Personalized Vaccines in the Adjuvant Setting

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Disclosures

- Advisor Boards: Merck, Bristol Myers Squibb, Novartis, Instil Bio, Delcath Systems, Regeneron
- Consultant: Clario
- I will be discussing non-FDA approved indications during my presentation.

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Pre-Test Question:

Personalized, mRNA-based neoantigen vaccines:

A. Have now been approved for melanoma, but not yet pancreatic cancer
B. Are easily mass produced, similar to COVID vaccines
C. Are well tolerated, but have not demonstrated substantial evidence of clinical benefit beyond checkpoint inhibitors
D. Have been associated with meaningful clinical benefit (HR 0.56) in patients with resected metastatic melanoma

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Outline

- Personalized Cancer Vaccine History and Conceptual Framework
- Modern development
- mRNA vaccines in melanoma and pancreatic cancer

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What is a vaccine? What is "personalized"?

- NCI: "A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms."
- Antigen + Immune Adjuvant

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Vaccine antigens:

- Peptide
- Protein
- Ganglioside
- mRNA/DNA
- Lysate
- Whole cell

Antigen Type	Pros	Cons
peptide	Easy preparation Easy storage Simple monitoring of immune response	Narrow antigen spectrum HLA restriction Challenges in cross presentation
protein	No HLA restriction Relatively simple preparation	Still fairly narrow antigen spectrum Challenges in cross presentation
ganglioside	Immune monitoring (antibody response) is relatively simple	Relies largely on humeral response for effect
DNA/RNA	Relatively simple preparation No HLA restriction	Delivery has been challenging
lysate	Broad antigen spectrum	Preparation/storage more difficult No antigen selection
whole cell	Most diverse antigen spectrum	Preparation/storage most difficult No antigen selection

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Vaccine history:

Author	year	n	Arms	HR	p-value	Notes:
Kirkwood	2001	880	HD-IFN vs GM-2KLH/QS-21	RFS: 1.47 OS: 1.52	0.0015 0.009	Favor IFN
Hersey	2002	700	VMCL vs. Obs	RFS: 0.86 OS: 0.81	0.17 0.068	
Sondak	2002	698	Melacine vs. Observation	RFS: 0.84	0.17	HLA-A2$^+$, C3$^+$ significant
Schadendorf	2006	108	DC+ peptides vs. DTIC	OS	0.48	Stage IV
Morton	2007	1160	Canvaxin vs. Placebo	OS: 1.26	0.040	Stage III (trend favor placebo)
Morton	2007	496	Canvaxin vs. Placebo	OS: 1.29	0.086	Stage IV
Testori	2008	322	hsp96 vaccine vs. BAC		0.316	Stage IV
Hodi	2010	676	ipilimumab vs. peptide vs. both	OS: 1.04	0.76	Favor Ipilimumab
Lawson	2010	398	GM-CSF +/- peptides	OS: 0.94 DFS: 0.93	0.670 0.709	
Schwartzentruber	2011	185	IL-2 +/- peptides	RR: 20% v. 10% PFS:2.2 v. 1.6 mo OS: 17.8 v. 11.1 mo	0.03 0.008 0.06	All favor vaccine
Eggermont	2013	1314	GM2-KLH/QS-21 vs Observation	RFS: 1.03 OS: 1.66	0.81 0.25	
Suriano	2013	250	VMO vs. Vaccinia	OS: 7.71 v. 7.95 yr	0.70	
Unpublished	2013	?	MAGE-A3 vs. placebo	OS	NS	

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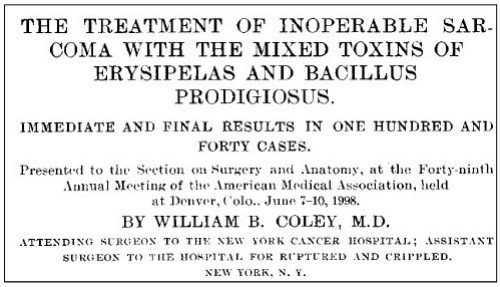
History: "Coley's Toxins"

William Bradford Coley

- **Late 19th Century, NY Surgeon**
- **Unresectable sarcomas regress after superinfection with erysipelas**
- **Injections of mixed toxins of erysipelas and bacillus prodigiousus**
- **Dose to 102-103º fever**



THE TREATMENT OF INOPERABLE SARCOMA WITH THE MIXED TOXINS OF ERYSIPELAS AND BACILLUS PRODIGIOSUS.

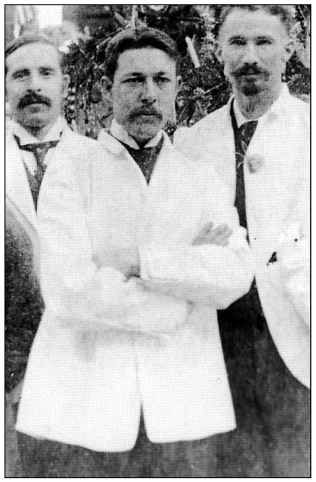
IMMEDIATE AND FINAL RESULTS IN ONE HUNDRED AND FORTY CASES.

Presented to the Section on Surgery and Anatomy, at the Forty-ninth Annual Meeting of the American Medical Association, held at Denver, Colo., June 7-10, 1898.

BY WILLIAM B. COLEY, M.D.

ATTENDING SURGEON TO THE NEW YORK CANCER HOSPITAL; ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED.

NEW YORK, N. Y.



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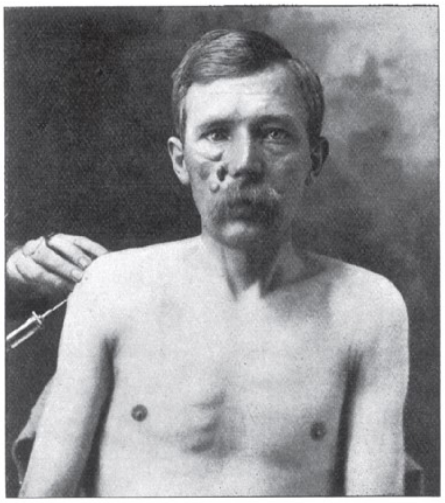
Example
"Round cell sarcoma" 1899

After 63 injections with Coley's toxins



After additional injections

Alive and well in 1910.

Balkwill Nat Rev Cancer 2010.

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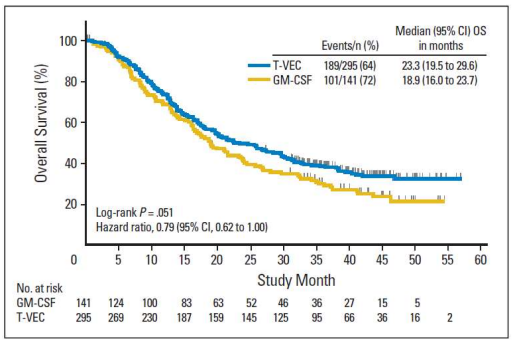
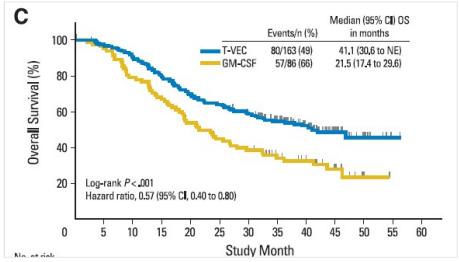
Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

Robert H.I. Andtbacka, Howard L. Kaufman, Frances Collichio, Thomas Amatruda, Neil Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Sanjiv S. Agarwala, Mohammed Milhem, Lee Cranmer, Brendan Curti, Karl Lewis, Merrick Ross, Troy Guthrie, Gerald P. Linette, Gregory A. Daniels, Kevin Harrington, Mark R. Middleton, Wilson H. Miller Jr, Jonathan S. Zager, Yining Ye, Bin Yao, Ai Li, Susan Doleman, Ari VanderWalde, Jennifer Gansert, and Robert S. Coffin

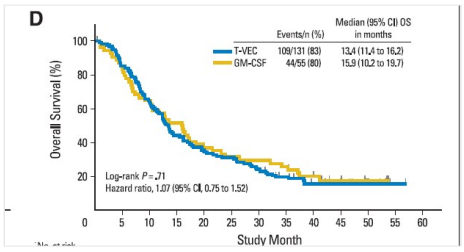
JOURNAL OF CLINICAL ONCOLOGY SEPTEMBER 1 2015



Stage IIIB/C, Stage IV M1a



Stage IV M1b/c



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T-VEC: Neoadjuvant Trial

Resectable Stage IIIB–IVM1a[6] Melanoma
- Injectable and measurable
- LDH ≤ 1.5 x ULN for IIIB/C and ≤ 1 x ULN for IVM1a
- ECOG PS 0 or 1
- Prior treatment completed ≥ 3 months prior

Stratification:
- Disease stage
- Planned adjuvant therapy

N = 150

R

1 : 1

Arm 1
T-VEC Intralesional
≤ 4 mL x 10^6 PFU/mL;
then after 3 weeks, ≤ 4 mL x 10^8 PFU/mL Q2W

n = 75

Surgical Resection

Follow-up ~5 Years

Week 1 | Week 6 | Week 13 | Week 18

Arm 2
Surgical Resection

Follow-up ~5 Years

n = 75

Primary Endpoint:	RFS
Key Secondary Endpoints:	RFS,* overall survival (OS),* overall tumor response, pathological complete response (pCR; in Arm 1), rates of histopathological tumor-free (R0) surgical resection, local RFS, regional RFS, distant metastases-free survival, safety
Exploratory Endpoints:	Analyses of tumor tissue biomarkers and correlations with clinical outcomes for T-VEC

5. Dummer R, et al. Presented at: ASCO 2019; Chicago, IL. Abstract 9520. **7.** AJCC Cancer Staging Manual, 7th Edition. 2015.

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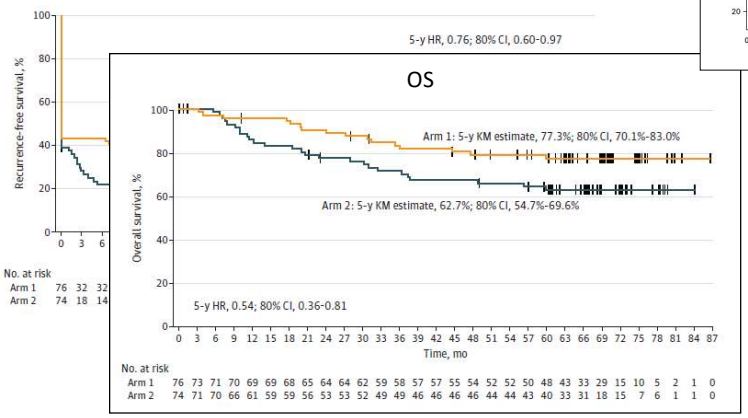
Final 5-Year Follow-Up Results Evaluating Neoadjuvant Talimogene Laherparepvec Plus Surgery in Advanced Melanoma: A Randomized Clinical Trial

Reinhard Dummer, MD David E. Gyorki, MD John R. Hyngstrom, MD Meng Ning, MS Tatiana Lawrence, MD Merrick I. Ross, MD

JAMA Oncology Oct 2023

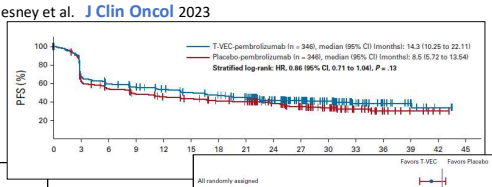
RFS

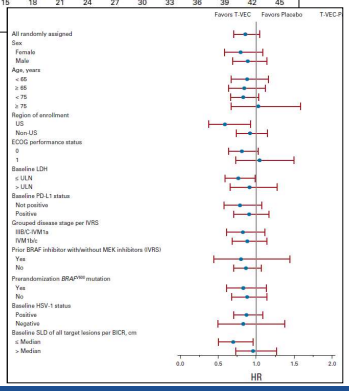


OS

Randomized, Double-Blind, Placebo-Controlled, Global Phase III Trial of Talimogene Laherparepvec Combined With Pembrolizumab for Advanced Melanoma

Chesney et al. J Clin Oncol 2023





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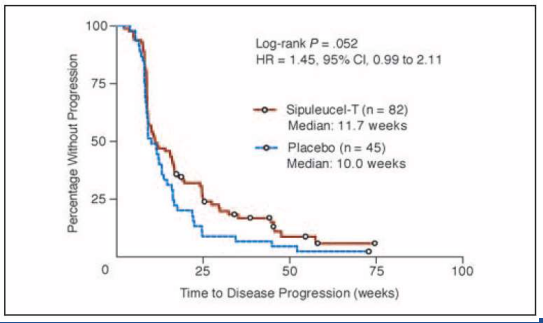
Placebo-Controlled Phase III Trial of Immunologic Therapy with Sipuleucel-T (APC8015) in Patients with Metastatic, Asymptomatic Hormone Refractory Prostate Cancer

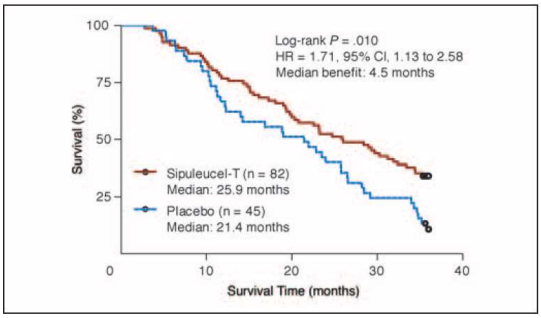
Eric J. Small, Paul F. Schellhammer, Celestia S. Higano, Charles H. Redfern, John J. Nemunaitis, Frank H. Valone, Suleman S. Verjee, Lori A. Jones, and Robert M. Hershberg

JOURNAL OF CLINICAL ONCOLOGY JULY 1 2006

TTP



OS



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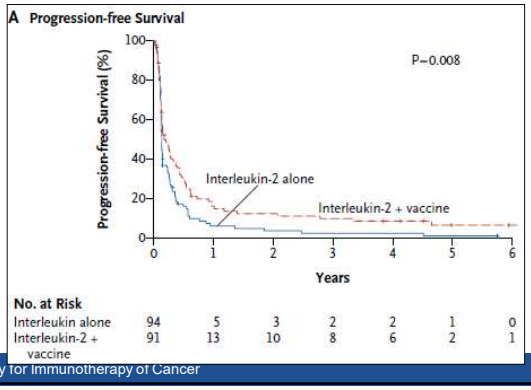
gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

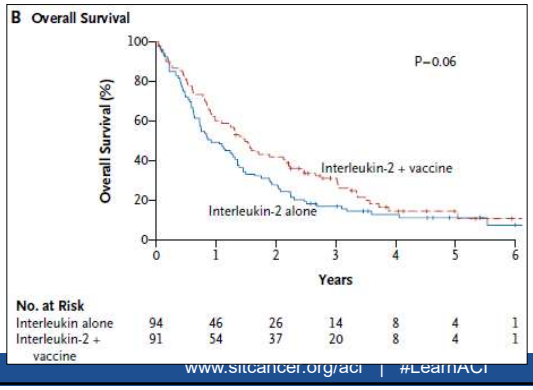
Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D., Jon M. Richards, M.D., Ph.D., Robert M. Conry, M.D., Donald M. Miller, M.D., Ph.D., Jonathan Treisman, M.D., Fawaz Gailani, M.D., Lee Riley, M.D., Ph.D., Kevin Conlon, M.D., Barbara Pockaj, M.D., Kari L. Kendra, M.D., Ph.D., Richard L. White, M.D., Rene Gonzalez, M.D., Timothy M. Kuzel, M.D., Brendan Curti, M.D., Phillip D. Leming, M.D., Eric D. Whitman, M.D., Jai Balkissoon, M.D., Douglas S. Reintgen, M.D., Howard Kaufman, M.D., Francesco M. Marincola, M.D., Maria J. Merino, M.D., Steven A. Rosenberg, M.D., Ph.D., Peter Choyke, M.D., Don Vena, B.S., and Patrick Hwu, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

364;22 June 2, 2011





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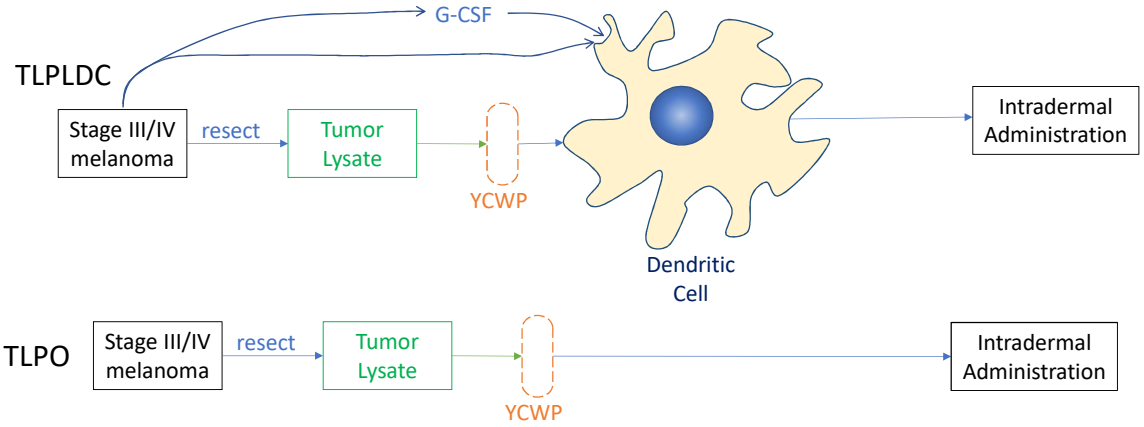
Journal for ImmunoTherapy of Cancer

Prospective, randomized, double-blind phase 2B trial of the TLPO and TLPLDC vaccines to prevent recurrence of resected stage III/IV melanoma: a prespecified 36-month analysis

Elizabeth I. Carpenter, Spencer Van Decar, AM Adams, AE O'Shea, P McCarthy ,3 RC Chick, GT Clifton, T Vreeland, FA Valdera, A Tiwari, D Hale, PK Bohan, A Hickerson, P Smolinsky, K Thomas, J Cindass, J Hyngstrom, AC Berger, J Jakub, JJ Sussman, MF Shaheen, X Yu, TE Wagner, Mark Faries, George E Peoples



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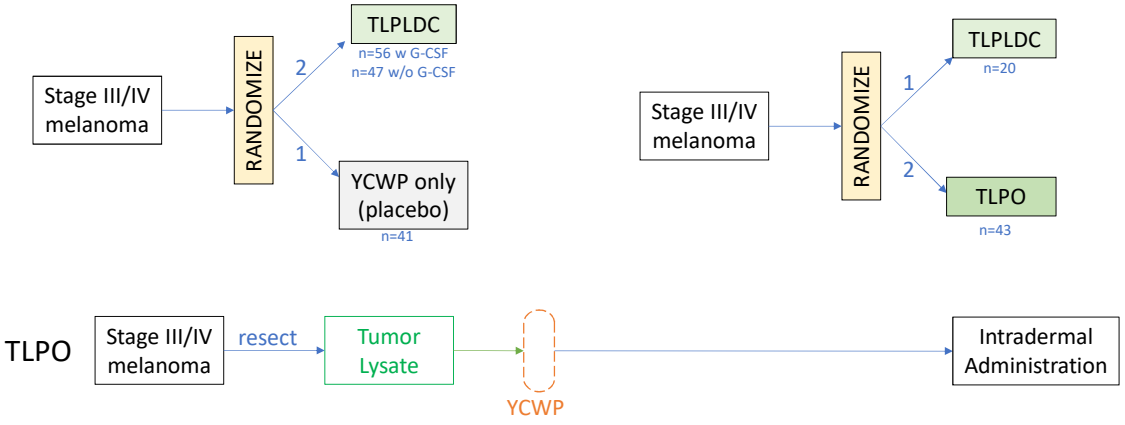

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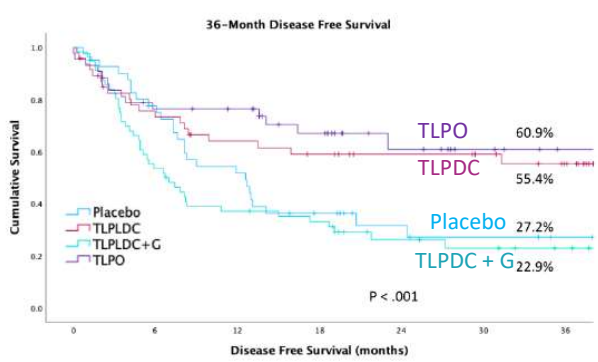

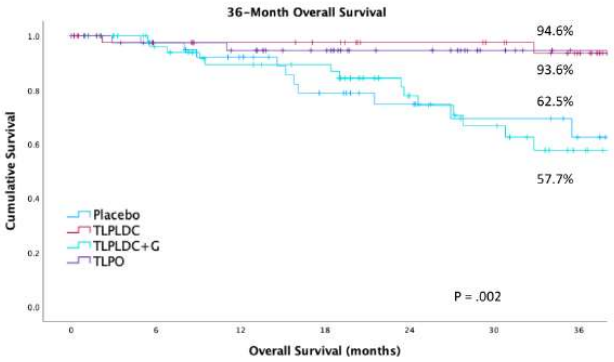

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mRNA Vaccines

- Advantages:
  - No potential for genetic integration
  - Non-infectious / non-immunogenic* vector
  - mRNA manipulations
  - ease of manufacture (for personalized vaccines)
- Challenges:
  - Delivery had been a problem.
    - naked mRNA is quickly degraded
  - Numerous strategies have been used for delivery
  - Time interval until vaccine is ready
  - Prediction of relevant antigens

mRNA Manipulations

- synthetic cap analogues/enzymes
- Regulatory elements in 5'-UTR and 3'-UTR
- Poly(A) tail stabilize mRNA, ↑ translation
- Modify nucleosides: ↓ immune activation, ↑ translation
- Sequence/Codon optimization
- Modulation of target cells: co-delivery

* if desired

Pardi, *Nat Reviews Drug Discov*, 2018

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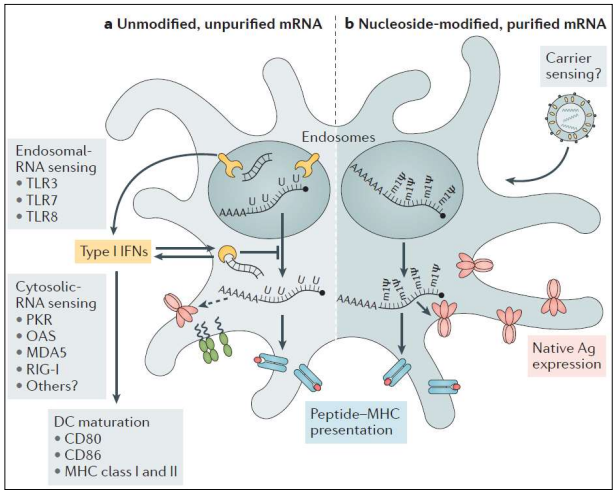

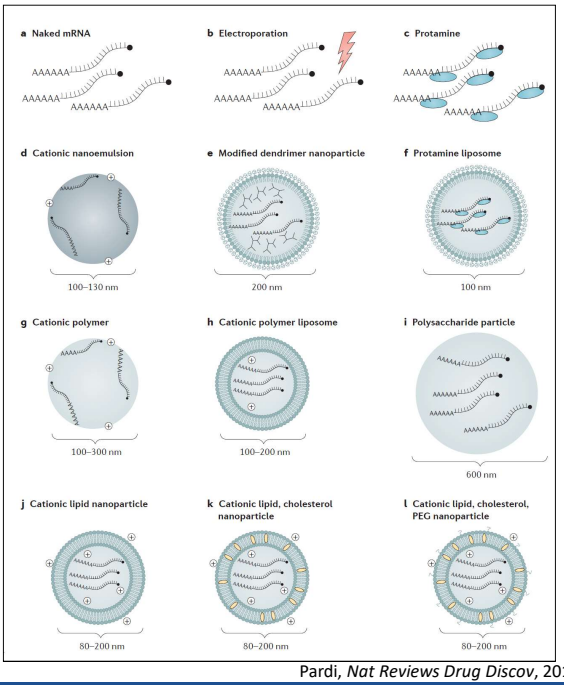

Pardi, *Nat Reviews Drug Discov*, 2018

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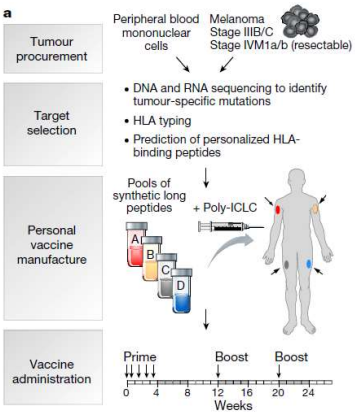
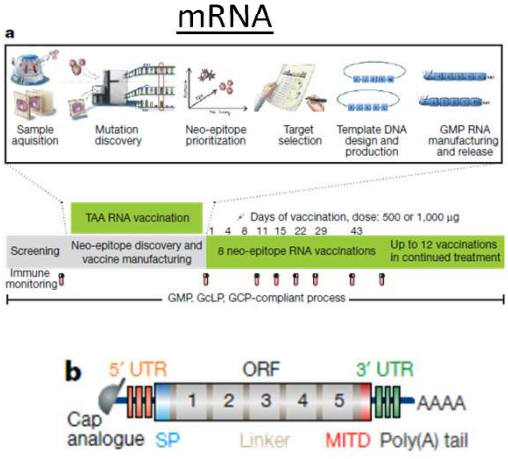
Selection of Neoantigens

Peptides



Ott, *Nature*, 2017

mRNA



Sahin, *Nature*, 2017

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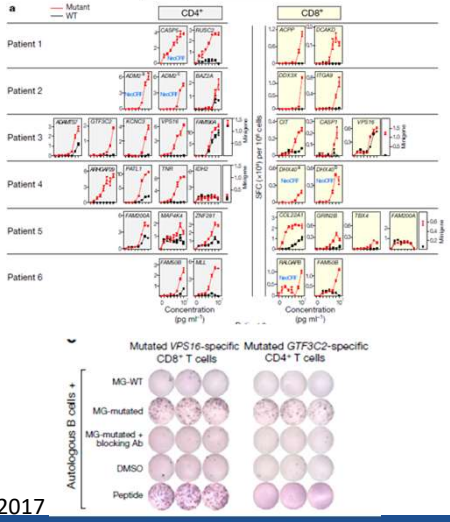
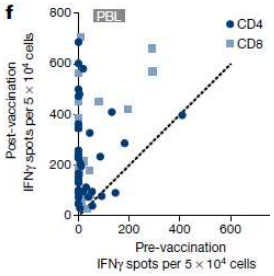
Immunization

Peptides



Ott, *Nature*, 2017

mRNA



Sahin, *Nature*, 2017

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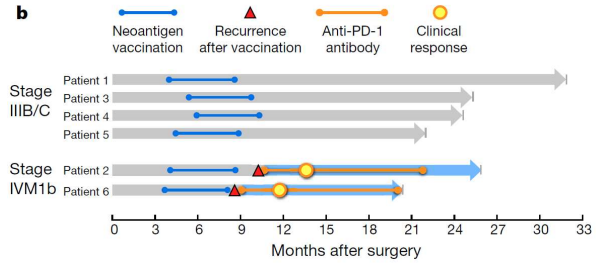
Clinical Effects

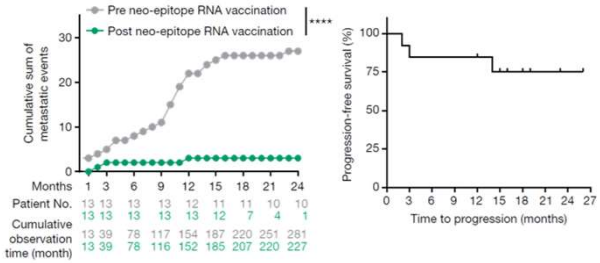
Peptides



- 4 of 6 without recurrence
- 2 with recurrence had complete response to anti-PD-1

Ott, *Nature*, 2017

mRNA



Sahin, *Nature*, 2017

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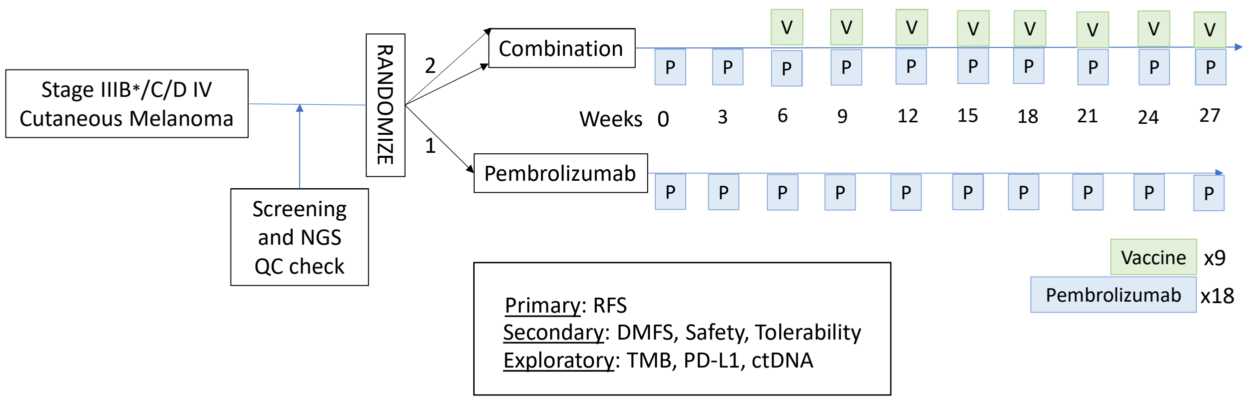
Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study

Jeffrey S Weber, Matteo S Carlino, Adnan Khattak, Tarek Meniawy, George Ansstas, Matthew H Taylor, Kevin B Kim, Meredith McKean, Georgina V Long, Ryan J Sullivan, Mark Faries, Thuy T Tran, C Lance Cowey, Andrew Pecora, Montaser Shaheen, Jennifer Segar, Theresa Medina, Victoria Atkinson, Geoffrey T Gibney, Jason J Luke, Sajeve Thomas, Elizabeth I Buchbinder, Jane A Healy, Mo Huang, Manju Morrissey, Igor Feldman, Vasudha Sehgal, Celine Robert-Tissot, Peijie Hou, Lili Zhu, Michelle Brown, Praveen Aanur, Robert S Meehan, Tal Zaks**

Lancet 2024; 403: 632–44



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Neoantigen Selection Algorithm

NGS sequencing

- **Patient tumour DNA-seq**
- **Patient normal DNA-seq**
- **Patient tumour RNA-seq**
- **Patient HLA typing**

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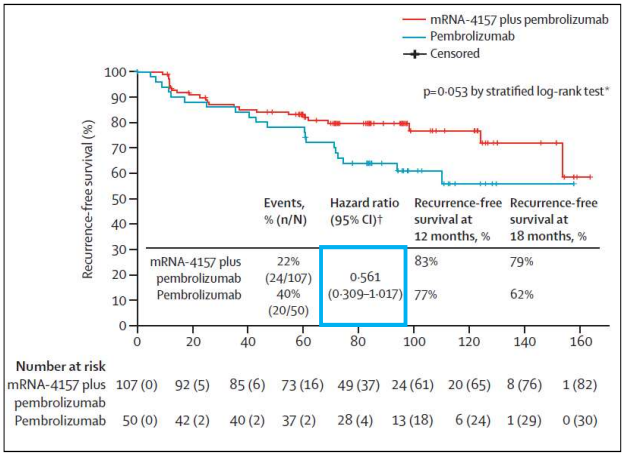
	mRNA-4157 plus pembrolizumab (n=107)	Pembrolizumab (n=50)
Sex*		
Male	70 (65%)	31 (62%)
Female	37 (35%)	19 (38%)
Age, years		
Median (IQR)	63·0 (53–72)	61·5 (51–69)
Mean (SD)	61·3 (13·5)	59·4 (14·3)
Age group		
<65 years	59 (55%)	28 (56%)
≥65 years	48 (45%)	22 (44%)
Eastern Cooperative Oncology Group performance status score		
0	90 (84%)	40 (80%)
1	15 (14%)	9 (18%)
Missing†	2 (2%)	1 (2%)
Disease stage at randomisation‡		
Stage IIIC	89 (83%)	42 (84%)
Stage IIID	2 (2%)	2 (4%)
Stage IV	16 (15%)	6 (12%)
Number of previous cancer-related surgeries		
1	41 (38%)	24 (48%)
2	36 (34%)	18 (36%)
≥3	30 (28%)	8 (16%)
Lymph node dissection	34 (32%)	15 (30%)
Lactate dehydrogenase (U/L), median (IQR)§	189 (166–211)	185 (162–204)
>upper limit of normal	5 (5%)	3 (6%)
Programmed death ligand 1 status		
Positive	69 (64%)	27 (54%)
Negative	13 (12%)	5 (10%)
Indeterminate¶	25 (23%)	18 (36%)
BRAF‖		
V600K or V600E mutation	41 (38%)	20 (40%)
Wildtype**	66 (62%)	30 (60%)



Weber et al, *Lancet*, 2024

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Table 2: Treatment-related adverse events occurring in ≥20% of patients*

	mRNA-4157 plus pembrolizumab (n=104)		Pembrolizumab (n=50)	
	Any grade	Grade ≥3†	Any grade	Grade ≥3
Any adverse event‡	104 (100%)	36 (35%)	47 (94%)	18 (36%)
mRNA-4157 treatment-related adverse events§				
Any	98 (94%)	12 (12%)	..	..
Fatigue	63 (61%)	5 (5%)	..	..
Injection-site pain	58 (56%)	0	..	..
Chills	52 (50%)	0	..	..
Pyrexia	50 (48%)	1 (1%)	..	..
Headache	33 (32%)	0	..	..
Injection-site erythema	33 (32%)	0	..	..
Influenza-like illness	32 (31%)	0	..	..
Nausea	26 (25%)	0	..	..
Myalgia	22 (21%)	1 (1%)	..	..
Pembrolizumab treatment-related adverse events¶				
Any	101 (97%)	24 (23%)	41 (82%)	9 (18%)
Fatigue	72 (69%)	6 (6%)	20 (40%)	0
Diarrhoea	31 (30%)	2 (2%)	5 (10%)	0
Pruritus	30 (29%)	0	10 (20%)	0
Nausea	23 (22%)	0	5 (10%)	0
Chills	22 (21%)	0	1 (2%)	0
Pyrexia	22 (21%)	0	0	0

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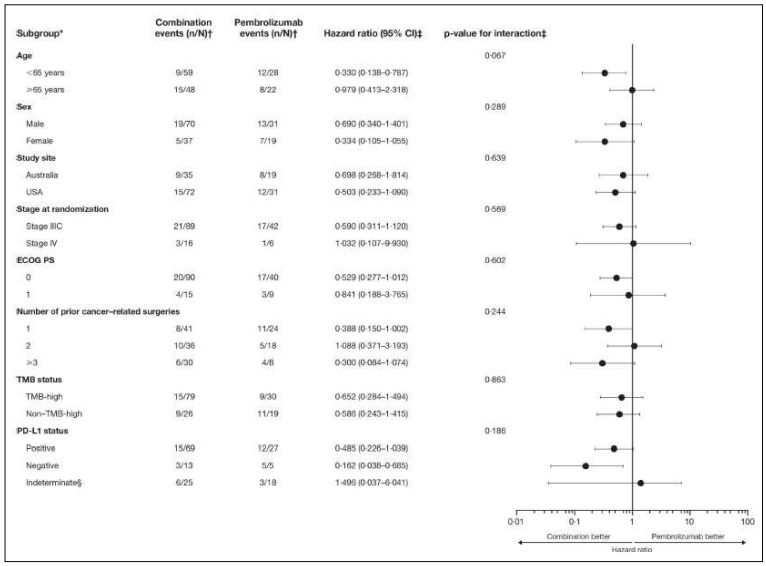
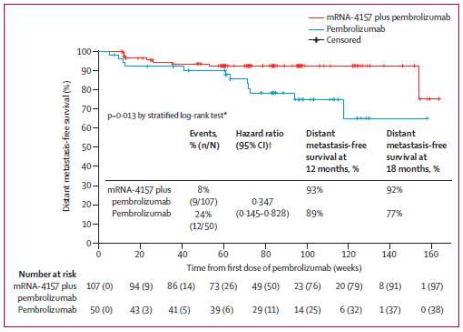


DMFS



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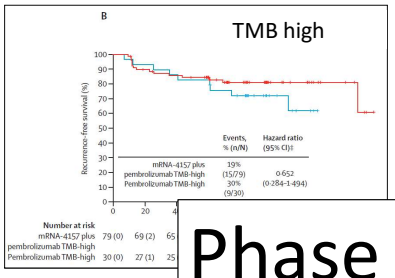
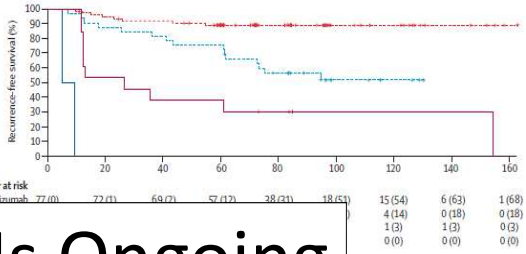
Phase 3 Trial Is Ongoing

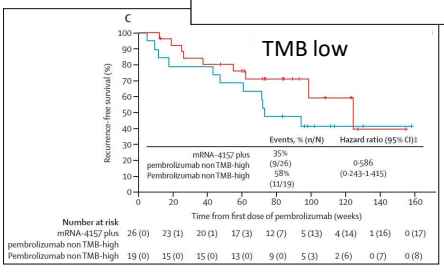
TMB high



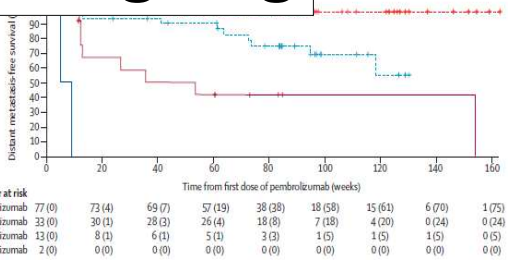
RFS by ctDNA status



TMB low



DMFS by ctDNA status



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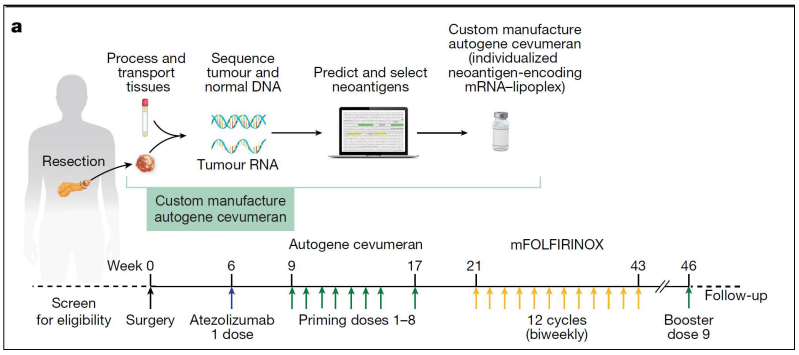
Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

Rojas LA, Sethna Z, Soares KC, Olcese C, Pang N, Patterson E, Lihm J, Ceglia N, Guasp P, Chu A, Yu R, Chandra AK, Waters T, Ruan J, Amisaki M, Zebboudj A, Odgerel Z, Payne G, Derhovanessian E, Müller F, Rhee I, Yadav M, Dobrin A, Sadelain M, Łuksza M, Cohen N, Tang L, Basturk O, Gönen M, Katz S, Do RK, Epstein AS, Momtaz P, Park W, Sugarman R, Varghese AM, Won E, Desai A, Wei AC, D'Angelica MI, Kingham TP, Mellman I, Merghoub T, Wolchok JD, Sahin U, Türeci Ö, Greenbaum BD, Jarnagin [illegible] Balachandran VP.

Nature | Vol 618 | 1 June 2023

Key inclusion criteria
- All surgically resectable PDAC
  - No borderline resectable
  - No locally advanced or metastatic disease
  - No neoadjuvant therapy
- ≥5 neoantigens



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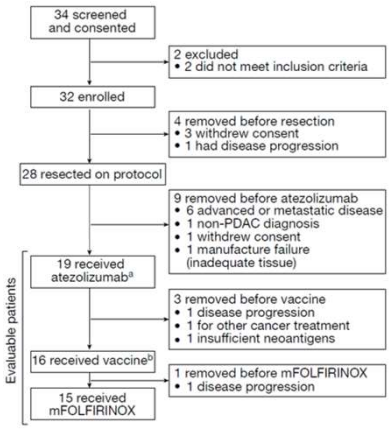
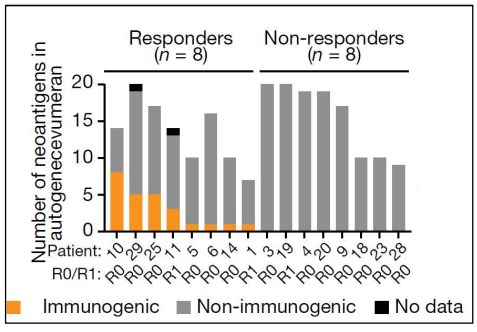
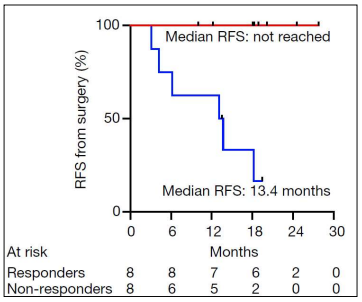
Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

Rojas LA, et al

Nature | Vol 618 | 1 June 2023







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Summary

- Personalized immunotherapy has a long history
- Improved understanding of tumor immunology and remarkable advances in technology have made truly individualized neoantigen vaccination possible
- Early indications are of major clinical benefit, though more study is needed
- Promise for less mutated tumors as well

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Post-Test Question:

Personalized, mRNA-based neoantigen vaccines:

A. Have now been approved for melanoma, but not yet pancreatic cancer
B. Are easily mass produced, similar to COVID vaccines
C. Are well tolerated, but have not demonstrated substantial evidence of clinical benefit beyond checkpoint inhibitors
D. Have been associated with meaningful clinical benefit (HR 0.56) in patients with resected metastatic melanoma

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