IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Fibroblast Growth Factor Receptor (FGFR)3 sustains acquired resistance to trastuzumab in gastric cancer patients

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1573665 since 2016-06-28T12:09:06Z

Published version:

DOI:doi:10.1016/S0959-8049(16)30134-4

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

03 May 2024

IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

This Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in European Journal of Cancer, Volume 51, Supplement 3, Pages S42–S43; September 2015
DOI: http://dx.doi.org/10.1016/S0959-8049(16)30134-4

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

(1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.

(2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.

(3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en), 10.1016/S0959-8049(16)30134-4

The publisher's version is available at:
http://www.ejcancer.com/article/S0959-8049(16)30134-4/pdf

When citing, please refer to the published version.

Link to this full text:
http://hdl.handle.net/2318/1573665

This full text was downloaded from iris-Aperto: https://iris.unito.it/

iris-AperTO

University of Turin's Institutional Research Information System and Open Access Institutional Repository

Link to full-text publisher PDF http://www.ejcancer.com/article/S0959-8049(16)30134-4/pdf

European Journal of Cancer, Volume 51, Supplement 3, September 2015, Pages S42–S43, Poster 248, presented at the European Cancer Congress on 28 September 2015; doi:10.1016/S0959-8049(16)30134-4

Fibroblast Growth Factor Receptor (FGFR)3 sustains acquired resistance to trastuzumab in gastric cancer patients

G. Piro[1], C. Carbone[1], I. Cataldo[2], F. Di Nicolantonio[3], S. Giacopuzzi[4], F. Boschi[5], M. Zanotto[1], V. Merz[1], M.M. Mina[1], A. Sbarbati[5], G. De Manzoni[4], A. Scarpa[2], G. Tortora[1], D. Melisi[1].

[1]University of Verona, Medicine, Verona, Italy; [2]University of Verona, Pathology and Diagnostics, Verona, Italy; [3]University of Turin, Oncology, Turin, Italy; [4]University of Verona, Surgery, Verona, Italy; [5]University of Verona, Neurological Sciences, Verona, Italy

Background: Trastuzumab has been recently demonstrated as valuable treatment in HER2+ gastric cancer (GC). However the majority of patients who achieve an initial response to trastuzumab-based regimens develop resistance within 1 year of treatment. This study was aimed at identifying the molecular mechanisms responsible for this resistance.

Material and Methods: A GFP+/luciferase+, HER-2 positive, trastuzumab sensitive NCI-N87 GC orthotopic nude mouse model was used to select resistant models to this agent. Tumor growth was measured by using an IVIS Spectrum Imaging System. Differentially expressed transcripts between trastuzumab-resistant and sensitive GC cell lines were measured by Illumina whole-genome microarray, and tested for network and functional interrelatedness by IPA software. Expression of FGFR3, HER2, total AKT, phosphorylated (p)AKT, and ZEB1 was measured by immunohistochemical staining in pre- vs. post-treatment biopsies from GC patients progressing under trastuzumab-based treatment.

Results: NCI-N87 orthotopic tumor bearing mice were kept under treatment until the tumors suddenly recurred while on continuous therapy with trastuzumab. Four NCI-N87 trastuzumab resistant (N87-TR) cell lines were established from different excised tumors by repeated GFP flow cytometry sorting and their effective resistance was verified in vitro and in vivo. Microarray analysis showed the dowregulation of HER2, the induction of epithelial-to-mesenchymal transition, and indicated FGFR3 as one of the top 10 upregulated genes in N87-TR cell lines. We found a significant and consistent association of N87-TR gene expression profiles with the activation of the mTOR signaling. Accordingly, N87-TR cell lines showed significantly lower expression of all HER family members, E-cadherin and pERK1/2, and higher levels of FGFR3, vimentin, ZEB1, and pAKT than did sensitive control. In vitro, N87-TR cell lines demonstrated a higher sensitivity to the FGFR3 inhibitor dovitinib than did trastuzumab sensitive control. Treatment with dovitinib reduced the expression of pAKT, ZEB1, and migration in N87-TR cell lines. Oral dovitinib significantly reduced tumor burden and prolonged mice survival duration in N87-TR mouse models, whereas it was ineffective on trastuzumab-sensitive GC tumors. A significantly higher expression of FGFR3 and a lower expression of HER2 was observed in biopsies from GC patients progressing under trastuzumab-based therapies if compared with respective pre-treatment biopsies.

Conclusions: This study identified the FGFR3/AKT axis as an escape pathway responsible for trastuzumab resistance in GC, thus candidating dovitinib as potential agent to modulate this resistance.