Phase 1 results from the combination of an immune-activating anti-CD27 antibody (varlilumab) in combination with PD-1 blockade (nivolumab): activation across multiple immune pathways without untoward immune-related adverse events

Rachel E Sanborn[1], Michael J Pishvain[2], Margaret K Callahan[3], Naiyer Rizvi[4], Harriet Kluger[5], Michael Yellin[6], Tracey Rawls[6], Laura Vitale[6], Abdel Halim[6], Thomas Davis[6], Tibor Keler[6]

1.Earle A. Chiles Research Institute, OR; 2. Georgetown University Medical Center, DC; 3. Memorial Sloan Kettering Cancer Center, NY; 4. Columbia University, NY; 5. Yale Cancer Center, CT; 6.Celldex Therapeutics, NJ

Abstract # CTO23

Background

- CD27 is a key costimulatory molecule expressed on CD4+ and CD8+ T cells and plays roles in T cell activation, proliferation, and effector function, including generation of cytolytic CD8+ T cells, and differentiation to memory T cells.
- Varlilumab is a fully human agonist IgG1k anti-CD27 mAb that has demonstrated biological and clinical activity in a Phase 1 study.
- Preclinical data suggests that a combination of varlilumab with checkpoint blockade will have synergistic anti-tumor activity.
- This Phase 1/2 clinical study explores the biological and clinical activity of combining varlilumab with nivolumab, a fully human anti-PD-1 mAb. We present safety and immune biomarker data from the Phase 1 portion of the study.

Phase 1 Trial Design & Patient Characteristics

- A 3+3+3 design with escalating doses of varlilumab (0.1, 1.0 & 10 mg/kg) in combination with nivolumab (3 mg/kg) for patients with advanced (unresectable or metastatic) colorectal cancer (CRC), melanoma (MEL), ovarian cancer, non-small cell lung cancer (NSCLC), or head & neck squamous cell carcinoma (SCCHN). Backfill of up to 9 additional patients per cohort was permitted, for a total of 15 patients per cohort. The 1.0 mg/kg and 10 mg/kg cohorts were backfilled.
- Primary Objectives:
  - Phase 1: To assess the safety and tolerability of varlilumab in combination with nivolumab, and to identify dose limiting toxicities (DLTs) and the recommended Phase 2 dose.
  - Phase 2: To assess the preliminary antitumor activity, of the combination of varlilumab and nivolumab, as measured by objective response rate (ORR), in all tumor types except GBM which will be measured by overall survival at 12-months (OS12).
- Patients were to have no more than 5 prior therapies; prior treatment with PD-1 or PD-L1 mAbs were excluded.
  - 24 (69%) patients had ≥3 prior regimens and all 4 patients with MEL had no prior treatments.
- Treatment was q 2 wks x 4, with repeat cycles of combination therapy permitted for 4 cycles for patients with SD or better. Subsequently, nivolumab monotherapy was permitted until PD or intolerance.
- 35 patients have been enrolled in the Phase 1 phase of the study.

Patient Characteristics	n=35
Age, years (range)	30-85
Females [n (%)]	18 (51%)
Males [n (%)]	17 (49%)
Race [n (%)]	
White	29 (83%)
Black, Native Hawaiian and Asian	3 (9%)
Unknown	3 (9%)
Tumor Types	
CRC	20 (57%)
Ovarian	8 (23%)
MEL	4 (11%)
SCCHN	3 (9%)

Safety

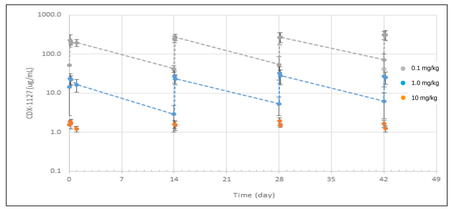
- All dose levels of the combination therapy were well tolerated, without identification of a MTD.
- Treatment-related AEs included infusion reactions, lymphopenia, fatigue, nausea, vomiting, rash, and elevated pancreatic enzymes, with the majority of AEs being low grade.
- Two patients with drug-related SAEs
  - Grade 4 hepatitis (DLT) and grade 3 renal insufficiency in a patient with ovarian cancer (varlilumab 10 mg/kg cohort).
  - Grade 2 paresthesia in a patient with CRC (varlilumab 10 mg/kg cohort).

Treatment Related AE Table >10%

	Overall (N=35)		
Preferred Term	Grade 1-2	Grade ≥ 3*‡	All
Fatigue	9 (25.7%)	0	9 (25.7%)
Lymphopenia	4 (11.4%)	3 (8.6%)	7 (20.0%)
Nausea	7 (20.0%)	0	7 (20.0%)
Chills	6 (17.1%)	0	6 (17.1%)
Arthralgia	5 (14.3%)	0	5 (14.3%)
Pruritus	5 (14.3%)	0	5 (14.3%)
Rash	3 (8.6%)	1 (2.9%)**	4 (11.4%)

*Additional grade ≥ 3 AEs: 2 (5.7%) patients with lipase increased 1 patient (2.9%) each with hepatitis, amylase and acute kidney injury.
**Patient discontinued study treatment due to grade 3 rash.
‡Beside the grade 4 hepatitis, none of the ≥ 3 AEs met DLT criteria

Varlilumab PK profile



Varli Dose (mg/kg)	CDX-1127 conc.	Cycle 1 Dose 1	Cycle 1 Dose 2	Cycle 1 Dose 3	Cycle 1 Dose 4
0.1	Cmax (ug/mL)	1.85	1.63	1.93	1.67
1	Cmax (ug/mL)	23.53	27.30	32.88	26.99
10	Cmax (ug/mL)	229.45	195.12	262.27	306.59

Changes in Serum Chemokine Levels

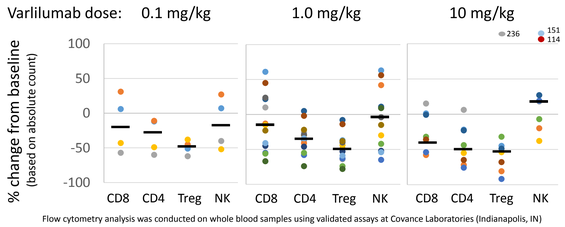
Chemokine	IP-10 (CXCL10)	MIP-1b (CCL4)	MCP-1 (CCL2)	MIG (CXCL9)
Median baseline	255 pg/ml	237 pg/ml	257 pg/ml	862 pg/ml
	Median (range) increase, pg/ml			
0.1 mg/kg varli	522 (114 - 2540)	1143 (233 - 3114)	263 (0 – 3179)	2042 (353 – 29,680)
1.0 mg/kg varli	308 (175 - 941)	935 (81 - 11,352)	410 (309 – 1217)	1938 (650 – 3930)
10 mg/kg varli	421 (76 - 4253)	2292 (1289 – 12,431)	380 (188 – 4726)	818 (-700 – 5231)

Serum biomarkers were analyzed on validated assays using Luminex multiplex platform at Myriad RBM (Austin, TX)

Transient increase in chemokines is observed across all dose levels of varlilumab.

- Peak responses for IP-10, MIP-1b and MCP-1 were generally early in treatment (post 1st dose).
- Peak responses for MIG generally increased with additional doses.
- The majority of patients (5 out of 6) in the 0.1 mg/kg cohort had low grade infusion reactions which may have increased the median levels for that cohort.

Changes in Circulating Lymphocytes

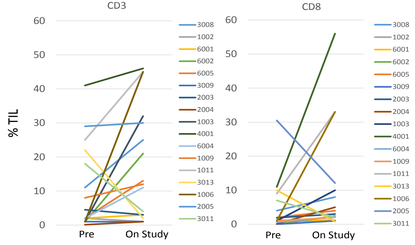


Flow cytometry analysis was conducted on whole blood samples using validated assays at Covance Laboratories (Indianapolis, IN)

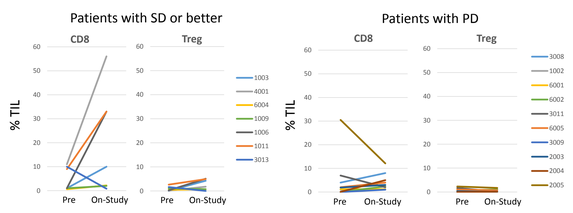
- Consistent pattern of decreased CD4 and Treg cells observed across all varlilumab dose levels.

Changes in Tumor Infiltrating Lymphocytes

Patients with results from pre- and on study biopsies (n=17)



Patients stratified by outcome (n=17)



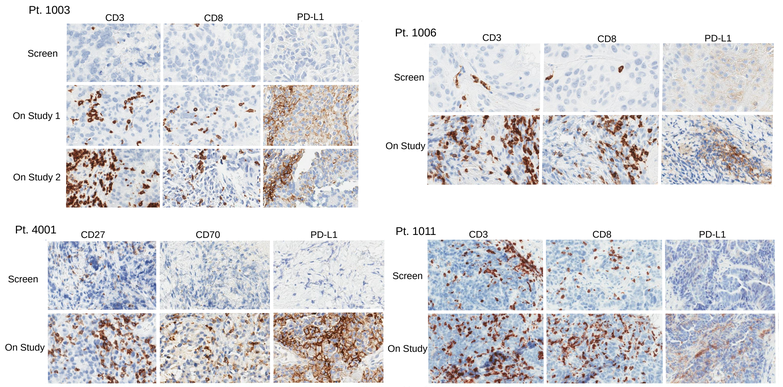
PD-L1 Expression by Tumor Cells

Percentage of Tumor Cells Expressing PD-L1			
Patient ID	Tumor Type	Screen	On Study
1001	CRC	0	unavailable
1002	CRC	0	0
1003	Ovarian	0	20
3002	CRC	0	0 (necrotic tumor)
3005	CRC	0	unavailable
6001	CRC	0	0
6002	Ovarian	0	0
1004	CRC	0	unevaluable
4001	Ovarian	0	20
6004	Ovarian	0	5
1005	SCCHN	9	unavailable
3008	CRC	0	0
3011	CRC	0	0
6005	CRC	0	0
3010	CRC	unevaluable	12
2005	MEL	0	3
1009	CRC	0	0
1011	Ovarian	0	2
3012	CRC	unavailable	0
3009	CRC	0	0
4002	Ovarian	0	unavailable
1006	SCCHN	5	5
4003	CRC	0	unavailable
2003	MEL	0	0
2004	MEL	0	35
2006	MEL	0	unavailable
3013	CRC	0	0
1012	Ovarian	unavailable	1
1013	CRC	0	unavailable

- 29 out of 35 patient samples have been tested
- PD-L1 testing was performed using the BMS developed PD-L1 IHC method

0.1 mg/kg varli cohort
1.0 mg/kg varli cohort
10 mg/kg varli cohort

Examples of Patients with Increase in TIL and PD-L1 Expression



Immunohistochemistry was performed on validated assays using monoclonal antibodies at Mosaic Laboratories (Lake Forest, CA)

- Increase in TILs observed at all varlilumab dose levels
- Trend toward increase in PD-L1 expression and CD8+ TILs in patients with SD or better responses

Summary

- The combination of varlilumab and nivolumab was well tolerated at all varlilumab dose levels in Phase 1. Toxicity has been similar to what was seen with varlilumab or nivolumab monotherapy.
- Circulating biomarkers show increase in inflammatory chemokines and decrease in CD4 and Treg cells.
  - Biomarker changes not related to varlilumab dose level.
  - Biomarker changes generally consistent with varlilumab monotherapy.
- Marked increases in tumor infiltrating lymphocytes.
  - Observed in select patients at each varlilumab dose level.
  - May correlate with clinical outcome.
- The Phase 1 varlilumab dose escalation is complete
  - Biological and safety data support a broad activity range for varlilumab (0.1-10 mg/kg).
  - 3 mg/kg varlilumab has been chosen for Phase 2 based on cumulative data with varlilumab across multiple studies.
- Phase 2 has initiated enrollment into the following indications:
  - CRC, RCC, SCCHN, Ovarian, NSCLC & GBM

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