

# World Federation of Neuro-Oncology Societies magazine

Neurology • Neurosurgery • Medical Oncology • Radiotherapy • Paediatric Neuro-Oncology  
• Neuropathology • Neuroradiology • Neuroimaging • Nursing • Patient Issues

## Editorial

W. Wick and Patrick Y. Wen

### **Challenges and Next Steps for CAR T-Cell Therapy for Glioblastoma**

Payal B. Watchmaker, Pavlina Chuntova, Kira M. Downey, Zinal S. Chheda, Maryam Shahin, Diego A. Carrera, and Hideho Okada

### **Alliance A071401: Molecularly driven trial in meningiomas**

Priscilla Brastianos and Evanthia Galanis

### **COGNO News and Activities**

Zarnie Lwin, Mustafa Khasraw, Hui Gan, Jenny Chow, and Anna Nowak

### **The Developing Chinese Society of Neuro-Oncology**

Peidong Liu, Xuejun Yang, and Zhongping Chen

### **Observations from the Sub-Saharan Africa Neuro-Oncology Meeting**

October 18–19, 2017 London, UK

Chas Haynes, Jason Huse, and Gelareh Zadeh

### **The Sub-Saharan Africa Neuro-Oncology Collaborative (S-SANOC)**

#### **Planning Meeting**

Kathy Oliver and Christine Mungoshi

### **First EANO Winter School in Athens: Complications of Primary and Secondary Brain Tumors**

Carina M. Thomé

### **2017 Society for Neuro-Oncology Annual Meeting Update**

Jennie W. Taylor, Roy E. Strowd, and Albert H. Kim

### **FOCUS ON: Long-Term Neurovascular Complications in Cancer Patients**

Joyce Wilbers

### **Clinical case discussion Multimodal Response Assessment in a Patient with Anaplastic Glioma: Tumor Or No Tumor?**

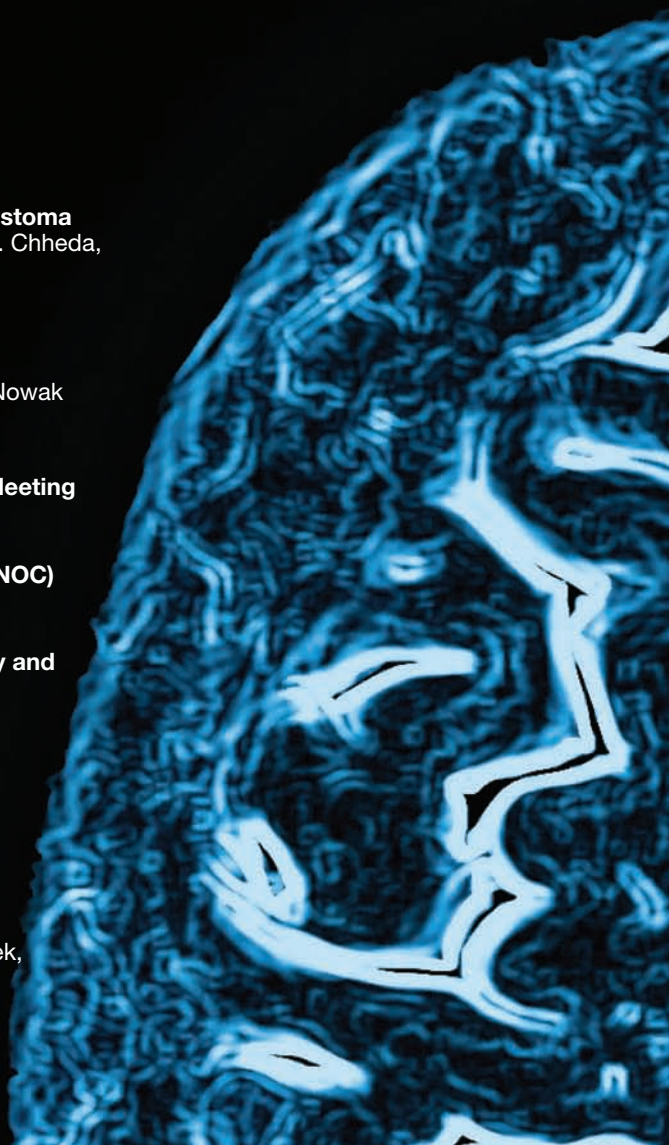
D. Eckmayr, F. Marhold, R. Brustbauer, M. Kitzwögerer, B. Calabek, E. Freydl, and S. Oberndorfer

### **Hotspots in Neuro-Oncology**

Riccardo Soffietti

### **Hotspots in Neuro-Oncology Practice 2017/2018**

Wolfgang Grisold



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OF THE SOCIETY  
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November 15-18, 2018

Marriott Hotel

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## Editorial

Dear readers of the WFNOS Magazine,

dear friends in Neurooncology,

What are the best assets we have in neuro-oncology? In my view these are the multidisciplinary collaboration, scientific strengths, and focus on development of young neuro-oncologists.

The present copy of the WFNOS Magazine provides great examples of these highlighted features of neuro-oncology. The review dives deep into immunotherapy for brain tumors. We lean on the structure and vision of well-established national societies in Australia and China, but

also get the chance to understand the challenges of building a new society for neuro-oncology in a nonprivileged area of the world. The development of a Society of NeuroOncology for Sub-Saharan Africa (SNOSSA), which is supported by the international Brain Tumor Alliance, SNO, and EANO, documents the relevance of neuro-oncology also outside the known foci.

The EANO Winter School has been our highlight in the education of young clinical and scientific neuro-oncologists. Carina Thomé

summarizes the first teaching course, focused on neurological complications of neuro-oncology and held in Athens under the auspices of the National Greek Society and the European Association of Neurology, organized by EANO. I wish all of you great personal and academic successes in the upcoming month and novel insights into neuro-oncology provided at one of the upcoming national or international meetings.

**Prof Dr W. Wick**  
EANO President

## Editorial

Dear Friends and Colleagues in Neuro-Oncology,

I would like to congratulate the Editors of the WFNOS magazine on another outstanding edition highlighting exciting areas of neuro-oncology. These include the challenges related to developing CAR T cells for glioblastomas, innovative trials for meningiomas, and neurovascular complications in cancer patients. This edition also emphasizes the importance of helping to foster the growth of neuro-oncology throughout the world with the description of the development of the Society of Neuro-Oncology for Sub-Saharan Africa (SNOSSA). This is a wonderful effort initially made possi-

ble through the collaborative efforts of the Society for Neuro-Oncology (SNO), the International Brain Tumor Alliance, and the Zimbabwe Brain Tumor Association, in association with Mark Bernstein, the Greg Wilkins-Barrick Chair of International Surgery at the University Health Network in Toronto. It is indeed encouraging to see the international brain tumor community come together to support SNOSSA's inaugural meeting that will take place later this year in Abuja, Nigeria.

As we all know, progress in finding better treatments for our patients has been unacceptably slow. There are many reasons for this but the poor rate of accrual to clinical trials and

the lack of sufficient high-quality studies are important contributing factors. A major goal of SNO, together with partners around the world and patient advocacy groups, is to identify the barriers to clinical trial accrual and map out a path to significantly improve this over the next 3–5 years. The 2018 SNO meeting in New Orleans (November 15–18) will have clinical trials as its main theme. In particular, Education Day will provide information on how to conduct better studies and improve accrual to trials. We look forward to seeing many of you there.

**Patrick Y. Wen**  
SNO President



# Challenges and Next Steps for CAR T-Cell Therapy for Glioblastoma

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## Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. The standard of care, which consists of maximal safe surgical resection, radiotherapy, and chemotherapy, is unable to prevent tumor recurrence. The outcome for patients with GBM is dismal, with the median overall survival of 14.6 months,<sup>1</sup> presenting an urgent unmet need for more efficacious treatment modalities that extend survival without compromising quality of life. Immunotherapeutic approaches present one such possibility. T cells engineered to express a T-cell receptor (TCR) specific for a tumor-antigen expressed solely by tumor cells represent a novel immunotherapeutic modality. Activation of T cells via their TCR is both antigen and human leukocyte antigen (HLA) specific. Furthermore, because the peptides displayed by HLA molecules may be derived from both intra- and extracellular proteins, both cell-surface and intracellularly localized proteins can potentially be used as neoantigen targets for TCR. As another approach of directing T cells to tumor surface antigens, chimeric antigen receptor (CAR) T cells make use of a class of synthetic receptors that reprogram lymphocyte function and specificity. CARs are able to bind surface-displayed antigens without the need for HLA presentation and are thus not affected by the tumor cells' downregulation of HLA, a commonly observed tumor immune-escape mechanism. In addition, the latest generation of CARs can elicit costimulatory signaling without the need for exogenous ligands, which are frequently absent in the tumor microenvironment (TME).

In this review, we present the most recent data which have emerged from clinical trials utilizing CAR T cells in GBM patients. Furthermore, we summarize the latest advances in the field aimed at making adoptive T-cell therapy safer and more efficacious, alongside a discussion of the biggest challenges facing present-day researchers in the field of GBM immunotherapy.

## Targeting glioma-specific mutations using engineered TCR-transduced cytotoxic T cells

In addition to the significance of malignant gliomas in adults, in children brain tumors are the leading cause of cancer-related mortality and morbidity.<sup>2</sup> In particular, the median overall survival for children with diffuse midline gliomas (DMG), including diffuse intrinsic pontine gliomas (DIPG), is less than one year.<sup>3,4</sup> Recent genetic studies

have revealed that malignant gliomas in children and young adults often show somatic missense mutations in the histone H3 variant H3.3.<sup>5</sup> A majority of DMG and over 70% of DIPG cases<sup>6</sup> harbor the amino acid substitution from lysine (K) to methionine (M) at position 27 of H3.3 (H3.3K27M mutation, hereafter). H3.3K27M mutation in DMG results in a global reduction of methylation at H3K27me3, leading to suppression of targets of polycomb repressive complex 2, thereby causing aberrant gene expression.<sup>7</sup> Patients with H3.3K27M+ DIPG have shorter survival times than those with nonmutated H3.3.<sup>6</sup>

We recently reported the identification of an HLA-A\*02:01-restricted CD8+ cytotoxic T-lymphocyte (CTL) epitope encompassing the H3.3K27M mutation.<sup>8</sup> Furthermore, we have cloned cDNA for TCR  $\alpha$  and  $\beta$  chains derived from an H3.3K27M-specific CD8+ T-cell clone. The TCR binds to the HLA-A\*02:01-peptide complex at excellent affinity levels, and HLA-A\*02:01+ donor-derived T cells transduced with the TCR recognize and lyse HLA-A\*02:01+ H3.3K27M+ glioma cells in a mutation- and HLA-specific manner. Adoptive transfer of TCR-transduced T cells but not mock-transduced T cells results in inhibition of intracranial H3.3K27M+ glioma in vivo. Importantly, alanine scan assays demonstrated that there are no known human proteins that share the set of key amino acid residues for recognition by the TCR. Our data strongly support development of vaccine- and TCR-transduced T-cell-based immunotherapy strategies in patients with H3.3K27M+ gliomas.<sup>8</sup> While the vast majority of neoantigens described to date are "private" (ie, not shared by multiple patients), the H3.3K27M presents one that is shared by the majority of patients with the same tumor type. Further investigations of shared neoantigens may lead to development of TCR-based approaches to other cancer types.

## Experience with epidermal growth factor receptor variant III, interleukin-13 receptor $\alpha 2$ , and human epidermal growth factor receptor 2 CAR T-cell therapy clinical trials

Recently concluded were the first human CAR T-cell clinical trials targeting GBM surface antigens, such as epidermal growth factor receptor variant III (EGFRvIII),<sup>9</sup>



interleukin-13 receptor (IL13R) $\alpha$ 2,<sup>10</sup> and human epidermal growth factor receptor 2 (Her2).<sup>11</sup> These clinical studies have established an initial safety profile and have helped us to understand some of the obstacles that neutralize the efficacy and function of CAR T-cell therapy and inform us in defining strategies to surmount these challenges.

**EGFRvIII CAR T cells:** The mutated extracellular domain of EGFR results in a glioma-specific, immunogenic epitope for CAR targeting (EGFRvIII). Most recently, O'Rourke and his team including us used a single intravenous dose of second-generation EGFRvIII-CAR to treat 10 patients with recurrent GBM.<sup>9</sup> We reported no objective radiographic responses, except for 1 patient who had stable disease that persisted for >18 months. The patients did not exhibit any cytokine release syndrome or cutaneous toxicity. Post-infusion brain biopsies from 7 patients provided information about CAR T-cell trafficking and its persistence and impact on the glioma TME. The persistence and expansion of EGFRvIII-CAR T cells in the glioma tissue inversely correlated with decrease in levels of EGFRvIII expression, suggesting the CAR T cells exhibited antitarget activity. However, immune activation in the glioma tissue was also associated with upregulation of compensatory adaptive resistance mechanisms such as increased expression of indoleamine-2,3-dioxygenase, programmed death receptor ligand 1 (PD-L1), and infiltration of immunosuppressive regulatory T cells. The lack of clinical efficacy despite the ability of EGFRvIII-CAR T cells to traffic to the brain could be attributed to the heterogeneous expression of EGFRvIII leading to antigen loss, as well as the inhibitory effects of the TME.

**IL13R $\alpha$ 2 CAR T cells:** In 2015, Brown et al reported a clinical study assessing intracavitary adoptive transfer of CD8<sup>+</sup> T cells expressing first-generation IL13R $\alpha$ 2-targeted CAR for patients with recurrent GBM.<sup>12</sup> Besides the site of injection, CAR T cells were detected at the secondary sites of recurrence, suggesting the potential for CAR T cells to traffic to sites of infiltrative disease. Brown and colleagues observed a significant decrease in IL13R $\alpha$ 2 expression, alongside transient radiologic responses following CAR T-cell therapy in 2 of the 3 GBM patients.<sup>12</sup> The same group reported a case study of a patient with recurrent GBM who received enriched central memory CD8<sup>+</sup> T cells transduced with a CAR comprising an IL13R-specific cytokine ectodomain, mutated immunoglobulin (Ig)G4-Fc linker, a transmembrane domain, costimulatory domain 4-1BB, and the CD3 $\zeta$  endodomain, which together constituted a modified second-generation construct.<sup>10</sup> The study showed marked regression of lesions following intracavitary and intraventricular infusion of CAR T cells; recurrent lesions had minimal or no expression of the CAR target IL13R $\alpha$ 2.

**Her2/CMV CAR T-cells:** A clinical trial utilizing second-generation Her2-CAR T cells assessed safety and efficacy in patients with recurrent Her2<sup>+</sup> GBM. A polyclonal, cytomegalovirus (CMV)-specific, central memory CD8<sup>+</sup>

T-cell population was selected for lentiviral CAR transduction, as the patients were CMV seropositive and could benefit from additional TCR/costimulation during the expansion of CAR T cells. However, the infused T cells persisted only in low levels in the periphery without expanding. There was no dose-limiting toxicity reported following repeated administration of Her2-specific CAR T cells. Objective radiographic response was seen in 1 patient and disease stabilization for >24 months was noted in 5 patients following CAR T-cell treatment.

The most important insight gained from these 3 trials is the loss of the antigen being targeted and relapse due to outgrowth of antigen null tumor cells. In addition to the complex and dynamically immunosuppressive TME, these observations make CAR T-cell therapy for GBM challenging. While these studies have provided insight, a variety of ongoing clinical trials (Table 1) will continue to inform our understanding of T-cell-based therapy in the setting of GBM.

## Strategies for improving the efficacy of CAR T cells

**Antigen targeting:** The primary challenge in designing CAR T-cell therapy is identifying tumor-restricted antigens that can be safely targeted without the risk of autoimmunity to normal tissues, which also may constitutively express the antigen. Importantly, the tumor-restricted antigen of interest must be expressed on the vast majority of tumor cells. None of the existing glioma-specific antigens, such as EGFRvIII, meet both of these criteria. Combinatorial antigen recognition and targeting strategies can bypass the limitations of antigen heterogeneity, antigen escape, and off-tumor toxicity. Given the heterogeneous expression pattern of antigens, simultaneous targeting of multiple GBM-restricted antigens has been investigated by several groups. Hegde and colleagues reported tandem CAR T cells targeting IL13R $\alpha$ 2 and Her2 produced in enhanced antitumor efficacy coupled with mitigated antigen escape in a preclinical model of GBM.<sup>13</sup> Biela and colleagues have conducted similar experiments using trivalent CAR T cells co-directed against Her2, IL13R $\alpha$ 2, and ephrin-A2 displayed potential in overcoming GBM variability.<sup>14</sup>

Due to the paucity of targetable tumor-specific antigens in GBM, it will be necessary to carefully design CAR T constructs targeting tumor-associated antigens. Engineering CARs with tumor-sensing mechanisms will allow for better differentiation between target antigens presented on tumor tissue and those expressed by healthy tissue. In order to achieve this, combinatorial receptor approaches integrating 2 different antigen inputs to control CAR T-cell function have been developed to

o **Table 1.** Ongoing clinical trials for T-cell-based therapies for GBM

Start Date Status	Trial Name	Study Phase	Participant Number	NCT#	Agent	Study Details
Jul 2016 Recruiting	Pilot Study of Autologous Anti-EGFRvIII CAR T-cells in Recurrent GBM	1	20	NCT02844062	Anti-EGFRvIII CAR T cells	<ul style="list-style-type: none"> <li>• Lentiviral vector containing CAR recognizing EGFRvIII tumor antigen</li> <li>• Establish safety and efficacy of autologous anti-EGFRvIII CAR T cells in patients with recurrent GBM</li> <li>• Lymphodepletion chemotherapy (fludarabine + cyclophosphamide) followed by autologous anti-EGFRvIII CAR T cells i.v. in a 3-day-split dose regimen</li> </ul>
Jan 2017 Recruiting	PD1-PIK Cell Therapy for Patients With GBM	1	40	NCT03347097	PD-1-PIK	<ul style="list-style-type: none"> <li>• Pluripotent immune killer (PIK) cells are transgenic T cells that express high level of full length anti-PD1 antibody</li> <li>• Establish safety and efficacy of autologous T cells in patients with GBM</li> <li>• 10 days post chemoradiotherapy, inject i.v. two times every 30 days</li> <li>• Combination of EGFR BATs and standard of care TMZ and RT</li> <li>• Establish safe dose and immune responses</li> </ul>
Feb 2018 Recruiting	Phase I EGFR BATs in Newly Diagnosed GBM	1	18	NCT03344250	EGFR BATs	<ul style="list-style-type: none"> <li>• First and second infusions of EGFR BATs on days 14 and 21 after finishing RT and TMZ; infusion on day 21 of first of 6 cycles of TMZ.</li> <li>• Up to 80% of GBMs are positive for Her2</li> <li>• Determine safety of Her2-CAR T cells</li> <li>• Safety profile 6 weeks following T-cell infusion; if disease is stable patients will receive additional dose at 6-12 week intervals a the highest safety established dose.</li> </ul>
Feb 2016 Recruiting	T-cells Expressing HER2-specific CAR for Patients With GBM	1	14	NCT02442297	Her2-specific T cells	



Feb 2018 Not yet recruiting	Administration of Autologous T-cells Genetically Engineered to Express T-cell Receptors Reactive Against Mutated Neoantigens in People With Metastatic Cancer	2	210	NCT03412877	Individual patient TCR-transduced PBL + high or low-dose aldesleukin	<ul style="list-style-type: none"> <li>Determine rate of objective response using autologous PBL transduced with genes encoding TCRs recognizing neoantigens</li> <li>Patients will undergo resection and biopsy to make autologous TIL cultures. T-cell cultures with reactivity against mutations will be identified, and retrovirus for transduction will be used to put TCR into patients autologous PBL</li> <li>Patients will receive non-myeloablative lymphocyte depleting regimen (cyclophosphamide + fludarabine) and then autologous transduced PBL and high or low dose aldesleukin.</li> <li>Phase I aims to find highest tolerable dose of CMV CTLs + TMZ</li> <li>Phase II aims to see if this regimen is efficacious</li> <li>Establish largest safest dose of Her2-CD28 CMV T cells</li> <li>Single i.v. dose</li> <li>If patients improve, they can continue to receive up to 6 additional treatments</li> <li>Establish safety; PD-L1 overexpressed in 88% GBM</li> <li>CSR modified T cells recognize PD-L1-expressing tumor cells which triggers T-cell activation; truncated EGFR also in this CSR vector which can be used to track T cells in vivo tracking and ablation of CSR T cells</li> <li>Lymphodepleting chemotherapy (fludarabine + cyclophosphamide) followed by i.v. anti-PD-L1 CSR T cells</li> </ul>
Jun 2016 Recruiting	Autologous Cytomegalovirus (CMV)-Specific Cytotoxic T-cells for GBM Patients	1/2	54	NCT02661282	CMV CTLs	
Oct 2010 Active, not recruiting	CMV-specific Cytotoxic T Lymphocytes Expressing CAR Targeting HER2 in Patients With GBM (HERT-GBM)	1	16	NCT01109095	Genetically modified Her2 CAR CMV-specific CTLs	
Jul 2016 Recruiting	Pilot Study of Autologous Chimeric Switch Receptor (CSR) Modified T-cells in Recurrent GBM	1	20	NCT02937844	Anti-PD-L1 CSR T cells	

Continued

∞ Table 1. Continued

Start Date Status	Trial Name	Study Phase	Participant Number	NCT#	Agent	Study Details
Feb 2018 Active, not yet recruiting	Memory-Enriched T-cells in Treating Patients With Recurrent or Refractory Grade III-IV Glioma	1	81	NCT03389230	HER2(EQ)BBζ/CD19t+ central memory T cells	<ul style="list-style-type: none"> <li>Establish side effects and best dose in recurrent or refractory GBM</li> <li>Intracavity/intratumoral, intraventricular, or dual delivery using autologous Her2(EQ)BBζ/CD19t+ central memory T cells</li> <li>Determine safe number of cells and establish safety and efficacy in recurrent or refractory histologically proven GBM or gliosarcoma expressing EGFRvIII</li> <li>Non-myeloablative but lymphocyte depleting preparative regimen (cyclophosphamide + fludarabine) followed by i.v. anti-EGFRvIII CAR transduced PBL + i.v. aldesleukin</li> <li>Newly diagnosed GBM post resection</li> <li>EGFRvIII CAR T cells administered i.v. prior to RT + TMZ; during third cycle TMZ, EGFRvIII CAR T cells infused i.v. in dose escalation cohorts</li> <li>Local administration of autologous T cells transduced with a retroviral vector containing CAR recognizing EGFRvIII tumor antigen</li> <li>Infusion of a single dose of anti-EGFRvIII CAR following surgical resection</li> <li>Establish safety and efficacy of autologous anti-EGFRvIII CAR T cells in patients with recurrent GBM</li> </ul>
Sept 2011 Recruiting	CAR T-cell Receptor Immunotherapy Targeting EGFRvIII for Patients With Malignant Gliomas Expressing EGFRvIII	1/2	107	NCT01454596	Anti-EGFRvIII CAR transduced PBL	
Feb 2017 Recruiting	EGFRvIII CAR T-cells for Newly-Diagnosed GBM (ExCel)	1	48	NCT02664363	EGFRvIII CAR T cells	
Apr 2018 Not yet recruiting	Intracerebral EGFRvIII CAR T-cells for Recurrent GBM (INTERCEPT)	1	24	NCT03283631	CAR EGFRvIII T cells	



Jul 2014 Active, not recruiting	Autologous T-cells Redirected to EGFRvIII-With a CAR in Patients With EGFRvIII <sup>+</sup> GBM	1	12	NCT02209376	EGFRvIII-CARs	<ul style="list-style-type: none"> <li>Administration of autologous T cells transduced with a lentiviral vector for CAR recognizing EGFRvIII tumor antigen</li> <li>Establish safety and efficacy of autologous anti-EGFRvIII CAR in patients with residual GBM or first GBM recurrence</li> <li>Administration of anti-IL13R<math>\alpha</math>2 CAR T cells intratumorally, intraventricularly, intracavitarily, or some combination thereof</li> <li>Establish safety and efficacy of IL13R<math>\alpha</math>2 CAR according to various administration sites</li> <li>CAR T cells infused weekly for 3 weeks in the absence of disease progression and followed by additional infusions as necessary</li> <li>Administration of autologous CAR-IgT cells targeting EGFRvIII tumor antigen. Upon CAR engagement, T cells produce anti-PD1 and anti-PD-L1 antibodies in addition to CAR-mediated tumor targeting.</li> <li>Evaluate safety and efficacy of anti-EGFRvIII CAR-IgT cells in lymphodepleted patients</li> <li>Evaluate proliferation and persistence of both anti-EGFRvIII CAR and checkpoint antibodies in the blood of GBM patients</li> </ul>
May 2015 Recruiting	Genetically Modified T-cells in Treating Patients With Recurrent or Refractory Malignant Glioma	1	135	NCT02208362	IL13R $\alpha$ 2-specific, 4-1BB costimulatory CAR/truncated CD19-expressing T cells	
May 2017 Enrolling by invitation	4SCAR-IgT Against GBM	1/2	20	NCT03170141	Anti-EGFRvIII CAR-IgT cells	

i.v., intravenous; PIK, pluripotent immune killer; PD1, programmed cell death-1; PD-L1, programmed death ligand; TMZ, temozolomide; RT, radiation therapy; BATs, bi-armed activated T cells; PBLs, peripheral blood lymphocytes; TIL, tumor infiltrating lymphocytes; CSR, chimeric switch receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

spatially distinguish between normal and tumor cells expressing target antigen. One such approach utilizes synthetic inhibitory CARs (iCARs), which contain components derived from inhibitory signaling domains of PD-1 or cytotoxic T-lymphocyte antigen 4 receptors, to switch off T-cell activation upon iCARs' recognition of antigen on normal cells but not on tumor tissues.<sup>15</sup> Another approach utilizes complementary signals split between 2 receptors, including a CAR for T-cell activation and a costimulatory chimeric receptor for costimulation. The selected 2 antigens must be coexpressed by tumor cells but found alone in normal cells.<sup>16</sup>

CAR T cells are potent antitumor cells, and several innovative strategies have been developed to address the safety concerns associated with excessive T-cell activity in the clinical setting. One such strategy is the inclusion of a latent suicide switch, such as the inducible caspase-9 (iCasp9) enzyme, which can be activated to induce T-cell apoptosis via the administration of a small molecule.<sup>17</sup> Preclinical studies with iCasp9+ CAR T cells have demonstrated successful elimination of the infused T cells.<sup>18,19</sup> Finally, a strategy for the in vivo elimination of CAR T cells involves the addition of an exogenously expressed surface tag molecule, such as the extracellular domain of EGFR. CAR T cells can thus be depleted via administration of the EGFR-specific antibody cetuximab.<sup>20</sup>

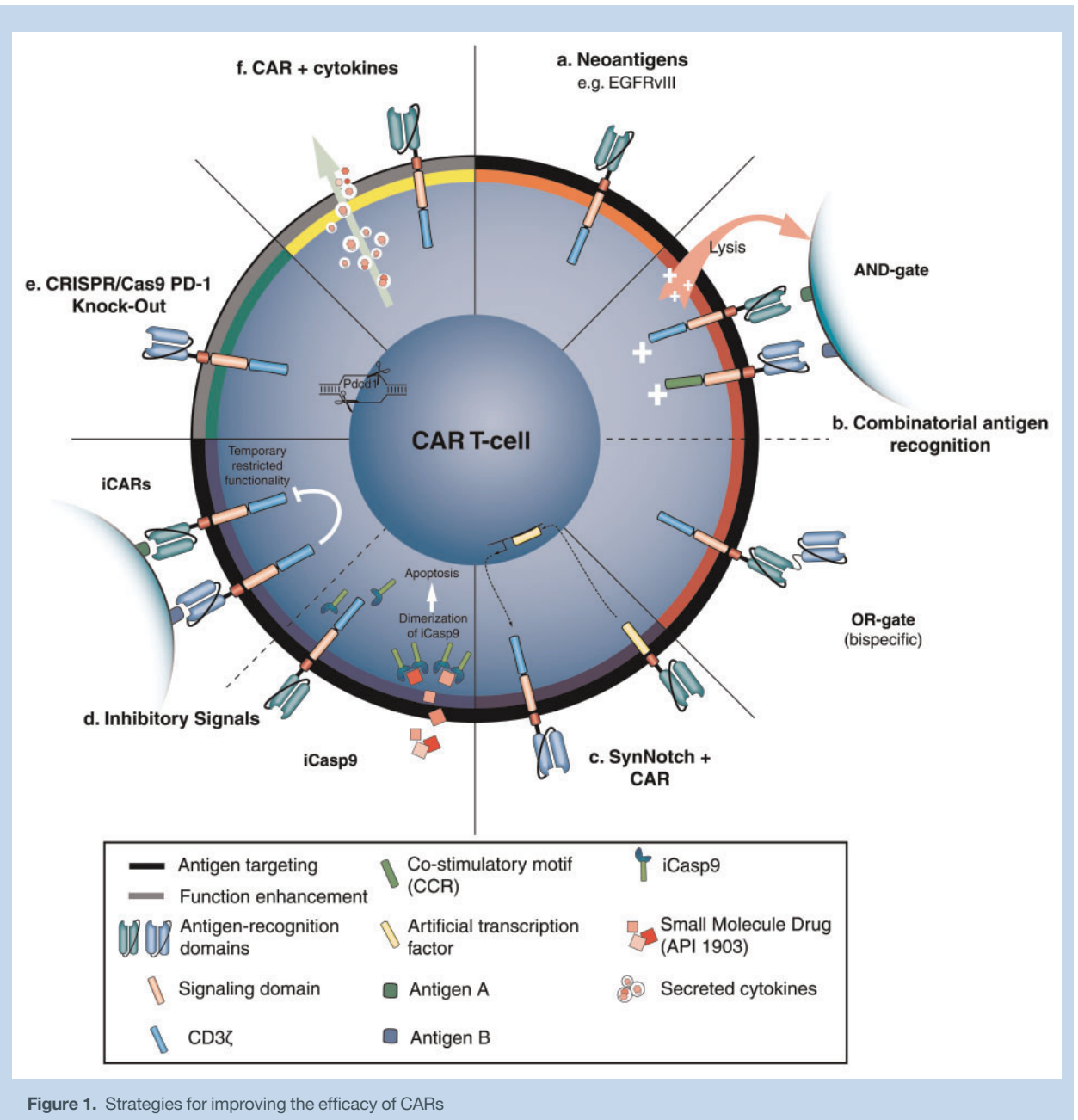
Taken together, these lines of investigations may allow us to develop safe and more effective CAR T-cell therapy approaches by reducing the risk of autoimmunity and addressing antigenic heterogeneity of solid cancer.

**Improving CAR T-cell trafficking to CNS while avoiding neurotoxicities:** While the central nervous system had been often considered to be immunologically privileged,<sup>21</sup> multiple recent trials have demonstrated the ability of systemically administered immune therapies to home to CNS tumor sites.<sup>9,22</sup> We have found critical roles for the integrin receptor very late activation antigen (VLA)-4<sup>23</sup> and the chemokine CXCL10<sup>24</sup> in efficient homing of CTLs to the brain tumor site. We subsequently found that a toll-like receptor-3 agonist, poly-ICLC (polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose), effectively induces expression of CXCL10<sup>25</sup> in glioma and VLA-4<sup>26</sup> on vaccine-activated CTLs, and integrated these findings into the design of vaccine clinical trials.<sup>27,28</sup> While these findings could be integrated into the design of CAR T cells to improve their homing abilities to CNS tumors, CNS toxicities by CAR T cells should be avoided. A recently study evaluating neurotoxicities following CD19 CAR T-cell therapy demonstrated the endothelial activation, capillary leak, and increased blood-brain barrier permeability.<sup>29</sup> Furthermore, a recent preclinical study evaluating a high-affinity CAR targeting GD2 ganglioside (GD2-CAR) induced fatal encephalitis in mice bearing syngeneic neuroblastoma, which was associated with GD2

expression in the cerebellum.<sup>30</sup> While further studies are warranted to totally delineate mechanisms and risk factors for CAR T-cell-related neurotoxicity, future development of CAR T-cell therapies should carefully consider prevention and management of possible neurotoxicities.

**Enhancing CAR T-cell functionality:** Once tumor-specific CAR T cells localize to the tumor site, they encounter a barrage of intrinsic and extrinsic factors that render them hypofunctional. One of the best-studied cell-intrinsic mechanisms known to limit CAR T-cell effectiveness is the upregulation of immune checkpoint (IC) molecules, such as PD-1, the engagement of which results in the phenotype known as T-cell exhaustion. In addition to combining CAR-T therapy with systemic administration of IC inhibitors, genetic engineering of the CAR T cells using the clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 method has been found to be an effective tool to overcome IC pathway activation. In a 2017 *Scientific Reports* article, Rupp et al demonstrated that human T cells can be modified through genome editing and viral transduction resulting in a population of cells that are PD-1 deficient and CD19-CAR.<sup>31</sup> These T cells showed increased levels of tumor cell killing and enhanced levels of tumor clearance in a xenograft model of CD19+ tumor.<sup>31</sup> Another mechanism known to result in suboptimal CAR-T effectiveness stems from the engagement of the surface receptor Fas (CD95) with its cognate ligands, which are often expressed on activated T cells, tumor, and endothelial cells. Fas-FasL interactions lead to activation-induced cell death and limit the number of CAR+ T cells within solid tumors. Utilizing the ability of synthetic T-cell receptors to drive controlled initiation of transcription, researchers have been working to engineer CAR T cells which upregulate pro-survival molecules known to overcome signals due to activation-induced cell death.<sup>32</sup> In addition to pro-survival molecules, synNotch T cells have been engineered to produce a variety of interleukins in an attempt to modulate the local microenvironment. For example, production of IL-12 by synNotch CD4+ T cells leads to increased production of interferon- $\gamma$  and enhanced T<sub>H</sub>1 differentiation, which has been linked to better CAR T-cell performance.<sup>33</sup> In addition to improving CAR vector design, optimizing vector delivery presents another important avenue of research. A recent study by Eyquem and colleagues provided strong evidence that the level of CAR expression, both basally and throughout the course of therapeutic intervention, is critical for prolonged tumor control and increased survival in a murine model of acute lymphoblastic leukemia. Using CRISPR/Cas9 and adenovirus-encoded CD19 CAR plasmid, the authors were able to achieve successful disruption of the  $\alpha$ -chain TCR locus and simultaneous expression of the CAR construct under the control of the endogenous TCR promoter.<sup>34</sup> This resulted in uniform CAR expression and significantly reduced in vivo tumor burden compared with what the authors observed when CAR





expression was achieved through T-cell transduction with  $\gamma$ -retrovirus. This suggests that novel methods of genome engineering might reveal methods yielding CAR T cells with superior in vivo persistence and therapeutic efficacy.

In regard to roles of cytokines that are produced by CAR T cells, polarization of CAR T cells into IL-17-producing  $T_H17$  CD4<sup>+</sup> cells through the addition of the intracellular costimulatory domain within the CAR expression vector has provided evidence that CD8<sup>+</sup> killer T cells may not

be sufficient for tumor eradication, and a more complete T-cell repertoire may be needed. Furthermore, a preclinical study demonstrated increased persistence, proliferation, and cytokine production of CAR T cells expressing the IL-15 transgene.<sup>35</sup> However, IL-15 expression also led to the emergence of antigen loss variants, implying that CAR T cells targeting GBM should be engineered to not only enhance proliferation and persistence but also simultaneously target multiple antigens. Figure 1 summarizes a variety of CAR systems discussed in this review.

## Concluding remarks

As we have discussed, strategies to overcome the obstacles in T-cell therapy for GBM should include, but not be limited to (i) targeting multiple antigens to avoid antigen loss and resistance; (ii) increasing the potency of CAR T cells, and (iii) overcoming the hostile TME. Combination strategies addressing all of the above issues will likely be necessary to achieve successful immunotherapy for GBM. Concurrent genetic engineering, such as CAR transduction and PD-1 knock out in the same T cells, may be attractive. On the other hand, it is also important to compare the efficacy of such strategies with the use of CAR T cells in conjunction with pharmacological (ie, antibody-mediated) inhibition of PD-1 because these two approaches may mediate different impacts on the physiological functions of PD-1. Finally, in regard to the evaluation of TME in CAR T-cell clinical trials, to date, tumor samples have been most typically obtained from recurrent cases after immunotherapy failure. However, this is not ideal for the study of CAR T-cell effects due to the inconsistency in the timing of sampling among the patients and the potential for acquired resistance of the tumor interfering with the evaluation of the therapy. In fact, the TME of most successful patients with positive response to the therapy will never be evaluated unless we implement prospective studies to evaluate the tumor following the study interventions. We advocate for integration of presurgical CAR T-cell administrations and prospective tumor procurement to study the therapeutic impact on the TME. Proper understanding of the effects and challenges of the current CAR T-cell therapy in GBM TME is essential to develop the next-generation CAR T-cell therapy that will integrate all the components that we discuss in this review.

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## Alliance A071401: Molecularly driven trial in meningiomas

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Meningiomas are the most common primary brain tumor, typically managed with surgery and/or radiation. Once surgery and radiation fail, systemic therapies historically have had dismal responses in recurrent or progressive meningiomas, largely because of our limited understanding of the therapeutic targets in these tumors. Recent advances in genomic technologies have allowed the comprehensive characterization of the genetic landscape of meningiomas.<sup>1–7</sup> Importantly, novel clinically actionable drivers have now been identified, which have paved the way for new and exciting trials in this arena.

The most frequent alteration in meningiomas is inactivation of neurofibromatosis type 2 (*NF2*), which occurs in approximately 50% of meningiomas.<sup>8,9</sup> A number of therapeutic approaches are being explored to target this large tumor suppressor gene. One such approach is inhibition of focal adhesion kinase (FAK). FAK is a nonreceptor protein tyrosine kinase that integrates signals from integrins and growth factor receptors; it regulates proliferation, survival, migration, invasion, and cancer stem cell renewal.<sup>10</sup> FAK is overexpressed in many cancers, including anaplastic meningiomas.<sup>11</sup> Low Merlin product, the protein product of *NF2*, is associated with sensitivity to FAK inhibition, likely because of the disrupted balance between cell-extracellular matrix and cell-cell interactions.<sup>12</sup>

Furthermore, oncogenic driver mutations in Smoothened (*SMO*), *Akt1*, and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) occur in a subset

of meningiomas. *SMO*, a member of the Hedgehog signaling pathway, is mutated in 3%–5% of meningiomas<sup>1,2</sup>; the *SMO* mutations reported in meningiomas are known activating mutations in other cancer types, including basal cell carcinoma, and for which targeted therapies have been approved for clinical use.<sup>13</sup> *Akt1* is a serine/threonine protein kinase in the phosphatidylinositol-3 kinase (PI3K) signaling pathway that regulates several cellular processes, including survival, proliferation, tissue invasion, and metabolism. Specifically, 8%–13% of meningiomas have recurrent oncogenic mutations in *Akt1* (E17K) and 15% exhibit immunohistochemical evidence of PI3K/Akt/mammalian target of rapamycin (mTOR) pathway activation.<sup>1,2</sup> Inhibitors of *Akt1* are showing promise in other cancers.<sup>14</sup> Additionally, 7% of *NF2*-wildtype meningiomas harbor oncogenic alterations in *PIK3CA*, also a member of the PI3K pathway.<sup>3</sup> Notably, *SMO*, *Akt*, and *PIK3CA* mutations occur in meningiomas of the skull base, which are historically the most difficult to treat surgically.

The Alliance for Clinical Trials in Oncology cooperative group has initiated a phase II umbrella trial of targeted therapy in recurrent or residual meningiomas (A071401). Tumors undergo central genetic screening and pathology review for the presence of specific genetic mutations and for confirmation of histopathologic diagnosis. Patients with *NF2* mutations are assigned to receive a FAK inhibitor; *SMO* or Patched (*PTCH*) mutations, a *SMO* inhibitor; and *Akt* or *PIK3CA* mutations, a PI3K inhibitor. The primary endpoints of the study are 6-month

# Study synopsis

progression-free survival and response rate. Secondary endpoints are overall survival, median time to progression, and toxicity of SMO, Akt, and FAK inhibitors. Twenty-four evaluable patients will be accrued to the SMO and Akt/PIK3CA arms, and 36 patients to the NF2 arm. Key inclusion criteria include: intracranial meningioma; presence of SMO, Akt, PIK3CA, or NF2 mutation; and progressive or residual measurable disease. The NF2 arm has completed accrual: a new NF2 arm will open later in 2018. The other arms will be actively accruing later in 2018. If successful, this trial could represent a paradigm shift for the management of meningiomas, which traditionally have been managed with surgery and radiation.

Questions concerning this protocol can be directed to the Study Chair, Priscilla Brastianos, pbrastianos@mgh.harvard.edu, Alliance Neuro-Oncology Chair, Eva Galanis, galanis.evanthia@mayo.edu, or Samantha Sublett, Protocol Coordinator, at ssublett@uchicago.edu.

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# COGNO News and Activities

Zarnie Lwin, Mustafa Khasraw,  
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Anna Nowak



It is certainly an exciting time for the Cooperative Trials Group for Neuro-Oncology (COGNO) as we share our news of change, major developments, and activities. Since its inception in 2007, COGNO has gone from strength to strength. In that time, it has grown to 656 members. COGNO continues to leverage upon a strong partnership between clinicians, scientists, researchers, and consumer representatives, sharing a common goal of “better health outcomes for patients and those affected by brain tumors through clinical trials research.”

## New COGNO Chair

At the Annual General Meeting in October 2017, COGNO members ratified and warmly welcomed Professor Anna Nowak as our new Chair.

We are indebted to Professor Mark Rosenthal, Professor John Simes, and Dr Elizabeth Hovey for their leadership and vision over the past 10 years. Under their leadership COGNO has built plenty of momentum moving in the right direction, securing new collaborators, and promoting mentorship and succession planning to cultivate the next generation of clinical trialists.

Professor Anna Nowak is no stranger to COGNO or the international brain tumor community. With a PhD in tumor immunology and a postdoctoral fellowship at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, Professor Nowak has been an established leader in COGNO activities since its inception—contributing to the very first Australian national high-grade glioma clinical practice guidelines, as an investigator on the original COGNO grant application to Cancer Australia and as a founding member of COGNO’s Scientific Advisory Committee. Under Anna’s inspiring leadership and navigation, COGNO looks forward to charter new avenues and opportunities, both nationally and internationally. As COGNO implements positive change, we also seek to raise our profile in government and the community.

## Australian Brain Cancer Mission—\$100 million fund to fight brain cancer

The most astounding news for brain cancer clinical trials has been the announcement of the Australian Brain Cancer Mission, a \$100 million fund established to fight brain cancer. This is the result of intense advocacy from a number of groups around Australia, which culminated in the “Brain Cancer Round Table” convened by the



Professor Anna Nowak accepts role as new COGNO Chair at the AGM

Minister for Health, The Honourable Greg Hunt, which Professor Mark Rosenthal and Professor Anna Nowak attended in August 2017. The result of this meeting was a Brain Cancer Roadmap, which incorporates clinical trials as one of the most important pillars that will help the Fund achieve the goals of improving brain cancer survival. COGNO will continue to play a lead role in brain cancer clinical trials in Australia and to contribute strongly to key international clinical trials. Further details of this fund can be accessed at the following factsheet: [https://canceraustralia.gov.au/sites/default/files/brain\\_cancer\\_research\\_roadmap\\_factsheet.pdf](https://canceraustralia.gov.au/sites/default/files/brain_cancer_research_roadmap_factsheet.pdf)

## Strategic Planning Day

COGNO held a strategic planning meeting in September 2017, with the goal of identifying what we are doing well, what we could do better, and what changes we might make to better serve our patients and the COGNO membership. With a change of Chair, the time is ripe for the COGNO committees to reevaluate our Articles of Association and committee procedures and how we engage with members and consumers. Armed with ideas and in-principle agreement from the Strategic Planning



COGNO strategic planning day

Meeting, we are looking at member engagement, how we develop junior clinicians, how we interact with the pharmaceutical industry, and what our “public face” looks like to our colleagues and consumers. This will include an overhaul of our website <http://www.cogno.org.au/default.aspx> and consideration of the best way to use social media to inform members and consumers about clinical trials and COGNO activities.

## Medical Research Future Funding: Lifting Clinical Trials and Registries Capacity (LCTRC)

There are new funding opportunities in Australia, including the Medical Research Future Funding to Lift Clinical Trials and Registries Capacity. These competitive grants will target public clinical trials and Clinical Quality Registries that address areas of health burden and unmet need. Novel and innovative methodologies will be encouraged, such as the application of precision medicine. In the first round, approximately 13 million Australian

dollars were awarded, including to a number of projects studying glioma.

## Trials updates

COGNO conducts several investigator initiated and collaborative group trials addressing important clinical questions in their clinical trials portfolio.

COGNO has two trials that are currently recruiting in high-grade gliomas (ACED) and GBM (VERTU), one in follow-up (CATNON), two new trials that are hoping to open in 2018 (NUTMEG and CODEL), and many more in the concept and development stage.

The ACED trial is a study looking at adults with recurrent or progressive high-grade glioma who require dexamethasone or dose increase for cerebral edema. The study design is acetazolamide and dexamethasone versus dexamethasone alone for cerebral edema.

The VERTU trial is looking at a combination of veliparib, radiotherapy, and temozolomide in glioblastoma patients with newly diagnosed resected glioblastoma with the unmethylated MGMT promoter gene.

The CATNON trial is an international collaboration run by the EORTC, which is currently in long-term follow-up. The Australian COGNO sites contributed 82 (11%) of the total number ( $n = 751$ ) of patients recruited for this trial, which was a huge achievement, given that we joined recruitment later in the study.

COGNO has two trials in the pipeline that are hoping to open in 2018:

The NUTMEG study is looking at whether the combination of adjuvant nivolumab with temozolomide improves overall survival outcomes of GBM patients who are 65 years of age or older. This study is currently in startup and is hoping to be open for recruitment in early 2018.

CODEL (N0577) is another International study led by ALLIANCE (USA) looking at temozolomide alone versus radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy with adjuvant PCV chemotherapy in patients with 1p/19q codeleted anaplastic glioma. This trial is hoping to open for recruitment in 2018.

## Funding acknowledgments

**ACED:** Perpetual (via Cure Brain Cancer Foundation) and Cancer Australia grants. Cancer Australia: This grant was funded through the 2015 round of the Priority Driven Collaborative Cancer Research Scheme and is funded by Cancer Australia. **VERTU:** This project was supported by a grant from the Cure Brain Cancer Foundation. This research was funded by Cancer Council NSW RG 16-13 drug management and by AbbVie. **CATNON:** First grant: This grant was co-funded by Cancer Council Australia and Cancer Australia. Second grant: This grant was funded through the 2014 round of the Priority Driven Collaborative Cancer Research Scheme and is funded by Cancer Australia. **NUTMEG:** This study was funded by an NHMRC project grant. **CODEL:** This grant #1130584 was awarded through the Priority Driven Collaborative Cancer Research Scheme and co-funded by Cancer Australia and Cancer Council NSW.

## 10th COGNO ASM 2017 and 11th ASM 2018

A big congratulations to A/Prof Hui Gan and the 2017 organizing committee for another successful Annual Scientific Meeting (ASM) with an outstanding program, world-renowned keynote speakers, and a very well received Patient Information Forum. A total of 149 delegates attended from across Australia as well as internationally. The meeting brought together a multidisciplinary group of clinicians, scientists, pharmaceutical representatives, and patients to discuss the theme of “Tailoring Therapies for Brain Tumours: Challenges and Opportunities.” It was two days of presentations and discussions about the latest in the fight against brain tumors, covering the latest scientific discoveries and the most

recent advances in treatment and valuable strategies to help patients and their families with the daily challenges of living with brain tumors.

Highlights of the meetings were the three invited international faculty. Professor Patrick Wen (Dana-Farber Cancer Institute, USA) provided insights into the most promising new drugs for patients with brain tumors. Professor Dan Kelly (John Wayne Cancer Center, USA) then provided a review of cutting-edge endoscopic approaches to skull base surgery, as well as other new neurosurgical techniques. Professor Koichi Ichimura (National Cancer Centre Research Institute, Japan) took us on a deep dive into the diagnostic and therapeutic potential of TERT biology in brain tumors. We also had two other international speakers: A/Prof Ben Ellingson (University of California, USA) and A/Prof Maciej Mrugala (University of Washington, USA), speaking on advances in imaging and chemoprotection, respectively.

The meeting also showcased the best of Australian talent and research, with multiple presentations about the work that was happening nationally in this space. We heard first about what was state-of-the-art in imaging and pathology in Australia, highlighting both our expertise and the challenges we face. Our scientists showed us where they thought there were opportunities to understand brain cancer better and new potential treatments for brain cancer. Lastly, we shared the collective wisdom of clinicians and patients about how we deal with legal and other day-to-day challenges of living with brain cancer. Patient issues are a strong and enduring focus of COGNO, and a patient education forum was led by Ms Dianne Legge on October 22, on behalf of the Brain Tumour Alliance Australia and the Olivia Newton-John Cancer Wellness and Research Centre, where some of our international experts (Professors Wen and Kelly) and national experts (Professor Jenny Philip and Dr Zarnie Lwin) engaged in an afternoon of discussion with patients about topics ranging from medical cannabis to personalized surgery.

A number of prizes were given out for outstanding presentations and posters. The COGNO-Roche Most Outstanding Poster Presentation was awarded to Dr Sarah Shigdar (Deakin University) for her abstract “Targeting Brain Cancer Metastases—A Double Targeted Strategy for Effective Drug Delivery”; the COGNO Most Outstanding Oral Presentation was awarded to A/Prof Hui Gan (Austin Health) for his presentation on “Efficacy Analysis of Depatuxizumab Mafodotin (ABT-414) +/- Temozolomide (TMZ) in Patients (Pts) with EGFR Amplified, Recurrent Glioblastoma (rGBM) from a Multicentre, International Phase 1 Clinical Trial”; and lastly the COGNO-Bristol-Myers Squibb Young Investigator Award was awarded to Dr Gurvinder Toor (Royal Melbourne Hospital) for his poster abstract “Health-Related Quality Of Life And Cognition Post-Resection Of Benign Brain Tumours.”

The meeting was capped by a wonderful conference dinner at the stunning Melbourne Aquarium. Delegates were





ASM organising committee and international guest speakers



A/Prof Hui Gan opening welcome on day 1 of ASM

wined and dined while sharks and other exotic fish swam within touching distance. It was also an opportunity to thank all our speakers, especially our international faculty. A number of announcements and awards were presented during the dinner. It was a chance to thank Professors Mark Rosenthal and John Simes for their invaluable contributions and leadership for the last 10 years while handing the baton over to Chair-elect Professor Anna Nowak. The MSD Hubert Stuerzl Memorial Educational Award was given to Dr James Whittle (Medical Oncologist, Peter MacCallum Cancer Centre) and the COGNO Outreach

Education Preceptorship was awarded to Dr Achiraya Teyateeti from Thailand.

We are all looking forward to the 11th COGNO Annual Scientific Meeting next year in Brisbane from Sunday, October 7 to Tuesday, October 9, 2018 and invite you all to join us there. Organization is well under way with conference convenor Dr Mark Pinkham and his team.

Save the date for the 2018 ASM to be held in Brisbane Oct 7–9!



## Ideas Generation Workshop (IGW)

COGNO's fourth Ideas Generation Workshop was held on May 2017 in Sydney, co-convened by Mustafa Khasraw, Zarnie Lwin, and Kathryn Field with the able support of Candace Carter. Nine interesting concepts were presented and discussed, with further development required on some before progression to consideration by the COGNO SAC. COGNO extended a special thank you

to Drs Khasraw and Lwin, who were the founders and co-convenors on all four of our very successful IGWs, and have now handed over to the very capable Drs Kathryn Field and Benjamin Chua. The 5th COGNO IGW is scheduled for May, in Sydney.

## Committees

COGNO is governed by a Management Committee, supported by various specialist committees as required.



Mustafa Khasraw, Zarnie Lwin, Kathryn Field and Candace Carter

# The Developing Chinese Society of Neuro- Oncology

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The Chinese Society of Neuro-Oncology (CSNO), which is affiliated to the Chinese Anti-Cancer Association (CACA), is a multidisciplinary organization that represents all the medical professionals and basic researchers involved in the management of CNS tumors in China. CSNO was founded in 2004 by a group of doctors in the field of neuro-oncology in China (Figure 1). Prof Zhongping Chen from Cancer Center of Sun Yat-sen University was the founder president. Prof Chao You from West China Hospital of Sichuan University is the current president, and Prof Shiguang Zhao from the First Affiliated Hospital of Harbin Medical University is a former president. Currently, there are more than a thousand active CSNO members and about 20 branch societies in provinces and main cities of China. The official website is [www.csno.cn](http://www.csno.cn).

CSNO is dedicated to promoting advances in neuro-oncology in China through research and education, to providing a platform for interaction and communication in the field of neuro-oncology. CSNO is also actively involved in communication and collaboration with neuro-oncology societies in Asia, Europe, North America, and all the world.

## Academic Conference

CSNO organizes a series of scientific meetings including the CSNO scientific annual meeting, CSNO-SNO joint meeting, Neuro-oncology Summit Forum: East Meets

West, and the Korea-China Neuro-Oncology Meeting. The CSNO scientific annual meeting is the biggest one, first held in Guangzhou in 2004 and hosted by Prof Zhongping Chen. In the CSNO scientific annual meeting, participants report the new research findings covered from all over the field of neuro-oncology. The approaching 15th annual meeting will be held at Shenyang this August. In 2007, the 1st Korea-China Neuro-Oncology Joint Meeting took place in Harbin, in North China, jointly with the 4th scientific annual meeting of CSNO. After that, this meeting has been held annually, and alternatively hosted by Korea (named the “China-Korea Neuro-Oncology joint meeting”) and China (named “Korea-China Neuro-Oncology joint meeting”) (Figure 2). The 12th China-Korea Neuro-Oncology Joint Meeting will be held this June in Gwangju, Korea. The CSNO-SNO joint meeting was first organized in Guangzhou in 2012 (Figure 3). It is one of the grandest meetings between China and the United States in the field of neuro-oncology. All attendees of the meeting are believed to gain abundant knowledge and frontier concepts over all aspects of neuro-oncology. The forthcoming CSNO-SNO Joint Meeting is going to take place this March in Guangzhou, China, and several eminent scholars from SNO already accepted the invitation, including Prof Mitchel S. Berger from UCSF, Prof Roger Stupp from Northwestern University, and Prof Michael Lim from Johns Hopkins University. Starting from 2015, the Neuro-oncology Summit Forum: East Meets West intends to promote academic exchange and friendship between CSNO and EANO. In 2016 during the EANO meeting in



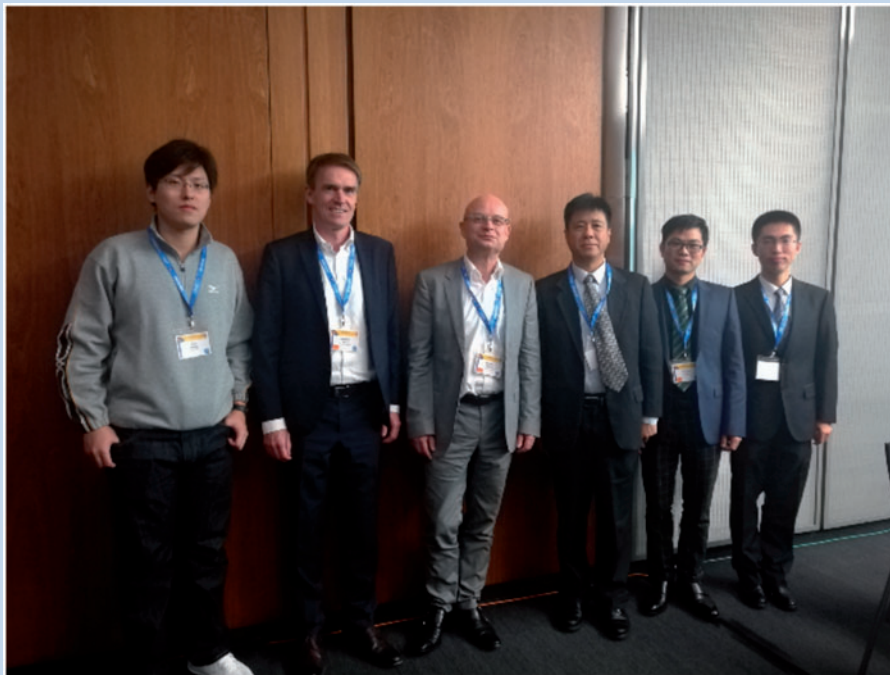
Figure 1. CSNO founder members.



**Figure 2.** The 11th Korea-China Neuro-oncology joint meeting, 2017, Tianjin, China.



**Figure 3.** CSNO-SNO meeting, 2012, Guangzhou, China.



**Figure 4.** Prof Yang met with Prof Weller and Prof Wick at EANO meeting, 2016, Mannheim, Germany.



**Figure 5.** Neuro-oncology Summit Forum: East Meets West, 2017, Shenyang, China.

Mannheim, Prof Xuejun Yang from Tianjin Medical University General Hospital representing CSNO met with Prof Michael Weller and Prof Wolfgang Wick to discuss the further collaboration and exchange between CSNO and EANO (Figure 4), and officially invited key members from EANO to join the East Meets West Forum 2017. Prof Wolfgang Wick, Prof Elizabeth Moyal, and Prof Colin Watts came to Shenyang and made wonderful presentations to Chinese colleagues (Figure 5) last October.

## Publication

GLIOMA, a publication of CSNO and a peer-reviewed bimonthly journal, will publish the first issue by Medknow this year. The editors-in-chief are Zhongping Chen and Mark D. Johnson from the University of Massachusetts Medical School. The journal's full text will be available online at [www.jglioma.com](http://www.jglioma.com), allows free access (Open Access) to its contents, and permits authors to self-archive the final

accepted version of the articles on any OAI-compliant institutional/subject-based repository. The Journal accepts original articles, reviews, meta-analyses, editorials, and case reports covering all subjects and topics on glioma.

## Research Foundation

The CSNO Neuro-Oncology Research Program has been in operation for almost 5 years, founded in 2015. This funding raises donations from social enterprises and aims to encourage and promote the development of clinical research on neuro-oncology in China. The funding has received more than 180 items, with topics covering the different fields of neuro-oncology from medical institutions all over the country. Among them, 71 projects have been officially funded with a total expenditure of 5.16 million yuan. As examples, one of the biggest tasks with a total amount of 1.4 million yuan is the project named “Temozolomide concurrent radiotherapy for more than 6 cycles: temozolomide adjuvant chemotherapy for newly diagnosed glioblastoma” recently has been

initiated by CSNO-CTCG (Chinese Society of Neuro-oncology–Clinical Trial Collaboration Group), led by Prof Zhongping Chen.

## International Relationships

CSNO bonds closely with WFNOS as well as ASNO, EANO, SNO, and other regional neuro-oncology societies. The CSNO members are also encouraged to attend scientific meetings held by ASNO, EANO, SNO, WFNOS and other important neuro-oncology meetings. China has hosted ASNO annual meetings twice, respectively in Shanghai in 2004 and in Suzhou in 2011. Approaching us is the 15th ASNO annual meeting. We are so proud to hold it in the historic and luminous city of Beijing, China, October 25–28, 2018. We believe this forthcoming conference will bring a brand-new horizon, and we are cordially waiting for your attending.



# Observations from the Sub-Saharan Africa Neuro-Oncology Meeting October 18–19, 2017 London, UK

Chas Haynes, Jason Huse, and Gelareh Zadeh

Society for Neuro-Oncology

## Introduction

The first sub-Saharan Africa Neuro-Oncology Collaborative (S-SANOC) planning meeting was held in London on October 18–19, 2017, at The Tower Hotel. The meeting was organized through the collaborative efforts of the Society for Neuro-Oncology (SNO), the International Brain Tumor Alliance (IBTA), and the Zimbabwe Brain Tumor Association (ZBTA), in association with Mark Bernstein, the Greg Wilkins-Barrick Chair of International Surgery at the University Health Network, University of Toronto, Canada.

## Background

Established in 2015, the SNO Wilkins-Barrick Course in Neuro-Oncology provides seed funding for neuro-oncology symposia or courses in the developing world. To date, SNO Wilkins-Barrick Courses have been held in Kuala Lumpur, Malaysia (2016), Marrakech, Morocco (2017), and Colombo, Sri Lanka (2017). A future course is currently being planned for Lima, Peru. Applications for SNO Wilkins-Barrick Course funding are made through a competitive application process and are reviewed by a committee comprising senior members of SNO.

As part of the current round of funding, a specific call for applications from sub-Saharan Africa was made. A number of strong applications were received from various health care professionals regarding proposed educational activities in that region. During the period of the grant

application process, SNO also became aware of the efforts of the IBTA in connection with brain tumor patients and advocacy communities in sub-Saharan Africa.

## Meeting Purpose

Recognizing the congruent interests of SNO (given the high quality of the applications received, and mindful of the disparities that exist across the region) and the IBTA and ZBTA (who are keen to advance brain tumor patient advocacy in sub-Saharan Africa), a decision was made to invite the SNO Wilkins-Barrick applicants and African patient advocates to a central location to examine the challenges and potential solutions for improving the care of brain tumor patients in sub-Saharan Africa. The S-SANOC meeting was therefore held in London, UK, so applicants could have the opportunity to present their proposals for achieving a high-quality, state-of-the-art symposium or educational course in sub-Saharan Africa in 2018. Additionally, brain tumor patient advocates from Zimbabwe, Cameroon, South Africa, and Uganda were given the opportunity to present their perspectives on the current situations for brain tumor patients in their countries. The IBTA also presented on its current work in the international advocacy and awareness-raising field. In addition, representatives of the following neuro-oncology societies were present at the S-SANOC meeting: the European Association of Neuro-Oncology (EANO), the Indian Society of Neuro-Oncology (ISNO), and the

Asian Society of Neuro-Oncology (ASNO). It was further hoped that bringing together key stakeholders from the region would be conducive to the development of a multi-stakeholder African neuro-oncology society that would take a leadership role in coordinating efforts to improve patient care in that area of the world.

## Meeting Program

After a welcome from Kathy Oliver of the IBTA, each of the applicant groups presented as follows:

- Thierry Muanza and Ekokobe Fonkem (Dar es Salaam, Tanzania Group 1)
- Daniel Fulkerson (Eldoret, Kenya Group)
- Trish Scanlan (Dar es Salaam, Tanzania Group 2)
- Alan Davidson (Cape Town, South Africa Group)
- James Balogun (Abuja, Nigeria Group)
- Teddy Totimeh (Accra, Ghana Group)
- Nimrod Juniahs (Lome, Togo Group) via taped message

A roundtable discussion followed during which participants were able to ask questions on specific aspects of the various proposals.

After lunch, representatives from patient advocacy groups presented on the state of brain tumor advocacy in sub-Saharan Africa and the challenges faced by patients and families:

- Christine Mungoshi and Linda Longwe (Zimbabwe Brain Tumor Association)

- Irene Azong-Wara (Jacob's Hope Foundation, Cameroon)
- Bonita Suckling (Rainbows and Smiles, South Africa)
- Wilson Mugarura (Uganda Brain Tumor Foundation)

The meeting concluded with a discussion of the logistical and administrative practicalities of organizing a neuro-oncology course in sub-Saharan Africa, with consideration given to the accessibility and infrastructure that may exist in the proposed locations.

## Observations

The funders of the SNO Wilkins-Barrick Course were very impressed with the quality of the various proposals. It was observed that:

- Collectively, the applicants demonstrated a strong commitment to improving patient care in sub-Saharan Africa and expressed a willingness to work collaboratively in this effort.
- There was general agreement that health care professionals and patient advocates would benefit from a mechanism providing the ability to communicate, network, and collaborate with their peers across the continent.

## Recommendations

With regard to organizing a SNO Wilkins-Barrick Course in sub-Saharan Africa, the funders hope that the meeting in London serves as a catalyst for positive and lasting change in the region.

The funders recommend that:

- Decisions regarding the planning and content of the course in 2018 would best be directed by the stakeholders in the region, and not by the funders.
- Mindful of the administrative challenges involved in organizing the first course, work to leverage the resources of an existing event that already has the necessary infrastructure in place may increase the prospects for success.
- To take account of the determination expressed by all the course applicants at the S-SANOC meeting that it was their wish to form a sub-Saharan neuro-oncology association, SNO accordingly recommends that the stakeholders in the region form a multi-disciplinary society or consortium to be known as the Society for Neuro-Oncology in Sub-Saharan Africa (SNOSSA).
- That SNOSSA should comprise neuro-oncology professionals and allied health care providers, and should reflect as broadly as possible the cultural and other needs of the brain tumor patient population within sub-Saharan Africa.
- That SNOSSA would necessarily include patient advocates as members.
- That SNOSSA should also reach out and establish a formal relationship with the EANO.
- As soon as is practical, that SNOSSA should join as a member of the World Federation of Neuro-Oncology Societies (WFNOS) and play an active role in the organization of the WFNOS quadrennial event.

## Commitments

The Wilkins-Barrick Chair in Neuro-Surgery and the Society for Neuro-

Oncology together commit to the following:

- Providing funding to offset the costs of organizing three neuro-oncology courses in sub-Saharan Africa over the next three years (one course per year).
- Development and launch of a web-based collection system of contact information of neuro-oncology professionals, allied health care providers, and patient advocates/patient advocacy organizations in sub-Saharan Africa, including email addresses, geographic location, practice area, and sub-specialty.

## Conclusion

The Greg Wilkins-Barrick Chair of International Surgery and the Society for Neuro-Oncology believe that the S-SANOC planning meeting held in London was a critical step toward the establishment of a sustainable neuro-oncology community across sub-Saharan Africa. This will result in improved care and better outcomes for patients with brain tumors and their families in that region. Since the conclusion of the meeting in London, a Steering Committee of stakeholders from sub-Saharan Africa have taken steps toward developing a formal constitution (charter) for the Society for Neuro-Oncology in Sub-Saharan Africa (SNOSSA). The Steering Committee is also organizing a one-day conference to be held in Abuja, Nigeria, in conjunction with the Continental Association of African Neurosurgical Societies (CAANS) in July of this year.

# The Sub-Saharan Africa Neuro-Oncology Collaborative (S-SANOC) Planning Meeting

**by Kathy Oliver, Chair and  
Co-Director**

*International Brain Tumour Alliance (IBTA)*

**Christine Mungoshi, Director**

*Zimbabwe Brain Tumour Association (ZBTA)*

A traditional African proverb about the value of teamwork says: “If you want to go fast, go alone. If you want to go far, go together.”

This sentiment was certainly in evidence at the first Sub-Saharan Africa Neuro-Oncology Collaborative (S-SANOC) planning meeting held in London, UK on 18 and 19 October 2017, where the spirit of “going far together” was palpable.

Thirty-three participants from 16 countries within and beyond sub-Saharan Africa attended this groundbreaking event, which saw brain tumor patient advocates from the region actively collaborating with neurosurgeons, researchers, and others to develop a strategy for improved outcomes in brain tumor treatment, care, and support in this part of the world.

The vision for this innovative meeting was to bring together key neuro-oncology stakeholders in sub-Saharan Africa. The meeting provided an opportunity to address unmet needs and key priorities and to find potential solutions to the many unique challenges for people with brain tumors in the region.

The practical goals of the S-SANOC meeting were to:

- organize a neuro-oncology educational course/conference in sub-Saharan Africa in 2018
- actively involve the sub-Saharan patient advocacy community in enhanced efforts to raise awareness of the challenges of brain tumors
- start building the foundations for a sub-Saharan Africa multi-stakeholder neuro-oncology society.

During the S-SANOC meeting, there were many inspirational stories of efforts by health care professionals, patient advocates, and others working tirelessly and selflessly in sub-Saharan Africa. It became apparent very quickly that the challenges are, in many cases, monumental and the resources with which to meet them are few.

The meeting also laid bare, in moving testimonies from sub-Saharan brain tumor patients and former caregivers, the devastating struggles they endure on the patient care journey: lack of access to accurate diagnosis; lack of access to treatments; cultural barriers; stigmatization (ie, discriminatory cultural attitudes to epilepsy); and fragmented delivery of services (ie, frequent breakdowns of equipment such as radiotherapy machines), to name just a few examples.

And yet, despite the inequities and huge unmet needs described by participants, the event pulsed with positivity, determination, and the promise of better things to come, thanks to plans for a new collaboration among stakeholders—The Society for Neuro-Oncology Sub-Saharan Africa (SNOSSA).

There is much to do, but the S-SANOC meeting was a vital start.

The overwhelming message from the event was that, working collaboratively and with one voice—health care professionals and patient advocates together—barriers can be broken down, the impossible may become possible, and dreams may turn into realities for those whose lives are touched by a brain tumor.



*The 2017 S-SANOC meeting participants. **Front row**, left to right: Dr James Balogun (Nigeria), Dr Gelareh Zadeh (Canada), Dr Thierry Muanza (Canada), Pastor Wilson Mugarura (Uganda), Kathy Oliver (IBTA, United Kingdom), Jenny Baker (IBTA, United Kingdom), Mary Lovely (IBTA United States), Irene Azong-Wara (Jacob's Hope Foundation, Cameroon), Bonita Suckling (Rainbows and Smiles, South Africa), Christine Mungoshi (Zimbabwe Brain Tumour Association), Dimitri Pouradier Duteil (Bristol-Myers Squibb). **Second row**, left to right: Chas Haynes (Society for Neuro-Oncology), Professor Geoff Pilkington (United Kingdom), Dr Rakesh Jalali (India), Dr Patrick Bankah (Ghana), Dr Stuart Farrimond (IBTA, United Kingdom), Anita Granero (Oscar's Angels, IBTA, France), Chris Tse (IBTA, New Zealand), Shade Adoh (United Kingdom). **Third row**, left to right: Dr Teddy Totimeh (Ghana), Dr Jason Huse (United States), Dr Edjah Nduom (United States), Gordon Oliver (IBTA, United Kingdom), Sally Payne (IBTA, Australia), Dr Daniel Fulkerson (United States). **Back row**, left to right: Professor Alan Davidson (South Africa), Jean Arzbaeher (IBTA, United States), Jan-Marc Lieskovsky (MagForce), Luke Mungoshi (Zimbabwe Brain Tumour Association). Photo by MVF Studios (<https://mvfstudios.biz/>)*





S-SANOC 2017 delegates (left to right): Pastor Wilson Mugarura (Uganda), Professor Alan Davidson (South Africa), Kathy Oliver (IBTA, United Kingdom), Dr James Balogun (Nigeria), Dr Teddy Totimeh (Ghana), Dr Thierry Muanza (Canada), Christine Mungoshi (Zimbabwe), Dr Edjah Nduom (United States), Dr Patrick Bankah (Ghana). Photo by MVF Studios (<https://mvfstudios.biz/>)


And so the work begins. We wish all of those who attended the first S-SANOC meeting the very best of luck in realizing the ambitious plans discussed. It was a great privilege and powerful learning experience to bear witness to the start of what we all hope will be a new and exciting journey—together.

Delegates at the 2017 S-SANOC meeting were reminded of words from the surgeon, writer, and public health researcher Atul Gawande, who said: *“Better is possible. It does not take genius. It takes diligence. It takes moral clarity. It takes ingenuity. And above all, it takes a willingness to try.”*

It was this “willingness to try” that brought delegates together in London and it will be this same “willingness to try” that will help inspire future directions for neuro-oncology in sub-Saharan Africa.

To read the complete S-SANOC Report, including the full program and participant biographies, please see: [https://issuu.com/ibta-org/docs/ibta\\_ssanoc-report\\_final\\_20mar2018](https://issuu.com/ibta-org/docs/ibta_ssanoc-report_final_20mar2018)

For further information on the S-SANOC initiative, please contact Kathy Oliver, Chair and Co-Director, International Brain Tumour Alliance—IBTA ([www.theibta.org](http://www.theibta.org)) at [kathy@theibta.org](mailto:kathy@theibta.org)

A blue decorative shape, resembling a stylized arrow or a corner piece, is located in the top left corner of the slide.

# First EANO Winter School in Athens: Complications of Primary and Secondary Brain Tumors

**Carina M. Thomé, PhD**

*Clinical Cooperation Unit Neurooncology/ G370,  
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The first European Association of Neuro-Oncology (EANO) Winter School, endorsed by the European Academy of Neurology (EAN), was held March 16–17, 2018 in Athens, Greece. The well-organized, two-day conference was chaired by Evangelia Razis, Matthias Preusser, and Riccardo Soffietti. This year's main topic was "Complications of primary and secondary brain tumors." The interdisciplinary course was addressed to scientists, nurses, and clinicians working in the field of neuro-oncology. Each session focused on one specific complication, such as "Infections in brain tumor patients" or "Radiation necrosis and pseudoprogression." After an introduction to the field, well-known and experienced lecturers such as Priscilla Brastianos, Evanthia Galanis, Roberta Rudà, and Wolfgang Wick provided guideline treatment options and outlined the current state of research. On the second day, complications like "Leptomeningeal carcinomatosis" and "Spinal cord compression" were presented. "Palliative and end-of-life care" and "Psychological impact of brain tumors on patients and caregivers" were also discussed. A very important and interesting course objective was the panel discussion on "Clinical trial participation: opportunities and challenges," headed by Matthias Preusser. The faculty members gave valuable advice on clinical trial design, shared their experiences, and mentioned common

obstacles and how to overcome them. In the last session, four younger clinicians were given the opportunity to present their own clinical cases, outlining complications like "Chemotherapy-induced pancytopenia," "Inflammatory myopathy," "Supplementary motor syndrome after resection," and "Cerebral venous thrombosis." Altogether 44 attendees arrived from many different countries to the first EANO Winter School: Albania, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, France, Germany, Greece, Israel, Jordan, the Netherlands, Norway, Romania, Russia, Spain, Turkey, and United Kingdom. The professions among the participants were also diverse. Nurses, molecular biologists, medical students, residents in radiation oncology, neurosurgery, neuro-oncology, medical oncology, and neurology attended the course in Athens. Besides the increase of knowledge in neuro-oncology, this course was a very good opportunity for youngsters to meet and network with experienced clinicians and scientists as well as connect with peers from other countries. Science transfer and sharing experience were among the main objectives. At the end of this educational, interactive, and fantastic course we can state the first EANO Winter School was a great success and look forward to further educational activities organized by EANO.



# 2017 Society for Neuro-Oncology Annual Meeting Update

**Jennie W. Taylor, MD, MPH<sup>1</sup>,  
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Albert H. Kim, MD, PhD<sup>3</sup>**

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Center, St Louis, MO*



The Society for Neuro-Oncology hosted its 22nd annual Scientific Meeting on November 16–19, 2017 in San Francisco, California. More than 2500 attendees from 42 countries were there, with a record 1024 abstracts submitted to the conference.

Both the Education Day and the Scientific Meeting featured several sessions focused on the Cancer Moonshot program. The Cancer Moonshot program is a national effort led by former Vice President Joe Biden, who lost his son to glioblastoma (GBM), with the bold aspiration to end cancer. Dr W. K. Alfred Young introduced the program, and keynote presentations throughout the Meeting all aligned with Moonshot initiatives—including Dr Walter Koroshetz's update on neuro-oncology initiatives at the National Institute of Neurological Disorders and Stroke (NINDS); Dr Carlo Croce's discussion of microRNAs as oncogenic drivers; Dr Ludmil Alexandrov's computational approach to mutational signatures across cancers; and Dr Jennifer Doudna's discovery of the CRISPR/Cas9 system.

Additionally, inspired by work led by Dr Terri Armstrong and colleagues on burnout in neuro-oncology practitioners, the SNO Cares program, which incorporates self-care activities such as morning yoga and massage stations into the meeting, was launched.

The Education Day focused on recommendations from the Moonshot Blue Ribbon Panel. Dr Donald Abram delivered a keynote presentation on incorporating integrative medicine into managing symptoms from cancer treatments. This was followed by breakout sessions on Practical and Applied Neuro-Oncology, including survivorship, measuring outcomes, and mitigating effects of treatment and disease. Dr Trever Bivona's keynote presentation addressed mechanisms for overcoming resistance and was followed by the Tumor Biology and Therapy breakout sessions on the biology of resistance as well as therapy-specific resistant mechanisms. The afternoon concluded with talks by Dr Gregory Armstrong on patient-reported outcomes in survivors of pediatric cancers; Dr E. Antonio Chiocca, current SNO president, who provided thoughtful reflections on resistance mechanisms and mentorship in neuro-oncology; and panel discussions on therapy resistance and burnout in neuro-oncology practitioners.

The Scientific Meeting spanned the following 2.5 days, from numerous Sunrise Sessions chaired by international experts in their fields to evening eTalks and poster sessions. Dr Susan Chang was the recipient of the Victor Levin Award. Dr Webster Cavenee received the Lifetime Achievement Award. The Public Service Award was renamed in recognition of Jan Esenwein and was presented to Carol Kruchko, President and founder of the central brain tumor registry of the United States (CBTRUS). All keynote presentations focused on Blue Ribbon Panel recommendations from the Cancer Moonshot and several award-winning abstracts were highlighted:

Dr Joydeep Mukherjee from the Pieper lab at University of California, San Francisco (UCSF), recipient of an Adult Basic Research Award and the Andrew Parsa Young Investigator Award, presented mechanistic data on mutant isocitrate dehydrogenase's (IDH) interaction with loss of alpha thalassemia/mental retardation syndrome X-linked protein (ATRX) to drive alternative lengthening of telomeres (ALT), thereby rescuing gliomas from telomere-induced cell death and cell immortality. They found mutant IDH1 or ATRX loss alone to be insufficient to drive the ALT phenotype, while the combination was tumorigenic. The mechanism of IDH1 and ATRX on ALT was mediated by downregulation of RAP1 and XRCC1 as part of the telomere capping sheltering complex and fusion of dysfunctional telomeres through alternative non-homologous end joining. These data suggest that agents altering linkage between mutant IDH and DNA repair pathway preferences may have therapeutic potential in IDH mutant gliomas.

Dr Ulrich Herrlinger of Tübingen, Germany, received an Adult Clinical Research Award for the CeTeG/NOA-04 study—a phase III trial combining CCNU and temozolomide (TMZ) in MGMT-methylated newly diagnosed glioblastoma (GBM). The study randomized 129 newly diagnosed patients to CCNU (100 mg/m<sup>2</sup>/d, D1) and TMZ (100 mg/m<sup>2</sup>/d, D2–6) every 6 weeks starting with radiotherapy versus standard radiotherapy with concurrent TMZ followed by 6 cycles of adjuvant TMZ. The primary outcome of overall survival (OS) was improved from 30.4 months (95% CI: 24–45) in the standard arm to 46.9 months (95% CI: 31–NA) in the combination, with increased toxicity.

Dr Ingo Mellinghoff from Memorial Sloan Kettering Cancer Center received the other Adult Clinical Research Award, for his update from the phase I study of AG-120, a first-in-class mutant IDH1 inhibitor, focusing on the exploratory imaging analysis of the non-enhancing glioma cohort. He presented on the 35 patients (11 in the dose escalation and 24 in the dose expansion cohorts) with non-enhancing gliomas demonstrating 83% with stable disease at a median duration on treatment of 16 months. They found the tumor growth rate to slow when using volumetric quantification of T2/FLAIR.

Dr David Raleigh from UCSF, the other recipient of the Adult Basic Research Award, presented data on the comprehensive genomic characterization of aggressive meningiomas. Using data from the UCSF Meningioma Database, they performed whole exome sequencing, DNA methylation arrays, RNA-seq, Nanostring, and immunohistochemistry on a discovery and validation set of aggressive grades I–III meningiomas. They validated prior results demonstrating poorer survival in tumors with increased somatic mutation burden and identified proto-oncogene *FOXM1* as a novel biomarker of aggressiveness, with implications for drug development.

Dr Yoshihiro Muragaki of Tokyo Women's Medical University of Japan discussed results of the phase IIb


study of an autologous formalin-fixed tumor vaccine (AFTV) for patients with newly diagnosed GBM, a late breaking abstract. This trial built on prior work demonstrating clinical activity and in vivo immunoactivation of AFTV from paraffin-embedded tissue. Patients with extensively resected GBM were randomized to AFTV versus placebo. Median overall survival (OS) did not differ between AFTV (25.6 mo) and placebo (31.5 mo, hazard ratio: 1.19, 0.57 – 2.47,  $P = 0.64$ ). However, there was a trend in 3-year OS for tumors with negative p53 immunostaining (79% vs 43%,  $P = 0.072$ ) or total resection (81% vs 46%,  $P = 0.067$ ), a finding that will be further evaluated in the planned phase III study.

Dr Martin van den Bent presented an additional late breaking abstract of the phase II EORTC-1410-BTG study of Depatux-m, a tumor-specific antibody–drug conjugate consisting of the antibody ABT-806 bound to monomethylauristatin-F toxin. This open-label study randomized 260 epidermal growth factor receptor (EGFR)–amplified GBMs at first recurrence to Depatux-m, Depatux-m with TMZ, or either lomustine or TMZ

monotherapy. Median survival of 9.6 months (1-year OS 39.7%) was longer in the Depatux-m/TMZ arm compared with 8.2 months (1-year OS 28.2%) in the placebo arm with a hazard ratio for death of 0.71 (95% CI: 0.50–1.02). A phase III in newly diagnosed EGFR-amplified GBM is under way.

Numerous lunch sessions were offered spanning topics from a more in-depth introduction to CRISPR-based technologies to a Neuro-Oncology Trainee Forum. The Meeting also included several concurrent sessions moderated by leaders in their field and was packed with exciting oral abstract presentations focusing on pediatric and adult clinical trials, radiation oncology, neurosurgical oncology, imaging, basic science from stem cells to immunology, and practical and applied neuro-oncology. Poster sessions and eTalks rounded out the evening activities.

The 23rd annual Scientific Meeting of the Society for Neuro-Oncology will be held later this year, November 15–18, 2018, in New Orleans, LA.



# FOCUS ON: Long-Term Neurovascular Complications in Cancer Patients

**Joyce Wilbers**

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## Cancer and vascular disease

Cancer and vascular diseases are the two leading causes of mortality and morbidity worldwide.<sup>1</sup> An autopsy study showed that 15% of patients with cancer had evidence of cerebrovascular disease.<sup>2</sup> The coexistence of these diseases may be explained by:

- (1) High prevalence of both diseases in the general elderly population.
- (2) Common population risk factors, particularly smoking.
- (3) Direct cancer effects, like cancer-induced hypercoagulable state, nonbacterial thrombotic endocarditis, or compression of blood vessels by the tumor.
- (4) Toxicity of anticancer treatments, either radiotherapy-related long-term vasculopathy or chemotherapy-related hypercoagulability.<sup>2,3</sup>

## Radiotherapy-induced neurovascular complications in head and neck cancer

Since the population of long-term cancer survivors is growing, long-term treatment-related complications become more important. In recent years, further insight into and attention to these late vascular complications in

survivors of specific cancers has increased. The underlying pathophysiology of radiotherapy-induced carotid vasculopathy is not completely clear. There are two lines of thought<sup>4</sup>:

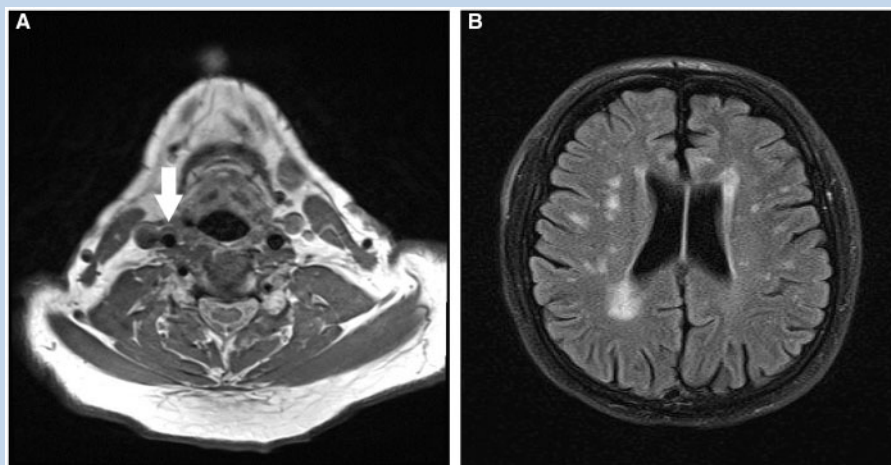
- (1) Acceleration of “common atherosclerosis”
- (2) A distinct disease entity starting with injury to the vasa vasorum

Radiotherapy induced carotid artery vasculopathy is a potential long-term complication after radiotherapy of the neck, with enhanced risk of ischemic stroke.<sup>5–7</sup> The intima media thickness of the carotid artery measured by ultrasonography is a widely used, validated, and reliable measure of atherosclerosis and is associated with the risk of cerebrovascular events.<sup>8</sup> Prior retrospective studies showed a larger intima media thickness in the irradiated, compared with the non-irradiated, carotid artery after a median follow-up period of 8–10 years after unilateral radiotherapy of the neck. Increased intima media thickness is associated with an increased risk of ischemic stroke.<sup>5,6,9</sup>

No long-term prospective studies are available. The time course of the development of radiotherapy-induced vasculopathy, the imaging characteristics and the spectrum of clinical implications, like ischemic stroke, vascular white matter lesions, and cognitive deficits are still unclear.

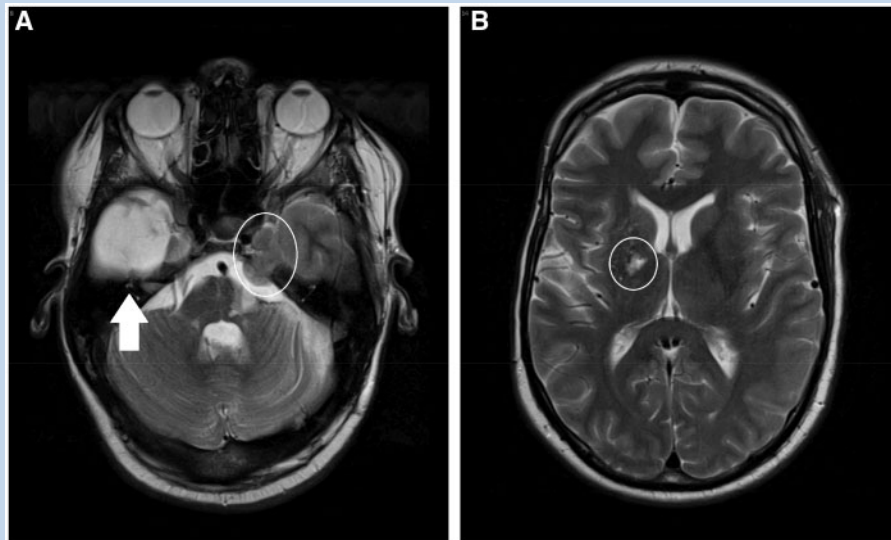
## Cancer prevalence in stroke patients

The short-term incidence of stroke in patients with active cancer has been studied retrospectively.<sup>10</sup> The most



**Figure 1.** (A) Proton density weighted MRI showing an increased vessel wall thickness of the right carotid artery. (B) MRI of the brain showing vascular white matter lesions, most prominent in the vascular territory of the right carotid artery.





**Figure 2.** (A) T2-weighted MRI showing a state after a right temporal resection of a low-grade glioma (arrow) and a left-sided skull base meningioma (circle). (B) T2-weighted MRI showing a lacunar infarction in the right internal capsule (circle).

frequent types of cancer in patients with stroke and cancer are lung (30%), brain (9%), and prostate (9%). A recent study among 327 389 pairs of cancer patients and matched controls showed a 3-month increased incidence of stroke in patients with lung, pancreatic, and colorectal cancers.<sup>11</sup> Furthermore, an observational study in 1105 Chinese patients who suffered from an ischemic stroke showed that 5.2% had a cancer history. Cancer history was an independent predictor of recurrent stroke.<sup>12</sup>

The cases below illustrate neurovascular complications in 2 cancer patients.

## Patient 1

A 61-year-old man had been treated with bilateral radiotherapy (70 Gy) of the neck because of a carcinoma of the oropharynx 6 years before. Vascular risk factors consisted of hypertension, smoking, diabetes, obesity, atrial fibrillation, and a positive family history for vascular diseases. MRI showed an increased vessel wall thickness of the right carotid artery (Figure 1A) and vascular white matter lesions, mostly in the right hemisphere (Figure 1B).

In such a patient it is unknown whether primary prevention of cardiovascular disease by treatment of classical cardiovascular risk factors is an effective strategy.

## Patient 2

A 42-year-old woman presented with a left-sided paresis due to a lacunar infarction in the right internal capsule (Figure 2). Medical history revealed a low-grade

astrocytoma in the right temporal lobe more than 30 years before, for which she underwent resection and radiotherapy. Furthermore, 2 years before presentation, the patient was treated for a left-sided skull base meningioma with a subtotal resection and additional gamma knife radiosurgery. Vascular risk factors consisted of hypertension and obesity.

It is not clear whether only cardiovascular risk factors or also prior resection and radiotherapy of the brain tumor caused this ischemic stroke.

## Radiotherapy-induced neurovascular complications in head and neck cancer: summary of a long-term prospective follow-up study<sup>(13,14,15,16,17)</sup>

Most studies assessing radiotherapy-induced carotid vasculopathy and ischemic stroke in head and neck cancer survivors were retrospective in design and mainly focused on carotid intima media thickness and ischemic stroke.<sup>5,6,18</sup> However, the natural course and imaging characteristics of this radiotherapy-induced vasculopathy were not clear. Furthermore, potential clinical

consequences of this carotid wall pathology, like vascular white matter lesions or cognitive deficits, were not studied before.

Therefore, we started a long-term prospective follow-up study in head and neck cancer patients treated with radiotherapy on baseline.<sup>14</sup> This study showed that within the course of the first 2 years, intima media thickness of the irradiated carotid arteries was not increased, whereas after 7 years it was. The prospective design of our study added to the understanding of the natural course of radiotherapy-induced vasculopathy by showing that this process takes several years to develop visual vascular wall changes on ultrasonography. As a consequence of the prospective study design, we assessed the beginning stage of these vessel wall changes and therefore found relative mild vessel wall thickening.

The results of the MRI study were in line with the results of the ultrasonography study and showed vessel wall thickening of the irradiated carotid arteries after 7 years.<sup>16</sup> Advantages of MRI above ultrasonography were the possibility to study a larger part of the carotid artery and to study the composition of plaques. Due to the relatively mild vascular thickening in the first years after radiotherapy, it was, however, more difficult to analyze plaques than in more advanced atherosclerosis. In future studies, the use of a dedicated neck coil and contrast-enhanced pictures can increase the distinctive character of the MRI to detect vessel wall changes.<sup>19</sup>

We hypothesized that radiotherapy-induced carotid artery changes could result in vascular white matter lesions of the brain with consequently cognitive deficits. We showed that head and neck cancer patients had cognitive deficits 7 years after radiotherapy, which were related to subjective complaints and fatigue and also to ischemic strokes on MRI.<sup>17</sup> In fact, these cognitive deficits were multifactorially influenced. It is not clear to what extent the ischemic strokes were a consequence of the relatively mild carotid artery wall thickening or probably more logically influenced by the co-occurrence of other vascular risk factors.

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# Clinical case discussion Multimodal Response Assessment in a Patient with Anaplastic Glioma: Tumor Or No Tumor?

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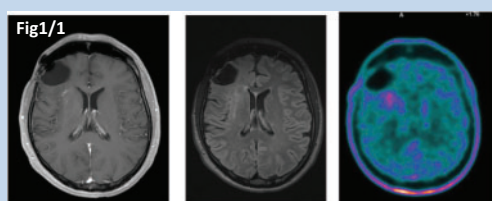
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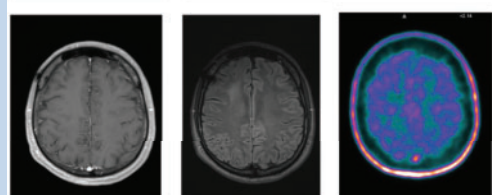
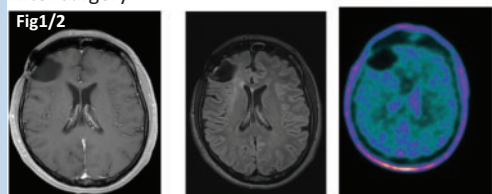
## Introduction

Follow-up in patients with glioma after surgery and concomitant radiochemotherapy according to the protocol of

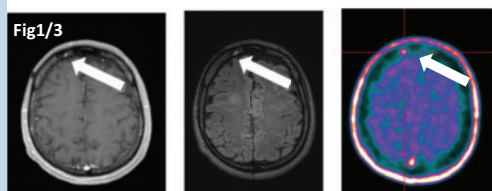
the European Organisation for Research and Treatment of Cancer (EORTC) (1) usually consists of brain MRI including contrast media, neurological evaluation, and Karnofsky (KPS) or Eastern Cooperative Oncology Group performance status, as well as assessment of quality of



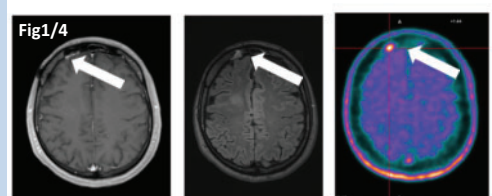
After surgery



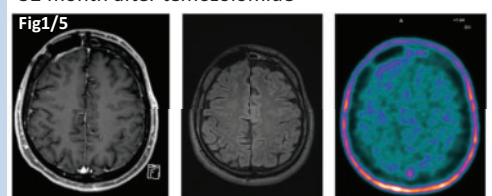
2 month after 6 adjuvant cycles of temozolomide



26 month after temozolomide



32 month after temozolomide



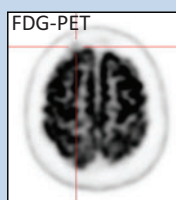
6 month post surgery; 41 month after temozolomide

Follow-up 1

Follow-up 2

Follow-up 3

Follow-up 4



**Figure 1.** MRI(Gd) – first row, MRI (FLAIR) – second row, FET-PET – third row, from follow-up 1 to follow-up 4.

Fig 1/1: tumor cavity after gross total resection; Fig 1/2: Imaging showing no signs of tumor activity; Fig 1/3: small right frontal contrast enhancing, T2 hyperintense and FET-PET hypermetabolic lesion; Fig 1/4: suspect lesion increasing in size on T2, contrast sequences as well as increased tracer uptake on FET-PET; Fig 1/5: Imaging after resection without residual abnormalities.



life issues. Some neuro-oncology centers also implement additional follow-up methods, such as cognitive testing and amino acid PET imaging.

Follow-up to assess tumor activity or effects of treatment is becoming even more complex using different therapies such as anti-angiogenic, immunological, or reirradiation techniques. The combination of multiple follow-up techniques works for the majority of glioma patients in an acceptable manner and contribute to an accurate disease assessment, which after all represents the basis for further treatment decisions.

However, despite comprehensive morphological, metabolic, and functional evaluation of tumor activity, some results may be puzzling and are indeed difficult to interpret.<sup>2-5</sup>

We report on a 44-year-old male patient with anaplastic glioma developing unclear imaging results during routine follow-up.

## Case history

In November 2012, a 44-year-old male patient underwent gross total resection for a right frontal anaplastic astrocytoma (**Figure 1**). Medical history so far was unremarkable. After surgery he received concomitant radiochemotherapy and 6 cycles of adjuvant temozolomide according to the EORTC protocol (1). At the end of 6 adjuvant temozolomide cycles, follow-up revealed stable disease according to the Response Assessment in Neuro-Oncology criteria (6) (**Figure 1/1**). Follow-up investigations, including neurological examination, KPS, cognitive testing MRI, and <sup>18</sup>F-fluoro-ethyl-tyrosine (FET)-PET imaging every 6

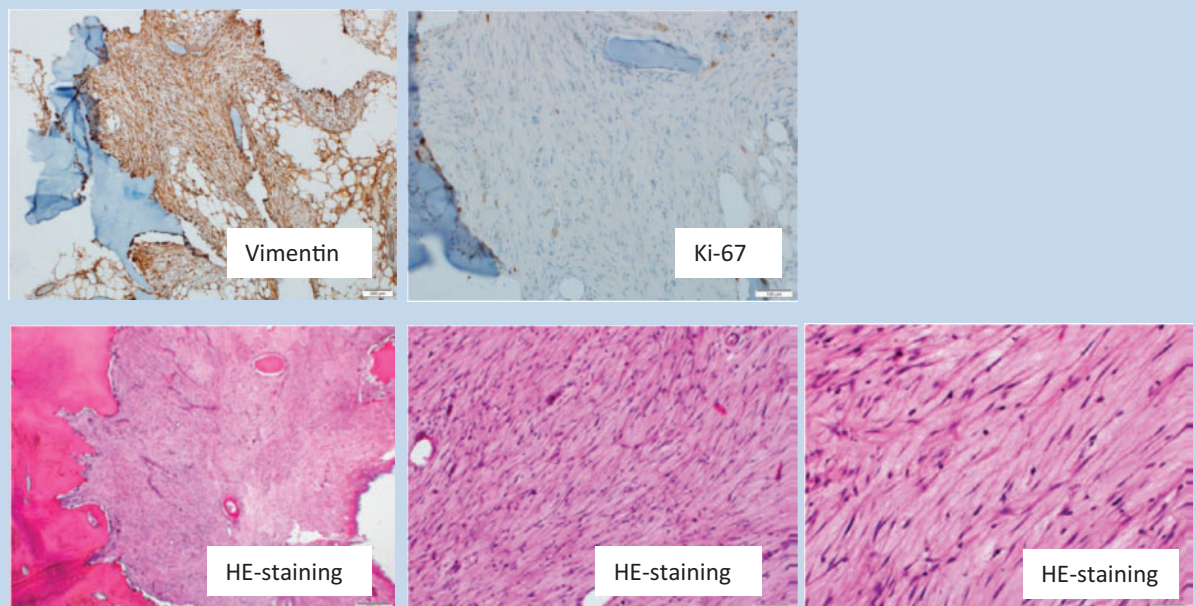
months, resulted in stable disease for almost another 3 years after glioma diagnosis.

In October 2015, twenty-six months after adjuvant temozolomide treatment, a new right frontal contrast-enhancing lesion was detected on MRI (**Figure 1/2**). Due to the unremarkable clinical and FET-PET results, a “wait and see” strategy was decided by an interdisciplinary neuro-oncological tumor board. Six months later, besides MRI, FET-PET showed now a corresponding new lesion in the right frontal area (standardized uptake value [SUV 10 min] 3.9 and SUV [60 min] 2.94) (**Figure 1/3**). In order to better characterize this unclear lesion and to possibly discriminate from inflammatory origin, an additional 2-fluoro-2-deoxy-D-glucose (FDG)-PET was performed. Results of the FDG-PET were unremarkable, which makes a possible inflammatory origin of the lesion unlikely (**Figure 1/4**). The patient had no seizures or any other clinical neurological signs or symptoms.

Considering the increasing contrast-enhancing lesion on MRI, as well as the increasing tracer uptake in FET-PET imaging over time, we suspected a malignant process and recommended a resection of the lesion.

Extensive histological examination exhibited reactive tissue most probably associated with late delayed radiation damage. No aspects of a malignant process were detected by means of histological and immunohistological examination (**Figure 2**).

At next follow-up, 6 months after the resection in January 2017, the area of the previous unclear lesion showed no contrast enhancement on MRI and no tracer uptake on FET-PET (**Figure 1/5**).



**Figure 2.** Histological examination without evidence of a malignant process.

## Discussion

Individual clinical courses and responses to treatment in patients with gliomas vary within histological grading and even within molecularly characterized subgroups. The new 2016 World Health Organization classification of central nervous system tumors summarizes only the tip of the iceberg with respect to the heterogeneity of gliomas.<sup>7–8</sup> Due to multiple possible pitfalls in clinical examination and follow-up imaging in glioma patients, such as pseudoprogression, pseudoresponse, edema, glioma-associated seizures, etc, multimodal assessment combining morphological, metabolic, and functional information can provide additional decisive information in some cases.<sup>9–11</sup> On the other hand, divergent results in multimodal testing can also lead to puzzling questions and may reflect the intratumor heterogeneity at the time of assessment as well as during the evolution of different tumor components in the course of the disease.<sup>2–5,10,12</sup>

This case illustrates late delayed imaging phenomena after radiochemotherapy, where discrimination toward tumor progression can be challenging. Clinical, MRI, and metabolic characteristics are demonstrated over time, which might support decision making in similar cases. Our report also highlights that even multimodal assessment is not always capable to entirely reflect the biology of the tumor and its associated phenomena. In these cases, a surgical approach can be recommended, although even tissue analysis may not always provide clear results.

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# Hotspots in Neuro-Oncology

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### **Patterns of response and relapse in primary CNS lymphomas after first-line chemotherapy: imaging analysis of the ANOCEF-GOELAMS prospective randomized trial**

*Tabouret E et al. Neuro Oncol. 2017;19(3):422–429.*

Data are scant on MRI characteristics in the assessment of primary CNS lymphoma (PCNSL) patients treated with standardized polychemotherapy in prospective trials.

The aim of the study by Tabouret et al was to review MRI characteristics of patients with PCNSL enrolled in a randomized phase II trial and to evaluate their potential prognostic value and patterns of relapse, including T2 fluid-attenuated inversion recovery (FLAIR) MRI abnormalities. Neuroimaging findings in 85 patients with PCNSL were reviewed blinded to outcomes. MRI characteristics and responses according to criteria of the International PCNSL Collaborative Group were correlated with progression-free survival (PFS) and overall survival (OS).

Multivariate analysis showed that objective response at 2 months ( $P < 0.001$ ) and at the end of treatment ( $P = 0.015$ ) were predictors of prolonged OS. Infratentorial location ( $P = 0.008$ ) and large ( $> 11.4 \text{ cm}^3$ ) enhancing tumor volume ( $P = 0.006$ ) were associated with poor OS and PFS, respectively. Ratio of change in product of largest diameters at early MRI evaluation but not timing of complete response achievement (early vs delayed) was prognostic for OS. Sixty-nine patients relapsed. Relapse in the brain ( $n = 52$ ) involved an initial enhancing site, a different site, or both in 46%, 40%, and 14% of patients, respectively. At baseline, non-enhancing T2-FLAIR hypersignal lesions distant from the enhancing tumor site were detected in 18 patients. These lesions markedly decreased ( $> 50\%$ ) in 16 patients after chemotherapy, supporting their neoplastic nature. Of these patients, 10/18 relapsed, half ( $n = 5$ ) in the initially non-enhancing T2-FLAIR lesions.

The findings of this study provide evidence that non-enhancing FLAIR abnormalities may add to overall tumor burden, suggesting that response criteria should be refined to incorporate evaluation of T2-weighted/FLAIR sequences.

### **Adult IDH wild-type lower-grade gliomas should be further stratified**

*Aibaidula A et al. Neuro Oncol. 2017;19(10):1327–1337.*

Astrocytoma of the isocitrate dehydrogenase (IDH) wild-type gene is described as a provisional entity within the new World Health Organization (WHO) classification. Some groups believe that IDH wild-type lower-grade gliomas, when interrogated for other biomarkers, will mostly turn out to be glioblastoma. The hypothesis of the study by Aibaidula et al was that not all IDH wild-type lower-grade gliomas have very poor outcome and the group could be substratified prognostically.

Seven hundred and eighteen adult WHO grades II and III patients with gliomas were re-reviewed and tested for

IDH1/2 mutations. One hundred and sixty-six patients with IDH wild-type cases were identified for further studies, and examined were epidermal growth factor receptor (EGFR) and myeloblastosis (MYB) amplifications and mutations of histone H3F3A, telomerase reverse transcriptase promoter (TERTp), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF). EGFR amplification and BRAF and H3F3A mutations were observed in 13.8%, 6.9%, and 9.5% of patients, respectively, in a mutually exclusive pattern in IDH wild-type lower-grade gliomas. TERTp mutations were detected in 26.8% of cases. Favorable outcome was observed in patients with young age, oligodendroglial phenotype, and grade II histology. Independent adverse prognostic values of older age, nontotal resection, grade III histology, EGFR amplification, and H3F3A mutation were confirmed by multivariable analysis. Tumors were further classified into “molecularly” high grade (harboring EGFR, H3F3A, or TERTp; median overall survival = 1.23 y) and lower grade (lacking all of the 3; median overall survival = 7.63 y) with independent prognostic relevance. The most favorable survival was noted in molecularly lower-grade gliomas with MYB amplification.

In conclusion, adult IDH wild-type lower-grade gliomas are prognostically heterogeneous and do not have uniformly poor prognosis. Clinical information and additional markers, including MYB, EGFR, TERTp, and H3F3A, should be examined to delineate discrete favorable and unfavorable prognostic groups.

### **Multicenter phase II study of temozolomide and myeloablative chemotherapy with autologous stem cell transplant for newly diagnosed anaplastic oligodendroglioma**

*Thomas AA et al. Neuro Oncol. 2017;19(10):1380–1390.*

Anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA) are chemotherapy-sensitive tumors with prolonged survival after radiochemotherapy. The study by Thomas et al reported a prospective trial in these tumors using induction temozolomide (TMZ) followed by myeloablative high-dose chemotherapy (HDC) with autologous stem-cell transplant (ASCT) as a potential strategy to defer radiotherapy.

Patients with AO/AOA received 6 cycles of TMZ ( $200 \text{ mg/m}^2 \times 5/28 \text{ day}$ ). Responding patients were eligible for HDC (thiotepa  $250 \text{ mg/m}^2/\text{day} \times 3 \text{ days}$ , then busulfan  $3.2 \text{ mg/kg/day} \times 3 \text{ days}$ ), followed by ASCT. Genomic characterization was performed using next-generation sequencing. Forty-one patients were enrolled, and 85% had 1p/19q codeleted tumors. After induction, 26 patients were eligible for HDC-ASCT and 21 agreed to proceed. There were no unexpected adverse events or toxic deaths. After median follow-up of 66 months, 2-year progression-free survival (PFS) for transplanted patients was 86%, 5-year PFS 60%, and no patient has died. Among all 1p/19q codeleted patients ( $N = 33$ ), 5-year



PFS was 50% and 5-year overall survival (OS) was 93%, with median time to radiotherapy not reached.

Next-generation sequencing disclosed typical oligodendroglioma-related mutations, including those of isocitrate dehydrogenase 1 (IDH1), TERT (telomerase reverse transcriptase), CIC (capicua transcriptional repressor), and FUBP1 (far upstream element-binding protein 1) in 1p/19q codeleted patients, and glioblastoma-like signatures in 1p/19q intact patients. Aside from IDH1, potentially oncogenic/actionable mutations were variable, depicting wide molecular heterogeneity within oligodendroglial tumors.

In conclusion, TMZ followed by HDC-ASCT can be safely administered to patients with newly diagnosed 1p/19q codeleted AO. This strategy was associated with promising PFS and OS, suggesting that a chemotherapy-based approach may delay the need for radiotherapy and radiation-related toxicities. Raw data for further genomic analyses and meta-analyses are publicly available at [http://cbioportal.org/study?id=odg\\_msk\\_2017](http://cbioportal.org/study?id=odg_msk_2017) (accessed January 6, 2017).

#### **Global incidence of malignant brain and other central nervous system tumors by histology, 2003–2007**

*Leece R et al. Neuro Oncol. 2017;19(11):1553–1564.*

Overall incidence of malignant brain and other CNS tumors varies significantly by country. The aim of this study was to estimate histology-specific incidence rates by global region and assess incidence variation by histology and age.

Using data from the Central Brain Tumor Registry of the United States and the International Agency for Research on Cancer's Cancer Incidence in Five Continents Vol. X (including over 300 cancer registries), Leece et al calculated the age-adjusted incidence rates (AAIRs) per 100 000 person-years and 95% CIs for brain and other CNS tumors overall and by age groups and histology.

There were significant differences in incidence by region. Overall incidence of malignant brain tumors per 100 000 person-years in the US was 5.74 (95% CI = 5.71–5.78). Incidences were lowest in Southeast Asia (AAIR = 2.55, 95% CI = 2.44–2.66), India (AAIR = 2.85, 95% CI = 2.78–2.93), and East Asia (AAIR = 3.07, 95% CI = 3.02–3.12). Incidences were highest in Northern Europe (AAIR = 6.59, 95% CI = 6.52–6.66) and Canada (AAIR = 6.53, 95% CI = 6.41–6.66). Astrocytic tumors showed the broadest variation in incidence regionally across the globe.

In conclusion, brain and other CNS tumors are a significant source of cancer-related morbidity and mortality worldwide. Regional differences in incidence may provide clues to genetic or environmental causes as well as a foundation for broadening knowledge of their epidemiology. Gaining a comprehensive understanding of the epidemiology of malignant brain tumors globally is critical to researchers, public health officials, disease interest

groups, and clinicians and contributes to collaborative efforts in future research.

#### **Outcome of patients with intracranial nongerminomatous germ cell tumors—lessons from the SIOP-CNS-GCT-96 trial**

*Calaminus G et al. Neuro Oncol. 2017;19(12):1661–1672.*

Following promising results to increase survival and reduce treatment burden in intracranial nongerminomatous germ cell tumors (NGGCTs), Calaminus et al conducted a European study using dose-intense chemotherapy followed by risk-adapted radiotherapy. All patients received 4 courses of cisplatin/etoposide/ifosfamide. Non-metastatic patients then received focal radiotherapy only (54 Gy); metastatic patients received 30 Gy craniospinal radiotherapy with 24 Gy boost to primary tumor and macroscopic metastatic sites. Patients with localized malignant NGGCT ( $n = 116$ ) demonstrated 5-year progression-free survival (PFS) and overall survival (OS) of  $0.72 \pm 0.04$  and  $0.82 \pm 0.04$ , respectively. Primary tumor sites were: 67 pineal, 35 suprasellar, 5 bifocal, 9 others. One patient died postsurgery in clinical remission; 3 patients progressed during treatment and 27 (23%) relapsed afterward. Fourteen were local, 6 combined, and 7 distant relapses (outside radiation field). Seventeen of the 27 relapsed patients died of disease. Patients with metastatic disease ( $n = 33$ ) demonstrated 5-year PFS and OS of  $0.68 \pm 0.09$  and  $0.75 \pm 0.08$ , respectively; 1 patient died following progression on treatment and 9 (27%) relapsed afterward (5 local, 1 combined, 3 distant). Only one metastatic patient with recurrence was salvaged. Multivariate analysis identified diagnostic alpha-fetoprotein level (serum and/or CSF level  $> 1000$  ng/mL, 19/149 patients, of whom 11 relapsed;  $P < 0.0003$ ) and residual disease following treatment, including after second-look surgery ( $n = 52/145$  evaluable patients, 26 relapsed;  $P = 0.0002$ ) as significant prognostic indicators in this cohort. In conclusion, in localized malignant NGGCT, craniospinal radiotherapy could be avoided without increased relapses outside the radiotherapy field. Chemotherapy and craniospinal radiotherapy remain the gold standard for metastatic disease.

#### **Brain volume reduction after whole-brain radiotherapy: quantification and prognostic relevance**

*Hoffmann C et al. Neuro Oncol. 2018;20(2):268–278.*

Recent studies have questioned the value of adding whole-brain radiotherapy (WBRT) to stereotactic radiosurgery (SRS) for brain metastasis treatment. Neurotoxicity, including radiation-induced brain volume reduction, could be one reason why not all patients benefit from the addition of WBRT.

In this study, Hoffmann et al quantified brain volume reduction after WBRT and assessed its prognostic significance. Brain volumes of 91 patients with cerebral metastases were measured during a 150-day period after commencing WBRT and were compared with their pre-treatment volumes. The average daily relative change in

brain volume of each patient, referred to as the “brain volume reduction rate,” was calculated. Univariate and multivariate Cox regression analyses were performed to assess the prognostic significance of the brain volume reduction rate, as well as of 3 treatment-related and 9 pretreatment factors. A one-way analysis of variance was used to compare the brain volume reduction rate across recursive partitioning analysis (RPA) classes.

On multivariate Cox regression analysis, the brain volume reduction rate was a significant predictor of overall

survival after WBRT ( $P < 0.001$ ), as well as the number of brain metastases ( $P = 0.002$ ) and age ( $P = 0.008$ ).

Patients with a relatively favorable prognosis (RPA classes 1 and 2) experienced significantly less brain volume decrease after WBRT than patients with a poor prognosis (RPA class 3) ( $P = 0.001$ ). There was no significant correlation between delivered radiation dose and brain volume reduction rate ( $P = 0.147$ ).

This retrospective study demonstrates that smaller decrease in brain volume after WBRT is an independent predictor of longer overall survival.

# Hotspots in Neuro-Oncology Practice 2017/ 2018

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**(1) Taylor JW et al. Clinical trial endpoints for patients with gliomas. *Neuro Oncology Practice* 2017;4 (4): 201–208**

Studies are the basis of research and treatment in neuro-oncology. The paper by Taylor et al focuses on other endpoints of studies than the commonly used overall survival (OS), progression-free survival, and radiographic endpoints in regard to the Response Assessment in Neuro-Oncology (RANO) and immunotherapy RANO (iRANO) criteria, quality of life, neurocognitive function, molecularly informed trials, and a new development: adaptive design studies. These adaptive design studies, as bucket and basket studies, will be aimed at common molecular features of tumors, rather than specific tumor entities. As gliomas are of marked heterogeneity, they can no longer be considered as a single disease entity, and choices will need to be made on patient genomic signatures.

It is hoped that the increase of emerging endpoints and new study designs will be useful to identify effective treatments for patients with glioma. While OS will remain as a gold standard, alternative endpoints need to be explored. This paper is a helpful resource as an update for the current development of trials.

**(2) Lukas RV et al. Pivotal therapeutic trials for infiltrating gliomas and how they affect clinical practice. *Neuro Oncology Practice* 2017;4(4): 209–219**

Lukas et al identify the key therapeutic trials for GBM, providing the present treatment paradigm of GBM patients. The development of drugs and combination therapies are described, and a very useful table helps to follow and understand the development of brain tumor treatment in the developmental context from 1992 onward.

Temozolomide (TMZ) has been the dominating drug since this time, but also older drugs such as procarbazine, the PCV scheme, and BCNU and CCNU reappear.

There is a useful Table 2 on side effects in TMZ, but it should also contain the toxicity of the older drugs.

More recent treatment options, such as bevacizumab, locally administered therapies (BCNU wafers), and tumor treating fields, are described and discussed. Also discussed, in addition to GBM, are treatments for anaplastic gliomas and high-risk low-grade gliomas.

This understanding of pivotal trials is important for the standard of care of glioma patients and is equally important for the clinician and researcher, providing a quickly accessible information.

**(3) Wasilweski A et al. Acute care in glioblastoma: the burden and the consequences. *Neuro Oncology Practice* 2017;4(4): 248–254**

In addition to the selection of the proper treatment and/or inclusion in adequate studies, patients with GBM experience several “acute” events, which need either outpatient attention or hospitalization. In a group of 158 GBM patients, acute care visits were necessary in 71% of

patients, and a large number of them also needed multiple visits.

The reasons were seizures, neurosurgical procedures, infections, focal neurological symptoms, and venous thromboembolism, among others, which are displayed graphically. It is important to see that also medical issues, orthopedic problems, and falls contribute to acute situations.

The authors were able to show that most visits took place in the first year following diagnosis, and were also able to demonstrate a correlation between acute hospital visits and survival. The times are demonstrated by a graphic display of cumulative frequency of acute care visits. The need for repeated “acute care” has a negative influence on survival. It is also alarming that 20% of this “acute care visit” group spent more than 10% of their remaining survival in acute care settings.

Earlier implementation of palliative care and hospice settings may be warranted.

**(4) Leeper HE et al. Survivorship care planning in neuro-oncology. *Neuro Oncology Practice* 2018;5(1): 1–10**

Due to improved therapies and longer survival, survivorship planning is becoming important, and is a topic linked to burden of disease and quality of life. It is also part of the transition from active treatment toward a posttreatment phase, which encompasses several issues.

The authors identify several treatment gaps in respect to knowledge in collaboration with patients and caregivers and in regard to their points of views and needs and with concerned institutions locally as well as those at larger distances.

Cultural preferences and particularities and need have to be implemented to provide patient-centered care. Furthermore there is a strong element of self-empowerment and self-advocacy to have a comprehensive overview of one’s medical care, with emphasis on including a basic plan to move forward from the active treatment phase.

Specific care plans have been created for breast, lung, prostate, and colon cancers, as well as for lymphoma, and these need also be developed and implemented for neuro-oncologic patients.

The improvement of therapies and increased survival times, as this is now commonly observed in several other oncologic disease entities, will need a focus on survivorship.

**(5) Vera E et al. Relationship between symptom burden and health status: analysis of the MDASI-BT and EQ-5D. *Neuro Oncology Practice* 2018;5(1)**

The authors describe the disease trajectory of glioma patients, using the EQ-5D health status. In addition, the MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT) is used measure symptom burden and interference.

Results : The sample included 100 patients (65% male, 78% with a glioblastoma, median age 52 [range, 20–75], 56% in active treatment). Seventy-two percent of patients reported functional limitations in at least one area. Extreme cases reported inability to perform usual



activities (8%), and significant anxiety/depression (5%) was apparent. The MDASI-BT neurologic factor and activity-related interference (walking/activity/work) explained 52% of the variability in the EQ-5D in this patient population while adjusting for the effect of tumor grade, recurrence status, and performance status.

Because of the demonstrated impact of symptom burden and the interference of symptoms on functional and survival outcomes, this project was undertaken to evaluate the relationship between patient-reported health status using the EQ-5D, and symptom severity and interference using the MDASI-BT in the primary brain tumor patient population.

The authors conclude that the majority of glioma patients reported at least one functional limitation on the EQ-5D. Over half of the variance in the EQ-5D was explained by the MDASI-BT, performance status, tumor grade, and recurrence status. The resultant model demonstrates the significant contribution of symptom burden on health status in glioma patients.

**(6) Kurian KM et al. Brain tumor research in the United Kingdom: current perspective and future challenges. A strategy document from the NCRI Brain Tumor CSG. Neuro Oncology Practice 2018;5(1)**

This is a very good template for future national research in brain tumors and metastases. National databases not only have the advantage of being able to overview large patient groups and material, but also have a useful effect on the formation of national cooperations and strategies.

The National Cancer Research Institute (NCRI) is a partnership of charity and government research funders whose purpose is to improve health and quality of life by accelerating progress in cancer-related research through collaboration.

Under this umbrella, the NCRI Brain Tumor Clinical Studies Group is focused on improving clinical outcomes for adult patients with brain and central nervous system tumors, including those with brain metastases from other primary sites. This document discusses the current state of clinical brain tumor research in the United Kingdom, the stakeholders, the burden of disease, and the challenges to increasing study and trial opportunities for patients.

The clinical research priorities are defined along with a strategy to strengthen the existing brain tumor research network, improve access to tissue and imaging, and develop the future leadership for brain tumor research in the United Kingdom.

A future strategy is developed and elements are defined as strengthening the existing tumor network and the brain tumor bio bank, and developing capacity as well as persons and infrastructure.

**(7) Prayongrat A et al. Outcomes of stereotactic radiosurgery of brain metastases from neuroendocrine tumors. Neuro Oncology Practice 2018;5(1)**

Stereotactic radiosurgery (SRS) is an established treatment for brain metastases, yet little is known about SRS for neuroendocrine tumors given their unique natural history.

The study was carried out to determine outcomes and toxicity from SRS in patients with brain metastases from neuroendocrine tumors. Thirty-three patients with brain metastases from neuroendocrine tumors who underwent SRS were retrospectively reviewed. The median age was 61 years and median Karnofsky performance status was 80.

The primary tumor sites were lung (87.9%), cervix (6.1%), esophagus (3%), and prostate (3%). Ten patients (30.3%) received an upfront SRS.

Kaplan–Meier survival and Cox regression analyses were performed to determine prognostic factors for survival.

Results: with median follow-up after SRS of 5.3 months, local and distant brain recurrence developed in 5 patients (16.7%) and 20 patients (66.7%), respectively. Median overall survival (OS) after SRS was 6.9 months. Patients with progressive disease per Response Assessment in Neuro-Oncology–Brain Metastases criteria at 4 to 6 weeks after SRS had shorter median time to developing recurrence at a distant site in the brain and shorter OS than patients without progressive disease: 1.4 months and 3.3 months versus 11.4 months and 12 months, respectively (both  $P < 0.001$ ).

Toxicity was more likely in lesions of small cell histology than in lesions of other neuroendocrine tumor histology, 15.7% versus 3.3% ( $P = 0.021$ ). No cases of grades 3 to 5 necrosis were noted.

Conclusions: SRS is an effective treatment option for patients with brain metastases from neuroendocrine tumors with local control despite slightly higher toxicity rates than expected. Progressive disease at 4 to 6 weeks after SRS indicates a poor prognosis.

**(8) Youland RS et al. Modern reirradiation for recurrent gliomas can safely delay tumor progression. Neuro Oncology Practice 2018;5(1)**

Despite advances in modern diagnostics and therapeutics, gliomas continue to confer a poor prognosis. In modern trials of high-grade gliomas, progression-free survival (PFS) remains short at approximately 7 months, with nearly all patients eventually experiencing tumor progression by 36 months.

While the prognosis of low-grade glioma tends to be significantly better than that of high-grade glioma, at least half of patients with low-grade glioma finally convert into a high-grade glioma. Thus, salvage therapies are commonly used in the majority of glioma patients. The anti-angiogenic agent bevacizumab is the most commonly used salvage chemotherapeutic option used in the treatment of recurrent glioma. In a study by Kreisl et al,<sup>4</sup> 48 patients with recurrent glioblastoma were treated with bevacizumab every 2 weeks until tumor progression, when they were transitioned to bevacizumab with irinotecan. A radiographic response was achieved in 71%, and 6-month PFS was 29%, with a median overall survival (OS) of 31 weeks.

Another study randomized 167 patients to receive bevacizumab alone or in combination with irinotecan after

tumor progression, which reported similar response rates in both arms (28% and 39%) and no significant difference in PFS or OS.

The conclusion is that reirradiation for recurrent glioma is feasible and outcomes compare favorably with salvage chemotherapy after progression on bevacizumab. Toxicity appears to be minimal,

particularly in patients receiving concurrent bevacizumab and those with limited recurrence volumes treated with hypofractionated, stereotactic radiation. Further research is needed to prospectively evaluate the impact of reirradiation on tumor progression and quality of life.

\*J Clin Oncol. 2009;27(5):740–745.