Insight into the molecular events underlying oncogenesis has prompted the development of new treatment approaches such as molecularly targeted therapies, which are overcoming the limited overall survival and severe side effects of traditional cytotoxic cancer therapeutics. At the same time, matured clinical trials have identified reliable biomarkers that predict the outcomes of such molecularly targeted cancer therapeutics. One of the most successful therapies with an associated biomarker is the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) in non–small cell lung cancer (NSCLC), including gefitinib and erlotinib, both of which compete with adenosine triphosphate (ATP) for binding to the tyrosine kinase pocket of the receptor. Several recent phase III trials, WJTOG3405 (1), NEJ002 (2), and subset analysis of IPASS (3) demonstrated that single-agent gefitinib has superior progression-free survival (PFS) to platinum-based doublets if NSCLC patients with somatic activating mutations in EGFR are selected. However, limitations of molecularly targeted therapies still exist even when using reliable biomarkers, because of heterogeneity within the same subtype as well as acquired resistance to these therapies. For example, 30% to 40% of NSCLC patients with EGFR mutation do not achieve Response Evaluation Criteria in Solid Tumors (RECIST) criteria for response (1–3). These studies suggest that one biomarker may not be sufficient to predict the outcome of a corresponding molecularly targeted therapy. Thus, there is a need to identify other biomarkers to provide patients with more personalized cancer therapeutics.

The B-cell lymphoma 2 (BCL-2) interacting mediator of cell death (BIM) is a member of the pro-apoptotic BCL-2 homology domain 3 (BH3)–only proteins, which have essential roles in the mitochondrial apoptosis pathway. BIM is able to bind to anti-apoptotic BCL-2 family members such as MCL-1 and BCL-2 to liberate and directly activate pro-apoptotic BAX and BAK, which cause mitochondrial outer membrane permeabilization (MOMP) followed by cytochrome c release and caspase-dependent apoptosis (Fig. 1A). Several preclinical studies have pointed out that BIM induction by inhibition of the MEK-ERK pathway plays a key role in apoptosis of oncogene-addicted solid cancer cells including EGFR-mutant NSCLC (4, 5), HER2-amplified breast cancer (5, 6), and BRAF-mutant colorectal cancer or melanoma cells (7). In this issue of Cancer Discovery, Faber and colleagues (8) demonstrate that knockdown of BIM expression protects HER2-amplified and PIK3CA-mutant breast cancer cells against apoptosis induced by the EGFR/HER2 TKI lapatinib and the PI3K/mTOR inhibitor NVP-BEZ235, respectively. These results not only confirm previous results (4, 6, 7), but also suggest that BIM expression is critical for apoptosis even in PIK3CA-mutant cells treated with NVP-BEZ235, which does not affect the MEK-ERK pathway. Most importantly, the basal expression of BIM is positively correlated with the amount of apoptosis induced by the corresponding TKI treatment within the same subtype of several oncogene-addicted cancer cell types, such as EGFR-mutant NSCLC cells treated with gefitinib, HER2-amplified breast cancer cells treated with lapatinib, PIK3CA-mutant breast cancer cells treated with NVP-BEZ235, and BRAF-mutant colorectal cancer cells treated with the MEK inhibitor AZD6244. Strikingly, high BIM expression is associated with longer PFS in EGFR-mutant NSCLC and HER2-positive breast cancer patients treated with TKI. These results suggest that pre-treatment assessment of BIM levels is able to identify patients who will benefit more from molecularly targeted therapies even after selecting patients based on mutated oncogene status.

However, as Faber and colleagues (8) discuss, strategies need to be developed for patients with low BIM expression in order to take advantage of the benefit of BIM in aiding death of tumors driven by mutant oncoproteins. Although their previous study suggested that the combination of NVP-BEZ235 and AZD6244 could be an alternative strategy for EGFR-mutant NSCLC cells (5), this combination failed to increase apoptosis in EGFR-mutant cells with low BIM expression in their current study. Another recent study demonstrated that NVP-BEZ235 combined with lapatinib increased apoptosis compared with each agent alone in PIK3CA-mutant breast cancer cells with high BIM expression (6). This combination should be assessed...
BIM and BH3 mimetics in the apoptotic pathway. A, BH3-only protein BIM binds to anti-apoptotic BCL-2 family members such as MCL-1 and BCL-2 to liberate and directly activate pro-apoptotic BAX and BAK, which cause caspase-dependent apoptosis through the mitochondrial apoptosis pathway. B, BH3 mimetics ABT-737 and ABT-263 bind to anti-apoptotic BCL-2 members resulting in the upregulation of free BH3-only protein BIM to increase apoptosis. Because ERK inhibition causes BIM induction, the use of BH3 mimetics combined with ERK inhibition by targeted therapies could be a strategy for patients with low BIM expression.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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The Potential Benefits of BIM in the Further Pursuit of Biomarker Discovery in Cancer Therapeutics

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