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Continuing Medical Education (CME) Questions

A novel *PDGFRB* mutation in TKI-resistant Ph-like ALL

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Zhang Y, Gao Y, Zhang H, Zhang J, He F, Hnízda A, Qian M, Liu X, Gocho Y, Pui C-H, Cheng T, Wang Q, Yang JJ, Zhu X, Liu X. *PDGFRB* mutation and tyrosine kinase inhibitor resistance in Ph-like acute lymphoblastic leukemia. *Blood.* 2018;131(20):2256-2261.

1. Your patient is a 5-year-old boy with Philadelphia-like (Ph-like) acute lymphoblastic leukemia (ALL) who has relapsed after chemotherapy and tyrosine kinase inhibitor (TKI) therapy. Your patient's genetic alterations are very similar to those in the case report and genomic analysis by Zhang and colleagues. Based on the case report, which of the following statements about the clinical characteristics and a novel oncogenic *PDGFRB* fusion gene in Ph-like ALL is correct?

- ☐ Imatinib monotherapy induced rapid leukemia clearance, which was a stable response at 1-year follow-up
- ☐ Cytogenetic analysis using fluorescence in situ hybridization suggested a possible *PDGFRB* rearrangement, and genomic analysis identified *AGGF1-PDGFRB*, a novel oncogenic fusion gene
- ☐ The novel oncogenic fusion gene in this patient was characterized by in-frame fusion of exon 7 to 10 of *PDGFRB* with exon 7 to 10 of the *AGGF1* gene
- ☐ *PDGFRB* rearrangement was unlikely to be the genomic abnormality driving leukemia pathogenesis

2. Based on the case report and genomic analysis by Zhang and colleagues, which of the following statements about *PDGFRB* mutation–mediated TKI resistance in Ph-like ALL is correct?

- ☐ The $PDGFRB^{C843G}$ mutation directly conferred resistance only to imatinib and not to other ABL TKIs
- ☐ Diagnostic blasts had a single *IKZF1* deletion at a subclonal level
- ☐ At relapse after imatinib treatment, only 1 of the 2 *IKZF1* deletions remained, and there was a new relapse-specific $IKZF1^{G158S}$ mutation
- ☐ Ponatinib was as effective in Ba/F3 cells expressing the mutant *AGGF1-PDGFRB* as in cells with wild-type fusion gene

3. Based on the case report and genomic analysis by Zhang and colleagues, which of the following statements about a potential therapeutic strategy to overcome TKI resistance in Ph-like ALL is correct?

- ☐ *PDGFRB*-mutant leukemia cells were highly sensitive to multitarget kinase inhibitor CHZ868, suggesting a potential therapeutic strategy for some patients with resistance to ABL TKIs
- ☐ CHZ868 was highly effective in cells expressing the *BCR-ABL1* fusion, but not in Ba/F3 cells with *AGGF1-PDGFRB* fusions
- ☐ Dasatinib has more proximal interactions with the wild-type PDGFRB kinase domain than does CHZ868
- ☐ The TKI resistance mechanism identified in this study is exclusive to Ph-like ALL

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