short review

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Best of ASCO 2022—central nervous system tumors

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Summary In this article, updates on novel therapy approaches in central nervous system tumors presented at the ASCO 2022 meeting are summarized. Promising outcome results on targeted therapies in rare entities such as neurotrophic tyrosine receptor kinase (NTRK) fusion-positive tumors [1] and in v-RAF murine sarcoma viral oncogene homolog (BRAF)V600 mutant pediatric glioma are reported [2, 3]. Furthermore, we shortly review data on additional administration of polyADP-ribose polymerase (PARP) inhibitor veliparib (Alliance A071102 trial) [4] and on a combinatorial immunotherapy regime (consisting of intramuscular administration of two synthetic DNA plasmids in combination with cemiplimab) in newly diagnosed glioblastoma patients [5].

Keywords Glioma · Targeted therapies · Immunotherapy · Glioblastoma · BRAF inhibition

Immunotherapy approaches

Several previous phase II and III trials have evaluated efficacy of checkpoint inhibition as monotherapy, especially using programmed death-1 (PD-1) inhibitors, in newly diagnosed and recurrent glioblastoma (GBM) patients. However, all these studies have failed to show improved outcome in glioma patients [6–10]. Therefore, the future value of immunotherapy approaches in primary central nervous system (CNS) tumors remains unclear. Thus, current research concentrates on investigation of several combinatorial immunotherapy regimes.

INO-5401 + INO-9012 with electroporation in combination with cemiplimab in glioblastoma

Utilization of vaccine platforms with checkpoint blockade may be able to achieve antitumor immune response by helping T-cells to migrate into the immunologically cold GBM tumor microenvironment. A phase I/II single arm study with two cohorts of newly diagnosed GBM (methylated MGMT versus unmethylated MGMT promotor) used an DNA plasmid approach with intramuscular injection of two synthetic DNA plasmids INO-5401 (encoding hTERT, WT-1, and PSMA) and INO-9012 (encoding IL-12) with combinatorial administration of IgG subclass 4 PD-1 blocking antibody cemiplimab. All patients received a hypofractionated radiation scheme (40 Gy) and concurrent temozolomide (TMZ) chemotherapy, but only the methylated group received adjuvant TMZ chemotherapy.

Primary aim was to assess safety. Secondary objectives included efficacy (18-month overall survival [OS]) and evaluation of immunogenicity including peripheral cellular immune reactions to the targeted antigens as well as changes in intratumoral gene expression.

In all, 52 patients, of whom 32 patients were unmethylated, were enrolled in the study. Study regime was well-tolerated with known single-agent toxicity profile. Most of adverse events (AE) were grade 1 or 2. Related AE grade ≥4 was not observed. In terms of

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efficacy, the 18-month OS endpoint for unmethylated and methylated patients was approximately 50% and 75%, respectively.

Immunogenicity measures via flow cytometry and interferon-γ ELISpot revealed activated, INO-5401-specific cellular immune responses. Regarding gene expression levels, significantly reduced markers associated with antiapoptosis, proproliferation and immune response suppression have been observed in patients who were alive at least 18 months compared to patients with OS less than 18 months.

In summary, this study with a novel combinatorial immunotherapy approach incorporating DNA plasmids plus cemiplimab together with radiotherapy and TMZ shows a good safety profile and encouraging survival benefit. However, further evaluation of this approach is needed in a randomized clinical trial.

Checkpoint inhibition in children with hypermutant tumors

The majority of pediatric cancers have low mutational burden and are considered as unresponsive to immune checkpoint inhibition. However, a small subset of cancers in children and young adults, mostly consisting of patients with an underlying germline DNA replication repair deficiency (e.g., Lynch syndrome), have ultrahypermutant tumors and high microsatellite insertion deletion burden. Data of this patient group were retrospectively and prospectively collected in an observational, registry-based study to investigate outcome to anti-PD-1 therapy. The trial enrolled 38 patients who developed 45 cancer types, whereof 33 (73%) were CNS tumors. High and durable response rates were observed across non-CNS solid tumors (100%) and CNS tumors (64%). Median OS for CNS tumors was 21.6 months and not reached for non-CNS solid tumors. In line with previous data in pediatric solid tumors or lymphoma, immune checkpoint inhibitors therefore presented with a favorable clinical activity [11]. However, efficacy of immune checkpoint inhibition appears especially effective in a small and rare patient group with hypermutant cancers and an underlined germline replication repair deficiency.

Targeted therapies in primary CNS tumors

Veliparib or placebo in combination with adjuvant temozolomide in newly diagnosed glioblastoma (Alliance A071102)

The Alliance A071102 clinical phase II/III trial was designed based on robust preclinical data of a study performed in patient-derived xenograft (PDX) models. PDX cancer models are created by engrafting patients' tumor tissue into immunodeficient mice. Results demonstrated outcome benefit of methylated GBM PDX models due to TMZ sensitization by polyADP-ribose polymerase (PARP) inhibition [12].

The trial design included a phase II with PFS as the primary endpoint and one interim analysis for futility. Accrual did to stop for the futility analysis and phase II patients were transferred to phase III with OS as primary endpoint. Overall, the Alliance A071102 trial randomized 447 newly diagnosed MGMT promotor hypermethylated GBM patients one to one to standard of care adjuvant treatment with TMZ (day 1–5 every 28 days) combined with either placebo or veliparib (administered day 1–7 every 28 days) after completion of concurrent radiation and TMZ. The additional administration of veliparib was not associated with significant improvement of OS (median OS 28.1 vs. 24.8 months for TMZ + veliparib vs. TMZ + placebo, $p = 0.15$; HR 0.89 [0.71–1.11]) or progression-free survival (PFS, median 13.2 vs 12.1 months, $p = 0.31$; HR 1.05 [0.86–1.30]). An unplanned exploratory analysis showed extension in survival across patients belonging to the experimental arm after retreatment of TMZ at first recurrence. The data are well in line with previous trials showing only limited efficacy of PARP inhibitors in glioma [13]. Therefore, PARP inhibition will rather unlikely find entry into clinical practice in treating glioma patients.

Long-term control and safety of larotrectinib in NTRK-fusion-positive primary CNS tumors

Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are known as oncogenic drivers in many tumor entities. Efficacy data of NTRK inhibition with the highly selective TRK inhibitor larotrectinib have been recently reported in adult and pediatric patients with TRK fusion primary CNS tumors [14]. Respective updated data of an expanded cohort were presented at ASCO 2022. The study evaluated objective response rate (ORR) as primary endpoint and safety of adult and pediatric patients with TRK fusion primary CNS tumors treated with larotrectinib. In all, 38 patients, of whom 28 patients (74%) were pediatric, were enrolled from two clinical trials (NCT02637687, NCT02576431). The majority of patients were diagnosed with high-grade gliomas (23/38, 60.5%), followed by low-grade gliomas (9/38, 23.7%) and other rare entities (6/38, 15.8%). The ORR and 24-week disease control rate (DCR) was 30% and 73%, respectively. The median time to response was less than 2 months and there was a high durability of response (64% 12-month duration of response rate). Toxicity profile was manageable.

BRAF/MEK inhibition in pediatric glioma

Gliomas account for the majority of brain tumors in the pediatric population, whereof approximately 90% are low-grade and 10% high-grade [15].

In low-grade glioma, treatment essentially consists of tumor resection. If surgery is not possible,

chemotherapy is applied as first-line treatment with highly variable response rates. V-RAF murine sarcoma viral oncogene homolog (BRAF) V600E mutation is identified among 15–20% of all pediatric low-grade glioma and less frequent in high-grade glioma (approximately 5%) [16]. In previous studies, BRAF inhibition using dabrafenib as monotherapy or a combinational approach with trametinib has shown clinical benefit in this population (NCT02684058).

Results of two phase II trials that evaluated outcome after usage of BRAF/MEK inhibition in BRAFV600-mutant pediatric gliomas were presented at ASCO 2022.

The first one enrolled 110 patients with diagnosis of newly diagnosed pediatric BRAFV600-mutant low-grade glioma. A 2-to-1 randomization between the experimental arm (combination dabrafenib and trametinib, $n=73$ patients) versus standard of care chemotherapy (carboplatin and vincristine, $n=37$ patients) was performed. ORR was 47% (95% CI 35–59%) with dabrafenib/trametinib and 11% (95% CI 3–25%) in the control arm ($p<0.001$; odds ratio, 7.2 [95% CI 2.3–22.4]). A significant difference in favor of the experimental arm was also seen in an increased clinical benefit rate (86% vs 46%) and prolonged median PFS (20.1 months vs 7.4 months, $p<0.001$; HR, 0.31 [95% CI 0.17–0.55]). Toxicity profile in the dabrafenib/trametinib arm was more favorable with fewer grade ≥3 adverse events (47% vs 94%) and lower discontinuation rate due to AEs (4% vs 18%).

The other phase II study evaluated outcome of dabrafenib and trametinib in 41 pediatric patients with relapsed/refractory BRAFV600 high-grade gliomas (WHO grade III/IV).

Administration of dabrafenib and trametinib resulted in an ORR of 56.1% and improvement in response durability and survival compared to current standard of care treatment in this patient population.

Findings of this pediatric study align with the encouraging experience of BRAF/MEK inhibition in the adult population [17].

The presented data showed that targeted therapies including NTRK and BRAF/MEK inhibition may be a feasible and effective approach in a small subgroup of CNS tumors in pediatrics and adults. Molecular testing should be sought early in the disease course in order to select patients for these treatment options. However, timing of the administration (first-line or in the recurrent setting) remains unclear.

Take home message

Immunotherapy approaches have still not found a breakthrough in successful treatment of primary central nervous system tumors. However, evidence of their value in improving outcome exists by using a combinatorial approach and in distinct patient groups (e.g. in children with hypermutant tumors). Recent performed studies on targeted therapies showed limited efficacy of PARP inhibitors in glioma patients, whereas BRAF and NTRK inhibition revealed promising results.

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