Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Brain Metastases

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Disclosures

- Steering Committee: *Genentech/Roche*
- Consultation: *Genentech/Roche, Novartis, and Bristol-Myers Squibb*

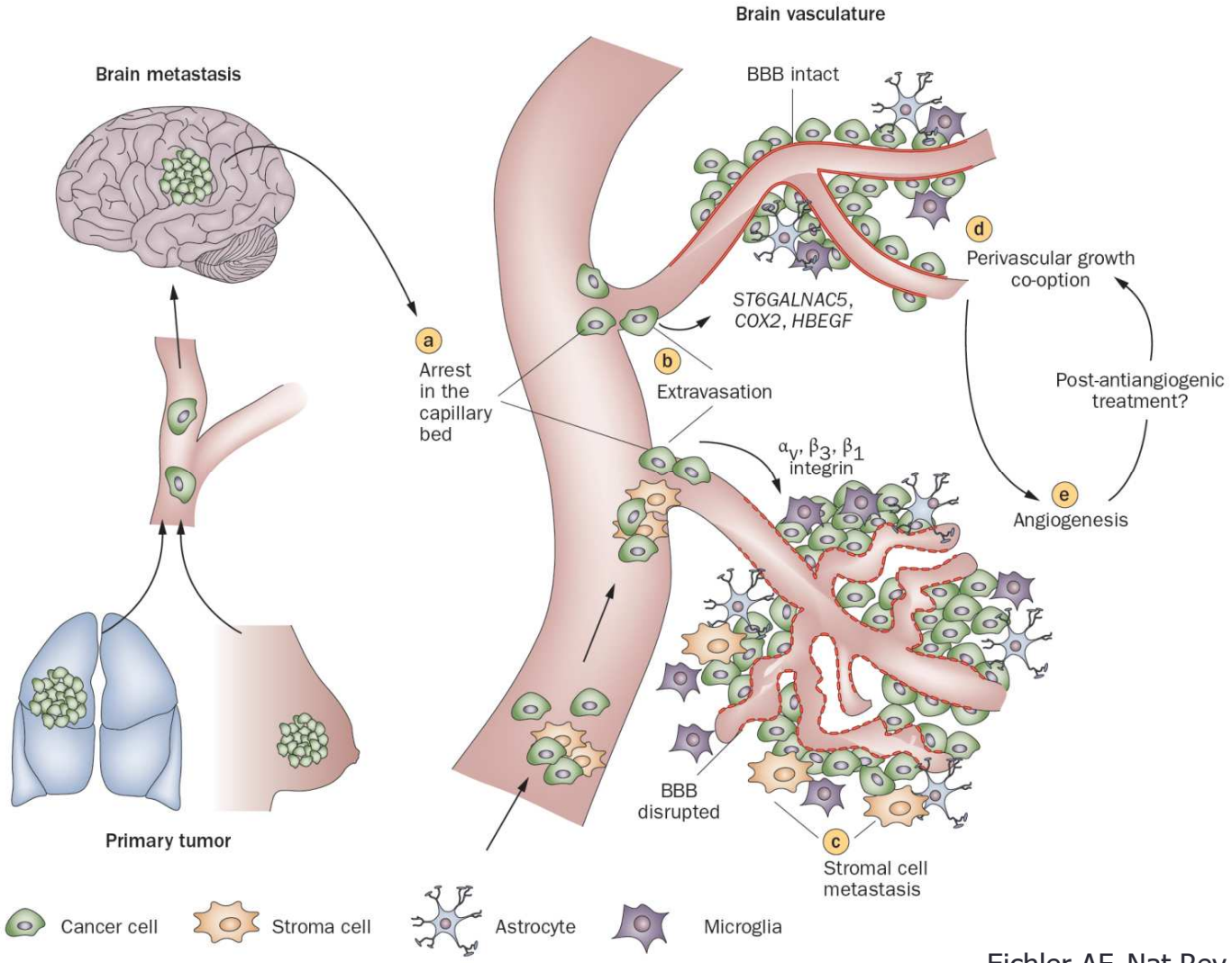
Objectives

Objective 1: To develop a better understanding of the clinical significance of brain metastases in oncology.

Objective 2: To learn about “immune privilege” of the CNS

Objective 3: To learn about the application of immunotherapies for management of brain metastases.

How do brain metastases develop?



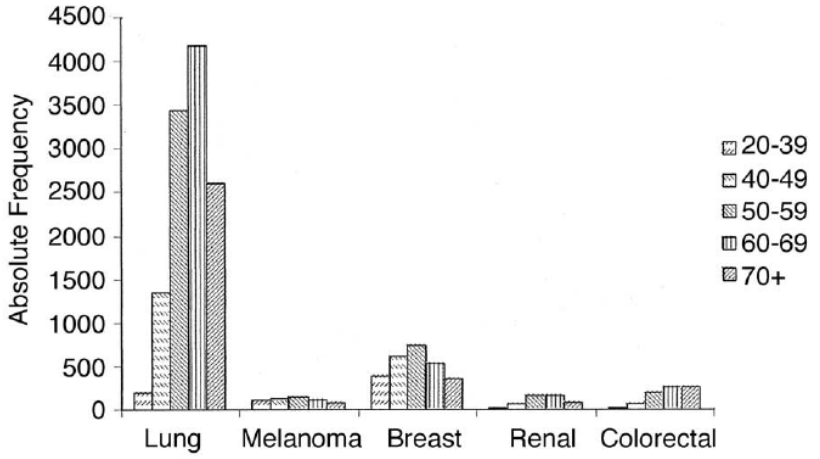
Eichler AF, Nat Rev Clin Oncol 2011

Breakdown of CNS metastases

- 7-11 new brain met pts/100,000 in USA yearly
- Approximately 170, 000 cases/year
- Autopsy reports show 15-41% of patients with known primary cancers have brain mets
- Most common cancers to metastasize to the brain: lung, breast, melanoma, and GI tract.

TABLE 1 Frequency of BM by primary cancer in 943 cases

Primary cancer	No. of cases	Sex ratio, M:F	Frequency, %
Lung	456	321:135	48.4
Breast	156	0:156	16.5
Renal	72	37:35	7.6
Colorectal	68	41:27	7.2
Uterus	38	0:38	4.0
Melanoma	35	24:11	3.7
Malignant lymphoma	27	15:12	2.9
Other known primary	41	23:18	4.4
Unknown origin	50	24:26	5.3
Total	943	485:458	100.00



Owonikoko TK, et al, Nat Rev Clin Oncol, 2014
Johnson JD, et al, Neurosurg Clin N Am, 1996
Barnholtz-Sloan JS, JCO 2004.
Zhang X, Ann Surg Oncol, 2012.

Impact of Brain Metastases (Melanoma)

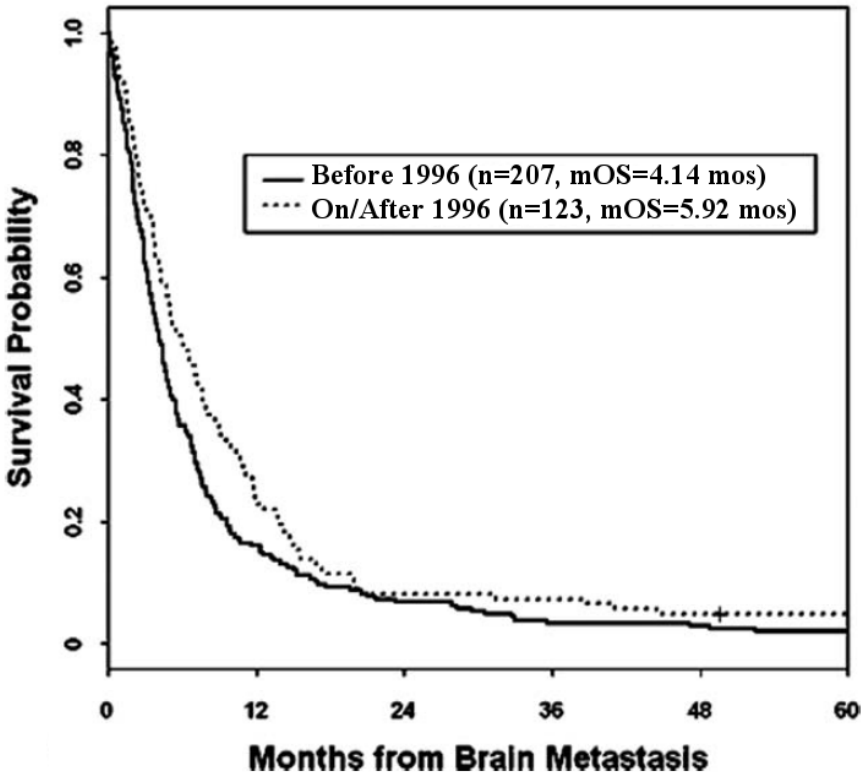
73,870 New Cases of melanoma

↓

9,940 Deaths From melanoma

↓ **Up to 50% rate**

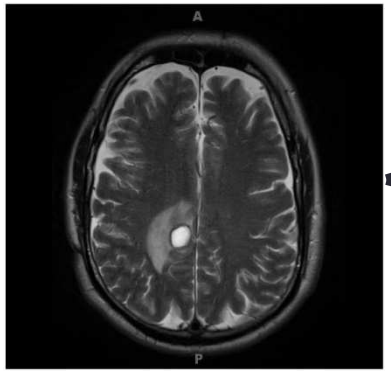
4,970 Deaths attributed to symptomatic brain mets



Siegal RL, et al, CA Cancer J Clin, 2015.
Davies MA, et al, Cancer, 2011.

General Management Strategies

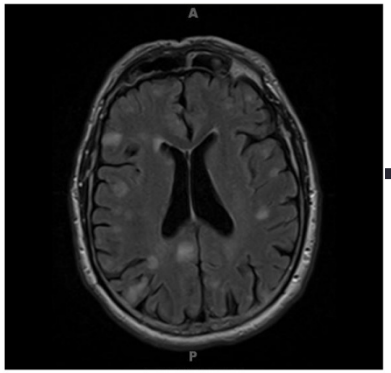
1 - 4 lesions



Surgery

Stereotactic Radiosurgery

≥ 5 lesions



Whole Brain Radiotherapy

Ewend MG, et al, J Natl Compr Canc Netw, 2008

Impact of standard melanoma BM management

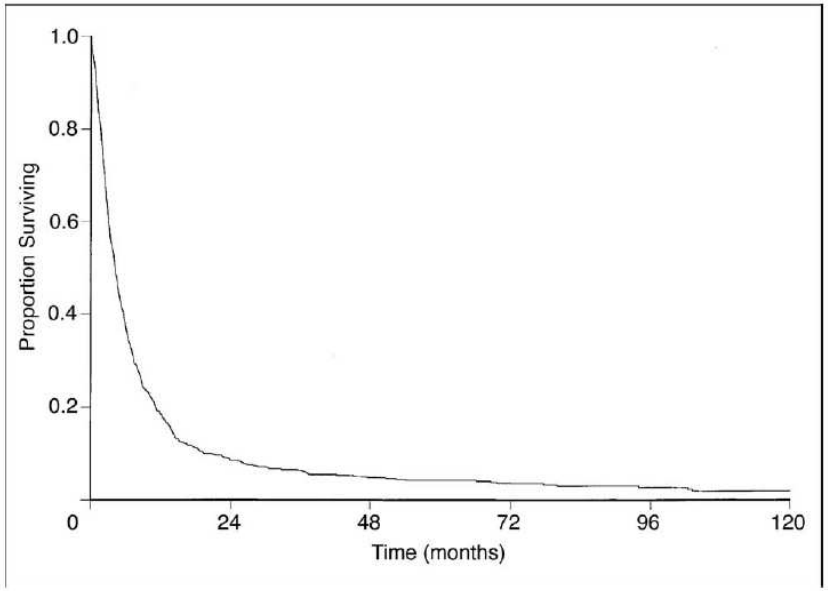


Fig 1. Cerebral metastases from melanoma (1985 to 2000 cohort); overall survival.

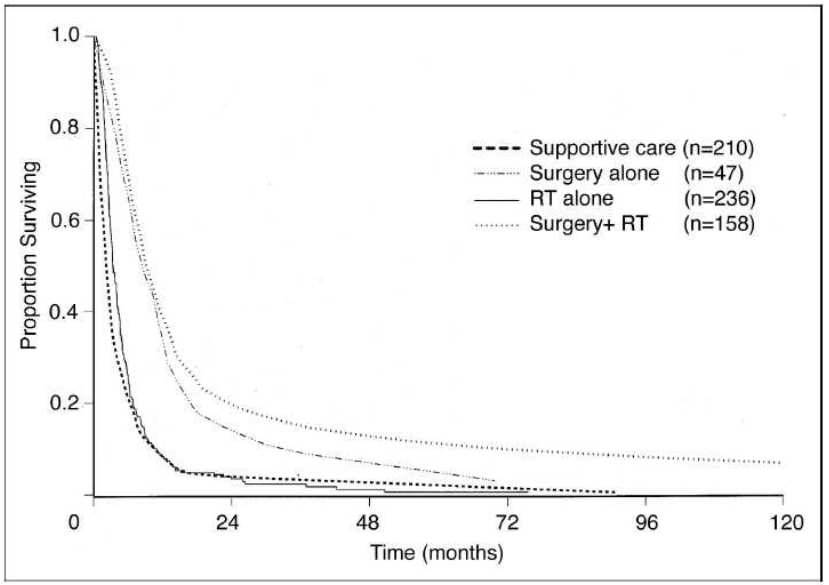


Fig 2. Cerebral metastases from melanoma (1985 to 2000 cohort); survival by treatment. RT, radiotherapy.

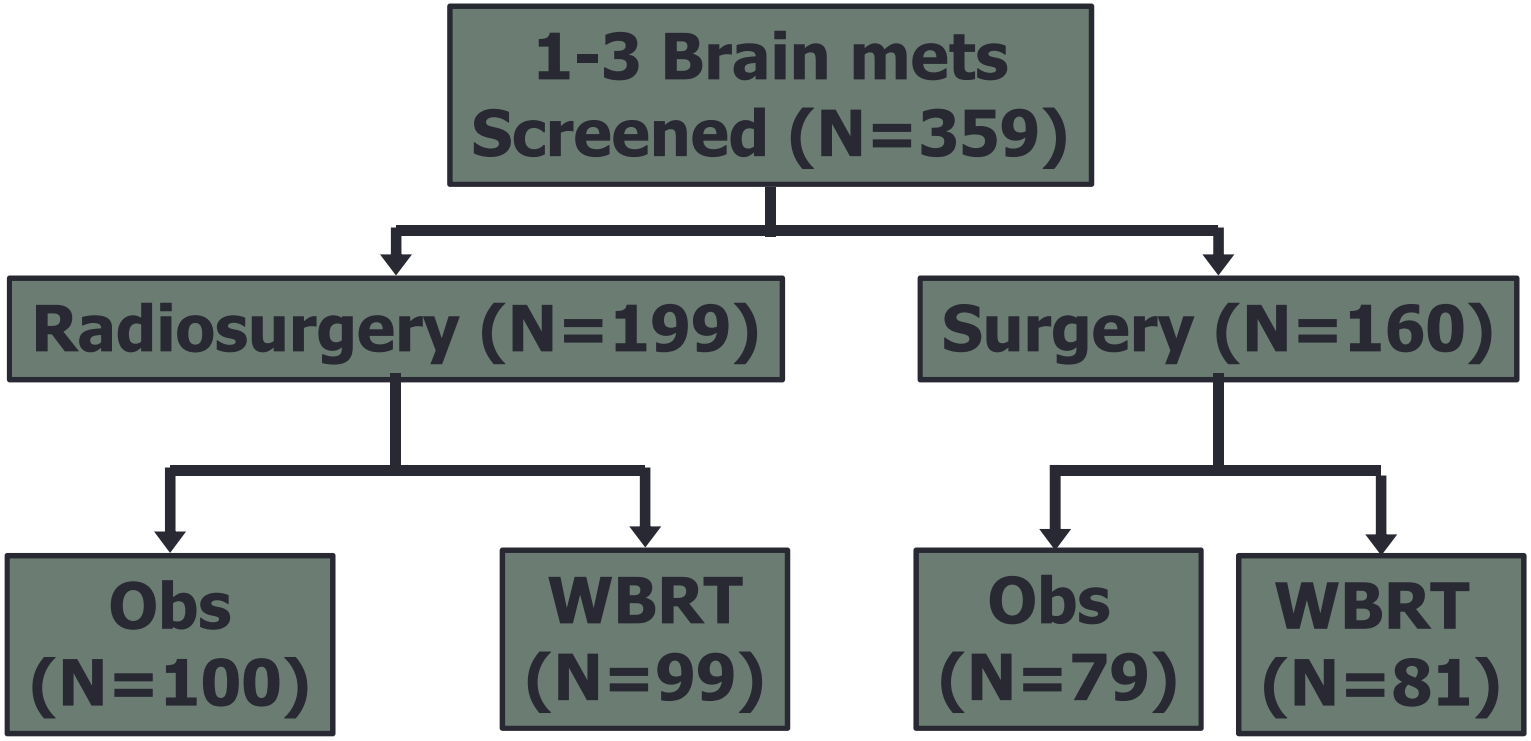
Table 5. Median Survival According to Treatment From the Three Largest Published Series of Patients With Cerebral Metastases

Treatment	Fife et al* (1985–2000 cohort)		Sampson et al*[1]		Lagerwaard et al†[4]	
	Median Survival (months)	No. of Patients	Median Survival (months)	No. of Patients	Median Survival (months)	No. of Patients
Supportive care	2.1	210	NA	178	1.3	118
Radiotherapy alone	3.4	236	4.0	180	3.6	1,079
Surgery alone	8.7	47	6.5	52		
Surgery and radiotherapy	8.9	158	8.9	87	8.9	95

Abbreviation: NA, not available.
*Series including melanoma patients only.
†Series including patients with breast cancer, lung cancer, melanoma, and other primary sites.

Reference: Fife KM, et al, J Clin Oncol, 2004

EORTC-22952 Protocol



NSCLC 53%, Breast 12%, Kidney 8%, Colorectal 8%, and Melanoma 5%

Reference: Kocher M, et al, J Clin Oncol, 2011.

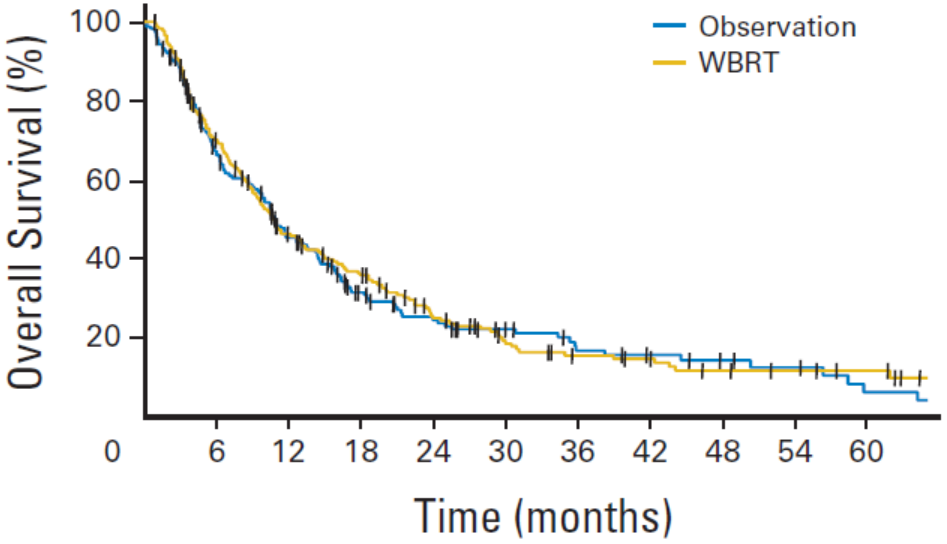
EORTC-22952 Protocol

Intracranial Recurrence At 2years

	Treated site relapse	New site relapse
Surgery + Obs	59%	42%
Surgery + WBRT	27%	23%
SRS + Obs	31%	48%
SRS + WBRT	19%	33%

P<0.05 for all paired comparisons of Obs vs WBRT

Survival



	Observation	WBRT
mOS	10.9 mos	10.7 mos

Reference: Kocher M, et al, J Clin Oncol, 2011.

Systemic therapies for BMs?

Chemotherapy → modest BM activity in patients

- 7% RR for temozolomide and fotemustine in melanoma patients
- 30% RR for cisplatin/etoposide in NSCLC patients
- 38% RR for cisplatin/etoposide in breast cancer patients

Targeted therapies → possibly more BM activity

- ~30% RR for dabrafenib/trametinib in BRAF mut melanoma
- upto 67% RR for erlotinib in EGFR mut NSCLC
- *6% RR for lapatinib in HER2+ breast cancer (20% when combined with capecitabine)*

What about immunotherapies?

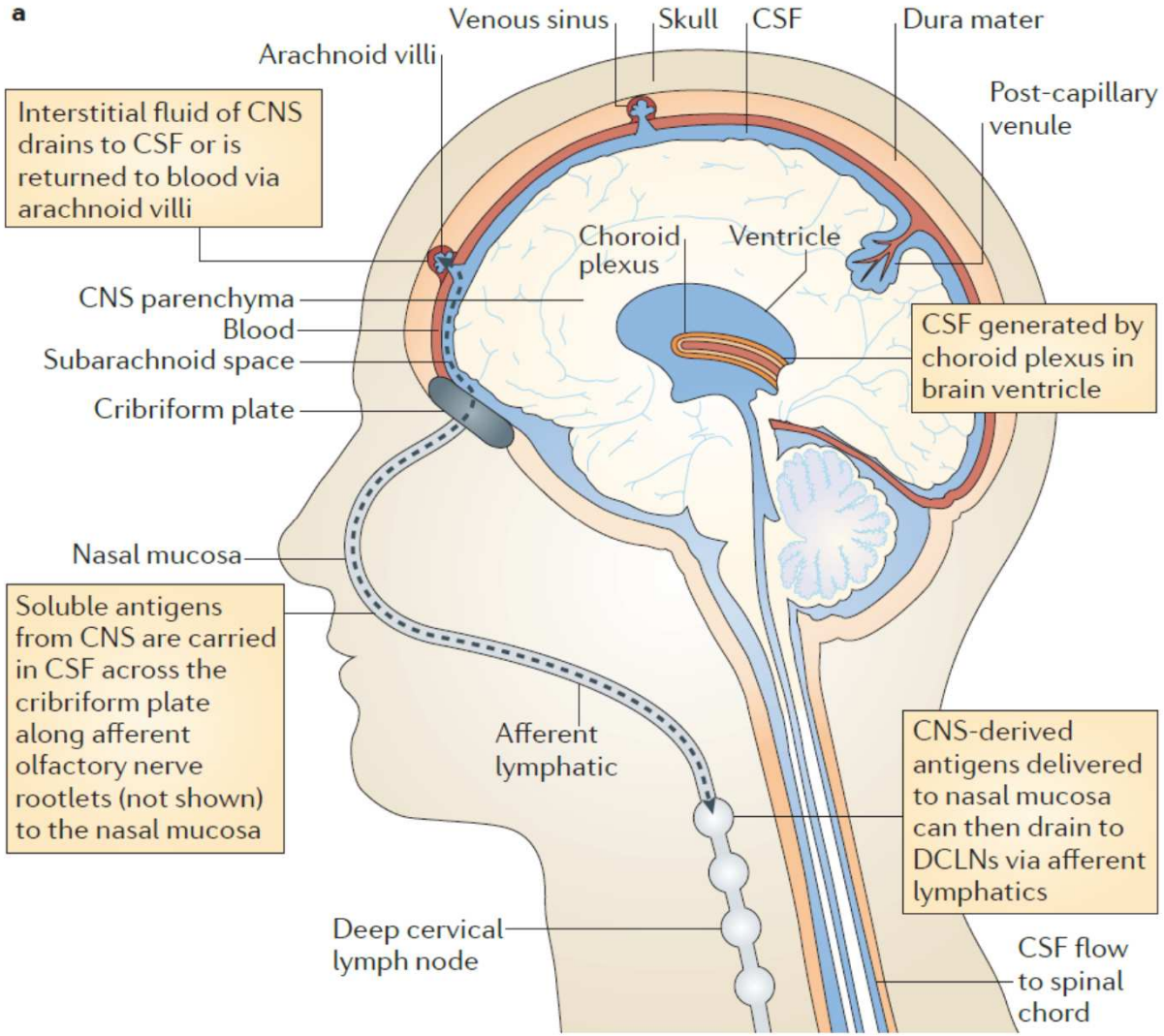
Gibney GT, et al, Mel Res, 2012.
Franciosi V, et al, Cancer, 1999.
Wu YL, et al, Ann Oncol, 2013.
Lin NU, et al, Clin Cancer Res, 2009.

Concept of immune privilege/sanctuary

- Few immune cells are within the brain parenchyma – primarily parenchymal microglial cell (a highly specialized tissue macrophage) and macrophages at the meninges
- CSF mainly contains trafficking populations of memory T cells (1000-3000/mL), small numbers of B cells and monocytes
- The BBB limits but does not prevent immune cells from crossing in the brain parenchyma
- Direct injection of tumor cells into brain parenchyma does not elicit an immune response
- Goal is to minimize inflammation and damage to CNS

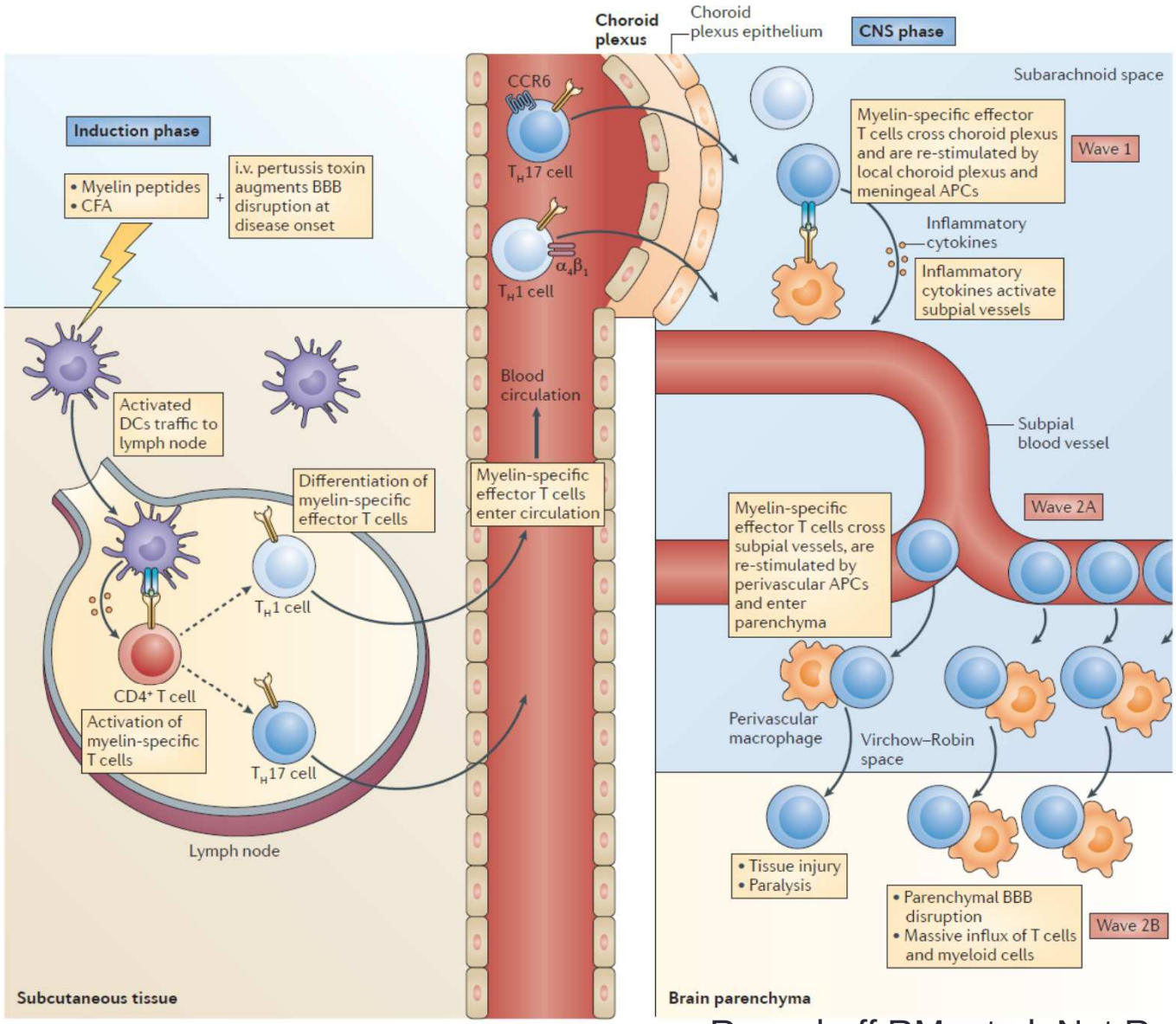
Ransonoff RM, et al, Nat Rev Immunol, 2012

Flow for CNS Antigen presentation



Ransohoff RM, et al, Nat Rev Immunol 2012

Model for immune response in the CNS

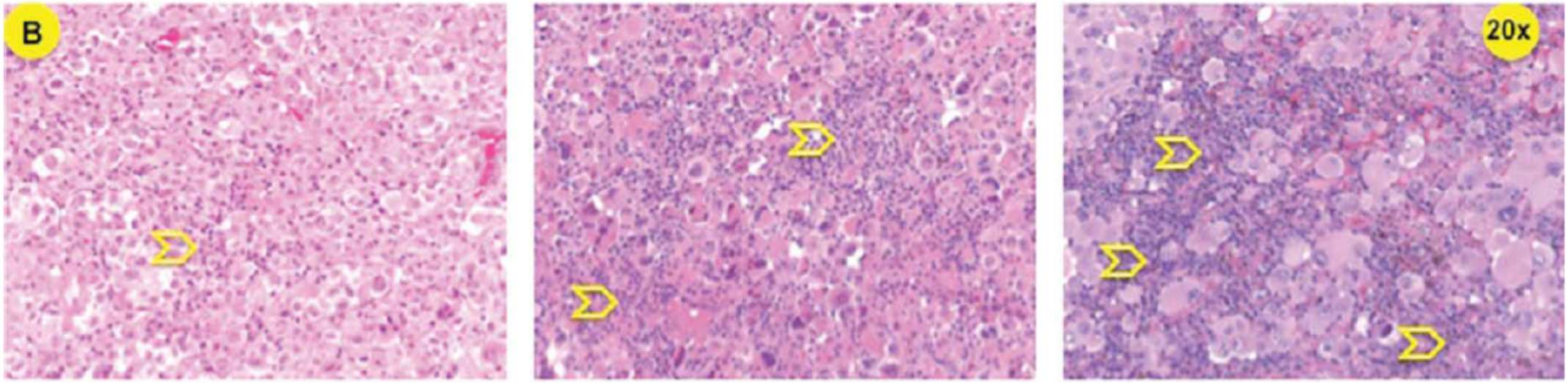


Ransohoff RM, et al, Nat Rev Immunol 2012

Are there immune responses in brain metastases?

- Retrospective study of 115 patients who underwent craniotomy for melanoma BM at the University of Pittsburgh
- 31 received immunotherapy prior to surgery (no prior radiation to the brain)
- Immune infiltrate was scored semi-quantitatively from 0 to 3+
  - Low = score of 0-1+, High = score of 2-3+
- 44 tumors out of 101 (44%) showed a high immune infiltrate

Low lymph infiltrate (1+) | Moderate lymph infiltrate (2+) | High lymph infiltrate (3+)



Hamilton R, et al, Cancer, 2013

High immune infiltrate and immune markers are associated with better melanoma BM survival

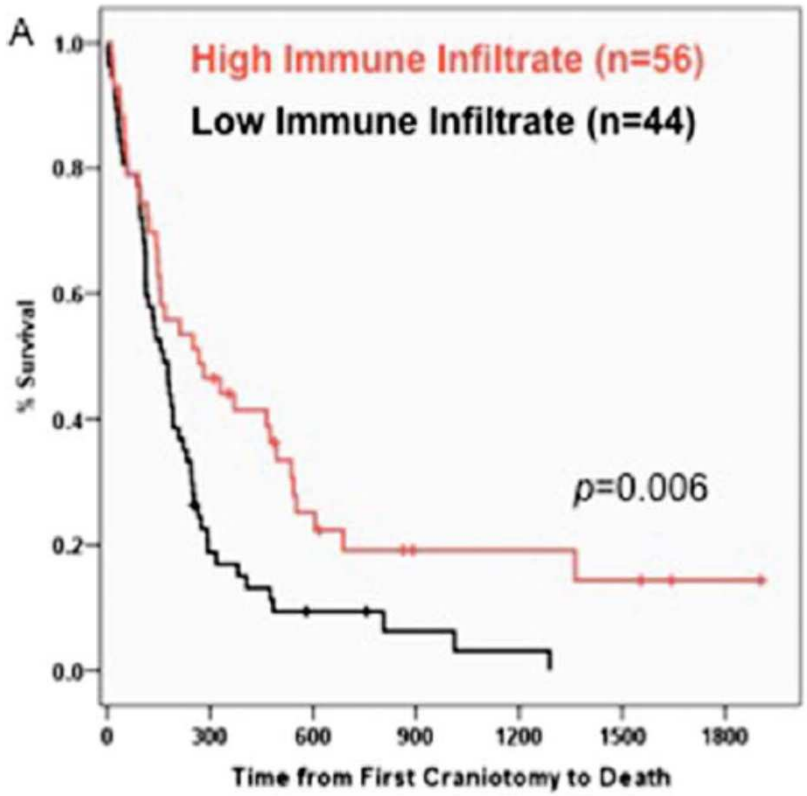


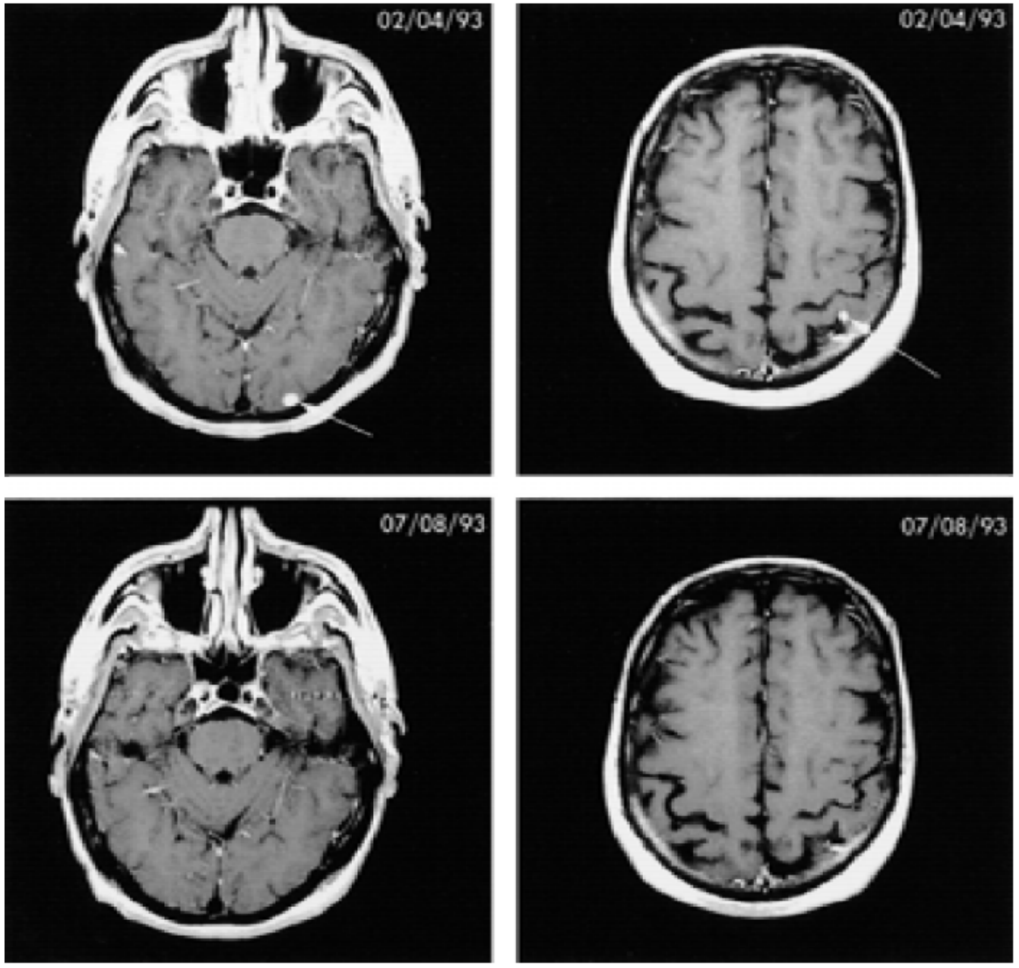
TABLE 3. Biocarta Pathways That Were Prognostically Significant in Metastatic Melanomas to the Brain.

	Pathways Associated With Good Prognosis	GSA Test *P* Value
1	CD3 complex	<.005
2	T helper (Th) surface molecules	<.005
3	HIV-induced T-cell apoptosis	<.005
4	B-cell surface molecules	<.005
5	Th1/Th2 differentiation	<.005
6	Role of Tob in T-cell activation	<.005
7	Activation of Csk inhibits signaling through the TCR	.005
8	Lck and Fyn kinases initiate TCR activation	.005
9	Cells/molecules involved in local acute inflammatory response	.005
10	Dendritic cells regulate Th1/Th2 development	.005

Hamilton R, et al, Cancer, 2013

Proof of principle – Interleukin 2

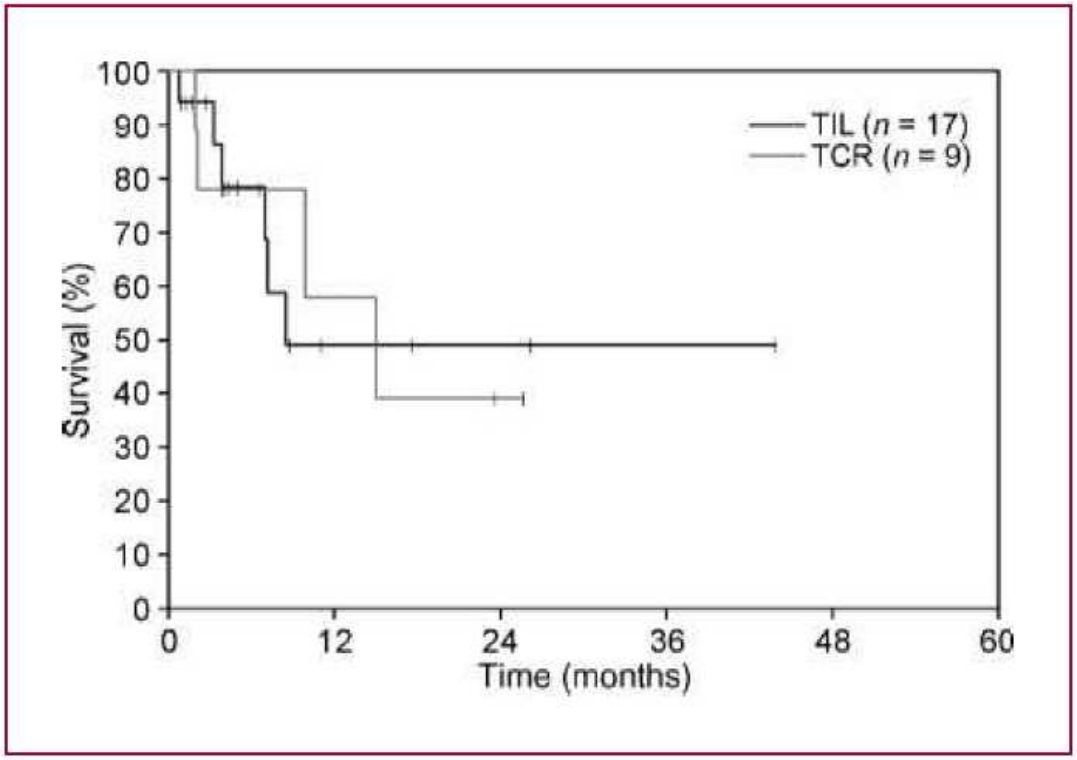
- Retrospective review of 1069 melanoma and RCC patients treated with IL-2 at the NCI → 37 with active, untreated BMs
- Safe: similar rate of neurotoxicities and # of IL-2 doses compared to BM-free patients
- 1 CR and 1 PR out of 36 evaluable BM patients (5.6% ORR)



Guirguis LM, et al, J Immunother, 2002

Proof of principle – Adoptive Cell Therapy

- Retrospective review of 264 melanoma patients treated with either TIL/IL-2 or autogolous TCR-transduced lymphocyte infusion/IL-2 at the NCI → 26 with active, untreated BMs
- Relatively safe – one pt developed SAH at 9mm brain met during thrombocytopenic phase requiring surgery
- 7 CRs, 6 PRs (ORR 50%)
- All responding BMs were 10mm or less in size



Hong JJ, et al, Clin Cancer Res, 2010

Ipilimumab for BM (melanoma)

Two prospective ipilimumab studies BM studies (also ipilimumab EAP study)

❖ **Phase II study of Ipilimumab 10mg/kg x 4 doses, followed by maintenance Ipilimumab Q12 weeks**

- **Cohort A N=51, asymptomatic, no steroids**
- **Cohort B N=21, symptomatic, requiring steroids, and/or edema**
  - **Prior SRS or WBRT allowed (as long on not index lesion)**

❖ **NIBIT-M1 – single arm phase II study of Ipilimumab 10mg/kg x 4 with fotemustine through 24, then maintenance ipilimumab and fotemustine if clinical response.**

- **20/80 patients enrolled with asymptomatic MBMs**

Margolin K, et al, Lancet Oncol, 2012
Di Giacomo AM, et al, Lancet Oncol, 2012

Immunotherapy for Brain Mets: Ipilimumab

ORR

Treatment	Complete Response	Partial Response	Stable Disease
Cohort A (asymptomatic, no steroids)			
CNS only	0%	16%	10%
Overall	0%	10%	16%
Cohort B (symptomatic, steroids)			
CNS only	5%	0%	5%
Overall	0%	5%	5%

*irRC after 12 weeks

mPFS

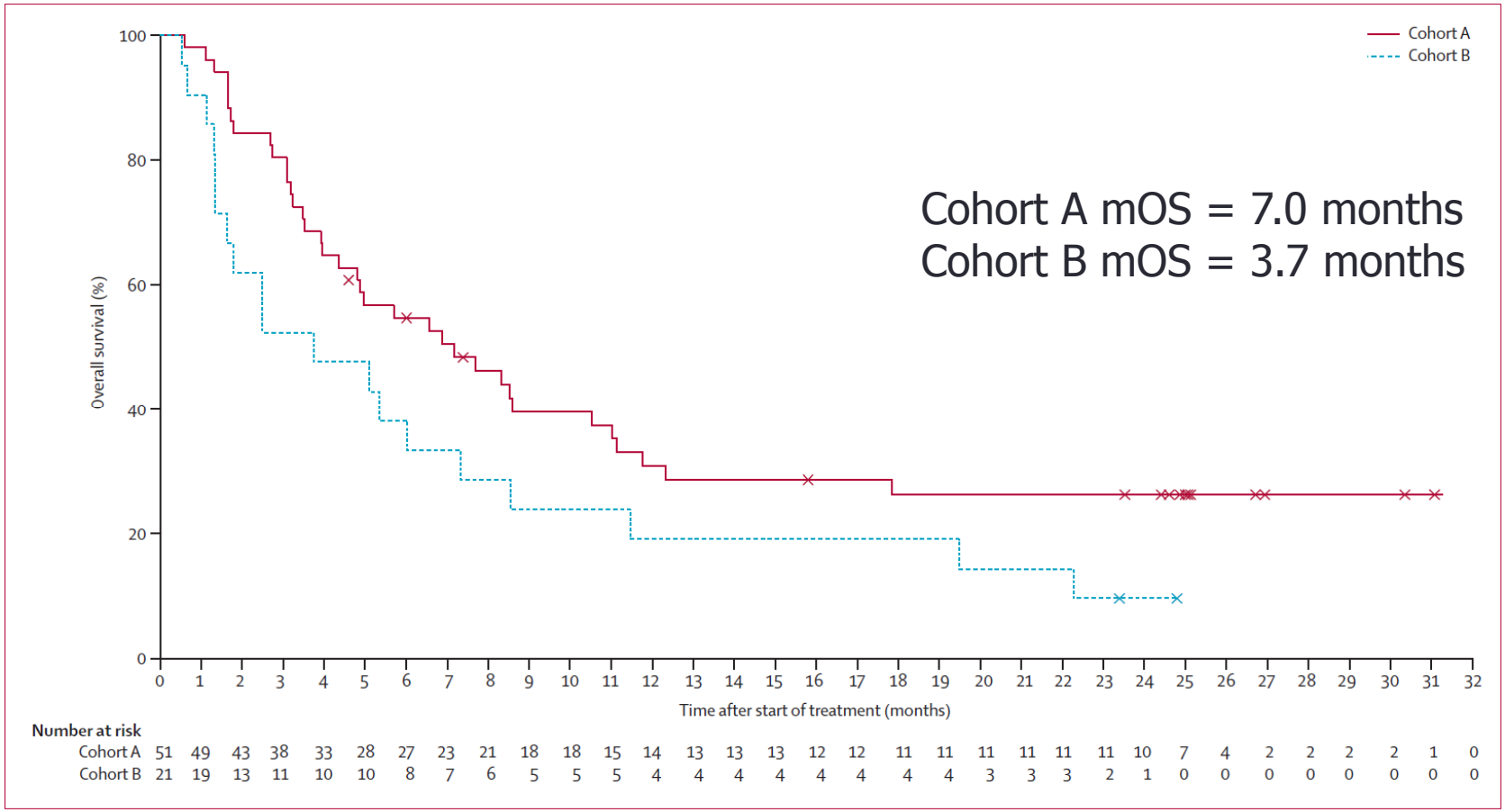
	Cohort A		Cohort B	
	mWHO	irRC	mWHO	irRC
Overall	1·4 (1·2–2·6)	2·7 (1·6–3·7)	1·2 (1·2–1·3)	1·3 (1·2–2·5)
Brain	1·5 (1·2–2·5)	1·9 (1·2–2·9)	1·2(1·2–1·3)	1·2 (1·2–1·3)
Non-CNS	2·6 (1·3–4·1)	3·3 (2·6–4·7)	1·3 (1·2–2·5)	1·3 (1·2–2·5)

Data are months (95% CI). mWHO=modified WHO criteria. irRC=immune-related response criteria.

Table 4: Median progression-free survival

Margolin K, et al,
Lancet Oncol, 2012

Ipilimumab for melanoma BM patients



Margolin K, et al, Lancet 2012

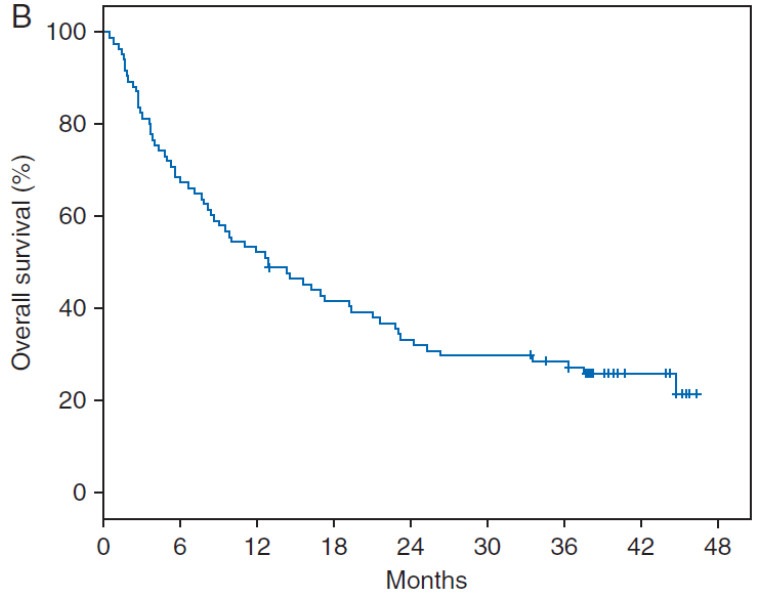
Adverse Events with Ipilimumab

	Cohort A (n=51)			Cohort B (n=21)		
	Any grade*	Grade 3	Grade 4	Any grade*	Grade 3	Grade 4
Any event						
Diarrhoea	25 (49%)	6 (12%)	0	9 (43%)	0	0
Nausea	22 (43%)	3 (6%)	0	4 (19%)	0	0
Vomiting	13 (25%)	3 (6%)	0	1 (5%)	0	0
Constipation	8 (16%)	0	0	4 (19%)	0	0
Fatigue	28 (55%)	6 (12%)	0	12 (57%)	1 (5%)	0
Oedema (peripheral)	4 (8%)	1 (2%)	0	5 (24%)	0	0
Headache	18 (35%)	2 (4%)	0	6 (29%)	0	0
Dizziness	11 (22%)	0	0	2 (10%)	0	0
Rash	19 (37%)	1 (2%)	0	7 (33%)	1 (5%)	0
Pruritus	16 (31%)	0	0	6 (29%)	0	0
Decreased appetite	14 (27%)	2 (4%)	0	4 (19%)	0	0
Dehydration	5 (10%)	2 (4%)	0	4 (19%)	2 (10%)	0
Hyperglycaemia	4 (8%)	2 (4%)	0	4 (19%)	2 (10%)	0
Back pain	8 (16%)	0	0	4 (19%)	1 (5%)	0
Cough	11 (22%)	0	0	2 (10%)	0	0
Aspartate aminotransferase increased	4 (8%)	1 (2%)	0	4 (19%)	2 (10%)	0
Confused state	9 (18%)	1 (2%)	1 (2%)	3 (14%)	1 (5%)	1 (5%)
Insomnia	8 (16%)	0	0	4 (19%)	0	0

Ipilimumab + Fotemustine for melanoma BM patients

Treatment	Complete Response	Partial Response	Stable Disease
Ipilimumab plus Fotemustine			
Treatment-Naïve (n=13)	5 (38%)	3 (23%)	
Prior Brain Met Radiation (n=7)	0%	3 (43%)	

- Median OS 12.7 months (similar to non-BM group)
- 5 CNS events (hemorrhage, seizure, headache) attributed to disease progression

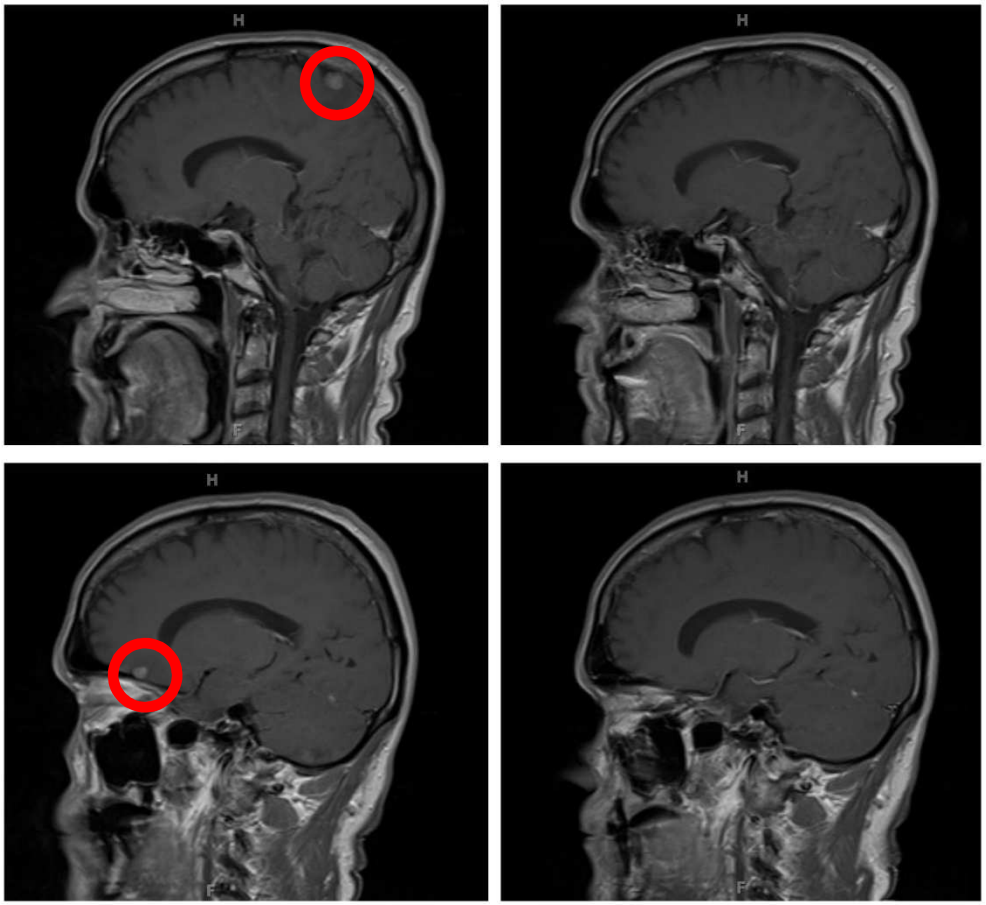


Di Giacomo AM, et al, Lancet Oncol, 2012
Di Giacomo AM, et al, Ann Oncol, 2015

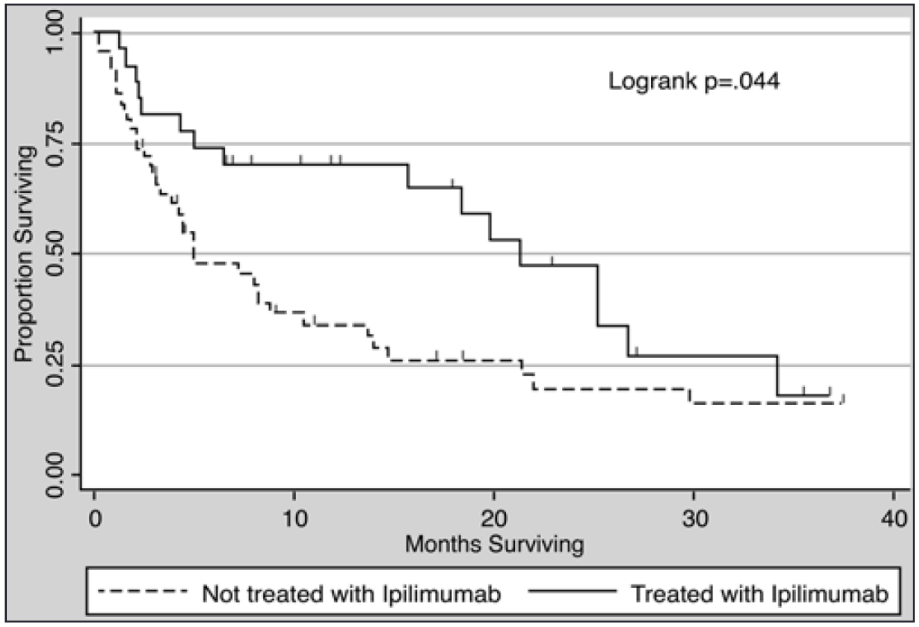
Patient example:

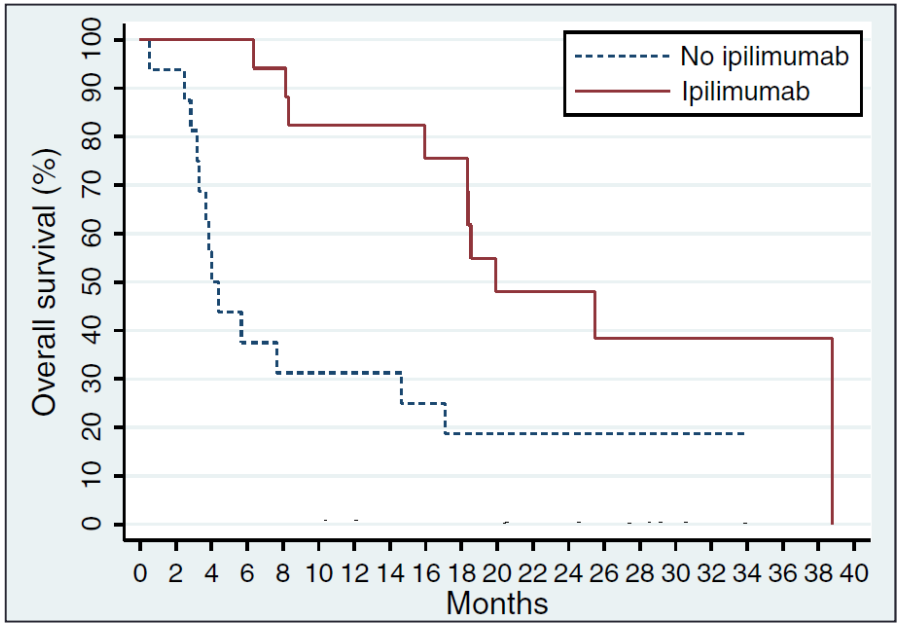
Ipilimumab plus Stereotactic Radiosurgery

s/p Ipi x 2 doses **s/p SRS + Ipi**



Retrospective data on melanoma BM patients treated sequentially with RT and Ipilimumab





mOS = 4.9 mos / mOS = 21.3 mos

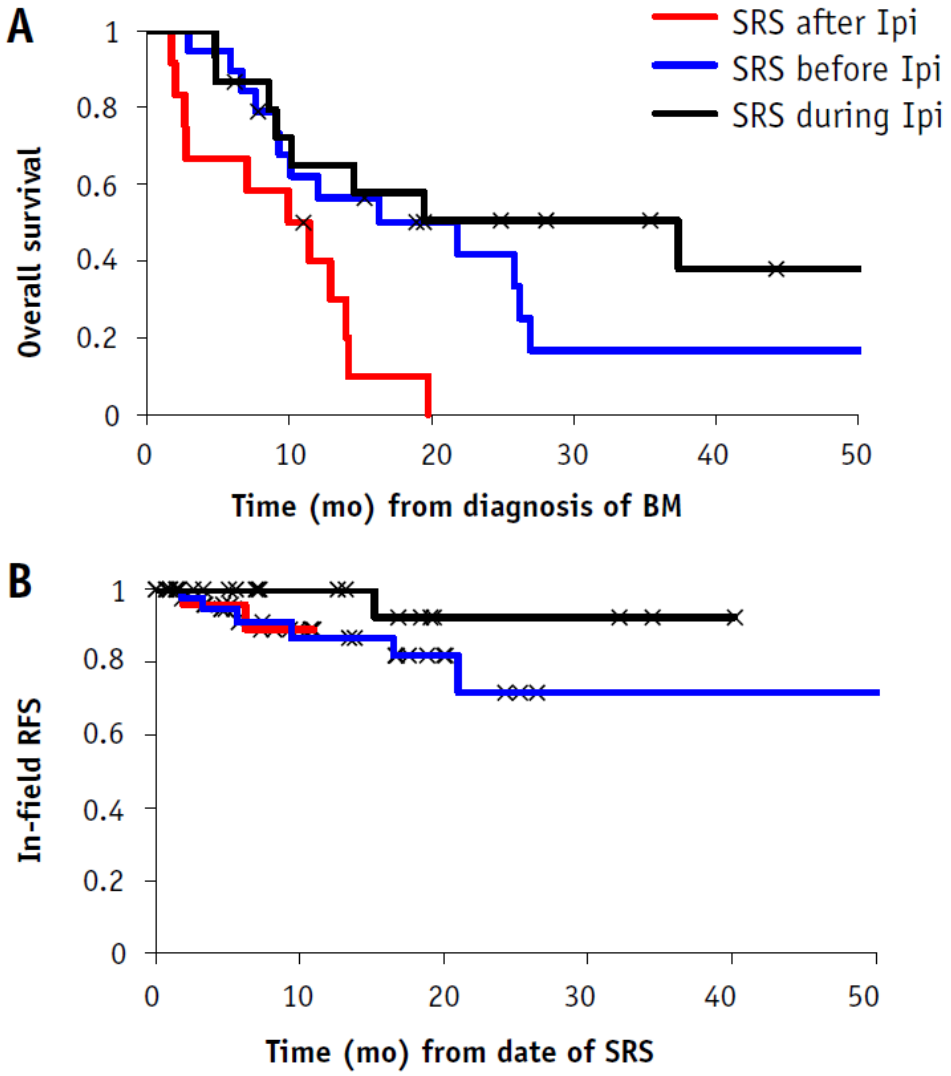
Knisely JP, et al, J Neurosurg 2012

mOS = 4.0 mos / mOS = 19.9 mos

Silk AW, et al, Cancer Med, 2013

Ipilimumab + SRS

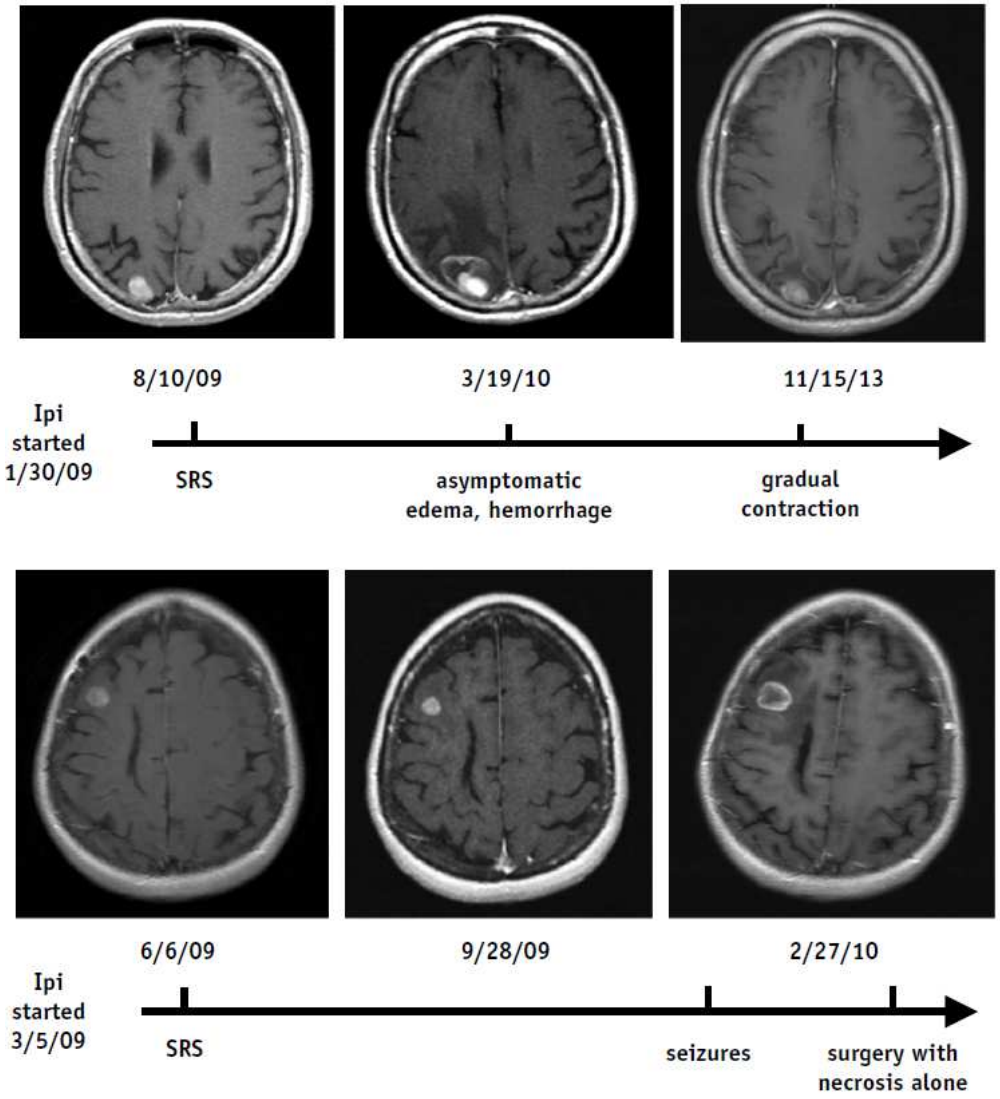
- Retrospective study of 46 melanoma BM patients treated with SRS prior to (n=19), concurrent with (n=15), or after (n=12) ipilimumab.
- 40/46 patients received prior systemic therapy
- 10 patients also received WBRT
- Median number BMs = 2 (range 1-6)
- Median OS 12.4 months



Kiess AP, et al, Int J Rad Oncol, 2015

SRS + Ipilimumab, toxicities

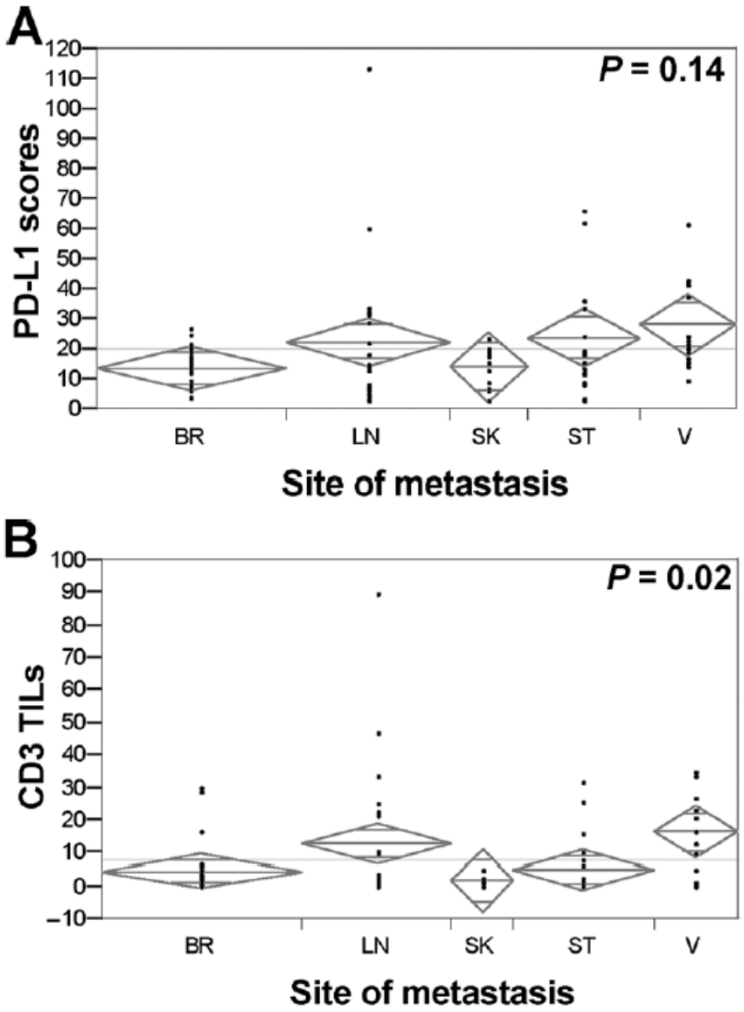
- Few significant neurotoxicities in patients receiving SRS before or during Ipilimumab –cognitive change, headaches, seizure, and CNS bleeding
- 11 pts required steroids for 2 or more weeks
- 50% of treated BMs increase >150% size if SRS was during or before Ipilimumab
- 82% of treated BMs had hemmorrhage and/or edema



Kiess AP, et al, Int J Rad Oncol, 2015

Is anti-PD-1/anti-PD-L1 a potential strategy?

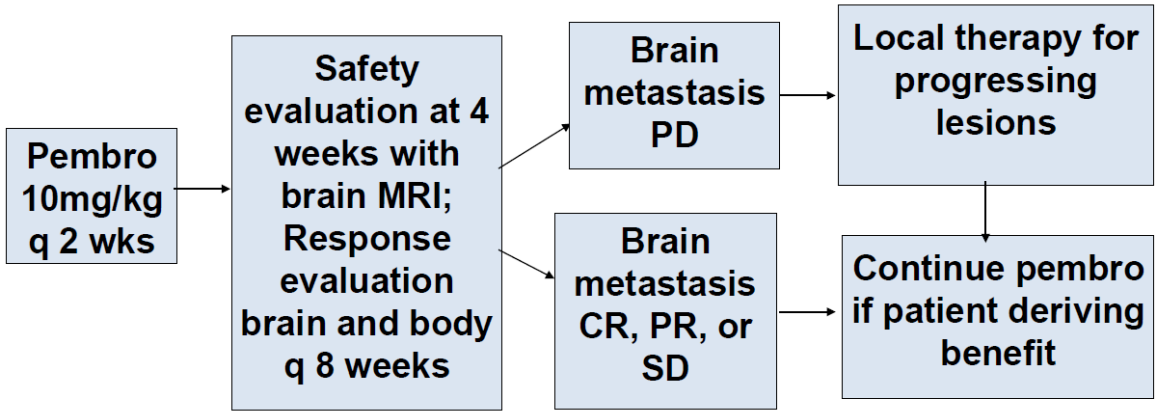
- Median PD-L1 aqua score of 14 (range 4-27)
- Dichotomous high/low = 41% high for brain mets vs 54% high for non-brain mets
- High TIL = 30% in brain mets compared to 57% in non-brain mets
- Other tumor types show BMs can have high PD-L1 expression and TIL (such as breast and lung)



Kluger HM, et al, Clin Cancer Res, 2015

Phase 2 study of pembrolizumab in NSCLC and melanoma patients with active BMs

- Requirements: at least one untreated BM measuring 5-20mm, asymptomatic; requires BM amenable to biopsy or availability of prior tissue
- Dose of pembro: 10mg/kg Q2weeks



- Enrolled 16 patients with NSCLC and 19 patients with melanoma
- Planned accrual 44 NSCLC patients, 24 melanoma patients

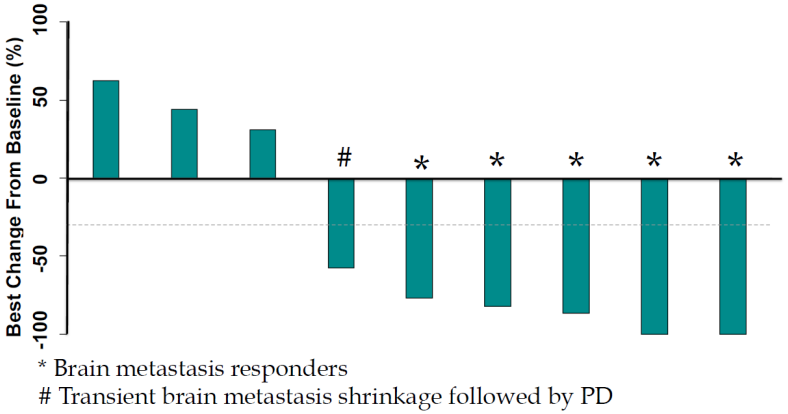
Goldberg S, et al, 2015 ASCO Annual Meeting, Abstract 8035
Kluger HM, et al, 2015 ASCO Annual Meeting, Abstract 9009

Phase 2 study of pembrolizumab in NSCLC and melanoma patients with active BMs

- Brain met responses:
  - NSCLC = 1 CR, 4 PRs out of 11 evaluable patients (ORR 45%)
  - Melanoma = 4 PRs out of 14 evaluable patients (ORR 29%)

NSCLC

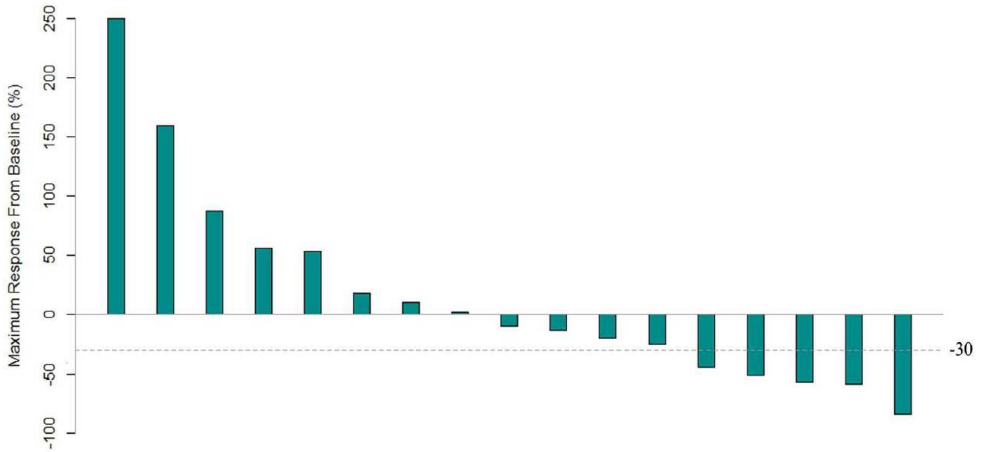
Figure 1. Best Change in Brain Metastasis Tumor Size by mRECIST



* Brain metastasis responders
\# Transient brain metastasis shrinkage followed by PD

Melanoma

CHANGES IN SUM OF DIAMETERS OF BRAIN LESIONS:



Goldberg S, et al, 2015 ASCO Annual Meeting, Abstract 8035
Kluger HM, et al, 2015 ASCO Annual Meeting, Abstract 9009

Ongoing trials

- Ipilimumab/Nivolumab in melanoma BM patients
  - **NCT02320058 (Checkmate 204)**, NCT02374242
- Fotemustine vs Ipilimumab/Fotemustine vs Ipilimumab/Nivolumab in melanoma BM patients
  - NCT02460068 (NIBIT)
- Ipilimumab + SRS or WBRT in melanoma BM patients
  - NCT01703507, NCT02115139, NCT01950195, NCT02097732
- Pembrolizumab in melanoma and NSCLC BM patients
  - NCT02085070
- GBM patient trials with immunotherapies
  - Ipilimumab/Nivolumab vs Nivolumab vs Bevacizumab (NCT02017717)
  - Pembrolizumab (NCT02337686)
  - Pembrolizumab +/- Bevacizumab (NCT02337491)

Take home points

- Brain metastases are a frequent occurrence and generally caries a poor prognosis in malignancies such as breast cancer, lung cancer and melanoma
- Immune responses are seen in brain metastases and are associated with improved survival
- Checkpoint immunotherapies, such as ipilimumab and pembrolizumab, have demonstrated objective BM responses in patients with melanoma and NSCLC
- Survival of BM patients treated with SRS and ipilimumab may be as good as BM-free patients treated with ipilimumab alone (at least in melanoma)