Therapeutic Cancer Vaccines: Successes and Failures in the Clinic

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Tumor Vaccines

- >100 years ago, W. B. Coley reported regression of tumors with injected bacterial extracts.
- Attempts to harness the immune system to mediate the rejection of tumors *in vivo*.
- Important discoveries in immunology and tumor cell biology: opportunities to explore the therapeutic potentials of cancer vaccines.

Tumor Vaccines

"To increase host's immunity to own tumor"

Tumor Vaccines:
The Successes

Tumor Vaccines Currently Being Used

- Peptide Vaccines
- Gene-Modified Cellular Vaccines
- Dendritic Cell Vaccines

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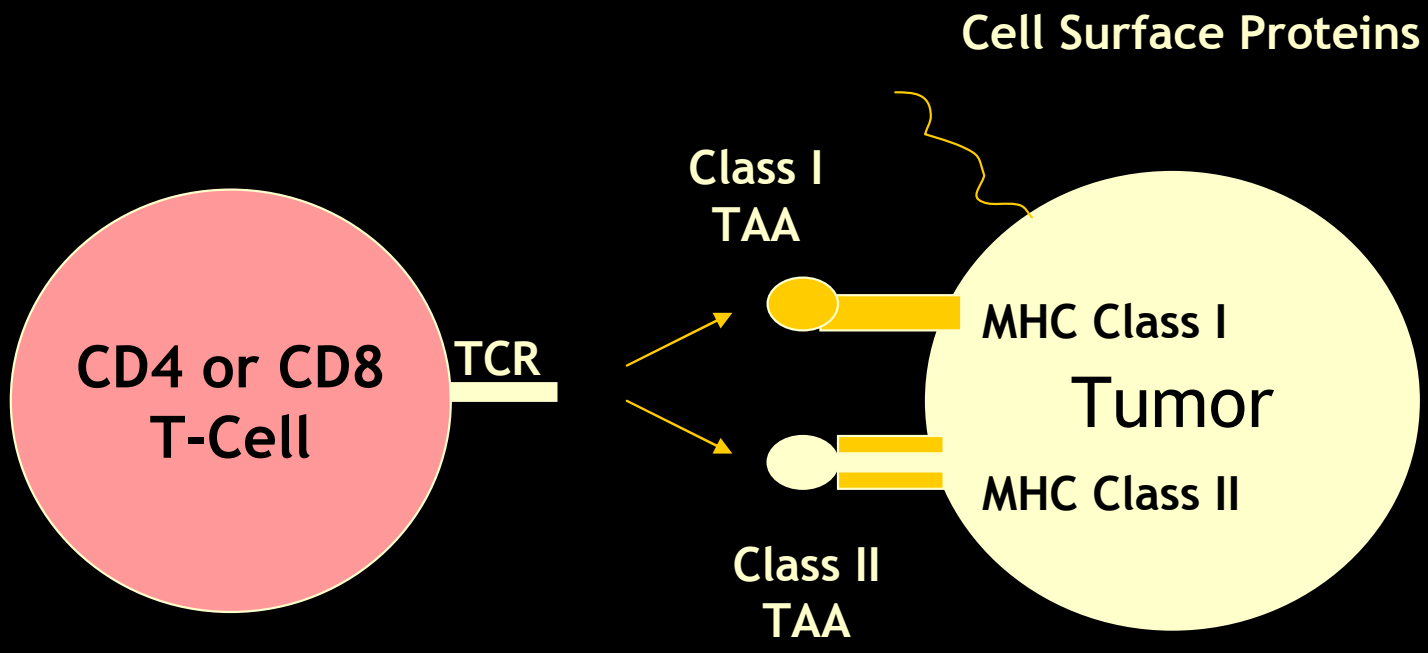
Peptide Vaccines



Peptide Vaccines

- Overexpressed proteins (HER-2/*neu*)
- Oncogenes (ras)
- Embryonic proteins (MAGE)
- Viruses (HPV, HBV)
- Tissue specific proteins (MART-1/Melan-A, gp100, tyrosinase, PSA, PSMA)
- Mutated tumor suppressors (p53)
- Modified proteins (MUC-1)
- Idiotypic epitopes (B cell lymphoma)

Clinical Trial Results of the HER-2/*neu* (E75) Vaccine to Prevent Breast Cancer Recurrence in High-Risk Patients:

From US Military Cancer Institute Clinical Trials Group Study I-01 and I-02

Elizabeth A. Mittendorf, MD[1], Guy T. Clifton, MD[2], Jarrod P. Holmes, MD[3], Kevin S. Clive, MD[2], Ritesh Patil, MD[4], Linda C. Benavides, MD[2], Jeremy D. Gates, MD[2], Alan K. Sears, MD[2], Alexander Stojadinovic, MD[5], Sathibalan Ponniah, PhD[6], and George E. Peoples, MD[2,6]

Cancer 2012 May 15; 118(10): 2594–2602

Timeline

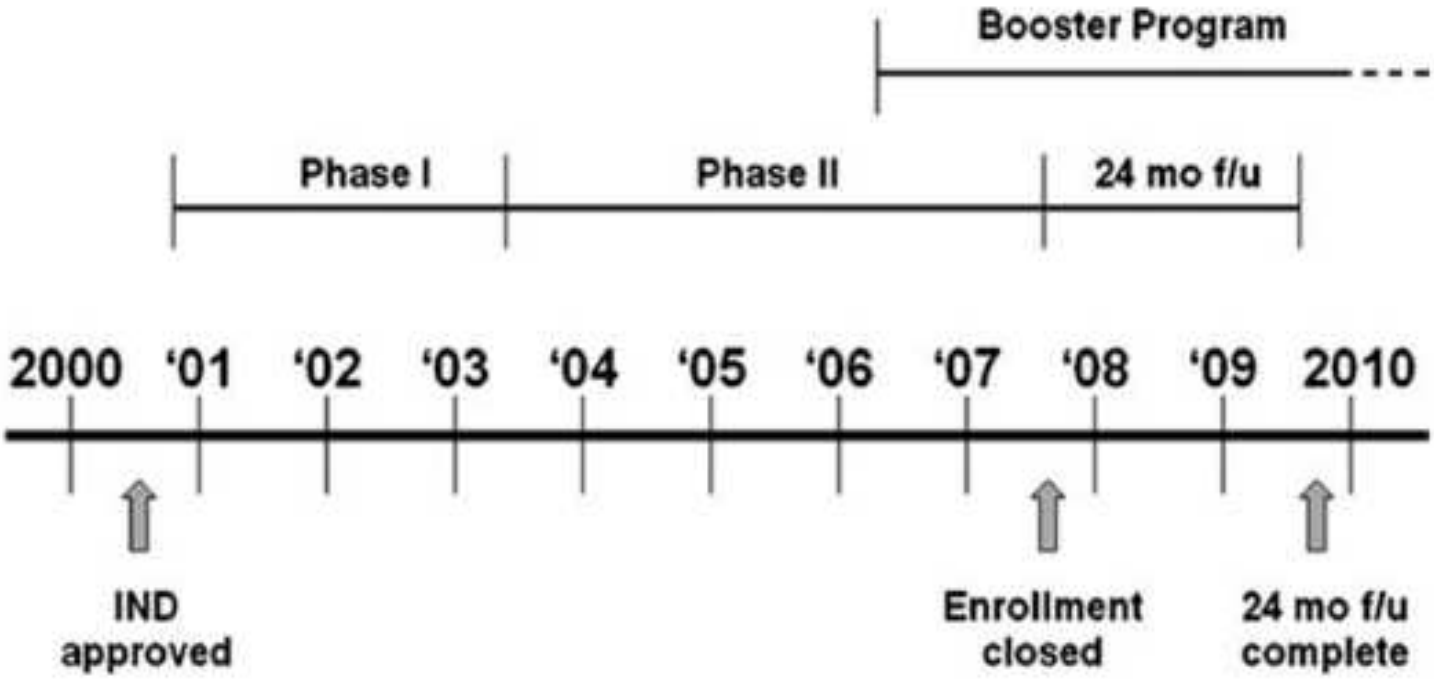


Figure 1.
E75 vaccine trial schema. IND = Investigational New Drug.

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Clinicopathologic Characteristics of Evaluable Patients in the E75 Vaccine Trials by Treatment Group at 24-Month Landmark Analysis

Characteristics	Vaccinated, n = 106, No. (%)	Controls, n = 76, No. (%)	*P*
Age, y			.38
Median	57	53	
Range	(28–78)	(32–83)	
Race			.19
White	95 (89.6%)	64 (81.2%)	
Black	5 (4.7%)	10 (13.2%)	
Other	6 (5.7%)	2 (2.6%)	
Time to enrollment in trial in days			
Median	472	435	.25
Tumor size			.45
T1	71 (67.0%)	46 (60.5%)	
T2	26 (24.5%)	18 (23.7%)	
T3	7 (6.6%)	8 (10.5%)	
T4	2 (1.9%)	4 (5.3%)	
Nodal status			.13
N0	55 (51.9%)	33 (43.4%)	
N1	39 (36.8%)	25 (32.9%)	
N2	9 (8.5%)	11 (14.5%)	
N3	3 (2.8%)	7 (9.2%)	
Other tumor characteristics			.45
Histologic grade 3	40 (38.8%)	30 (41.1%)	.88
ER and PR negative	33 (31.7%)	14 (18.4%)	.06
HER2 overexpression[a]	30 (30.3%)	18 (26.5%)	.61
Trastuzumab	12	3	
Treatment			.13
Hormonal therapy	70 (66.0%)	57 (76.0%)	.19
Chemotherapy	79 (74.5%)	54 (71.1%)	.62
Radiation therapy	77 (72.6%)	62 (81.6%)	.22
Received optimal dose of vaccine[b]	37 (34.9%)		N/A
Yes	37 (34.9%)	N/A	
No	69 (65.1%)	N/A	

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E75 Dosing Regimens for Breast Cancer Node-Positive and Node-Negative Patient Groups by Trial Design

Patient Group	Patients, No.	Peptide Dose, µg	GM-CSF Dose, µg	Months Vaccinated
Node positive				
100.250.6[a]	2[b]	100	250	0, 1, 2, 3, 4, 5
500.250.4	6	500	250	0, 1, 2, 5
500.250.6	5	500	250	0, 1, 2, 3, 4, 5
1000.250.4	11	1000	250	0, 1, 2, 5
1000.250.6	27[c]	1000	250	0, 1, 2, 3, 4, 5
Node negative				
500.125.3	10	500	125	0, 1, 5
500.125.4	9	500	125	0, 1, 2, 5
500.250.4	12	500	250	0, 1, 2, 5
500.250.6	13	500	250	0, 1, 2, 3, 4, 5
1000.250.6	11	1000	250	0, 1, 2, 3, 4, 5
Total	**106**			

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Disease-Free Survival

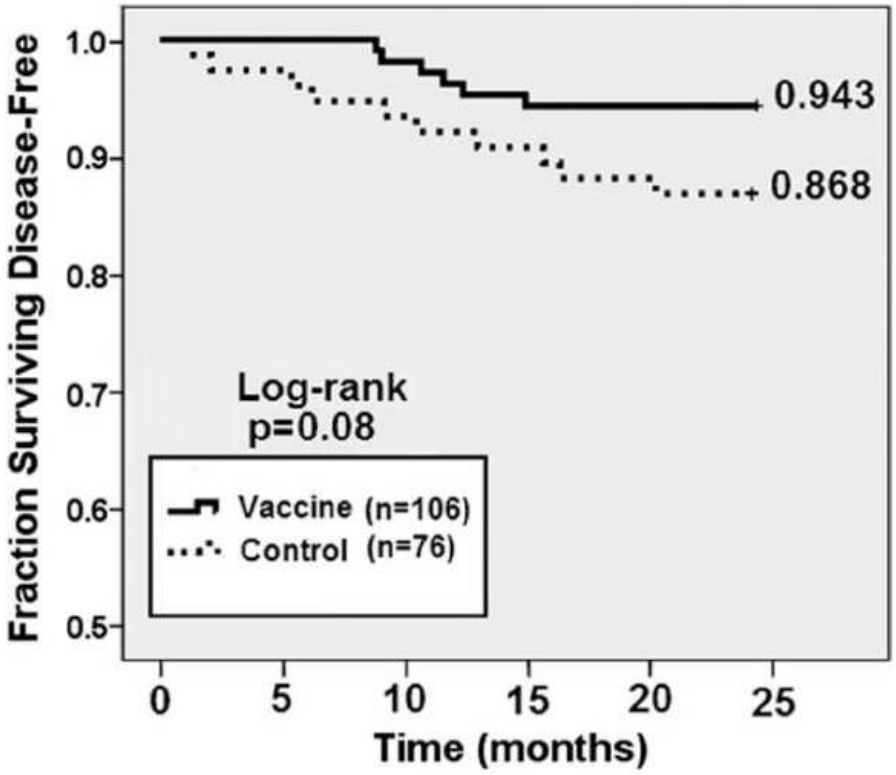

Figure 2.
24-month disease-free survival for all vaccinated patients compared with unvaccinated control patients.

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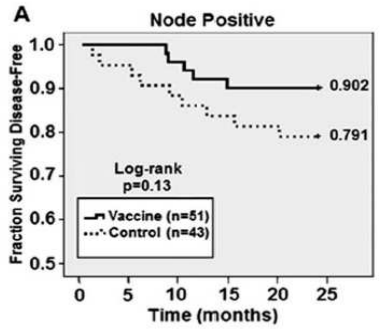
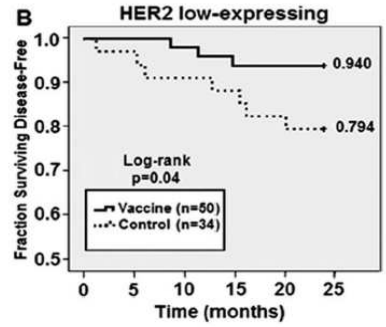
DFS by Subgroups





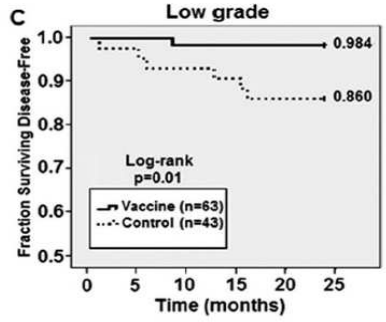


Figure 3.
24-month disease-free survival (DFS) determined for clinicopathologic subgroups. DFS was compared between vaccinated patients and unvaccinated controls in patients with (A) node-positive breast cancer, (B) HER2 low-expressing (IHC 1+ or 2+ or FISH < 2.0) breast cancer, and (C) low-grade (grade 1 or 2) breast cancer.

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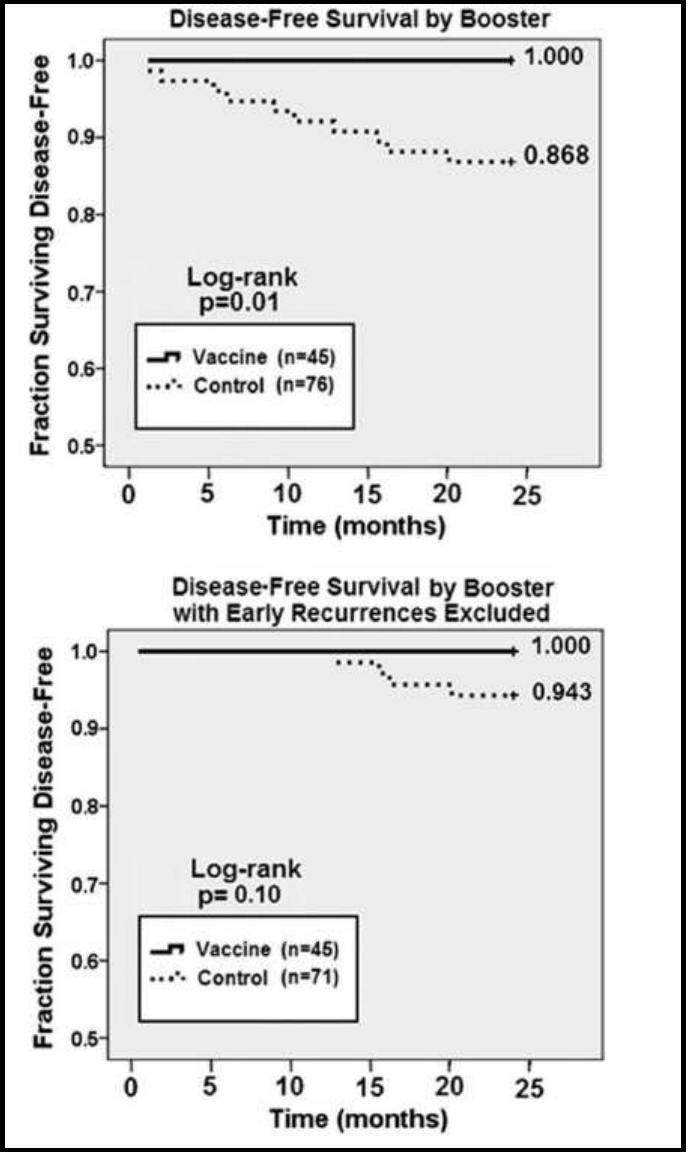
DFS by Booster



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Conclusion

- E75 + GM-CSF vaccine effective in certain subsets of patients (HER2 low, positive LN, low grade)
- Boosting is beneficial
- Ongoing phase 3 trial comparing E75 + GM-CSF to GM-CSF alone in HLA-A2+/A3+ patients

Tumor Vaccines Currently Being Used

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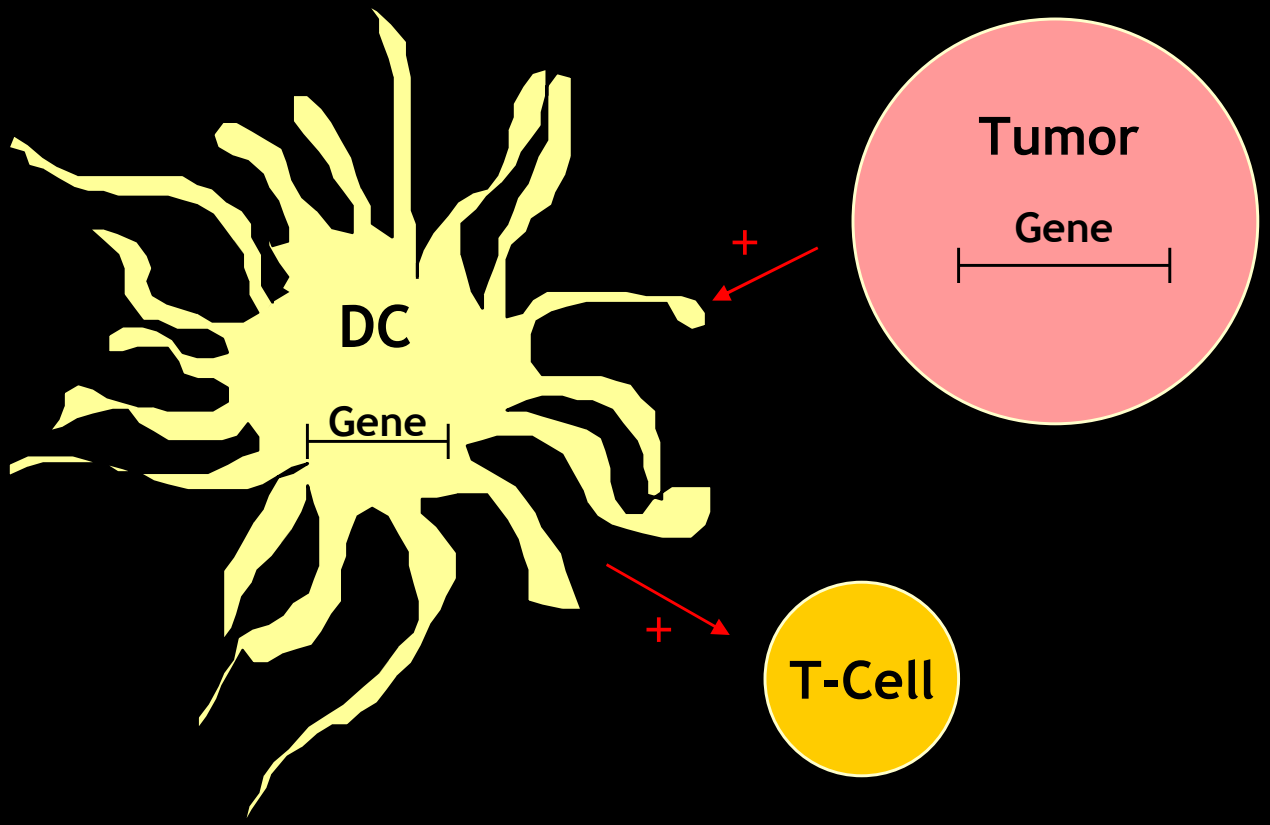
- Gene-Modified Cellular Vaccines
- Dendritic Cell Vaccines

Gene-Modified Cell Therapy



Gene Therapy

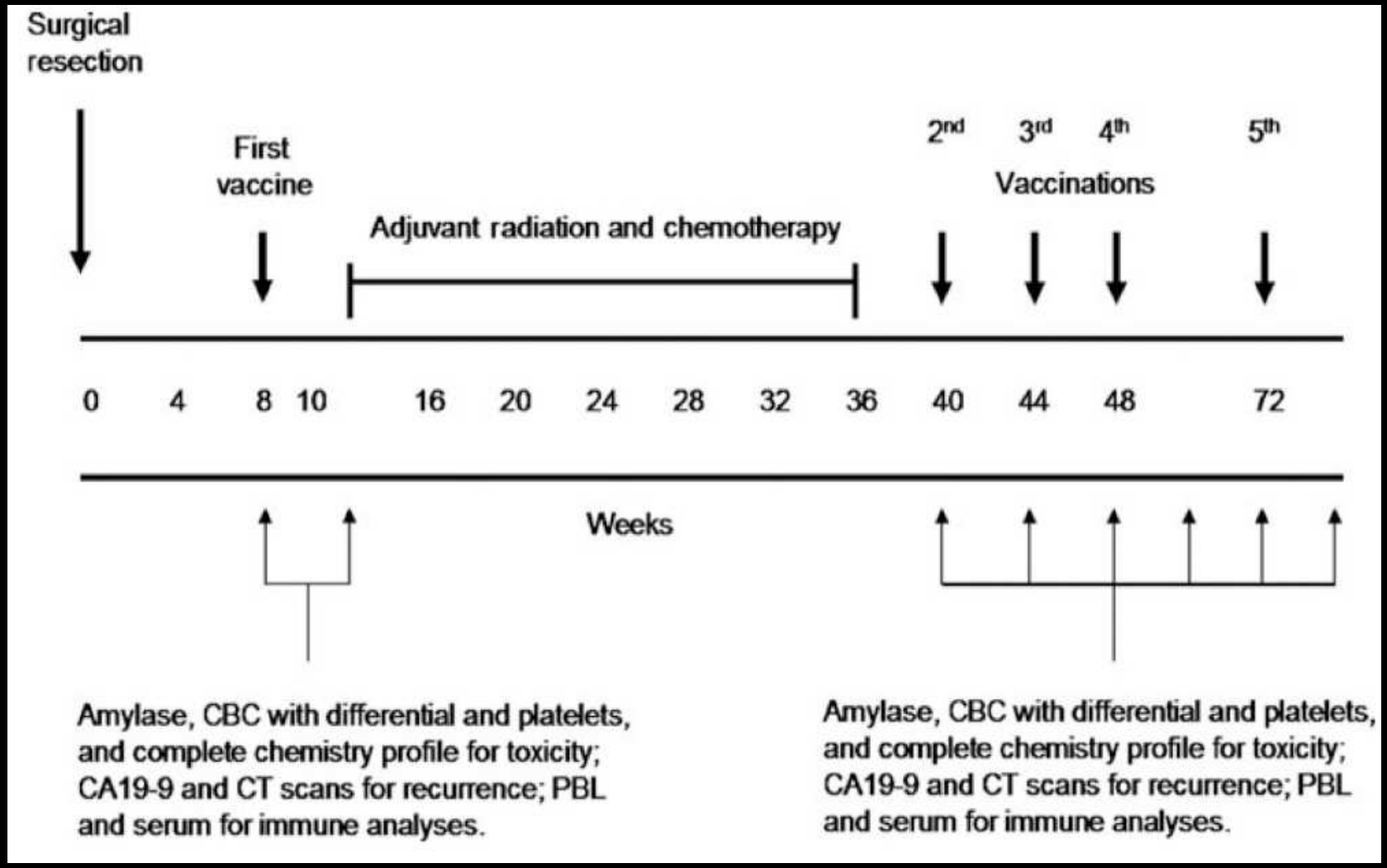
- Cytokines (GM-CSF, IL-12)
- Tumor Antigens
- Viral Genes
- MHC Genes
- Co-Stimulatory Molecules

A Lethally Irradiated Allogeneic Granulocyte-Macrophage Colony Stimulating Factor-Secreting Tumor Vaccine for Pancreatic Adenocarcinoma: A Phase II Trial of Safety, Efficacy, and Immune Activation

Eric Lutz, PhD[*,§§], Charles J. Yeo, MD[**], Keith D. Lillemoe, MD[††], Barbara Biedrzycki, NP[*], Barry Kobrin, PhD[*], Joseph Herman, MD, MSc[†], Elizabeth Sugar, PhD[¶], Steven Piantadosi, MD, PhD[***], John L. Cameron, MD[‡], Sara Solt, BS[*], Beth Onners, RN[*], Irena Tartakovsky, MS[*], Miri Choi, BS[*], Rajni Sharma, PhD[§], Peter B. Illei, MD[§], Ralph H. Hruban, MD[*,§], Ross A. Abrams, MD[‡‡], Dung Le, MD[*], Elizabeth Jaffee, MD[***,§§,¶¶], and Dan Laheru, MD[*]

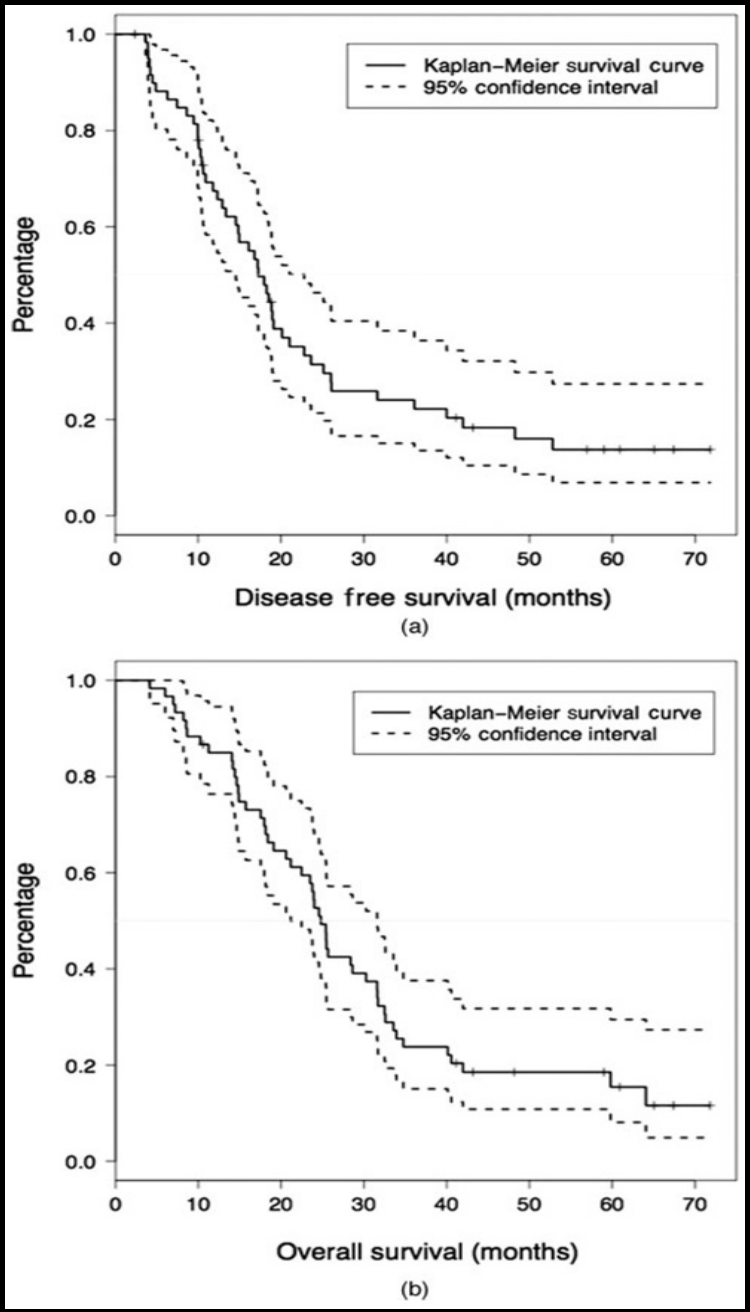
Ann Surg. 2011 February ; 253(2): 328–335.

Methods



Ann Surg. 2011 February ; 253(2): 328–335.

DFS and OS

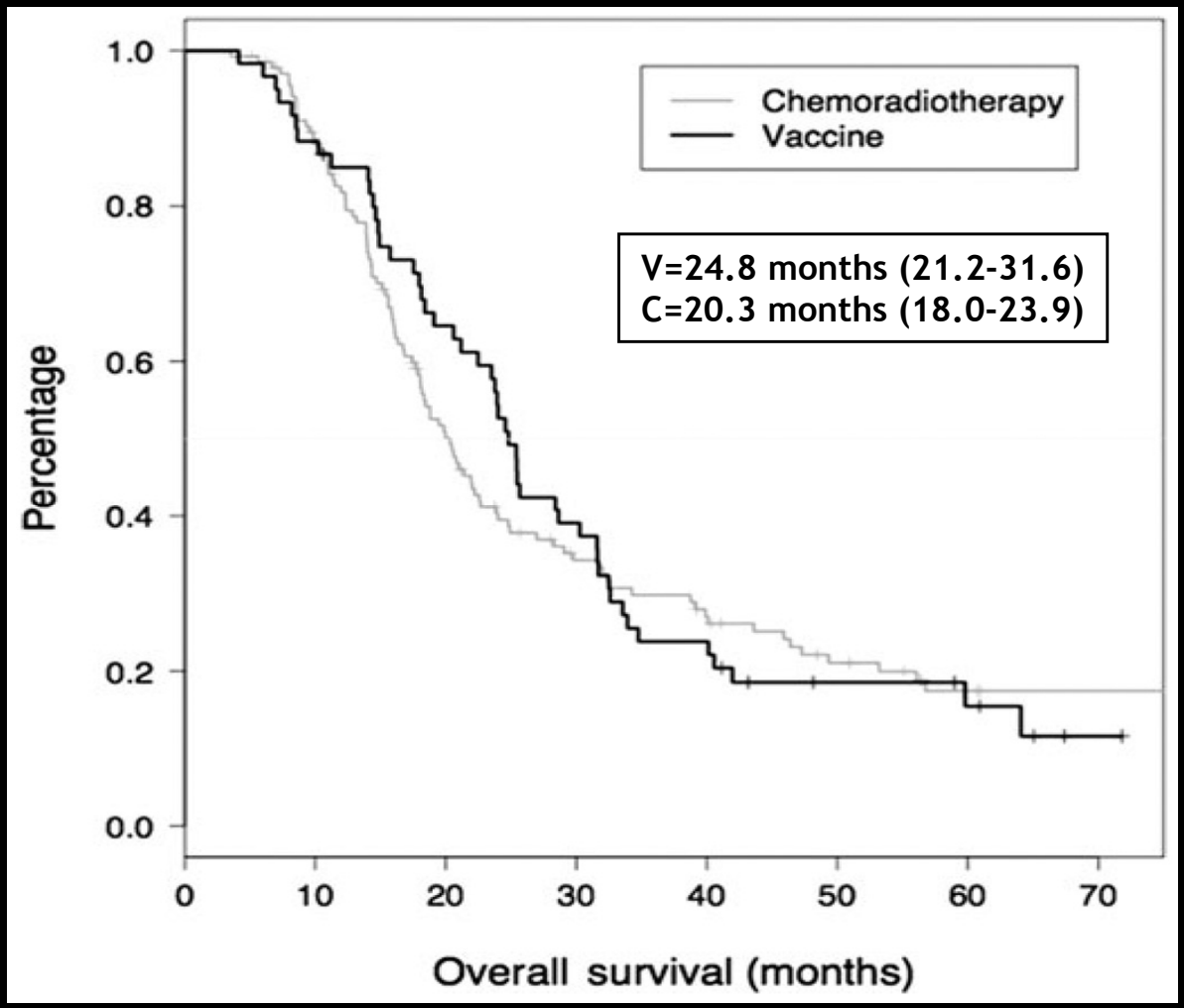


17.3 months (14.6-22.8)

24.8 months (21.2-31.6)

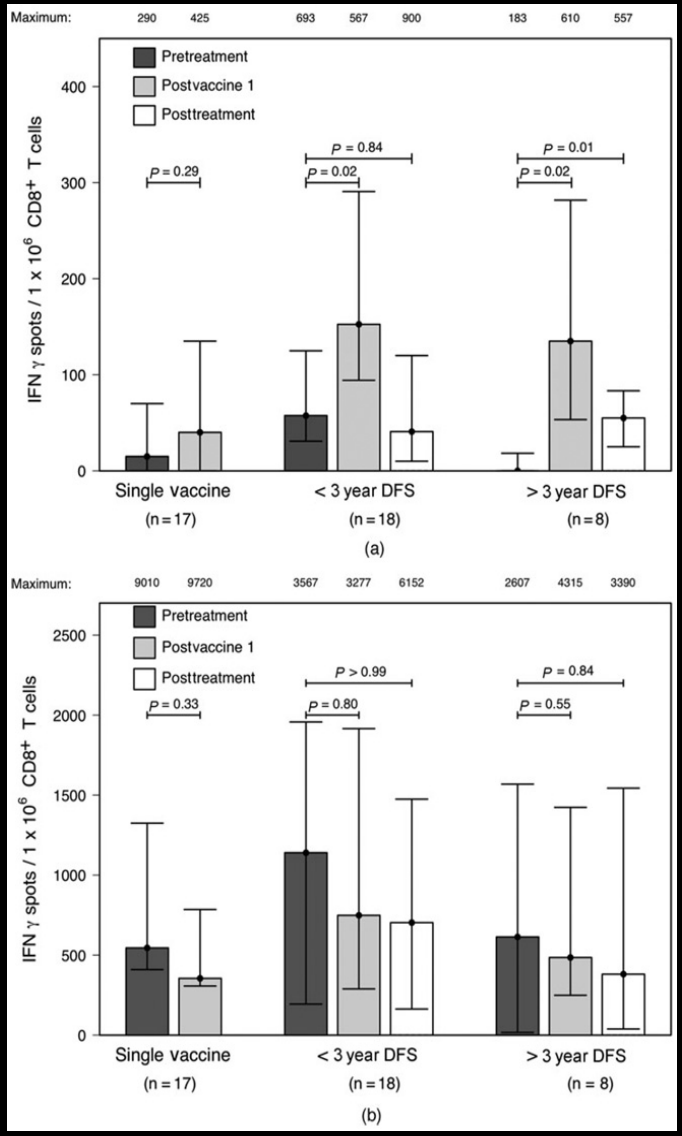
Ann Surg. 2011 February ; 253(2): 328–335.

OS compared to SOC



Ann Surg. 2011 February ; 253(2): 328–335.

Postimmunotherapy enhancement of mesothelin-specific CD8+ T cell responses in HLA-A0101+ and HLA-A201+ patients correlates with disease-free survival.



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Tumor Vaccines Currently Being Used

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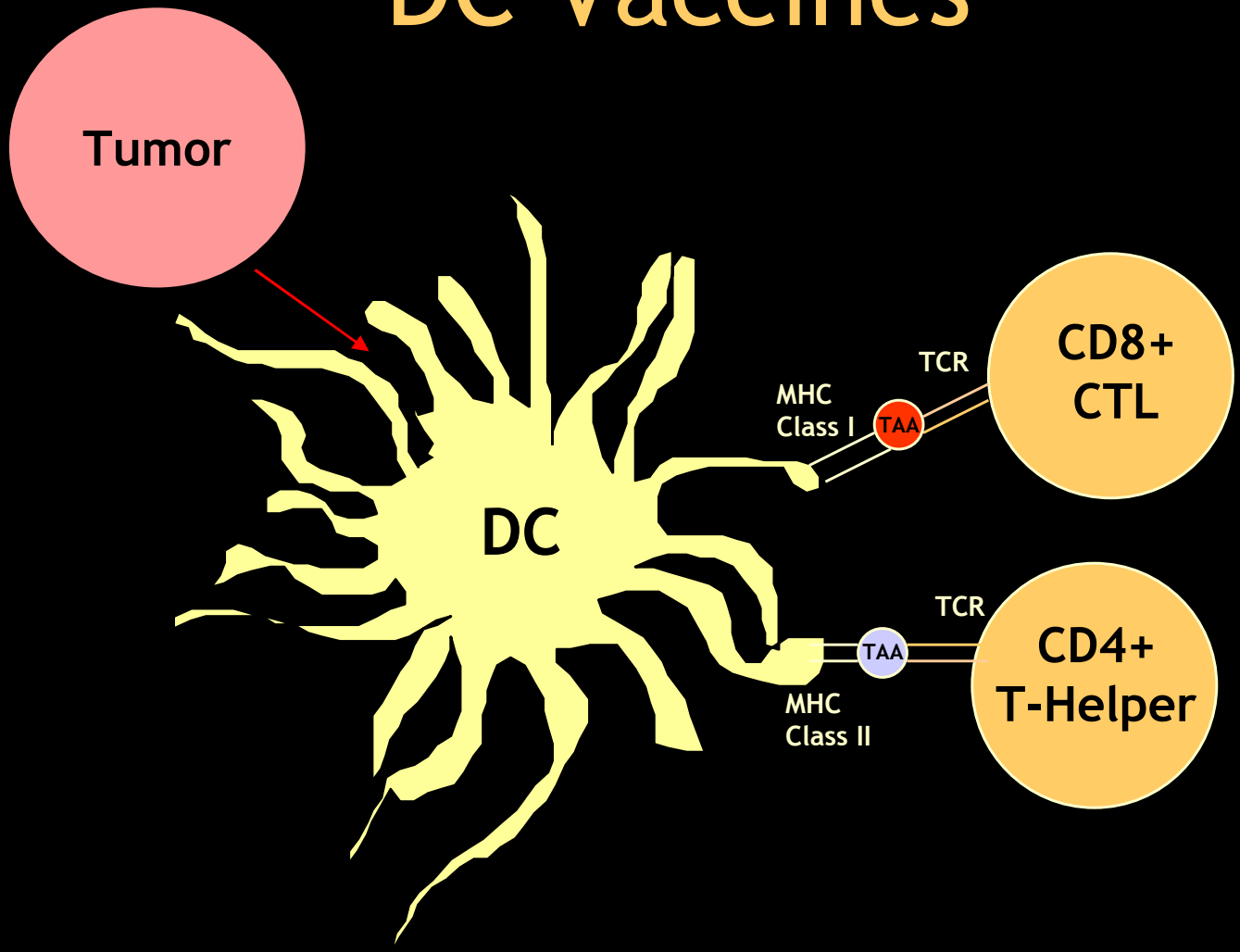
DC Vaccines

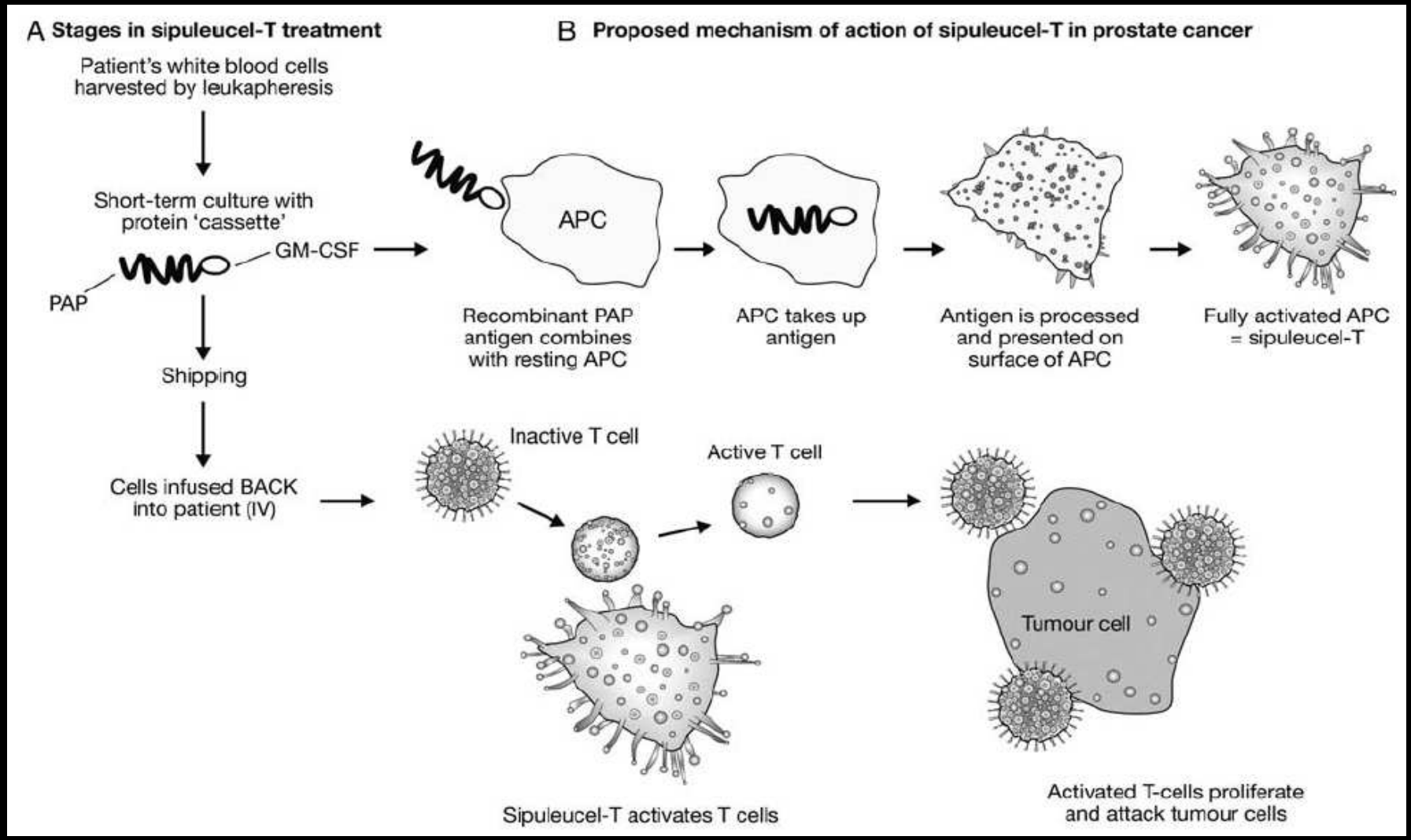

Tumor
DC
MHC
Class I
TAA
TCR
CD8+
CTL
TCR
TAA
CD4+
T-Helper
MHC
Class II

Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory PC.

Small EJ, Schellhammer PF, Higano CS et al

J Clin Oncol 2006; 24: 3089–3094

Methods



J Clin Oncol 2006; 24: 3089–3094

Results

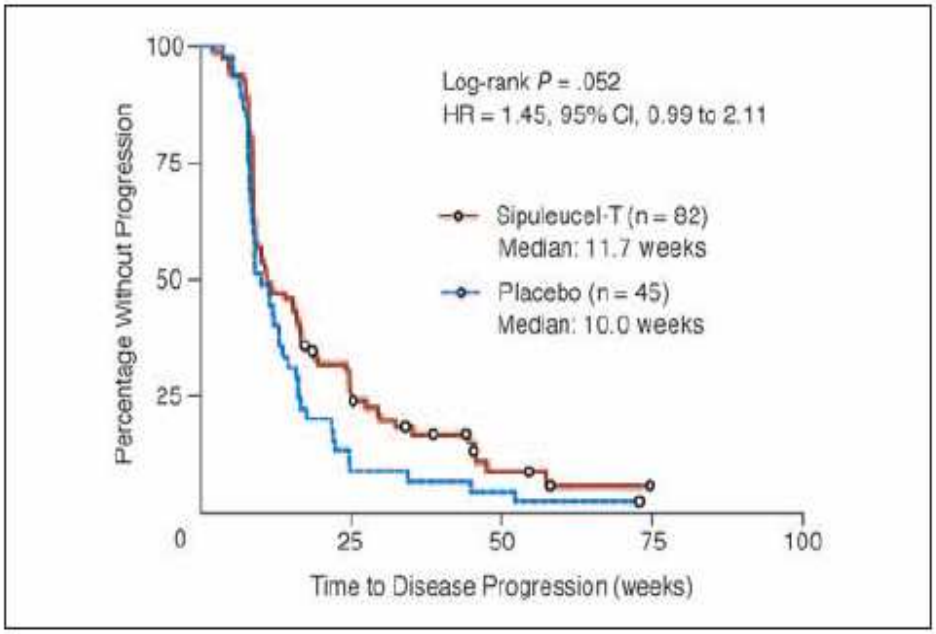


Fig 2. Primary end point, time to disease progression (intent-to-treat population). HR, hazard ratio.

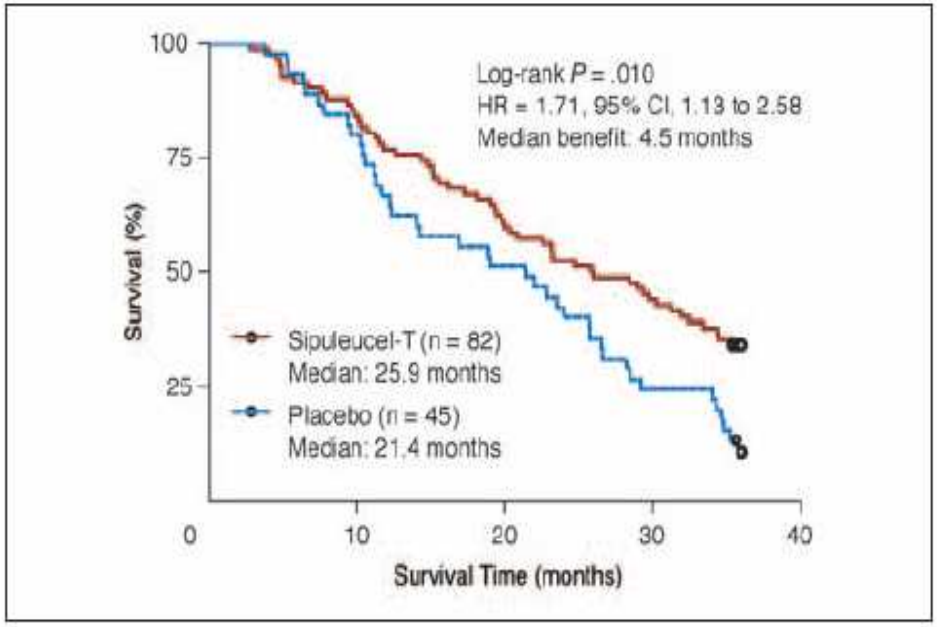
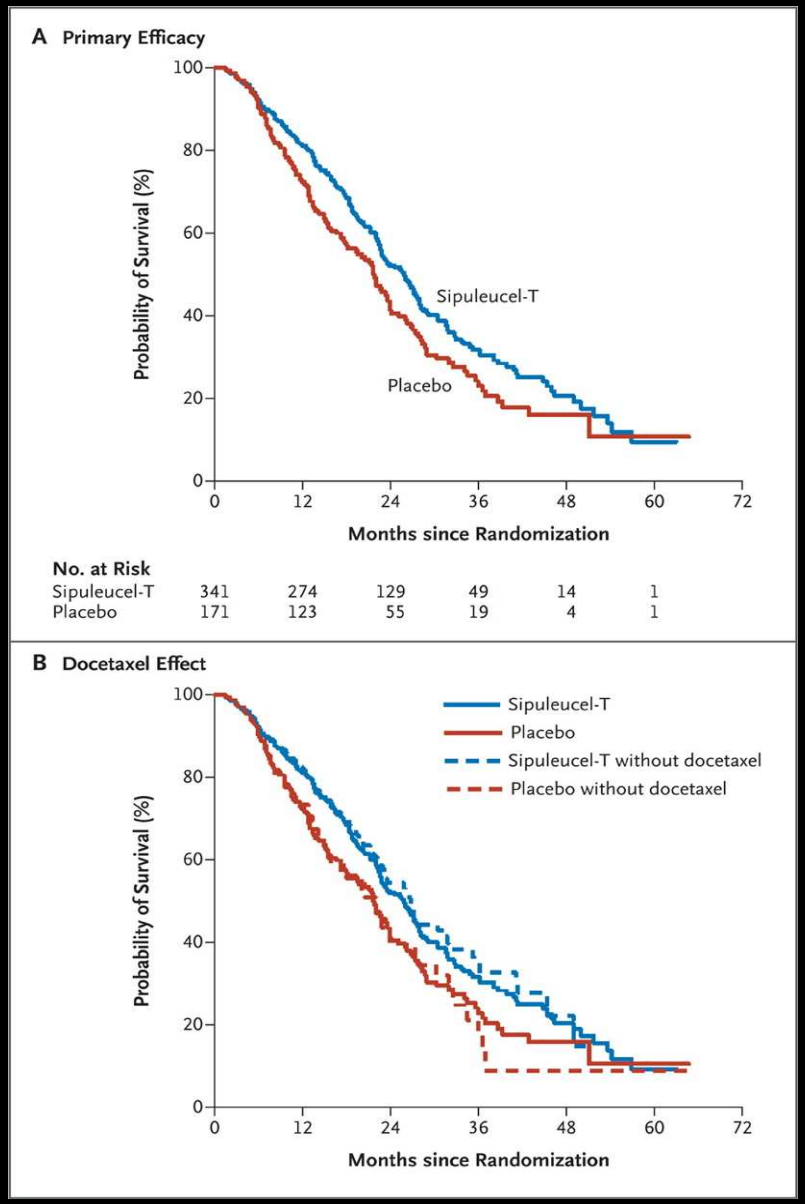


Fig 3. Final overall survival (intent-to-treat population). HR, hazard ratio.

J Clin Oncol 2006; 24: 3089–3094

Kaplan–Meier Estimates of Overall Survival

N= 512
2:1 randomization
1º endpoint: OS



HR: 0.78 (0.61-0.98)
P=0.03

HR: 0.65 (0.47-0.90)
P=0.009

Kantoff PW et al. N Engl J Med 2010;363:411-422.

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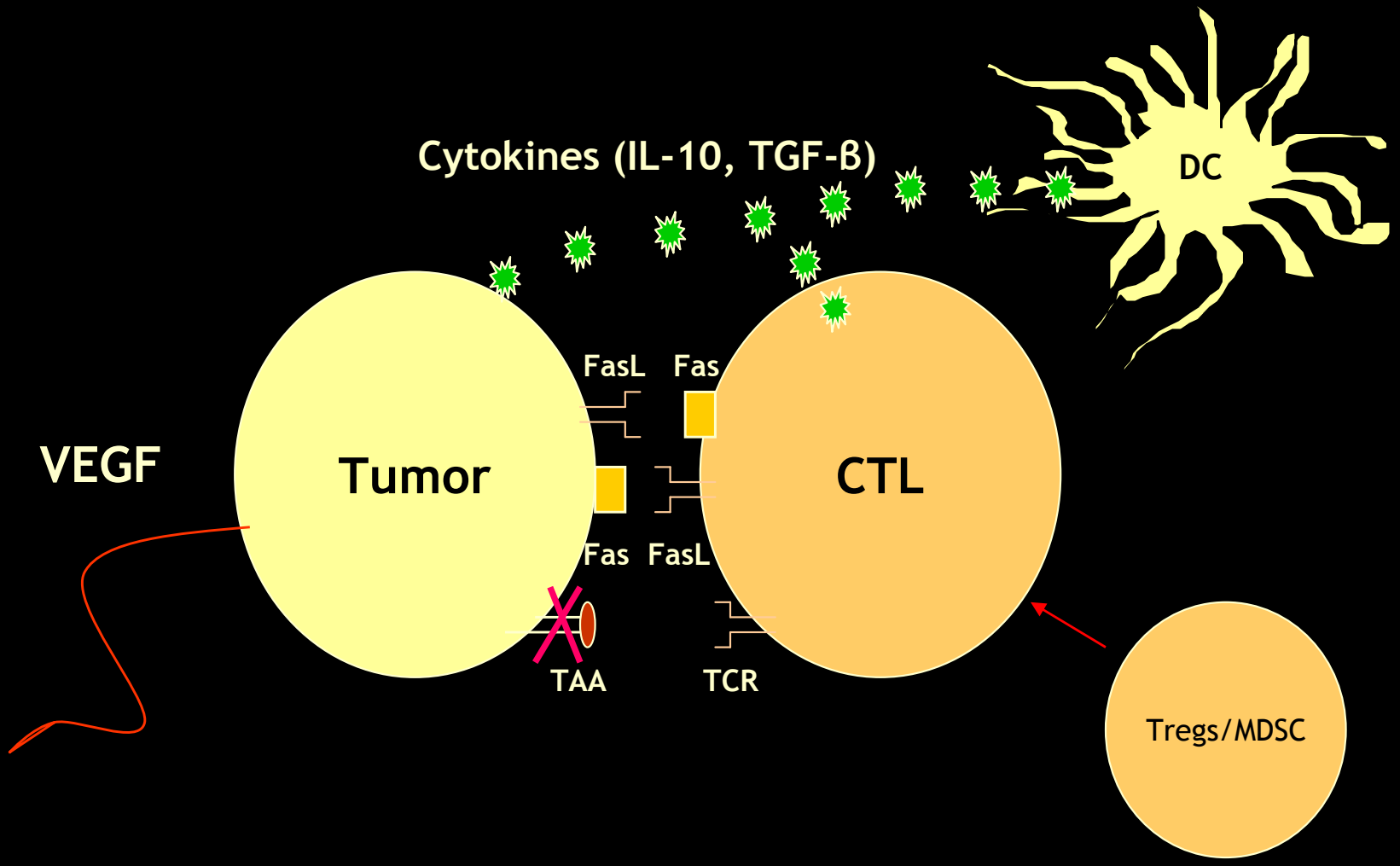
Vaccines: The Challenges



Summary

- Significant advances in the basic science of tumor immunology
- Some clinical trials report sustained responses and survival advantage in patients with advanced cancer

Future Directions

- Patients who have failed conventional cancer treatment $\rightarrow$ Patients who have completed conventional treatment
- HLA-restricted $\rightarrow$ HLA-unrestricted
- Preventive vaccines
- CMT: Sx + CT + RT + BT

Thank you