short review

memo (2023) 16:100–104
https://doi.org/10.1007/s12254-023-00879-0

memo
magazine of european medical oncology

ESMO 2022: spotlight on new emerging treatment options in central nervous system tumors

Invited short review

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Received: 10 January 2023 / Accepted: 14 February 2023 / Published online: 20 March 2023

Summary Nearly 40 abstracts regarding tumors of the central nervous system were presented at the European Society for Medical Oncology (ESMO) Congress in September 2022. While no practice-changing data were shown, interesting early phase clinical trial results on immune-modulating agents, targeted treatments and other therapeutic modalities were revealed (Table 1). In this short review, we aim to summarize our personal highlights of the presented data and outline future perspectives in the field.

Keywords CNS neoplasms · Glioma · Glioblastoma · Targeted therapy · Immunotherapy

Abbreviations

CCNU	Lomustine
ESMO	European Society for Medical Oncology
IDO	Indoleamine-2,3-dioxygenase
IFN	Interferon
MGMT	O6-methylguanine methyltransferase
mTOR	Mammalian target of rapamycin
OS	Overall survival
PFS	Progression-free survival
PI3K	Phosphoinositide-3-kinase
RANO-BM	Response Assessment in Neuro-Oncology for Brain Metastases
T-DXd	Trastuzumab deruxtecan

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Immunotherapeutic approaches

So far, immune-modulating agents such as immune checkpoint inhibitors have failed to show an overall benefit in glioblastoma both in newly diagnosed disease and in the recurrent setting [1–3]. Ongoing research is therefore focusing on combinatorial approaches, the improvement of patient selection, or myeloid cells as treatment targets, as macrophages constitute the majority of tumor-infiltrating immune cells in glioma [4]. While no practice-changing study results were delivered, promising early phase data covering these aspects were presented at ESMO 2022.

Combination of retifanlimab (anti-PD-1) ± epacadostat (IDO inhibitor) in patients with recurrent glioblastoma

Indoleamine-2,3-dioxygenase (IDO) is an enzyme catalyzing the conversion of tryptophan to kynurenine and exerts immune-suppressive properties via a plethora of metabolic and nonmetabolic mechanisms. Indeed, IDO is expressed in the microenvironment of glioblastoma and is associated with infiltration of regulatory T cells which inhibit antitumoral immune responses [5], providing the rationale for the evaluation of IDO inhibitors.

Bevacizumab is frequently used in recurrent glioblastoma for symptomatic perifocal edema, although exerting only little (if any) antitumoral activity [6]. However, inhibition of vascular endothelial growth factor (VEGF) was shown to modulate the tumor microenvironment, providing the rationale for investigating the combination of immune-modulating agents with bevacizumab [7, 8]. In a phase 2 study, the combination of hypofractionated radiotherapy, bevacizumab and the anti-PD-1 antibody retifanlimab ± the IDO inhibitor epacadostat is being evaluated in patients

Table 1 Overview on selected therapeutic approaches covered by presented abstracts at ESMO 2022

Entity	Drug(s)	Main results
Immunotherapeutic approaches		
Recurrent glioblastoma [9]	Retifanlimab (anti-PD-1) ± epacadostat (IDO inhibitor) (+ bevacizumab + hypofractionated radiotherapy)	*Cohort A (without epacadostat):*
		Favorable side effect profile (1 grade 3 event in 24 patients)
		ORR: 62.5%
		DCR: 87.5%
		Durable responses in 37.5%
		Median PFS: 7.6 months
		Median OS: 11.1 months
Newly diagnosed, MGMT promoter-unmethylated glioblastoma [12]	Genetically engineered macrophages expressing IFN-alpha	Translational results: low serum IFN-alpha levels, enrichment of IFN-alpha-related pathways, repolarization of macrophages
		Favorable side effect profile: no systemic IFN-alpha-related adverse events
		Median OS: 15 months
		Median PFS: 8.3 months
Glioblastoma at first progression [15]	L19TNF (conjugate of TNF-alpha and antibody targeting fibronectin)	Objective responses in 2/6 patients
		Synergistic, immune-dependent effect with lomustine in murine models
Targeted therapies		
Newly diagnosed, MGMT promoter-unmethylated glioblastoma [16]	Paxalisib (PI3K- and mTOR inhibitor)	Higher systemic exposure in fed (vs. fasted) patients
		Maximum tolerated dose: 60 mg
		Median PFS: 8.6 months
		Median OS: 15.9 months
Active HER2+ breast cancer brain metastases [20]	Trastuzumab deruxtecan (HER2-targeted antibody drug conjugate)	Maintained quality of life during treatment
		Maintained emotional, social, cognitive and physical functioning during treatment
Radiotherapy		
Recurrent glioma [18]	Nanoliposomal rhenium-186	Up to > 10-fold higher local radiation doses compared to conventional beam radiotherapy
		Significant survival benefit in patients with effective dose > 100 Gy
		High heterogeneity in absorbed doses, tumor/treated volume ratios, placed catheters

DCR disease control rate, *Gy* Gray, *HER2* human epidermal growth factor receptor 2, *IDO* indoleamine-2,3-dioxygenase, *IFN-alpha* interferon alpha, *MGMT* O6-methylguanine methyltransferase, *mTOR* mammalian target of rapamycin, *ORR* objective response rate, *OS* overall survival, *PD-1* programmed death receptor 1, *PI3K* phosphoinositide-3-kinase, *PFS* progression-free survival, *TNF-alpha* tumor necrosis factor alpha

with recurrent glioblastoma [9]. After confirming the favorable side effect profile of hypofractionated radiotherapy + bevacizumab + retifanlimab in cohort A, the addition of epacadostat is assessed in cohort B. At ESMO 2022, the results of cohort A were presented. In 24 included patients, only one grade 3 toxicity was seen (myositis), and overall response rate was 62.5%, whereas disease control rate reached 87.5%, with durable responses in 37.5% of patients. The median progression-free survival (PFS) and overall survival (OS) times were 7.6 months and 11.1 months, respectively. These results are well in line with other trials evaluating bevacizumab either as control group or as experimental arm in combination with other agents [1, 10]. Data on the addition of epacadostat remain to be awaited as enrollment of patients to cohort B is still ongoing.

Delivery of interferon alpha using genetically engineered macrophages

Recently, it was shown that intratumoral release of interferon alpha (IFN-alpha) leads to potent antitumoral immune responses within the tumor microenvironment which may even lead to tumor eradication in murine models [11]. Based on this and previous work, autologous hematopoietic stem cells were *ex vivo* transfected with a lentiviral vector encoding for IFN-alpha under the Tie2 promoter, which is active in tumor-infiltrating monocytes that contribute to a growth-promoting milieu in the glioma microenvironment. At ESMO 2022, early clinical and translational data of a phase 1/2a trial enrolling patients with newly diagnosed, O6-methylguanine methyltransferase (MGMT) promoter-unmethylated glioblastoma (NCT03866109) were shown [12]. The expression of transgenic IFN-alpha was well controlled, as serum IFN-alpha levels were low and no systemic, potentially IFN-alpha-related adverse events were seen. In addition, persistence of transduced cells was observed up to 18 months after administration. Whereas median OS (15 months after first surgery) and PFS (8.3 months) were comparable to historical controls [13], some long-term survivors were observed. Providing mechanistic insights, single cell RNA sequencing of tumor-infiltrating leukocytes at second surgery

showed an enrichment of IFN-alpha-related pathways and indicated repolarization of macrophages. Still, superiority over the current standard of care remains to be proven in well-designed randomized controlled trials.

Antibody-targeted tumor necrosis factor in recurrent glioblastoma

L19TNF is a compound consisting of tumor necrosis factor alpha and an antibody targeting fibronectin (L19). Preclinical and early clinical data have shown that L19TNF causes intratumoral necrosis and accumulation of proinflammatory cytokines within the tumor microenvironment [14]. At ESMO 2022, data on the combination between L19TNF and the alkylating agent lomustine (CCNU) were presented [15]. In murine models, a synergistic effect was observed which seemed to be immune-dependent, as long-term antitumoral immunity was observed. Moreover, the combination was paralleled by an increase of lymphocyte infiltration. Of the first 6 patients enrolled in the phase 1 part of the phase 1/2 trial (NCT04573192), 2 patients achieved objective responses; further data on efficacy remain to be awaited for the phase 2 stage, where patients are currently 1:1 randomized to CCNU alone or CCNU + L19TNF.

Targeted therapies and beyond

Paxalisib in newly diagnosed, MGMT promoter-unmethylated glioblastoma

Based on data showing that the phosphoinositide-3 kinase (PI3K) pathway is activated in a large fraction of glioblastomas, the NCT03522298 phase 2 trial explored the use of the PI3K and mammalian target of rapamycin (mTOR) inhibitor paxalisib in newly diagnosed, MGMT promoter unmethylated glioblastoma [16]. After temozolomide-based concurrent radiochemotherapy, patients received adjuvant paxalisib at either 60 mg or 75 mg in a fed and fasted state. Based on safety data, the maximum tolerated dose was 60 mg, and systemic exposure to paxalisib was marginally higher in a fed as compared to fasted state, whereas there were no differences in other pharmacokinetic parameters. Of note, median PFS and OS were 8.6 and 15.9 months, respectively, comparing favorable to historical data on MGMT promoter-unmethylated glioblastoma receiving radiochemotherapy. Further data on efficacy will be generated within GBM AGILE (NCT039070447), an ongoing platform trial assessing the use of various targeted agents in glioblastoma [17].

Nanoliposomal rhenium-186 via convection-enhanced delivery in recurrent glioma

Regarding radiotherapeutic treatments, data on a nanoliposomal formulation of the radionuclide rhenium-186 (^{186}RNL) were shown [18]. In this trial, ^{186}RNL was locally delivered via convection-enhanced delivery in recurrent glioma, utilizing pressure gradients via intratumoral/-cavitary catheters to improve tumor tissue penetration. Local application of radionuclides allows to achieve considerably higher radiation doses which are limited by radiation exposure of healthy tissue in conventional external beam radiotherapy. Indeed, absorbed radiation dose in the trial reached up to 740 Gy which is more than 10-fold compared to conventional radiotherapy, and a significant survival benefit was observed in patients with an effective dose > 100 Gy. Still, there was high heterogeneity in absorbed doses (range 9–740 Gy) and tumor/treated volume ratios (13–100%). Moreover, the number of placed catheters differed considerably, underscoring the need for standardized protocols and optimal patient selection. Although survival data are promising, the superiority towards other methods remains to be proven in randomized controlled trials.

Data on quality of life and neurocognitive function of the TUXEDO-1 trial

Antibody–drug conjugates are increasingly used in a wide array of solid tumor entities. Recently, an increasing body of evidence showing intracranial activity also in active brain metastases has emerged. One of these trials was the TUXEDO-1 phase 2 trial, evaluating the intracranial efficacy of trastuzumab deruxtecan (T-DXd) in HER2+ breast cancer brain metastases [19]. Here, an intracranial response rate of 73.3% according to Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) criteria was observed as presented at the ESMO Breast Cancer Congress in May 2022. Further data on quality of life followed at ESMO 2022 [20]. Here, maintained quality of life was observed during T-DXd treatment as determined using the EORTC QLQ-C30 questionnaire. Moreover, specific subdomains such as emotional, social, cognitive and physical functioning remained stable over time, justifying further evaluation of antibody–drug conjugates for active brain metastases.

Conclusion

The treatment of brain tumors remains challenging. The efficacy of many drugs is complicated by the blood–brain barrier, limiting active concentrations of these agents in the tumor, and the success of immune-modulating agents is further challenged by the unique inflammatory microenvironment. In addition, there were no practice-changing results revealed at ESMO 2022, but further insights on innovative combinato-

rial approaches in immunotherapy as well as novel targeted agents including antibody drug conjugates were presented. The combination of these innovative strategies with a more personalized approach may set the scene for meaningful outcome improvements in neuro-oncology.

Take home message

At ESMO 2022, no practice-changing results were presented. Still, novel immunotherapeutic and targeted therapy approaches underscore the variety of innovative treatment methods under investigation.

Funding Open access funding provided by Medical University of Vienna.

Conflict of interest M.J. Mair received travel support from Pierre Fabre. A.S. Berghoff has received research support from Daiichi Sankyo, Roche, and honoraria for lectures, consultation or advisory board participation from Roche, Bristol-Meyers Squibb, Merck, Daiichi Sankyo as well as travel support from Roche, Amgen, and AbbVie.

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