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 spit 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.

A. Uguen1,2,3*, M. Talagas3,4, S. Andrieu-Key2, S. Costa2, I. Quintin-Roué2, M. De Braekeleer1,5 & P. Marcorelles2,3,4

1Inserm, U1078, Brest;
2Department of Pathology, CHRU Brest, University Hospital Morvan, Brest;
3European University of Brittany, Rennes;
4EA4685, Brest University, Brest;
5Cytogenetics and Reproduction Biology Laboratory, CHRU Brest, Brest, France

(*E-mail: arnaud.uguen@chu-brest.fr)

disclosure

The authors have declared no conflicts of interest.

references


doi: 10.1093/annonc/mdv210
Published online 28 April 2015

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
additional TKIs and cancer types. Following informed consent, \textit{BIM} genotype and clinical response data were analyzed in self-reported Asian patients treated with the VEGFR-targeted TKIs pazopanib and sunitinib in renal cell carcinoma (RCC), pazopanib in ovarian cancer (OC), or the HER2/EGFR-targeted TKI lapatinib (plus paclitaxel) in HER2-overexpressing metastatic breast cancer (MBC). The association of \textit{BIM} deletion carriage with progression-free survival (PFS) in patients for each TKI/disease subset was analyzed by Cox regression. With more than 60 PFS events for each subset, there was 60\%–80\% power to identify an effect with hazard ratio (HR) >2, similar in size to the original report [1].

The \textit{BIM} deletion allele was present in 11\%–15\% of patients analyzed (Figure 1). Seven of the 74 carriers were homozygous for the deletion allele and were not analyzed separately due to small sample size. \textit{BIM} deletion carriage was not significantly associated with PFS response to TKI treatment in RCC and MBC (Figure 1, \textit{P} > 0.05), but was weakly associated with shorter PFS in pazopanib-treated OC patients [Figure 1, HR = 1.73 (95\% confidence interval 0.91–3.30), \textit{n} = 129, one-tailed \textit{P} = 0.048].

The 2.9-kb, intron 2 deletion polymorphism confers preferential splicing of exon 3 over exon 4 and expression of \textit{BIM} isoforms lacking the proapoptotic BH3 domain [1]. The different association results for the \textit{BIM} deletion polymorphism on different TKIs might reflect variable relative expression of deletion and full-length isoforms in heterozygous carriers in different TKI treatment and disease settings, or may reflect differences in the importance of \textit{BIM}-mediated apoptosis relative to other antitumor mechanisms (such as signaling blockade and angiogenesis inhibition). Our results suggest that future studies should explore the \textit{BIM} deletion in a broader range of disease and TKI treatment settings.


\textit{GlaxoSmithKline Research and Development, Stevenage, UK;} 2\textit{G}2\textit{Health} International, Durham; 3\textit{GlaxoSmithKline Research and Development, Philadelphia, USA;} 4\textit{Klinikum Essen-Mitte, Essen, Germany}  

(*E-mail: colin.f.spraggs@gsk.com)

acknowledgements

Editorial support was provided by ProEd Communications, Inc.

data bias

The clinical studies were funded and conducted by GlaxoSmithKline.

disclosure

AdB has received advisory board honoraria from Astra Zeneca, MSD, Roche, AMGEN, Eisai, Mundipharm, and Pharmamar (all unrelated to the submitted work). CFS, LRP, LPB, KS, TJ, MR, HT and CFX are employees of GlaxoSmithKline and hold stock. This report is not under consideration for publication elsewhere and all named authors have agreed to its submission.

references


doi: 10.1093/annonc/mdv211
Published online 28 April 2015