THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Immunotherapy for the Treatment of Breast Cancer

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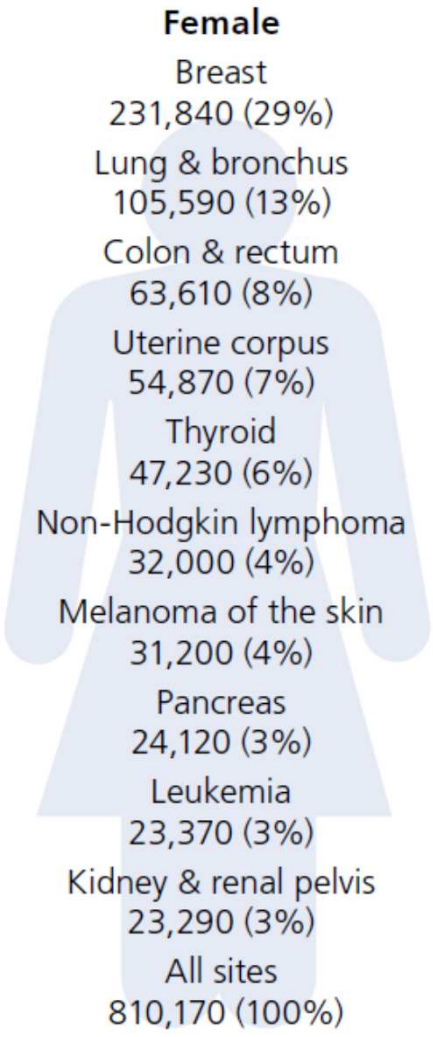
Disclosures

- Clinical trial support:
  - Galena Biopharma
  - Antigen Express
  - Norwell
  - Merck
  - Genentech

Breast Cancer

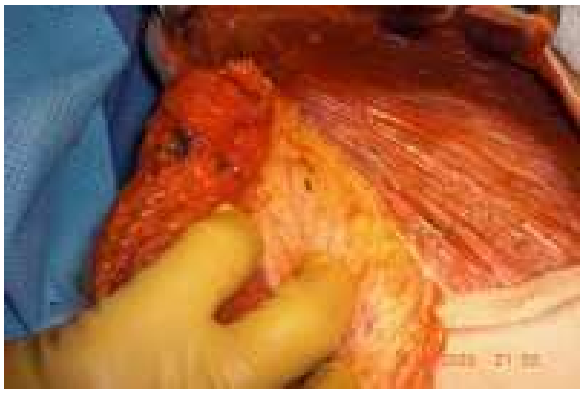


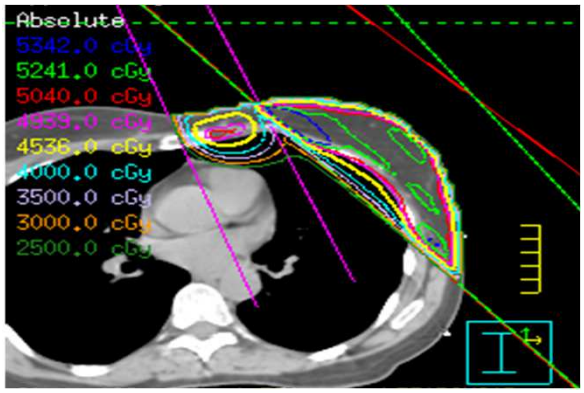
- Most frequently diagnosed cancer in women
- 231,840 invasive cases
- 40,290 estimated deaths

American Cancer Society Facts & Figures 2015

Breast Cancer - Treatment

- Surgery
- Systemic therapy
  - Chemotherapy
  - Endocrine therapy
  - Other targeted therapy
- Radiation

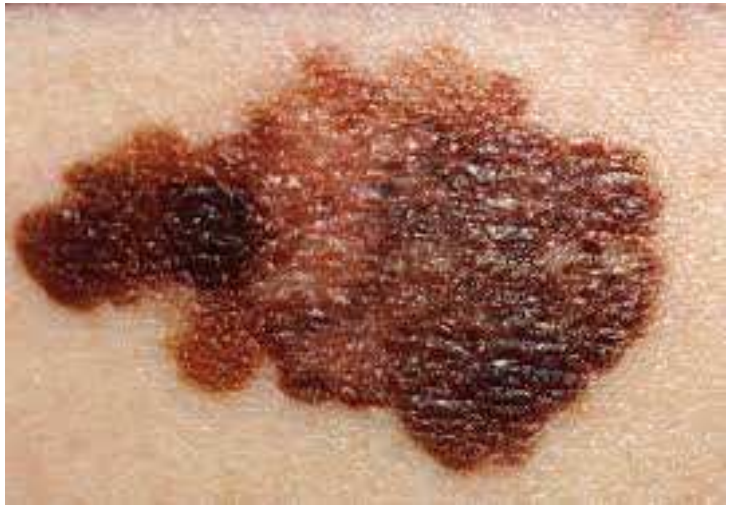


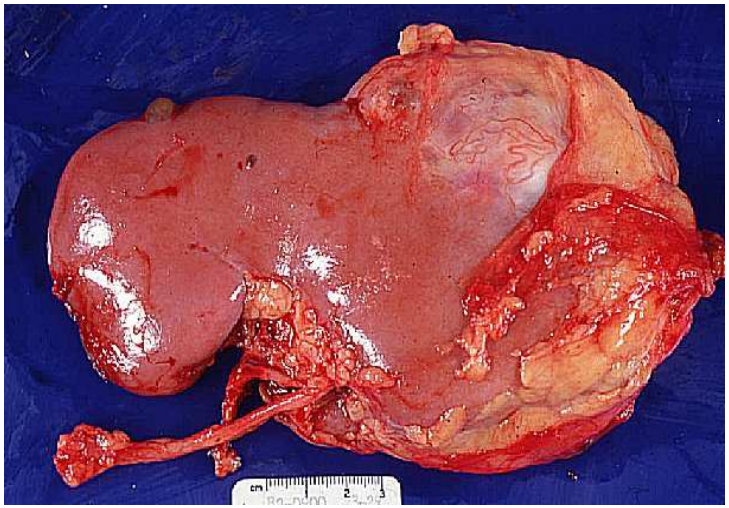


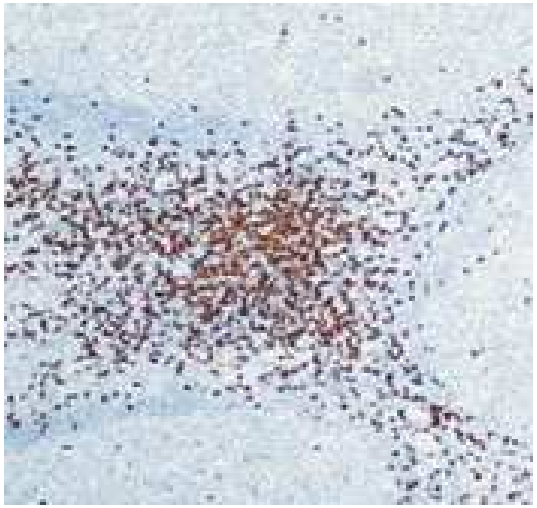
Despite advances in treatment, approximately 20% of patients recur and ultimately succumb to their disease

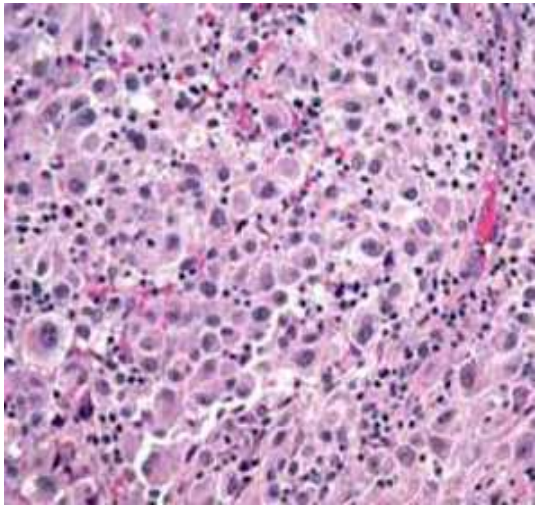
Immunotherapy

Immunogenic Tumors





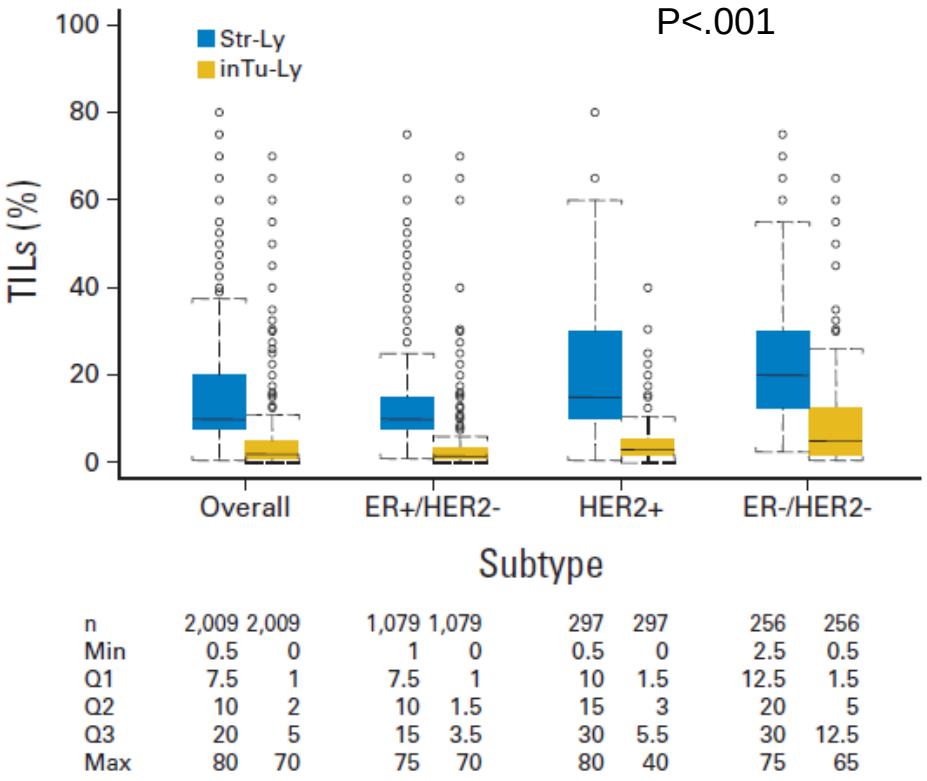




Is breast cancer immunogenic?

Prognostic Value of TIL

- N=2009 node positive breast cancer samples from BIG 02-98 adjuvant phase III trial
- TIL identified on full-face H&E sections, pre-treatment
  - Evaluated stromal and intratumoral TIL
  - LPBC = ≥ 50% lymphocyte infiltration

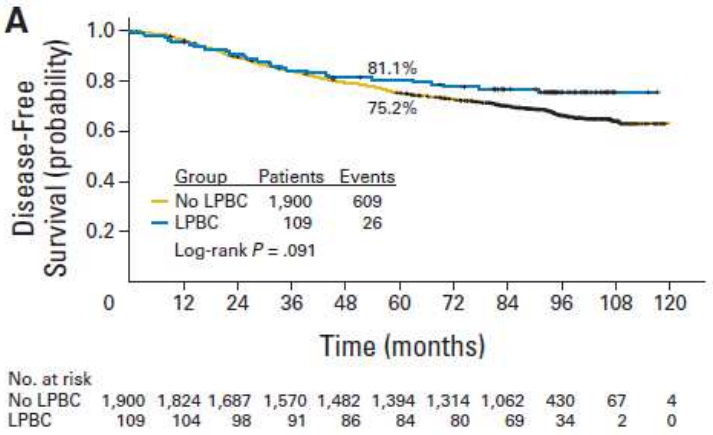


n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65

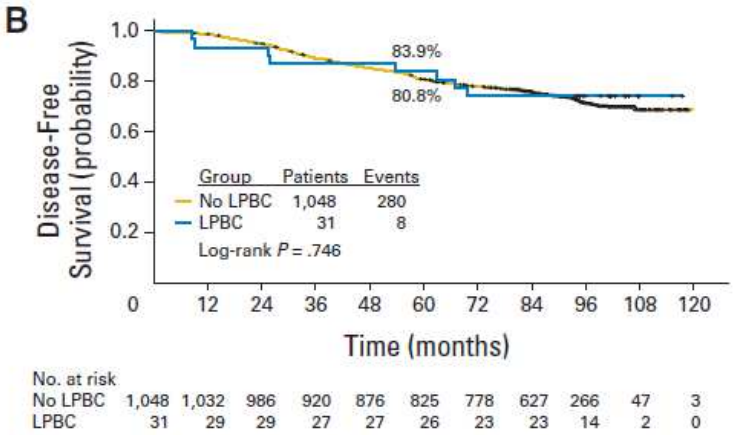
Loi S, et al. *J Clin Onc* 2013; 31:860-867

Prognostic Value of TIL

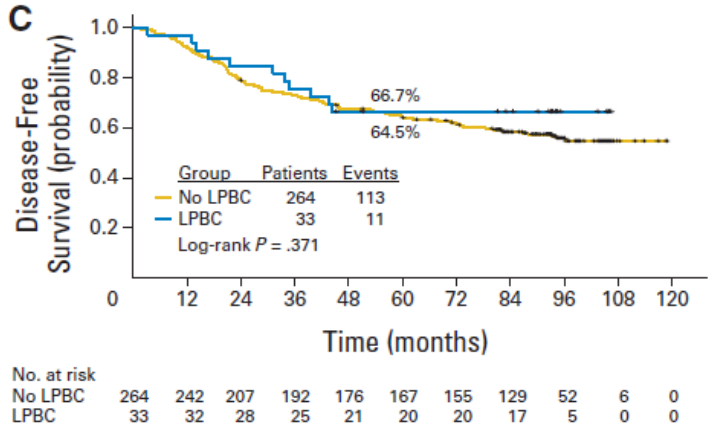
All Patients



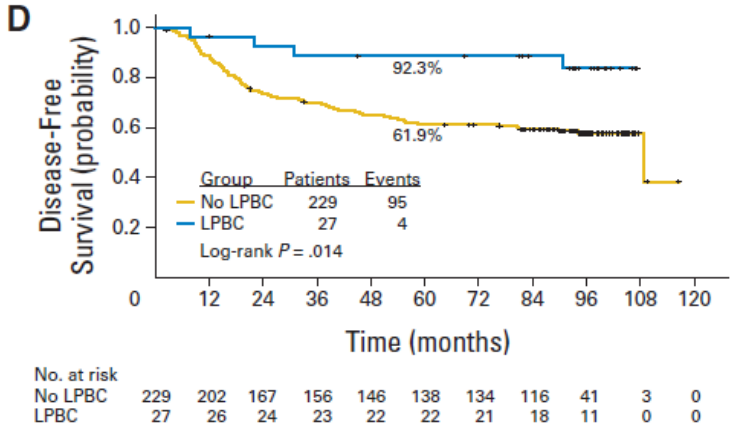
ER+/HER2-



HER2+

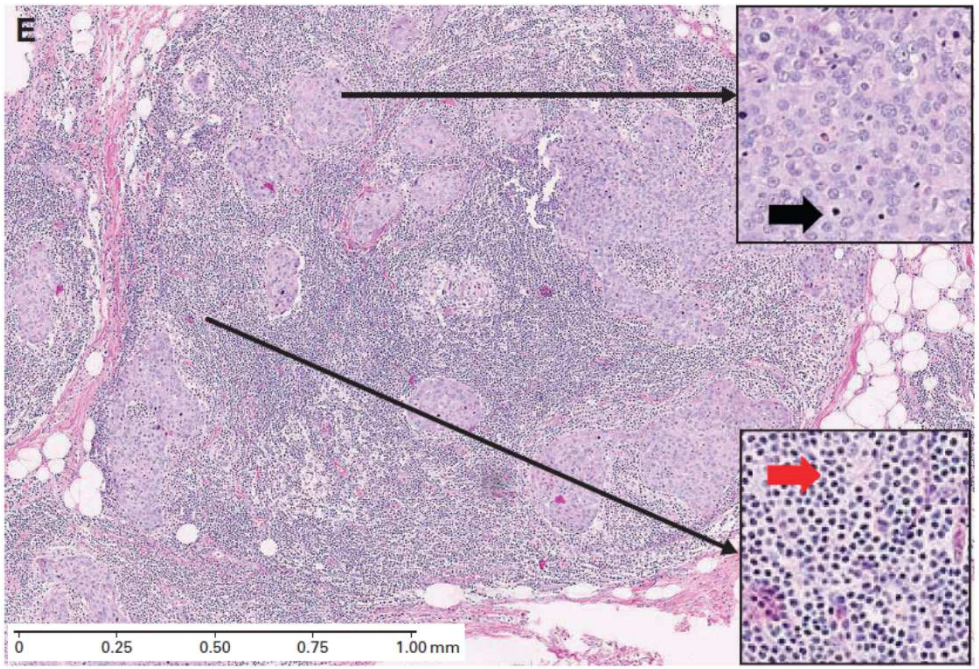


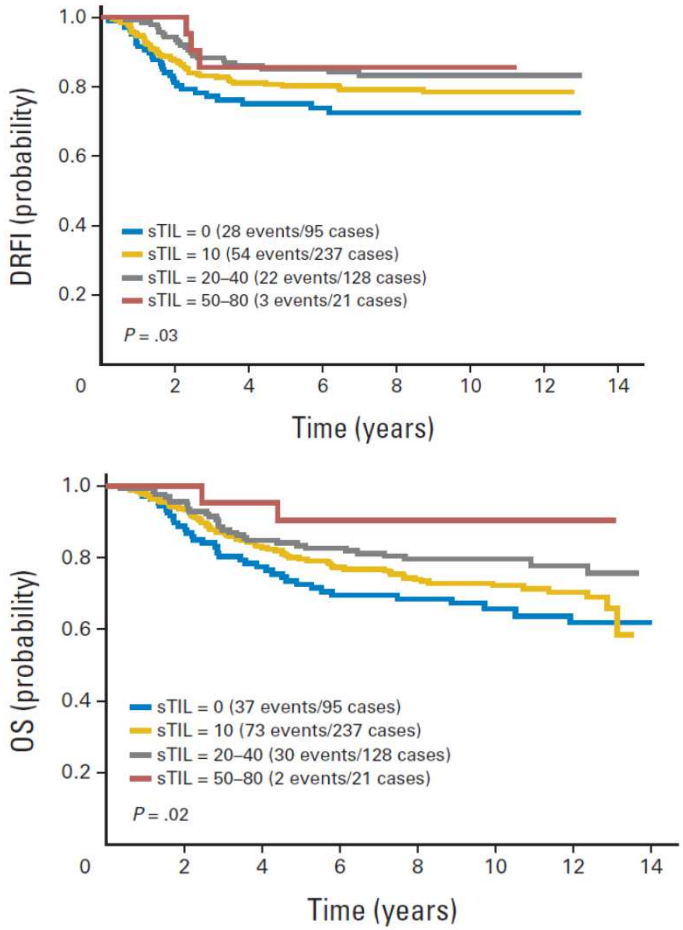
TNBC



Loi S, et al. *J Clin Onc* 2013; 31:860-867

Prognostic Value of TIL





Adams S, et al. *J Clin Onc* 2014; 32:2959-2966

Breast cancer is immunogenic……

Is there a role for immunotherapy?

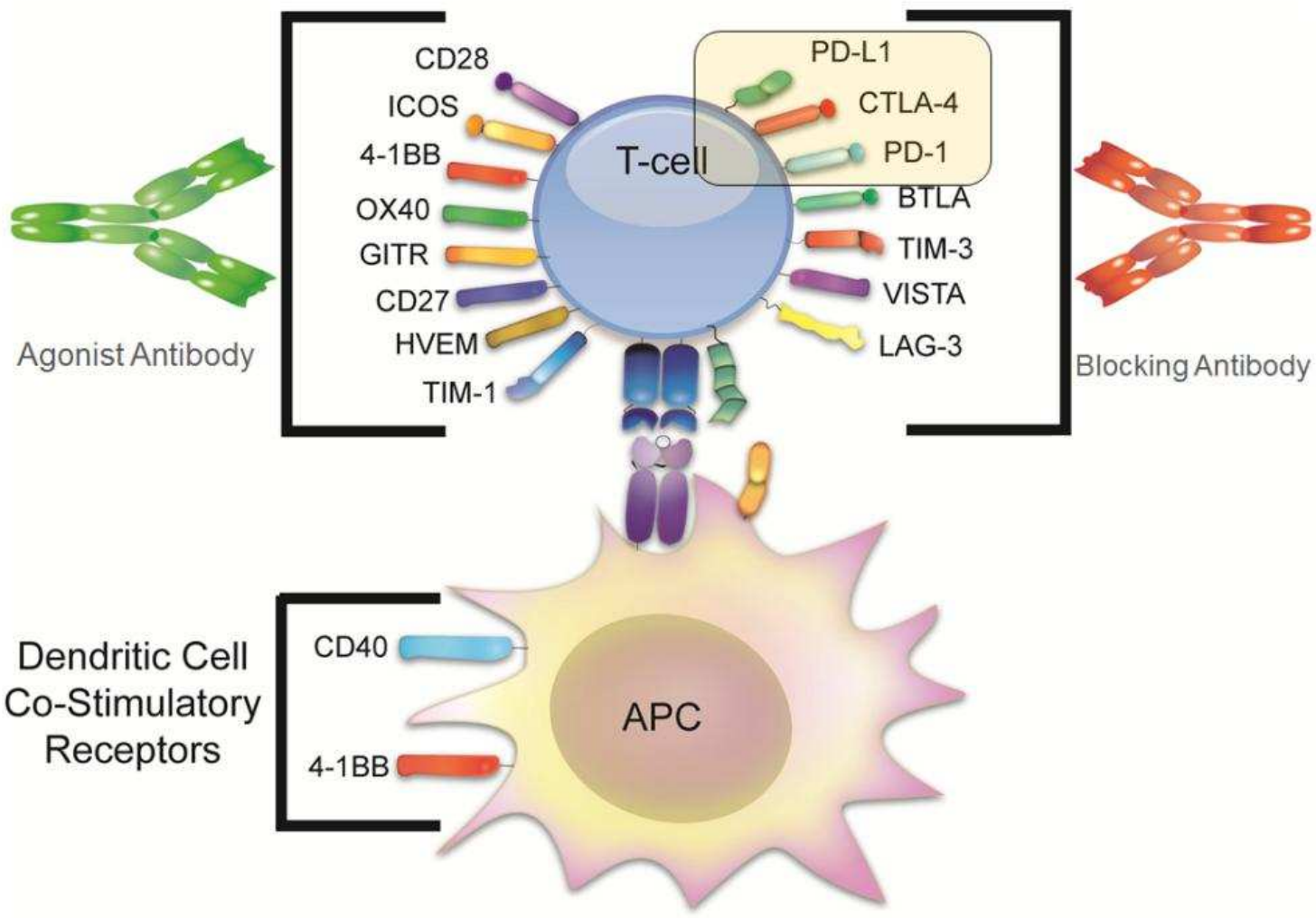
Immunotherapy

- Checkpoint blockade
- Adoptive T cell therapy
  - –CAR+ T cells
- Vaccines

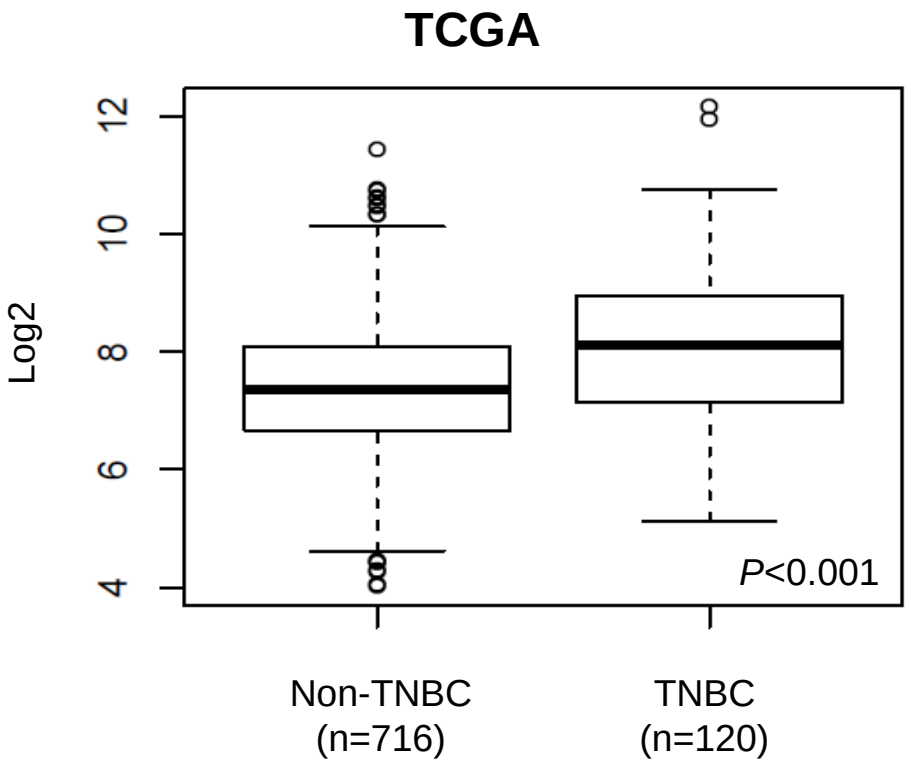
Immunotherapy

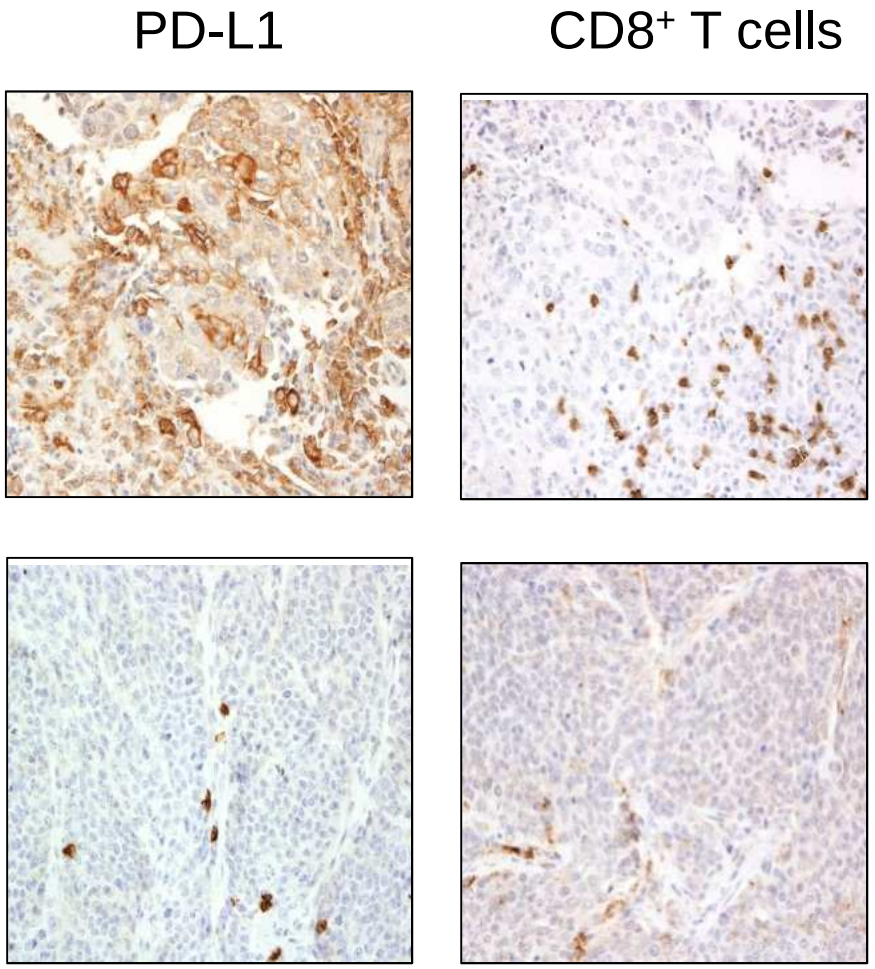
- Checkpoint blockade
- Adoptive T cell therapy
  - –CAR+ T cells
- Vaccines

Novel agents in clinical trials



PD-L1 in TNBC

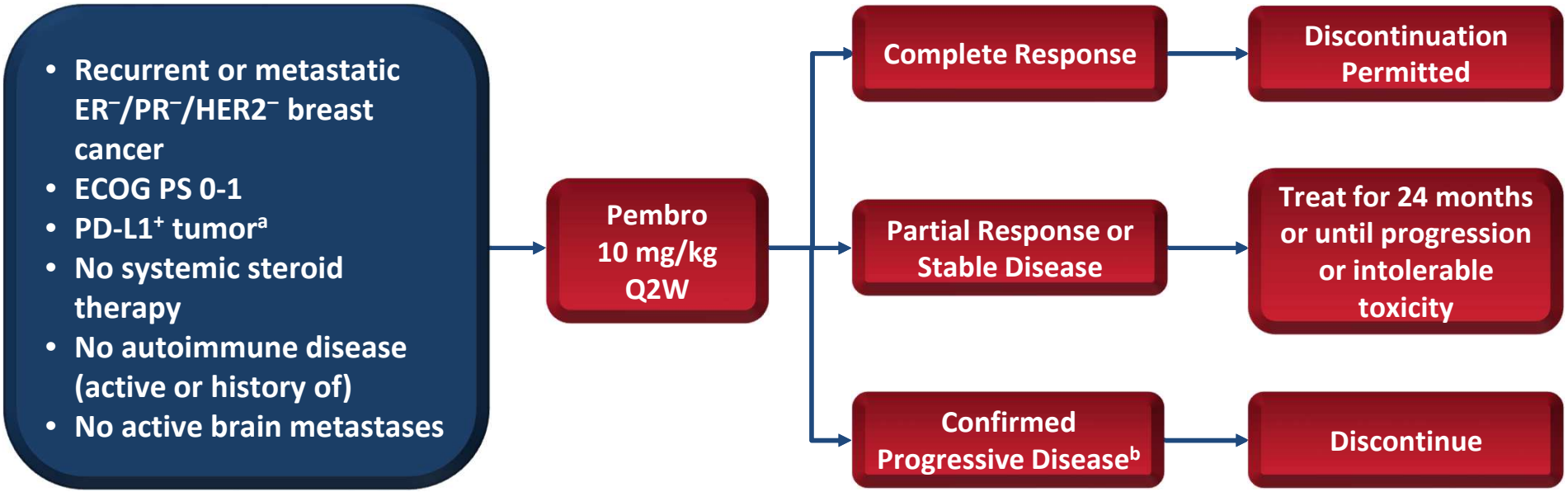




Mittendorf EA, et al. *Cancer Immunol Res*, 2014;2:361-370

Anti-PD-1

KEYNOTE-012: Triple-Negative Breast Cancer Cohort



- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

Nanda R, et al. *SABCS* 2014

Treatment-related AEs

	N=32	
	Any Grade	Grade 3-5
Arthralgia	6 (18.8%)	0
Fatigue	6 (18.8%)	0
Myalgia	5 (15.6%)	0
Nausea	5 (15.6%)	0
ALT increased	2 (6.3%)	0
AST increased	2 (6.3%)	0
Diarrhea	2 (6.3%)	0
Erythema	2 (6.3%)	0
Headache	2 (6.3%)	1 (3.1%)

AEs of a potentially immune-mediated nature, regardless of attribution, included pruritis (n=3; all grade 1-2), hepatitis (n=1; grade 3), and hypothyroidism (n=1; grade 2)

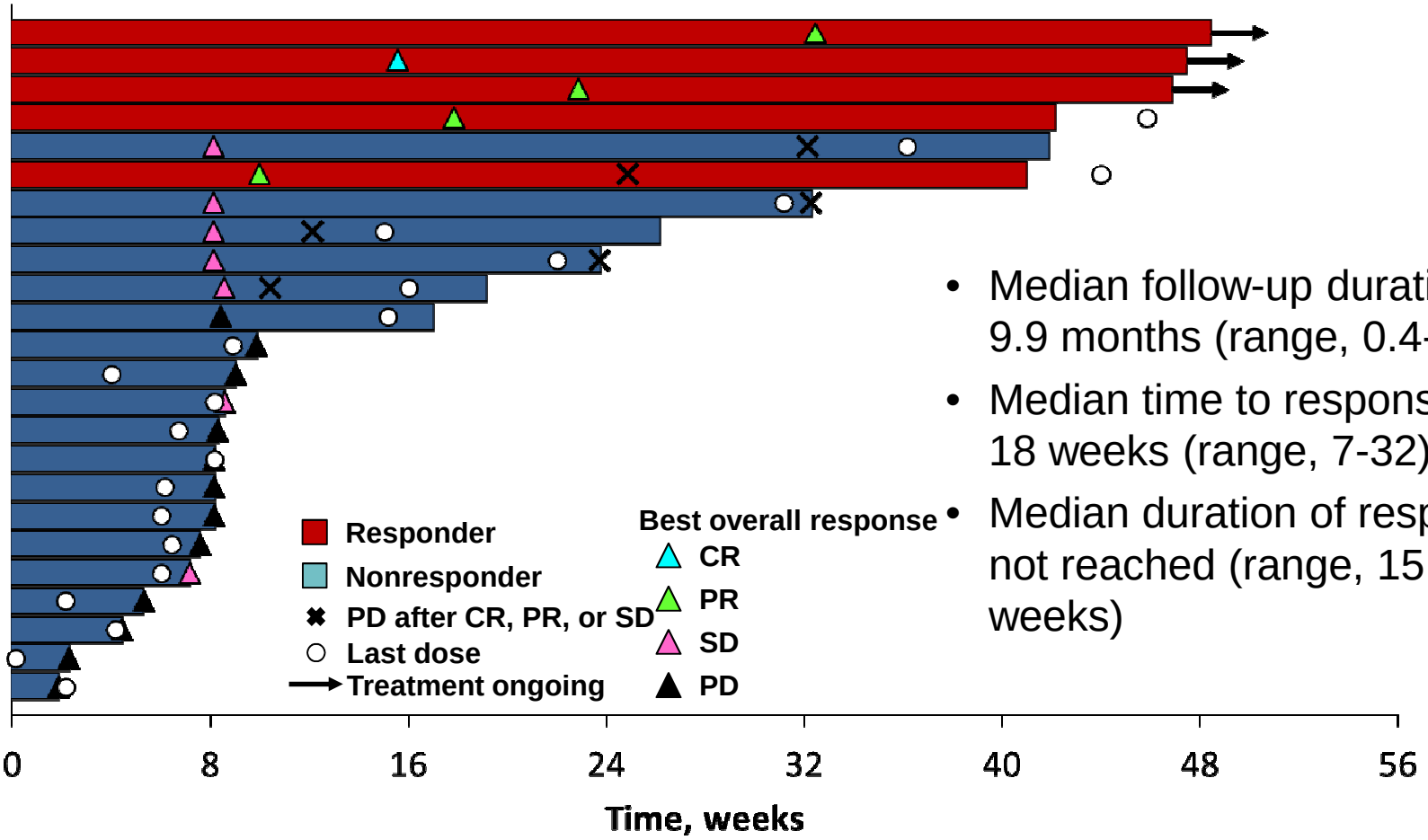
Nanda R, et al. *SABCS* 2014

Treatment Response

- Response assessed by RECIST v1.1
- Overall response rate 5 (18.5%)
- Best overall response
  - Complete response 1 (3.7%)
  - Partial response 4 (14.8%)
  - Stable disease 7 (25.9%)
  - Progressive disease 12 (44.4%)
  - No assessment 3 (11.1%)

Nanda R, et al. *SABCS* 2014

Time to and Durability of Response

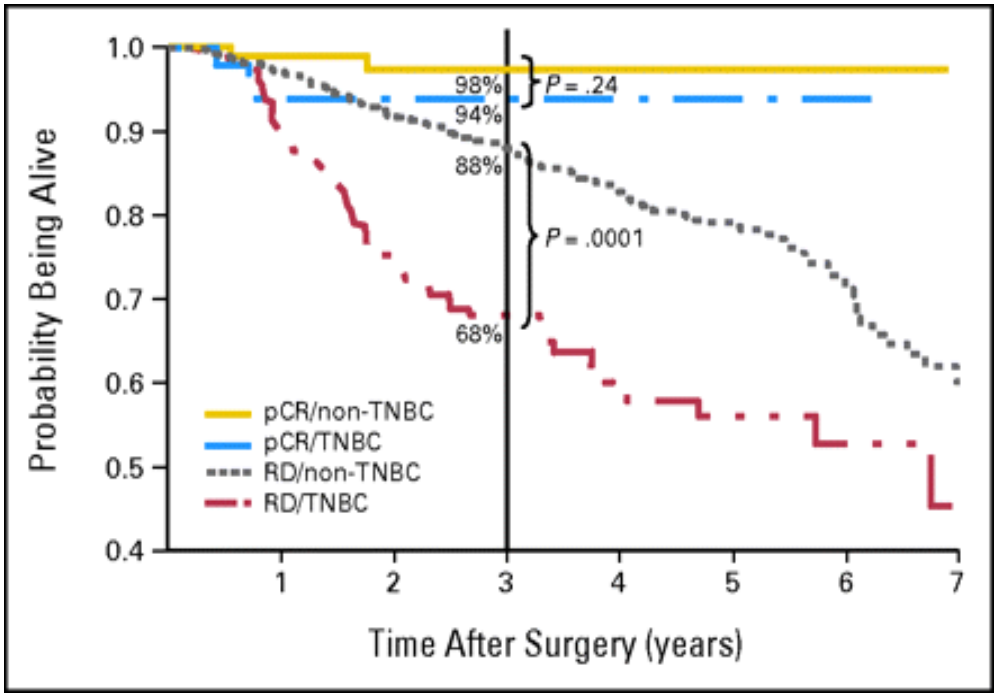


- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response[a]: not reached (range, 15 to 40+ weeks)

Nanda R, et al. *SABCS* 2014

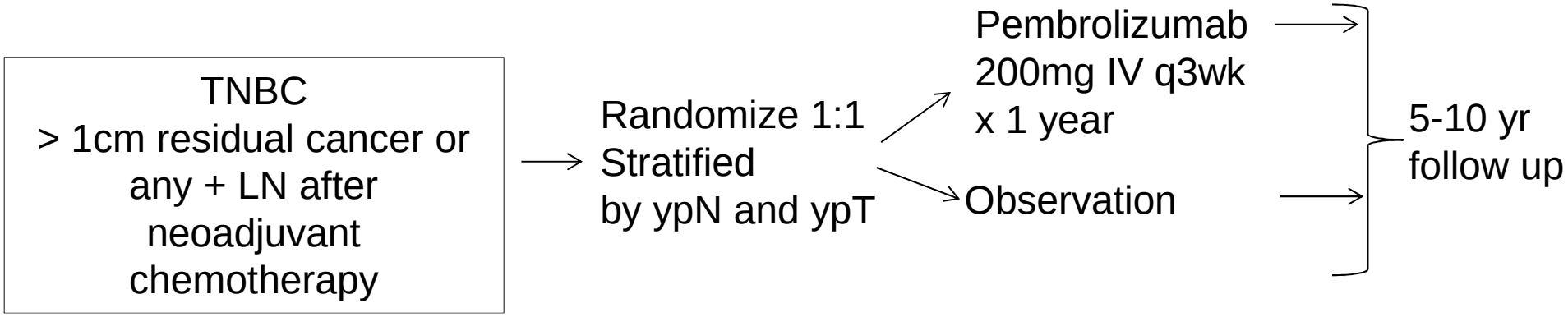
SWOG S1418

- Phase III trial
- Evaluating pembrolizumab as adjuvant therapy for TNBC patients with ≥ 1cm residual invasive cancer or + lymph nodes after neoadjuvant chemotherapy
- PI: Lajos Pusztai, MD, PhD, Yale University



Liedtke C, et al. *J Clin Onc* 2008; 26:1275-1281

SWOG S1418



Primary Objective: DFS in patients who receive 1 year of trastuzumab vs observation

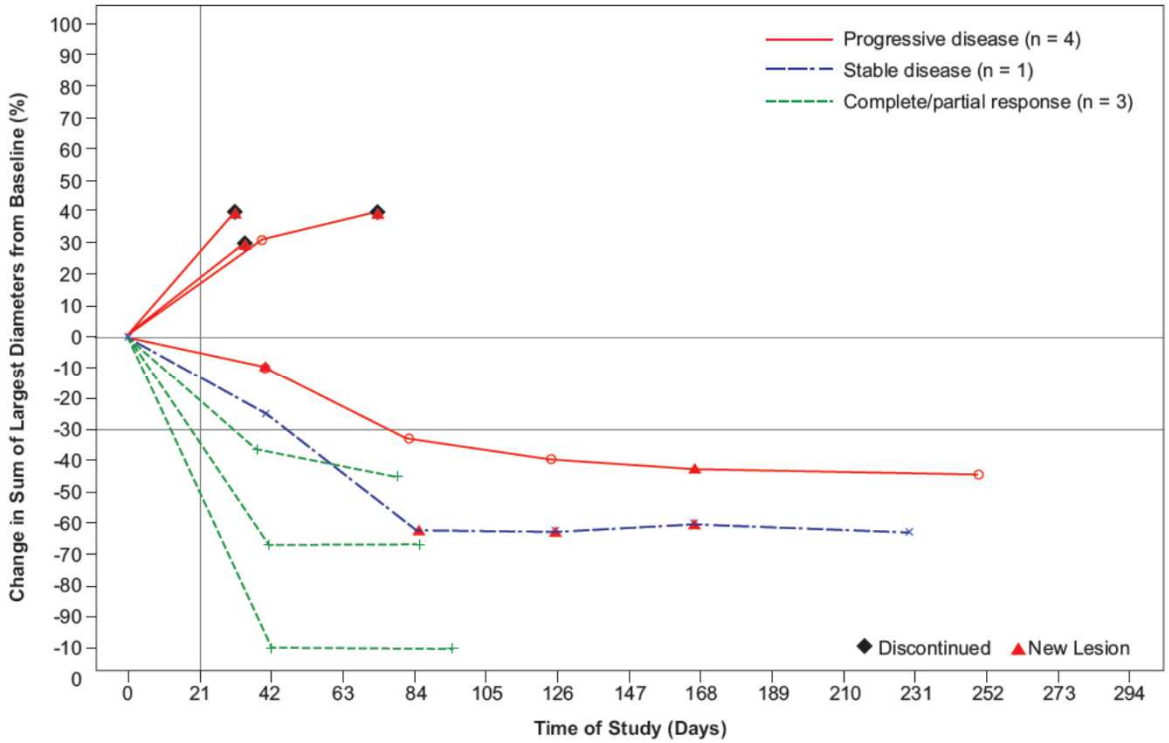
Secondary Objectives:

- OS
- DRFS
- Toxicity & tolerability

PI: Lajos Pusztai

Anti-PD-L1

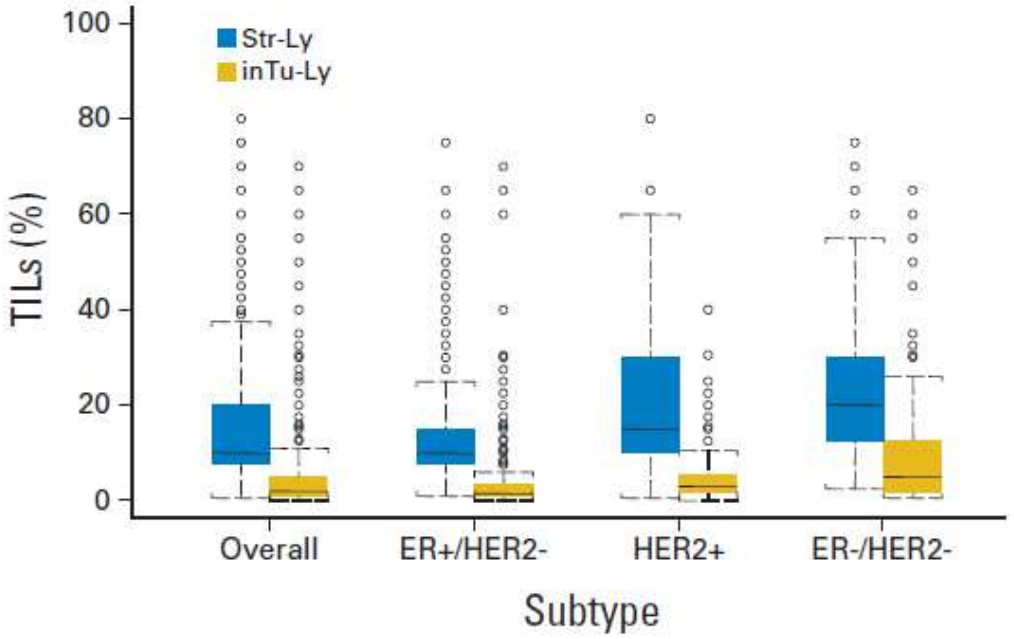
- MPDL3280A
- N=12
- Well tolerated with only 1 grade 3-4 treatment-related AE
- Responses seen in patients previously treated with multiple lines of therapy



Emens L, et al. *SABCS* 2014

PD-1/PD-L1 Pathway

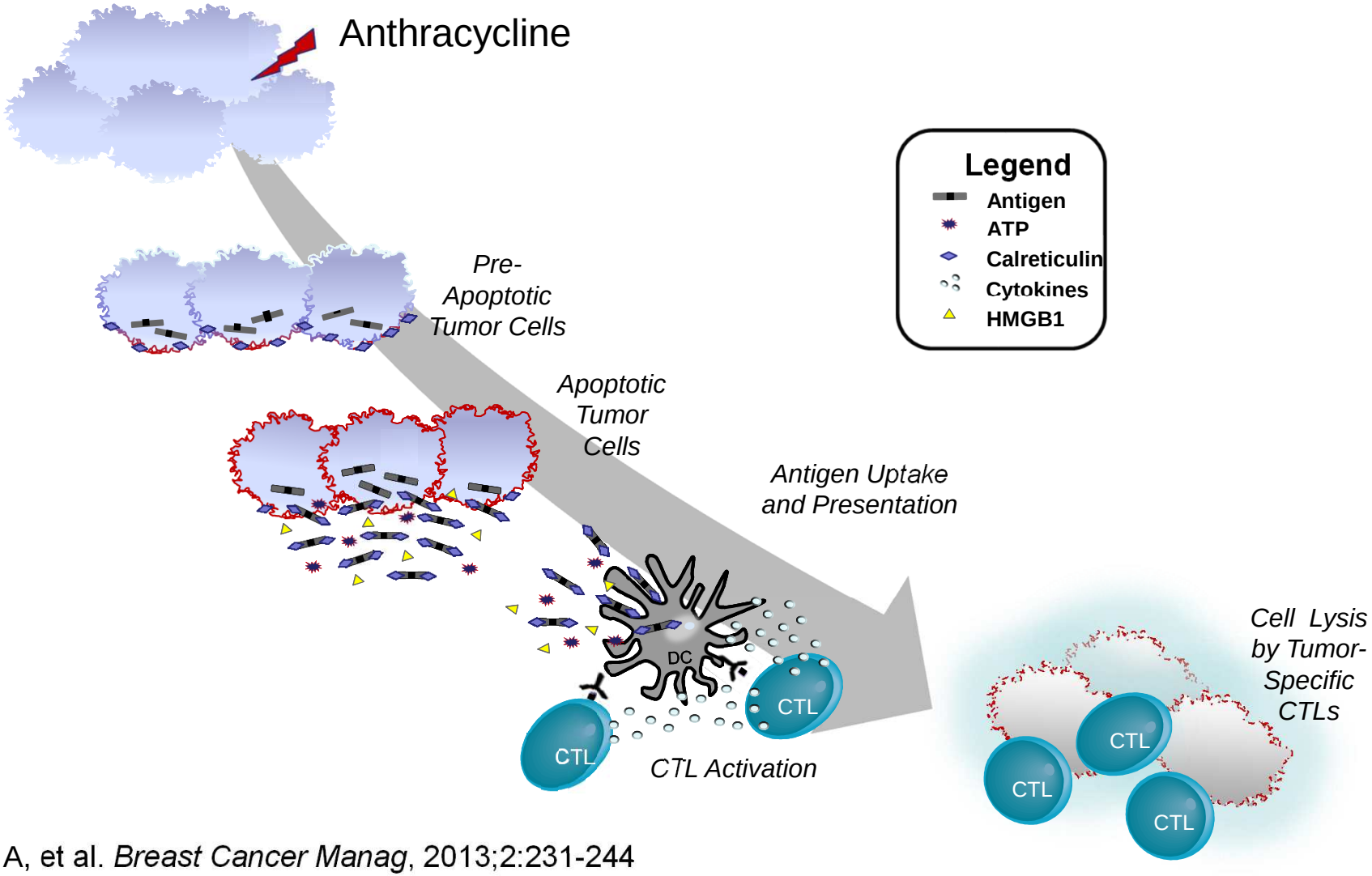
- Response to anti-PD-1 or anti-PD-L1 therapy requires:
  - PD-L1 expression
  - Presence of T cells



Strategies to Augment T cell Infiltrate

- Chemotherapy
  - –“immunogenic cell death”
- Vaccines

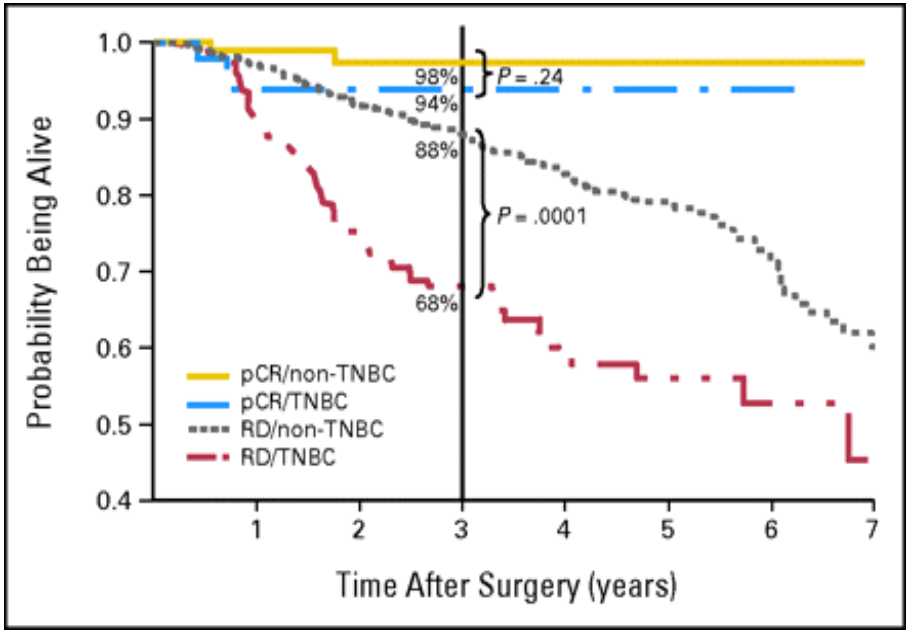
Chemotherapy – Immunogenic Cell Death

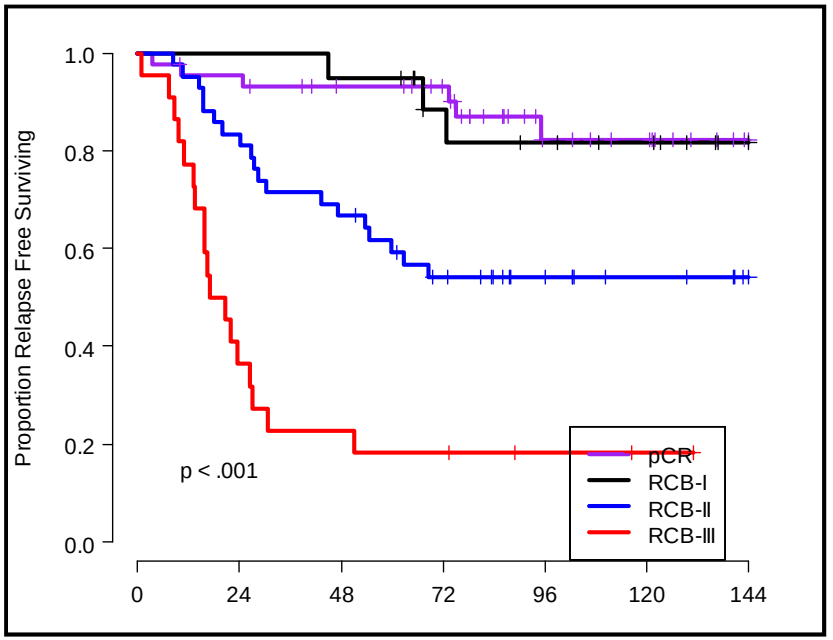


Chawla A, et al. *Breast Cancer Manag*, 2013;2:231-244

Clinical Trial

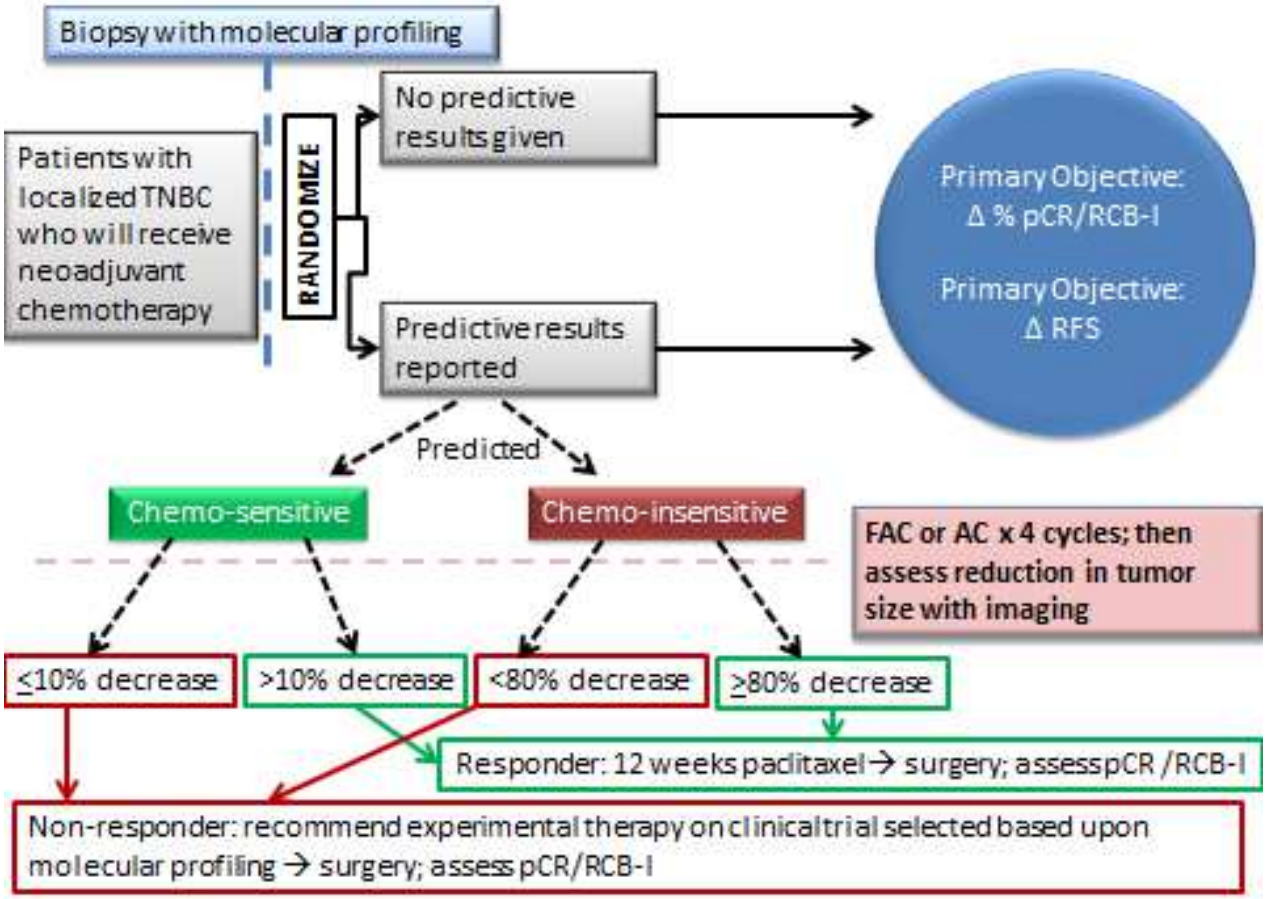
TNBC with residual cancer after neoadjuvant chemotherapy has a poor prognosis





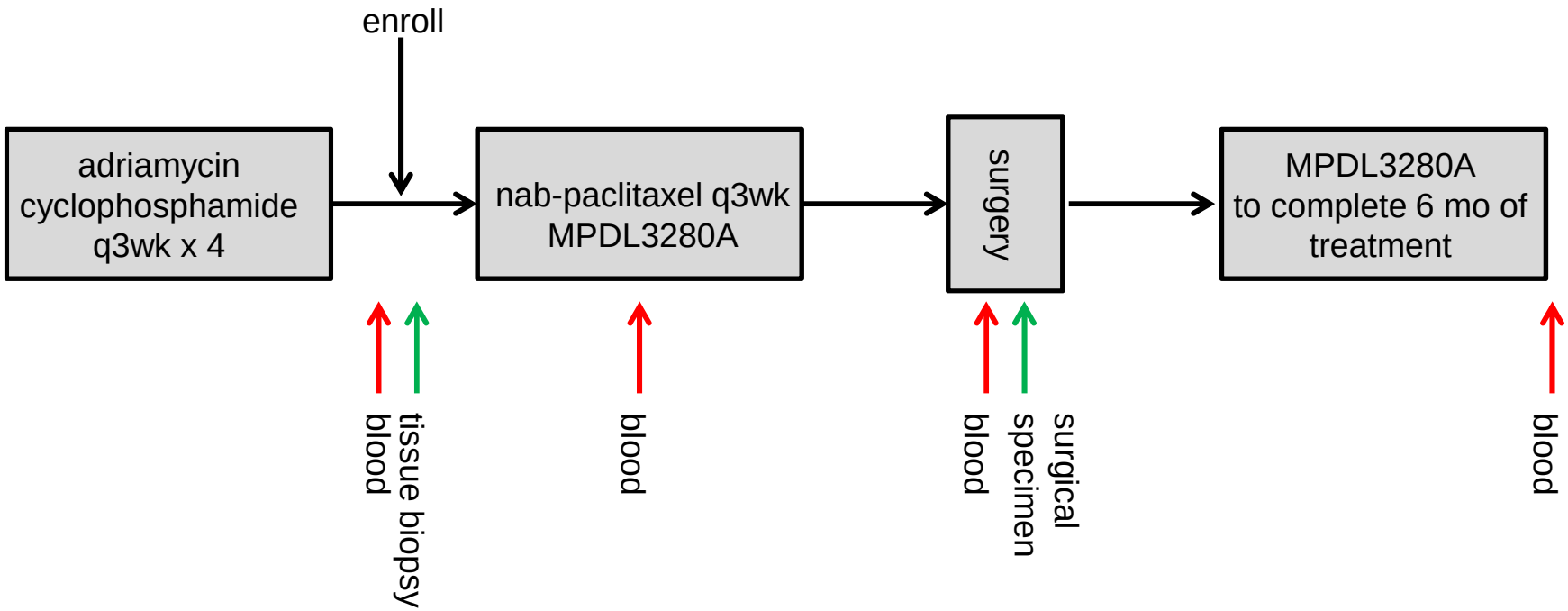
Liedtke C, et al. *J Clin Onc* 2008; 26:1275-1281
Symmans WF, et al. *J Clin Onc* 2007; 25:4414-4422
Symmans WF, et al. *SABCS* 2013

Triaging Protocol



Slide courtesy of Dr. Stacy Moulder, MD Anderson Cancer Center

Targeting PD-L1 in TNBC



- N=37 to detect ↑ in rate of pCR or RCB-I from 5% to 20%
- Primary endpoint:
  - Determine safety of MPDL3280A in combination with nab-paclitaxel
  - pCR/RCB-I rate
- Secondary endpoint:
  - DFS
- PIs: Jennifer Litton, MD and Elizabeth Mittendorf, MD, PhD

Strategies to Augment T cell Infiltrate

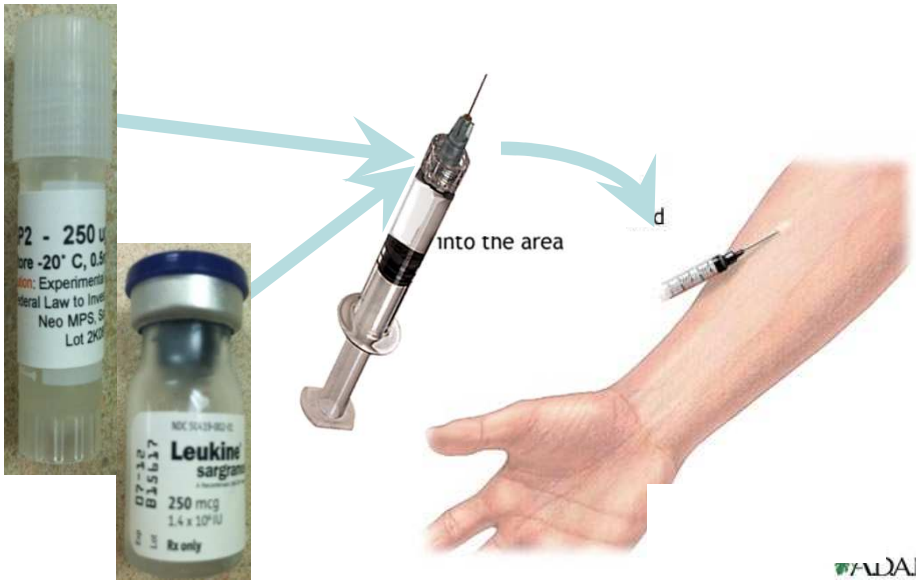
- Chemotherapy
  - –“immunogenic cell death”
- Vaccines

Vaccines

- Inject an antigen that stimulates a specific immune response
- Lymphocytes – B cells and T cells

Peptide Vaccines

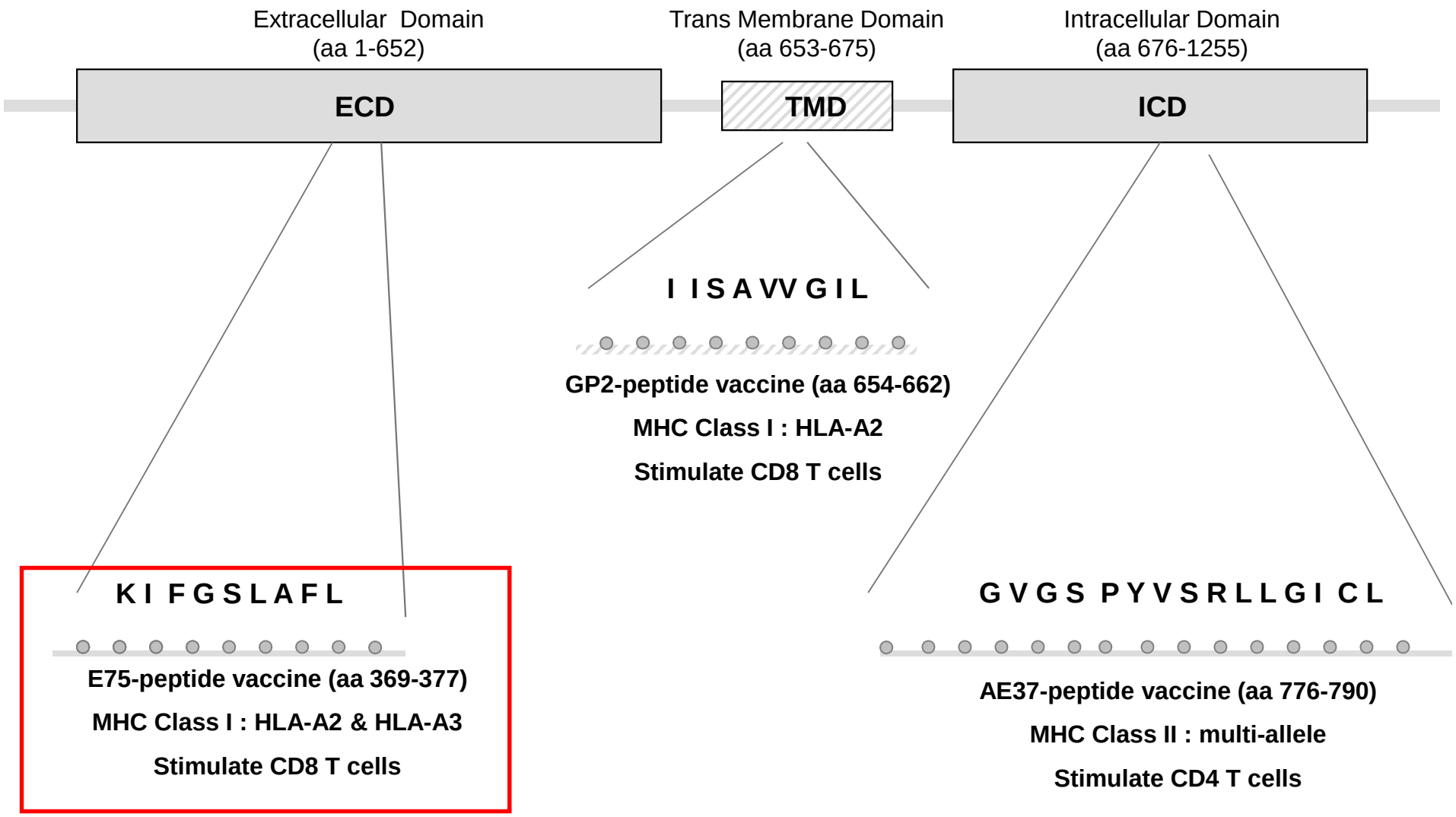
- Use antigenic peptides derived from tumor associated antigens (TAA)
- Stimulate peptide-specific immune regulators



Peptide Vaccines

- Pros:
  - Simple to construct
  - Easy to manufacture large scale
  - Inexpensive
  - Exportable to the community

HER2

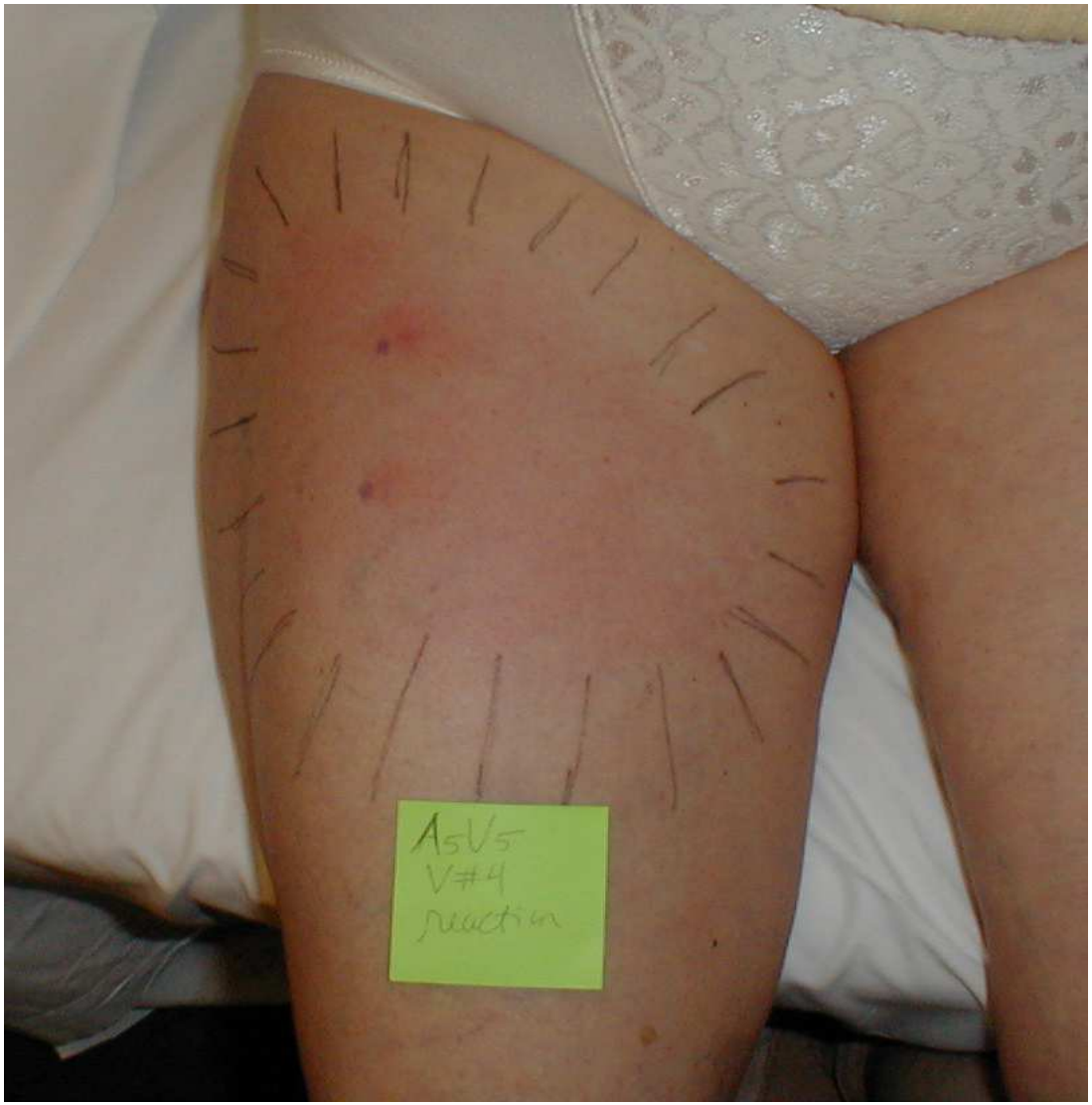

Extracellular Domain
(aa 1-652)
Trans Membrane Domain
(aa 653-675)
Intracellular Domain
(aa 676-1255)
ECD
TMD
ICD
I I S A VV G I L
GP2-peptide vaccine (aa 654-662)
MHC Class I : HLA-A2
Stimulate CD8 T cells
K I F G S L A F L
E75-peptide vaccine (aa 369-377)
MHC Class I : HLA-A2 & HLA-A3
Stimulate CD8 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

E75 Phase I/II Trial

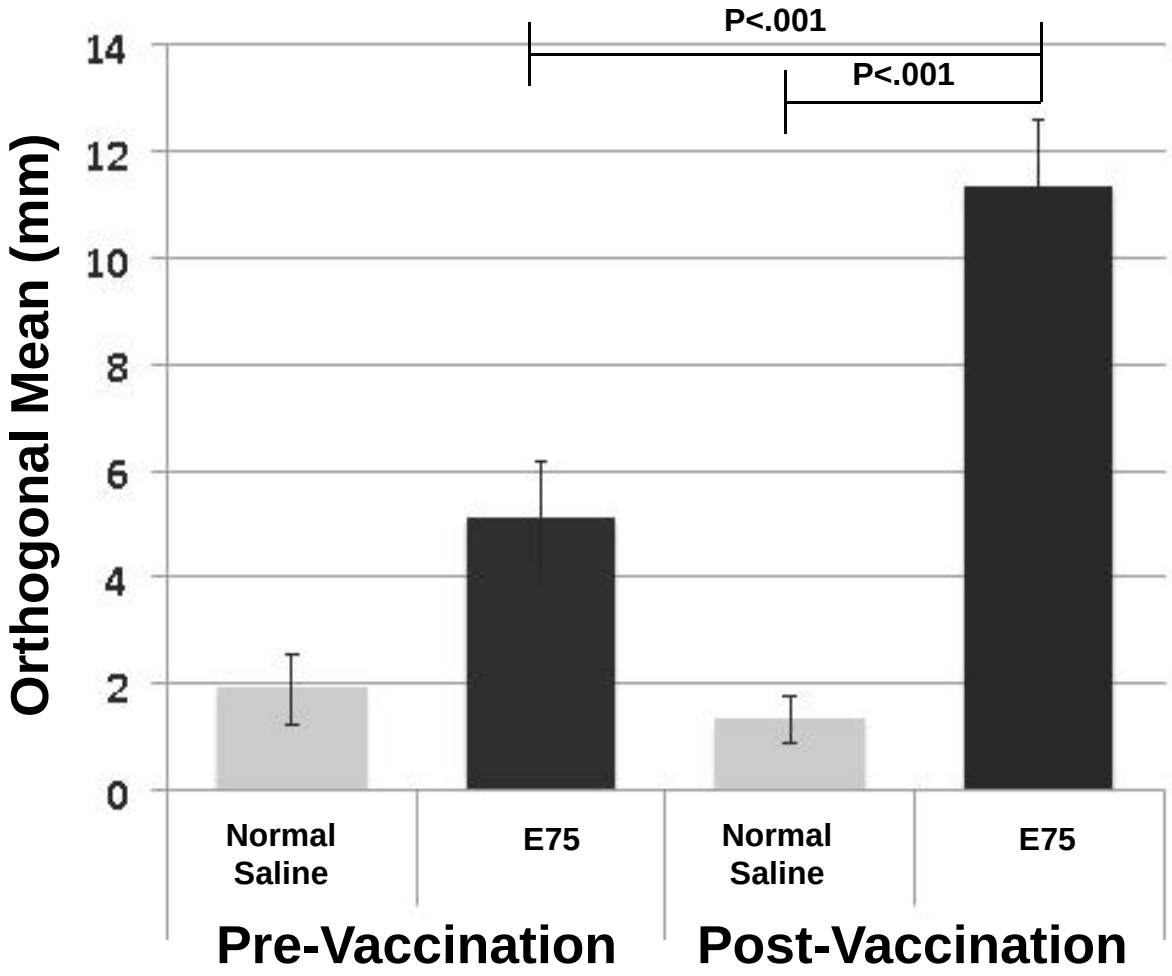
	Vaccine n=108	Control n=79	p value
Age (median)	57	53	0.49
Node Positive	49%	56%	0.37
Tumor Size (T2-T4)	30%	39%	0.51
Histologic Grade 3	41%	38%	0.85
ER/PR negative	**31%**	**18%**	**0.03**
HER2 overexpression	31%	25%	0.53
Chemotherapy	76%	73%	0.70

Mittendorf EA et al. *Ann Oncol* 2014;25(9):1735-1742

Local Toxicity

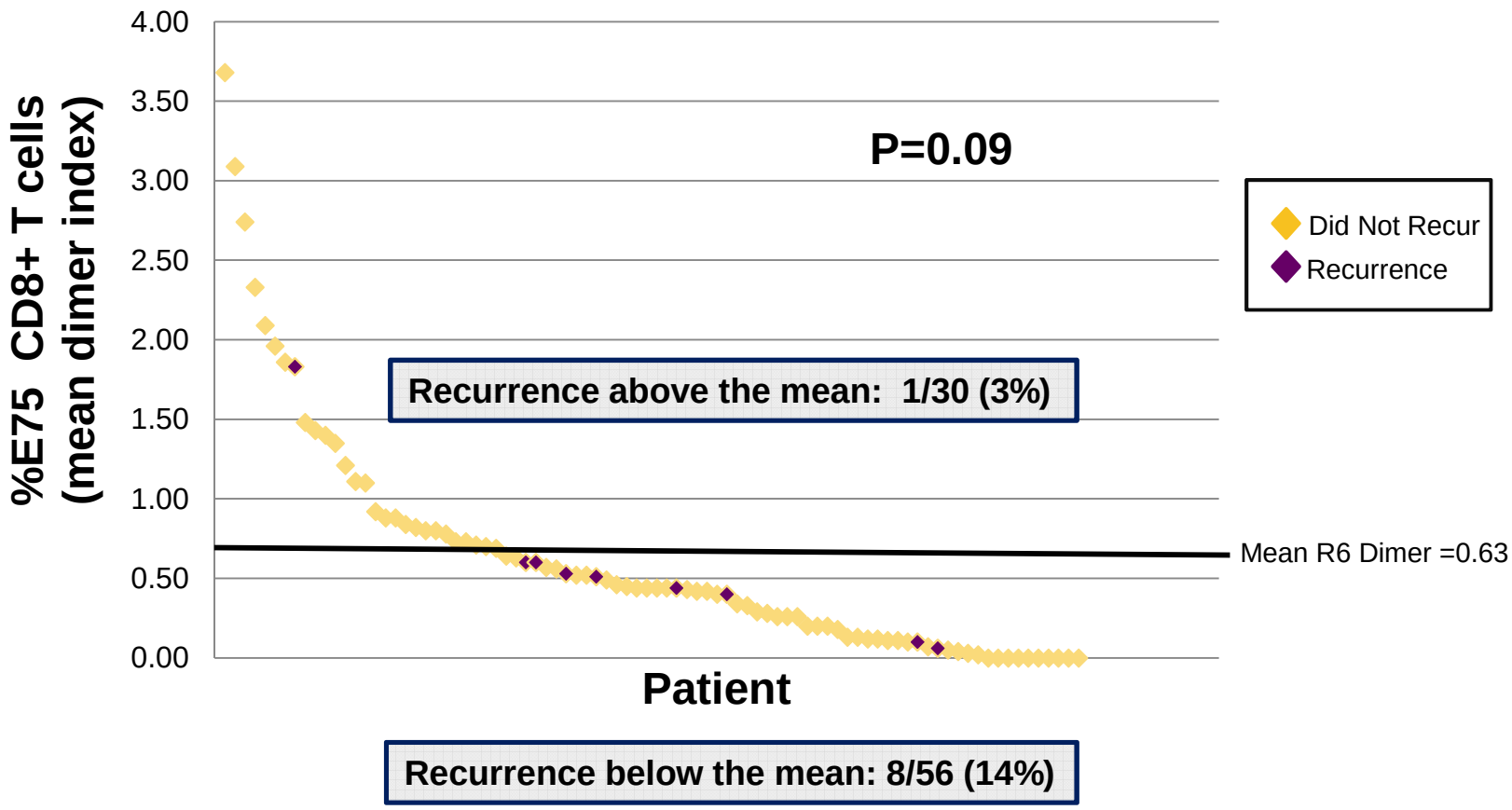


In Vivo Immune Response: DTH



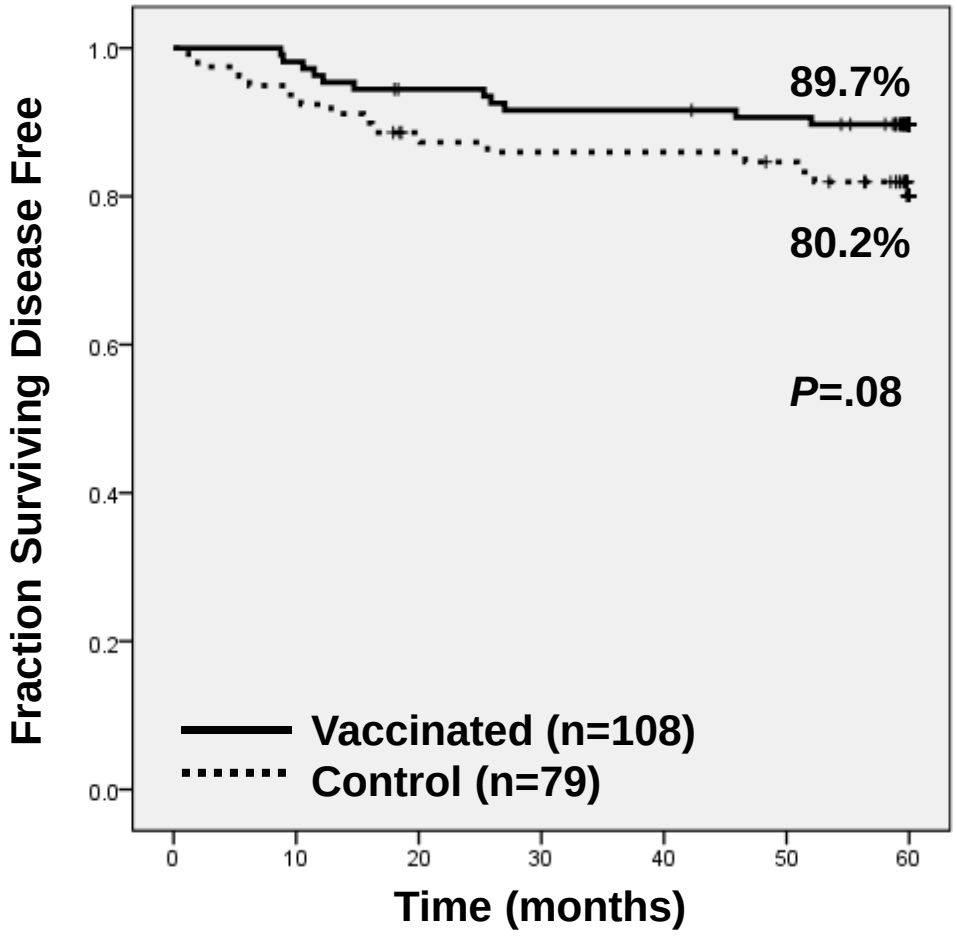
Mittendorf EA et al. *Ann Oncol* 2014;25(9):1735-1742

Vaccine Induced E75 CTL



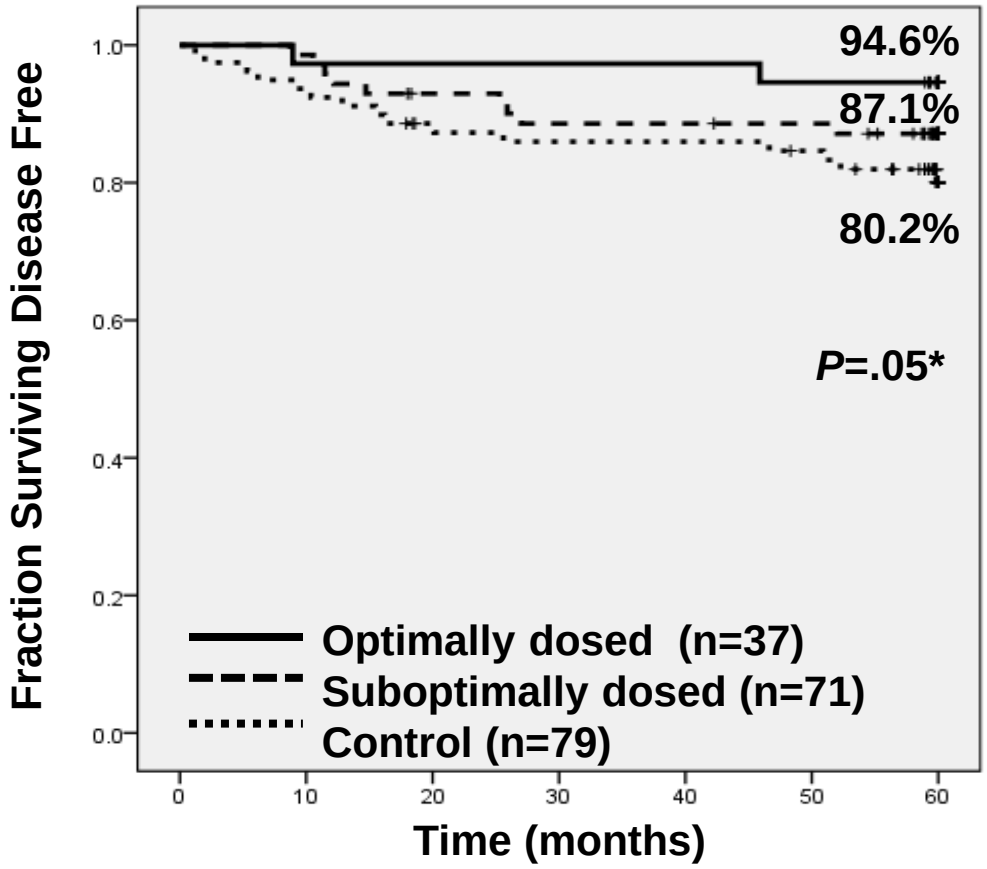
Schneble EJ et al. *Immunotherapy* 2014;6(5):519-531

DFS – 60 mo f/u



Mittendorf EA et al. *Ann Oncol* 2014;25(9):1735-1742

DFS – Optimal Dosing



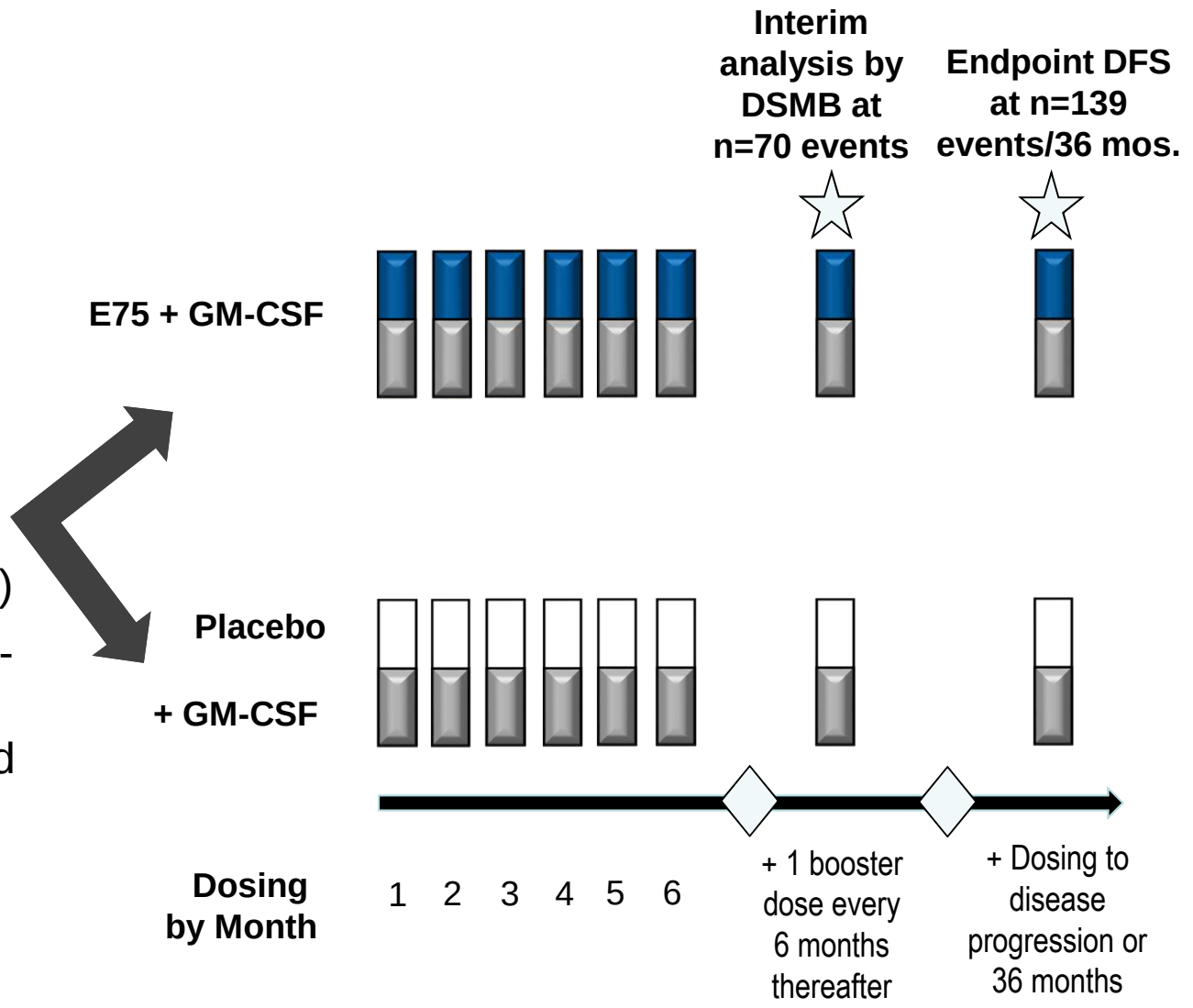
Mittendorf EA et al. *Ann Oncol* 2014;25(9):1735-1742

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 +/- E75



PI: E.A. Mittendorf

Phase II Trial of Combination Immunotherapy with E75+GM-CSF and Trastuzumab in high-risk HER2+ Breast Cancer Patients

Study Sponsors:
Department of Defense
Galena Biopharma

Mechanisms of Synergy

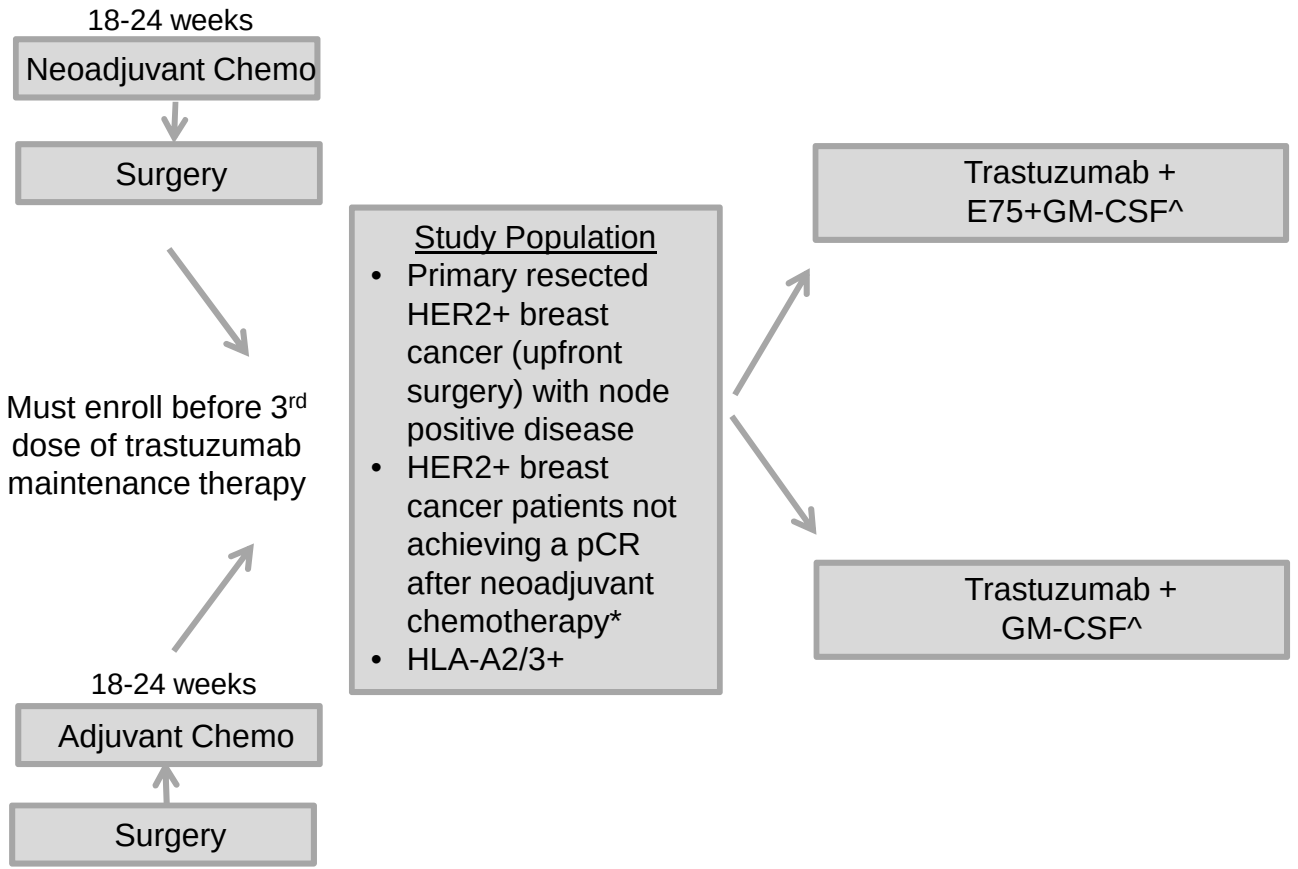
- ADCC → ↑ $CD8^+$ T cell response
- Broad stimulation of HER2-specific immunity
  - $CD4^+$ T cell response
  - Antibody response
- ↑ antigen availability/presentation

High-risk HER2+ Breast Cancer

- Did not achieve a pCR after neoadjuvant chemotherapy + HER2-targeted therapy
- Upfront surgery patients that are path node-positive
  - ≥ 4+ LN
  - 1-3+ LN if HR negative

Neoadjuvant Therapy						
Study	N	Regimen	Results			
TECHNO	217	EC→taxol + Tz	3-yr DFS from randomization pCR = 88% no pCR = 73%			
MD Anderson (2009)	142	Included a taxane, anthracycline and concomitant Tz	3-yr RFS from date of diagnosis pCR = 96% no pCR = 80%			
MD Anderson (2013)	229	Included a taxane, anthracycline and concomitant Tz	5-yr RFS from date of diagnosis pCR = 96% no pCR = 79%			
Adjuvant Therapy						
BCIRG-006	3222	Randomized to: AC-T AC-T + Tz TCH	5-yr DFS			
				NN	NP	≥4+ LN
			AC-TH	93%	80%	73%
			TCH	90%	78%	72%

Schema



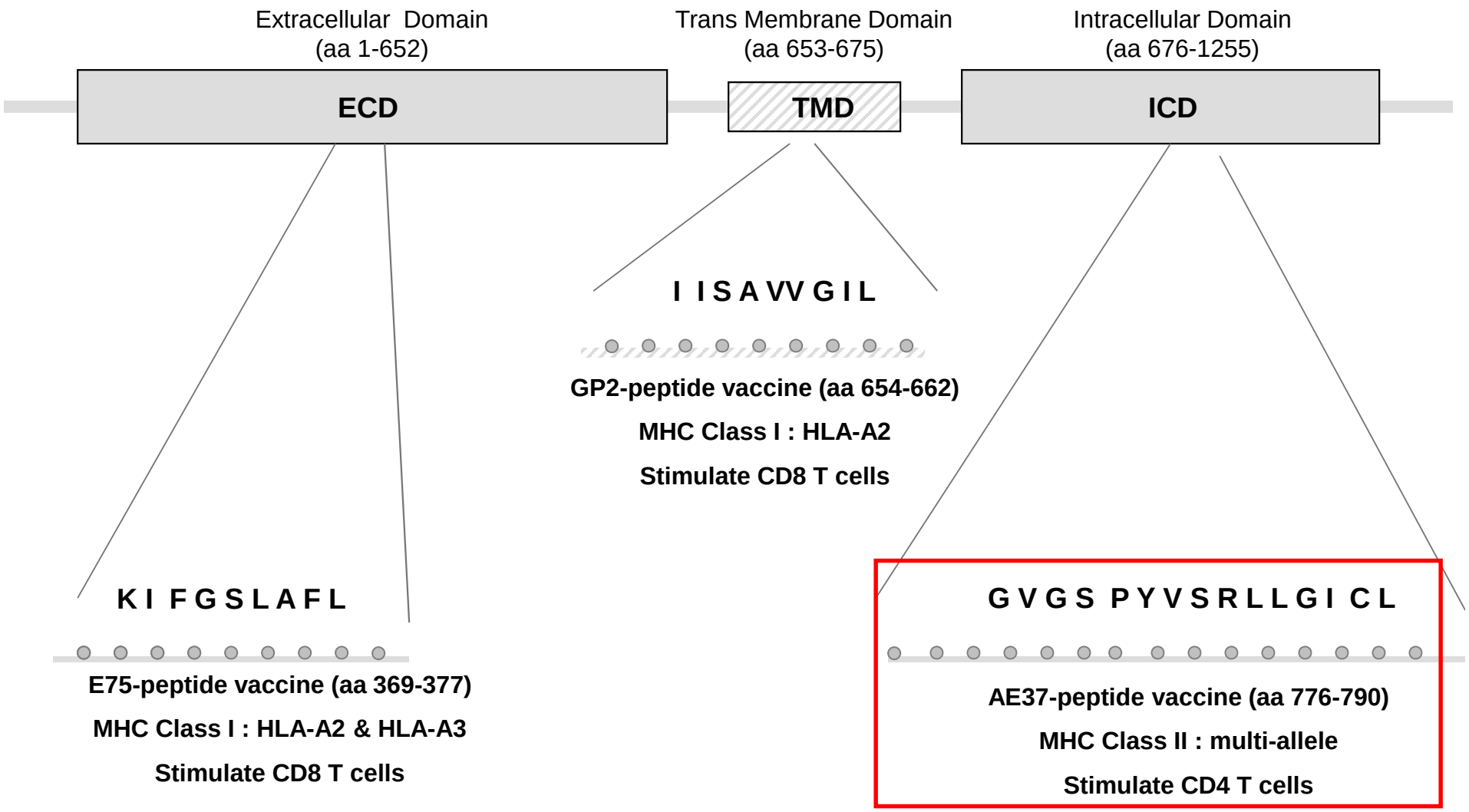
*neoadjuvant chemotherapy regimen must include trastuzumab and at least four cycles (12 weeks) of taxane-containing therapy

^inoculations to begin with 3rd dose of trastuzumab maintenance therapy

Endpoints

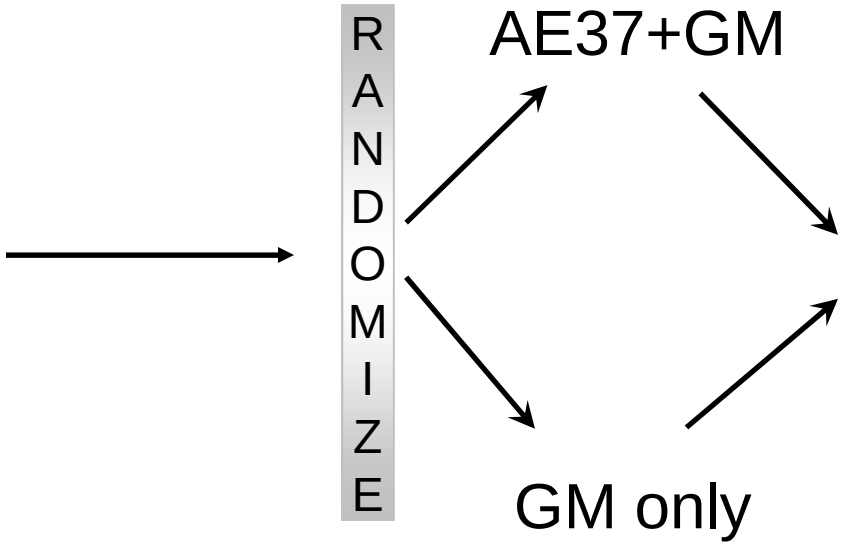
- Primary
  - Compare invasive DFS between treatment groups
- Secondary
  - Distant RFS
  - Assess local and systemic toxicities
  - Evaluate in vivo and in vitro immune responses

HER2


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 Phase II Trial

- NP or high-risk NN
- HER2 IHC 1+, 2+ or 3+
- NED after SOC therapy



Specific Aims

1. Recurrence
2. Time to Recurrence
3. Immunologic response correlation

National PI: E Mittendorf, MD, PhD

AE37 Phase II Trial

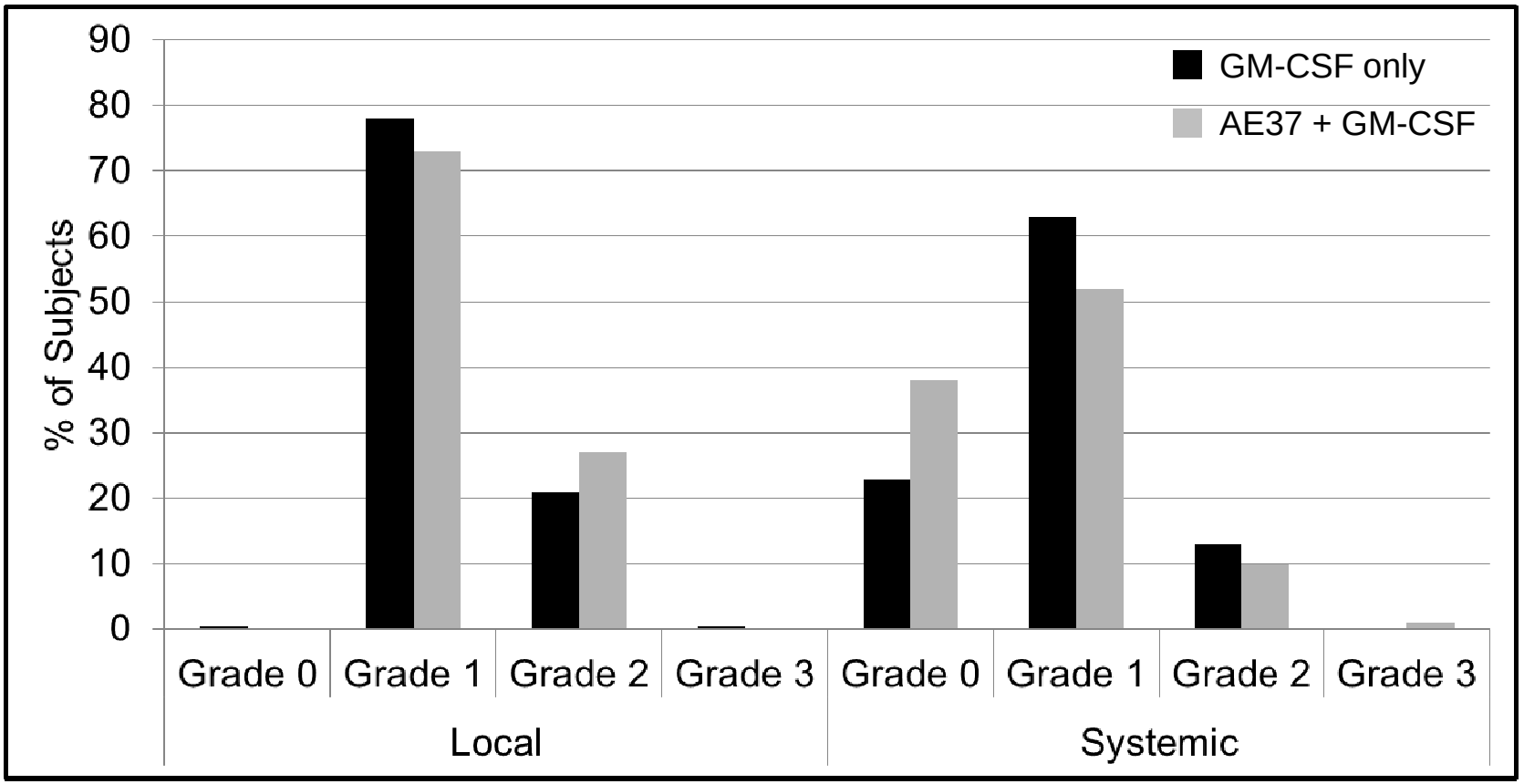
- Inclusion criteria
  - Node-positive or high-risk node-negative breast cancer
  - Any degree of HER2 expression (IHC 1-3+)
  - NED after SOC therapy
- Objective
  - Determine if the AE37+GM-CSF vaccine reduces the recurrence rate
- Primary analysis to occur after 39 events

AE37 – Clinicopathologic Characteristics

	Vaccine N=153	GM-CSF alone N=145	P value
Age (median)	49 yrs	51 yrs	0.22
Node positive	65%	66%	0.32
Grade 3	51%	54%	0.36
T2-T3	56%	66%	0.06
ER/PR negative	39%	38%	0.46
HER2 positive	50%	46%	0.36

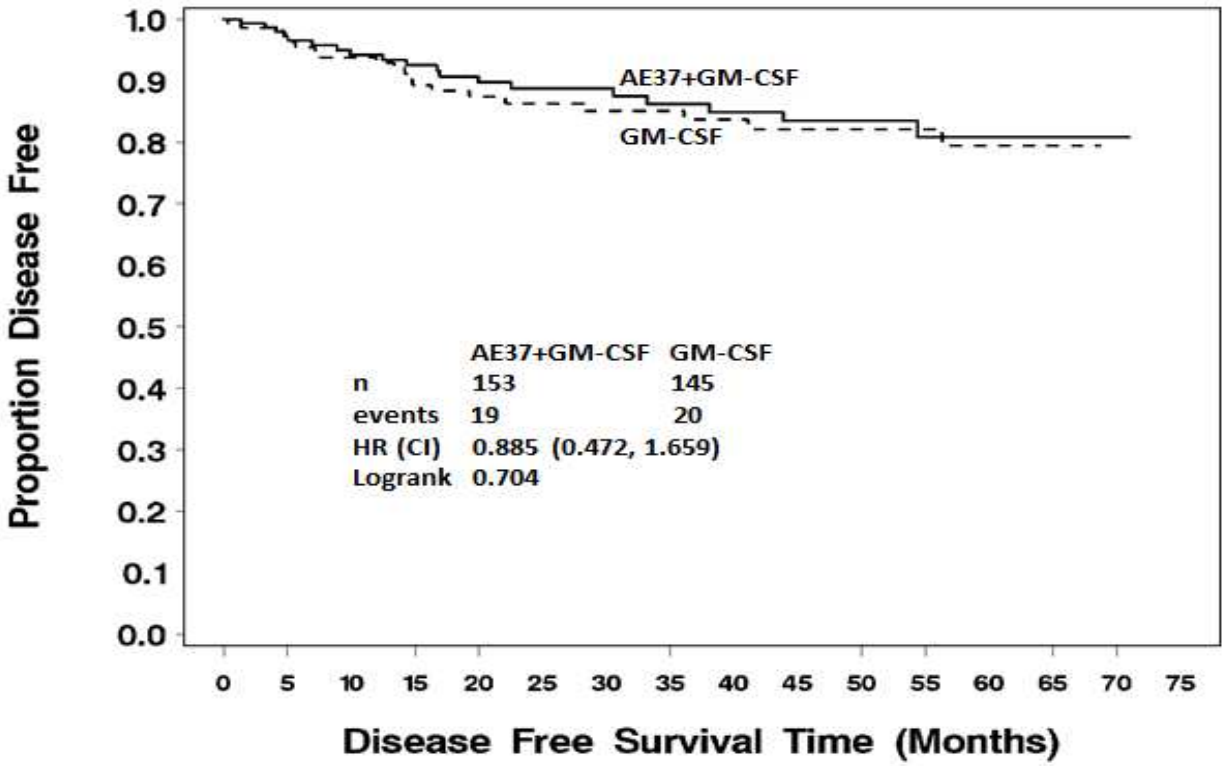
Mittendorf EA, et al. *ASCO* 2014

AE37 – Toxicity



Mittendorf EA, et al. *ASCO* 2014

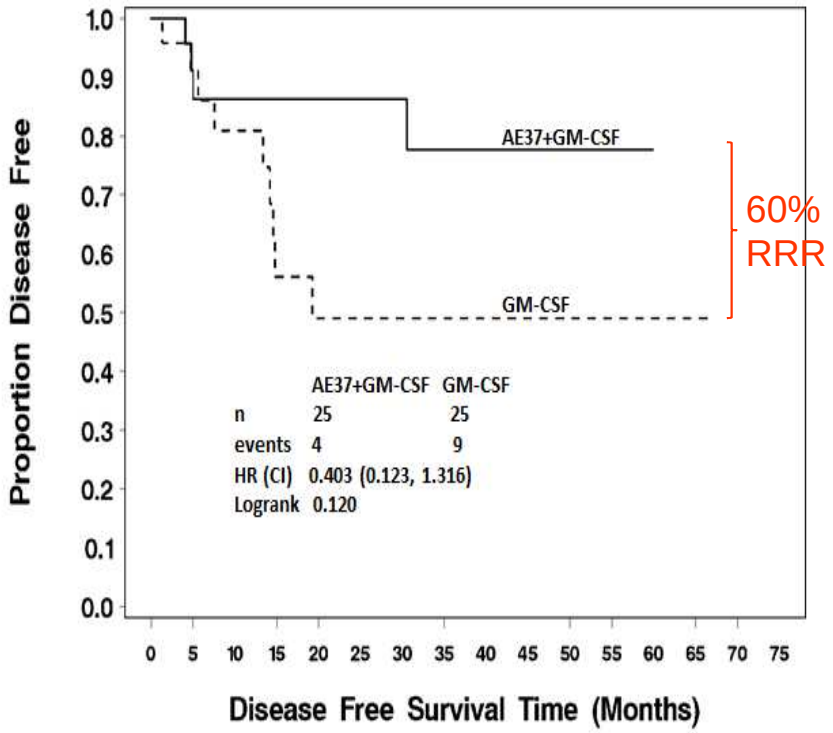
AE37 – Primary Analysis



Mittendorf EA, et al. *ASCO* 2014

AE37 – Primary Analysis

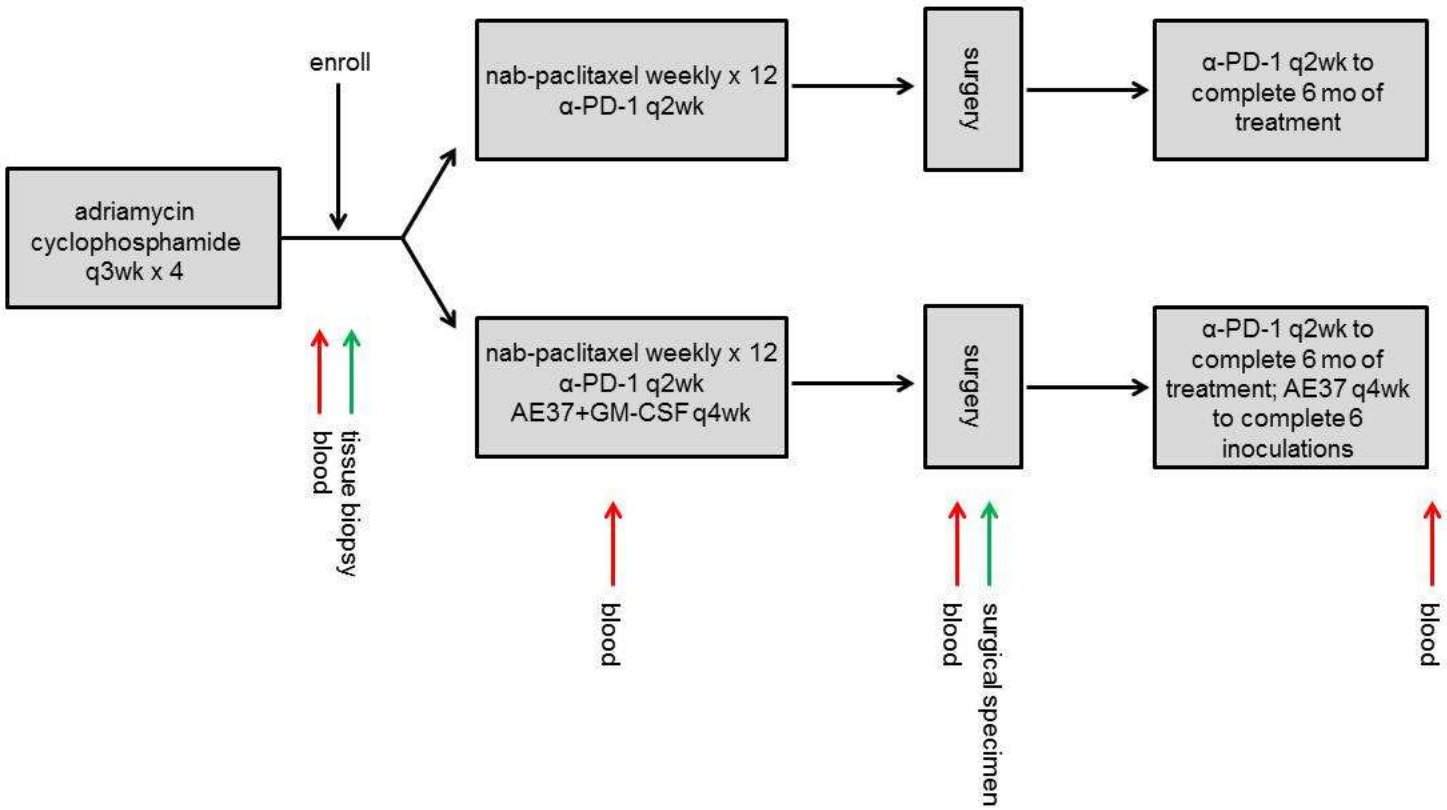
TNBC



Mittendorf EA, et al. *ASCO* 2014

AE37

- Proposed trial



Conclusions

- Breast cancer is an immunogenic tumor
- Multiple ongoing trials are evaluating immunotherapy strategies
- Novel combinations are the likely way forward

Is immunotherapy ready for prime time in breast cancer?

Yes

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Injecting Hope