Melanoma brain metastases (MBM) present a significant clinical challenge. Molecular profiling of MBM is useful to identify molecular pathways, such as the PI3K pathway, that are specifically and differentially altered in MBM. Therapeutic studies should recruit patients with MBM and prospective tissue collection will lay the foundation for further advances. Clin Cancer Res; 20(21); 5346–8. ©2014 AACR.

How can this finding be translated into therapeutic targeting of the PI3K pathway in MBM and ultimately clinical benefit for melanoma patients with brain metastases? Despite the fact that multiple small-molecule inhibitors of the PI3K pathway are in development, including those of Novartis, GlaxoSmithKline, Oncothyreon, Pfizer, Bayer, and others, the path to patients with MBM is fraught with difficulty. The paradigm to date remains to establish safety and therapeutic efficacy in clinical trials designed for patients with ECM, reflexively excluding MBM. A combination of BRAF inhibitor with PI3K inhibitor will have to find success in ECM before it is explored in patients with MBM, effectively putting the cart before the horse because MBM may be more suited for such combinations.

Several scientific and logistic challenges have hampered progress in the management of patients with MBM and made it consistently trail advances in the management of melanoma. Scientific challenges include (i) the inherent difficulty in measuring the pharmacokinetic and pharmacodynamic (PK/PD) effects in the brain, leading to limited knowledge of central nervous system drug penetration at concentrations that effectively inhibit the target; (ii) the unique tumor microenvironment in the brain where melanoma cells seem to thrive through potentially epigenetic modulation; and (iii) lack of characterization of tumor–host interactions in a site traditionally considered an "immune sanctuary," despite recent evidence of immune cell infiltration into MBM (3). Logistic challenges include the feasibility of MBM-specific studies in a single center or limited center studies, the lack of safety data for this population despite evidence that patients with MBM can be safely included in phase I trials, and the lack of interest from big pharma in pursuing drug development in this population (7). The lag time in translating active therapy from ECM to MBM is best exemplified by the combination of dabrafenib and trametinib, which met its safety and efficacy endpoints (8), finalized its two large phase III studies, and received FDA approval in January 2014, before a phase II study of the combination in MBM (COMBI-MB) was opened to enrollment (NCT02039947). Conversely, when early-phase clinical trials allow patients with MBM, progress can happen at a much more satisfying pace. The phase I
study of the BRAF inhibitor dabrafenib was a groundbreaking experience in which intracranial activity was noted in melanoma patients with active MBM as they were enrolled on a study that did not specifically exclude them (9). This prompted a phase II study (BREAK-MB) that was completed before dabrafenib had achieved FDA approval and confirmed that dabrafenib has intracranial activity that closely parallels its extracranial activity (10). Margolin and colleagues (11) confirmed that immunotherapeutic advances can be translated to MBM, with the anti-CTLA antibody ipilimumab demonstrating intracranial activity. Phase II studies are ongoing or planned to assess the activity of anti-PD1 antibodies alone or in combination in MBM (12). In both instances, MBM-specific studies are similarly being initiated after large phase III registration studies have been concluded.

Looking beyond the specific findings of this study, the authors should be commended for helping to establish a new paradigm in which extensive molecular profiling of matched MBM–ECM pairs becomes of increasing utility to decipher the underlying biological differences between MBM and ECM and to pave the way for more effective therapeutic targeting of MBM. The current study represents a significant step in an all-encompassing strategy required to conquer this most daunting challenge in the management of metastatic melanoma (Fig. 1). MBM are becoming increasingly prevalent, and patients often find themselves excluded from clinical trials that carry the most promise in this disease. Elucidating MBM-specific pathways and gaining further insights into the microenvironment and tumor–host interactions will lead to the development of direly needed MBM-specific clinical trials. On the other hand, a far more efficient approach is to allow the inclusion of patients with MBM onto clinical trials designed to bring the most promising therapies to patients with ECM. Although the caveats of including such a population with a distinctly worse prognosis are understandable, they could be easily addressed in randomized settings in which the presence of active untreated MBM is used as a stratification factor, thereby isolating its impact on the overall outcome of studies. This strategy may not be favored by pharmaceutical companies but should be advocated for by investigators and patients alike.

Prospective collection of resected intracranial tumors should be a priority of translational research in MBM, especially if matched ECM can be concurrently obtained. A concerted effort potentially nested in ongoing clinical trials will fuel the next generation of discoveries for MBM as it helps to characterize MBM-specific mechanisms of resistance to active therapy (NCT02058953). In light of
emerging data implicating the tumor microenvironment in the development of therapeutic resistance. MBMs are likely to have resistance pathways distinct from ECM. Prospective collection of intracranial tissue should coincide with the application of novel imaging techniques such as 3D MRI, MR spectroscopy, and dynamic PET imaging. Advances in the imaging science of MBM can be harnessed to allow noninvasive monitoring of tumor response and perhaps early detection of emerging resistance. Finally, a direct assessment of the intracranial PK/PD of drug therapy is essential to further MBM drug development and is being tested in a novel translational study design pioneered by the International Melanoma Working Group (IMWG; NCT01978236).

In conclusion, uncovering the differences between primary melanoma, ECM, and MBM is critical to developing strategies to disrupt the relentless march of melanoma from skin to the brain. Our role is to outwit a cancer with the highest propensity for metastasizing to the brain. The interrogation of matched pairs with all available tools will not only advance knowledge of MBM biology but also accelerate therapeutic advances in immunotherapy, targeted therapy, and combinatorial strategies for this melanoma population in need.

References


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Matching Wits with Melanoma Brain Metastases: From Biology to Therapeutics

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