



## A new *KIF5B-ERBB4* gene fusion in a lung adenocarcinoma patient

To the Editor:

In cancer patients, *ERBB4* fusions have been reported in the literature with various gene partners (*IKZF1*, *B4GALT5* and *EZR*) [1–3] allowing dimerisation and constitutive activation of the *ERBB4* tyrosine kinase domain. Here, we report a new fusion of *ERBB4* with the coiled-coil domain encoded by *KIF5B*, a universal partner in lung cancer gene fusions, in a patient with a stage IV lung adenocarcinoma.

A 69-year-old female former smoker of 40 pack-years, who had ceased smoking 9 years ago, was diagnosed with an upper right lobe nonmucinous lung adenocarcinoma with symptomatic cystic brain metastases (cT2aN0M1c, 8th edition of the TNM classification for lung cancer) (figure 1a). Immunohistochemistry analyses on computed tomography (CT)-guided lung biopsy sample revealed positive TTF1 immunostaining (figure 1b) but negative PD-L1, ROS1, and ALK staining. A first next-generation sequencing (NGS) analysis was performed on tumour sample DNA (Oncomine Tumor solid DNA kit (OST panel) and complementary panel (OST+V2); Thermo-Fisher Scientific, San Francisco, CA, USA) and RNA extract (Oncomine Focus Assay (OFA); Thermo-Fisher Scientific) failed to detect any additive gene alteration. Since initial general condition was poor, with Eastern Cooperative Oncology Group performance status 2, she first received whole-brain radiation therapy and was then treated with weekly paclitaxel plus carboplatin (four cycles) in the first line setting, with stable disease as the best tumour response according to Response Evaluation Criteria in Solid Tumours 1.1. Because of early relapse at 3 months, she then received single-agent pemetrexed as a second-line treatment with disease progression after two cycles. A third line consisted of nivolumab with rapid metastatic progression (lung and liver) and, finally, single-agent gemcitabine was proposed without any clinical benefit while general condition worsened after one cycle. Taking into account the long period elapsed since smoking cessation and since tumour disease failed to show any response to four lines of treatment, even showing fast progression upon checkpoint inhibitor and a pulmonary miliary pattern of progression on CT scanning, we suspected that patient's tumour could contain a yet unknown additive mutation. We thus decided during our monthly institutional Molecular Multidisciplinary Tumor Board (MTB) meeting (North-Paris TMB, Assistance Publique-Hôpitaux de Paris, at Bichat University Hospital) to investigate the patient's sample using a new, enlarged NGS panel for further additive mutations and potential therapeutic targets. Two different analysis panels were used to maximise the likelihood of significant results. First, we used the Oncomine Comprehensive Assay (version 3; Life Technologies–Thermo Fisher Scientific) for DNA and RNA analyses (including 86 hotspot gene mutations, 48 full-length genes, 47 copy number variations and gene fusions across 45 genes with 760 possible fusions) and second, FusionPlex Lung Tumor for Ion Torrent (Archer DX, Boulder, CO, USA), which allows the identification of additional gene fusions involving 14 genes.

The Oncomine Comprehensive Assay kit only identified a new *KIF5B* (15)–*ERBB4* (18) fusion transcript (figure 1c). To check that this fusion was not an artefact, we performed an additional RNA sequencing analysis with the FusionPlex Pan-Solid Tumor panel for Ion Torrent (Archer DX), which allows analysis



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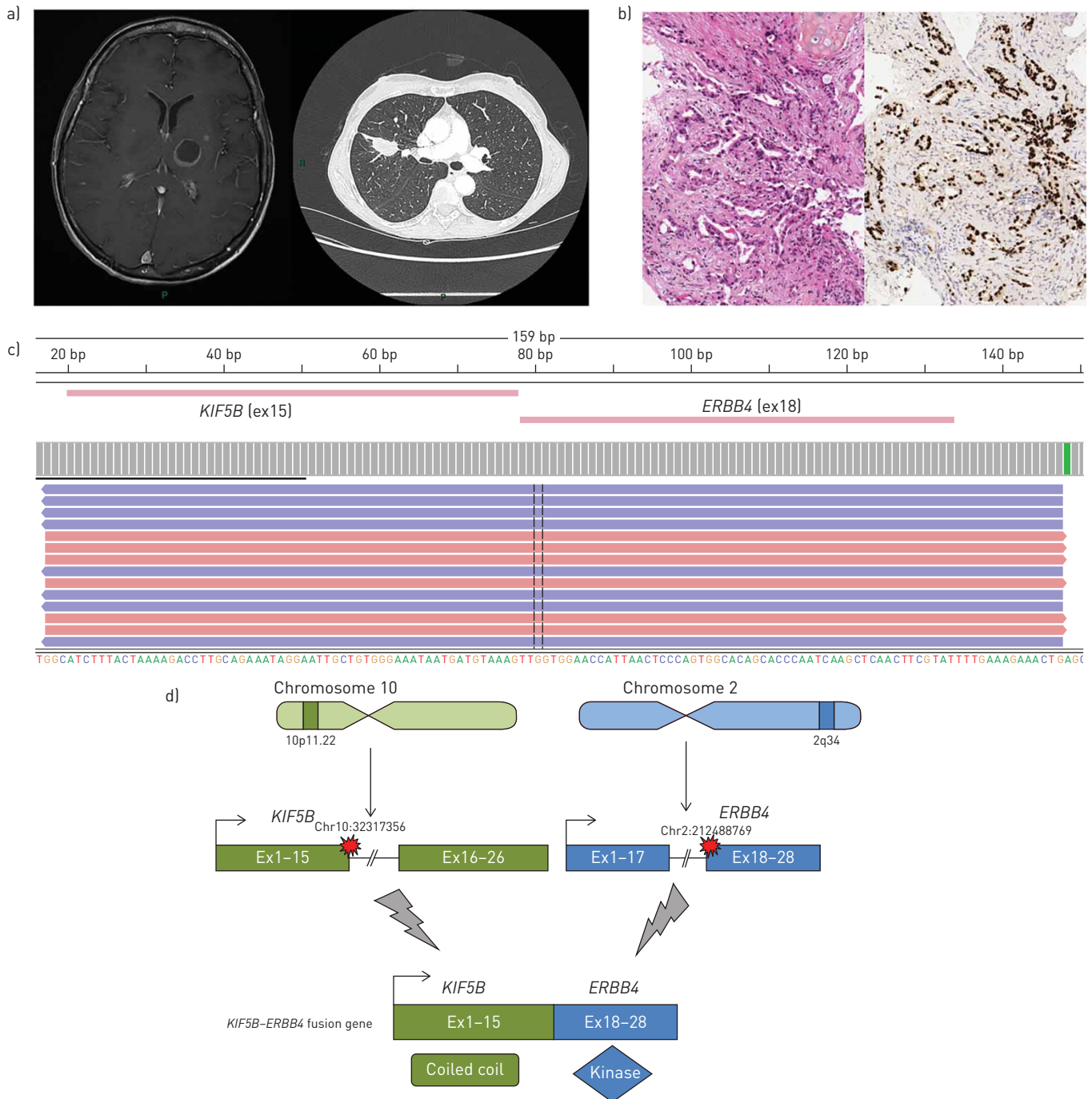
***ERBB4* fusion is a rare, novel oncogenic event involved in the development of lung adenocarcinoma that is not routinely looked for, although *ERBB4* fusion is a potential target for existing pan-ErbB tyrosine kinase and must be implemented in the laboratory**

<https://bit.ly/3nYmGQ9>

**Cite this article as:** Guenzi E, Pluvy J, Guyard A, *et al.* A new *KIF5B-ERBB4* gene fusion in a lung adenocarcinoma patient. *ERJ Open Res* 2021; 7: 00582-2020 [https://doi.org/10.1183/23120541.00582-2020].

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**FIGURE 1** a) Baseline imaging characteristics with upper right lobe mass on computed tomography, and multiple nodular and cystic brain metastasis (magnetic resonance imaging T1 sequence with gadolinium). b) Bronchial biopsy showing an acinar adenocarcinoma (haematoxylin and eosin staining,  $\times 100$  magnification). The tumoral cells display a diffuse nuclear immunostaining of TTF1 ( $\times 100$  magnification). c) Alignment of sequence reads mapping to *KIF5B* and *ERBB4* from RNA sequencing data issue of OncoPrint Comprehensive Assay (version 3) panel. The vertical line indicates the fusion point. d) A schematic of fusion genes with exons (ex) from *KIF5B* and *ERBB4*, and the genomic position of the breakpoint.

of fusions across 103 genes, including *ERBB4*. This expanded third analysis did confirm the existence of the *KIF5B* (Chr10:g.32317356)–*ERBB4* (Chr2:g.212488769) fusion.

*ERBB4* (also known as HER4) belongs to the ErbB/HER family of protein tyrosine kinases, which also includes EGFR (ErbB1), HER2 (ErbB2) and HER3 (ErbB3). These cell membrane receptor proteins can dimerise upon ligand stimulation and then activate multiple signalling pathways, including PI3K/AKT and Ras/Raf/MAPK cascades, transmitting signals that could trigger cell mitosis and proliferation or cell

differentiation. ERBB4 dysfunction has been reported to be involved in multiple human cancers, such as colorectal adenocarcinoma, breast carcinoma, gastric adenocarcinoma and melanoma [4]. *ERBB4* was also reported to carry missense mutations in 4.8% of lung carcinomas [5]. Only rare *ERBB4* fusions have been described so far in human cancers, notably with *EZR* [3] (in a mucinous lung adenocarcinoma), *IKZF2* [1] (in T-cell lymphoma and ovarian tumours) or *B4GALT5* [2] (in a human papillomavirus-positive oropharyngeal squamous cell carcinoma). All these protein fusions retained the full ERBB4 kinase domain and either the polypeptide corresponding to the coiled-coil domain of *EZR* or *IKZF2*, leading to dimerisation of two ERBB4-containing fusion proteins and, most probably, transphosphorylation of their kinase domains or the protein fragment encoded by the first exon of *B4GALT5*, the function of which remains unclear, but in each case probably causing aberrant activation of the ERBB4 kinase domain. NAKAOKU *et al.* [3] reported that *EZR-ERBB4* fusions constitutively activated the ERBB4 kinase function by showing downstream signalling pathways activation. Moreover, fusion-induced anchorage-independent growth and tumorigenicity of NIH3T3 cells stably expressing such plasmid-encoded fusions were shown to be efficiently suppressed by already approved, but repositioned, tyrosine kinase inhibitors (TKIs).

KIF5B (kinesin family member 5B) is involved in the normal distribution of mitochondria and lysosomes in cells, and regulates centrosome and nuclear positioning during mitotic entry. It is also a well-known fusion partner in non-small cell lung cancer (NSCLC) gene fusions, especially with *RET*, *MET* and *ALK* [6]. Fusions with these genes include the KIF5B coiled-coil domain involved in protein dimerization, leading to transphosphorylation and constitutive activation of RET, ALK or MET kinase domains. In this new *KIF5B* (15)–*ERBB4* (18) fusion transcript, the *KIF5B* component encodes the KIF5B coiled-coil domain that should lead to dimerisation and thus abnormal ERBB4 kinase activation (figure 1d).

With respect to this finding, the MTB, based on scarce literature data and taking into account the lack of other validated efficient drugs in a fifth-line setting for NSCLC, suggested to offer the patient Afatinib treatment, a second generation pan-ErbB TKI, at 40 mg·day<sup>-1</sup>, as already described in NSCLC with *EGFR* mutation [7]. This treatment had actually been reported to display some efficacy in a lung squamous cell carcinoma patient with a tumour missense mutation in the *ERBB4* gene (p.Arg847His) [8] and in an urothelial carcinoma patient with *ERBB3* missense mutations [9]. Indeed, afatinib inhibits all members of the ErbB family *in vitro*. Unfortunately, due to worsening neurological condition, the patient never received afatinib and passed away.

Other treatments could also be considered for *ERBB4* alterations, such as lapatinib or tarloxotinib. However, *ERBB4* gene mutations seem to confer a resistance mechanism to lapatinib in breast cancers with *HER2* amplifications [10]. Tarloxotinib (EGFR/HER inhibitor) is currently being tested for NSCLC in cases of *ERBB* fusions, including *ERBB4* fusion (<https://clinicaltrials.gov/show/NCT03805841>).

In conclusion, we report a new *ERBB4* fusion transcript in a nonmucinous lung adenocarcinoma with *KIF5B* as partner, which has never previously been described, to our best knowledge. Other *ERBB4* fusion transcripts were previously shown to be oncogenic and targetable but they are probably underdiagnosed, since the current genetic tests do not explore this gene. In fact, routine genetic tests lack several unusual or rare genetic alterations that could be targeted, especially in never- or former smoker patients. We think such an enlarged second-line panel strategy should be discussed more systematically in MTBs when no common genetic alteration is found in the first-line NGS (especially, with no *EGFR*, *ROS*, *ALK*, *KRAS*, *MET* or *RET* alterations), possibly earlier than in the current case. A second-line NGS approach could lead to treating these patients with registered oral TKI initially developed to target other related genes or with drug in clinical trials, with the potential to prolong patient survival.

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Received: 7 Sept 2020 | Accepted: 12 Jan 2021

Conflict of interest: E. Guenzi has nothing to disclose. J. Pluvy reports personal fees from BMS, nonfinancial support from MSD and personal fees from AstraZeneca, outside the submitted work. A. Guyard has nothing to disclose.

M. Nguenang has nothing to disclose. K. Rebah has nothing to disclose. Z. Benrahmoune has nothing to disclose. J. Lamoril has nothing to disclose. A. Cazes reports personal fees from AstraZeneca, Boehringer Ingelheim, Roche and MSD, outside the submitted work. V. Gounant reports personal fees from AstraZeneca, BMS, Chugai, MSD and Roche, outside the submitted work. S. Brosseau has nothing to disclose. C. Boileau has nothing to disclose. G. Zalzman reports nonfinancial support from Roche; personal fees and nonfinancial support from AstraZeneca; grants, personal fees and nonfinancial support from BMS; and nonfinancial support from MSD, Pfizer, Takeda, Abbvie and Da Volterra, all outside the submitted work. N. Théou-Anton reports grants and personal fees from AstraZeneca and Takeda, outside the submitted work.

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