effective management options which need to be considered in the context of the patient’s individual needs and preferences.

Let’s not expend any further stomach acid on this issue, agree that we all are ethical and capable physicians trying to bring the best solutions to our patients and continue to collaborate on meeting the real unmet needs of our patients.

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ALK FISH rearranged and amplified tumor with negative immunohistochemistry: a rare and challenging case concerning ALK status screening in lung cancer

We read with interest the study by Ilie et al. concerning the discrepancies between fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) for assessment of the ALK status in nonsmall-cell lung cancer (NSCLC) [1]. The authors not only reported FISH+ IHC− and FISH− IHC+ cases, as

Figure 1. Metastasis analysis. (A) Adenocarcinomatous tumor cells. (B) Negative ALK immunohistochemistry. (C) A tumor cell with ALK split and single 3’ rearranged signals and numerous ALK copies. (D) Tumors cells only contain ~3.5 mean number of chromosome 2 per nucleus.
previously reported, but also introduced the notion of ALK FISH ‘borderline’ tumors (i.e. 15%–20% of rearranged nuclei) emphasizing potential issues in ALK FISH analysis [2]. They especially reported the particular cases of two FISH–IHC+ tumors with ALK amplification (i.e. high copy number corresponding to more than six copies per nucleus). Within 26 ALK FISH+ tumors (i.e. with more than 15% of rearranged FISH nuclei using the FDA-approved ALK break-apart FISH probe), no tumor presented ALK amplification.

ALK copy number gains have been described in NSCLC. Although ALK amplification in ALK-rearranged tumors seems to be rare, few studies have been conducted in these tumors [3–5]. We report here a case of ALK-rearranged and amplified tumor that was ALK IHC negative.

We identified a single case of both ALK-rearranged and amplified tumor among ~70 cases of ALK FISH positive NSCLC (~7% of the NSCLC samples analyzed in our institutional cancer molecular genetics platform). This represents <2% of ALK-rearranged NSCLC and 0.1% of unselected NSCLC in our institution. The sample was a metastasis from the abdominal wall in a patient with a voluminous lung tumor. The ALK rearrangement consisted in both FISH split and single 3' signals in 30% of tumor cells (mean 2.8 split and 1.5 single 3' signals per nucleus). There was a mean number of 4.5 fused signals per nucleus. Adding split and single 3' signals resulted in a mean number of 8.8 ALK copies per nucleus whereas the mean number of chromosome 2 per nucleus was 3.5 with an ALK/chromosome 2 ratio of 2.5. This was consistent with an ALK amplification. The ALK IHC analysis (clone 5A4, 1:25, CliniSciences) was negative (score 0) (Figure 1). To date, this 46-year-old smoker woman, with KRAS, EGFR and BRAF nonmutated status, has not been treated by crizotinib.

This particular case illustrates some challenges in ALK rearrangement screening. First, ALK amplification, with FISH clusters in some cells as encountered in our case can impair the detection of positive signals within tumor cells and in this manner requires careful examination of these cases. Second, if ALK copy number gains are frequent in ALK nonrearranged tumors, ALK-amplified tumors are rare in ALK-rearranged tumors, as previously described [1, 3–5]. Finally, as previously mentioned in some studies, we agree with Ilie et al. and think that both IHC and FISH analyses should be carried out to avoid ALK status misdiagnosis [1, 2]. We should be aware of these particular cases because this rare ALK double alteration would have been missed by an IHC-based prescreening, as proposed in some studies.

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**References**


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**Different effects of the BIM deletion polymorphism on treatment of solid tumors by the tyrosine kinase inhibitors (TKI) pazopanib, sunitinib, and lapatinib**

An inherited 2.9-kb deletion polymorphism in the proapoptotic protein Bcl-2-like 11 (BIM) may have a role in tumor response to tyrosine kinase inhibitor (TKI) treatment [1]. Preclinical studies have correlated apoptosis response induced by a range of TKIs with BIM expression and with loss activity conferred by RNA interference [2] or the deletion polymorphism [1]. BIM deletion carriage allele is common in East Asian individuals (10%–19%), but has not been observed in African and European populations [1]. Recently, a few studies in Asian patients consistently demonstrated that the BIM deletion polymorphism was associated with clinical resistance to EGFR-targeted TKI therapy in EGFR-mutated nonsmall-cell lung cancer [1, 3]. In contrast, inconsistent results for this genetic association have been reported for imatinib in chronic myeloid leukemia [4], and the BIM deletion showed no effect for sorafenib efficacy in patients with hepatocellular carcinoma [5].

The availability of germline DNA, collected prospectively during clinical trials (supplementary Table S1, available at Annals of Oncology online), provided us the opportunity to extend evaluation of the BIM deletion polymorphism to...