Translational development of Therapeutic Lymphoma Vaccines

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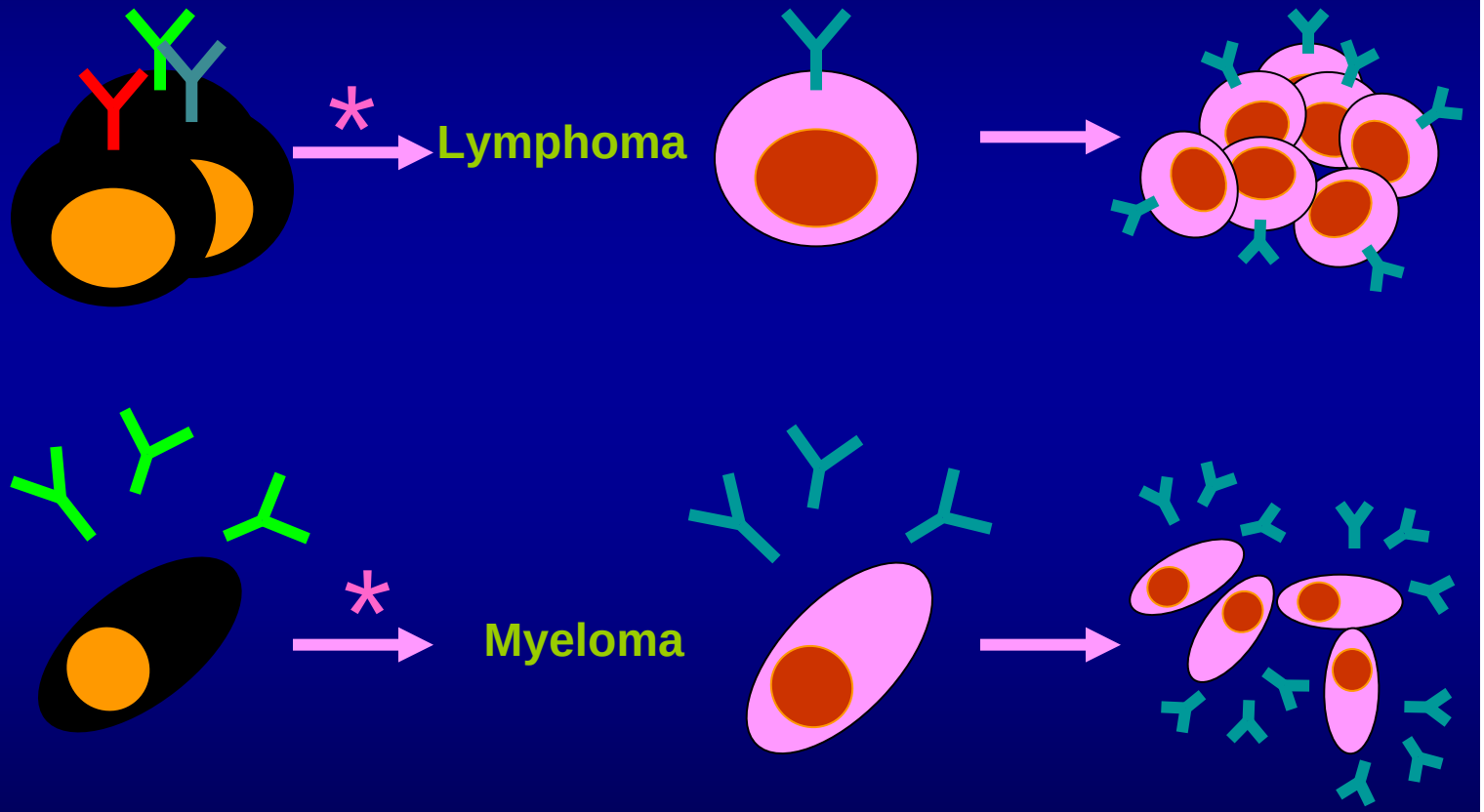
CME Disclosures

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

Types of vaccines

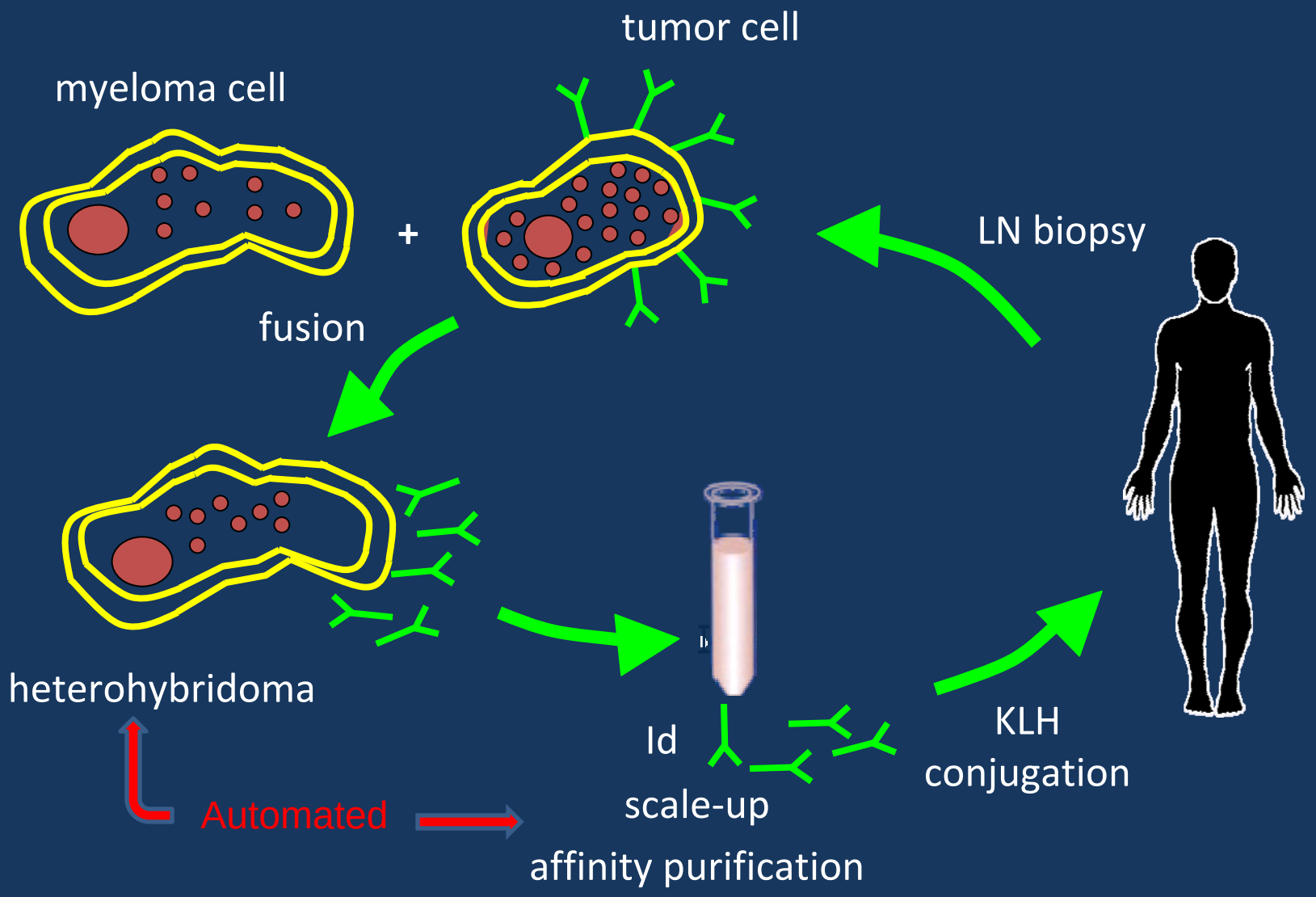
- Prevention
- Secondary prevention
- Therapeutic (e.g. Provenge)

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



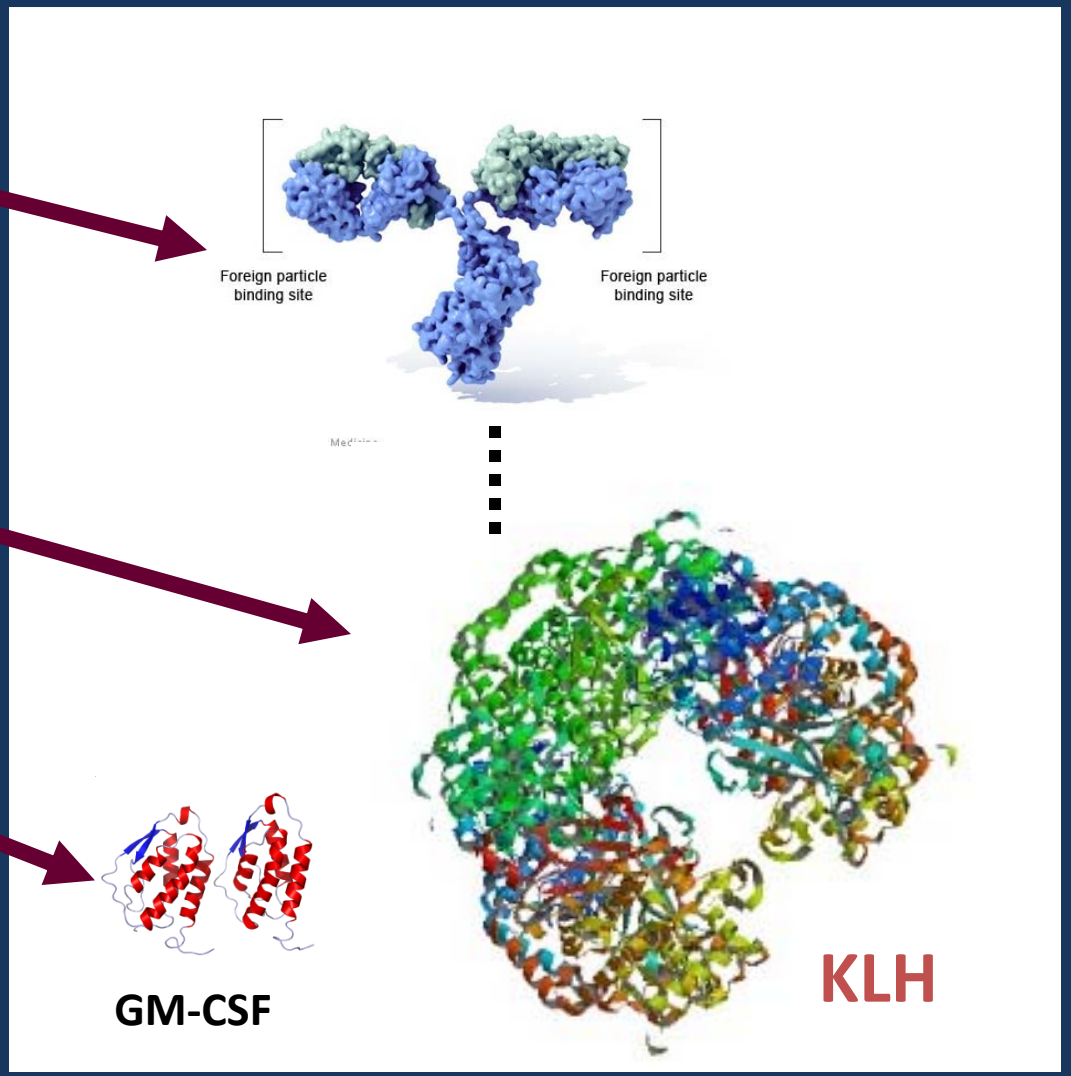
* = malignant transformation

Personalized Human Vaccine Production



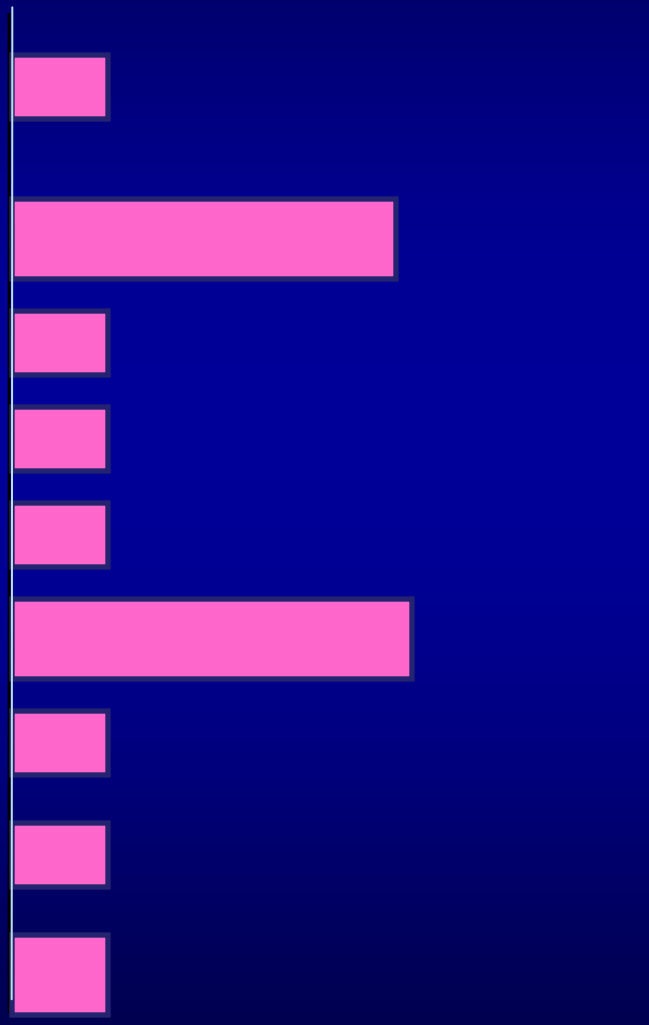
Vaccine components

- Idiotype of the Ig antigen of a B-cell lymphoma can be used as a tumor-specific immunogen
- Keyhole lympet hemocyanin (KLH) carrier serves as an immune stimulant
- GM-CSF administered concurrently at site of injection as an adjuvant



Id Vaccination: Early Phase Clinical Trials

Publication	Vaccine	No. Patients	Histology
Kwak, NEJM 1992 Hsu, Blood 1997	Id-KLH + Adjuvant	41	FL
Bendandi, Nat Med 1999	Id-KLH + GMCSF	20	FL
Timmerman, Blood 2002	Id - DC	35	FL
Timmerman, Clin Can Res 2002	Plasmid DNA	12	FL
Barrios, Hematologica 2002	Id-KLH + adjuvant	9	FL
Neelapu, Nat Med 2005	Id – KLH + GMCSF	26	MCL
Inoges, JNCI 2006	Id – KLH + GMCSF	25	FL
Bertinetti, Can Res 2006	Fab + MF59 + GMCSF	18	various
Redfern, JCO 2006	Id – KLH + GMCSF	31	indolent

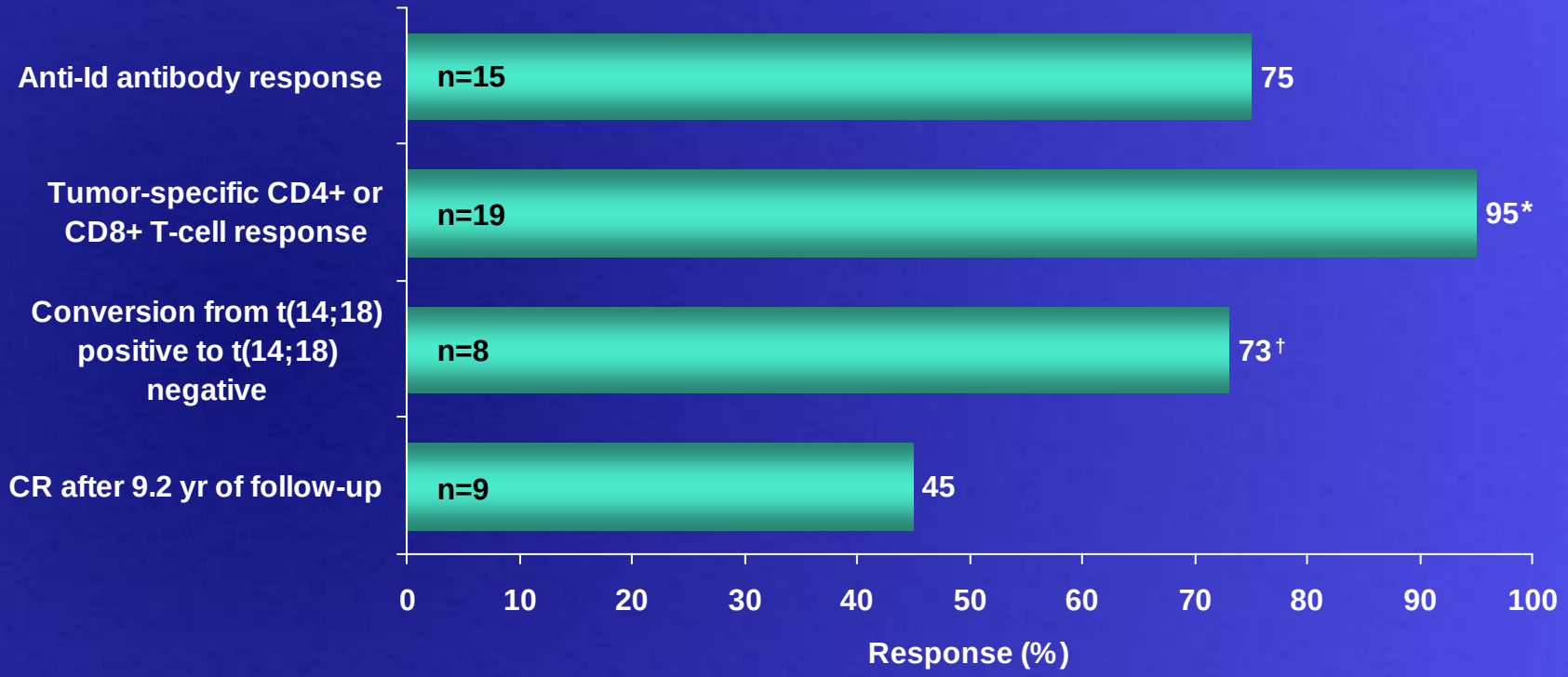


First IND-supported Phase II Trial of Id Vaccine During Clinical Remission (NCI)

- Single-arm prospective study in 20 patients with follicular lymphoma
- Homogeneous group of patients in first remission after uniform induction chemotherapy *
- Vaccine treatment in setting of minimal residual disease
- Regimen
  - Started 6 months after completion of chemotherapy
  - Vaccine (Id-KLH 0.5 mg SC day 0 + GM-CSF 100 µg/m^2 SC days 0–3) injected monthly for 5 cycles

* PACE= prednisone, Adriamycin (doxorubicin), cyclophosphamide, and etoposide.

First IND-supported Phase II Vaccine Trial During 1st Complete Remission (CR): Results



- DFS after 9.2 yr of follow-up

Bendandi et al. *Nat Med.* 1999;5:1171-1177.

NCI/Biovest Phase III Vaccine Study Objectives

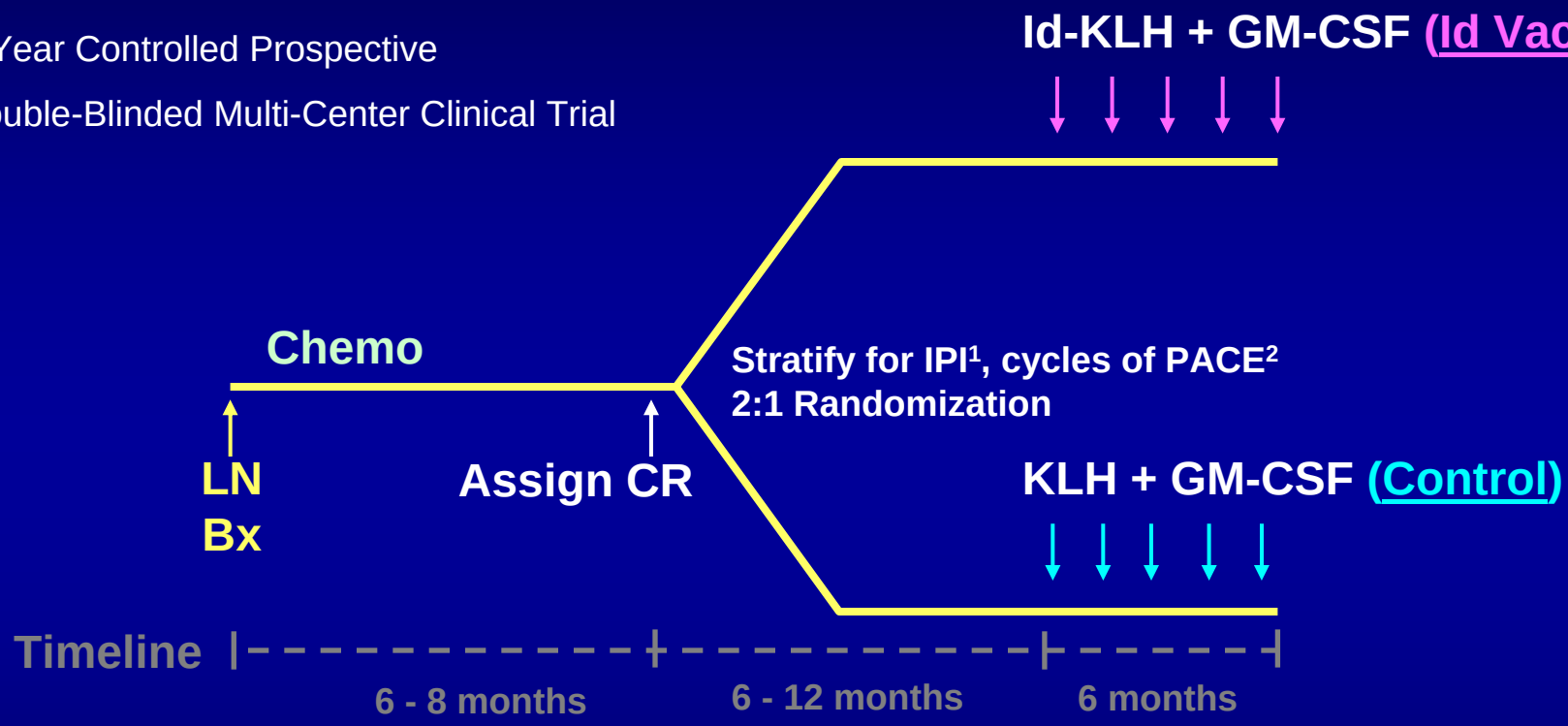
- Primary Objective:
  - To determine whether Id vaccine prolongs disease free survival (DFS) compared to control in patients with follicular lymphoma in complete remission (CR) after uniform standard chemotherapy

- Secondary Objectives:
  - Evaluate safety of Id vaccine
  - Immune response and biomarker assessment

NCI/Biovest Phase III Vaccine Study Design

8-Year Controlled Prospective

Double-Blinded Multi-Center Clinical Trial



- Primary endpoint: disease-free survival
- 14 sites enrolled patients from 2000-2007

[1]low, low-intermediate or high-intermediate, high groups

[2] < 8 or ≥ 8 cycles

Statistical Design

Two Prospective Efficacy Analyses

- Intent-to-Treat Analysis (ITT) compared DFS in treatment arms for all randomized pts

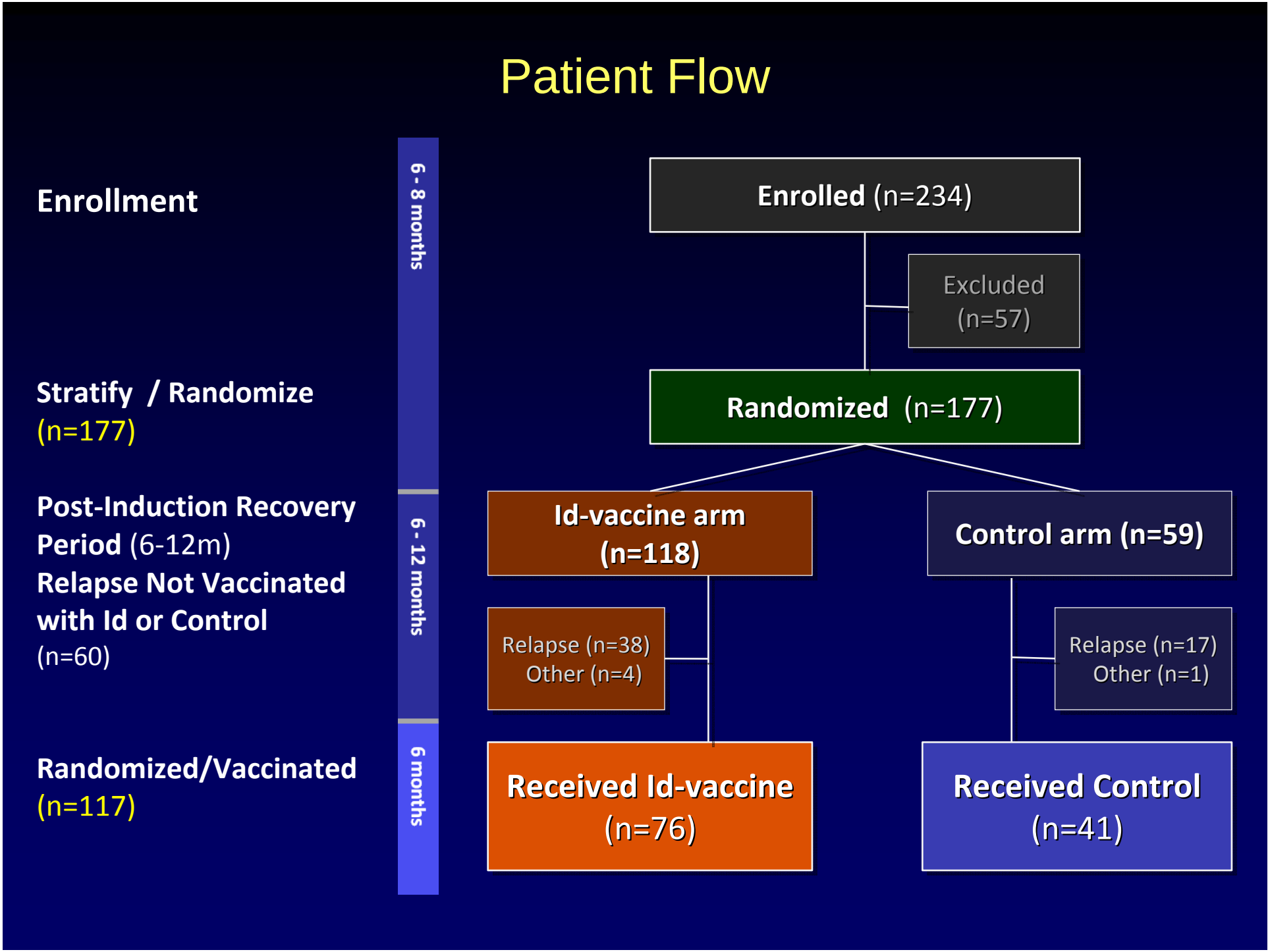
- Modified Intent-to-Treat Analysis (mITT) compared DFS in treatment arms for randomized pts who remained in CR/CRu and received either Id- or control vaccine

Vaccine Isotype Subset Analysis (unplanned)

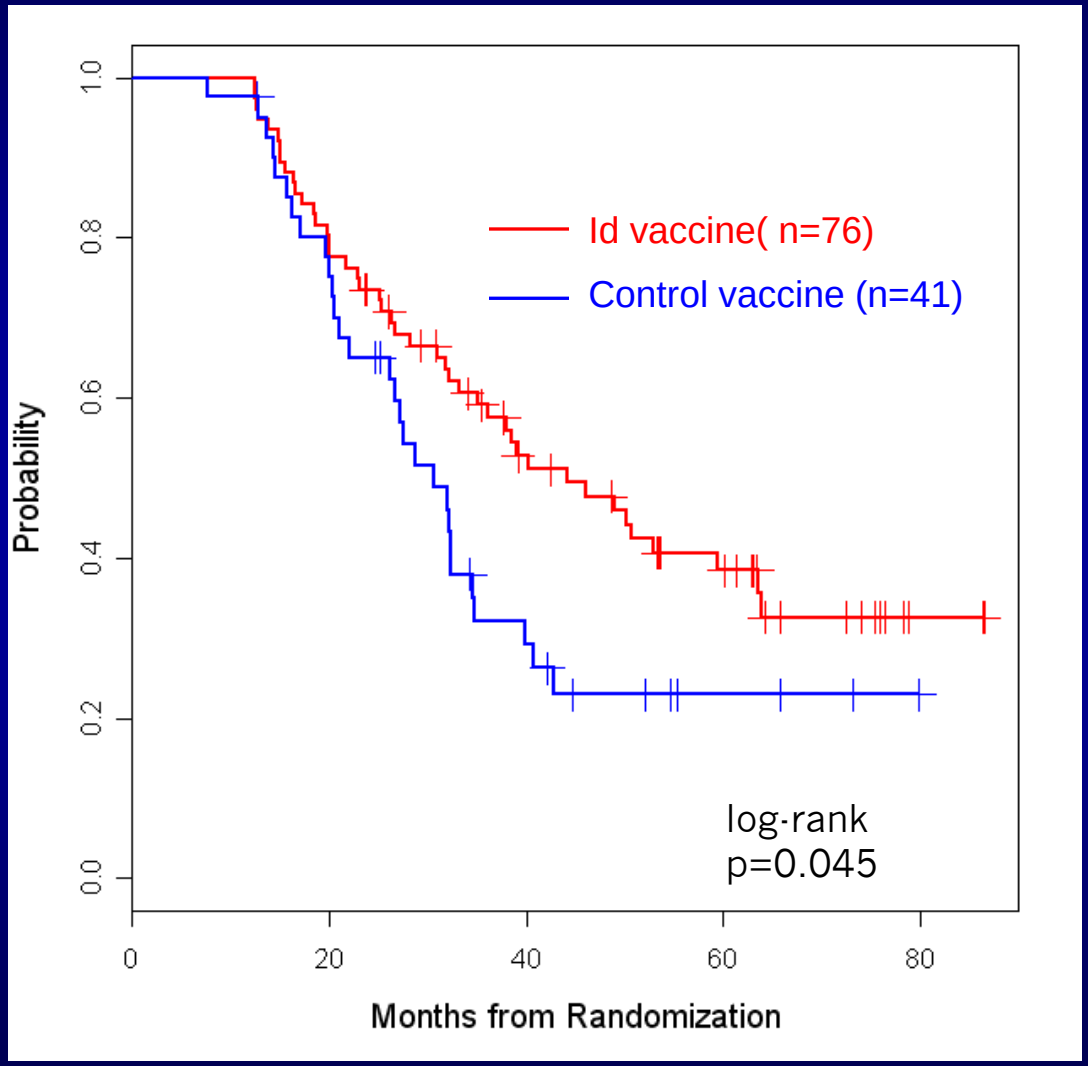
- DFS by vaccine isotype (IgM or IgG) for patients receiving Id vaccine

Schuster , Neelapu et al. (Kwak) *J Clin Oncol* 29:2787, 2011

Patient Flow



Disease Free Survival from Randomization (mITT)



Median Follow-up

56.6 mo (range 12.6 – 89.3)

Median DFS

Id vaccine = 44.2 mo

Control vaccine = 30.6 mo

Events

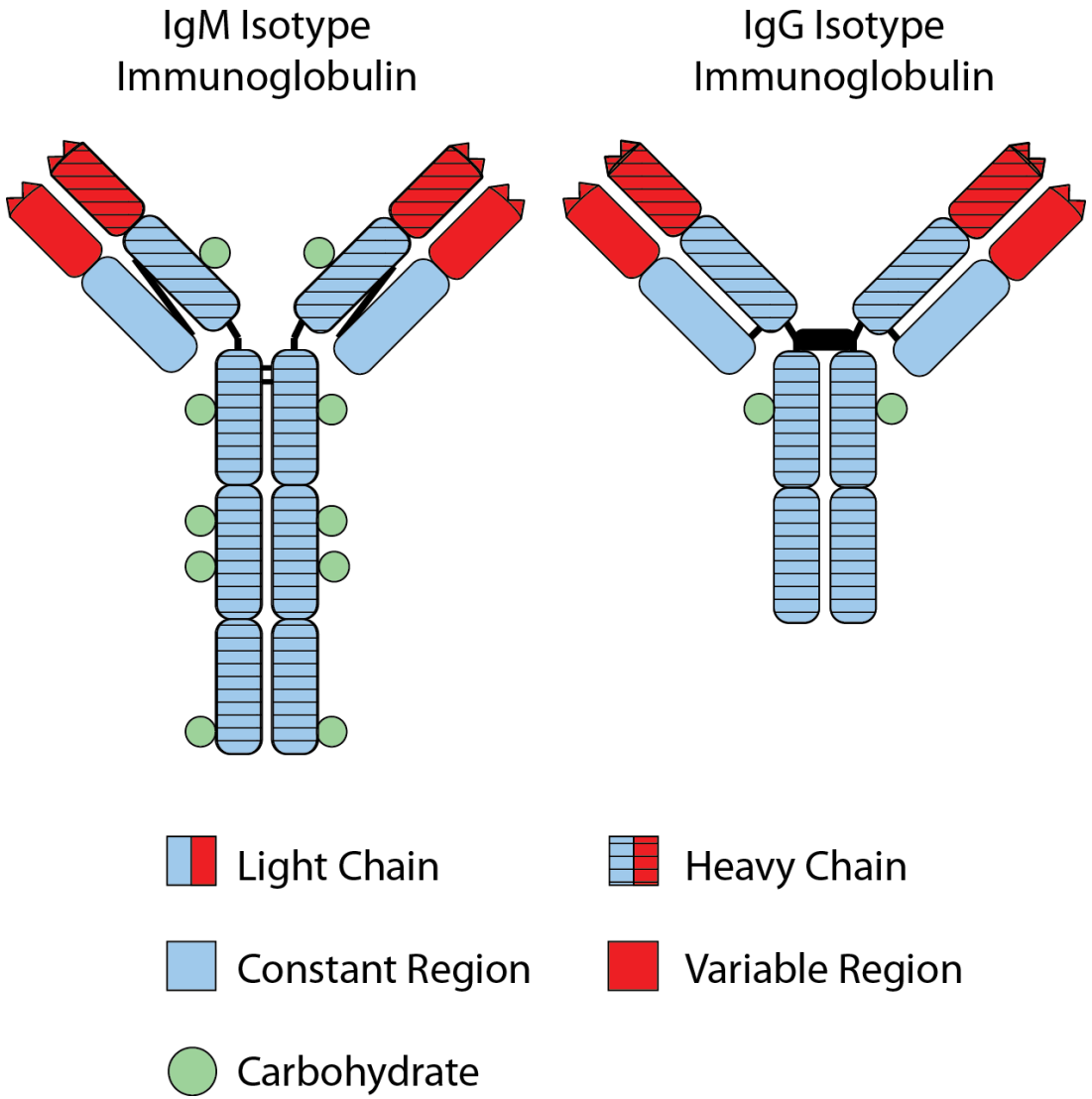
Id vaccine = 44

Control vaccine = 29

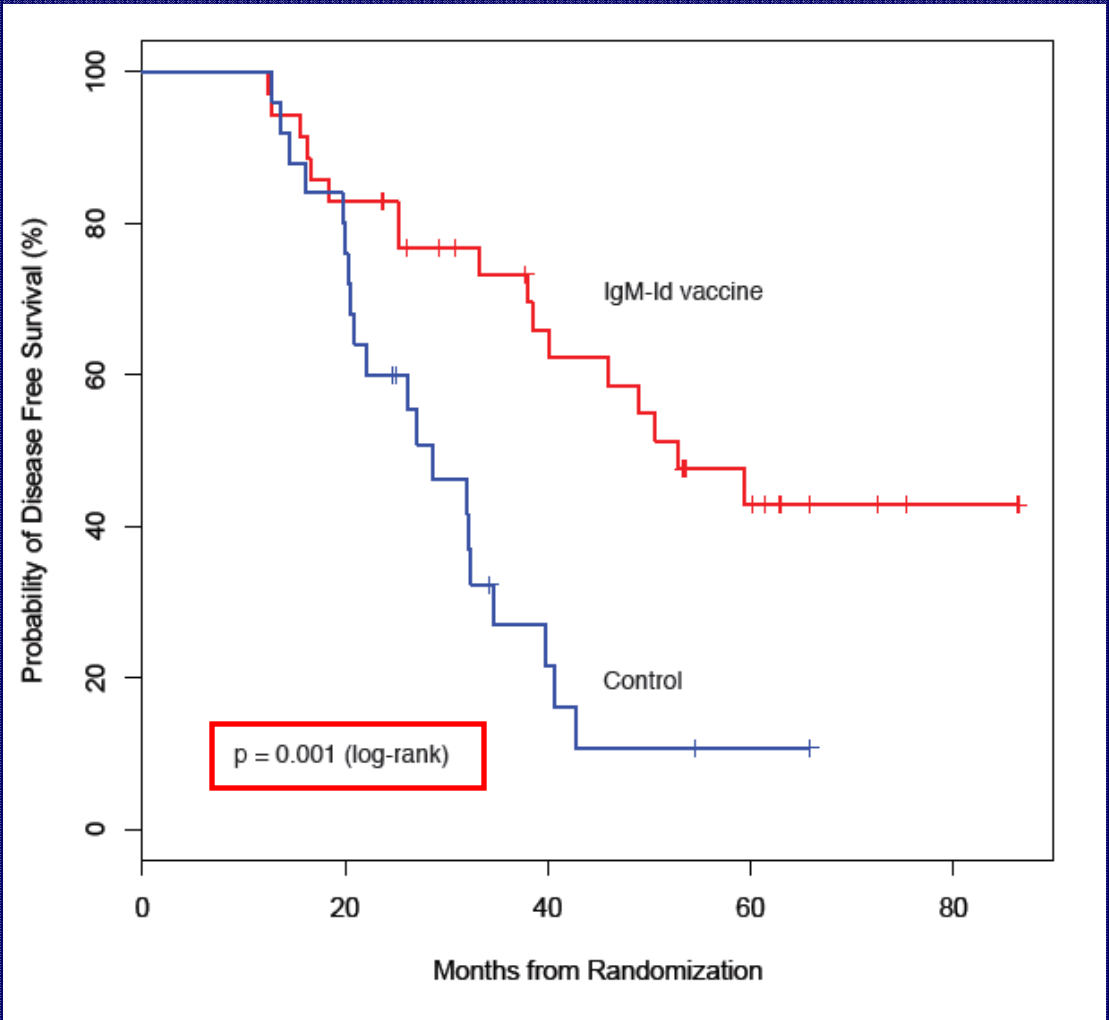
Cox PH Model

HR = 0.62; [95% CI: 0.39,0.99] (p=0.047)

FL surface Ig can be either IgG or IgM Isotype



Disease Free Survival for Patients with IgM-isotype lymphomas (n = 60)



Median Follow-up

56.6 mo (range 12.6 – 89.3)

N = 60

IgM-Id vaccine N = 35

Control N = 25

Median DFS

IgM-Id vaccine = 52.9 mo

[95% CI:40.2,NA]

Control = 28.7 mo

[95% CI:21.0,39.8]

Events

IgM-Id vaccine = 17

Control = 20

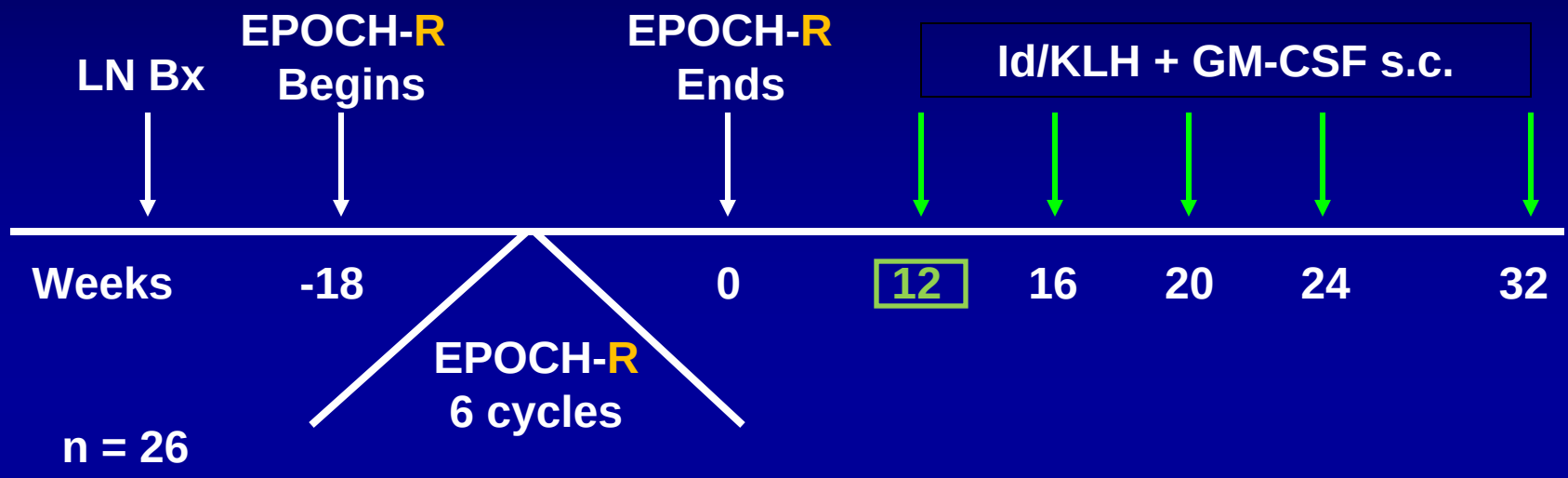
Positive Phase III trial: Potential challenges to “Delivery”

- Patient accrual stopped early/treatment effect apparent only in modified ITT
- requirement for biopsy and personalized manufacture
- optimal treatment requires sustained complete remission

Future directions

- Identify/stratify the subgroup of patients most likely to benefit from this vaccine (e.g. MRD?; predictive biomarkers) and determine the mechanism underlying the observed clinical effects
- Make further improvements in the vaccine product (e.g. 2nd generation DNA fusion vaccines)
- Additional clinical trials combining this vaccine with anti-CD20 mAb (rituximab)-containing chemotherapy regimens

Mantle cell lymphoma clinical trial schema



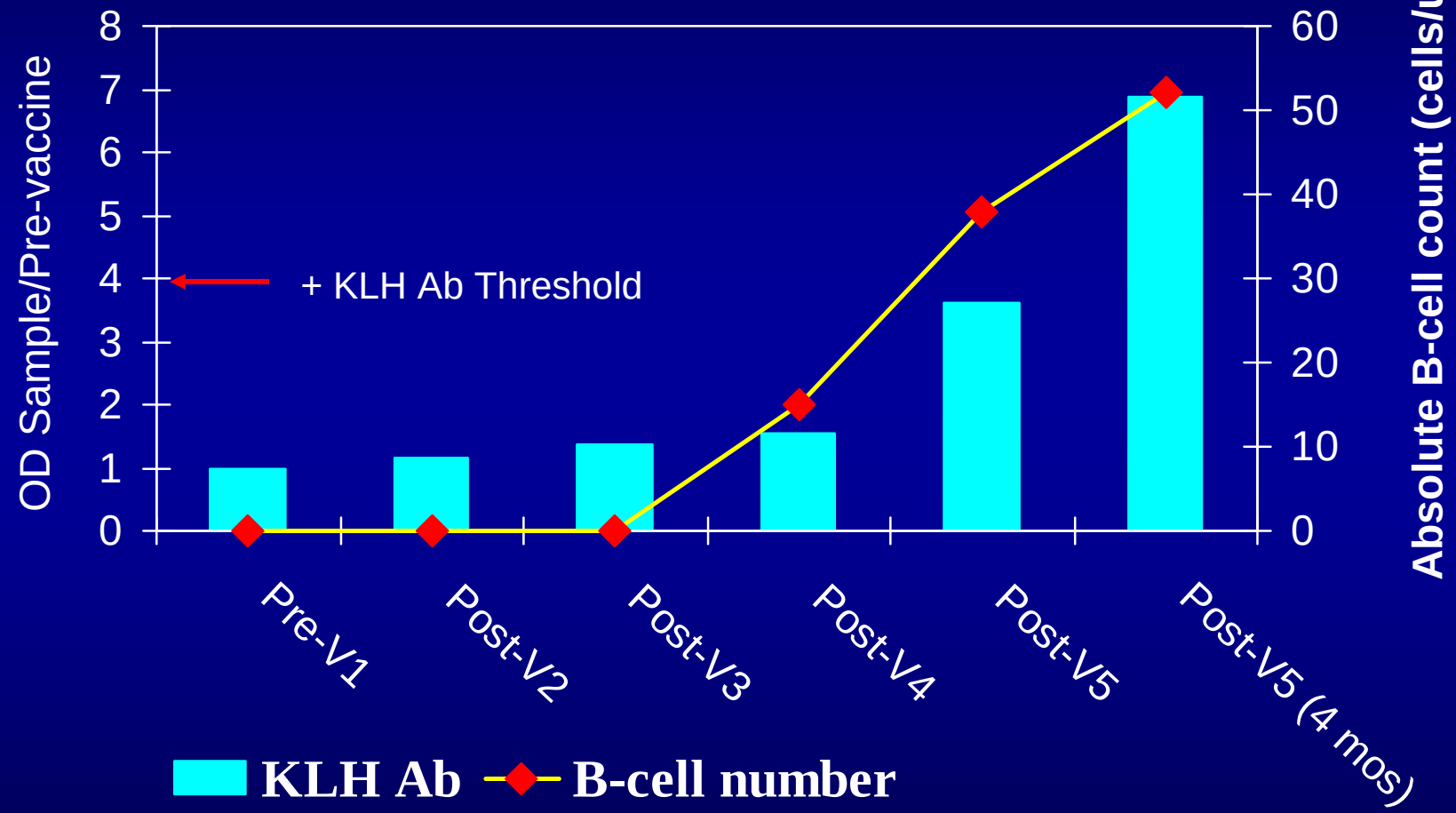
- **EPOCH-R – Rituximab on day 1**
  - **-- Continuous iv infusion of Etoposide, Doxorubicin and Vincristine over 96 hrs (days 1-5)**
  - **-- Cyclophosphamide iv on day 5**
  - **-- Prednisone days 1-5.**

- **Id-KLH+GM-CSF – 0.5 mg autologous Id + 0.5 mg KLH + 100 μg/m² GM-CSF**

Neelapu et al. (Kwak, Wilson) *Nature Med* 11:986, 2005

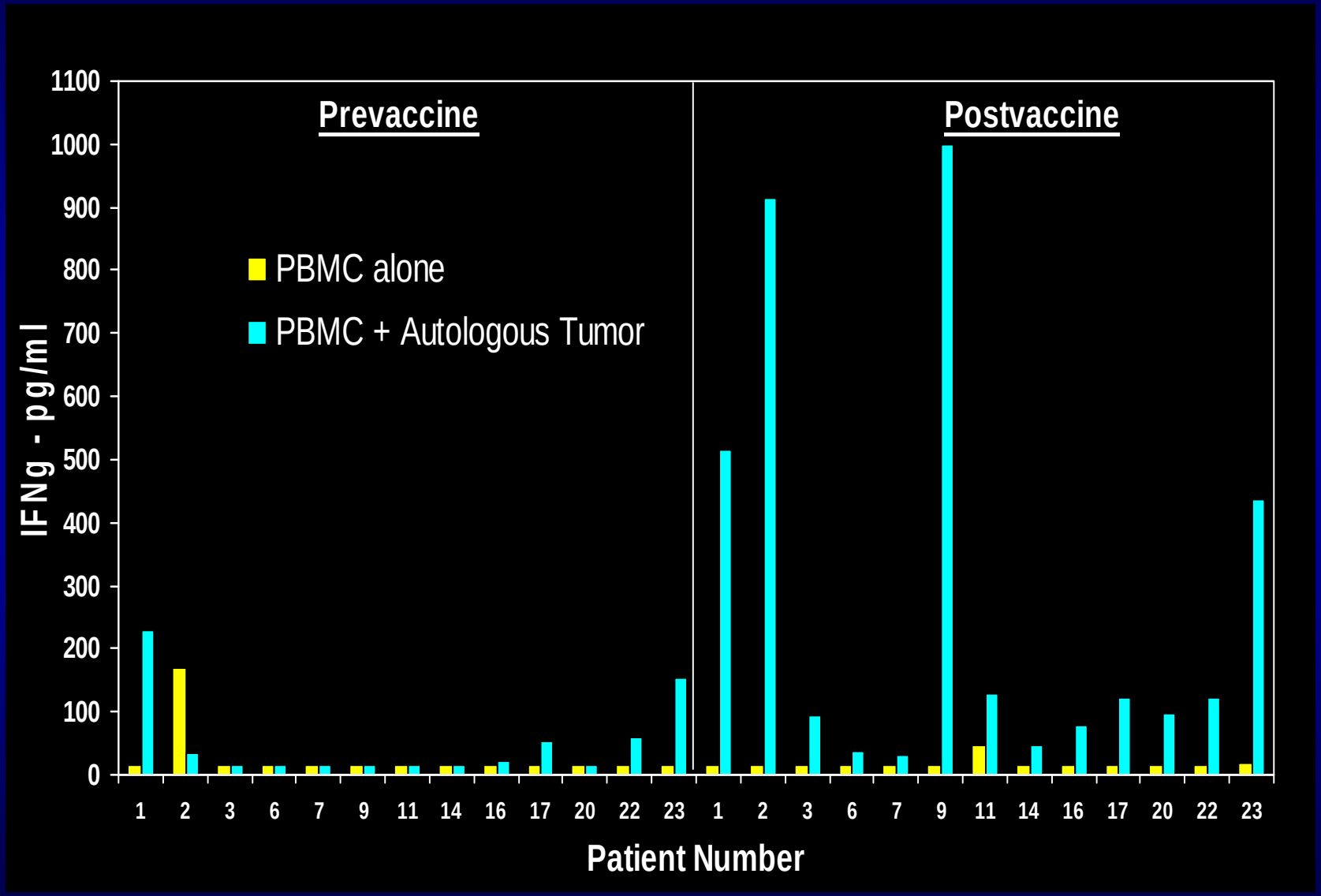
KLH Ab and B-cell recovery

Representative patient



- **17/23 (74%) patients were positive for anti-KLH antibody.**

Response to autologous tumor - IFNg



- **20/23 (87%) patients had a positive T cell response by cytokine induction assay.**

Conclusions – MCL vaccine study

- Antibody responses to KLH carrier were delayed but present in 17/23 (74%) patients, and Id-specific antibody responses were detected in 8/23 (35%) patients.
- Tumor-specific T cell responses were detected in 20/23 (87%) patients following rituximab containing chemotherapy regimen
- These results suggest that severe B-cell depletion does not impair induction of T-cell responses

Conclusions

- Administration of vaccine following immunosuppressive chemotherapy is feasible (duration of recovery period required unknown)
- In a Phase III trial vaccination improved disease-free survival (DFS) following chemotherapy in patients already in complete remission at time of vaccination (secondary prevention)
- The clinical effect of the vaccine is validated by the subgroup analysis of patients expressing the IgM isotype
- Long-term clinical experience with idiotype protein vaccines demonstrates low toxicity profile, making it ideal for consolidation or maintenance therapy

Factors which may explain differences in outcomes between randomized Phase III studies

Critical variable	NCI Phase 2	NCI/Biovest	Genitope	Favrille
Pre-requisite to vaccine	CR only	CR only	CR or PR	CR or PR or SD
Induction therapy	PACE	PACE	CVP	rituximab
Id protein	Native protein from hybridoma	Native protein	Recombinant protein	Recombinant protein
Isotype of Id-vaccine	IgM and IgG (tumor-matched)	IgM and IgG	IgG	IgG
Stratification		Prognostic index; # cycles chemotherapy		

Schuster SJ, et al. *J Clin Oncol. 29:2787, 2011* ;
Freedman A, et al. *J Clin Oncol.* 27:3036, 2009; Levy, et al. *AACR Meeting Abstracts*. 2008: LB-204

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