



UniversitätsSpital
Zürich

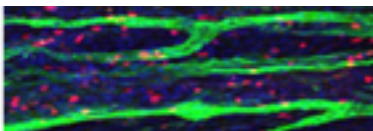
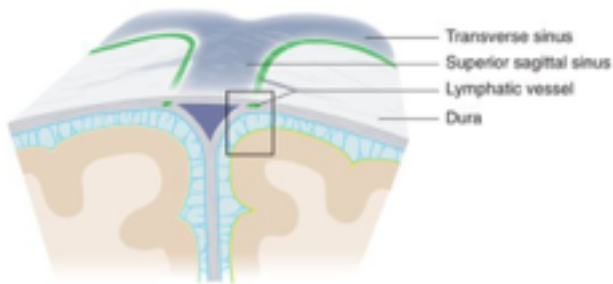
Interactive Case Reports on Immunotherapy

Tobias Weiss

University Hospital & University of Zurich

Immune surveillance of the CNS

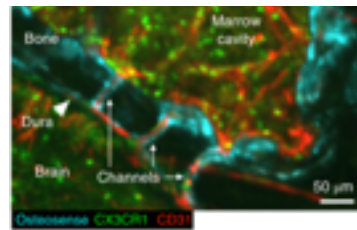
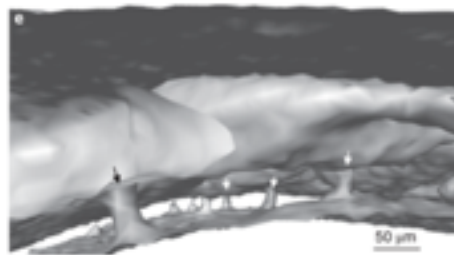
Meningeal lymphatics



Lymphocytes

Louveau *et al. Nat.* 2015

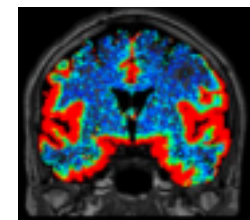
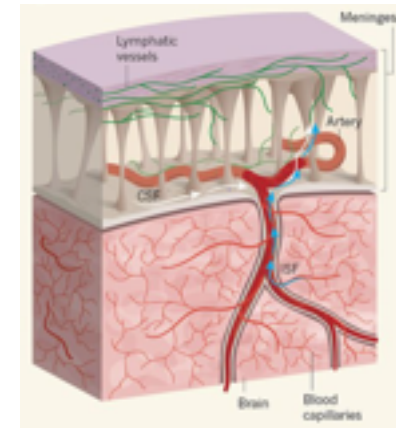
Skull - Dura channels



Myeloid cells

Herisson *et al. Nat. Neurosci.* 2018

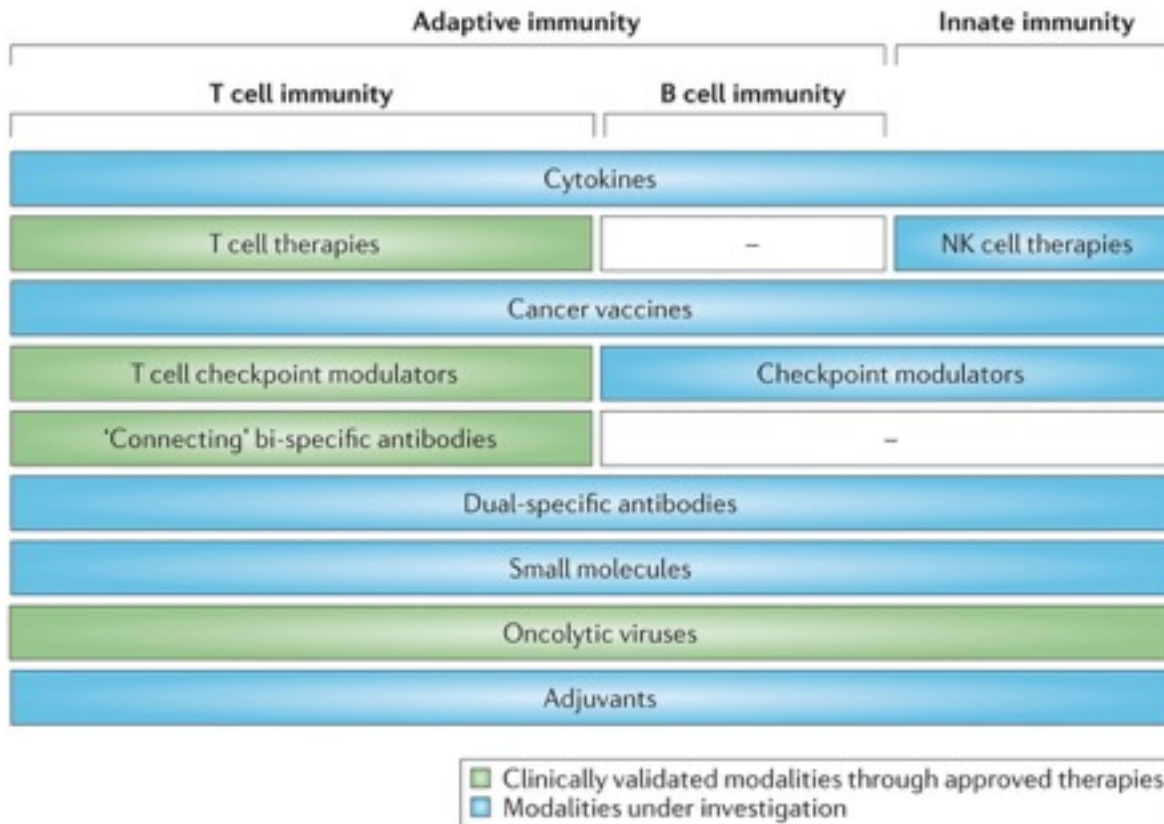
Glymphatic system



Cytokines

Sweeney *et al. Nat.* 2018

Cancer Immunotherapy



Brain metastases were excluded from most phase III immunotherapy trials

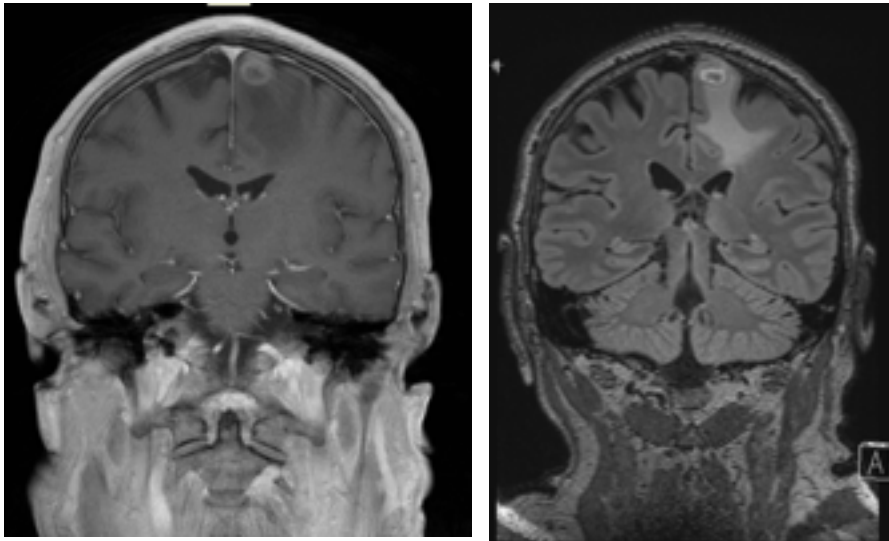
Experience with IT for patients with BM?



Case 1

- 60 y/o man
- 08/2015 right hemiparesis

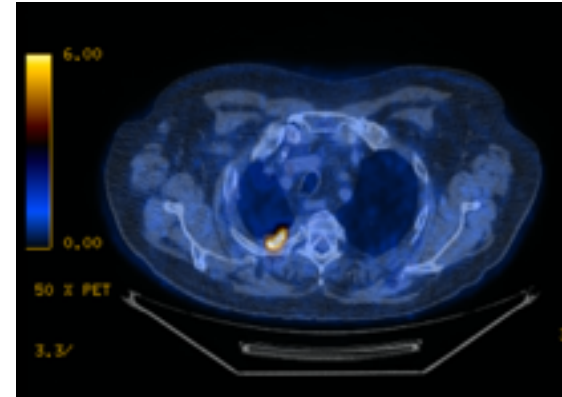
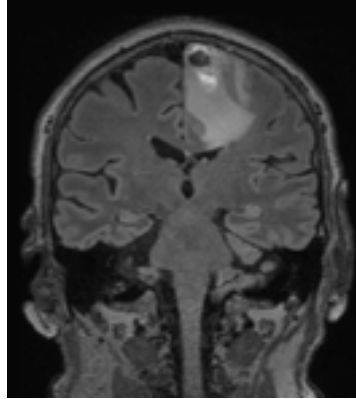
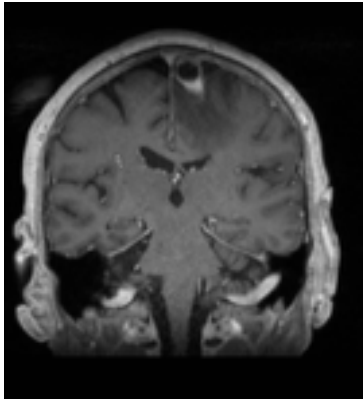
Adenocarcinoma of the lung
(*EGFR* wt, *ALK* neg., *KRAS* mut.)



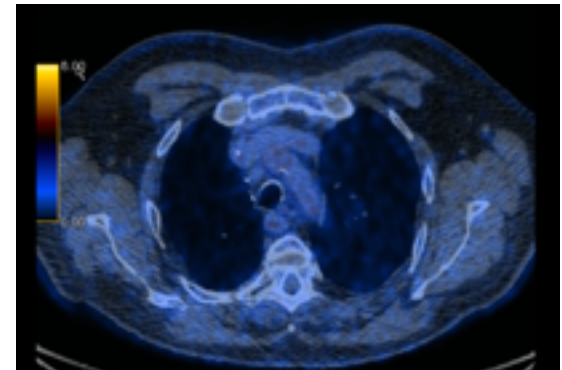
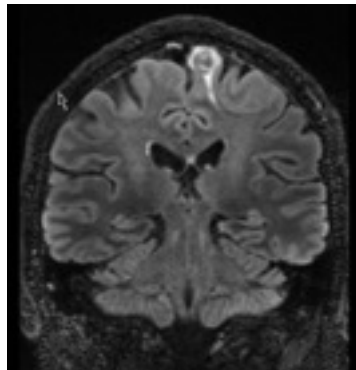
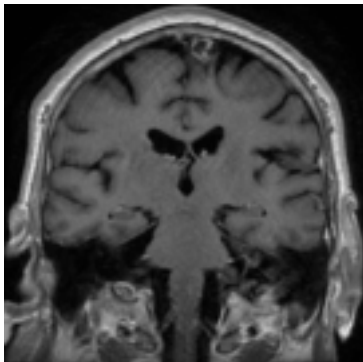
- 9-10/2015: SRS of brain metastasis
- 9/2015 – 4/2016: Dexamethasone 8 - 4 mg/day
- 10-12/2015: 4 x Carboplatin / Pemetrexed

Case 1

12/2015 disease progression



01/2016 stopp CP + Pem → start Nivolumab





Interactive Questions

- **Steroids and Immunotherapy?**
- **Single / sequential treatments vs. combination IT?**

Activity of IT in BM: what we know

CTLA-4

- Margolin *et al. Lancet Oncol.* 2012
 - IPI, Phase II
 - melanoma BM, asympt. + sympt.
 - Activity in asympt. BM, no steroids (ORR 26%, mOS 7 mo., 2y OS 24% vs. ORR 10%, mOS 3.7 mo., 2y OS 10%)

PD-1

- Goldberg *et al. Lancet Oncol.* 2016
 - Pembro, Phase II
 - asympt. melanoma / NSCLC BM, no steroids
 - ORR 22% MBM, 33% NSCLC
 - mOS for MBM not reached (FU 12 mo.), mOS for NSCLC 6.8 mo.

CTLA-4 + PD-1

- Tawbi *et al. NEJM* 2018
 - Nivo. + IPI. -> Nivo, Phase II
 - asympt melanoma BM., < 10d of steroids
 - ORR 57% MBM
 - mOS not reached (FU 12 mo.), OSR at 12 months 81.5%
- Long *et al. Lancet Oncol.* 2018
 - Nivo. + IPI. vs Nivo., Phase II
 - A/B: asympt melanoma BM., C: sympt., LM.
 - ORR 46% (A), 20% (B), 6% (C)
 - mOS not reached (A), 18.5 mo. (B), 5.1 mo. (C), OSR at 6 months 80% (A/B), 44% (C)

1. Asymptomatic BM / no steroids can derive most benefit
2. Concordance CNS / systemic responses
3. Rationale for combination IT (IPI + Nivo) for melanoma BM

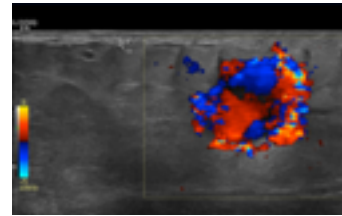
Case 2: 61 y/o female

06/2012



Melanoma (pT2bN0M0)
→ excision

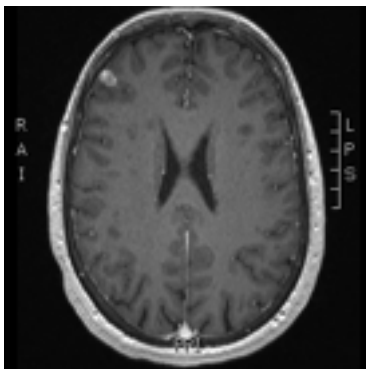
06/2015



Melanoma (pT2bN2cM0), *BRAF* mut.
→ excision + adjuvant therapy
(CTLA-4 vs. anti-PD1 clinical trial)

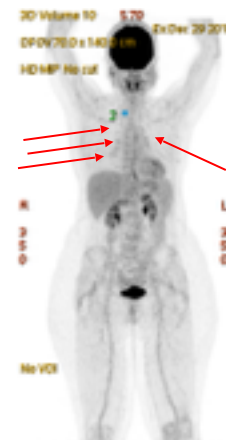


08/2015



Melanoma (pT2bN2cM1c)
→ excision + RT + IPI

02/2016



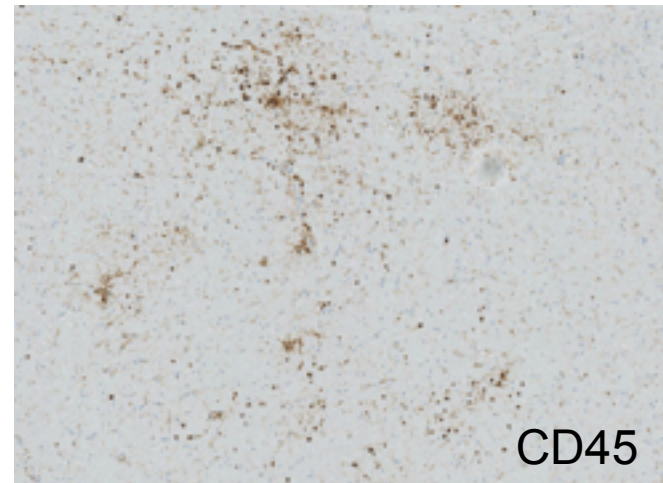
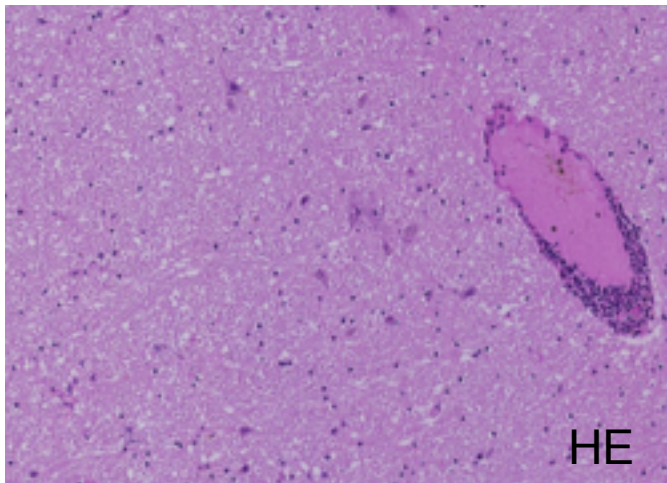
Switch from IPI to Pembro
1st Infusion 4th of April 2016

16th of April 2016: tel. „not feeling well“ → what would you do?

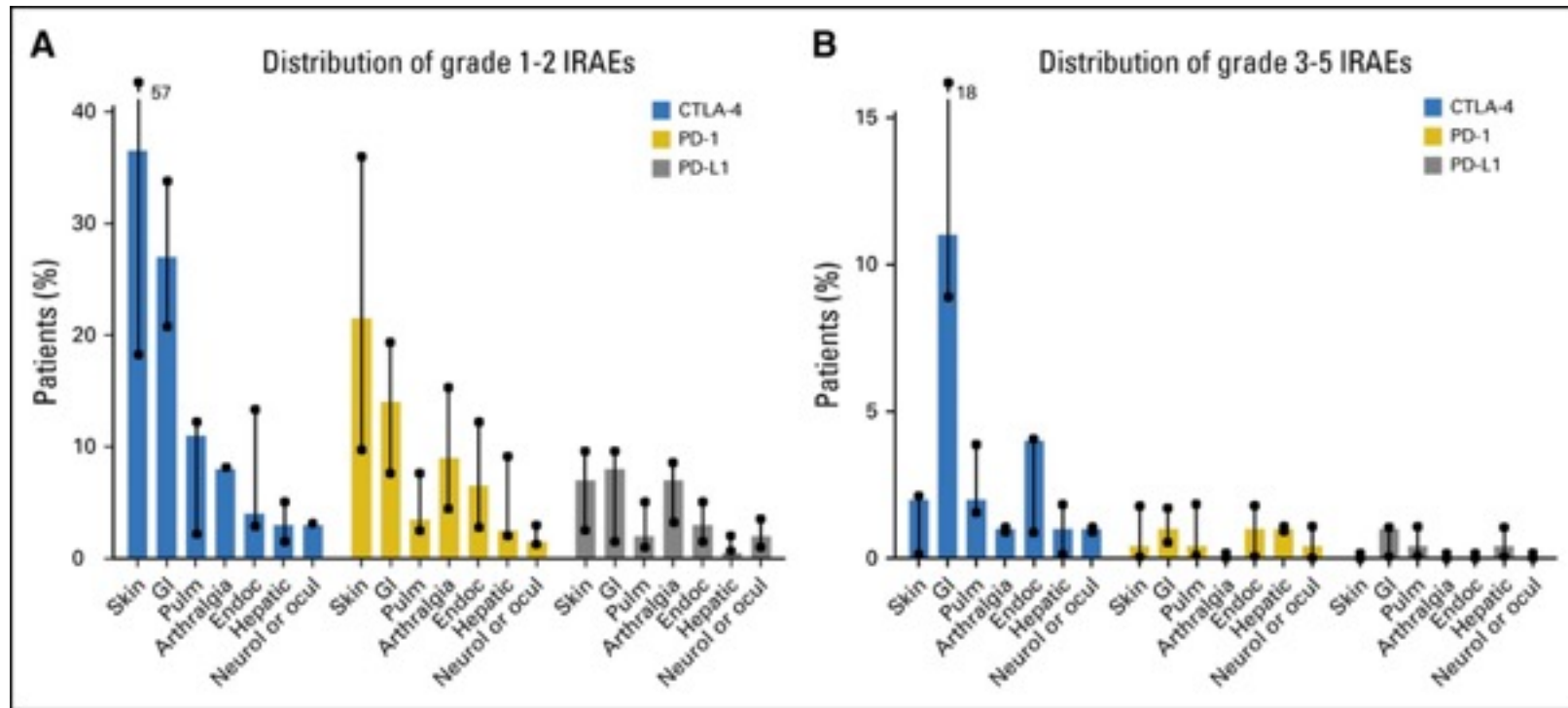
18th of April 2016 death

Autopsy

- Pulmonary edema
- Encephalitis (CD8 T cells)
- CD4 T cells infiltrate in thyroid, heart, lung, liver, adrenal gland, pituitary gland
- Infection excluded (such as HHV6)



Toxicities of IT for BM: what we know

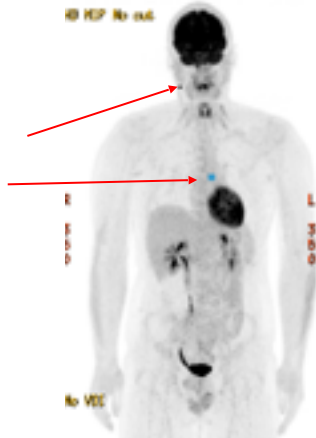


Brahmer *et al. J. Clin. Oncol.* 2018

Similar toxicities in BM: Tawbi *et al. NEJM* 2018, Long *et al. Lancet Oncol.* 2018

Case 3: 38 y/o man

05/2013



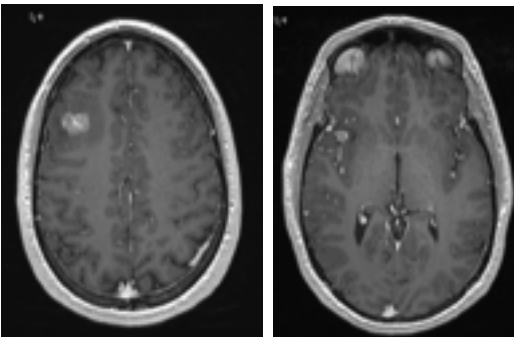
Melanoma (T4N0Mx), *NRAS* mt., *BRAF* wt.
→ excision, Ipilimumab

10/2013



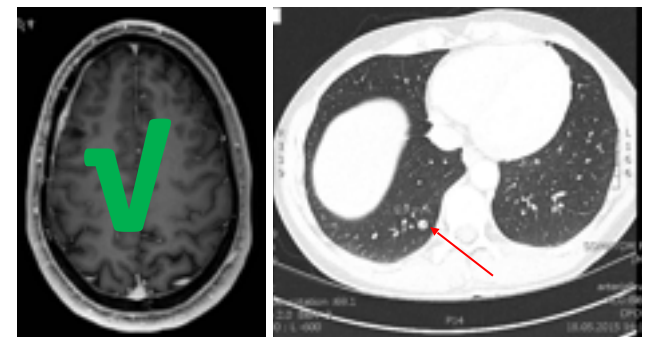
Lung metastases PD
→ stopp IPI, start anti-PD1

05/2014



Seizure, 2 BM
→ excision, RT
anti-PD1 stopp, start MEKi

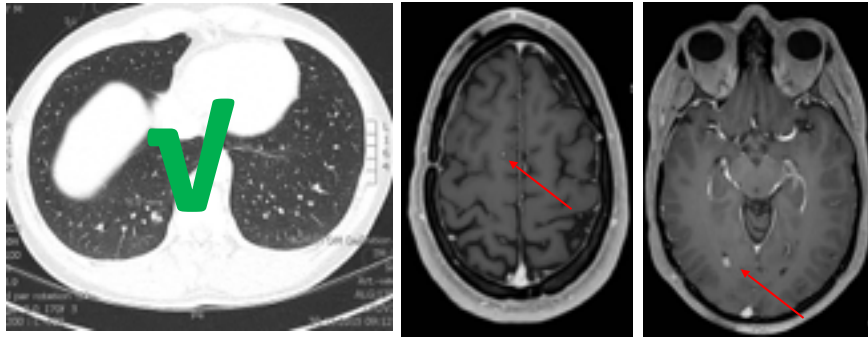
03/2015



Lung metastases PD
→ SRS, MEKi stopp, re-start IPI

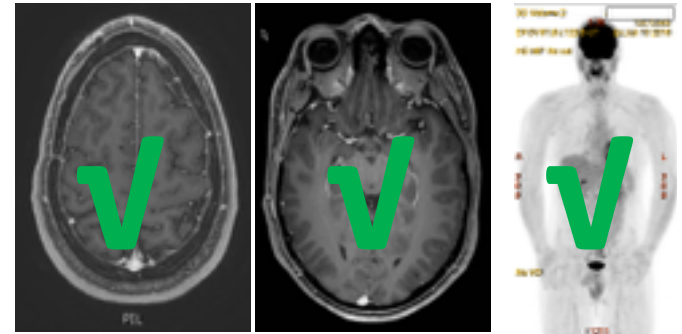
Case 3

12/2015



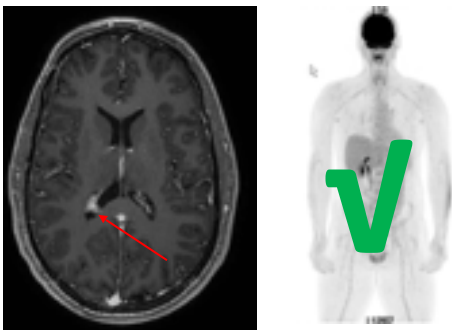
new BM
→ SRS, re-start anti-PD1

06/2016



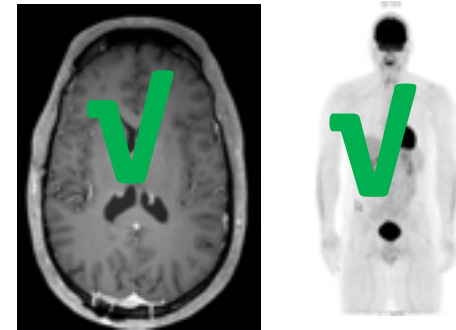
CR

05/2018



new BM
→ excision, SRS, continue anti-PD1

09/2018



→ continue anti-PD1

Conclusions

- **Many open questions (efficacy, integration/combination, etc.)**
- **Need for better understanding of the biology of parenchymal BM and LeptoM (basic science / transl. research)**
- **Exchange of experiences with IT for BM/LeptoM**
- **Need for phase III clinical trials with IT for patients with BM/LeptoM**