ReACT: Overall Survival from a Randomized Phase II Study of Rindopepimut (CDX-110) Plus Bevacizumab in Relapsed Glioblastoma

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Celldex therapeutics

BACKGROUND & METHODS

EGFR Mutation Variant III (EGFRvIII) and Rindopepimut Vaccine

- EGFRvIII is a tumor-specific oncogene expressed in one-third of primary GBM, seldom expressed with IDH mutations but not in normal tissue
- EGFRvIII(+) cells may induce growth in EGFRvIII(-) cells via paracrine signaling, membrane-derived microvesicles, and tumor stem cells[1-4]
- Rindopepimut consists of EGFRvIII peptide conjugated to Keyhole Limpet Hemocyanin (KLH)
  - Generates a specific immune response against EGFRvIII-expressing GBM
  - "Ready to use" formulation
  - Delivered as intradermal injection of 500 µg rindopepimut with 150 µg GM-CSF as an adjuvant

EGFRvIII Linked To Poor Long Term Survival

Dataset	EGFRvIII+ Median OS (mos)	EGFRvIII+ 3-year OS	EGFRvIII- Median OS (mos)	EGFRvIII- 3-year OS
Heimberger 2005	12	<5%		
Pelloski 2007	12.7	6%		
RTOG 0525, TMZ 5/28	14.2	7%	18.2	25%
RTOG 0525, matched*	16.0	13%	22.2	36%
Lai 2010, matched*	15.2	6%		
German glioma network, all patients	11.3	8%	11.9	17%
German glioma network, matched*	17.0	17%	15.4	26%

* Matched for eligibility for Phase II rindopepimut trials (EGFRvIII+, GTR, radiation/TMZ, no progression through ~3 months post-diagnosis)

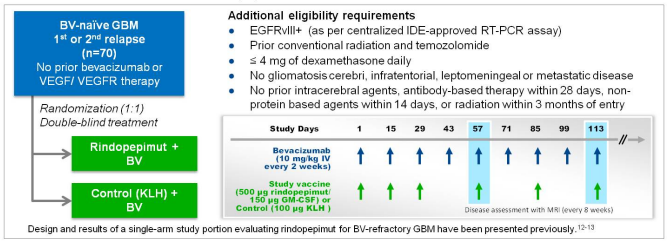
Rationale for Rindopepimut Plus Bevacizumab in Relapsed GBM

- Promising PFS/OS from Phase 2 studies in newly diagnosed, resected, EGFRvIII-expressing GBM[5-7]
- Anecdotal evidence suggests that rindopepimut may induce specific immune responses and regression in multifocal and bulky tumors
  - Marked tumor regression with rindopepimut in combination with standard treatments (compassionate use experience)
- Bevacizumab (BV) may optimize EGFRvIII-specific immune response[8-10]
  - VEGF may mediate immunosuppression (impairs DC maturation, alters tumor endothelium, potentially decreasing immune cell infiltration)
  - BV enhances immune-mediated anti-tumor effect in tumor models

Expected Outcome for Relapsed GBM Treated with BV[11]	
ORR (%)	28
PFS6 (%)	43
Median PFS (months)	4.2
Median OS (months)	9.2

Study Design and Analyses

Randomized Phase 2 study designed to estimate outcome for patients with relapsed EGFRvIII+ GBM treated with standard of care +/- rindopepimut



Additional eligibility requirements
- EGFRvIII+ (as per centralized IDE-approved RT-PCR assay)
- Prior conventional radiation and temozolomide
- ≤ 4 mg of dexamethasone daily
- No gliomatosis cerebri, infratentorial, leptomeningeal or metastatic disease
- No prior intracerebral agents, antibody-based therapy within 28 days, non-protein based agents within 14 days, or radiation within 3 months of entry

Design and results of a single-arm study portion evaluating rindopepimut for BV-refractory GBM have been presented previously.[12-13]

- Primary Analysis: PFS at 6 mos (PFS6) for intent-to-treat (ITT) population
  - Study Design: PFS6 of 40%[11] vs 60%, 1-sided α = 0.2, power = 80%
  - Assessed by a blinded independent review committee (IRC)
- Secondary Analyses: ORR, PFS, OS, safety and tolerability, EGFRvIII-specific immune response
- Supportive/sensitivity analyses: Per-Protocol (PP) population
  - Excludes patients with significant protocol deviations:
    - Randomized but did not receive study treatment (n=1)
    - Screening scan after initiation of BV (n=2)
    - Screening scan > 28 days prior to Day 1 (n=3)
- Tumor response evaluation by RANO criteria: assessment incorporates radiographic data, steroid use and clinical status[14]

RESULTS

Patient Characteristics

		Rindopepimut + BV (n=36)	Control + BV (n=37)
Age, years (median [range])		59 (44-79)	55 (30-75)
≥50 years (n [%])		35 (97%)	27 (73%)
Male (n [%])		19 (53%)	22 (59%)
KPS (n [%])	100	2 (6%)	5 (14%)
	90	13 (36%)	13 (35%)
	80	14 (39%)	12 (32%)
	70	7 (19%)	7 (19%)
Primary GBM (n [%])		35 (97%)	35 (95%)
Time from diagnosis to study entry, months (median [range])		10.8 (3.7-55.2)	11.6 (4.7-38.3)
Relapses (n [%])	1	33 (92%)	28 (76%)
	2	3 (8%)	9 (24%)
Surgery after last relapse (n [%])		15 (42%)	10 (27%)
Gross-total resection		14 (39%)	6 (16%)
Partial resection/unspecified		1 (3%)	4 (11%)
On steroids at study entry (n [%])		18 (50%)	19 (51%)

RESULTS (continued)

- Mean (range) number of vaccinations:
  - Rindopepimut + BV: 9.1 (3, 35)
  - Control + BV: 6.3 (2, 23)
- Rindopepimut + BV was well-tolerated
  - No unexpected toxicity associated with BV administration
  - No SAEs attributed to rindopepimut
  - No discontinuations due to rindopepimut treatment-related AEs
  - Frequent grade 1-2 injection site reactions
  - One G2 hypersensitivity reaction
  - No evidence of increased cerebral edema

Safety

Most Frequent Adverse Events (Regardless of relationship to study treatment)

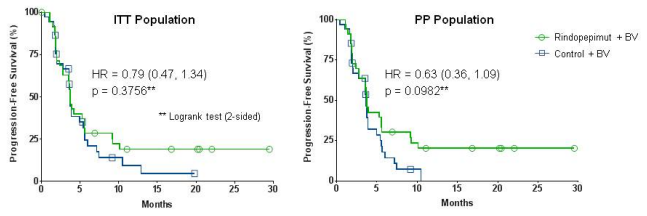
	Rindopepimut + BV (n=35) ≥Grade 3	Rindopepimut + BV (n=35) Overall	Control + BV (n=37) ≥Grade 3	Control + BV (n=37) Overall
Arthralgia	-	8(23%)	1(3%)	2(5%)
Back pain	2(6%)	6(17%)	-	3(8%)
Convulsion	4(11%)	7(20%)	-	9(24%)
Diarrhea	-	6(17%)	-	2(5%)
Fatigue	-	9(26%)	2(5%)	9(24%)
Headache	-	8(23%)	2(5%)	9(24%)
Hemiparesis	-	2(6%)	2(5%)	6(16%)
Hyperglycaemia	-	3(9%)	3(8%)	4(11%)
Hypertension	1(3%)	8(23%)	3(8%)	9(24%)
Musculoskeletal pain	-	-	2(5%)	4(11%)
Nausea	-	8(23%)	1(3%)	4(11%)
Vomiting	-	6(17%)	-	2(5%)

Includes any adverse event occurring at ≥15% frequency, or in >2 patients at severity Grade ≥3, in either treatment group (excluding injection site reactions).

Progression-Free Survival

	Primary Endpoint: PFS6 (Crude rate) ITT population		PP population	
Rindopepimut + BV	10/36 (28%)	p = 0.1163*	10/33 (30%)	p = 0.0310*
Control + BV	6/37 (16%)		4/34 (12%)	

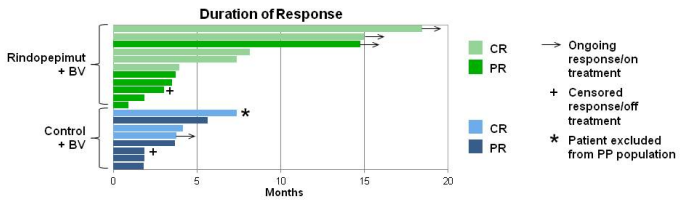
* Chi-square test (1-sided). Study is designed to detect a PFS6 difference with 1-sided α = 0.2. Data based on independent expert radiographic review.



Radiographic Response

	ITT Population Rindopepimut + BV	ITT Population Control + BV	PP Population Rindopepimut + BV	PP Population Control + BV
ORR (confirmed CR/PR)	9/30 (30%)	6/34 (18%)	9/29 (31%)	5/32 (16%)
Any response (≥50% shrinkage) including those not sustained at subsequent assessment	11/30 (37%)	8/34 (24%)	11/29 (38%)	7/32 (22%)

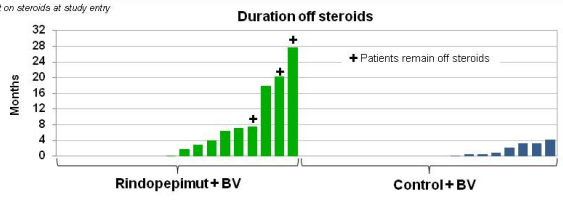
Response-evaluable patient subset with measurable disease. Data based on independent expert radiographic review.



Reduction in Steroid Use

	Rindopepimut + BV	Control + BV
Able to stop steroids for any duration*	10/18 (56%)	8/19 (42%)
Able to stop steroids for ≥2 months*	8/18 (44%)	4/19 (21%)

*Subset on steroids at study entry

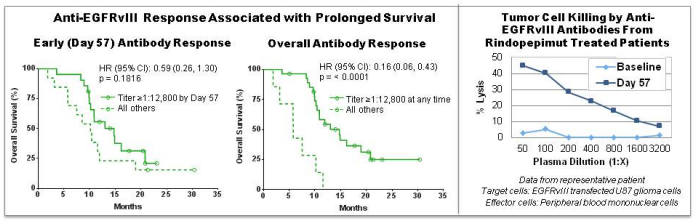


Anti-EGFRvIII Immune Response

Robust Anti-EGFRvIII Immunity Induced by Rindopepimut + BV

- 4-fold increase in anti-EGFRvIII Ab titers in 89% of patients (nearly all remaining patients treated for < 1-2 months)
- High-titer response (1:12,800 to 1:6,553,600) in 80% of patients
- Robust humoral response similar to that seen in studies of newly diagnosed patients, despite advanced disease, use of steroids, presence of bulky tumor
- The prominent isotype is IgG1
- Titer correlates with binding to EGFRvIII+ glioma cells
- Antibodies can mediate tumor cell killing via ADCC and CDC.

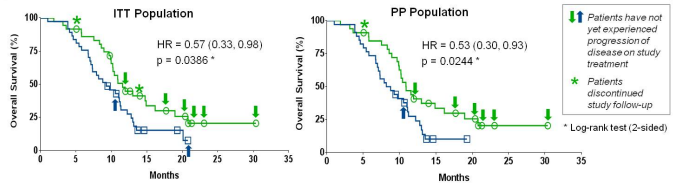
Anti-EGFRvIII Response Associated with Prolonged Survival



RESULTS (continued)

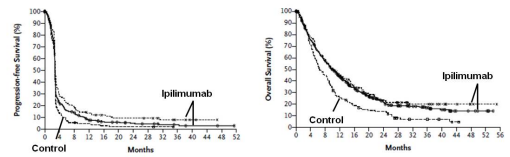
Overall Survival

	ITT Population Median (95% CI)	ITT Population OS 12	ITT Population OS 18	PP Population Median (95% CI)	PP Population OS 12	PP Population OS 18
Rindopepimut + BV	11.6 (10.0, 16.2)	45%	30%	10.9 (9.7, 16.2)	41%	30%
Control + BV	9.3 (7.1, 11.3)	31%	15%	8.5 (6.8, 11.1)	28%	10%

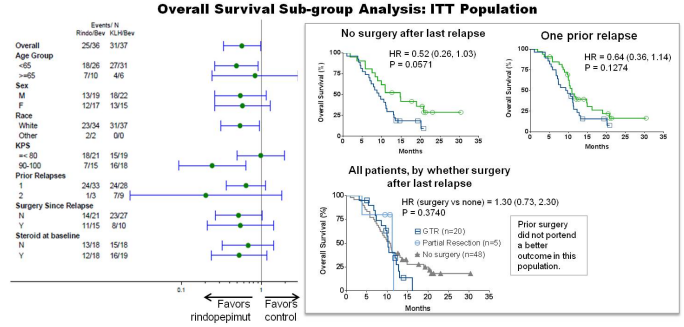


ReACT Results are Consistent with Immunotherapy Experience

FDA approval data – ipilimumab for metastatic melanoma[15]



Overall Survival Sub-group Analysis: ITT Population



CONCLUSIONS

- Rindopepimut was very well tolerated without additive toxicity to bevacizumab
- Bevacizumab-naïve patients:
  - The randomized Phase 2 study met its primary endpoint of PFS6: 28% vs 16% (p = 0.1163)
  - Overall survival advantage (HR=0.57, p=0.0386) with apparent long-term survival benefit
  - Advantage to rindopepimut therapy across multiple endpoints including long-term progression-free survival, objective response rate and steroid requirement
- Bevacizumab-refractory patients: Evidence of rare and prominent tumor regression
  - Up to 11% objective response rate
- Activity profile consistent with prior immunotherapy experience[15]
- Remarkable frequency and level of anti-EGFRvIII immune responses despite prior chemotherapy and growing tumor
  - Development of anti-EGFRvIII titer may be a biomarker of improved outcome
- The Phase 3 trial in newly diagnosed patients (ACT IV) has completed accrual

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