Src Inhibition Is Still a Relevant Target in Pancreatic Cancer

THOMAS J. GEORGE JR.,^a JOSE G. TREVINO,^b CHEN LIU^c

Departments of ^aMedicine, ^bSurgery, and ^cPathology, University of Florida, Gainesville, Florida, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

It is with great interest and anticipation that Dr. Chee and colleagues report their phase II study results of dasatinib in the first-line treatment of patients with metastatic pancreatic cancer (PCa) [1]. The authors should be applauded for successfully conducting an important “window of opportunity” study with high hopes of demonstrating benefit. Unfortunately, the study failed to meet the prespecified primary endpoint of improving overall survival. However, we respectfully disagree with the authors’ conclusion that dasatinib has no clinical activity in metastatic PCa. Although it is true that this agent as monotherapy failed to achieve a meaningful composite outcome of overall survival in the patients treated, there were a number of individuals who had durable and sustained response to relatively brief therapy exposure. Whether due to the biologic agent or inherent in the individual patient’s disease biology, such findings are consistent with the National Cancer Institute’s recently reported goal of identifying exceptional responders to therapies. Such identification of clinical responders allows for the pursuit of deep interrogation of their cancer biology to determine a mechanistic rationale that might be exploited further for the benefit of all patients [2]. Thus, efforts should be made to better understand the outcomes and biologic “-omics” associated with the heterogeneous nature of the disease among individual patients with pancreatic cancer.

There are significant preclinical data to support the rationale for Src inhibition as a potentially effective therapeutic target in PCa [3–6]. However, the presumption that a single biologic agent would significantly improve survival in

metastatic PCa is inconsistent with prior clinical investigation and preclinical data. It may be more therapeutically effective and scientifically rational to consider Src inhibition in combination with cytotoxic therapies based on the following caveats: (a) Constitutively active Src is associated with increased chemoresistance in pancreatic cancer cells [7–9]. (b) Inhibition of Src reduces tumor expression of thymidylate synthase, the target enzyme of 5-fluorouracil; thus, lowering thymidylate synthase levels is associated with subsequent 5-fluorouracil chemoresistance reversal, resulting in substantially decreased in vivo tumor growth and inhibition of progressive distant metastases [10, 11]. (c) Dasatinib can synergistically inhibit oxaliplatin-induced Src activation, and Src inhibition can also increase oxaliplatin activity both in vitro and in vivo [12].

Therefore, we recommend continued investigations for our patients with PCa by developing rational combination therapies that capitalize on therapeutic Src inhibition. A combination clinical trial of Src inhibition with cytotoxic therapies to explore these hypotheses, with correlative molecular tumor and surrogate tissue analyses, is ongoing with active enrollment (NCI ClinicalTrials.gov #NCT01652976).

DISCLOSURES

Thomas J. George Jr.: Bristol-Myers Squibb (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

1. Chee CE, Krishnamurthi S, Nock CJ et al. Phase II study of dasatinib (BMS-354825) in patients with metastatic adenocarcinoma of the pancreas. *The Oncologist* 2013;18:1091–1092.
2. Kaiser J. Biomedicine. Rare cancer successes spawn “exceptional” research efforts. *Science* 2013;340:263.
3. Ito H, Gardner-Thorpe J, Zinner MJ et al. Inhibition of tyrosine kinase Src suppresses pancreatic cancer invasiveness. *Surgery* 2003;134:221–226.
4. Yezhelyev MV, Koehl G, Guba M et al. Inhibition of Src tyrosine kinase as treatment for human pancreatic cancer growing orthotopically in nude mice. *Clin Cancer Res* 2004;10:8028–8036.
5. Nagaraj NS, Smith JJ, Revetta F et al. Targeted inhibition of Src kinase signaling attenuates pancreatic tumorigenesis. *Mol Cancer Ther* 2010;9:2322–2332.
6. Trevino JG, Summy JM, Lesslie DP et al. Inhibition of Src expression and activity inhibits tumor progression and metastasis of human pancreatic adenocarcinoma cells in an orthotopic nude mouse model. *Am J Pathol* 2006;168:962–972.
7. Duxbury MS, Ito H, Zinner MJ et al. Inhibition of Src tyrosine kinase impairs inherent and acquired gemcitabine resistance in human pancreatic adenocarcinoma cells. *Clin Cancer Res* 2004;10:2307–2318.
8. Ischenko I, Camaj P, Seeliger H et al. Inhibition of Src tyrosine kinase reverts chemoresistance toward 5-fluorouracil in human pancreatic carcinoma cells: An involvement of epidermal growth factor receptor signaling. *Oncogene* 2008;27:7212–7222.
9. Treviño JG, Pillai S, Kunigal S et al. Nicotine induces inhibitor of differentiation-1 in a Src-dependent pathway promoting metastasis and chemoresistance in pancreatic adenocarcinoma. *Neoplasia* 2012;14:1102–1114.
10. Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: The combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul* 1984;22:27–55.
11. Griffiths GJ, Koh MY, Brunton VG et al. Expression of kinase-defective mutants of c-Src in human metastatic colon cancer cells decreases Bcl-xL and increases oxaliplatin- and Fas-induced apoptosis. *J Biol Chem* 2004;279:46113–46121.
12. Kopetz S, Lesslie DP, Dallas NA et al. Synergistic activity of the SRC family kinase inhibitor dasatinib and oxaliplatin in colon carcinoma cells is mediated by oxidative stress. *Cancer Res* 2009;69:3842–3849.

Correspondence: Thomas J. George Jr., M.D., F.A.C.P., Department of Medicine, University of Florida, 1600 SW Archer Road, Gainesville, Florida 32610, USA. Telephone: 352-273-8008; E-Mail: tgeorge@ufl.edu Received October 23, 2013; accepted for publication November 11, 2013; first published online in *The Oncologist Express* on January 23, 2014. ©AlphaMed Press 1083-7159/2014/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2013-0410>