Professor Enrico De Toni: my thoughts on immune checkpoint inhibitors and hepatocellular carcinoma

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Editor's note

Between December 6th and 7th, 2019, the 4th Pearl River International Academic Conference on GI Disease and Cancer was successfully held in Foshan, China. Many Chinese and international experts were invited to share and discuss the latest research on gastroenterology, precision medicine and ERAS. During the conference, *Digestive Medicine Research* (*DMR*) had the great honor to invite Professor Enrico De Toni (*Figure 1*), Professor from the Department of Internal Medicine at the University of Munich, to share his perspectives on immune checkpoint inhibitors and hepatocellular carcinoma (HCC).

Expert's introduction

Prof. Enrico De Toni's major interests are the interdisciplinary treatment of hepatobiliary tumors, the treatment of acute and chronic liver failure and liver transplantation. He is member of the Liver Centre Munich, of its transplantation committee, and of the Comprehensive Cancer Centre Munich (CCC) and head of the unit for hepatobiliary and GI-Tumors at the second medical clinic at the University of Munich. His bench-research activity focuses on alternative therapeutic approaches for the therapy of gastrointestinal tumors and in particular the field of kinase inhibition and the immune-mediated induction of apoptosis in cancer treatment.

Interview

***DMR**: You gave an excellent presentation on the topic "Treatment of HCC in the age of immune checkpoint inhibitors". Would you like to summarize some main points of your speech? How would the immune checkpoint inhibitors change the treatment of HCC?*

Prof. De Toni: The use of checkpoint inhibitors represented a turning point in cancer treatment for many tumor entities. In these days, experimentation of these agents has reached

Figure 1 Prof. Enrico De Toni on the 4th Pearl River International Academic Conference on GI Disease and Cancer held in Foshan, China.

HCC, and the results are unprecedented in terms of objective response rates and survival. We desperately needed these new treatment options for HCC, since the latest advances in systemic treatment date back to 2007 when sorafenib was established as first systemic treatment for this tumor and because HCC is one of the most common causes of tumor-related dead worldwide. Immune checkpoint inhibitors represent an entirely new category of drugs: in contrast to cytotoxic agents or kinase inhibitors, they do not possess per se an antitumoral effect, but delegate to the immune system the function of recognizing cancer cells as non-self and rely on inborn mechanisms to kill them. This explains the fact that these agents are generally very good tolerated, which is another important aspect to consider about the results of IMBRAVE 150 trial presented today.

There is a further aspect—perhaps a bit theoretical, but on my opinion nevertheless important—which has to

be considered about CPI: These agents do not interfere with the typical mechanisms which regulate the biology of malignant behavior from within the cells, such as the intracellular mechanisms of cell proliferation or of resistance to apoptosis. By killing a cell from outside we do not need to fully understand the entangled complex of redundant mechanisms governing the biology of a malignant cell. This reduces the amount of things we need to understand about the biology of cancer cell before we are able to cure cancer. In a way, immune-mediated killing of cancer cells represents a simplification in the approach to cancer treatment.

***DMR**: What is your opinion on the future development in the treatment of HCC?*

Prof. De Toni: It's very likely that the use of checkpoint inhibitors, which will most likely be approved as a front-line treatment of advanced HCC, will be extended to the treatment of patients in earlier tumor stages. In fact, we already have studies ongoing with CPI in the neoadjuvant and adjuvant setting. Recently data have been published on the use of combined treatment with nivolumab and ipilimumab showing high rates of complete pathological responses. These are impressive results, which open the perspective for the use of immunological treatment to downstage tumors e.g., prior to a surgery. In addition, there are other studies for HCC in intermediate stage, such as the DEMAND study, a randomized trial which we are about to initiate on the use of atezolizumab/bevacizumab either up-front, and followed by on-demand TACE in one arm, or direct combination with TACE in the other treatment arm.

DMR: Looking forward, which problems do you think will still need to be addressed in the treatment of HCC?

Prof. De Toni: To fully exploit the therapeutic potential of these new drugs for the treatment of HCC, we will have to establish the correct sequence and combination of treatment with respect to locoregional options like TACE, may be also SIRT, and find out which the ideal combination of these agents is. Should they be combined with VEGF inhibitors as in the IMBRAVE 150 study? With another CPI? Or used in sequence? Also, we will have to find predictors of response to their action.

At the same time, while we celebrate the success of these new drugs, we must be aware that, at some point, we will have to confront the problem of the increasing cost of this kind of treatment. How many patients will have access to a CPI-based treatment? Will the financial burden sustainable in the long term? How can we make this treatment affordable? These are important questions which we have to address in the future.

Finally, I would like to remind the fact that—if treatment is important, prevention is even more important. For HCC this means for instance using vaccination against hepatitis B virus to prevent the development of chronic hepatitis, something you are already doing excellently in China. This is the so-called primary prevention, which means trying to avoid tumor formation in the first place. The second most important thing to fight HCC related mortality is the early detection of HCC. This can be done by systematically performing ultrasound investigation in patients at-risk for HCC. Prevention and early diagnosis will abate cancer-related mortality by a fraction of the costs—in terms of efforts, financial burden and quality of life—necessary to development and use specific tumor therapies.

DMR: What are you most looking forward to at this conference?

Prof. De Toni: I'm really very excited to be here. When we start a talk or a lesson to the students about HCC in Europe, we begin by saying that HCC is a common tumor with rising incidence on the global scale, and that half of patients are in China. So, there is no better way to learn about HCC than being here and talking to practitioners who have a lot of experience in the treatment of these patients. I'm very looking forward to talking to them and to all scientists attending the meeting in the coming days, and I really appreciate your invitation.

Acknowledgments

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Footnote

Conflicts of Interest: Prof. De Toni has served as a paid consultant for AstraZeneca, Bayer, BMS, EISAI, Eli Lilly & Co, Pfizer, IPSE, and Roche, the manufacturer of atezolizumab and bevacizumab. He has received reimbursement of meeting attendance fees and travel expenses from Arqule, BMS, Bayer, Celsion and Roche, and lecture honoraria from BMS and Falk. He has received

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(Science Editor: Wymen Chen, DMR, dmr@amegroups.com)

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