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**PROGRESS IN VACCINE IMMUNOTHERAPY**  
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**Disclosures**

- Biovest International (consultant)
- Antigenics (consultant)
- Xeme Biopharma, Inc. (stockholder)
- Celgene (research support)

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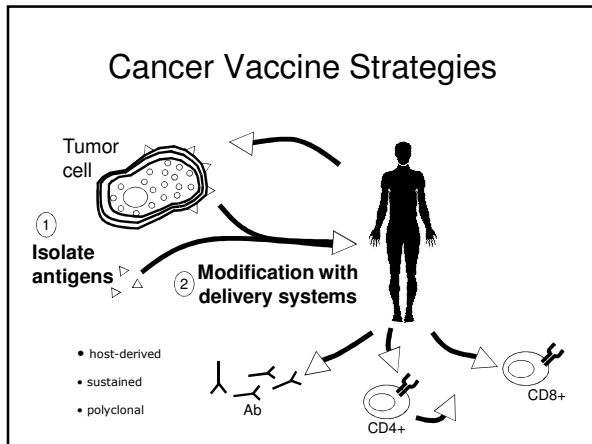
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### The Challenge – Harnessing the Immune System to Fight Cancer

- Unique target (antigen)
- Technology to deliver the target to the immune system (delivery system)
- Release from immune suppression

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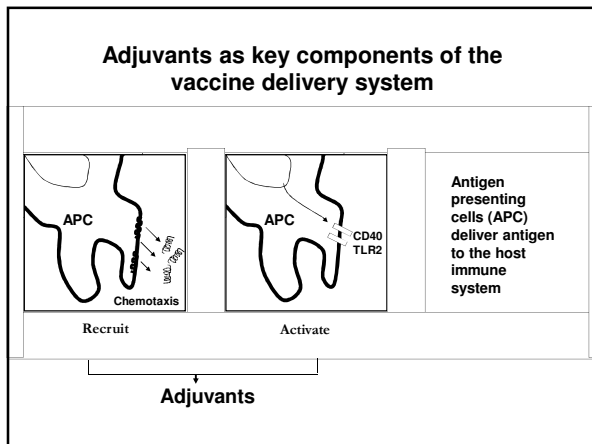
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Hematologic cancers are ideal disease models to study immunotherapy

- Some lymphomas are associated with waxing and waning natural history, occasionally with spontaneous regressions of tumors
- [Opat et al. #2923] Percentage of cytotoxic T cells in 122 mantle cell lymphoma biopsies predicted response to rituximab
- [Hilchey et al. #758] Increased proportions of infiltrating T regulatory cells contributed to T-cell hyporesponsiveness within 3 of 6 FL samples
- [Homsy et al. #3031] Factors derived from a myeloma cell line generated tolerogenic DC

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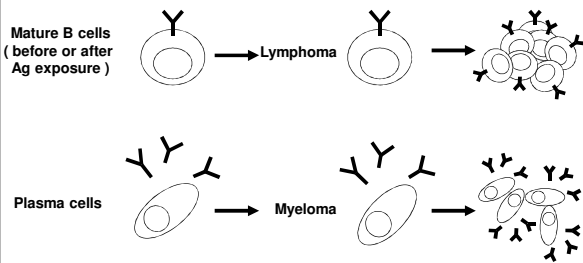
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Idiotype (Id): A clonal marker and model tumor antigen




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Id Vaccination: Early Phase Clinical Trials

Publication	Vaccine	No. Patients	Histology	Phase I	Phase II	Phase III
Kwak, NEJM 1992 Hsu, Blood 1997	Id-KLH + Adjuvant	41	FL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bendandi, Nat Med 1999	Id-KLH + GMCSF	20	FL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Timmerman, Blood 2002	Id - DC	35	FL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Timmerman, Clin Can Res 2002	Plasmid DNA	12	FL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Barrios, Hematologica 2002	Id-KLH + adjuvant	9	FL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Neelapu, Nat Med 2005	Id - KLH + GMCSF	26	MCL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Inoges, JNCI 2006	Id - KLH + GMCSF	25	FL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bertineti, Can Res 2006	Fab + MF59 + GMCSF	18	various	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Redfern, JCO 2006	Id - KLH + GMCSF	31	indolent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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## Lymphoma idiotype protein vaccines in completed Phase III clinical trials

Product	Adjuvant	Disease	Chemo	Status	Sponsor
• Hybridoma Id	GM-CSF	FL	PACE	CR	NCI/Biovest
• Recomb. Id	GM-CSF	FL	Rituximab	CR/PR	Favrille
• Recomb. Id	GM-CSF	FL	CVP	CR/PR/SD	Genitope

Schuster SJ, et al. *J Clin Oncol*. 27(18s): Abstract 2.  
 Freedman A, et al. *J Clin Oncol*. 2009;27(18):3036-3043.  
 Levy, et al. *AACR Meeting Abstracts*. 2008: LB-204.

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## NCI/Biovest-Sponsored Phase III Vaccine Study Objectives

- Primary Objective:
  - To determine whether Id-KLH + GM-CSF prolongs disease free survival (DFS) compared to KLH + GM-CSF (control vaccine) in patients with follicular lymphoma in CR/CRu after PACE
  
- Secondary Objectives:
  - Evaluate safety of Id-KLH + GM-CSF
  - Immune response and biomarker assessment

Schuster SJ, et al. *J Clin Oncol*. 27(18s): Abstract 2.

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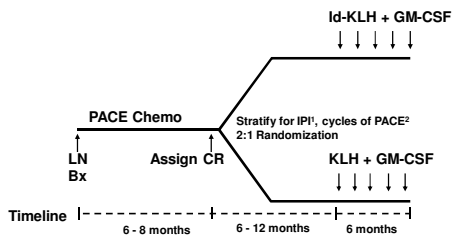
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## NCI/Biovest-Sponsored Phase III Vaccine Study Design



- Primary endpoint: disease-free survival
- 14 sites enrolled patients from 2000-2007
- <sup>1</sup>low, low-intermediate or high-intermediate, high groups
- <sup>2</sup>< 8 or ≥ 8 cycles

Schuster SJ, et al. *J Clin Oncol*. 27(18s): Abstract 2.

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### Statistical Design: Projected sample size calculations

563 pts required for 2:1 randomization of 375 pts to either Id-KLH arm (250) or control vaccine arm (125)

Assumptions:

- 80% power to detect a 20% difference between DFS curves with an initial hazard ratio of 1.0 and an intended hazard ratio of 0.5 after the first 8 months
- 2/3 CR/CRu response rate to PACE chemotherapy
- Vaccine production failure rate not exceeding 10%

Schuster SJ, et al. J Clin Oncol. 27(18s): Abstract 2.

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### Study monitoring

- Central pathology review (E. Jaffe, NCI)
- Contract data collection (EMMES Corp.)
- Independent DSMB

Schuster SJ, et al. J Clin Oncol. 27(18s): Abstract 2.

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### Statistical Design: Two Prospective Efficacy Analyses

- Intent-to-Treat Analysis (ITT) compared DFS in treatment arms for all randomized pts
- Modified Intent-to-Treat Analysis (mITT) compared DFS in treatment arms for randomized pts who remained in CR/CRu and received either Id-KLH or control vaccine

Schuster SJ, et al. J Clin Oncol. 27(18s): Abstract 2.

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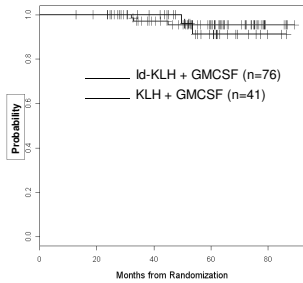
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### Overall Survival from Randomization (mITT)



**Overall Survival**  
 Id-KLH = 95.4%  
 Control vaccine = 91.2%

**Median OS**  
 not yet reached at median  
 follow-up 56.6 months

**Events**  
 Id-KLH = 3  
 Control vaccine = 2

**Cox PH Model**  
 HR = 0.7 (p=0.7)

Schuster SJ, et al. *J Clin Oncol*. 27(18s): Abstract 2.

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### Safety Summary: AEs During Vaccination

System	KLH + GMCSF N (%)		Id-KLH + GMCSF N (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Allergy	0	0	1 (1%)	0
Cardiovascular	1 (2%)	0	1 (1%)	1 (1%)
Constitutional	0	0	2 (3%)	0
Dermatology	1 (2%)	0	4 (5%)	0
Gastrointestinal	1 (2%)	0	3 (4%)	0
Infection	1 (2%)	0	0	0
Musculoskeletal	1 (2%)	0	1 (1%)	0
Neurological	1 (2%)	0	1 (1%)	0
Pain	6 (15%)	0	5 (7%)	0
Pulmonary	1 (2%)	0	0	0
Secondary Malignancy	1 (2%)	0	0	1 (1%)

CTCAE Version 2

Schuster SJ, et al. *J Clin Oncol*. 27(18s): Abstract 2.

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### Results: Local Injection Site Reactions

Maximum Local Reaction	Severity	KLH + GMCSF (%)	Id-KLH + GMCSF (%)
Erythema	No reaction	12%	3%
	< 1 cm	0%	0
	1-10 cm	39%	51%
	> 10 cm	49%	46%
Induration	No reaction	24%	14%
	< 1 cm	2%	4%
	1-10 cm	46%	62%
	> 10 cm	27%	20%
Ulceration	No reaction	98%	93%
	< 1 cm	2%	3%
	1-10 cm	0%	3%
	> 10 cm	0%	1%

Schuster SJ, et al. *J Clin Oncol*. 27(18s): Abstract 2.

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## Lymphoma vaccine: Potential regulatory caveats

- patient accrual stopped early
- treatment effect associated with marginal statistical significance
- induction chemotherapy did not include anti-CD20 mAb rituximab (standard of care changed)
- treatment effect apparent only in mITT

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## Characteristics of Excluded Patients [Relapsed After Randomization and Before Vaccination (n=60)]

	Id-KLH N (%)	Control N (%)		Id-KLH N (%)	Control N (%)	
<b>Sex</b>						
Female	21 (50%)	11 (61%)	<b>Age</b>			
Male	21 (50%)	7 (39%)	Mean (SD)	49.1 (10.4)	46.1 (10.8)	
<b>Race</b>						
Am Indian or AK Native	1 (2%)	0 (0%)	<b>Histology</b>			
Asian	1 (2%)	0 (0%)	Follicular, grade 2	22 (52%)	10 (56%)	
Black	3 (7%)	2 (11%)	Follicular, grade 1	20 (48%)	8 (44%)	
Caucasian	37 (88%)	14 (78%)	<b>LDH</b>			
Hispanic or Latino	0 (0%)	1 (6%)	High-int or high	6 (14%)	2 (11%)	
Other	0 (0%)	1 (6%)	Low or low-int	36 (86%)	16 (89%)	
<b>ECOG PS</b>						
0	30 (71%)	16 (89%)	<b>Cycles of PACE</b>			
1	11 (26%)	1 (6%)	< 8	22 (52%)	7 (39%)	
2	1 (2%)	1 (6%)	≥ 8	20 (48%)	11 (61%)	
<b>LDH</b>						
				Mean (SD)	428.4 (301.9)	304.6 (173.6)

No statistically significant ( $P > 0.05$ ) differences between the two arms for any patient characteristics

Schuster SJ, et al. *J Clin Oncol*. 27(18s): Abstract 2

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## Conclusions

- Id-KLH + GM-CSF vaccination improves DFS following PACE chemotherapy in patients in CR/CRu at time of vaccination
- The magnitude of the treatment effect is substantial (14 mo increase in median DFS)
- Long-term clinical experience with idiotype vaccination demonstrates low toxicity profile

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Factors which may explain differences in outcomes between randomized phase III studies of Id-KLH /GM-CSF vaccination in FL

- Requirement for CR or CRu status prior to vaccination
  - higher CR rates associated with PACE (vs. CVP, Rituxan monotherapy)
  - immune stimulatory effects of anthracycline (chemo-induced immune activation)
- Trial design issues: e.g. stratification by prognostic factors
- Intact B-cell numbers (no prior Rituxan)
- Inherent complexity of vaccine manufacturing techniques (not a simple commodity)

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Future directions

- Identify the subgroup of patients most likely to benefit from this vaccine
- Determine the mechanism underlying the observed clinical effects
- Additional clinical trials of this vaccine following rituximab-containing chemotherapy regimens
- Make further improvements in the vaccine product (e.g. improved adjuvant in Phase IV)

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Potential roles for a vaccine in the management of lymphoma patients

- requirement for biopsy and personalized manufacture
- optimal treatment requires sustained CR
- high risk subgroup of FL patients (unmet need)
- as maintenance therapy (non-toxic)

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## Phase III Clinical Trial Sites

- National Cancer Institute
- Duke University Medical Center
- Emory University Winship Cancer Institute
- H. Lee Moffitt Cancer Center
- New England Medical Center
- New York University Medical Center
- Virginia Oncology Associates
- North Mississippi Hem & Oncology Associates
- Northwestern University
- St. Mary's/Duluth Clinic (SMDC) Health System
- University of Pennsylvania
- The University Of Texas MD Anderson Cancer Center
- Westchester Oncology & Hematology Group
- Southern Oncology Research

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