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TIC10/ONC201—a potential therapeutic in glioblastoma

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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

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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.

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