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Prospect of rindopepimut in the treatment of glioblastoma

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Abstract

Introduction—Rindopepimut (CDX-110) is a peptide vaccine that targets epidermal growth factor receptor variant III (EGFRvIII), a tumor-specific epitope expressed in the most common and lethal primary malignant neoplasm of the brain – glioblastoma (GBM).

Areas covered—The EGFRvIII mutation introduces an 801 base pair in-frame deletion of the extracellular domain of the transmembrane tyrosine kinase, resulting in constitutive kinase activity, amplification of cell growth, and inhibition of apoptosis. Rindopepimut contains a 14mer amino acid peptide spanning the EGFRvIII mutation site that is conjugated to keyhole limpet hemocyanin (KLH). The EGFRvIII neoantigen is exclusively present on GBM cells, providing rindopepimut tumor-specific activity. The authors review rindopepimut's clinical efficacy, administration, safety, and prospects in the treatment of GBM.

Expert opinion—Rindopepimut showed clinical benefit and significant efficacy in phase II clinical trials, including as part of a multi-immunotherapy approach. A phase III clinical trial was terminated early, however, as it was deemed likely the study would fail to meet its primary endpoint. Longer term and sub-group analyses will be necessary to better understand rindopepimut's future role in GBM therapy.

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Declaration of interest

JH Sampson is a consultant/has an advisory role with Celldex Therapeutics. His institution also has the potential to receive patent-related royalties from Celldex Therapeutics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Keywords

Glioblastoma; immunotherapy; clinical trials; rindopepimut; peptide vaccine; EGFRvIII

1. Introduction

Intracranial primary tumors lead to approximately 13,000 deaths per year and collectively possess a 5-year survival rate of just 29.1% [1,2]. Glioblastoma (GBM) is the most common primary malignant neoplasm, comprising approximately half of all primary malignant brain tumor diagnoses in the USA [3]. Defined as a World Health Organization (WHO) Grade IV astrocytoma, GBM is also the most lethal malignant brain neoplasm, with a median survival of approximately 14.6 months despite advances in surgical and medical care [4–6]. While the only unequivocal risk factor was previously thought to be ionizing radiation, recent evidence suggests increased rates associated with genetic mutations in gene loci such as *p53*, mutations in *isocitrate dehydrogenase (IDH) 1/2*, and amplification of the *epidermal growth factor receptor (EGFR)* gene [7–10].

2. Market overview

2.1. Current standard of care therapy

In the early 20th century, the treatment for GBM involved aggressive surgical resection with primary goals of palliation; often, just the operative mortality rate was as high as 60% [11]. As Harvey Cushing improved surgical techniques, medical management simultaneously underwent significant progress, and chemotherapeutic regimens were added to treatment regimens. An evidence-based treatment protocol of chemotherapy, radiation, and surgery was standardized in a 2005 *New England Journal of Medicine* article, establishing what is now known as the Stupp protocol [5].

The Stupp protocol states that patients first undergo gross total resection and histologic confirmation of a GBM diagnosis. Six weeks post-operatively, patients begin to receive fractionated focal irradiation at a dose of 2 Gy, 5 days per week, until a cumulative radiation dose of 60 Gy is achieved. While the patients undergo radiation therapy, they are concurrently prescribed oral temozolomide (TMZ) chemotherapy at 75 mg/m²/day, given 7 days a week for a maximum of 49 days. After a 4-week break, patients undergo 6 cycles of subsequent TMZ therapy in 5-day cycles every 28 days, at an initial dose of 150 mg/m²/day, later increased to 200 mg/m²/day if tolerated for the first cycle.

2.2. Developing therapeutic classes

Despite optimal management with the Stupp protocol, the median survival after diagnosis with GBM is less than 15 months and ranks among the most expensive therapies per quality adjusted life year in the USA [12]. Furthermore, incapacitating toxicity to the normal brain remains a significant concern. This has garnered significant interest into the development of additional and more specific therapeutic classes [4,5,13]. A few interventions include anti-angiogenesis drugs, small molecule inhibitors of i.e. tyrosine kinases and signal transduction molecules, and novel cytotoxic agents [14–16]. Furthermore, creating novel drug delivery

mechanisms to improve delivery within the brain, such as Convection-Enhanced Delivery (CED), has also enhanced our therapeutic efficacy.

One of the broadest and fastest-growing classes of GBM treatment is immunotherapy, which leverages the patient's immune system against the tumor. Immunotherapy comprises a wide variety of approaches, including but not limited to: (1) monoclonal antibodies and targeted toxins, including newer approaches such as bi-specific antibodies (BiTEs); (2) antigenic, tumor cell, and dendritic cell (DC) vaccines; (3) adoptive T cell therapies, including chimeric antigen receptor (CAR) T cells; (4) oncolytic viruses; and (5) checkpoint inhibitors [17].

3. Introduction to rindopepimut

In rapidly growing tumor cells, dysregulation of normal DNA repair and replication yields novel mutations that can disinhibit cell growth or increase cell proliferation to further increase a cell's neoplastic potential [18,19]. In the early 1960s, Stanley Cohen and colleagues discovered epidermal growth factor (EGF), which has led way to the discovery and advances of genetic alterations that occur in a variety of tumors [20]. Particularly, genetic modification of the EGFR gene, ensuing an overexpression of EGFR, is found to be one of the most common genetic alterations in malignant gliomas with a frequency of 40% [21–23]. The consequences of the rearrangement of over-expressing EGFR genes in GBM is the expression of a mutated EGFR gene, most commonly EGFR-variant III (EGFRvIII) [24–26]. The EGFRvIII neoantigen is mostly expressed on primary GBM tumors, with a prevalence of 20–30% [27–29]. The most common and accurate detection of EGFRvIII are formalin fixation plus paraffin embedding (FFPE) and immunohistochemistry (IHC) of preserved tissue, and less common are real-time reverse transcription-polymerase chain reaction (RT-PCR) and Southern blot assay [29–31]. EGFRvIII mutation is known to increase proliferation of both the cell and its neighbors; therefore, eradicating EGFRvIII-positive cells may reduce a neoplasm's overall tumorigenicity [23,32].

Targeting the EGFRvIII mutation in intracranial tumors with active immunotherapies began to show promise in 2002 when a study demonstrated an antigen-specific immune response toward EGFRvIII following immunizations with DCs pulsed with tumor-specific peptides in a model of murine intracerebral melanoma [33]. Furthermore, the authors determined that expression of EGFRvIII in GBM is an independent predictor of inferior outcomes [34]. Of note, along with GBM, EGFRvIII has been found to have varying degrees of expression in head and neck squamous cell carcinomas, non-small cell lung cancers, melanomas as well as breast and ovarian carcinomas [27,29,35–38]. There are currently various immunotherapeutic approaches to target EGFRvIII, including monoclonal antibodies, DC vaccines, and genetically modified T cells. Rindopepimut (also called Rintega®, Pep-3-KLH, and CDX-110) is a peptide vaccine toward EGFRvIII that has shown the greatest promise and is the focus of this review. Upon administration of the vaccine, the EGFRvIII antigen is phagocytized by host Antigen Presenting Cells (APCs) and subsequently presented on Major Histocompatibility Complexes I and II to CD8+ (cytotoxic) and CD4+ (helper) T cells, generating an inflammatory response within the brain against tumor cells

[39]. In 2010, Rindopepimut was licensed by Celldex Therapeutics, and is currently an investigational agent (Box 1).

4. Rindopepimut properties

4.1. Chemistry

The wild-type Epidermal Growth Factor Receptor (EGFR) is a 170-kDa transmembrane tyrosine kinase, containing both an extracellular and cytoplasmic ligand-binding domains [27,40]. The EGFRvIII mutation introduces an 801 base pair in-frame deletion of the extracellular domain, resulting in constitutively active Ras signaling to increase the cell's growth potential and amplification, while also inhibiting apoptosis [41,42]. The mutation forms a neoepitope by fusing two normally distant sequences, creating a distinct antigen on the extracellular cell surface marked by a glycine residue at the fusion site.

A 14-amino acid sequence surrounding the fusion site was used to chemically synthesize a peptide (LEU-GLU-GLU-LYS-LYS-GLY-ASN-TYR-VAL-VAL-THR-ASP-HIS-CYS), conjugated to keyhole limpet hemocyanin (KLH) at the peptide's carboxyterminal cysteine to generate the peptide vaccine rindopepimut [43]. KLH, a large copper-containing immunogenic carrier glycoprotein, serves as an adjuvant for rindopepimut that activates both the humoral and cellular immune system [44,45].

4.2. Pharmacology

4.2.1. Mechanism of action—Early preclinical experiments targeting the EGFRvIII antigen with dendritic cell and peptide vaccines in GBM models increased median survival in mice [33,34]. Administering the Pep-3-KLH vaccine resulted in a significant humoral response, with elevated titers of anti-PEP-3 IgG within 8 weeks of vaccination. However, antitumor response was reduced after NK and CD8⁺ T cell depletion, suggesting a key element to the treatment response is antibody-dependent cell-mediated cytotoxicity (ADCC) [34]. Importantly, tumor relapse in murine models tended to occur in a delayed fashion; immunohistochemistry of such relapses demonstrated a loss of EGFRvIII expression, suggesting treatment failure in EGFRvIII^{POS} tumors could be associated with antigen escape and a proliferation of EGFRvIII^{NEG} tumor cells [34,46,47].

4.2.2. Dosing—In the successful 'ACT III' phase II clinical trial, 500 µg of the conjugated peptide vaccine rindopepimut with 150 µg of the adjuvant granulocyte-macrophage colony-stimulating factor (GM-CSF) was administered systemically by an intradermal injection at the groin. Patients initially received the vaccine on days 0, 14, and 28 of treatment; thereafter, the vaccine was delivered monthly and concurrently with the temozolomide regimen described previously. Similar dosing and peptide conjugation was used in the recently discontinued 'ACT IV,' phase III clinical trial. Furthermore, in the completed 'ReACT' phase II clinical trial, 500 µg of the conjugated peptide vaccine rindopepimut with GM-CSF or KLH is being administered. These current dosing regimens have been well tolerated, with minimal toxicities associated with the vaccine.

5. Clinical efficacy

Overall, rindopepimut has shown clinical efficacy in phase I and II clinical trials, with a phase III clinical trial recently discontinued. Described are the clinical trials, phase I–III, and efficacy of rindopepimut for the treatment of GBM (Table 1).

5.1. Phase I

After the success of rindopepimut in preclinical animal studies, the first clinical study conducted to evaluate safety and efficacy in human subjects was a small-scale phase I safety trial ‘VICTORI.’ Inclusion criteria for patient selection were newly diagnosed GBM patients, treated with current standard of care: surgical resection, radiation, and temozolomide (TMZ), age 18-years old, with a KPS of 80. Eligibility, however, did not include tumor EGFRvIII expression. In this study, 12 patients underwent 3 vaccinations in the upper thigh, once every 2 weeks, with peripheral blood mononuclear cell (PBMC)-derived autologous DCs pulsed with 500-μg rindopepimut and evaluated without other treatments until tumor progression was detected. The maximum dose of 1×10^8 rindopepimut-DCs was well tolerated with minimal toxicity. The results suggested that T cells from vaccinated patients underwent antigen-specific proliferation *in vitro*, with T cells from 83.3% and 91.7% of patients responding to PEPvIII and KLH, respectively. Delayed type hypersensitivity (DTH) skin tests were used to determine the presence of a cellular immune response. All patients were positive for tetanus toxoid both pre- and post-vaccination. No patient was responsive to PEPvIII or KLH prior to vaccination; however, 56% and 100% of patients had a positive response to PEPvIII and KLH post-vaccination, respectively. The median progression-free survival (PFS) was 10.2 months, while the median overall survival (OS) was 22.8 months after histopathological diagnosis [48].

5.2. Phase II

In a small single-arm phase II multicenter trial ‘ACTIVATE,’ 18 patients with newly diagnosed GBM, with EGFRvIII-expression and KPS of 80, completing standard-of-care therapy were vaccinated 3 times, once every 2 weeks, with 500-μg rindopepimut and with 150-μg GM-CSF as an adjuvant (NCT00643097). Vaccinations were then administered once a month, thenceforward, until evidence of tumor progression or death. DTH skin tests indicated that, after vaccination, only 18% of patients had a positive response against PEPvIII [49]. Additionally, humoral responses were assessed, and 43% had positive responses post vaccination [49]. Although the sample size of this study is too small to draw any meaningful conclusions, patients with positive DTH response and antibodies against PEPvIII exhibited a prolonged OS compared to those that were negative for these responses. Median PFS and OS from histopathological diagnosis for GBM patients receiving rindopepimut vaccine were 14.2 and 24.6 months, respectively [49,51]. Among GBM patients with recurrent tumors where histopathological tissue could be obtained, 82% lost all EGFRvIII expression. One of the two recurrent tumors that expressed EGFRvIII revealed <1% of total cells staining positive for EGFRvIII [49]. Four patients vaccinated with rindopepimut survived beyond the end of this study.

Similarly, another phase II trial ‘ACT II’ was performed to evaluate rindopepimut vaccination in the context of standard dosing (STD) and dose intensified (DI) of temozolomide (TMZ) chemotherapy regimens. Patient inclusion criteria were similar to those of ACTIVATE, with 22 patients recruited for this study. Rindopepimut was administered, with 150-µg GM-CSF, on the 21st day of a 28-day TMZ cycle. STD resulted in predominantly Grade 2 lymphopenia (<800 cells/µL), and DI resulted in frequently Grade 3 lymphopenia (<500 cell/µL) by the 6th cycle [50]. Though, TMZ treatment diminished both T cell and B cell counts, GBM patients treated with DI regimen had an unexpected increase in regulatory T cells [50]. DTH responses and antibody titers were also remarkably increased in DI-treated patients [50]. The median PFS and OS of all vaccinated patients from study entry date were 15.3 months and 24.4 months, respectively [51].

Following these clinical trials, a randomized multicenter-phase II trial, ‘ACT III,’ was conducted at 24 centers in the USA (NCT00458601). 65 newly diagnosed GBM patients with EGFRvIII expression were recruited for this trial, regardless of HLA subtype. Selection criteria included 18 years of age, no progression after gross tumor resection and chemoradiation treatment, and a KPS score of 70. Patients were administered with 500-µg rindopepimut and 150 µg of the adjuvant GM-CSF, and treated with STD maintenance regimen. Patients were vaccinated bimonthly, for the first 3 doses, and then on the 21st day of a 28-day treatment cycle until intolerance, tumor progression, or death. 85% of patients developed enhanced humoral responses against EGFRvIII, which increased 4-fold over baseline [51]. Cellular responses were also assessed; however, the results were obscured by TMZ-induced lymphopenia [51]. No correlation was found among the various HLA types. Median PFS and OS from histopathological diagnosis were 12.3 and 24.6 months, respectively [51]. EGFRvIII was eliminated in 4/6 (67%) of tumor samples obtained after >3 months of treatment [51].

Concurrently with these phase II clinical trials, novel immunotherapeutic approaches combining rindopepimut with monoclonal antibodies targeted toward vascular endothelial growth factor (VEGF) have shown promise against GBM. ‘ReACT’ was a randomized phase II clinical trial in patients with recurrent EGFRvIII-positive GBM (NCT01498328). 73 bevacizumab-naïve patients in first or second relapse with EGFRvIII positive GBM were randomized one-to-one to bevacizumab plus double-blinded injection of rindopepimut or control (KLH). There were advantages of rindopepimut across the multiple endpoints, including: OS, long-term PFS, objective response rate (ORR) and cessation of steroids greater than 6 months [52]. For the cohort receiving rindopepimut plus bevacizumab versus the cohort receiving KLH plus bevacizumab, the PFS at 6 months was 28% (10/36) and 16% (6/37), respectively, with median OS being 11.3 and 9.3 months, respectively [52]. Moreover, the ORR was 30% (9/30) and 18% (6/34), respectively, and the cessation of steroids greater than 6 months was 33% (6/18) and 0%, respectively [52]. Overall, the rindopepimut-arm of the clinical trial has shown great promise as a combinatory therapy with bevacizumab.

5.3. Phase III

Due to the positive results of the phase II clinical trials, an international, randomized, double-blind, controlled phase III clinical trial, 'ACT IV' (NCT01480479) was initiated. The trial included rindopepimut plus GM-CSF added to standard of care in EGFRvIII positive newly diagnosed GBM patients who have received current standard of care treatment and have not progressed following chemoradiation therapy. While patients were allowed to be enrolled in study regardless of the extent of residual disease, only those with minimal residual disease or less were included in the primary end point analysis. This study was carried out in nearly 200 locations worldwide, with more than 700 patients enrolled. Patients received vaccinations with 500µg rindopepimut plus GM-CSF or KLH alone, each along with maintenance TMZ treatment. The trial was discontinued in March 2016 based on the recommendation of the independent Data Safety and Monitoring Board that the study was unlikely to meet its primary OS end point in patients with minimal residual disease as both the treatment and control arm were comparable. Intriguingly, the control arm surpassed expectations with a median OS of 21.1 months, while the rindopepimut minimal residual disease cohort performed similarly to prior clinical trials with a median OS of 20.4 months.

6. Safety and tolerability

Rindopepimut has been well tolerated throughout all the clinical trials, with minimal toxicities observed. In the 'ACTIVATE' trial of 18 patients, toxicities were all grade 2 adverse events, including neurological symptoms (i.e. parasthesia, 11%), pain (11%), constitutional (11%), GI (17%), dermatologic (6%), and allergic (11%) [49]. In the 'ACT II' trial of 22 patients, the adverse events included dermatologic (rash, itching, flushing: 23%), constitutional (diaphoresis, malaise, fever: 14%), GI (nausea, hypersalivation: 9%), cardiovascular (hypotension, chest pain: 9%), and blood/bone marrow (leukopenia: 5%) [50]. In the 'ACT III' trial of 65 patients, the most prevalent toxicities included injection site-erythema (86%), pruritus (62%), swelling (29%), fatigue (26%), pain (20%), and rash (18%) which were all considered minor [51]. Even though 'ACT IV' was discontinued and 'ReACT' has been completed, there were no major adverse events reported with the administration of rindopepimut for both trials, with Grade 1–2 injection site reaction being common [52].

7. Regulatory and financial affairs

Rindopepimut received the FDA 'Breakthrough Designation' approval in 2015 to be used in clinical trials as a potential treatment for GBM. Due to the recent discontinuation of 'ACT IV' phase III clinical trial, longer term and subgroup analyses of the phase III trial will be necessary to better understand rindopepimut's future role as a monotherapy for GBM. Depending on the results of potential follow up or confirmatory trials based on the 'ReACT' study, there may still be a path for rindopepimut to enter the market and become FDA approved as part of this combinatory approach.

8. Conclusion

The development of a well-tolerated, selective tumor-specific antigen peptide vaccine targeting the EGFRvIII mutation represents a novel therapeutic approach to targeting GBM. Rindopepimut is a 14mer amino acid peptide, conjugated to KLH that spans EGFRvIII mutation site. Rindopepimut showed clinical benefit and significant efficacy in phase II clinical trials, including as part of a multi-immunotherapy approach. A phase III clinical trial was terminated early; however, as it was deemed likely the study would fail to meet its primary end point. Subgroup analyses and follow-up studies will be necessary to better understand rindopepimut's future role in GBM therapy.

9. Expert opinion

Rindopepimut demonstrated potential efficacy in treating GBM as a monotherapy peptide-vaccine in phase II clinical trials that showed promising OS. While, in a phase III clinical trial, patients with minimal residual disease receiving rindopepimut also experienced a comparable increase in survival (median OS 20.4 months); however, the Data Safety and Monitoring Board concluded that rindopepimut would not reach statistical significance for OS due to the control arm surpassing expectations (median OS 21.1 months). Further longitudinal and subgroup analysis is necessary to understand the effects of rindopepimut and the clinical role the peptide will have in GBM therapy.

There may have been several variables and factors that may have contributed to the overall efficacy of rindopepimut in the trial that warrant discussion. One contributing variable may have been the extent of tumor resection performed. There was no established standardization of the extent of resection necessary for the patients enrolled into the clinical trial. Therefore, the efficacy of rindopepimut may not have been consistent due to the inconsistency resection. Another contributing variable may have been the percentage threshold to be considered 'EGFRvIII positive.' There was not an established threshold; therefore, rindopepimut administered to patients with <1% EGFRvIII-positive mutation will not be as efficacious as in patients with >50% EGFRvIII-positive mutation. In the early preclinical studies demonstrated that mice with deficient or decreased EGFRvIII expression by IHC had an unsuccessful response toward rindopepimut vaccination [34]. Therefore, suggesting that low expression of EGFRvIII, either on the tumor or that decreases due to antigen escape may contribute to the overall inefficacy of rindopepimut. Overall, patient selection is important in creating an efficacious response to rindopepimut. Maximizing the tumor resection and having an increased percentage of EGFRvIII-positive mutation cells are important factors in amplifying the therapeutic response of rindopepimut. Furthermore, patients' current health status, comorbidities, and genetic predispositions are also important patient variables that either heighten or decrease the efficacy immunologic therapies. Identifying variables that may reduce the efficacy of rindopepimut is important to understand for both the future of rindopepimut and other peptide-vaccines used to target malignant gliomas.

However, while there may have been several factors that may have hindered the efficacy of rindopepimut, the use of KLH as the control may have demonstrated that even just an

enhanced nonspecific immune response could cause an improved OS. Further understanding of the effects of KLH on the immune system is important to investigate. There may be certain immunogenic responses that are stimulated by KLH that may have a role in treating patients with malignant gliomas.

The use of immunotherapy toward GBM will be a multimodality approach with a variety of immunotherapies targeting different aspects of malignant gliomas. While advances in both understanding and investigation of novel immunotherapies continue to develop, we expect to see an increase in combinatory therapy to effectively target GBM. In the phase II clinical trial 'ReACT,' rindopepimut has shown promise as part of a multi-immunotherapeutic approach. This multi-therapy approach indicates the potential rindopepimut has to continue having a role in the treatment of GBM in the future. However, until 'ACT IV' results are better understood and clinical studies are conducted to confirm ReACT results, the role of rindopepimut remains undetermined.

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Box 1**Drug summary box**

Drug name	Rindopepimut
Phase	Discontinued
Indication	Primary glioblastoma in adult patients who have the EGFRvIII-positive mutation
Pharmacology description	Peptide vaccine that target EGFRvIII antigens expressed by GBM.
Route of administration	Intradermal injection. 500 µg injection dosed at weeks 0, 2, 4 and once monthly thereafter. Dosing regiment based on phase II and III clinical trials
Pivotal trial(s)	ACTIVATE [49] ACT II [50] ACT III [51] ACT IV (NCT01480479)

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Table 1

Summary of rindopepimut clinical trials.

Acronym (Identifier)	Phase	Number of patients	Treatment groups	PFS (Months)	OS (Months)	Ref.
VICTORI	I	12	3 id. doses in inguinal area, once every 2 weeks, with (PBMC)-derived autologous DCs pulsed with 500-µg rindopepimut	Median: 10.2	Median: 22.8	[48]
ACTIVATE (NCT00643097)	II	19	3 injected id. doses in inguinal area once every 2 weeks, with 500-µg rindopepimut with 150-µg GM-CSF, followed by monthly doses.	Median: 14.2	Median: 26	[49]
ACTII	II	22	3 id. doses in inguinal area biweekly, with 500-µg rindopepimut plus 150µg GM-CSF, followed by monthly doses in standard dosing and dose intensified TMZ chemotherapy	Median: 15.2	Median: 23.6	[50]
ACTIII (NCT00458601)	II	65	3 id. doses in inguinal area biweekly, with 500-µg rindopepimut plus 150-µg GM-CSF, followed by monthly doses in standard dosing and dose intensified TMZ chemotherapy	Median: 12.3	Median: 24.6	[51]
ReACT (NCT01498328)	II	72	Bevacizumab-naïve patients in 1st or 2nd relapse with EGFRvIII positive GBM were randomized 1:1 to bevacizumab plus double-blinded injection of rindopepimut or control (KLH)	Median: 12	Median: 12	[52]
ACT IV (NCT01480479)	III	745	500-µg rindopepimut plus GM-CSF or KLH alone, each along with maintenance TMZ treatment		Median: 20.4	