Methods behind oncolytic virus-based DC vaccines in cancer: Toward a multiphase combined treatment strategy for Glioblastoma (GBM) patients

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Chapter outline

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Abstract

Glioblastoma (GBM) remains an orphan cancer disease with poor outcome. Novel treatment strategies are needed. Immunotherapy has several modes of action. The addition of active specific immunotherapy with dendritic cell vaccines resulted in improved overall survival of patients. Integration of DC vaccination within the first-line combined treatment became a challenge, and immunogenic cell death immunotherapy during chemotherapy was introduced. We used a retrospective analysis using real world data to evaluate the complex combined treatment, which included individualized multimodal immunotherapy during and after standard of care, and which required adaptations during treatment, and found a further improvement of overall survival. We also discuss the use of real world data as evidence. Novel strategies to move the field of individualized multimodal immunotherapy forward for GBM patients are reviewed.

List of abbreviations

ATMP	advanced therapy medicinal product
AYLL	average years of life lost
BBB	blood brain barrier
CAR	chimeric antigen receptor
CMV	cytomegalovirus
CPI	checkpoint inhibitor
DAMPs	damage-associated molecular patterns
DC	dendritic cell
EBV	Epstein-Barr virus
EVs	extracellular vesicles
GBM	glioblastoma
GM-CSF	granulocyte/macrophage colony-stimulating factor
GMP	good manufacturing practice
HHV-6	human herpesvirus 6
HMGB1	high-mobility group box 1

HPV	human papillomavirus
HRQoL	health-related quality of life
ICD	immunogenic cell death
IDH1	isocitrate dehydrogenase 1
IFN	interferon
IL	interleukin
IMI	individualized multimodal immunotherapy
MDSC	myeloid-derived suppressor cells
mEHT	modulated electrohyperthermia
MGMT	O^6-methylguanine-DNA methyltransferase
NDV	Newcastle disease virus
NK	natural killer
OS	overall survival
OV	oncolytic virus
PFS	progression-free survival
PGE2	prostaglandin-E2
POH	perillyl alcohol
R&D	research and development
RCT	randomized controlled trial
RWD	real world data
TLR	toll-like receptor
TMB	tumor mutational burden
TME	tumor microenvironment
TMZ	temozolomide
TMZm	maintenance chemotherapy with TMZ
TNFa	tumor necrosis factor-α
Treg	regulatory T cell
TTF	tumor treating field
VOL	viral oncolysate
wt	wild-type

In the invitation to contribute to a new thematic edition in Methods in Cell Biology (MCB), entitled "**Cell-based Cancer Immunotherapy**," the guest editor suggested to write a chapter with the putative title "**Methods behind oncolytic virus-based DC vaccines in cancer**," because of the "*existing expertise and outstanding contributions to the field*." The book chapter should provide "*a systematic overview of proven, state-of-art techniques, along with relevant historical background and theory, to aid researchers in efficient design and effective implementation of experimental methodologies*."

1 Introduction

Cancer is the second leading cause of death worldwide, accounting for almost 20 million new cases and about 10 million deaths in 2020 (Ferlay et al., 2021; World Health Organization, 2022). The International Agency for Research on Cancer

provided in their All-Cancer-Factsheet 2020 (The Global Cancer Observatory: International Agency for Research on Cancer, 2020) further details on the prevalence of types of newly diagnosed cancers in patients: Breast (11.7%), Lung (11.4%), Colorectum (10%), Prostate (7.3%), Stomach (5.6%), Liver (4.7%), Cervix (3.1%), Oesophagus (3.1%) and others (42.9%). A slightly different distribution was present when looking to cancer-related fatality: Lung (18%), Colorectum (9.4%), Liver (8.3%), Stomach (7.7%), Breast (6.9%), Oesophagus (5.5%), Pancreas (4.7%), Prostate (3.8%) and others (35.7%). These are identified as the big cancer types, substantiating the main economic interest and thus directly influencing health policies. A completely different distribution of important cancer types emerged when looking to the average years of life lost (AYLL) due to cancer (Burnet, Jefferies, Benson, Hunt, & Treasure, 2005). The term "Years of life lost" reflects the difference in years between the life expectancy age for a given sex in a given community and the effective age of death due to cancer. The AYLL for all cancers was 12.5 years. Prostate cancer had the lowest AYLL (6.1 years), while brain tumors had the highest AYLL (20 years). When plotting the sorted simple percentage of death for the different types of cancer *versus* the percentage AYLL due to that particular cancer type, four types of cancer had a higher contribution in the percentage AYLL than compared to the simple percentage of death from that tumor. The population burden for Brain tumors, Cervix and Ovary cancers, and Melanoma, exceeded their simple mortality ranking. Of note comparing AYLL to research spending pointed to high individual cancer burden but low research spending for Brain tumors, Cervix and Kidney cancers, and Melanoma. Rouse *et al.* confirmed the particularly high cancer burden calculated as years of life lost for brain tumors relative to other cancers in adults (Rouse, Gittleman, Ostrom, Kruchko, & Barnholtz-Sloan, 2016).

The remarkable community burden of brain tumors is not only based on the years of life lost being highest of all cancers, but also due to the morbidity caused by the disease itself and the treatment modalities. Co-morbidity emerges sometimes right from the diagnosis on, sometimes later as irreversible long-term sequelae in survivors. One extra challenge is the growing insight in the biology of brain tumors, which requires a repetitive update of their categorization (Kleihues et al., 2002; Louis et al., 2007, 2016, 2021).

In this chapter, we aim to meet the goals of the inviting editor. We explain the specific characteristics and challenges of glioblastoma (GBM), a grade 4 malignant glioma in the central nerve system. We review how dendritic cell (DC) vaccination entered the clinical field as a therapeutic option, and what evidence is obtained. We explain how DC vaccination became an experimental intervention studied during the first-line combined treatment for GBM, and the challenges faced, both biologic and clinical as regulatory and financial. We introduce how immunogenic cell death (ICD) became a critical mechanism within a multimodal immunotherapy strategy, and how exciting improvements in overall survival (OS) for patients with GBM were reached. At this stage we have to reflect about the notion of "evidence" of the therapeutic role of individualized multimodal immunotherapy (IMI) as part of the combined treatment for GBM patients and how health-related quality of life

(HRQoL) came into the picture as part of the assessment of treatment effectiveness. Finally, we outline further strategies in the domain of adoptive anticancer immunotherapy that we plan to set-up and implement in the near future.

2 Methods

Literature data and own experiences were summarized in a narrative and educative review. The domain of "Oncolytic virus-based DC vaccines in cancer" is very broad. That is the reason why we focussed on GBM. GBM as disease entity has been described with highlight in relation to immunotherapy aspects. Similarly, the different modes of immunotherapy have been described only with a focus to GBM. The DC vaccination trials for GBM have been sampled from January 2000 till March 2023 from a weekly personalized update of the literature by PubMed with Search: ("glioblastoma"[MeSH Terms] OR "glioblastoma"[All Fields]) AND ("immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields]). Since about 10 years, a personalized update of the literature is obtained with Search: ("Oncolytic Viruses"[Mesh] OR "Oncolytic Virotherapy"[Mesh]) AND "Glioblastoma"[Mesh], and with Search: "Newcastle disease virus"[Mesh]. We focussed on the methods to produce these vaccines. More importantly from a clinical point of view, we focussed on the method to implement DC vaccines into clinical reality as part of the first-line treatment of patients with GBM, and how scientific clinical research challenges and regulatory issues played a role. We reviewed the available literature on ICD immunotherapy, and how and why ICD immunotherapy became scheduled in connection to maintenance chemotherapy, and again after DC vaccination. The obtained OS data were put in the light of available OS data derived from randomized controlled clinical trials. It became necessary to introduce the readership into public health frameworks that allow individualized treatments, and to explain how clinical research evidence might be different from but strengthened by medical evidence.

3 Glioblastoma

GBM is the most frequent primary malignant brain tumor in adults, with the worst prognosis. GBM belongs to the diffuse gliomas. The incidence is no higher than 4 to 5 patients per 100.000 adults per year (Thakkar et al., 2014). Although GBM can be part of cancer predisposition syndromes (Ostrom et al., 2014), most GBM are sporadic. Only brain irradiation has been identified as a potential cause of brain tumors like GBM (Izycka-Swieszewska et al., 2018) and meningiomas (Timmermann & Kortmann, 2022). Alternatively, aging, immunosuppression, viral infections like cytomegalovirus (CMV), or prolonged exposure to higher doses of non-ionizing irradiation are associated with the incidence of GBM, though without proof of causality (Batich et al., 2017; Hardell, Carlberg, & Hansson, 2013; Ladomersky et al., 2019). In spite of the extreme poor prognosis and high community burden, there is almost no

evolution in the standard of care to improve the prognosis. This is certainly due to the orphan disease status, making big investments for innovative treatments not lucrative. However, the particular biology of GBM, including the relative low tumor mutational burden (TMB) in untreated tumors (Alexandrov et al., 2013), the tumor heterogeneity itself (Aum et al., 2014; Dirkse et al., 2019; Jain, 2018; Suter, Rodriguez-Blanco, & Ayad, 2020), the role of glioma cancer stem cells (Johnson, Laterra, & Lopez-Bertoni, 2022; Lombard et al., 2020; Maugeri-Sacca, Di Martino, & De Maria, 2013), the blood brain barrier (BBB) (Papademetriou & Porter, 2015) and the tumor microenvironment (TME) (Zhang et al., 2022; Zhao et al., 2022), makes the development of new therapeutic approaches very challenging. Indeed, there are much more gaps to be bridged than only killing tumor cells. Finally, the high plasticity and dynamic character of GBM, the dynamic changes in the TME, and the changes in the systemic compartment in the patient, challenge the value of the standard and generally accepted clinical trial methodology, which is principally based on comparisons of fixed treatment protocols in an adapted trial design (Sprenger, Schirrmacher, Stucker, & van Gool, 2020; Van Gool et al., 2021).

Immunotherapy in cancer has become a hot topic in general for basic science, translational, and clinical research, and for GBM in particular. The introduction of the domain of immunology in oncology has been extremely facilitated by providing the Nobel Prize for Medicine 2011 to Ralph Steinman for his discovery of the DC and its role in adaptive immunity, and to Bruce Beutler and Jules Hoffmann for their discoveries concerning the activation of innate immunity. The American Association for the Advancement of Science appointed cancer immunotherapy as the breakthrough of the year 2013, with the appropriate cover in Science. Finally, the Nobel Prize for Medicine 2018 was awarded to James Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation.

The recognition that the brain is an immune-special site instead of an immune-privileged site, and that the central nervous system undergoes constant immune surveillance (Louveau et al., 2015), supports research to target GBM with immunotherapeutic strategies. Recent advances in oncolytic virotherapy and immunotherapy create a glimmer of hope in the search for an effective therapy for GBM (Stepanenko & Chekhonin, 2018). In this chapter, the authors, who treated the first GBM patients with DC vaccines in Europe (De Vleeschouwer et al., 2004; Rutkowski et al., 2004), describe the evolution of the DC vaccine approach for GBM, the introduction of oncolytic viruses (OVs) and modulated electrohyperthermia (mEHT) in the IMI concept, the development of a combined treatment strategy for GBM, the level of Evidence-based Medicine reached thus far, and some perspectives for the future.

4 Anticancer immunotherapy

Immunotherapy is defined by the American Cancer Society as "a treatment that uses a person's own immune system to fight cancer. Immunotherapy can boost or change how the immune system works so it can find and attack cancer cells"

Table 1 Modes of immunotherapy.

Mode of immunotherapy	Non-cellular—Cellular immunotherapy
1. Restorative immunotherapy	Non-cellular
2. Passive immunotherapy	Non-cellular
3. Immunogenic cell death immunotherapy	Non-cellular
4. Modulatory immunotherapy	Non-cellular
5. Adoptive immunotherapy	Cellular
6. Active specific immunotherapy	Non-cellular or cellular

(American Cancer Society, 2019). Anticancer immunotherapy consists of a lot of different immunotherapy modalities, amongst which the term "cellular immunotherapy" covers a few of them. Therefore, it is extremely important to understand about which modality of immunotherapy physicians talk when using the term "immunotherapy" (Table 1).

1. Restorative immunotherapy consists of the administration of cytokines with the aim to generate an aspecific immune activation, thereby also reaching anticancer effector cells. Multiple applications for the treatment of GBM have been used in the past (reviewed in (De Vleeschouwer, Van Gool, & Van Calenbergh, 2005)). The common characteristic of these approaches is the high adverse reactions in patients with a low efficacy profile, due to which most of these approaches are nowadays abandoned.
2. For passive immunotherapy, monoclonal antibodies are used against one specific target on the tumor cells. With this opsonization, complement-mediated cytotoxicity or antibody-dependent cell-mediated cytotoxicity mechanisms against the target cells are generated. Nimotuzumab and Cetuximab targeting epidermal growth factor receptor (EGFR) are the best known antibodies used for the treatment of GBM (Hasselbalch et al., 2010; Li et al., 2017). Because the BBB hinders antibody transport into the brain, different delivery systems using nanoparticles and routes like intra-arterial administrations for antibody therapy have been explored (Ferreira et al., 2021; Kulason et al., 2018). The concept of targeting membrane structures with antibodies has moved toward adoptive immunotherapy with Chimeric Antigen Receptor (CAR) technology, whereby scFv binding domains and modified Fc parts are transduced into T cells and coupled to a T cell activating machinery (Zhang, Zhang, & Ji, 2022). Further developments in the domain of passive immunotherapy are immunotoxins, in which immune-active substances are bound to radioactive substances or to chemotherapeutic drugs, thereby bringing the anticancer treatment activity close to the target-positive tumor cells (Han & Kim, 2022; Sharma & Debinski, 2018).
3. A third immunotherapy modality is the ICD immunotherapy. ICD is a separate mechanism of cell death, belonging to Regulated Cell Death. As a consequence of ICD, an immune response is generated against antigens of dying cells (Galluzzi et al., 2018, 2020). A great variety of medical interventions

can cause ICD, including OVs (Brown et al., 2017; Donnelly et al., 2013; Fournier, Arnold, Wilden, & Schirrmacher, 2012; Koks et al., 2014; Liikanen et al., 2013; Qu et al., 2018), chemotherapeutics (Obeid et al., 2007), epigenetic modifiers (West et al., 2013), targeted therapies (Liu et al., 2019), and numerous physical interventions, such as ionizing irradiation (Golden et al., 2014), mEHT (Minnaar, Kotzen, Ayeni, Vangu, & Baeyens, 2020; Vancsik et al., 2018), tumor-treating electric fields (TTF) (Voloshin et al., 2020), photodynamic therapy (PDT) (Garg et al., 2016). Several mechanisms play a combined role in ICD, like the production of danger signals, release of "find me"-signals, increased membrane expression of "eat me"-signals, and increased expression of tumor antigens ("recognize me"-signals).

4. The final non-cellular immunotherapy is the modulatory immunotherapy. Nowadays, this is the best known type of immunotherapy, because the immune checkpoint blockers (ICB), also called immune checkpoint inhibitors (ICI) or checkpoint inhibitors (CPI), belong to this modality (Korman, Garrett-Thomson, & Lonberg, 2021). The immune system is regulated by a large number of checkpoints, both at the activation and the effector phase of the immune response. The best known checkpoints are the interaction between CD28 and CTLA4, and the interaction between PD1 and PDL1. Currently, several monoclonal antibodies are produced and applied in patients to combat the immune resisting abilities of the tumor and its microenvironment (Arrieta et al., 2023; Kreatsoulas et al., 2022). The prerequisite here is that functional immune cells are present and an anticancer immune response occurs but is blocked by immune checkpoints exhibited by the tumor to evade the immune system. The metronomic dosing of cyclophosphamide to deplete regulatory T cells (Le & Jaffee, 2012), or of capecitabine to deplete myeloid-derived suppressor cells (Peereboom et al., 2019) are other immune modulatory strategies. Further approaches that fall under the category of modulatory immunotherapy are bisphosphonates, aimed to stimulate gamma-delta T cells (Fowler, Copier, Dalgleish, & Bodman-Smith, 2014; Lo Presti et al., 2017), and anti-histamine receptor H1 blockers which block M2-like macrophages and stimulate M1-like macrophages (Li et al., 2022). Administration of Cox2 inhibitors (Exley, Garcia, Zellander, Zilberberg, & Andrews, 2022) and/or curcumins (Paul & Sa, 2021) is also aimed to influence the inflammatory myeloid compartment in tumors.

   All these treatment strategies are non-cellular immunotherapies. The fifth and the sixth modality of immunotherapy belong almost exclusively to the category of cellular immunotherapy.

5. The fifth modality of immunotherapy is the adoptive immunotherapy. For this, anti-cancer effector cells are created and/or expanded *ex vivo*, and re-infused. Again, this category is comprised of several distinct approaches. Lymphokine-Activated Killer (LAK) cells and Tumor-Infiltrating Lymphocytes (TIL) have been explored in the past and showed some efficacy (Vauleon, Avril, Collet, Mosser, & Quillien, 2010). Novel approaches of adoptive cellular immunotherapy consist of CAR-transduced T cells, T cell receptor

(TCR)-transduced T cells, CAR-transduced natural killer (NK) cells, expanded NK cells, expanded NKT cells and expanded gamma-delta T cells (Wang & Wang, 2022). Because of a potential role of CMV in the pathophysiology of GBM, expanded CMV-specific T cells have been used to treat GBM patients (Duinkerken, van Kooyk, & Garcia-Vallejo, 2016; Schuessler, Walker, & Khanna, 2014; Smith et al., 2020; Soderberg-Naucler & Johnsen, 2012; Weathers et al., 2020).

6. The last modality of immunotherapy is the active specific immunotherapy. In this modality of immunotherapy, an antigen is injected into the patient, with the aim that the patient actively creates an anticancer immune response to that specific antigen. Three critical factors have to be considered: (i) the antigen, (ii) the vehicle to bring the antigen into the body, and (iii) the danger signal generated to set up the immune response. The antigen used consists of well-defined amino-acid sequences linked to particular tumors (Dutoit et al., 2018; Phuphanich et al., 2013; Pollack et al., 2016; Wen et al., 2019), or predicted specifically for a given tumor and presented in the context of a given MHC class I and MHC class II phenotype of a single patient (tumor-specific neo-antigens) (Keskin et al., 2019; Shraibman et al., 2018). The selected antigen can also be a mixture of known and unknown antigens derived from tumor tissue (Bota et al., 2022; Rapp et al., 2018; Van Gool, 2015). The amino-acid content of short and/or long peptides can be generated based on DNA (Adhikari et al., 2022; InSug, Blaszczyk-Thurin, Shen, & Ertl, 2003), RNA (Wu et al., 2022), *ex vivo* generated peptides (Sampson et al., 2009), or proteins derived from tumor lysate or apoptotic tumor cells (Bota et al., 2022; Rapp et al., 2018; Van Gool, 2015). The vehicle and the danger signals can be separated when using antigen vaccines with an adjuvant like Poly-ICLC (Dutoit et al., 2018; Keskin et al., 2019) or Montanide + Poly-ICLC (Pollack et al., 2016). A 50 μg granulocyte/macrophage colony-stimulating factor (GM-CSF) adjuvant injection can be given as danger signal, eliciting a response against the vaccine (Bota, Taylor, Lomeli, et al., 2022). The vehicle and the danger signals come together in the form of Dendritic Cells, primed with antigens and stimulated with selected danger signals *ex vivo* to become mature DCs for appropriate antigen presentation accompanied by essential signals from costimulatory molecules and cytokines. DCs serve as antigen-presenting cells specialized for the induction of a primary T cell response (Banchereau & Steinman, 1998). These cell-based anti-cancer vaccines are a broadly used type of cellular immunotherapy for different types of cancer (Figdor, De Vries, Lesterhuis, & Melief, 2004).

5 The immune-editing in GBM

Using autologous tumor antigens in DCs might raise questions in view of the classical hypothesis of Elimination–Equilibrium–Escape of tumor cells in interaction with a functioning immune system. This hypothesis is summarized as cancer

immune-editing (Dunn, Bruce, Ikeda, Old, & Schreiber, 2002). A similar hypothesis has also been proposed for malignant glioma (Dunn, Fecci, & Curry, 2012). The possibility of cancer immune-editing in glioma has been re-discussed later-on (Arrieta et al., 2018; Sonabend, Stupp, Lee-Chang, & Okada, 2021). Several immune escape mechanisms have been suggested, and all belong to the complex and dynamic interaction between tumor and host in the TME (Pearson et al., 2020; Virtuoso et al., 2022). Part of these mechanisms are located at the side of the tumor, like low TMB in GBM, downregulation of MHC class I molecules, upregulation of PDL1 and other potential checkpoint molecules, and secretion of immunosuppressive substances like interleukin (IL)-10, Transforming Growth Factor-b (TGFb), indoleamine 2,3-dioxygenase (IDO), or Prostaglandin-E2 (PGE2). Part of the mechanisms are located at the side of the host, with the particular role of resident microglia, the influx of immune suppressive myeloid cells like myeloid-derived suppressor cells (MDSCs), and the influx of regulatory T cells (Tregs). The influx of tumor-promoting macrophages aids further cancer development. Remarkably, epigenetic subtypes of GBM and even intracellular signaling pathways affect the cellular influx of immune cells in the TME (Dejaegher et al., 2021) and how the tumor-host interaction can be modulated (Arrieta et al., 2021). Finally, Glioma Cancer Stem Cells are located in the poorly accessible subventricular zone and have a strong immunosuppressive potency (Johnson et al., 2022; Lombard et al., 2020; Maugeri-Sacca et al., 2013). This all raised the hypothesis that due to the immunosuppressive TME, the weakly expressed tumor antigens in GBM are less immune-edited and hence more immune-naïve. The use of tumor lysate from primary GBM tumor tissue can therefore likely be used as source of not-immune-edited tumor antigens, to which the immune system can still be stimulated when the appropriate danger signals are provided. It might also explain why modulatory immunotherapy with only CPI did not provide the expected result in tumor control (Adhikaree, Moreno-Vicente, Kaur, Jackson, & Patel, 2020), except in hypermutant GBM where an anti-cancer immune response had occurred and the escape mechanism was based on checkpoints (Bouffet et al., 2016), or in relapsed GBM where Temozolomide (TMZ)-induced hypermutation had occurred (Daniel et al., 2022). The classic immune-editing that occurs during and after passive and/or active immunotherapy, with the appearance of new tumoral subclones with different antigens, is meanwhile also a recognized and researched technical challenge (O'Rourke et al., 2017; Sampson et al., 2010; Van Gool et al., 2023).

6 Dendritic cell vaccines as active specific immunotherapy for GBM

In the period 1995 to 2000, the standard of care for GBM was neurosurgery and radiotherapy. At that time, phase I and phase II trials were running to detect the toxicity and efficacy of TMZ in patients with relapsed malignant glioma (Bower et al., 1997; Newlands et al., 1992). It was evident that novel treatment strategies

had to be developed, and neuro-oncology clinical researchers took advantage by the translational and clinical research on DC vaccination performed for other cancer diseases like lymphoma (Hsu et al., 1996), melanoma (Nestle et al., 1998), prostate cancer (Murphy, Tjoa, Ragde, Kenny, & Boynton, 1996) and renal cell carcinoma (Holtl et al., 1999). In pre-clinical models, bone marrow-derived DCs were loaded with tumor extracts or tumor RNA (Ashley et al., 1997), acid-eluted tumor antigens (Liau et al., 1999) or tumor homogenate (Heimberger et al., 2000) and these vaccines elicited an immune response against orthotopic glioma. The know-how to culture human DCs was already established in 1994 (Romani et al., 1994). Patient-derived T cells could be stimulated with patient-derived DCs loaded with lysate from patient-derived GBM tissue, and showed a tumor-specific MHC-restricted cytotoxicity against patient-derived cultured GBM tumor cells or MHC class I-compatible cell lines (De Vleeschouwer et al., 2001, 2005; De Vleeschouwer, Spencer, Ceuppens, & Van Gool, 2007). Although the preclinical evidence and mechanistic insights were still extremely limited at that time, the first clinical report came out, already in 2000, demonstrating the clinical efficacy of a DC vaccine loaded with peptides eluted from a primary allogeneic MHC class I-matched GBM cell culture (Liau et al., 2000). One year later, two phase I trials were published, one from Tokyo, Japan, where DCs were fused with autologous tumor cells (Kikuchi et al., 2001), and one from Los Angeles, California, where DCs were loaded with autologous MHC class I peptides (Yu et al., 2001). A group from Niigta, Japan, presented their phase I/II study in 2003, and used DCs loaded with tumor lysate (Yamanaka et al., 2003). The group from Los Angeles published a larger series of GBM patients vaccinated with DCs loaded with tumor lysate (Wheeler et al., 2003). That cascaded into a whole series of case reports and phase I, phase I/II and phase II clinical trials, summarized in Table 2.

Reviewing the literature, we detected in total 77 reports on clinical trials, of which one was originally designed as a phase IIb randomized controlled trial (RCT) but ultimately reported as a phase III study with an external control arm (Liau et al., 2018, 2023). These publications were derived from 31 research groups located in 15 countries in 5 of the 7 continents. One can conclude that world-wide research in this domain has occurred. The median number of patients reported was 22, ranging from 1 till 366. Results from DC vaccination as part of first-line treatment or at time of relapse were reported in 56 respectively 41 publications. Hence 21 publications described results reached in both patients treated in first-line and patients treated at time of relapse. In almost all papers, DCs were differentiated out of monocytes in the presence of GM-CSF and IL-4. One group in Japan included Tumor Necrosis Factor-α (TNFa) at this stage (Kikuchi et al., 2001, 2004). A Russian group used the combination of GM-CSF and interferon-α (IFNa) (Leplina et al., 2007). In one paper, the cytokine mixture was optimized but kept proprietary (Parney et al., 2022). As far as the authors know, only monocyte-derived DCs have been used till now. We did not find publications using purified conventional DC1 (Bottcher & Reis Sousa, 2018) for immunotherapy for GBM, although such cell-based products are used for treatment of high risk melanoma (Bhardwaj et al., 2020).

Table 2 Reports on DC vaccination for patients with glioblastoma (two studies: DC vaccination for DIPG).

First author	Year	Number of patients	First-line	Integration	Recurrent	Cao (Cao etal., 2014)	Wang (X. Wang etal., 2014)	Eagles (Eagles etal., 2018)	Vatu (Vatu etal., 2019)	Lv (Lv, Huang, Xi, & Zhou, 2020)	Cozzi (Cozzi etal., 2022)	DC differentiation	DC maturation	Tumor cells	Tumor lysate	Peptides	Tumor RNA	TL/EV	CMV RNA
Liau (Liau et al., 2000)	2000	1		N/A	X							GM-CSF/IL4	Not mentioned			X			
Yu (Yu et al., 2001)	2001	9	X	S→RT→DC				X				GM-CSF/IL4	Not mentioned			X			
Kikuchi (Kikuchi et al., 2001)	2001	8		N/A	X	X		X				GM-CSF/IL4/TNFa	Not mentioned	X					
Yamanaka (Yamanaka et al., 2003)	2003	10		N/A	X	X		X				GM-CSF/IL4	Not mentioned		X				
Wheeler (Wheeler et al., 2003)	2003	17	X	S→RT→DC	X							GM-CSF/IL4	Not mentioned		X				
Kikuchi (Kikuchi et al., 2004)	2004	15		N/A	X			X				GM-CSF/IL4/TNFa	Not mentioned	X					
Caruso (Caruso et al., 2004)	2004	9		N/A	X			X				GM-CSF/IL4	Not mentioned				x		
Wheeler (Wheeler, Das, Liu, Yu, & Black, 2004)	2004	25	X	S→RⒸT→DC		X			X		X	GM-CSF/IL4	Not mentioned		X				
Yu (Yu et al., 2004)	2004	14	X	S→RT→DC	X	X	X	X	X		X	GM-CSF/IL4	Not mentioned		X				
Rutkowski (Rutkowski et al., 2004 #4723)	2004	12		N/A	X			X				GM-CSF/IL4	Tnfa/IL1b/PGE2		X				
De Vleeschouwer (De Vleeschouwer et al., 2004)	2004	1		N/A	X							GM-CSF/IL4	TNFa/IL1b/PGE2		X				
Liau (Liau et al., 2005)	2005	12	X	S→RT→DC	X	X	X	X	X			GM-CSF/IL4	Not mentioned		X				
Yamanaka (Yamanaka et al., 2005)	2005	24		N/A	X	X	X	X	X		X	GM-CSF/IL4	Not mentioned		X				
Khan (Khan & Yaqin, 2006)	2006	1	X	S→CT→DC								GM-CSF/IL4	Not mentioned		X				
Leplina (Leplina et al., 2007)	2007	39	X	S→RT→DC							X	GM-CSF/IFNa	LPS		X				
Okada (Okada et al., 2007)	2007	7	X	S→RT→DC	X			X				GM-CSF/IL4	TNFa/IL1b/IFNg		X				
Walker (Walker, Laherty, Tomlinson, Chuah, & Schmidt, 2008)	2008	13	X	N/A	X							GM-CSF/IL4	MoCM		X				

Prins (Prins, Cloughesy, & Liau, 2008)	2008	1	X	S→RCT→DC								GM-CSF/IL4	Not mentioned		X			
Wheeler (Wheeler et al., 2008)	2008	32	X	No data available	X							GM-CSF/IL4	Not mentioned		X			
De Vleeschouwer (De Vleeschouwer et al., 2008)	2008	56		N/A	X							GM-CSF/IL4	TNFa/IL1b/PGE2		X			
Sampson (Sampson et al., 2009)	2009	12	X	S→RT→DC								GM-CSF/IL4	TNFa/IL1b/IL6			X		
Ardon (Ardon et al., 2010)	2010	8	X	S→RCT→DC+CT								GM-CSF/IL4	TNFa/IL1b/PGE2		X			
Ardon (Ardon et al., 2010)	2010	45		N/A	X							GM-CSF/IL4	TNFa/IL1b/PGE2		X			
Prins (Prins et al., 2011)	2011	23	X	S→RCT→DC	X						X	GM-CSF/IL4	Not mentioned		X			
Chang (Chang et al., 2011)	2011	17	X	S→RT→DC	X	X	X		X		X	GM-CSF/IL4	Not mentioned	X				
Okada (Okada et al., 2011)	2011	22		N/A	X							GM-CSF/IL4	TNFa/IL1b/IFNa/ IFNg/Poly-I:C			X		
Fadul (Fadul et al., 2011)	2011	10	X	S→RCT→DC+CT								GM-CSF/IL4	TNFa/PGE2		X			
Cho (Cho et al., 2012)	2012	34	X	S→RCT→DC+CT		X	X		X	X	X	GM-CSF/IL4	Not mentioned		X			
Qin (Qin et al., 2012)	2012	13		N/A								GM-CSF/IL4	TNFa	X				
Valle (Valle et al., 2012)	2012	5	X	S→DC→RCT→DC + CT								GM-CSF/IL4	TNFa/IFNa/Poly-I:C		X			
Akiyama (Akiyama et al., 2012)	2012	9		N/A	X							GM-CSF/IL4	TNFa/IL1b/IFNa/ IFNg/Poly-I:C			X		
Iwami (Iwami et al., 2012)	2012	8		N/A	X							GM-CSF/IL4	TNFa/IL1b/IL6			X		
Fong (Fong et al., 2012)	2012	24	X	S→RCT→DC+ CT	X							GM-CSF/IL4	TNFa/IL1b/IL6/ PGE2		X			
Jie (Jie et al., 2012)	2012	25	X	DC during S→RCT→CT		X	X		X	X	X	GM-CSF/IL4	TNFa/IL1b/PGE2		X			
Ardon (Ardon et al., 2012)	2012	77	X	S→RCT→DC+ CT								GM-CSF/IL4	TNFa/IL1b/PGE2		X			
Elens (Elens, De Vleeschouwer, Pauwels, & Van Gool, 2012)	2012	39		N/A	X							GM-CSF/IL4	TNFa/IL1b/PGE2		X			
De Vleeschouwer (De Vleeschouwer et al., 2012)	2012	117		N/A	X							GM-CSF/IL4	TNFa/IL1b/ PGE2orImiquimod		X			
Lasky (Lasky III et al., 2013)	2013	7	X	S→RCT→CT→DC	X							GM-CSF/IL4	Not mentioned		X			
Prins (Prins et al., 2013)	2013	34	X	S→RCT→DC+CT	X							GM-CSF/IL4	Not mentioned		X			
Phuphanich (Phuphanich et al., 2013)	2013	21	X	S→RCT→DC+CT	X							GM-CSF/IL4	TNFa		X			
Vik-Mo (Vik-Mo et al., 2013)	2013	7	X	S→RCT→DC+CT					X		X	GM-CSF/IL4	TNFa/IL1b/IL6/ PGE2				x	
Pellegatta (Pellegatta et al., 2013)	2013	15		N/A	X							GM-CSF/IL4	TNFa/IL1b/IL6/ PGE2		X			

Continued

Table 2 Reports on DC vaccination for patients with glioblastoma (two studies: DC vaccination for DIPG).—cont'd

First author	Year	Number of patients	First-line	Integration	Recurrent	Cao (Cao etal., 2014)	Wang (X. Wang etal., 2014)	Eagles (Eagles etal., 2018)	Vatu (Vatu etal., 2019)	Lv (Lv, Huang, Xi, & Zhou, 2020)	Cozzi (Cozzi etal., 2022)	DC differentiation	DC maturation	Tumor cells	Tumor lysate	Peptides	Tumor RNA	TL/EV	CMV RNA
Buchroithner (Buchroithner et al., 2014)	2014	65	X	S→RCT→DC+CT						X	X	GM-CSF/IL4	IFNg/LPS		X				
Eyrich (Eyrich et al., 2014)	2014	146		N/A	X							GM-CSF/IL4	TNFa/IL1b/ Imiquimod		X				
Mitchell (Mitchell et al., 2015)	2015	12	X	S→RCT→DC+CT								GM-CSF/IL4	Not mentioned						x
Hunn (Hunn et al., 2015)	2015	14		N/A	X							GM-CSF/IL4	Not mentioned		X				
Sakai (Sakai et al., 2015)	2015	10	X	?								GM-CSF/IL4	OK-432 or LPS or TNFa		X				
Müller (Muller et al., 2015)	2015	117	X	N/A	X						X	GM-CSF/IL4	TNFa/IL1b/PGE2 or Imiquimod		X				
Van Gool (Van Gool, 2015)	2015	366	X	S→RCT→DC+CT	X							GM-CSF/IL4	TNFa/IL1b/PGE2 or Imiquimod		X				
Akasaki (Akasaki et al., 2016)	2016	32	X	S→RCT→DC+CT	X							GM-CSF/IL4	TNFa		X				
Batich (Batich et al., 2017)	2017	14	X	S→RCT→DC+CT							X	GM-CSF/IL4	IL1b/GM-CSF						x
Sakai (Sakai et al., 2017)	2017	2		N/A	X							GM-CSF/IL4	OK-432			X			
Inoges (Inoges et al., 2017)	2017	32	X	S→DC→RCT→DC + CT								GM-CSF/IL4	TNFa/IFNa		X				
Buchroithner (Buchroithner et al., 2018)	2018	76	X	S→RCT→DC+CT						X	X	GM-CSF/IL4	IFNg/LPS		X				
Erhart (Erhart et al., 2018)	2018	43	X	S→RCT→DC+CT								GM-CSF/IL4	IFNg/LPS		X				
Yao (Yao et al., 2018)	2018	43	X	S→RT+DC	X					X	X	GM-CSF/IL4	Not mentioned		X				
Liau (Liau et al., 2018)	2018	331	X	S→RCT→DC+CT								GM-CSF/IL4	Not mentioned		X				
Jan (Jan et al., 2018)	2018	47	X	S→DC+ RCT→DC + CT								GM-CSF/IL4	Not mentioned		X				

Van Gool (Van Gool et al., 2018)	2018	15	X	S→RCT→CT +ICD→DC								GM-CSF/IL4	TNFa/IL1b/IL6/ NDV					x	
Pellegatta (Pellegatta et al., 2018)	2018	24	X	S→RCT→DC+CT								GM-CSF/IL4	TNFa/IL1b/IL6/ PGE2		X				
Benitez-Ribass (Benitez-Ribas et al., 2018)	2018	9	X	DIPG								GM-CSF/IL4	TNFa/IL1b/IL6/ PGE2/Poly-I:C		X				
Wen (Wen et al., 2019)	2019	124	X	S→RCT→DC+CT						X	X	GM-CSF/IL4	IFNg/LPS		X				
Antonopoulos (Antonopoulos, Van gool, Dionysiou, Graf, & Stamatakos, 2019)	2019	101	X	S→RCT→DC+CT or S→RCT→CT→DC								GM-CSF/IL4	TNFa/IL1b/ Imiquimod		X				
Rudnick (Rudnick et al., 2020)	2020	28	X	S+Gliadel→DC	X							GM-CSF/IL4	Not mentioned		X				
Van Gool (Van Gool, Makalowski, Domogalla, et al., 2020)	2020	15	X	S→RCT→CT +ICD→DC								GM-CSF/IL4	TNFa/IL1b/IL6/ NDV					x	
Van Gool (Van Gool, Makalowski, Bonner, et al., 2020)	2020	41	X	DIPG	X							GM-CSF/IL4	TNFa/IL1b/IL6/ NDV					x	
Wang (Wang et al., 2020)	2020	5	X	S→RCT+DC	X							GM-CSF/IL4	TNFa/IL1b/IL6/ PGE2/Imiquimod				x		
Van Gool (Van Gool et al., 2021)	2021	70	X	S→RCT→CT+ ICD→DC								GM-CSF/IL4	TNFa/IL1b/IL6/ NDV					x	
Dejaegher (Dejaegher et al., 2021)	2021	93	X	S→RCT→DC+CT or S→RCT→CT→DC								GM-CSF/IL4	TNFa/IL1b/ Imiquimod		X				
Heugenhauser (Heugenhauser et al., 2022)	2022	76	X	S→RCT→DC+CT								GM-CSF/IL4	IFNg/LPS		X				
Hu (Hu et al., 2022)	2022	36	X	S→RCT→DC+CT	X							GM-CSF/IL4	IFNg/LPS		X				
Bota (Bota et al., 2022)	2022	57	X	S→RCT→DC+CT								GM-CSF/IL4	Not mentioned		X				
Pinho (Pinho et al., 2022)	2022	1		N/A	X							GM-CSF/IL4	Not mentioned	X					
Parney (Parney et al., 2022)	2022	21	X	S→RCT→DC+CT								Proprietary	Proprietary		X				
Van Gool (Van Gool et al., 2022)	2022	32	X	S→RCT→CT +ICD→DC								GM-CSF/IL4	TNFa/IL1b/IL6/ NDV					x	
Liau (Liau et al., 2023)	2023	331	X	S→RCT→DC+CT	X							GM-CSF/IL4	Not mentioned		X				
Van Gool (Van Gool et al., 2023)	2023	32	X	S→RCT→CT +ICD→DC								GM-CSF/IL4	TNFa/IL1b/IL6/ NDV					x	

CMV, cytomegalovirus; DC, DC vaccination; DIPG, diffuse intrinsic pontine glioma; GM-CSF, granulocyte macrophage colony stimulating factor; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MoCM, monocyte-conditioned medium; N/A, not applicable; NDV, Newcastle disease virus; PGE2, prostaglandin E2; RCT, radiochemotherapy; RT, radiotherapy; S, surgery; TNFa, tumor necrosis factor-a; TV/EV, tumor lysate/extracellular vesicles.

In 54 publications, DCs were loaded with tumor lysate. Loading with peptides was reported in 7 studies. Irradiated tumor cells and cell fusion technologies were used in 5 studies, and RNA loading was used in 3 studies. Loading with mRNA for CMV was used in 2 studies. Our team from Cologne reported in 6 studies the technology of loading DCs with ICD immunotherapy-induced serum-derived antigenic extracellular microvesicles and apoptotic bodies. The rationale for this will be worked out later in the text. All reports, except one (Pinho et al., 2022), used autologous DCs as carrier for the antigens. In 28 papers, we could not deduce if maturation signals were used, half of them being published before 2010. In 49 papers, the use of DC maturation signals was described. Maturation signals were diverse but consisted of cytokines, without or with Toll-Like Receptor (TLR) signaling.

Since 2014, 6 meta-analyses and systematic review papers have been published covering in median 8 reports on DC vaccination for GBM patients, ranging from 6 to 15 (Cao et al., 2014; Cozzi et al., 2022; Eagles et al., 2018; Lv, Huang, Xi, & Zhou, 2020; Vatu et al., 2019; Wang et al., 2014). In total, 23 of the 77 publications (30%) were included in at least one meta-analysis or systematic review, 7 original papers were included into 2 reviews, 1 paper was included into 3 reviews, 2 papers were mentioned by 4 reviews, and 4 papers were included in 5 review papers. Table 2 shows which publication (row) is included in which meta-analysis or systematic review (column 7 to 12). Three major conclusions can be drawn when reviewing the literature and the reviews. (1) The literature clearly points to a significant prolongation of the OS in patients who received DC vaccination in comparison to the available control population. The repetitive finding of the significant effect in systematic reviews on OS offers level 2a evidence for efficacy according to the Oxford Criteria for Evidence-based Medicine (Centre for Evidence-Based Medicine, 2009). (2) One meta-analysis explicitly mentioned the lack of increase of adverse events as compared to the data in the control group (Lv et al., 2020). A significant prolongation of OS by a treatment without additive toxicity is an extremely important point in the context of a cancer disease with virtually no chances for long-term OS. (3) No paper discussed a potential difference in the progression-free survival (PFS), induced by the DC vaccination. This is partially due to the potential induction of pseudoprogression due to DC vaccination, which makes the interpretation of magnetic resonance images very challenging. Several publications illustrated this topic and provided guidelines for clinicians (Aquino, Gioppo, Finocchiaro, Bruzzone, & Cuccarini, 2017; Heugenhauser et al., 2022; Okada et al., 2015).

7 The changing landscape of immunotherapy of GBM

Since the hallmark publication in 2005, the standard of care for GBM patients changed from neurosurgery+radiotherapy toward neurosurgery+radiochemotherapy+maintenance chemotherapy with TMZ (TMZm) (Stupp et al., 2005, 2009). The vital role of the O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation

status was demonstrated (Hegi et al., 2005), showing that MGMT promoter-methylated GBM patients have a better prognosis than MGMT promoter-unmethylated patients. The higher MGMT enzyme activity in promoter-unmethylated patients neutralizes the genetic damage of radiotherapy and chemotherapy, resulting in a worse prognosis. Researchers had to take the new standard of care of combined treatment into account when bringing DC vaccination into first-line treatment. It became a point of consideration to stratify randomizations for MGMT promoter-methylation status, to use this status as inclusion or exclusion criteria in a study, or to perform *post-hoc* analyses using this prognostic factor.

Another major challenge occurring in the same period was the installation of the EU Directive 2001/83/EC and EU Regulations 726/2004 and 1394/2007, and their implementation in the Member States in the next years. These regulations appointed DC vaccines as Advanced Therapy Medicinal Products (ATMP), to be produced under strict Good Manufacturing Practice (GMP) conditions. In the same period, the Clinical Trial Directives 2001/20/EC and 2005/28/EC also entered the medical field, referring to Good Clinical Practice (GCP) for conducting clinical trials. The way how DC vaccination of GBM patients had started in the beginning would never have been possible after the implementation of the current combination of directives and regulations. Increasing the quality at the level of DC vaccines production and their clinical testing was aimed to increase the benefit for patients. In reality, especially the administrative burden and costs to conduct clinical trials with ATMPs increased, so that it became extremely difficult for academic and industrial researchers alike. The uncontrolled not-evidence-based permanent increase of quality requirements actually resulted in reduced accessibility for patients. This is exemplified in the industry-driven studies with DCVax®-L (NCT00045968), which could not recruit patients for years due to financial issues (Liau et al., 2018, 2023). Another example of an industrial DC vaccine trial of which completion failed due to financial reasons is the ICT-107 phase III trial (NCT02546102). Similarly, the academia-driven phase IIb RCT HGG-2010 (EudraCT 2009-018228-14) was prematurely terminated by the sponsor without comments. Fortunately, the high quality data from this trial were published later on under the name of Glioma Translate Study, and demonstrated favorable OS in comparison to published data (Stupp et al., 2005, 2009), even in the worst epigenetic subgroups of mesenchymal and RTK I GBM (Dejaegher et al., 2021).

8 Integration of DC vaccination within the first-line combined treatment for GBM

Active specific immunotherapy reportedly has the best results in minimal residual cancer disease status (De Vleeschouwer et al., 2008; Lasky III et al., 2013). This status is usually reached at best after the first neurosurgery and radiochemotherapy. This clinical condition makes patients with first-line GBM diagnosis the optimal patient group to perform larger RCTs, in which DC vaccination as experimental

treatment is included in a combined treatment approach. The available experiences with DC vaccination in relapsed patients supported the step to study DC vaccination as part of the first-line combined treatment. Reviewing all clinical trials in which DC vaccination was given as part of first-line combined treatment, DC vaccination was given mostly after radio(chemo)therapy, and was continued during the TMZm. Multiple arguments have been discussed in placing DC vaccination after radiochemotherapy (Van Gool & De Vleeschouwer, 2012). In addition, other data suggested increased sensitivity of GBM to TMZ after DC vaccination (Wheeler et al., 2004), making the sequence of the treatment modalities in the combined treatment approach obvious. In spite of the observed significant shift in OS demonstrated in the meta-analyses, the overall clinical benefit from DC vaccination for OS, when given as part of combined first-line treatment after radiochemotherapy, remained disappointing. This might be due to the hematotoxic effect of TMZ impeding primed T cells multiplication during their proliferative phase (Buchroithner et al., 2018; Dutoit et al., 2020). Furthermore, radiochemotherapy is associated with changes in regulatory and effector peripheral blood mononuclear cells that tilt the balance toward an immunosuppressive state (Fadul et al., 2011). Only in the phase IIb HGG-2010 trial (EudraCT 2009-018228-14) (Antonopoulos et al., 2019; Dejaegher et al., 2021; Van Gool, 2015), patients were randomized between DC vaccination after radiochemotherapy and boost vaccines during TMZm, *versus* a similar immunotherapy schedule after the 6 TMZm cycles. The final results for the primary question, PFS, were not published. The OS data were published for different epigenetic subgroups irrespective of the randomization arm (Dejaegher et al., 2021). As part of the European project Computational Horizons in Cancer (Stamatakos et al., 2014), a subset of OS data from patients, including information about their randomization, became available (Antonopoulos et al., 2019). In both the complete resected and less than complete resected subgroups of patients, there was a trend for better 2-year OS when the DC vaccines were given after the chemotherapy instead of before and during chemotherapy. These findings are compatible with the suggestion that TMZ might affect the T cell response upon vaccination (Buchroithner et al., 2018; Dutoit et al., 2020). DC vaccination was thus definitively placed after chemotherapy.

9 Challenges to design randomized clinical trials with dendritic cell vaccines as part of first-line treatment of GBM

For the design of an optimal combined treatment strategy that includes neurosurgery, radiochemotherapy, maintenance chemotherapy, different modes of immunotherapy, and complementary medicines, several considerations and challenges came together.

1. The low numbers of immune cells and the T cell dysfunction at time of diagnosis (Brooks, Roszman, Mahaley, & Woosley, 1977; Chongsathidkiet et al., 2018;

Dunn, Dunn, & Curry, 2007) and the urgent clinical need to start pre-operative steroids in this patient group should be taken into account as such, and especially when designing combined treatment strategies with immunotherapy as experimental arm. An association of the global composition of the peripheral immune compartment with the ultimate OS was suggested in the phase IIb HGG-2010 trial (EudraCT 2009-018228-14) (Antonopoulos et al., 2019).

2. The unpredictable effect of radiochemotherapy and maintenance chemotherapy on the immune function of each patient (Buchroithner et al., 2018; Dutoit et al., 2020) has not only an impact for designing the best combination when DC vaccination is aimed to be included into the first-line treatment; it also strongly complicates the set-up of RCTs with immunotherapy as experimental arm, because the same unpredictable and uncontrolled effect is present in the control arm.
3. Similarly, the eventually transient but certainly unpredictable clinical need for steroids at a certain time point during first-line treatment might affect results when immunotherapy is the experimental intervention, and its effect on OS has to be analyzed in an RCT. So far, steroid requirement causes patients to drop-out of the study, affecting the representability of the study population.
4. A major consideration in the domain of GBM is the dynamic evolution of the tumor cells and the TME during treatment (Jain, 2018; Suter et al., 2020). Subclones of GBM tumor cells change over time, all having potentially different antigens. Radiotherapy and chemotherapy with alkylating agents like TMZ or Lomustin can increase the TMB in tumor cells and hence their antigenic profile (Daniel et al., 2022). These are all biologic processes that cannot be controlled in control arms of RCTs.

   The authors acknowledge that these elements are all supposed to be so-called equally distributed in both control and experimental arms of RCTs. Still, due to these dynamic changes of the tumor, the tumor-host interaction and the host during treatment, the question arises whether highly dynamic biologic processes can be treated with *a priori* fixed treatment protocols to obtain the best outcome, and whether comparing an experimental protocol with a control protocol in an RCT is the best method in clinical research to move the field forward. Do we interpret differences in treatment efficacy, or are we still at least partially mislead by uncontrolled differences in the biologic kinetics in each patient, in spite of stratified randomizations? Therefore the set-up of RCTs for immunotherapy to treat patients with GBM has been challenged (Van Gool et al., 2021). This particular concern may not only be implied as unique to immunotherapy, but applies to any experimental anticancer therapy.
5. One further consideration at the technical level arises when the tumor is not completely resected. GMB tumor cells always infiltrate into the brain parenchyma, most likely even beyond the radiotherapy field. These cells might also become resistant to chemotherapy. Similarly, glioma cancer stem cells are supposed to be resistant to radiotherapy and chemotherapy, and are the potential source of newly emerging tumor cell clones. When using a vaccine in

which tumor antigens used are derived from the resected tumor, one might miss part of the antigens on tumor cells that are still in the body and that persist in spite of radiochemotherapy and chemotherapy. Adding to this problem, the swift development of GBM heterogeneity and the effects of tumor treatment on tumor composition, combined the time it takes between resection and actual application of tumor lysate in treatment, mean not all current tumor cells can be targeted with past tumor lysate.

6. Finally, if data suggest that the placement of DC vaccines is probably better after TMZm, then the tumor control during the period of monotherapy with TMZm has to be strengthened. This could be realized with the addition of ICD immunotherapy during TMZm chemotherapy.

10 Immunogenic cell death immunotherapy for GBM

ICD is recently described as a specific form of Regulated Cell Death, which causes an adaptive immune response specific for endogenous (cellular) or exogenous (viral) antigens expressed by the dying cells (Galluzzi et al., 2018, 2020). Several cell-killing mechanisms can induce ICD, like viral infections, some chemotherapeutics (like anthracyclines), particular techniques of radiotherapy, hypericin-based PDT, and electromagnetic waves (TTF or mEHT). The mechanism of ICD is based on timely release of Damage Associated Molecular Patterns (DAMPs) whose recognition by Pattern Recognition Receptors (PRR) expressed by innate and adaptive components of the immune system warns the organism of a situation of danger, resulting in the elicitation of an immune response generally associated with the establishment of immunological memory. Six DAMPs seem to play a crucial role for ICD: (1) expression of calreticulin on the membrane ("eat me"-signal for phagocytosis by macrophages, neutrophils and DCs), (2) secretion of ATP ("find me"-signal for macrophages and DC precursors), (3) secretion of high-mobility group box 1 (HMGB1) which binds mainly on TLR4 ("approach me"-signal), (4) secretion of broadly immune stimulatory type I interferon (IFN), (5) release of cancer cell-derived nucleic acids which are taken up by DCs, macrophages and neutrophils, and (6) annexin A1 (ANXAI) which specifically engages DCs via Formyl Peptide Receptor 1 ("recognize me"-signal). Of note, dysregulated cancer cells usually make less IFN type I, a mechanism that can be used through oncolytic Newcastle Disease Virus (NDV) to target a broad spectrum of solid tumors (Bommareddy, Shettigar, & Kaufman, 2018).

10.1 Newcastle disease virus

NDV is a single strand RNA virus. It binds to TLRs in particularly TLR3, 7 and 8. NDV also binds to the cytoplasmic Retinoic acid Inducible Gene I (RIG-I) receptors which ultimately causes an IFN type I response (Fournier, Wilden, & Schirrmacher, 2012). Healthy human cells use this mechanism to protect them against NDV,

whereas cancer cells fail and remain sensitive to the lytic effect (Bommareddy et al., 2018). At the same time, one can use this mechanism in DCs to polarize the mature DCs toward a DC1-type response (Fournier, Arnold, & Schirrmacher, 2009; Qian et al., 2017).

This all means that NDV can be used as ICD immunotherapy in patients, eventually during TMZm chemotherapy, and as an *ex vivo* danger signal for making DC vaccines thereby also delivering NDV antigens into the DCs. The use of OVs as platform to target DC-activating pathways emerges in preclinical models and clinical applications (Zheng et al., 2023).

The first report of a cancer response in acute leukemia after exposure to NDV was published in 1964, almost 60 years ago (Wheelock & Dingle, 1964). Since then, a lot of basic scientific knowledge, translational work and clinical experiences have been realized (Schirrmacher, 2016). NDV is a member of the Avulavirus genus in the Paramyxoviridae family (Zamarin & Palese, 2012). There are three pathotypes, depending on the severity of the respiratory and gastrointestinal disease that it causes in birds: lentogenic (avirulent), mesogenic (intermediate) or velogenic (virulent) types. The latter two types are oncolytic. The reported inability of human cancer cells to produce type I IFN mean they cannot mount a primary defense against this type of virus (Bommareddy et al., 2018).

About 30 years after its discovery as an oncolytic virus, the first research letter about the use of intravenous NDV for the treatment of an adolescent with GBM was published (Csatary & Bakacs, 1999). Five years later, the same group published a first small series of 3 children (12 year, 12 year, 1.5 year) and one adult (42 year) with GBM treated with intravenous NDV (Csatary et al., 2004). In the same year, a small non-randomized study was published which demonstrated beneficial effects (induction of immune response and improvement of OS) of an intratumoral application of autologous tumor cells, which were *ex vivo* expanded and lysed with NDV (Steiner et al., 2004). The first more formal phase I/II trial for the use of intravenous NDV in patients with recurrent GBM was published two years later (Freeman et al., 2006). The combined intravenous and inhalation route was used in a pediatric GBM patient (Wagner et al., 2006). Overall, there was no maximal tolerated dose, and an obvious absence of major toxicity beyond grade II, conclusively appointing NDV as a safe and effective treatment for GBM patients.

While GBM patients, including children, had already profited from NDV treatment, studies to understand the working mechanisms of NDV against GBM tumor cells came later. It became clear that the treatment of tumor cells with NDV induced the requirements necessary for the induction of an anticancer immune response (Fournier, Arnold, et al., 2012; Koks et al., 2014; Qu et al., 2018), reflecting ICD. Immunologic insights were then worked out in several different strategies for clinical use in different cancer types (Schirrmacher, 2015). In one strategy, cultures of tumor cells were infected with NDV, and viral oncolysates (VOL) were used as vaccine. A variant strategy was the use of autologous irradiated tumor cells modified by infection with non-lytic lentogenic NDV, called autologous-tumor-vaccine-NDV (ATV-NDV). The major challenge in this strategy is a GMP-approved culture of

autologous GBM tumor cells, which should keep the antigenic profile of the *in vivo* tumor during *in vitro* culture passages. Therefore, *in vivo* ICD induction creating *in vivo* VOL and triggering an *in vivo* immune response seemed to be a more relevant approach, and in fact supported the already available older clinical experiences (Csatary et al., 2004; Csatary & Bakacs, 1999; Freeman et al., 2006; Steiner et al., 2004; Wagner et al., 2006). The application of oncolytic NDV is now considered an effective immunotherapeutic strategy against GBM (Cuoco, Rogers, & Mittal, 2021; Meng et al., 2021). NDV mediates tumor cell killing, regulates autophagy by tumor cells, counteracts the immunosuppression in the TME, and activates the immune response (Huang et al., 2022; Schirrmacher, van Gool, & Stuecker, 2022). NDV can even be manipulated to enhance and direct the immune response (Vijayakumar, McCroskery, & Palese, 2020; Xu, Sun, Mei, Liu, & Zhao, 2018). Of particular interest is the discovery that NDV enhances the growth-inhibition and pro-apoptotic effects of TMZ on GBM cells (Bai et al., 2018).

10.2 Electromagnetic fields

In the search to find new treatment modalities against GBM, the use of radiofrequency electromagnetic fields became of interest. Electromagnetic fields induce thermal and non-thermal effects on cancer cells (Minnaar & Szasz, 2022; Wust et al., 2022). Alternating electric fields induce cell cycle arrest in human GBM tumor cells (Kirson et al., 2007). The use of TTF (100 to 300 kHz with a minimum field intensity of 1 to 3 V/cm for >85% of the time) entered the clinical field, and a RCT could demonstrate its efficacy in GBM patients (Branter, Basu, & Smith, 2018; Stupp et al., 2017). The effect of TTF in combination with TMZm did raise the question about its working mechanism, because the induction of cell cycle arrest in combination with TMZ, which requires cell cycling for its effect, remained unclear. Later on, increased membrane permeability in GBM cells (Chang et al., 2018), the induction of ICD (Voloshin et al., 2020), and the activation of inflammasomes to induce adjuvant immunity (Chen et al., 2022) emerged as potential working mechanisms.

A similar attempt to induce an anticancer effect was performed with local mEHT (13.56 MHz with a power of 40 to 100 Watt for 20 to 60 min). The rationale and mechanisms to kill cancer cells have been worked out (Hegyi, Szigeti, & Szasz, 2013; Szasz, 2007, 2019), the mechanism of ICD due to mEHT has been reviewed (Lee et al., 2018), and preclinical models (Vancsik et al., 2018) and clinical experiences (Minnaar et al., 2020) have demonstrated the ICD effect. The first experiences with mEHT for GBM were already presented almost two decades ago (Fiorentini et al., 2006). More recently, this same group published an update of their experiences (Fiorentini et al., 2018). Of note, the combination with alkylating chemotherapy showed safety, feasibility and efficacy (Roussakow, 2017; Wismeth et al., 2010).

10.3 ICD immunotherapy at the IOZK

Both intravenous bolus injections with NDV (1 to 10×10^7 infectious particles), and sessions of mEHT (40 to 60 Watt for 50 min), are applied together as ICD immunotherapy (Van Gool et al., 2023). For GBM patients, 100 mL Mannitol 10% is infused

immediately before NDV administration in order to facilitate blood brain barrier penetration. The bolus injection of NDV is aimed to reach a high peak concentration for the infection of tumor cells, because the virus is cleared out of the blood very fast after injection. The mEHT sessions were originally performed over three consecutive days, but for about 5 years 5-day treatment cycles are given.

11 Extracellular microvesicles and apoptotic bodies: A new source of tumor antigens for DC vaccines?

Communication between cells in an organism is crucial for regulation of all biologic processes, survival of the cells and ultimately the organism. Besides intercellular communication via hormones, cytokines and chemokines, and released molecules, a complete new domain of extracellular vesicles (EVs) opened in the last decennium (Hendrix, 2021). Their notable role in tumor biology has been recognized (Willms, Cabanas, Mager, Wood, & Vader, 2018). Because of their novelty and complexity, the International Society of Extracellular Vesicles (ISEV) classified the diverse types of EVs based on size, occurrence and function as exosomes (30–100 nm), extracellular microvesicles (100–1000 nm), and apoptotic bodies (>1000 nm). Different biologic roles of the different EVs should be interpreted in the light of the accurate definition. EVs play a role in GBM biology (Broekman et al., 2018; Giusti, Di Francesco, & Dolo, 2017), in particular a role in immune suppression in the TME (Domenis et al., 2017; Himes et al., 2020, 2021; Ricklefs et al., 2018; Wang, Jia, Cui, Peng, & Jiang, 2021). The release of small exosomes can have pro-inflammatory and anti-inflammatory effects (Othman, Jamal, & Abu, 2019). On the other hand, EVs can be used as anti-cancer therapeutics (Jurj et al., 2020; Lener et al., 2015). Finally, the plasma concentration of EVs can be used to obtain information about diagnosis, response to treatment and identification of relapse in GBM, independently from the GBM molecular subtype (Ab Razak, Ab Mutalib, Mohtar, & Abu, 2019; Del Bene et al., 2022; Osti et al., 2019). The potential translation of plasma EV concentration in a clinical setting has been called "vesiclemia" (Sabbagh, Andre-Gregoire, Guevel, & Gavard, 2020). In this context, liquid biopsy for diagnostics and disease monitoring was redirected by the authors to include liquid biopsy for therapy. Upon ICD, EVs are released, which potentially contain tumor antigen/MHC molecules on membrane fragments as well as DAMPs like HMGB1, heat shock proteins and S100 proteins (Abu, Rus Bakarurraini, & Nasir, 2021). These microvesicles and apoptotic bodies can serve as source of tumor antigens (Van Gool et al., 2021) obtained without the need for tissue sampling. Most interestingly, antigens yielded through ICD immunotherapy reflect the current antigenic spectrum of the tumor cells in the body.

For vaccine production, monocytes are purified via adherence, and are differentiated toward immature DCs in the presence of IL-4 and GM-CSF. Immature DCs are then loaded with tumor antigens derived either from tumor lysate, but mostly from ICD immunotherapy (5 NDV intravenous bolus injections plus 5 sessions of mEHT)-induced serum-derived antigenic extracellular microvesicles and apoptotic bodies.

Finally, loaded DCs are matured in the presence of IL1b, TNFa, IL-6 and NDV. This is our IO-Vac® vaccine. IO-Vac® is to be administered intradermally. The IOZK received the formal approval to produce this patient-specific vaccine as ATMP for use in human at 27/05/2015: "specific autologous anti-tumor dendritic cell vaccine for intradermal application: patient-autologous monocyte-derived dendritic cell, loaded with tumor antigens from lysates from autologous tumor cells and matured with danger signals from Newcastle Disease Virus" (Authorization numbers: DE_NW_04_MIA_2015_0033 and DE_NW_04_MIA_2020_0017).

12 Individualized multimodal immunotherapy as part of first-line multiphase combined treatment for GBM

Taking all the above-mentioned considerations into account, we designed a rational novel combined treatment strategy for GBM patients, starting from the standard of care (neurosurgery, radiochemotherapy, TMZm). The standard of care was strengthened with IMI, and includes three treatment phases (Schirrmacher, Lorenzen, Van Gool, & Stuecker, 2017; Van Gool, Makalowski, Domogalla, et al., 2020; Van Gool et al., 2018, 2021, 2022, 2023).

1. The first phase is aimed to optimize anti-cancer activity beyond monotherapy with only alkylating agents. Whereas TMZ with or without Lomustin kills tumor cells via genetic damage and subsequent cell killing during cell cycling, ICD immunotherapy with bolus injection of NDV and sessions of mEHT kills tumor cells via their specific ICD mechanisms. Combination therapies with other OVs different from NDV for the treatment of GBM have been reviewed (Qi, Long, Liu, & Cheng, 2022), pointing to the general principle behind the treatment strategy. Already in this phase, inflammation should be maximally suppressed by treatment with Curcumin, which we can deliver as an oil-holding spray for buccal resorption resulting in high blood concentrations. The beneficial role of curcumin in polarization of myeloid cells has been suggested in preclinical research models for GBM (Mukherjee et al., 2016). The use of the Cyclooxygenase-2 inhibitor Celecoxib is well known, and has been included as part of combination drugs in a recent phase Ib/IIa clinical trial (Halatsch et al., 2021). Blockage of M2 macrophages is reached with Histamine Receptor-1 antagonists (Li et al., 2022), and the potency of this strategy for GBM treatment was suggested (Chryplewicz et al., 2022).
2. The second phase starts after all chemotherapy is finished, and is the immunization phase. DC vaccines are generated and administered intradermally. By loading autologous monocyte-derived DCs with ICD immunotherapy-induced serum-derived antigenic extracellular microvesicles and apoptotic bodies, the antigenic spectrum of *in vivo* existing tumor cells, which persist in spite of radiochemotherapy and TMZm, is covered by the vaccine. Recently, this antigenic spectrum has been further expanded with long-peptide vaccines covering some more generally present tumor antigens (Cheever et al., 2009) like

WT1 (Hashiba et al., 2007) and survivin (Chakravarti et al., 2002), in combination with local application of NDV and imiquimod. Both WT1 (Sakai et al., 2015) and survivin (Ahluwalia et al., 2022) have been explored as antigens in vaccines for patients with malignant glioma.

Besides the active specific immunotherapy with vaccines, modulatory immunotherapy is implemented during this phase. The inflammation remains blocked with the combination of Curcumin, Celecoxib and anti-histamin Receptor-1 blockers. Bisphosphonates trigger gamma-delta T cells to target monocytes and down-modulate inflammatory homing (Fowler et al., 2014; Lo Presti et al., 2017). Finally, if PDL1 is detected on tumor tissue, or if the mRNA expression for PDL1 is increased in comparison to mRNA expression for the housekeeping gene GAPDH, the use of pembrolizumab in its standard dose is recommended (Arrieta et al., 2023; Kreatsoulas et al., 2022).

3. The third phase of treatment is aimed to maintain the anticancer immune control, and to expand the covered antigenic spectrum. Repetitive 5-day ICD immunotherapy courses keep targeting and killing new developments of tumor cell clones. Since 2021, a boost vaccine, at least 6 months after the second IO-Vac®, is recommended to increase a memory response to tumor antigens. During this phase, the modulatory immunotherapy strategies continue as well.

The proof of principle for this multiphase combined treatment strategy, which ultimately resulted in the generation of a tumor neo-antigen-specific immune response without the use of tumor lysate and without the use of tumor neo-antigen-specific neo-peptides, has been published (Van Gool et al., 2021). In this case report, neurosurgery, radiochemotherapy and chemotherapy with TMZm alone did not result in anti-tumor immune responsiveness. The addition of ICD courses in connection to further TMZm chemotherapy courses, and one vaccination with IO-Vac® in which ICD immunotherapy-induced serum-derived antigenic extracellular microvesicles and apoptotic bodies were used as antigen, could induce a tumor neo-antigen-specific immune response to some peptides as predicted in the original tumor tissue.

The combined treatment strategy against GBM aims to kill tumor cells, build up an anti-GBM immune response and change the local TME to allow immune access to the tumor cells, and finally to maintain and expand the anticancer immune protection. We implemented several further complementary treatment strategies, which we do not consider as effective against GBM on their own, but which might be of help in controlling GBM. (1) A combination of metformin, atorvastatin and mebendazole has been suggested as metabolic treatment strategy useful in patients with GBM (Agrawal et al., 2019; Shah & Stonier, 2019). The effect of gabapentin on the enzymes in metabolic pathways of glutamate and GABA is to be considered (Goldlust, Su, Welty, Taylor, & Oxender, 1995). (2) The interaction between neurons and glioma cells via AMPA receptor-dependent neuron-glioma synapses (Keough & Monje, 2022; Venkatesh et al., 2019) lead to the investigation of the role of drugs like Perampanel in the treatment of GBM patients (Salmaggi et al., 2021; Venkataramani et al., 2019). (3) The psychoneuroendocrine immunotherapy might contribute to improved OS (Lissoni, Messina, Lissoni, & Franco, 2017).

Outside the combination of the standard of care, IMI and the complementary treatment strategies, some further combination treatment approaches, for which the authors gained experience, are worth to be mentioned. (1) Whereas most chemotherapies affect the immune functioning, the intranasal application of perillyl alcohol (POH) does not, and has been successfully combined with IMI. The working mechanism of POH on glioma cells is diverse (Chen, Fonseca, & Schonthal, 2015; da Fonseca et al., 2016). Its effect to control malignant glioma and so prolong OS has been described (da Fonseca et al., 2011, 2013). During intranasal POH inhalation treatment, IMI can be delivered without additional toxicity. In our hands, such combined treatment could induce disease stabilization and even response to treatment in several patients (unpublished data). (2) Another interesting combination is the application of IMI together with Bevacizumab. It is known that Vascular Endothelial Growth Factor (VEGF) creates an immune suppressive TME through four mechanisms: inhibition of antigen presentation and DC maturation, inhibition of CD8+ T cell proliferation trafficking and infiltration, promotion of aberrant tumor vasculature and recruitment of immune suppressive cells like MDSC, Tregs and M2 macrophages (Hack, Zhu, & Wang, 2020). This knowledge creates a strong rationale to combine different modes of immunotherapy with Bevacizumab treatment. (3) Dietary measurements like ketogenic diet can influence GBM tumor growth in combination with IMI (Hirschberger et al., 2021; Santos et al., 2018; Seyfried et al., 2019; Woolf, Syed, & Scheck, 2016).

13 IMI integrated during and after standard of care improves OS in adults with IDH1 wild-type GBM

Whereas all patients were treated on an individualized basis ("*individueller Heilversuch*," a German legal framework that will be explained below) in a single private non-profit day-care facility, we were able to retrospectively analyze data of a group of 50 adults with isocitrate dehydrogenase 1 (IDH1) wild-type (wt) GBM (Van Gool et al., 2023). The data reflect real-world data (RWD). Patient characteristics are described in Table 3. The methodology to limit biased selection of patients, and the data on the treatment details are available (Van Gool et al., 2023). We now aim to put the data on OS of this real-world patient group in the light of OS data reported in RCTs that focussed on the efficacy of TMZ (Stupp et al., 2005, 2009), of TTF (Stupp et al., 2017) and of DC vaccination (Liau et al., 2018, 2023). They all fall back on the basis RCT to introduce TMZ as part of the standard of care published by Stupp et al. in 2005 and 2009 (Stupp et al., 2005, 2009). The standard of care with TMZ served as basis for the new RCT with TTF as experimental arm (Stupp et al., 2017). Although treatment is basically similar, the median OS and 2-year OS increased from 12.6 months respectively 14.8% to 14.7 months respectively 22.1% for the MGMT promoter unmethylated patients (Table 4). This might be due to better treatment at relapse, thereby causing a slight prolongation of the OS. In contrast, the median and 2-year OS for MGMT promoter-methylated

Table 3 Patient characteristics in the selected publications.

Reference	Number of patients	Median age (year)	F/M (%)	Median KPI	Meth (%)	Unmeth (%)	Macroscopic complete resection (%)	<Macroscopic complete resection (%)	ND (%)
Gilbert (Gilbert et al., 2013)	411	>50	42/58	>90	30	62	46	44	0
Gilbert (Gilbert et al., 2014)	309	>50	37/63	>90	28	69	59	41	0
Stupp (Stupp et al., 2017)	229	57	31/69	90	42	51	54	46	0
Weller (Weller et al., 2017)	374	58	39/61	>70	35	58	56	44	0
Wen (Wen et al., 2019)	43	60	28/72	>90	42	56	74	26	0
Liau (Liau et al., 2018, 2023)	232	56	41/59	>90	39	56	63	37	0
Van Gool (Van Gool et al., 2023)	50	48	46/54	80	44	56	28	52	20

F, female; KPI, Karnofsky performance index; M, male; Meth, MGMT promoter-methylated; ND, not documented; Unmeth, MGMT promoter-unmethylated.

Table 4 Overall survival reported in selected publications.

		Unmethylated		Methylated	
Reference		mOS (m)	2y OS (%)	mOS (m)	2y OS (%)
Stupp (Stupp et al., 2009) RCT	S + RT	11.8	1.8	15.3	23.9
	S + RCT + CT	12.6	14.8	23.4	48.9
Stupp (Stupp et al., 2017) RCT	**S + RCT + CT**	**14.7**	**22.1**	**21.2**	**37.7**
	S + RCT + CT + TTF	16.9	26.8	31.6	59.1
Liau (Liau et al., 2023) ECA	**S + RCT + CT**	**14.6**	**21**	**21.3**	**42**
	S + RCT + CT + DCVax®-L	14.9	19	30.2	58
Van Gool (Van Gool et al., 2023) RWD	S + RCT + CT + IMI	22.1	39	37.7	80.5

IMI, individualized multimodal immunotherapy; m, months; mOS, median overall survival; RCT, randomized controlled trial; RDW, real-world data; S + RT, surgery + radiotherapy; S + RCT + CT, surgery + radiochemotherapy + chemotherapy; TTF, tumor-treating fields; 2y OS, 2-year overall survival. Expected OS with standard of care treatment anno *2023 are marked in bold and gray background.*

patients did not change: 23.4 months respectively 48.9% in 2009 and 21.2 respectively 37.7% in 2017. The first and only phase III RCT for DC vaccination, published by Liau et al. (2018, 2023), used an external control arm for comparison, including the TTF RCT (Stupp et al., 2017), besides others (Gilbert et al., 2013, 2014; Weller et al., 2017; Wen et al., 2019). Reported results on the expected OS with standard of care treatment, at time of writing this manuscript, are marked in bold and gray background in Table 4.

Overall, our real-world patient group was a bit younger than the patients in the RCTs, with a slightly higher percentage of females. On the other hand, the Karnofsky performance index (KPI) was lower, and the proportion of less than macroscopic complete resected patients was higher. The extent of resection is an important prognostic factor (Stummer et al., 2006). The dynamics of immune variables and tumor characteristics over time during treatment are nicely illustrated (Van Gool et al., 2023). Table 4 shows the published median OS and percentage 2-year OS of the patient groups reported (Liau et al., 2023; Stupp et al., 2009, 2017; Van Gool et al., 2023). TTF significantly prolonged the median OS and percentage 2-year OS in both MGMT promoter-unmethylated and -methylated patients. Induction of ICD by TTF (Voloshin et al., 2020) combined with the standard of care might explain this effect. DCVax®-L during standard of care appeared to significantly improve the median OS and percentage 2-year OS in MGMT promoter-methylated patients, but not in MGMT promoter-unmethylated patients. The retrospectively sampled real-world data on OS of patients in which the standard of care was combined with IMI, including both ICD immunotherapy and DC vaccination in a unique combination approach, and administered with personalized adaptations during treatment, are included in Table 4. Though no scientific research evidence can be drawn out of the RWD from this retrospective analysis of patients treated within the "*individueller Heilversuch,*" the clinical meaning is obvious.

14 Individualized multimodal immunotherapy in the current health care systems

In most countries, the standard of care is organized and paid for by the community. How the national health insurance is organized differs from country to country. Once the standard of care is not giving an appropriate solution toward cure anymore, the patient moves to a new level of care: palliative treatment, euthanasia, or inclusion into a clinical trial (Fig. 1). Palliative treatment and, nowadays available in some countries, euthanasia, are considered as belonging to the standard of care and are again paid for by the society. In contrast, pre-clinical and clinical research is paid for by the researcher who receives the necessary funds to do research. Research can be done by industry or academia. Clinical trials are usually financed by the pharmaceutical or biotech company developing the drug or medical device being tested. The cost of conducting clinical trials can be substantial, running into millions of dollars, and companies generally cover these costs themselves or with the help of investors. In some cases, government agencies or non-profit organizations may also provide funding for clinical trials. Study-selected patients become an anonymized number to allow unbiased gain of knowledge for the researcher. By definition, the patient can or cannot profit from the research, being randomly assigned to the test or control group without their knowledge. It is ethically correct that the patient delivers the data from their own body as an alternative method of payment for the research-treatment. Clinical trial participants may receive compensation for their time and expenses. The extreme high costs for the use of a GMP facility, production

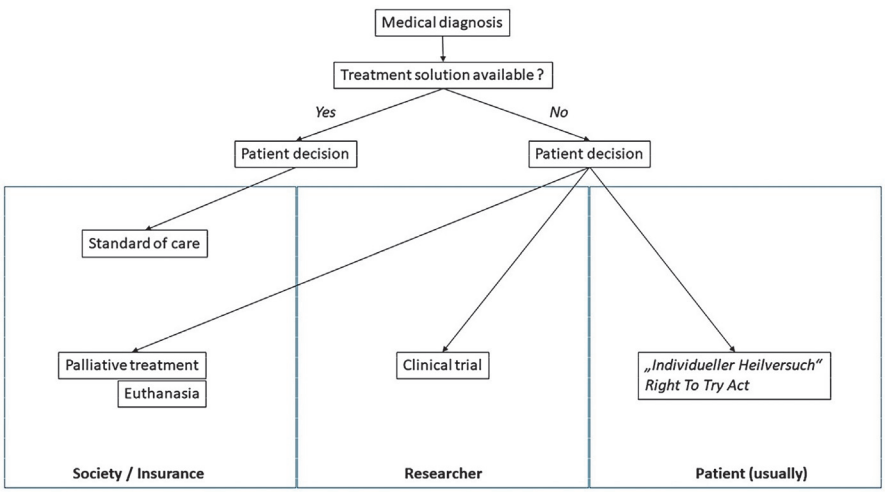

FIG. 1

The health care system.

of DC vaccines for each individual patient, and corresponding clinical trial challenges and documentation, make it virtual impossibility to further develop DC vaccination for GBM in large scale RCTs for both industry, here usually functioning as contract manufacturing organization, as well as academia (Van Gool et al., 2021).

In the last decade, it became clear that the progress to combat cancer with the existing methodologies is insufficient. However, patients in need of future treatment today, as well as patients who do not fit a narrowly defined trial inclusion profile, should have the right to be treated, the right to try, because they have a deadly tumor. In the US, The Cancer Moonshot initiative was launched in 2016 to accelerate scientific discovery in cancer, foster greater collaboration and improve sharing of cancer data (National Cancer Institute, n.d.). The "Right To Try Act" was signed May 30th 2018, creating a uniform system for terminal patients seeking access to investigational drugs that passed Phase I clinical trials and are scheduled for further clinical research (Agarwal & Saltz, 2020; Walker, 2020). When the patient and the drug meet the qualifications of the federal law, the drug can be provided. The federal law bans companies from making a profit on any drug or treatment that has not been approved by the FDA, but the law does allow companies to recover costs that are directly related to providing the individual treatment. Insurance companies and taxpayer-funded healthcare programs are thus not required to cover the costs of investigational treatments in the context of Right To Try, but may choose to do so (Goldwater, 2014).

A prior-existing solution for these patients in Germany is the German legislation framework of the "*individueller Heilversuch*": individualized treatment (Huber, 2014). In this framework, a patient and a doctor discuss together all possible treatment options, design a treatment plan agreed upon by both sides, and sign the informed consent and treatment contract, so that treatment can be given. Such personalized treatment is aimed to be of maximal benefit for the individual patient. There are no scientific questions to be answered during treatment. Only through retrospective analyses of treatment results on these patients, reflections about the approach in the context of "*individueller Heilversuch*" can be obtained.

Whereas the standard of care is paid for by the society/insurance, and research being paid for by the researcher, treatment within "*individueller Heilversuch*" is usually paid for by the patient. In this way, the three financial schemes for the three different frameworks for medical care are clearly distinct (Fig. 1). One question remains: who pays the researcher? Academic research is usually funded by grants or charities, money from the society. Sometimes, academia research is supported by industry. In turn, industry can be supported through grants and investments: again from the society. Most industrial research and development (R&D) is taken on at own risk with private investments. However, once a medicinal product comes on the market, a strong return of investment, including all investments in unsuccessful R&D, is realized. This is again paid for via national health systems by the society. This means that all successful developments of medicinal products, but also all failed R&D, are ultimately paid for by the society. In the "*individueller Heilversuch*," all failed individualized treatments without clinical benefit are paid for by the individual

patient. However, all successful treatments with good clinical results, allowing patients with deadly cancer disease to return to a normal life, are paid for exclusively by the patient, without solidarity or support from the society. The question emerges whether that is ethically correct. Usually, the discussion about reimbursement of successful (individualized) treatment is reduced to the specific evidence defined by the national health systems and insurance companies.

15 The evidence

The fundamental aim of healthcare is to improve overall health of the population by providing state-of-the-art healthcare for individuals at an affordable cost. The foundation for this system is largely referred to as "Evidence-based Medicine." Evidence-based Medicine is defined as the "conscientious, explicit, judicious and reasonable use of modern, "best" evidence in making decisions about the care of individual patients," and integrates clinical experience and patient values with the "best" available research information (Sackett, 1997). In practice it means integrating individual clinical expertise and patient values with the best available external clinical evidence from systematic research (Masic, Miokovic, & Muhamedagic, 2008). Important to note, however, is that external clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all, and, if so, how it should be integrated into a clinical decision (Masic et al., 2008). Evidence-based Medicine constitutes a complex process to allow doctors and patients to select the best possible solutions for each individual patient.

The Oxford Centre for Evidence-based Medicine—Levels of Evidence are typically referred to as standard to assess the level to which a clinical intervention meets scientific evidence (external clinical evidence from systematic research). The levels range from 5 (expert opinion without critical appraisal, based on physiology, bench research or "first principles") to 1 (systematic review of RCTs or pivotal RCT) (Centre for Evidence-Based Medicine, 2009).

Policy makers tend to only accept level 1 evidence for decision-making on "standard of care," and subsequent cost reimbursements or coverage (Jones & Podolsky, 2015). The original intent of the term "Standard of Care" was to define a minimum level of care considered acceptable and without committing malpractice. Over time, the term has evolved to be considered the "appropriate" or "best" care, a level of care that balances risk and benefit, outcomes and costs, and legal fears, and that is based on scientific evidence. Because the RCT, and especially the systematic review of several RCTs, is commonly accepted as the highest level of scientific evidence, it has become the "gold standard" for judging whether a treatment does more good than harm. With this justification, regulators and insurers are (too) often connecting reimbursements of treatment costs to data retrieved from RCT (Marshall, 2006). However, evidence-based guidelines are sometimes untrustworthy when their reliability is measured (Iannone et al., 2017).

A few reflections on why individualized medicine and real-world data should guide decision-making in addition to and beyond RCT methodology:

1. Traditional RCTs focus on hypothesis testing by comparing an experimental arm (e.g. therapeutic intervention) to a control arm (no intervention). By nature, these are study designs, not treatment designs. Aside the financial and logistical complications (such trials take years to design and run, time these patients simply do not have), it implies that patients in the control arm that might benefit from a promising experimental intervention are restricted to the best available treatment and hence refrained such promising benefit, in order to meet scientific design criteria. This is a pertinent ethical concern, given that the Helsinki Declaration requires that "the well-being of the individual research subject must take precedence over all other interests" (Kyr, Svobodnik, Stepanova, & Hejnova, 2021; Nardini, 2014).
2. As RCTs are study designs in support of Evidence-based Medicine, it is important that "all" evidence should be available, both published and non-published, to avoid performing Evidence-biased Medicine. It is often mentioned that about 50% of research is not published, with a vast majority of the publications reporting positive effects, which means that at least half of the research results we can access is biased (publication and reporting bias (EUnetHTA JA2 Authoring Team, 2015)).
3. Traditional clinical trials produce "average" results for a given outcome variable, and sometimes do not answer questions related to why therapies work in some situations and not in others. Ironically, these questions are of most interest to clinicians and of most benefit to patients, especially in oncological research where the idea of proceeding from the genetic and molecular hallmarks of common diseases in order to situationally design and administer the least harmful and most effective treatment (tailored treatment) gains momentum out of apparent necessity (Ellis et al., 2014; Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996).
4. Traditional clinical trials require clear (and multiple) eligibility criteria to ensure that the study population is similar in all baseline factors that may affect the potential benefits and risks from the intervention studied. This not only requires large study populations, with a tendency to get bigger and larger, but it also implies that patients considered at greater risk of adverse events from the trial, and patients not expected to benefit, will be excluded. This might make sense to eliminate bias and balance for unknown covariates. However, overly strict eligibility criteria can cause a lower patient accrual rate. This becomes a challenge for orphan diseases like GBM, where the sample sizes are small and overall survival is low. The result is increased length, complexity and costs of the trial. Ultimately, it can lead to trial results to be less generalizable. These are all pertinent issues in oncology research, resulting in study populations to be unrepresentative of the actual clinical population of patients with cancer, misrepresenting concerns and complications occurring in real-life treatment and

limiting patient access to new treatments (Deaton & Cartwright, 2018; Jin, Pazdur, & Sridhara, 2017; Kyr et al., 2020; Skaga et al., 2021).

5. Traditional clinical trials do not consider the rapidity of advances in tumor biology, which is slicing and dicing cancer into ever smaller subsets. Indeed, an assumption is made that all randomized individuals are, and will remain, homogenous, and that no change within the set of investigated subjects occurs during the study period except the changes due to treatment. This is not true for cancers, which are known to evolve through continuously accumulating additional genomic alterations through high mutation rates. This calls for smaller, shorter, and more focused approaches (Catani, Riechelmann, Adjemian, & Strauss, 2017; Rodon et al., 2015). Especially in oncology, the current strict clinical trial design paradigm needs to be revisited. An extra argument is the hard fact that the "Standard of Care" oncology treatments are associated with over 90% mortality at two years for some metastatic cancers, despite a multitude of clinical trials (Stewart & Kurzrock, 2013).

So, with the objective of increasing the magnitude of treatment effects, there is steadily growing interest in tailoring assessments and interventions to better match individual needs (Lawler et al., 2022; Schork, 2015). Accrual to trials as set out above is slow, if feasible. This calls for innovation and so-called precision-oncology "to offer the right drug for the right patient at the right time" (Subbiah & Kurzrock, 2018). This is possible as we have entered into a new era, with novel insights leading to new, more effective treatment options with higher success rates. This includes opportunities for advanced malignancies, which improve HRQoL, are less toxic, are tailored to specific patient and disease characteristics, and are potentially less expensive.

Lead authorities such as the US Department of Health and Human Services—Food and Drug Administration (US FDA, responsible for all approvals of clinical studies in the US) and the EU Policy Department for Economic, Scientific and Quality of Life Policies therefore called for a review of the current decision-making process on the basis of clinical trials, and recommended—amongst others—for data collected in a non-RCT setting and for well-designed retrospective studies to be considered in future decision making (Couespel & Price, 2020; Food and Drug Administration, 2017). RWD collected at an individual level provide critical evidence that can be used to inform health care decisions, improve treatment, or refine theories (Ismail, 2022). First and foremost, RWD include findings from patients that are often not eligible for trial participations (for reasons explained above). Such data, however, are of utmost importance and relevance for daily clinical practice. Second, RWD can also be used to monitor new systemic treatments, such as interventions for rare diseases (too small samples for trials), awaiting study trial outcomes (given length of study and associated costs), or in case of dynamic pathology processes (e.g. oncology). Therefore, information on real-world effectiveness of treatments is key for daily clinical practice, health technology assessment bodies and insurers, since a broader—more representative—population in clinical practice is treated

using these therapies. Both the FDA and the EU make reference to the rate at which innovative therapies—including immunotherapy—are being developed as an example where RWD shows great value. The current report (Van Gool et al., 2023) about 50 adults with IDH1 wild-type GBM treated with IMI in connection to the standard of care should be considered in this context.

16 Quality of life

The application of Evidence-based Medicine, as defined above, implies decision-making to maximize the individual patient's health. The aim of a medical intervention should indeed no longer be to just extend peoples' lives, but also to improve or maintain their HRQoL. Longer-term surviving patients with cancer often have a chronic disease that requires long-term treatment with potential negative effects on patient's quality of life. HRQoL is defined as "a patient's general subjective perception of the effect of illness and intervention on physical, psychological and social aspects of daily life" (EUnetHTA., 2013). Indeed, professionals and patients are first and foremost interested in the dimensions of life that are affected by a disease, and will be affected by an intervention. Including HRQoL in clinical or epidemiological studies and in clinical practice therefore (1) facilitates an understanding of the patient's perspectives on what is lost or gained as a result of a disease or a medical intervention; (2) can give insight into the balance between therapeutic benefits and adverse effects of an intervention from the perspective of patients; and (3) may aid in defining response in the absence of quantifiable endpoints such as tumor regression (Bottomley, 2002; Cella, Chang, Lai, & Webster, 2002; Wiklund, 2004). Inclusion of HRQoL therefore might be particularly relevant to oncologic treatment, where the downside of intense chemotherapeutic protocols as worldwide standard of care contains multiple side effects both short- and long-term (Niraula et al., 2014), has associated compliance problems (Mooney, Berry, Whisenant, & Sjoberg, 2017), and offers only marginal gains with (expensive) new drugs (Haslam, Herrera-Perez, Gill, & Prasad, 2020).

Challenged by many patients thanks to an increasing number of therapeutic options and personalized approaches as never before, it is becoming increasingly important to address treatment value from a holistic perspective with careful attention given to patients' subjective experience and HRQoL (Reale et al., 2020). As such, HRQoL data have been found to be strong predictors of survival (Sprangers, 2002). A multicenter quality study (Sibeoni et al., 2018) revealed that treatment side effects were the (sole) factor negatively affecting patient's quality of daily life during treatment. These side effects were outweighed by the benefits of having optimal supportive care that make patients feel good. The subjective perception of the efficacy of the anticancer treatment, and the positive effects of good supporting relationships, including with the treating physician, were listed as positive contributions to quality of life. Casali already stated in 1997: "Thus, when a clinical choice is to be made from among different treatment options, the ethical principle of respect for the

patient's autonomy would require that the patient be informed of their possible respective outcomes, and allowed to provide his/her own assessment of the quality of life associated with these outcomes" (Casali et al., 1997). Health state data, combined with data on duration of life, becomes increasingly important as a measure of clinical effectiveness of interventions.

IMI is usually well tolerated and without serious adverse events (Schirrmacher, 2020). The systematic recording of HRQoL was introduced before and during treatment at our institution since October 2021. The registration of self-reported multidimensional health outcomes are important novel assets to evaluate patient welfare, quality of life, and quality of survival. Future research and policy recommendations should consider not just short-term HRQoL outcomes but HRQoL outcomes until the end of life (Haslam et al., 2020). They should be incorporated in global assessments of treatments by medical associations and health insurance companies.

17 Perspectives

IMI in connection to the standard of care was shown to be effective to improve OS in adults with GBM, without increase of adverse reactions. However, the promise of IMI does not stop there. Two innovative and promising adoptive immunotherapies require the development of novel ATMPs: oncogenic virus-specific T cells, and tumor-specific memory T cells derived from bone marrow.

17.1 Tumor-associated virus-specific T cells

The infiltration of tumor-reactive T cells, especially CD8+ T cells, strongly correlates with tumor regression and improves prognosis in cancer patients (Clemente et al., 1996; Gooden, de Bock, Leffers, Daemen, & Nijman, 2011; Kawai et al., 2008; Nakano et al., 2001; Schumacher, Haensch, Roefzaad, & Schlag, 2001; Sharma et al., 2007; Shibuya et al., 2002; van Houdt et al., 2008; Webb, Milne, & Nelson, 2014). Tumor immunosuppressive qualities reduce tumor-reactive T cell infiltration, and those few present have often become anergic (Azimi et al., 2012; Clark et al., 1989; Pages et al., 2010; Sharma et al., 2007; van Houdt et al., 2008; Webb et al., 2014). Autologous T cells can be reactivated through adoptive T cell therapy, during which T cells are extracted from patient blood, reactivated and expanded *in vitro*, and transferred back into patients (Besser et al., 2013; Dudley et al., 2008; Rosenberg et al., 2011; Schumacher et al., 2001; Somerville & Dudley, 2012). As the generation of tumor-specific infiltrating T lymphocytes has proven complex and time-consuming, tumor-associated viruses provide an alternative tumor-specific target.

CMV is a contributing factor to tumor expansion and progression, shown to exclusively occur in cancer tissue (Cinatl, Scholz, Kotchetkov, Vogel, & Doerr, 2004;

Cobbs et al., 2002; Johnsen, Baryawno, & Soderberg-Naucler, 2011; Klyushnenkova et al., 2012; Michaelis et al., 2011; Qiu et al., 2015). A DC vaccine pulsed with autologous tumor lysate elicited a robust CD8+ CMV-specific T cell response (Prins et al., 2008), and low levels of CMV presence have been associated with significantly improved GBM survival rates (Ghazi et al., 2012). Together, this led to the development of CMV-specific adoptive T cell therapy (ATCT): the isolation, *in vitro* restimulation and expansion of CMV-specific T cells for patient reintroduction. Cell-based immunotherapy directed against human CMV has been studied (Duinkerken et al., 2016; Schuessler et al., 2014; Smith et al., 2020; Soderberg-Naucler & Johnsen, 2012; Weathers et al., 2020). A broad spectrum of CMV peptides to cover all potential CMV antigens and further T cell modulation is considered mandatory to improve the success of this approach (Weathers et al., 2020).

CMV-targeting adoptive T cells have been administered to patients in multiple consecutive rounds within RCTs. Cancer patients treated with the CMV-specific adoptive T cells tolerated the T cell infusions well with no to minor serious adverse events related to the treatment (Brestrich et al., 2009; Einsele, Kapp, & Grigoleit, 2008; Mackinnon, Thomson, Verfuerth, Peggs, & Lowdell, 2008; Peggs et al., 2003; Riddell & Greenberg, 1997; Schuessler et al., 2014; Smith et al., 2019, 2020; Weathers et al., 2020). The CMV-expanded T cells can additionally be loaded with NDV, to transport the virus directly to the tumor (Pfirschke & Schirrmacher, 2009).

Other than CMV, Epstein–Barr virus (EBV), Human herpesvirus 6 (HHV-6: a roseolovirus), Adenovirus, Herpes simplex virus type 1 and 2 (HSV 1 and 2), Human papillomavirus (HPV), John Cunningham Virus (JCV: a polyomavirus) and Simian Virus 40 (SV40) have been linked to central nervous system tumors like gliomas based on various molecular biology techniques (Akhtar, Vranic, Cyprian, & Al Moustafa, 2018; Moore & Chang, 2010). For HPV and EBV, adoptive T cell therapy has already been published (Shibata et al., 2021; Straathof et al., 2005; Yang, Farmer, Lin, Wu, & Hung, 2017), as well as a broad-spectrum approach, in which within a single culture an adoptive virus-specific T cell therapy was prepared against 12 immunogenic antigens from 5 different tumor-associated viruses (EBV, adenovirus, CMV, BK virus, and HHV-6) (Papadopoulou et al., 2014).

17.2 Bone marrow-derived T cells

Tumor immunosuppression causes T lymphocyte dysfunction, which is especially severe in GBM patients (Brooks et al., 1977; Chongsathidkiet et al., 2018; Dunn et al., 2007). Where most people have an average blood-circulating CD4 helper T cell count of 962 cells/μL, a substantial number of GBM patients (24.7% compared to 10.9% of control patients) suffer from lymphopenia, with on average 411 cells/μL, of which 15% even had levels comparable to HIV patients, of <200 cells/μL. CD8+ T cells are also severely diminished in number. Lymphoid organs are depleted of immune cells and decreased in size. The missing T cell population was found sequestered in the bone marrow. The sequestered cells lack cell surface receptor S1P1, key to exiting the bone marrow (Chongsathidkiet et al., 2018).

The bone marrow is capable to recruit antigen-loaded DCs from peripheral sites, prime T cells against local and systemic antigens, and generate and recruit memory T cells. Its pivotal role in orchestrating a highly effective antitumor response was defined after detection of tumor antigen-reactive cytotoxic and type-1 memory T cells. Upon restimulation, these cells exert a particularly high proliferative potential and sustain the generation of secondary effector T cells to mediate long-term tumor regression.

Adoptive bone marrow-derived T cell therapy is a highly relevant adjuvant therapy for cancer patients in general and GBM patients in particular. T cells are directly extracted from bone marrow, reactivated using a heterogeneous mix of tumor-antigen pulsed DCs and/or tumor-associated viruses, and expanded *in vitro* before intravenous patient reapplication. Multiple murine and clinical studies have already demonstrated the potential of this approach, which resulted in an increased activated circulating type-1 tumor-reactive T cell population (Domschke et al., 2013; Feuerer et al., 2001, 2003; Schuetz et al., 2009).

18 The model of multiphase combined treatment for patients with GBM

Although GBM is an orphan disease, the community burden is highest amongst all cancer types (Burnet et al., 2005; Rouse et al., 2016). Over the last two decades, only little progress has been made to improve OS with good HRQoL. This is due to the complex biology of the tumor. Old-fashioned clinical research methodologies and excessive regulations and costs in the field of translational and clinical research hinder fast development of scientific innovations. Still, developing a smart combination of treatment approaches with focus on the tumor, on the TME and on the patient might offer a glimpse of hope (Fig. 2). Such combined treatment should be individualized at all possible levels, and each component of the combined treatment should be prone to adaptations along the complete treatment period because of the dynamic character of the tumor, the tumor-host interaction, and the host. The latter requires not only very careful monitoring of the patient with imaging technologies, but also with repetitive liquid biopsies, with attention to molecular biology of the tumor and to all components of the immune system. One should not anymore treat dynamic tumors in dynamic environments with fixed treatment protocols. The three established standard of care anticancer pillars remain of utmost importance: neurosurgery, radiochemotherapy and chemotherapy, but complete treatment should include a fourth pillar composed of novel anticancer strategies in the form of targeted therapies, including immune-targeted therapies (adoptive T cell therapy modalities). A fifth anticancer pillar consists of the physics therapies (electromagnetic waves) and the biologic treatments (OVs), both inducing ICD of cancer cells. All components of these five anticancer pillars are aimed to kill tumor cells and reduce the tumor load. They might already induce an anticancer immune response with the

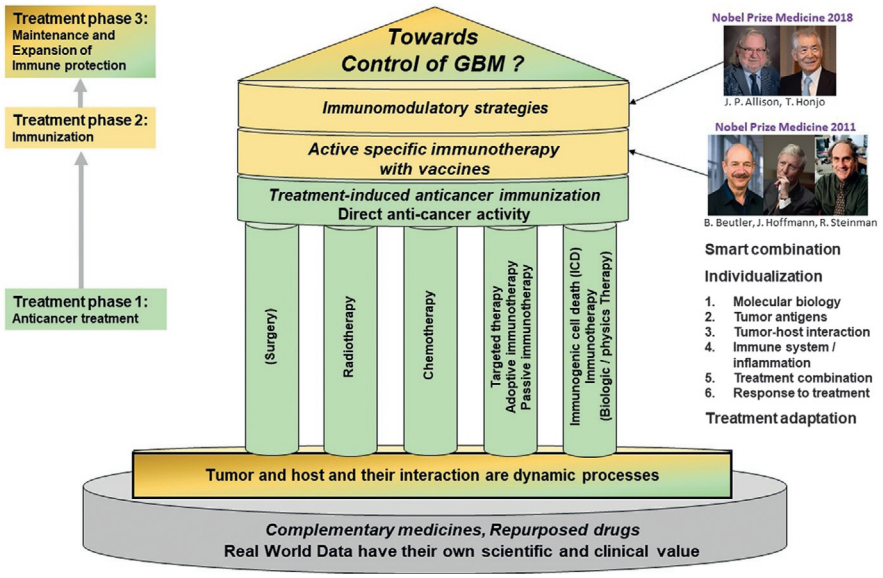

FIG. 2

The model of multiphase combined treatment for patients with GBM.

generation of anticancer immunity. Unfortunately, in almost all cases, this is not enough to sustain control of GBM. That is why we believe that a new layer of treatment is needed after the first phase of anticancer treatment: a second phase of active immunization with vaccines against the cancer. At time of minimal cancer burden, the physician should train the immune system with active specific immunotherapy using current tumor antigens yielded from ICD immunotherapy-killed tumor cells. This layer of treatment has been supported by the Nobel Prize awarded in 2011 to Bruce Beutler, Jules Hoffmann and Ralph Steinman. On top of that, a third layer of treatment should be designed: the modulatory immunotherapy. The generated immune response against the cancer should be modulated so that it can function at the cancer site. This layer of treatment has been supported by the Nobel Prize awarded in 2018 to Tasuku Honjo and James Allison. After the anticancer phase and immunization phase, the maintenance and expansion of the anticancer immune protection is the third phase in the treatment model proposed in this chapter. Finally, a lot of patients are treated with complementary medicines and repurposed drugs. These might only facilitate the multiphase combined treatment efficacy within the body, but cannot be considered as anticancer treatment as such.

The role of RWD in the development of innovative anticancer treatment and in Health Technology Assessment later-on remains a matter of debate (Ismail, 2022). The generation of RWD based on such multiphase combined treatment model should be recognized for its own scientific and clinical value, given the strengths and weaknesses on how they were generated. RWD should be analyzed and reported

so that the medical community ultimately can make progress in controlling GBM in patients, and that multiphase combined treatment approaches can enter the public health environment. The medical community should inform the patients about treatment strategies documented by RWD, certainly when the patient has a life-threatening disease, so that ultimately the patient can make an independent informed decision about treatment.

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