IN THE SPOTLIGHT

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

Takeshi Yoshida and Eric B. Haura

Summary: In this issue of *Cancer Discovery*, Faber and colleagues demonstrate that the basal expression of BIM is positively correlated with the amount of apoptosis induced by the corresponding tyrosine kinase inhibitor treatment within the same subtype of several oncogene-addicted cancer cell types. Their results suggest that pre-treatment assessment of BIM levels can identify patients who would benefit from molecularly targeted therapies even after biomarker-based patient selection. *Cancer Discovery; 1(4);* 289–90. *©2011 AACR.*

Commentary on Faber et al., p. 352(8).

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 oncogenes. 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

Authors' Affiliation: Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

Corresponding Author: Eric B. Haura, Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL 33612. Phone: 813-903-6827; Fax: 813-903-6817; E-mail: eric.haura@moffitt.org

doi: 10.1158/2159-8290.CD-11-0193

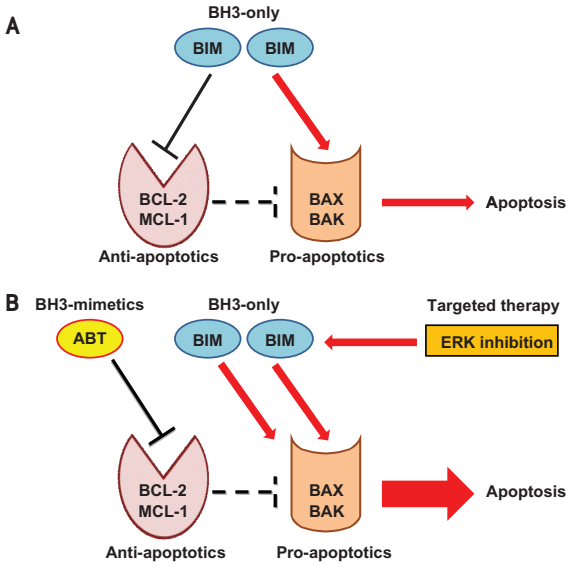

Figure 1. Model of involvement of BIM and BH3 mimetics in the apoptosis of cancer cells. **A,** BH3-only protein BIM binds to anti-apoptotic BCL-2 family members such as MCL-1 and BCL-2 to liberate and directly activate pro-apoptotic BAX and BAK, which cause caspase dependent apoptosis through the mitochondrial 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.

in *PIK3CA*-mutant cells with low BIM expression, since NVP-BEZ235 itself does not lead to BIM induction, unlike EGFR-TKI, AZD6244, or lapatinib (6). Faber and colleagues (8) also show that BIM knockdown does not rescue *HER2*-amplified or *PIK3CA*-mutant breast cancer cells from apoptosis induced by paclitaxel, gemcitabine, or cisplatin, in line with their results indicating that BIM expression is not correlated with the amount of apoptosis induced by these cytotoxic agents in *EGFR*-mutant NSCLC cells. In addition, lapatinib combined with paclitaxel induced tumor regression compared with each agent alone in ZR7530 *HER2*-amplified breast cancer xenografts with low BIM expression. Given these results, it is possible that *EGFR*-mutant NSCLC patients with low BIM expression may benefit from the combination of cytotoxic chemotherapy plus EGFR-TKI over single-agent EGFR-TKI alone, despite the results of recent phase III trials showing that single-agent gefitinib has a better outcome in NSCLC patients with *EGFR* mutation (1–3). Although previous clinical trials in unselected patients did not show any additive effects of EGFR-TKI when combined with platinum-based doublets in NSCLC patients (9), such combination should be reconsidered in the setting of *EGFR*-mutant NSCLC with low BIM expression. According to the results showing that BIM induction in cells with low BIM expression sensitizes them to targeted therapies, another potential strategy is employing BH3 mimetics that bind to anti-apoptotic BCL-2 members, resulting in the upregulation of free BH3-only proteins including BIM (Fig. 1B). Indeed, a previous study demonstrated that gefitinib combined with BH3 mimetic ABT-737 substantially increases apoptosis compared with each agent alone in *EGFR*-mutant H1650 cells with low BIM expression (4). A phase I trial of erlotinib with BH3 mimetic ABT-263 is currently ongoing to translate this strategy to the clinic (ClinicalTrials.gov identifier NCT01009073). Since it remains unclear whether BIM is a useful biomarker in other populations including NSCLC patients with the *EML4-ALK* fusion gene (10) or EGFR-TKI resistance, additional retrospective cohorts as well as prospective clinical trials are also needed to provide cancer patients with second-generation biomarker-based personalized molecularly targeted therapeutics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Published online September 15, 2011.

REFERENCES

1. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121–8.
2. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380–8.
3. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
4. Cragg MS, Kuroda J, Puthalakath H, Huang DC, Strasser A. Gefitinib-induced killing of NSCLC cell lines expressing mutant EGFR requires BIM and can be enhanced by BH3 mimetics. PLoS Med 2007;4:1681–9.
5. Faber AC, Li D, Song Y, Liang MC, Yeap BY, Bronson RT, et al. Differential induction of apoptosis in HER2 and EGFR addicted cancers following PI3K inhibition. Proc Natl Acad Sci U S A 2009;106:19503–8.
6. Tanizaki J, Okamoto I, Fumita S, Okamoto W, Nishio K, Nakagawa K. Roles of BIM induction and survivin downregulation in lapatinib-induced apoptosis in breast cancer cells with HER2 amplification. Oncogene. 2011 Apr 18. [Epub ahead of print]
7. Cragg MS, Jansen ES, Cook M, Harris C, Strasser A, Scott CL. Treatment of B-RAF mutant human tumor cells with a MEK inhibitor requires Bim and is enhanced by a BH3 mimetic. J Clin Invest 2008;118:3651–9.
8. Faber A, Corcoran RB, Ebi H, Sequist LV, Waltman BA, Chung E, et al. BIM expression in treatment-naïve cancers predicts responsiveness to kinase inhibitors. Cancer Discovery 2011;1:352–65.
9. Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. J Clin Oncol 2004;22:777–84.
10. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693–703.