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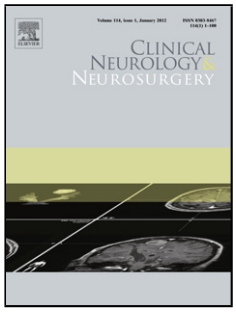

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Update on Glioma Biotechnology

Madeline Abrams, BS[a], Noah Reichman, BS[a], Deepak Khatri, MD[a], Nitesh V. Patel, MD[a], Randy S. D'Amico, MD[a], Tamika Wong, MPH[a], Sherese Fralin, MSN FNP-BC[a], Mona Li, BA[a], Marc Symons, PhD[b], David Langer, MD[a], Christopher G. Filippi, MD[c], John A. Boockvar, MD[a]

[a]Department of Neurosurgery, Lenox Hill Hospital, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New York, NY, USA
[b]The Feinstein Institute for Medical Research, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY, USA
[c]Department of Radiology, Lenox Hill Hospital, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New York, NY, USA

Corresponding Author:

Madeline Abrams, BS

Department of

Neurosurgery Lenox Hill

Hospital

Zucker School of Medicine at Hofstra/Northwell

New York, NY

mabrams3@pride.hofstra.edu

HIGHLIGHTS:

- The future of brain tumor treatment necessitates development of innovative approaches
- Areas of progress include immunotherapy, precision medicine and other novel technologies
- Collaboration between cancer specialists, biotechnology industry leaders and investors is key

ABSTRACT

Neuro-oncological research is at the forefront of the rising cancer therapy market, as evidenced by its growing revenue and the multitude of clinical trials investigating innovative treatment approaches. The Feinstein Institute for Medical Research, in conjunction with the Department of Neurosurgery at Lenox Hill Hospital and the Zucker School of Medicine at Hofstra / Northwell, sponsored The Brain Tumor Biotech Summit in New York City in June 2019. The aim of the Summit was to provide a forum that encourages collaboration between cancer specialists, biotechnology and pharmaceutical industry leaders, and the investment community in order to promote innovation and advance emerging therapies for brain tumors. Areas highlighted during the Summit included immunotherapy, precision medicine, and novel applications and experimental treatments such as receptor targeting, methods for improved drug delivery, and innovative intraoperative techniques and technologies. This review synthesizes the recent breakthroughs in brain tumor research as presented at The Brain Tumor Biotech Summit.

Keywords: Glioma; Brain Tumor; Glioblastoma; Biotechnology; Industry

1. INTRODUCTION

Nearly 50 years of research and 1500 clinical trials later, the prognosis of malignant brain tumors remains dismal. Glioblastoma multiforme (GBM), accounting for a majority of malignant brain tumors, carries a poor prognosis despite best treatment practices. Previous research has been hindered at the national level by budget cuts; by 2016, the National Cancer Institute (NCI) suffered budget losses of nearly 25% since 2003 [1]. Although recent NCI budgets show a slight increase, great necessity remains for funding [2]. Therefore, financial support from the private sector, including biotechnology and pharmaceutical companies, angel investors, and philanthropic and nonprofit contributors, is crucial.

The Brain Tumor Biotech Summit, hosted bi-annually in New York City, was established to provide a forum encouraging collaboration among neuro-oncology, biotechnology and financial industry experts. These parties attend the Summit to discuss the state of brain tumor research and areas of advancement [3-5]. The following report discusses progress in brain tumor biotechnology, highlighting innovative advances in the treatment of malignant brain tumors. While some technologies discussed in the report have been previously presented in the literature, here we emphasize new information regarding their use, including updated results and new and ongoing trials [3-5]. The report follows and expands on the agenda presented at the Brain Tumor Biotech Summit in June 2019, and the topics covered in this report reflect the various presentations at the Summit. Research and publications referenced by the Summit presenters formed the basis for this review. Supplementary articles providing further background and support for each technology were identified using PubMed searches with keywords relevant to each topic. This report contains up to date information through mid-2020. All information presented is publicly available and listed in the references. Table 1 summarizes the current status of clinical trials in the areas of malignant glioma research discussed herein.

2. STANDARD OF CARE

Current standard management of GBM adheres to Stupp protocol: maximal safe resection and adjuvant radiation with concurrent chemotherapy using temozolomide (TMZ) [6]. Despite this protocol, GBM typically proves to be relatively refractory and development of innovative treatment modalities is critical.

3. IMMUNOTHERAPY

3.1 Anti-PD-1 Monoclonal Antibody

Although immunotherapy is considered a practical treatment target for GBM, it has shown relatively little success [7]. CheckMate 143 (NCT02017717), sponsored by Bristol-Myers Squibb (New York, NY), evaluated Nivolumab, a human IgG4 monoclonal antibody inhibitor of the programmed death receptor-1 (PD-1) [8]. PD-1 is a cell-surface receptor expressed on T cells and,

upon binding to its ligands (PD-L1/PD-L2), diminishes receptor signaling, suppressing T cell activity [9]. The CheckMate 143 phase III study failed to demonstrate improved median overall survival (OS) in recurrent GBM patients treated with Nivolumab (9.8 months) compared with Bevacizumab (10 months) [8]. Nevertheless, the future of immunotherapy with PD-1 inhibitors for GBM holds potential, and a recent small randomized clinical trial demonstrated that neoadjuvant immunotherapy with Pembrolizumab, an anti-PD-1 monoclonal antibody, amplifies antitumor immune responses and promotes survival [10].

Further research has aimed to integrate anti-PD-1 monoclonal antibody inhibitors into combination immunotherapy. One study evaluated different combinations of agents, including an anti-PD-1 monoclonal antibody, agonist anti-OX40 monoclonal antibody and GVAX [11]. GVAX is a vaccination technique involving irradiated autologous tumor cells modified to express granulocyte-macrophage colony stimulating factor (GM-CSF). GVAX has been shown to amplify antitumor immunity and survival in mouse models [12]. A phase I human clinical trial evaluated a GVAX-like vaccine with irradiated autologous tumor cells mixed with GM-K562 cells. This vaccination was well tolerated in patients with malignant glioma and conferred antitumor immunity [13]. GVAX, in combination with an agonist anti-OX40 monoclonal antibody, has demonstrated improved OS in mouse models [14]. OX40 is a tumor necrosis factor (TNF) receptor expressed on T cells. Binding to OX40 results in upregulation of T cell activity, potentially enhancing antitumor immunity [15]. Triple combination therapy with all three agents – anti-PD-1 antibody, agonist anti-OX40 antibody and GVAX – is associated with increased antitumor immunity and survival compared to any agent alone [11].

In 2017, Regeneron (Eastview, NY) and Inovio (Plymouth Meeting, PA) announced a Phase I/II study, GBM-001 (NCT03491683), for newly diagnosed GBM. The GBM-001 study aims to evaluate Cemiplimab (LIBTAYO), a PD-1 inhibitor, in conjunction with INO-5401, a T cell activating agent encoding for over-expressed GBM antigens, and INO-9012, an immune activator coding for T cell stimulating factor IL-12 [16]. Preliminary findings demonstrated a 6-month progression-free interval (PFS) in 80% and 75% of patients with and without MGMT methylation, respectively [17].

3.2 Dendritic Cell-Based Vaccine

Northwest Biotherapeutics (Bethesda, MD) is a biotechnology credited for developing the DCVax-L technology, a dendritic cell-based vaccine platform used in surgically resectable tumors. Dendritic cells play an important role as antigen-presenting cells in immunotherapy [18]. DCVax-L is produced by preparing autologous dendritic cells with tumor lysate. The final product is administered as a vaccine [19]. The phase I/II clinical trials enrolled newly diagnosed and recurrent GBM patients who received three biweekly intradermal vaccinations. The study demonstrated that newly diagnosed patients who received DCVax in addition to standard of care experienced significantly longer median PFS and OS, 2 years and 3 years, respectively, than historical controls [20]. A randomized, placebo-controlled, double-blinded, phase III trial is ongoing (NCT00045968). At the time of interim analysis, nearly 90% of enrolled patients had received DCVax-L, with the overall patient population demonstrating a median OS of 23.1 months from surgical resection [19].

3.3 Retroviral Replicating Vectors

Tocagen (San Diego, CA) has developed Toca 511, a novel retroviral replicating vector (RRV) which selectively infects rapidly dividing malignant cells and subsequently undergoes replication [21]. Toca 511 encodes yeast-derived cytosine deaminase (CD), which converts the prodrug 5-fluorocytosine (5-FC) into 5-fluorouracil (5-FU). Administration of Toca 511 with oral Toca FC, a formulation of 5-FC, leads to preferential tumor cell infection, resulting in accumulation of 5-FU formed from conversion of Toca FC [21]. Toca 511 and Toca FC kill infected tumor cells via cytotoxic effects of 5-FU, and as 5-FU can traverse cell membranes, it may also induce cell death in neighboring, non-infected malignant cells [21, 22]. Additionally, 5-FU induces antitumor immunity and diminishes levels of immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs), with a consequent increase in local T cell populations [22, 23]. Three phase I clinical trials were initiated to evaluate Toca 511 in recurrent high-grade gliomas. Each trial utilized a different approach for Toca 511 delivery: injection into the resection cavity (NCT01470794), direct intratumoral injection (NCT01156584), and intravenous injection (NCT01985256). The resection cavity study enrolled 56 patients, of

whom 23 were deemed a "phase III eligible subgroup". From this subgroup, 5/23 patients demonstrated complete response with OS between 33.9 and 52.2 months after Toca 511 administration. Interestingly, median OS for this phase III eligible subgroup was 14.4 months [24]. A multicenter, randomized open-label phase II/III trial, the Toca 5 Trial (NCT02414165), comparing Toca 511 and Toca FC against standard of care for recurrent high-grade glioma recently terminated. Analysis demonstrated no significant difference in OS between the treatment group (11.07 months) and those receiving standard of care (12.22 months) [25].

4. PRECISION MEDICINE

4.1 Diagnostic Subtyping Technology and Treatment

ISOMA Diagnostics (Philadelphia, PA), a biotechnology company spun out of the Wistar Institute, is devising diagnostic technology to stratify GBM into subtypes. An existing gene-based system divides GBM into four subcategories: proneural, neural, classical, and mesenchymal [26]. Further research at Wistar Institute aimed to classify GBM into these subtypes not based on gene expression, but at the level of transcript variants, or isoforms [27]. Researchers developed a novel isoform-based stratification system that classifies GBM into the four known molecular subtypes at the transcript level. This model demonstrates increased accuracy and prognostic value, validated by translating the model to a reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) based assay, displaying 92% predictive accuracy [27]. This system may have important implications for personalized treatment and has been licensed to ISOMA Diagnostics.

ISOMA recently acquired Rindopepimut, a previously studied immunotherapeutic agent targeting a mutant receptor tyrosine kinase, EGFRvIII, implicated in 20-30% of GBM cases [28]. Rindopepimut is an injectable EGFRvIII-specific peptide conjugated to an immunogenic protein, keyhole limpet hemocyanin (KLH) [29]. Following several phase II clinical trials that suggested Rindopepimut imparts benefit in both PFS and OS, a phase III clinical trial (NCT01480479) was conducted to assess survival benefit using Rindopepimut in conjunction with standard chemotherapy in patients with newly diagnosed EGFRvIII-expressing GBM [29]. However, the

trial was terminated after interim analysis deemed the treatment futile with no significant difference in median OS between the treatment group (20.1 months) and control group (20.0 months) [29].

4.2 Precision Oncology Platform

Through the use of artificial intelligence (AI) and collaboration, xCures (Los Altos, California) operates a trial that acquires real-world evidence (RWE) to constantly learn from its patients and their medical care. The network integrates treatment suggestions across its patients and hospitals to determine the most effective therapies [30]. As expense of clinical trials can differ depending on various factors, some estimates cite the total cost as up to $600 million to implement and manage a large multicenter trial to completion [31]. With this in mind, xCures aims to reduce the financial burden of clinical trials while strengthening the bridges between scientific research and clinical application.

Unlike traditional trials, xCures has no inclusion or exclusion criteria or randomized control groups, and takes a year on average to complete. The platform offers virtual tumor boards and is beneficial to companies and physicians, supplying businesses with global data to expedite approvals and reimbursements, and providing doctors with administrative support.

xCures recently collaborated with the drug development company Oncoceutics to address the unmet needs of pediatric patients with high-grade gliomas, including diffuse intrinsic pontine glioma (DIPG). The anatomic location of these tumors coupled with prior failed trials highlights the need to establish new therapeutics. In 2019 this partnership carried out an Expanded Access program for ONC201 in H3 K27M-mutant gliomas to provide patients with immediate access to promising drugs and generate real-world data for pharmaceutical companies [32].

4.3 Investigational Medical Devices

EMulate Therapeutics (Seattle, WA), formerly Nativis, has focused on developing its proprietary investigational medical device, the EMulate Therapeutics Voyager ulRFE System, for treatment

of GBM. This device consists of a headpiece containing an electromagnetic coil for targeted ultra-low radio frequency energy (ulRFE) [33]. RFE cognates have been shown to mimic the action and effect of molecules in vitro and in vivo [34, 35]. A preclinical study demonstrated that RFE derived from the magnetic field measurements of paclitaxel, a chemotherapeutic agent, resulted in a molecular outcome reflective of the mechanism of action of paclitaxel itself [34]. A second study utilized an RFE cognate derived from an siRNA molecule for the epidermal growth factor receptor (EGFR) gene and delivered it to a human derived GBM cell line, U-87 MG with an overall decrease (30-70%) in EGFR mRNA production [35].

5. NOVEL APPLICATIONS AND EXPERIMENTAL TREATMENTS

5.1 Blood Brain Barrier (BBB) Disruption with Intra-Arterial Drug Delivery

Cancer stem cells (CSC) may persist within the tumor perivascular niche despite gross total resection and adjuvant treatment, expressing high levels of vascular endothelial growth factor (VEGF) and promoting angiogenesis and proliferation [36]. Bevacizumab, an anti-angiogenic agent, disrupts the CSC micro-environment killing persister cells in a dose-dependent manner [37].

Several methods of BBB disruption to facilitate drug delivery have been utilized, including superselective intra-arterial cerebral infusion (SIACI) of mannitol for transient BBB disruption followed by bevacizumab [Fig. 2] Opening the BBB selectively in the tumor region before drug delivery has been proven safe, feasible and more effective than intravenous bevacizumab [38]. Use of SIACI with bevacizumab in our ongoing phase I/II trials show promising results (NCT01811498; NCT01269853). Recently EnterTroy Bio (New York, NY), a spinoff from the Feinstein Institute/Northwell Health, began developing a novel BBB permeability kit for SIACI of bevacizumab. [Fig. 2]

5.2 Nanotechnology for Improved Drug Delivery

Lauren Sciences LLC (New York, NY) developed V-Smart® Nanomedicines to treat central nervous system diseases. They designed a non-invasive method to encase and deliver agents across

the BBB. This platform offers unique benefits including high encapsulation for a multitude of agents, oral and parenteral options, regulated release, and no loss of agent fidelity [39].

In February 2017, Lauren Sciences was awarded a grant to finance the continued development of LAUR-401, customized for irinotecan (CPT-11), a chemotherapeutic agent, for targeted release in-vitro. Studies suggest that CPT-11 is the most potent chemotherapeutic as a single agent on patient-derived cells implanted in-vitro [40]. There is also evidence that CPT-11 is capable of synergizing with TMZ against GBM [41]. Though CPT-11 has been studied in clinical trials with TMZ with minimal efficacy, this was likely because of inadequate brain penetration of CPT-11 [42]. LAUR-401 is also capable of transporting CPT-11 to GBM cells with low toxicity due to its high release rate of CPT-11, and because the CPT-11 metabolite (SN38) is synthesized solely in GBM cells [39].

5.3 EGFR Targeting

EnGeneIC (Lane Cove West, Australia) is a biopharmaceutical company focused on advancing its proprietary EnGeneIC Dream Vector (EDV) that facilitates targeted drug delivery. EDV technology uses bacterially-derived antibody-coated nanocells packaged with chemotherapeutic agents or gene-silencing molecules (e.g. siRNA) [43]. A human phase I study was conducted utilizing EDV technology to deliver Doxorubicin to adults with EGFR-positive recurrent GBM, and established a safe maximum tolerated dose at $5x10^9$ [44]. A follow-up open-label Phase I clinical trial was approved in 2016 and is still ongoing (NCT02766699). Current advancements are using a second-generation EDV containing a cytotoxic nemorubicin derivative (D682) or an immune adjuvant to further stimulate an immune response (ACTRN12619000385145).

5.4 Dopamine Receptor Targeting

Oncoceutics (Philadelphia, PA) is credited for generating ONC201, an oral BBB-penetrable dopamine receptor D2 (DRD2) antagonist [45]. Antagonism by ONC201 induces apoptosis through several mechanisms, including cell signaling disruption and transcription factor-mediated upregulation of pro-apoptotic factors [46]. Studies have demonstrated DRD2 expression in GBM

[47]. ONC201 previously demonstrated safety and tolerability in human subjects [48]. Oncoceutics sponsored a phase II clinical trial (NCT02525692) evaluating the use of oral ONC201 for recurrent GBM. PFS at 6 months was 11.8%, and OS at 6 and 9 months was 71% and 53%, respectively [49].

ONC201 has been studied in H3 K27M-mutant gliomas, which exhibit dopamine receptor dysregulation and commonly overexpress DRD2 [50]. Preliminary reporting from a phase II, open-label trial in adults with H3 K27M-mutant glioma (NCT03295396; NCT02525692) demonstrated 3/29 partial responses, 1/29 complete regression at >14 months, and 10/29 patients with stable disease [51]. A phase I, open-label clinical trial (NCT03416530) of ONC201 in pediatric H3 K27M-mutant gliomas is ongoing.

5.5 Enhanced Brain Tumor Visualization using 5-Aminolevulinic Acid

NX Development Corporation (Lexington, KY) recently launched Gleolan, an optical imaging agent of 5-aminolevulinic acid hydrochloride (ALA HCl). 5-aminolevulinic acid (5-ALA) is an endogenous substance which generates protoporphyrin IX through the heme biosynthetic pathway [52] [Fig. 3] Intracellular accumulation of protoporphyrin IX occurs preferentially in neoplastic tissues and when exposed to violet-blue light, emits red fluorescence [53]. This technique has consistently displayed high diagnostic accuracy in identifying tumor tissue, ultimately leading to FDA approval in 2017 [54]. By applying violet-blue light, tumor margins and residual tissue may be more easily discerned, enabling more complete resections [55]. In one phase III trial, patients who underwent 5-ALA fluorescence-guided surgery experienced a higher 6-month PFS rate of 41% compared to 21.1% in the control group who underwent conventional resection [55].

5.6 Imaging Frontiers in Neuroradiology

Deep-learning convolutional neural networks (CNN), an emerging technology of artificial intelligence (AI), have made progress in image recognition and classification in diagnostic radiology [56]. Traditionally, physicians determine the underlying genetic and molecular

mutations of gliomas by analyzing tumor tissue collected by biopsy. However, this technique carries risks, including excessive bleeding [57]. Though tissue analysis is the criterion standard, deep-learning CNNs may provide a less invasive means for classifying mutation status and offer additional insight into how these genetic mutations drive tumor biology and treatment response. Researchers involved in one study developed a machine algorithm to predict molecular mutation status in gliomas [58]. This CNN system was trained to classify glioma mutation status by automatically learning and analyzing specific patterns of gliomas on magnetic resonance imaging (MRI), identifying the most predictive imaging characteristics that correlate with specific genetic mutations in order to predict mutation status. The CNN classification performed well, accurately identifying IDH1 mutation status (94%), 1p/19q codeletion (92%), and MGMT promoter methylation status (83%) through analysis of imaging features of gliomas in patients with previously available molecular genetic information [58]. Researchers were also able to extract those specific imaging features which the CNN algorithm had identified as most predictive for each molecular genetic classification. Imaging characteristics that correlated with the IDH1 wild-type status included irregular tumor enhancement, while IDH1 mutant status typically demonstrated absent or minimal enhancement. Similar unique features were identified for 1p/19q codeletion and MGMT promoter methylation status as well [58].

5.7 New Developments in Intraoperative Radiotherapy

Although methods such as fluorescence-guided resection may boost visible GBM resection rates, there is currently no technique targeting the microscopic tumor cells surrounding the tumor cavity. Intraoperative radiotherapy (IORT) may offer a solution, delivering low energy x-rays directly to the tumor bed, with minimal radiation exposure to adjacent healthy tissue [59].

Carl Zeiss Meditec AG (Jena, Germany) is a technology company developing therapeutic technologies including IORT. INTRAGO I, a phase I/II, single-arm 3+3 dose escalation study (NCT02104882), assessed the safety and tolerability of IORT combined with standard therapy in newly diagnosed GBM patients [60]. PFS was divided into local PFS (L-PFS) and distant (D-PFS; less than 1 cm to the cavity). The IORT doses ranged from 20 Gy to 40 Gy. There were 0 dose-limiting toxicities within the first 3 months post-surgery, 21 Grade 2 events, 27 Grade 3 events, 2

grade 4 events, and 1 grade 5 event. The median follow-up was 13.8 months with median OS of 16.2 months and PFS of 11.2 months for all patients [60]. Zeiss has initiated a follow-up phase III study, INTRAGO-II, (NCT02685605), that is ongoing.

5.8 Tumor Treating Fields

Novocure (Jersey), an international oncology company, launched Optune® in 2011. This portable, noninvasive machine contains transducer arrays which apply tumor treating fields (TTFields) to the brain when placed on the scalp. TTFields are low-intensity, intermediate-frequency alternating electric fields that halt GBM cell proliferation and kill resulting tumor cells. The fields disrupt microtubule spindle formation during mitosis, delaying cell division and inducing apoptosis [61]. An interim analysis from a randomized phase III clinical trial to compare maintenance TMZ with maintenance TMZ plus TTField in 315 patients showed significantly increased PFS and OS [62].

6. FUTURE DIRECTIONS

The Brain Tumor Biotech Summit is an interactive hub, bringing together physicians, scientists, biotechnology companies, small and large pharma, foundations, patients and investors to develop novel treatments for malignant brain tumors. This review highlights potential new tools and technologies to improve treatment of these tumors. Collaboration between the aforementioned groups is integral to improving the future of neuro-oncology by securing funds and enhancing the current paradigm for treating brain tumors.

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Conflicts of Interest: None

Disclosures: None

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Fig. 1 Therapeutic Drug Targets in the Treatment of GBM

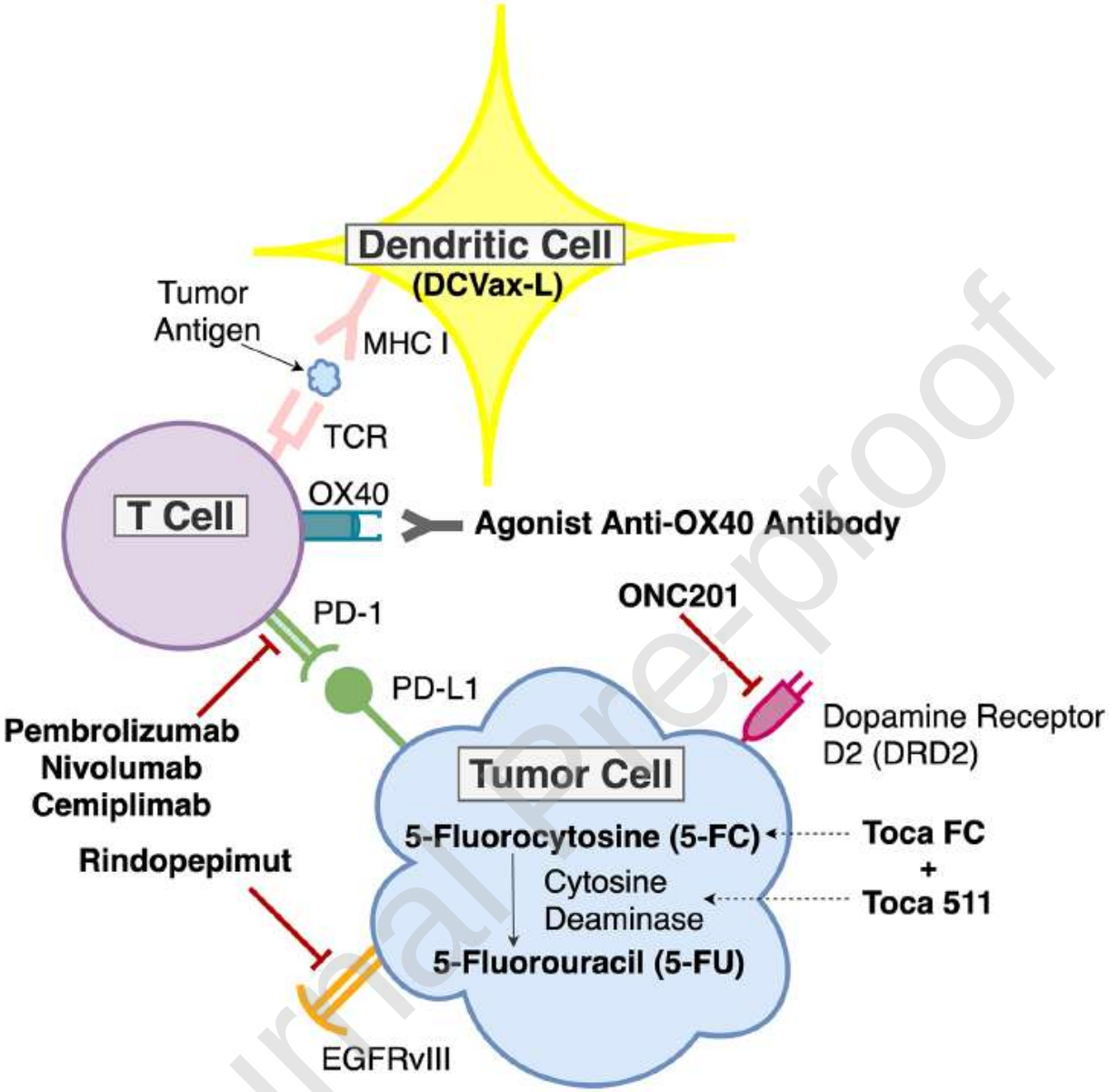

Fig. 2 Blood Brain Barrier Disruption with Intra-Arterial Drug Delivery performed in a temporo-parietal glioblastoma. Selective catheterization of the vascular supply is performed (marked by arrows) and IA bevacizumab is injected after blood brain barrier disruption using mannitol. **(A-C)** The Blood Brain Barrier disruption kit developed at our center. **(D)** Intra-procedural photograph showing SIACI bevacizumab for GBM. (**E)**

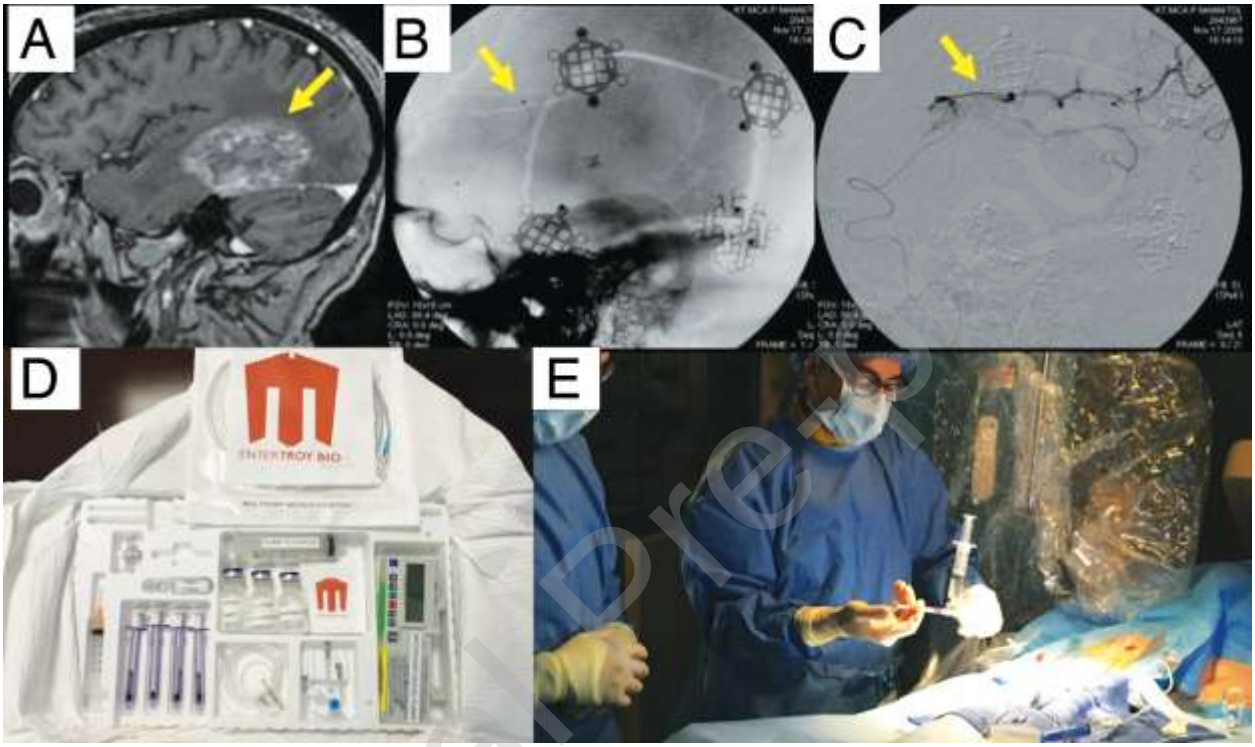

Fig. 3 Mechanism of Action of 5-ALA in Fluorescence-Guided Resection

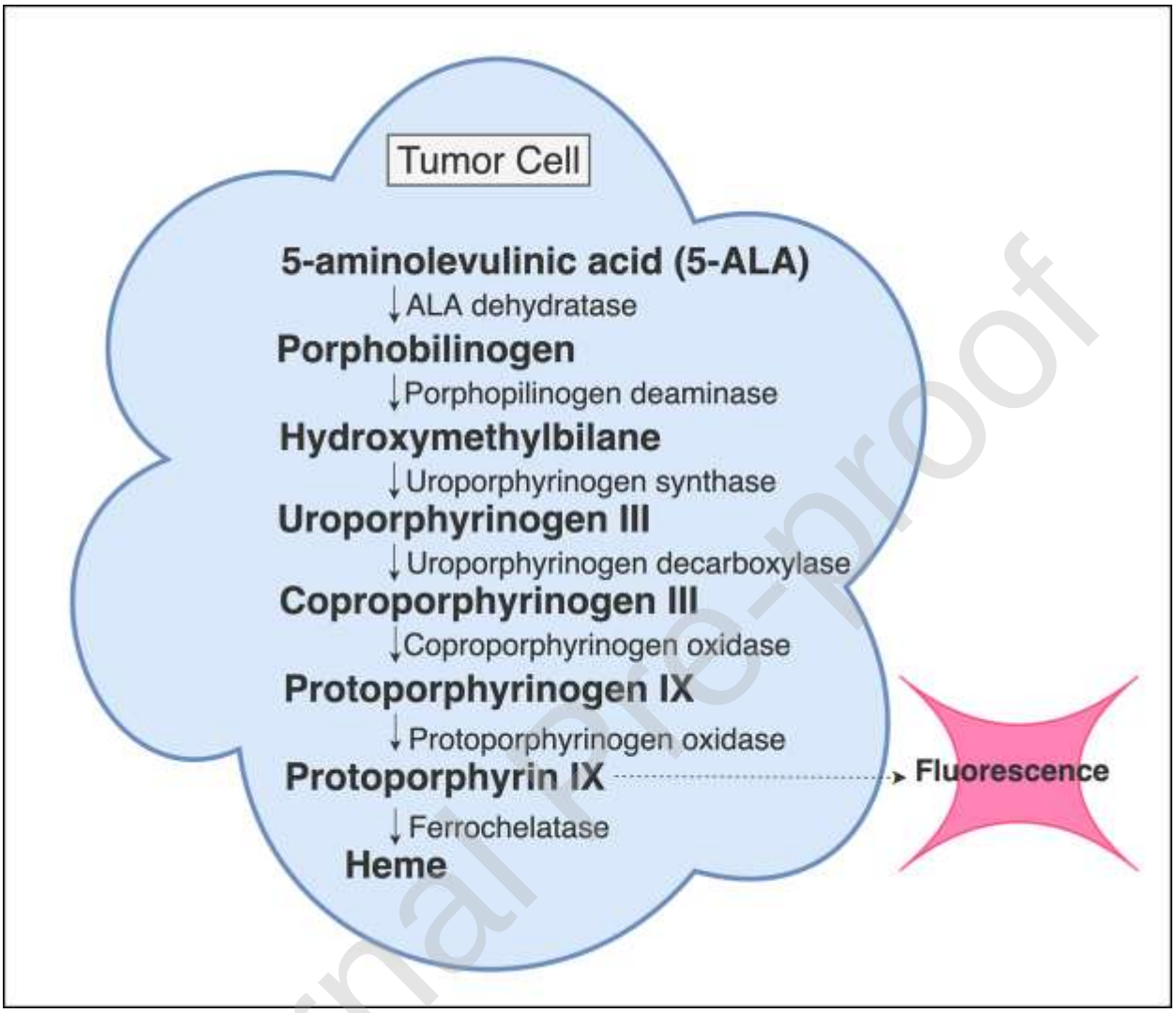

Table 1. Summary of Clinical Trials for Malignant Gliomas Included in this Report

Trial	Sponsor	Product	Mechanism	Phase, Status
Immunotherapy				
NCT02017717	Bristol-Myers Squibb	Nivolumab	Inhibits PD-1 on T cells; Suppresses T cell activity	III, Active
NCT03491683	Inovio Pharmaceuticals	Cemiplimab (REGN2810)	Inhibits PD-1 on T cells; Suppresses T cell activity	I/II, Active
NCT00045968	Northwest Biotherapeutics	DCVax(R)-L	Vaccine containing dendritic cells prepared with tumor lysate	III, Unknown
NCT01470794	Tocagen, Inc.	Toca 511	Converts 5-FC to cytotoxic 5-FU in tumor cells	I, Completed
NCT01156584	Tocagen, Inc.	Toca 511	Converts 5-FC to cytotoxic 5-FU in tumor cells	I, Completed
NCT01985256	Tocagen, Inc.	Toca 511	Converts 5-FC to cytotoxic 5-FU in tumor cells	I, Completed
NCT02414165	Tocagen, Inc.	Toca 511	Converts 5-FC to cytotoxic 5-FU in tumor cells	II/III, Terminated
Precision Oncology Platform				
NCT02296580	Nativis, Inc.	Voyager System	Delivers ulRFE derived from magnetic field measurements of drugs and molecules to mimic their actions	N/A, Active
Novel Applications and Experimental Treatments				
NCT01811498	Northwell Health	SIACI of Bevacizumab	Intra-arterial disruption of BBB for drug delivery targeting VEGF	I/II, Recruiting
NCT01269853	Northwell Health	SIACI of Bevacizumab	Intra-arterial disruption of BBB for drug delivery targeting VEGF	I/II, Recruiting
NCT01480479	Celldex Therapeutics	Rindopepimut	Targets EGFRvIII (a mutant tyrosine kinase)	III, Completed

NCT02766699	Engeneic Pty Limited	EnGeneIC Dream Vector	Facilitate transport of doxorubicin to tumor cells overexpressing EGFR	I, Recruiting
ACTRN12619000385145	EnGeneIC Pty Limited	EnGeneIC Dream Vector	Facilitate transport of doxorubicin to tumor cells overexpressing EGFR	I/IIa, Recruiting
NCT03134131	Oncoceutics, Inc.	ONC201	Inhibits dopamine receptor D2 expressed on tumor cells	N/A, Available
NCT02525692	Oncoceutics, Inc.	ONC201	Inhibits dopamine receptor D2 expressed on tumor cells	II, Recruiting
NCT03295396	Oncoceutics, Inc.	ONC201	Inhibits dopamine receptor D2 expressed on tumor cells	II, Recruiting
NCT03416530	Oncoceutics, Inc.	ONC201	Inhibits dopamine receptor D2 expressed on tumor cells	I, Recruiting
NCT00241670	Medac GmbH	5-ALA	Generates fluorescent porphyrins in tumor cells	III, Completed
NCT02104882	Universitätsmedizin Mannheim	IORT	Delivers low energy x-rays directly to the tumor bed	I/II, Completed
NCT02685605	Universitätsmedizin Mannheim	IORT	Delivers low energy x-rays directly to the tumor bed	III, Recruiting
NCT00916409	NovoCure Ltd.	NovoTTF-100A Device	Applies alternating electric fields that inhibit tumor cell proliferation and induce apoptosis	III, Completed