THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Cancer Vaccines and Cytokines

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Disclosures

- I serve as the PI on a phase III trial sponsored by Galena BioPharma investigating NeuVax
- I serve as the PI on a phase II trial sponsored in part by Antigen Express investigating the AE37 vaccine

Goals

- Discuss considerations in vaccine construction/development
- Review specific vaccines currently being evaluated in later stage clinical trials

A vaccine is used for induction of humoral and/or cellular immune responses against an antigen or set of antigens

Considerations in Vaccine Development

- Target (tumor antigen)
- Effective adjuvant
- Delivery platform
- Clinical setting in which vaccine will be effective
- Patients likely to benefit from vaccination
- Feasibility of large-scale vaccine production
  - Cost
  - Preparation time

Tumor Antigen

- Allows tumor cells to be distinguished from normal
- Overexpressed or abnormally expressed in tumors
- Critical for the survival of the tumor

Tumor Antigen

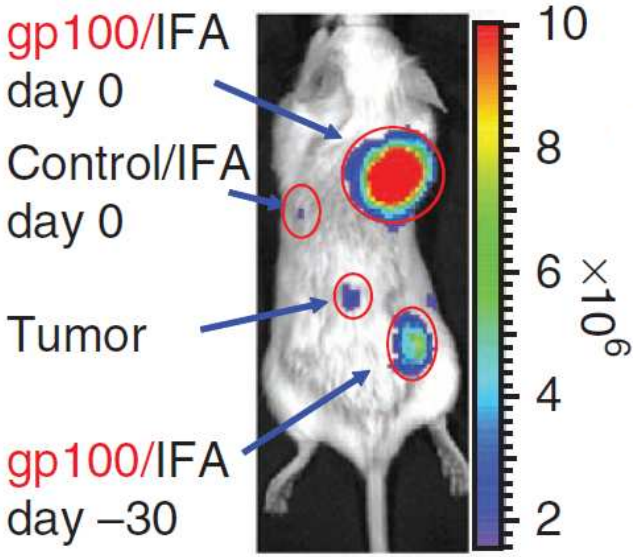
- Cancer testis
  - MAGE, NY-ESO-1
- Oncogenes
  - HER2, WT1, p53
- Differentiation antigens
  - gp 100, MART-1, tyrosinase
- Glycoproteins
  - MUC-1
- Oncofetal antigens
  - AFP, CEA

Immunoadjuvant

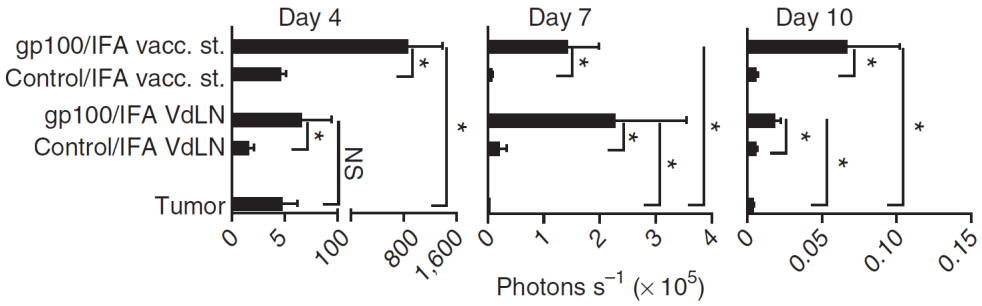
- Nonspecific substance acting to enhance the immune response to an antigen with which it is administered
- Examples
  - Incomplete Freund’s adjuvant (IFA)
  - GM-CSF
  - Monophosphoryl lipid A
  - CpG oligonucleotides

IFA

- Evaluated immune responses to gp100 + IFA
- Peptide/IFA primed tumor-specific CD8+ T cells
- Primed T cells remained at the vaccination site; not tumors



Kinetics of pmel-1 T cell luminescence



Hailemichael Y et al. *Nat Med* 2013;19(4):465-472

Platforms

- Dendritic cell vaccines
- Peptide vaccines
- Protein vaccines
- Whole tumor cell vaccines
- DNA vaccines
- Recombinant viral vectors

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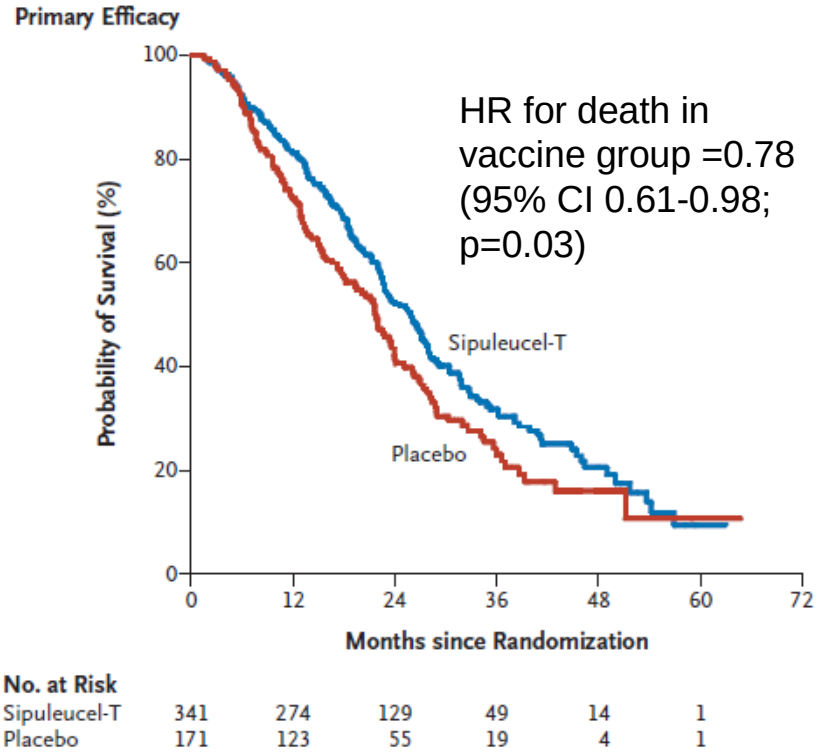
Dendritic Cell Vaccines

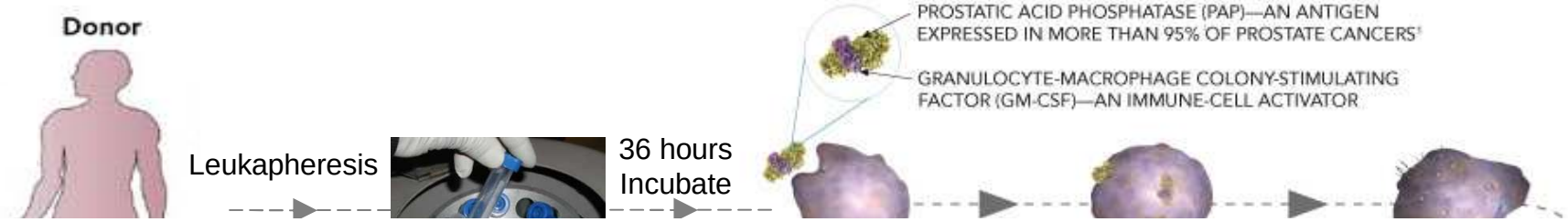
- Sipuleucel-T (Provenge)
- Approved by FDA in 2010 for metastatic castration resistant prostate CA
- Improves OS by 4.1 months

IMPACT Study

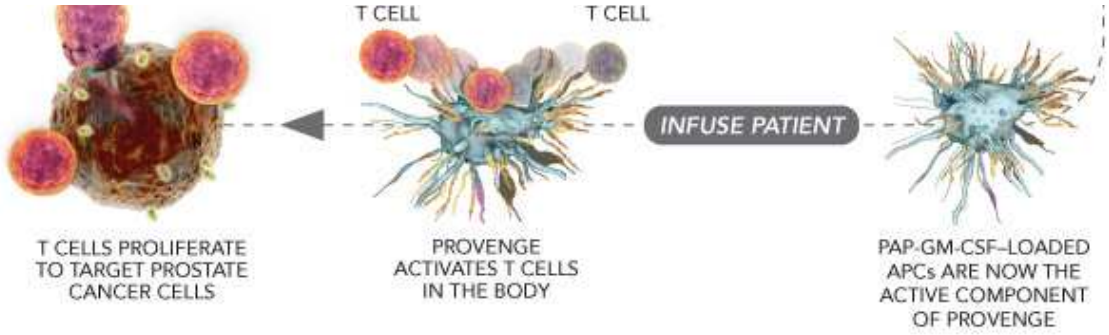


Kantoff PW et al. *NEJM* 2010;363(5):411-422

Dendritic Cell Vaccines



$93,000/patient

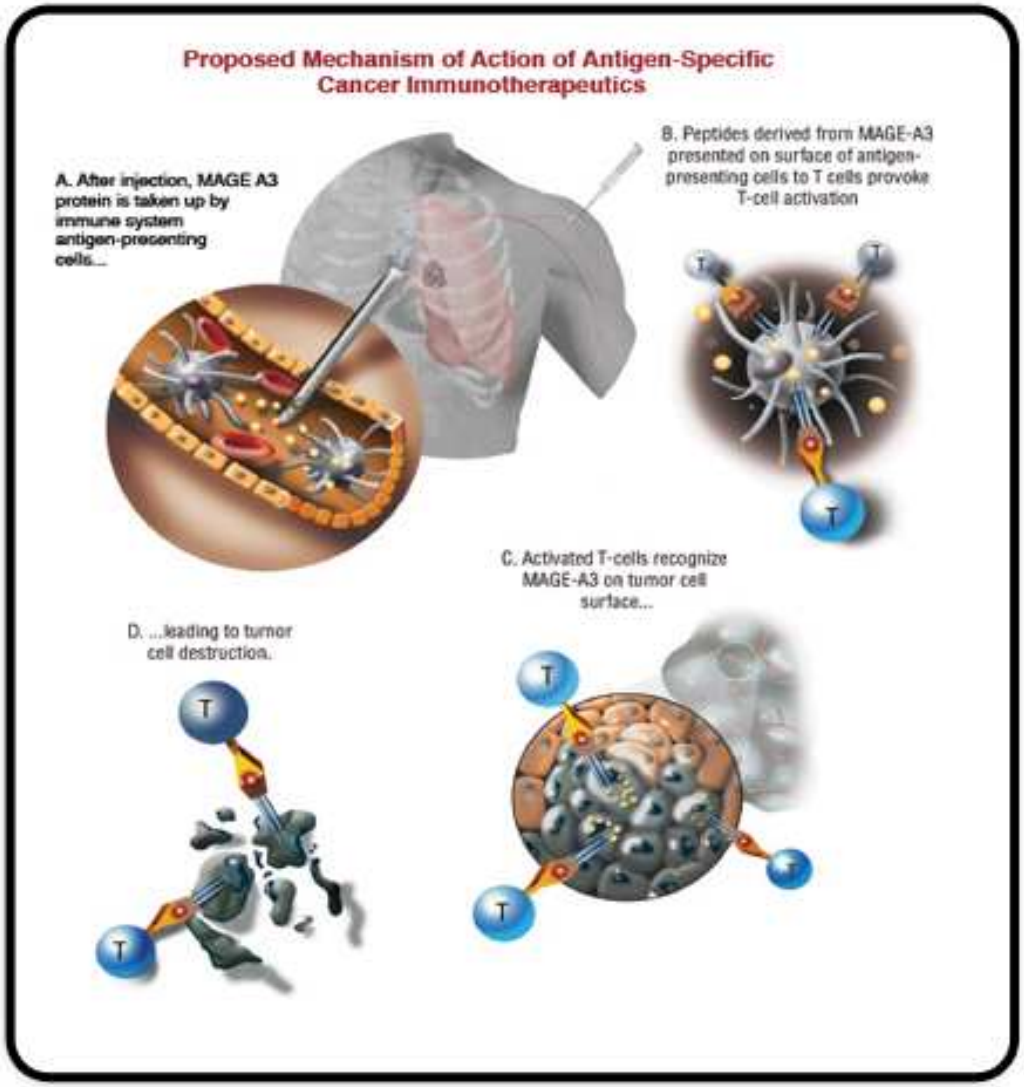


Dendritic Cell Vaccines

- Pros
  - Ex vivo DC maturation step
  - ↑ immune activation of infused product over time
- Cons
  - Complex manufacturing process
  - Expensive
  - Inconsistent results

GSK MAGE-A3

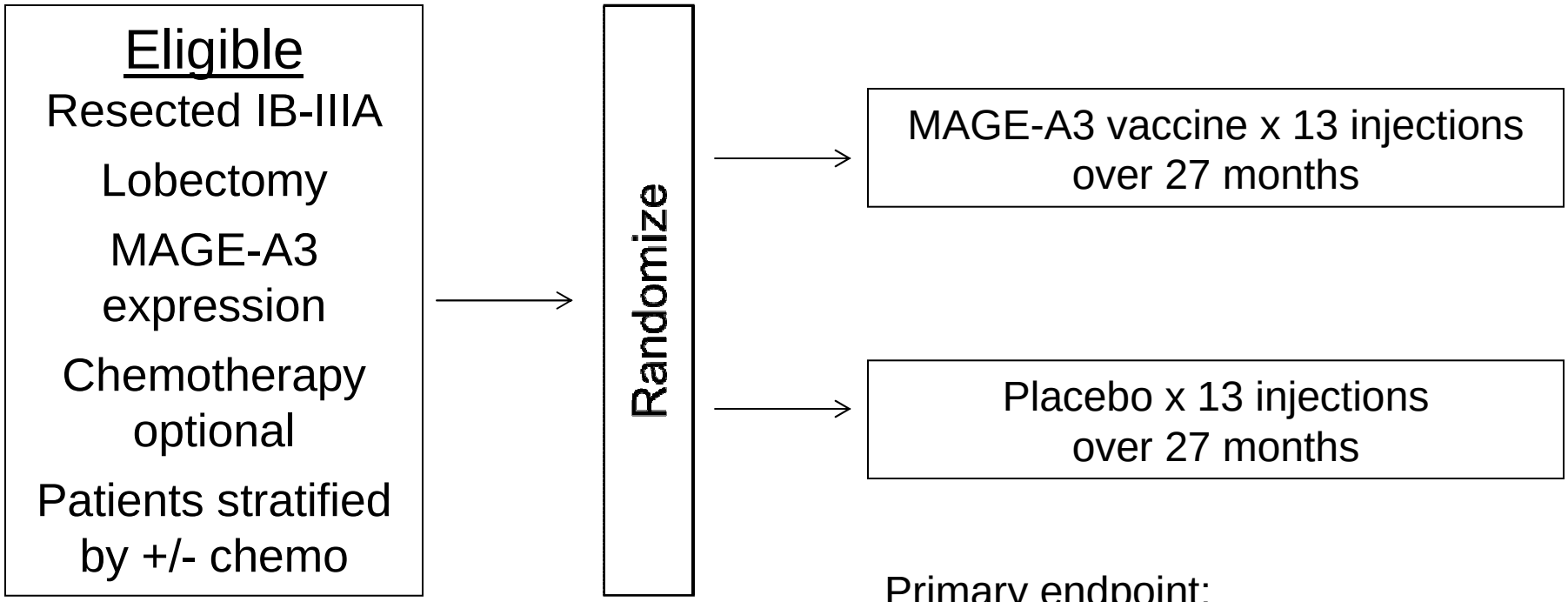
- Recombinant protein
- MAGE-A3
  - Tumor specific
  - Expressed in testis and placenta where spermatogonia and trophoblasts lack MHC molecules
- AS15 = GSK proprietary immunologic Adjuvant System



GSK MAGE-A3

- Phase II (n=182)
- Resected stage IB or II NSCLC
- Randomized to post-op vaccine or placebo
- Median f/u = 44 months
- Trend towards improved DFS and OS in vaccine group
- Identified possible gene signature that correlated with clinical activity

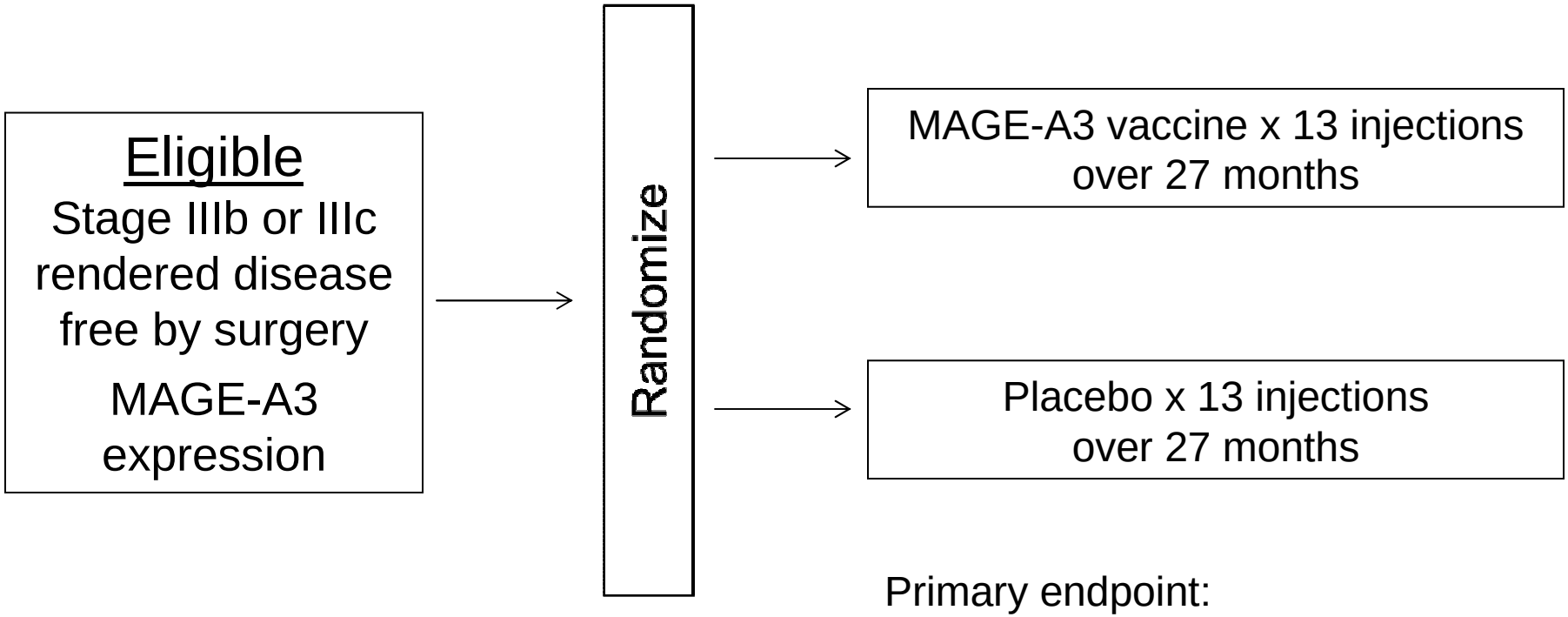
MAGRIT - NSCLC



Primary endpoint:
Disease-free survival

Secondary endpoint:
Validation of predictive gene signature

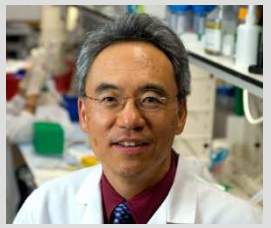
DERMA - Melanoma



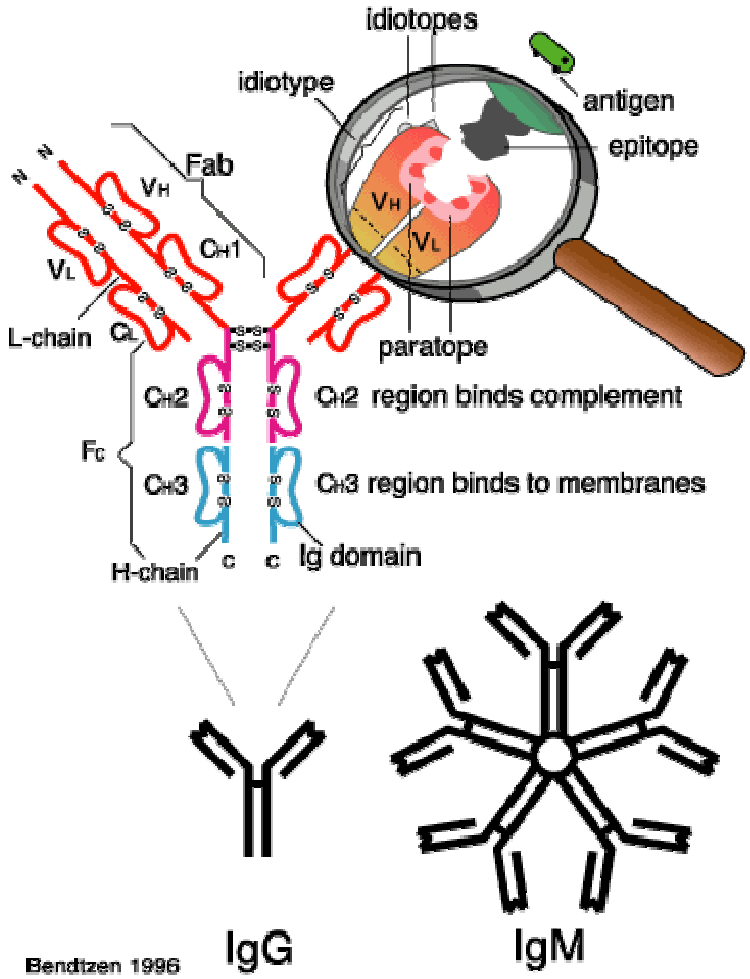
Primary endpoint:
Disease-free survival

Secondary endpoint:
Validation of predictive gene signature

Idiotype Vaccine

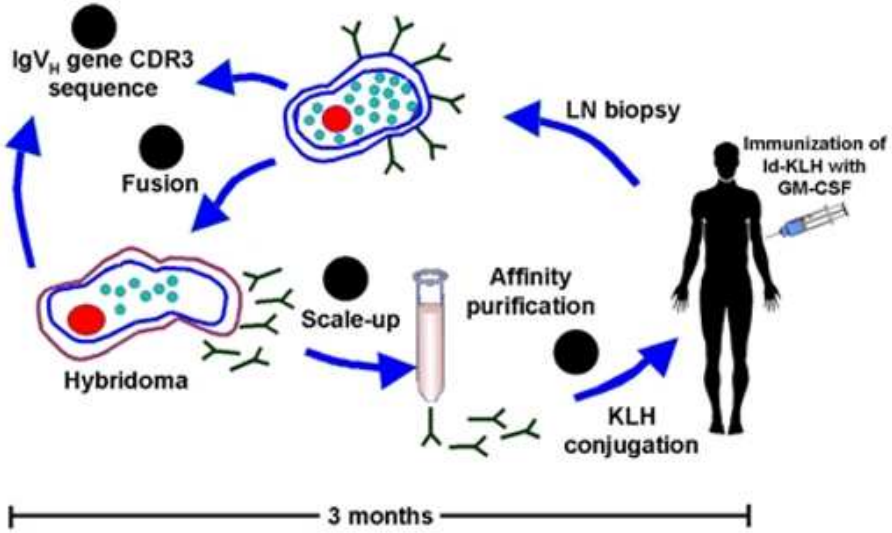


- Idiotype
  - Molecular determinant on the variable regions of surface Ig on a B-cell
  - Unique to each Ig
  - Can be recognized as antigens



Idiotype Vaccine

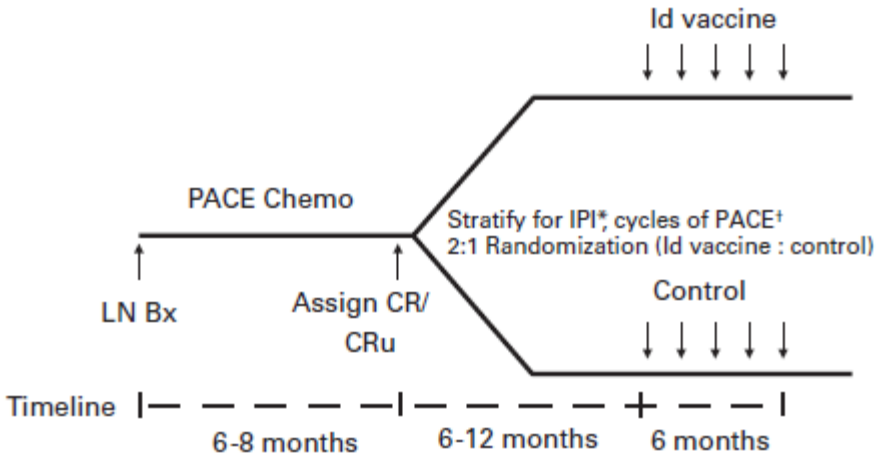
- Double-blind, RCT
- Follicular lymphoma
- Bulky stage II, III or IV disease with LN > 2cm accessible for biopsy
- Chemo naïve
- Patients achieving a complete response after chemotherapy were randomized

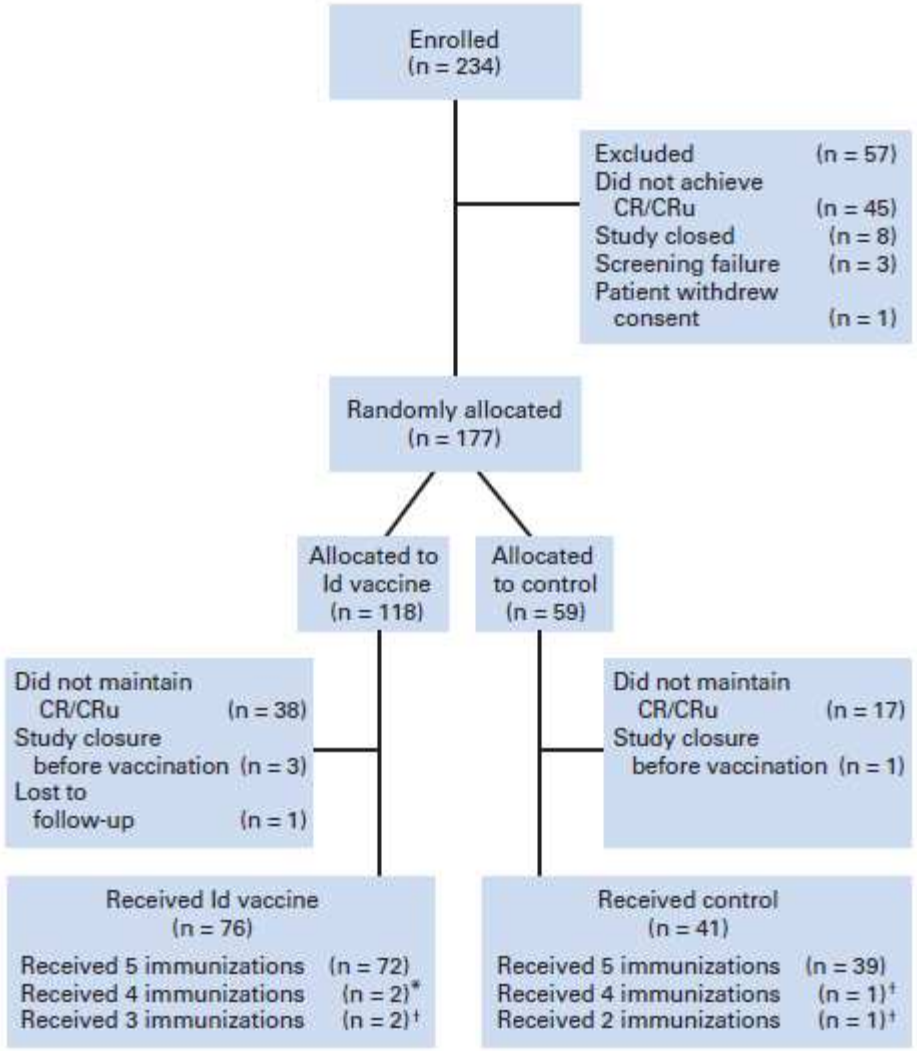


Vaccine: tumor isotype-matched Id protein manufactured by hybridoma technology.

Schuster SJ et al. *J Clin Oncol* 2011;29(20):2787-2794

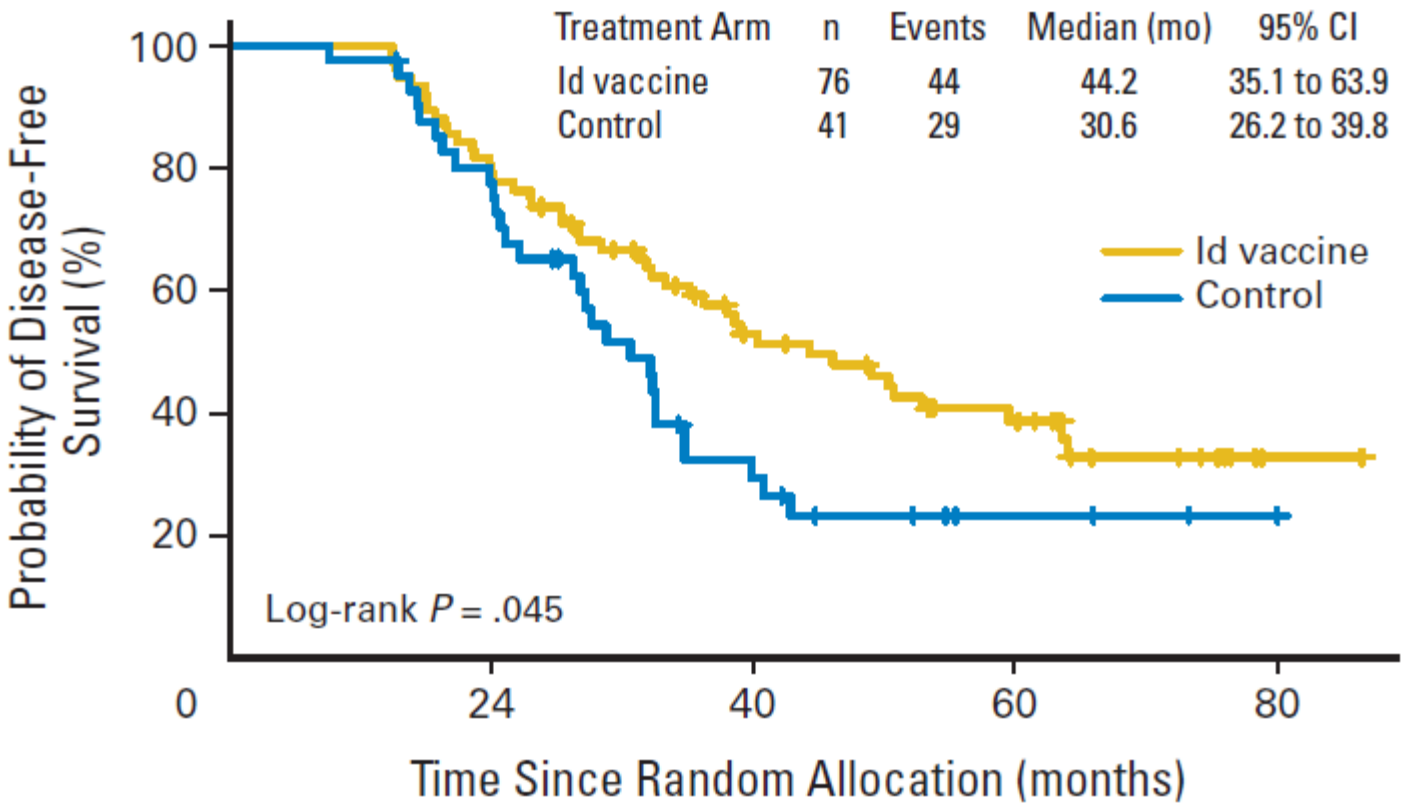
Idiotype Vaccine





Schuster SJ et al. *J Clin Oncol* 2011;29(20):2787-2794

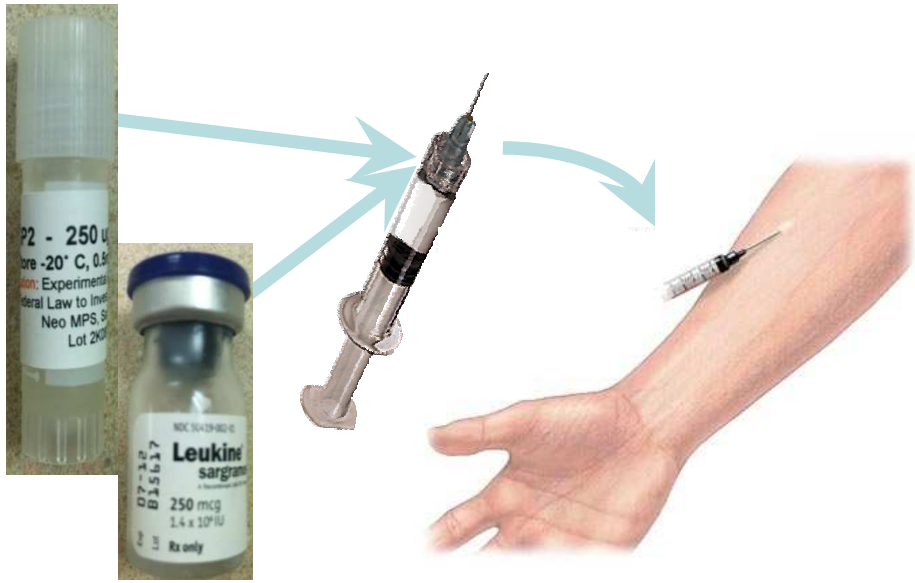
Idiotype Vaccine



Schuster SJ et al. *J Clin Oncol* 2011;29(20):2787-2794

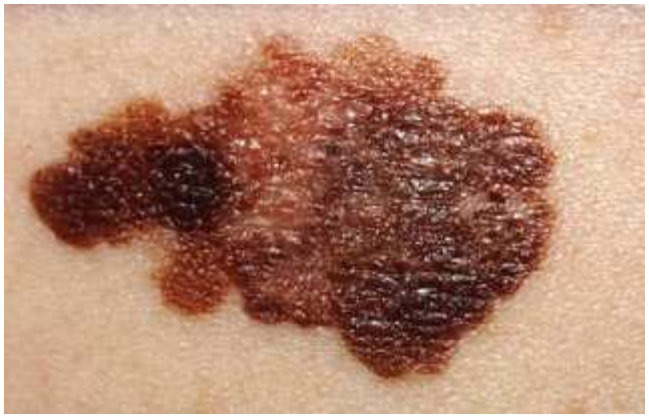
Peptide Vaccines

- Use antigenic peptides derived from tumor associated antigens (TAA)
- Stimulate peptide-specific immune regulators



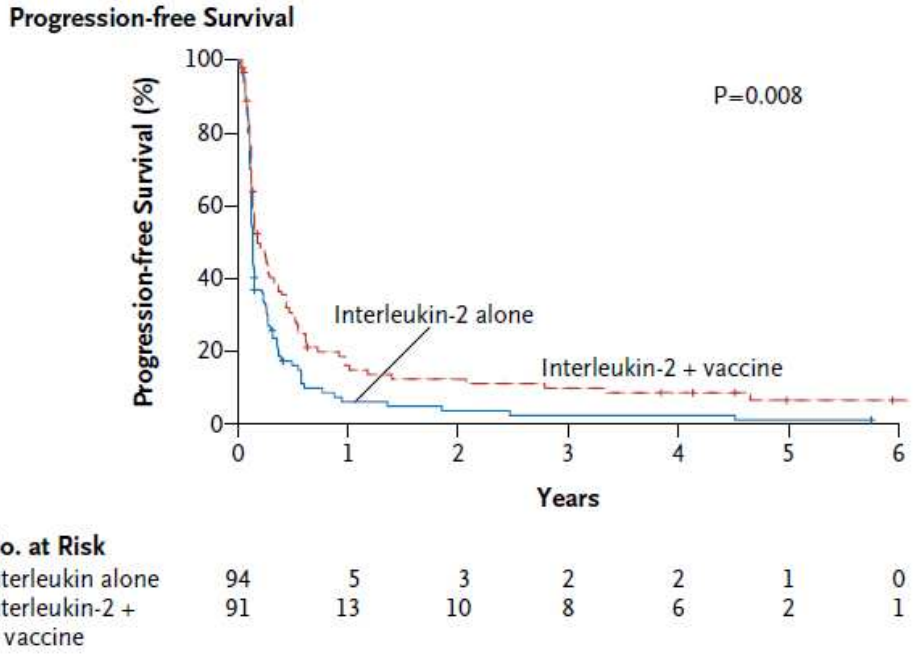
gp100

- Randomized phase 3
- N=185
- Stage IV or locally advanced stage III melanoma
- HLA-A2+
- Patients randomized to:
  - IL-2 alone
  - Gp100 + IFA followed by IL-2
- Primary endpoint: clinical response

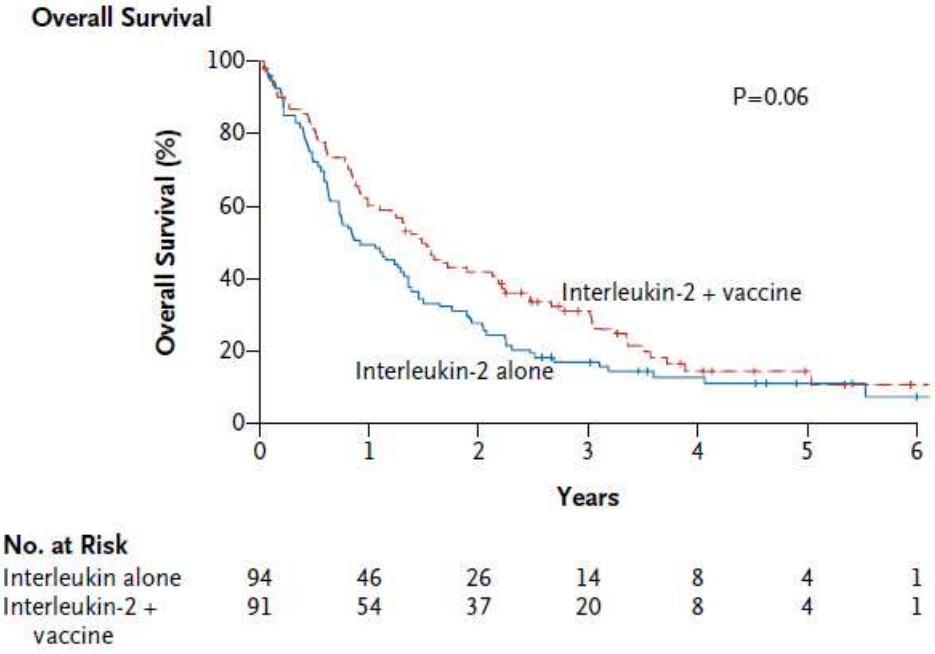


Schwartzentruber D, et al. *NEJM* 2011;364(22):2119-2127

gp100



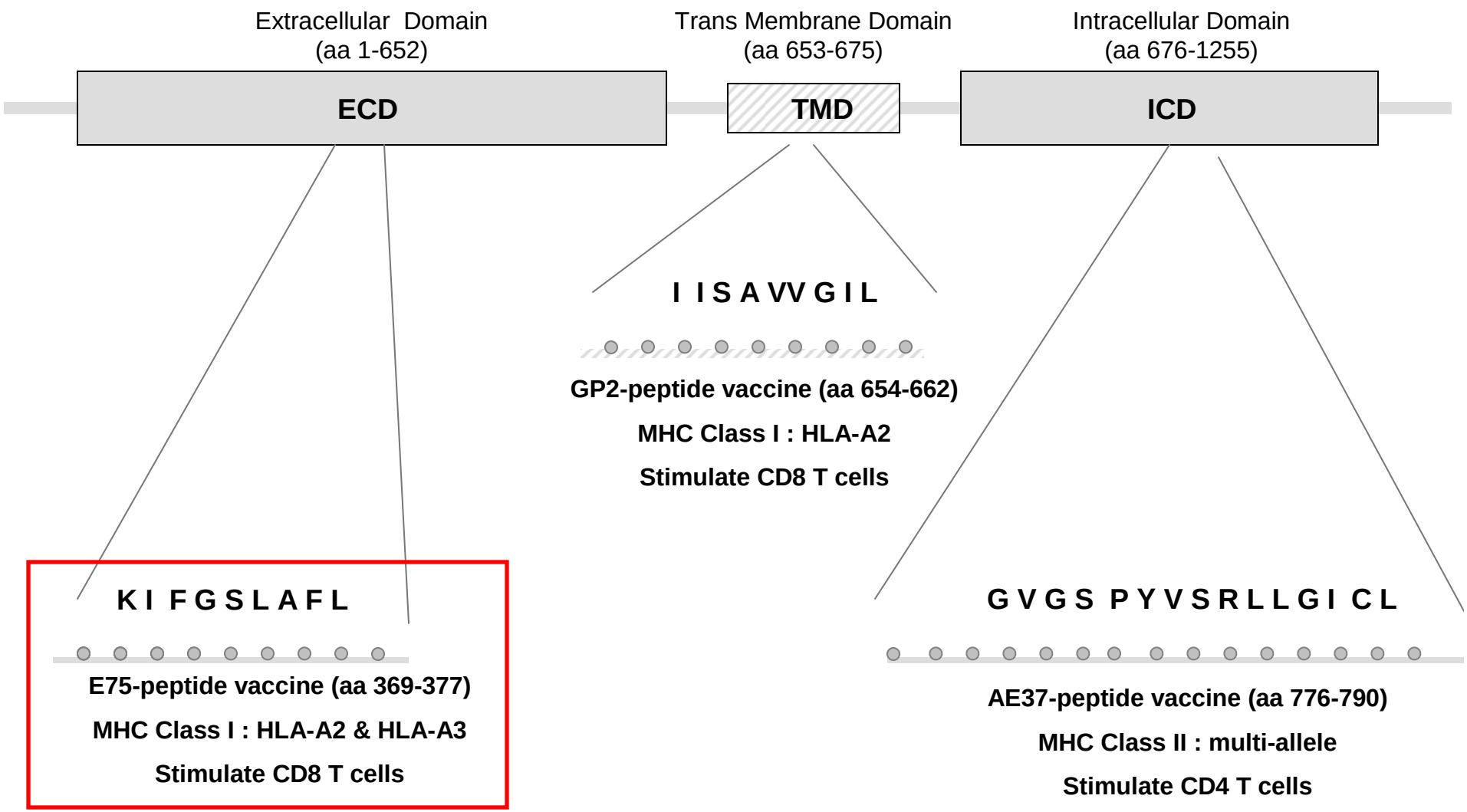
No. at Risk							
Interleukin alone	94	5	3	2	2	1	0
Interleukin-2 + vaccine	91	13	10	8	6	2	1



No. at Risk							
Interleukin alone	94	46	26	14	8	4	1
Interleukin-2 + vaccine	91	54	37	20	8	4	1

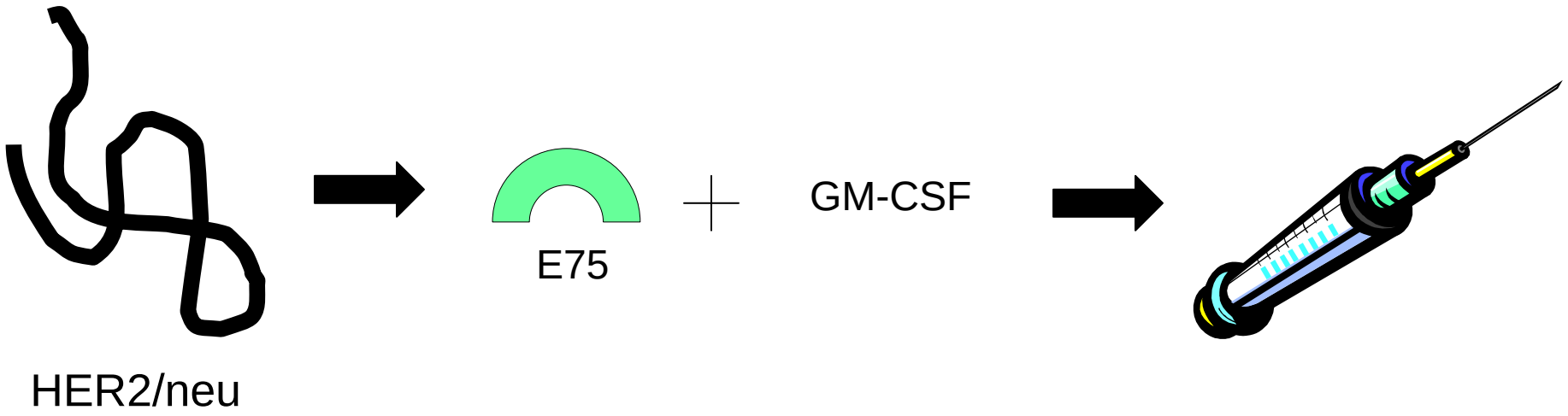
Schwartzentruber D, et al. *NEJM* 2011;364(22):2119-2127

HER2/neu

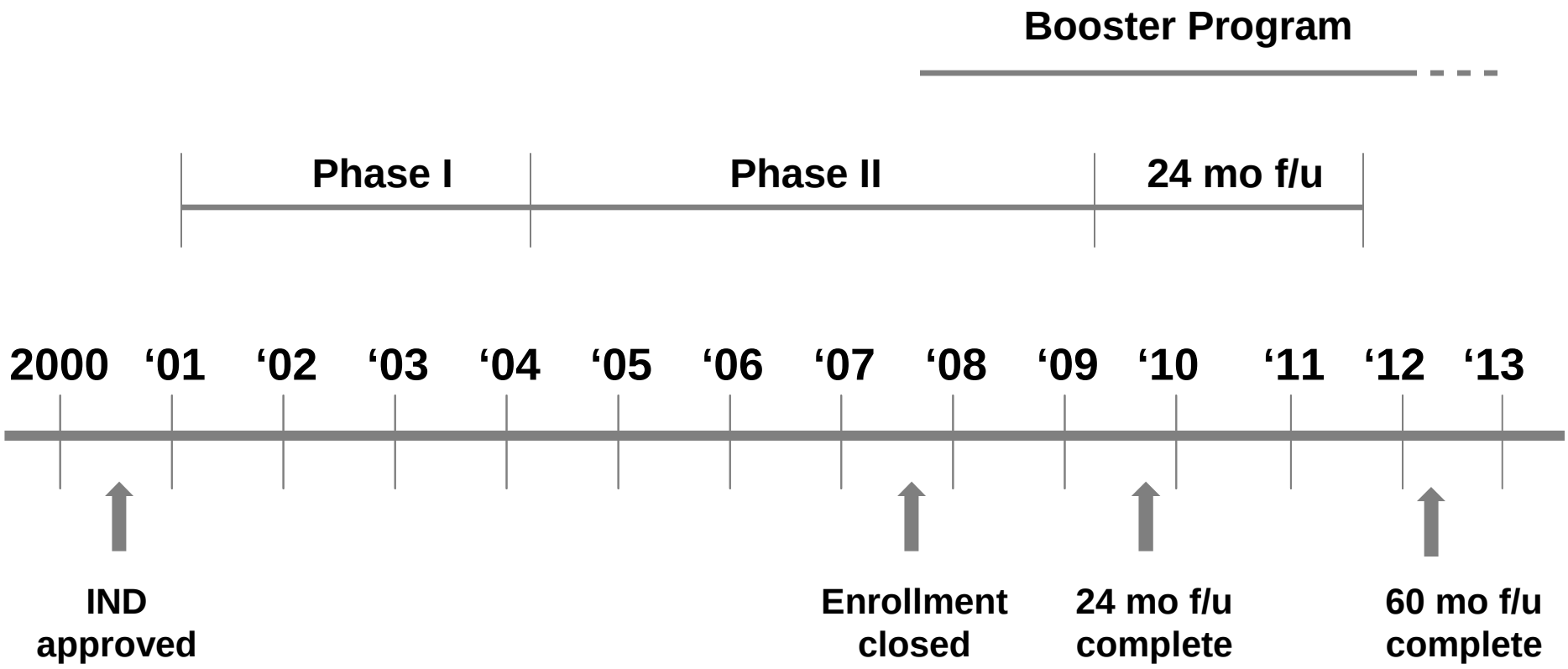

Extracellular Domain
(aa 1-652)
Trans Membrane Domain
(aa 653-675)
Intracellular Domain
(aa 676-1255)
ECD
TMD
ICD
I I S A VV G I L
GP2-peptide vaccine (aa 654-662)
MHC Class I : HLA-A2
Stimulate CD8 T cells
K I F G S L A F L
E75-peptide vaccine (aa 369-377)
MHC Class I : HLA-A2 & HLA-A3
Stimulate CD8 T cells
G V G S P Y V S R L L G I C L
AE37-peptide vaccine (aa 776-790)
MHC Class II : multi-allele
Stimulate CD4 T cells

HER2-Derived Peptide Vaccine

- E75
  - 9 aa peptide from extracellular domain
  - Immunodominant epitope of HER2/*neu*
  - MHC class I peptide → stimulated $CD8^+$ T cells
  - High affinity for HLA-A2 /A3



Trial Design



Mittendorf E et al. *Cancer* 2012;118(10):2594-2602

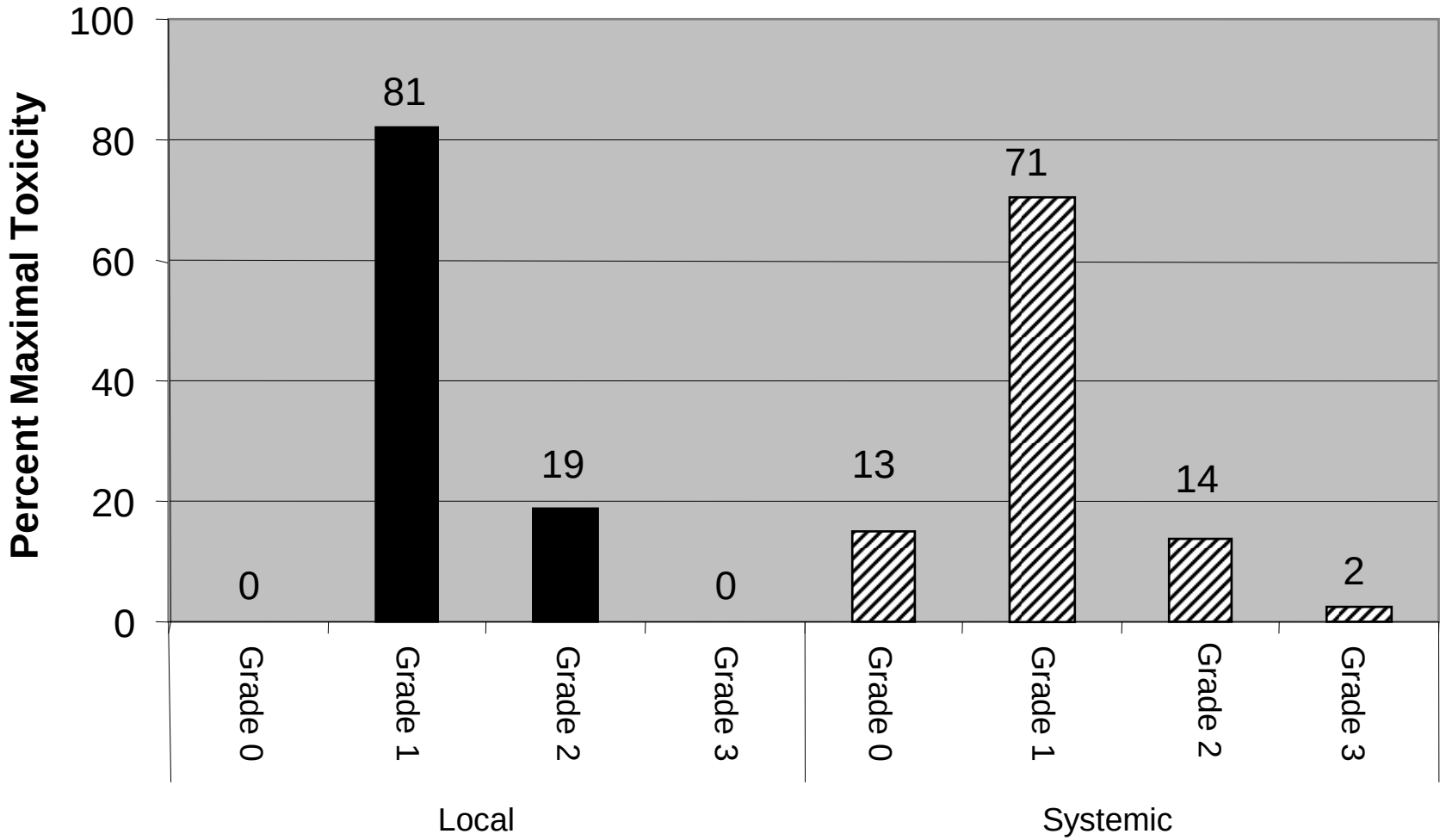
Inclusion Criteria

- Histologically confirmed breast cancer
- Node positive or high-risk node negative
- Completed SOC surgery, chemotherapy and radiation
- Immunocompetent
- Any level of HER2 (IHC 1+, 2+, 3+)

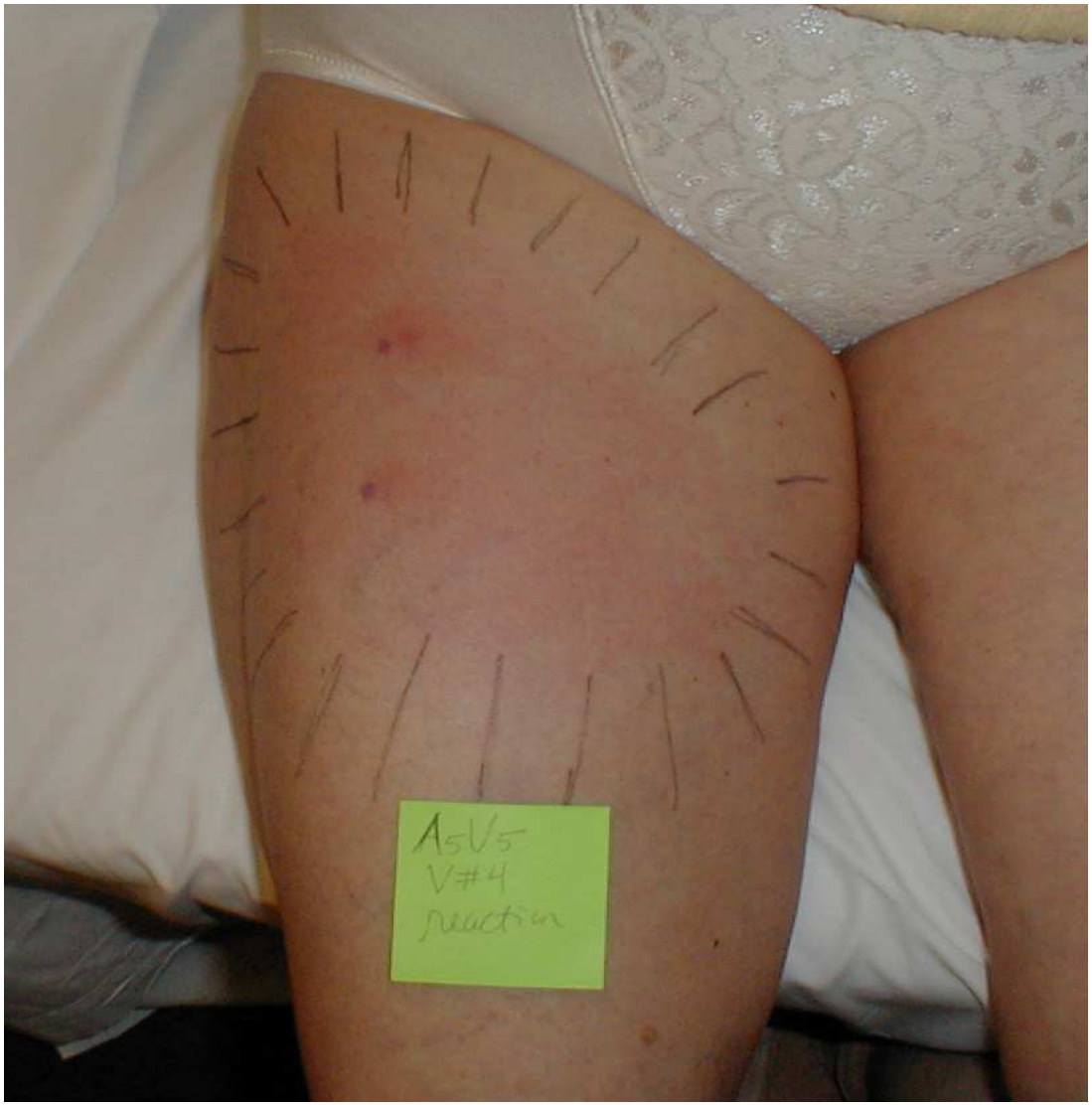
E75 Phase I/II Trial

n=	Vaccine 108	Control 79	p value
Age (median)	57	53	0.26
Node Positive	49.1%	55.7%	0.38
Tumor Size (T2-T4)	34.3%	46.2%	0.13
Histologic Grade 3	40.0%	39.5%	1.00
ER/PR negative	**31.1%**	**17.7%**	**0.04**
HER2/*neu* overexpression	31.7%	26.8%	0.50
Hormonal Therapy	66.7%	76.9%	0.14
Chemotherapy	75.0%	72.2%	0.74
XRT	72.2%	81.0%	0.17
Trastuzumab Therapy	11.1%	3.8%	0.10
Optimal dose	34.3%	0.0%	n/a

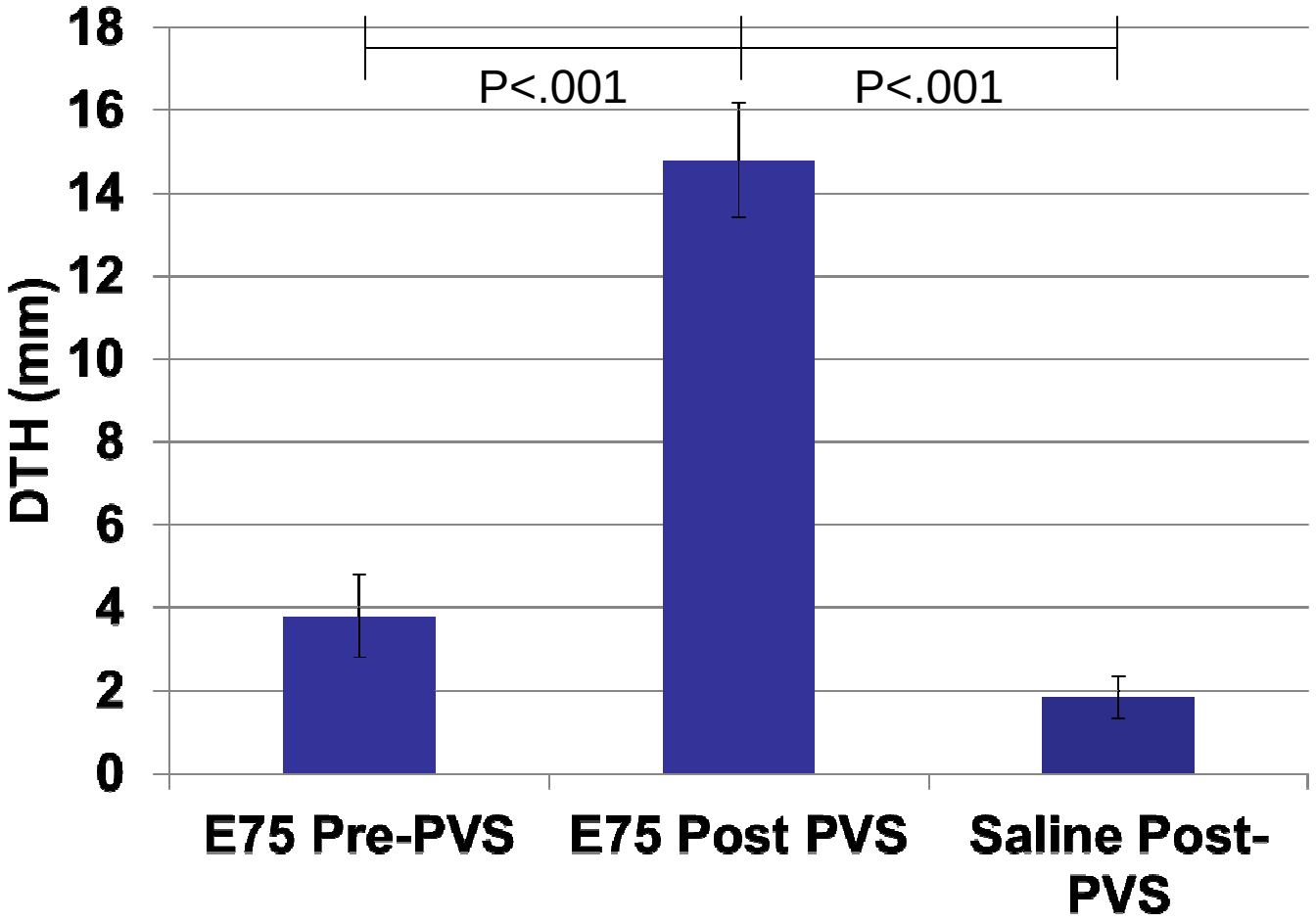
Safety and Toxicity



Local Toxicity



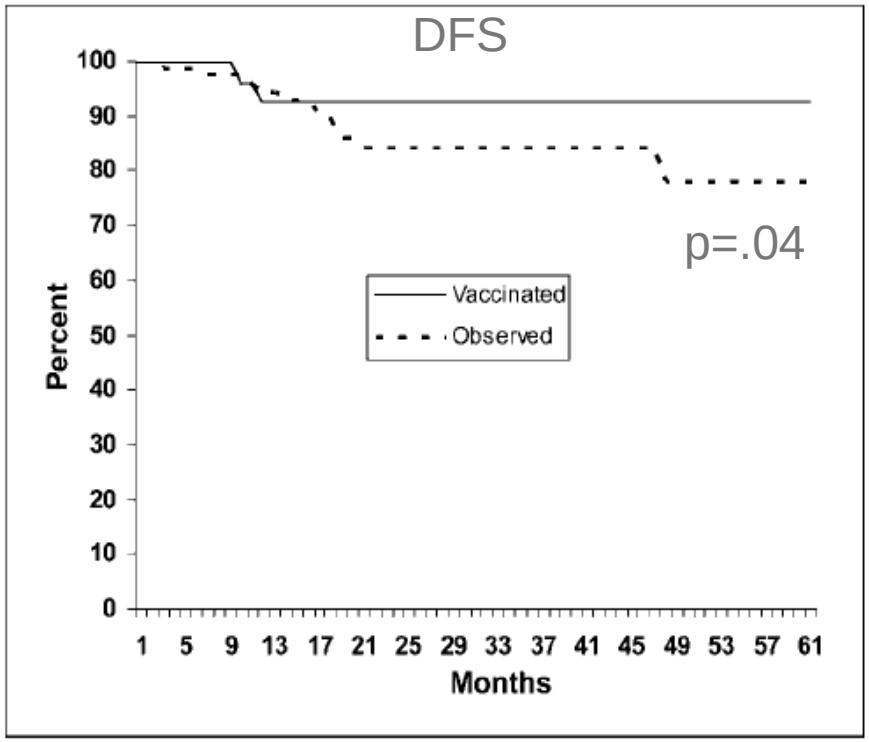
In Vivo Immune Response



Clinical Benefit to Vaccination

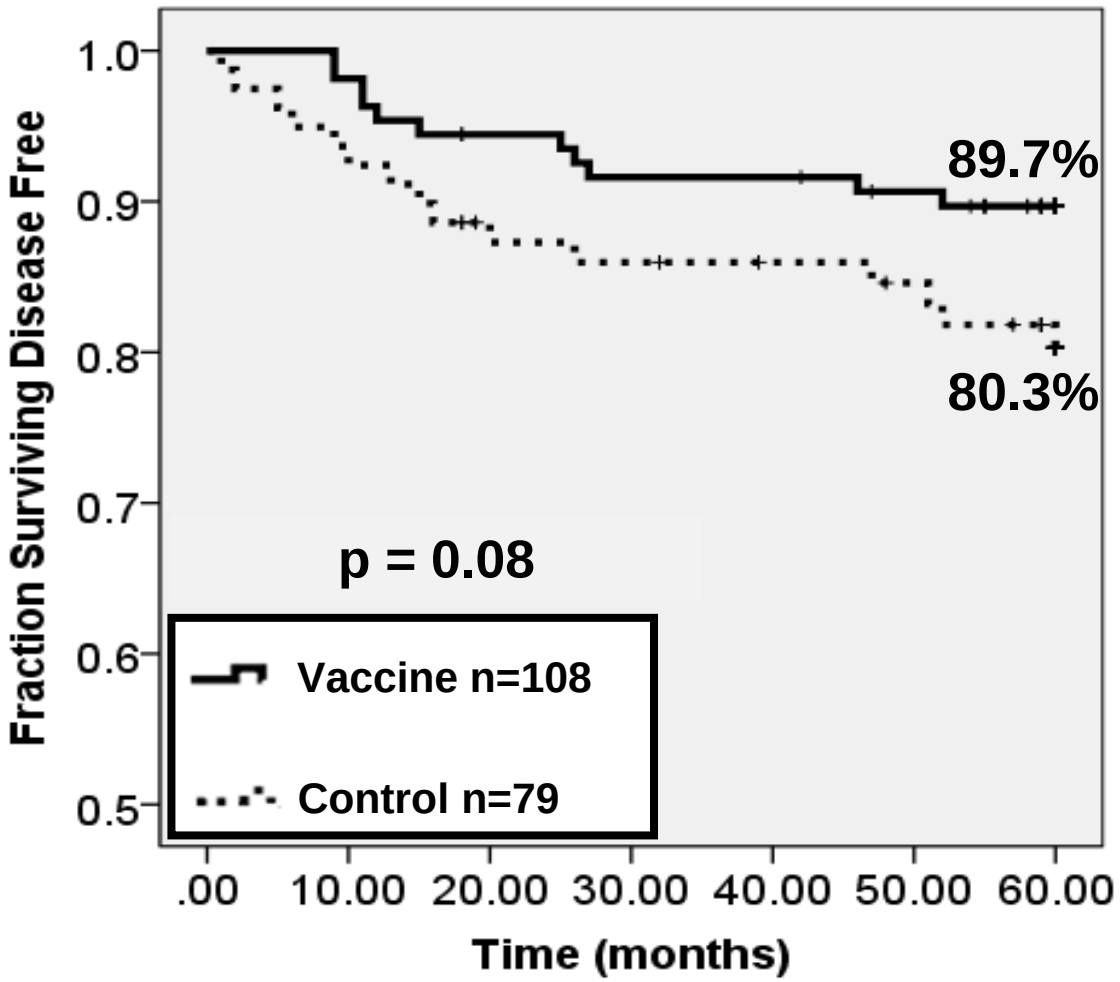
Primary analysis at 18 months median follow-up

	Vaccinated	Control	P-value
Recurrence Rate	5.6%	14.2%	0.04
Disease Free Survival	92.5%	77.0%	0.04
Overall Survival	99.0%	95.1%	0.10



Peoples GE et al. *Clin Cancer Res* 2008;14(3):797-803

DFS – 60 mo median f/u



Vreeland T, et al. SABCS 2012

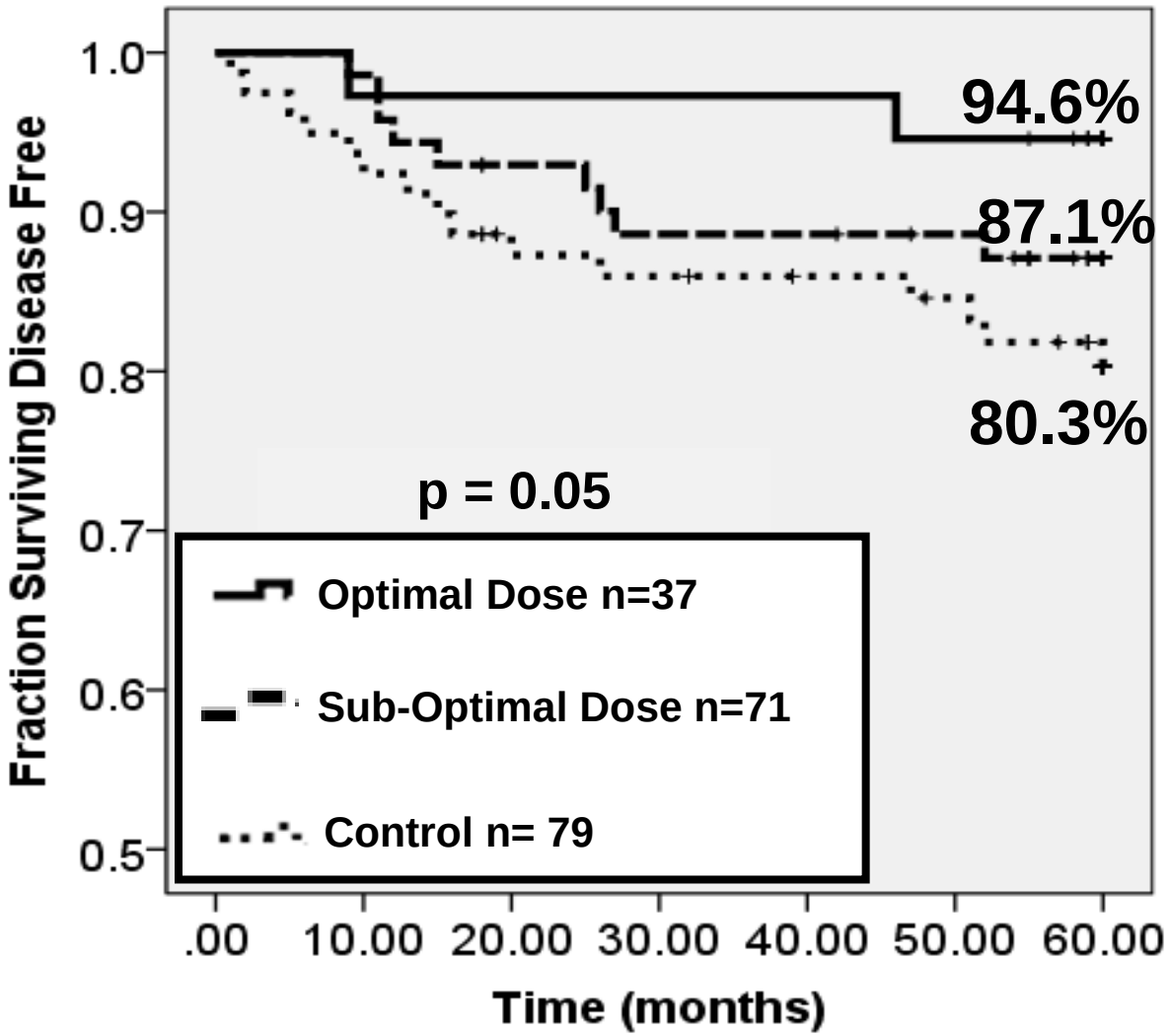
E75 Trial Summary

- Largest breast cancer adjuvant vaccine trial
- Safe and effective in raising HER2 immunity
- Appears to have clinical impact
- HER2 low expressing patients with best immunologic response

Data Limitations

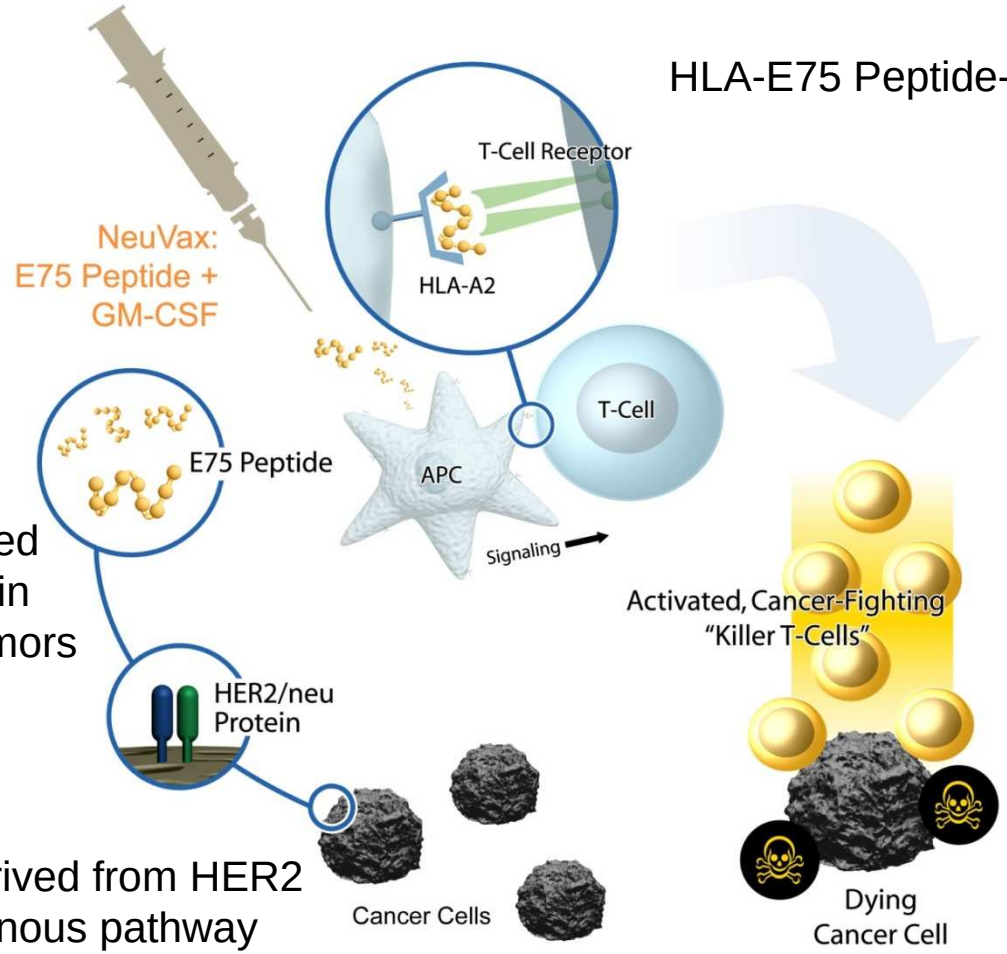
- No true control group (HLA-A2/3+ vaccinated, A2/A3- controls)
- No GM-CSF alone group
- Analyzed phase I/II together
  - Not all patients received optimal dose
  - Not all patients received booster

DFS – Optimal Dosing



Vreeland T, et al. SABCS 2012

NeuVax™



HLA-E75 Peptide-TCR complex

Induces proliferation of E75-specific T-cell clones

Millions of HER2-targeted "CTL" clones seek and destroy HER2 expressing cancer cells

E75 isolated from HLA in human tumors

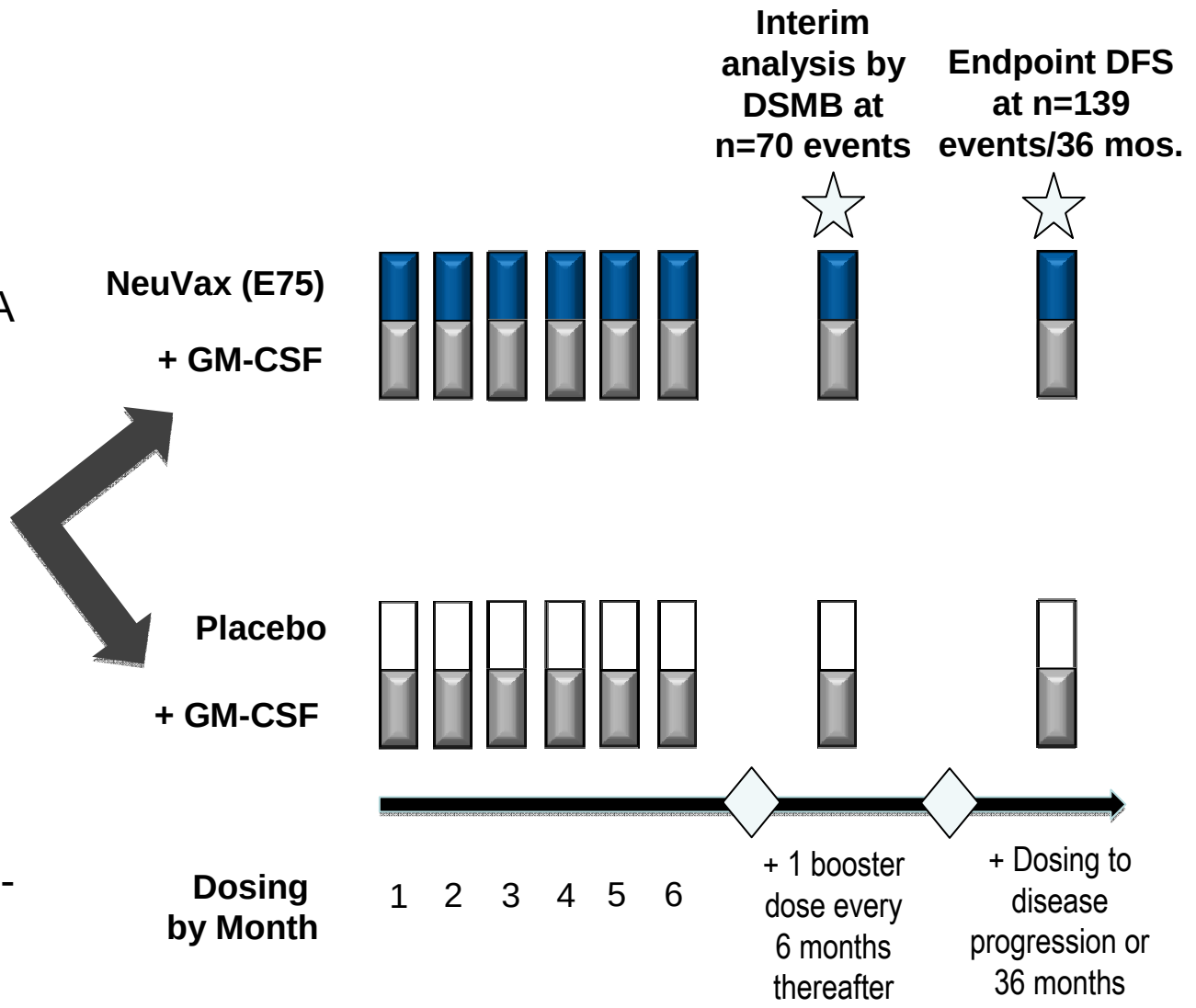
E75 derived from HER2 endogenous pathway

Phase III Study Schema: PRESENT (Prevention of Recurrence in Early Stage Node-Positive Breast Cancer with Low to Intermediate HER2 Expression with NeuVax Treatment

Study Population

Adjuvant Breast cancer (BC) patients, n=700, randomized 1:1

- Node positive (NP), HLA A2/A3+, low and intermediate HER2 expression
- Achieve CR with standard of care (SOC)
- Stratified by Stage (IIA-IIIA), Type of Surgery, Hormone Receptor and Menopausal status
- Single dose level of GM-CSF +/- NeuVax

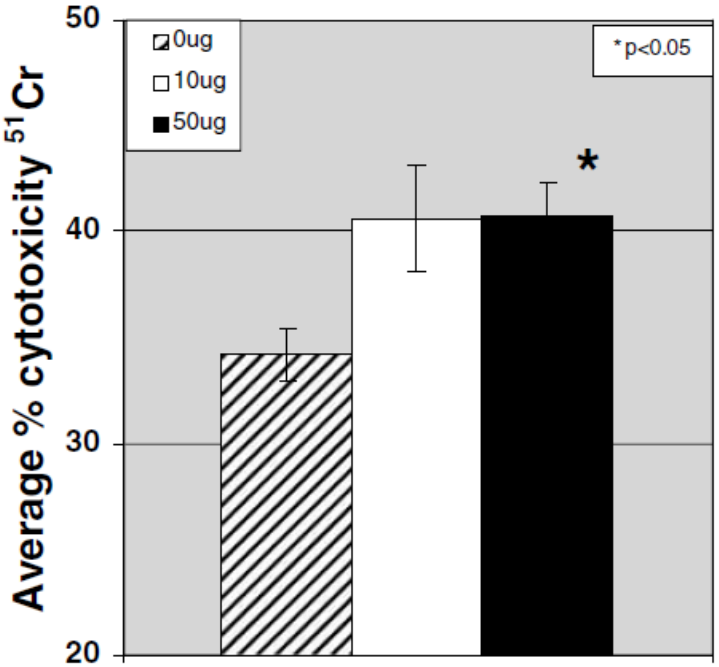


NeuVax™

PI: E.A. Mittendorf

Combination Immunotherapy

- Pretreatment of tumor cells with trastuzumab results in increased specific cytotoxicity



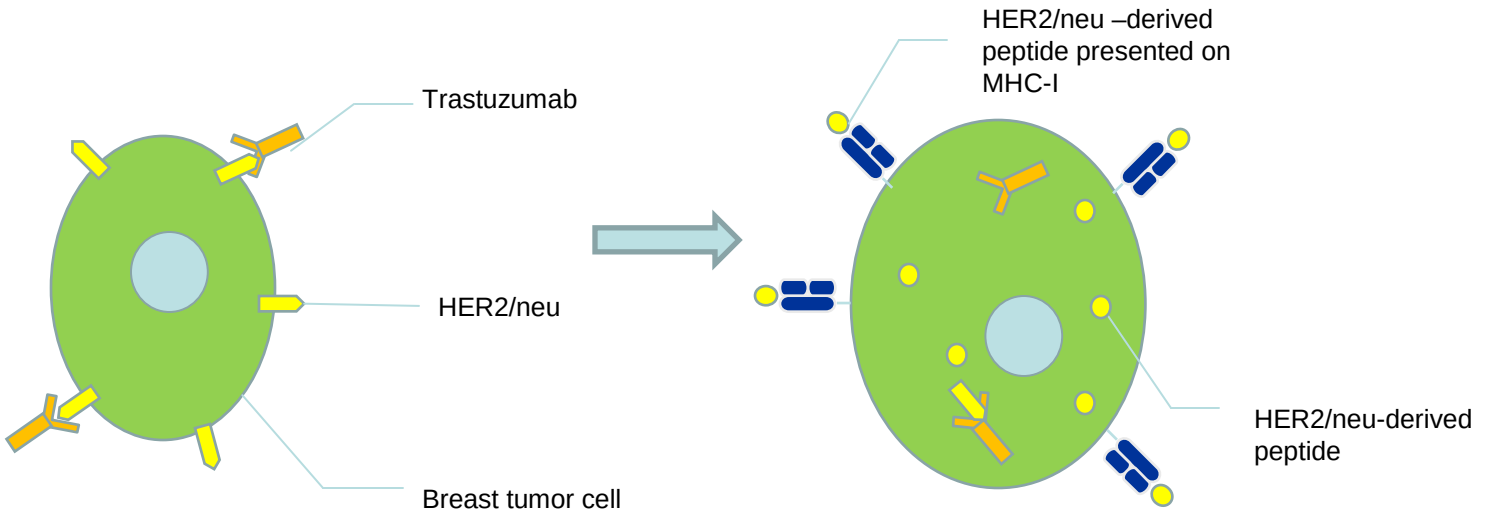
Mittendorf et al. *Ann Surg Oncol* 2006

Possible Mechanisms

- Increased antigen availability
- Altered MHC class I expression
- Altered APM
- Antibody response

Combination Immunotherapy

Enhanced antigen presentation

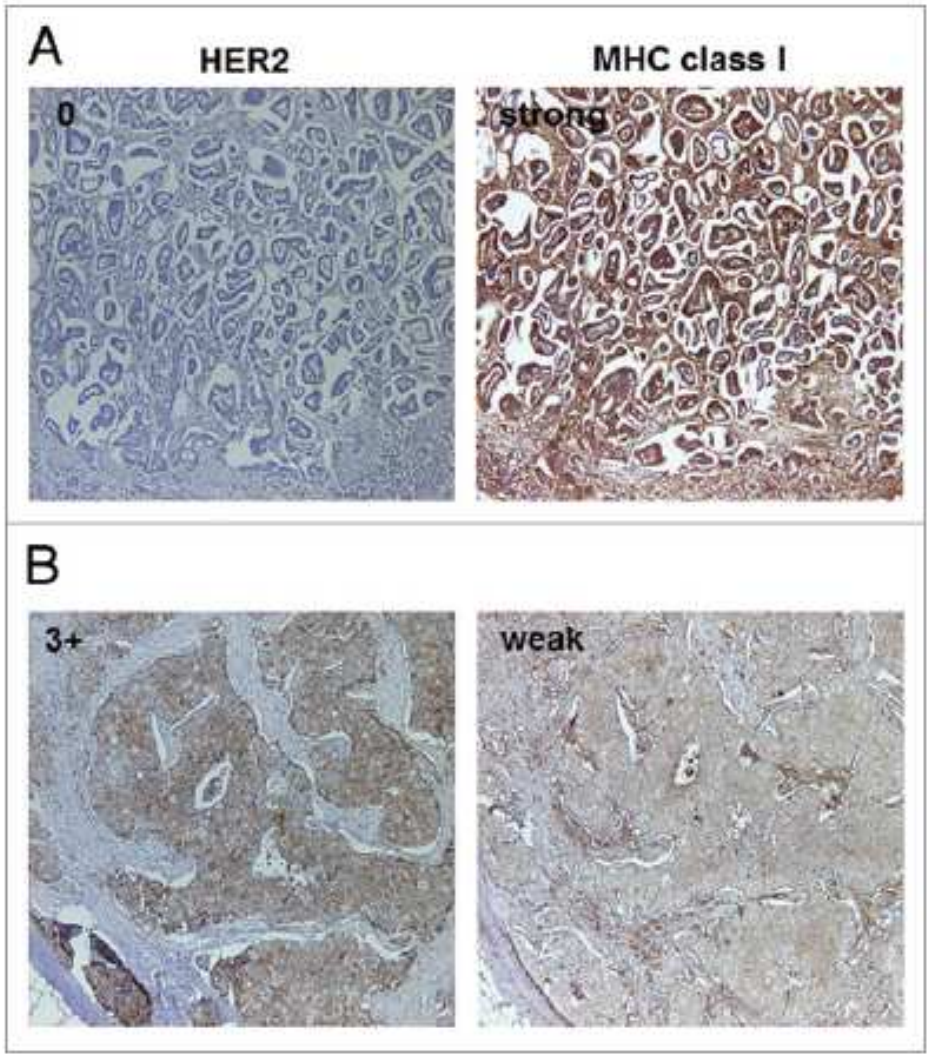


Trastuzumab binds to HER2/neu receptors on breast cancer cell

Trastuzumab/HER2 complexes are internalized and processed by proteasomes into short peptides (such as E75 or GP2), which are then presented on MHC class I molecules.

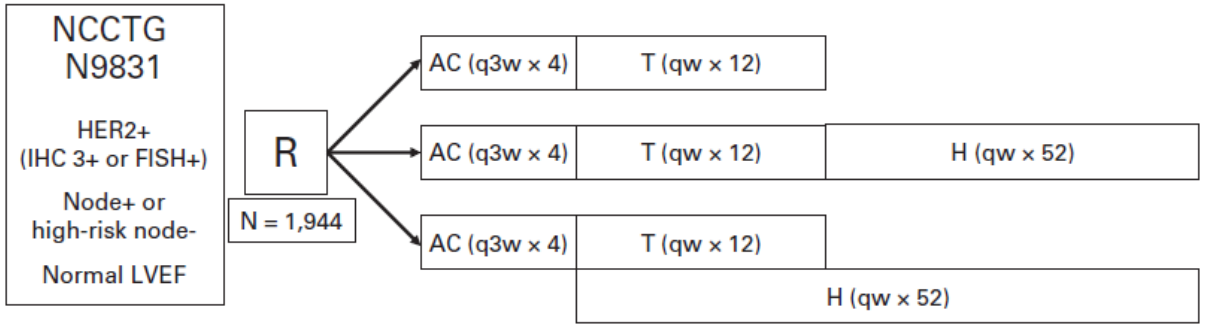
Mittendorf et al. *Ann Surg Oncol* 2006

Correlation between HER2 and MHC-I

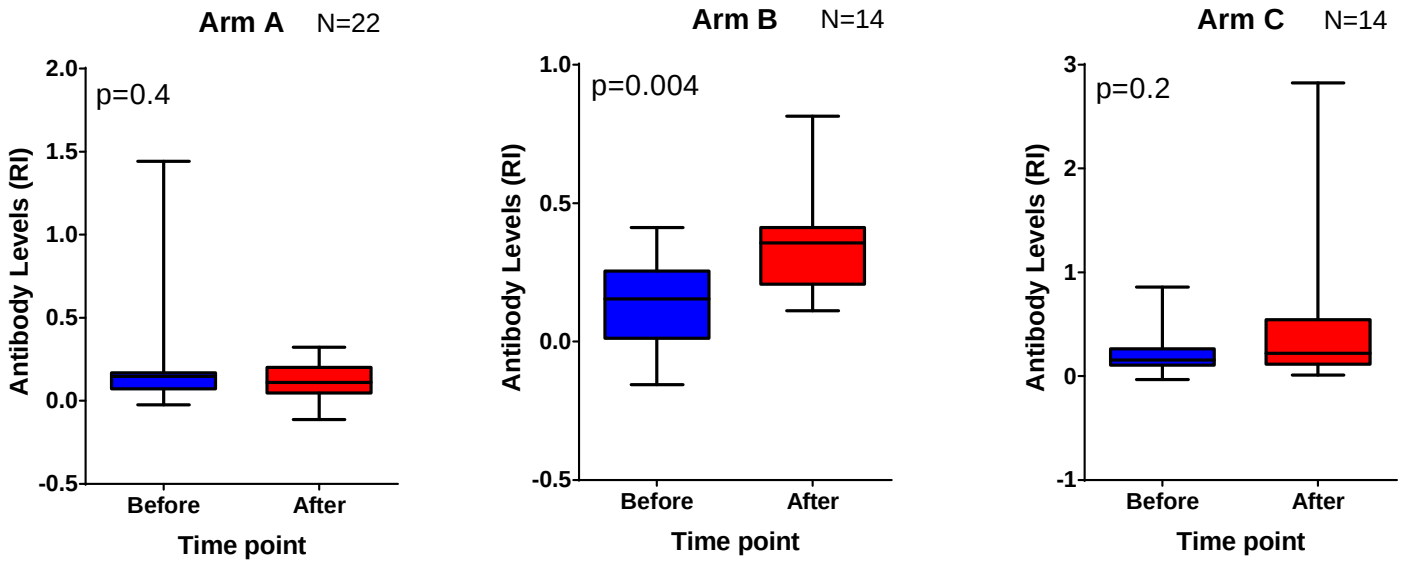


Inoue M, et al. *Oncoimmunology* 2012;1(7):1104-1110

Antibody Response



HER2-specific IgG Ab response



Knutson, et al. ASCO 2013

Phase I Trial

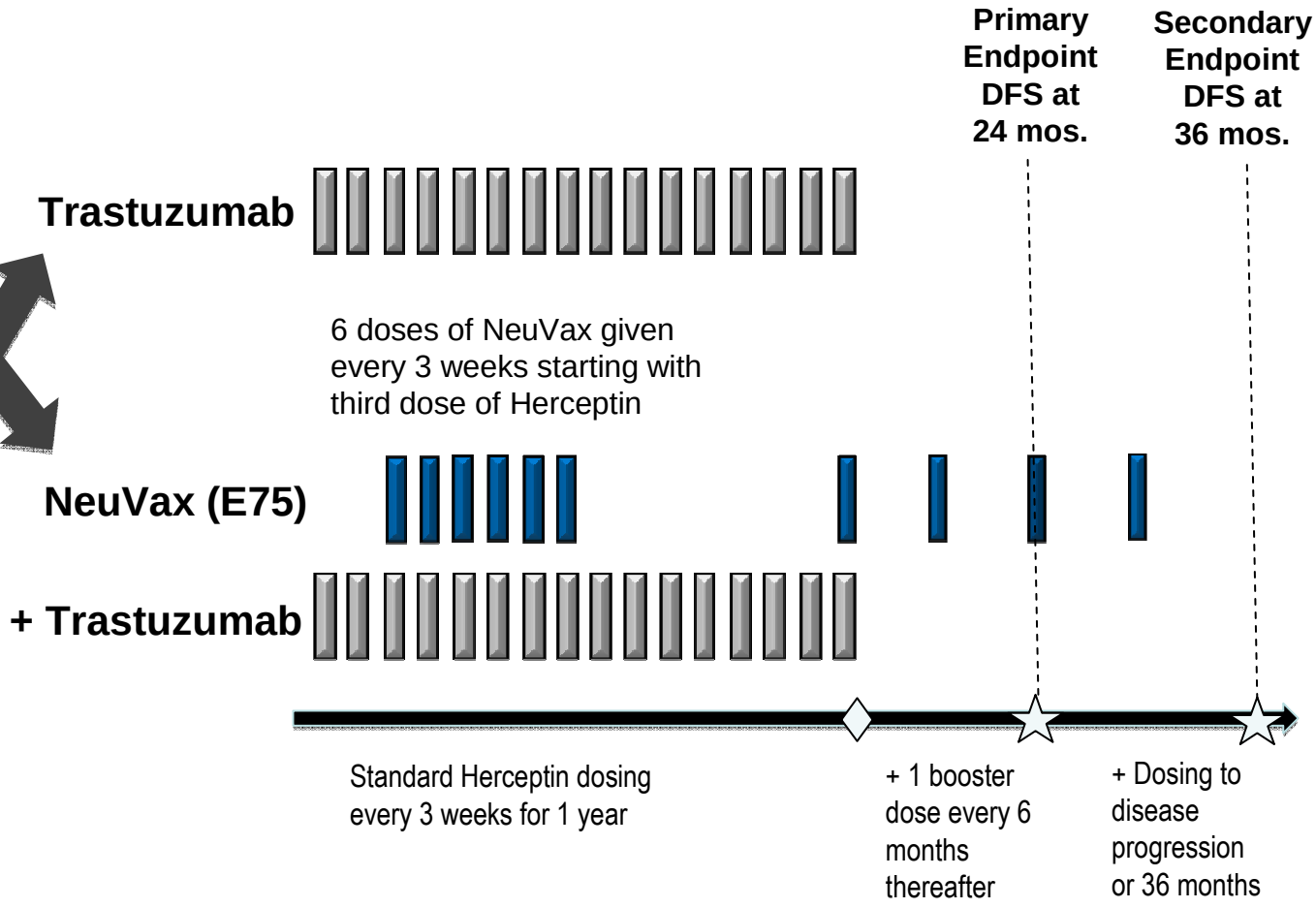
- Combination therapy with vaccine + trastuzumab is:
  - Safe
  - Immunogenic
  - No dose limiting toxicity or cardiac events

Phase II: NeuVax (E75) + Trastuzumab v. Trastuzumab alone in HER2 IHC 1+/2+, early-stage breast cancer

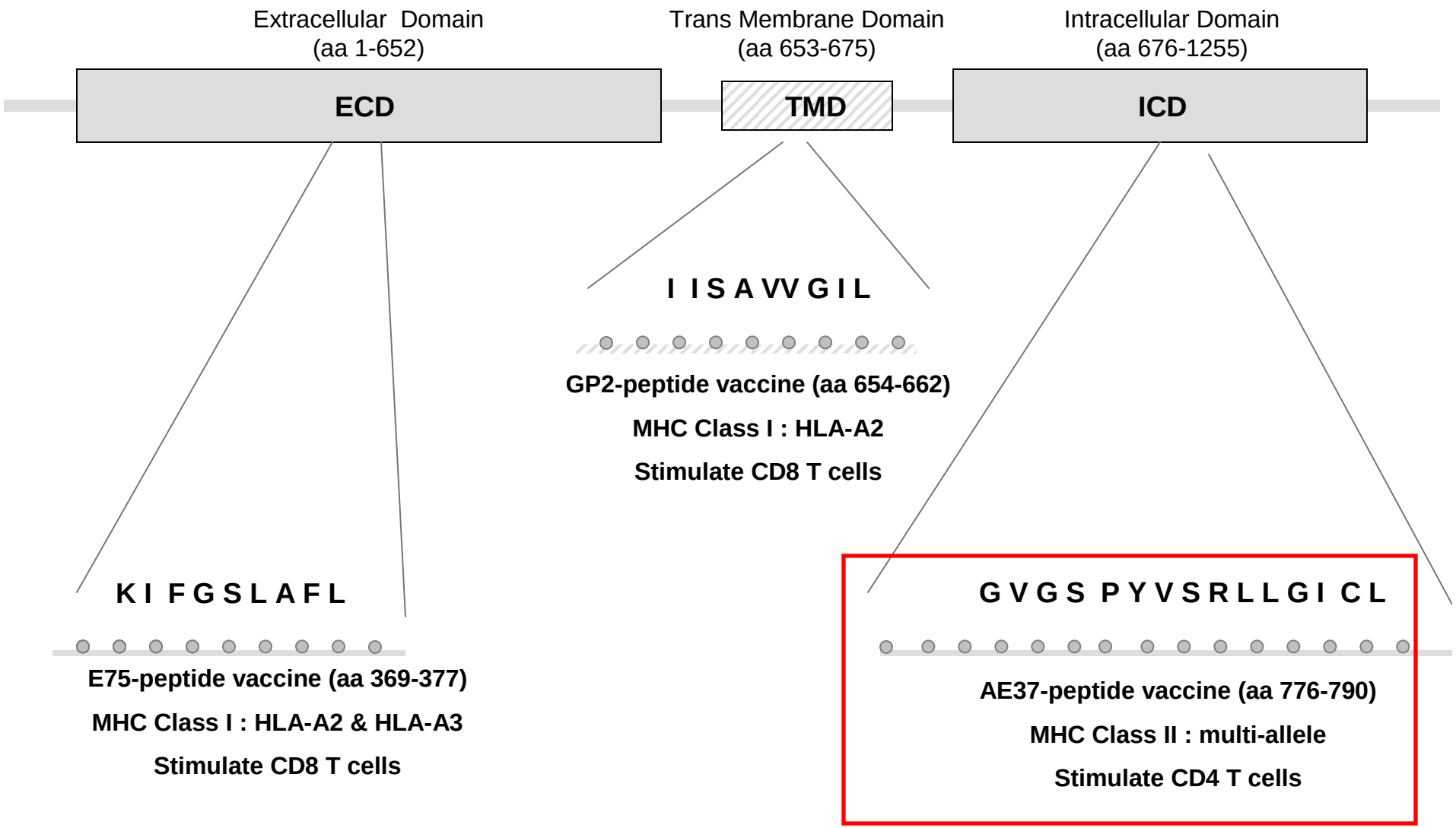
Study Population

Adjuvant Breast cancer (BC) patients, n=300, randomized 1:1

- HLA A2/A3+, low and intermediate HER2 (IHC 1+/2+) expression; node positive (HR+/-) or node negative (HR-)
- Stratified by nodal status and HER2 status
- Single dose level of Trastuzumab + NeuVax vs Trastuzumab + GM-CSF alone



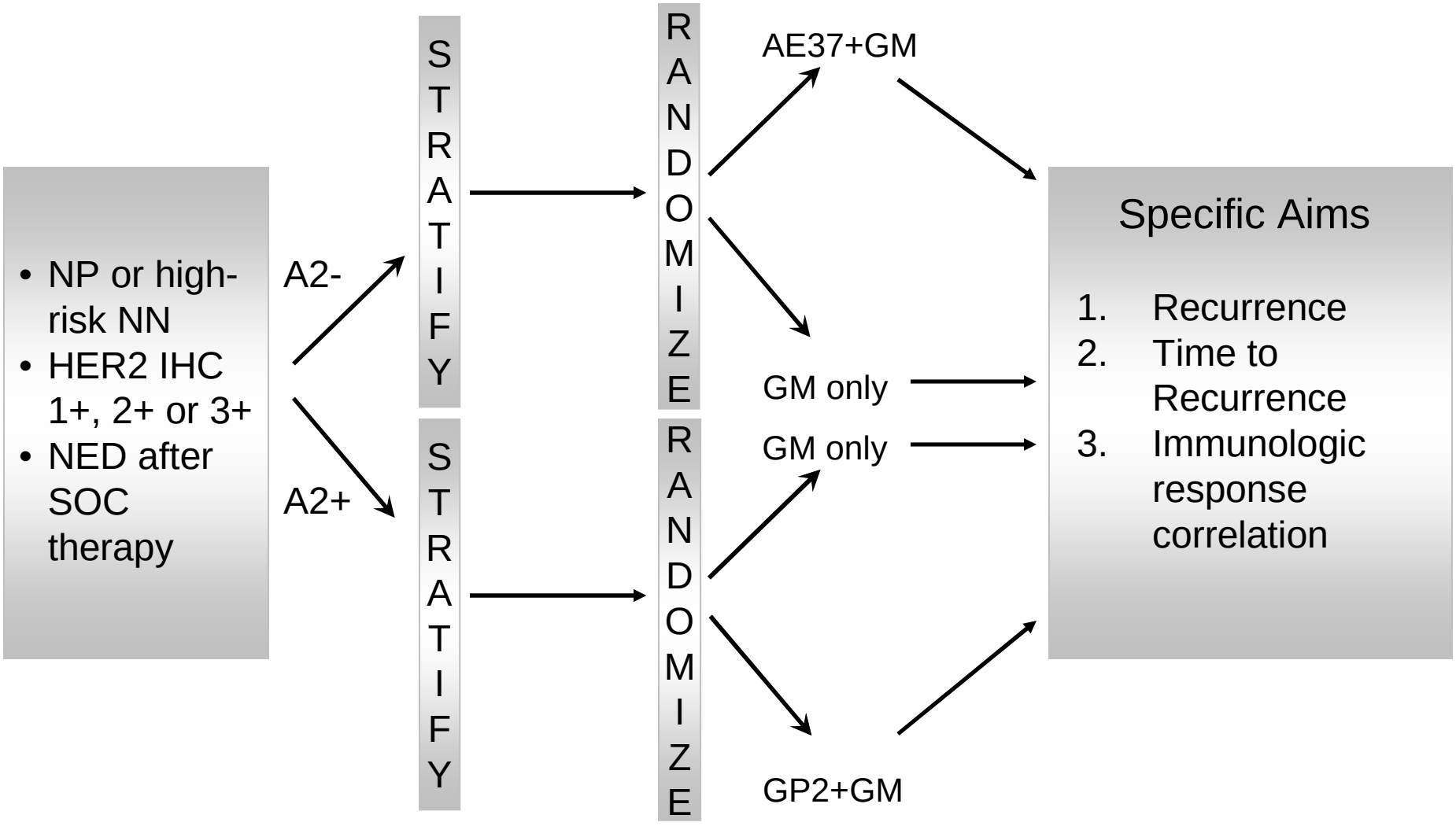
HER2/neu


Extracellular Domain
(aa 1-652)
Trans Membrane Domain
(aa 653-675)
Intracellular Domain
(aa 676-1255)
ECD
TMD
ICD
I I S A VV G I L
GP2-peptide vaccine (aa 654-662)
MHC Class I : HLA-A2
Stimulate CD8 T cells
K I F G S L A F L
E75-peptide vaccine (aa 369-377)
MHC Class I : HLA-A2 & HLA-A3
Stimulate CD8 T cells
G V G S P Y V S R L L G I C L
AE37-peptide vaccine (aa 776-790)
MHC Class II : multi-allele
Stimulate CD4 T cells

AE37

- Modified HER2/neu class II epitope
  - Naturally occurring AE36
  - Linked to Ii-Key moiety of the invariant chain
    - Facilitates epitope charging of MHC class II molecules
    - ↑ antigen presentation
    - ↑ potency to > 250 times that of unmodified class II epitope in vitro

AE37/GP2 Phase II Trial



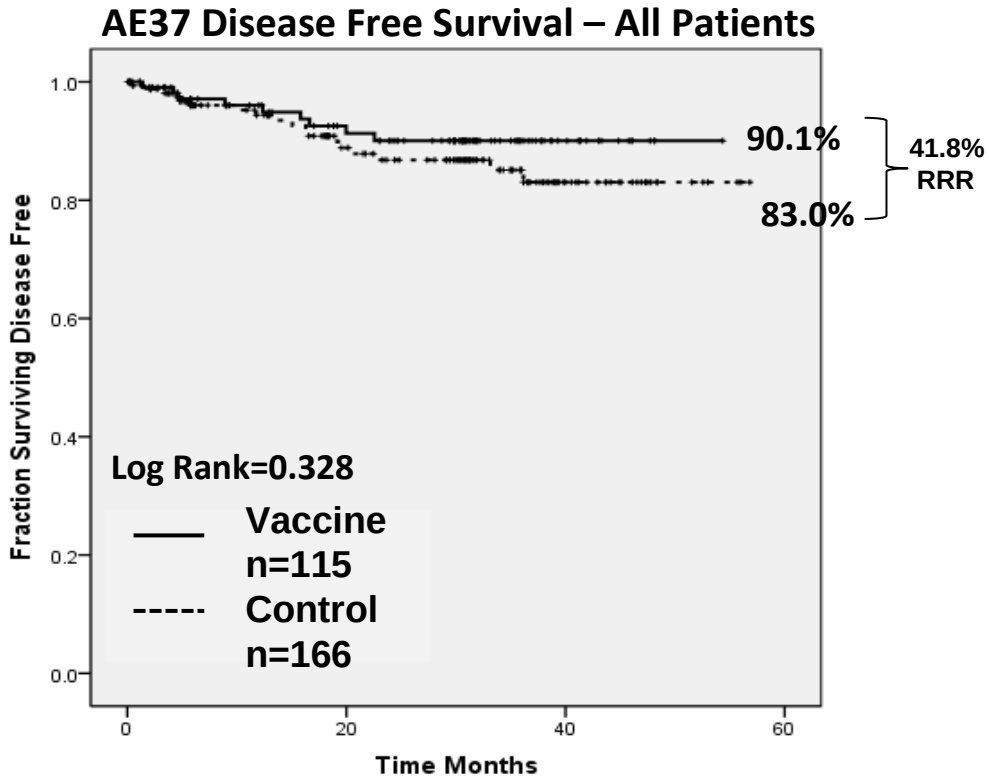
National PI: E.A. Mittendorf

AE37/GP2 Phase II Trial

- What are we learning?
  - Toxicity is due primarily to GM-CSF
  - GM-CSF alone is not responsible for the immune response
  - DTH continues to be a good predictor of clinical response

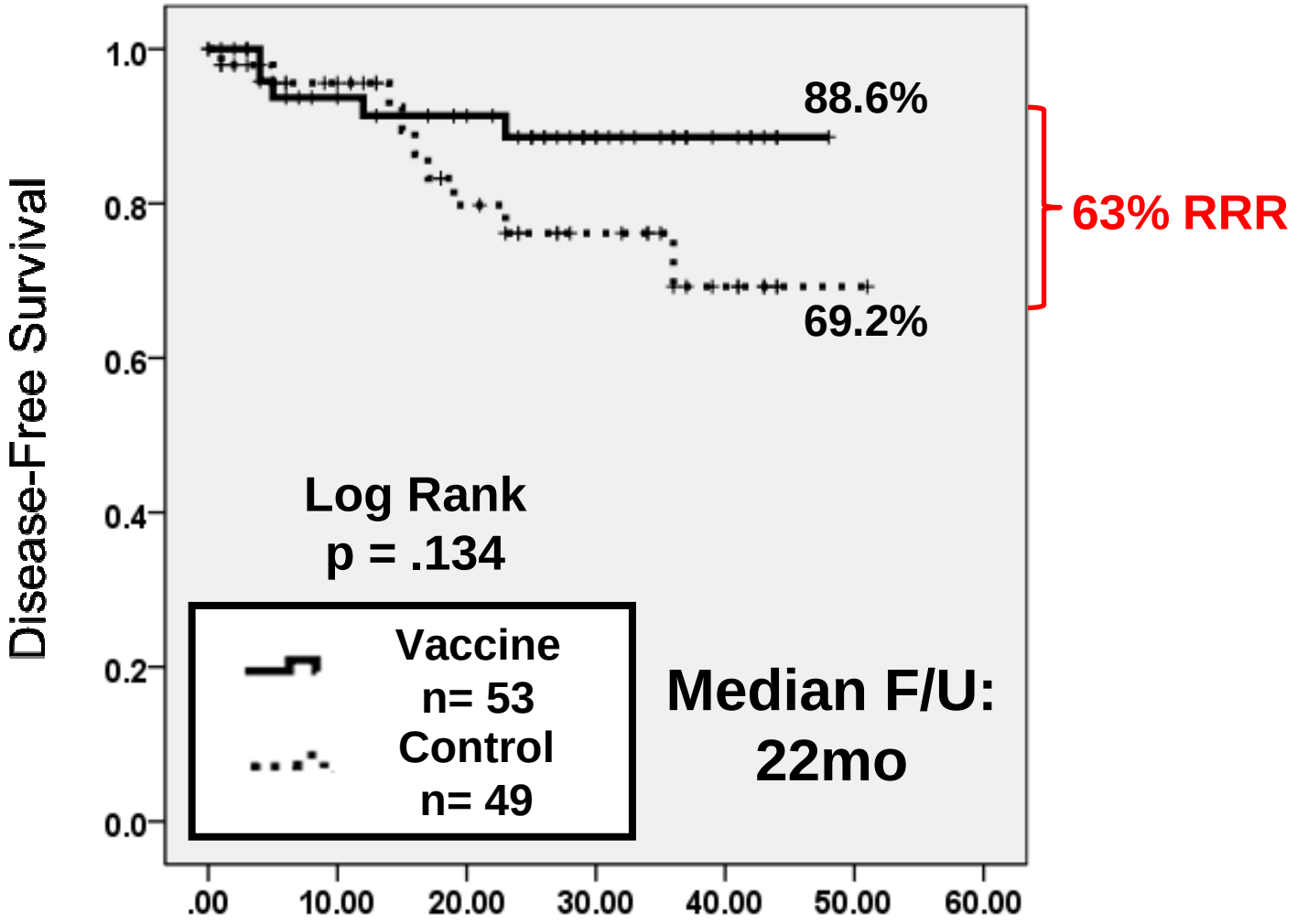
Interim Analysis: AE37

	Vaccine (n=115)	Control (n=166)	P value
Median age	49	51	.13
Tumor ≥ 2 cm	57%	63%	.42
Grade 3	50%	54%	.52
Node positive	73%	66%	.24
ER/PR neg	40%	38%	.73
HER2 pos	50%	48%	.75



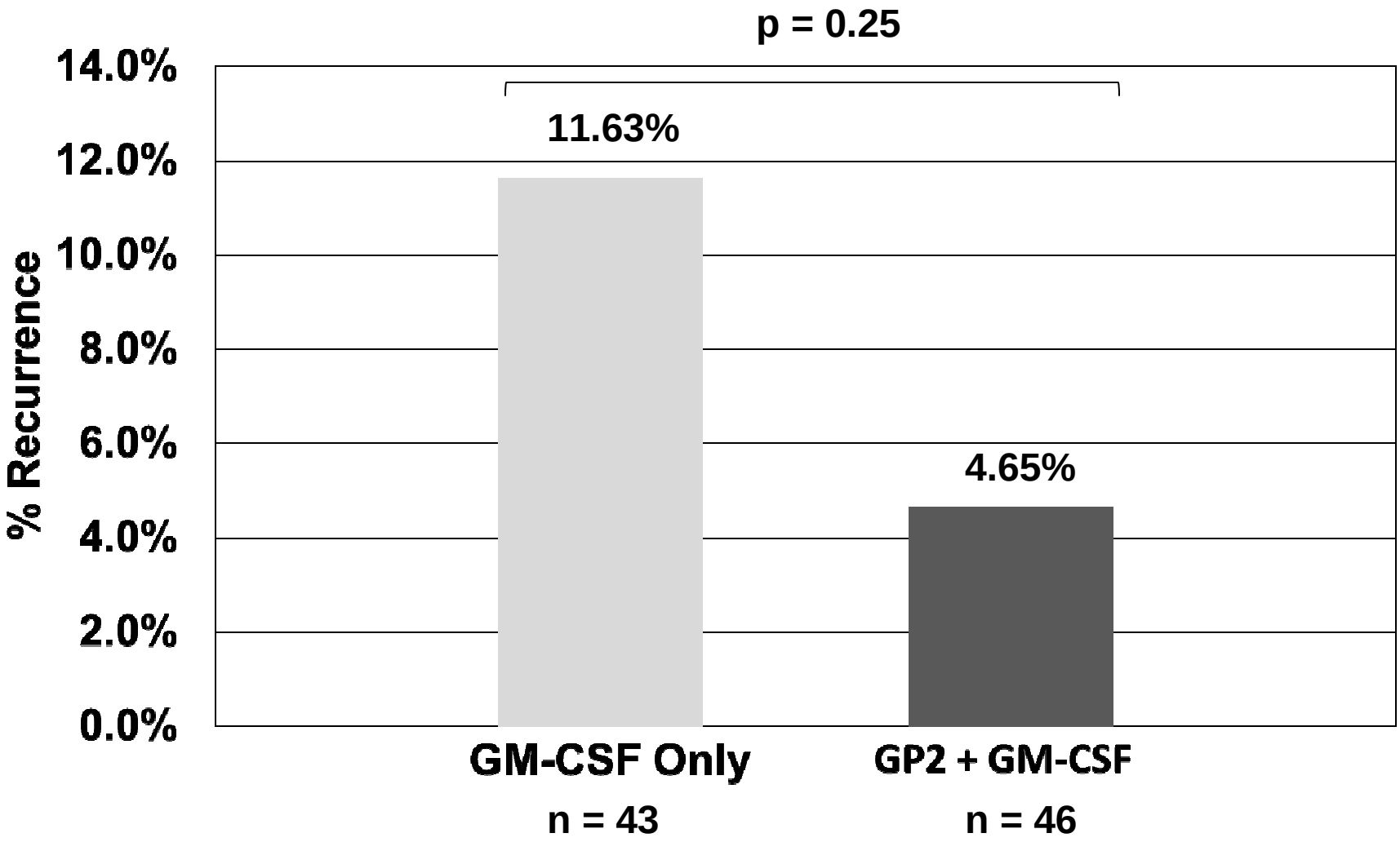
Vreeland T, et al. ASCO 2012

DFS: HER2 low-expressors



Vreeland, et al. ASCO 2012

Interim Analysis: GP2



Trappey, et al. ASCO 2013

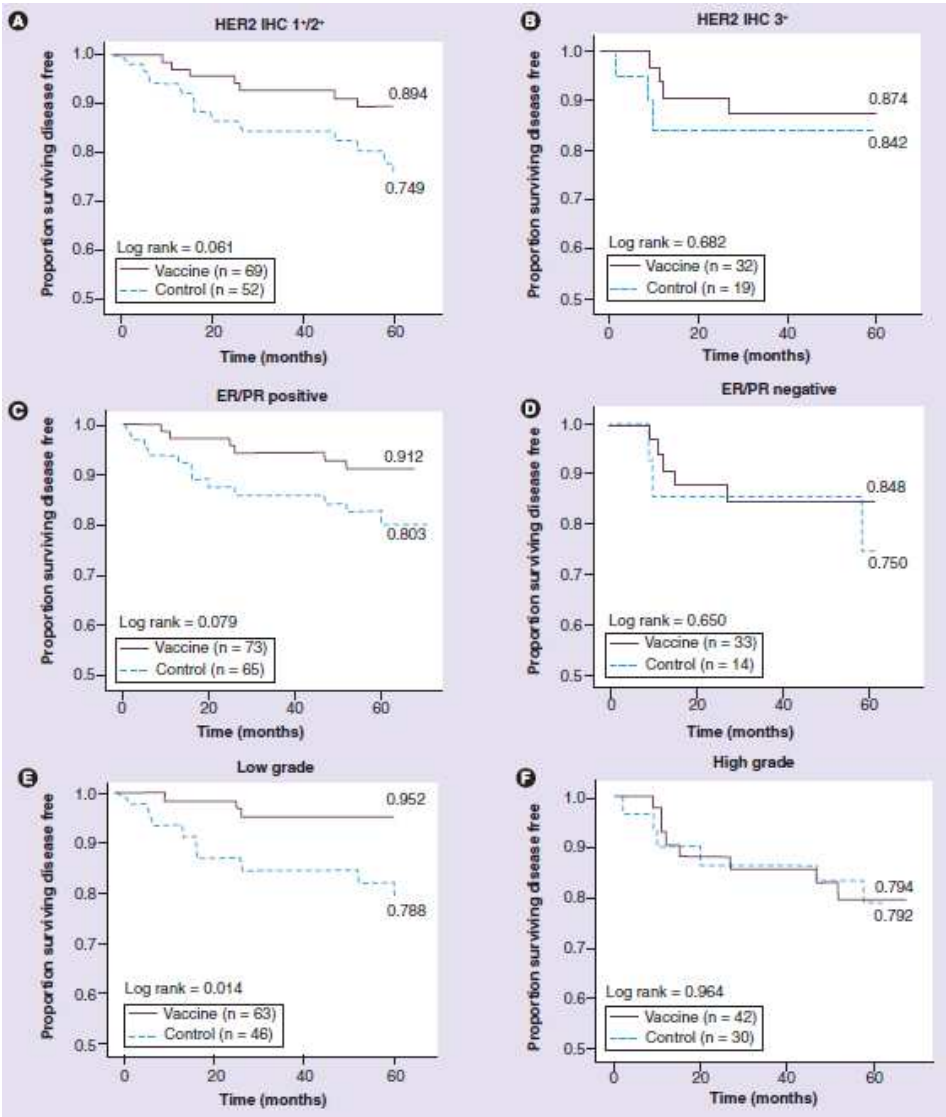
Conclusions

- Cancer vaccines represent a nontoxic therapeutic modality with great specificity
- Multiple ongoing phase III trials to assess efficacy

Conclusions

- Ongoing challenges
  - Identification of appropriate patient populations
  - Integration into current treatment algorithms
  - Determination of immune response that correlate with outcome
  - Elucidation of gene signatures predictive of response

Vaccination in Less Aggressive Disease



Hale DF et al. *Expert Rev Vaccines* 2012;11(6):721-731

Vaccines for Solid Tumors

Table 2 Peptide vaccine immunization of patients with metastatic cancer

Peptide	HLA restriction	Total patients	NR	PR	CR
MART-1_{27-35}	A2	23	22	1	0
MART-1_{27-35} + IL-12	A2	12	12	0	0
MART-1_{26-35}(27L)	A2	6	6	0	0
TRP-$2_{180-188}$	A2	20	19	1	0
$gp100_{209-217}$	A2	9	8	0	1
$gp100_{209-217}$(210M)[a]	A2	32	32	0	0
$gp100_{209-217}$(210M) + IL-12	A2	28	28	0	0
$gp100_{209-217}$(210M) + GM-CSF	A2	18	18	0	0
$gp100_{280-288}$	A2	9	9	0	0
$gp100_{280-288}$(288V)[b]	A2	5	5	0	0
$gp100_{154-162}$	A2	10	0	0	0
gp100ES:$_{209-217}$(210)	A2	9	9	0	0
g209-2M + MART-27L	A2	23	23	0	0
g209-2M, g280-9V, MART-27L[c] + tyr3D[d]	A2	16	14	2	0
$gp100_{44-59}$	DR4	4	4	0	0
$gp100_{44-59}$ + g209-2M + MART-27L	A2/DR4	22	21	0	1
$Tyrosinase_{240-251}$	A1	16	15	1	0
$gp1001_{7-25}$	A3	12	12	0	0
$Tyrosinase_{206-214}$	A2	8	8	0	0
TRP-1 ORF1-9	A31	5	5	0	0
Combination peptides	Non-A2	15	15	0	0
MAGE-$12_{170-178}$	Cw7	9	8	1	0
NY-ESO-$1_{157-165}$(165V)	A2	19	19	0	0
NY-ESO-$1_{161-180}$	DP4	6	5	1	0
NY-ESO-$1_{161-180+157-165}$(165V)	A2/DP4	11	11	0	0
$Her2/neu_{369-378}$	A2	6	6	0	0
$Telomerase_{540-548}$	A2	13	13	0	0
Dendritic cells + g209-2M + MART-27L	A2	15	13	2	0
Total		381	370	9	2

Overall objective response rate = 2.9%. HLA, human leukocyte antigen; CR, patients showing complete response; PR, patients showing partial response; NR, patients showing no response. [a]g209-2M. [b]g280-9V. [c]MART-1_{26-35}(27L). [d]$Tyrosinase_{368-376}$(370D).

Overall objective response rate = 2.9%

Rosenberg SA et al. *Nat Med* 2004;10(9):909-915

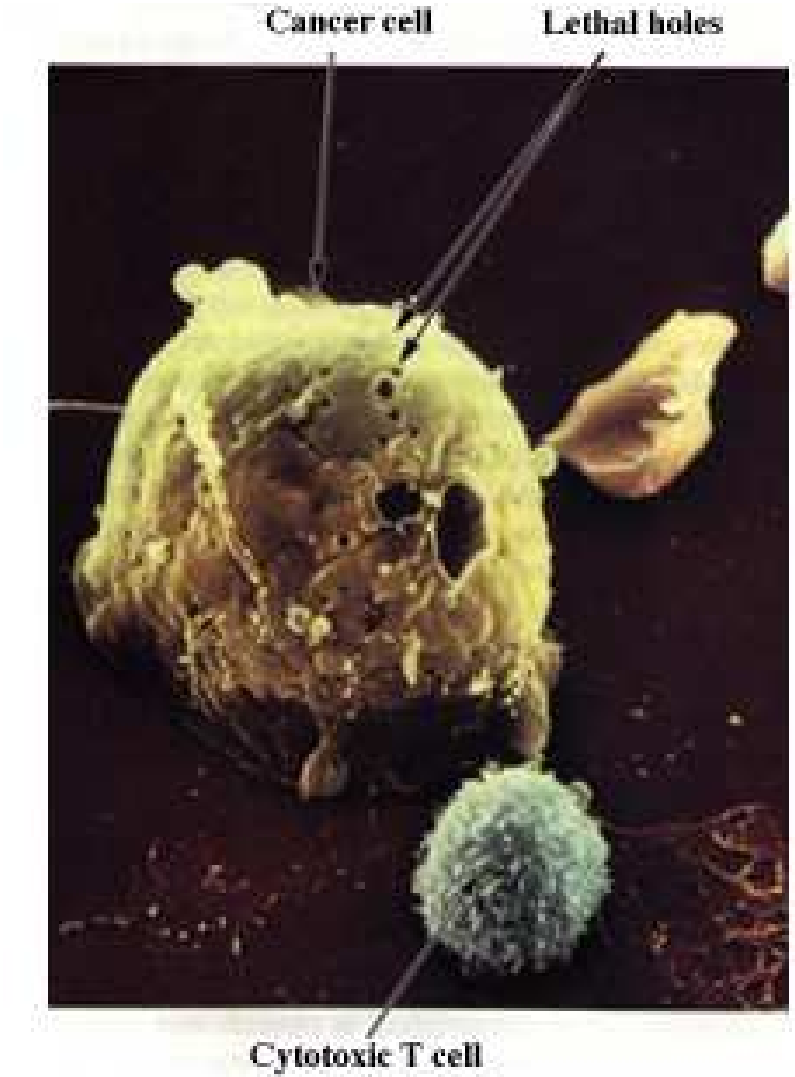
Vaccines for Solid Tumors

- 440 patients
  - 422 metastatic melanoma
    - 65% visceral disease
    - 20% lymph node disease ± subcutaneous disease
    - 15% subcutaneous or cutaneous disease only
  - 18 with other metastatic CA

Rosenberg SA et al. *Nat Med* 2004;10(9):909-915

Minimal (Residual) Disease

- Idiotype vaccines
- GSK MAGE-A3
- HER2



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Thank You