

Answer 1:

### Bibliographic Information

**Enhancement of the antitumor activity of tamoxifen and anastrozole by the farnesyltransferase inhibitor lonafarnib (SCH66336).** Liu, Gonjigie; Marrinan, Cindy H.; Taylor, Stacey A.; Black, Stuart; Basso, Andrea D.; Kirschmeier, Paul; Robert Bishop, W.; Liu, Ming; Long, Brian J. Department of Biological Research - Oncology, Schering-Plough Research Institute, Kenilworth, NJ, USA. *Anti-Cancer Drugs* (2007), 18(8), 923-931. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 147:203228 AN 2007:833451 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Lonafarnib is an orally bioavailable farnesyltransferase inhibitor. Originally developed to block the membrane localization of Ras, subsequent work suggested that farnesyltransferase inhibitors mediate their antitumor activities by altering the biol. activities of adnl. farnesylated proteins. Breast tumor models that express wild-type Ras have been shown to be sensitive to farnesyltransferase inhibitors. We have detd. the effects of combining lonafarnib with the antiestrogen 4-hydroxy tamoxifen on hormone-dependent breast cancer cell lines in vitro. The effects of combining lonafarnib with tamoxifen or the aromatase inhibitor anastrozole on the growth of two different MCF-7 breast tumor xenograft models were also evaluated. In four of five human breast cancer cell lines, lonafarnib enhanced the antiproliferative effects of 4-hydroxy tamoxifen. The combination prevented MCF-7 cells from transitioning through the G1 to S phase of the cell cycle and augmented apoptosis. This was assocd. with reduced expression of E2F-1 and a redn. in hyperphosphorylated retinoblastoma protein. Lonafarnib plus 4-hydroxy tamoxifen also inhibited the mammalian target of rapamycin signal transduction pathway. In nude mice bearing parental MCF-7 or aromatase-transfected MCF-7Ca breast tumor xenografts, lonafarnib enhanced the antitumor activity of both tamoxifen and anastrozole. These studies indicate that lonafarnib enhances the efficacy of endocrine agents clin. used for treating hormone-dependent breast cancer.

Answer 2:

### Bibliographic Information

**Aromatase Inhibitors in Human Lung Cancer Therapy.** Weinberg, Olga K.; Marquez-Garban, Diana C.; Fishbein, Michael C.; Goodglick, Lee; Garban, Hermes J.; Dubinett, Steven M.; Pietras, Richard J. Departments of Medicine, University of California at Los Angeles School of Medicine, Los Angeles, CA, USA. *Cancer Research* (2005), 65(24), 11287-11291. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 144:80771 AN 2005:1311906 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Lung cancer is the most common cancer in the world. It is a highly lethal disease in women and men, and new treatments are urgently needed. Previous studies implicated a role of estrogens and estrogen receptors in lung cancer progression, and this steroidal growth-stimulatory pathway may be promoted by tumor expression and activity of aromatase, an estrogen synthase. We found expression of aromatase transcripts and protein in human non-small cell lung cancer (NSCLC) cells using reverse transcription-PCR and Western immunoblots, resp. Aromatase staining by immunohistochem. was detected in 86% of archival NSCLC tumor specimens from the clinic. Further, biol. activity of aromatase was detd. in NSCLC tumors using radiolabeled substrate assays as well as measure of estradiol product using ELISA. Significant activity of aromatase occurred in human NSCLC tumors, with enhanced levels in tumor cells compared with that in nearby normal cells. Lung tumor aromatase activity was inhibited by anastrozole, an aromatase inhibitor, and treatment of tumor cells in vitro with anastrozole led to significant suppression of tumor cell growth. Similarly, among ovariectomized nude mice with A549 lung tumor xenografts, administration of anastrozole by p.o. gavage for 21 days elicited pronounced inhibition of tumor growth in vivo. These findings show that aromatase is present and biol. active in human NSCLCs and that tumor growth can be down-regulated by specific inhibition of aromatase. This work may lead to development of new treatment options for patients afflicted with NSCLC.