AZD1390 with radiotherapy shows manageable safety profile and preliminary efficacy for patients with glioblastoma

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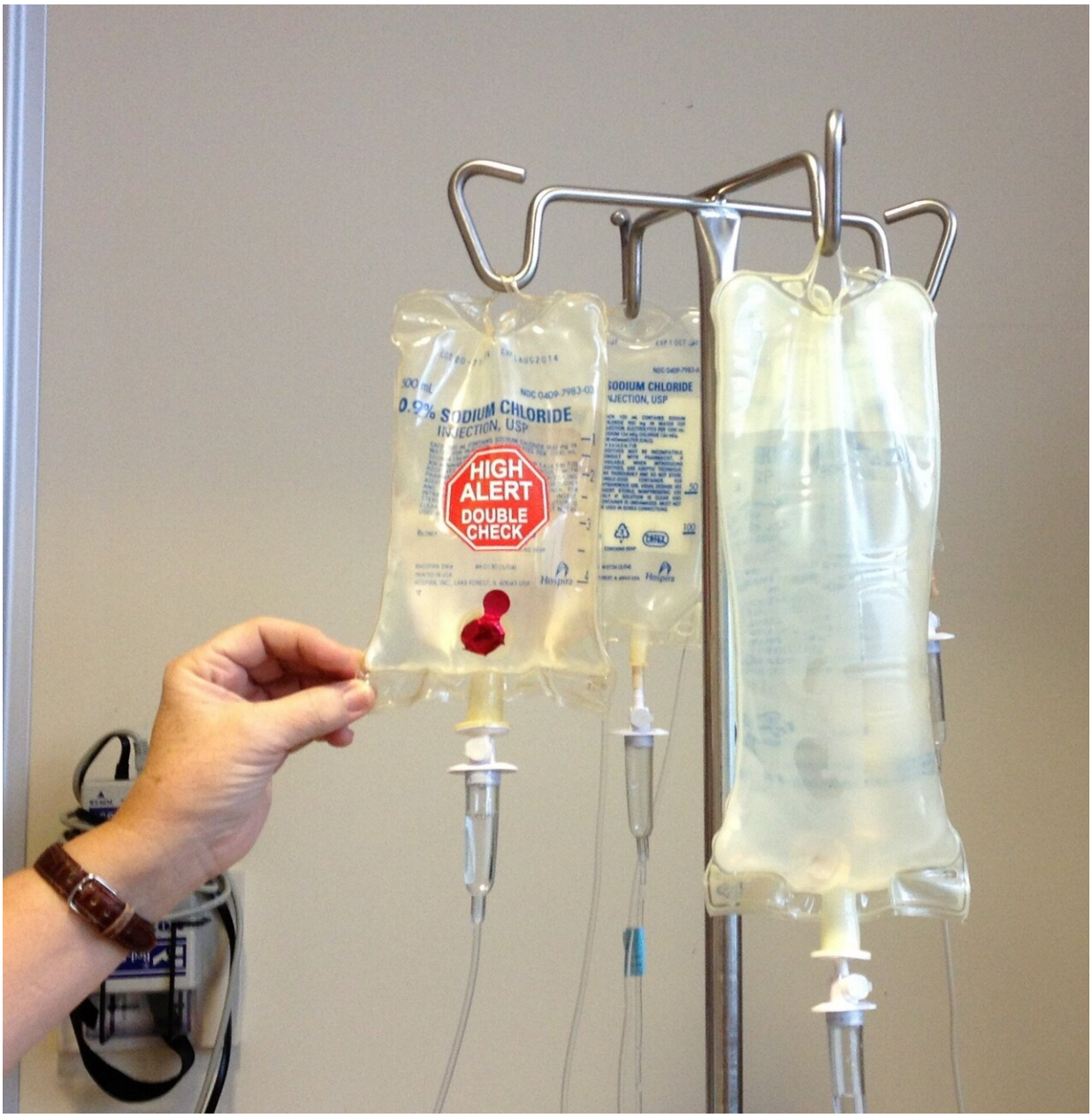

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AZD1390, an ataxia telangiectasia mutant (ATM) kinase inhibitor, demonstrated a manageable safety profile in both recurrent and newly diagnosed glioblastoma (GBM) patients when given in combination with

standard-of-care radiotherapy and showed preliminary efficacy in recurrent GBM patients, according to results from a global phase I trial presented at the American Association for Cancer Research (AACR) Annual Meeting 2024, held April 5–10.

"Glioblastoma is a lethal cancer with the majority of patients not surviving past two years from diagnosis," said Jonathan T. Yang, MD, Ph.D. of Memorial Sloan Kettering Cancer Center, who presented the results of the trial. "Despite efforts to improve survival, the current standard of care continues to be a backbone of radiotherapy with or without temozolomide [Temodar] without much innovation in the past two decades. This context highlights both the urgent need to develop new medicines and the historical challenges of developing novel therapeutics for this devastating disease."

Intensity-modulated radiation therapy (IMRT), which is the standard of care in newly diagnosed GBM patients, causes the death of cancer cells by damaging the DNA inside of the cell. But the ATM cell signaling pathway is activated to help repair the DNA double-strand breaks (DSBs) caused by radiation therapy, thus impeding its effectiveness. An ATM inhibitor prevents the repair of DSBs, thereby enhancing the cancer-killing effect of radiation therapy, Yang said.

GBM accounts for approximately 50% of primary malignant brain tumors. One reason brain tumors have been difficult to treat is because the blood-brain barrier prevents some therapies from penetrating into the brain and reaching the cancers they aim to treat. Because of this challenge, AZD1390 was designed to penetrate the blood-brain barrier, and a healthy volunteer study recently showed that AZD1390 crossed through an intact barrier. Other pre-clinical experiments demonstrated the potential antitumor effects of AZD1390 without exacerbating IMRT

toxicity in surrounding areas by not causing harm to normal, healthy brain tissue.

Yang and his colleagues assessed the safety, tolerability, early efficacy, and maximum tolerated dose of AZD1390 with IMRT in humans. As of February 2024, 115 patients were given AZD1390 in the phase I trial, including 75 patients with recurrent GBM in Arm A and 36 patients with newly diagnosed, MGMT unmethylated GBM in Arm C. In both Arms, patients received escalating once-daily doses of AZD1390; patients in Arm A were given 35 Gy of IMRT in 10 fractions over two weeks while those in Arm C were given 60 Gy of IMRT in 30 fractions over six weeks. Additionally, following the completion of IMRT, patients were given adjuvant AZD1390 for two weeks.

Out of the 115 patients, 18 (15.7%) experienced an AZD1390-related adverse event (AE) of a grade 3 or 4; there were no grade 5 treatment-related AEs. Additionally, 4.3% of patients discontinued AZD1390 treatment due to an AE related to AZD1390 only.

"Most adverse effects experienced by patients during the study were low grade, readily manageable, and reversible in nature," Yang said.

Patients in Arm C experienced a higher frequency and severity of radiation-related skin injury due to longer exposure to radiation, and most instances were easily managed and fully reversed following treatment with topical steroids and moisturizers, Yang said.

The researchers identified 400 mg in Arm A and 300 mg in Arm C as the maximum tolerated doses.

While Yang said they are still collecting efficacy data in both arms, an encouraging median overall survival (OS) of 12.7 months was observed in Arm A patients at doses demonstrating target engagement. Prior

studies have shown the current standard of care leads to an OS of 6 to 10 months. The OS data for Arm C is still maturing.

"Drug development in GBM is generally challenging due to the rarity of the disease and lack of robust early clinical indicators of efficacy," Yang said. "If the preliminary efficacy benefit observed in this trial is proven in a pivotal study, it would be a critical, biologically supported approach to address the high unmet need in GBM."

Yang said the planning for the next phase of development is currently underway.

Limitations of this study include the single-arm and open-label nature of the study with a small sample size.

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