Brain Metastases

Therapy and Perspectives

Nuria Kotecki, MD

BSMO Meeting, 2/12/2022

OUTLINE

- Epidemiology

- General considerations for the treatment of CNS metastases

- Clinical trials in CNS metastases

- Systemic treatments for CNS metastases

- Perspectives

ONCODISTINCT NETWORK

Brain Storm

Nuria Kotecki, MD
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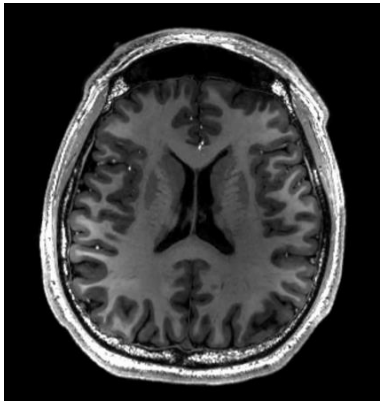
Brain Storm

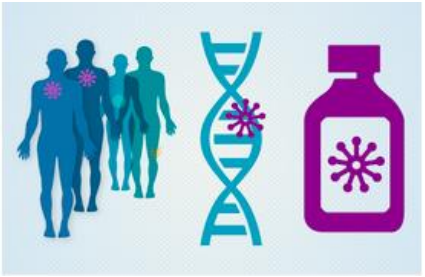
Nuria Kotecki, MD
BSMO Meeting, 1/12/2022

Brain metastases: a growing issue

Most common CNS tumors in adults

Incidence is increasing due to both improved **diagnostic techniques** and **prolonged survival** following the progress systemic treatments





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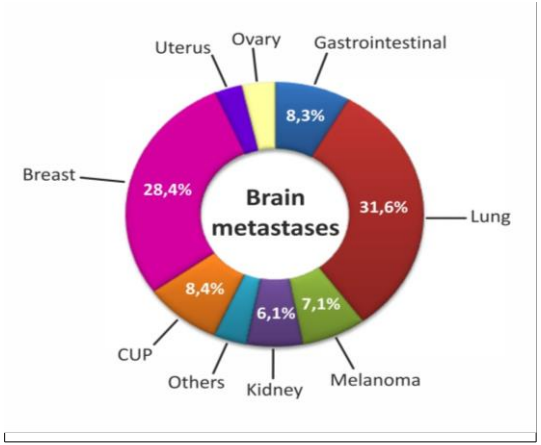
Brain metastases in solid tumours

	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 rearrangement			4-18 months
SCLC		50%	3-4 months
Melanoma		15-50%	4-8.3 months



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

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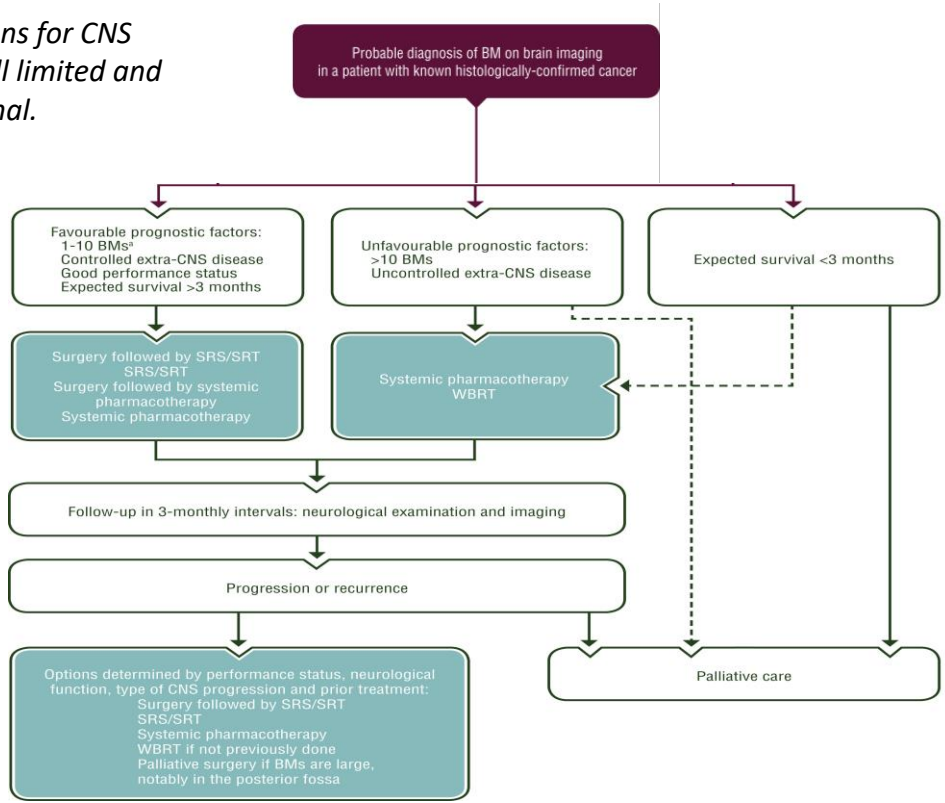
Nuria Kotecki, MD
BSMO Meeting, 1/12/2022

EANO/ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours

Treatment options for CNS metastases are still limited and suboptimal.



Depending on:

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

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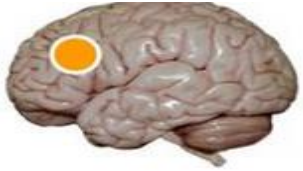
Adapted from Annals of Oncology 2021 321332-1347DOI: (10.1016/j.annonc.2021.07.016)

When to favor systemic therapy options for BM ?



Singular

Small, no critical location, clinical asymptomatic

↓

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

↓

Progression

Multiple

Surgery or Radiosurgery; WBRT if multiple

Surgery or Radiosurgery if <4; Systemic Therapy? (Re-)WBRT

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Adapted from F.Winkler, ESMO 2018

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It ‘s all about optimizing the treatment sequence

Multidisciplinary brain metastasis tumor boards

Are emerging as an optimal method for discussing clinical options for patients presenting with intracranial disease

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Nuria Kotecki, MD
BSMO Meeting, 1/12/2022

Clinical trials in CNS metastases : a recent paradigme shift

- *Brain metastases have been historically excluded from clinical trials*
- *Huge unmet medical need and increasing prevalence*
- *Demonstration of CNS activity of systemic therapies in various tumor types*

Recommendation for inclusion of patients with treated/stable brain metastasis	Include such patients in all phases of trials except if there is a strong justification to exclude In early exploratory studies, inclusion should not be based on the investigational drug's property of penetrating the BBB Include patients who have neurologically stable CNS disease, to be able to correctly verify if the toxicity is due to the drug itself or underlying disease Limit enrolment of patients who are receiving a stable/decreasing dose of steroid during 1 week before study entry
Recommendation for inclusion of patients with active brain metastasis	Should not be automatically excluded from trials; should be included in trials if immediate CNS-directed treatment is not necessary and is unlikely to be required Describe the justification of exclusion in cases where the investigated drug is l have CNS-related adverse events

FDA recommendations for clinical trial eligibility criteria for cancer patients with CNS metastases

Curr. Treat. Options in Oncol. (2021) 22:78
DOI 10.1007/s11864-021-00875-8

Neuro-oncology (GJ Lesser, Section Editor).

Clinical Trial Considerations in Neuro-oncology

Eudocia Q. Lee, MD, MPH

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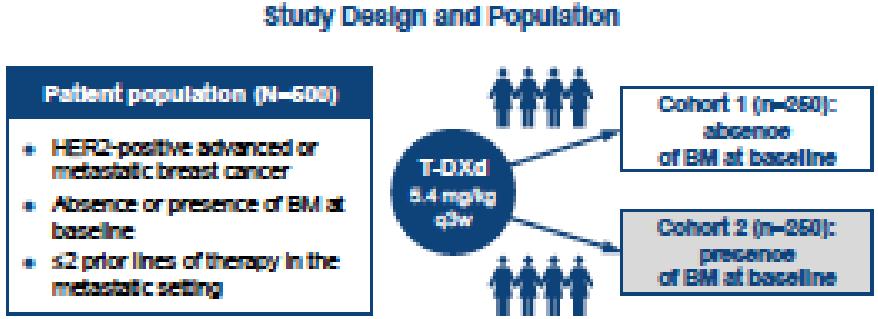
A phase IIIb/IV study of T-DXd in patients with previously treated advanced/metastatic HER 2 positive breast cancer **with or without baseline brain metastasis**

DESTINY BREAST12



Participants should have pathologically documented BC that is: unresectable/advanced or metastatic; confirmed HER2+ expression ***must have either: no evidence of BM, or untreated BM not needing immediate local therapy, or previously treated stable or progressing***

BM Participants with BM ***must be neurologically stable***

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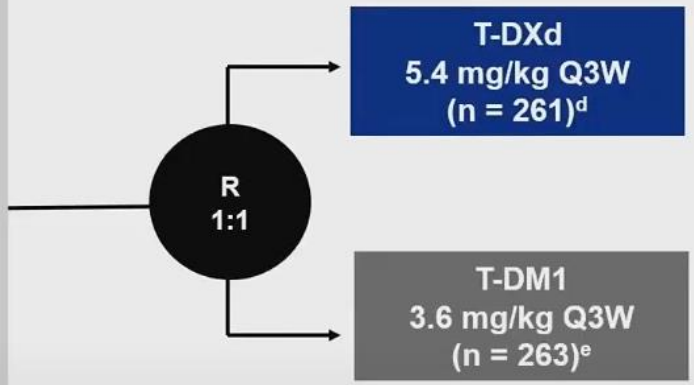
SYSTEMIC TREATMENT OF PATIENTS WITH HER2+ BCBMs

	Trial	n =	Intracranial ORR	CNS PFS	Median OS
Lapatinib + Capecitabine	Landscape *(no prior WBRT)*	45	65,9%		
Neratinib + Capecitabine	*TBRC 022* *(active CNSm* *- prior RT allowed)*	37	49%		13,3 months
Tucatinib + Trastuzumab + Capecitabine	ONT 380 005 *(including active CNSm)* HER2CLIMB *(including active CNSm)*	23 198	42% 47,7% (75 pts) *Risk of IC progression or death reduced by 68%*	9,9 months	OS - 18,1 months *Risk of death reduced by 42%*
Trastuzumab-Deruxtecan	DESTINY Breast 03 *(treated and stable)* DEBBRAH *(active BM cohort 2/3)*	43 13	63,9% (36 pts) 46.2% in active BM.		

DESTINY-Breast 03 trial

Patients (N = 524)
- Unresectable or metastatic HER2-positive[a] breast cancer that has been previously treated with trastuzumab and a taxane[b]
- Could have clinically stable, treated brain metastases[c]
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

	T-DXd	T-DM1
History of BM, n (%)		
Yes | No	62 (23.8) | 199 (76.2)	52 (19.8) | 211 (80.2)
BM at baseline,[b] n (%)		
Yes | No	43 (16.5) | 218 (83.5)	39 (14.8) | 224 (85.2)

Baseline characteristics

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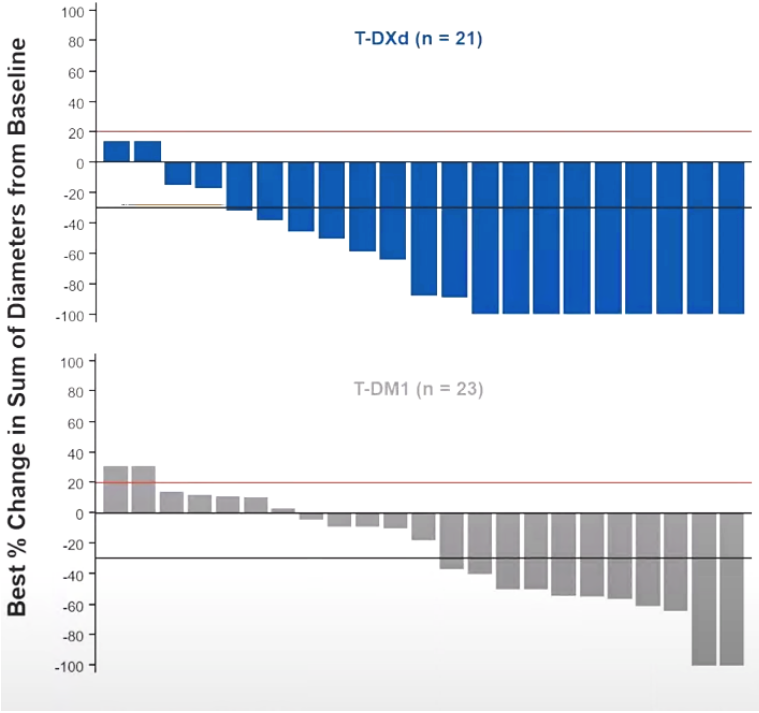
Hurvitz S et al. SABCS 2021

DESTINY-Breast 03 trial – CNS activity

Intracranial Response per BICR using RECIST 1.1



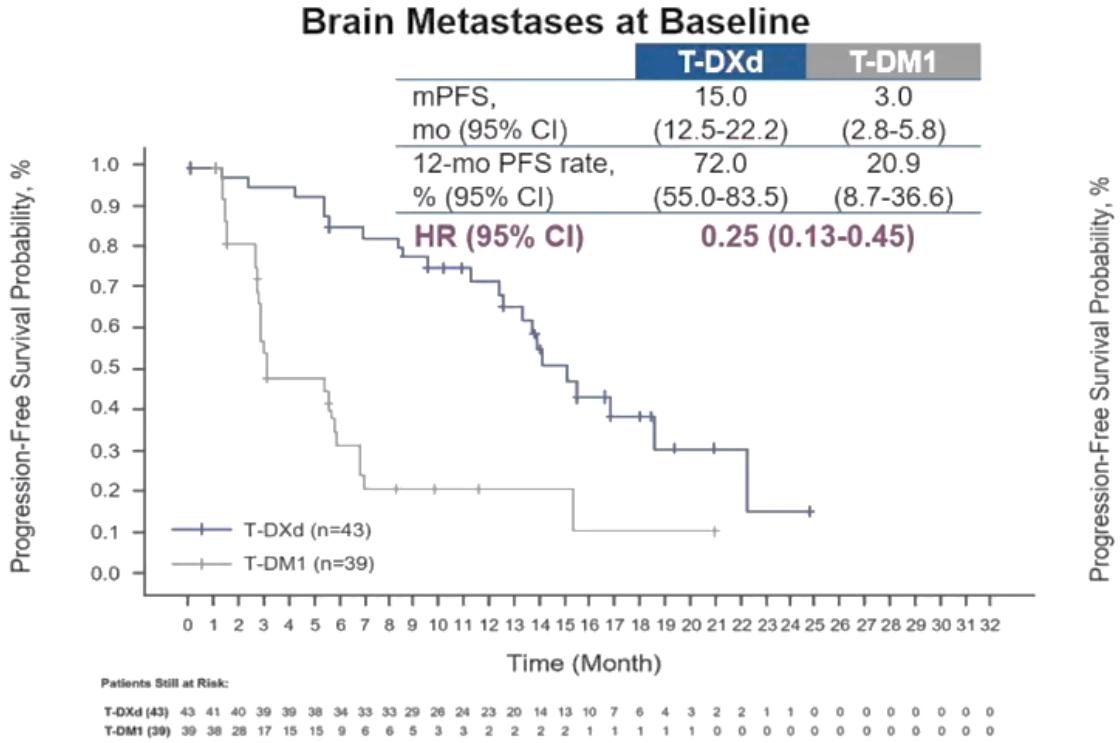
	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

IC ORR 63%

Hurvitz S et al. SABCS 2021

DESTINY-Breast 03 trial – CNS activity



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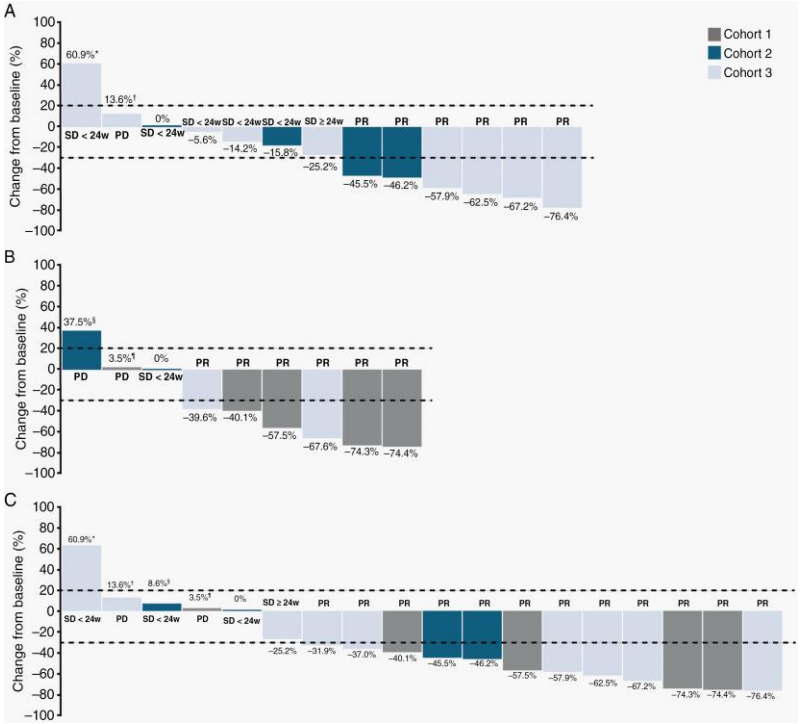
Hurvitz S et al. SABCS 2021

DEBBRAH trial – T-DXd in pts with breast cancer and CNS involvement

	Cohort 1	Cohort 2	Cohort 3
Inclusion criteria	*HER2+BC with treated and non-progressing BM*	*HER2+or HER2-low BC with asymptomatic untreated BM*	*HER2+BC with progressing BM after local treatment*
Number of patients	8	4	9
Primary endpoint and results	16w PFS 87,5%	IC ORR 50%	IC ORR 44%

- *Cohort 4: HER2-low expressing BC with progressing BM after local treatment*
- *Cohort 5: HER2+or HER2-low expressing BC with LMC*



Pérez-García, et al. Neuro Oncol. May 2022

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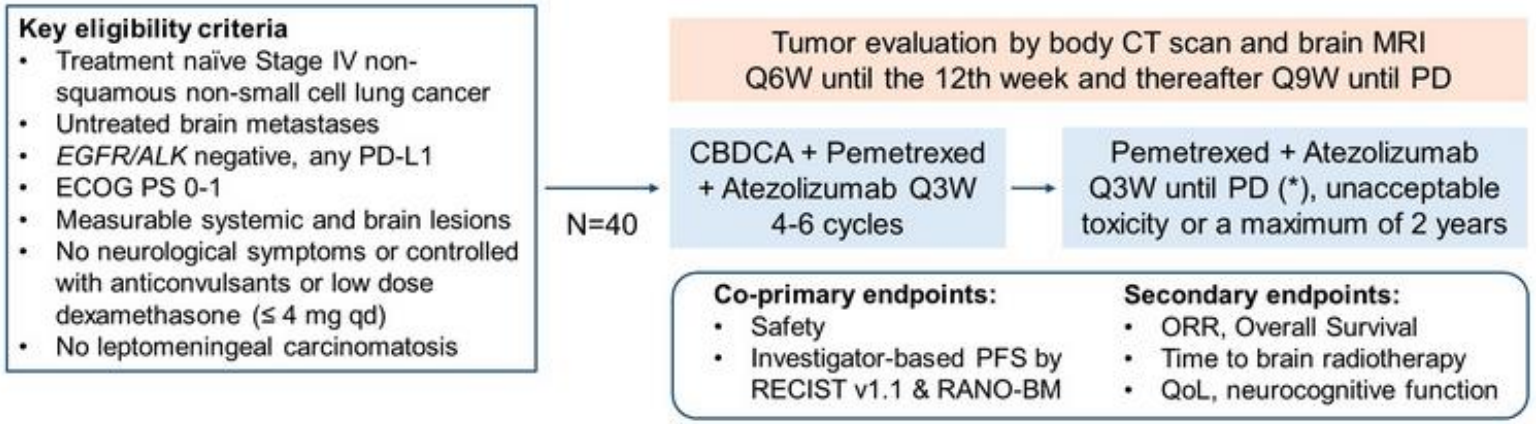
Systemic treatment for NSCLC cancer

	Drug	Trial	n =	Intracranial ORR	CNS PFS	Median OS
NSCLC	Pembrolizumab	NCT02086070 *Not previously treated or progressing after RT*	37 PDL1 ≥ 1% 5 PDL1 ≤ 1%	29,7% 0%		
NSCLC Adk	Atezolizumab + Carboplatine + Pemetrexed	ATEZO Brain *(untreated BM)*	40	42,5%	6,9 mo	13,6 mo
EGFRm	Osimertinib	AURA3 (stable aS) BLOOM (LM) FLAURA (stable aS)	116 32 128	70% (efr) 40% (fas) 32% 91% (mes.d) 68%		
ALK/ROS1	Ceritinib	ASCEND-7 *Prior Brain RT Prior ALKi* *Prior ALKi* *Prior Brain RT* *ALKi/RT naive*	 42 40 12 44	 39% 27,6% 28,5% 51,5%		
	Alectinib	ALEX (stable aS CNS/LM) Prior RT	122	85,7% 78,6%		
	Brigatinib	ALTA (prior crizotinib – aS) 90mg OD 180mg OD	 112 110	 46% 56%		 29,5 mo 34,1 mo
	Lorlatinib	CROWN aS treated or untreated CNSm	38	66% 82% (mes.d)	96% at 12mo	

ATEZO Brain



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Nadal et al, ASCO 2022

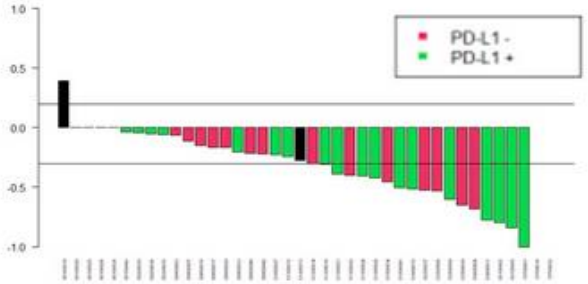
ATEZO Brain

Event	
Any brain RT	24 (60%)
Death before brain RT	13 (32.5%)
Median time to brain RT (95% CI)	10.9 (7.8 – 15.9)

Type of brain RT	
WBRT	16 (40%)
Stereotactic RT	8 (20%)

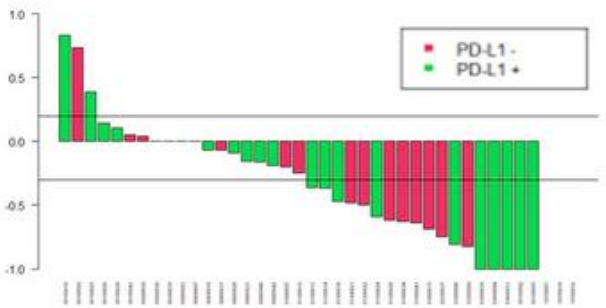
	Systemic ORR	Intracranial ORR
CR	1 (3%)	5 (12.5%)
PR	17 (43%)	12 (30%)
SD	16 (40%)	17 (42.5%)
PD	4 (10%)	5 (13%)
NE	2 (5%)	1 (3%)
ORR	**18 (45%)**	**17 (42.5%)**

Best ORR by RECIST v1.1 according to PD-L1 expression



No differences in systemic ORR between PD-L1 positive vs negative (p = 0.264)

Best ORR by RANO-BM according to PD-L1 expression



No differences in brain ORR between PD-L1 positive vs negative (p = 0.104)

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Nadal et al, ASCO 2022

Systemic treatment for melanoma

	Drugs	Trial	n =	Intracranial ORR	Extracranial ORR
	Ipilimumab/Nivolumab	Checlmate 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 V600D/E/K/R	 76 16 16 17	 68% 56% 44% 59%	 55% 44% 75% 41%

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WHAT IS THE OPTIMAL TREATMENT STRATEGY ?

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

Clinical Trial	Location	Phase	Tx	Treatment Arms	Primary Outcome Measure	Secondary Outcome Measure
ABC-X NCT03340129	Multicenter, Australia	II	Nivo + Ipi + SRS	Two arms, one of Nivo + Ipi with or without SRT or hypofractionated for larger lesions	Proportion of patients dead at 1 year from randomization and whose immediate cause of death is neurologic	Best response of IC metastases, best response of EC disease; ORR; etc.
IPI+RTS NCT02662725	Multicenter, France	II	Ipi + SRS	73 patients	OS	Adverse events; ORR in brain; global ORR; disease control rate in brain; global disease control rate; PFS
BEPCOME-MB NCT04074096	Multicenter, France	II	SRS +/– Bini + Enco + Pembro	*BRAF* V600-mutant Arm A: Bini + Enco + Pembro Arm B: SRS followed by Bini + Enco + Pembro	IC PFS	IC RR; IC disease control; EC RR; ORR; PFS; OS; etc.
NCT02858869	Emory University, USA	I	Pembro + SRS	Arm A: Pembro + SRS 6 Gy Arm B: Pembro + SRS 9 Gy Arm C: Pembro. + SRS 18–21 Gy	DLTs	ORR; OS; rate of LMD; etc.
RadioCoBRIM NCT03430947	Multicenter, Germany	II	Vemu + Cobi	Vemu + Cobi after radiosurgery in *BRAF* V600-mutant	Best IC ORR	EC best ORR; best ORR; IC duration of response; EC duration of response; PFS; OS; etc.

A Randomised Phase II Trial of Osimertinib With or Without SRS for EGFR Mutated NSCLC With Brain Metastases (OUTRUN)

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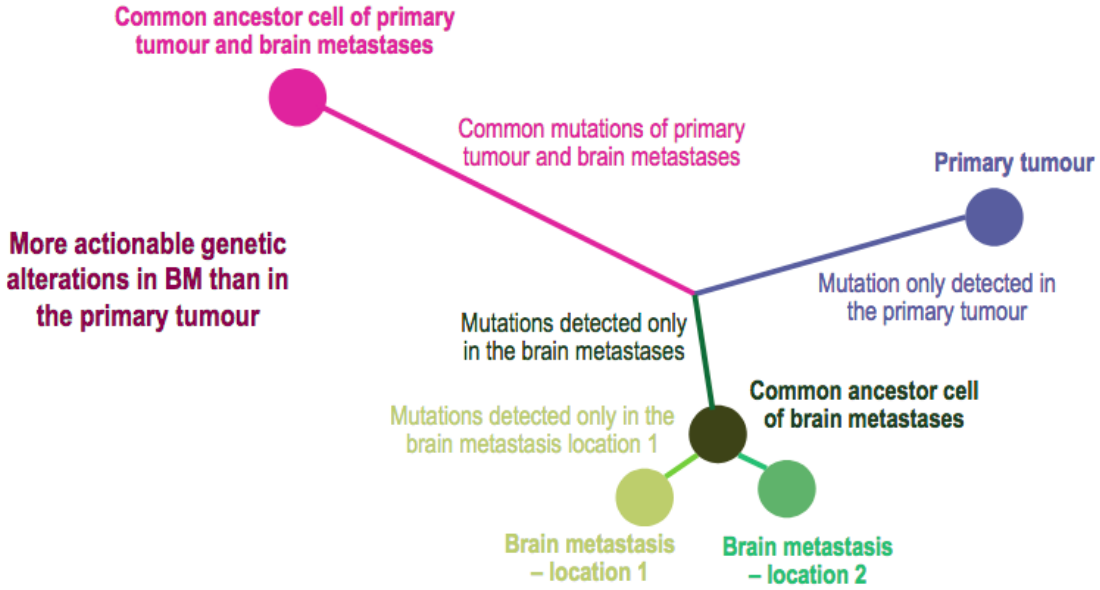
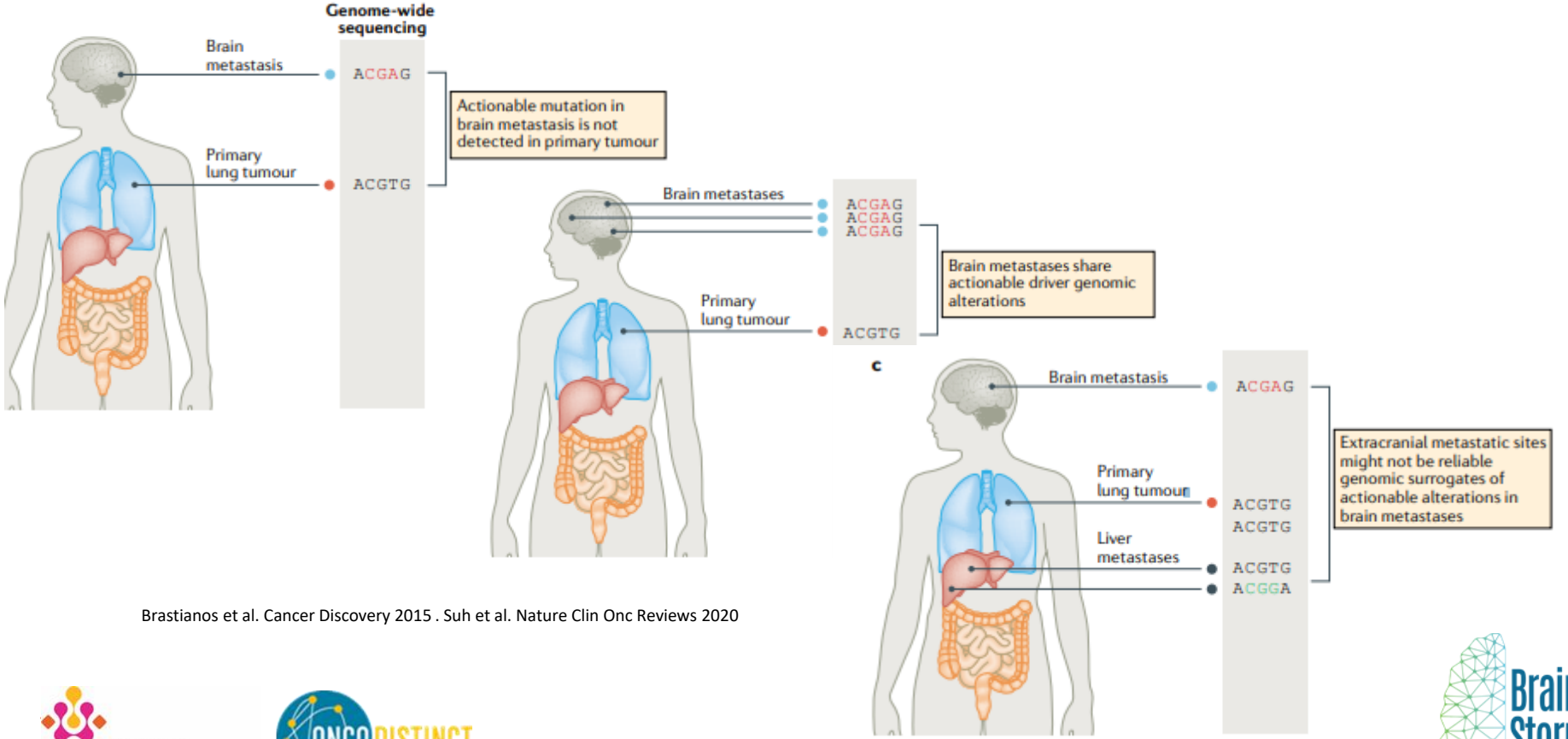
BSMO Meeting, 1/12/2022

CNS metastases: A branched evolution



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

Actionable mutations in BM, primary tumor and extracranial metastases



Brastianos et al. Cancer Discovery 2015 . Suh et al. Nature Clin Onc Reviews 2020

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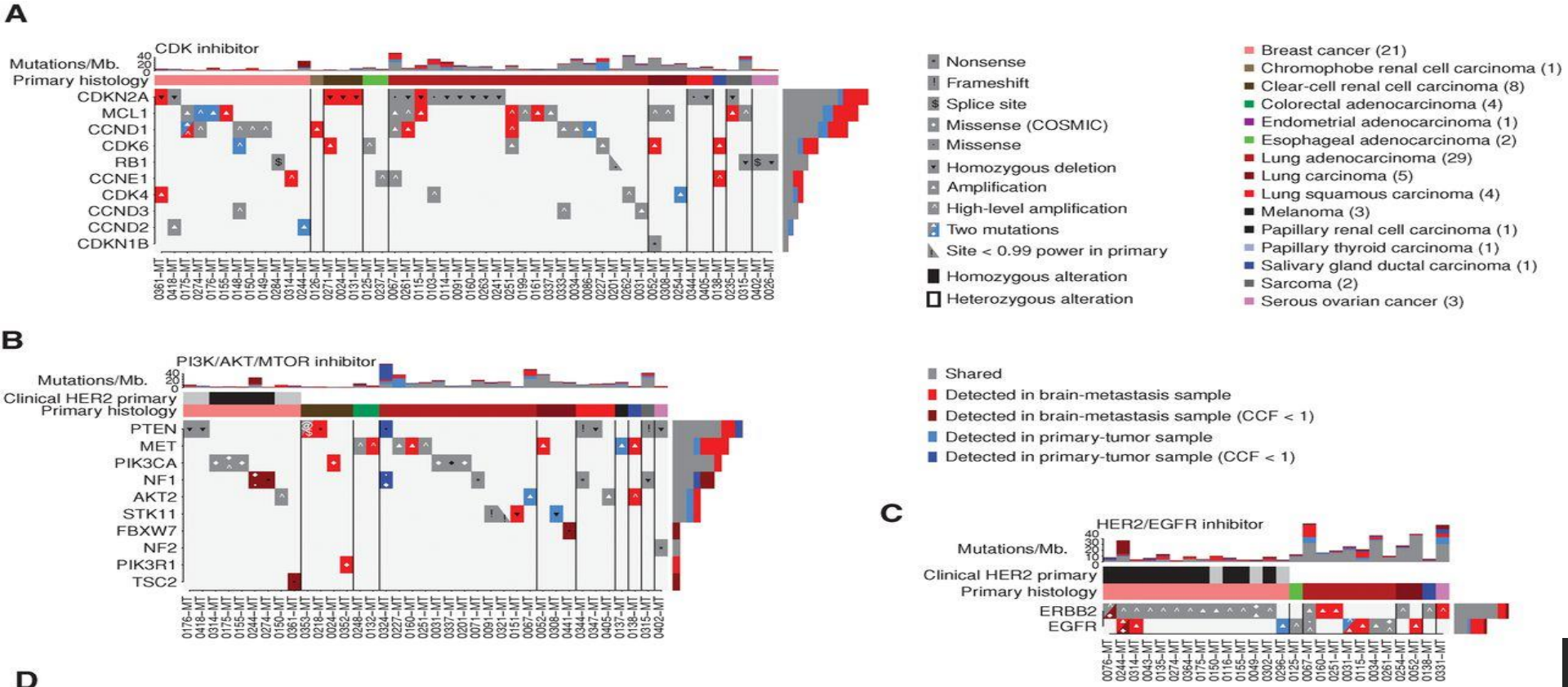
From: **Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets**

Cancer Discov. 2015;5(11):1164-1177. doi:10.1158/2159-8290.CD-15-0369



BRIEF COMMUNICATION
https://doi.org/10.1038/s43018-021-00198-5
nature cancer

Check for updates

Palbociclib demonstrates intracranial activity in progressive brain metastases harboring cyclin-dependent kinase pathway alteratio

Priscilla K. Brastianos[1,4]✉, Albert E. Kim[1,4], Nancy Wang[1], Eudocia Q. Lee[2], Jennife
Justine V. Cohen[1,3], Ugonma N. Chukwueke[2], Maura Mahar[1], Kevin Oh[1], Michael D. Wh
Helen A. Shih[1], Deborah Forst[1], Justin F. Gainor[1], Rebecca S. Heist[1], Elizabeth R. Gers
Tracy T. Batchelor[1], Donald Lawrence[1], David P. Ryan[1], A. John Iafrate[1], Anita Giobbie-
Sandro Santagata[2], Scott L. Carter[2], Daniel P. Cahill[1,5] and Ryan J. Sullivan[1,5]

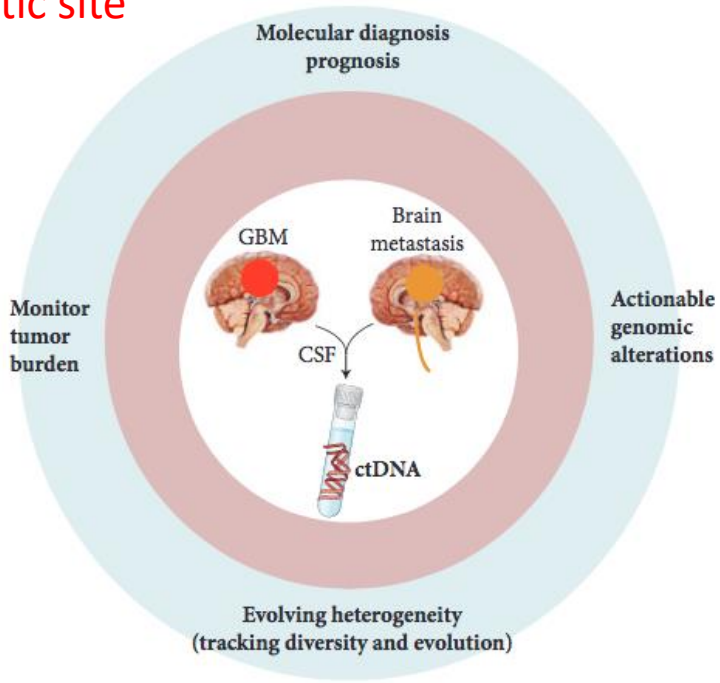
Table 2 | Summary of response data (RANO and RECIST)

Patient ID	Tumor histology	RANO response (intracranial disease)	RECIST response (extracranial disease)
1[a]	**Breast**	**Stable disease**	**Stable disease**
2	Breast	Progressive disease	Stable disease
3[a]	**Breast**	**Stable disease**	**Unevaluable**
4	Melanoma	Progressive disease	Progressive disease
5[a]	**Melanoma**	**Stable disease**	**Stable disease**
6	Esophageal	Progressive disease	Unevaluable
7[a]	**Lung**	**Stable disease**	**Progressive disease**
8[a]	**Lung**	**Stable disease**	**Progressive disease**
9	Breast	Progressive disease	Missing
10	Melanoma	Progressive disease	Stable disease
11[a]	**Esophageal**	**Stable disease**	**Partial response**
12[a]	**Esophageal**	**Stable disease**	**Progressive disease**
13[a]	**Breast**	**Stable disease**	**Stable disease**
14[b]	**Melanoma**	**Progressive disease**	**Missing**
15[b]	**Melanoma**	**Progressive disease**	**Missing**

[a]These patients had intracranial benefit (that is, complete response, partial response or stable disease, as defined by RANO). [b]These patients were enrolled using extracranial tissue (no intracranial tissue was available at the time of enrollment).

Genotyping of primary tumor or extracranial metastatic site **might miss** actionable oncogenic driver mutations…

- **Mutation** related to drug resistance
- **Activation** of an alternative signalling pathway
- **Alteration** in the drug activating site



Brain biopsies are often considered as an invasive approach:

CSF ctDNA as a surrogate for BM DNA ?

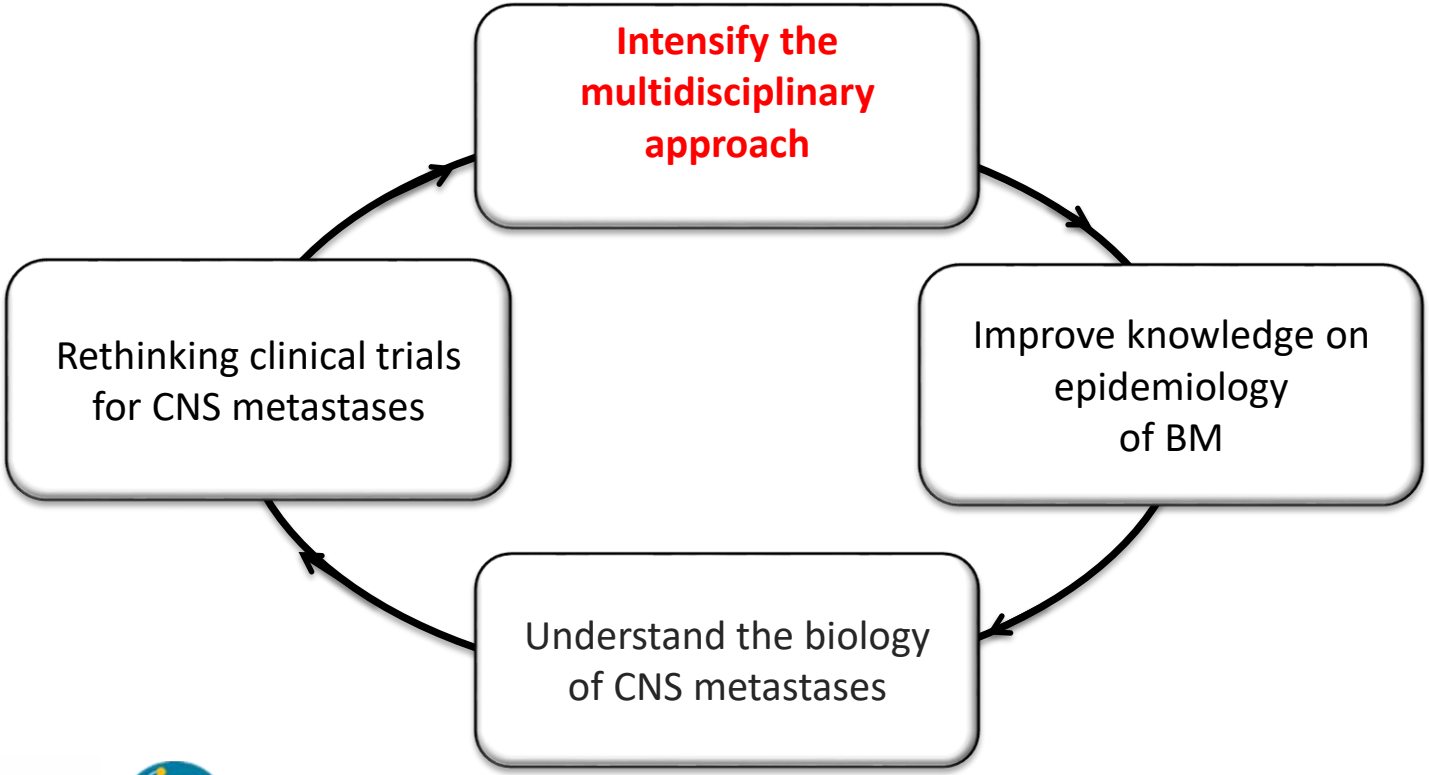
Seone et al, Annals of oncol 2019

Studies on ctDNA sequencing in CSF of CNS metastases

Study	Site of CNS malignancy	n	Primary	Biological fluid sampled	Sequencing method	CNS malignancy mutation detection rate
Swinkels et al, 2000	LM	2	Lung Adenocarcinoma	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, WES	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 *BRAF*m malignancies	CSF	Targeted sequencing	*BRAF*m 6/11 54%
Pentsova et al; 2016	P, LM	41	11 LC, 11 BC, 6 melanoma, 1 BC, 2 GI, 2 OC, 1 NE, 2 Thyroide, 2 prostate, 2 RCC, 1 sarcoma	CSF	Targeted sequencing	Mutations detectable in CSF 20/32 (63%) with BM and 75% pts with LM
Marchio et al, 2017	LM	2	Lung Adenocarcinoma	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	*EGFR*m 11/11 (100%) , not concordant (1/11)
Li et al, 2018	LM	42	*EGFR*-mutated NSCLC	CSF	Targeted sequencing	*EGFR*m 92% (28)
Huang et al, 2018	LM	1	Adenocarcinoma of unknown primary	CSF	Targeted sequencing	*HER2* and *MPL* amplification *PIK3CA*, *CDKN2A*, *P53*m

BC: breast cancer; LC: Lung cancer, GBM: Glioblastoma; GI: gastrointestinal, OC: ovarian cancer; NE: neuro-endocrine; RCC: renal cell cancer

Challenges for the management of CNS metastases



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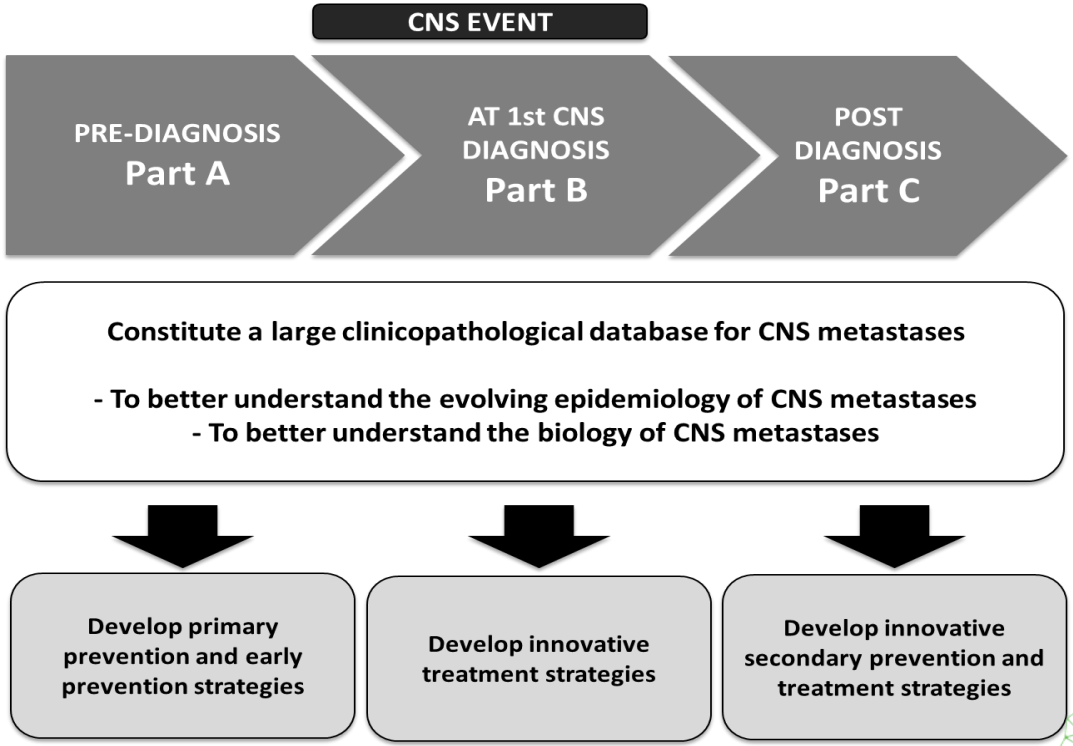
Brain Storm

Brainstorm Program Objectives

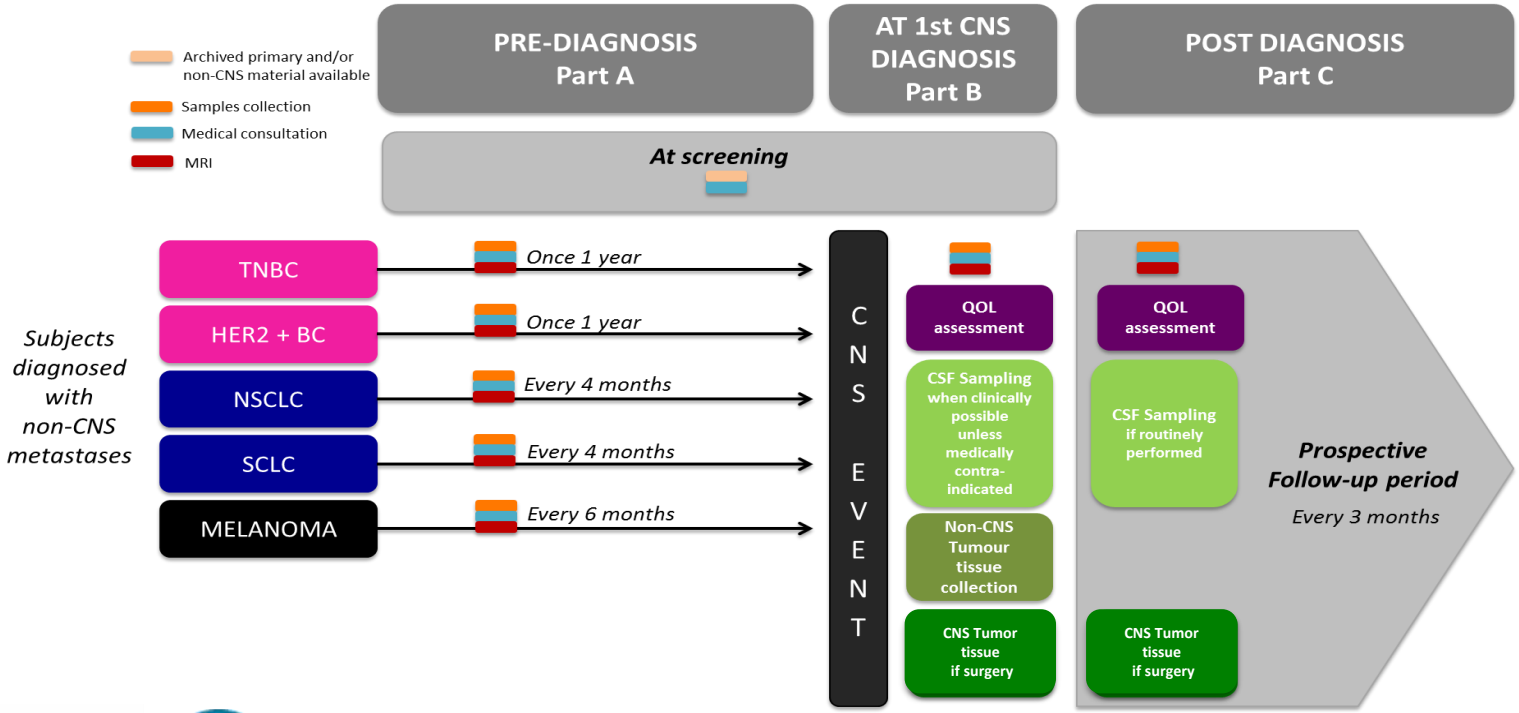
Cohort 1:TNBC
Cohort 2: HER2+ BC
Cohort 3: NSCLC
Cohort 4: SCLC
Cohort 5: Melanoma

Cohort 6: Other solid tumours
Cohort 7: LMC

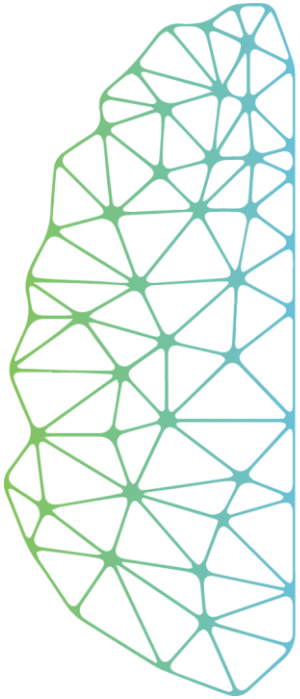
Implementation of clinical trials



Study Design



Sponsor Protocol Number: IJB-BS-ODN-006
ClinicalTrials.gov Number: NCT04109131



Brain Storm

Thank you for your attention!

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