Anti-CD27 agonist antibody varlilumab in combination with nivolumab for recurrent glioblastoma: Phase 2 clinical trial results

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BACKGROUND

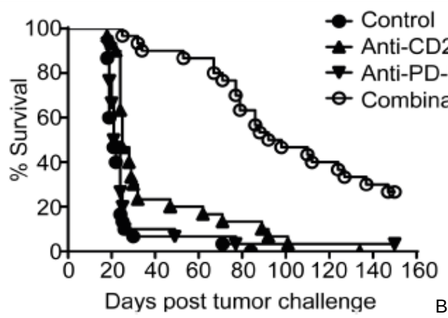
CD27: Member of the TNF-receptor superfamily

- Single ligand is CD70 (tightly regulated)
- Constitutively expressed on most T cells/subset of B and NK cells
- Key immunostimulatory molecule that enhances T cell survival, activation and effector function, as well as NK cell proliferation and cytotoxic activity

Varlilumab: Fully human IgG1 CD27 agonist mAb

- Potent antitumor activity as monotherapy and combination therapy in preclinical models[1,2]
- Well tolerated as single agent, no MTD identified[3,4]
- Single-agent antitumor activity demonstrated in advanced, refractory solid tumors and hematologic malignancies (n=90)[3,4]

Combining CD27 agonist Abs with PD-(L)1 blockade improves antitumor responses[2]



- Reported here are results from GBM-specific phase 2 cohort from a phase 1/2 study of varlilumab with nivolumab (NCT02335918)[5,6]

STUDY DESIGN

Patients
- Recurrent GBM after prior first line TMZ chemoradiation
- Bevacizumab- and check-point inhibitor naïve
- Corticosteroid dose <2 mg/kg dexamethasone

- Up to 32 weeks of combination treatment (varlilumab 3 mg/kg & nivolumab 240 mg q2w), then nivolumab monotherapy until intolerance or progression
- Disease assessments every 8 weeks

Objectives
- Primary: Estimation of OS12
- Secondary: ORR, PFS (iRANO), PK/PD, Tolerability

- 22 patients enrolled between Jun 2016 to Feb 2017
- As of an analysis cut off of 22 Oct 2018: 4 patients remain in survival follow-up, including 3 continuing treatment on nivolumab monotherapy

Abbreviations: NK, natural killer; DLT, dose-limiting toxicity; GBM, glioblastoma; mAb, monoclonal antibody; MGMT, O^6-methylguanine DNA methyltransferase; ORR, objective response rate; OS12, 12-month survival; PFS, progression free survival; PK, pharmacokinetic; PD, pharmacodynamic; TMZ, temozolomide; CI, confidence interval; SRS, stereotactic radiosurgery; RT, radiation therapy

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Celldex therapeutics

RESULTS

Baseline Patient and Disease Characteristics

	All Patients (N=22)
Age, years (median [range])	58 (35-75)
Male	15 (68%)
ECOG PS: 0	8 (36%)
1	14 (64%)
Duration of disease prior to entry, mos (median [range])	13.0 (5.4, 58.1)
PD-L1 expression[a,b]	4/18 (22%)
EGFR amplification/mutation[a]	9/14 (64%)
IDH1 mutation[a]	3/21 (14%)
MGMT promoter:[a] Methylated	5/21 (24%)
Unmethylated	16/21 (72%)
On corticosteroids at entry	6 (27%)

Data shown as n (%) unless otherwise specified.
a. Denominator represents patients with tumor assessed.
b. PD-L1+ criteria: ≥ 1% tumor cells staining positive, using the BMS developed PD-L1 IHC method (Dako PD-L1 IHC 28-8 pharmDx assay) at a central lab

Exposure and Tolerability

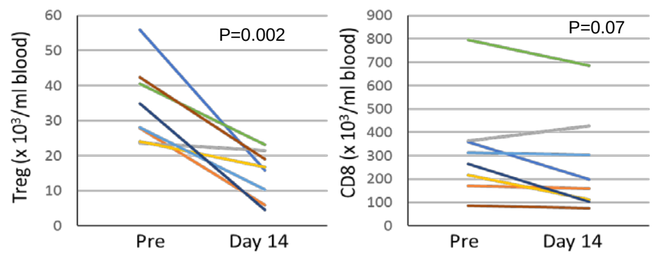
- Patients received a median (range) of 6.5 (1, 16) varilumab doses and 6.5 (1, 50) nivolumab doses
- No DLT or treatment-related deaths
- Two treatment-related serious events (grade 2 gait disturbance, headache and personality changes; grade 4 thrombocytopenia)

Treatment-Related Toxicity

	Any Severity	Grade ≥3
Any treatment-related toxicity	18 (81%)	9 (41%)
Lymphocyte count decreased	10 (45%)	8 (36%)
Headache	4 (18%)	0
Rash maculo-papular	4 (18%)	0
Pruritus	4 (18%)	0
Rash	3 (13%)	0
Hypothyroidism	3 (13%)	0
Amylase increased	3 (13%)	1 (5%)
Nausea	3 (13%)	0
Platelet count decreased	2 (9%)	1 (5%)
Lymphopenia	1 (5%)	1 (5%)
Lipase increased	1 (5%)	1 (5%)

Table presents all treatment-related adverse events with overall incidence >10% or with at least one event of grade ≥3 severity.

Preferential Depletion of T-regulatory Cells



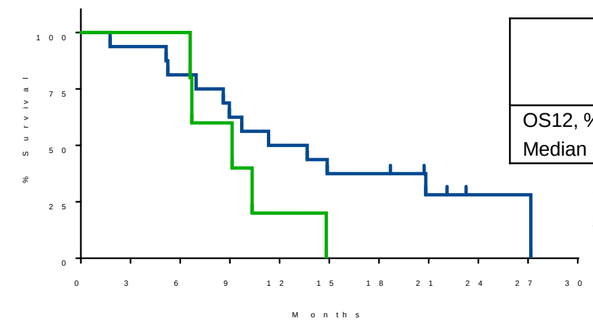
Whole blood was stained for T cell markers and analyzed by flow cytometry for 8 patients. Treg defined as CD4+CD25+FoxP3+.

Clinical Activity

	OS12, % (95% CI)	Median OS, mos (95% CI)	Median PFS, mos (95% CI)	ORR[1]
All Patients (N=22)	41 (21, 60)	10.0 (6.7, 14.9)	1.9 (1.6, 7.3)	2/20 (10%)

1. ORR for response-evaluable population, excluding two patients without measurable disease at study entry

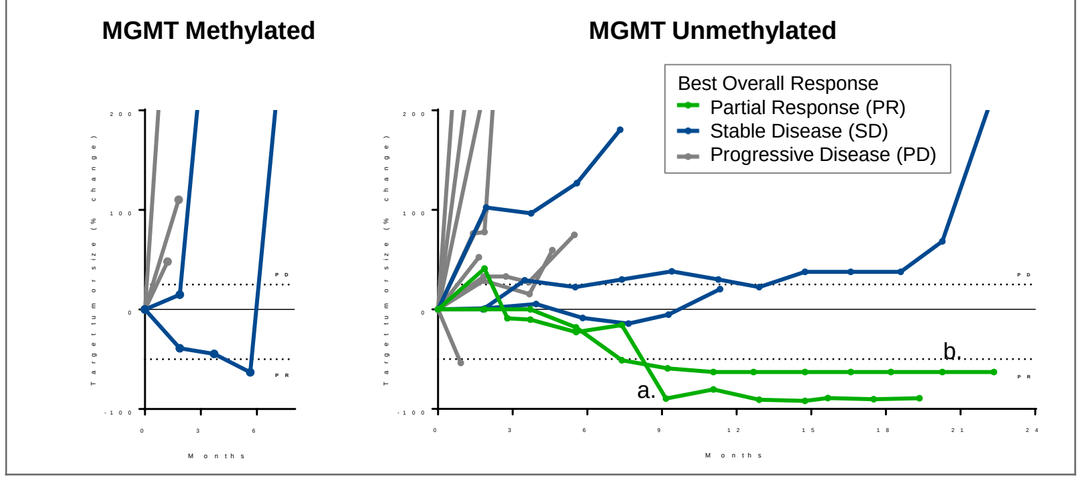
Overall Survival



	MGMT methylated (n=5)	MGMT unmethylated (n=16)
OS12, % (95% CI)	20 (1, 58)	50 (25, 71)
Median OS, mos (95% CI)	9.1 (6.6, 14.8)	12.5 (7.0, 27.2)

9 patients (1 with MGMT methylation, 8 without) survived ≥ 12 months

Tumor Burden



a.
- 60-year-old female with IDH1(-), PD-L1(+; 5%) GBM
- Prior treatments: Partial resection; TMZ/SRS → TMZ/Wee inhibitor (~6 months); relapse ~13 months later
- No steroid use prior to or during the study
- On study: initial pseudoprogression followed by an evolving response. 1st PR at 9.1 months; maximum 92% shrinkage.
- Completed varlilumab; continues nivolumab at 20.7 months

b.
- 71-year-old man with IDH1(-), PD-L1(-) GBM
- Prior treatments: GTR; TMZ/RT → TMZ w/ DCVAX or placebo (~11 months); relapse ~2 months later
- Started steroids (prednisone, 10 mg daily), during the study
- On study: 1st PR at 7.4 months; maximum 63% shrinkage
- Completed varlilumab; continues nivolumab at 23 months

No measurable disease at study entry, therefore subject is not represented on above figure:
- 70-year-old man with MGMT unmethylated, PD-L1 (-) GBM
- Prior treatments: TMZ/RT → TMZ (1 cycle); relapse ~6 weeks later; GTR
- No steroid use prior to or during the study
- Completed varlilumab; continues nivolumab at 21 months

CONCLUSIONS

- Varlilumab with nivolumab was generally well tolerated by patients with recurrent GBM; safety profile is consistent with that of each agent alone
- Durable therapeutic benefit achieved in a subset of patients
- Outcome among glioblastoma patients with unmethylated MGMT promoter (OS12 = 50%), appears encouraging
- Without taking into account MGMT status or other prognostic factors, overall results are similar to nivolumab monotherapy in recurrent GBM (OS12 = 42%)[7]

References:
1. *Wasiuk, et al. JI 2017*
2. *Buchan, et al. CCR 2018*
3. *Bullock, et al. SITC 2014*
4. *Burris, et al. JCO 2017*
5. *Sanborn, ASCO 2017*
6. *Sanborn, ASCO 2017*
7. *Reardon, WFNOS 2017*