Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Brain Metastases

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Advances in Cancer Immunotherapy™
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Disclosure

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-Trans Target, Inc.

Contracted Research

-Dendreon

-Millenium

-Pharmacyclics

Ownership Interest

-Seattle Genetics

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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*

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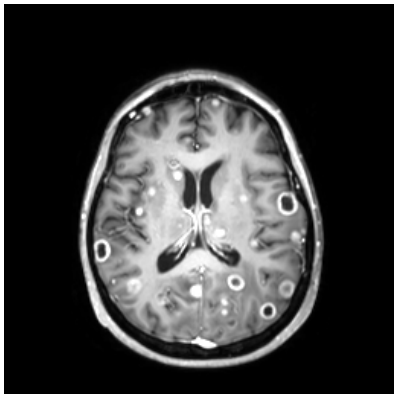
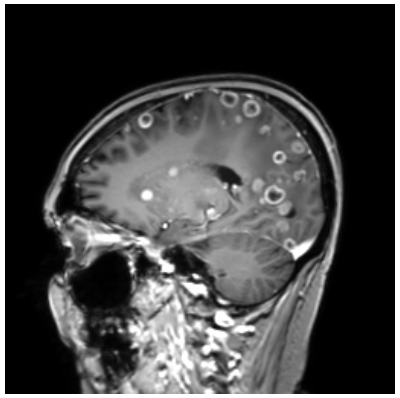
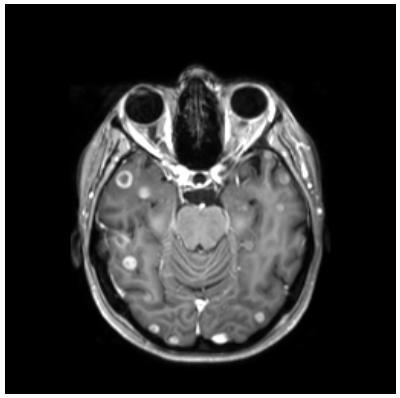
Brain Metastases (BM)

- 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







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Radiation Therapy is the Backbone of Treatment

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

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Limits of cytotoxic and targeted therapy

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

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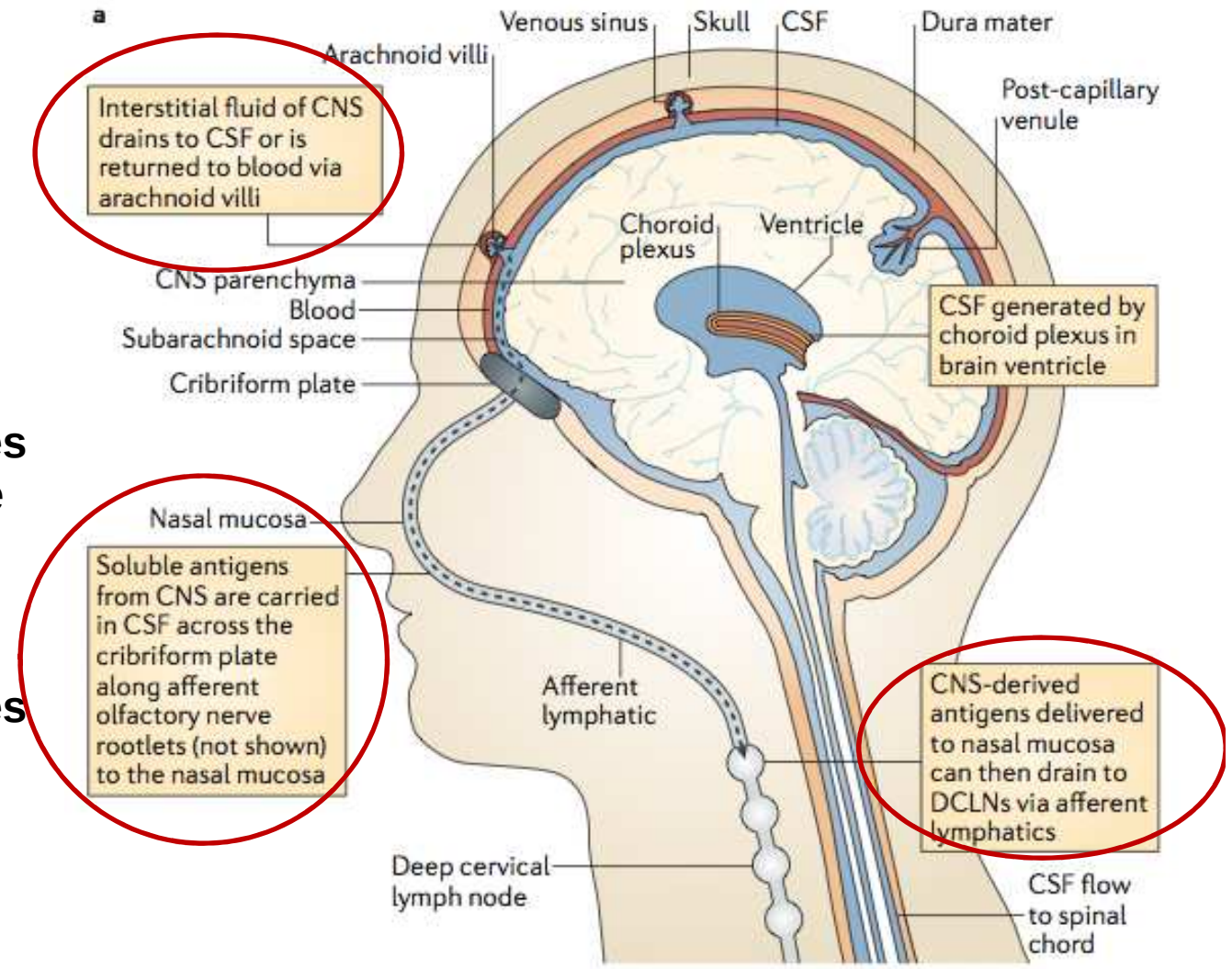
CSF drains to blood and lymph

- 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



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Ransohoff and Engelhardt, 2012. Nat Rev Immunol

Outline

1. *Background*
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*

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Is the brain a sanctuary?

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

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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.

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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

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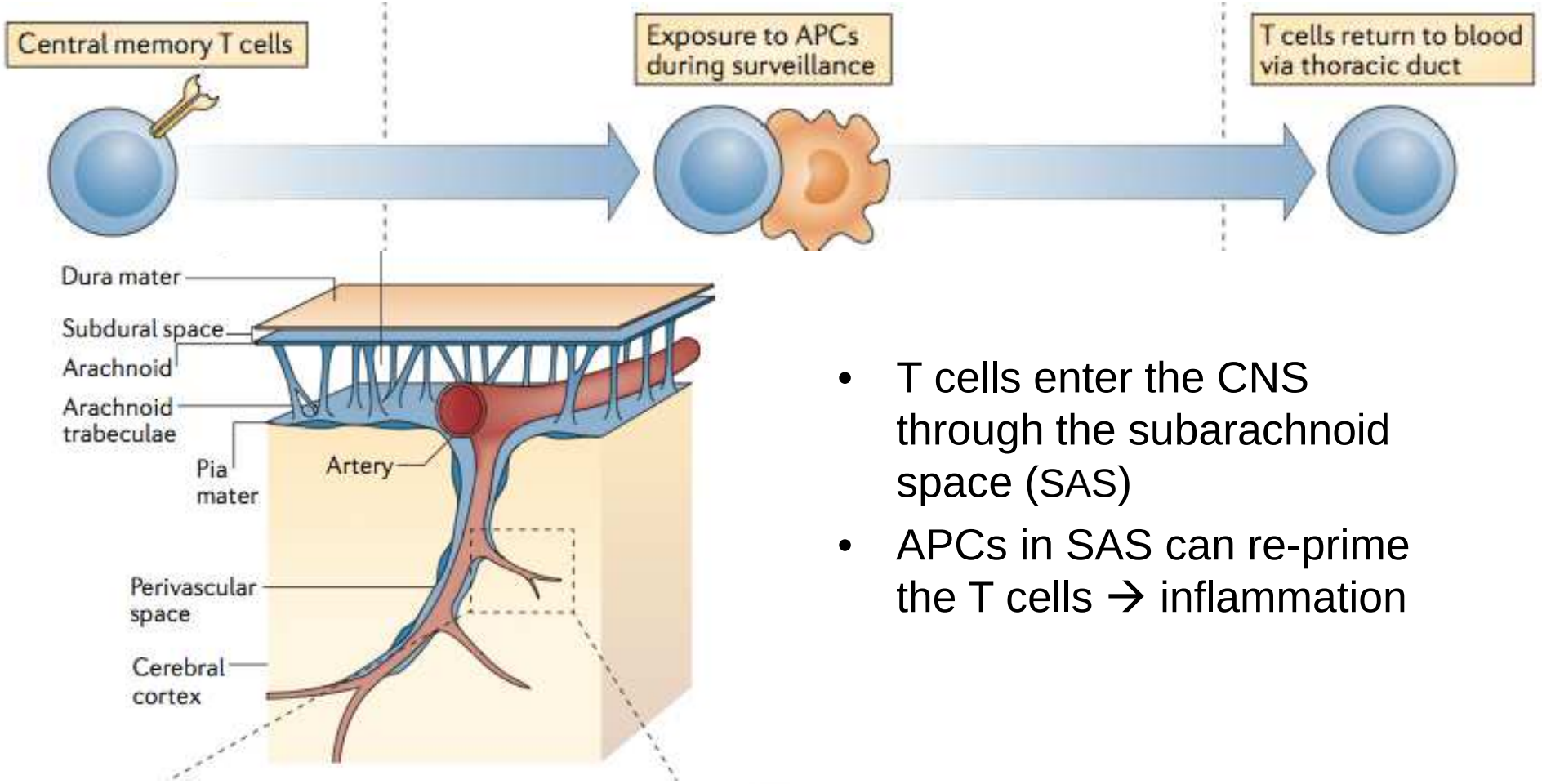
Memory T cells are responsible for immune surveillance in CNS



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

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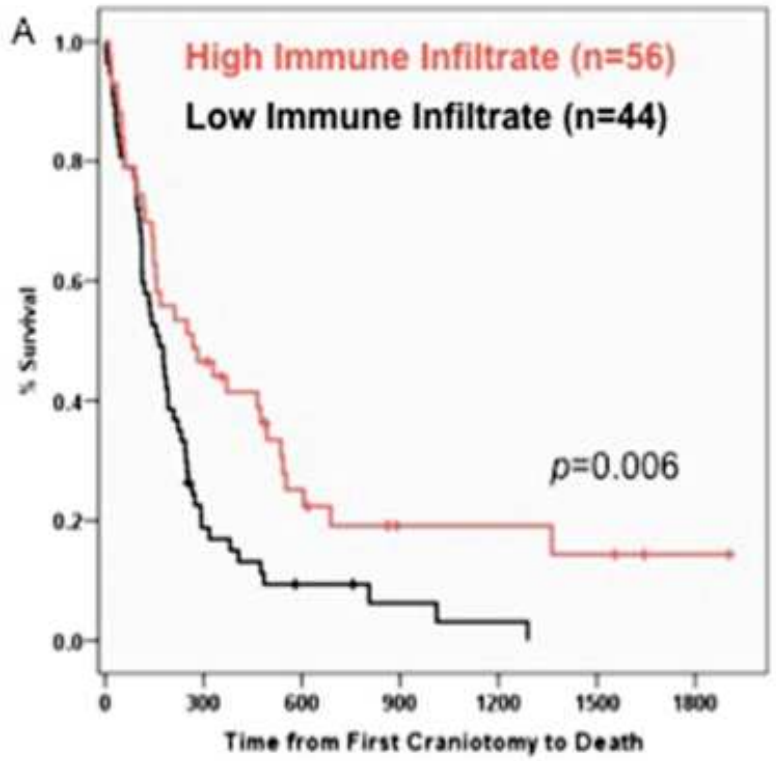
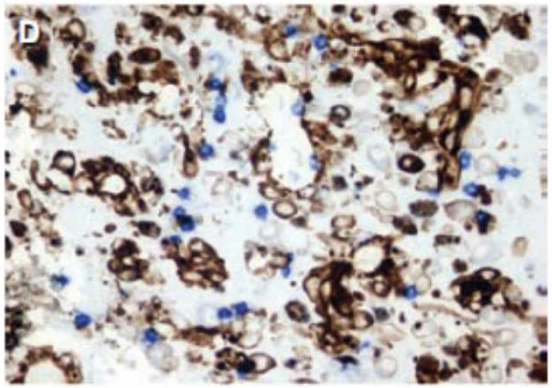
Ransohoff and Engelhardt, 2012. Nat Rev Immunol

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)

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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

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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

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Guirguis, et al 2002
Powell and Dudek, 2009

Activity of Ipilimumab in BM in 51 neurologically asymptomatic pts

- 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)
- Treated with ipilimumab 10 mg/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

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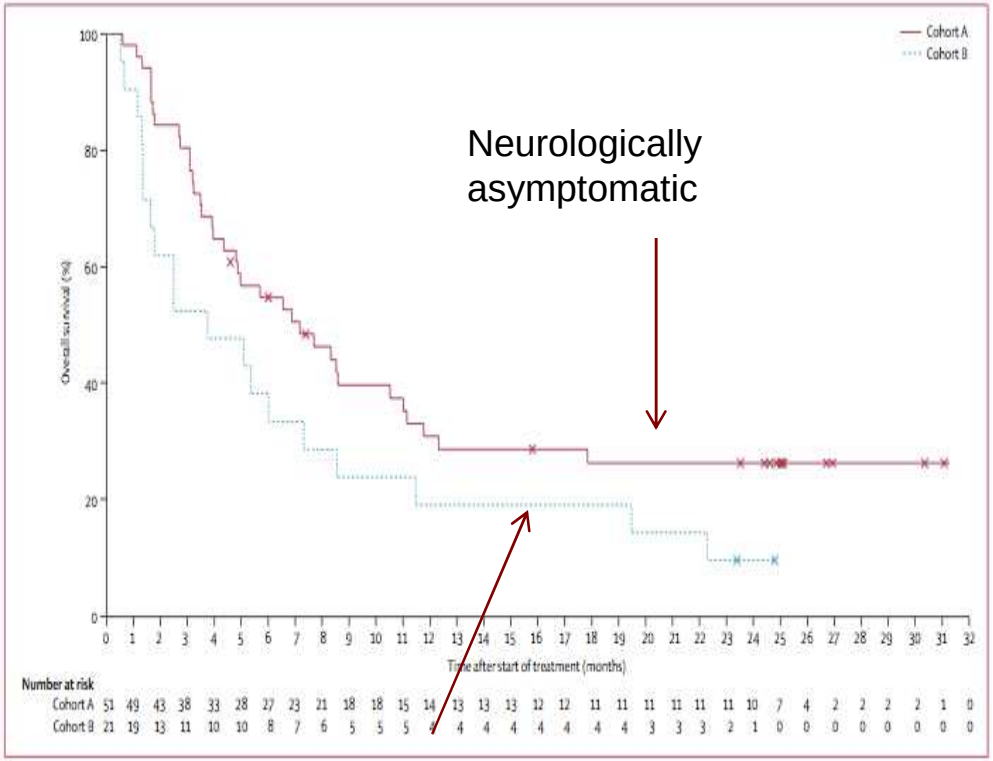
Margolin, et al 2012 Lancet Oncol

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



Neurologically symptomatic

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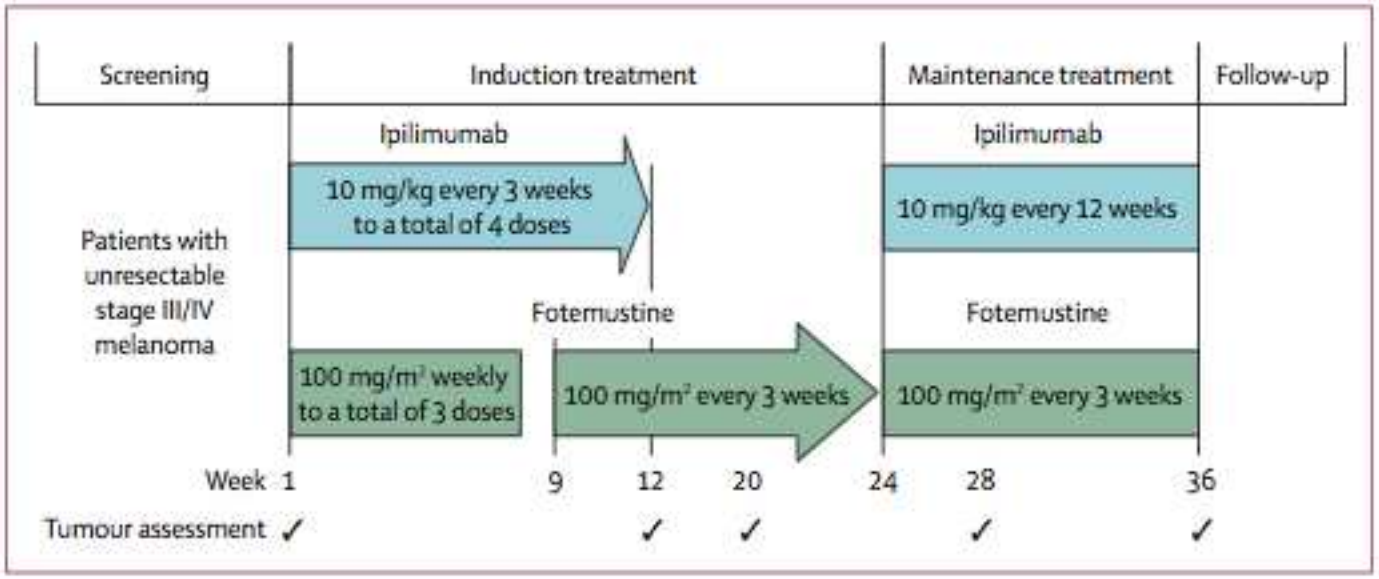
Margolin, et al 2012 Lancet Oncol

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



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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

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DiGiacamo 2012 Lancet Oncol

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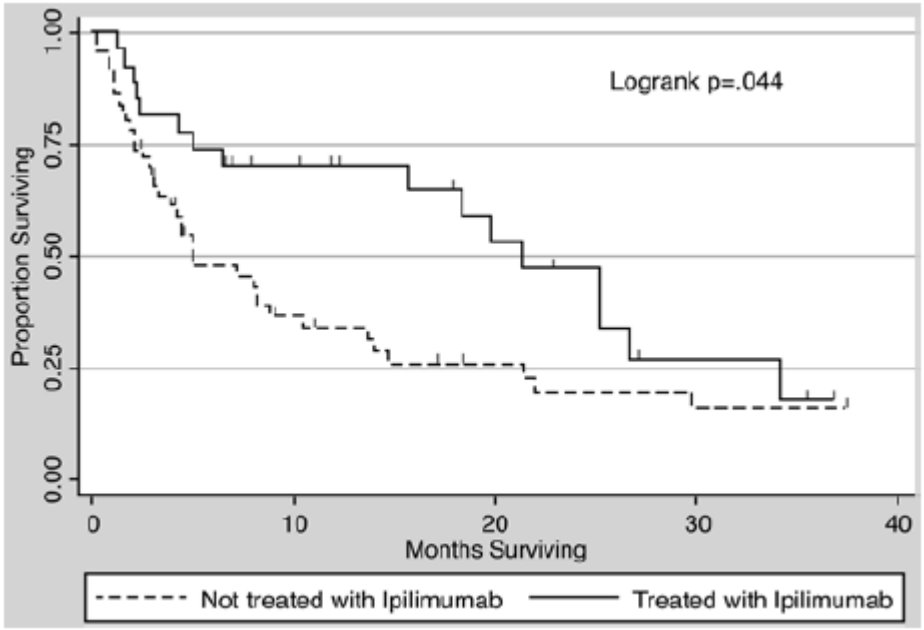
Combinations: Radiation therapy (RT)

- 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**



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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

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Silk, et al, 2013, Cancer Medicine

Improved survival with ipilimumab and SRS

	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
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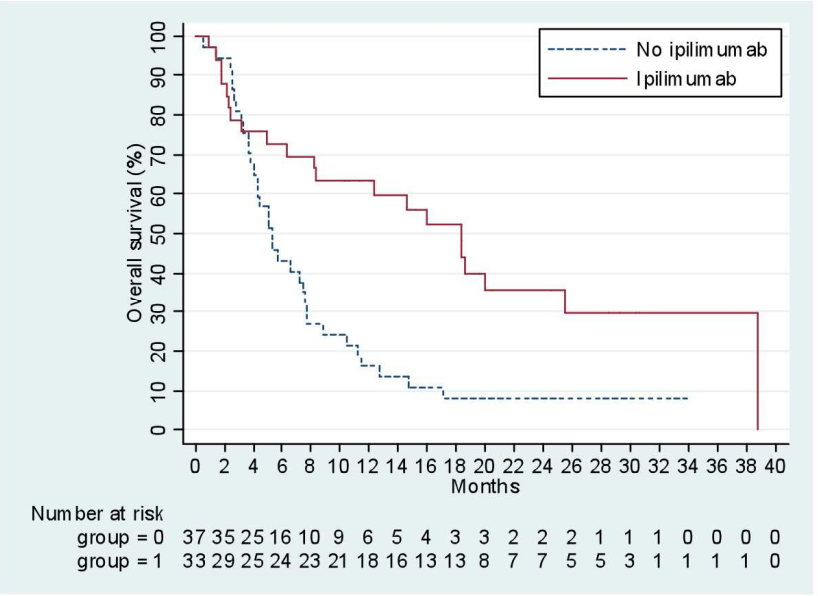

Ipilimumab is associated with significantly decreased risk of death
HR= 0.43, p=0.005

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Silk, et al, 2013, Cancer Medicine

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

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Future directions

- PD-1 and PD-L1 antibodies
- Checkpoint inhibitors + RT
- Vaccines: DC/cell-based vaccines, oncolytic viruses
- Adoptive T cell strategies:
  - a) CAR-T targeting EGFR
  - b) Anti-CD3 X anti-EGFR armed T cells (EGFR BATs)
- Combination therapies of checkpoints, adoptive T cells, RT, and/or vaccines

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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 for preventing or treating BM in many types of cancer

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THANK YOU!!

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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