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Novel Receptor Tyrosine Kinase Pathway Inhibitors for Targeted Radionuclide Therapy of Glioblastoma

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Glioblastoma (GB) remains the most fatal brain tumor with a median survival of approximately 14 months and less than 10% of patients living longer than 5 years from diagnosis. GB tumors are characterized by a high infiltration rate and treatment resistance. At recurrence, there is no consensus on the standard of care as no therapeutic options thus far could demonstrate a substantial survival benefit. An improved understanding of the underlying disease pathology and the causes for these treatment challenges might aid the development of new GB therapy strategies. One particular strategy is the development of theranostic agents that combine diagnostic molecular imaging with therapy using the same agent. The theranostic agent thereby investigates the presence of a certain target on the tumor cells of the patient while the therapeutic version of the agent (commonly a radioactive derivative) binds to the same target and induces tumor cell death by emitting radiation, while sparing healthy normal tissues. The latter approach is called targeted radionuclide therapy (TRT). Mutations in receptor tyrosine kinases (RTKs) and aberrant activation of their intracellular signaling pathways have been linked to malignant transformation and therapy resistance and have driven the development of a new generation of drugs that block or attenuate RTK activity. Overexpression and/or mutation of RTKs is common in GB, and therefore receptor tyrosine kinase inhibitors (RTKIs) have been investigated to improve the dismal prognosis of GB in an effort to evolve into a personalized targeted therapy strategy. RTKIs consist of mainly two categories, monoclonal antibody-based drugs that bind to the extracellular domain of the receptor and small molecule inhibitors acting intracellularly, both of which result in blocking the downstream signal trans-duction cascade. Numerous RTKIs have been approved in the clinic and several radiopharmaceuticals are part of (pre)clinical trials as a non-invasive method to identify patients who could benefit from RTKI. The latter opens up the scope for theranostic applications.
In this work, recently published in MDPI Pharmaceuticals, the option to use the tyrosine kinase pathway as a target for GB radiopharmaceutical development, and specifically for TRT, was explored. The focus was on seven tyrosine kinase receptors, based on their central role in GB: EGFR, VEGFR, MET, PDGFR, FGFR, Eph receptor and IGF1R. Finally, by way of analyzing structural and physiological characteristics of the RTKIs with promising clinical trial results, four small molecule RTKIs were selected based on their potential to become new therapeutic GB radiopharmaceuticals.

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