JMEA Journal of Modern Educational Achievements
Volume 10, 2024 https://scopusacademia.org/

HIGH-GRADE ASTROCYTOMA TREATMENT: EFFICACY OF ZOTIRACICLIB AND TEMOZOLOMIDE COMBINATION THERAPY IN A PHASE I CLINICAL TRIAL

Abdulvohid Pazliddinov
[1]Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS), University of Strathclyde, Glasgow, United Kingdom
Xolmatov Jasurbek
[2]Department of the pharmaceutical sciences, Andijan State Medical Institute

ABSTRACT

High-grade astrocytoma is common and aggressive type of the brain tumor it causes cancer-related death in most times. The earliest diagnosis and effective anti-tumor agents can help to prolong the survival time of the patients. Zotiraciclib a cyclin-dependent kinase 9 (CDK9) inhibitor is known as potential agent for treating high-grade astrocytoma. This two-stage phase 1 clinical trial established maximum tolerated dose (MTD) of Zotiraciclib with the Temozolomide. The study conducted in to branch dose-dense (Arm1) and metronomic (Arm2). 53 percents were covered during the study and 10% of initial patients finished the entire course of treatment. Zotiraciclib and Temozolomide used in high-grade astrocytoma treatment process represented synergetic effect. These combined drugs are safe in the treatment of HGA.

KEY WORDS

High-grade astrocytoma, Zotiraciclib, Temozolomide, Cyclin-dependent kinase 9 (CDK9), Drug synergy, Progression-free survival

INTRODUCTION

Nowadays, Cancer is the serious health problem and cause of every one death out of six in globally. The therapy of tumor is challenging because of its variety of biology and high rate of heterogeneity. The several types of drug resistances lead to facing with extra challenges during the cancer treatment. Currently available treatment methods like immunotherapies, stem cell transplantation, targeted therapies, hormonal therapies, precision medicine, and palliative care, and traditional therapies such as surgery, radiation therapy, and chemotherapy are insufficient to successfully treat all types of this disease.

Brain cancer also has a high level of mortality. The median survival time is <12-15 months in several patients with brain cancer. Tumors appearing in the central nervous system can affect the behavior of patients. Uncontrolled growth of cell proliferation starting in spinal cord can lead to weakness and disability. The closeness of the tumors to the vital brain regions and their complexity of proliferation is one of

the main limitations of the successful treatment of brain cancer.[2] The treatment processes with conventional and weakly targeted anticancer drugs did not give expected results. In the last years few research institutions have explored specialized receptor-targeted nanomedicines and drug delivery systems but there is no effective treatment in the in the today's pharmaceutical markets. In this situation both in-vitro and in-vivo research should be conducted.[4] High-grade astrocytoma is the widely spread tumor of central nervous system (CNS) within the patients. The tumor formed in the brain because of proliferation of nerve cells called astrocytes. High-grade astrocytoma is one of the most aggressive tumors and has a short median survival time.

Astrocytoma is known as a common type of gliomas. According to the World Health Organization classification there are divided into four groups. First and second groups are call pilocytic astrocytoma and low-grade diffuse astrocytoma respectively. Their survival time is approximately 10-5 years. Anaplastic astrocytoma and glioblastoma are mostly aggressive tumors with a short survival time, and they belong to the third and fourth groups of the classification. Anaplastic astrocytoma (AA) is described in some literature as High-grade astrocytoma and these terms means one disease.[7] In some cases, glioblastoma (GBM) also same to High-grade astrocytoma because of the approximately equal length (up to 14 months) of survival factor of patients suffering with Anaplastic astrocytoma. Glioblastomas account for 17.1% of all brain tumors and account for 49.8% of all neuroepithelial tumors. The early diagnosis and treatment of high-grade astrocytoma is the first and urgent factor to extent patients live. No highly histologically differs between low-grade astrocytoma and high-grade astrocytoma but the growth of cells is different from each other. In the state of high-grade astrocytoma, the cells start more aggressively growth. The main symptoms are headaches because of increased intracranial pressure, visual problems,

neck stiffness and vomiting.

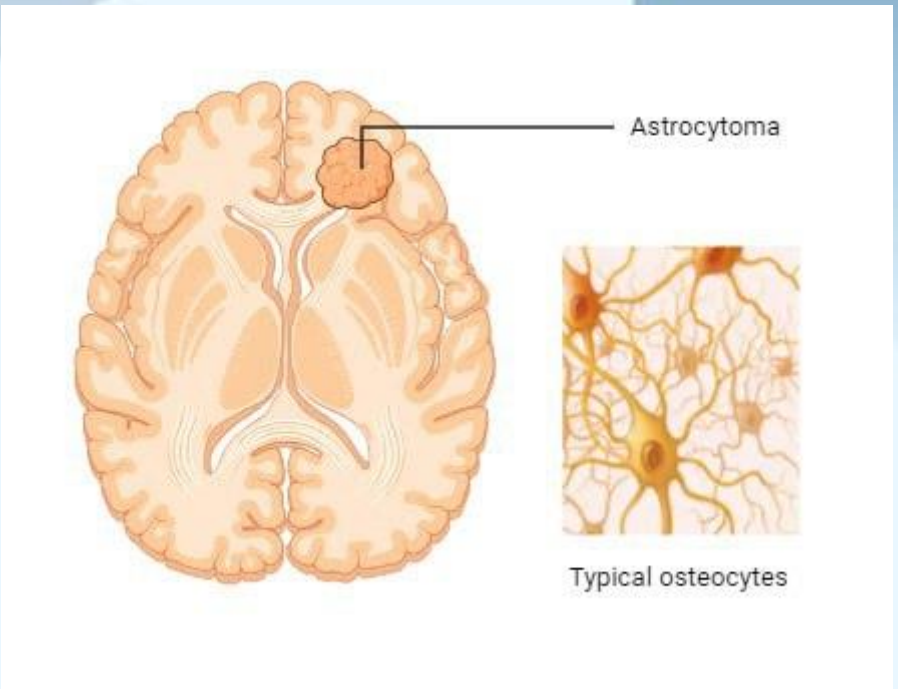

Figure 1 Human Brain with Astrocytoma.

MR spectroscopy and CT scanning are the most useful methods of diagnosis of brain tumors with high accuracy of location, size, degree of oedema, contrast enhancement.[10] Surgery, radiation therapy, observation, chemotherapy are widely used for treatment of high-grade astrocytoma, but method of treatment should be specially selected depending on the condition of every patient. Tumor recurrence may occur in nearly hundreds of treated patients despite using several methods. There are two main challenges in the treatment process. They are molecular/genetic heterogeneity of tumor as well as poor and limited targeting drug delivery in central nervous system.

Temozolomide used a novel standard chemotherapy drug. The results of several research approved that temozolomide considerably extended survival time of patients when used together radiotherapy with this approach temozolomide started new stage of neuro-oncology therapy. Today exist several strategies that manage to improve the effectiveness of Temozolomide.[11,12]

The next novel anti-cancer drug widely used in treatment of brain cancers is Zotiraciclib (TG02). Zotiraciclib is an effective multi-kinase inhibitor, and it can inhibit several subtypes of cyclin-dependent kinases (CDK)− 1, − 2, − 5, − 7 and – 9. A little amount of TG02 in nanomolar concentration capable for (CDKs)− inhibiting

process. Inhibiting CDK-9 function is the main target of the TG02 by protecting RNA polymerase II from phosphorylation process.[13] By inhibiting signaling pathways TG02 effects CDKs, JAK2 and FLT3 in tumor cells. The benefits of the TG02 compared to other CDKs blockers is blocking several CDKs, JAK2 and FLT3 pathways at the same time. After oral dosing of TG02 shows effective phArmacokinetic results in in vivo models by effectively inhibiting both CDK and STAT signaling pathways. This process is the main cause of reducing cancer cells proliferation rate in patients.[13]

Zotiraciclib (TG02) can be used effectively because of multi-kinase inhibiting function. Because single-agent kinase inhibiting is one of the main limitations of other anti-cancer agents. Drug resistance also the problematic drawbacks of the several anti-cancer drugs. By inhibiting the multiple kinases such as CDK1, CDK2, CDK5, CDK7 and especially CDK9 Zotiraciclib can overcome or considerably delay the drug resistance and cancer cell proliferations in patients with High-grade astrocytoma.[13,14]

METHODS

Clinical trials divided into 4 phases and cover hull process of evaluation of novel drug efficiency, pharmacokinetics and pharmacodynamics, side effects, safe dose of drugs and other main quality indicators of novel drug in the patients. The phases differ from each other with quantity of patient participating in the study. In this phase 1 study enrolled 53 patients.

The main aim of the study was to evaluate the drug safety and anti-tumor function of Zotiraciclib and temozolomide together which were used before separately. For this reason, the actual dose schedule should be created. Patients were divided into 2 groups which is the dose-dense (DD) temozolomide called group 1 and metronomic (MN) second group. Each Arm combined with 4 dose- levels of Zotiraciclib in 150mg, 200mg, 250mg, 300mg. Bayesian Optimal Interval (BOIN) method was used for establishing the maximum tolerated dose of Zotiraciclib.[15]

After successfully establishing of the MTD in both groups patients randomized and started to take Zombination of drugs orally until the number of treated patients reaching up to 18 in each group. Two dosing schemes of TMZ and Zotiraciclib were tested by using “Pick the Winner” design. “Pick the Winner” design is statistical

analyzing method of effective drug to carry forward into more extensive testing in the next phase when used several drugs in clinical trials.[16]

All patients aged over 18 suffered with recurrent anaplastic astrocytoma and the disease was histologically approved. Because of the unknown effects of TG02 on fetus or infant pregnant and nursing women excluded in the study. The special dose of TMZ and TG02 were used during the study. The suitable dose schedule of the agents mentioned in the protocol of the clinical trial on the under the supplementary materials subtitle.[17] The daily treatment dose was 125mg/m2 on days 1–7 and 15–21 orally in DD TMZ Arm and 50mg/m2 daily in MN TMZ Arm. The dose of administrated Zotiraciclib was 200 mg daily based on 1,12,15,26 days. The dosage plan was created mainly using encounters, with Zotiraciclib and carfilzomib in blood related cancers considering the likelihood of side effects, in patients treated with Zotiraciclib and TMZ. After establishing the tolerated dose (MTD) of Zotiraciclib, in both groups a cohort expansion phase was initiated. Patients were then randomly assigned to receive Zotiraciclib at the MTD along with either dose (DD) of TMZ in Arm 1 or monthly dose (MN) of TMZ in Arm 2. The treatment plan consisted of 12 cycles unless an experienced disease progression, intolerable side effects, pregnancy or chose to discontinue participation in the study. Prior, to and after each Zotiraciclib dose administration all patients were given premedication to prevent nausea, vomiting and diarrhea.

The research involved using a variety of evaluation methods to analyze how the treatment impacted patients with recurring high grade astrocytomas. These methods included examinations, assessments of any effects and different laboratory tests that were carried out before each treatment session and, at the start. Additionally blood count (CBC) tests with counts were done on the 14th day of every cycle. Brain MRIs were used to determine how well the treatment worked based on criteria set by the Response Assessment in Neuro Oncology Guidelines. Any negative effects were categorized according to the Common Terminology Criteria for Adverse Events version 4.0. The definitions for dose limiting toxicities (DLT) were clearly stated, encompassing conditions like neutropenia and other harmful effects, on blood cells and other parts of the body.

Pharmacokinetics (PK), pharmacogenetics (PG), and neutrophil analysis were conducted in patients which participated during the cohort extension process. Blood samples combined before the taking the first dose during the cycle fallowing 3 days and at 1, 2, 4, 12, 24, 48, and 72-hour after taking the initial dose. Every sample collected at the times mentioned above were tested for CBC. CellaVision instrumentations were used for blood testing. Neutrophil chemotaxis, reactive oxygen species (ROS) production and neutrophil cell surface marker index of the blood conducted in the blood samples which collected at 0,24 and 72 hours. By using either N-formylmethionyl-leucyl-phenylalanine the quick test was conducted for *in vitro* chemotaxis measurement.

At the same time with neutrophil analysis Pharmacokinetics index of the collected blood samples were analysed. The concentration of the Zotiraciclib in the plasma measured using liquid chromatography-tandem mass spectrometry assay. By using the date collected in the test the following indicators concentration (Cmax); and half-life (T1/2), determined by the terminal elimination rate constant (λz) were calculated. Part of the baseline of blood samples used for analysing the genotype of drug metabolizing enzymes and transporters from the genomic DNA which more usual than other metabolizing enzymes. Each polymorphism in CYP1A2 and CYP3A4 was compared to (AUC_{inf}) which analysed in the patients because CYP1A2 and CYP3A4 genotype groups participate in the mobilizing of zotiracilib.[19]

RESULTS

Authors of this Phase 1 clinical trail aimed to design assessing the safety, tolerance and initial effectiveness of Zotiraciclib combined with Temozolomide in individuals which have high-grade astrocytoma. Initially the Maximum Tolerated Dose (MTD) of Zotiraciclib was established. During the study 2 type of dosing schedule of studying agents' dose-danse DD and metronomic MN were used. Within December 2016 and December 2019 fifty-three patients were covered in the cercle of this study.

Drug safety assessing provided by conducting the dose limiting toxicity analysis. This test suitable for both exploring Arms of patients. Fatigue, elevated liver enzymes and diarrhea are the non-haematological toxicity types meanwhile only neutropenia mentioned as an exhibited hematologic toxicity. According to the dates provided in

the article 2 patient participated in the high level 300 mg dose test. One of these patients transferred to intensive care unit because of febrile neutropenia, thrombocytopenia, and hepatic dysfunction. The health condition of the second patient which received 300 mg zotiracilib was good than first one. This patient felled mild fatigue, but this result shows that high level of zotiracilib is interacts individually. Thats why this dose missed out the next studies. DLT index was observed in 28.9% of patients within 38 DLT evaluated patients.

DLT test was conducted withe other dose 200mg and 250 mg of Zotiracillib. For Arm1 received 200 level of dose DLT rate was 16.7% and non-hematologic DLT was diarrhea with the 3rd level of grade. After increasing dose to 250mg overall DLT level reached 25%. Neutropenia with grade 4, level three alanine aminotransferase (ALT) elevation and last one level three fatigue.

The same DLT types were explored for the Arm2. DLT rate for 200 mg Zotiracillib receiving patients was same 16.7% but DLT rate at 250 mg significantly increased up to 41.7% the DLT indicators were same with amr1, but the level of neutropenia showed grade three. The level of DLT for dose II was 50% with grade 4 neutropenia and liver enzyme elevations which explained above separately for each patient.

As a part of the results 250 mg of zotiracilib was approved as the maximum tolerated dose MTD for both groups of study. The continue of the study 36 patients followed treating with Zotiracilib at least 1 cycle of maximum tolerated dose and one dose type of temozolomide dose-dance or metronomic.

The term progression-free survival PFS is one of the main indicators of the effectiveness of the anti-cancer drugs. PFS is important every cancer research because it indicate stabilisation of the health condition of patients under the study or deterioration of the.[20] That is why PFS4 was evaluated in this research. PFS4 rate was overall 0.40 with 95% confidence interval 0.17 to 0.63 and 0.25 with 95% confidence interval 0.08 to 0.47 respectively Arm1 and Arm2 studies. After statistically and pharmacologically data analysing 250mg dose of zotiracilib was chosen as the most optimal dose within the other studied one.

The next evaluated factor in patients is absolute neutrophil count (ANC) and this term is clinically significant in the several type of disease such as cancer because it explains

the patient's immune system status.[21] The result showed that after oral administration of the zotiracilib absolute neutrophil count (ANC) temporary decreased. At the 12-24 hours after receiving the dose analysis showed the lowest point of ANC. The reverse level of neutrophil was observed after 72 hours at the same time with drug concentration decreasing in the patient's plasma. As well as zotiracilib decreased the production of reactive oxygen species which responsible for bacterial killing and working as anti-inflammatory system but the level of ROS restored after 72 hours. Changings appeared on the cytokines also restored at the same time of other indexes. Several cytokine types such asIL-6, MIP-1α, MIP-1β, IP-10, and MCP-1 were explored. All types of cytokines reached their pick in plasma at 24 hours and recovering process of the normal level occurred approximately at 72 hours.

Pharmacokinetic and Pharmacogenetics test of the blood samples also analysed. During the analysis individual concentration of drugs and time profile was provided. Results show that absorption process and elimination of Zotiraciclib was same in all 13 patient which participated in the second state of the research, but PK parameters varied among patients. For example, CV range fluctuated 31-52%. Several genetic variations were analysed but final PG data showed that *rs2470890* "C" allele effects to the Zotiraciclib metabolism process by reducing CYP1A2 expression.

DISCUSSION

Approaching novel malignant gliomas therapeutic targets is remain challenging. There several astrocytes targeted research was conducted.[22] High-grade astrocytoma account 20% of all central nervous systems tomos.[23] the second suffering fact that 70% to 90% of patients with several subtype High-grade gliomas die within 2 years after diagnosing this connected with aggressive proliferation of tumour cells.[24]

Temozolomide commonly used as a standard treatment of anaplastic astrocytoma as well as recurrent anaplastic astrocytoma.[25,26] Nowadays several specialists mention that combination treatment of the cancer is more effective than using unique medicine. The recent phase 1 clinical study represents combinatory using Zotiraciclib and Temozolomide against recurrent high-grade astrocytoma. The research findings indicated that the combined treatment was well tolerated with manageable side effects such as neutropenia, diarrhea, increased liver enzymes and fatigue. Notably, correctly

scheduled dose of temozolomide and Zotiraciclib showed 40% progression survival rate at 4 months (PFS4) in the dose-dense Arm meanwhile PFS rate was 25% in metronomic Arm.

All type of tumour has a complex biology, and several normal cells life cycle processes faced with changes after starting tumour cells growth. During the cancer several pathway disfunctions may occur in the patient's body. Some type of anti-cancer drugs work as a signalling pathway inhibitor. The represent of the study can be used a single agent in the diagnosed glioblastomas. Synergism of Zotiraciclib and TMZ used as a novel agent for treating high-grade astrocytoma. The effect of these two combinate drugs appears by reducing O^6-methylguanine-DNA methyl-transferase expression.

Because of high efficiency and low toxicity these drugs can be used aa an effective agent compere to existing therapeutics. Conventional treatments, like surgery and radiation therapy along with chemotherapy often prolong survival period for one year for individuals with glioblastoma. Zotiraciclib and TMZ can be use alternatives supportive treatment during HGA.

Strengths of the Study

The research used a two-stage phase trial approach to establish the maximum tolerated dose (MTD) Zotiraciclib when combined with dose-dense or metronomic temozolomide. The results of this research provide a valuable information about the safety and efficacy of the combination treatment of HGA. A Bayesian Optimal Interval design was used for determining the maximum tolerated dose to ensure systematically correcting of founded dosing schedule. Pharmacokinetic and pharmacogenomic analysis were conducted for assessing specific polymorphisms and drug metabolism by providing this personalized dosage plans can be approved. By focusing on patient reported outcomes and monitoring symptom burdens over time the study offers a view of how the treatment impacts patients' quality of life.

Limitations of the Study

The one of the main limitations of the current study is that on July 30, 2020, 41 patients were deceased which is 82% of the total number of patients and 72% of patients terminated treatment because of cancer progression. Only 5 patient completed full treatment course this number equal 10% of the initial patients who started treatment course. This results from the data obtained from a small number of patients, which makes it impossible to completely predict the next stages of the study.

What is already known about this subject?

- High-grade astrocytomas, such as anaplastic astrocytoma and glioblastoma, are aggressive and often deadly forms of brain cancer with a high rate of mortality and limited effective treatments.
- Common treatments include surgery, radiation, chemotherapy, and targeted therapies, but they often do not significantly extend survival.
- Temozolomide is the standard chemotherapy used for these cancers, often in combination with radiotherapy, offering some improvement in survival times..

What does this study add?

- Introduces a combination treatment approach using Zotiraciclib with Temozolomide, which was previously used separately, assessing their efficacy in treating recurrent high-grade astrocytoma.
- Demonstrates that this combination can be well-tolerated by patients with manageable side effects like neutropenia and diarrhea.
- Provides new data on the maximum tolerated doses of Zotiraciclib in combination with two dosing schemes of Temozolomide (dose-dense and metronomic), contributing to personalized treatment planning.
- pharmacokinetic and pharmacogenetic insights, potentially guiding more tailored and effective therapeutic strategies based on individual patient profiles

The research did not discover exact variances differences of symptom across the different treatment groups, which could make it challenging to distinguish the impacts of the two treatment plans. Polymorphism n=17 in CYP1A2, n=25 in CYP3A4 was identified at the study they suggested a potential impact on Zotiraciclib metabolism, but the validation of this finding not mentioned on the repot and protocol.

Pregnant and nursing women as well as individuals who has cognitive health problems were excluded this may was limited some groups from participating in the study. The research lasted a short time compared to other studies this limitation impacts to investigate long time survival time research.

In conclusion, the results Zotiraciclib cyclin-dependent kinase 9 (CDK9) inhibitor can be used for treating glioblastomas. Zotiraciclib showed synergistic anti-

glioma effects, and these effects approved during the study. The side effect of the drugs can be controlled and stabilized.

REFERENCES

1. Patil, P. C., Kaleem, M., Mishra, R., Ray, S., Ahmad, A., Verma, D., Bhayye, S., Dubey, R., Singh, H. N., & Kumar, S. (2024). Anticancer drug discovery based on natural products: From computational approaches to clinical studies. *Biomedicines*, *12*(1), 201. https://doi.org/10.3390/biomedicines12010201
2. Chauhan, M., Sonali, Shekhar, S., Yadav, B., Garg, V., Dutt, R., Mehata, A. K., Goswami, P., Koch, B., Muthu, M. S., & Singh, R. P. (2024). AS1411 aptamer/RGD dual functionalized theranostic chitosan-PLGA nanoparticles for brain cancer treatment and imaging. *Biomaterials Advances*, *160*, 213833. https://doi.org/10.1016/j.bioadv.2024.213833
3. Raucher, D. (2019). Tumor targeting peptides: novel therapeutic strategies in glioblastoma. *Current Opinion in Pharmacology*, *47*, 14–19. https://doi.org/10.1016/j.coph.2019.01.006
4. Aldape, K., Brindle, K. M., Chesler, L., Chopra, R., Gajjar, A., Gilbert, M. R., Gottardo, N. G., Gutmann, D. H., Hargrave, D., Holland, E. C., Jones, D., Joyce, J. A., Kearns, P., Kieran, M. W., Mellinghoff, I. K., Merchant, M. S., Pfister, S. M., Pollard, S. M., Ramaswamy, V., . . . Gilbertson, R. J. (2019). Challenges to curing primary brain tumours. *Nature Reviews. Clinical Oncology*, *16*(8), 509–520. https://doi.org/10.1038/s41571-019-0177-5
5. Sathornsumetee, S., Rich, J., & Reardon, D. A. (2007). Diagnosis and treatment of High-Grade Astrocytoma. *Neurologic Clinics*, *25*(4), 1111–1139. https://doi.org/10.1016/j.ncl.2007.07.004
6. Moini, J., Avgeropoulos, N. G., & Samsam, M. (2021). Astrocytoma. In *Elsevier eBooks* (pp. 111–127). https://doi.org/10.1016/b978-0-12-821736-8.00017-0
7. Rakopoulos, P., & Hawkins, C. (2014). Genetic alterations in paediatric high grade astrocytomas. *Diagnostic Histopathology*, *20*(2), 84–90. https://doi.org/10.1016/j.mpdhp.2014.01.003

8. Schneider, T., Mawrin, C., Scherlach, C., Skalej, M., & Firsching, R. (2010). Gliomas in adults. *Deutsches Ärzteblatt International*. https://doi.org/10.3238/arztebl.2010.0799
9. Christoforidis, G. A. (2022). Low-grade astrocytomas. In *Elsevier eBooks* (pp. 521–545). https://doi.org/10.1016/b978-0-12-822835-7.00065-2
10. Béhin, A., Hoang-Xuan, K., Carpentier, A. F., & Delattre, J. (2003). Primary brain tumours in adults. *Lancet*, *361*(9354), 323–331. https://doi.org/10.1016/s0140-6736(03)12328-8
11. Sathornsumetee, S., Rich, J., & Reardon, D. A. (2007b). Diagnosis and treatment of High-Grade Astrocytoma. *Neurologic Clinics*, *25*(4), 1111–1139. https://doi.org/10.1016/j.ncl.2007.07.004
12. Chan, T. A., Weingart, J., Parisi, M., Hughes, M., Olivi, A., Borzillary, S., Alahakone, D., Detorie, N., Wharam, M. D., & Kleinberg, L. (2005). Treatment of recurrent glioblastoma multiforme with GliaSite brachytherapy. *International Journal of Radiation Oncology, Biology, Physics*, *62*(4), 1133–1139. https://doi.org/10.1016/j.ijrobp.2004.12.032
13. Goh, K. C., Novotny-Diermayr, V., Hart, S., Ong, L. C., Loh, Y. K., Cheong, A., Tan, Y., Hu, C., Jayaraman, R., William, A. D., Sun, E. T., Dymock, B., Ong, K. H., Ethirajulu, K., Burrows, F., & Wood, J. M. (2011). TG02, a novel oral multi-kinase inhibitor of CDKs, JAK2 and FLT3 with potent anti-leukemic properties. *Leukemia*, *26*(2), 236–243. https://doi.org/10.1038/leu.2011.218
14. Cai, D., Latham, V. M., Zhang, X., & Shapiro, G. I. (2006). Combined depletion of cell cycle and transcriptional Cyclin-Dependent kinase activities induces apoptosis in cancer cells. *Cancer Research*, *66*(18), 9270–9280. https://doi.org/10.1158/0008-5472.can-06-1758
15. Biard, L., Andrillon, A., Silva, R. B., & Lee, S. M. (2024). Dose optimization for cancer treatments with considerations for late-onset toxicities. *Clinical Trials*. https://doi.org/10.1177/17407745231221152
16. Chen, D., Huang, P., Lin, H., Chiappori, A., Gabrilovich, D. I., Haura, E. B., Antonia, S., & Gray, J. E. (2017). A Bayesian pick-the-winner design in a

randomized phase II clinical trial. *Oncotarget*, *8*(51), 88376–88385. https://doi.org/10.18632/oncotarget.19088

17. *CCR-20-4730R1 Supplementary Materials*. (n.d.). [Dataset]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8197750/bin/NIHMS1690334-supplement-1.pdf
18. Hofmeister, C. C., Berdeja, J. G., Vesole, D. H., Suvannasankha, A., Parrott, T., & Abonour, R. (2015). TG02, an Oral CDK9-Inhibitor, in Combination with Carfilzomib Demonstrated Objective Responses in Carfilzomib Refractory Multiple Myeloma Patients. *Blood*, *126*(23), 3052. https://doi.org/10.1182/blood.v126.23.3052.3052
19. Pasha, M., Jayaraman, R., Reddy, V. P., Yeo, P., Goh, E. M. L., Williams, A. P., Goh, K., & Ethirajulu, K. (2012). Preclinical metabolism and pharmacokinetics of SB1317 (TG02), a potent CDK/JAK2/FLT3 inhibitor. *Drug Metabolism Letters*, *6*(1), 33–42. https://doi.org/10.2174/187231212800229336
20. Shameer, K., Zhang, Y., Jackson, D., Rhodes, K., Neelufer, I. K. A., Nampally, S., Prokop, A., Hutchison, E., Ye, J., Malkov, V., Liu, F., Sabin, A., Weatherall, J., Duran, C., Iacona, R., Khan, F., & Mukhopadhyay, P. (2021). Correlation between early endpoints and overall survival in Non-Small-Cell lung Cancer: A Trial-Level Meta-Analysis. *Frontiers in Oncology*, *11*. https://doi.org/10.3389/fonc.2021.672916
21. Yoon, C. H., Park, S., Jin, Y., Lee, H. S., Bae, S. J., Hwan, C., Lee, D. Y., Ahn, S. G., & Lee, J. E. (2020). Associations between absolute neutrophil count and lymphocyte-predominant breast cancer. *Breast*, *50*, 141–148. https://doi.org/10.1016/j.breast.2019.09.013
22. Osama, M., Mostafa, M. N., & Alvi, M. A. (2020). Astrocyte elevated gene-1 as a novel therapeutic target in malignant gliomas and its interactions with oncogenes and tumor suppressor genes. *Brain Research*, *1747*, 147034. https://doi.org/10.1016/j.brainres.2020.147034
23. Rakopoulos, P., & Hawkins, C. (2014b). Genetic alterations in paediatric high grade astrocytomas. *Diagnostic Histopathology*, *20*(2), 84–90. https://doi.org/10.1016/j.mpdhp.2014.01.003

24. Paugh, B. S., Qu, C., Jones, C., Liu, Z., Adamowicz-Brice, M., Zhang, J., Bax, D. A., Coyle, B., Barrow, J. H., Hargrave, D., Lowe, J., Gajjar, A., Zhao, W., Broniscer, A., Ellison, D. W., Grundy, R. G., & Baker, S. J. (2010). Integrated Molecular genetic profiling of pediatric High-Grade GlIomas reveals key differences with the adult disease. *Journal of Clinical Oncology*, *28*(18), 3061–3068. https://doi.org/10.1200/jco.2009.26.7252

25. Wesolowski, J., Rajdev, P., & Mukherji, S. (2010). Temozolomide (Temodar). *American Journal of Neuroradiology*, *31*(8), 1383–1384. https://doi.org/10.3174/ajnr.a2170

26. Villanó, J. L., Seery, T. E., & Bressler, L. (2009). Temozolomide in malignant gliomas: current use and future targets. *Cancer Chemotherapy and Pharmacology*, *64*(4), 647–655. https://doi.org/10.1007/s00280-009-1050-5