BASTION

From Basic to Translational Research in Oncology

Report on active participation in

17th ECCO - 38th ESMO - 32nd ESTRO

European Cancer Congress

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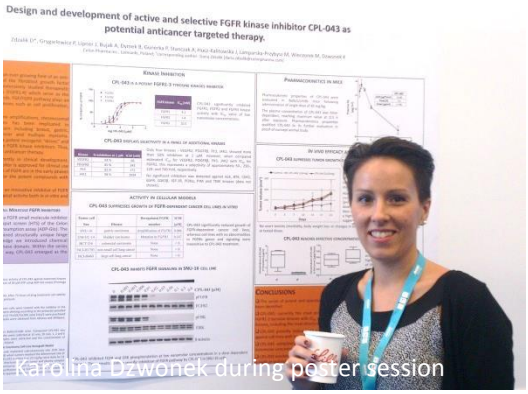
Karolina Dzwonek participated in European Cancer Congress as an author of two poster presentations, presented during the session “Drug Discovery” on Sep 29th:

Design and development of active and selective FGFR kinase inhibitor CPL-043 as potential anticancer targeted therapy.

Zdzalik D, Grygielewicz P, Lipner J, Bujak A, Dymek B, Gunerka P, Stanczak A, Lamparska-Przybysz M, Wieczorek M, Dzwonek K

Background

Fibroblast growth factor receptors (FGFRs) family of receptors with tyrosine kinase activity comprises a group of extensively studied targets for small molecule inhibitors development. Alterations in gene copy number of different FGFRs and their point mutations have been correlated with many types of cancer, making FGFR kinases an interesting target for novel anticancer therapy. There are several FGFR inhibitors in clinical development but there is still a niche for the drug with properly balanced selectivity profile.



Karolina Dzwonek during poster session

Material and Methods

Using sophisticated drug design methods we have designed CPL-043 – a small molecule FGFR kinase inhibitor with high potency in vitro. To establish the activity and the selectivity of the compound we have used kinase activity assay based on recombinant kinases and cell proliferation assay, using the cell lines dependent on FGFR signaling – SNU-16 and UM UC-14. To confirm biological activity of the inhibitor we performed immunoblot assay detecting the level of FGFR pathway related proteins.

Results

Our results indicate that CPL-043 inhibits FGFR1, 2 and 3 activity in vitro in low nanomolar concentrations. Concurrently the IC50 for the most common FGFR off-targets – KDR and PDGFR is over ten times higher. CPL-043 inhibits proliferation of FGFR-dependent cell lines including SNU-16 and UM-UC-14. Treatment of cells with CPL-043 for 1h evokes dramatic decrease in the level of pFGFR, pFRS and pErk proteins in a dose dependent manner. Moreover the inhibitor has no effect on the lines with low FGFR activity like HCT-116 or H1703, suggesting that the compound is not cytotoxic.

Conclusion

We have designed a very potent and selective FGFR inhibitor, which displays biological activity in selected cellular models without evoking cytotoxic effects on the FGFR-independent cell lines. The compound has proper ADME predicted profile as is currently under investigation in the in vivo study.

Epithelial-mesenchymal transition confers resistance to FGFR inhibitors in gastric cancer cell line.

Grygielewicz P, Zdzalik D, Dymek B, Bujak A, Gunerka P, Stanczak A, Lamparska-Przybysz M, Wieczorek M, Dzwonek K.

Background

Targeted therapies based on kinase inhibitors may bring encouraging results but they frequently elicit resistance that makes the therapy ineffective and is often accompanied with cross-resistance to other drugs. Understanding and anticipation of the resistance mechanism for novel targeted drugs provides new approaches to use alternative or combine therapy which would improve patients' chances for recovery.

Fibroblast growth factor receptor (FGFR) comprises a promising target for anticancer therapy as it's amplification, mutation or overexpression is considered to be an oncogenic driver in various types of human neoplasms. Several clinical trials are currently carried out with the use of FGFR inhibitors but there still lacks the information about possible mechanisms of resistance to therapy in treated patients. The aim of the study was to define the mechanisms of acquired resistance to FGFR inhibitors: AZD-4547, BGJ 398 and PD173074 in selected in vitro models.

Karolina Dzwonek during poster session

Material and methods

To explore the mechanism of acquired resistance to FGFR inhibitors we have applied SNU16 human gastric cancer cell line with FGFR2 amplification. The cells were cultured with increasing concentrations of each inhibitor: AZD-4547, BGJ398 or PD173074 until reaching a concentration exceeding the IC50 value ten times. The mechanism of resistance was verified using immunoblotting techniques.

Results

In the following study we have established three gastric cancer cell lines SNU16R AZD, SNU16R BGJ, SNU16R PD, resistant to selective FGFR inhibitors AZD-4547, BGJ398 or PD173074, respectively. Since we found the loss of FGFR phosphorylation in all three lines we concluded that the resistance results from activation of alternative signaling pathways and is not evoked by mutation in FGFR kinase gene. We found however loss of several cell surface growth factor receptors like cMet or EGFR in these lines. Concurrently, the protein profile of established cell lines indicated epithelial-mesenchymal transition (EMT). We found the decrease in E-cadherin level and an increase of vimentin which are markers of EMT.

Conclusion

Our results reveal that one of the mechanisms of acquired resistance to FGFR selective inhibitors can be epithelial-mesenchymal transition. To our best knowledge it is the first time to show EMT as mechanism of resistance to the therapy targeting at FGFR. This finding indicates that EMT could emerge in patients treated with FGFR inhibitors.

Karolina Dzwonek with the first authors of presented posters – Daria Zdzalik (left) and Paulina Grygielewicz (right) at the conference venue

During the conference Ms Dzwonek had several business talks on possible cooperation between BASTION research groups and pharmaceutical companies. She also aimed at getting to the right people within the companies, in order to invite them for upcoming BASTION Pharma Day next year, Spring. Ms Dzwonek spoke to the representatives of:

Amgen, Ariad, Astellas, Bayer, Boehringer Ingelheim, Bristol Meyers Squib, Exelixis, GE Healthcare (Breast Cancer), Glaxo Smith Klein, Hospira, Novartis, Pfizer, PharmaMar, Roche, SANDOZ, Sanofi, Takeda, TEVA

Certificate of Participation

The undersigned hereby certifies that

Karolina Dzwonek (Poland)

has registered for and attended the 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress from 27 September – 1 October 2013 in Amsterdam, the Netherlands.

C.J.H. van de Velde
Congress Chair