https://doi.org/10.1038/s41591-023-02595-y

BrainStorm: a multicenter international study to tackle CNS metastases in solid tumors

Clinical outcomes of patients with central nervous system (CNS) metastases remain disappointing despite recent advances. This medical condition represents an important unmet clinical need in the care of patients with cancer. The occurrence of CNS metastases is increasing along with prolonged survival of patients with metastatic disease owing to improved diagnostic techniques and advanced systemic treatment approaches. The incidence of CNS metastases differs by primary cancer, varying from approximately 5% to 50%[1]. The most common cancers presenting dissemination to the CNS are lung cancer, breast cancer, melanoma and renal cell carcinoma[1]. The diagnosis of CNS metastases is associated with a poor prognosis, with overall survival varying from 3 to 25 months depending on the primary cancer[1]. Treatment options are limited and usually involve multimodality approaches that include surgery, radiotherapy, radiosurgery and sometimes systemic therapy, depending on the number of CNS lesions, location and primary tumor type, as well as the patient's performance status based on validated prognostic indexes[2,3]. Several challenges are limiting the advances in this field, including: incomplete knowledge of the CNS metastasis evolving epidemiology; scarce data about the tumor biology of CNS metastasis and its interaction with the tumor microenvironment; and inappropriate preclinical and clinical research methodology and experiments in this field.

In this context, a multidisciplinary Brain Metastases Clinical Research Platform named the BrainStorm program was launched in 2020 by the Institut Jules Bordet, within the Oncodistinct network (ClinicalTrials.gov ID NCT04109131). The BrainStorm program is an international, multicenter, prospective interventional study that is focused on individuals with newly diagnosed non-CNS metastatic solid tumors with a high risk of developing CNS metastases. This program is building a large clinico-pathological database of around 600 patients to investigate the development and epidemiology of CNS metastases, focusing on three time periods: before the diagnosis; at diagnosis; and after the diagnosis of CNS metastases (Table 1).

Table 1 | BrainStorm study design

Part	Assessment	Timing
Part A: non-CNS metastases	Consultation Blood sample Brain MRI	At screening and then once a year for patients with triple-negative or HER2$^+$ breast cancer; every 4 months for patients with NSCLC or SCLC; and every 6 months for patients with melanoma
Part B: first CNS event	Consultation Blood sample Brain MRI QoL questionnaire CSF sample	At the diagnosis of the first CNS event
	Non-CNS tumor sample CNS tumor sample	When available
Part C: after first CNS event	Consultation Blood sample Brain MRI QoL questionnaire	Every 3 months
	CSF sample CNS tumor sample	When available

QoL, quality-of-life.

BrainStorm is recruiting adult patients with newly diagnosed non-CNS metastases or up to 24 months from diagnosis of non-CNS metastases from triple-negative breast cancer, human epidermal growth factor receptor 2-positive (HER2$^+$) breast cancer, small-cell lung cancer (SCLC), non-small-cell lung cancer (NSCLC), and melanoma for a prospective follow-up period before a first CNS event (part A). Availability of either primary and/or non-CNS metastatic archival tumor tissue is mandatory for inclusion. Enrolment of exceptional cases surpassing 24 months from diagnosis is allowed for patients with HER2$^+$ breast cancer or NSCLC containing driver mutations. Included patients undergo a baseline magnetic resonance imaging (MRI) analysis at inclusion to exclude CNS metastases, and are followed up (once a year for triple-negative breast cancer and HER2$^+$ breast cancer, every 4 months for NSCLC or SCLC, and every 6 months for melanoma) with medical consultation, blood samples collection, and brain MRI until the diagnosis of the first CNS event, death, or up to 48 months after inclusion if there is no development of CNS metastases.

The program also includes patients at presentation of a first CNS event (part B) who were not previously enrolled in part A, regardless of the tumor type, with a separate cohort for patients with leptomeningeal carcinomatosis. A lumbar puncture for the collection of cerebrospinal fluid (CSF) will be performed in patients directly enrolled in part B and in those who were included in part A and develop CNS metastases. Non-CNS tumor tissue collection at the presentation of the first CNS event is highly recommended. CNS tumor tissue should be collected when the patient is submitted to neurosurgery. A quality-of-life assessment using the EORTC QLQ-C30 version 3.0, EORTC QLQ BN20 and EQ-5D-5L is performed at diagnosis of CNS metastases (part B) and then every 3 months after the first CNS event (part C), together with medical consultation, blood samples collection, and brain MRI. Patients will be followed until death or up to 48 months after diagnosis of CNS metastases, and new CSF and CNS tumor samples will be collected during part C if clinically indicated.

This study aims to collect valuable data about the epidemiology and biology of CNS metastases from solid tumors, which should enable the identification of risk factors for CNS metastases, the discovery of new

therapeutic targets for future clinical trials, and innovative treatments for quality-of-life improvement of these patients.

The collection of clinico-demographic baseline characteristics will define clinical subgroups of patients with higher risk of CNS metastases, and the analyses of biological samples will identify potential biomarkers for the development of CNS metastases. The BrainStorm study will assess the role of neuron-specific serum enolase as a non-invasive predictive biomarker of brain damage due to CNS metastases[4] and its prognostic baseline value when CNS metastases are diagnosed. Molecular profiling of non-CNS tumor DNA and plasma circulating tumor DNA (ctDNA) will identify molecular signatures as biomarkers for higher risk of CNS metastases. These clinico-demographic characteristics and biomarkers may identify a target population for diagnostic imaging and the early detection of CNS metastases and their progression.

CNS metastases display molecular alterations that differ from primary tumors and other metastatic sites, which might confer special CNS sensitivity for targeted treatments[5]. Brain biopsies are an invasive approach and liquid biopies are therefore being investigated as a potential tool for detecting these molecular alterations in CSF ctDNA[6–10]. Tumor DNA was shown to be more abundant in CSF than in plasma of patients with brain tumors, and to characterize the genomic alterations of brain tumors more comprehensively than plasma[10]. The BrainStorm platform will analyze the molecular landscape of CSF ctDNA in a larger dataset, and explore CSF ctDNA as a surrogate for CNS tumor tissue DNA, which may identify promising therapeutic targets for clinical trials and innovative treatment strategies. The prospective quality-of-life assessment of patients with brain metastases will provide a robust description of the effect of this condition on patient's lives.

We expect BrainStorm to lead to subsequent clinical studies in the prevention of CNS events, including primary prevention, in which CNS metastases do not occur, and secondary prevention, in which CNS events are delayed. This study will also benchmark disease control rates, quality-of-life, and survival patterns to identify future personalized treatment strategies in this setting.

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Published online: 19 October 2023

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Acknowledgements

This study is funded by L'Association Jules Bordet, Fonds Gaston Ithier, Fondation Cancer du Luxembourg, Fondation Contre le Cancer, and Fund iris-Research from King Baudouin Foundation. The study was developped with the help of the Oncodistinct network investigators.

Competing interests

D.M.B. received honoraria from Daiichi Sankyo, Novartis, Merck Sharp & Dohme, Janssen, Pfizer, Angelini and AstraZeneca; meeting or travel grants from Novartis, Merck Sharp & Dohme, LEO Farmacêuticos, Ipsen, Janssen, Roche, Laboratórios Vitória and Gilead Sciences; and institutional grants from Novartis and F. Hoffmann-La Roche Ltd (outside the submitted work); G.N.M. received travel grants for meetings from Roche and Bayer (outside the submitted work); A. Gombos has served on the advisory board for AstraZeneca, Daiichi Sankyo and Seattle Genetics; received travel grants from Pfizer and Astra Zeneca; and educational fees from Eli Lilly; E.B. received honoraria from Eisai, Merck Sharp & Dohme, Sandoz and Amgen; meeting or travel grants and non-financial support from Daiichi Sankyo, Eisai, Amgen, Sandoz, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, Pfizer and Roche; and has consulted for Egle Tx; F.C. received honoraria or travel grants from Astra Zeneca, BMS, Merck, MSD, Lilly, Roche, Novartis, Pfizer and Gilead (outside the submitted work); S.H. received honoraria from Brystol Myers Squibb, and travel grants from Roche; C.C. received travel grants for meetings from Lilly Oncology and Pfizer; and honoraria from Lilly Oncology (outside the submitted work); F.P.D. received a postdoctoral research grant from Fondation Belge Contre le Cancer; consulting fees from Amgen, Astrazeneca, Daiichi Sankyo, Eli Lilly, Gilead Sciences, MSD, Novartis, Pfizer, Pierre Fabre, Roche and Seagen; and travel support from Amgen, Daiichi Sankyo/AstraZeneca, Gilead Sciences, Pfizer, Roche and Teva (outside the submitted work); L.D. received consulting fees to UZ Brussel from MSD, BMS, Astra Zeneca, Roche and Servier; and travel support from MSD and Roche; H.D. received consulting fees (advisory role) paid to their institution by Pfizer, Roche, PharmaMar, AstraZeneca, Eli Lilly, Novartis, Amgen, GSK, MSD, Seagen, Gilead; and other fees paid to their institution (travel, accommodations, expenses) by Pfizer, Roche, PharmaMar, Teva, AstraZeneca, MSD, GSK and Gilead (all outside the submitted work); P.M.C. reports study budget funds from AstraZeneca; and was an advisory board member for AbbVie, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Leo Pharma, Merck Serono, MSD, Rakuten and Vifor Pharma; J.G. received honoraria from Astra Zeneca, Daiichi, Eisai, Exact Science, Eva Pharm, Lilly, Menarini, Merck Sharp & Dohme, Novartis, Onxeo, Pfizer, Roche Genentech, Seattle Genetics and Sothema; meeting or travel grants from Astra Zeneca, Daiichi, Eisai, Eva Pharm, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche Genentech, Seattle Genetics and Sothema; and research support from Eisai, Exact Science and Roche Genentech; A.A. had an advisory role for Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Hengrui, Innate, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Viatris and Menarini; speaker fees from Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer and Seattle Genetics; and received research grants to their institution from BMS and Roche; N. Kotecki received meeting or travel grants from Ose Immunotherapeutics (outside the submitted work). P.B., A. Goncalves, E.D.E., V.V., C.D., F.L., J.L.C., M.P. and N. Kindt have no conflicts of interest to declare.