The *BIM* deletion polymorphism cannot account for intrinsic TKI resistance of Chinese individuals with chronic myeloid leukemia

To the Editor:

We read with great interest the research of Ng *et al.*[1], which established an association between a BCL2-like 11 (*BIM*) gene deletion polymorphism in East Asian populations and clinical resistance to imatinib, a tyrosine kinase inhibitor (TKI). They showed that the deletion resulted in expression of BIM isoforms lacking the proapoptotic BCL2-homology domain 3 (BH3). Therefore, patients with chronic myeloid leukemia (CML) with the polymorphism had markedly inferior responses to TKIs (especially imatinib) than did patients without it. This discovery could be of great importance for the treatment of CML because the use of BH3 mimetics in patients harboring this polymorphism might allow for personalized treatment that would overcome this TKI resistance or even prevent its emergence.

In order to identify the influence of this polymorphism on TKI responses in Chinese patients with CML, we examined a group of 220 newly diagnosed patients with chronic-phase CML whose first-line therapy was a standard dose of imatinib (400 mg per day) and determined whether they had the *BIM* deletion polymorphism. We classified individuals as resistant or sensitive to imatinib in a similar manner to Ng *et al.*[1] on the basis of the European LeukemiaNet (ELN) criteria (detailed criteria are shown in **Supplementary Table 1**). We detected the *BIM* deletion polymorphism by a single PCR using three primers that were designed to amplify the 244-bp wild-type and 138-bp deletion *BIM* segments. We subsequently sequenced the amplified products to ensure the specificity of the PCR (primer and product sequences and PCR conditions are in **Supplementary Methods** and **Supplementary Figure 1**).

We found that 30 patients were heterozygous for the deletion polymorphism and the other 190 patients did not harbor the deletion. Of the 30 individuals with this polymorphism, 23 (76.7%) were sensitive to imatinib and only seven (23.3%) were resistant to it. Among the individuals without the polymorphism, 117 (61.6%) were sensitive to imatinib and 73 (38.4%) were resistant to it (**Supplementary Table 2**). Baseline characteristics of all patients with CML and clinical features of patients with CML and the *BIM* deletion polymorphism are shown in **Supplementary Tables 3** and **4**, respectively. Our results did not show that patients with the *BIM* deletion polymorphism were more likely to be resistant to imatinib compared to those without it. Additionally, we screened 200 healthy individuals and found the deletion polymorphism in 41 of them. One of them was homozygous, and the other 40 were heterozygous. The overall carrier frequency of the *BIM* deletion polymorphism in our study (16.9%, $n = 420$) was higher than that reported by Ng *et al.*[1] (12.3%).

We then carried out statistical analysis to test for the association between the *BIM* deletion polymorphism and clinical resistance to imatinib using logistic regression. The overall odds ratio for resistant disease among individuals with the polymorphism compared to those without it was 0.488 ($P = 0.116$, 95% confidence interval 0.199–1.194). This showed that the association between the polymorphism and clinical resistance to imatinib was not statistically significant. Therefore, we conclude that the *BIM* deletion polymorphism cannot account for intrinsic TKI resistance of Chinese individuals with CML, although the conclusion is limited to our patient population. Further studies on a larger sample size and populations of other genetic backgrounds are needed to verify this association.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nm.3638).

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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1. Ng, K.P. *et al. Nat. Med.* **18**, 521–528 (2012).

Ong *et al.* reply:

We acknowledge the interest of Chen *et al.*[1] in our recent publication on the discovery of an East Asian–specific *BIM* deletion polymorphism that mediates intrinsic resistance to tyrosine kinase inhibitors (TKIs) in patients with chronic myeloid leukemia (CML) and epidermal growth factor receptor (EGFR)-mutated non–small-cell lung cancer (EGFR NSCLC)[2]. Mechanistically, the *BIM* deletion results in the generation of *BIM* splice isoforms lacking the proapoptotic BH3 domain and is sufficient to cause partial, but not absolute, resistance to TKI monotherapy[2]. Further, *BIM* deletion–mediated TKI resistance can be overcome by increases in TKI concentration or the use of more potent TKIs (T.K.K., C.T.H.C., J.W.J. Huang, K.P. Ng & S.T.O., unpublished data). In their correspondence, Chen *et al.*[1] evaluated the response of 220 Chinese patients with CML to imatinib. They found the frequency of the *BIM* deletion polymorphism to be 13.6% in patients (30/220) and that there was no difference between *BIM* deletion carriers and noncarriers in the clinical response to imatinib.