Editorial commentary: Society for Neuro-Oncology 2021 Annual Meeting updates on primary central nervous system tumors

Lauren Singer, Priya Kumthekar

Malnati Brain Tumor Institute at the Robert H. Lurie Comprehensive Cancer Center, Department of Neurology, The Feinberg School of Medicine/Northwestern University, Chicago, IL, USA

Correspondence to: Lauren Singer. Malnati Brain Tumor Institute at the Robert H. Lurie Comprehensive Cancer Center, Department of Neurology, The Feinberg School of Medicine/Northwestern University, Chicago, IL, USA. Email: lauren.singer@nm.org.

Submitted Jan 01, 2022. Accepted for publication Jun 07, 2022.

doi: 10.21037/cco-22-2

View this article at: https://dx.doi.org/10.21037/cco-22-2

Introduction

The Annual Meeting for the Society for Neuro-Oncology (SNO) was held in November 2021. The meeting caters to the multidisciplinary field of neuro-oncology, including future growth and advances. During the conference, several key clinical trials and research were presented with respect to the diagnostic and therapeutic advances. Several emerging themes were observed from these presentations, including immunotherapy, targeted therapy, and focus on meningioma. These topics are at the forefront of current research for treatment of central nervous system (CNS) tumors and shed light on new therapeutic agents as treatment options. Here, we present a brief editorial of several key abstracts (*Table 1*) within these themes and relevant data to be interpreted in the context of continued evolution and progress of treatment of primary CNS tumors.

Immunotherapy in glioma

The current standard of care for treatment of newly diagnosed glioblastoma remains radiotherapy (RT) with concurrent temozolomide (TMZ) followed by adjuvant TMZ (8). While this first line therapy is well established, nearly all patients go on to have recurrence. Many clinical trials have aimed to determine therapeutic alternatives to prolong survival. Immunotherapy is one such therapeutic option which has been widely researched. One such phase III trial (NCT02667587) was presented at SNO 2021 looking at the addition of nivolumab to current standard of care (1). In this study, 716 patients with newly diagnosed glioblastoma were randomized 1:1 to experimental and control arm regardless of programmed death-ligand 1 (PD-L1) expression. All patients were O^6-methylguanine-DNA-methyltransferase (MGMT) methylated or indeterminate. Individuals in the experimental arm received nivolumab (first dosed at 240 mg every 2 weeks for 8 doses followed by 480 mg every 4 weeks) with concurrent standard of care consisting of RT with concurrent TMZ followed by six cycles of adjuvant TMZ. The control arm received only standard of care with a placebo infusion. Primary endpoints of the trial included progression free survival (PFS) and overall survival (OS). Overall, no improved survival was seen in patients who received nivolumab with PFS 10.6 months for the group who received Nivolumab *vs.* 10.3 months for standard of care (HR 1.06, 95% CI: 0.9–1.25) and OS 28.9 months with addition of nivolumab *vs.* 32.1 months in the control group (HR 1.1, 95% CI: 0.91–1.33). There was further characterization of OS for patients who were not on baseline corticosteroids, which showed OS 31.2 months in experimental arm *vs.* 33.0 months, which does show prolonged survival if not on baseline corticosteroids. Additional endpoint included safety, with 52.4% of patients receiving nivolumab reporting grade 3–4 adverse events as compared to 33.6% of patients who did not receive nivolumab. Thus, patients who received nivolumab showed increase risk of adverse events but no improvement in survival in the newly diagnosed setting.

While treatment at diagnosis has been well described in the literature, there is no current standard of care exists for treatment of recurrence of glioblastoma (9). Therapeutic options often used include lomustine, an alkylating agent with similar properties to TMZ, as well as bevacizumab, a

© Chinese Clinical Oncology. All rights reserved.

Table 1 Summary of clinical trials presented

Author	Trial phase	Tumor type	Therapy	Therapy type	Results
Weller *et al.* (1)	III	GBM	Nivolumab	Immunotherapy	No improvement in PFS or OS
Desjardins *et al.* (2)	I/II	GBM	PVSRIPO	Immunotherapy	No significant toxicity, prolonged OS
Arrillaga-Romany *et al.* (3)	II	H3K27 DMG	ONC201	Targeted therapy	Prolonged ORR, PFS, and OS
Doz *et al.* (4)	I/II	Primary CNS tumors with NTRK fusion	Larotrectinib	Targeted therapy	Prolonged ORR, PFS, and OS
Brastianos *et al.* (5)	II	Meningioma	Pembrolizumab	Immunotherapy	Prolonged PFS
Yust-Katz *et al.* (6)	II	Meningioma and HPC	Pembrolizumab	Immunotherapy	Lack of generalizable data
Plotkin *et al.* (7)	II	Meningioma	Vistusertib	Targeted therapy	Prolonged PFS

GBM, glioblastoma; DMG, diffuse midline glioma; CNS, central nervous system; NTRK, neurotrophic tyrosine receptor kinase; HPC, hemangiopericytoma; PFS, progression free survival; OS, overall survival; ORR, overall response rate.

vascular endothelial growth factor (VEGF) inhibitor which is often used for symptom control at time of recurrence (10). Immunotherapy has also been pursued as a treatment option at time of recurrence. One such study was presented using PVSRIPO, which is an immunotherapy agent which targets CD155 via poliovirus on malignant cells of solid tumors (2). In preclinical models, this agent has been shown to elicit a tumor antigen-specific T-cell mediated anti-tumor response (11). A phase 1 study showed prolonged survival with PVSRIPO compared to control in patients with recurrent GBM (12). The data presented at SNO 2021 included updates to phase I safety and efficacy and interim results of the phase II trial (2). In this trial, patients with recurrent, histologically-confirmed recurrent glioblastoma (n=149) were given PVSRIPO intratumorally versus convection-enhanced delivery on day 1. Follow-up was done at 12 and 24 months. Of these patients, 30 received doses of PVSRIPO in phase I. Safety was assessed, with no dose-limiting toxicities and 97% of patients experiencing grade 1–2 adverse events. OS was the primary endpoint assessed, with 12 months OS 54% for phase I and 50% for phase II and 24 months OS 18% and 17% for phase I and phase II, respectively. Both smaller lesions and MGMT methylation were associated with prolonged survival, which is consistent with prior data (13). Overall, PVSRIPO was shown to be associated with prolonged long-term survival as compared to historic controls and was shown to be well tolerated, which suggests that this may be a promising therapeutic agent for recurrent glioblastoma in the future pending further studies.

Targeted therapy in glioma

Recent research in the field of neuro-oncology has emphasized the importance of molecular classification of glioblastoma in development of targeted therapies (14). One trial presented specifically looked at treatment for H3K27 mutant diffuse midline gliomas (DMGs) (3). This trial looked at drug efficacy of ONC201, which is an anti-cancer DRD2 antagonist and CIpP agonist (15). Efficacy analysis was reported on 50 patients, both pediatric and adult, with H3K27 mutant DMG. Results reported included overall response rate (ORR) of 20% with median duration of response of 11.2 months and median time to response of 8.3 months. The ORR by RANO-LGG criteria was 26.0%. Additionally, PFS at 6 months was 35.1% and median OS was 13.7 months (median follow-up 18 months) with OS at 24 months 34.7%. Overall, this trial showed that ONC201 monotherapy showed meaningful radiographic and clinical response in recurrent H3K27 mutant DMGs and should be considered in the management of these patients.

Data was also presented on larotrectinib as a treatment for primary CNS tumors. larotrectinib is a selective tyrosine receptor kinase (TRK) inhibitor which has been shown to be beneficial for patients with TRK-fusion malignancies (16). At the SNO 2021 conference, data from two clinical trials (NCT02637687, NCT02576431) including 33 patients with TRK fusion-positive CNS tumors treated with larotrectinib was presented (4). Tumor etiology included 19 high-grade gliomas (HGG), 8 low-grade gliomas (LGG), 2 glioneuronal tumors, 2 neuroepithelial tumors, 1 CNS neuroblastoma, and 1 small round blue cell tumor. In these

© Chinese Clinical Oncology. All rights reserved.

patients, ORR was 30% with three patients with complete response (all pediatric), 7 with partial response, 20 with stable disease, and 3 with progressive disease. Median time to response was 1.9 months irrespective of number of prior systemic therapies. The ORR in patients with HGG was 26% and 38% in LGG. Median PFS was 18.3 months with median OS 85% at 12 months and not reached at 16.5 months median-follow-up. Three patients reported grade 3–4 treatment-related adverse events. Overall, this data demonstrated sustained response in patients with TRK fusion-positive tumors receiving larotrectinib with a favorable safety profile, and should be considered in the treatment of primary brain tumors, especially in the pediatric population.

Meningioma

While many trials focus on gliomas, more research efforts have been placed on other primary CNS tumor subtypes, including meningioma. Meningiomas are the most common primary CNS tumor in adults (17). One abstract presented at SNO 2021 highlighted the importance of molecular classification of meningiomas (18). Four molecular groups were presented based on DNA copy-number mutations, DNA point mutations, DNA methylation, and mRNA abundance. These groups each had a unique biology and included immunogenic (MG1), benign NF2 wild-type (MG2), hypermetabolic (MG3), and proliferative (MG4) (18). The MG1 subtype demonstrates the highest frequency of NF2 and SMARCB mutations with high percentage of S100 protein expression. Of these subtypes, the MG3 and MG4 subtype show the most variability in terms of mutations and variability in chromosomal copy numbers. There was decreased PFS described in progression from MG1 to MG4 subtype, with the MG4 subtype showing the most unfavorable outcomes. The importance of these mutations is underscored by the unique behavior of each group which ultimately predicts clinical outcomes and determines therapeutic options.

Current treatment includes surgical resection as medical therapies have proven to be limited (19). At SNO 2021, three phase II trials were presented, including two trials looking at the therapeutic benefit of Pembrolizumab and a third trial looking at the therapeutic benefit of vistusertib (5-7). In one phase II trial presented at SNO 2021, 24 patients with recurrent grade II and III meningiomas were treated with Pembrolizumab (5). Of the 24 patients, 20 underwent more than one surgical resection and 12 received more than one round of RT. The trial data showed 6 months PFS rate of 0.5 and median PFS of 8.3 months. Median PFS for the 12 patients who achieved primary 6 months PFS endpoint showed overall PFS of 17.3 months from start of treatment. As the primary endpoint of 6 months PFS was met, this suggest the need to conduct further trials on the efficacy of pembrolizumab as a treatment option for anaplastic meningiomas.

A second phase II trial presented further assessed the efficacy of pembrolizumab in recurrent anaplastic meningioma and hemangiopericytoma (6). In this study, 12 patients (2 hemangiopericytoma, 10 refractory anaplastic meningioma) who had undergone prior treatment were treated with pembrolizumab. Primary endpoint included 6 and 12 months PFS with median follow-up of 18.5 months. The PFS was 25% at 6 months and 16.7% at 12 months with a median PFS of 2.75 months. The ORR was 16.7% with only 2 patients showing partial response. Median survival was not yet reached, but 1 year survival was noted to be 82.5%. Despite the previous trial demonstrating some clinical efficacy, this trial showed a low ORR. There is some data to suggest a subset of patients might benefit, given that two patients did show partial response, but there was lack of generalizable response data among the population tested.

The third trial presented was a phase II study looking at the efficacy of vistusertib, an mTOR inhibitor (7). The *NF2* gene, a regulator of the mTOR complex, is inactivated in more than half of meningiomas, which has been suggested to be associated with meningioma growth (20). Thus, targeting the mTOR complex was studied as a potential treatment for recurrent meningiomas. In this phase II trial, 28 patients with recurrent grade II and III meningiomas were enrolled (NCT03071874). Of these patients, 50% harbored pathogenic *NF2* variants. The primary endpoint was measured as PFS with progression defined radiographically with a 25% increase in size. The 6 months PFS was 47% and 12 months was 72%. PFS, but not OS, was overall decreased in patients with grade III meningioma, but there was no different in PFS or OS between genetic groups in regards to *NF2* mutation. Overall, vistusertib treatment was associated with 6 months PFS exceeding target 35%, which suggests that further research and trial of mTOR inhibitors is warranted in treatment of recurrent meningiomas.

Conclusions

The SNO annual meeting provided a platform for the

© Chinese Clinical Oncology. All rights reserved.

presentation and discussion of diagnostic and therapeutic research in the field of neuro-oncology. The trials discussed highlight a small subset of the data presented. Overall, several themes emerge from this data regarding the potential therapeutic benefit of various treatment modalities. Results from one phase III study showed no improved survival with nivolumab in patients with newly diagnosed glioblastoma while a phase II study showed potential efficacy of a different immunotherapy, PVSRIPO, in regards to OS. This suggests that while currently available immunotherapy may not be the answer to prolonged survival, novel immunotherapy agents warrant further evaluation for potential benefit. Additionally, more targeted therapy with ONC201 did show benefit in a subset of patients with H3K27M mutant DMG. Additionally, TRK fusion targeted therapy with larotrectinib did show response in patients with positive primary CNS tumors. This further emphasizes the importance of individualized molecular classification of tumors and highlights the importance of a more individualized, targeted approach. Future clinical trials should be designed around this targeted approach. Finally, two potential treatments for recurrent meningioma were studied, including pembrolizumab and vistusertib which both showed some potential for survival benefit in a subset of patients. The trials presented lay the groundwork for future directions of clinical trials in the advancement of therapeutics for primary CNS tumors.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Chinese Clinical Oncology*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-22-2/coif). PK receives consulting fees from Biocept, Affinia, Enclear, Angiochem and Bioclinica; and payment or honoraria from Novocure, and Sintetica. PK holds European Patent 3307327, August, 12 2020 and US Patent Pending 15/737,188. PK served on advisory boards/advised Berg, Janssen, Mirati, Orbus Therapeutics, Celularity, and SDP Oncology. PK has stock or stock options of Enclear. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Weller M, Lim M, Idbaih A, et al. A Randomized phase 3 study of nivolumab or placebo combined with radiotherapy plus temozolomide in patients with newly diagnosed glioblastoma with methylated MGMT promoter: CheckMate 548. Neuro-Oncol 2021;23:vi55-6.
2. Desjardins A, Gromeier M, Friedman H, et al. Safety and efficacy of PVSRIPO in recurrent glioblastoma: long-term follow-up and initial multicenter results. Neuro-Oncol 2021;23:vi97.
3. Arrillaga-Romany I, Kurz S, Tarapore R, et al. Clinical efficacy of ONC201 in recurrent H3 K27M-mutant diffuse midline glioma patients. Neuro-Oncol 2021;23:vi230.
4. Doz F, van Tilburg CM, Geoerger B, et al. Efficacy and safety of larotrectinib in TRK fusion-positive primary central nervous system tumors. Neuro Oncol 2022;24:997-1007.
5. Brastianos PK, Kim AE, Giobbie-Hurder A, et al. Phase 2 study of pembrolizumab in patients with recurrent and residual high-grade meningiomas. Nat Commun 2022;13:1325.
6. Yust-Katz S, Amiel A, Limon D. A Phase II, open-label, single arm trial of Pembrolizumab for Refractory Atypical and Anaplastic Meningioma and Hemangiopericytoma. Neuro-Oncol 2021;23:vi57.
7. Plotkin S, Kumthekar P, Wen P, et al. A single arm phase II study of the dual mTORC1/mTORC2 inhibitor vistusertib provided for sporadic patients with grade II-III meningiomas that recur or progress after surgery and radiation. Neuro-Oncol 2021;23:vi72.

© Chinese Clinical Oncology. All rights reserved.

8. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
9. Gallego O. Nonsurgical treatment of recurrent glioblastoma. Curr Oncol 2015;22:e273-81.
10. Wick W, Gorlia T, Bendszus M, et al. Lomustine and Bevacizumab in Progressive Glioblastoma. N Engl J Med 2017;377:1954-63.
11. Gromeier M, Lachmann S, Rosenfeld MR, et al. Intergeneric poliovirus recombinants for the treatment of malignant glioma. Proc Natl Acad Sci U S A 2000;97:6803-8.
12. Desjardins A, Gromeier M, Herndon JE 2nd, et al. Recurrent Glioblastoma Treated with Recombinant Poliovirus. N Engl J Med 2018;379:150-61.
13. Martinez R, Schackert G, Yaya-Tur R, et al. Frequent hypermethylation of the DNA repair gene MGMT in long-term survivors of glioblastoma multiforme. J Neurooncol 2007;83:91-3.
14. Singer LS, Feldman AZ, Buerki RA, et al. The impact of the molecular classification of glioblastoma on the interpretation of therapeutic clinical trial results. Chin Clin Oncol 2021;10:38.
15. Stein MN, Bertino JR, Kaufman HL, et al. First-in-Human Clinical Trial of Oral ONC201 in Patients with Refractory Solid Tumors. Clin Cancer Res 2017;23:4163-9.
16. Hong DS, Italiano A, Briggs A, et al. Intra-patient comparison from larotrectinib clinical trials in TRK fusion cancer: An expanded dataset. J Clin Oncol 2021;39:abstr 3114.
17. Buerki RA, Horbinski CM, Kruser T, et al. An overview of meningiomas. Future Oncol 2018;14:2161-77.
18. Nassiri F, Liu J, Patil V, et al. A clinically applicable integrative molecular classification of meningiomas. Nature 2021;597:119-25.
19. McMullen KP, Stieber VW. Meningioma: current treatment options and future directions. Curr Treat Options Oncol 2004;5:499-509.
20. James MF, Han S, Polizzano C, et al. NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth. Mol Cell Biol 2009;29:4250-61.

Cite this article as: Singer L, Kumthekar P. Editorial commentary: Society for Neuro-Oncology 2021 Annual Meeting updates on primary central nervous system tumors. Chin Clin Oncol 2022;11(3):18. doi: 10.21037/cco-22-2

© Chinese Clinical Oncology. All rights reserved.