Immunotherapy for Brain Metastasis

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Disclosures

- Grant/Research support: Merck, BMS, Apexigen

Honoraria: Genentech, Corvus, Nektar, Alexion, Biodesix, Celldex, Immunocore, Merck, Array Biopharma

Background – Brain Metastases

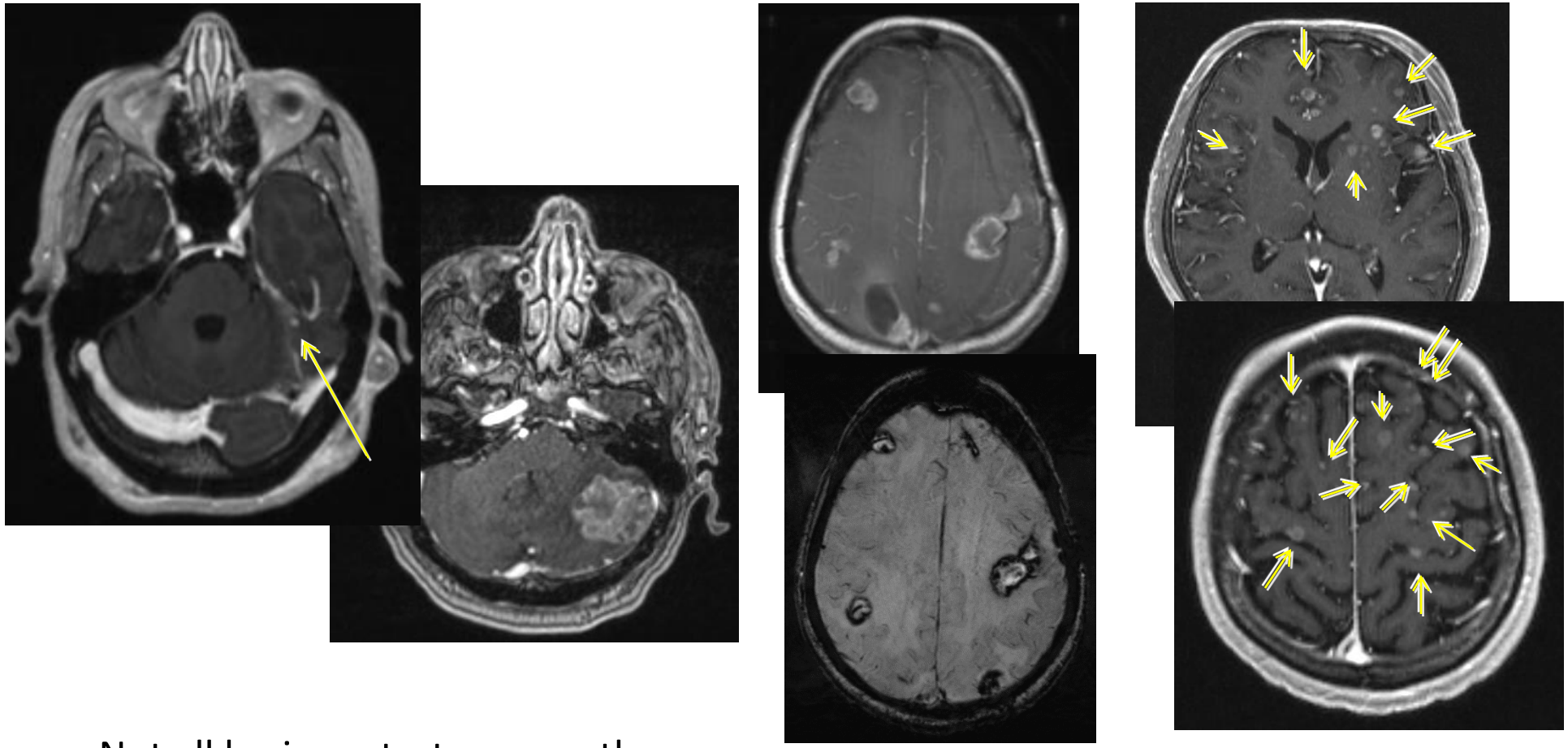
- Most common intracranial tumors in adults (>50% of brain tumors)
- In patients with systemic metastases, brain metastases occur in 10-50%
- Incidence is increasing due to improved imaging and survival of metastatic patients

Metastatic Lung cancer— 30 %
Metastatic Melanoma — 40 %
Metastatic Renal cell cancer — 15%
Metastatic Breast cancer — 10 %

Rationale behind studying systemic therapies and the TME in brain metastasis

- Historically considered ominous: e.g., for melanoma and lung cancer survival ~2-4 months.
- However with modern imaging and local therapy (stereotactic radiosurgery) - median survival ~8.3 months, even prior to approval of PD-1 and CTLA4 inhibitors
- Incorporation of systemic therapy could potentially help both with CNS disease and extracerebral disease, and understanding the tumor microenvironment in the brain is key given the concern that the brain **might be** a site of immune privileged
- Landmark trials using recently approved drugs for melanoma enrolled >6,000 patients, none with active brain metastasis; brain met specific trials only enrolled a few hundred patients
- **Challenges to studying brain metastasis include limited availability of animal models and human tumors for analysis**

Variable brain metastasis phenotypes

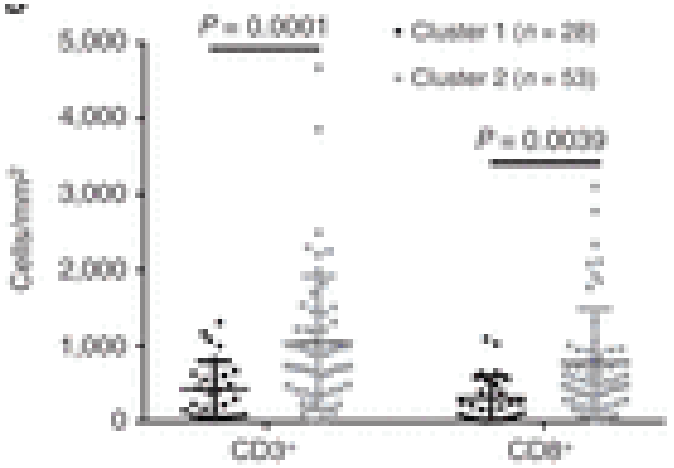


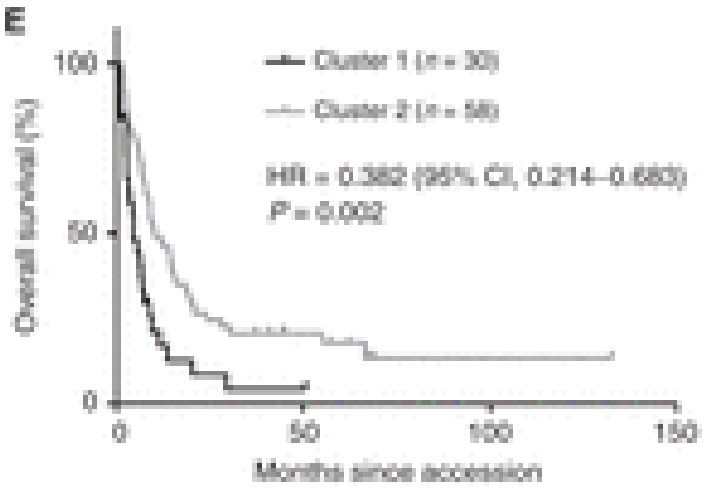
- Not all brain metastases are the same
- No obvious clinical features (age, gender, histologic type, etc) are associated with size, number and survival in Yale cohort

Brain metastasis profiling studies

- Davies group conducted RNA-seq on matched cranial and extracranial metastases and showed an oxidative-phosphorylation gene expression profile in CNS metastasis

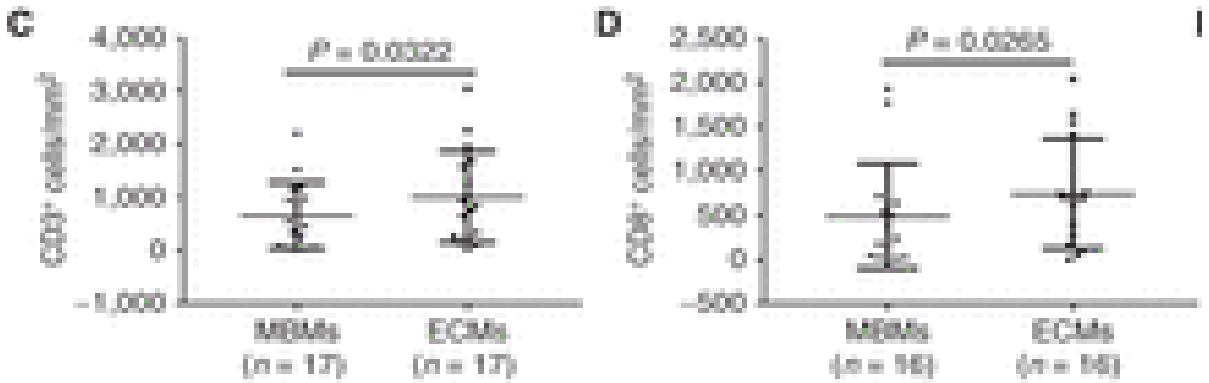
- Importantly, variability was seen in immune profiling; patients with more CD3+ and CD8+ cells had better survival





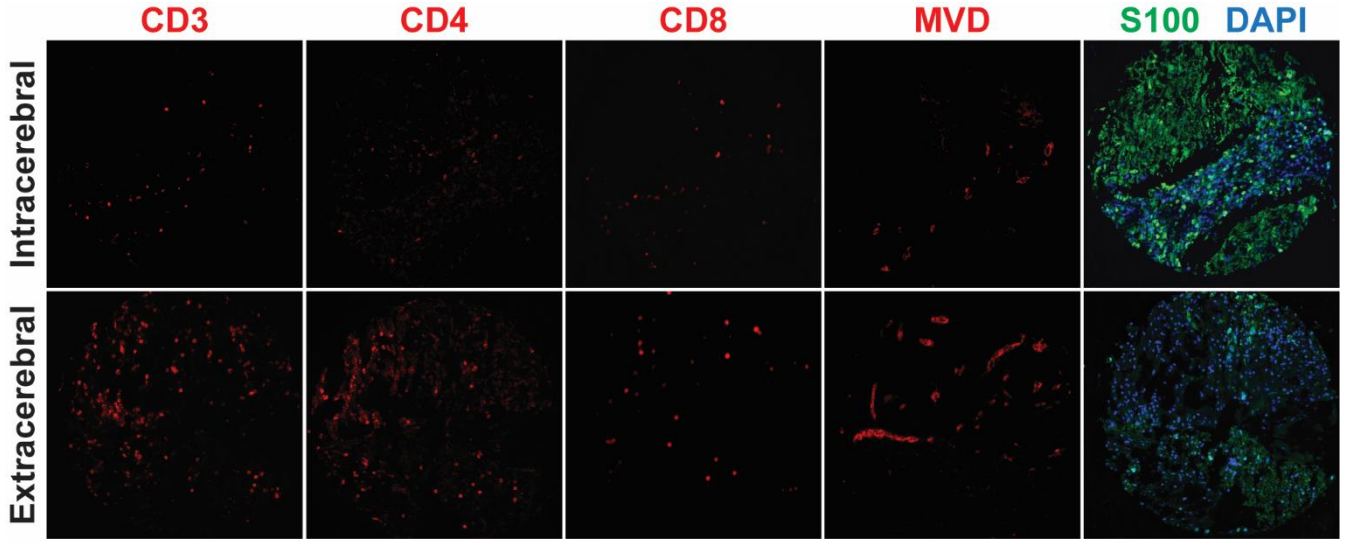
Fischer et al, Cancer Discovery, 2019

- Tumor immune cell infiltrate was lower in brain compared with matched extra-cerebral metastases



Fischer et al, Cancer Discovery, 2019

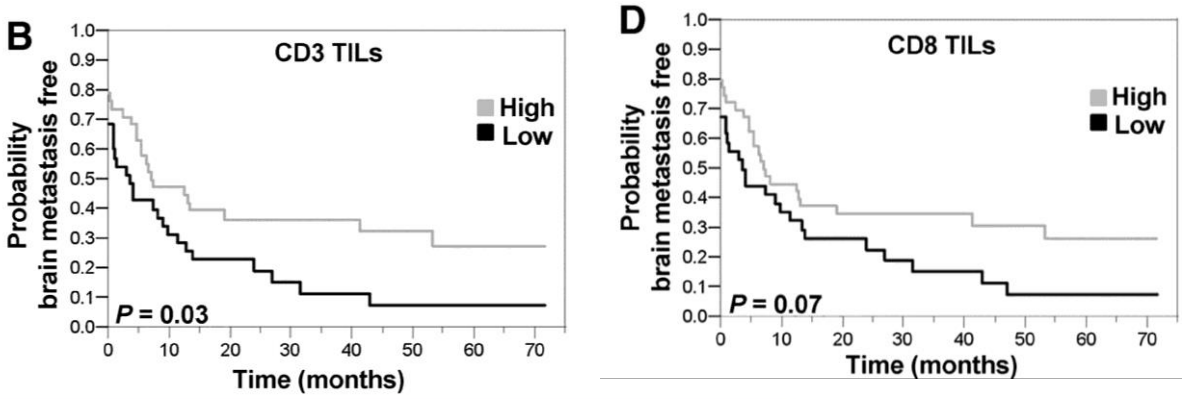
- Corroborated by studies in our lab



- Density of infiltrating CD3+ cells was lower in brain compared with matched extra-cerebral metastases, P=0.01, N=32

- Density of FOXP3 positive cells higher in the brain than matched extracerebral metastases, P=0.01

- Furthermore, melanomas from extra-cerebral sites that have less T cell infiltrate are more likely to disseminate to the brain



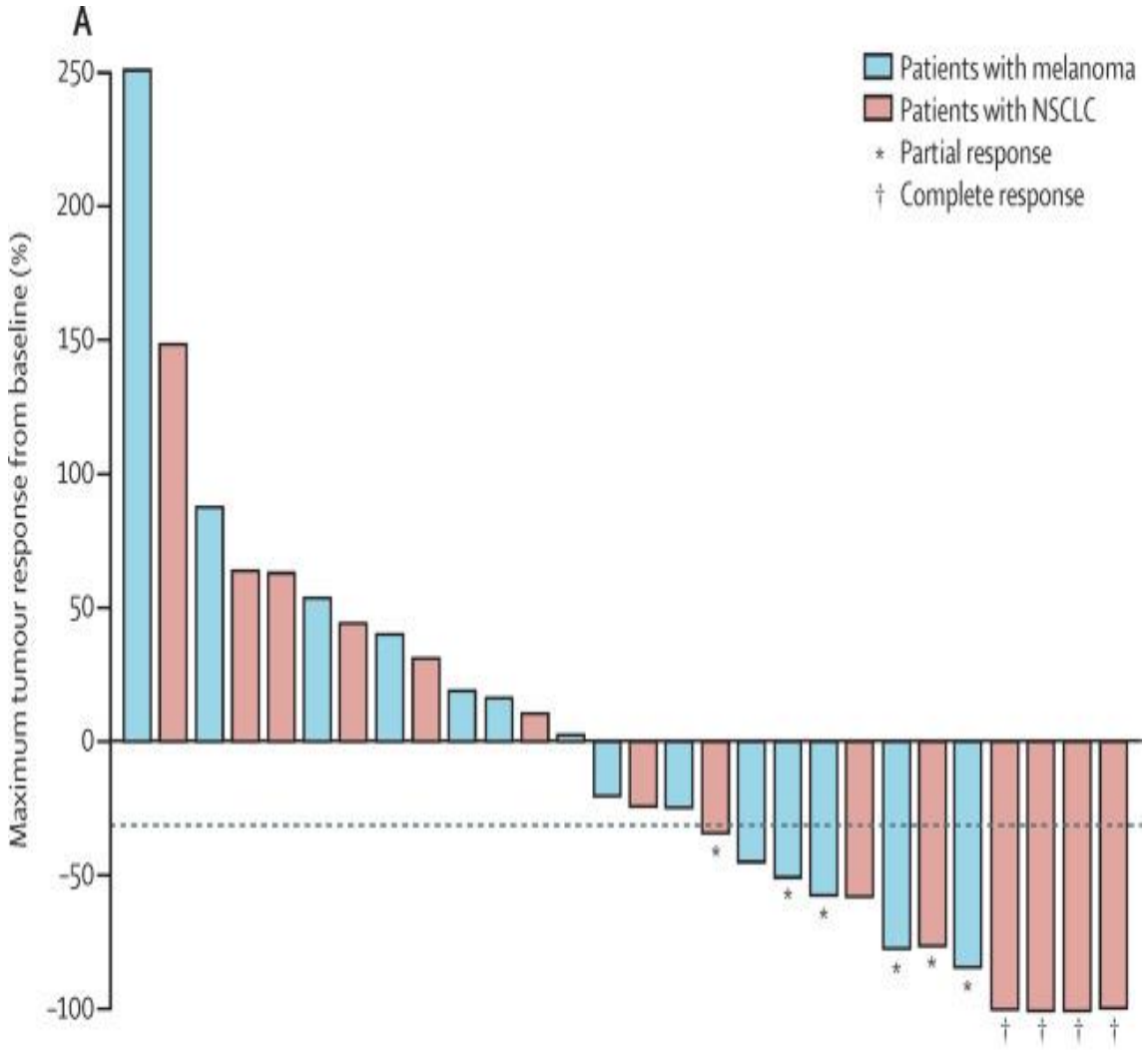
Kluger et al, Clinical Cancer Research, 2015

Is the brain a site of immune privilege?

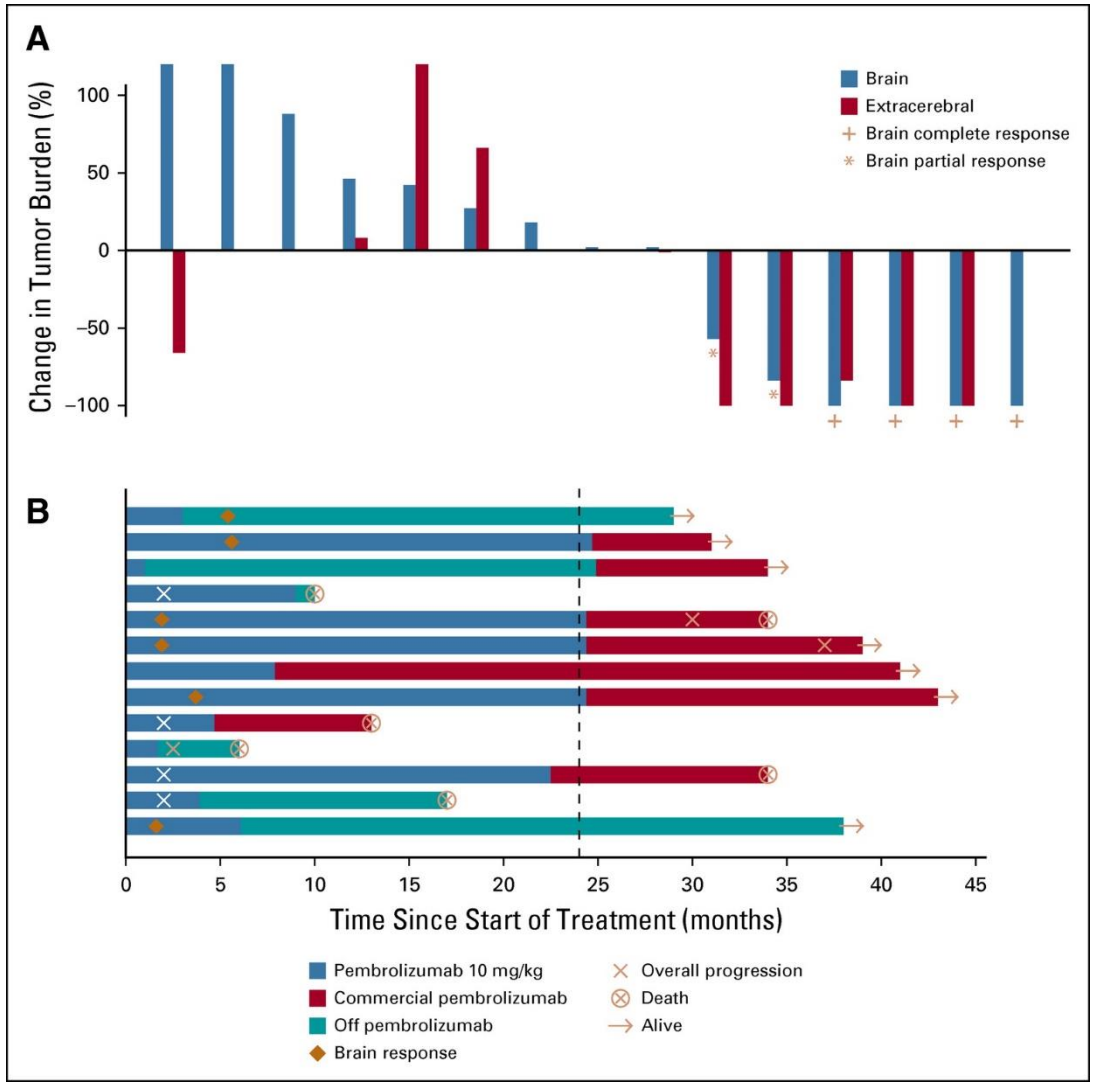
- Margolin et al, Lancet Oncology, 2012, ipilimumab in melanoma patients with brain metastasis, 16% PR rate in the brain

- Goldberg et al, Lancet Oncology 2016, pembrolizumab in patients with either non-small cell lung cancer or melanoma showed a brain metastasis response rate > 30% in lung cancer patients, 26% in melanoma patients (updated in Kluger et al, JCO 2019)

- **RESPONSES ARE LARGELY CONCORDANT BETWEEN BODY AND BRAIN**



Goldberg et al, Lancet Oncology, 2016

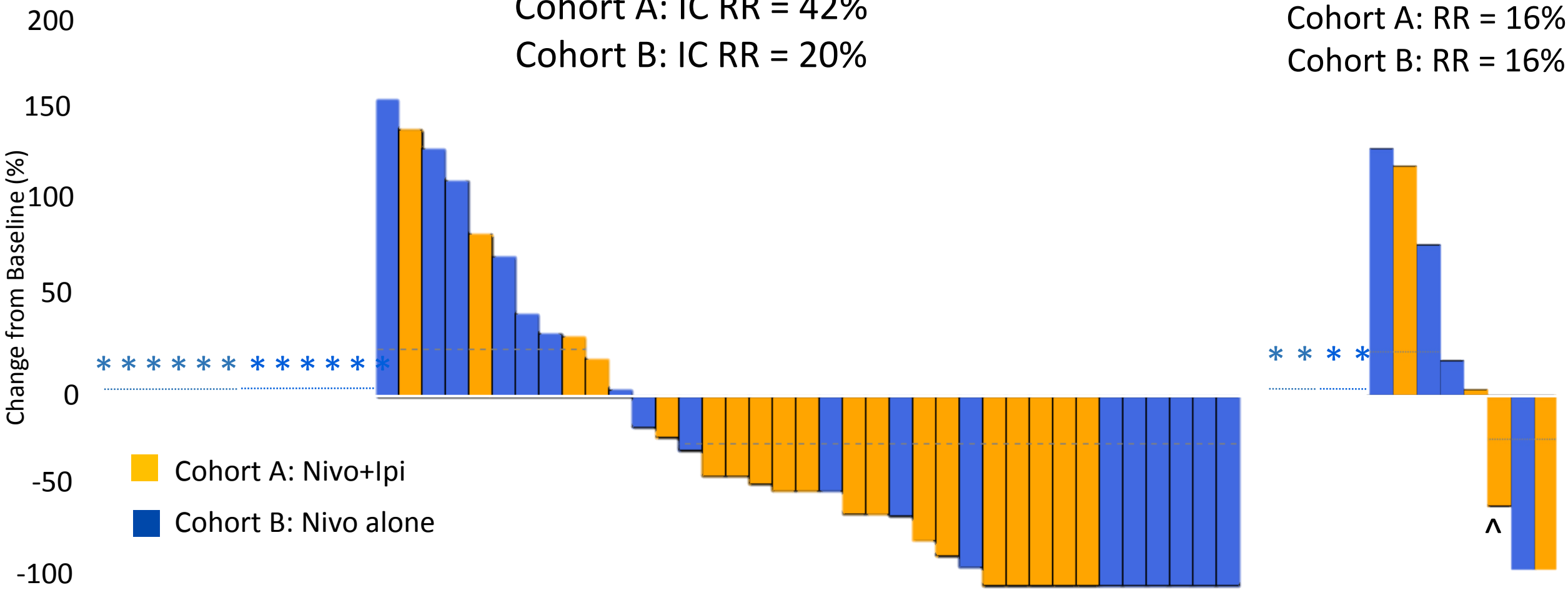


Kluger et al, Journal of Clinical Oncology, 2019

Ipilimumab+nivolumab vs. nivolumab – Long et al Lancet Oncology 2018; Intracranial Response

All Patients
Cohort A: IC RR = 42%
Cohort B: IC RR = 20%

BRAFi+MEKi Pretreated
Cohort A: RR = 16%
Cohort B: RR = 16%



Deceased prior to week 12 assessment

^PD

Tawbi H. et al, New England Journal of Medicine 2018, Checkmate 204 ipilimumab plus nivolumab (N = 75)

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41–65)	55 (43–66)	49 (38–61)
Clinical benefit rate[c], % (95% CI)	59 (47–70)	60 (48–71)	52 (40–64)

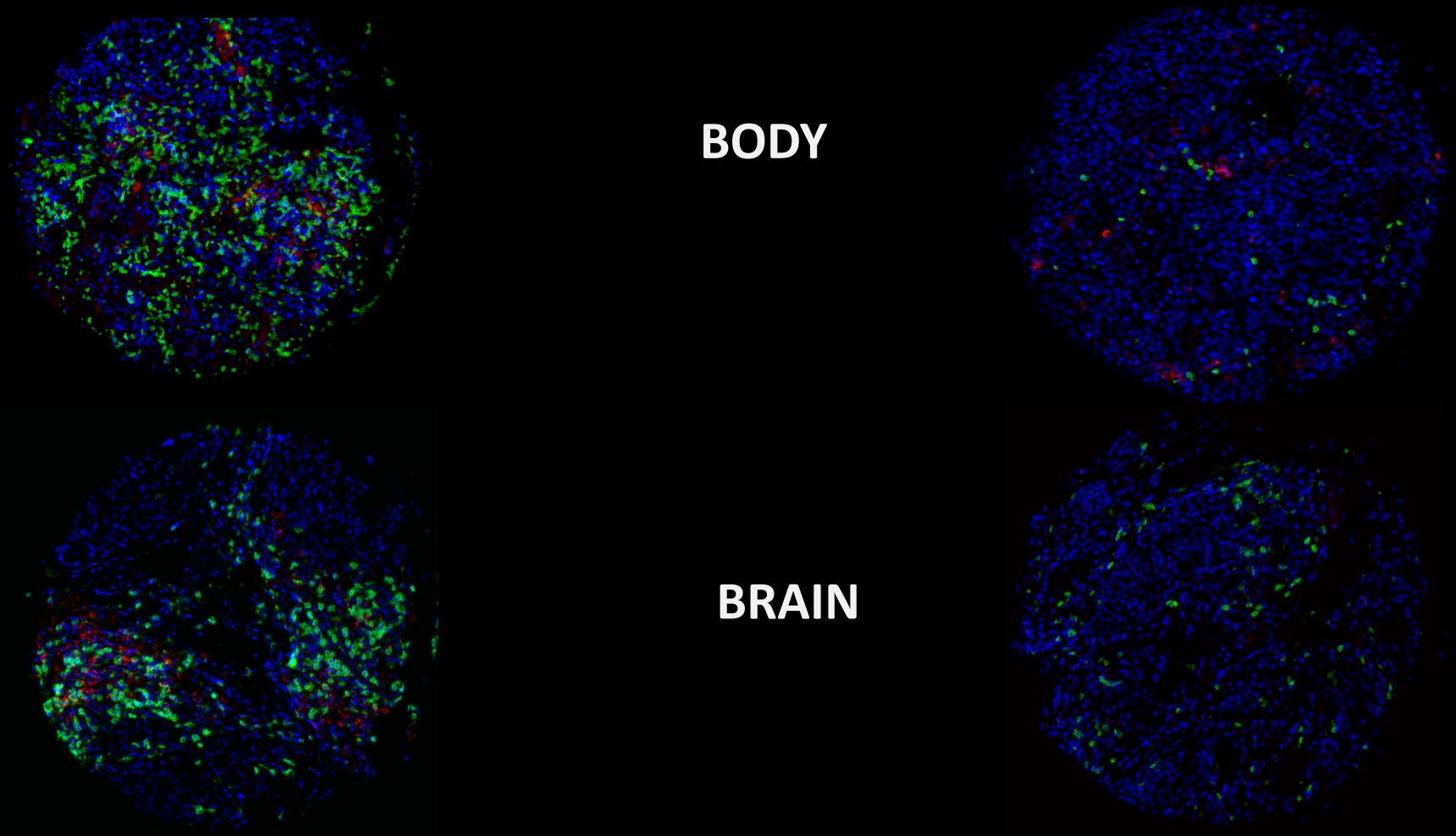
[a]Confirmed and unconfirmed progressive disease

[b]Includes unconfirmed responses

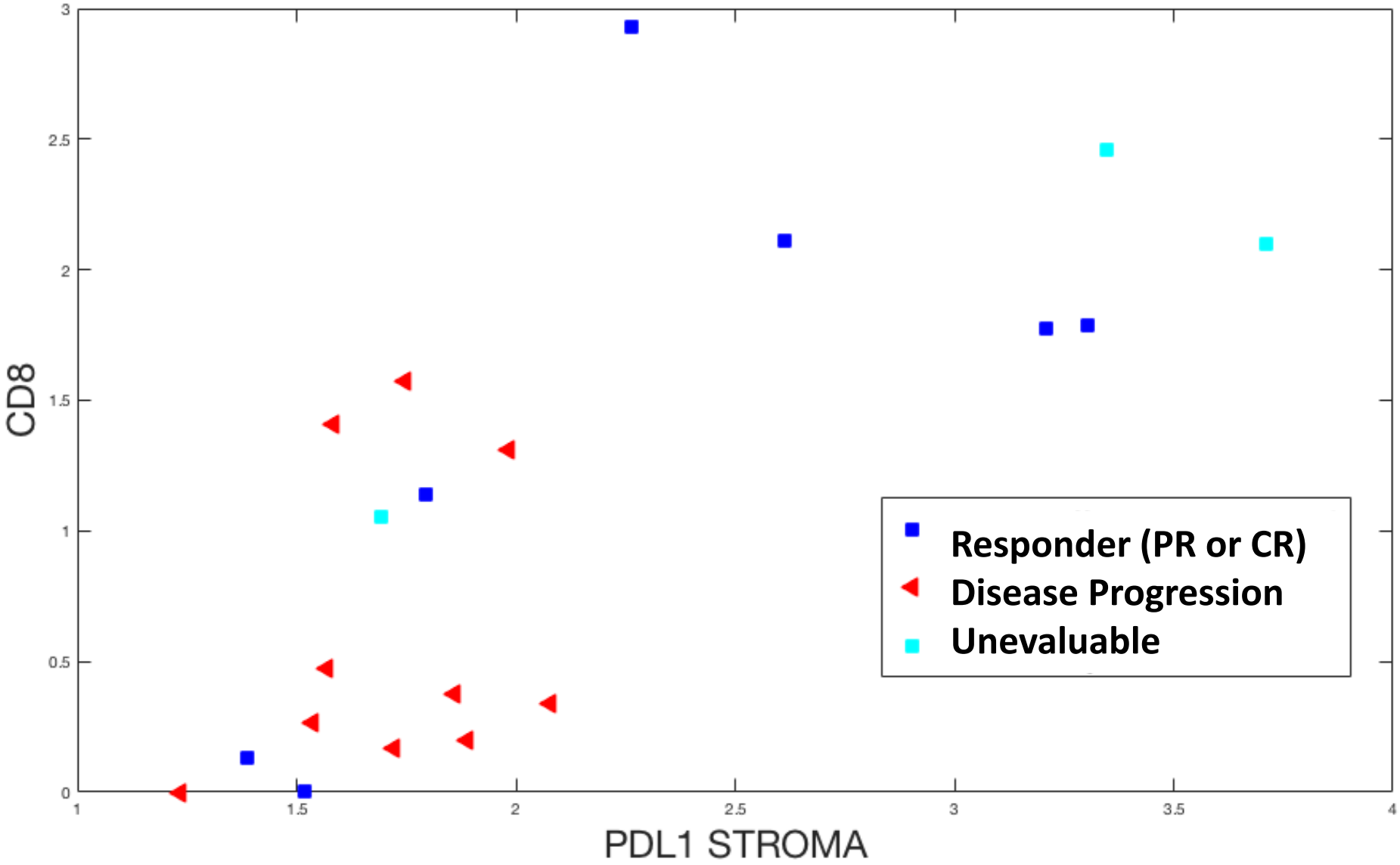
[c]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months

Complete response to pembro, tumor with high PD-L1 and CD8 cell density

Disease progression on pembro, tumor with low PD-L1 and CD8 cell density



PDL1 red, CD8 green, DAPI blue



PEMBROLIZUMAB; MELANOMA PATIENTS

Kluger et al, Journal of Clinical Oncology, 2019

Tumor microenvironment characteristics unique to brain metastasis

- Peri-lesional edema – due to limited lymphatic or venous drainage, vessel leakage or immune infiltrates?
- Role of astrocytes and microglial cells and how do the latter differ from other tissue resident macrophages
- Tumor vessel characteristics – tight junctions are impaired in brain metastasis
- Radiation necrosis occurs more commonly in the brain at doses of 22Gy than in other organs

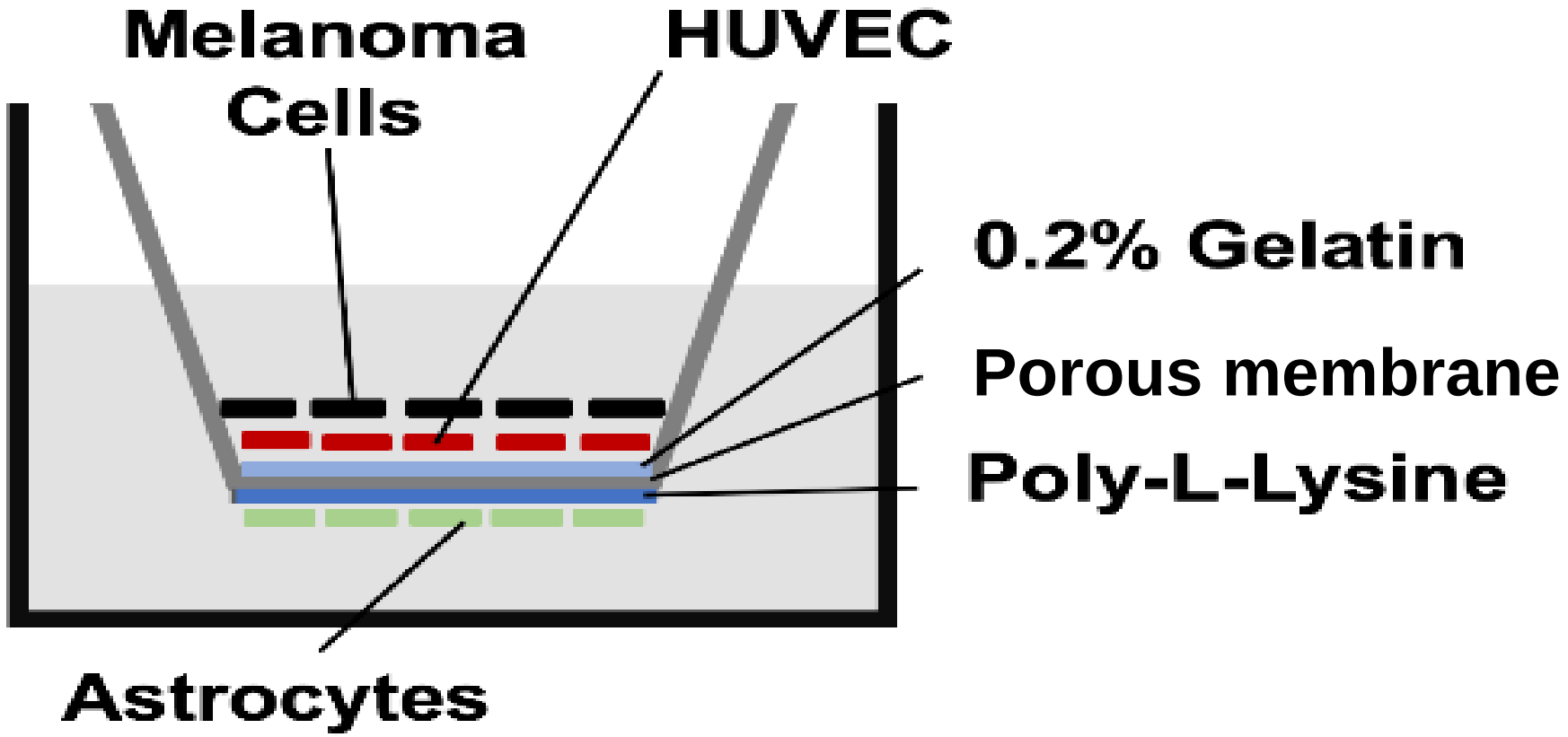
Questions regarding edema, Tran et al, JITC 2019

- No difference between lung cancer and melanoma
- Larger tumors tended to have more peri-lesional edema,

but the correlation was weak

- No association between degree of edema and PFS or OS
- Vessel density was not associated with the degree of edema, and in fact brain lesions had lower vessel density than matched extra-cerebral lesions

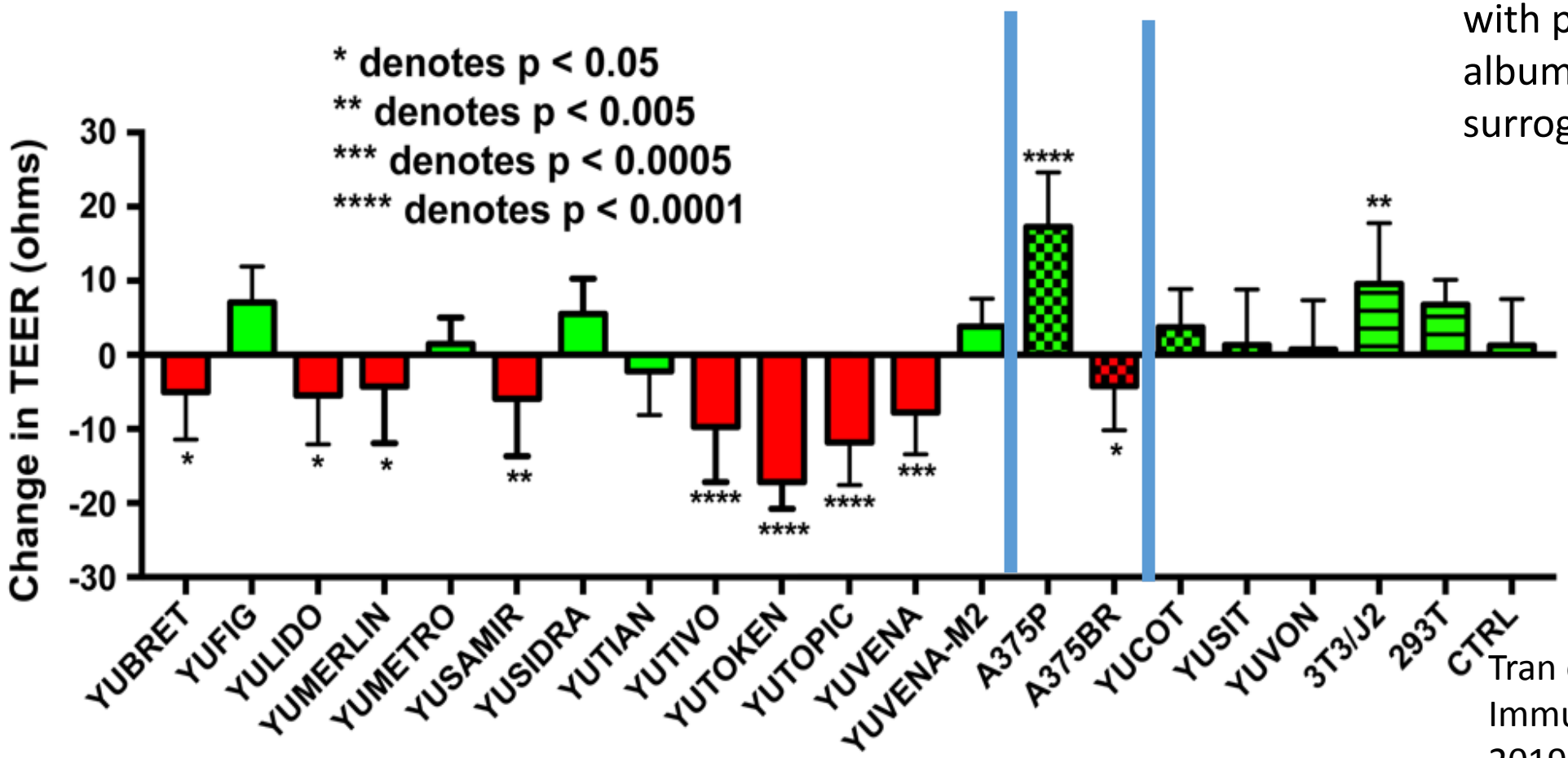
Is vascular leakiness caused by tumor cells themselves? *In vitro* studies of effects of tumor cells on tight junctions



Method described by Jilaveanu and Kluger, CCR 2015

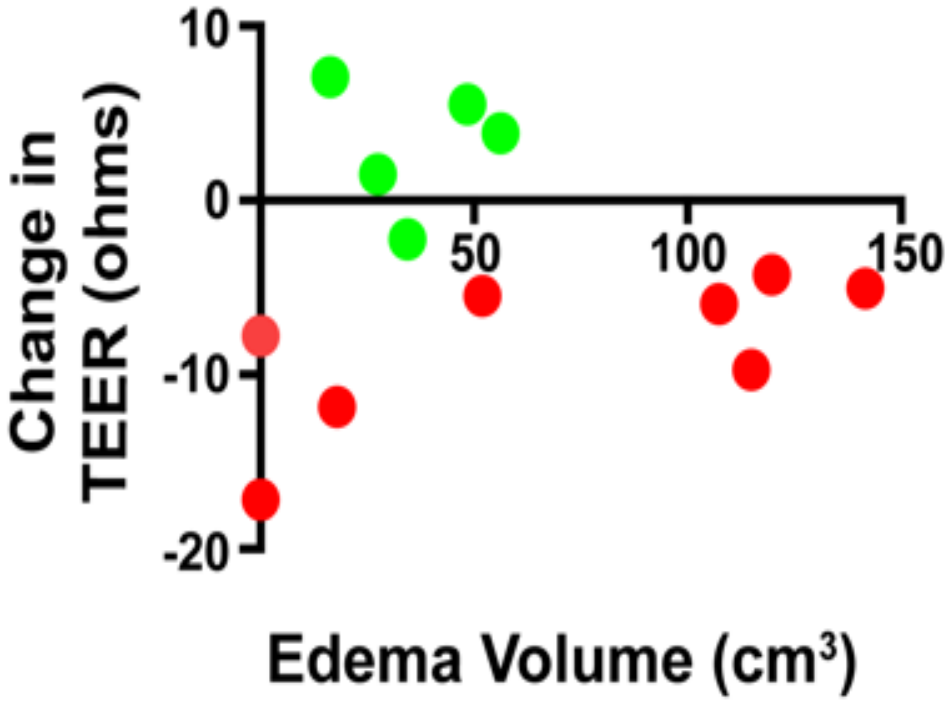
TEER (transendothelial electrical resistance)* changes caused by cerebral vs. non-cerebral melanoma cells

* TEER correlated well with passage of labelled albumin and serves as a surrogate for leakiness



Tran et al, Journal of Immunotherapy of Cancer, 2019

Does vasogenic edema correlate with disrupted tight junctions *in vitro*?



- Some cell cultures capable of inducing leakiness *in vitro* were from more edematous tumors, but not all.
- Cells can induce edema in an *in vitro* system in the absence of immune cells.
- Factors other than tumor cells likely play a role.
- Future studies will incorporate autologous T cells

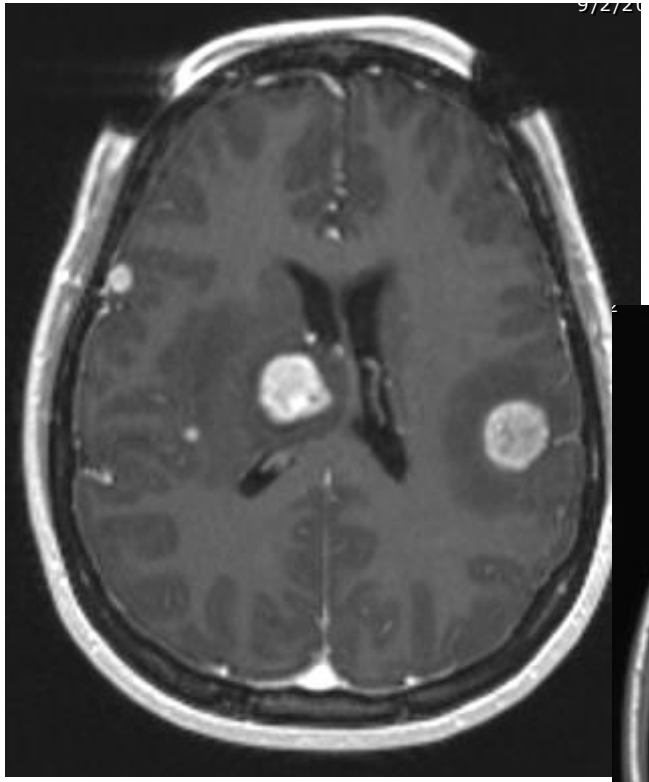
A Phase 2 Study of pembrolizumab plus bevacizumab in patients with melanoma or non-small cell lung cancer and untreated brain metastases

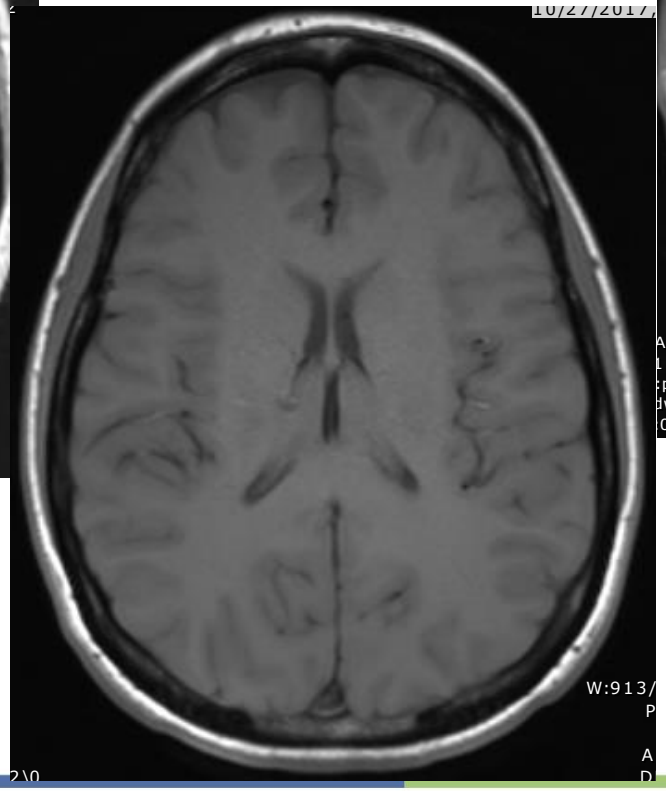
- Same trial design as pembrolizumab monotherapy trial; bevacizumab given cycles 1-4

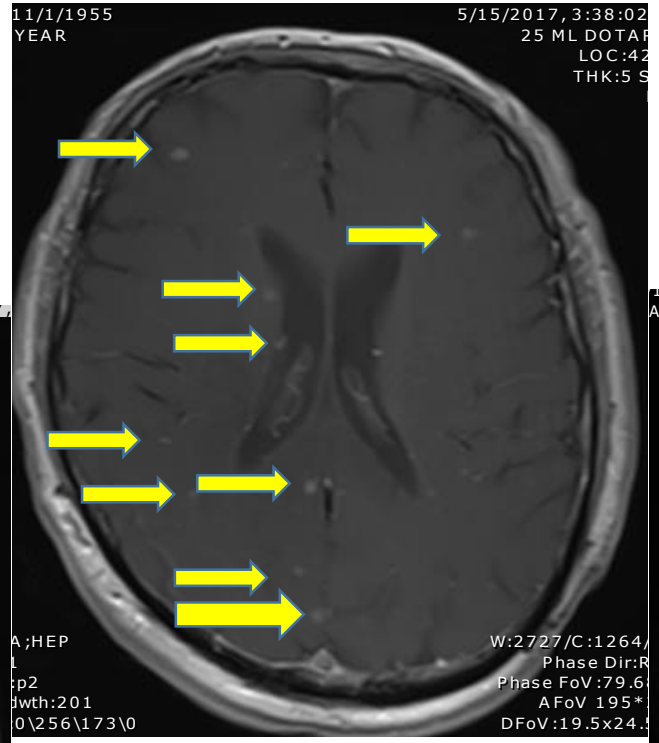
RATIONALE:

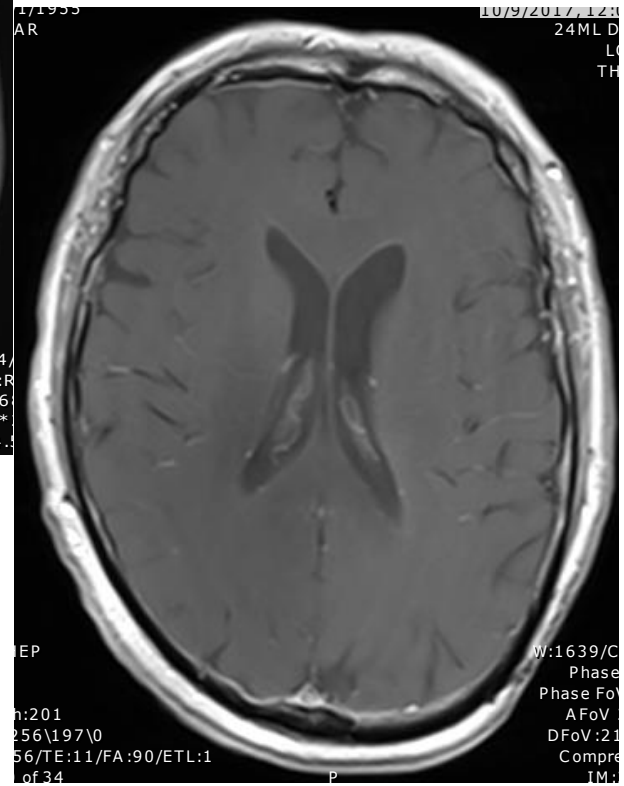
- VEGF decreases dendritic cell function and consequently antigen presentation
- VEGF promotes activity of myeloid-derived suppressor cells
- VEGF in the tumor microenvironment alters tumor vasculature to reduce lymphocyte adhesion and decrease lymphocyte trafficking across endothelium into tumor deposits
- In the Cloudman murine melanoma model and the MC38 colon cancer models, the combination of VEGF blockade and anti-PD-1 was synergistic

Response rate to date > 50%: Melanoma Pts 002 and 005









Conclusions

- While brain metastasis have less T cell infiltration and less PD-L1 they are not completely void of either
- Response rates to systemic immune therapy in brain metastases are similar to extra-cranial metastases; higher with combined CTLA4 and PD1 inhibitors
- The tumor micro-environment in the CNS is unique and poses challenges seen less in other organs such as edema and radiation necrosis
- Peri-lesional edema is more pronounced in larger tumors, but should not be a barrier to use of immune therapy, as both tumors and edema shrink in responsive tumors, although in the short term it can cause morbidity
- Peri-lesional edema is likely a result of factors secreted by tumor cells and immune cells, and can be pharmacologically modified
- VEGF inhibitors may add benefit to PD-1 inhibitors in brain metastasis; studies are ongoing

Acknowledgements

- Yale Melanoma and Lung Cancer Clinical Research Unit: **Mario Sznol, Sarah Weiss, Sarah Goldberg, Scott Gettinger, Roy Herbst,** Amanda Ralabate, Barbara Johnson, Gail Anderson

- Pharma collaborators: **Merck**

- **Patients and their families**

- Kluger lab members: **Thuy Tran**, Meaghan Barr, Gabriella Turcu, Marina Baine, **Christopher Zito**, Justine Cohen

- Other collaborators at Yale: **Lucia Jilaveanu, Sarah Weiss**, **Marcus Bosenberg**, Lieping Chen, Yuval Kluger, David Rimm, Robert Camp, Adebowale Adeniran, **Veronica Chiang, Amit Mahajan**, James Yu, **Richard Carson**

- SPORE specimen Core – Ruth Halaban, Antonella Bacchiocchi

- MRA, Lungevity (to Lucia Jilaveanu), DOD (Sarah Goldberg) and the NIH (to Lucia Jilavenu and Harriet Kluger)