ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

BRAIN METASTASES

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DISCLOSURES

Dr Hofer has reported receiving congress travel support from Astellas in 2019, honorarium for Advisory Board role from MSD in 2019. Financial support paid directly to her institution by Roche for Advisory Board role in 2019.

Dr Kotecki has reported no conflicts of interest

BRAIN METASTASES (BM)

Key points

BM are increasing in incidence since systemic tumour therapies have improved, resulting in longer patient survival, better control of metastases in distant organs and also due to better diagnostic techniques

The pathogenesis of BM has not been completely characterised to date

Prognosis of patients with BM depends on patient characteristics (i.e. age, KPS), tumour entity and molecular profile. Years with good quality of life are attainable, especially in molecularly altered tumours, where targeted therapies are available (e.g. EGFRmut and ALK rearranged NSCLC, HER 2- amplified Breast Cancer)

Treatment of BM is primarily local with neurosurgery and/or stereotactic radiotherapy (depending on criteria such as immediate relief of brain pressure, need of a histology, number of metastases, performance status and systemic disease control). Whole-brain irradiation (WBRT), is largely abandoned, exceptions remain for prophylactic CNS irradiation (PCI) in SCLC, diffuse leptomeningeal disease and for palliative reasons (salvage radiotherapy)

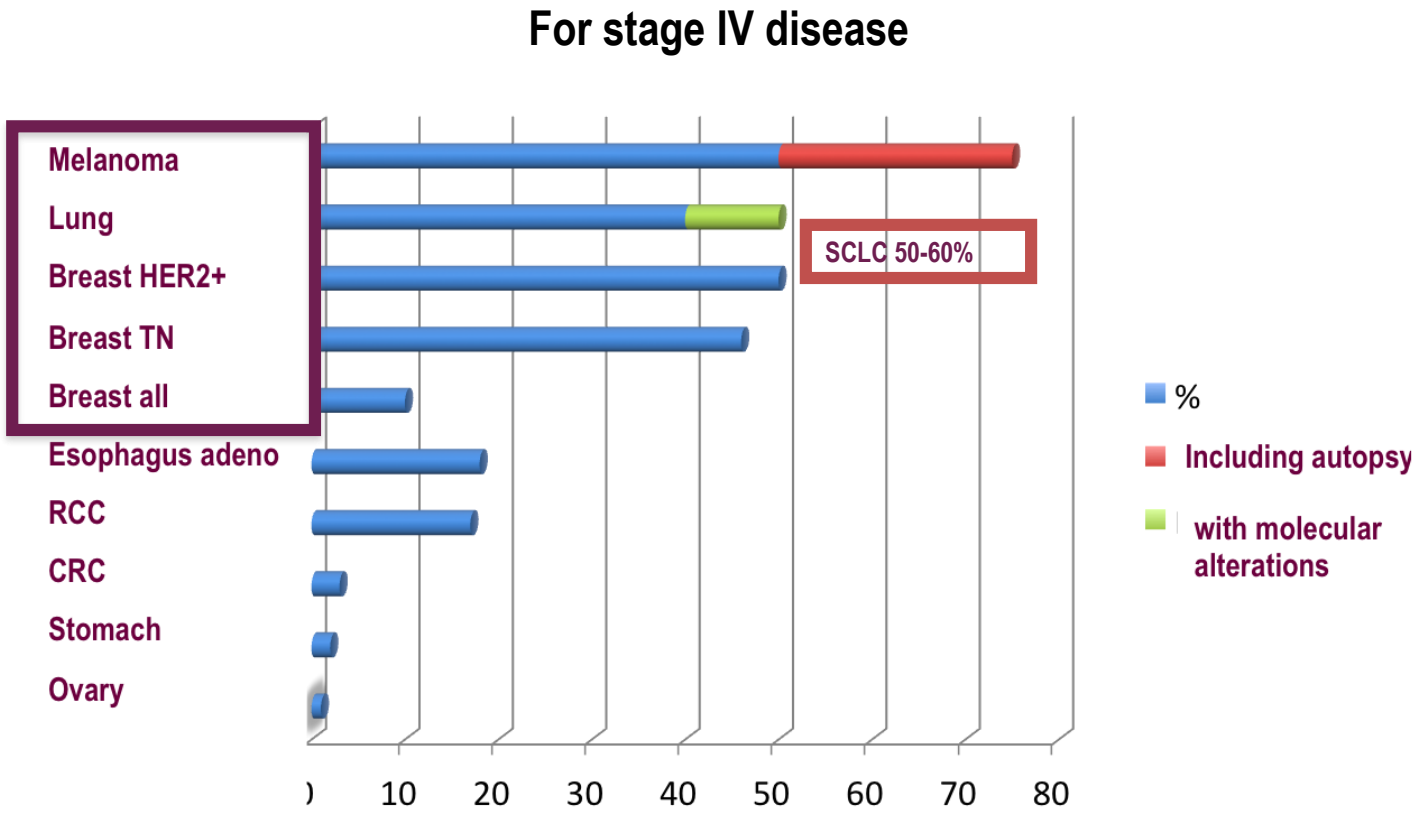
Since patients with BM are no longer excluded from clinical trials, there is increasing evidence that newer generation TKIs and immuno-therapies (IO) are also effective in the brain. The brain is not immune-isolated

AGENDA

1. Epidemiology
2. Pathogenesis of BM & Blood Brain Barrier
3. Prognostic scores
4. Therapeutic options for BM
5. Histologic entities
6. Summary

1. EPIDEMIOLOGY OF BM

CUMULATIVE INCIDENCE OF BM

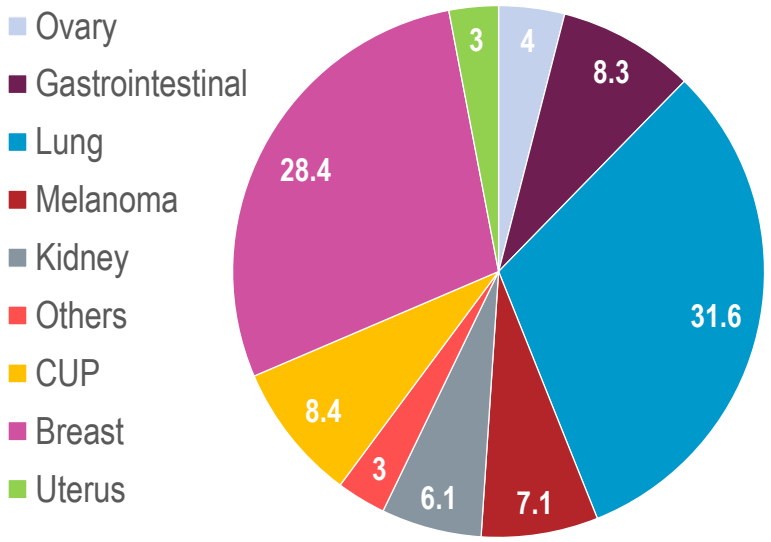


TN, triple negative.
Courtesy of Dr S Hofer, University Hospital, Zürich.

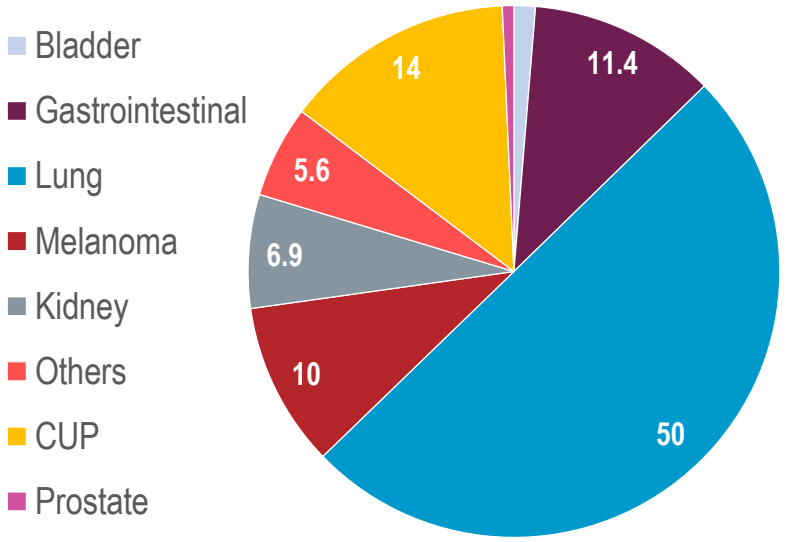
RELATIVE FREQUENCIES OF TUMOUR TYPES

Brain metastases (%)

Females

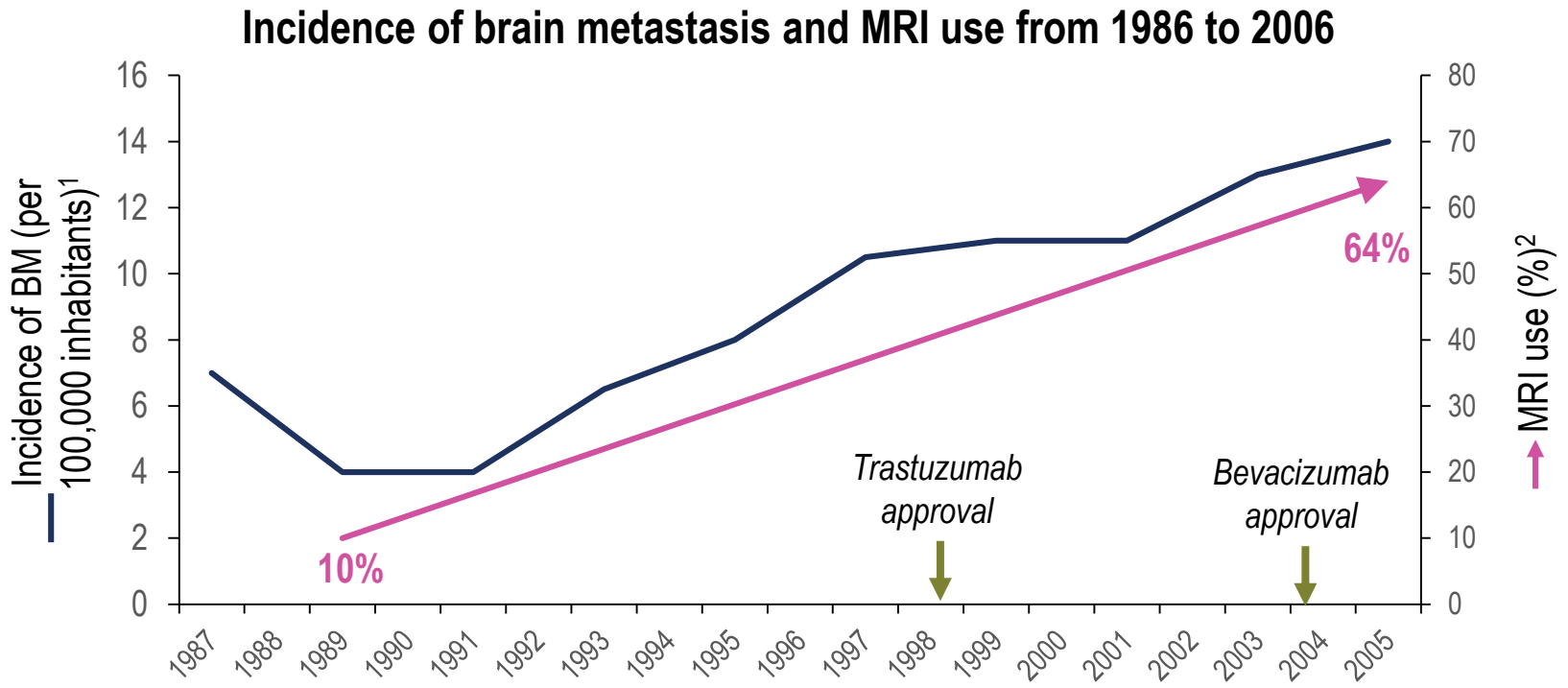


Males



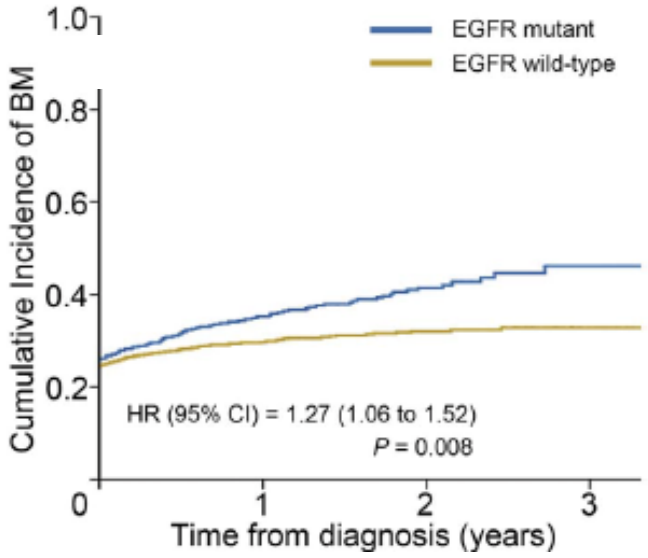
Preusser M, *et al*, Acta Neuropathol 2012;123(2):205–22.

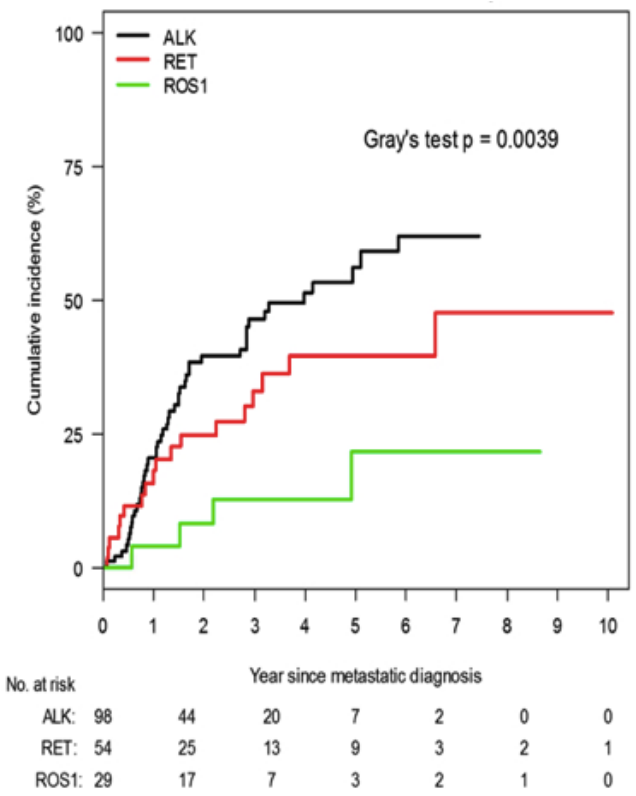
BM: AN INCREASING ISSUE



Adapted from: 1. Smedby KE, *et al*. Br J Cancer 2009;101:1919–24; 2. Nieder C, *et al*. Cancer 2010;117:2505–12.

Cumulative incidence of BM according to molecular subtype

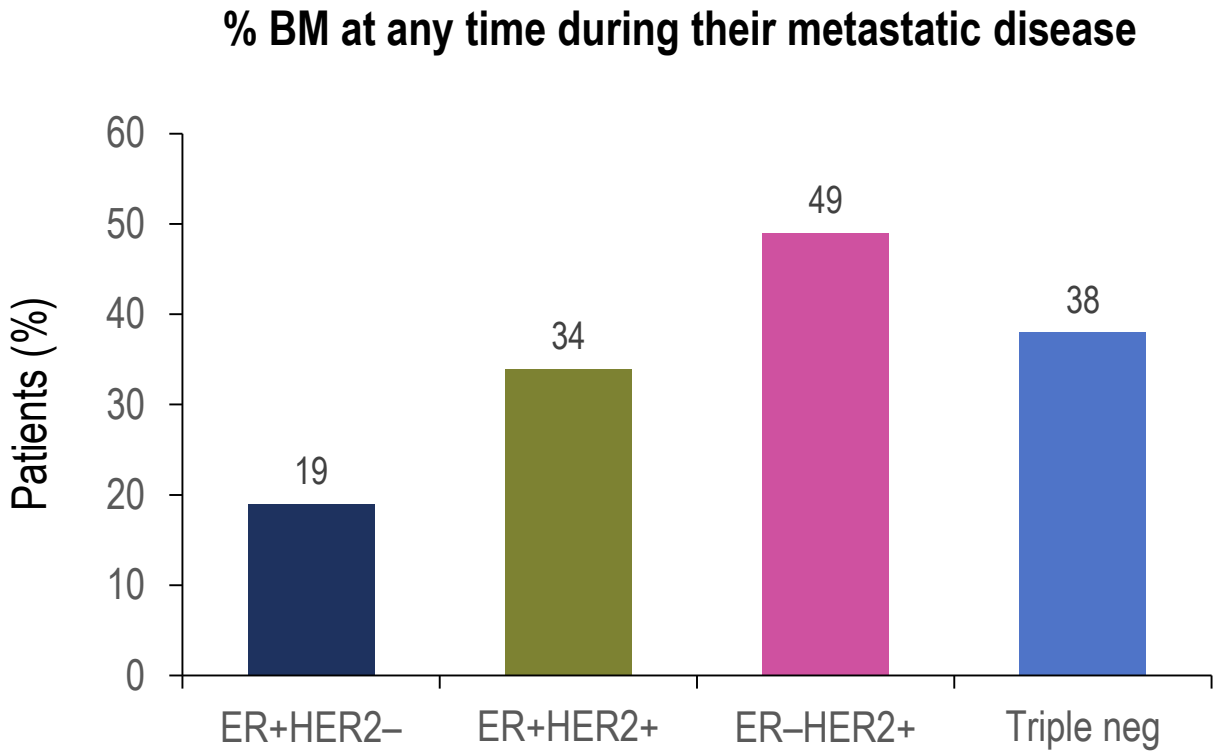




1. Reprinted from Clin Neurol Neurosurg , 160:, Wang B-X, Impacts of EGFR mutation and EGFR-TKIs on incidence of brain metastases in advanced non-squamous NSCLC, P96–100, Copyright , with permission from Elsevier;
2. Reprinted from Journal of Thoracic Oncology 13(10), Drilon A, *et al.* Frequency of Brain Metastases and Multikinase Inhibitor Outcomes in Patients With RET–Rearranged Lung Cancers, 1595–601, Copyright 2018, with permission from Elsevier.

BREAST

Cumulative incidence of Stage IV disease



Darlix A, *et al*. Br J Cancer 2019;121:991-1000; Pasquier D, *et al.* Eur J Cancer 2020;125:22e30.

MELANOMA

20–25% of patients with BM at diagnosis

Cumulative incidence in Stage IV disease 40–60%

At autopsy, up to 80%

SCREENING FOR BM

Recommended for:

NSCLC stage II–IV

SCLC any stage

Melanoma stage IIIc–IV

Breast stage IV or recurrent disease[1,2]

Germ-cell tumours with lung metastases

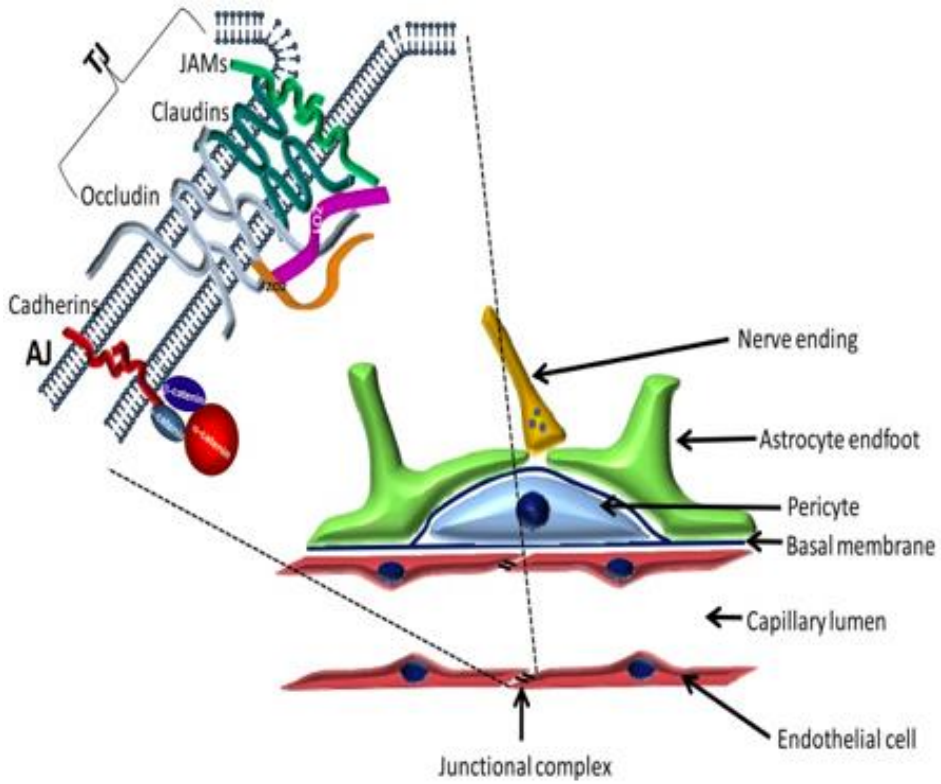
Alveolar soft part sarcoma (ASPS) any stage

1. Cagney D, *et al.* JAMA Oncol 2018; 2. NCCN 01.2020, ESMO 2019

2. PATHOGENESIS OF BM AND BLOOD BRAIN BARRIER

THE BLOOD BRAIN BARRIER (BBB)

Anatomy and physiology (1)

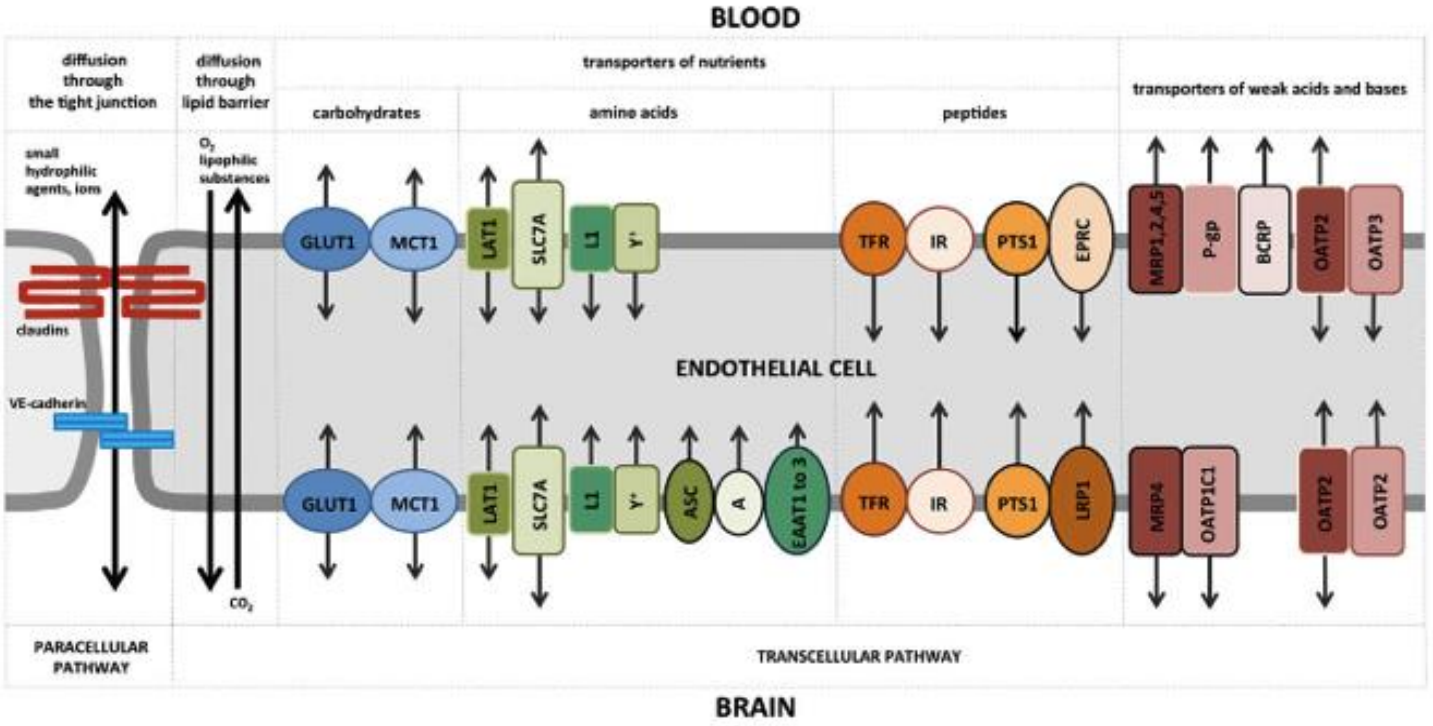


The BBB is a selective barrier formed by endothelial cells, interconnected by tight junctions, pericytes, astrocytes, neuronal end-foots and other cells from the microglia forming the neurovascular unit, which separates the bloodstream circulation from the brain and the cerebrospinal fluid (CSF)

TJ, tight junctions; AJ adherence junctions.

THE BLOOD BRAIN BARRIER

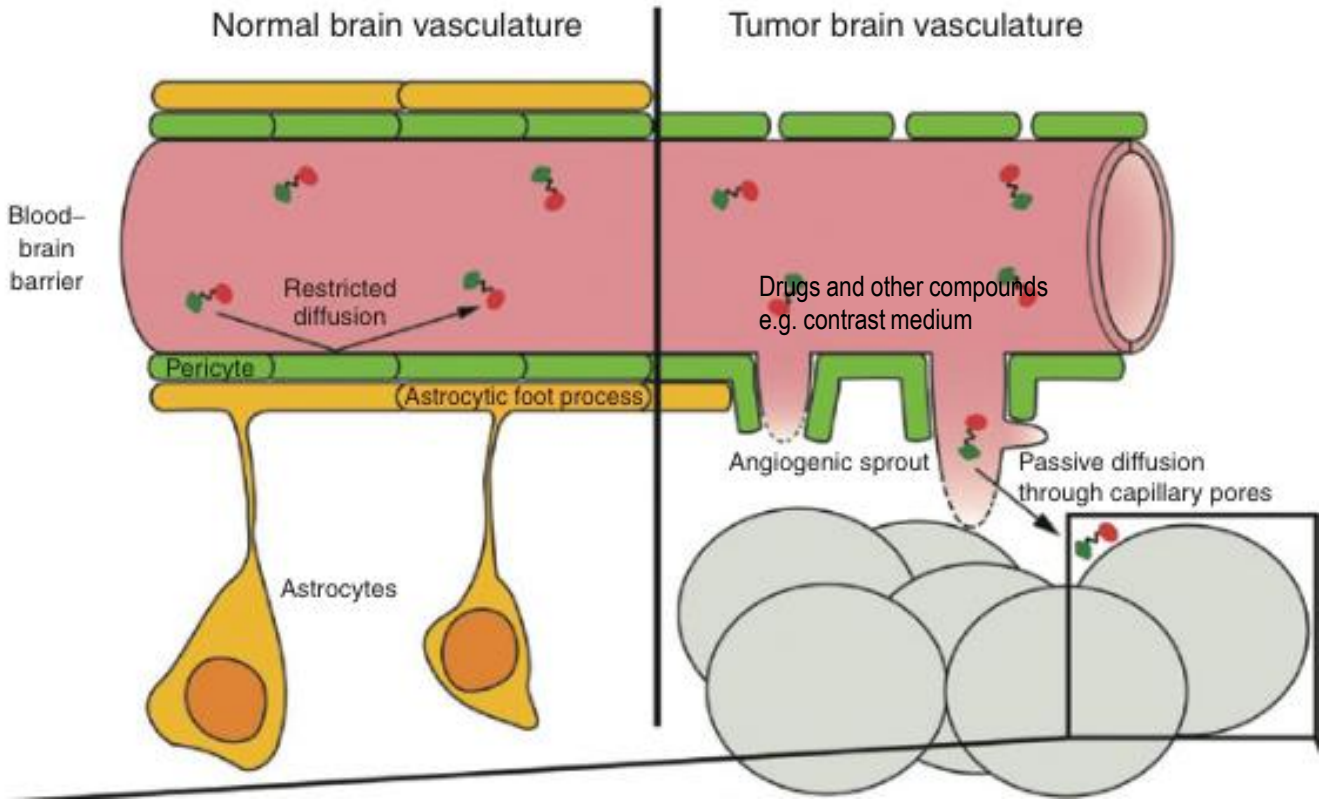
Anatomy and physiology (2)



Transport across the BBB is highly regulated, however, less so in the presence of BM. It includes paracellular transport, passive and active transport and cell-mediated transcytosis thus limiting- at least partly- the passage of many drugs, some of which are dependent on P-glycoprotein (P-gp), an efflux transporter

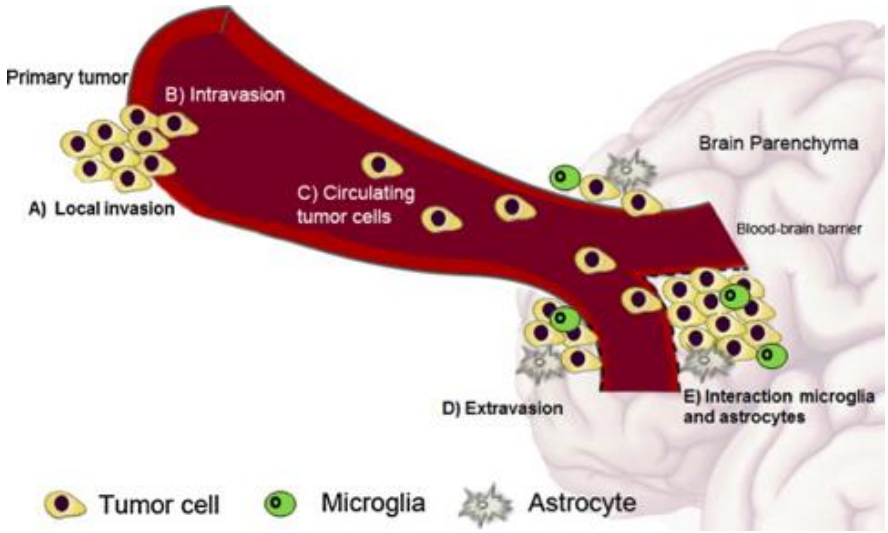
Reproduced from Blecharz KG, *et al.* Current concepts and management of Glioblastoma. Biol Cell 2015;107(10):342–71, with by permission of John Wiley and Sons, Copyright 2015 Société Française des Microscopies and Société de Biologie Cellulaire de France.

BLOOD BRAIN BARRIER AND DRUGS (3)



Reprinted from Mol Cancer Ther, 2013, 12(11):2389–99, Mittapalli RK, et al. Paclitaxel–Hyaluronic NanoConjugates Prolong Overall Survival in a Preclinical Brain Metastases of Breast Cancer Model, with permission from AACR.

PATHOGENESIS OF BM



Tumour cells spread from the primary tumour or from metastatic lesions and colonise the brain parenchyma, involving several biological processes:

A. local invasion

B. intravasation into the bloodstream

C. circulating tumour cells

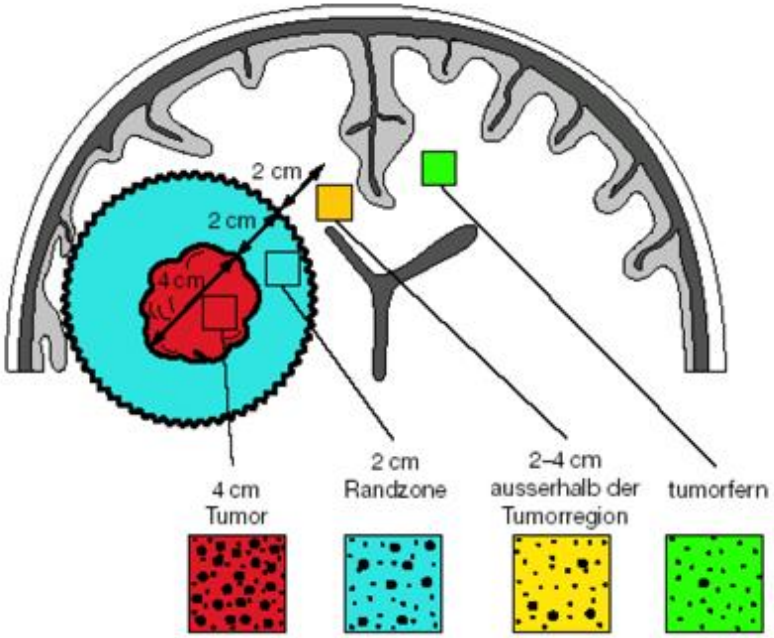
D. extravasation into the brain parenchyma through the blood brain barrier (BBB)

E. interaction with the CNS microenvironment

Mol Oncol 2014 Brain metastasis: new opportunities to tackle therapeutic resistance/, Seoane J, *et al.* Mol Oncol 2014;8(6):1120-–1. Published under a Creative Commons Attribution (CC BY) License (available at: https://creativecommons.org/licenses/by/4.0/; accessed Oct 2020).

GROWTH PATTERNS OF BM

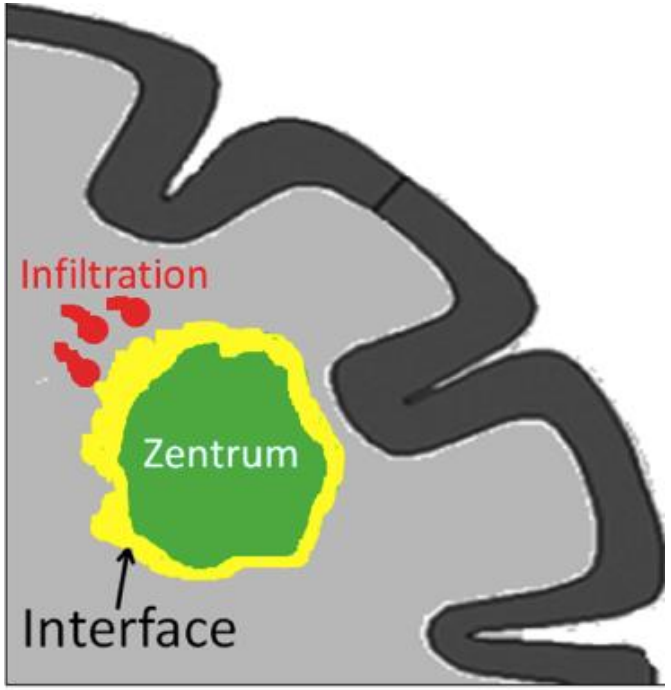
Glioma growth pattern[1]



main tumour

Infiltrative zone with decreasing tumour cell density

Brain metastases up to 50% show a glioma-like infiltrative pattern[2]



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1. Courtesy Dr S Hofer, University Hospital, Zurich; 2. Courtesy Prof. Dr. med.Tobias Pukrop, Universitaetsklinikum Regensburg.

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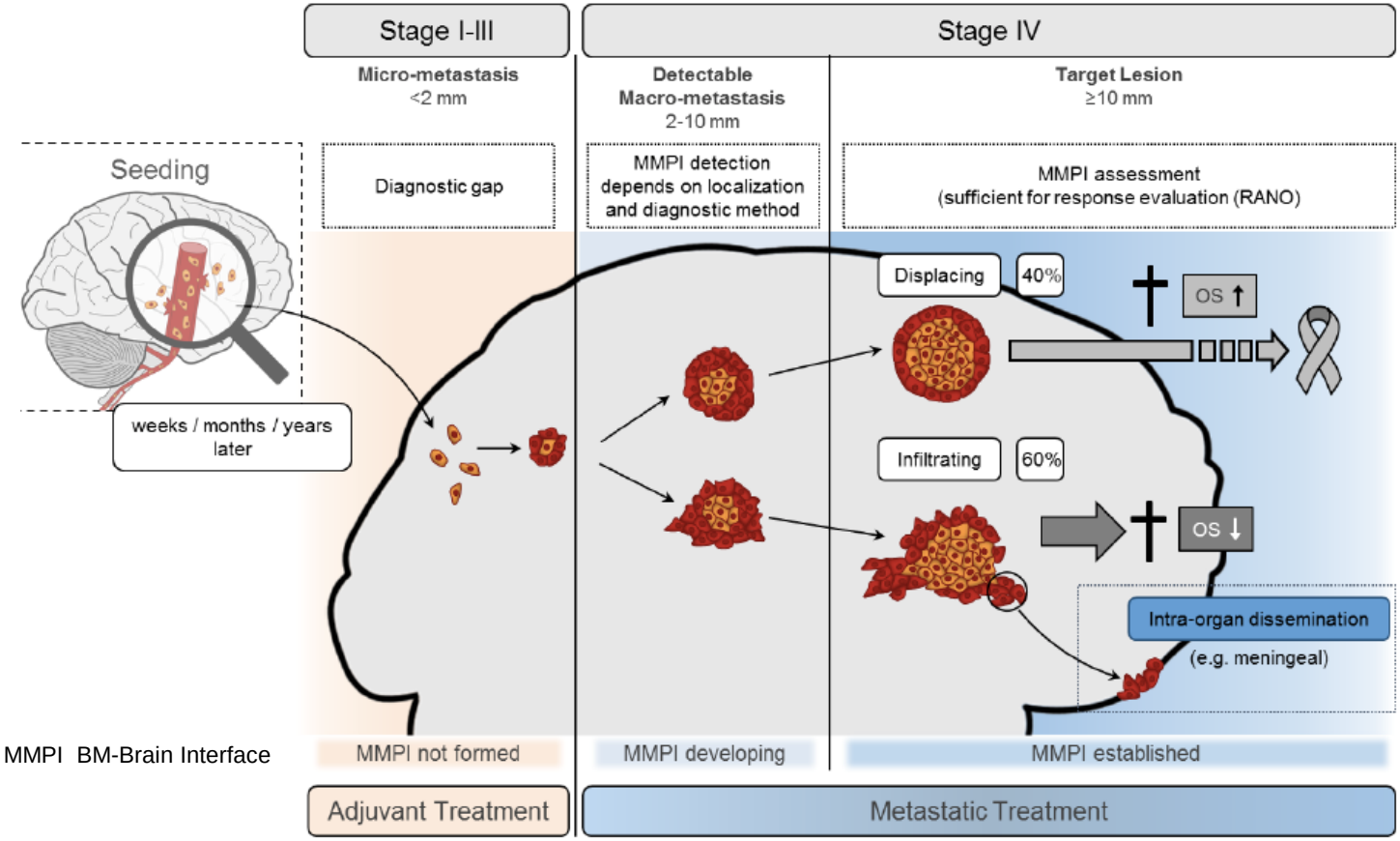
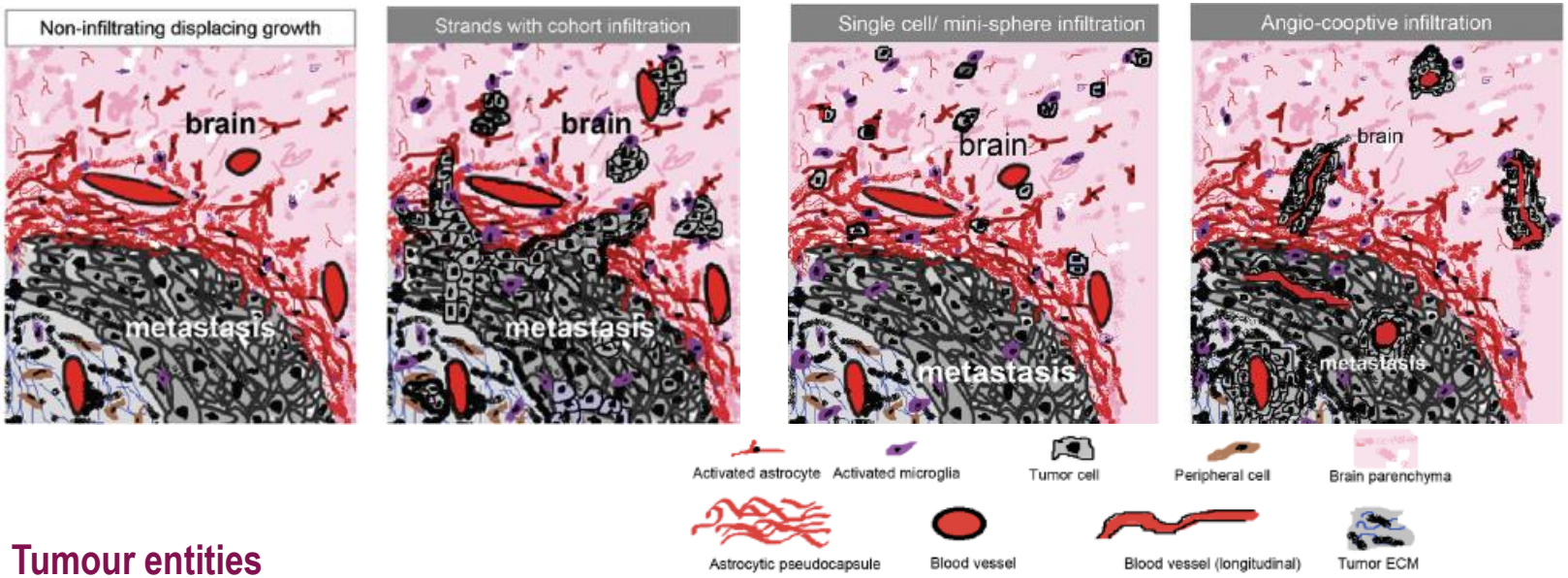
TYPES OF BRAIN COLONISATION



MMPI BM-Brain Interface

Blazquez R, *et al.* Semin Cancer Biol 2020;60:324–33. Reproduced under the terms of the Creative Commons Attribution (CC BY) License (available at: https://creativecommons.org/licenses/by/4.0/; accessed Oct 2020).

TUMOUR ENTITIES WITH DIFFERENT TYPES OF INFILTRATION



Tumour entities

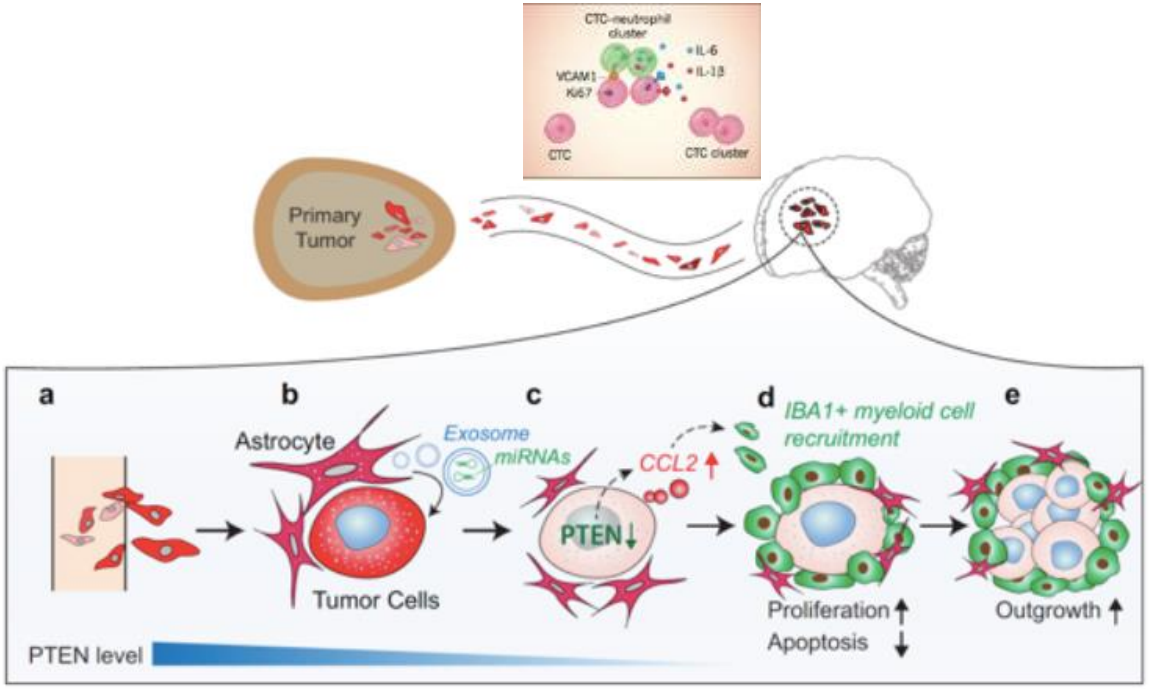
NSCLC SCLC **Breast** Melanoma **RCC**	**NSCLC** Breast	**NSCLC** **SCLC** Breast	**Melanoma**

Siam L, *et al.* The metastatic infiltration at the metastasis/brain parenchyma-interface is very heterogeneous and has a significant impact on survival in a prospective study. Oncotarget 2015;6:29254–67. Retrieved from https://www.oncotarget.com/article/4201/text/ Reproduced under the terms of the Creative Commons Attribution 3.0 License.(available at: https://creativecommons.org/licenses/by/3.0/; accessed Oct 2020).

BRAIN SPECIFIC MICROENVIRONMENT

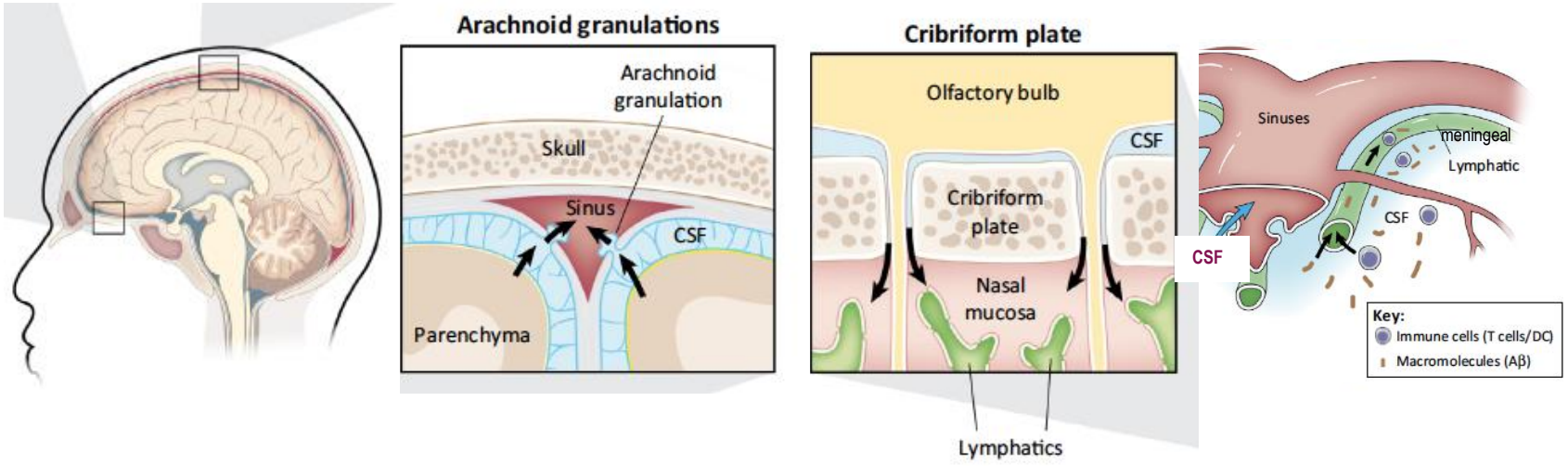
Interactions between brain resident cells and tumour cells promote BM growth pathways (example)

PTEN loss induced by astrocyte-derived exosomal microRNA primes brain metastasis outgrowth via functional cross-talk between disseminated tumour cells and brain metastatic microenvironment



CNS & IMMUNE SYSTEM

Paths of CSF drainage for macromolecules and immune cells

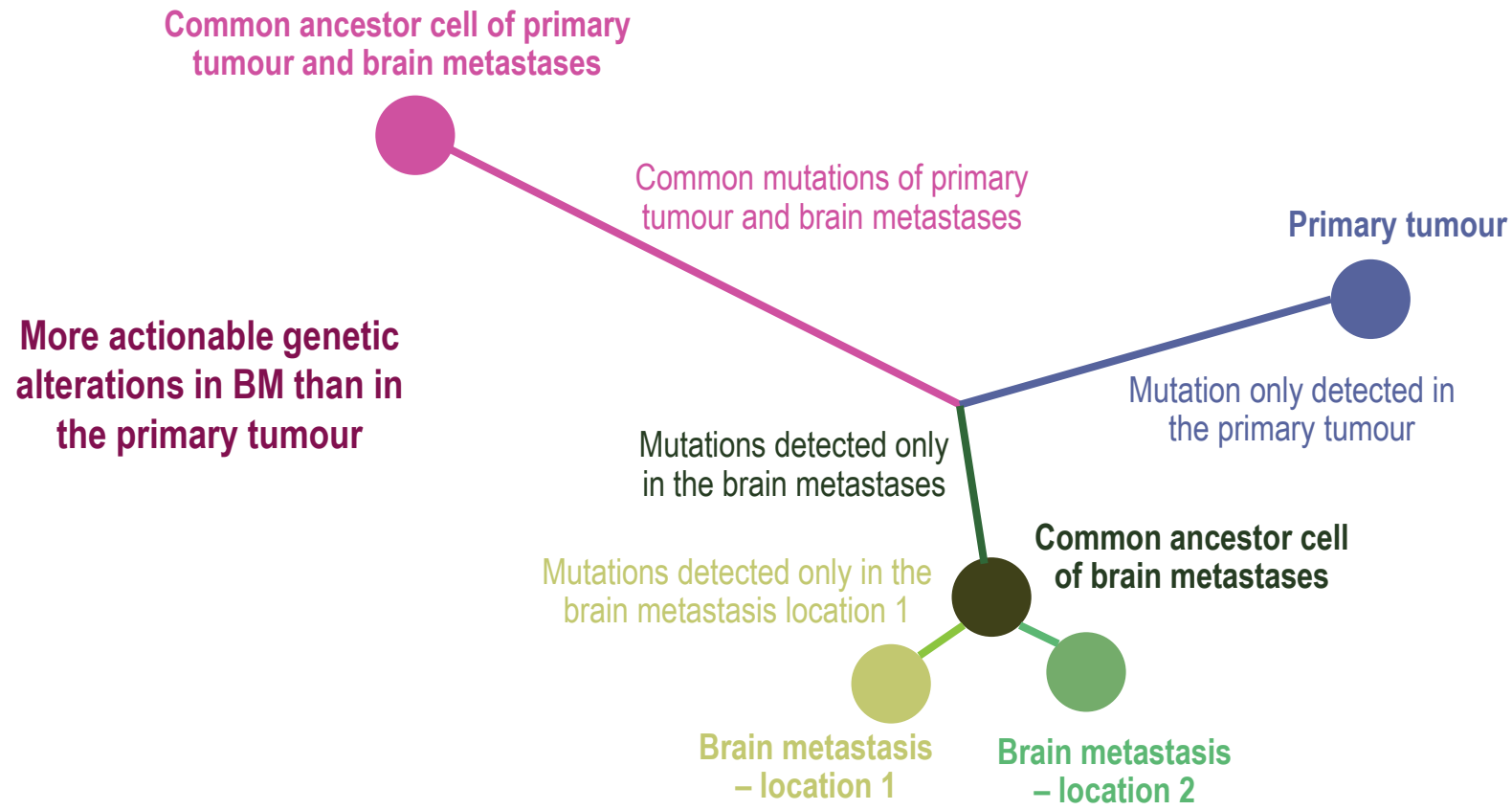


Immune cells can cross the BBB to gain access to the brain parenchyma and can leave the CNS during inflammation or tumour manifestation to reach the cervical lymph nodes

Reprinted from Trends in Immunology, 36(10), Louveau A,*et al*. Revisiting the Mechanisms of CNS Immune Privileger, 569–77, Copyright 2015, with permission from Elsevier.

BRANCHED EVOLUTION

Primary tumour and brain metastases



Berghoff AS, Brastianos PK. Seminar Neurol 2018;35:95–103.

CSF-DERIVED CIRCULATING TUMOUR DNA BETTER REPRESENTS THE GENOMIC ALTERATIONS OF BRAIN TUMOURS THAN PLASMA

N=12 patients (4 GBM, 6 BM from BC, 2 BM from LC)

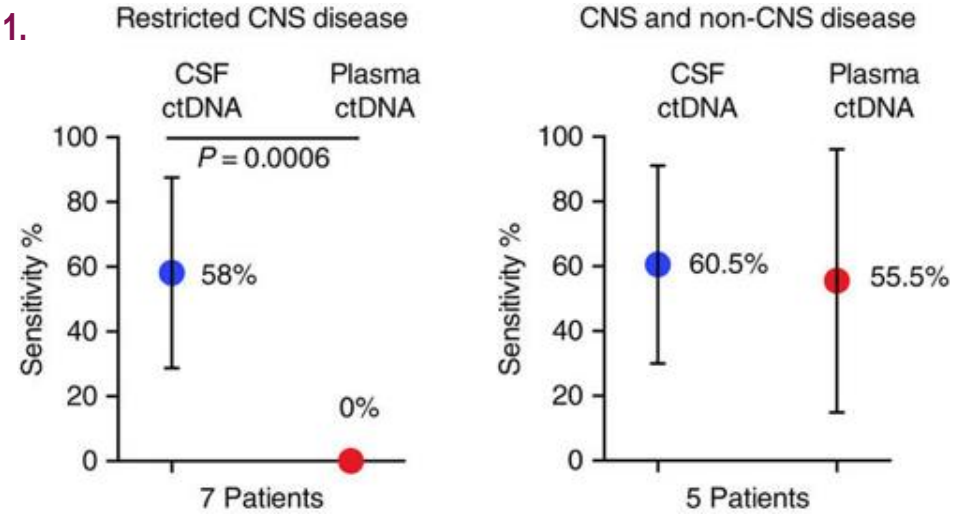
Methodology:

- Targeted capture massively parallel sequencing DNA samples from CNS tumours, non-CNS metastases, CSF and plasma samples as well as germline DNA MSK-IMPACT – 341 genes
- Exome (germline and tumour DNA)
- Droplet Digital (dd)PCR on CSF ctDNA and plasma ctDNA designed to specifically detect point mutations selected by exome sequencing

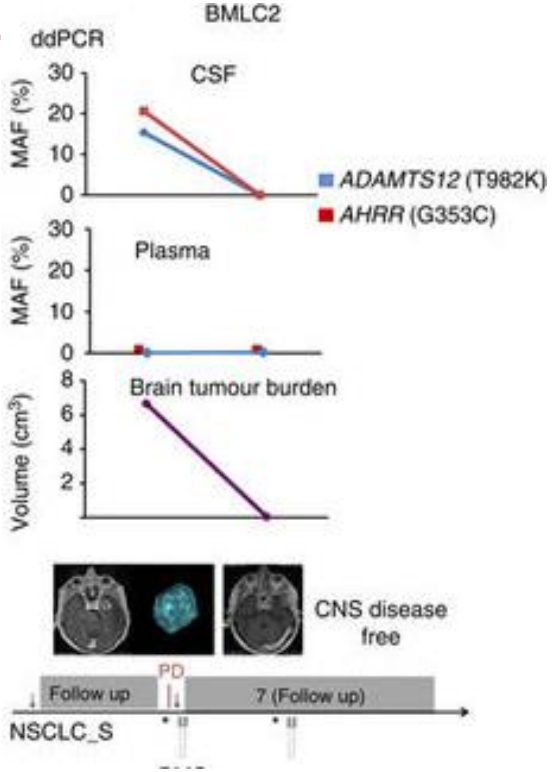
De Mattos-Arruda L, *et al.* Nat Commun 2015;6:8839.

CSF-DERIVED CIRCULATING TUMOUR DNA BETTER REPRESENTS THE GENOMIC ALTERATIONS OF BRAIN TUMOURS THAN PLASMA

1.



2.



1. ctDNA derived from CNS tumours is more abundantly present in the cerebrospinal fluid (CSF) than in plasma
2. CSF ctDNA levels longitudinally fluctuate in time and follow the changes in brain tumour burden providing biomarkers to monitor brain malignancies

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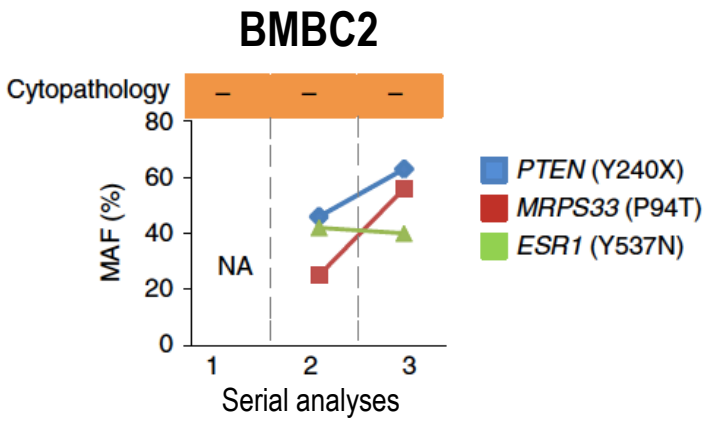
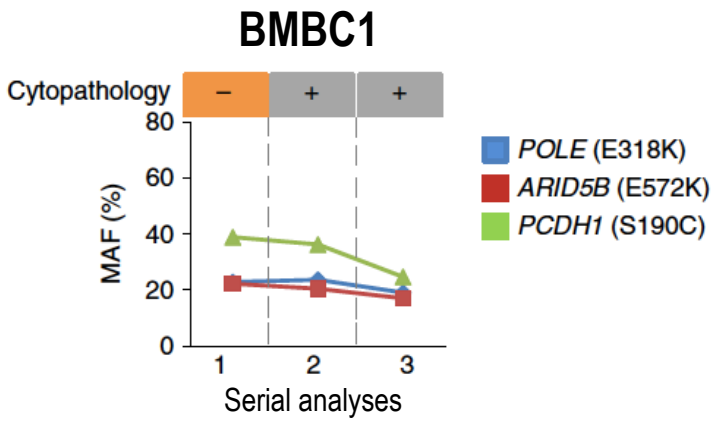
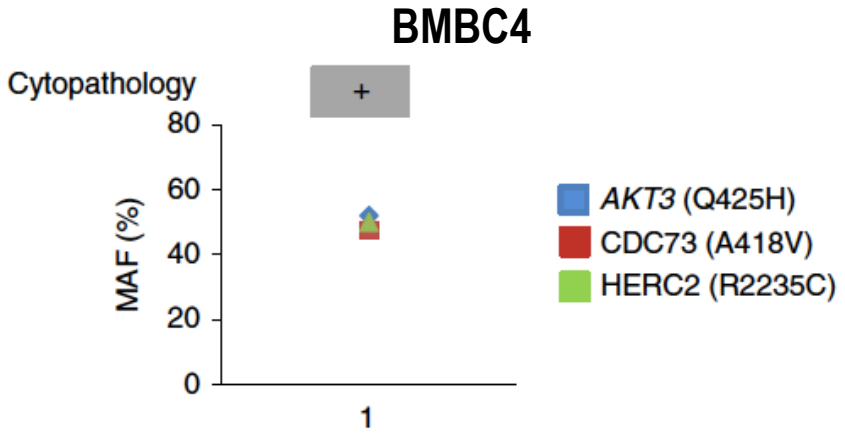
CSF CIRCULATING TUMOUR DNA COMPLEMENTS THE DIAGNOSIS OF LEPTOMENINGEAL METASTASES (LM)





Results build a proof-of-concept that opens the possibility to use CSF ctDNA to complement the diagnosis of LM



ct DNA circulating tumour DNA
MAF mutant allelic frequencies, measured by ddPCR
BMBC Brain metastases from three breast cancer patients (1,2,4)
NA not assesssed

3. PROGNOSTIC SCORES – DS-GPA (DISEASE SPECIFIC-GRADED PROGNOSTIC ASSESSMENT)

www.brainmetgpa.com

Guidance to estimate survival of patients with BM available for the following tumour entities:

- Lung cancer (including molecular marker)
- Melanoma (including molecular marker)
- Breast cancer (including molecular marker)
- Renal cell cancer
- Gastrointestinal cancer
- Sarcoma[1]

Sperduto P, *et al.* J Clin Oncol 2012;30(4):419–25
Sperduto P, *et a.l* J Clin Oncol 2020; 38(32):3773-84
[1]Patrikidou A, *et al.* BMC Cancer 2020;20:117

DISEASE SPECIFIC-GRADED PROGNOSTIC ASSESSMENT (DS-GPA)

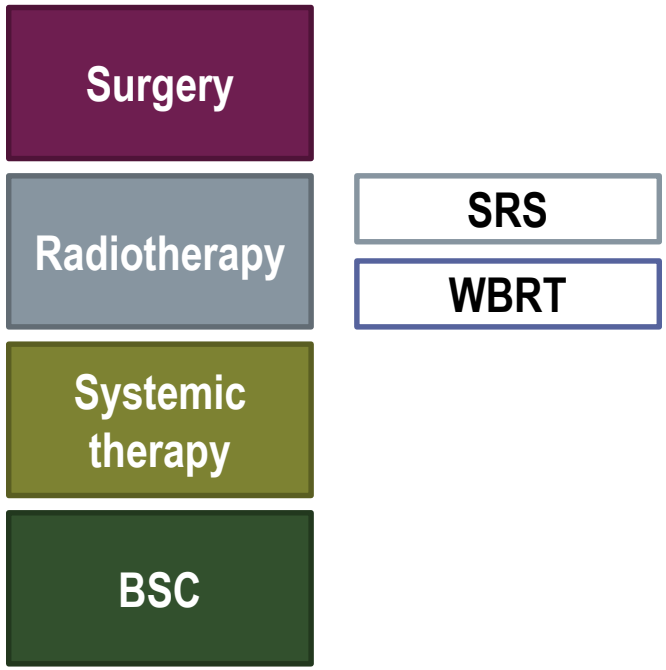
Summary of diagnosis-specific GPA indices, which estimates survival from brain metastases

Diagnosis	Prognostic factors	Median survival (mo)			
		GPA 0.0-1.0	GPA 1.5-2.0	GPA 2.5-3.0	GPA 3.5-4.0
Breast cancer	KPS Subtype (triple negative, HR+, HER2+, HR/HER2+) Age (y)	3.4	7.7	15.1	25.3
GI cancers	KPS	3.1	4.4	6.9	13.5
Melanoma	KPS Number of BM	3.4	4.7	8.8	13.2
NSCLC (adenocarcinoma)	Age (y) KPS Presence/absence of extracranial metastases Number of BM EGFR or ALK positive	6.9	13.7	26.5	46.8
NSCLC (nonadenocarcinoma)	Age (y) KPS Presence/absence of extracranial metastases Number of BM	5.3	9.8	12.8	N/A
Renal cell carcinoma	KPS Number of BM	3.3	7.3	11.3	14.8
SCLC	Age (y) KPS Presence/absence of extracranial metastases Number of BM	3.0	5.5	9.4	14.8

Sperduto P, *et al.* J Clin Oncol 2012;30(4):419–25; Sperduto P, *et al.* JAMA Oncol 2017;3(6):827–31

4. THERAPEUTIC OPTIONS FOR BM

THERAPEUTIC OPTIONS FOR BM



Depending on:

- Intracranial pressure
- Symptoms
- Number, size & site of metastases
- Extra-CNS disease control
- Performance status
- Sensitivity to systemic therapy
- Prognostic index: DS-GPA (disease specific-graded prognostic assessment)

Lin X, DeAngelis LM. J Clin Oncol 2015;33(30):3475–84.

LOCAL THERAPIES

Surgery and Stereotactic Radiotherapy (SRT)

Surgery is the most efficient method to immediately reduce mass effect and oedema from BM

For effective local control, surgery followed by SRT plays an integral role for oligometastatic BM

Repeat SRT may be offered for multiple BM

LOCAL THERAPEUTIC OPTIONS FOR BM

	SRS/SRT	Neursurgery	WBRT
Indication	Small lesions (up to 3 cm) and a limited number (<10)	Surgically accessible lesions Controlled extra-CNS disease Good PS Acute decompensation due to a significant mass effect	Multiple BM Leptomeningeal metastases Palliation (salvage RT)
Advantages	Better preservation of NC function compared to WBRT, no OS advantage for either radiation modality[1]	Tissue for histology	Significant risk for neurocognitive decline
Disadvantages	Will not treat microscopic tumour manifestation No tumour tissue collection	Not always appropriate in the palliative setting	Side effects

NC, neurocognition; WBRT, whole brain RT; SRS/SRT, stereotactic radio-surgery/ radiotherapy.
Adapted from Winkler, *et al.* ESMO 2018. 1. Brown P, *et al*. Lancet Oncol 2017;18(8):1049–60

LOCAL THERAPEUTIC OPTIONS FOR LEPTOMENINGEAL METASTASES (LM)

There are no randomised trials assessing efficacy and tolerance of RT in LM

Focal RT is an option for symptomatic nodular disease, to resolve CSF flow obstruction or hydrocephalus

WBRT may be considered for extensive nodular and symptomatic disease, coexistent BM and for palliation

Cerebrospinal RT is rarely an option due to its toxicity

Surgery is rarely an option, except for the insertion of a reservoir or ventriculo-peritoneal shunt

Adapted from E. Le Rhun, ESM0 2018. EANO-ESMO guidelines 2017

INTRATHECAL THERAPY FOR LM OF SOLID TUMOURS

There are no randomised trials assessing response to intra-CSF treatment for solid tumours *versus* best supportive care

Drug used intrathecally: Methotrexate, thiotepa, liposomal cytarabine (no longer available!), gemcitabine, etoposid, topotecan and the monoclonal antibody trastuzumab. The chemotherapeutic drugs are usually not first choice for the most common tumours with LM

Intra-CSF therapy has limited penetration (1-2 mm) in case of nodular disease, most drugs have a short half-life and are associated with considerable neurotoxicity, with the exception of trastuzumab[1]

Adapted from E. Le Rhun, ESM0 2018, EANO-ESMO guidelines 2017.
1. Bonneau C, *et al* EJC 2018, Zagouri F, *et al.* Cancer Treat Rev 2020.

SYSTEMIC THERAPY FOR BM

BM from highly chemotherapy-sensitive primary tumours (e.g. SCLC)

BM from primary tumours with identified molecular alteration, amenable to targeted therapy that cross the BBB (e.g. osimertinib for EGFRmut or alectinib for ALK altered NSCLC)

Asymptomatic BM found on screening MRI with planned systemic treatment

After exhaustion of other therapeutic options and availability of a drug (investigational or not)

Adapted from Lin, *et al*. J Clin Oncol 2015

TARGETED TREATMENTS FOR BM

	Treatment type	Trial (setting)	n	Intracranial ORR	Extracranial ORR
NSCLC					
EGFRm	Osimertinib	AURA3 (Stable asymptomatic CNSm)	116	70% MD, 40% NM/MD 30%	
		BLOOM (Confirmed LM)	32	91% MD , 66% NM/MD	
		FLAURA (Stable asymptomatic CNSm)	128		
ALK/ROS1	Ceritinib	ASCEND-7			
		Prior Brain RT, prior Alki (Alk-Inhibitor)	42	39%	31%
		Prior Alki only	40	27.6%	42.5%
		Prior Brain RT only	12	28.5%	41.7%
		Alki/RT naive	44	51.5%	61.4%
	Alectinib	ALEX (Stable asymptomatic CNS/LMm)	122	85.7%	
		(prior RT)		78.6%	
HER2+ BC					
	Lapatinib/capecitabine	LANDSCAPE (no prior WBRT)	45	65.9%	
	Neratinib/Capecitabine	TBRC 022 (prior RT allowed)	37	49%	
	Tucatinib/Trastuzumab/ Capecitabine	ONT 380 005 (including PD CNS)	23	42%	60%
		HERCLIMB ONT-380-206 (including PD CNS)	(480)	52% RR of PD	
Melanoma					
	Ipi/Nivo	Checkmate 204 (prior RT allowed)	94	57%	56%
		ABC trial (no prior RT)	25	44%	38%
BRAFm	Dabrafenib/Trametinib	COMBI-MB			
		V600E no prior RT	76	58%	55%
		V600E prior RT	16	56%	44%
		V600K/D/R	16	44%	75%
		V600 D/E/K/R	17	59%	41%

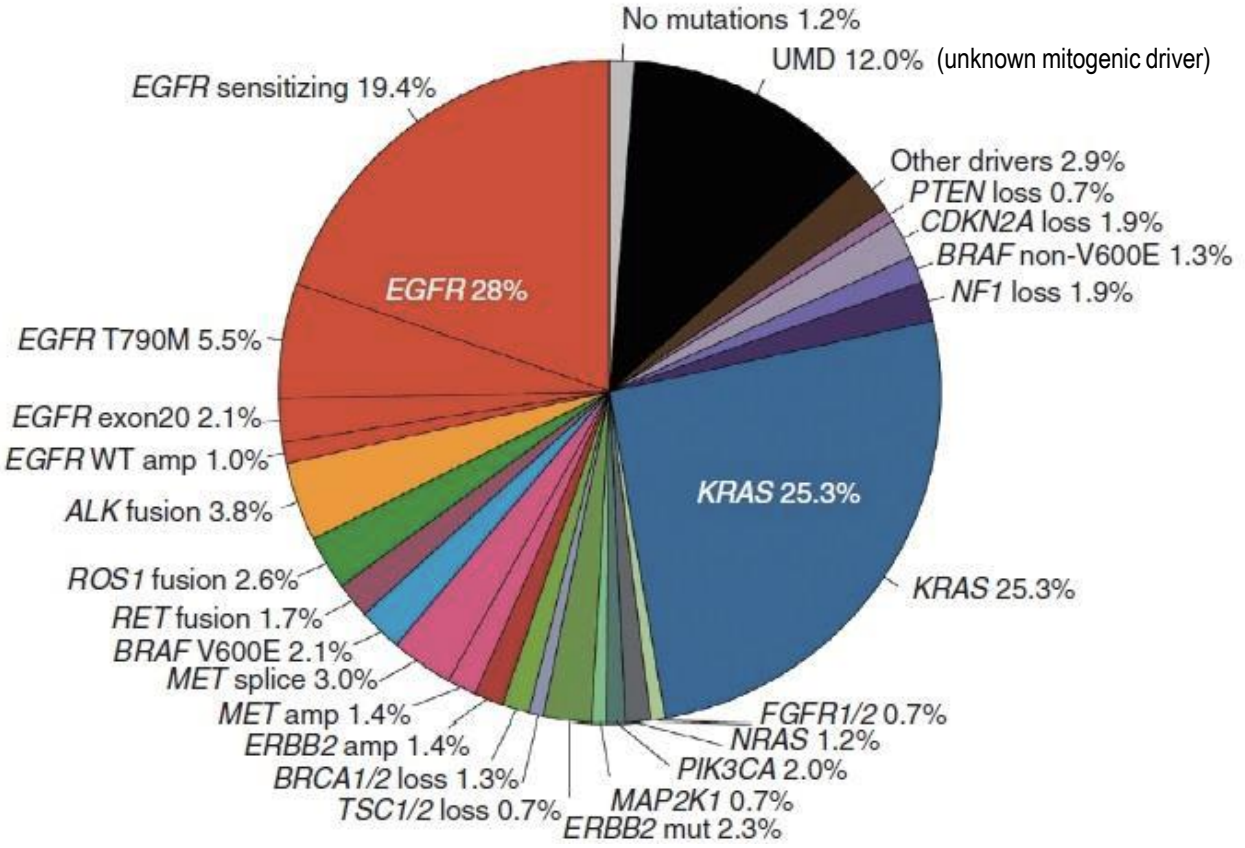
RT, Radiotherapy; CNSm, Central nervous system metastases; PD, Progressive disease; WBRT, whole brain radiotherapy; MD, mesurable CNS disease; NM/MD, non mesurable/mesurable CNS disease

5. TUMOUR AND MOLECULAR ENTITIES

LUNG

LUNG

Driver mutations in NSCLC adenocarcinomas



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Reprinted from Cancer Discov 2017;7(6):596–609, Jordan EJ, *et al.* Prospective Comprehensive Molecular Characterization of Lung Adenocarcinomas for Efficient Patient Matching to Approved and Emerging Therapies, with permission from AACR.

ESMO

LUNG

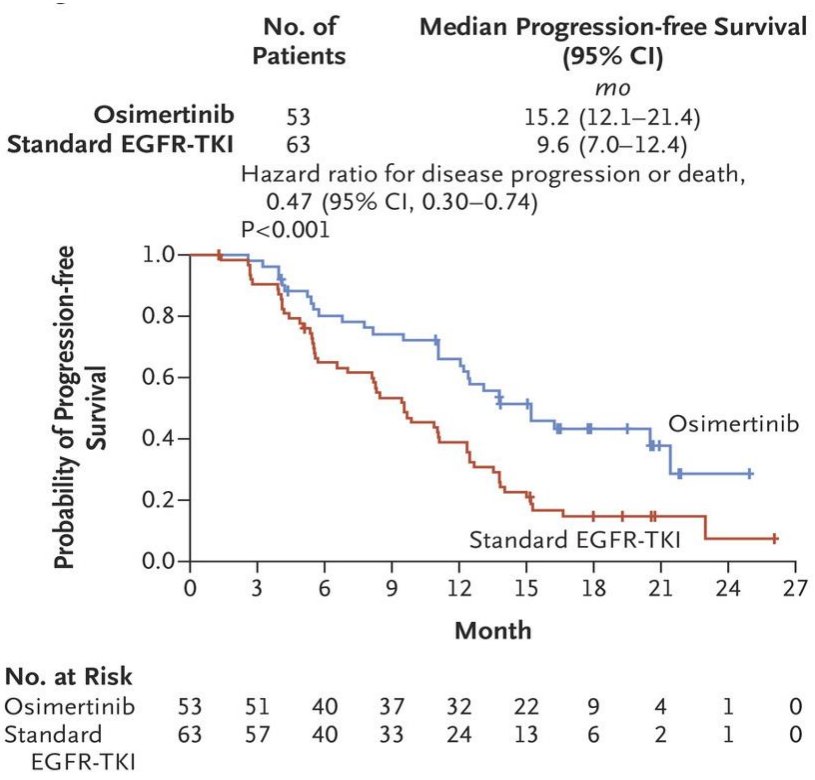
Systemic treatment options

- Asymptomatic patients with BM can be considered for systemic therapy
- For *EGFR*mut BM, first line osimertinib is the treatment of choice. EGFR-dependent & independent mechanisms of osimertinib failure e.g. MET alterations (7%–24%), EGFR C797X (0%–29%), SCLC transformation (2%–15%), and oncogene fusions (1%–10%) are the most common mechanisms of resistance. Circulating tumour (ct)DNA in the CSF is currently evaluated for monitoring
- The timing of additional SRT is not precisely defined; however, RT seems to play an essential role despite good responses to targeted therapies
- Alectinib is first choice for ALK– altered BM. On target mutations are common, in this case next generation ALK– inhibitors are recommended (e.g. lorlatinib)
- For RET– altered BM, selpercatinib seems promising with good brain penetrance
- Immunotherapies (IO) work in the brain as well as in the periphery, SRT may enhance the effect as might combination with chemotherapy (CT). Steroids required for BM, diminish effectiveness
- Patients with a good KPS and NSCLC without molecular alterations and those progressive on IO can be offered CT, which takes into account previous therapies and extra-CNS disease

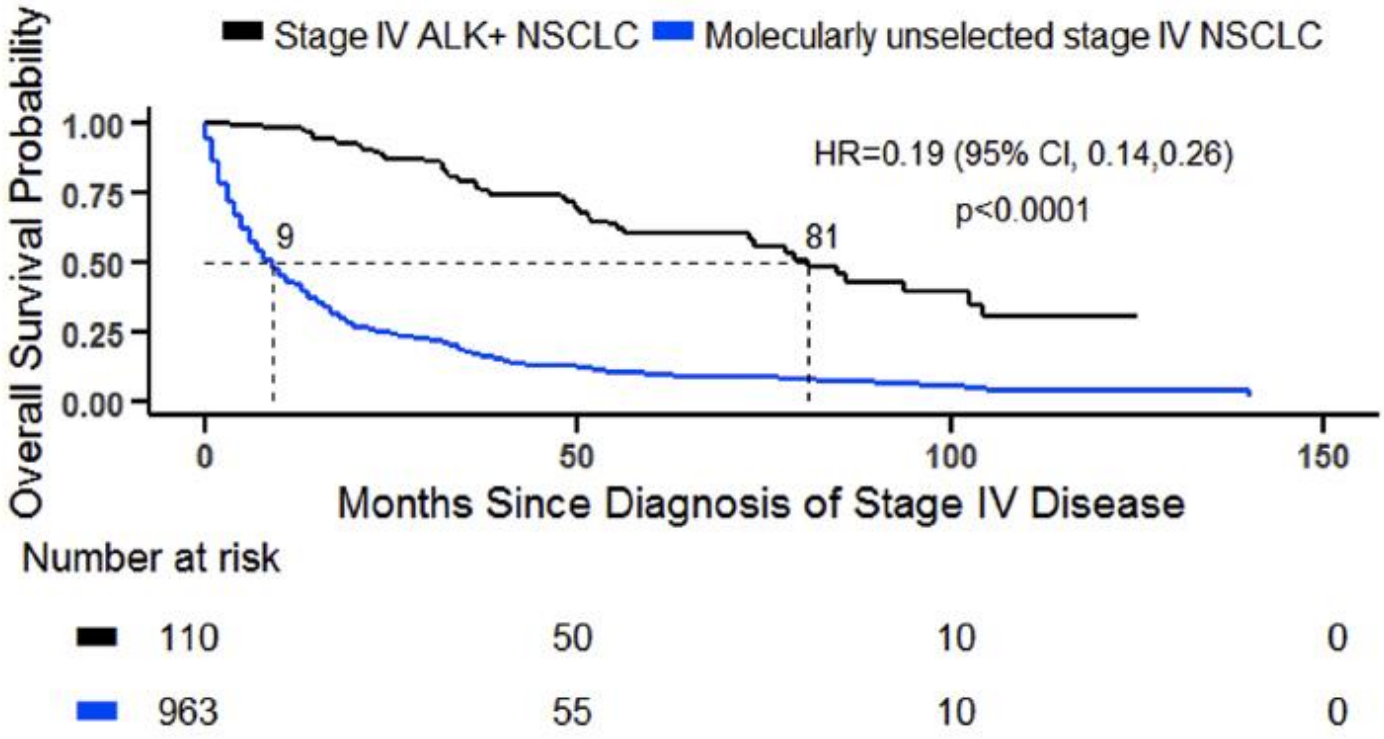
FLAURA TRIAL

Osimertinib in untreated *EGFR*$_{mut}$ advanced NSCLC

Progression-free survival in patients with CNS metastases



Median survival of NSCLC with and without ALK alterations



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LUNG ALK-POSITIVE NSCLC

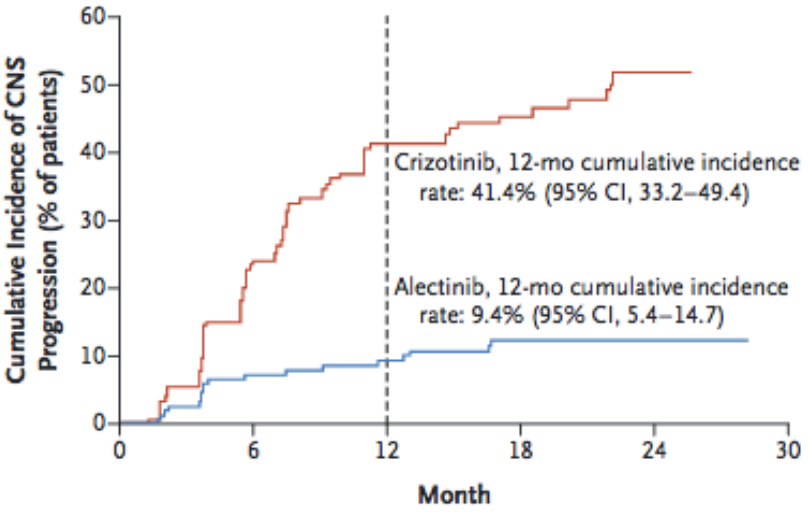
ALEX trial: Alectinib *versus* crizotinib first-line

CNS ORR
Measurable CNS lesions at baseline

	Crizotinib (n=22)	Alectinib (n=21)
CNS responders, n (%) (95% CI)	11 (50) (28, 72)	17 (81) (58, 95)
CNS complete response, n (%)	1 (5)	8 (38)
Median DOR in the CNS, months, (95% CI)	5.5 (2.1, 17.3)	17.3 (14.8, NR)

RR in the CNS of 81% with alectinib against 50% with crizotinib for measurable lesions

Cumulative incidence of BM



12% had an event of CNS progression with alectinib vs 68% with crizotinib

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Peters *et al.* ASCO 2017. From New Engl J Med, Peters S, et al. Alectinib *versus* Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer, 377(9), 829–38. Copyright ©2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

ESMO

BREAST

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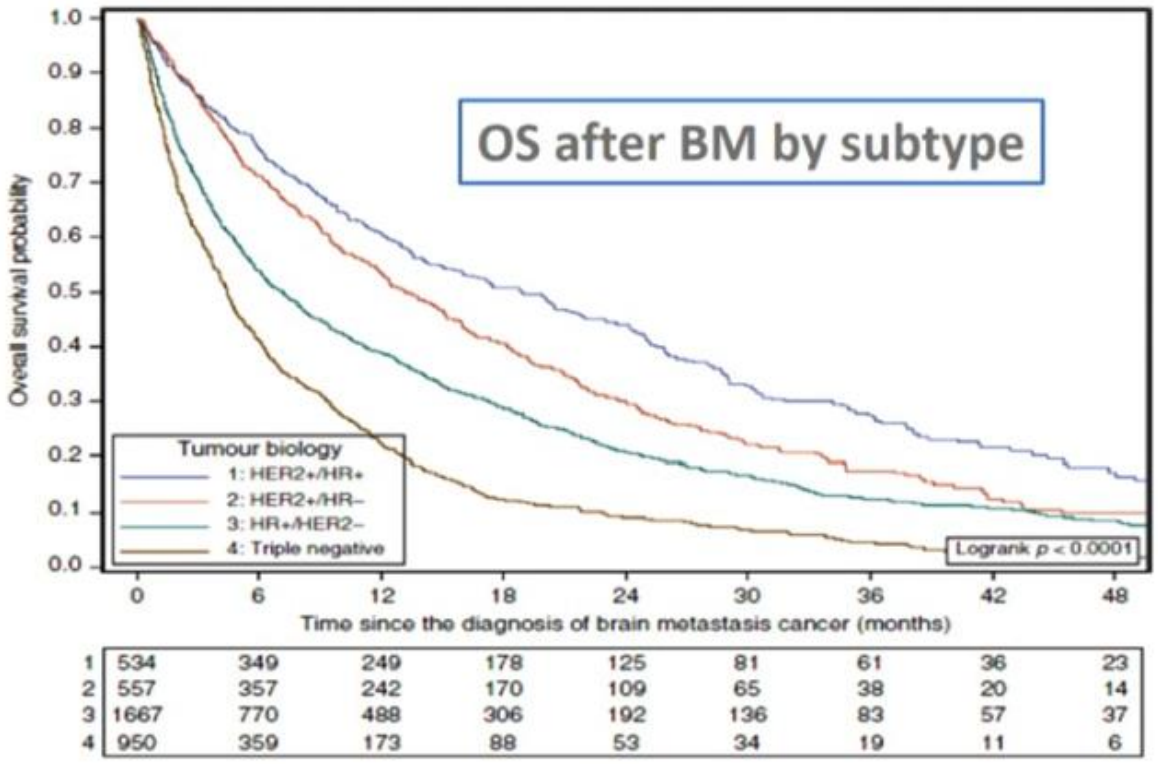
Survival probability according to breast cancer subtype



ER+ HER2+ => med. 19 months
ER- HER2+ => med. 13 months
ER+ HER2- => med. 7 months
ER- HER2- => med. 4.4 months

Darlix A, *et al*. Br J Cancer 2019;121(12):991–1000.

BREAST

Oestrogen-, Progesterone- and HER2- receptor discordance between primary tumour and BM

	1º tumour	BM	Gain
Hormone-receptors	Negative	Positive	25%
HER-2	Negative	Positive	13%

Adapted from Sperduto P, *et al.* Neuro-Oncol 2020;22(9):1359–67.

Emerging systemic therapies in HER2 positive breast cancer BM

Neratinib[1]: irreversible HER2/HER1 inhibitor

Tucatinib[2]: highly selective HER2 inhibitor

While both drugs are working effectively against BM, in combination with chemotherapy (capecitabine), tucatinib has a much safer side-effect profile and reaches median PFS of 7.6 months

1. Freedman RA, *et al.* J Clin Oncol 2019;37(13):1081–9. 2. Murthy RK, *et al.* N Engl J Med 2020;382(7):597–60.

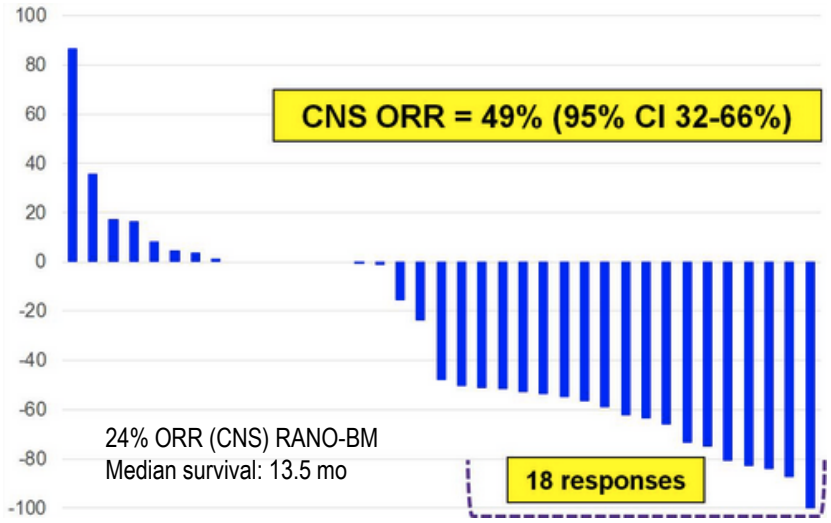
BREAST HER-2 POSITIVE
NERATINIB

Results of the Phase II TBRC 022 trial

Capecitabine/Neratinib cohort

- 39 patients with measurable BM from BC
- No prior lapatinib or capecitabine
- All but 3 had CNS PD after local CNS treatment

Best CNS volumetric response (n=31)*



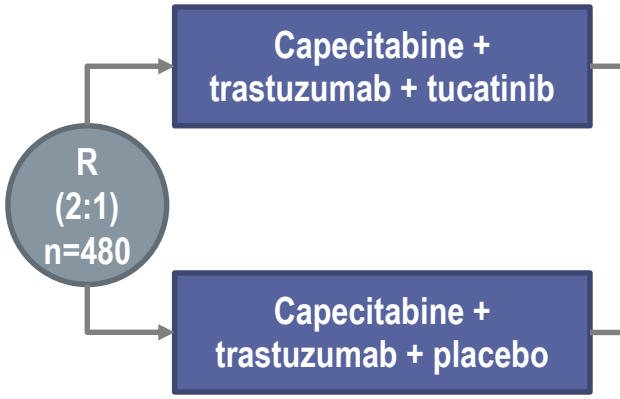
Freedman RA, *et al.* J Clin Oncol 2019;37(13):1081–9. Reproduced under the terms of the Creative Commons Attribution 4.0 License (available at: https://creativecommons.org/licenses/by/4.0/, accessed Oct 2020).

BREAST HER2 POSITIVE
TUCATINIB

HER2CLIMB study design

Eligibility criteria

- HER2+ metastatic breast cancer
- Stable or progressive brain metastases, or no evidence of CNS lesions
- Prior treatment with a taxane, trastuzumab, pertuzumab, or T-DMI1 allowed
- ECOG performance status of 0 or 1



Endpoints

Primary endpoint

- PFS

Secondary endpoints

- ORR, DOR, CBR, safety and tolerability

Therapies administered on 21-day cycle

- Tucatinib at 300 mg twice daily
- Capecitabine at 1000 mg/m^2 twice a day on Days 1 through 14 of each cycle
- Trastuzumab as a loading dose of 8 mg/kg, followed by 6 mg/kg once every 21 days; can be given weekly if needed to compensate for treatment modifications

Murthy RK, *et al.* N Engl J Med 2020;382:597-609

HER2CLIMB PRIMARY ANALYSIS RESULTS

TUCATINIB

The HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis

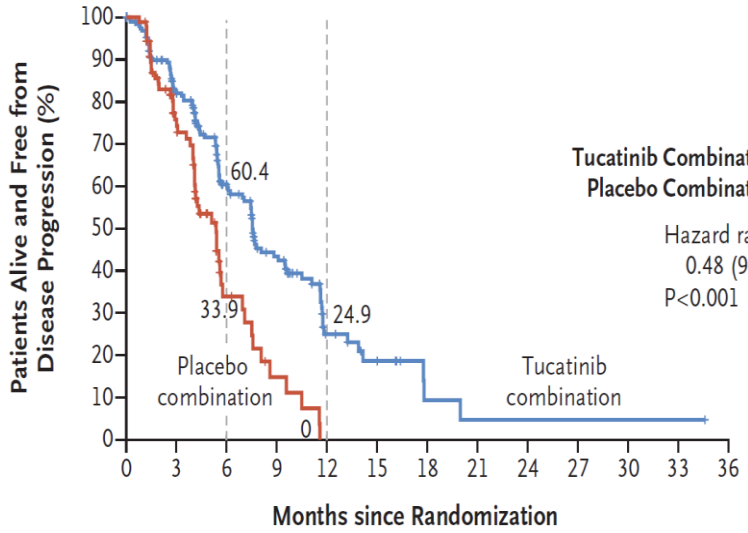
Importantly, the secondary endpoint of PFS in patients with brain metastases was met

PFS by BICR N=480*	Overall survival N=612	PFS by BICR in patients with brain metastases N=291
Risk of progression or death was reduced by ↓ 46%	Risk of death was reduced by ↓ 34%	Risk of death was reduced by ↓ 52%
95% CI: 0.42 to 0.71, P<0.001	95% CI: 0.50 to 0.88, P=0.005	95% CI: 0.34 to 0.69, P<0.001

PFS, progression-free survival; BICR, blinded independent central review.
*The primary endpoint of PFS was assessed in the first 480 patients.
Murthy RK, *et al.* N Engl J Med 2020;382:597–609. Murthy RK, ASCO 2020, Abs #1005.

PROGRESSION-FREE SURVIVAL* IN PATIENTS WITH BRAIN METASTASES

Alpha-controlled secondary endpoint in the HER2CLIMB trial



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	106/198	7.6 (6.2–9.5)
Placebo Combination	51/93	5.4 (4.1–5.7)

Hazard ratio for disease progression or death, 0.48 (95% CI, 0.34–0.69)
P<0.001

No. at Risk													
Tucatinib combination	198	144	78	45	14	8	2	1	1	1	1	1	0
Placebo combination	93	49	12	4	0	0	0	0	0	0	0	0	0

Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

One-year PFS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
25% (17, 34)	0%
Median PFS (95% CI):	
7.6 months (6.2, 9.5)	5.4 months (4.1, 5.7)

Prespecified efficacy boundary for PFS-brain metastases (P=0.0080) was met at the first interim analysis. Data cut off: Sep 4, 2019

Whether tucatinib might delay additional SRS or salvage WBRT will have to be evaluated

*PFS, defined as time from randomisation to documented disease progression (assessed by blinded independent central review) or death from any cause. Analysis does not include patients with dural lesions only.

BREAST HER-2 POSITIVE

Phase I feasibility study for intrathecal (IT) administration of Trastuzumab for HER-2 positive leptomeningeal disease

N=16

No DLT of IT trastuzumab

Eleven patients had no toxicity attributed to IT trastuzumab.

Three patients achieved a clinical response, seven patients had stable disease and four patients had PD

Conclusions

The MTD and recommended Phase II weekly dose of IT trastuzumab in patients with HER2-BC and MC is 150 mg. Phase II using this dose regimen in MC from HER2-BC is ongoing.

Comments[1]

IT trastuzumab in a 3-week schedule at a dose of 150 mg should be sufficient to treat HER2-positive non-bulky LM due to PK and outcome in a small series (n=3).

Intravenous trastuzumab may be omitted to control extra-CNS disease, since high systemic concentrations of trastuzumab could be measured by IT administration alone

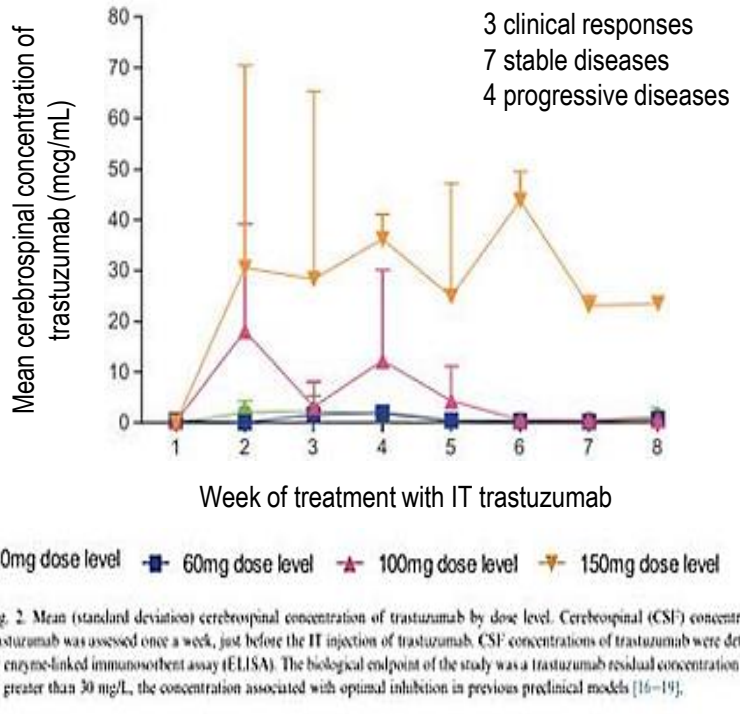


Fig. 2. Mean (standard deviation) cerebrospinal concentration of trastuzumab by dose level. Cerebrospinal (CSF) concentration of trastuzumab was assessed once a week, just before the IT injection of trastuzumab. CSF concentrations of trastuzumab were determined by enzyme-linked immunosorbent assay (ELISA). The biological endpoint of the study was a trastuzumab residual concentration equal to or greater than 30 mg/L, the concentration associated with optimal inhibition in previous preclinical models [16–19].

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Reprinted from European Journal of Cancer, 95, Bonneau C, *et al.,* Phase I feasibility study for intrathecal administration of trastuzumab in patients with HER2 positive breast carcinomatous meningitis, 75–84, Copyright 2018, with permission from Elsevier; 1. Hofer S,and Aebi S, EJC 2018 (comments).

ESMO

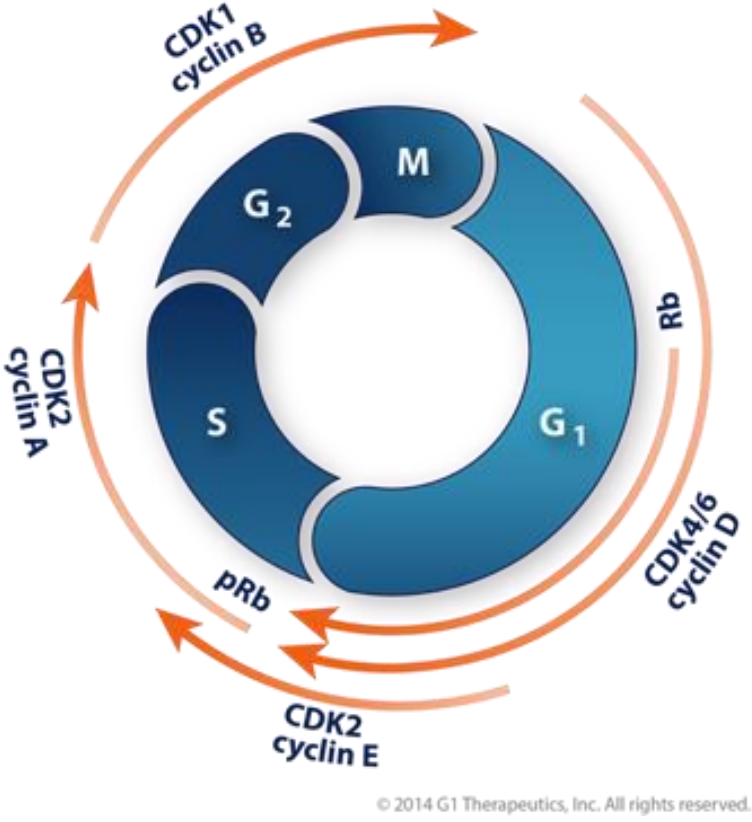
BREAST
CDK 4/6 INHIBITORS

Abemaciclib

Abemaciclib is a selective CDK4/6 inhibitor

It crosses the BBB and reaches concentrations that are 10x higher than palbociclib

Effective against BM in xenograft models



Raub TJ, *et al*. Drug Metab Dispos 2015;43(9):1360–71; Figure from G1 Therapeutics. Presentation for Wedbush PacGrow Healthcare Conference; August 15, 2017. ©2014. All rights reserved.

BREAST
CDK 4/6 INHIBITORS
Abemaciclib

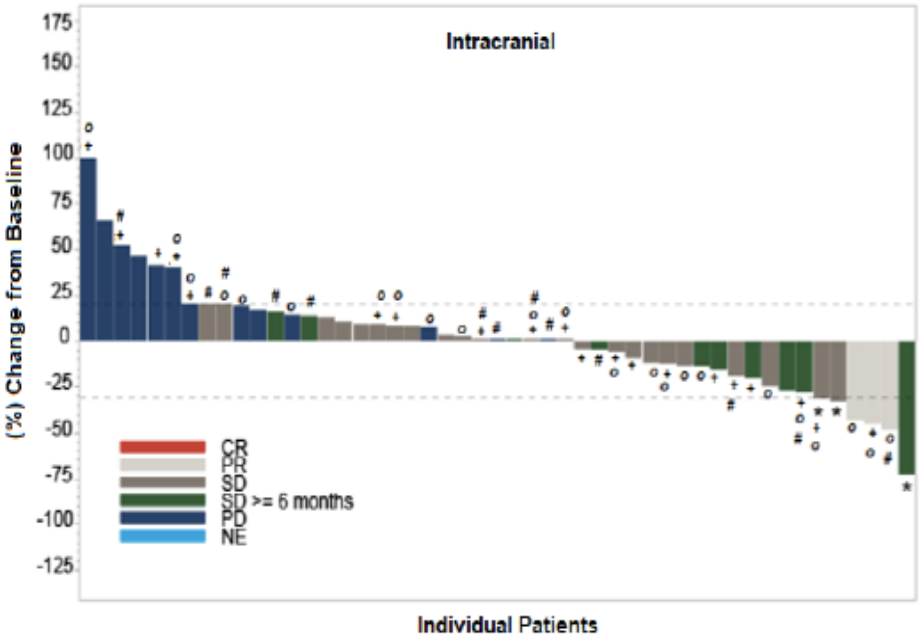
Phase 2 trial for Hormone-Receptor positive (HR+) mBC

Cohort A: HR+, HER2- (n=58)

Cohort B: HR+, HER2+(n=27)

Cohort C: HR+, LM (n=10)

Primary endpoint: Intracranial ORR was not met. Intracranial clinical benefit rate of 24% in patients with heavily pretreated HR+, HER2– mBC



ºPrior WBRT; *tumour shrinkage, no PR; #concomitant endocrine therapy.

Reprinted from Clin Cancer Res 2020;26(20):5310–9, Tolaney S, *et al.* A Phase II Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor–Positive Breast Cancer, with permission from AACR.

BREAST

Triple negative (TN)

Chemotherapy such as paclitaxel, eribulin, capecitabine, anthracyclins, vinorelbine platins may work

Trials with Immunotherapy, PARP inhibitors and antibody-drug conjugates are ongoing

MELANOMA

MELANOMA

Immunotherapy (IO) and BM

Best results with IO doublets (Checkmate 204[1]) nivolumab and ipilimumab

Patients not in need of steroids fare better[1,2]

Sustainable remissions could be achieved (i.e. ORR up to 59%[3]), comparable to effects in the periphery[1,2]

TKI-naive patients show better results (ABC trial[3])

1. Tawbi H, *et al*. NEJM 2018; 2. Long G, *et al*. Lancet Oncol 2018; 3. Long G, *et al*. ESMO 2019.

MELANOMA

BRAF^{V600} mutant

High concordance of *BRAF*^{V600} mutations in CNS and primary tumour

Dabrafenib plus trametinib are working fast and achieve response rates up to 60% (COMBI-MB[1]), the same holds true for newer TKI combinations

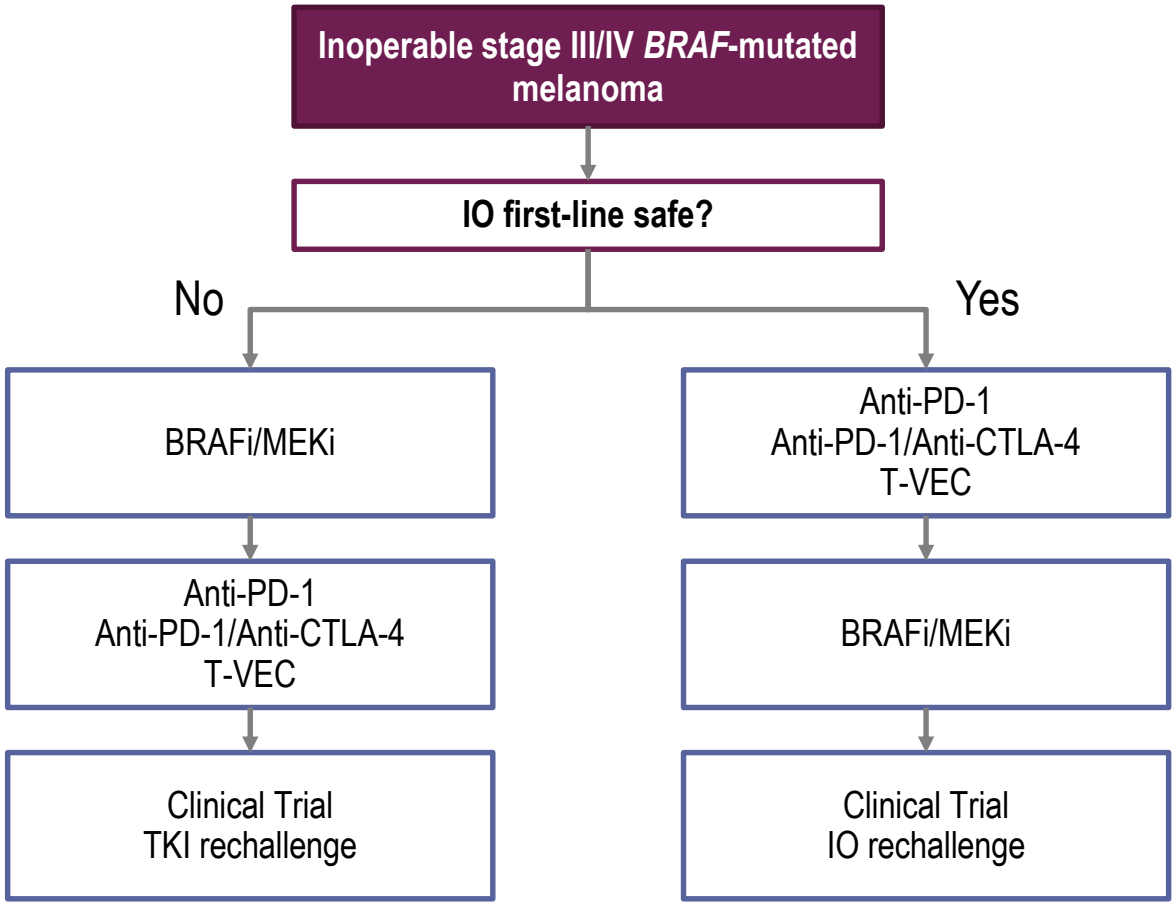
While ORRs in the CNS are similar to the periphery, duration of response in CNS is less sustained (median duration 6–8 mo vs 6– >10 mo)

Current trials are exploring triplets (TKI combinations plus IO) remission rates are expected to increase, as will grade 3 and 4 toxicities

1. Davies M, *et al.* Lancet Oncol 2017.

MELANOMA

Treatment algorithm



Michielin O, *et al.* Ann Oncol 2019;30:1884–901.

MELANOMA
SYSTEMIC TREATMENTS FOR BM

	Treatment type	Trial (setting)	n	Intracranial ORR	Extracranial ORR
Melanoma					
Immunotherapy	Ipi/Nivo	[1]**Checkmate 204** (Prior RT allowed)	94	57%	56%
		[2]**ABC trial** (No prior RT)	25	44%	38%
***BRAF*$_{mut}$**	Dabrafenib/ Trametinib	[3]**COMBI-MB**			
		V600E no prior RT	76	58%	55%
		V600E prior RT	16	56%	44%
		V600K/D/R	16	44%	75%
		V600 D/E/K/R	17	59%	41%

1. Tawbi H, et al. NEJM 2018; 2. Long G, et al. Lancet Oncology 2018; 3. Davies M, *et al*. Lancet Oncology 2017.

IMMUNE CHECK-POINT(S) IN BM

Authors	Phase	No. of pts	Tumour types	Characteristics	Treatment(s)	CNS ORR
Goldberg, *et al.* ASCO 2017	II	18 18	A. Melanoma B. NSCLC	At least 1 untreated or progressive BM	Pembrolizumab	A: 22% B: 33%
Margolin, *et al.* Lancet Oncol 2012	II	72	Melanoma	Cohort A: neurologically asymptomatic Cohort B: neurologically symptomatic and on a stable dose of corticosteroids	Ipilimumab	A: 24% B: 10%
Tawbi, *et al.* Checkmate 204	II	75	Melanoma	Asymptomatic/non pretreated BM	Ipilimumab + nivolumab	56%
Long, *et al.* ASCO 2017 ABC trial	II	66 A: 25 B: 25 C: 16	Melanoma	Cohort A/B: Asymptomatic/ non pretreated BM Cohort C: failed local therapy, neurologically symptomatic and/or with LM involvement	Ipilimumab + nivolumab (Cohort A/B) Nivolumab (Cohort C)	A: 42% B: 20% C: 6%
Escudier, *et al.* ASCO 2017	II	44/58 8	mRCC	BM previously treated or not, but not requiring steroids	Nivolumab	23%

Courtesy of Mariana Brandao, Institut Jules Bordet, Brussels

BEVACIZUMAB IN BM

Positive effects due to reduction of brain oedema, reduction of steroid use

Potential of synergy with Immunotherapy

Improvement of symptomatic radiation necrosis

INNOVATIVE TREATMENT STRATEGIES

Focus on prevention endpoints

Current failure rates of available treatments

Early detection strategies

Primary prevention

- Predictive biomarkers for BM (ctDNA, CTC, homing signatures)

Use of effective screening tools: treat before symptoms and deterioration of QoL

Secondary prevention: avoid the next CNS event

Based on better knowledge of pathogenesis of brain metastasis (e.g. Brainstorm program – https://clinicaltrials.gov/ct2/show/NCT04109131)

6. SUMMARY

Brain metastases (BM) are an increasing challenge confronting multiple disciplines

Development of effective therapies to treat BM requires greater understanding of the means by which metastatic cells adapt to the distinct metabolic, chemical, and cellular composition of the brain microenvironment

Likewise, greater insight is needed into the mechanisms blocking passage of therapeutic agents across the BBB, as well as into the immunologic proclivities of the brain microenvironment and the immune-evasive strategies implemented by BM

BBB, blood-brain barrier