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EORTC
European Organisation for Research and Treatment of Cancer

Meeting Report: EORTC Brain Metastases Strategic Meeting 2012

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On February 9, 2012, the EORTC Brain Metastases Strategic Meeting 2012 took place in Vienna, aiming to identify potential study designs that may advance therapy of patients with brain metastases. Brain metastases are the most common brain tumours and affect up to 40 % of cancer patients with incidences varying between tumour types and molecular subtypes. Currently, therapy relies mainly on surgery and radiotherapy (whole-brain radiotherapy and/or stereotactic radiosurgery-fractionated radiotherapy). The pathobiology of brain metastases is only partially understood so far, but recent advances have identified potential drugable targets such as the V600E-mutated BRAF protein in melanomas, HER2 in breast cancer, and EGFR in lung cancer brain metastases. Brain metastasis pathway analysis could be studied by investigating the effects of selected drugs in the preoperative setting for oligometastatic patients not requiring emergency surgery. This exploratory methodology for identifying pathway activation and drug penetration may be a new paradigm for biomarker-driven clinical trials for brain metastases. The meeting featured lectures by 15 international experts, who elucidated aspects of trial design, study endpoints, pathobiology, and provided up-to-date information on the trial landscape in the most common tumour types spreading to the brain with a focus on breast cancer, lung cancer, and melanoma (Table 1). After these lectures, potential study initiatives were discussed in a workshop session. Over 60 attendees took part in the meeting and made it a lively and stimulating scientific event.

Table 1. Speakers and meeting programme.

Speaker	Topic
Frank Winkler (Heidelberg)	Biology of brain metastases and translational research
Laurence Collette (Brussels)	Trial design
Sven Haller (Geneva)	Response evaluation
Sandrine Marreaud (Brussels)	Challenges to developing a brain met trial
Riccardo Soffietti (Torino)	Endpoints
Martin Klein (Amsterdam)	Neurocognitive function
Jaap Reijneveld (Amsterdam)	Quality of life
Jörg-Christian Tonn (Munich)	Surgery
Brigitta Baumert (Maastricht)	Radiotherapy
Paula Mulvenna (Newcastle)	NSCLC
Dirk Schadendorf (Essen)	Melanoma: BRAF inhibitors and ipilimumab
Renata Duchnowska (Warsaw)	Biomarkers predictive for brain relapse in HER2-positive patients
Nancy Lin (Boston)	Lapatinib
Yazid Belacemi (Paris)	PCI for high-risk patients
Jacek Jassem (Gdansk)	Triple-negative breast cancer

The lectures and discussions made clear that there is a great need for well-conducted trials in the field of brain metastases. Particular attention needs to be drawn to an adequate trial design, which in many cases is complicated by a lack of data on the incidence and the natural course of brain metastases, especially regarding molecular tumour subtypes. This issue may necessitate flexible and adaptive trial designs that allow for modifications during the trial. Of central importance is the selection of sound trial endpoints. So far, radiological readouts have been poorly standardized in brain metastases and there is a need for generation of diagnostic algorithms that also consider novel therapeutics and their impact on neuroimaging features. All trials on brain metastasis patients should include neurocognitive and quality-of-life (QoL) measurements. Various pitfalls have been identified with the latter endpoints, not limited to but including compliance issues, patients' cognitive impairment, and liberal time windows for QoL evaluation. Proxy measurements for QoL evaluation were discussed for patients in clinical trials and a new QoL questionnaire containing 15 items divided in global health status, functional, and symptom scales, was detailed. In melanomas, recent data from early clinical studies indicate high efficacy of novel drugs such as BRAF inhibitors and ipilimumab against brain metastases. The question of how these drugs compare to standard treatment regimens should be addressed in randomized trials. Furthermore, the appearance of secondary resistant tumours in many patients calls for studies investigating novel multi-targeted agents and strategies in the recurrent setting. In breast cancer, 2 tumour types are characterized by increased propensity for brain colonization: HER2-positive and triple-negative tumours. In these indications, novel radiotherapy regimens such as whole brain radiotherapy with hippocampal sparing may provide feasible and safe options for brain metastasis (BM) prophylaxis or therapeutic management. Alternatively, patients with diagnosed BM could be treated systemically; a potential phase-III trial could randomize HER-2-positive breast cancer patients to WBRT vs lapatinib plus capecitabine. In addition, novel compounds have been promising in preclinical and early clinical studies and provide promising trial opportunities. In non-small cell lung cancer, trials evaluating whole-brain radiotherapy and EGFR inhibitors as well as optimal palliative approaches are ongoing. Based on preclinical data, prophylactic administration of anti-angiogenic agents may be feasible in this tumour type. The feasibility, the high-cross-over rate, and the potential toxicity of systemic treatment were discussed during the meeting.

In summary, several brain metastasis study designs in breast cancer, lung cancer, and melanoma were discussed which could be potential EORTC prospective trials. A bevacizumab

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prophylactic trial for high-risk lung cancer patients and a WBRT vs capecitabin plus lapatinib phase-III trial for high-risk HER-2 breast cancer could be foreseen. Alternatively, a prophylactic WBRT with hippocampal sparing and concomitant trastuzumab trial could be developed for these patients. Finally, a BRAF inhibitor study for metastatic melanoma could be developed for patients with 1–3 (focal radiotherapy) and > 3 brain (WBRT) metastases.

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