Immunotherapy for Brain Metastases

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Disclosures

- Cellworks- consultant

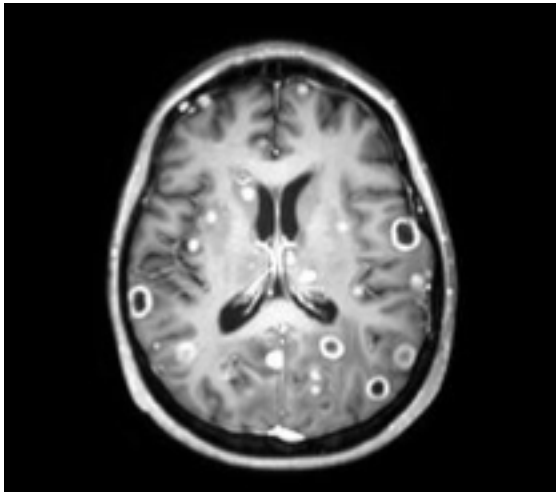
Outline

- Background and Current Treatment of Brain Metastases
- Blood Brain Barrier & CNS Immune Surveillance
- Clinical experience: BM Immunotherapy
- Rationale and update on Combination Therapies

Brain Metastases (BM)

20-40% of cancer patients will develop BM

300,000 plus new cases in the US each year



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

Brain Metastases from Melanoma: Background

- Brain metastasis develops in ~60% of patients with metastatic melanoma
- Progressive disease in the brain is the major cause of tumor-related death in these patients
- Median overall survival (OS) after MEL brain metastasis is only 4 months

Brain Metastases Treatment

- One BM- Surgery
- A few BM- Stereotactic radiosurgery (SRS)
- Numerous BM- Whole Brain Radiotherapy (WBRT)
- Radiation Therapy is the Main Stay.
- Why not chemo?

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

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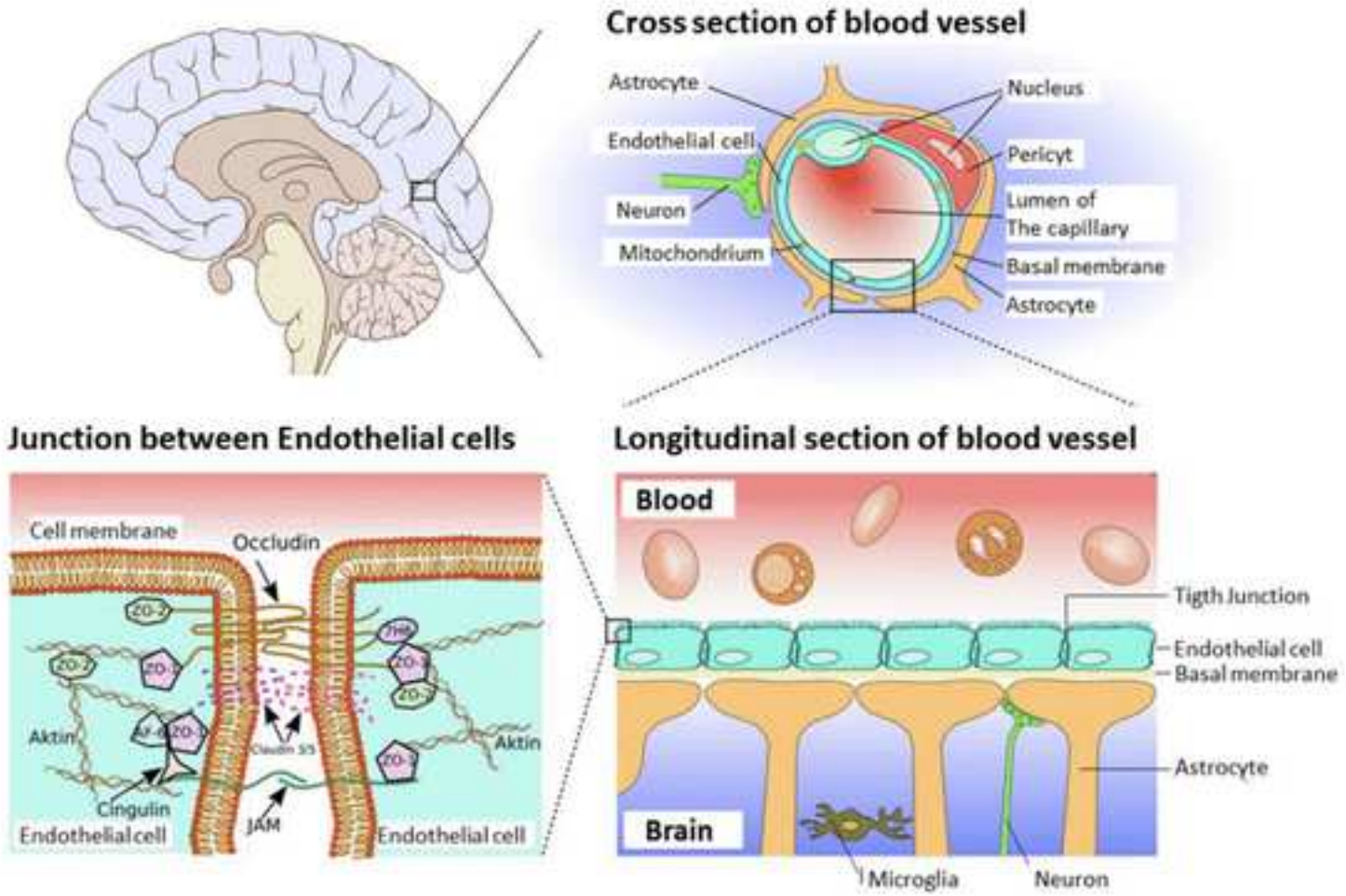
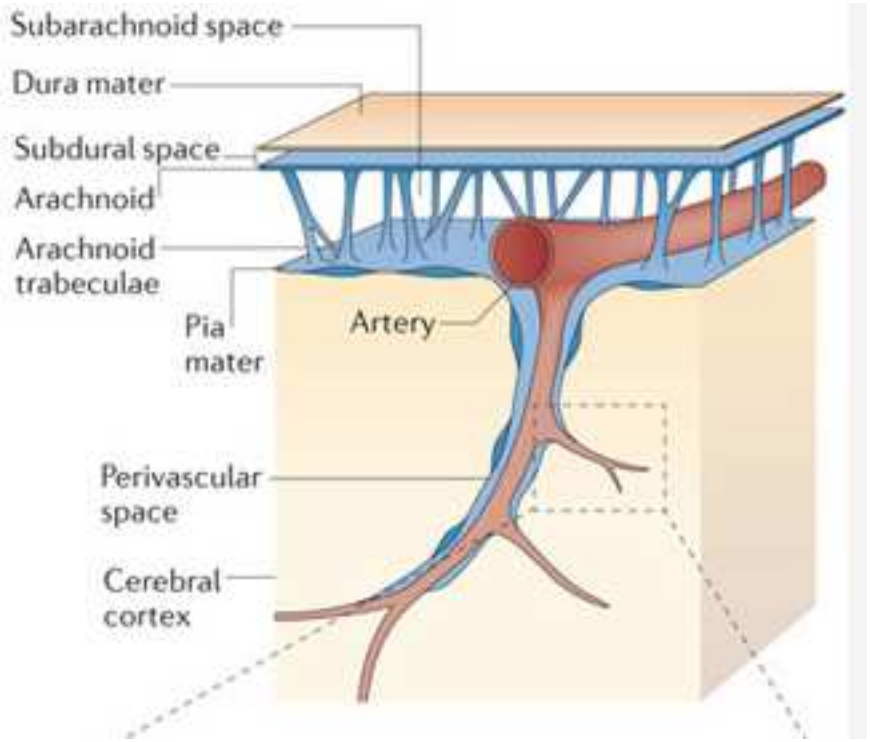
Blood-Brain Barrier

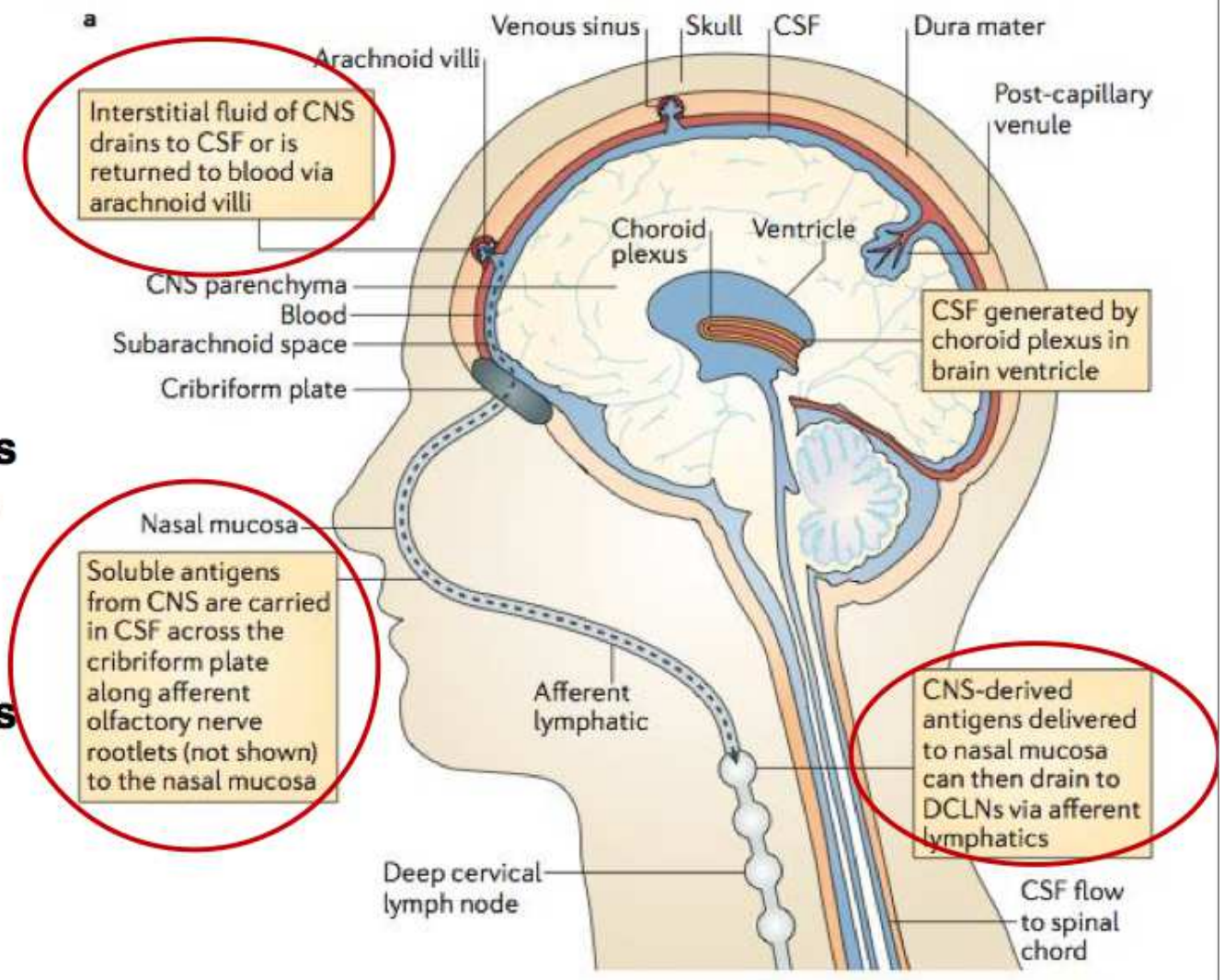


Cerebrospinal fluid (CSF): “lymph in the brain”

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



- 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

Memory T cells: CNS immune surveillance

- Memory T cells enter CNS independent of antigen specificity
- T cells enter the CNS through the subarachnoid space (SAS)
- Exposed to APC-like cells in the perivascular space
- T cells exit the CNS with the CSF via nasal mucosa to deep cervical lymph nodes

Edema is caused by fluid in the tissue around the tumor

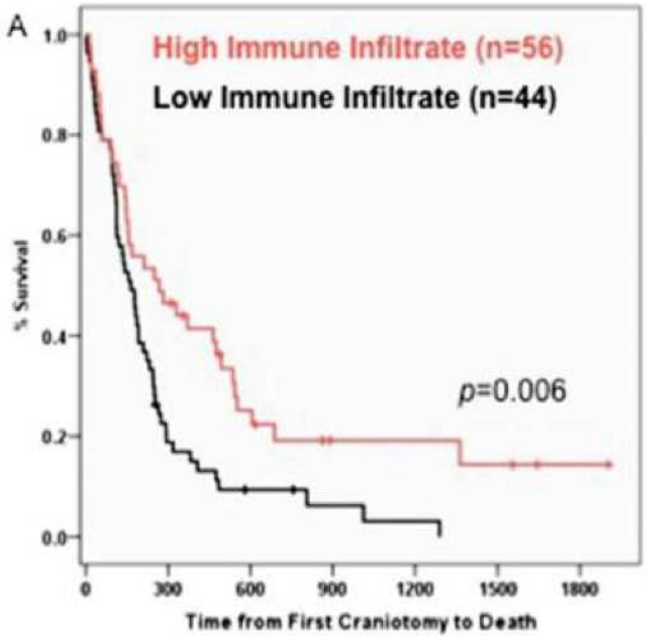
– Mediated by VEGF
– Perivascular space expands to accommodate edema
– Soluble tumor antigens may be contained in the CSF
– CSF drains into blood and/or lymph activates T cells

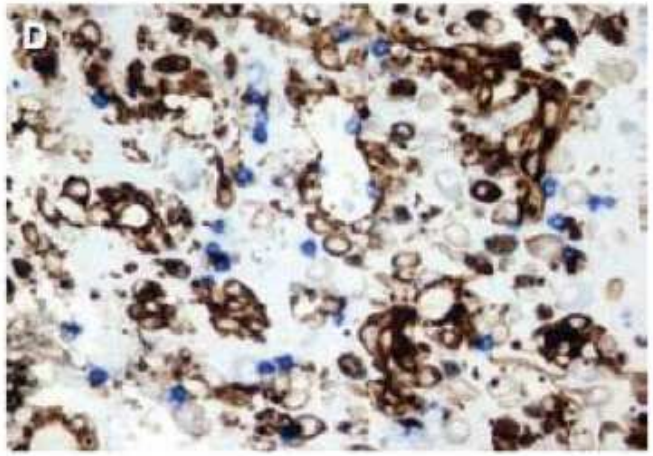
Activated T cells can cross the blood–brain barrier

- Can antigen presenting cells and Memory T cells mount an adaptive immune response in CNS mets?

High Immune Infiltrate equals better survival!

- 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

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Early Clinical experience: 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

- But 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)

- Treated with ipilimumab 10mg/kg IV Q3 weeks x 4, followed by Q12 week maintenance

- Activity of Ipilimumab in BM

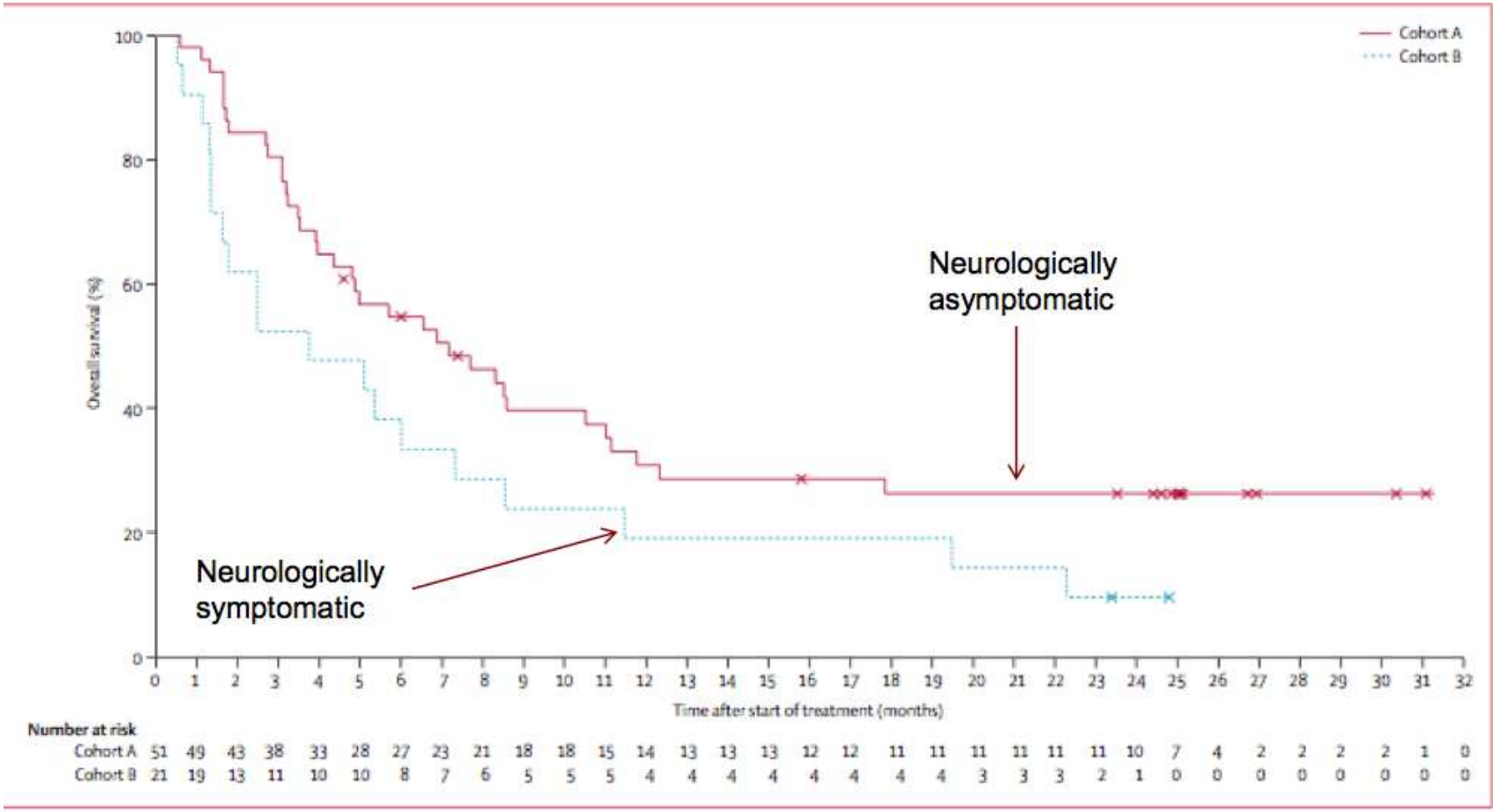
  Response rate in the CNS:

  - **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

Ipilimumab in melanoma 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

- 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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Combinations: Radiation therapy plus immunotherapy

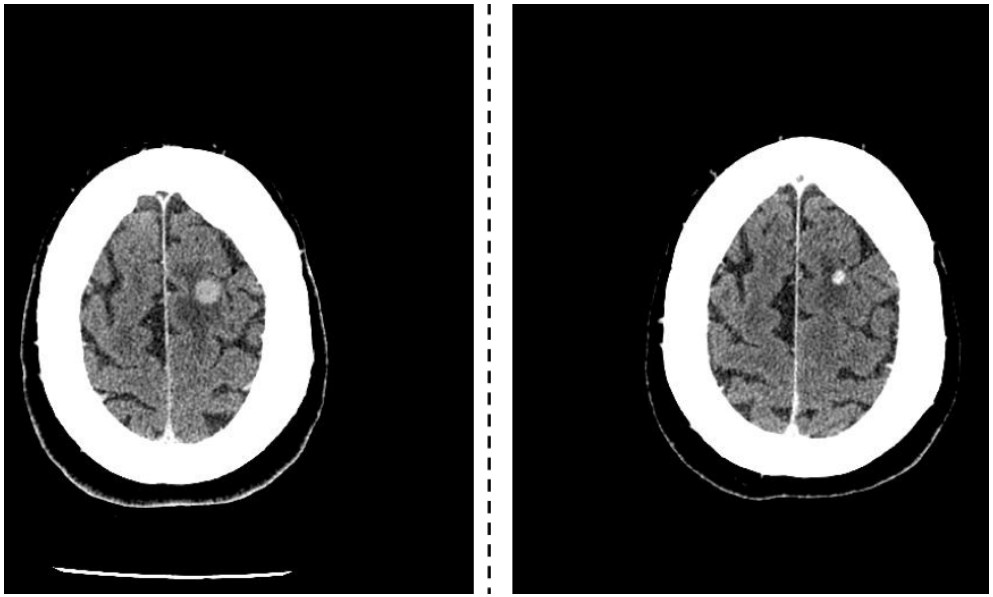
Ipilimumab + SRS

- 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



Ipilimumab appears to impact survival in patients treated with SRS

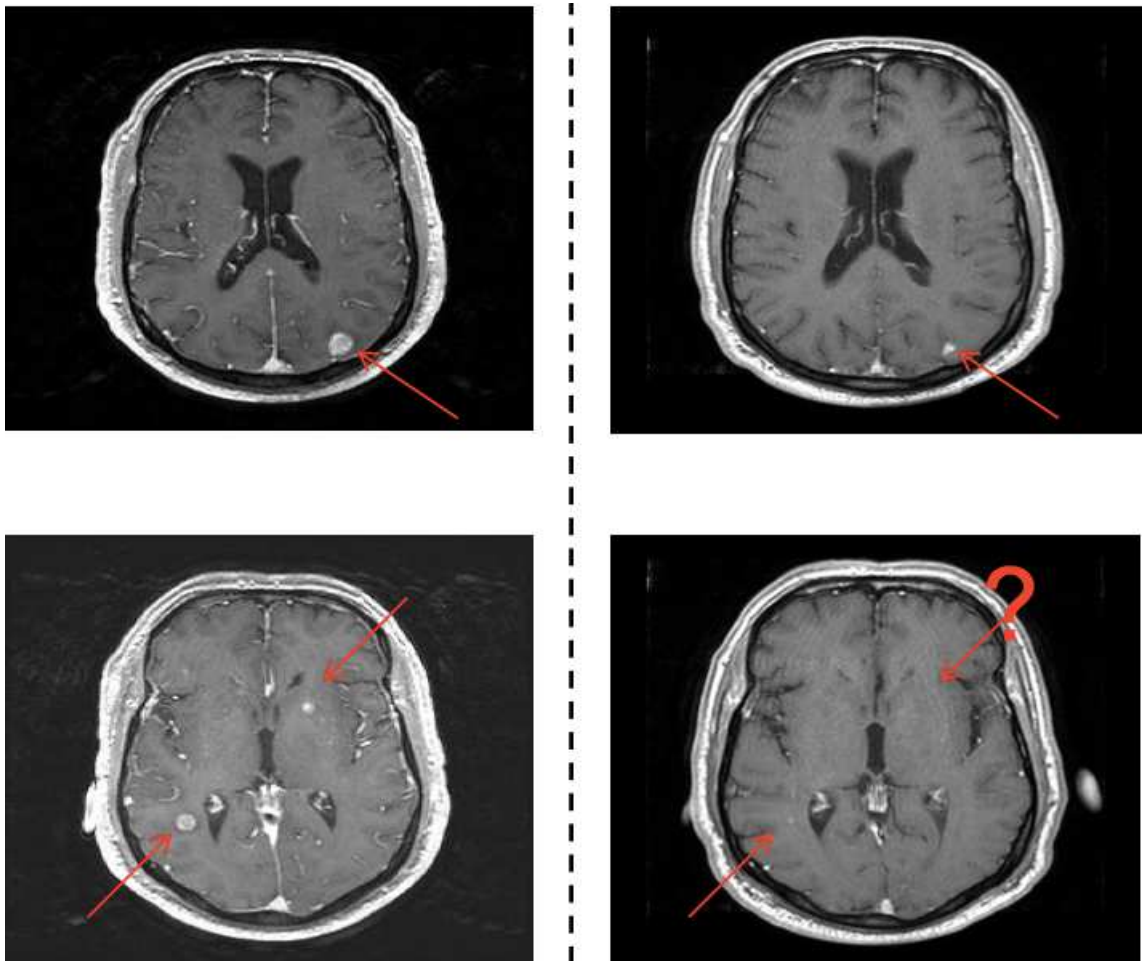
Median survival (in months) from the date of RT

	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

Radiation and the Immune Response: Brain Mets

- In melanoma brain mets: Silk et al showed:
  - ✓ 40% response for IPI + RT

  versus
  - ✓ 9% response for RT alone.[1]



[1]Silk et al. *Cancer Med* 2013.

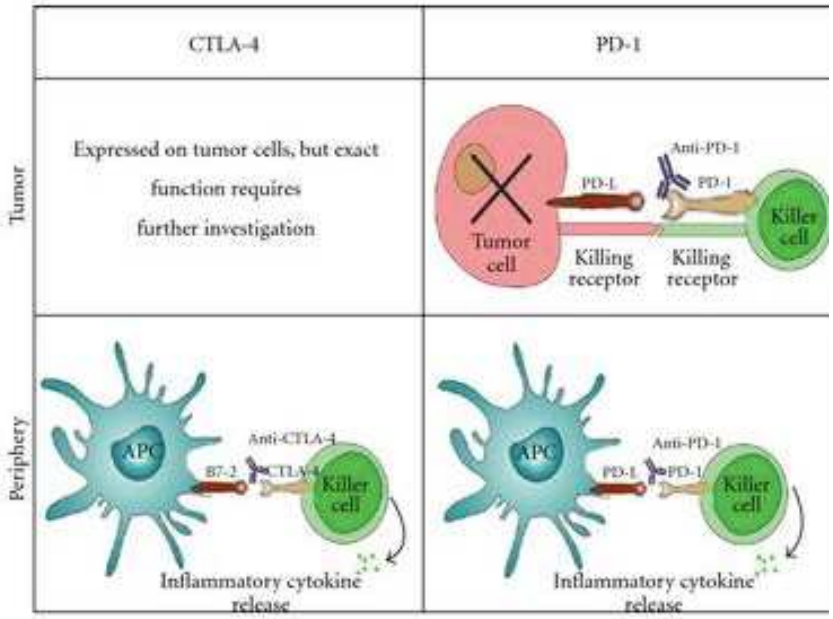
Future Directions: Anti-PD-1 plus Radiosurgery

Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial tumors.

- Lim M et. al, 2013

Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen.

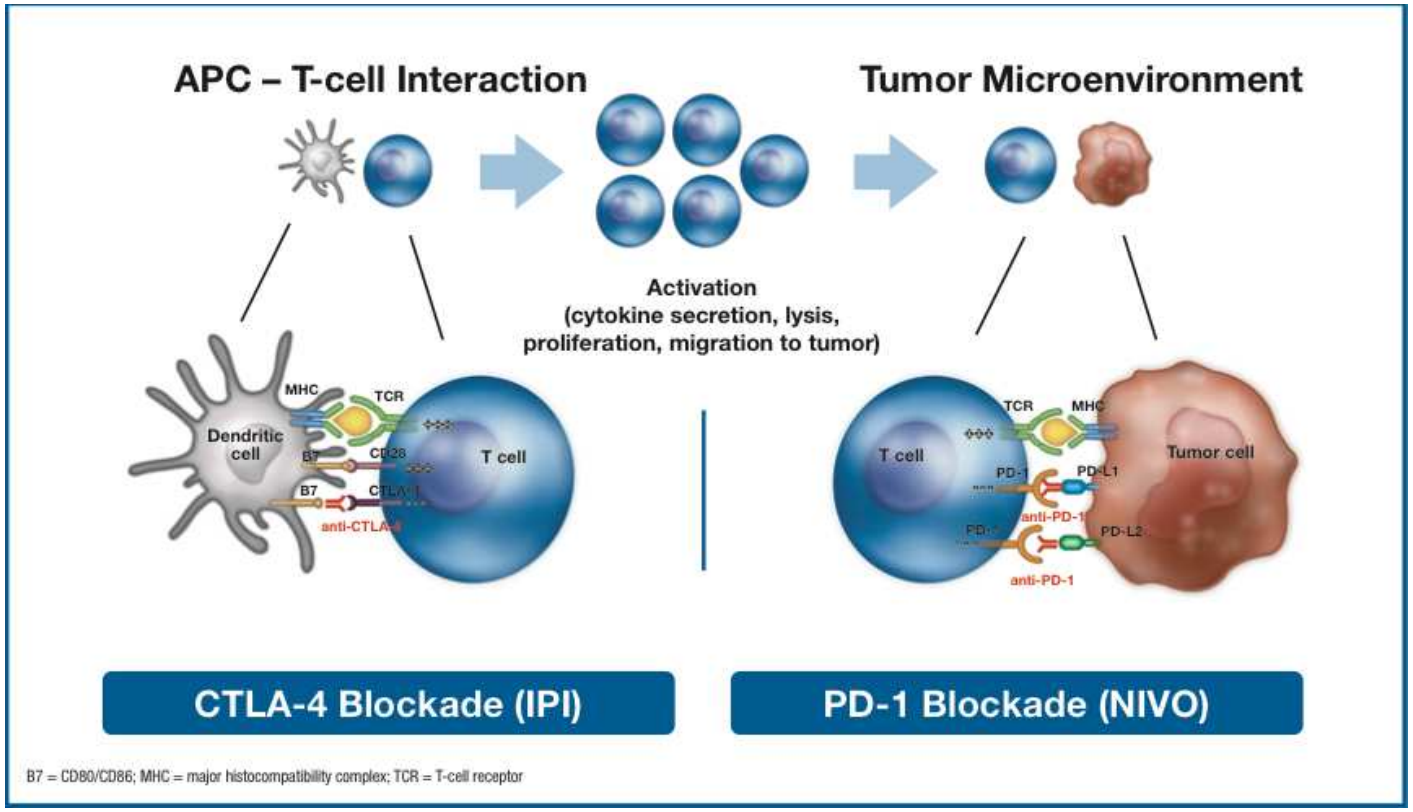
- Sharabi AB et. al, Cancer Immunol Res. 2014



Immune-stimulating effects of SRS were significantly increased when it was combined with anti-PD-1.

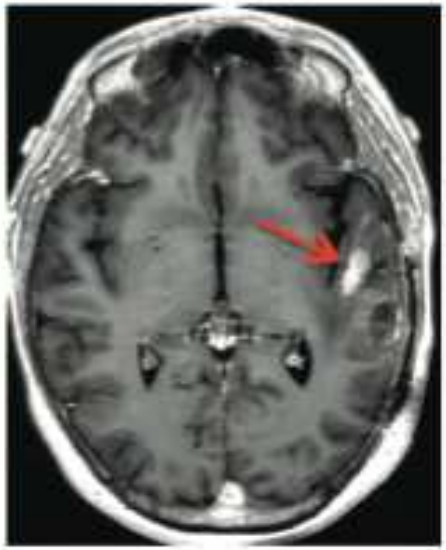
Clinical trials are being planned between Angeles Clinic and Cedars-Sinai to evaluate the safety and efficacy of this combination.

Combination CTLA-4 plus Anti-PD-1 Blockade

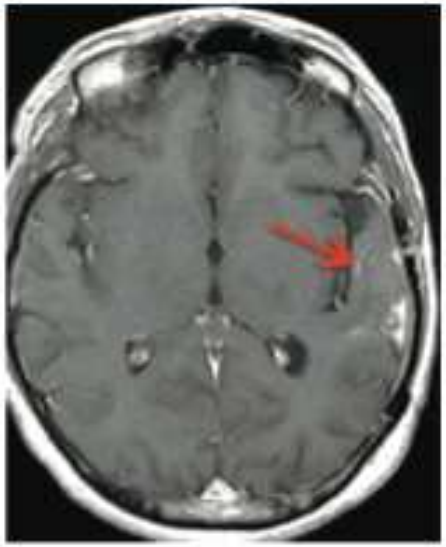


- **NIVO Plus IPI Combination in Advanced MEL**
- • In a phase II, double-blind study (CheckMate 069) with treatment-naïve pts with advanced MEL, combination therapy with NIVO 1 mg/kg plus IPI 3 mg/kg provided greater benefits than IPI monotherapy, with a manageable safety profile

Preliminary Safety and Activity of Nivolumab and its Combination With Ipilimumab in Recurrent Glioblastoma: CHECKMATE-143



Baseline
27-mm left temporal lobe lesion



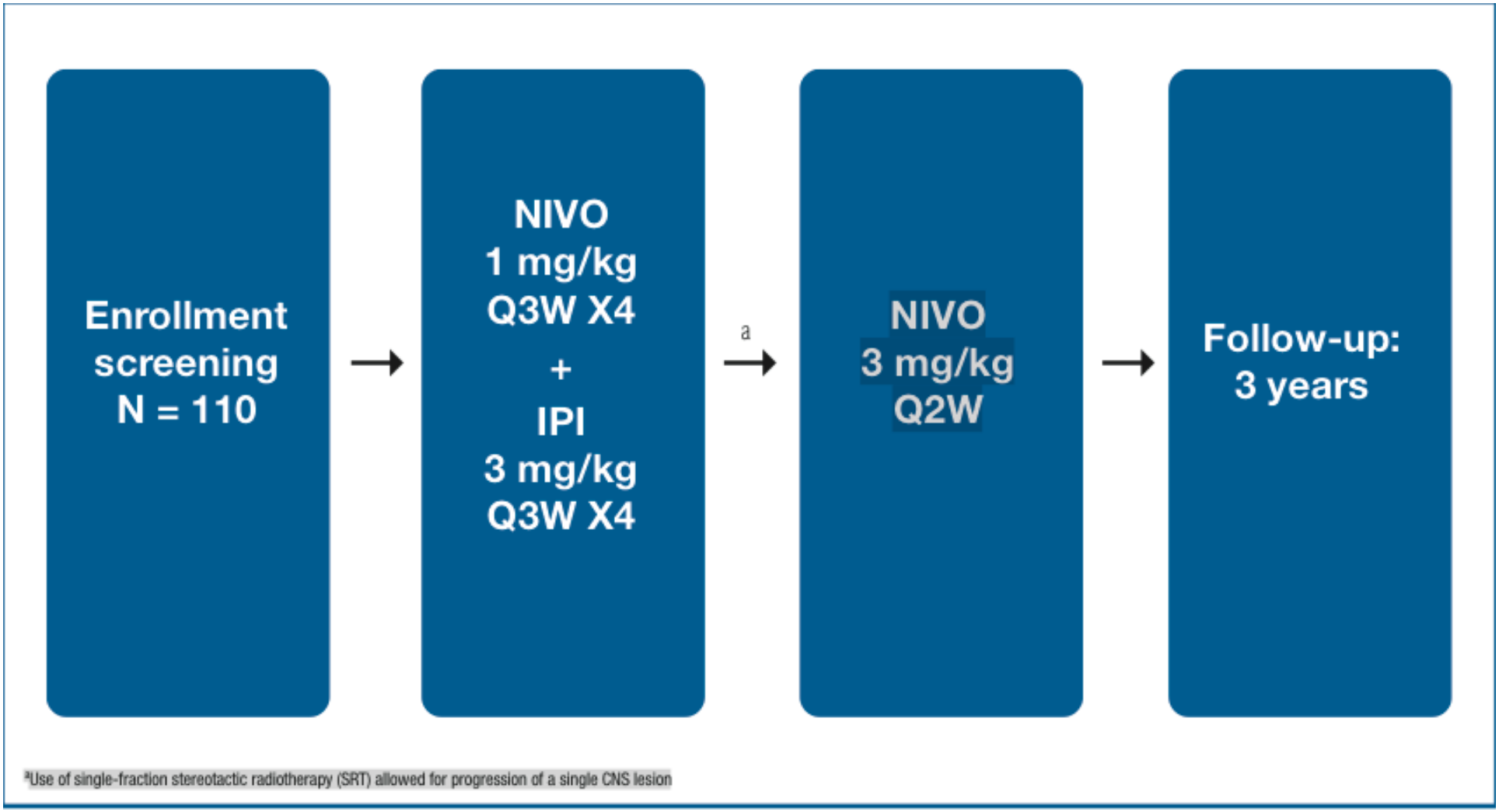
After 10 nivolumab doses
6-mm left temporal lobe lesion

- Patient was a 42-year-old white male with MGMT-methylated, epidermal growth factor receptor variant III+ GBM and prior radiochemotherapy
  - Last dose of radiotherapy received 108 days before study; last dose of temozolomide received 47 days before study
- Patient achieved confirmed partial response lasting 22 weeks
  - Response began after 3 doses of nivolumab with original lesion reduced to 24 mm
  - Response was maintained after 6 doses at 24 mm and after 10 doses at 6 mm
- Patient progressed with the appearance of new 11-mm temporal lobe lesion after 14 doses of nivolumab
- KPS remained stable at 90 throughout treatment
- Patient remains alive as of February 20, 2015, and continues to be followed

- **Study Rationale**
  - Since IPI has activity against MEL metastatic to the brain[11] and NIVO plus IPI provides greater systemic activity than IPI alone in advanced MEL,[12] NIVO plus IPI may also have improved antitumor effects in the brain than IPI alone for pts with MEL brain metastases.

- **Study Hypothesis**
  - NIVO plus IPI followed by NIVO monotherapy will provide clinical benefit to pts with MEL metastatic to the brain, improving on the results reported with IPI alone.[11]

Study Design



Inclusion/Exclusion Criteria

- **Key Inclusion Criteria**
  - Men and women aged >18 years
  - Previously treated or treatment-naïve, histologically confirmed malignant MEL with measurable metastases in both brain and extracranial sites
  - Measurable brain metastasis 0.5cm–3cm in longest diameter that has not been previously irradiated
  - Allowable prior therapy

- Approved adjuvant regimen
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

- **Key Exclusion Criteria**
  - Leptomeningealmetastasis
    - >3CNSlesionspreviouslytreatedwithSRT

Study Objectives

- **Primary Objective**
  - Assess the CNS Clinical Benefit Rate (CBR = CR + PR + >6-months SD) in pts with MEL metastatic to the brain treated with NIVO plus IPI followed by NIVO monotherapy

- **Secondary Objectives**
  - Extracranial CBR • OS
    • Global CBR • Safety and tolerability

- **Exploratory Objectives**
  - Predictive values of biomarkers (eg, PD-1, PD-L1, and other markers related to immune cell populations) and pharmacogenomics (eg, natural genetic variation in select genes)

Challenges for Immunotherapy in Brain Tumors

- The brain immune micro-environment is different
- Brain Edema
- Steroid management
- Appropriate patient selection is critical
- Optimal Immune therapy for brain metastases in the future may be different from systemic immune strategy

Take Home Messages

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

- The BBB and BTB 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.