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Tackling the challenge of CNS metastases
The BrainStorm Program

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BSMO 22.11.2019

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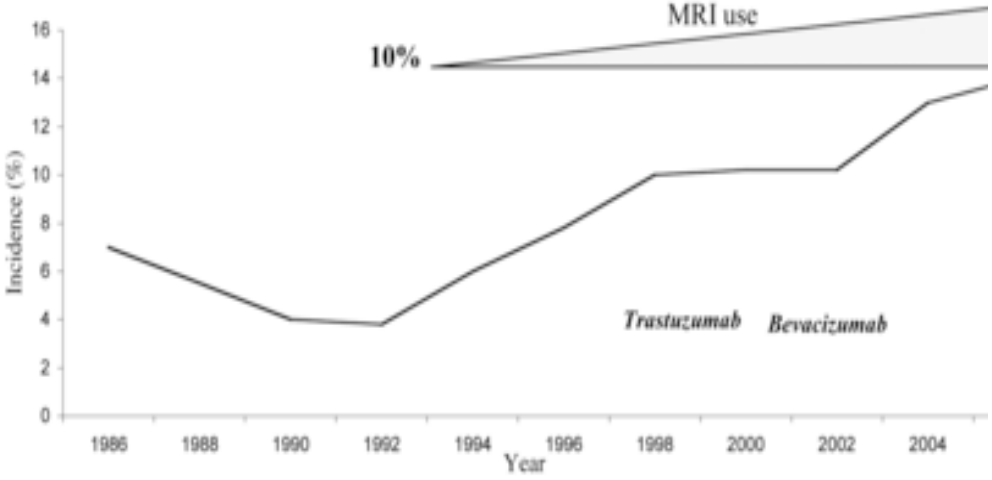
Disclosures:

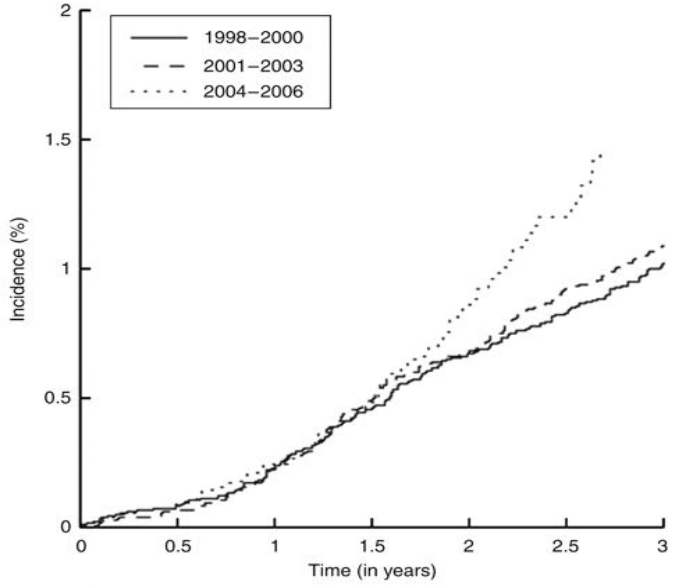
- Seattle Genetics, BMS, Puma Biotechnologies, Lilly, Astra Zeneca

CNS METASTASES: an increasing issue



Incidence of brain metastasis from 1986 to 2006

Smedby *et al*. Br J Cancer 2009, Nieder *et al.* Cancer 2010, Tabouret *et al.* Anti cancer research 2012



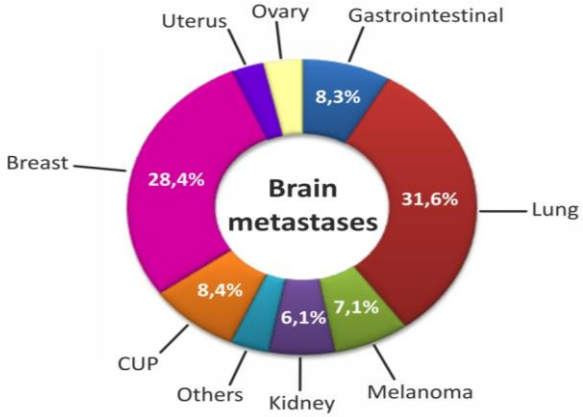
Cumulative incidence of admissions for BM in pts BC pts from 1998 to 2006 in Sweden

Frisk et al, Br J Cancer 2012

BRAIN METASTASIS IN SOLID TUMORS

	Median time to BM (mo)	Incidence	Median survival
Breast cancer		12-17%	3-25 months
- Subtypes -			
Triple negative	27.5	25-27%	7.3 months
Her2/neu	35.8	11-30%	17.9 months
Luminal A	54.4	8-15%	10 months
Luminal B	47.4	11%%	23 months
Lung cancer			
NSCLC		13-30%	4-16 months
EGFRm, ALK +			4-18 months
SCLC		50%	3-4 months
Melanoma		15-50%	4-8.3 months

Most common CNS tumors in adults



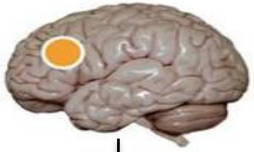
Preusser et al, Acta Neuropathol 2012

Adapted from:
Taillibert *et al.* Cancer/Radiotherapie 2015
Witzel et al.BreastCancerResearch (2016) 18:8
Sperduto et al. Journal of Neuro Oncol. 2013

BRAIN METASTASIS IN SOLID TUMORS

- Incidence of CNS metastases is increasing and prognosis remains poor
- The epidemiology data currently available are unclear and sometimes contradictory
- To date, there is no prospective database to obtain reliable information in the field.

Current therapeutic options for BM



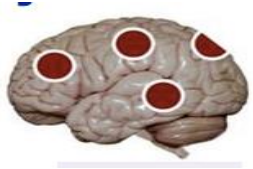
Singular

Surgery or SRS

Consider adjuvant SRS/local RX

Small, no critical location, clinical asymptomatic

Follow course under new systemic therapy if likely to be brain-active



Up to 4

> 4

Multiple

Surgery or SRS

WBRT

Consider adjuvant WBRT

Progression

Adapted from F.Winkler ESMO 2018

Surgery or Radiosurgery
WBRT if multiple
Systemic therapy
BSC

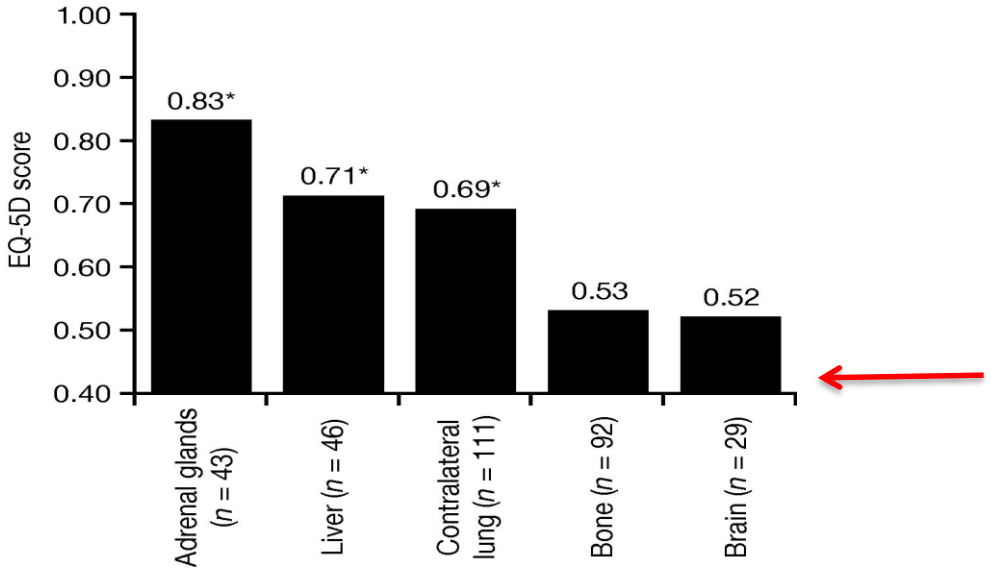
Depending on:

- Performans status
- Number, size and site of metastases
- Extra-CNS disease control
- Prognostic index (GPA/RPA)

Systemic treatments for BM ?

	Treatment type	Trial (setting)	n =	Intracranial ORR	Extracranial ORR
NSCLC					
EGFRm	Osimertinib	AURA3 (Stable aS CNS) BLOOM (Confirmed LM) FLAURA (Stable aS CNSm)	116 32 128	**70% (efr))40% (Fas)** **30%** **91% (mes.d) 68%**	
ALK/ROS1	Ceritinib	ASCEND-7 *Prior Brain RT Prior Alki* *Prior Alki only* *Prior Brain RT only* *Alkl/RT naive*	 42 40 12 44	 **39%** **27.6%** **28.5%** **51.5%**	 31% 42.5% 41.7% 61.4%
	Alectinib	ALEX (Stable aS CNS/LMm) (prior RT)	122	**85.7%** **78.6%**	
HER2BC					
	Lapatinib/capecitabine	LANDSCAPE (no prior WBRT)	45	**65.9%**	
	Neratinib/Capecitabine	TBRC 022 (prior RT allowed)	37	**49%**	
	Tucatinib/herceptine/Capecitabine	ONT 380 005 (including PD CNS) HERCLIMB ONT-380-206 (including PD CNS)	23 (480)	**42%** **52% RR of PD**	60%
Melanoma					
	Ipi/Nivo	Checkmate 204 (Prior RT allowed) ABC trial (No prior RT)	94 25	**57%** **44%**	56% 38%
BRAFm	Dabrafenib/trametinib	COMBI-MB *V600E no prior RT* *V600E prior RT* *V600K/D/R* *V600 D/E/K/R*	 76 16 16 17	 **58%** **56%** **44%** **59%**	 55% 44% 75% 41%

IMPACT OF BM IN QOL DUE TO BM AND TREATMENT



Peters et al. Cancer treat Rev 2016

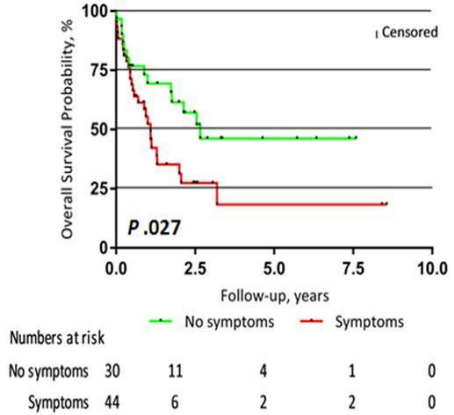
QoL and neurocognition is often impaired in pts with BM compared to extra-CNS M+

Value of early detection of CNS metastases ?

Local Treatment Approaches for the First BM

Treatment modality	Asymptomatic patients (n = 30) No. (%)	Symptomatic Patients (n = 44) No. (%)	*P* Value
WBRT	15 (50)	31 (70.5)	.075
SRS	15 (50)	9 (20.5)	.0077
WBRT+SRS	4 (13.3)	2 (4.6)	.17
Surgery	2 (6.7)	9 (20.5)	.11
None	4 (13.3)	5 (11.4)	.8

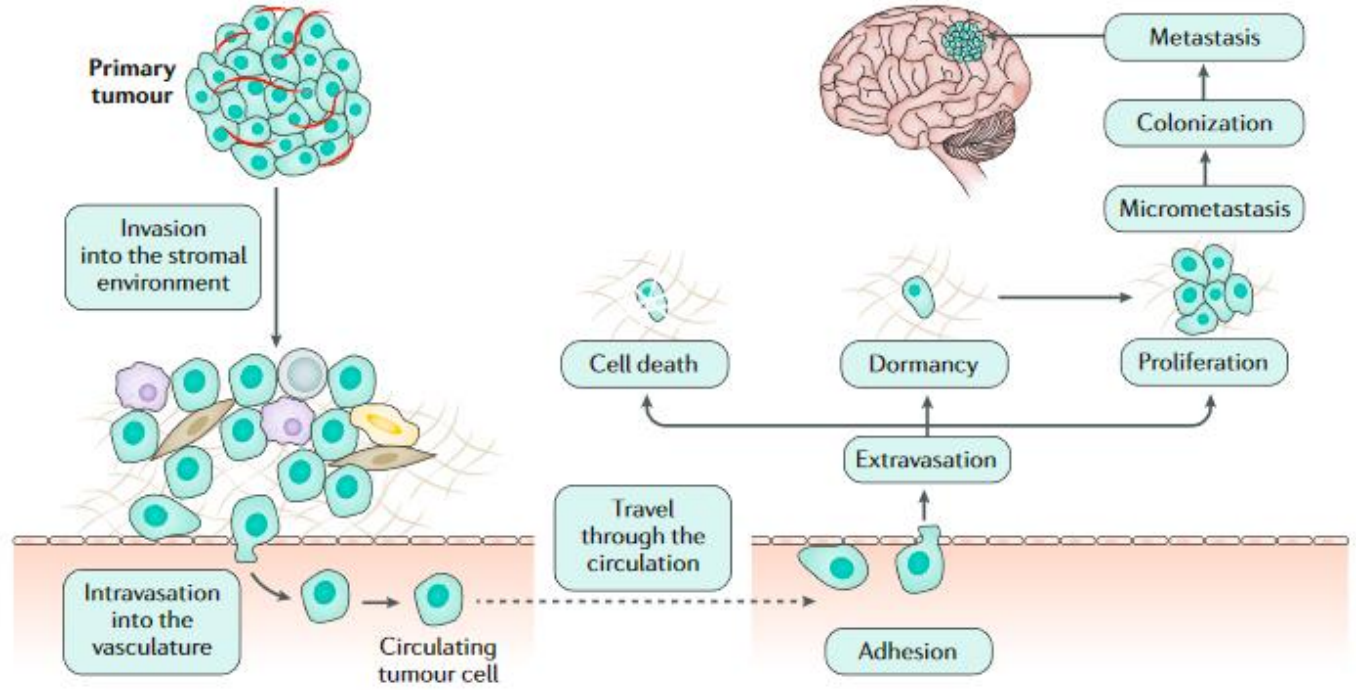
OS Estimates according to Clinical Symptoms related to 1st BM



- Early detection of CNS metastases using systematic Brain MRI screening in HER2+BC has not yet proven to improve outcome.

- Recent retrospective study results are suggesting a clinical impact of detecting asymptomatic BM in patients with HER2^{+} BC in terms of avoidance of further invasive local treatment including WBRT.

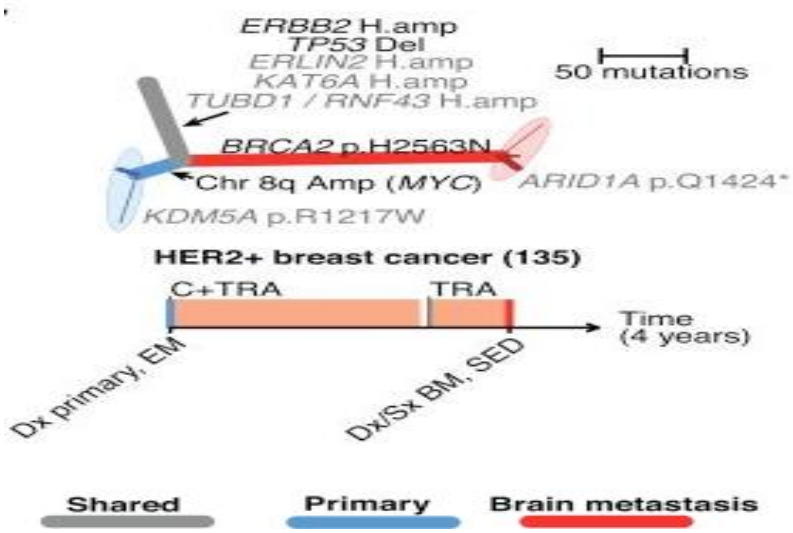
The pathogenesis of BM has not been completely characterized …



Achrol AS et al. Nat Rev Dis Primers. 2019

Heterogeneity between the primary tumor and the BM

Brastianos et al. Cancer Discovery 2015

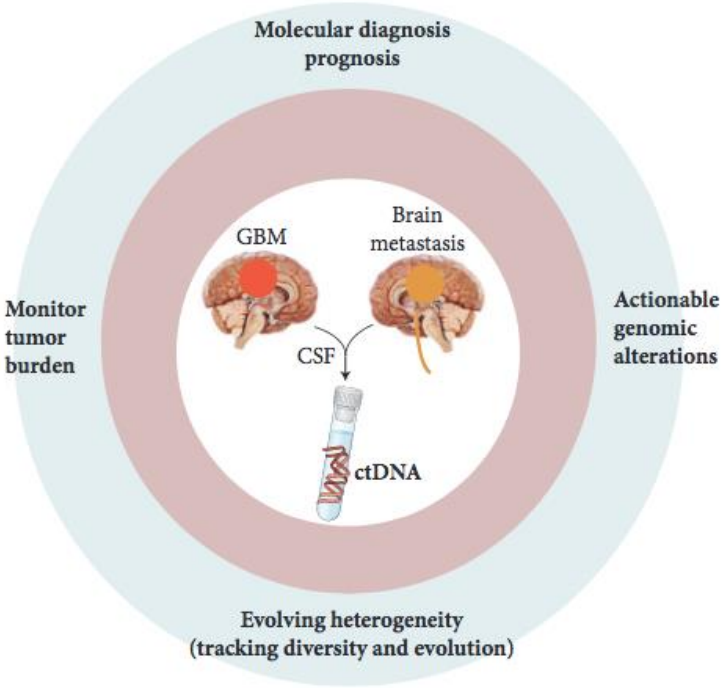


WES of 86 matched BM with primary tumors and normal tissue.

BM share alterations that are not necessarily detected in primary tumors, regional lymph nodes, or extracranial metastases

Primary tumor or extracranial metastatic site genotyping can miss actionable oncogenic driver mutations…

Brain biopsies are often considered as an invasive approach: **CSF ctDNA as a surrogate for BM DNA ?**



Seone et al, Annals of oncol 2019

Studies on cfDNA sequencing in CSF of CNS metastases

Study	Site of CNS malignanvy	n	Primary	Biological fluid sampled	Sequencing method	CNS malignancy mutation detection rate
Swinkels et al, 2000	LM	2	Lung ADK	CSF	Mutation allele-specific amplification (PCR)	KRAS mutation detectable in CSF (2/2) (100%)
De Mattos et al, 2015	P	12	6 BC, 2 LC, 4 GBM	CSF, Plasma	Targeted sequencing 341 genes	CNS disease only 58% CSF, 0% plasma, CNS / Non CNS disease 60% CSF, 55.5% plasma
Momtaz et al, 2016	P, LM	11	Patients with BRAFm malignancies	CSF	Targeted sequencing	BRAFm 6/11 54%
Pentsova et al; 2016	P, LM	41	11 LC, 11 BC, 6 melanome, 1 BC, 2 GI, 2 OC, 1 NE, 2 Thyroide, 2 CRPC, 2 RCC, 1 sarcoma	CSF	Targeted sequencing	Mutations detectable in CSF 20/32 (63%) with BM and ¾ (75%) pts with LM
Marchio et al, 2017	LM	2	Lung ADK	CSF, plasma	Targeted sequencing	Kras mutation in the CSF (2/2 -100%)
Siravegna et al, 2017	P	1	HER2+ breast CSF adenocarcinoma	CSF plasma	ddPCR	ERBB2, CNYC, TP53; PIK3CA
Fan et al, 2018	LM	11	EGFR-mutated NSCLC	CSF	Targeted sequencing	EGFRm 11/11 (100%) , not concordant (1/11)
Li et al, 2018	LM	42	EGF-mutated NSCLC	CSF	Targeted sequencing	EGFRm 92% (28)
Huang et al, 2018	LM	1	CUP ADK	CSF	Targeted sequencing	HER2 and MPL amplification PIK3CA, CDKN2A, P53m

ARTICLE

Received 25 Mar 2015 | Accepted 8 Oct 2015 | Published 10 Nov 2015

DOI: 10.1038/ncomms9839 OPEN

Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma

n = 12 patients (4 GBM, 6 BMBCs, 2 BMLCs)

METHODOLOGY:

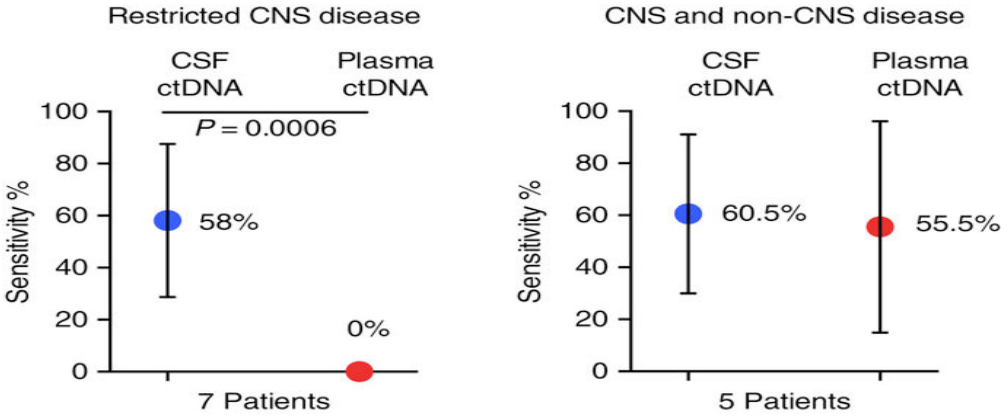
1-Targeted capture massively parallel sequencing DNA samples from CNS tumours, non-CNS metastases, CSF and plasma samples as well as germline DNA MSK-IMPACT – 341 genes

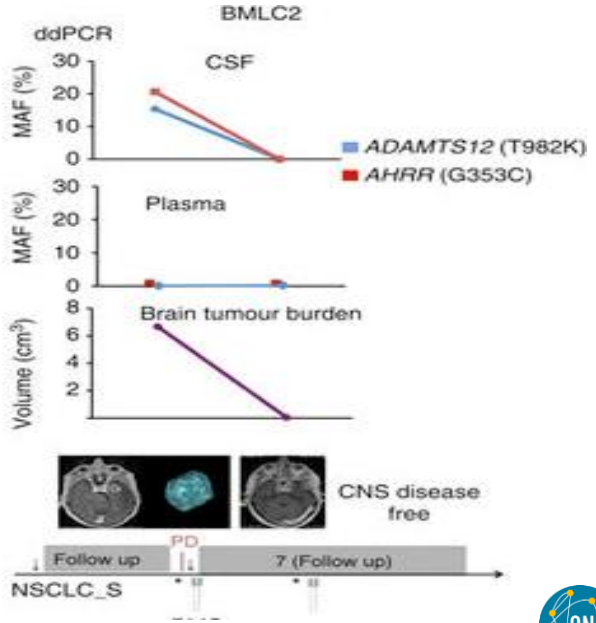
2- Exome (germline et tumor DNA)

3- ddPCR on CSFctDNA et ctDNA designed to specifically detect point mutations selected by exome sequencing

De Mattos-Arruda L,. Nat Commun. 2015

CSF-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma

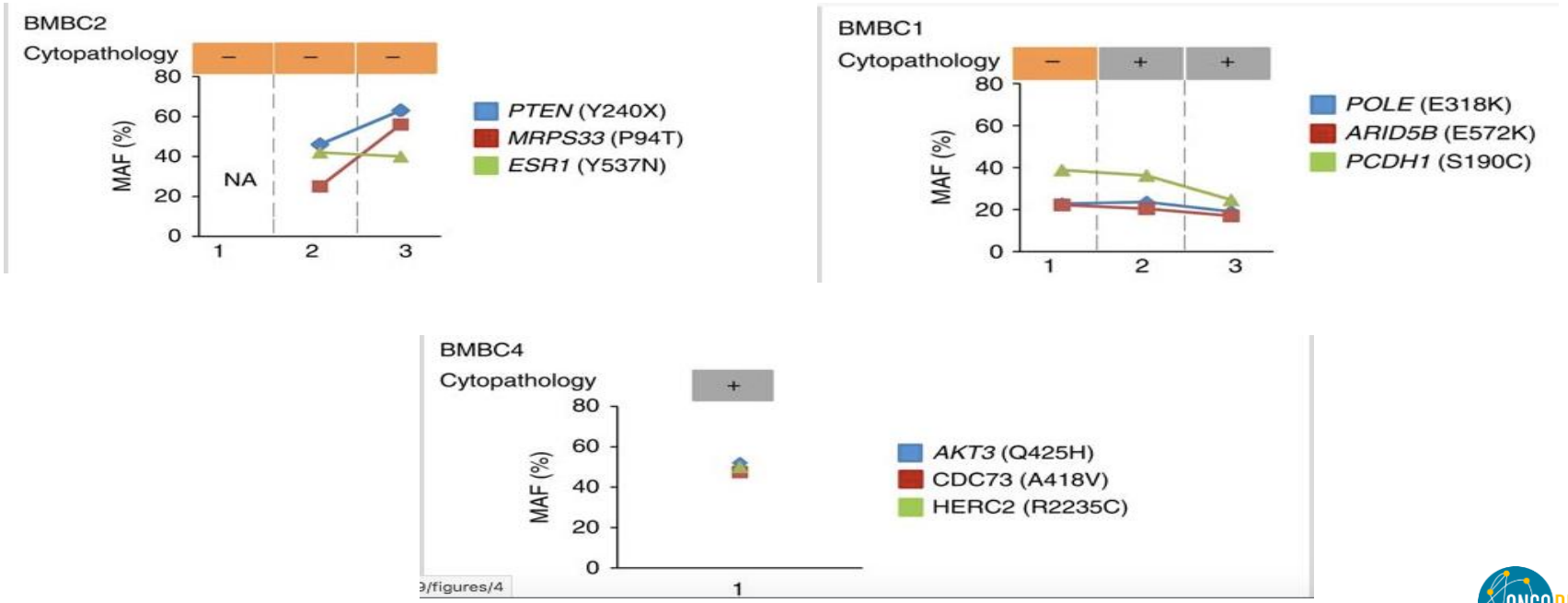




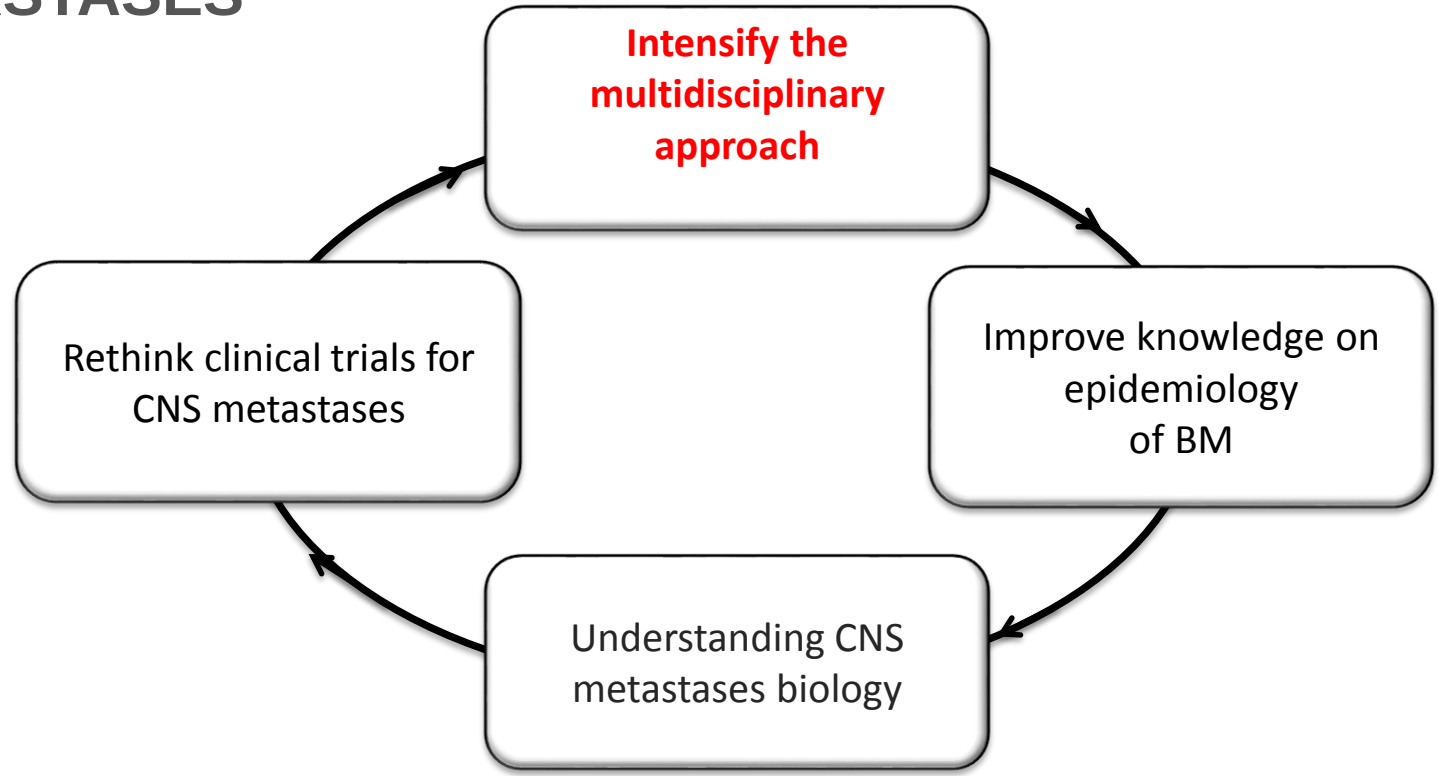
De Mattos-Arruda L,. Nat Commun. 2015

CSF ctDNA complements the diagnosis of LM

De Mattos-Arruda, Nature Com, 2015



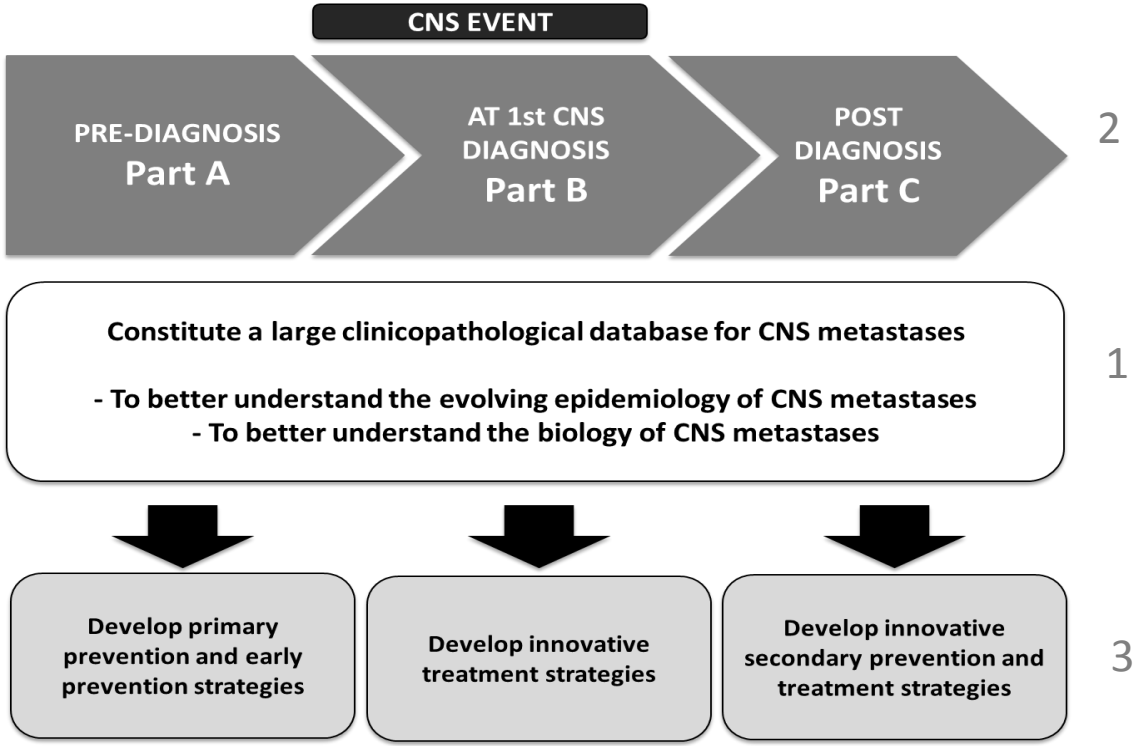
CHALLENGES FOR THE MANAGEMENT OF CNS METASTASES



Brainstorm Program

Cohort 1:TNBC
Cohort 2: HER2+ BC
Cohort 3: NSCLC
Cohort 4: SCLC
Cohort 5: Melanoma

Cohort 6: Other solid tumours
Cohort 7: LMC



Implement clinical trials

Inclusion criteria

- Age ≥ 18 years old
- ECOG≤ 2
- Eligible for part A: Subjects (from cohorts 1 to 5) with newly diagnosed non-CNS metastases or up to 24 months from diagnosis of non-CNS metastases
- Eligible for part B: Subjects (from cohorts 1 to 7) presenting with a first CNS event and not yet enrolled in the program
- Availability of either primary and/or non-CNS metastatic archival tumour tissue is mandatory for inclusion.
- Willingness to undergo lumbar puncture at diagnosis of CNS metastases unless medical contra-indications
- Predicted life expectancy > 3 months.

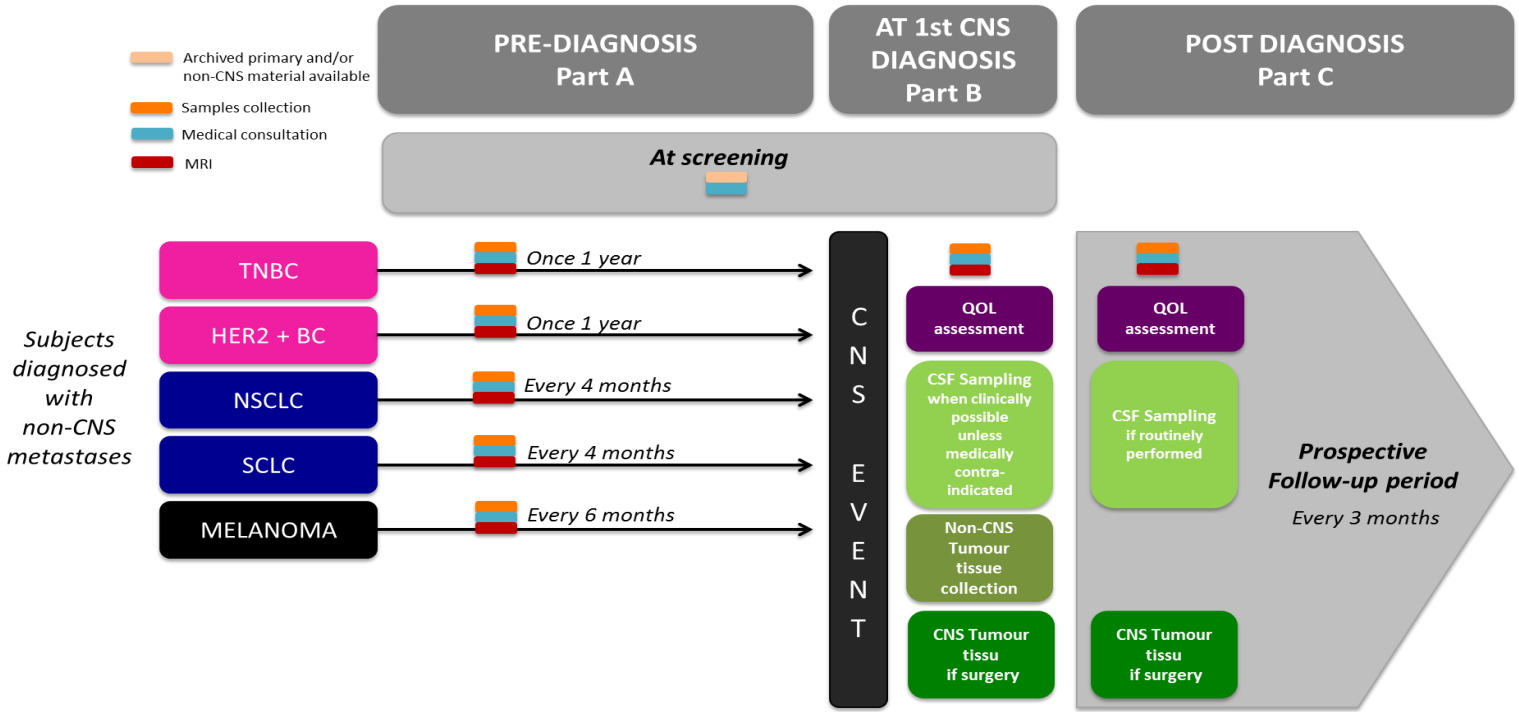
Exclusion criteria

•Pregnant and/or lactating women.

•Previous or current malignancies of other histologies within the last 5 years, with the exception of in situ carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin.

•Subject with a significant medical, neuro-psychiatric, or surgical condition, currently uncontrolled by treatment, which, in the principal investigator's opinion, may interfere with completion of the study.

STUDY DESIGN



Translational research

Better understand the biology of CNS metastases using CSF-ctDNA as a surrogate endpoint for CNS tumour tissue DNA.

Endpoints

- Presence of CSF-ctDNA at diagnosis of CNS metastases
- Presence of plasma ctDNA at diagnosis of CNS metastases
- Molecular landscape of CSF-ctDNA as compared to CNS metastases tumour DNA (if surgery), non-CNS tumour DNA and plasma ctDNA
- Actionable mutations in CSF-ctDNA and/or CNS metastases tumour DNA
- Potential molecular predictive biomarkers for the development of CNS metastases in plasma ctDNA and non-CNS tumour DNA
- Value of CSF-ctDNA and plasma-ct DNA for prognostic, predictive and monitoring purposes

Brainstorm statistics and number of patients:

The design will provide a 80% power (at a one-sided 5% alpha level) to detect that the rate of patients with CSF-ctDNA in case of a CNS event is higher than 10% (the power is reached in case the true rate is at least 30%).

To roughly take into account a 30% rate of inevaluable patients for the Brainstorm-CSF study, 40 patients with CNS metastases will be requested per cohort to obtain **29 evaluable patients.**

Taking into account the incidence of CNS metastases and patients who will directly enter Part B of the program in each cohort the approximative number if patient to enroll in Part A of the program will be:

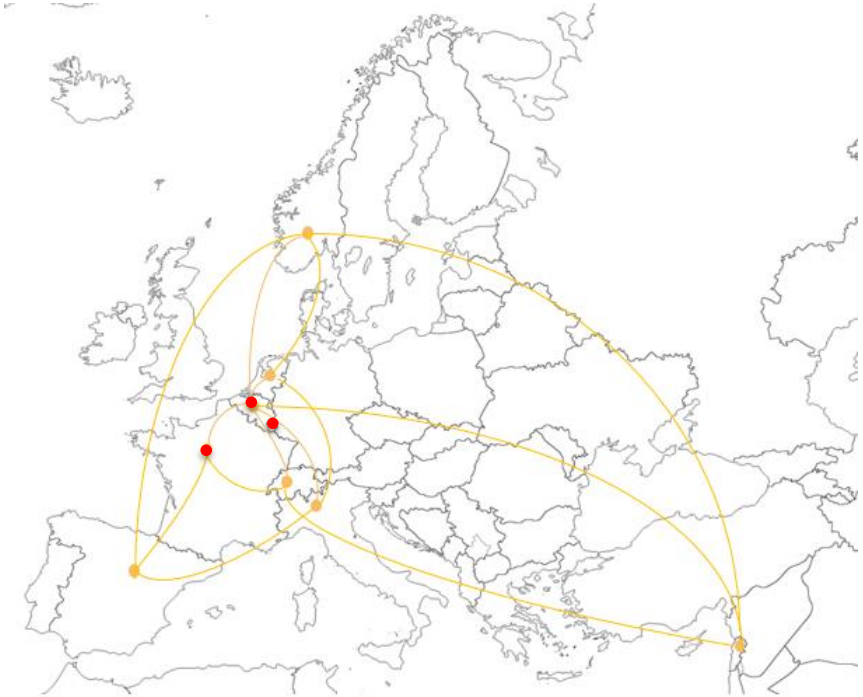
Triple-negative breast cancer: approximately 120 patients
HER 2 positive breast cancer: approximately 120 patients
Non-small cell lung cancer: approximately 80 patients
Small cell lung cancer: approximately 80 patients
Melanoma: approximately 120 patients

Additional 40 patients will be enrolled for Part B/C in the 2 following cohorts:

6. Cytologically or radiologically confirmed leptomeningeal carcinomatosis
7. Other solid tumors

Participating sites

1. Institut Jules Bordet – Dr Gombos
2. Ambroise Paré CHU Mons – Holbrechts Stephane
3. UCL Saint Luc – François Duhoux
4. Saint Elisabeth Namur – Donatienne Taylor
5. GHDC Site Notre Dame (Charleroi)- JL Canon
6. UZ Brussel – Lore Decoster
7. ULB Erasme – S.Luce /F.Lefranc
8. UZ Leuven – Kevin Punie
9. Centre Oscar Lambret – Raphaelle Mouttet Audouard
10. CHU Strasbourg – Philippe Barthelemy
11. Saint Lous Paris – Luis Teixeira
12. Institut Curie – Edith Borcoman
13. Centre Henri Becquerel – Florian Clatot – Rouen
14. Centre Jean François Leclerc (Dijon) – François Ghiringhilli
15. IUCT Toulouse – JP Delord
16. Institut Paoli Calmette – Marseille _ A. Gonçalves
17. CH Luxembourg – Caroline Duhem



Study start – FPI February 2020

Timelines

•May 2019 – October 2019 : Protocole writing – site selection – ICF – CRF – TR activities logistic

•December 2019: Regulatory submission

•February 2020: FPI

•Recruitment period : 48 months

•in the same time - Implement clinical trials in primary as well as secondary prevention of CNS metastases and innovative treatment strategies

Aknowledgements

- Ahmad Awada
- Oncodistinct investigators
- Project Managers: Chloe Velghe and Diane Delaroche
- Julie Gaye & IJB team
- Michail Ignatiadis
- Marie Guglielminetti

With the financial support of :

Fonds Gaston Ithier