ESMO Advanced Course on Unsolved Questions in Immuno-Oncology
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Special Situation: Brain metastases

Matthias Preusser, MD
Associate Professor of Medicine
Department of Medicine I
Comprehensive Cancer Center Vienna
Medical University of Vienna

CNS Tumor Program

Disclosures

Research support:

Böhringer-Ingelheim, GlaxoSmithKline, Merck Sharp & Dome and Roche

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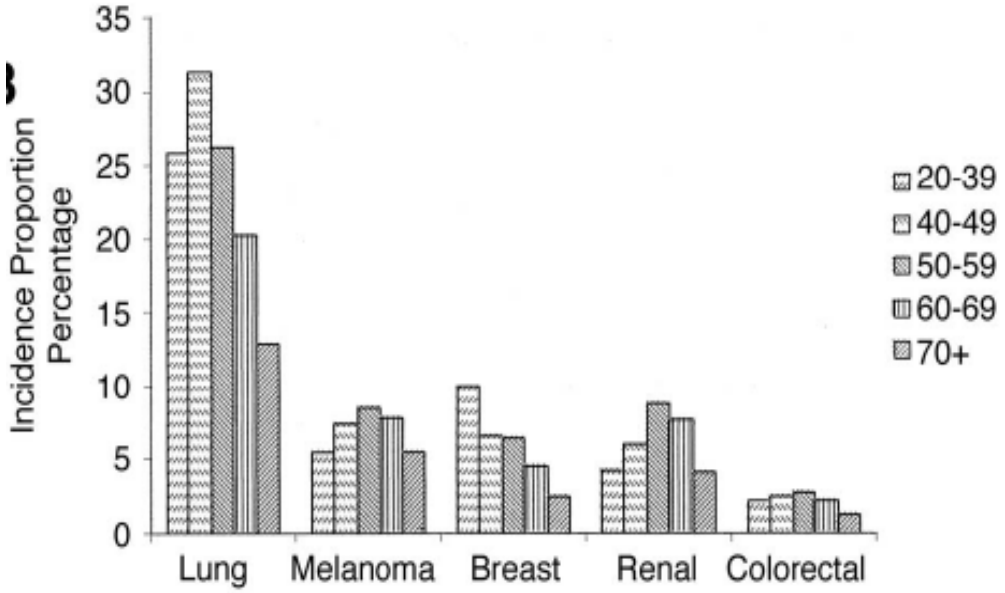
Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, Astra Zeneca and AbbVie.

Incidence of brain metastases

- Occur in 10-30% of all adult cancers
- Approx. 10 times more frequent than primary brain tumors
- Relative incidence increasing, due to
  - Effective systemic treatments → with longer survival
  - Improved imaging techniques and their increased availability
- Approx. half of all brain mets due to NSCLC, others:
  - Breast cancer
  - Melanoma
  - Unknown primary
  - Renal cell carcinoma

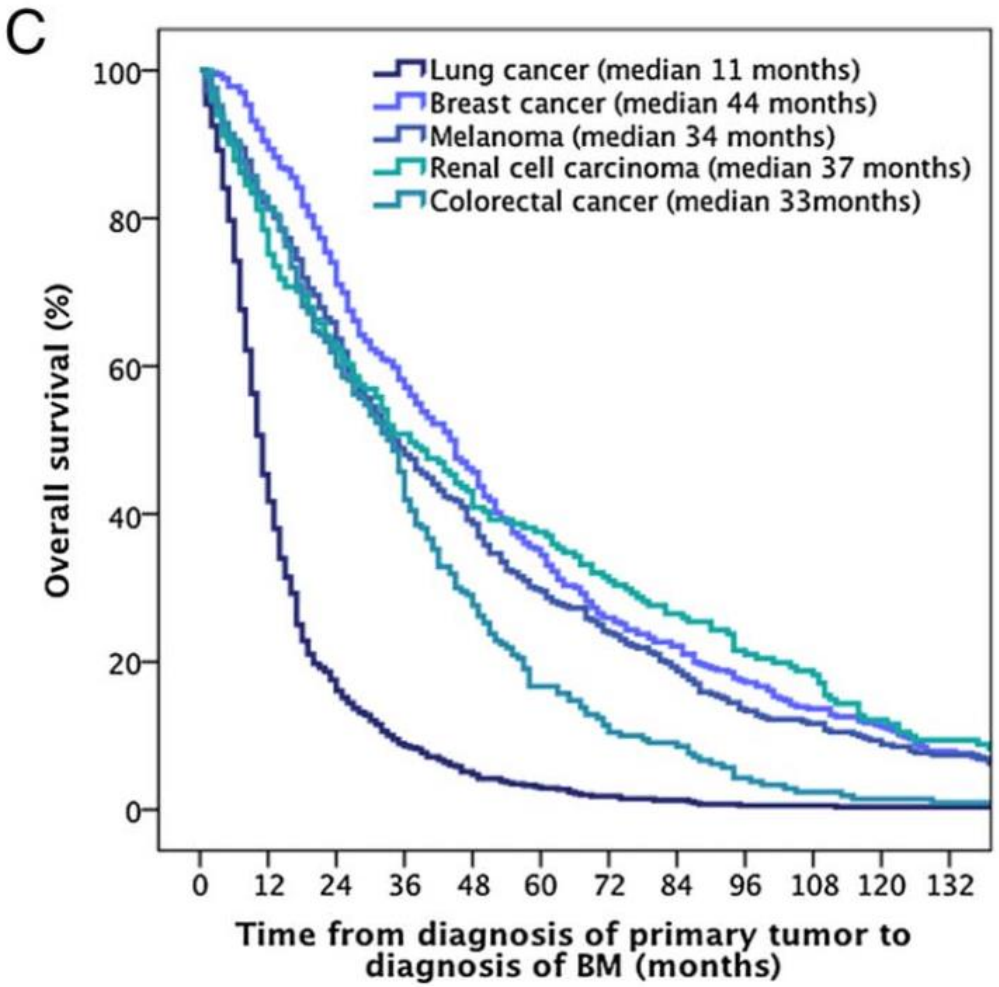


Barnholtz-Sloan… Sawaya RE.
J Clin Oncol 22:2865-72, 2004

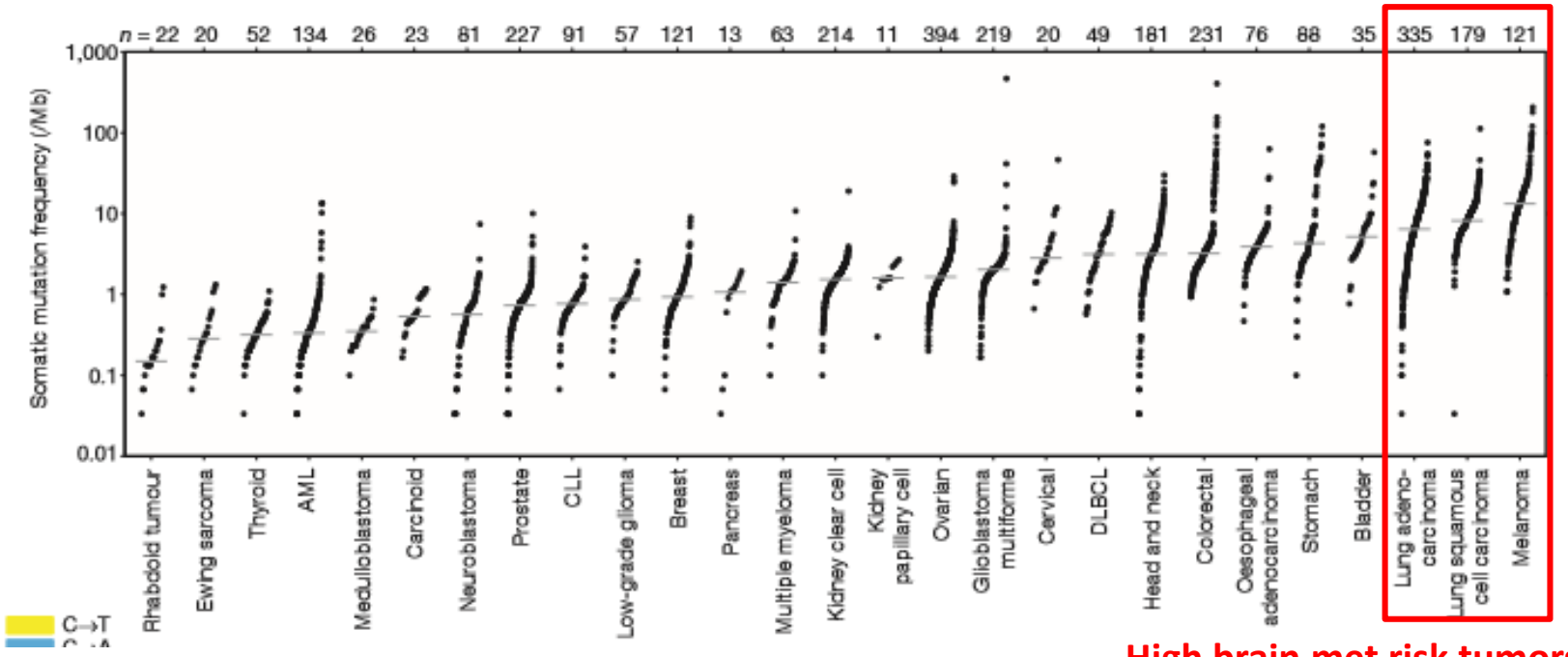
ESMO Open
Cancer Horizons

Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers

Anna S Berghoff,[1,2] Sophie Schur,[1,2] Lisa M Füreder,[1,2] Brigitte Gatterbauer,[2,3] Karin Dieckmann,[2,4] Georg Widhalm,[2,3] Johannes Hainfellner,[2,5] Christoph C Zielinski,[1,2] Peter Birner,[2,6] Rupert Bartsch,[1,2] Matthias Preusser[1,2]



Mutational heterogeneity in cancer



High brain met risk tumors!

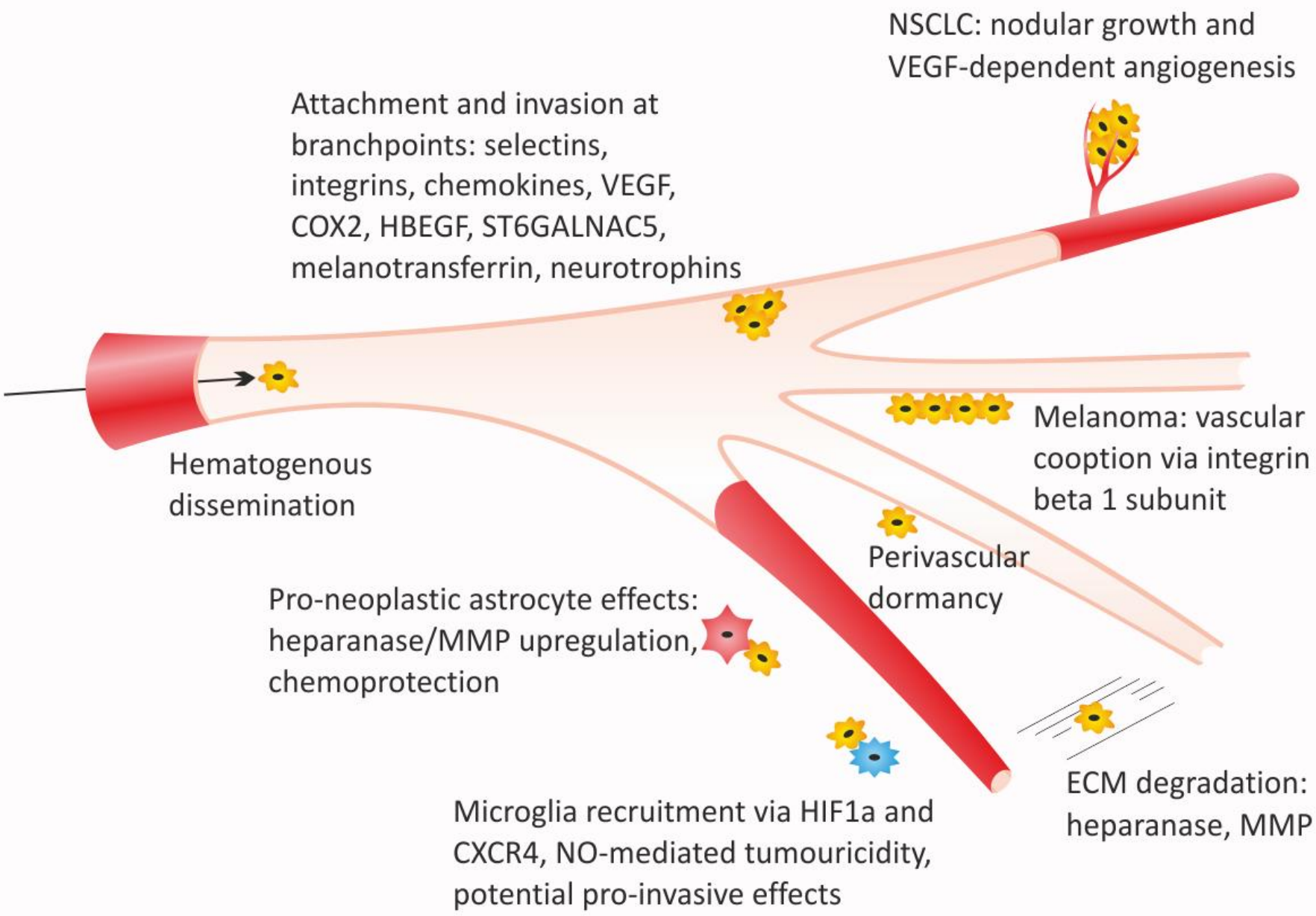
Lawrence, Nature 2013

Treatment approaches

- Neurosurgery
- Radiotherapy
  - Whole brain radiotherapy (WBRT)
  - Stereotactic radiosurgery/radiotherapy (SRS/SRT)
- Systemic therapy
  - Chemotherapy
  - Targeted therapies, e.g. tyrosine kinase inhibitors, antibodies
- Supportive therapy
  - Edema control
  - Anticonvulsants
  - Pain

Preusser et al, Oxford University Press 2015

Brain-metastatic cascade



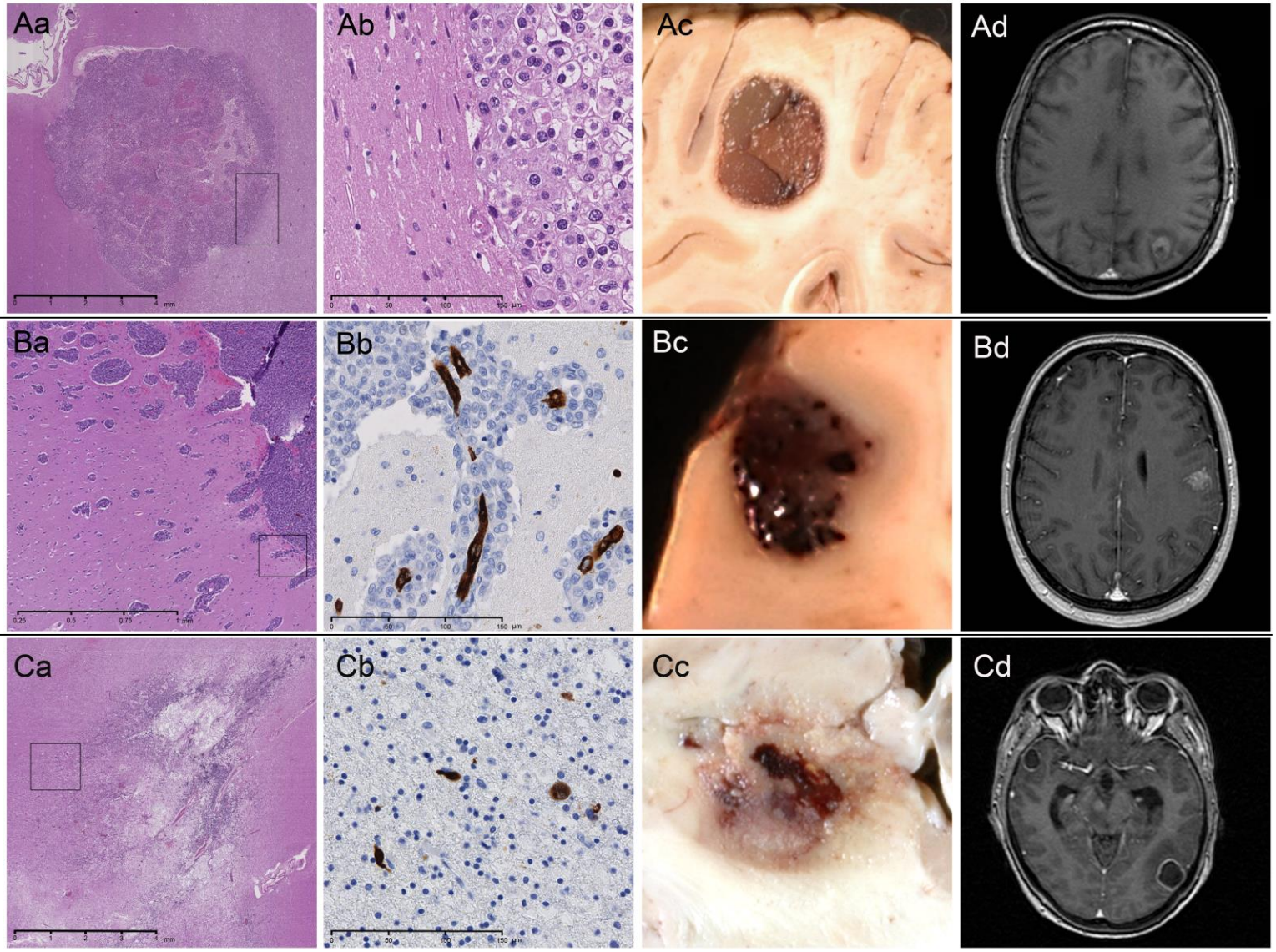
Preusser et al, Acta Neuropathol 2012

Growth patterns of brain metastases

Delineated
51%

Perivascular
18%

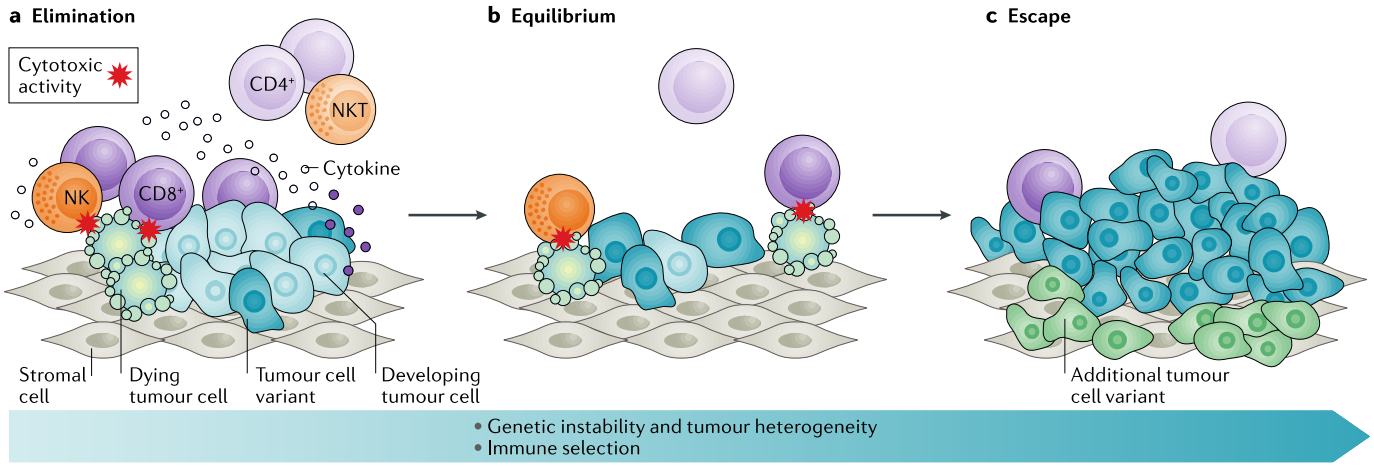
Diffuse
32%



Berghoff A (...) Preusser M. Neuro-Oncol 2013

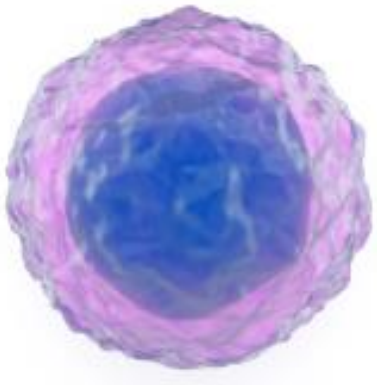
The role of immune cells in the brain metastatic cascade

- Immune evasion is a hallmark of cancer
- Metastasis initiating cells have already performed immune evasion



Van der Burg et al, Nat Rev 2016

Different characteristics of the inflammatory microenvironment between primary tumor and metastasis?

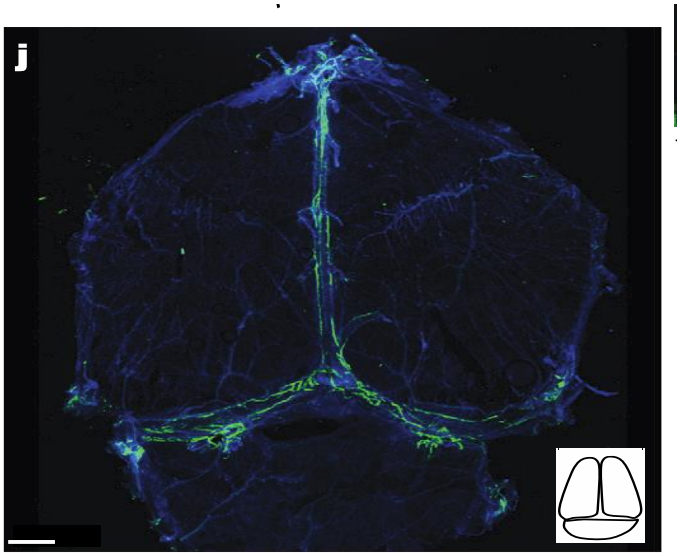


Lymphatic Drainage of the CNS Redefined

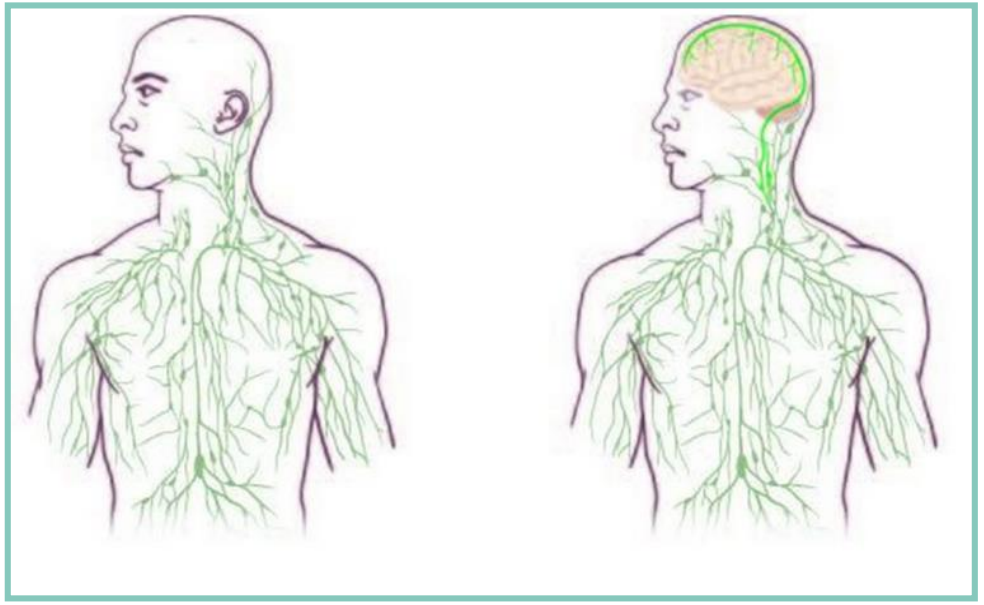
LETTER

doi:10.1038/nature14432

Structural and functional features of central nervous system lymphatic vessels

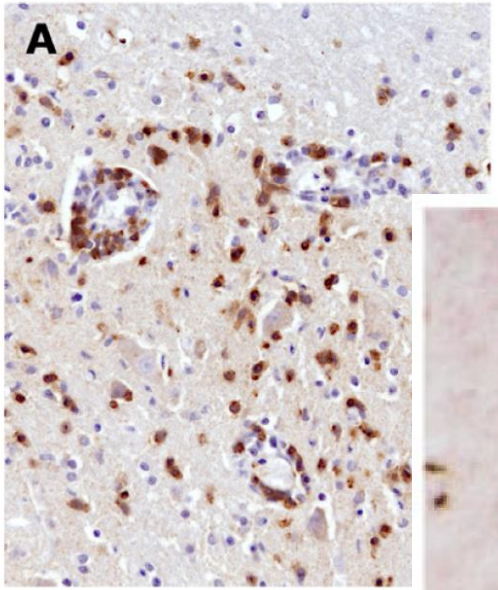


Lyve-1 DAPI

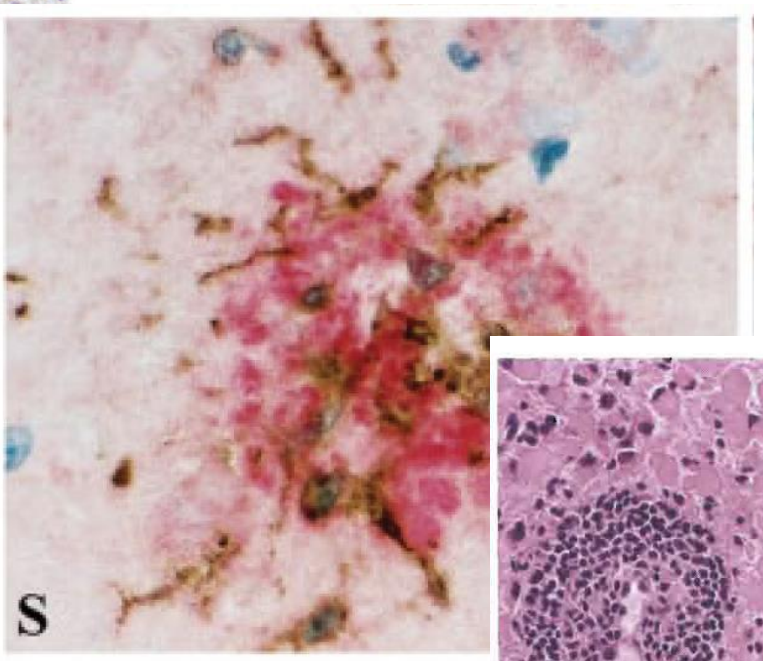


Louveau et al., Nature. 2015

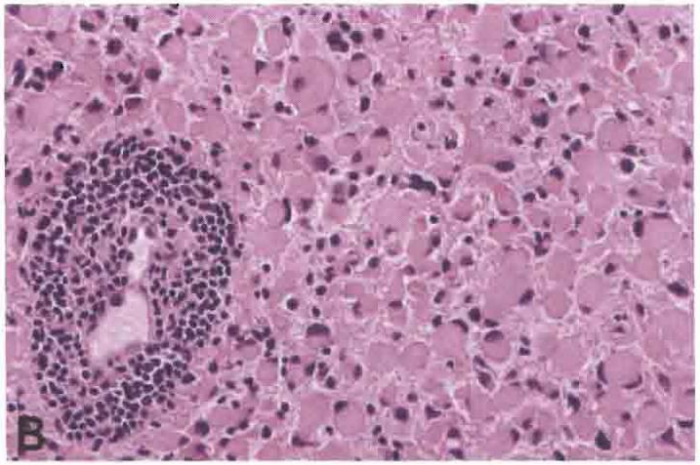
Inflammation in CNS diseases



Encephalitis

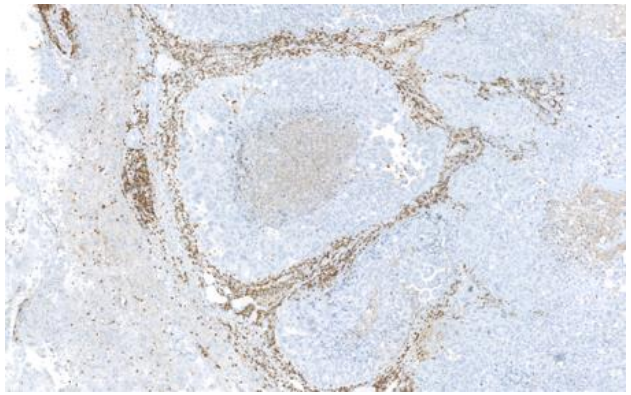


Multiple sclerosis

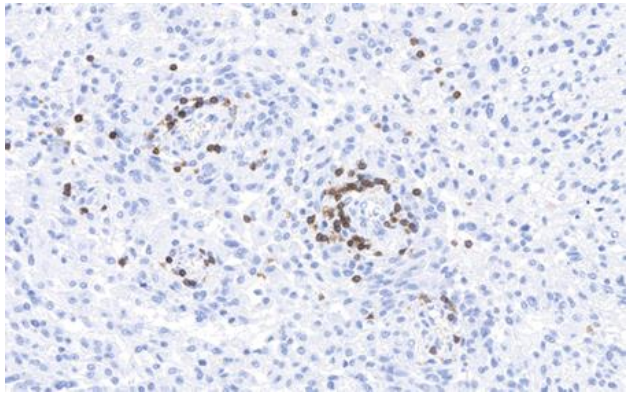


Gemistocytic astrocytoma

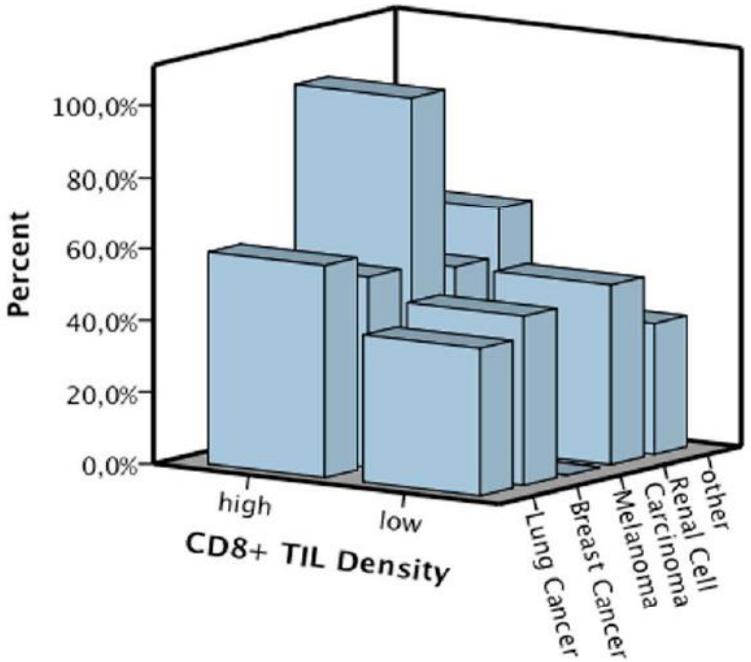
Tumor-infiltrating lymphocytes in brain tumors



Gehirnmetastase Lungenkarzinom

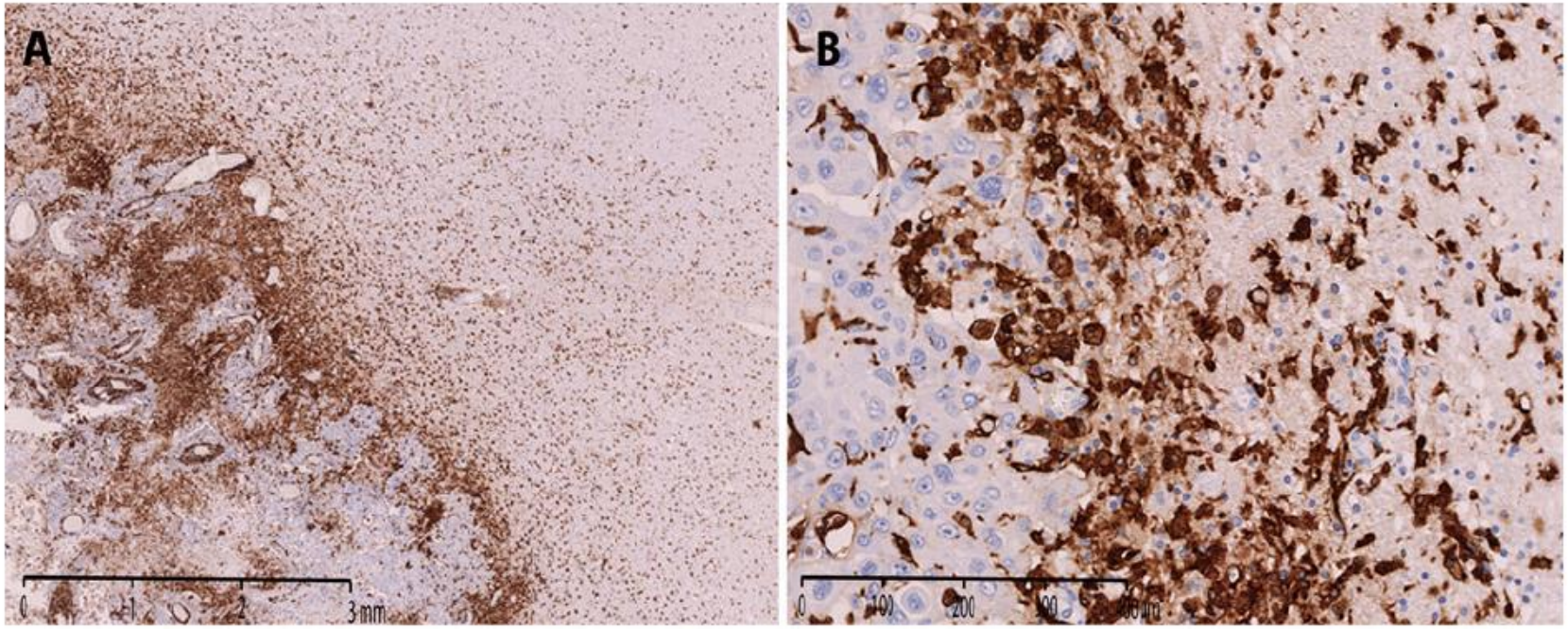


Glioblastom



Berghoff A (...) Preusser M. Onco-Immunol 2016

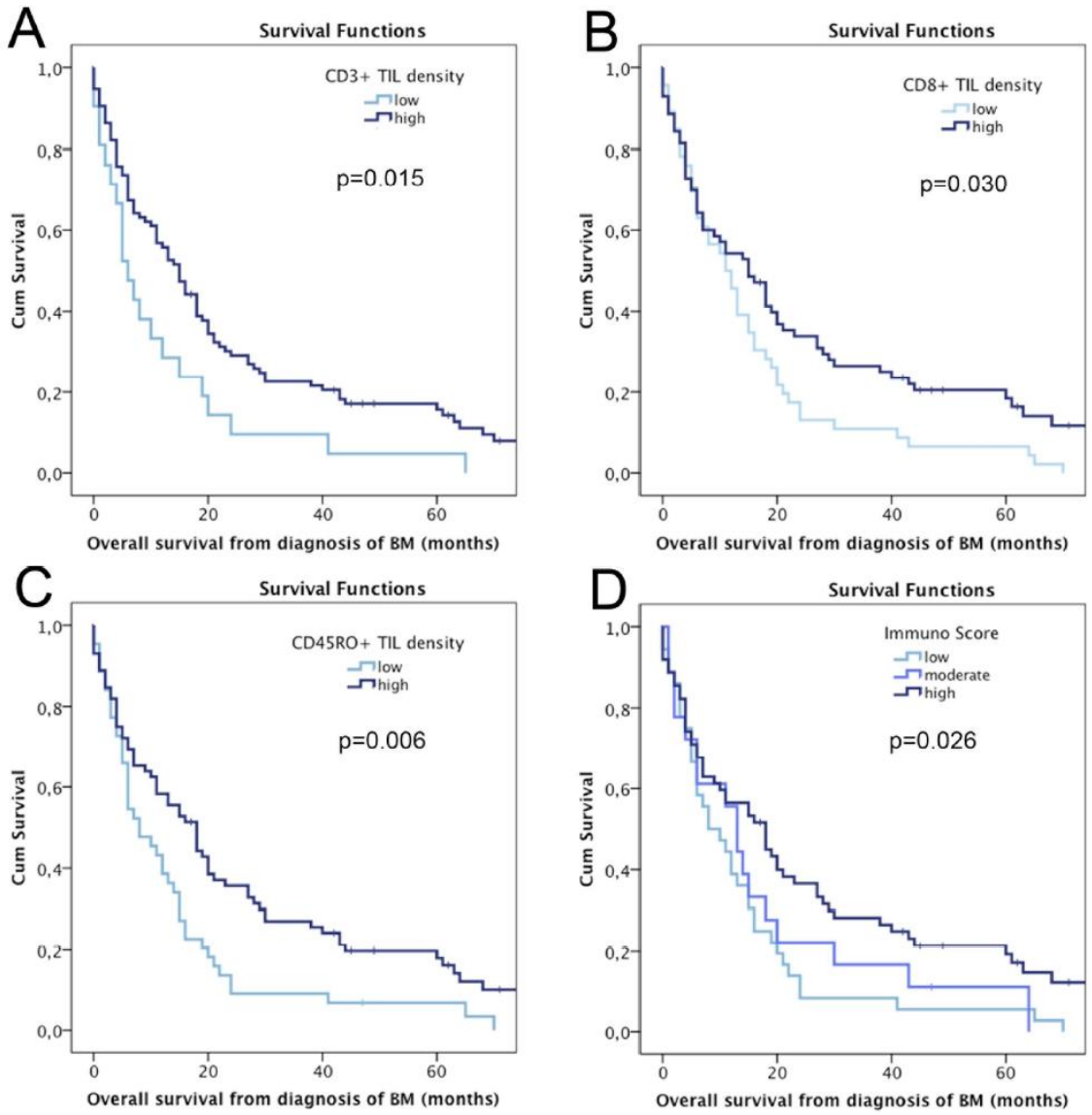
Microglia/macrophages in brain metastases



CD68

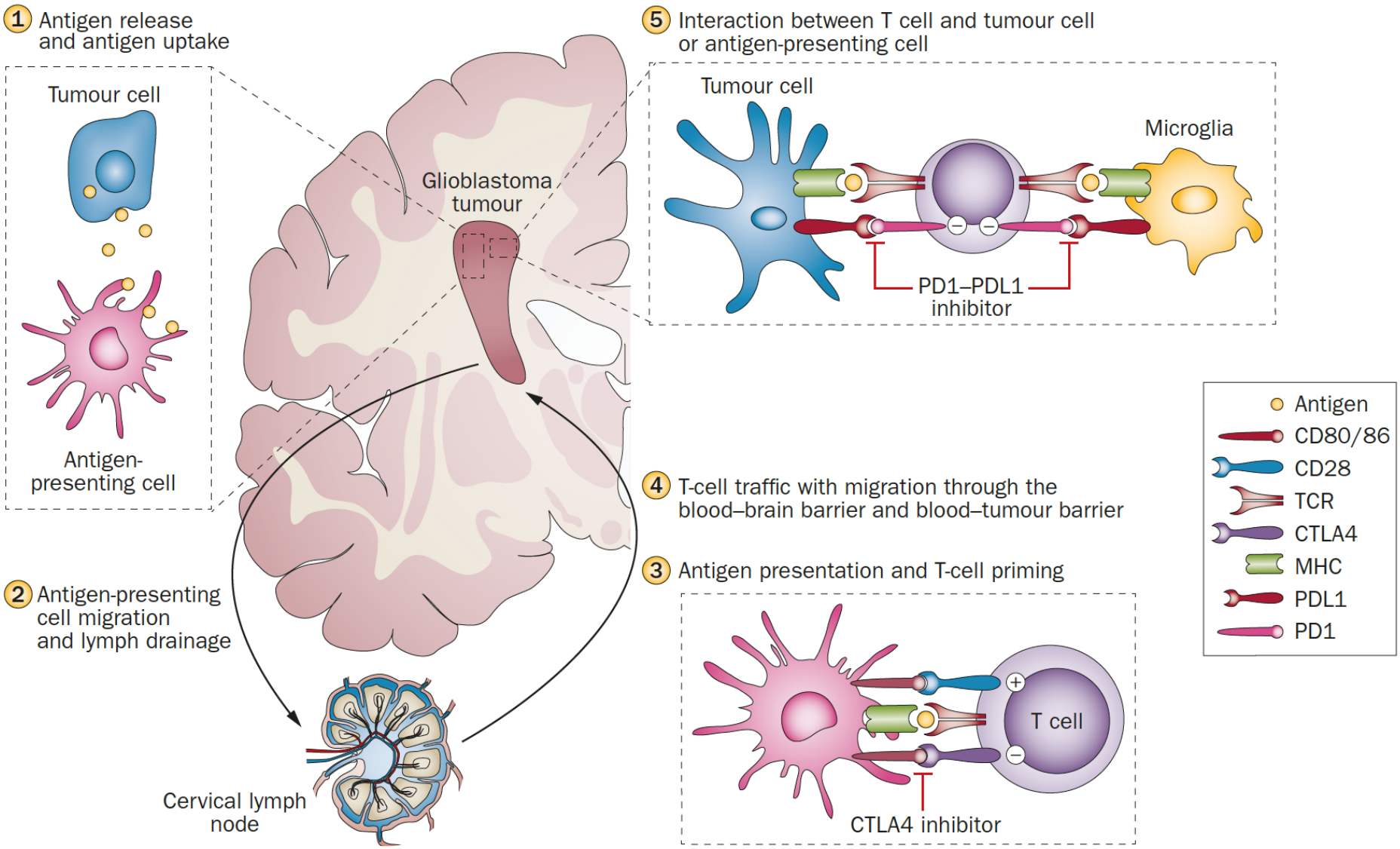
Berghoff et al, Clin Exp Metastasis 2012

Prognostic role of TILs in brain metastases



Berghoff, Onco-Immunol 2015

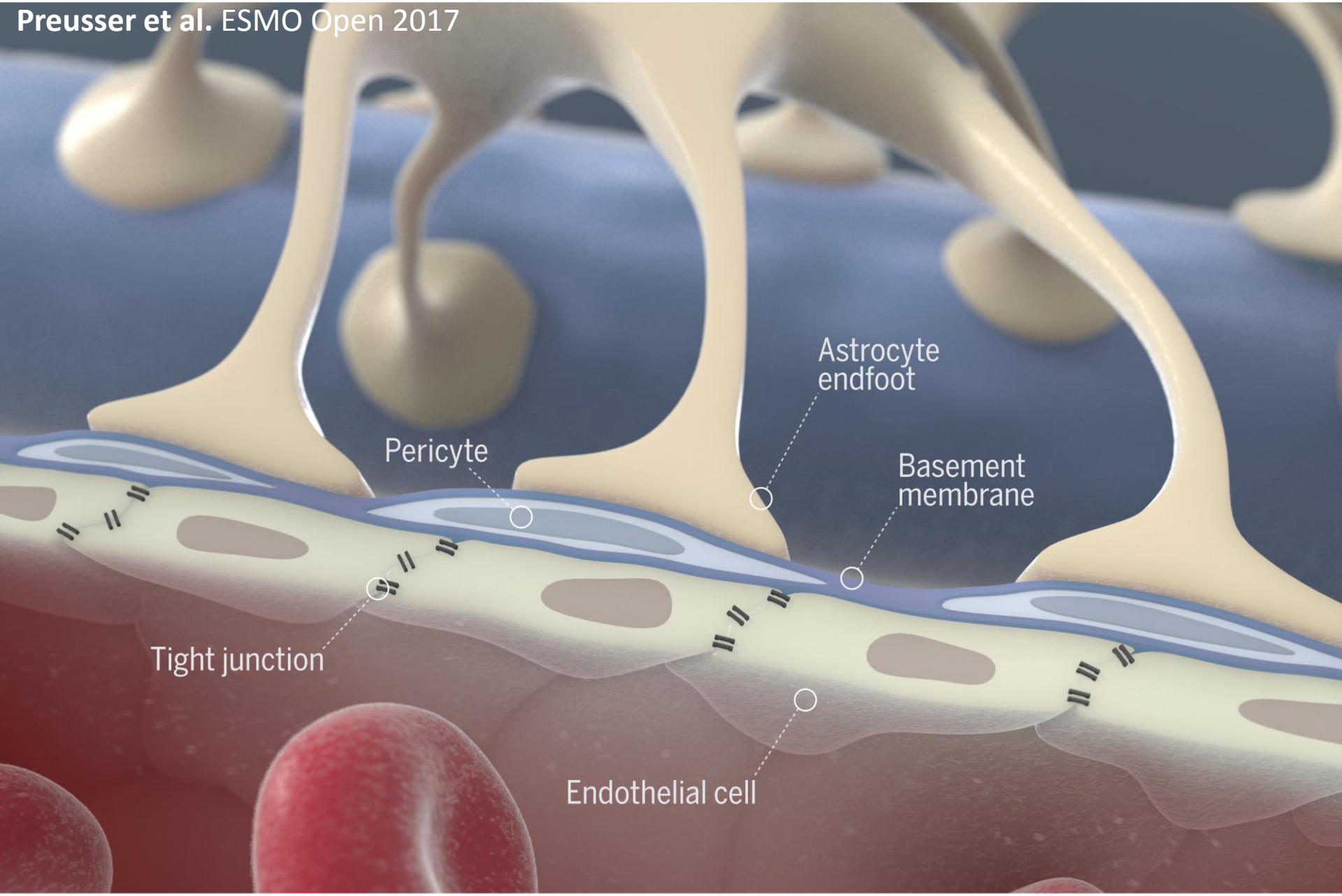
Immune cycle in brain tumors



Preusser et al, Nature Rev Neurol 2015

Blood brain barrier

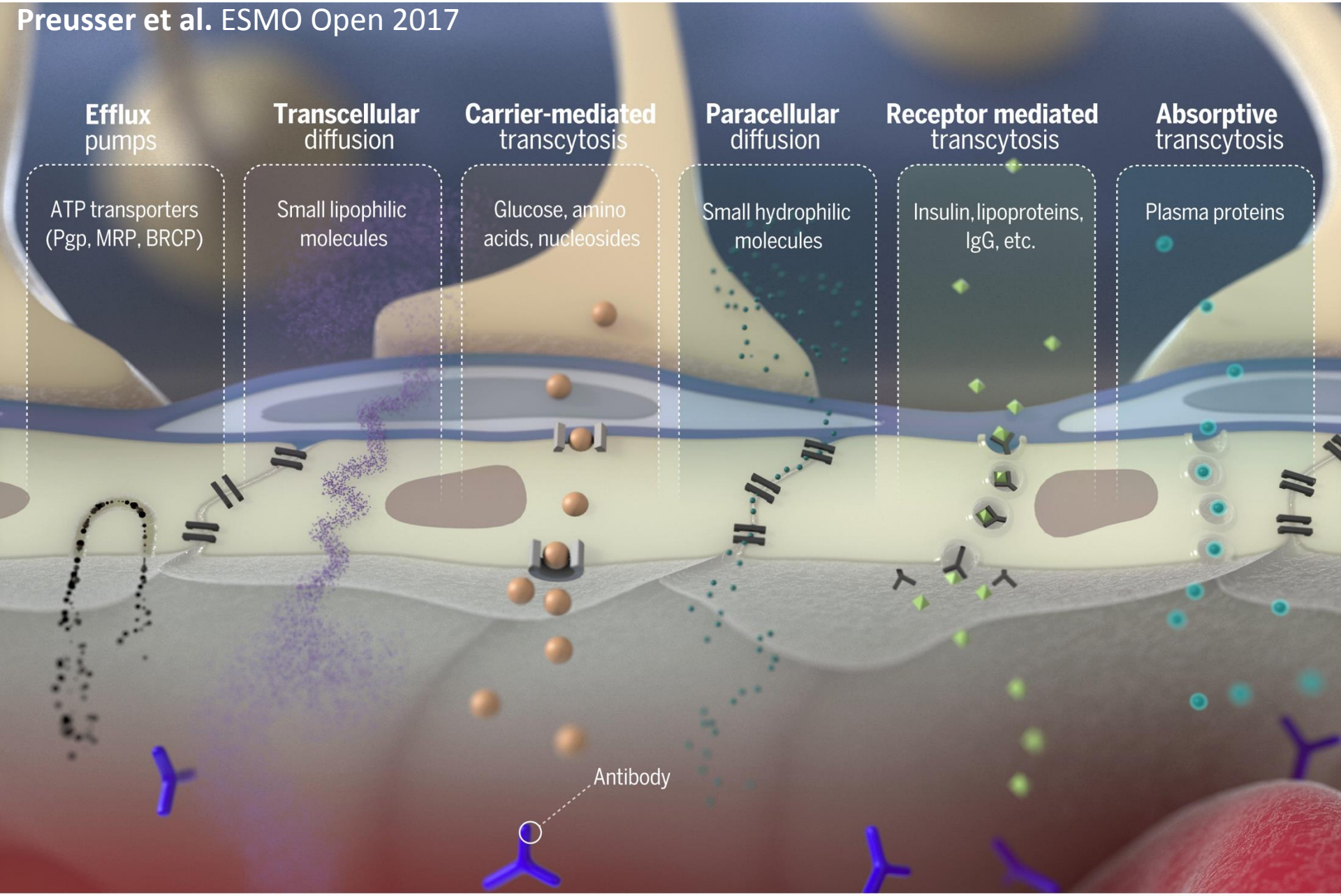
Preusser et al. ESMO Open 2017



Blood brain barrier constituents

CECOG
Central European Cooperative Oncology Group

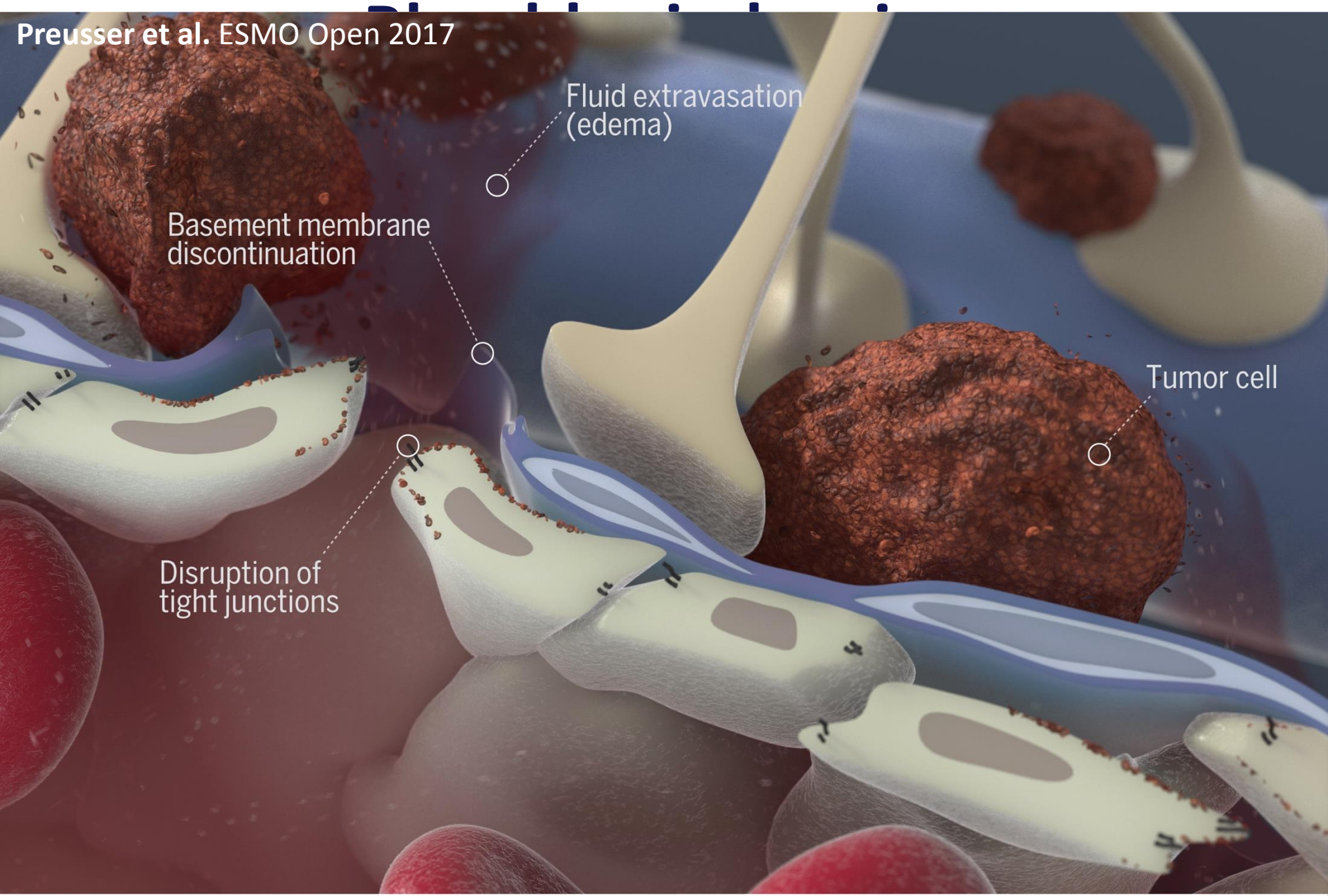
Preusser et al. ESMO Open 2017



Transport routes across the intact blood brain barrier

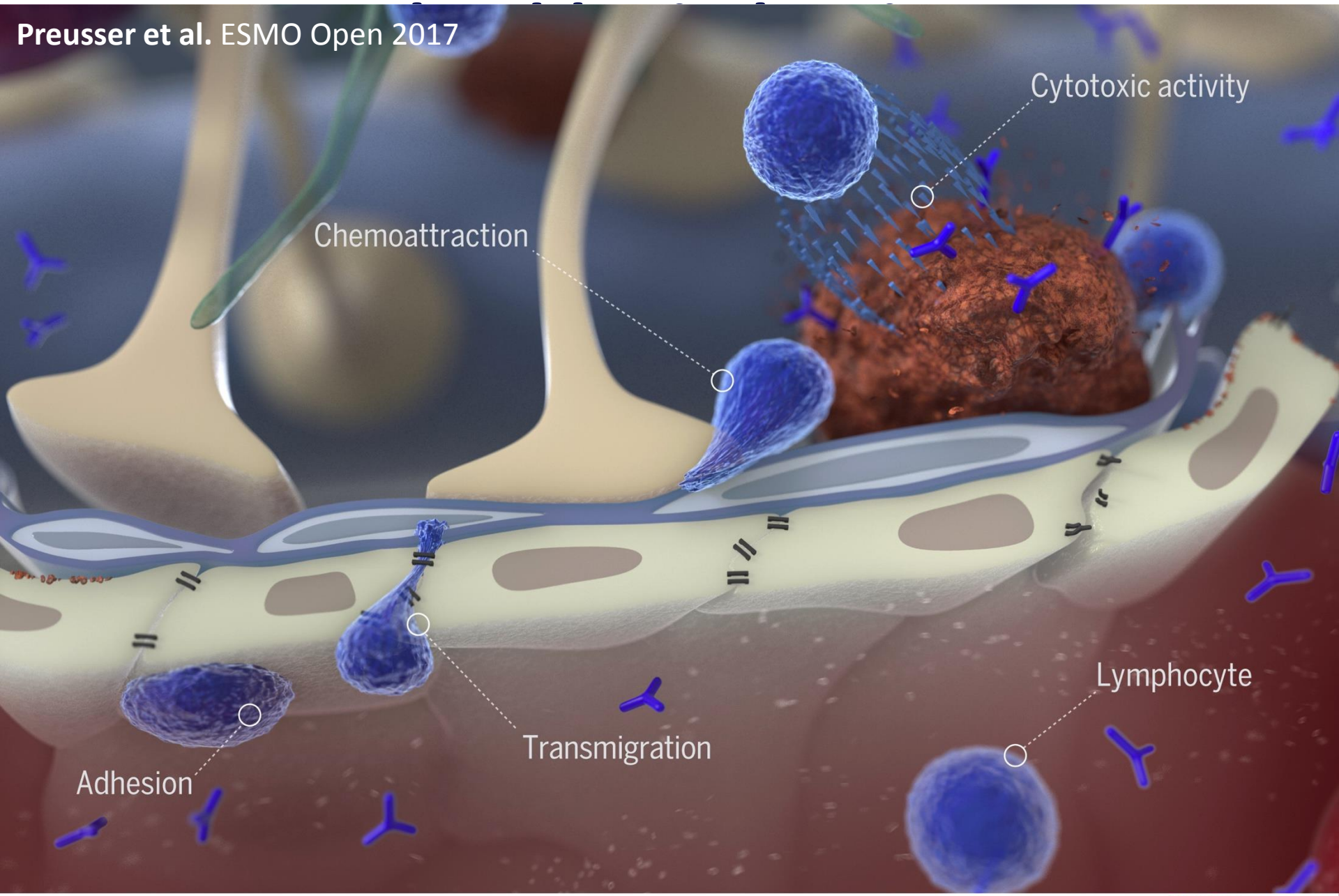
CECOG
Central European Cooperative Oncology Group

Preusser et al. ESMO Open 2017



Blood brain barrier disruption

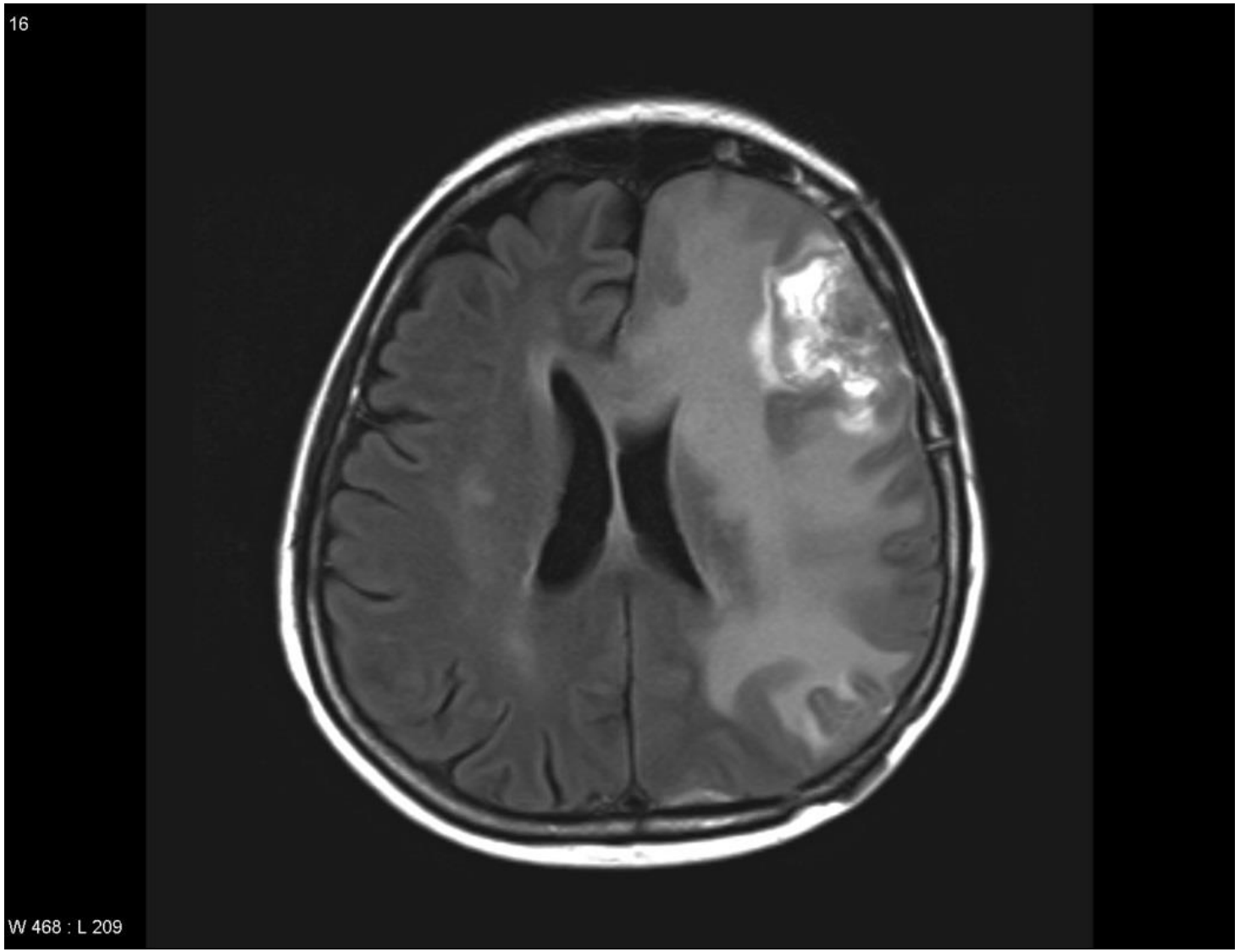
CECOG
Central European Cooperative Oncology Group



Lymphocyte extravasation

CECOG
Central European Cooperative Oncology Group

Immune checkpoint inhibitors for brain metastases?



Anti-CTLA4

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

Lancet Oncol **2012; 13: 459–65**

	Cohort A (n=51)		Cohort B (n=21)	
	mWHO	irRC	mWHO	irRC
Global disease control	9 (18%, 8–31)	13 (25%, 14–40)	1 (5%, 0·1–24)	2 (10%, 1–30)
CNS disease control	12 (24%, 13–38)	13 (25%, 14–40)	2 (10%, 1–30)	2 (10%, 1–30)
Non-CNS disease control	14 (27%, 16–42)	17 (33%, 21–48)	1 (5%, 0·1–24)	2 (10%, 1–30)
Global objective response	5 (10%, 3–21)	5 (10%, 3–21)	1 (5%, 0·1–24)	1 (5%, 0·1–24)
CNS objective response	8 (16%, 7–29)	8 (16%, 7–29)	1 (5%, 0·1–24)	1 (5%, 0·1–24)
Non-CNS objective response	7 (14%, 6–26)	7 (14%, 6–26)	1 (5%, 0·1–24)	1 (5%, 0·1–24)

Data are n (%, 95% CI). mWHO=modified WHO criteria. irRC=immune-related response criteria.

Table 3: **Disease control and objective response after 12 weeks**

Cohort A: asymtomatic, no corticosteroids (n=51)
Cohort B: symptomatic, stable dose of corticosteroids (n=21)

4x Ipi 10 mg/kg every 3 weeks, then maintenance every 12 weeks

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

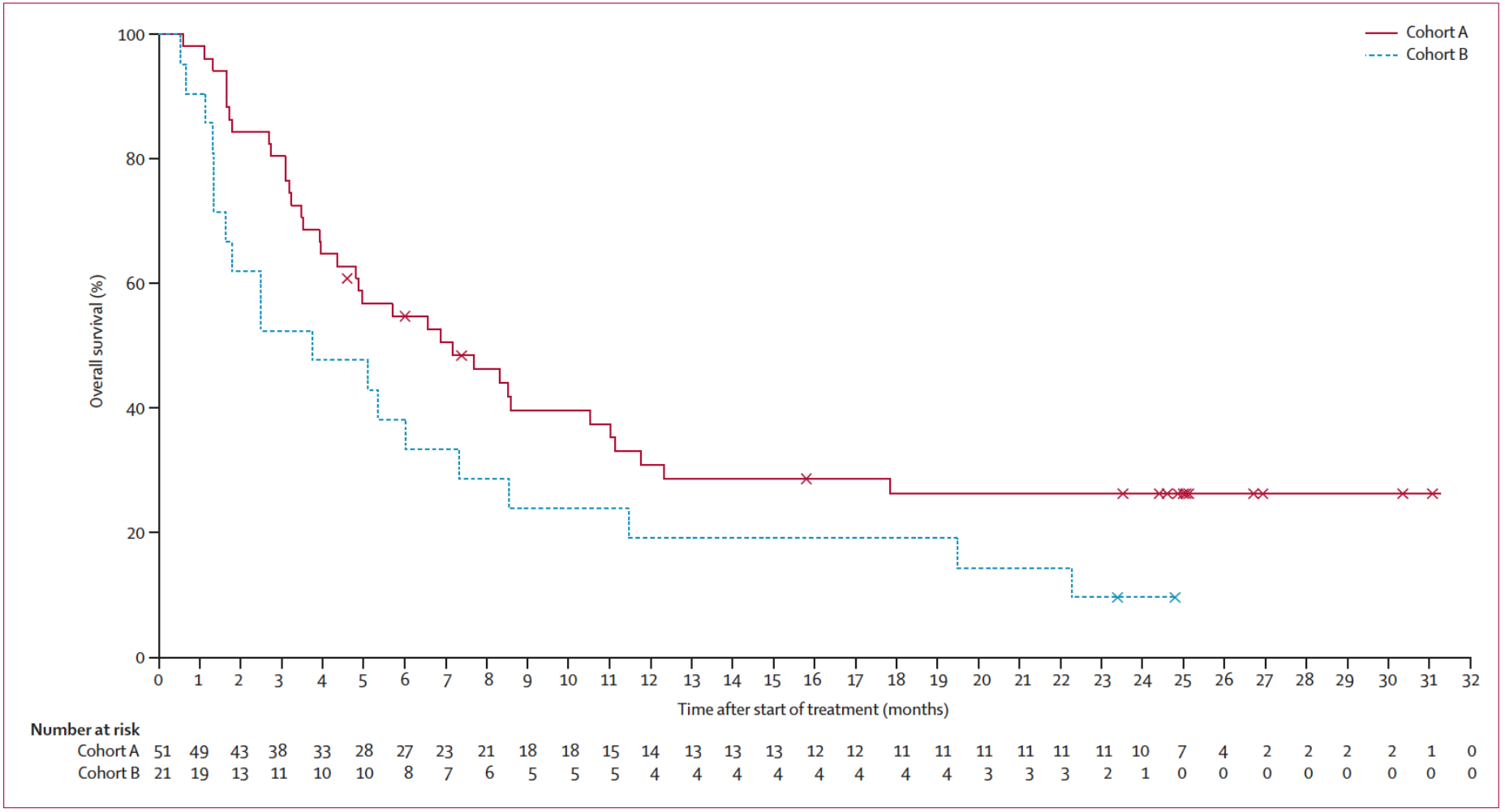


Figure: **Overall survival**
Crosses indicate censored patients.

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

Lancet Oncol 2012; 13: 459–65

Immune-related events						
Diarrhoea	22 (43%)	6 (12%)	0	8 (38%)	0	0
Rash	17 (33%)	1 (2%)	0	6 (29%)	1 (5%)	0
Pruritus	16 (31%)	0	0	5 (24%)	0	0
Aspartate aminotransferase increased	3 (6%)	0	0	4 (19%)	2 (10%)	0
CNS-related events						
Headache	18 (35%)	2 (4%)	0	6 (29%)	0	0
Dizziness	11 (22%)	0	0	2 (10%)	0	0

Data are n (%). Events occurring in at least 15% of patients in either cohort. *Grades 1–5 with National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0.

Table 5: **Adverse events**

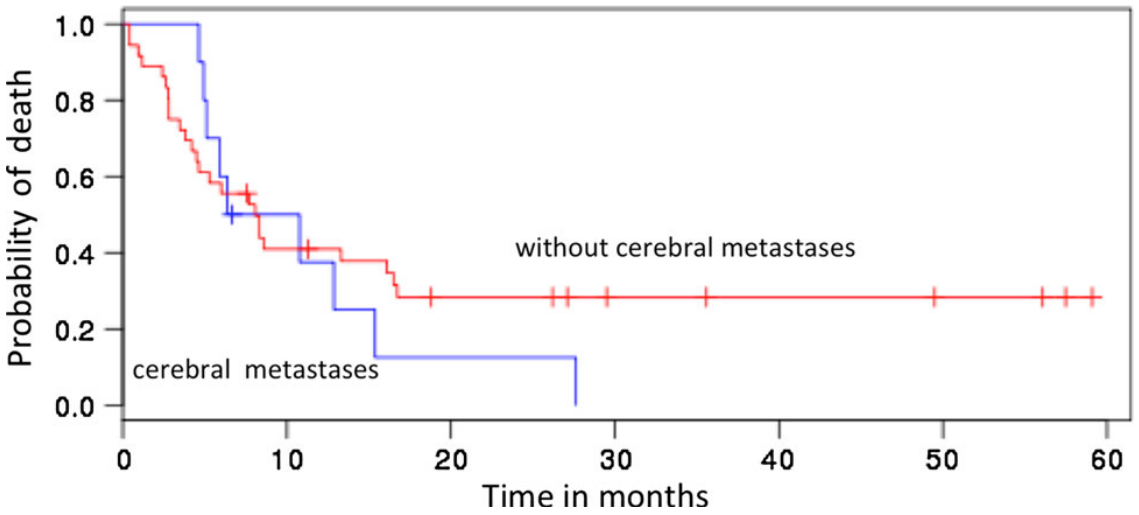
Does anti-CTLA4 have a prophylactic effect for brain metastases?

Development of brain metastases in patients with metastatic melanoma while receiving ipilimumab

C. Frenard[1] · L. Peuvrel[1] · M. Saint Jean[1] · A. Brocard[1] · A. C. Knol[1] · J. M. Nguyen[1] · A. Khammari[1] · G. Quereux[1] · B. Dreno[1]

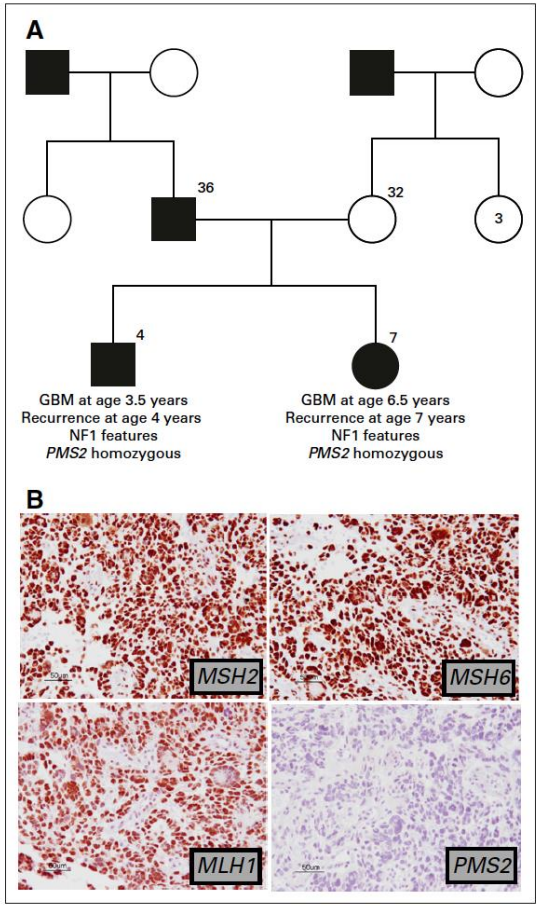
	Ipilimumab (46 patients)	Vemurafenib (87 patients)	p
% Cerebral metastases	21.7	29.9	0.4124
Sex ratio M/W	0.6	1.3	0.044
Mean age	58.07 years (±14.83)	59.6 years (±15.61)	0.59
Mean breslow thickness	3.3 mm (±3.1)	4.5 mm (±3.9)	1.5
Histological subtype	NM: 14	NM: 28	0.005
	SSM: 16	SSM: 40	
	ALM: 5	ALM: 1	
	Mucosal: 5	Mucosal: 1	
		Desmoplastic: 1	
Unknown primary melanoma	6	16	0.43

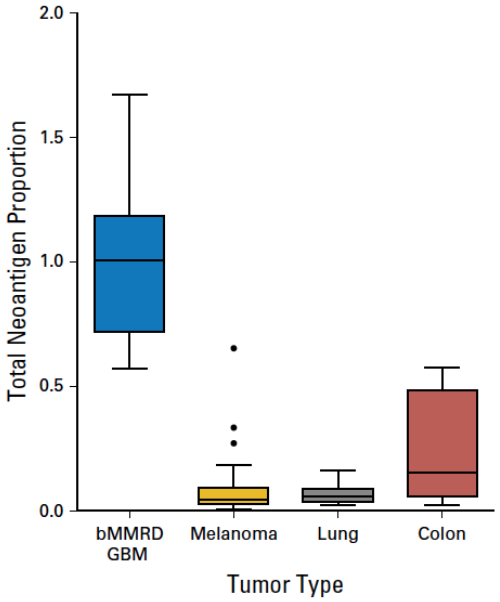
NM nodular melanoma, *SSM* superficial spreading melanoma, *ALM* acral lentiginous melanoma

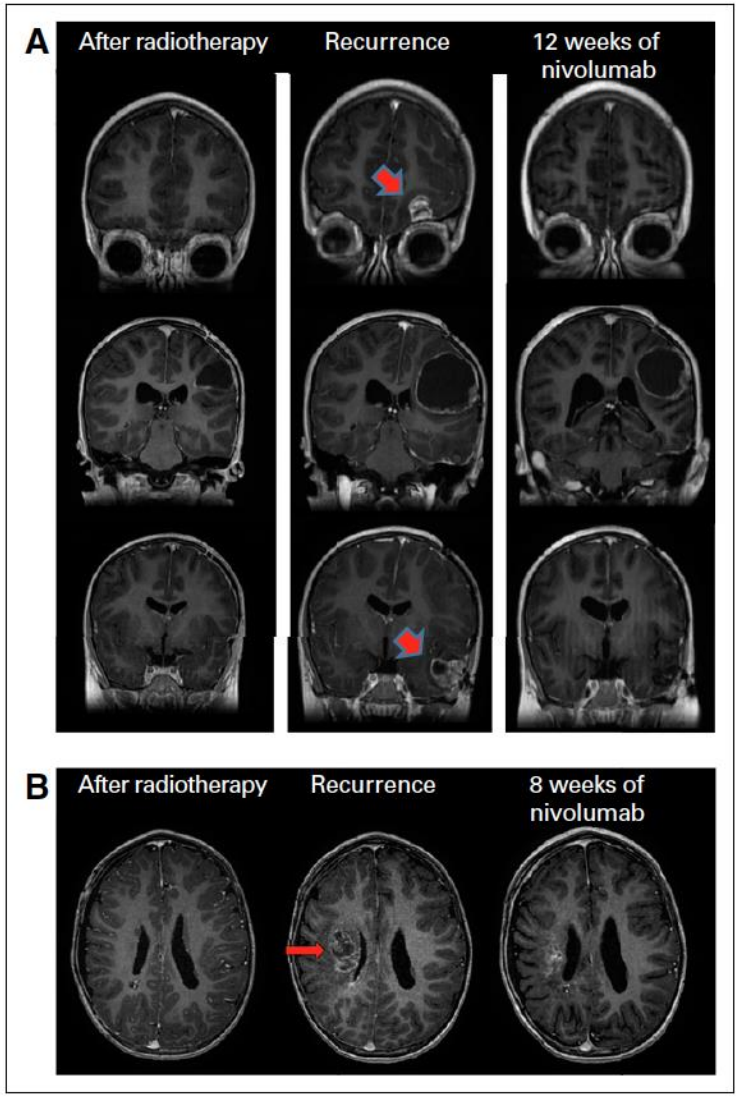


Anti-PD1

Response to nivolumab in two brothers with biallelic mismatch repair deficiency (bMMRD)



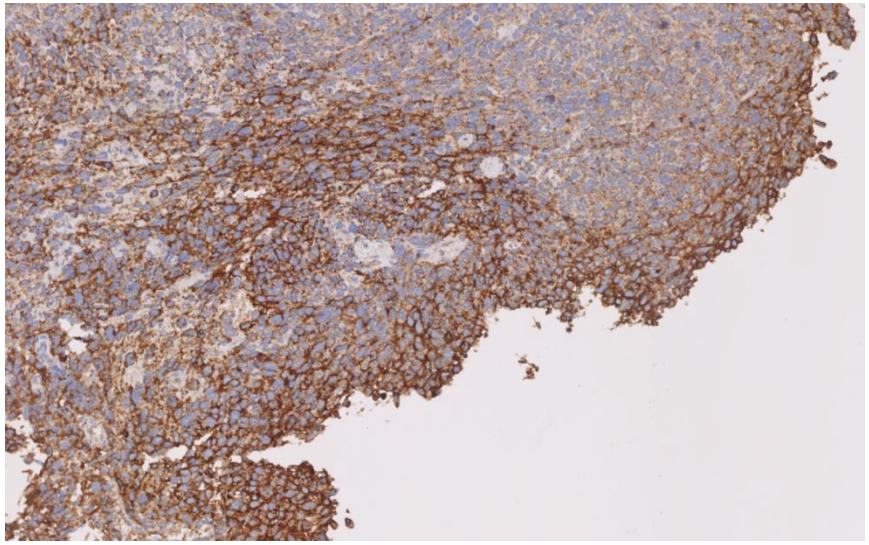




Bouffet, JCO 2016

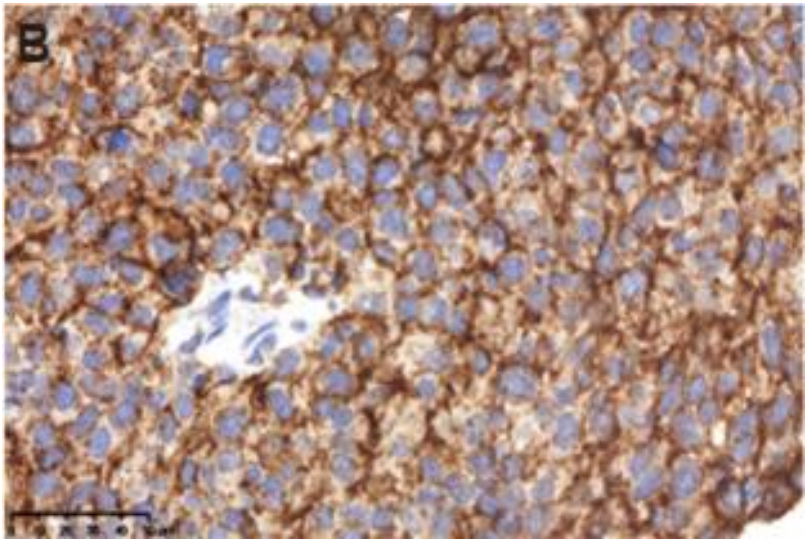
PD-L1 expression in brain metastases

NSCLC brain metastasis



52.0% PD-L1 positive

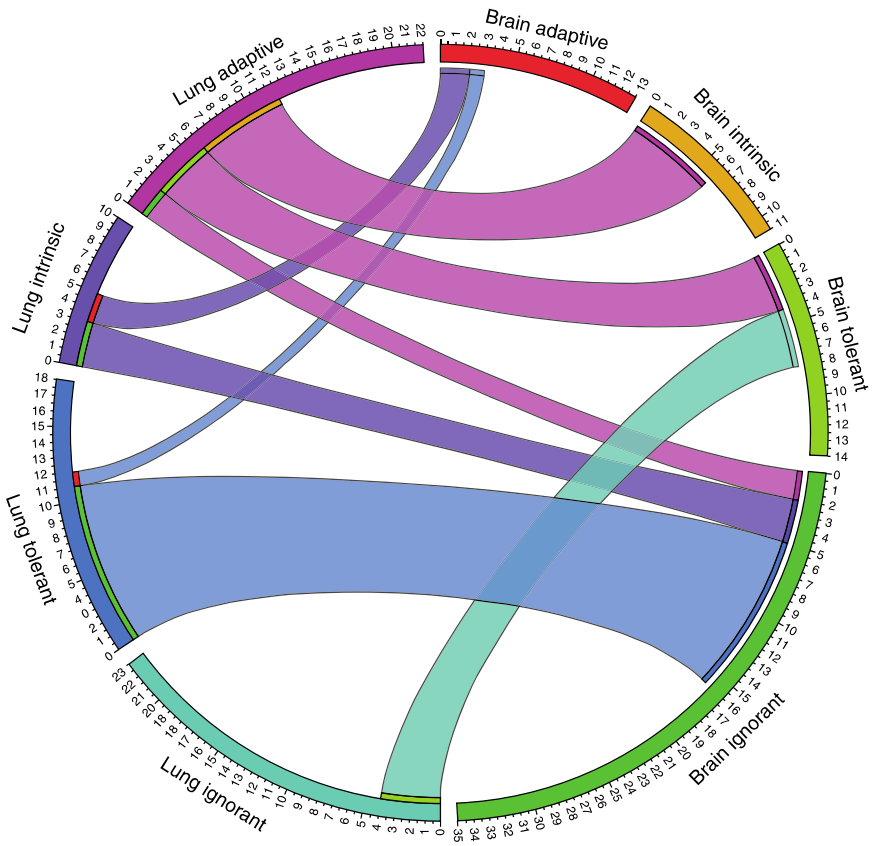
Melanoma brain metastasis



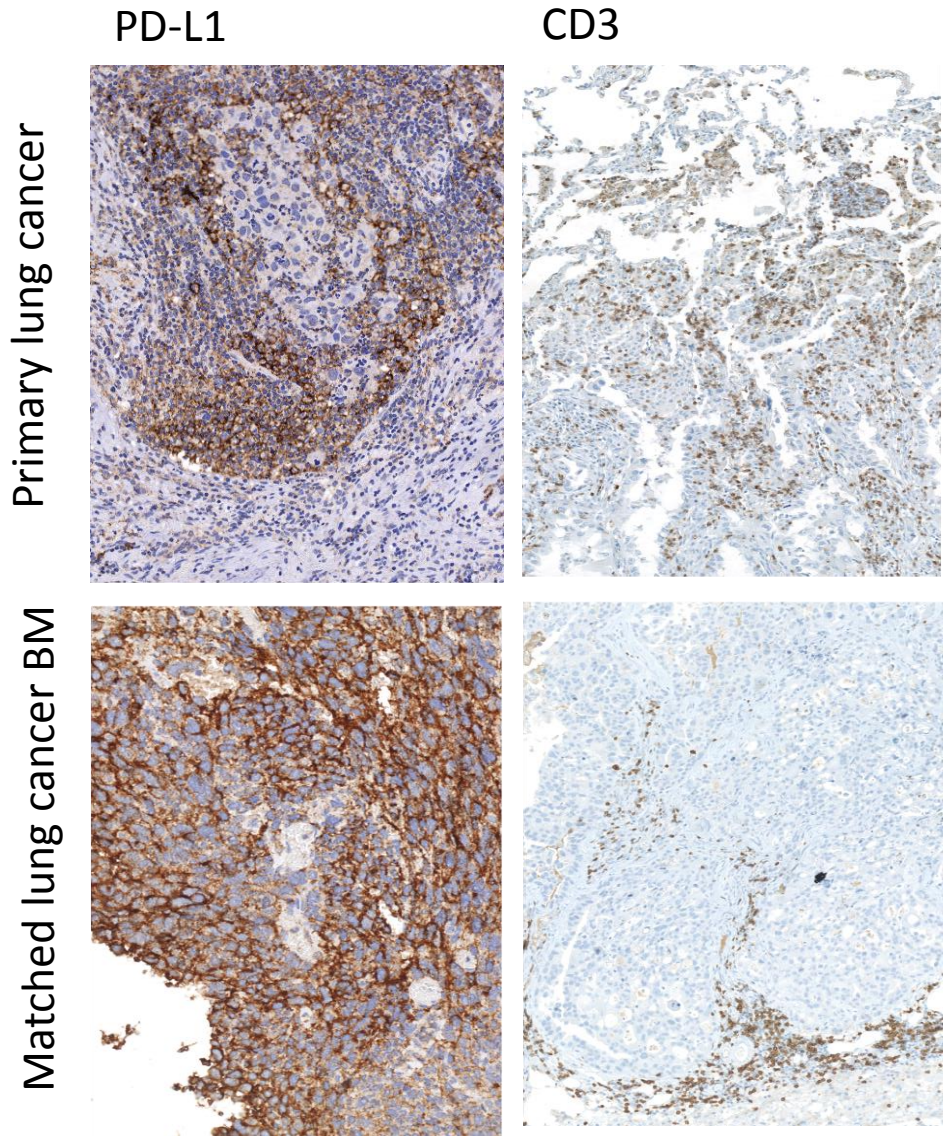
45.7% PD-L1 positive

Berghoff et al, Histopathol 2014

Does the inflammatory microenvironment differ between primary tumor and brain metastasis?

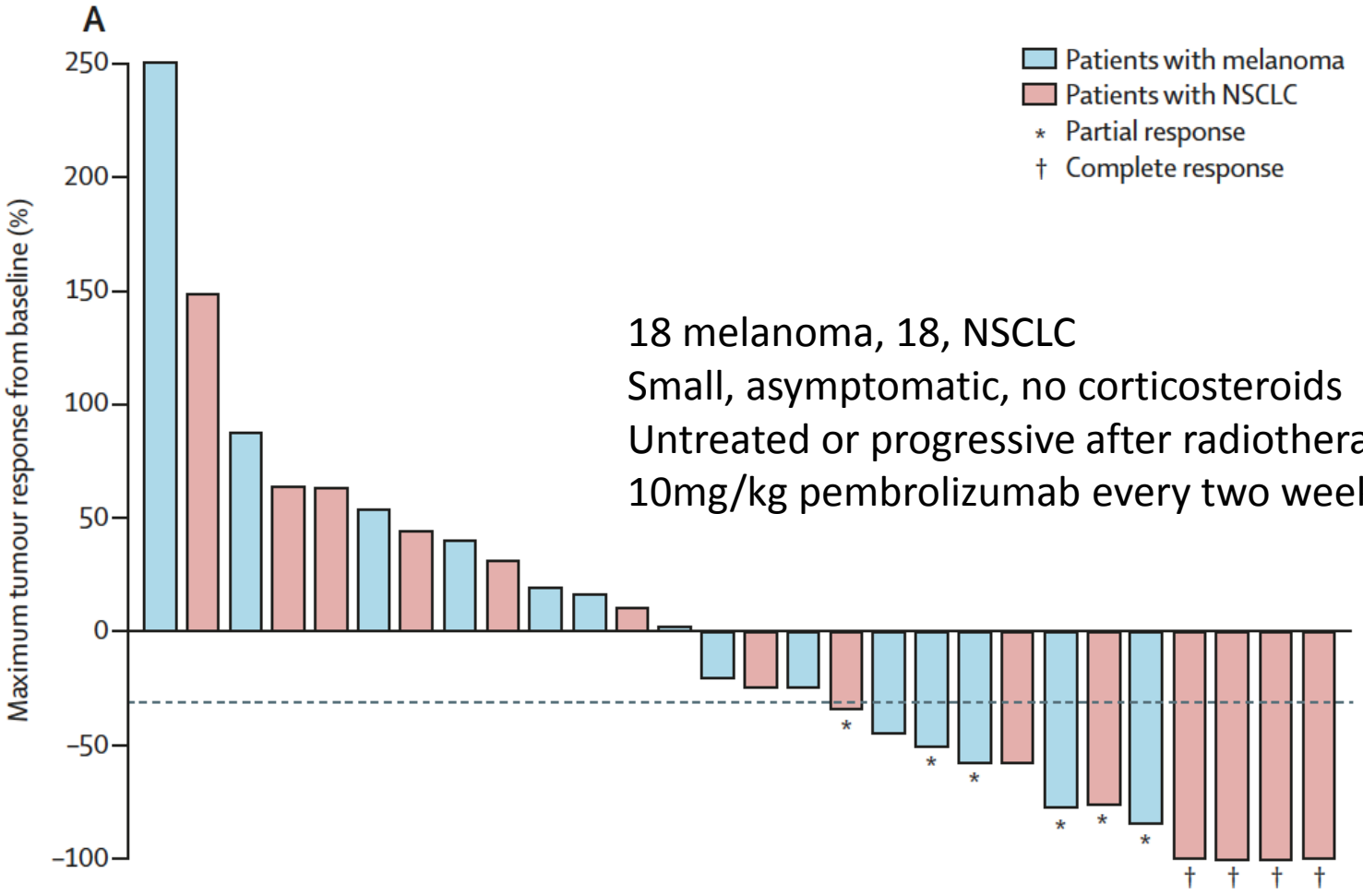


Mansfield et al, Ann Oncol 2016



PD-1 Inhibitor Pembrolizumab

NSCLC and melanoma brain metastases



18 melanoma, 18, NSCLC
Small, asymptomatic, no corticosteroids
Untreated or progressive after radiotherapy
10mg/kg pembrolizumab every two weeks

Goldberg S. Lancet Oncol 2016

PD-1 Inhibitor Pembrolizumab

NSCLC and melanoma brain metastases

	Melanoma (n=18)			NSCLC (n=18)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neurological*						
Cognitive dysfunction	0	1 (6%)	0	1 (6%)	0	0
Headache	3 (17%)	0	0	4 (22%)	0	0
Dizziness	1 (6%)	0	0	2 (11%)	0	0
Stroke	0	0	0	1 (6%)	0	0
Seizure	3 (17%)	0	0	0	0	0
Treatment-related non-neurological						
Colitis or diarrhoea	0	0	0	3 (17%)	1 (6%)	0
Pneumonitis	0	0	0	0	1 (6%)	0
Acute kidney injury	0	0	0	1 (6%)	0	0
Fatigue	8 (44%)	0	0	5 (28%)	1 (6%)	0
Anorexia	1 (6%)	0	0	2 (11%)	0	0
Dermatological	6 (33%)	0	0	4 (22%)	0	0
Arthralgias	2 (11%)	0	0	1 (6%)	0	0
Endocrine	1 (6%)	0	0	5 (28%)	0	0
Hyperkalemia	0	0	0	0	0	1 (6%)
Haematological	0	0	0	2 (11%)	0	0
Elevated aminotransferases	0	1 (6%)	0	0	0	0

NSCLC=non-small-cell lung cancer. There were no treatment-related deaths. *Irrespective of attribution to study drug.

***Table 3*: Neurological adverse events and treatment-related non-neurological adverse events in all treated patients with melanoma or NSCLC**

Goldberg S. Lancet Oncol 2016

What about anti-PD1 in symptomatic brain metastases?

Table 2. Baseline tumour characteristics

Characteristics	*N* (%)
Total number of IC metastases	
1	7 (10)
2–4	34 (52)
5–10	19 (29)
>10	6 (9)
Median SoD of IC targets (mm; range)	23.5 (5–153)
Median number of EC metastatic sites (range)	3 (0–7)
Symptomatic BM	
No	46 (70)
Yes	20 (30)
On steroids for symptomatic BM	
No	51 (77)
Yes	15 (23)

Abbreviations: BM = brain metastases; EC = extracranial; IC = intracranial; SoD = sum of dimensions.

Parakh S. Br J Cancer 2017

Response to anti-PD-1 in symptomatic melanoma brain metastases

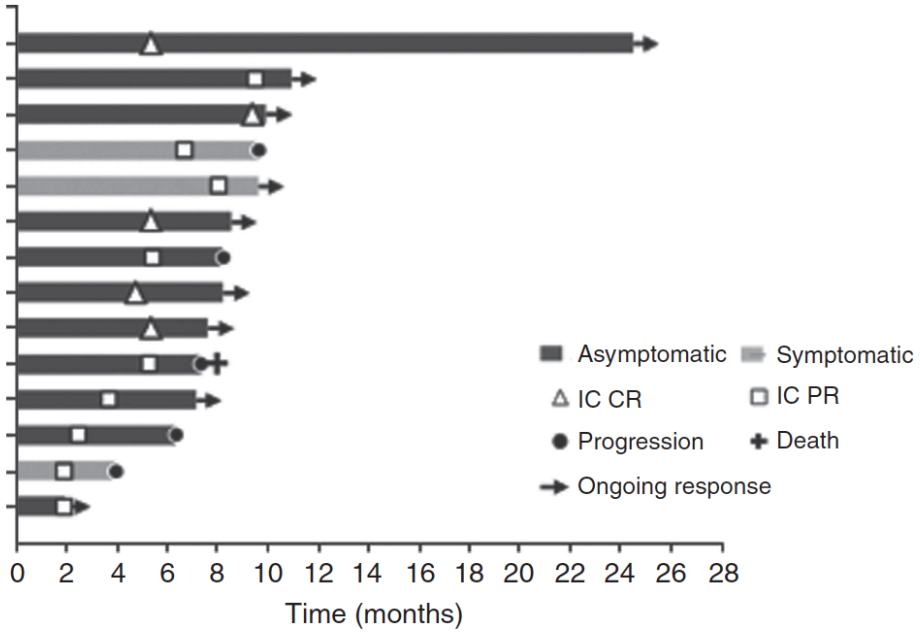
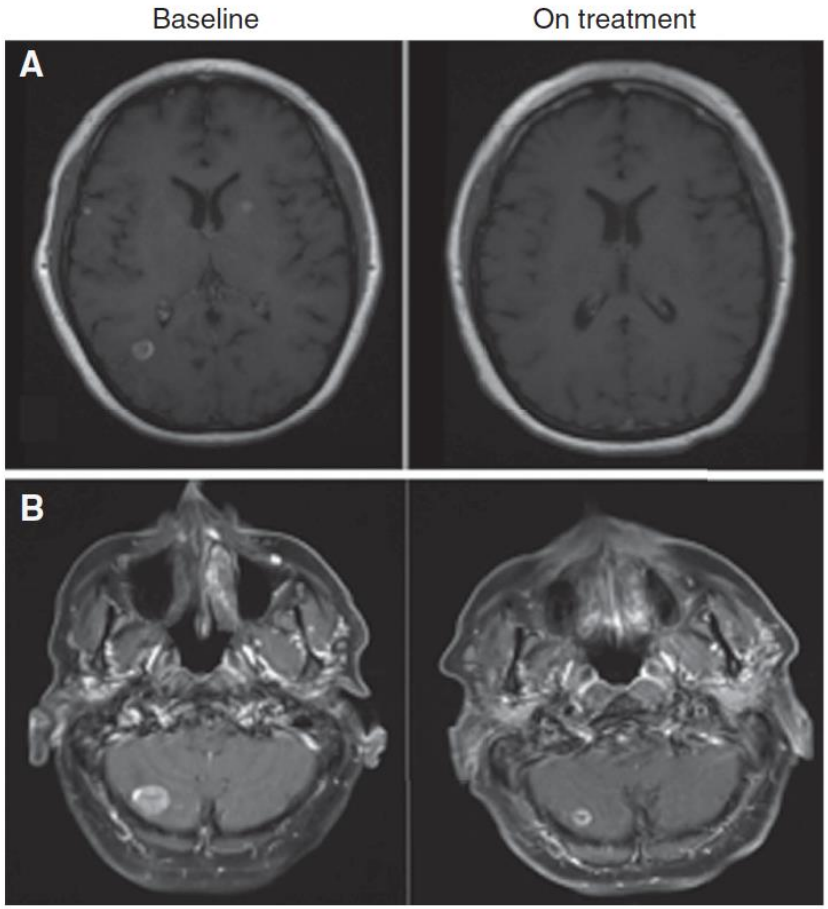
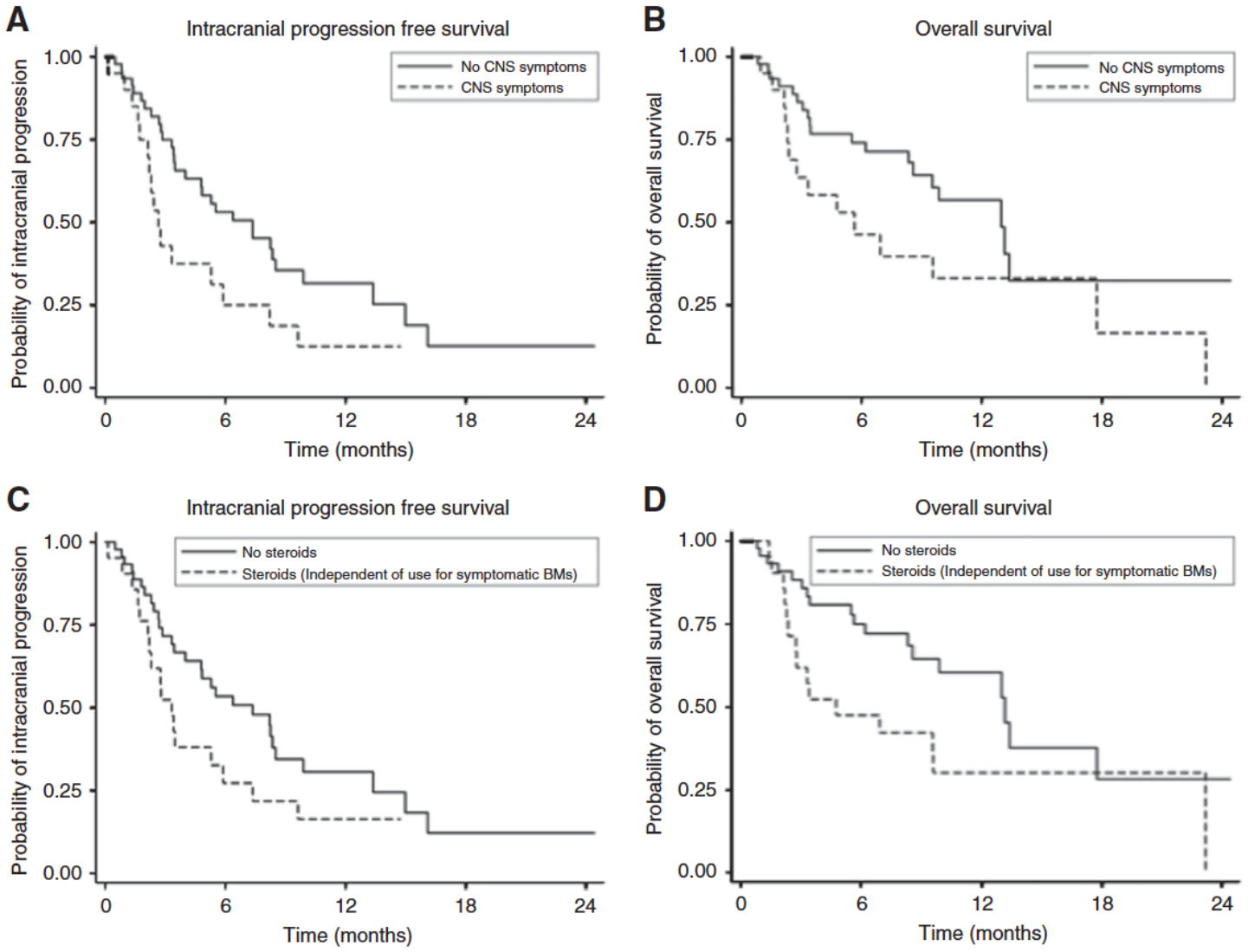


Figure 2. Swimmer's plot showing durable responses in patients who achieved an objective response to anti-PD1 therapy.



Parakh S. Br J Cancer 2017

Impact of symptoms and baseline steroids



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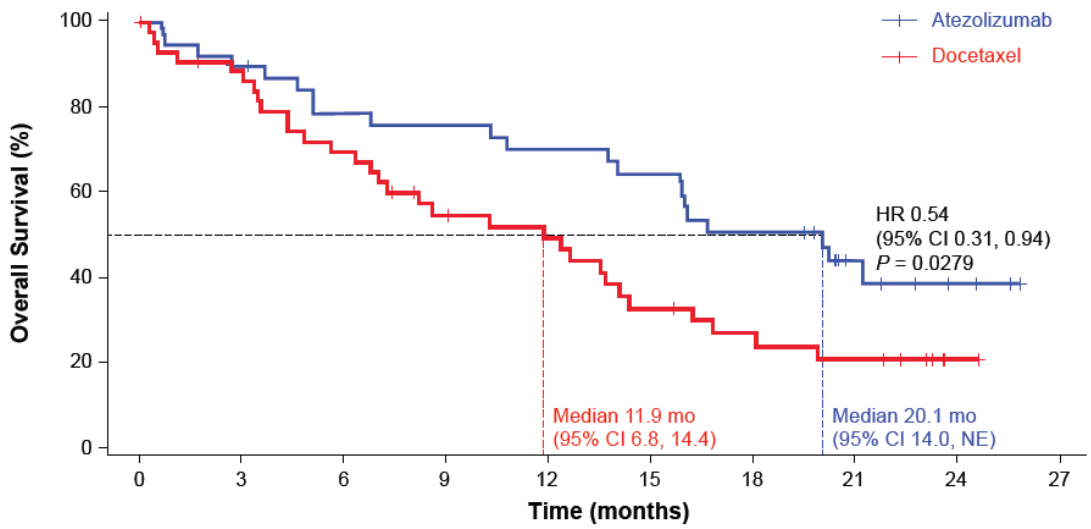
Anti-PDL1

Atezolizumab in Advanced NSCLC Patients with Baseline Brain Metastases: a Pooled Cohort Safety Analysis

Rimas Lukas,[1] Mayank Gandhi,[2] Carol O'Hear,[2] Sylvia Hu,[2] Marcus Ballinger,[2] Catherine Lai,[2] Jyoti D. Patel[3]

[1]Department of Neurology, The University of Chicago Medicine, Chicago, IL, USA
[2]Genentech, Inc., South San Francisco, CA, USA
[3]Section of Hematology/Oncology, The University of Chicago Medicine, Chicago, IL, USA

Figure 2. Kaplan-Meier Curve of OS From OAK in Patients With Baseline Brain Metastases: Atezolizumab vs Docetaxel



Combination of immune checkpoint inhibitors

Efficacy and safety of nivolumab plus ipilimumab in patients with melanoma metastatic to the brain: Results of the phase II study CheckMate 204

	Global	Intracranial	Extracranial
Best overall response, n (%, 95% CI)			
CR	2 (3, 0–9)	14 (19, 11–29)	4 (5, 1–13)
PR	40 (53, 41–65)	28 (37, 26–49)	33 (44, 33–56)
SD >6 months	5 (7, 2–15)	6 (8, 3–17)	2 (3, 0–9)
ORR, n (%, 95% CI)	42 (56, 44–68)	42 (56, 44–68)	37 (49, 38–61)

Brain met size max 3cm
No neurological symptoms or baseline steroids
NIVO 1 mg/kg + IPI 3 mg/kg Q3W x 4, then NIVO 3 mg/kg Q2W until progression or toxicity

Tawbi et al. ASCO 2017

A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients with melanoma brain metastases: The Anti-PD1 Brain Collaboration (ABC)

	A N = 25 nivo+ipi	B N = 25 nivo	C N = 16 nivo
ICR % (95% CI)	44 (24, 65)	20 (7, 41)	6 (0, 30)
ICR Complete Response	16 (24, 65)	12 (7, 41)	0
ECR % (95% CI)	38 (18, 62)	26 (10, 48)	21 (5, 50)
6-mo PFS % (95% CI)	50 (33, 75)	29 (15, 56)	0
6-mo OS % (95% CI)	76 (59, 97)	59 (41, 86)	44 (25, 76)

Reduced activity in patients who progressed on BRAF inhibitors

Poor response in patients with neurological symptoms, leptomeningial disease or prior local therapy

Long et al. ASCO 2017

Combination of immune checkpoint inhibitors with radiotherapy

Combination of immune checkpoint inhibitor and radiotherapy in brain metastases

Table 5. Immune checkpoint Inhibitors and RT

Study	Primary	*n*	RT	Drug	Brain control		Median survival	Toxicity	Median follow-up (months)
Patel et al. [85]	Melanoma	*20*	SRS	Ipilimumab *1 during SRS* *12 before SRS* *7 after SRS*	Not improved versus SRS alone		Not improved versus SRS alone (8 versus 9.1 mo)	No increased toxicity	7.3
Knisely et al. [83]	Melanoma	*77*	SRS	Ipilimumab 27 +SRS: *11 before SRS* *16 after SRS*	Brain 37%	local NR	21.3 mo (versus 4.9 without ipi) No ≠ before/after	NR	NR
Silk et al. [86]	Melanoma	*70*	WBRT (16) SRS (17)	Ipilimumab 33 +RT: *12 before RT* *21 after RT*	Not significantly increased in Ipi group		18.3 mo (versus 5.3 without ipi) 8.1 mo 18.4 mo	No neuro-toxicity (ipi)	10
Mathew et al. [84]	Melanoma	*58*	SRS	Ipilimumab 25 + SRS *4 before SRS* *7 during SRS* *10 after SRS* 33 without ipi		65% 63%	(OS 6 mo) 56% 46% (NS)	No increased toxicity	6
Kiess et al. [82]	Melanoma	*46*	SRS	Ipilimumab *15 during SRS,* *19 before SRS,* *12 after SRS*	brain 31% 36% 8%	Local 100% 87% 89%	(1-y OS) 65% 56% 40%	*during* SRS : no relevant toxicity *before* SRS: ITH (13%/0[a]), seizure (13%/0[a]) *after* SRS: ITH (6/3[a])	22
Tazi et al. [87]	Melanoma	*10*	SRS	Ipilimumab *During or after SRS*			16.5 mo 3-y OS: 50%	No increased toxicity	NR
Gerber et al. [88]	Melanoma	*13*	WBRT	Ipilimumab *4 before WBRT* *6 during WBRT* *3 after WBRT*	56%		4 mo	1 grade 3 cognitive change 100% new or worsening ITH	4
Cohen-Inbar et al. [89]	Melanoma	*46*	SRS	Ipilimumab *14 before SRS* *32 during/after SRS*	33.6% 50.4%	16.5% 72.6%	6.4 mo 13.8 mo	RN and post-SRS edema increased when Ipi was administered during or after SRS	7.9
Alomari et al. [90]	Melanoma NSCLC	*2*	SRS	Pembrolizumab Nivolumab + ipilimumab	100%		NA	pseudo clinical and radiological progression	6
Ahmed et al. [91]	Melanoma	*26*	SRS	Nivolumab *During (washout 6d)/ before/after*	(1-y) 53%	(1-y) 85%		ITH: 5% Grade 3 oedema: 10%	9.4

[a]x%/x%= grade 3/grade 4.

ipi, ipilimumab; RT, radiation therapy; SRS, stereotactic radiosurgery; OS, overall survival; WBRT, whole-brain radiation therapy; NSCLC, non-small-cell lung cancer; NR, not reported; NS, non-significant; NA, not applicable; ITH, intra-tumor hemorrhage.

Tallet et al. Ann Oncol 2017

Summary

New treatment apporaches for brain tumors are urgently needed

Preclinical and clinical data support imunotherapy as therapeutic opportunity in brain metastases

Immunotherapies seem to be active in tumor types commonly causing brain metastases (lung cancer, melanoma)

Many open questions on biomarkers and combination/sequencing strategies

Thank you!