

This is the peer reviewed version of the following article:

Sorafenib and Regorafenib in HBV- or HCV-positive hepatocellular carcinoma patients: Analysis of RESORCE and SHARP trials / Casadei Gardini, Andrea; Frassinetti, Giovanni Luca; Foschi, Francesco Giuseppe; Ercolani, Giorgio; Ulivi, Paola. - In: DIGESTIVE AND LIVER DISEASE. - ISSN 1590-8658. - 49:8(2017), pp. 943-944. [10.1016/j.dld.2017.04.022]

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

08/05/2026 12:28

(Article begins on next page)

Accepted Manuscript

Title: Sorafenib and Regorafenib in HBV- or HCV- positive hepatocellular carcinoma patients: analysis of RESORCE and SHARP trials

Authors: Andrea Casadei Gardini, Giovanni Luca Frassinetti



PII: S1590-8658(17)30854-X
DOI: <http://dx.doi.org/doi:10.1016/j.dld.2017.04.022>
Reference: YDL D 3445

To appear in: *Digestive and Liver Disease*

Author: Francesco Giuseppe Foschi

PII: S1590-8658(17)30854-X
DOI: <http://dx.doi.org/doi:10.1016/j.dld.2017.04.022>
Reference: YDL D 3445

To appear in: *Digestive and Liver Disease*

Author: Giorgio Ercolani

PII: S1590-8658(17)30854-X
DOI: <http://dx.doi.org/doi:10.1016/j.dld.2017.04.022>
Reference: YDL D 3445

To appear in: *Digestive and Liver Disease*

Author: Paola Ulivi

PII: S1590-8658(17)30854-X
DOI: <http://dx.doi.org/doi:10.1016/j.dld.2017.04.022>
Reference: YDL D 3445

To appear in: *Digestive and Liver Disease*

Received date: 21-4-2017

Please cite this article as: Ulivi Paola.Sorafenib and Regorafenib in HBV- or HCV- positive hepatocellular carcinoma patients: analysis of RESORCE and SHARP trials.*Digestive and Liver Disease* <http://dx.doi.org/10.1016/j.dld.2017.04.022>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Sorafenib and Regorafenib in HBV- or HCV- positive hepatocellular carcinoma patients: analysis of RESORCE and SHARP trials

Andrea Casadei Gardini ¹, Giovanni Luca Frassinetti ¹, Francesco Giuseppe Foschi ², Giorgio Ercolani ³⁻⁴, Paola Ulivi ⁵

¹*Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS, Meldola, Italy;*

²*Department of internal medicine, Ospedale per gli Infermi di Faenza, Faenza, Italy;*

³*Department of General Surgery, Morgagni-Pierantoni Hospital, AUSL Romagna, Forlì, Italy;*

⁴*Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.*⁵

⁵*Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS, Meldola, Italy;*

Address reprint requests to: Andrea Casadei Gardini, MD, Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS, Via Piero Maroncelli 40, 47014 Meldola, Italy.

E-mail: andrea.casadei@irst.emr.it; tel. +39 0543 739970, fax +39 0543 739249

Keywords: sorafenib, Regorafenib, hepatocellular carcinoma, hepatitis B, hepatitis C.

Dear editor,

In the RESORCE trial ¹, Bruix and colleagues reported the data of regorafenib in patients with hepatocellular carcinoma (HCC) who progressed after sorafenib treatment. Regorafenib improved overall survival (OS) with an hazard ratio (HR) of 0.63 (95% CI 0.50-0.79) . In the subgroup analysis, the HR for OS in HBV-positive patients was 0.58 (95% CI 0.41-0.82 p=0.0009) with respect to 0.79 (95% CI 0.49-1.26 p=0.1583) observed in HCV-positive patients. Similar data were observed for progression free survival (0.39 vs 0.59 respectively) and time to progression (0.38 vs 0.57 respectively). Different results were observed in relation to first line treatment with sorafenib. In the subgroup analysis of the SHARP study², HR relative to OS was 0.76 in HBV-positive patients (95% CI 0.38-1.50 p= not significant), with respect to 0.50 (95% CI 0.32-0.77) observed in HCV-positive patients, and the data were similar for time to progression (HR 1.03 and 0.43 for HBV-positive and HCV-positive patients, respectively). Similar data were obtained in HBV positive- HCC patients by the subgroup analysis of the phase III study of Sorafenib Asia–Pacific trial, where the HR for OS was 0.74 (0.51-1.06, not significant) respect to patients with other etiology, for which the HR was 0.57 (0.29-1.33). These results seem to suggest a different efficacy of sorafenib and regorafenib in HCV or HBV – positive HCC. HCV-mediated hepatocarcinogenesis seems to be strongly mediated by type I and III IFN, which induce a plethora of IFN stimulated genes, together with the ability of HCV core to modulate intracellular pathways and cellular metabolism, through the induction of kinases phosphorylation⁴. In this setting the multikinase inhibitor sorafenib seems to be more efficacious. On the other hand, HBV-positive HCC seem to be characterized by a IL-6 dependent inflammatory process, together with different genomic perturbations due to viral DNA integration⁴. Regorafenib, an anti-VEGFR2-TIE2 and multikinase inhibitor, seems to be more efficacious in this type of HCC, in which may be there is a more

intensive involvement of the angiogenic process. Differences in the mechanisms of action of the two drugs , together with the diversity in tumor microenvironment characteristics on the basis of HBV or HCV infection could explain the different antitumor profile.

In conclusion, these observations lead to hypothesize a different treatment strategy based on tumor etiology. Future studies should be made to evaluate if the use of first line regorafenib in HBV-positive HCC patients may be the best strategy for improving the outcome of these patients.

Another interesting point that has not been taken in consideration in the subgroup analysis of both RESORCE and SHARP trials is the effect of the drugs in patients with metabolic syndrome.

Specific studies aimed to understand the efficacy of drugs in relation to HCC etiology are warranted to clarify this aspect.

Authors contributions

Conception: Andrea Casadei Gardini

Manuscript writer: Andrea Casadei Gardini, Paola Ulivi.

Final approval of manuscript: Andrea Casadei Gardini, Giovanni Luca Frassinetti, Francesco Giuseppe Foschi, Giorgio Ercolani, Paola Ulivi.

We declare no competing interests.

References

1. Bruix J, Qin S, Merle P. et al Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2016 Dec 5.
2. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: Subanalyses of a phase III trial. Bruix, Jordi et al. *Journal of Hepatology* , Volume 57 , Issue 4 , 821 – 829
3. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: Subset analyses of the phase III Sorafenib Asia–Pacific trial. Cheng AL. *Eur J Cancer*. 2012 Jul;48(10):1452-65. doi: 10.1016/j.ejca.2011.12.006. Epub 2012 Jan 10.
4. Hepatocarcinogenesis associated with hepatitis B, delta and C viruses. Shirvani-Dastgerdi E, Schwartz RE, Ploss A.. *Curr Opin Virol*. 2016 Oct;20:1-10