Editorial

TIC10/ONC201—a potential therapeutic in glioblastoma

Georg Karpel-Massler[1], Markus D. Siegelin[2]

[1]Department of Neurological Surgery, Ulm University Medical Center, Ulm, Germany; [2]Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY, USA

Correspondence to: Georg Karpel-Massler, MD, PhD. Department of Neurological Surgery, Ulm University Medical Center, Albert-Einstein-Allee 23, D-89081 Ulm, Germany. Email: georg.karpel@uniklinik-ulm.de; georg.karpel@gmail.com.

Comment on: Arrillaga-Romany I, Chi AS, Allen JE, *et al.* A phase 2 study of the first imipridone ONC201, a selective DRD2 antagonist for oncology, administered every three weeks in recurrent glioblastoma. Oncotarget 2017;8:79298-304.

Submitted Oct 01, 2017. Accepted for publication Oct 17, 2017.
doi: 10.21037/tcr.2017.10.51
View this article at: http://dx.doi.org/10.21037/tcr.2017.10.51

Glioblastoma represents the most frequent primary brain tumor in adults and despite great efforts it remains to be an incurable disease. Advances in surgical techniques, radiotherapy and chemotherapy resulted only in a small improvement of patient survival as manifested by a median overall survival of only 14.6 months following best standard of care (1). This desperate situation forces researchers and clinicians into new venues. The identification of specific oncogenic signaling pathways which are aberrantly activated in cancer leads to the development of targeted therapies. This strategy was successfully applied in chronic myeloid leukemia using imatinib or in HER2/EGFR-positive breast cancer using trastuzumab. In glioblastoma, this approach did not hold up to the expectations when targeting for instance HER1/EGFR or VEGF. However, the identification of new targets and the development of novel compounds continue.

TIC10/ONC201 represents one such promising novel agent. It was identified in a small molecule screen of the National Cancer Institute Diversity Set II, a chemical library (2). The purpose of this search was to find compounds that would lead to endogenous up-regulation of Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) in order to circumvent the limitations related to treatment with exogenous death receptor ligands such as TRAIL. In this study, Allen *et al.* provided proof for the anti-neoplastic activity of TIC10/ONC201 in different cancer entities including data showing enhanced therapeutic efficacy in an orthotopic glioblastoma model *in vivo*. More studies followed to confirm and extend the initial findings providing further proof for the anti-cancer activity of TIC10/ONC201 in colorectal cancer stem cell, pancreatic cancer or non-Hodgkin's lymphoma models (3-5). In a multi-targeting approach, our own group was able to show that TIC10/ONC201 synergizes with ABT263, an inhibitor of anti-apoptotic Bcl-2 family proteins Bcl-2 and Bcl-xL, against glioblastoma and that the combination therapy causes tumor regression *in vivo* (6).

Based on these promising preclinical data, TIC10/ONC201 was taken into a phase 2 clinical trial (7). Seventeen patients with glioblastoma WHO grade IV which had previously received standard radio-/chemotherapy and presented with progressive disease according to RANO criteria were included in this study. Prior treatment with bevacizumab and mutated IDH1/2 status were exclusion criteria. The primary endpoint of this study was defined as a progression-free survival at 6 months (PFS6) greater than 30% with a planned enrolment of 30 patients. A dose of 625 mg of TIC10/ONC201 was administered per os every 3 weeks. Follow-up included clinical and imaging evaluation every 8 weeks to monitor response and toxicity. The study was terminated preterm after the enrolment of 17 patients since a futility interim analysis revealed that the primary endpoint of this study would not be met. Median overall survival was reported to be 41.6 weeks with a PFS6 of 11.8%. One patient showed partial response for more than 6 months with regression of two lesions and a second patient remained disease-free for more than 11 months. With respect to toxicity, TIC10/ONC201 was well tolerated with only two transient adverse events in the same patient. Pharmacodynamic studies showed that the treatment reached plasma concentrations above 1 μg/mL

which is reported to be above the target threshold and a rise in prolactin levels was noted in response to DRD2 antagonism, one proposed mechanism by which TIC10/ONC201 exerts its antineoplastic activity. Even though this study had to be closed before completion of planned patient accrual, the results are at least in part encouraging: In two patients a therapeutic response was noted in a disease that is so difficult to treat and the toxicity profile was favorable.

Where to go on from here? In the era of precision medicine identification of reliable molecular markers guiding targeted therapeutic measures is key and represents one of the major challenges. DRD2 might represent one such molecular marker and shaping treatment regimens accordingly, respecting the individual tumor specific genetic profile of the disease, will likely add beneficial therapeutic effects as seen for the two responders in this study. However, due to the complexity of the disease involving such a heterogeneous and diversely dysregulated molecular signature a mono-targeted approach will likely not succeed. Therefore, multi-targeted strategies should be encouraged based on the individual molecular profile. Hopefully this approach will lead to a more successful therapy of patients with glioblastoma and TIC10/ONC201 may well be part of it.

Acknowledgments

Funding: G Karpel-Massler was supported by a scholarship from the Dr. Mildred Scheel foundation of the German Cancer Aid. MD Siegelin received the American Brain Tumor Association, ABTA Discovery Grant (ABTA DG1700013), the 2013 AACR-National Brain Tumor Society Career Development Award for Translational Brain Tumor Research (13-20-23-SIEG), the BCURED Fighting Brain Cancer (16-0992), the NIH NINDS K08NS083732 and R01NS095848.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Ning Huang (Department of Neurosurgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.10.51). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
2. Allen JE, Krigsfeld G, Mayes PA, et al. Dual inactivation of Akt and ERK by TIC10 signals Foxo3a nuclear translocation, TRAIL gene induction, and potent antitumor effects. Sci Transl Med 2013;5:171ra17.
3. Talekar MK, Allen J, Dicker D, et al. ONC201 induces cell death in pediatric non-Hodgkin's lymphoma cells Cell Cycle 2015;14:2422-8.
4. Prabhu VV, Allen JE, Dicker DT, et al. Small-Molecule ONC201/TIC10 Targets chemotherapy-resistant colorectal cancer stem-like cells in an Akt/Foxo3a/TRAIL-dependent manner. Cancer Res 2015;75:1423-32.
5. Zhang Q, Wang H, Ran L, et al. The preclinical evaluation of TIC10/ONC201 as an anti-pancreatic cancer agent. Biochem Biophys Res Commun 2016;476:260-6.
6. Karpel-Massler G, Ba M, Shu C, et al. TIC10/ONC201 synergizes with Bcl-2/Bcl-xL inhibition in glioblastoma by suppression of Mcl-1 and its binding partners in vitro and in vivo. Oncotarget 2015;6:36456-71.
7. Arrillaga-Romany I, Chi AE, Allen JE, et al. A phase 2 study of the first imipridone ONC201, a selective DRD2 antagonist for oncology, administered every three weeks in recurrent glioblastoma. Oncotarget 2017;8:79298-304.

Cite this article as: Karpel-Massler G, Siegelin MD. TIC10/ONC201—a potential therapeutic in glioblastoma. Transl Cancer Res 2017;6(Suppl 9):S1439-S1440. doi: 10.21037/tcr.2017.10.51

