Therapeutic and Preventive Vaccines for Triple-Negative Breast Cancer

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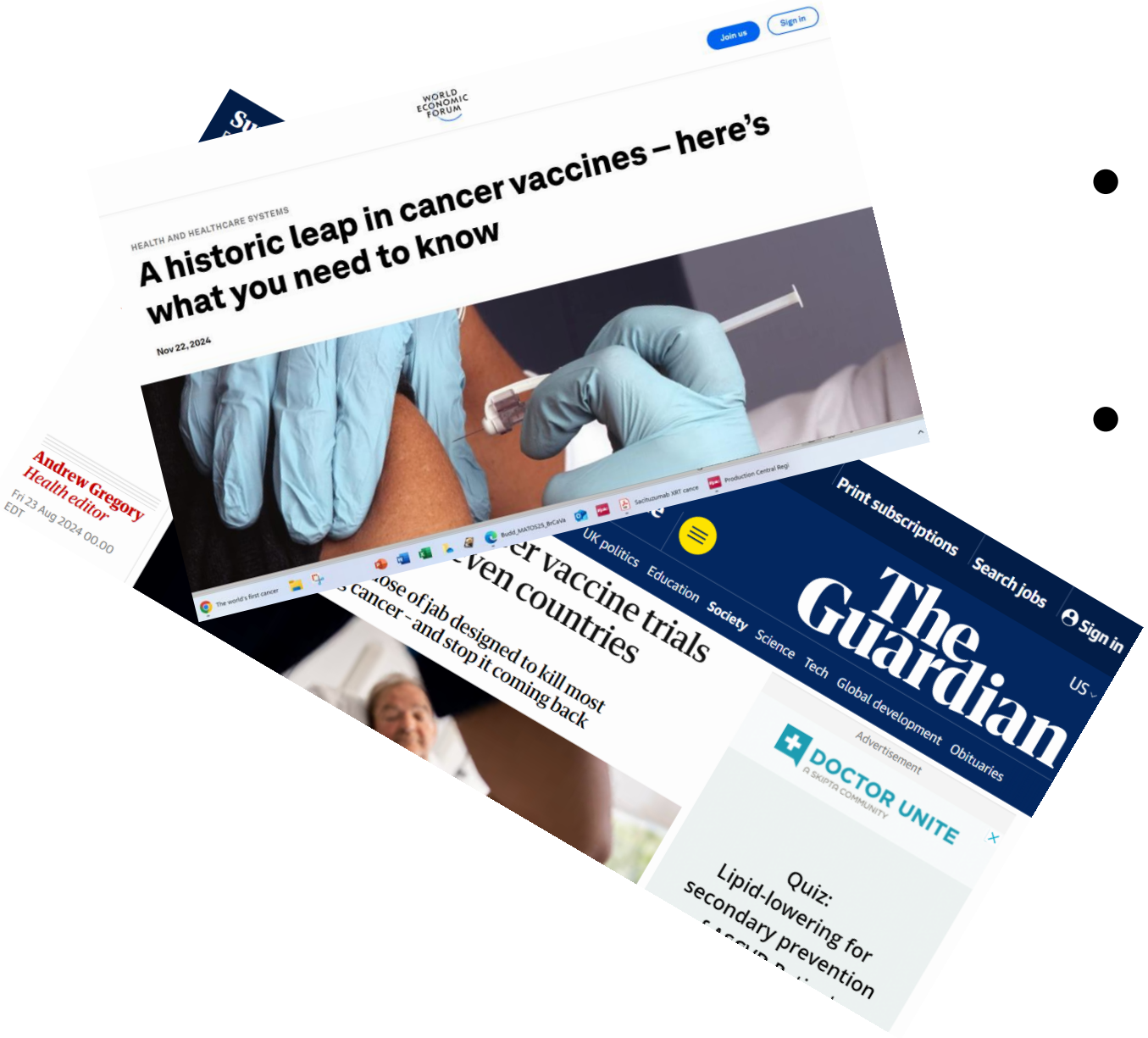
MaTOS

29 March 2025

Cancer Vaccines: Why Now?



- Cancer vaccines are not a new idea
- Why Now?
  - Activity of Immunotherapy in Early Breast and Other Cancers
  - Technical Advances in Vaccines (e.g.mRNA)

Human papillomavirus vaccine effectiveness by age at vaccination: A systematic review

Mallory K. Ellingson, Hassan Sheikha, Kate Nyhan, Carlos R. Oliveira & Linda M. Niccolai

https://doi.org/10.1080/21645515.2023.2239085

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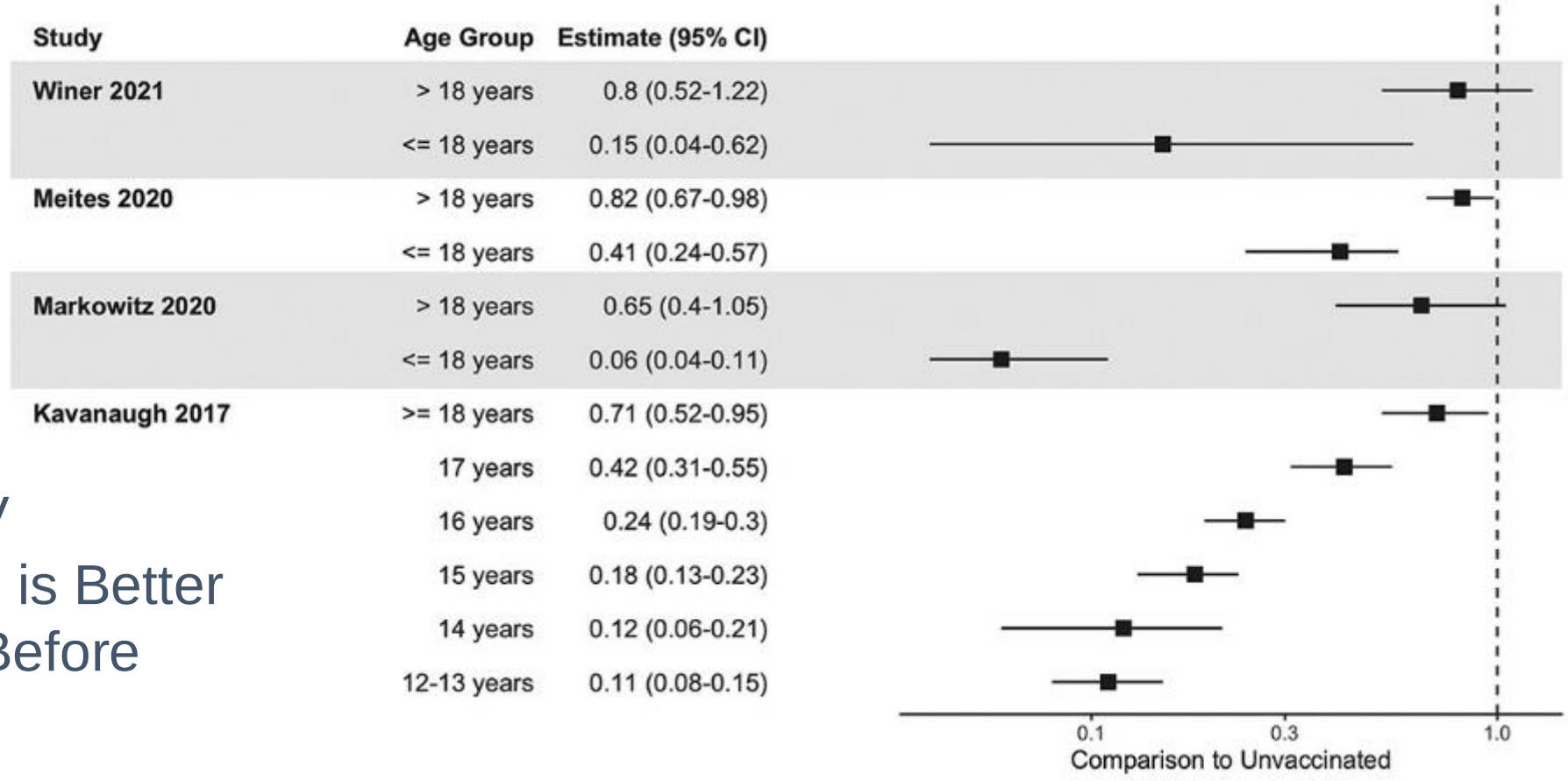
Figure 2 of 5

Figure 2. Effectiveness of HPV vaccination against vaccine-type HPV infection by age at vaccination.



- Earlier HPV Vaccination is Better
- Immunize Before Exposure

Categorization of Antigen Targets

Tumor-Specific Antigens vs Tumor-Associated Antigens

Table 1 TSAs and TAAs classified into four groups with examples

From: Cancer vaccines: the next immunotherapy frontier

TSA		TAA	
Viral	**Mutated self**	**Development specific**	**Tissue specific**
LMP1, LMP2	EGFRvIII	WT1	HER2/Neu
HPV E6/E7	$KRAS^{G12C}$	MAGE-A3	MUC1
	$BRAF^{V600E}$	NY-ESO-1	gp100

$BRAF^{V600E}$, v-raf murine sarcoma viral oncogene homolog B1 V600E mutation; MUC1, mucin 1.

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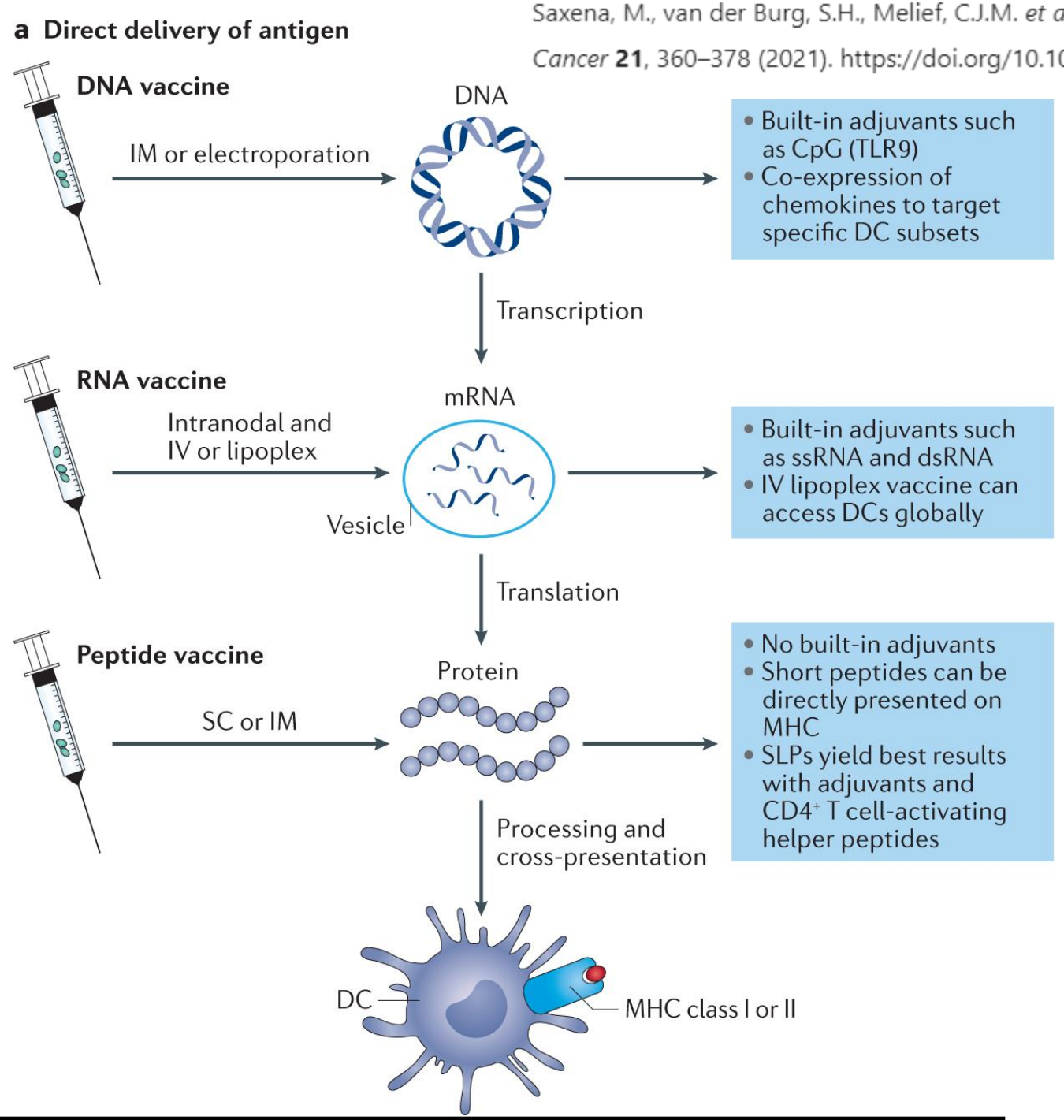
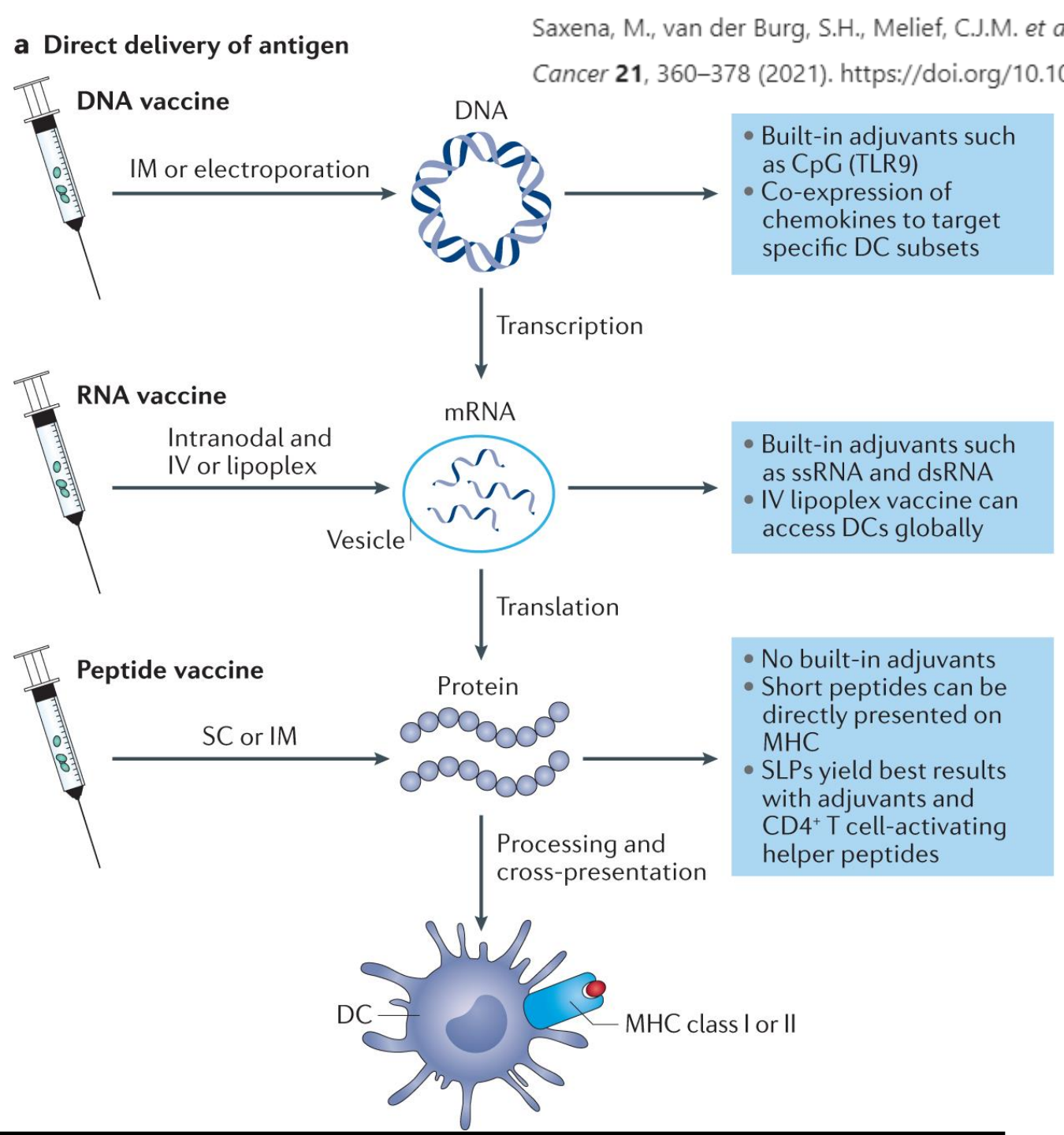
Nature Cancer (*Nat Cancer*) | ISSN 2662-1347 (online)

Types of Cancer Vaccines

Saxena, M., van der Burg, S.H., Melief, C.J.M. *et al.* Therapeutic cancer vaccines. *Nat Rev Cancer* **21**, 360–378 (2021). https://doi.org/10.1038/s41568-021-00346-0





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Types of Cancer Vaccines

→ -Anti-HER2 vaccines
-Polyvalent vaccine

From: **Safety and Outcomes of a Plasmid DNA Vaccine Encoding the ERBB2 Intracellular Domain in Patients With Advanced-Stage ERBB2-Positive Breast Cancer: A Phase 1 Nonrandomized Clinical Trial**

JAMA Oncol. 2023;9(1):71-78. doi:10.1001/jamaoncol.2022.5143

Table Title:

Table 1. Baseline Patient Characteristics

Characteristic	No. (%) 10 µg	100 µg	500 µg
No.	22	22	22
Age, median (range), y	50 (38-68)	51 (34-72)	53 (42-77)
Stage and status			
III	15 (68)	15 (68)	12 (55)
IV			
NED	3 (14)	4 (18)	7 (32)
SBO	4 (18)	3 (14)	3 (14)
ER/PR status			
ER^+ and/or PR^+	14 (64)	15 (68)	8 (36)
ER^-/PR^-	8 (36)	7 (32)	14 (64)
Trastuzumab therapy			
Prior			
No	4 (18)	2 (9)	2 (9)
Yes	18 (32)	20 (91)	20 (91)
Concurrent			
No	14 (64)	12 (55)	9 (41)
Yes	8 (36)	10 (45)	13 (59)

Abbreviations: ER, estrogen receptor; NED, no evidence of disease; PR, progesterone receptor; SBO, stable bone-only disease.

Baseline Patient CharacteristicsAbbreviations: ER, estrogen receptor; NED, no evidence of disease; PR, progesterone receptor; SBO, stable bone-only disease.

JAMA Network™

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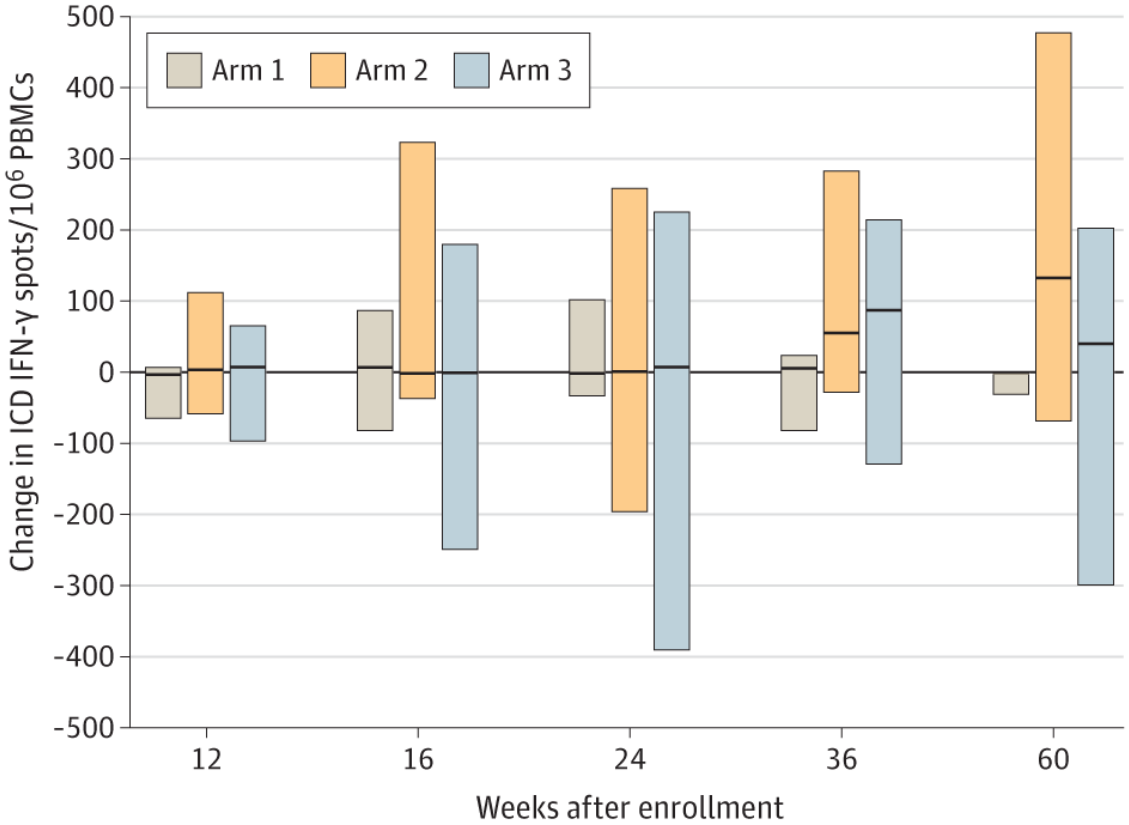

Figure Legend:

Association of Magnitude and Duration of Vaccine-Associated ERBB2 ICD T-Cell Immunity With DoseChange in magnitude of ERBB2 intracellular domain (ICD) interferon (IFN)-γ responses (y-axis) from baseline over time from enrollment (x-axis) for arms 1, 2, and 3 (10, 100, and 500 µg, respectively). Box plots represent the mean and IQR (25th and 75th percentiles). The number of postenrollment ERBB2 ICD response measures collected per patient ranged from 1 to 5, with a median of 5 measurements; 9 patients had 1 to 3, 11 had 4, and 41 had 5 measurements each. Five patients from arm 1 were excluded from this analysis due to insufficient samples. PBMCs indicates peripheral blood mononuclear cells.

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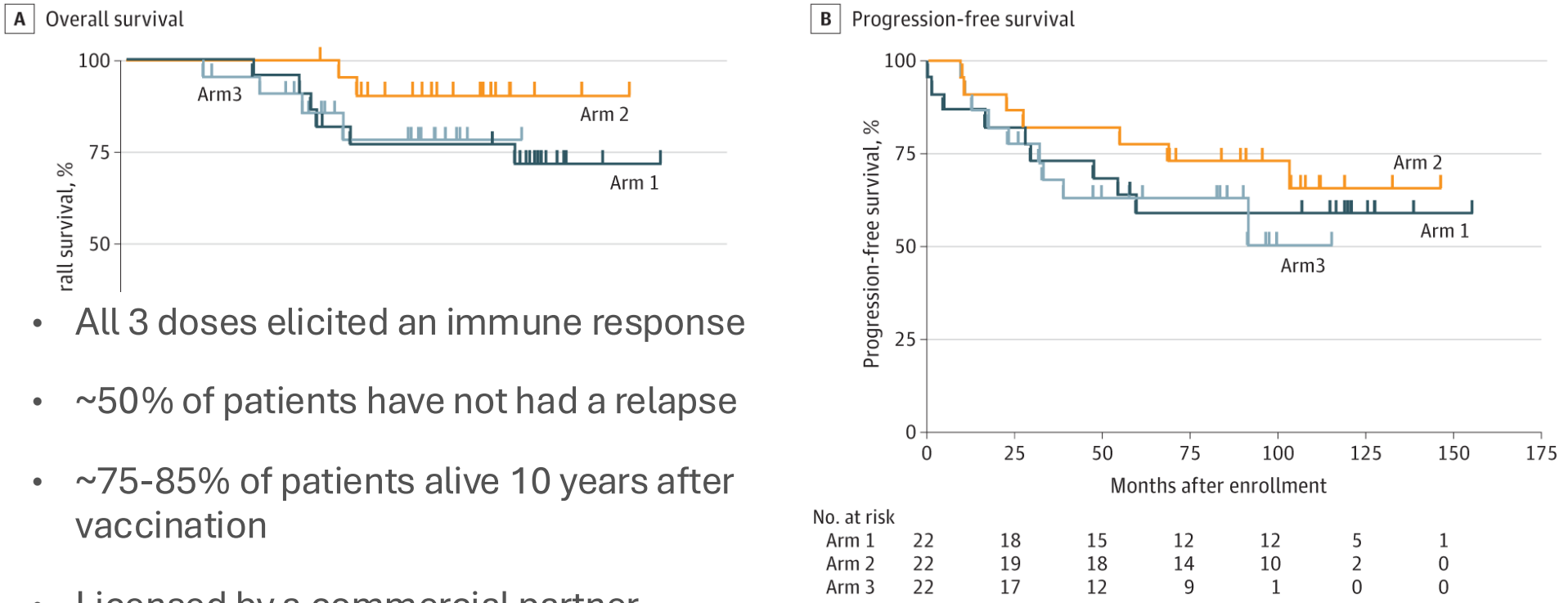


- All 3 doses elicited an immune response
- ~50% of patients have not had a relapse
- ~75-85% of patients alive 10 years after vaccination
- Licensed by a commercial partner
- Basket trial for different types of HER2+ cancers (uterine, gastric, lung, etc)

obability of overall survival (A) and progression-free survival (B) by
10, 100, and 500 µg, respectively). Tick marks indicate censored

NIH STUDY ID: NCT05455658 | FRED HUTCH STUDY ID: RG1122380

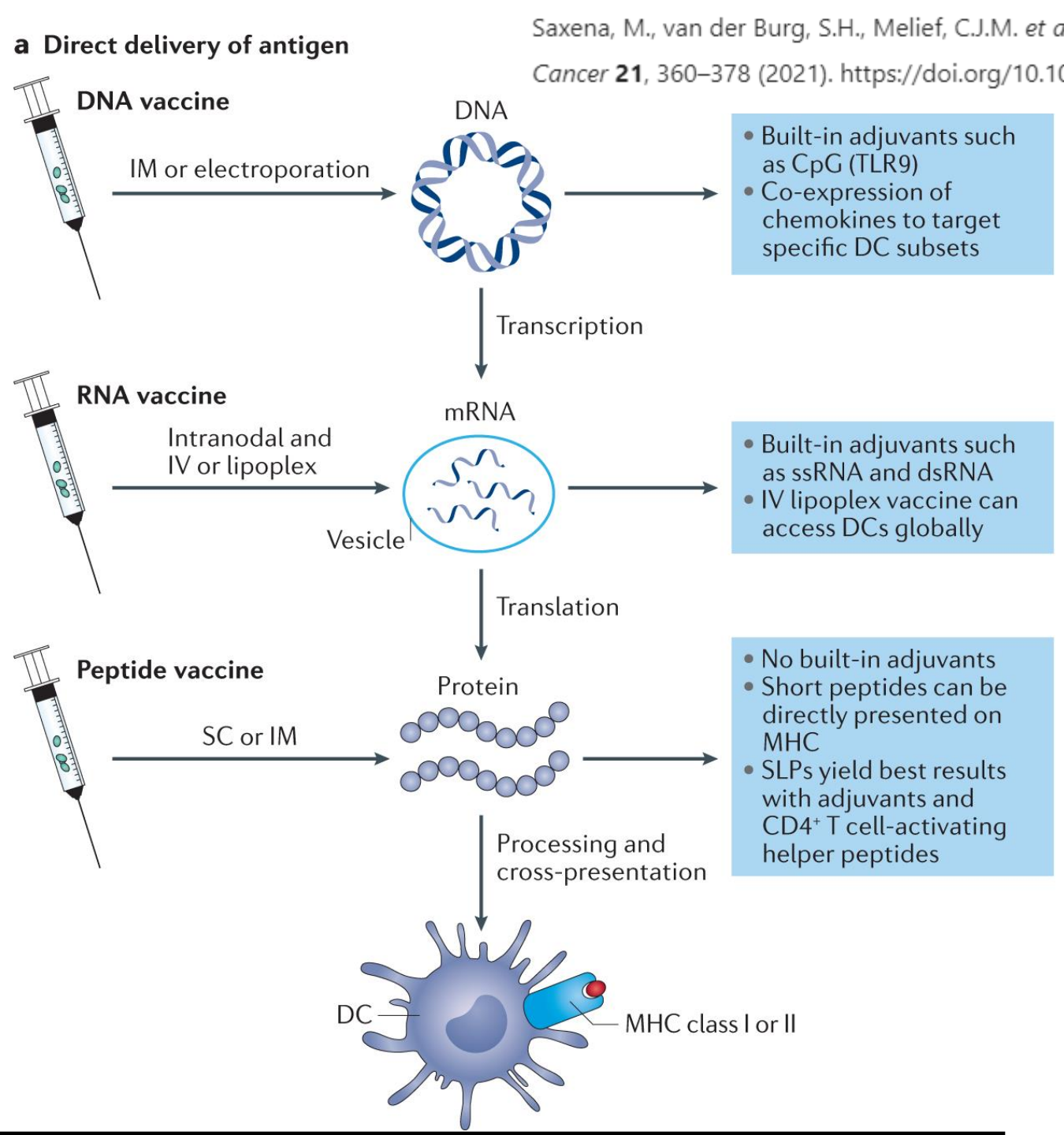
STEMVAC in Patients With Early Stage Triple Negative Breast Cancer

Complete Title: A Phase II Trial of the Immunogenicity of a DNA Plasmid Based Vaccine (STEMVAC) Encoding Th1 Selective Epitopes from Five Antigens Associated with Breast Cancer Stem Cells (MDM2, YB1, SOX2, CDH3, CD105) in Patients with Triple Negative Breast Cancer

Trial Phase: II

Investigator: Nora Disis

This phase II trial studies the effect of DNA plasmid based vaccine (STEMVAC) in treating patients with patients with stage IB-III triple negative breast cancer. STEMVAC may wake up the immune system in patients who have had a diagnosis of triple negative breast cancer and have been treated. STEMVAC targets proteins that are expressed on breast cancer cells and works by boosting the immune system to recognize and destroy the invader cancer cell proteins that are causing the disease. The purpose of this trial is to test the immune system`s response to STEMVAC.



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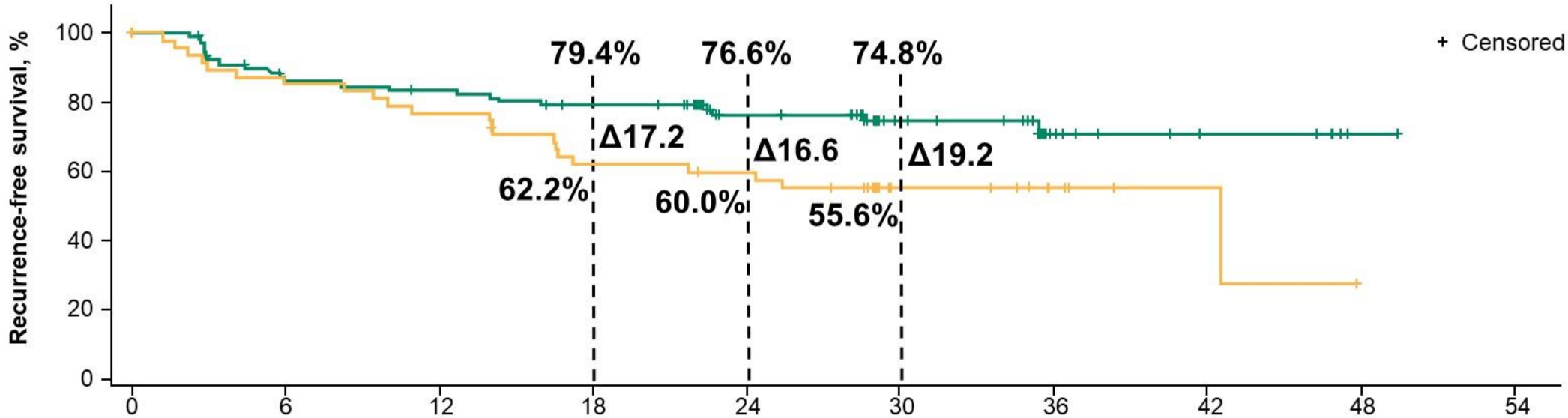
Types of Cancer Vaccines

→ -Anti-HER2 vaccines
-Polyvalent Vaccine

→ -Moderna - Melanoma
-BioNTech - Pancreatic Cancer
-Lung Cancer

Sustained improvement of RFS primary efficacy endpoint



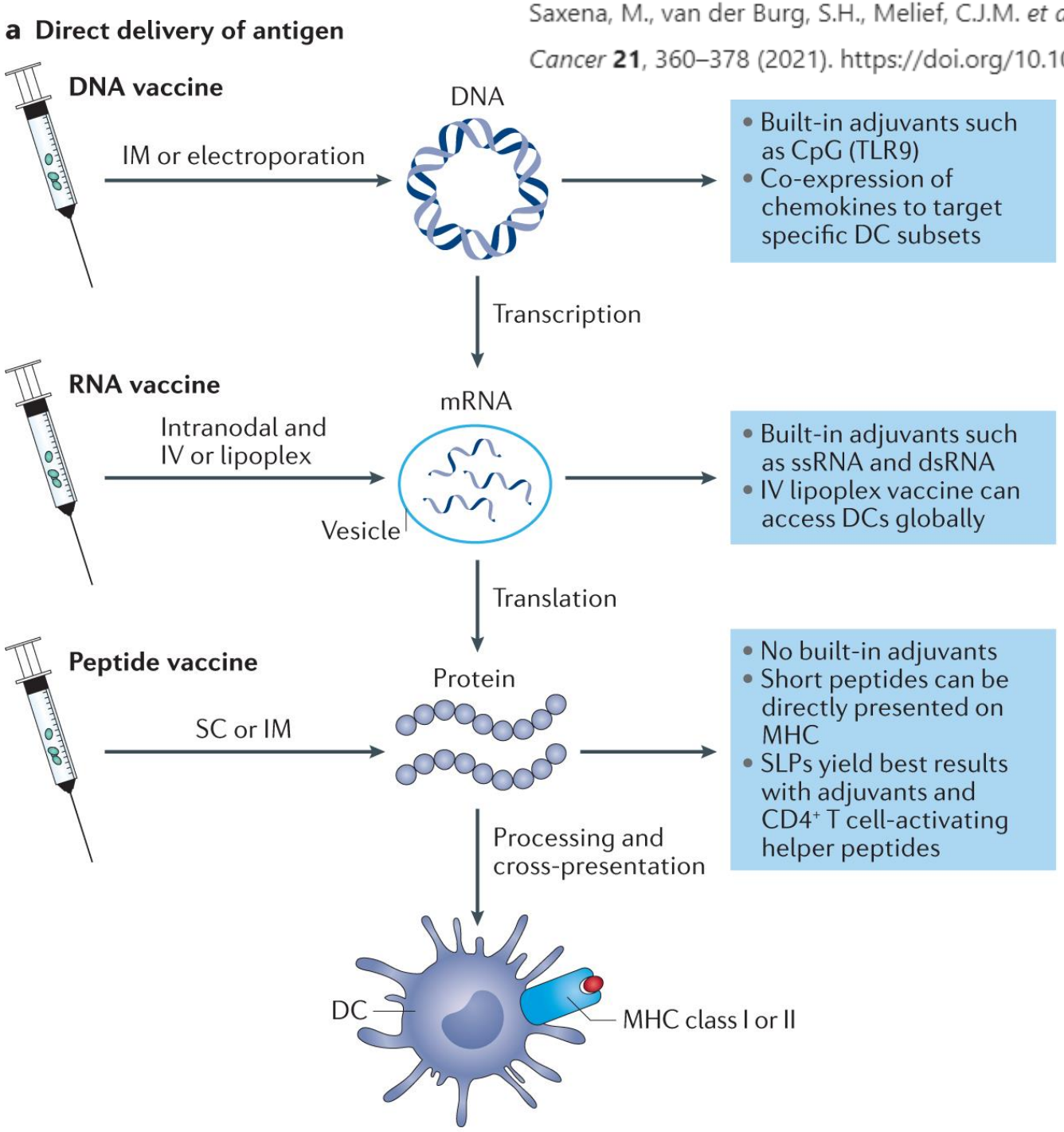
Patients at risk										
mRNA-4157 (V940) + pembrolizumab	107	87	83	77	52	29	12	6	1	0
Pembrolizumab	50	41	37	29	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	23.4 (25/107)	0.510 (0.288–0.906) *P* = 0.019[b]
pembrolizumab	42.51 (16.59–NE)	44.0 (22/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) + pembrolizumab versus pembrolizumab were estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization; [b]Formal hypothesis testing of RFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut; it's nominal and not for formal hypothesis testing. NE, not estimable.

Table 1 | Selected personalized neoantigen vaccines in clinical development

Vaccine	Platform	Number of neoantigens	Phase	Lead indication
mRNA-4157	Modified mRNA	Up to 34	II	Adjuvant melanoma
Autogene cevumeran	Unmodified mRNA	Up to 20	II	Metastatic melanoma, adjuvant colorectal cancer, adjuvant pancreatic cancer
GRANITE	Chimpanzee adenovirus prime, self-amplifying RNA boost	Up to 20	II	Untreated metastatic colorectal cancer
EVX-01	Peptide	Up to 10	II	Metastatic melanoma
EVX-02	DNA	Up to 13	I	Adjuvant melanoma
SW1115C3	Modified mRNA	10–30	I	Advanced solid tumours
GNOS-PV02	DNA	Up to 40	I	Metastatic liver cancer
VB10.NEO	DNA	Up to 40	I	Advanced solid tumours
NOUS-PEV	Gorilla adenovirus prime, modified vaccinia Ankara boost	Up to 60	I	Metastatic non-small-cell lung cancer and melanoma
TG4050	Modified vaccinia Ankara	Up to 30	I	Adjuvant head and neck cancer and ovarian cancer
YE-NEO-001	Yeast	Up to 24	I	Adjuvant solid tumours
iNeo-Vac-P01	Peptide	5–20	I	Adjuvant pancreatic cancer and oesophageal cancer



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Types of Cancer Vaccines

-Anti-HER2 vaccines
-STEMVac

-Moderna - Melanoma
-BioNTech -Pancreatic Cancer
-Lung Cancer

-MUC1 Vaccines
-Cleveland Clinic Vaccine "Retired Protein Hypothesis"

Vaccination with MUC-1-Targeting Tecemotide Improves Survival of Patients Receiving Neo-Adjuvant Chemotherapy for Early Breast Cancer: Results from the Prospective Randomized ABCSG 34 Trial by Christian F. Singer

- MUC1 expressed in >90% BC and Tecemotide (Liposomal Peptide) vaccine induces cellular immune response to cancer cells expressing MUC1
- 400 HER2-negative early BC with neoadjuvant SOC chemotherapy or endocrine therapy
- Negative primary endpoint of difference in RCB 0/1 rates/pCR
- However, 7-year follow-up data

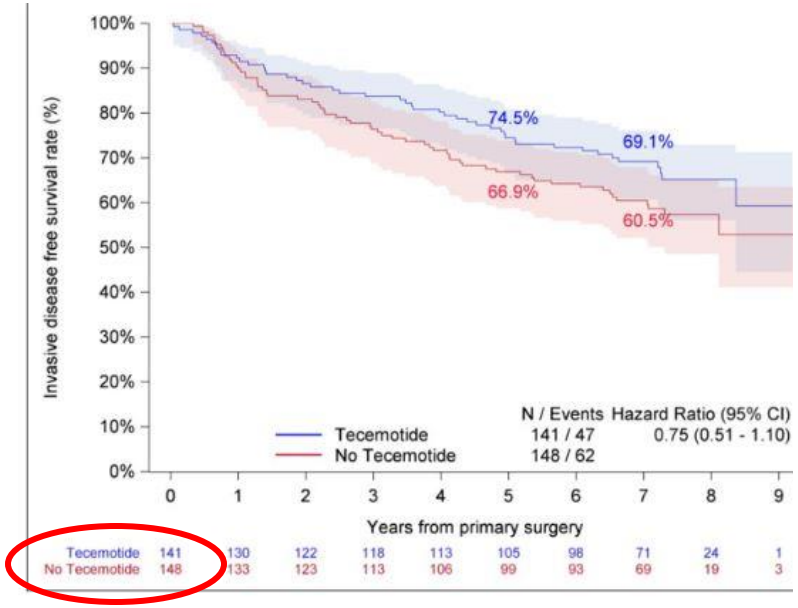


Figure 2 Invasive disease-free survival

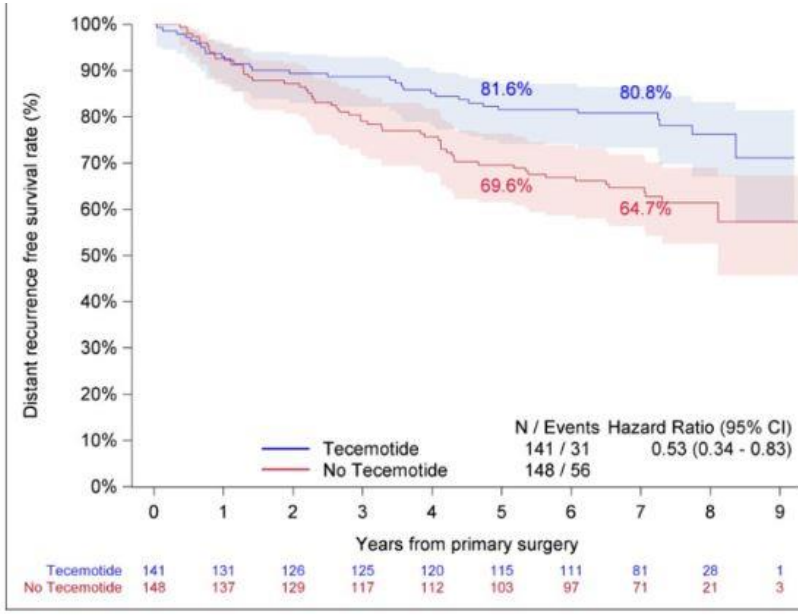


Figure 3 Distant recurrence-free survival

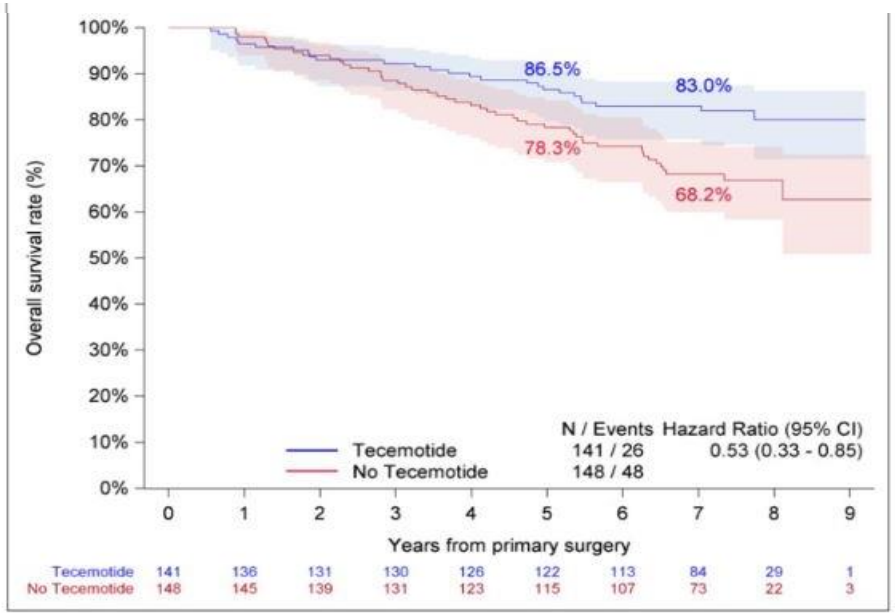
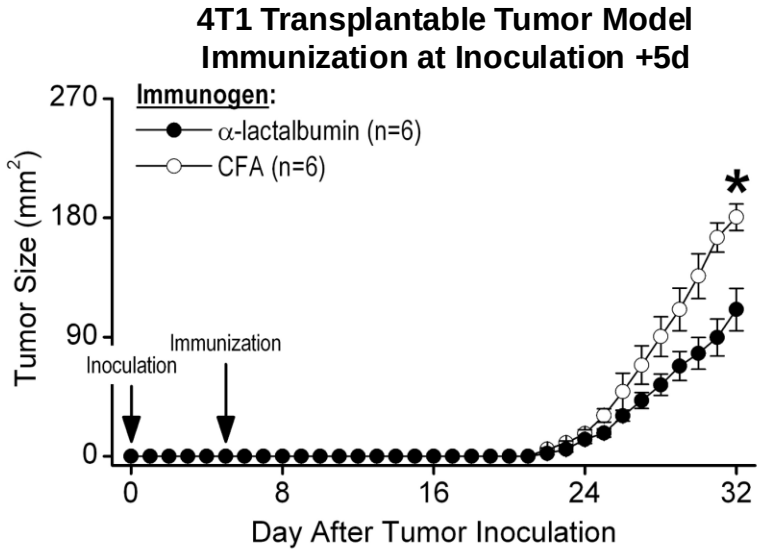


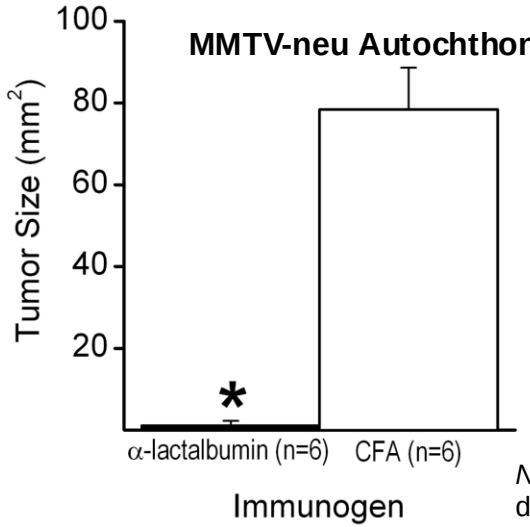
Figure 4 Overall survival

The “Retired Protein” Hypothesis

Hypothesized by the late Vincent Tuohy, PhD

- With age, we “retire” proteins no longer required
- Many of these retired proteins are organ-specific and associated with reproduction
- These organs have high incidence of cancer
- These conditions provide a strategy for autoimmune-based cancer vaccines
- α-Lactalbumin Vaccine is 1st Candidate for this approach
  - α-Lactalbumin is a protein in human milk produced only by the mammary gland and only during lactation; after childbearing years there is very little risk of α-lactalbumin expression in healthy women
  - Breast cancer, especially triple negative breast cancer (TNBC), expresses significant levels of α-lactalbumin



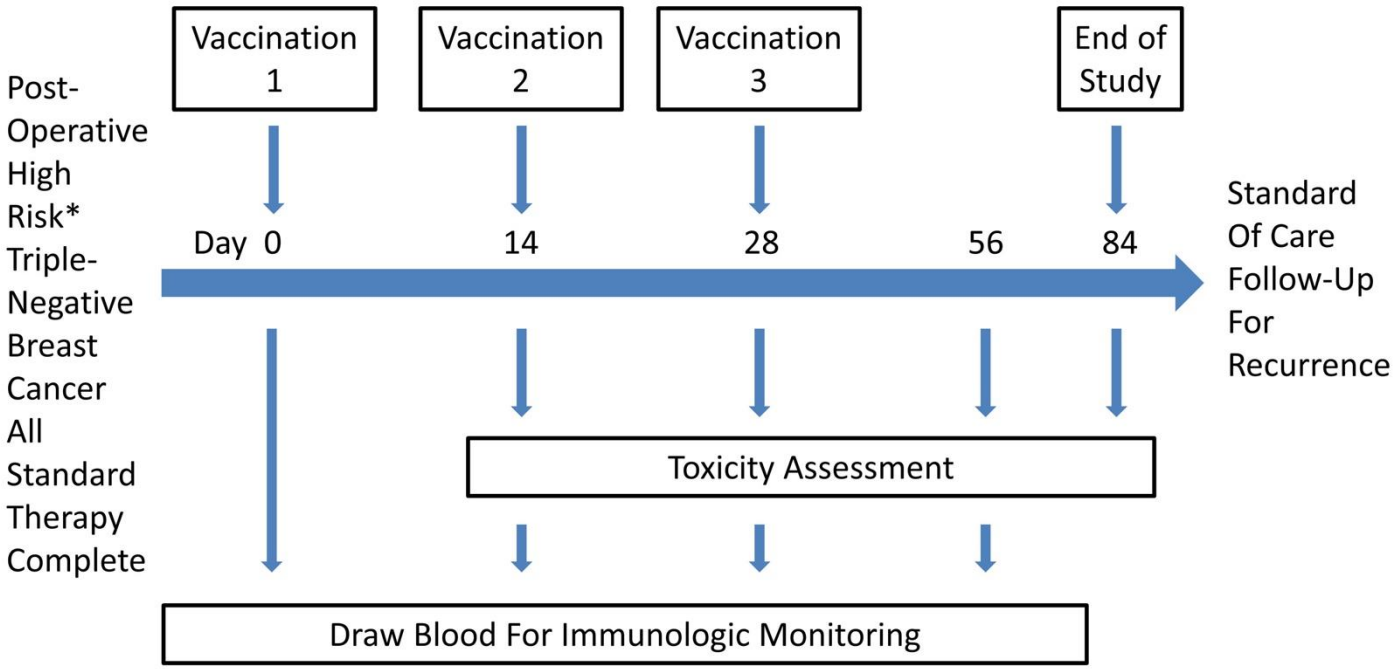


Nature medicine (2010)
doi:10.1038/nm.2161

Phase 1 Clinical Trial

Funded by the Department of Defense
Partnering PI Mechanism
Vincent K. Tuohy, PhD Award # W81XWH-17-1-0592
G. Thomas Budd, MD Award # W81XWH-17-1-0593

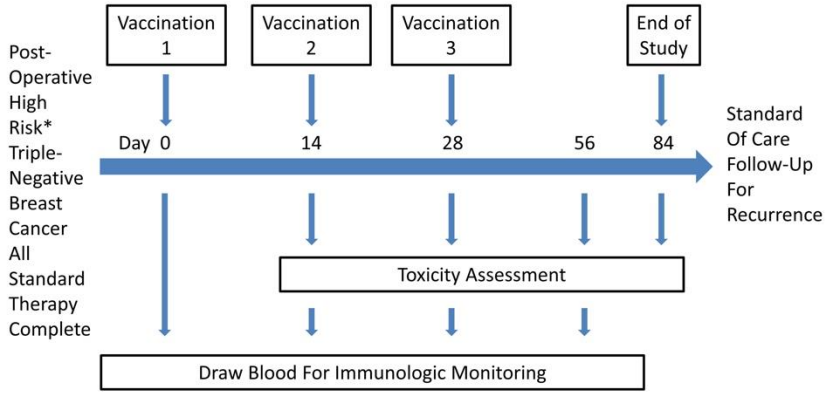
Study Schema — Phase Ia



*Stage IIA-IIIC or residual disease following neo-adjuvant chemotherapy

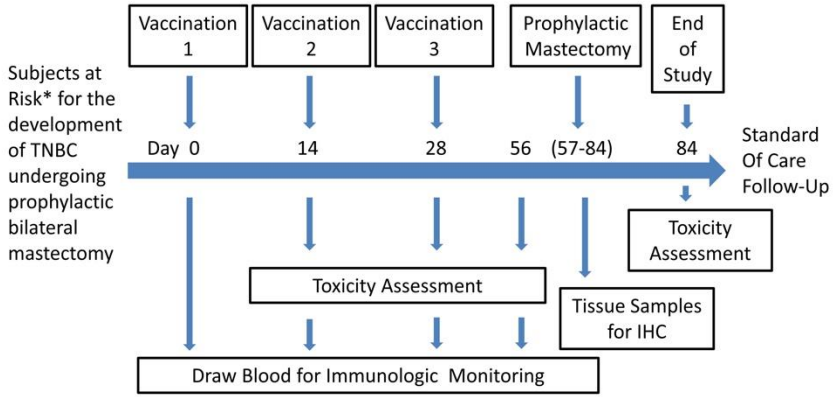
Study Schema — Phase Ic

Pre-Operative Chemo + pembrolizumab



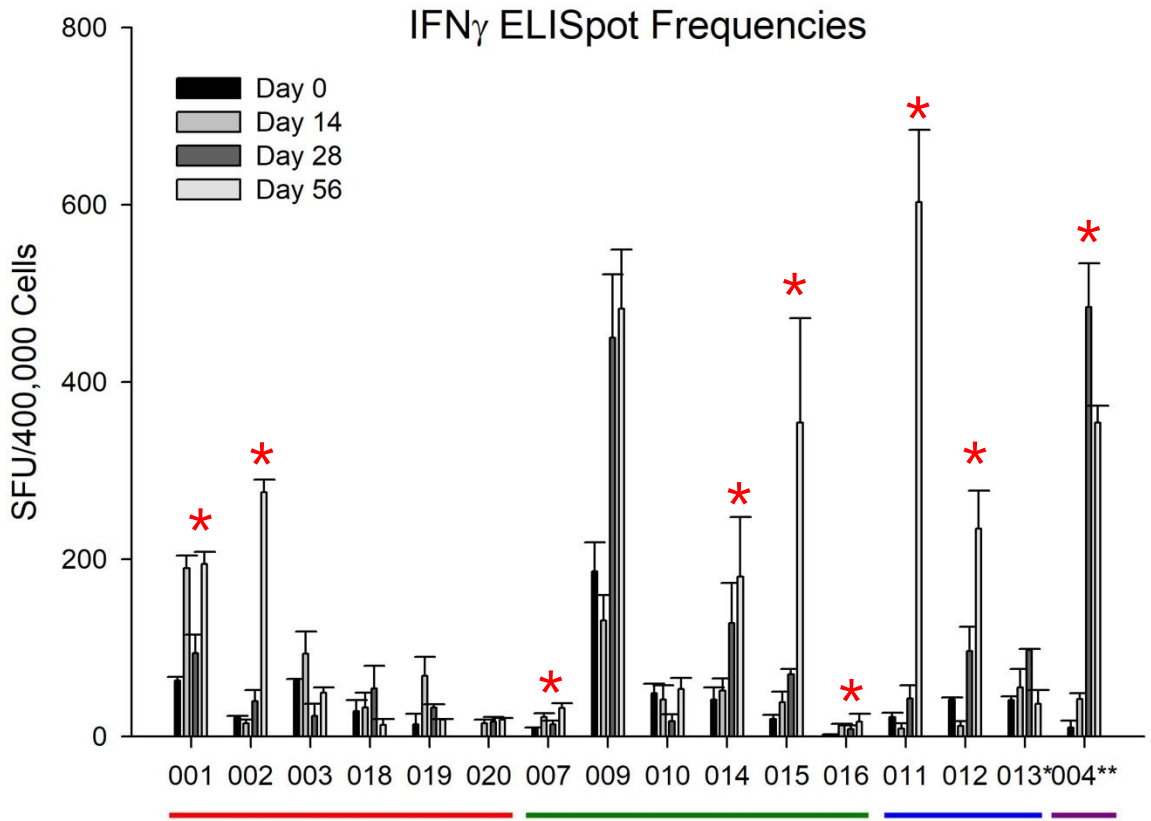
*Stage IIA-IIIC or residual disease following neo-adjuvant chemotherapy

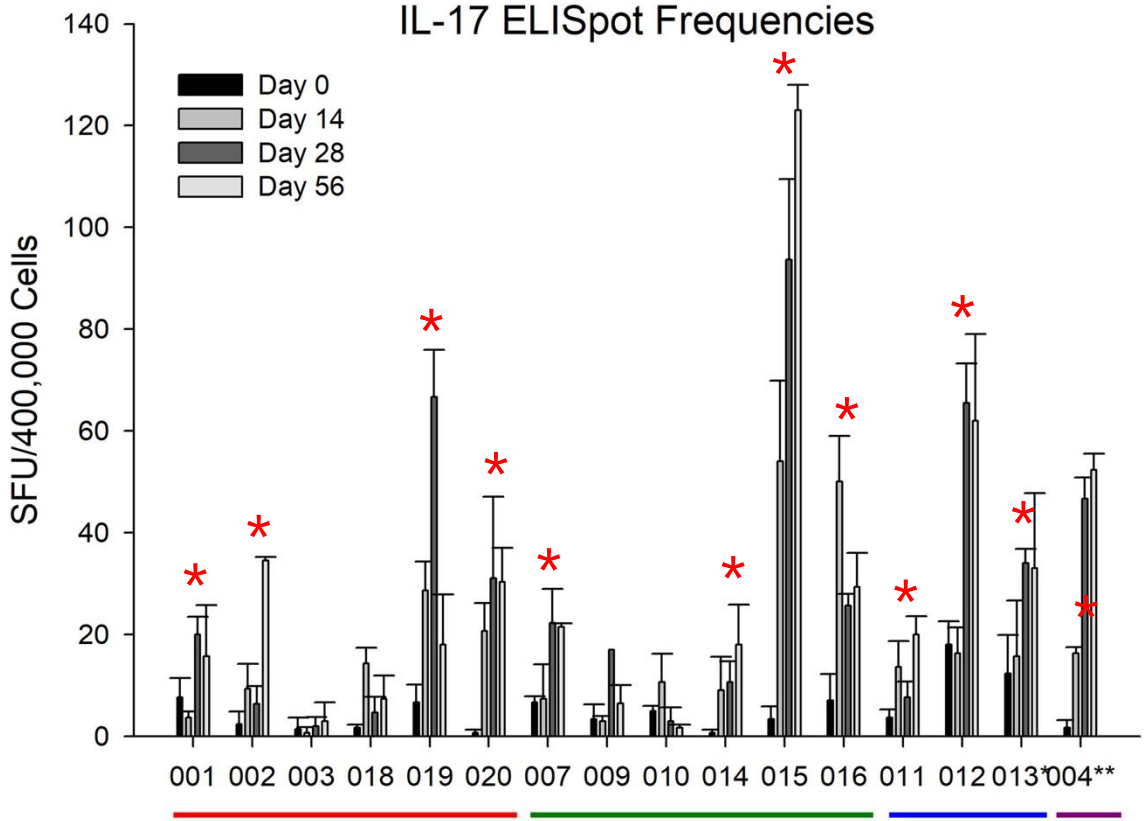
Study Schema — Phase Ib



*Having ≥1 deleterious mutation (BRCA1, PALB2)

Immunologic Assessment: ELISpot Assays





Dose Level	DL1	DL2	DL3	DL2 (old)
Zymosan	10 µg	10 µg	10 µg	100 µg
α-Lactalbumin	10 µg	100 µg	500 µg	100 µg

Dose Level	DL1	DL2	DL3	DL2 (old)
Zymosan	10 µg	10 µg	10 µg	100 µg
α-Lactalbumin	10 µg	100 µg	500 µg	100 µg

*Immunologic Response per Protocol Criteria

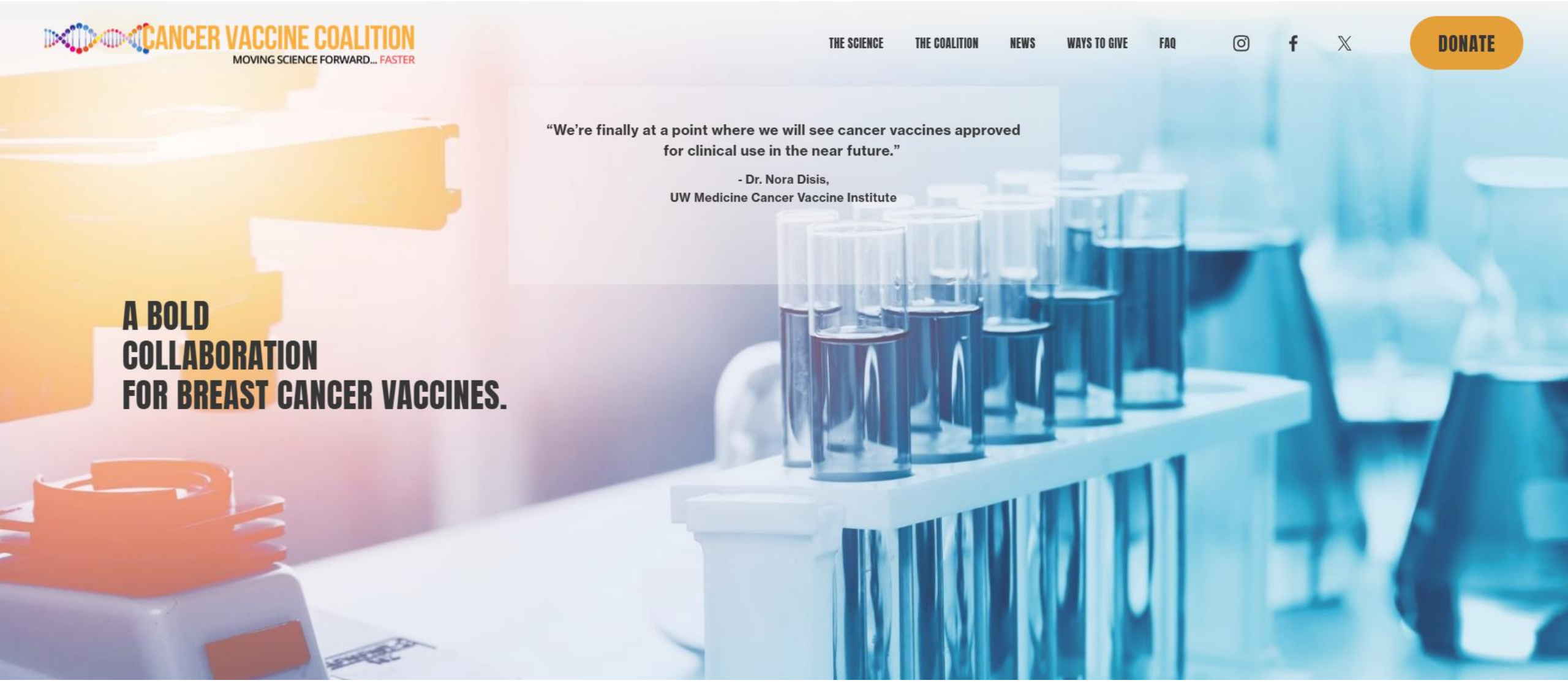
*3rd dose reduced in 1 subject after Grade 3 event in a different patient at that dose level
**3rd dose held

Future Plans

- Determine HLA type for all Phase I subjects
- Epitope mapping of alpha-lactalbumin
- Assess α-lactalbumin expression in Phase Ia/c and recurrence cases
- Long-term immunity testing of all Phase I subjects
- Identify and validate additional vaccine targets for breast, ovarian, prostate, lung, and colon cancers

- Phase II Neoadjuvant setting
- Randomized Phase II/III Post Neo-Adjuvant setting
  - For patients with RCB II+ following chemo-immunotherapy for TNBC
- High-Risk DCIS
- Prevention Trial
  - High risk for TNBC: BRCA, ?Polygenic Risk Score?
  - ?Randomized to vaccine vs not?
  - ?With ctDNA (multi-cancer) early cancer detection test?

CANCER VACCINE COALITION
MOVING SCIENCE FORWARD... FASTER



"We're finally at a point where we will see cancer vaccines approved for clinical use in the near future."

- Dr. Nora Disis,
UW Medicine Cancer Vaccine Institute

A BOLD COLLABORATION FOR BREAST CANCER VACCINES.