Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Brain Metastases

Ann W. Silk, MD
Rutgers Cancer Institute of New Jersey &
Robert Wood Johnson Medical School

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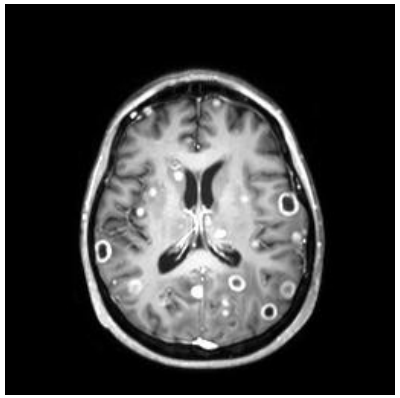
Society for Immunotherapy of Cancer

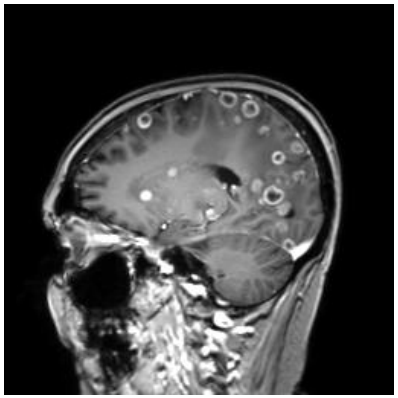
Outline

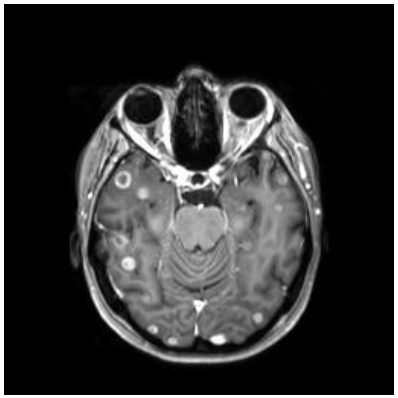
1. *Background*
2. *Immune surveillance and response in the CNS*
3. *Clinical experience with immunotherapy for the treatment of brain metastases*
4. *Rationale for combination therapies*

Brain Metastases (BM)

- 20-40% of cancer patients will develop BM
  - Lung (50%)
  - Breast (15%)
  - Melanoma (50-65%)
- The incidence of BM is increasing
  - HER2-positive breast cancer (30-55%)
  - ALK mutated NSCLC







Radiation therapy is the backbone of treatment

One BM	A few BM	Numerous BM
Surgery	Stereotactic radiosurgery (SRS)	Whole Brain Radiotherapy (WBRT)

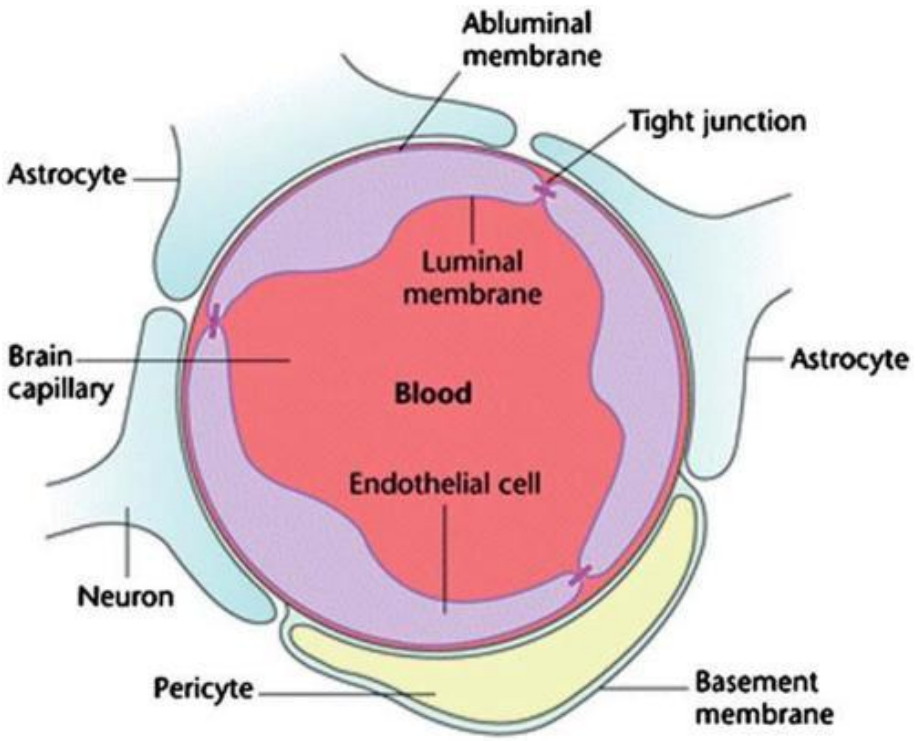
Limits of cytotoxic and targeted therapy

- Level of most cytotoxic and targeted drugs in brain metastases is a fraction of level in blood due to the blood brain barrier

The Blood Brain Barrier

Anatomy of the Blood Brain Barrier (BBB)

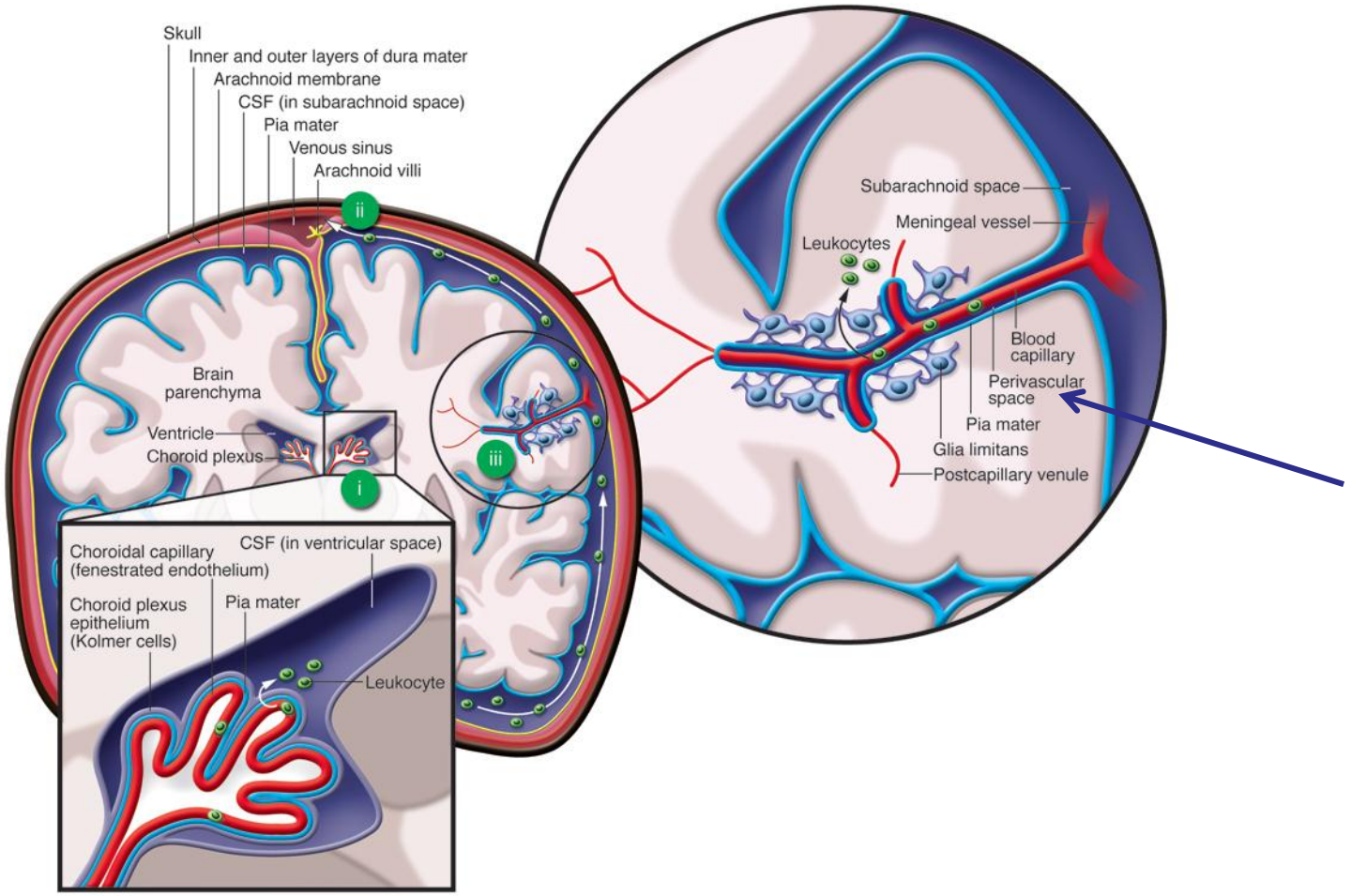
- Tight junctions
- Glia limitans – foot processes of astrocytes
- P-glycoprotein pumps



Cerebrospinal fluid (CSF) acts as lymph in the brain

- CSF is made by the choroid plexus
- Fills the ventricles and diffuses through the brain parenchyma
- Carries soluble antigens derived from the CNS
- Collects in the perivascular (Virchow Robin) spaces and drains to the subarachnoid space

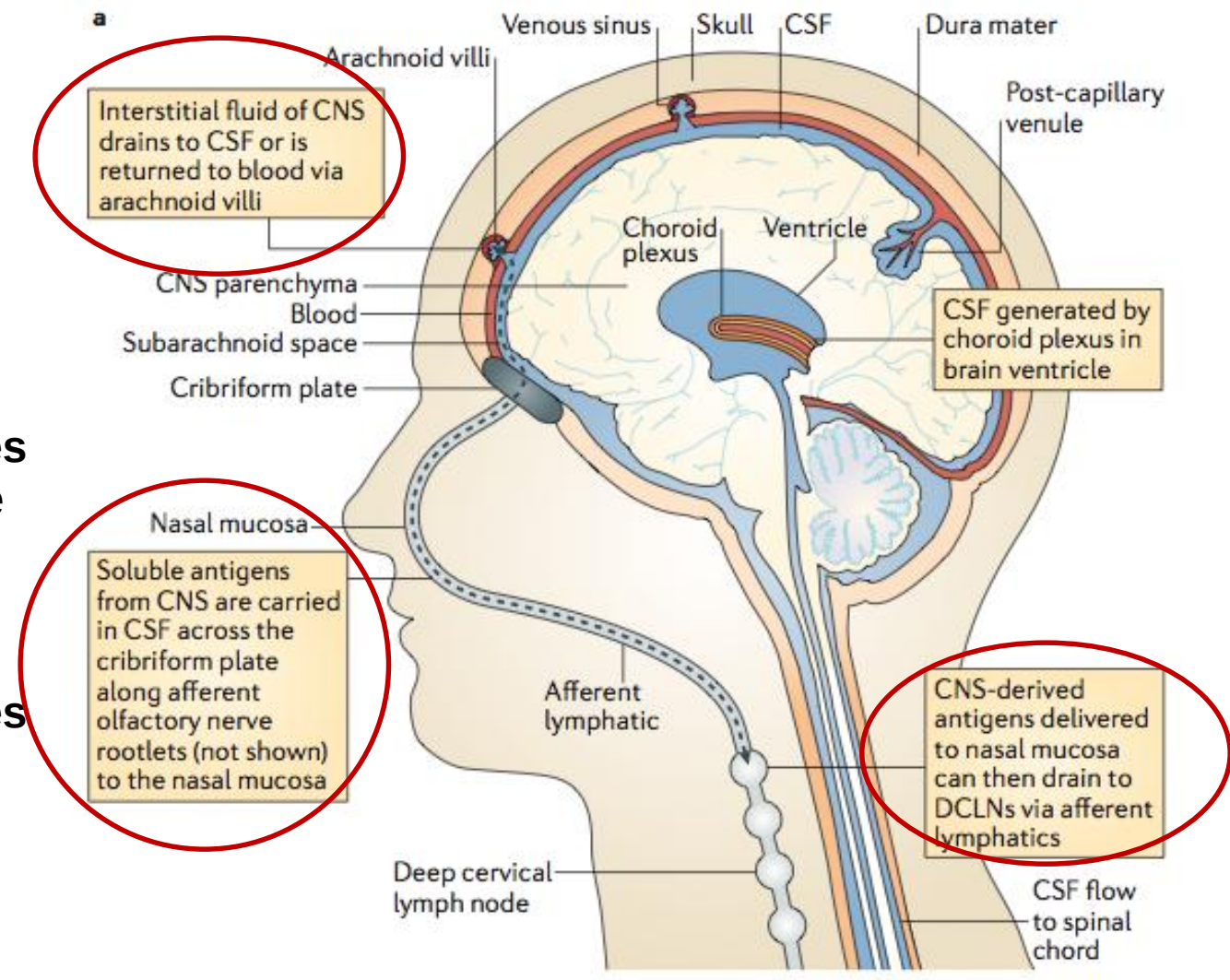
CSF carrying soluble antigens flows out through perivascular (Virchow-Robin) spaces



Wilson, Weninger and Hunter 2010 JCI

CSF drains to blood and lymph

- CSF drains from the subarachnoid space
  - To venous blood
  - To lymph
- Antigen presenting cells in the **deep cervical lymph nodes** can recognize soluble antigens in the CSF
- APCs in the **deep cervical lymph nodes** prime T cells → adaptive immunity



Ransohoff and Engelhardt, 2012. Nat Rev Immunol

Outline

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2. *The Blood Brain Barrier (BBB)*
3. *Immune surveillance and response in the CNS*
4. *Clinical experience with immunotherapy for the treatment of brain metastases*
5. *Rationale for combination therapies*

Is the brain a sanctuary?

- The brain contains no lymph nodes
- The parenchyma of the brain does not have conventional antigen presenting cells

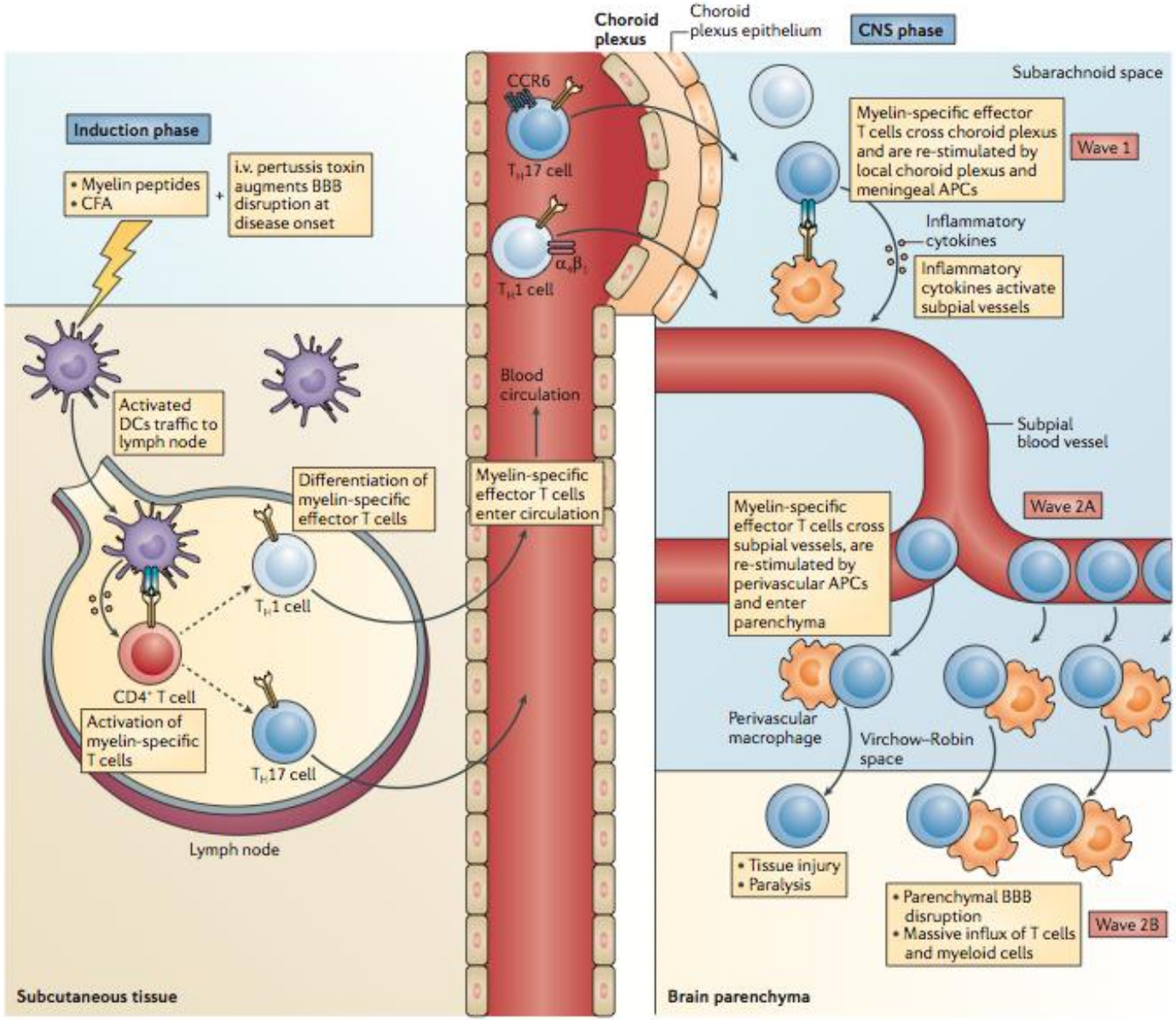
Evidence for immune privilege

1. In experimental models, antigens such as tumor cells, viruses, bacteria that are placed inside the brain parenchyma will not trigger a cell-mediated immune response

2. Peripheral immunization with an intra-parenchymal self antigen will trigger a brisk and robust immune response.

Ransohoff and Engelhardt, 2012. Nat Rev Immunol

Experimental autoimmune encephalomyelitis: A mouse model of multiple sclerosis



- Peripheral immunization with myelin
- Myelin-specific effector T-cells
- T cells enter the CSF in the SAS
- T cells enter brain parenchyma
- Brain injury

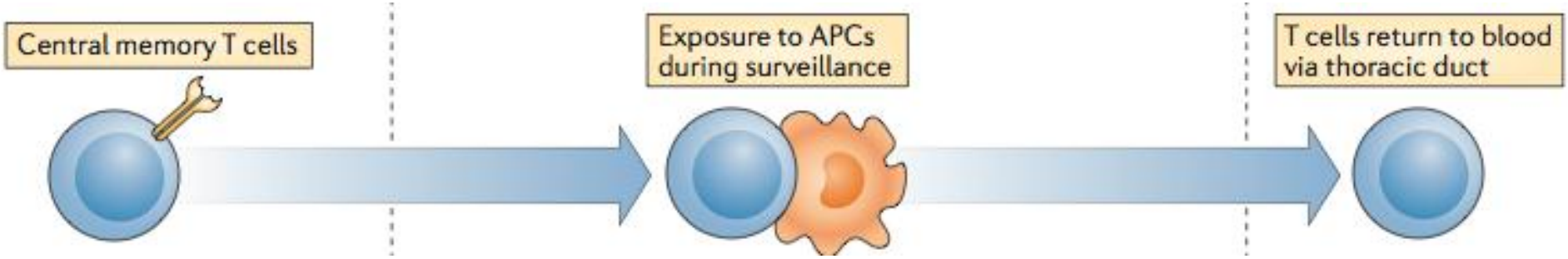
Ransohoff and Engelhardt, 2012.
Nat Rev Immunol

Clearly immune privilege in the brain is not absolute

- T-cells can cross the BBB
  - In health
    - Surveillance
  - In response to pathogens and cancer
    - Infectious meningitis and encephalitis
    - Brain metastases
  - In autoimmune disease
    - Multiple sclerosis
    - Ipilimumab-related hypophysitis

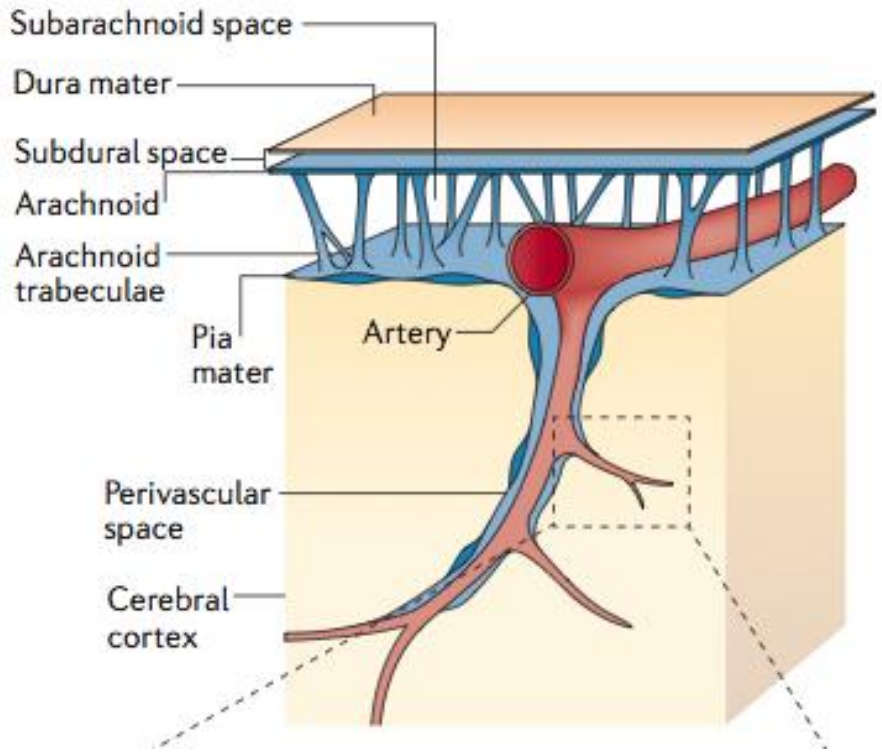
Memory T cells cross the BBB

How does immune surveillance in the CNS occur?



- Memory T cells enter CNS independent of antigen specificity
- Exposed to APC-like cells in the perivascular space
- In the absence of a non-self antigen, T cells flow with the CSF into the subarachnoid space
- T cells exit the CNS with the CSF via nasal mucosa to deep cervical lymph nodes

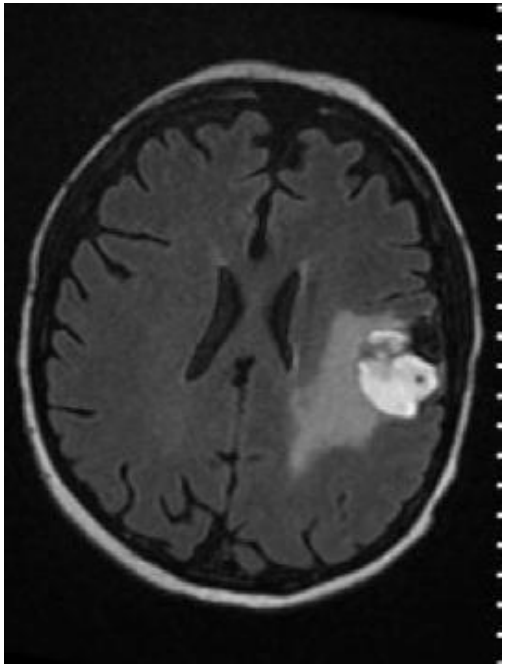
Memory T cells are responsible for immune surveillance in CNS



- T cells enter the CNS through the subarachnoid space (SAS)
- APCs in SAS can re-prime the T cells → inflammation

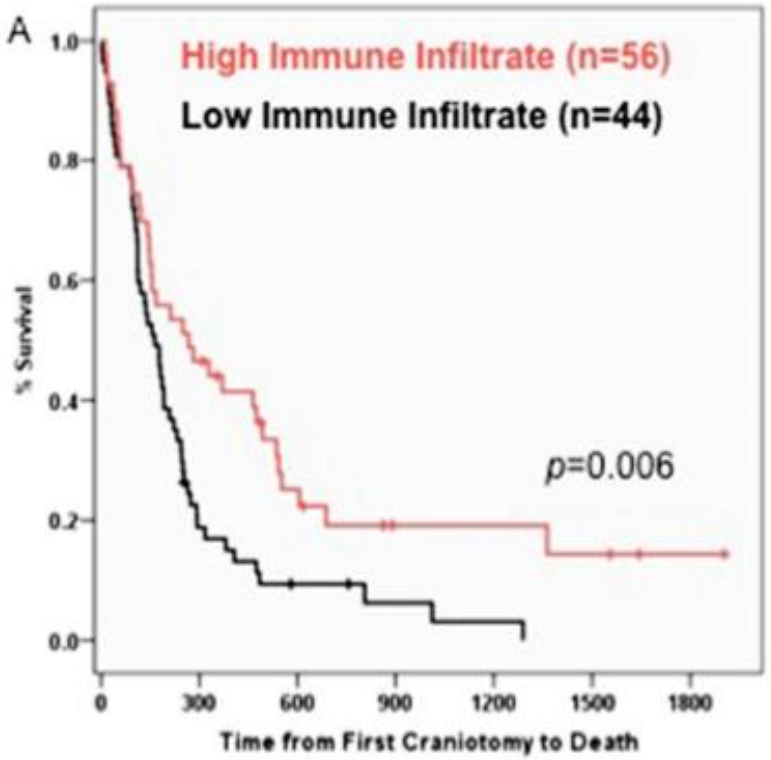
Ransohoff and Engelhardt, 2012. Nat Rev Immunol

BM often associated with edema

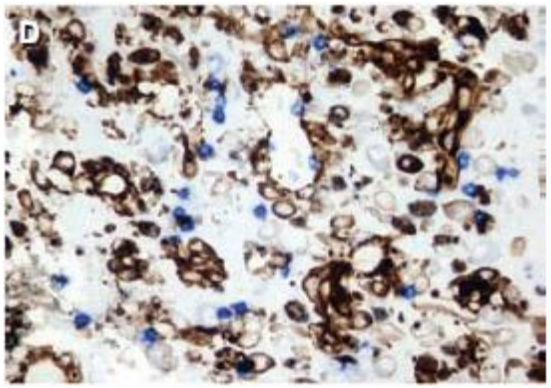


- Edema is caused by fluid in the tissue around the tumor
  - Mediated by VEGF
  - Perivascular space expands to accommodate edema
  - Soluble tumor antigens may be contained in the CSF
  - CSF drains into blood and/or lymph
- *Can an antigen presenting cell in the draining lymph nodes initiate an adaptive immune response?*

Immune infiltrate in BM and more favorable survival



- Resected brain metastases of patients with melanoma
- Peritumoral CD3+ and CD8+ cells were associated with prolonged survival



CD8+ T cells (blue)

Hamilton et al 2013 Cancer

Immune infiltrate in BM and more favorable survival

- Immunostaining study of 287 brain tumors
  - 170 BM (77 Lung, 44 Melanoma, 22 Others, 10 Renal)
  - 117 glioblastoma multiforme (GBM)

	BM	**GBM**	
Dense CD3+ TILs	**+++**	**+**	**p < 0.001**
Dense CD8+ TILs	+++	+	p < 0.001
Dense PD-1+ TILs	+++	+	p < 0.001

- Dense CD3+ tumor infiltrating lymphocytes (TILs) correlated with more favorable survival in BM patients (12 vs. 9 months; p = 0.015)
- Suggests that immunotherapy may be a viable strategy for BM

Berghoff, et al. ESMO abstract 2014

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Interleukin-2 for BM

- IL-2 has not been used extensively in patients with untreated BM due to the risk of cerebral edema
- Patients with stable previously irradiated or asymptomatic BM do not appear to have excess toxicity with IL-2 therapy
- The response rate in previously untreated brain metastases was 5.6% in one series
- Complete responses in the CNS have been reported

Guirguis, et al 2002
Powell and Dudek, 2009

Ipilimumab in melanoma BM

- Phase II in 72 patients with BM
- n=51 were neurologically asymptomatic, n=21 were neurologically symptomatic
- 40% had received previous radiation therapy (wash-out period 2 weeks)

Margolin, et al 2012 Lancet Oncol

Ipilimumab in BM

- Treated with ipilimumab 10mg/kg IV Q3 weeks x 4, followed by Q12 week maintenance
- Response was assessed after 12 weeks using modified WHO and immune related response criteria
- Previously irradiated brain lesions could not be index lesions unless they were progressive despite radiation therapy

Margolin, et al 2012 Lancet Oncol

Activity of Ipilimumab in BM
in 51 neurologically asymptomatic pts

	Modified WHO criteria	**Immune-related Response Criteria**
Global objective response	5/51 (10%)	5/51 (10%)
CNS objective response	8/51 (16%)	8/51 (16%)
Non-CNS objective response	7/51 (14%)	7/51 (14%)

- No patients had a discordant (CNS *vs.* non-CNS) response status
- Response rate was similar using either set of response criteria

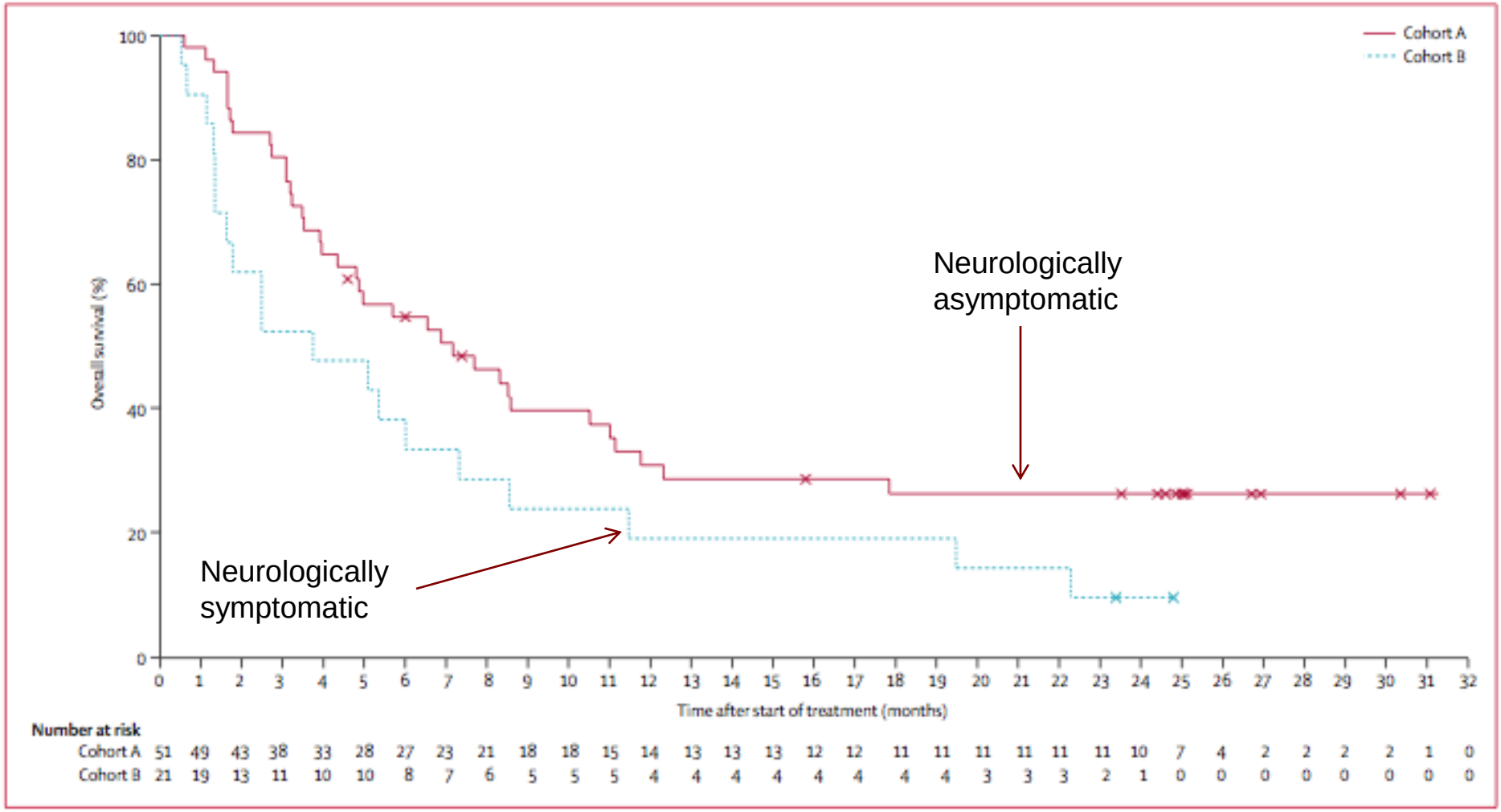
Margolin, et al 2012 Lancet Oncol

Activity of Ipilimumab in BM

- Response rate in the CNS
  - 16% in asymptomatic subjects
  - 5% in symptomatic subjects
    - 1 CR, 0 PR
- 2 year overall survival ~25% in the asymptomatic subjects

Margolin, et al 2012 Lancet Oncol

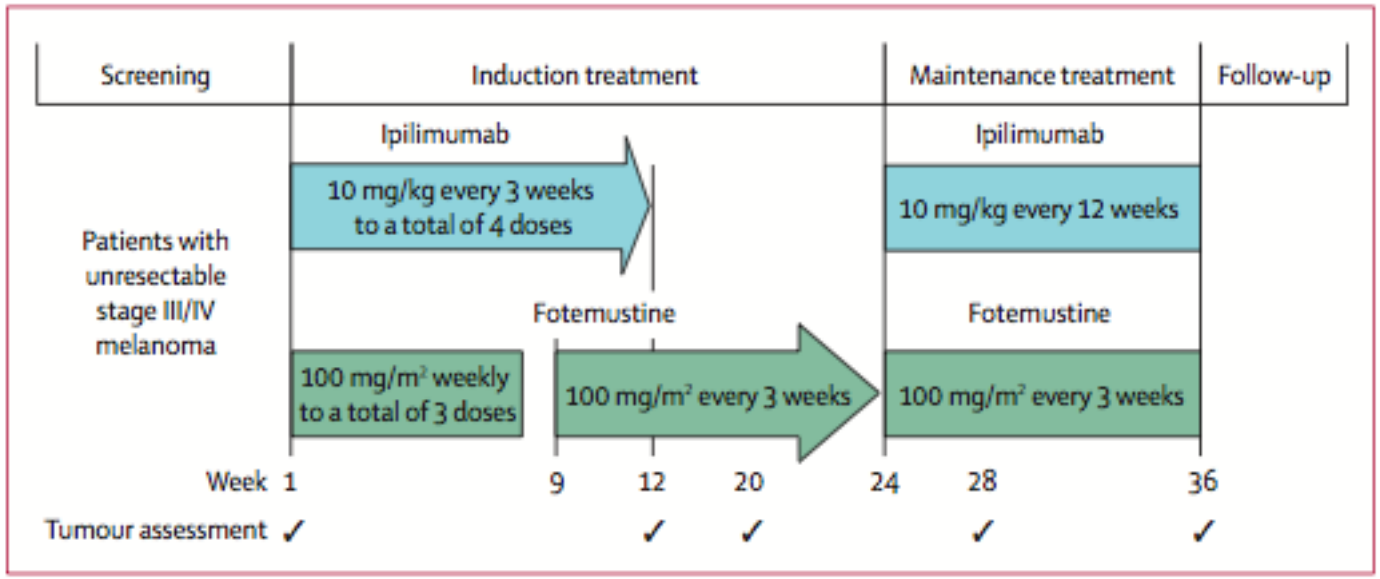
Activity of Ipilimumab in BM



Margolin, et al 2012 Lancet Oncol

Ipilimumab + Fotemustine

- Fotemustine can cross the BBB
- 86 patients with metastatic melanoma were treated with ipi + fotemustine
  - including 20 with asymptomatic BM
  - 35% of the patients with BM had received previous RT to the brain



DiGiacamo 2012 Lancet Oncol

Ipilimumab + Fotemustine

- 40 patients in the study population achieved disease control (47%), as did 10/20 patients with BM (50%).
- Of the 13 patients with BM who did not have previous radiotherapy, 5 (38%) of them had a complete response in the brain

DiGiacamo 2012 Lancet Oncol

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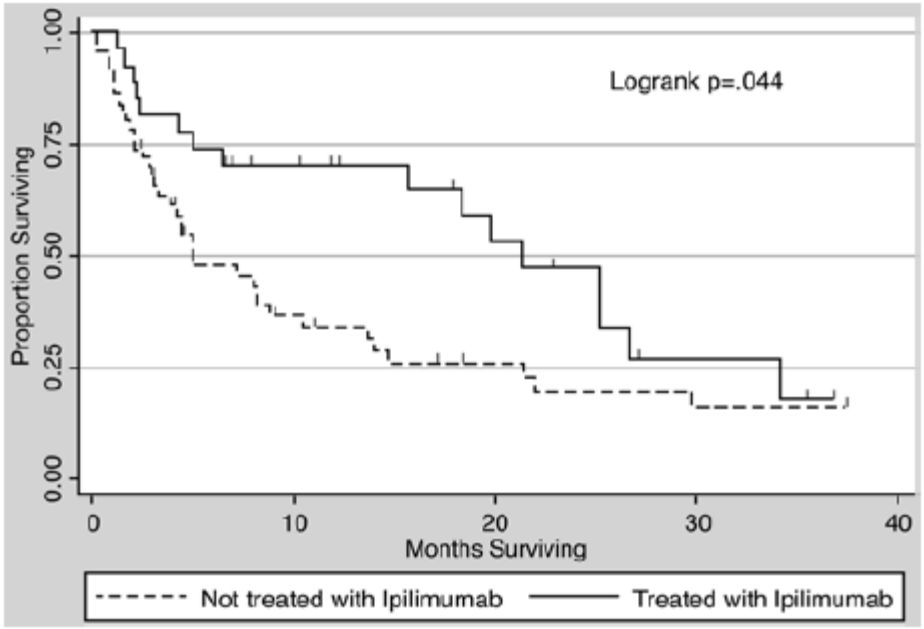
Combinations: Radiation therapy (RT)

- RT induces damage to the BBB and the tumor DNA → increases tumor immunogenicity
- Clinical experience: Ipilimumab + stereotactic radiosurgery (SRS)
- 77 patients with metastatic melanoma underwent SRS
  - 27 of them had ipilimumab (before or after SRS)
- Median survival
  - 21.3 *vs.* 4.9 months in those who received ipilimumab *vs.* those who did not



Knisely 2012 J Neurosurg

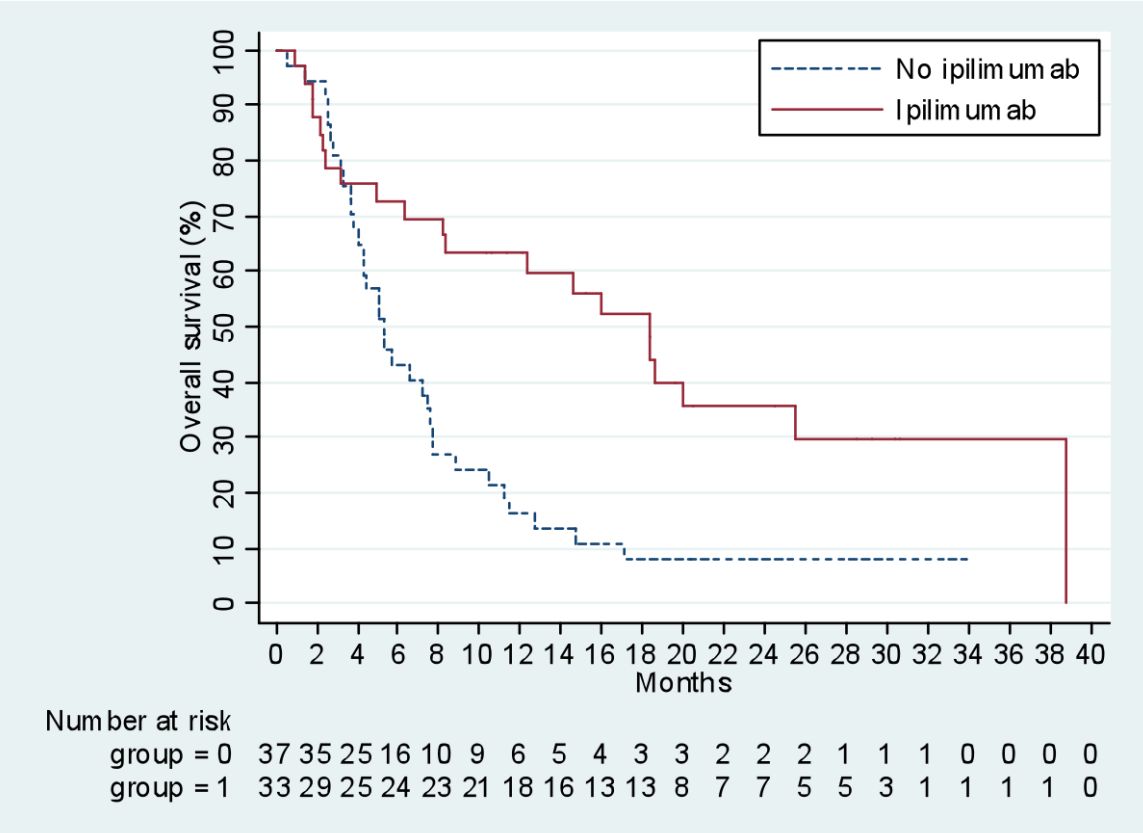
Combinations: Ipilimumab + RT

	No Ipilimumab (n=37)	Ipilimumab (n=33)
WBRT	21	16
SRS	16	17

- A retrospective study of 70 patients with melanoma brain metastases treated with RT
- 33 patients received ipilimumab
  - Either before or after RT
  - Mostly sequential, 5 patients treated concurrently

Silk, et al, 2013, Cancer Medicine

Improved survival with ipilimumab and SRS



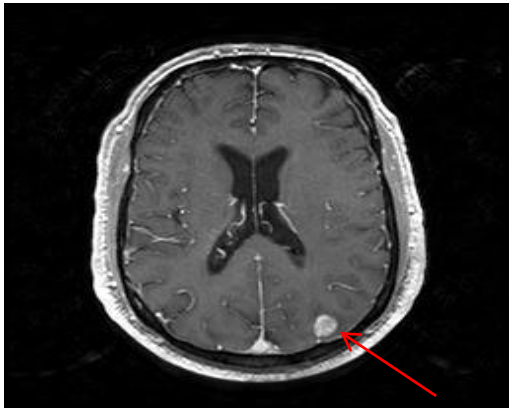
Ipilimumab is associated with significantly decreased risk of death
HR= 0.43, p=0.005

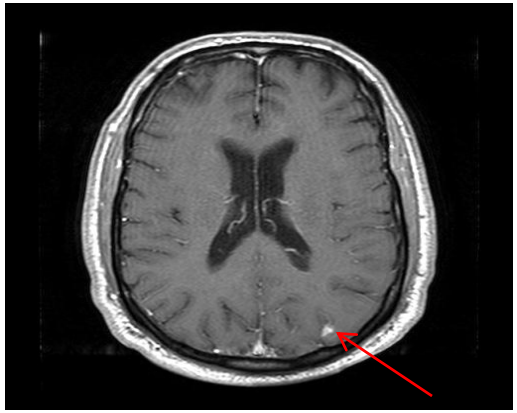
Silk, et al, 2013, Cancer Medicine

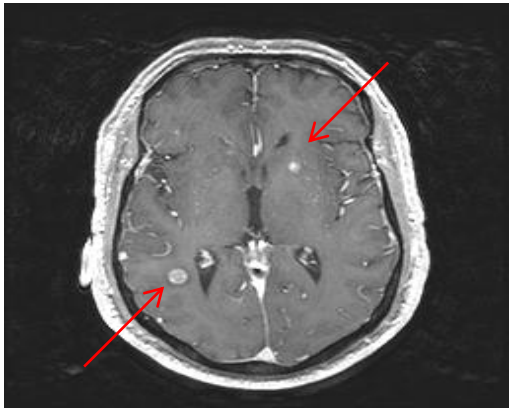
62M: Concurrent Ipi and WBRT

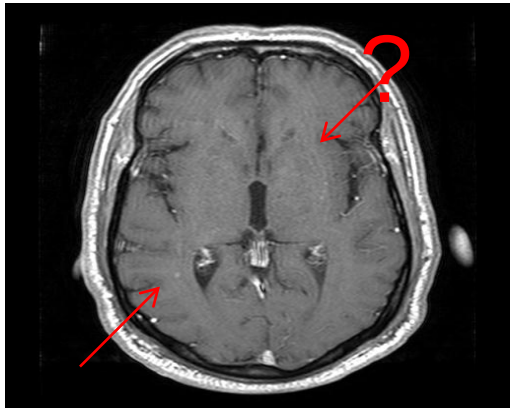
PRE-WBRT

POST-WBRT



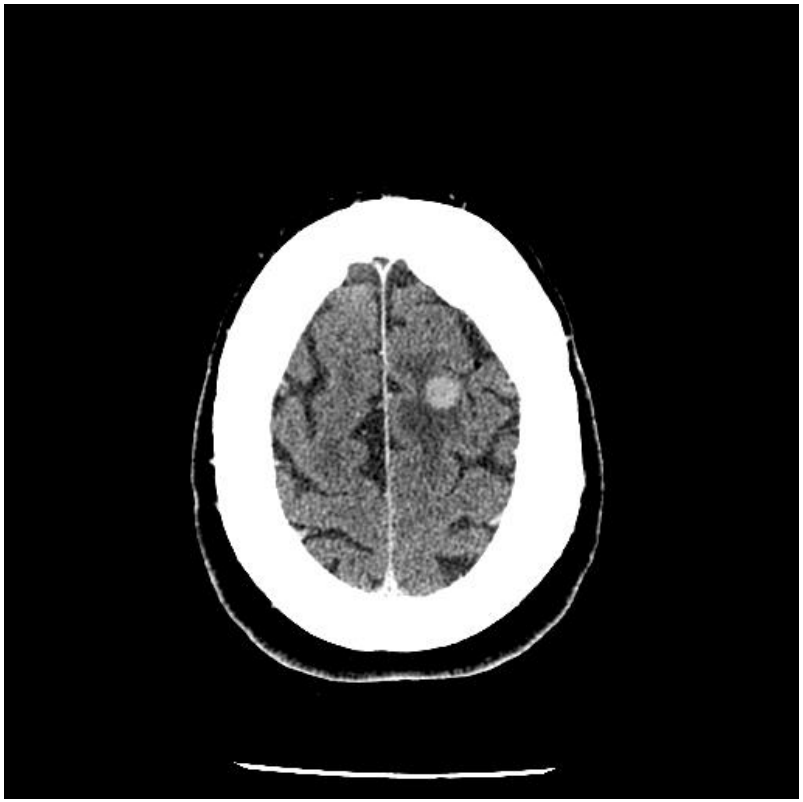




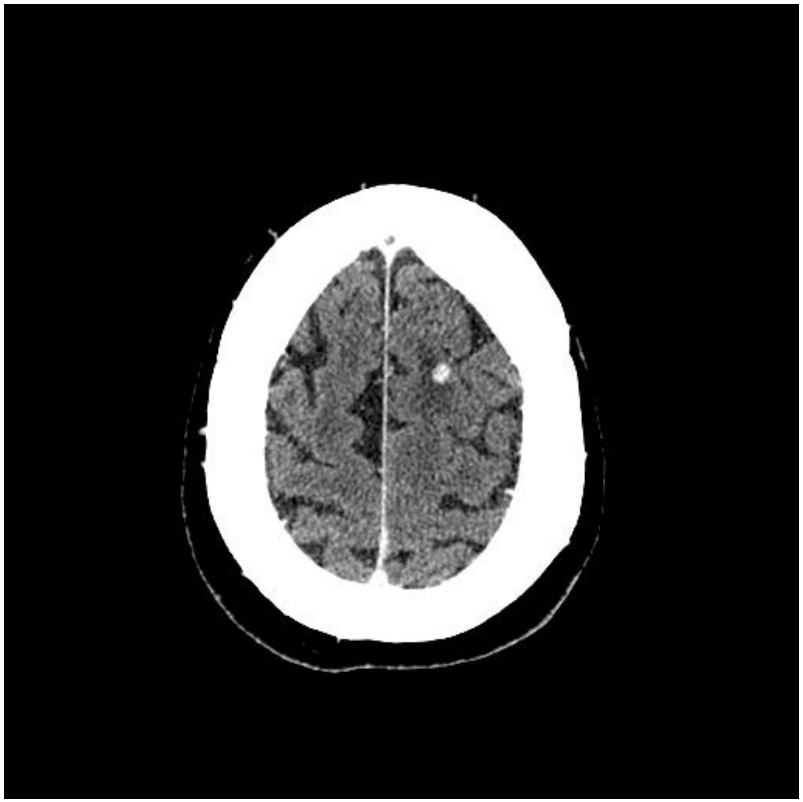


82F: Concurrent Ipi and SRS

PRE-SRS



POST-SRS



Ipilimumab appears to impact survival in patients treated with SRS

Median survival (in months) from the date of RT

	N=	Not treated with Ipilimumab	Treated with Ipilimumab	Difference
Knisely *et al* 2012	77	4.9	21.3	16.4 months
Silk *et al* 2013	70	4.0	19.9	15.9 months

Future directions

- PD-1 and PD-L1 antibodies
- Checkpoint inhibitors + RT
- Vaccines: cell-based vaccines, oncolytic viruses
- Adoptive T cell strategies

Select anti-PD-1 studies in BM

- MK-3475 (Pembrolizumab) in Melanoma and NSCLC Patients With Brain Metastases
  - ClinicalTrials.gov Identifier: NCT02085070

- A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects With Melanoma Metastatic to the Brain Treated With Nivolumab in Combination With Ipilimumab Followed by Nivolumab Monotherapy (CheckMate 204)
  - ClinicalTrials.gov Identifier: NCT02320058

Lessons and Take Home Messages

- Immunotherapy has a therapeutic advantage over cytotoxic drugs in CNS tumors because T-cells can cross the BBB

- The BBB is not absolute. Memory T cells provide immune surveillance in the CNS and mediate inflammation in response to antigens

- Combinations of immunotherapies and/or immunotherapy in combination with radiation therapy may be effective at treating and even preventing BM in many types of cancer

Thank You