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LETTER TO THE EDITOR

ROS1 translocations and amplifications in lung cancer brain metastases

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To the Editor,

ROS1 gene rearrangements occur in less than 3 % of primary lung cancers (1.2–2.6 % of adenocarcinomas and 0–1.4 % of squamous cell carcinomas) and define a new molecular subtype of lung cancer that is sensitive to therapy with specific inhibitors such as the ALK/MET inhibitor crizotinib [1, 2]. We investigated the *ROS1* gene status in a large series of lung cancer brain metastases (BM), which represent a common and serious disease manifestation for which new treatment options are needed.

All patients who underwent surgery for lung cancer BM at the Medical University of Vienna, Austria, between March 1990 and February 2011 were eligible for this retrospective study. A histologically confirmed primary lung cancer had to be evident for inclusion in this study. Institutional review board approval was obtained. Tissue micro arrays were constructed using two 1.5 mm spots per BM specimen, 3–5 micrometer thick sections were cut from the tissue micro arrays [3].

ROS1 gene status was investigated by fluorescent in situ hybridization (FISH) using a commercially available probe containing a double color break apart probe (Cytocell, Cambridge, UK). FISH was performed and analyzed according to the manufactureŕs instructions, two hundred cells were investigated in each case. *ROS1* amplification was defined if 6 or more gene copies/nucleus were observed, in analogy to *HER2*-FISH in breast cancer.

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We successfully investigated by FISH a total of 153 samples of lung cancer BM (99 adenocarcinomas, 11 squamous cell cancers, 3 adenosquamous carcinomas, 4 large cells carcinomas, 1 large cell neuroendocrine carcinoma, 35 small cell cancers). We found one case of adenocarcinoma BM with *ROS1* translocation (0.6 % of all samples, 1 % of adenocarcinomas, Fig. 1) and one case of squamous cell carcinoma with *ROS1* amplification (0.6 % of all samples), while 151 BM (98.7 % of all BM cases) samples showed neither *ROS1* translocation nor *ROS1* amplification. In the squamous cell lung cancer BM with the *ROS1* amplification 6 gene copies/nucleus were observed.

Our data show that translocations and amplifications of *ROS1* gene occur at a similarly low rate in lung cancer BM as reported for primary tumors. Thus, *ROS1* gene alterations seem not to represent a risk factor for BM development in lung cancer. Nevertheless, ROS1 fusion proteins might represent feasible therapeutic targets in selected lung cancer patients with brain-metastatic disease. Our findings should be validated in further studies.

Conflict of interest The authors declare that they have no conflict of interest.

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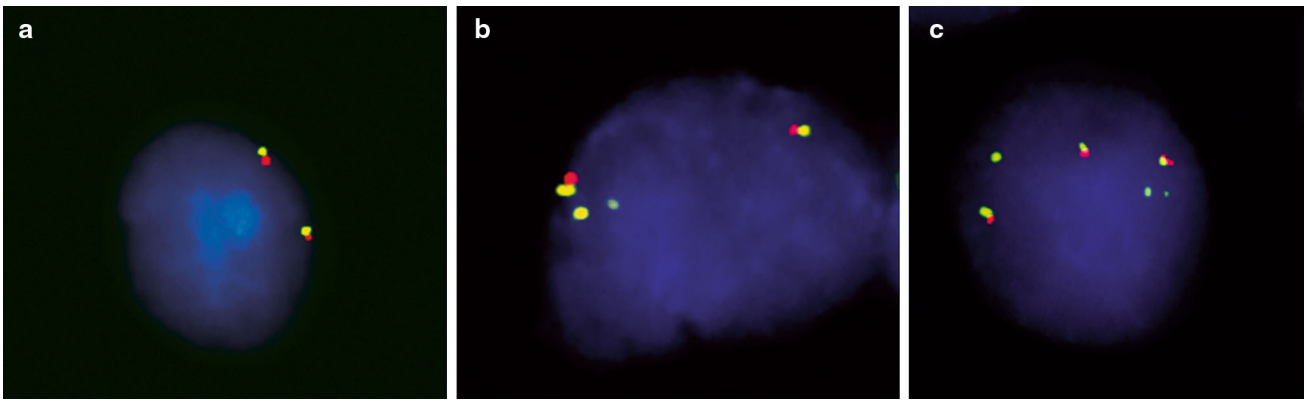

Fig. 1 FISH findings in the lung adenocarcinoma brain metastasis (*green signal* probes flanking the *ROS1* gene on the telomere-side; *red signal* probes flanking the *ROS1* gene on the centromere-side). **a** 66/200 of tumor cells showed 2 normal fusion signals. **b** 76/200 tumor cells showed two normal fusion signals and 1–2 additional *green signals* in close vicinity to one fusion signal: in these cells a rearrangement of *ROS1* occurred with a break in *ROS1* and a suspected rearrangement within the same chromosome. **c** 58/200 tumor cells showed an additional green signal randomly distributed within the nucleus, presumably resembling a subclone with an additional rearrangement with another chromosome

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