

European Association of NeuroOncology Magazine

Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-
oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

Report on a Completed EANO

Research Fellowship

Preusser M

*European Association of
NeuroOncology Magazine 2012; 2 (1)*

41-42



Homepage:

[www.kup.at/
journals/eano/index.html](http://www.kup.at/journals/eano/index.html)



THE EUROPEAN ASSOCIATION OF
NEUROONCOLOGY

Online Database Featuring
Author, Key Word and
Full-Text Search

Member of the



Report on a Completed EANO Research Fellowship

Matthias Preusser

Department of Medicine I & Comprehensive Cancer-Center – CNS Tumors Unit, Medical University of Vienna, Austria



Recently, the EANO has launched a new fellowship programme specifically aiming at supporting the mobility of young brain tumour researchers within Europe. Motivated by the wish to gain research experience abroad and to increase my professional network in the field, I applied for such an EANO Fellowship Grant and am very proud to have been selected as the first awardee in early 2011. The EANO Fellowship Grant gave me the opportunity to carry out the project “BRAF V600E mutations in brain metastases of solid cancers” from April to September 2011 at the Department of Neuropathology, Ruprecht-Karl-University, Heidelberg, Germany (Chair: Dr Andreas von Deimling), a distinguished laboratory well-known for its groundbreaking work on brain tumour neuropathology and biology including the recent establishment of isocitrate dehydrogenase 1 (IDH1) R132H immunostaining for neuropathological work-up of gliomas.

In the funded project, we investigated expression of the mutated BRAF V600E protein in a large series of tumours from patients with brain metastases of solid cancers. Brain metastases are common (up to 10 times more common than gliomas), have a poor prognosis, and, surprisingly enough, are so far grossly underrepresented in the scientific literature [1]. Current treatment algorithms comprise mainly neurosurgery and radiotherapy, while systemic therapies have not shown much efficacy so far. There is a strong need to single out novel therapeutic targets and strategies for patients with brain metastases. Activating mutations of the serine threonine kinase v-RAF murine sarcoma viral oncogene homolog B1 (BRAF), most commonly of the V600E type, are found in a wide range of tumours, and specific inhibitors targeting BRAF V600E protein have been developed [2]. Based on the available data on BRAF mutations in primary tumours, we hypothesized that a proportion of brain metastases also harbours the mutation and therefore may be amenable to BRAF-inhibiting therapeutics. We analyzed BRAF V600E-mutant protein expression using a recently generated mutation-specific antibody [3] in a series of 1120 tumour specimens (885 brain metastases, 157 matched primary tumours, and 78 matched extracranial metastases) of 874 brain metastasis patients. The aim of our study was to define the target population for BRAF-inhibiting therapies among brain metastasis patients and to analyze the tumoural expression patterns of BRAF V600E protein. In 85 cases, we performed validation of immunohistochemical results by BRAF exon 15 gene sequencing. BRAF V600E protein was found in brain metastases of 55.3 % of melanoma cases, 6.7 % of ovarian cancer cases, 5.5 % of colorectal cancer cases, 0.3 % of lung cancer cases, 2/6 of thyroid cancer cases, and 1/2 chorioncarcinoma cases. BRAF V600E expression showed high intratumoural homogeneity and was consistent among different tumour manifestations of individual patients, thus providing a rationale for

targeted BRAF inhibitor therapy in selected patients. VE1 immunohistochemistry and BRAF exon 15 sequencing were congruent in 97 % of cases. VE1 immunostaining was more sensitive than gene sequencing in our series, as it identified small BRAF V600E expressing tumour cell aggregates in 10/15 cases with inconclusive genetic results. In general, we found homogenous anti-BRAF V600E immunostaining intensity throughout well-preserved tumour tissue. In none of the cases, we saw focal BRAF V600E expression, providing evidence for a monoclonal origin of BRAF V600E mutated metastases. However, we detected variability of immunostaining intensity among different tumours. It remains to be clarified whether these differences relate to tissue preservation, qualitative differences of the immunostaining reaction, or whether they reflect true differences in BRAF V600E protein expression. It will be of interest to correlate immunostaining intensity to response to treatment with BRAF inhibitors within clinical trials and we have begun to design appropriate trials in cooperation with the European Organization for Research and Treatment of Cancer (EORTC) Brain Tumour Group. Interestingly, in our series, melanoma patients with BRAF V600E mutant protein expressing tumours were significantly younger at diagnosis of the primary tumour and at operation of brain metastases than patients with non-mutated tumours. From our work, we concluded that expression of BRAF V600E mutant protein is found in approximately 6 % of brain metastases and that immunohistochemical visualization of V600E-mutant BRAF protein is a promising tool for patient stratification for BRAF-inhibiting therapies and may facilitate molecular tumour characterization in the clinical setting [4].

My research stay in Heidelberg was a very valuable and scientifically productive time. I could not only profit by increasing my knowledge and scientific experience through the work and interaction with my colleagues in Heidelberg, but am also happy to have made many new friends during my fellowship. Dr von Deimling and his colleagues made me feel very welcome at their institute and were very supportive throughout my entire stay. I am very grateful for this and for the opportunity the EANO Fellowship Grant provided me with and truly hope that the EANO continues this programme to support the careers of more young scientists interested in the fascinating field of neuro-oncology. I feel that we need strong collaborative efforts to make more progress and to fight brain cancer more efficiently. To my mind, interaction and mobility of European researchers are pivotal for the establishment of strong networks for powerful scientific co-operations. Therefore, I strongly encourage all brain tumour researchers interested in a research stay in another European laboratory to apply for an EANO Fellowship Grant and would be happy to share my experience with the organisation of such an exchange or the development of the grant application.

References:

1. Kamar FG, Posner JB. Brain metastases. *Semin Neurol* 2010; 30: 217–35.
2. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364: 2507–16.
3. Capper D, Preusser M, Habel A, et al. Assessment of BRAF V600E mutation status by immunohistochemistry with a mutation-specific monoclonal antibody. *Acta Neuropathol* 2011; 122: 11–9.
4. Capper D, Berghoff AS, Magerle M, et al. Immunohistochemical testing of BRAF V600E status in 1120 tumor tissue samples of patients with brain metastases. *Acta Neuropathol* 2012; 123: 223–33.

Correspondence to:

Matthias Preusser, MD

*Department of Medicine I & Comprehensive Cancer Center –
CNS Unit (CCC-CNS), Medical University of Vienna
A-1090 Vienna*

Währinger Gürtel 18–20

e-mail: matthias.preusser@meduniwien.ac.at