The immunological aspects of immune checkpoint blockade

The role of immunotherapy in brain metastasis

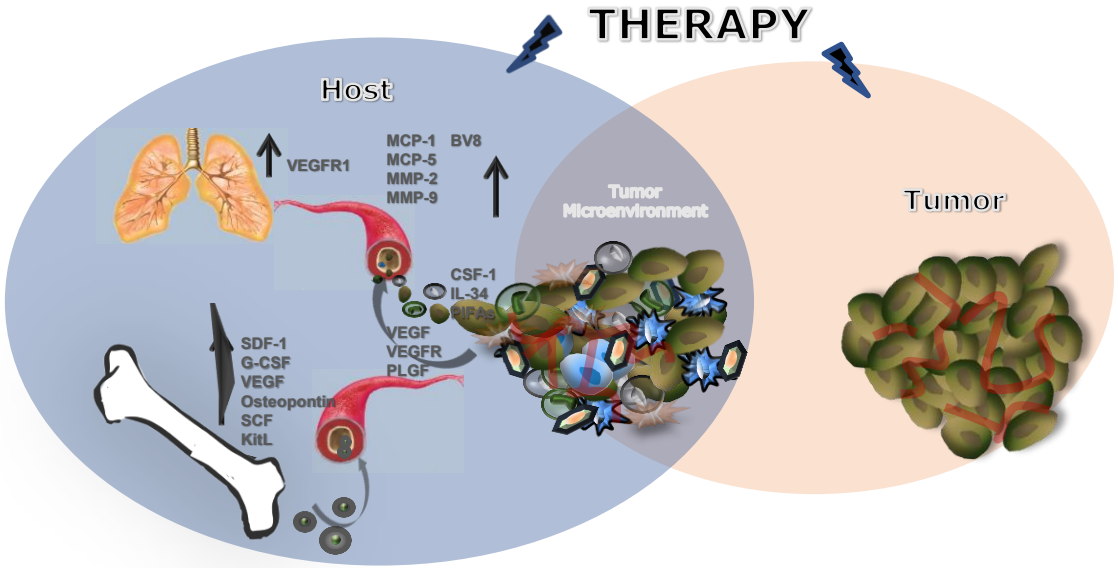
July 13-18 2025

Yuval Shaked, Technion

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

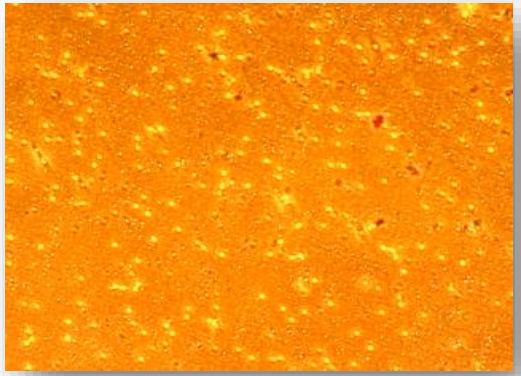
Mechanisms of tumor resistance are not only tumor- but also host-dependent



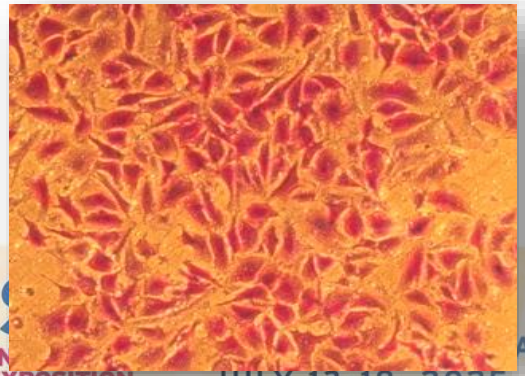
The host response to anti-cancer therapy

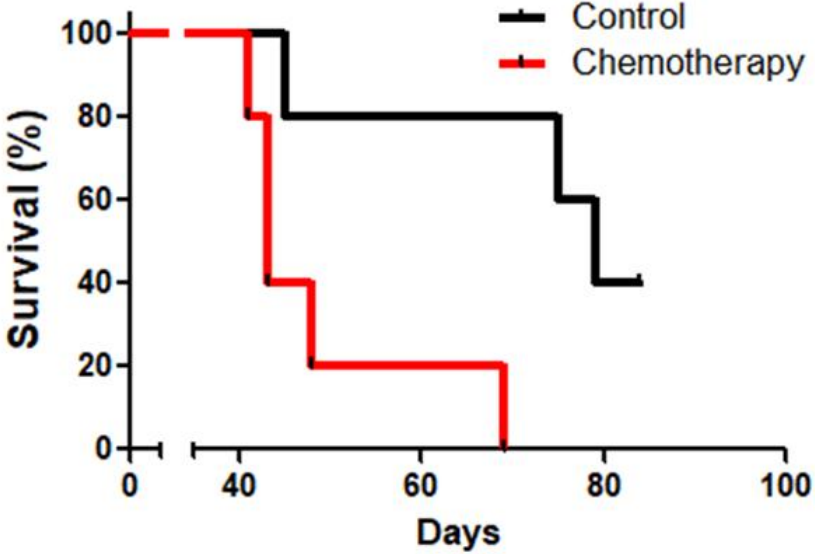
Therapy induces host effects promoting tumor cell dissemination and acceleration of metastasis

Plasma from control mice



Plasma from PTX treated mice

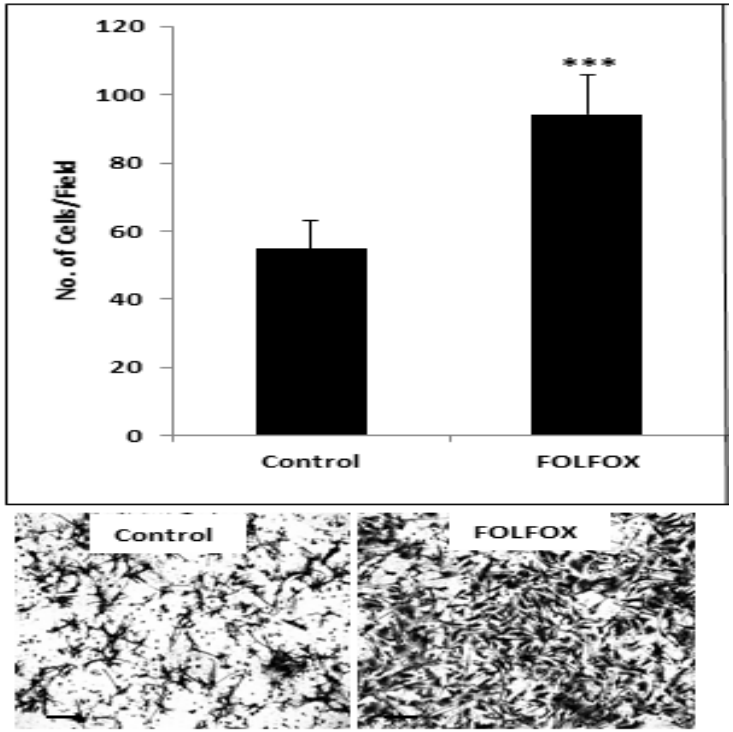




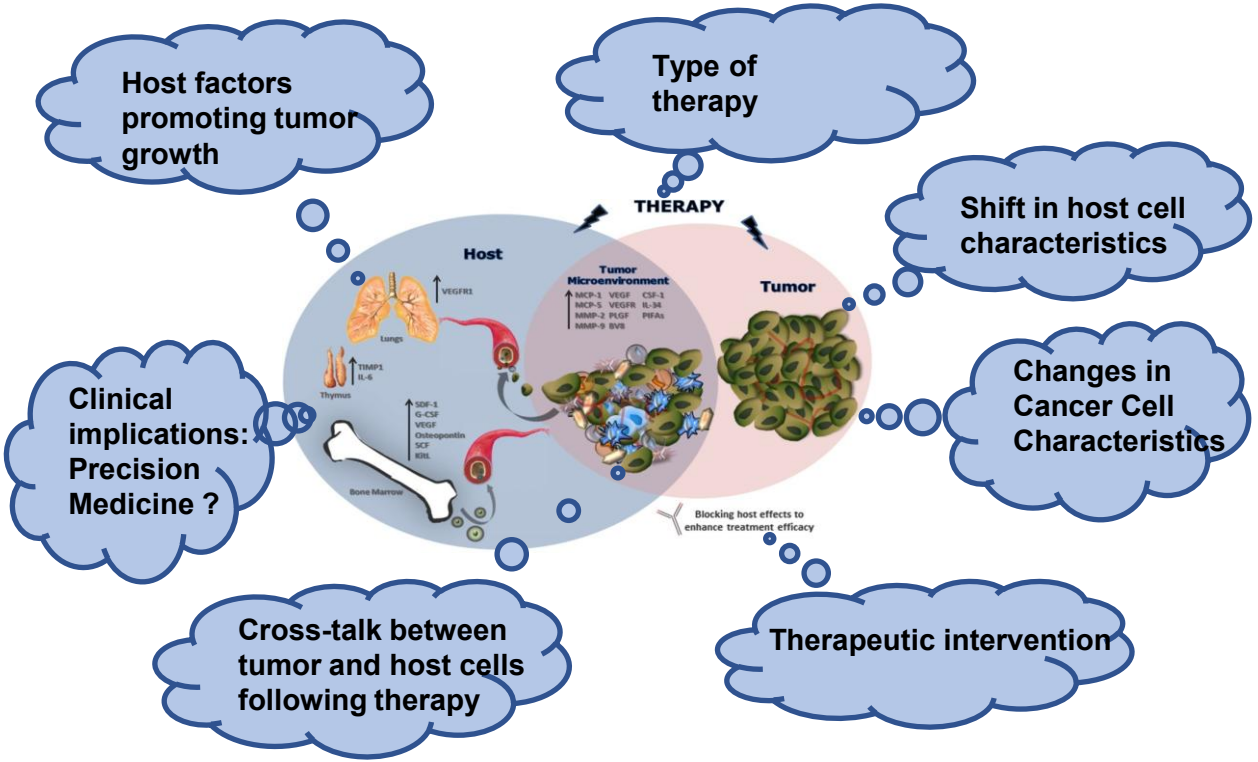
Adopted from Velitski-Gingis et.al., Cancer Research 2011

Plasma samples from colon cancer patients or mice following treatment with FOLFOX

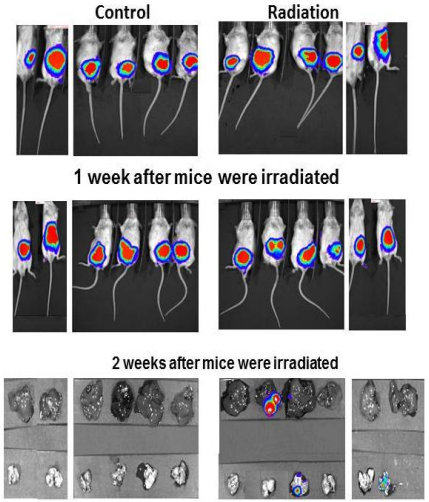
Mice



Questions

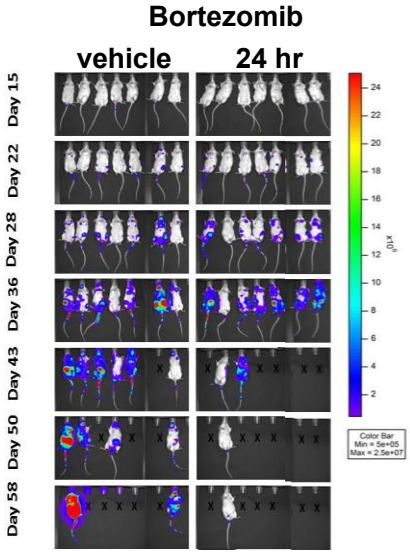

Host factors promoting tumor growth
Type of therapy
Shift in host cell characteristics
Changes in Cancer Cell Characteristics
Therapeutic intervention
Cross-talk between tumor and host cells following therapy
Clinical implications: Precision Medicine ?
THERAPY
Host
Tumor Microenvironment
Tumor
VEGFR1
Lungs
TIMP1
IL-6
Thymus
SDF-1
G-CSF
VEGF
Osteopontin
SCF
RRL
Bone Marrow
Blocking host effects to enhance treatment efficacy

Radiation



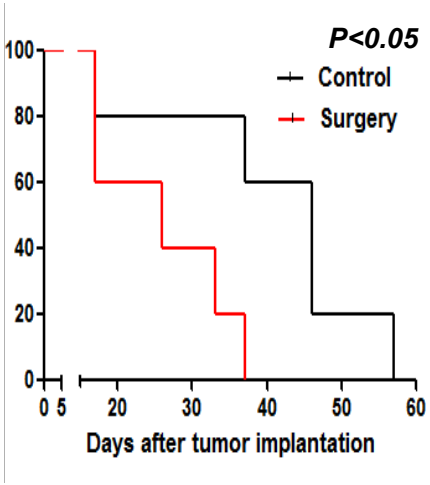
Timaner et.al.
Oncotarget 2015

Targeted drugs



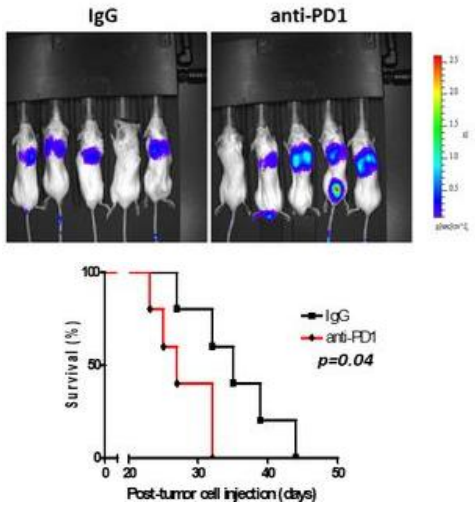
Beyar Katz et.al.
J. of Pathology 2016

Surgery



Rachman et.al.
Cell Reports 2017

Immunotherapy

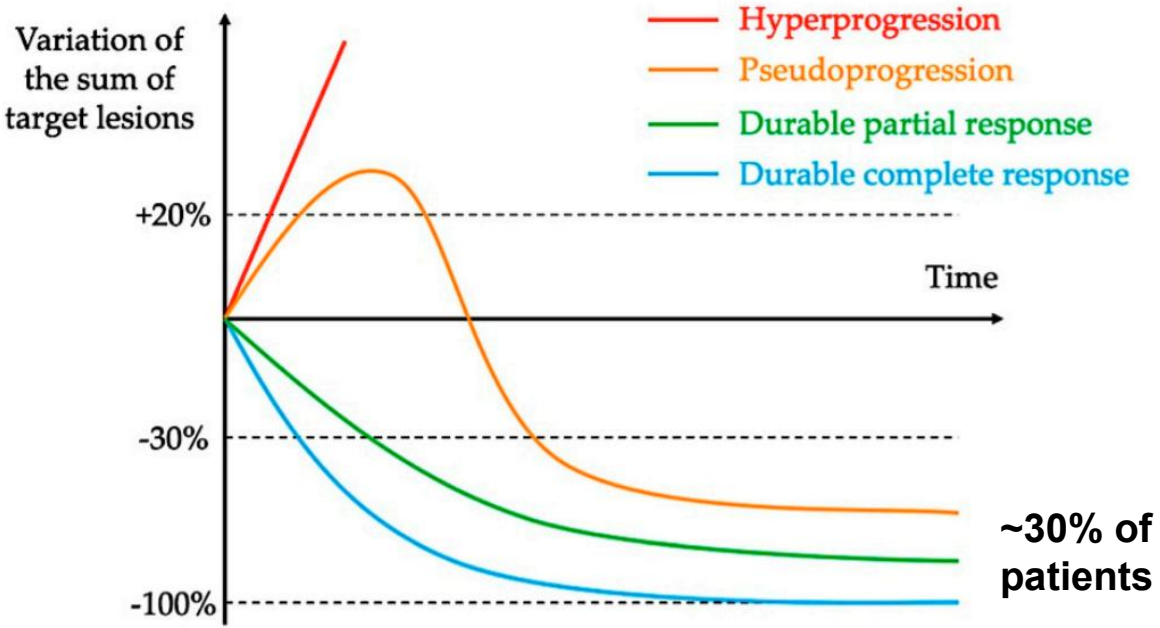


Khononov et.al.
J Immu. Ther. Can. 2021

Question

What is the clinical utility of these findings?

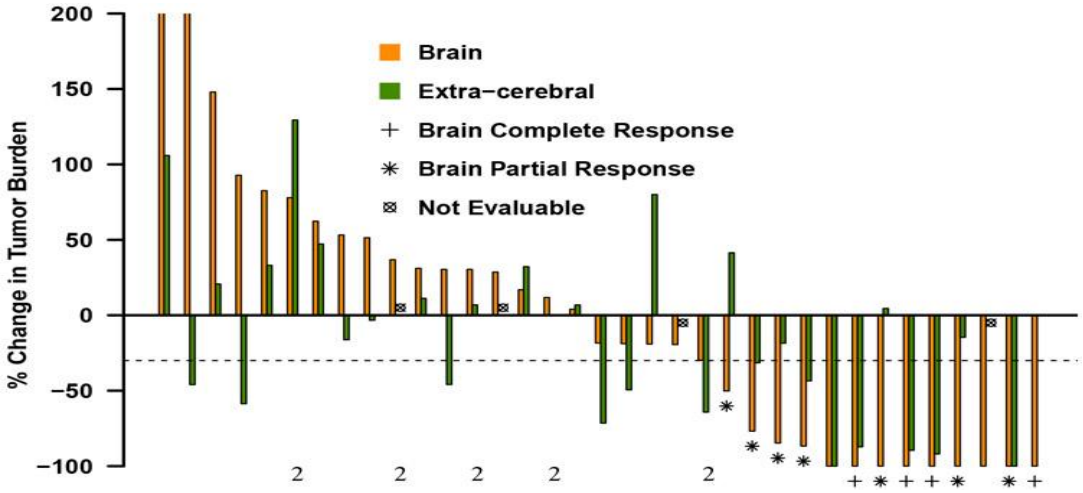
Low response rate in patients treated with immunotherapy



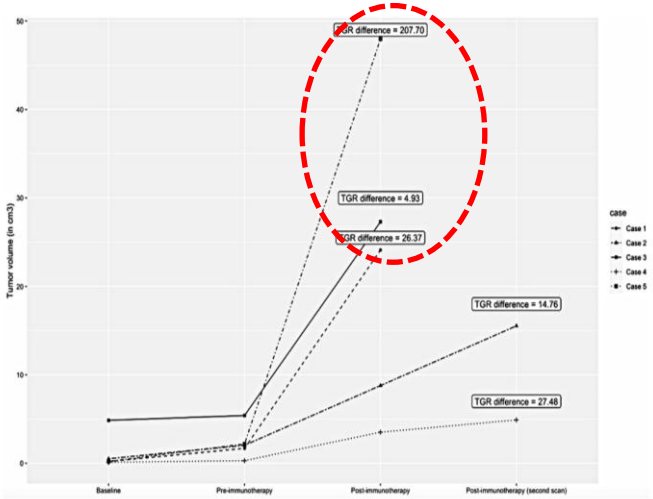
~30% of patients

Adopted from Frelaut et al., Int. J. Mol. Sci. 2019

Heterogenous response of brain metastasis to immunotherapy



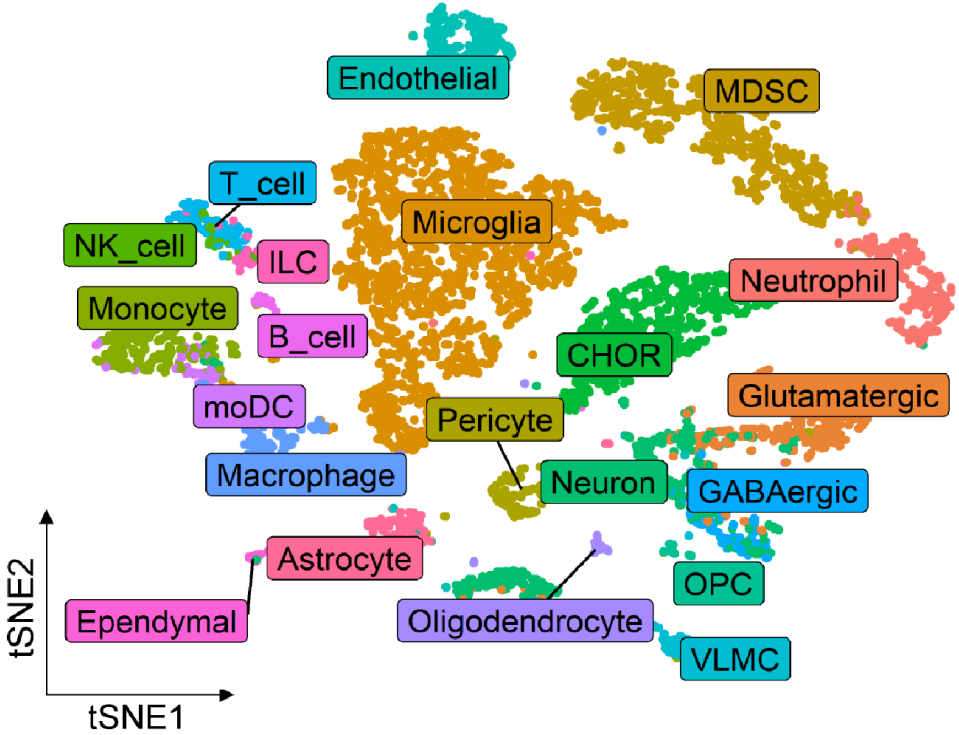
Goldberg et al., The Lancet Oncology, 2020; Randall et al., The Oncologist, 2021



Jessurun et al., J. of Neuro-oncology, 2025

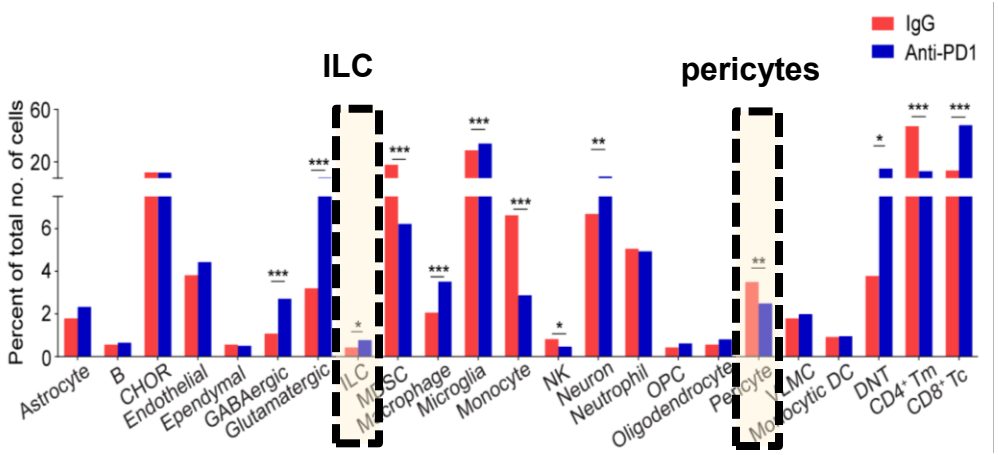
How does immunotherapy affect the development of brain metastasis?

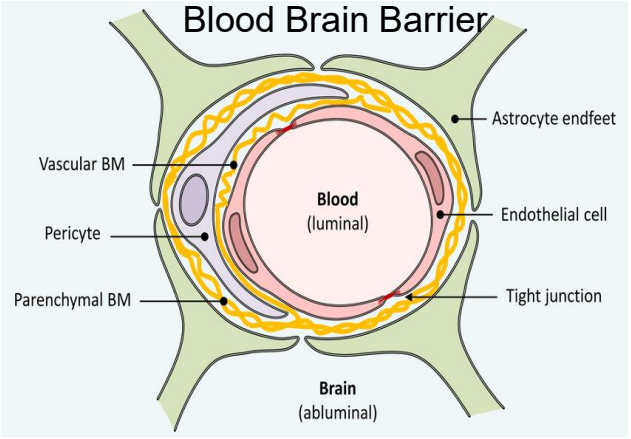
Effect of immunotherapy on the microenvironmental changes in the brain in pre-metastatic phase



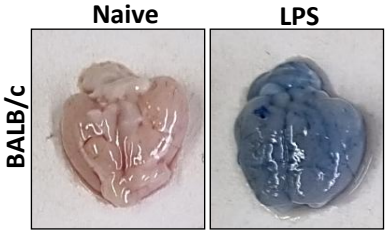
Unpublished

scRNA-seq data suggesting structural and functional changes in the barrier function of anti-PD1 treated brain



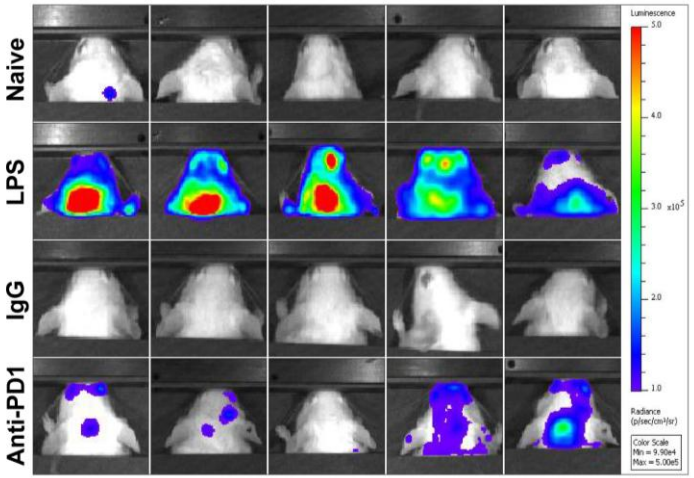


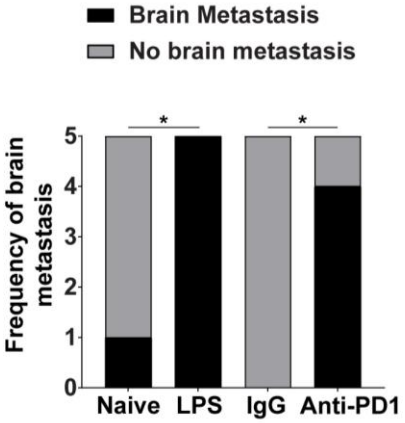
Effect of anti-PD1 treatment on the integrity of the blood brain barrier



Unpublished

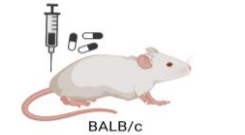
Anti-PD1 treatment promotes infiltration of circulating breast cancers to the brain





*p<0.05 as determined by Fisher's exact test

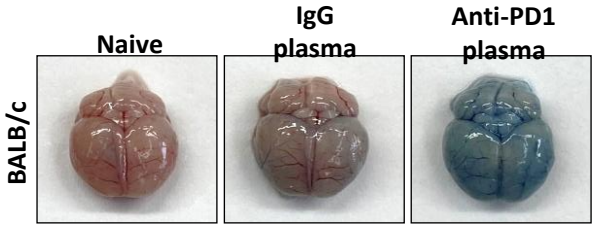
Host factors induced to anti-PD1 treatment cause disruption of the blood brain barrier and brain metastasis

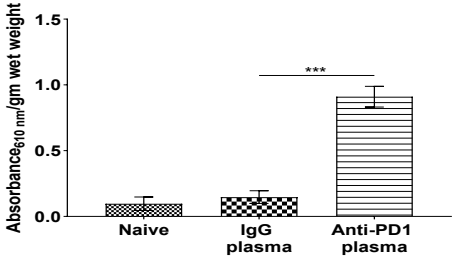


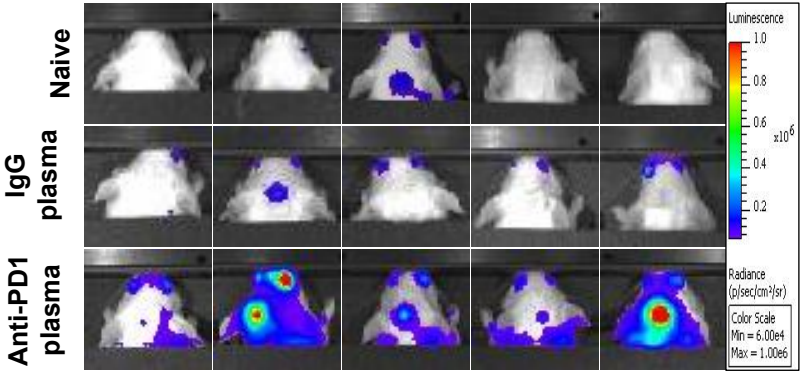
IgG/Anti-PD1 treatment

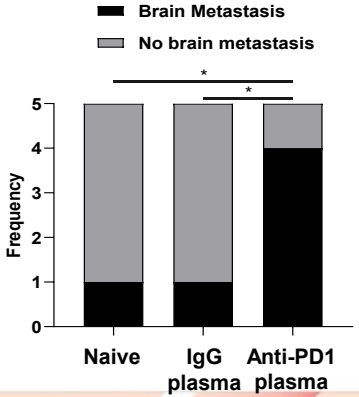
3 doses over a week

Plasma transfusion to BALB/c

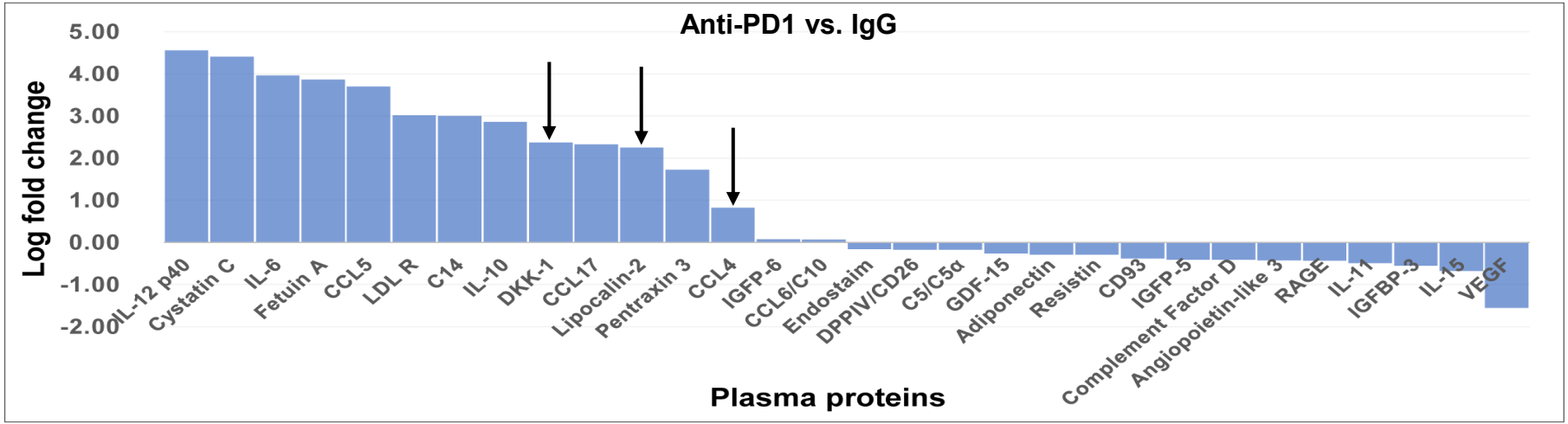




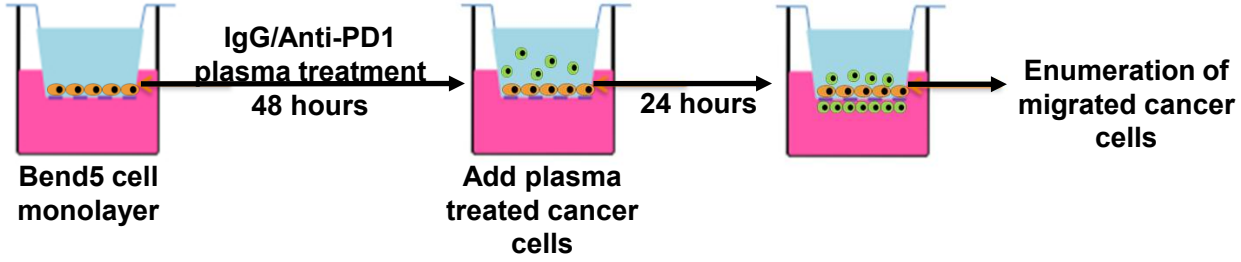


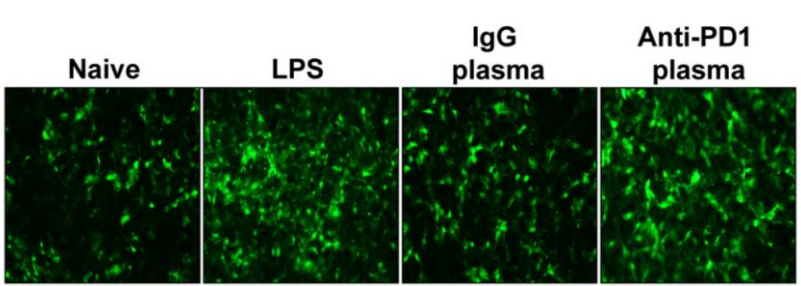


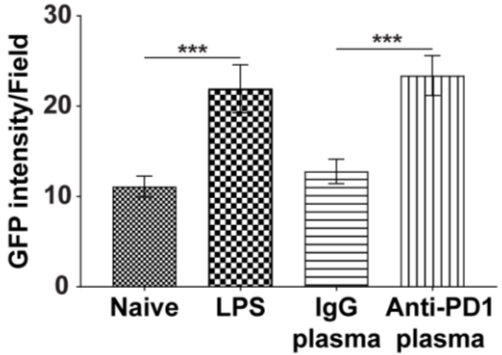
Protein array screen to identify putative candidates responsible for BBB disruption



Anti-PD1 treated plasma promotes trans-endothelial migration of breast cancer cells *in vitro*

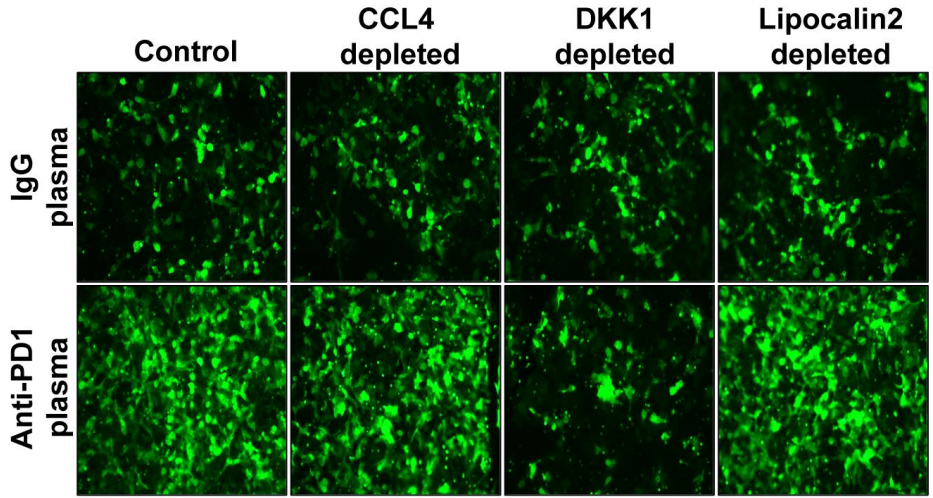


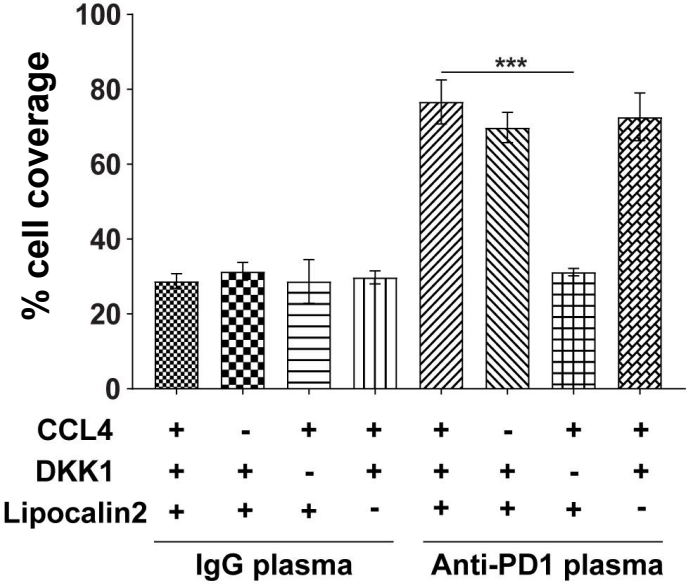




***p<0.001 as determine by ANOVA

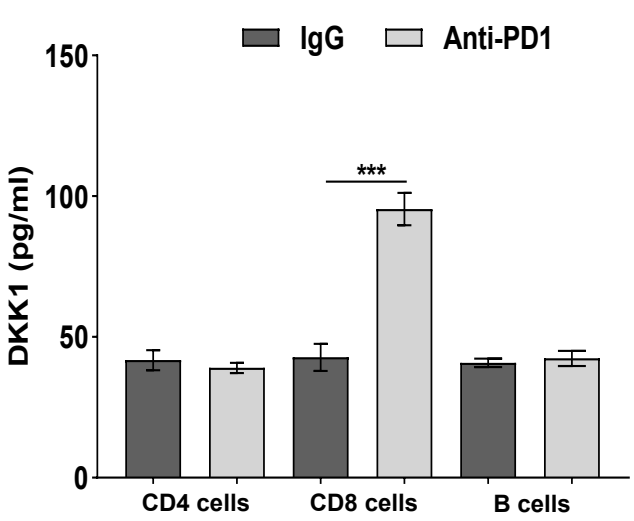
DKK1 depletion in anti-PD1 treated plasma preserved the integrity of the endothelial cells

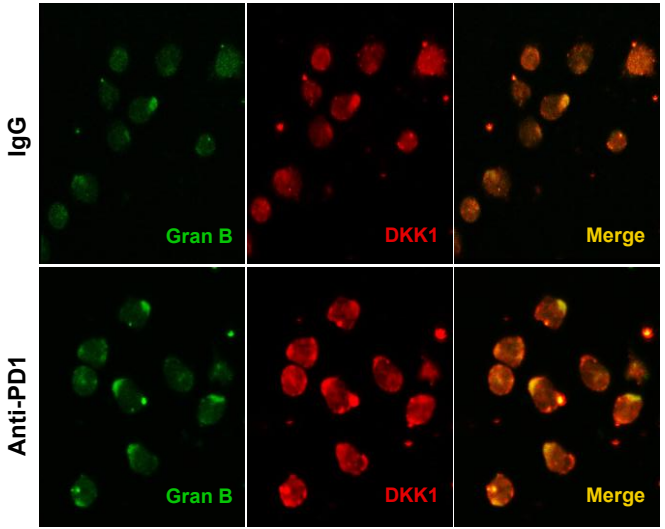


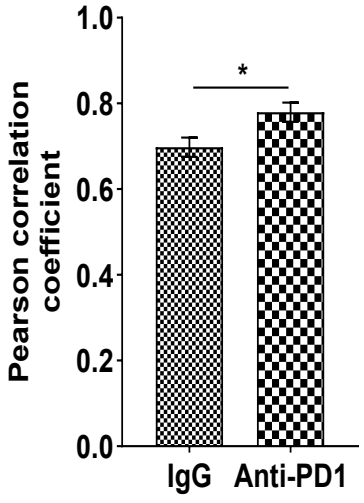


***p<0.001 as determined by one way ANOVA

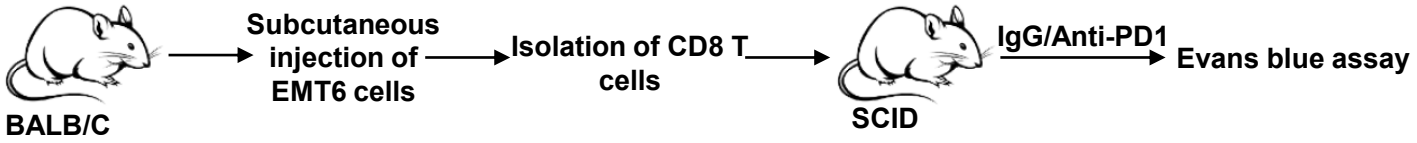
DKK1 is secreted from activated CD8+ T cells

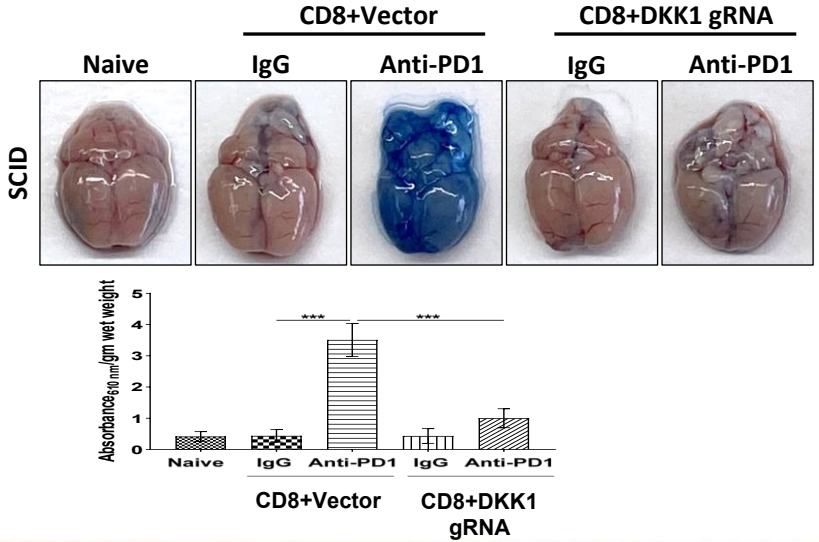


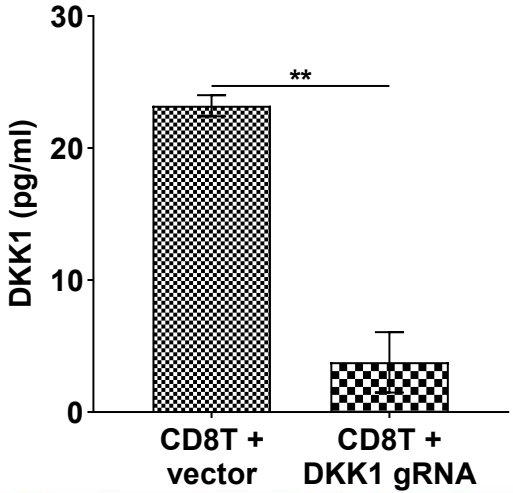




DKK1 KO in adoptively transferred CD8-T+ cells prevents BBB disruption in SCID mice







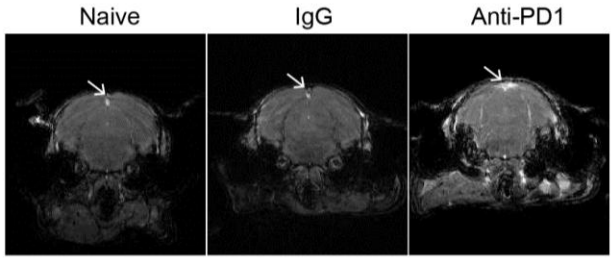
Interim conclusions

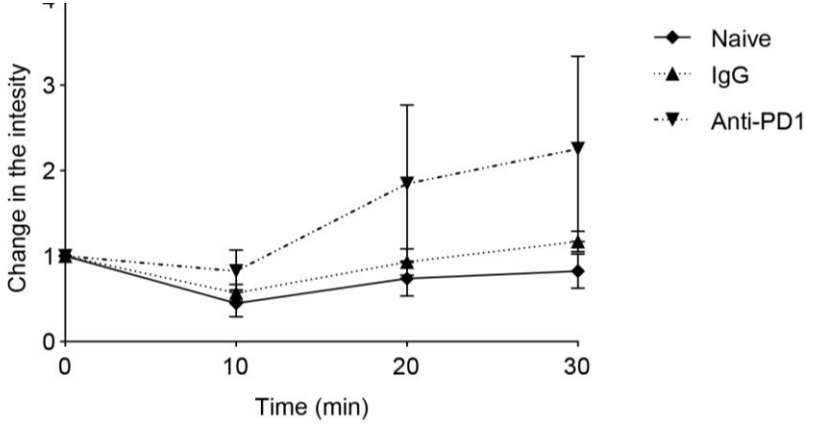
- Anti-PD1 resulted in BBB opening.
- Circulating DKK1 mediates BBB opening.
- The source of DKK1-induced BBB opening is activated CD8+ T cells.
- Blocking DKK1 expression solely in CD8+ T cells retain BBB integrity even after anti-PD1 therapy.

Question

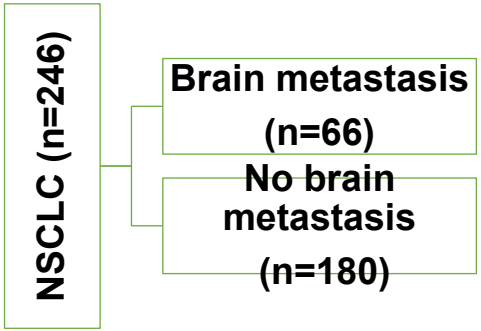
What can be the potential clinical implications of this phenomenon?

Evidence for permeable BBB in mouse and human following anti-PD1 therapy





Elevation in plasma DKK1 is associated with the incidence of brain metastasis in NSCLC patients undergoing immunotherapy

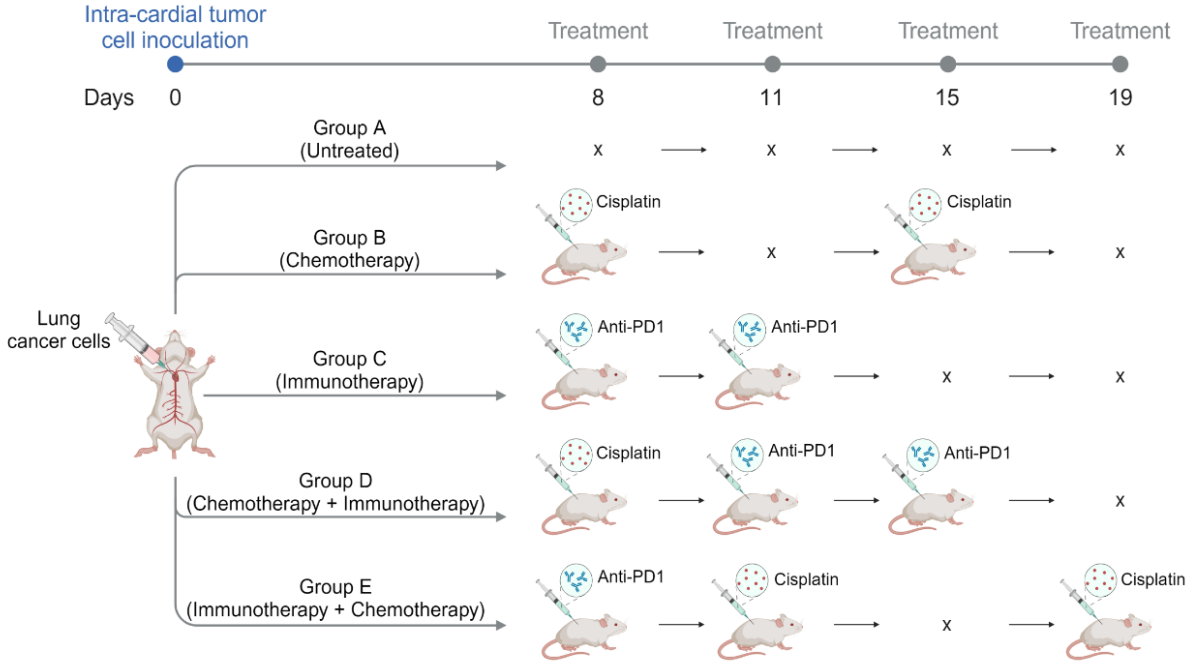


Harel et al., *J Immunother Cancer*, 2022

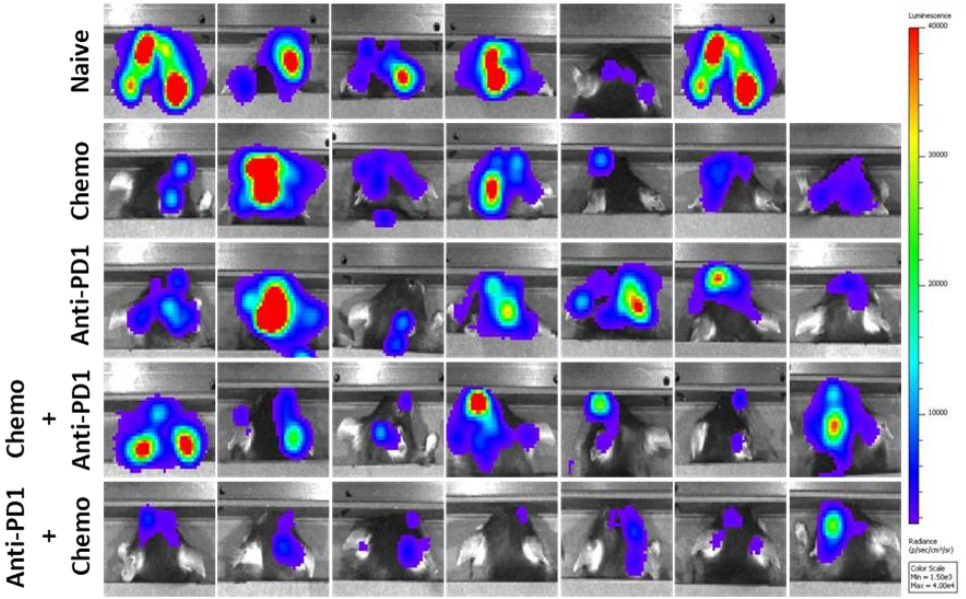
Progression free survival event	Plasma DKK1 elevation after anti-PD1 treatment	Incidence of brain metastasis	p-value
No progression (102)*	≤ 1.5-fold (87)	26.4% (23)	
	>1.5-fold (15)	33.3% (5)	0.5804
Progression (144)	≤ 1.5-fold (121)	23.1% (28)	
	>1.5-fold (23)	43.4% (10)	**0.0425**

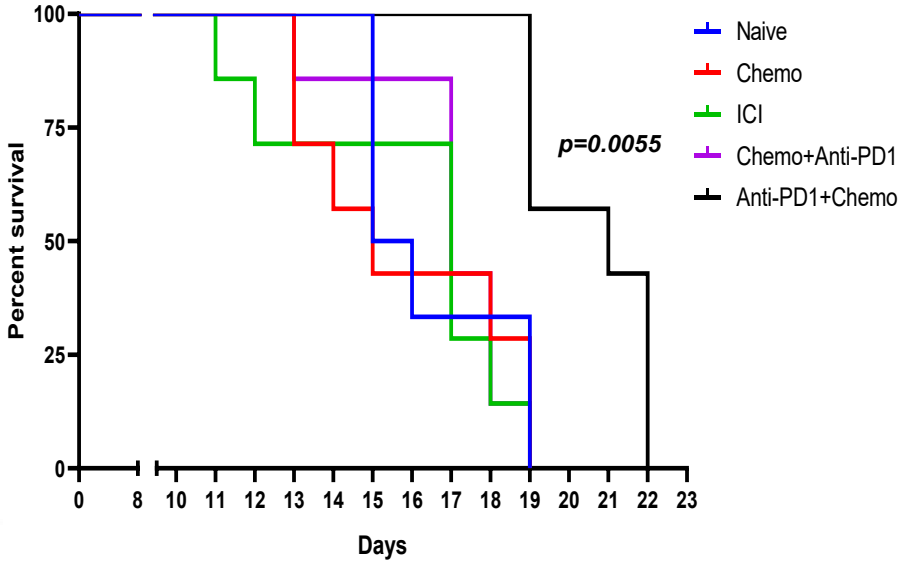
Overall survival event	Plasma DKK1 elevation after anti-PD1 treatment	Incidence of brain metastasis	p-value
Alive (129)	≤ 1.5-fold (108)	25.0% (27)	
	>1.5-fold (21)	33.3% (7)	0.4277
Dead (117)	≤ 1.5-fold (100)	24.0% (24)	
	>1.5-fold (17)	47.0% (8)	**0.0486**

Does an induction with anti-PD1 improve the intra-cranial efficacy of systemic therapy?



Single dose induction with anti-PD1 increases intracranial efficacy of cisplatin





Conclusions

- **Anti-PD1 promotes disintegration of the blood brain barrier**
- **Circulating DKK1 induced in response to anti-PD1 therapy contributes to the disintegration of the BBB and may support brain metastasis**
- **The effect is systemic and is primarily contributed by CD8+ T cells expressing DKK1**
- **Cancer patients treated with anti-PD1 display an induction in circulating DKK1 associated with brain metastasis which support BBB disintegration**
- **An upfront treatment with anti-PD1 can enhance anti-tumor chemotherapy activity against brain metastasis**

Acknowledgements

Technion

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Anat Grinfeld (Rambam)

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Michal Harel (OncoHost)

Coren Lahav (OncoHost)