Kanserde Koruyucu Aşılamalar

Dr Polat OLGUN

In the case of diseases caused by viruses (e.g., measles, polio, and smallpox) and bacteria (e.g., diphtheria, tetanus, and tuberculosis), vaccines work by exposing people to a weakened or inactivated version of the threat. This enables their immune system to identify these threats according to their specific markers—known as "antigens"—and mount a response against them. These vaccines typically work best in the preventive setting, when an individual is given the vaccine before being infected by the bacteria or virus.

In the case of cancer, however, the situation is more complicated for several reasons (more below), which has made it more difficult to develop vaccines to prevent or treat cancer. In particular, unlike bacteria and viruses, which appear foreign to our immune system, cancer cells more closely resemble our normal, healthy cells. Furthermore, each individual's tumor is in some sense unique and has its own distinguishing antigens. As a result, more sophisticated approaches are necessary to develop effective cancer vaccines.

Preventive Cancer Vaccines

Viral infections are responsible for the development of several cancers, and preventive vaccines play an important role in reducing risk. For instance, cervical cancer and head and neck cancer can be caused by human papillomavirus, or HPV, whereas liver cancer can be caused by hepatitis B virus or HBV. Several vaccines have been developed that can prevent HBV and HPV infection and, as a result, protect against the formation of HBV- and HPV-related cancers. Four of these preventive cancer vaccines have been approved by the U.S. Food and Drug Administration (FDA).

Preventive Cancer Vaccines

- **Cervarix®**: a vaccine approved for use in preventing infection by the two strains of HPV that cause most cervical cancers, HPV types 16 and 18; can help prevent the development of HPV-related anal, cervical, head and neck, penile, vulvar, and vaginal cancers
- **Gardasil®**: a vaccine that protects against infection by HPV types 16, 18, 6, and 11; can help prevent the development of HPV-related anal, cervical, head and neck, penile, vulvar, and vaginal cancers
- **Gardasil-9®**: a vaccine approved for the prevention of infection by HPV types 16, 18, 31, 33, 45, 52, and 58, and for the prevention of genital warts caused by HPV types 6 or 11; can help prevent the development of HPV-related anal, cervical, head and neck, penile, throat, vulvar, and vaginal cancers
- **Hepatitis B (HBV) vaccine (HEPLISAV-B®)**: a preventive vaccine that protects against infection by the hepatitis B virus; can help prevent the development of HBV-related liver cancer

Therapeutic Cancer Vaccines

Each individual's tumor is in some sense unique and has its own distinguishing antigens. As a result, more sophisticated cancer vaccine approaches are necessary.

Fortunately, doctors can now identify targets on patients' tumors that can help distinguish cancer cells from their normal cells. Sometimes these targets are normal proteins that are produced at abnormally high levels by cancer cells, such as prostatic acid phosphatase (PAP), which is often overexpressed by prostate cancer cells. Taking advantage of that insight, the sipuleucel-T vaccine was developed and received FDA approval in 2010 for the treatment of patients with advanced prostate cancer. Additionally, virus-derived proteins expressed by virus-infected cancer cells offer another promising source of markers that can be targeted through vaccines.

Another exception is Bacillus Calmette-Guérin, or BCG, a tuberculosis vaccine that acts as a general immune stimulant. In 1990, BCG became the first immunotherapy of any type to be approved by the FDA and is still used for the treatment of early-stage bladder cancer.

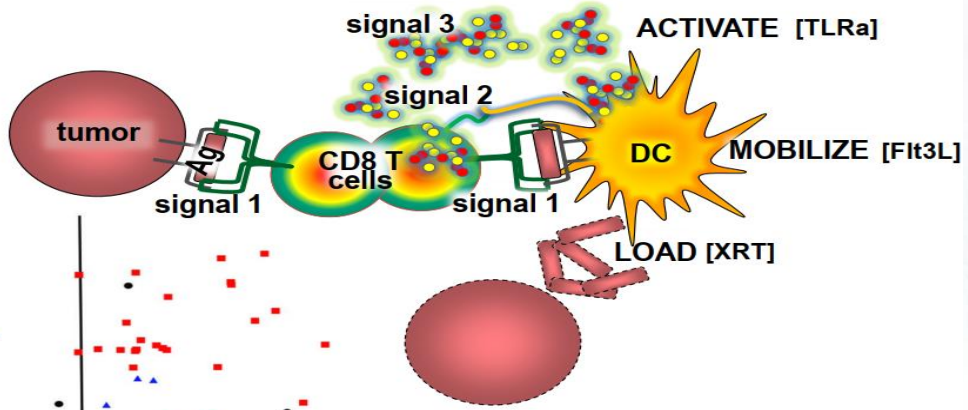
Therapeutic Cancer Vaccines

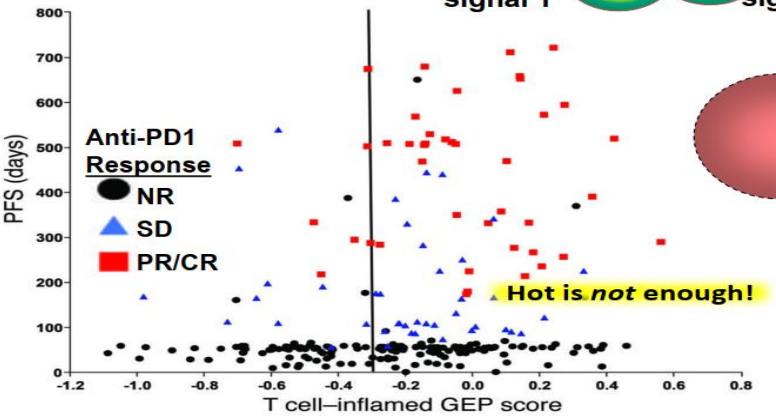
- **Bacillus Calmette-Guérin (BCG):** a vaccine that uses weakened bacteria to stimulate the immune system; approved for patients with early-stage bladder cancer
- **Sipuleucel-T (Provenge®):** a vaccine composed of patients' own stimulated dendritic cells; approved for prostate cancer

Over 40 years cancer *vaccines* have *not* been successful!

(So… give up? Or *keep going*?)

Priming anti-tumor T cells requires signal 1+2



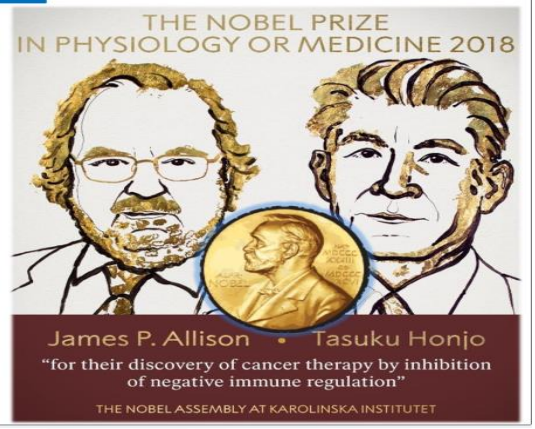


Ayers M et al., *J Clin Invest* 2017

The great -but limited-benefit of Immunotherapy

Checkpoint (PD1) antibodies helps 10,000s of patients each year.

	Incidence	Deaths	anti-PD1 Response Rate%	cancer incidence
1. Breast	276,480	42,170	5	
2. Lung	228,820	135,720	25	
3. Prostate	191,930	33,330	4	
4. Colorectal	147,950	53,200	5	
5. Melanoma	100,350	6,850	40	
6. Bladder	81,400	17,980	21	
7. Lymphoma (NHL)	77,240	19,940	8	
8. Kidney	73,750	14,830	25	
9. Uterine	65,620	12,590	6	
10.Leukemia	60,530	23,100	5	



Adams et al., Annals Oncol 2019
Garon EB, et al., N Engl J Med. 2015
De Bono JS. et al., J Clin Oncol 2018
O'Neil BH et al., PLoS One. 2017
Robert C, et al., N Engl J Med. 2015
Bellmunt J et al., N Engl J Med . 2017
Ansell SM et al., J Clin Oncol. 2019
Motzer RJ et al., N Engl J Med. 2015
Ott PA et al., J Clin Oncol . 2017

İmmünoterapi direnci (%50-70)

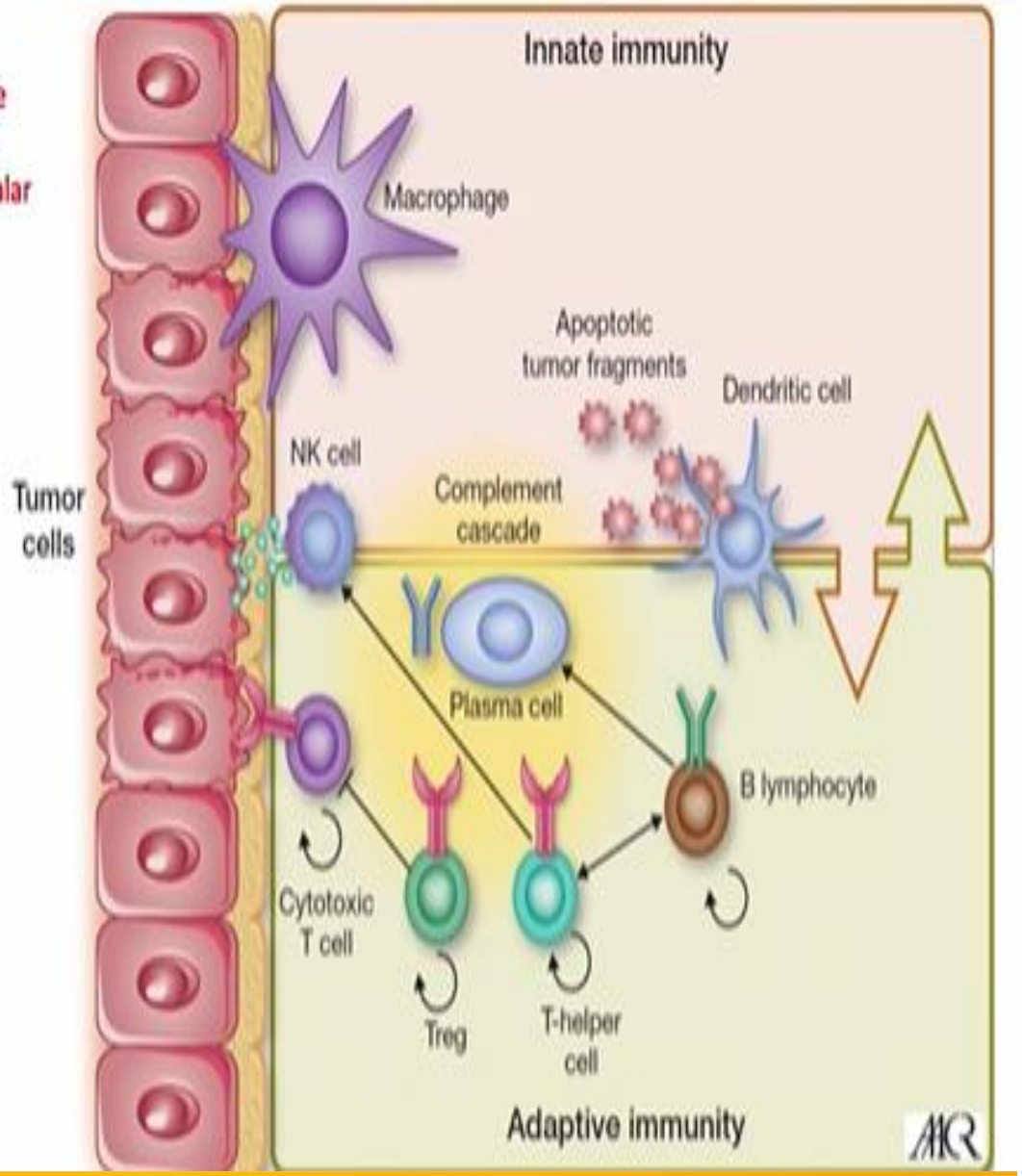
- Primer direnç (%30-50)
  - İmmünoterapiye yanıt yok, sağkalım uzamıyor
- Adaptif immün direnç (%30-40)
  - Kaser immün sistem tarafından tanınıyor fakat tümör immün sistem için önlem almış (klinkte primer direnç, mikst cevap, edinsel direnç olarak karşımıza çıkıyor)
- Edinsel direnç (%20-30)
  - (Başlangıçta cevap var sonrasında nüks/progresyon)

Personalized Neoantigen Vaccines

In contrast to normal-yet-overexpressed proteins like PAP, tumors also display unique targets that arise as a result of mutations. These are referred to as neoantigens ("new antigens"), and they are expressed exclusively by tumor cells and not by any of a patient's healthy cells. With neoantigen vaccines, therefore, it is conceivable that immune responses could be directed precisely against patients' tumor cells while sparing their healthy cells from immune attack, thus possibly preventing side effects.

In addition to the previously mentioned vaccines, several types of neoantigen vaccines are currently being evaluated, both alone and in combination with other treatments, in a variety of cancer types in clinical trials.

Kanserde immün mekanizmalar



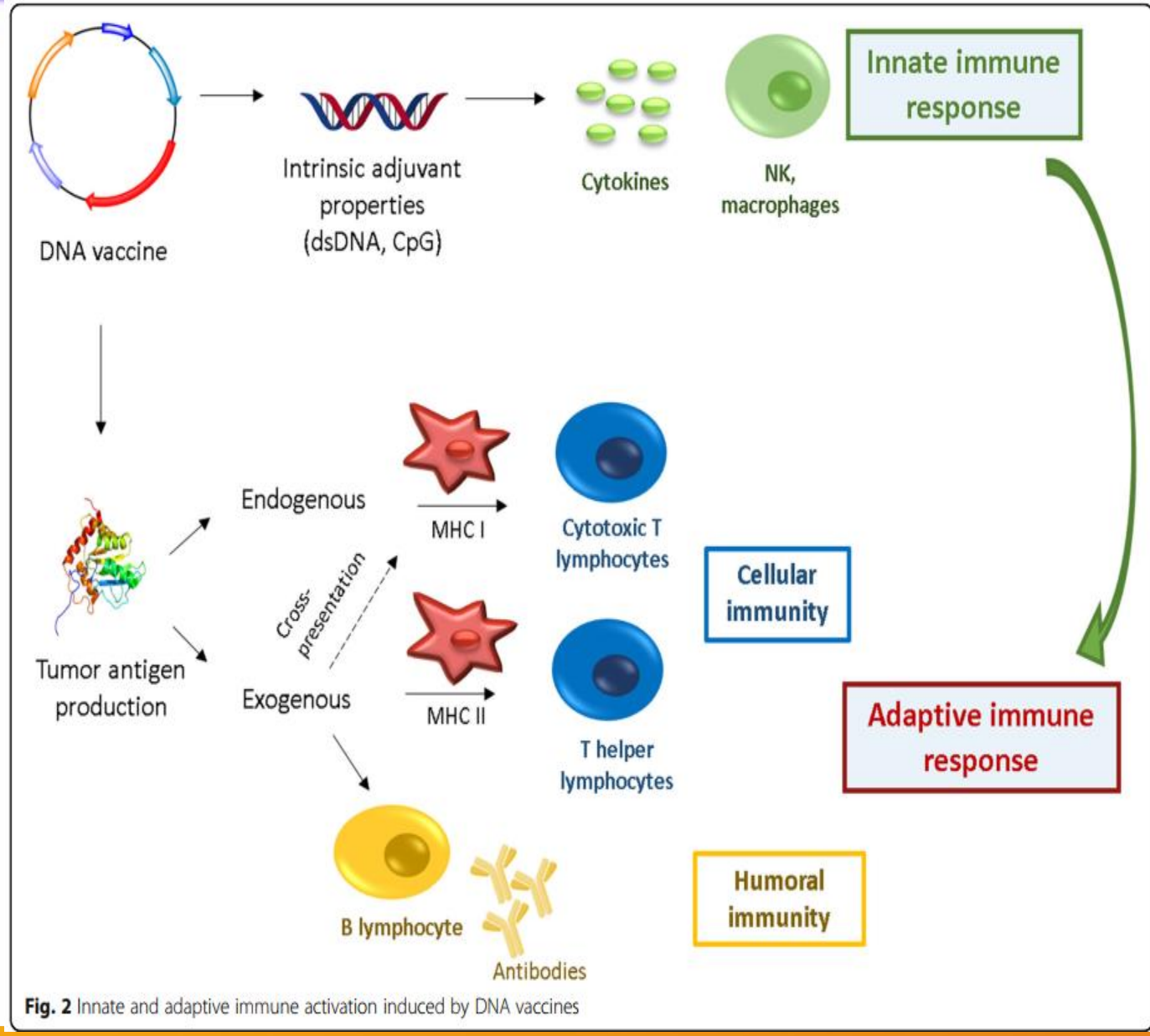
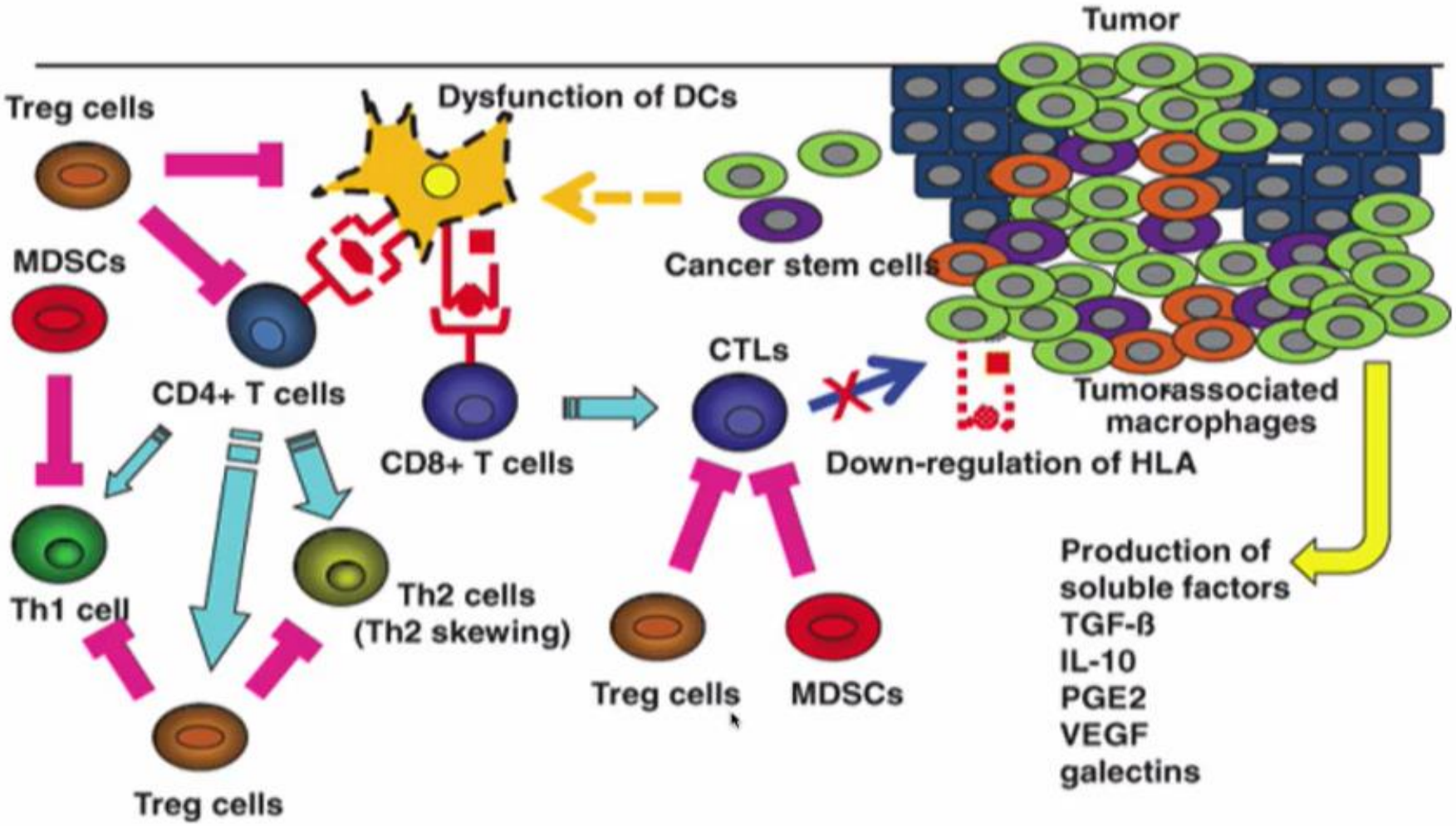


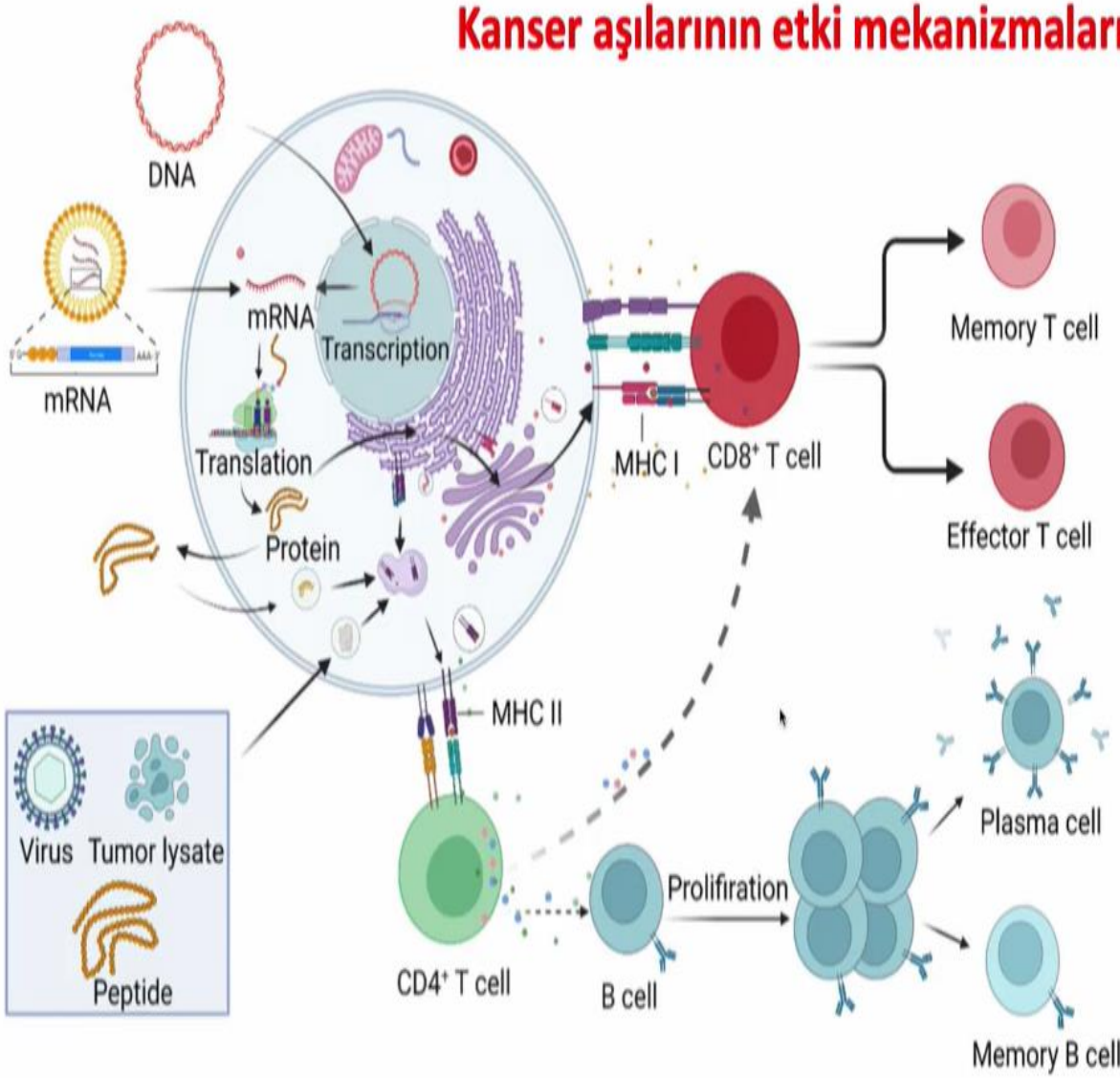
Fig. 2 Innate and adaptive immune activation induced by DNA vaccines

Immunosuppressive mechanisms

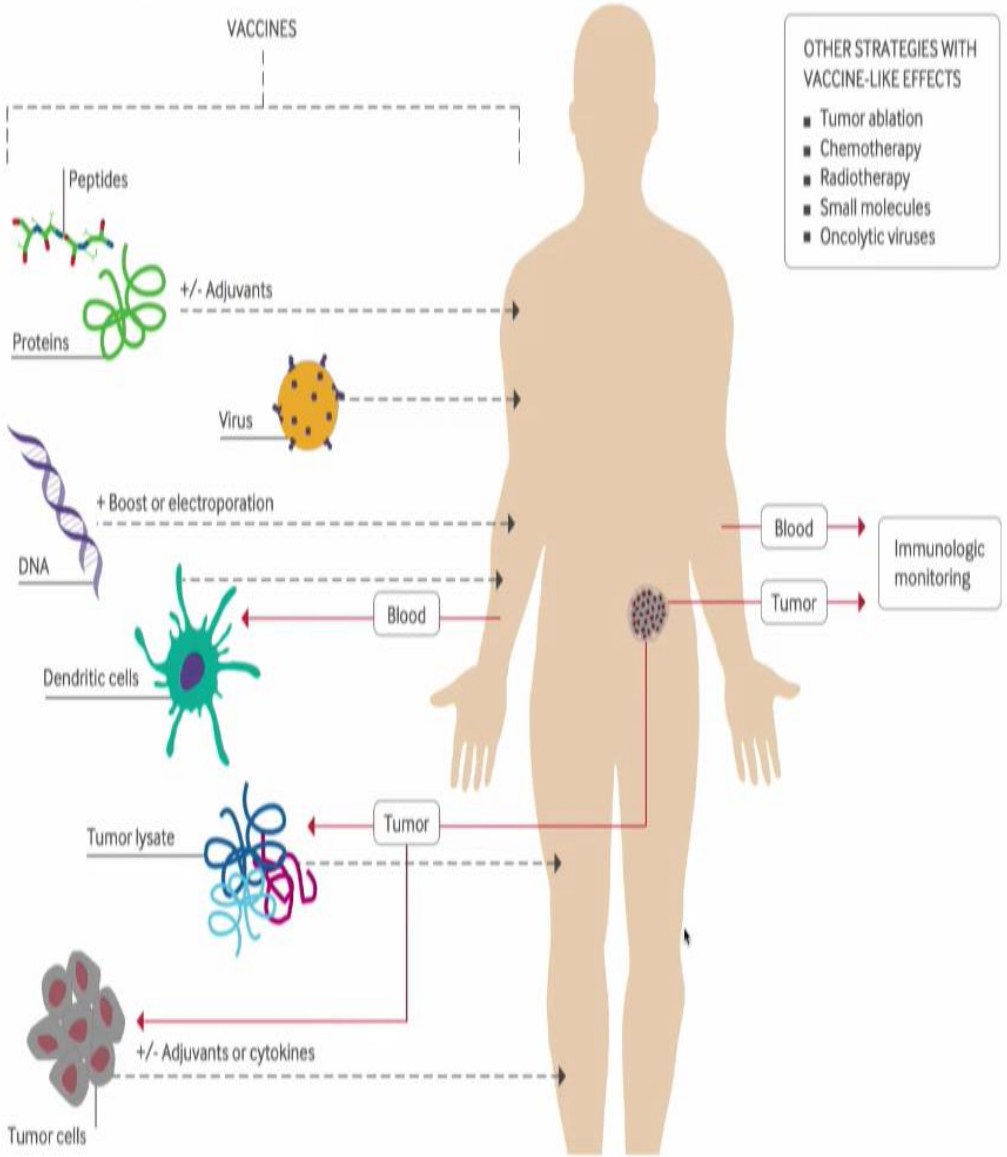


Chikamatsu K, et al 2013

Kanser aşılarının etki mekanizmaları



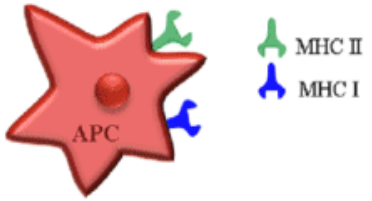
Liu et al, 2022



KANSER AŞI PLATFORMLARI

- Hücre tabanlı aşılar
  - *Tümör hücre tabanlı aşılar (Tam tümör hücre aşıları)*
  - *İmmün hücre tabanlı aşılar (DC, DC eksozomlar)*
- Peptid tabanlı aşılar
  - *Tümör antijenleri (büyük ve küçük polipeptidler)*
  - *VLP*
- Nükleik asit tabanlı aşılar
  - *DNA aşıları*
  - *mRNA tabanlı aşılar*
- Virüs tabanlı aşılar
  - *İnaktive virüs aşıları*
  - *Canlı atenüe veya subunit vürüs aşıları (EBV, HBV, HCV, HPV)*
  - *Onkolitik virüs aşıları/ viral vektör aşıları*

Cell-based vaccines



Pros (+):
- High immunogenicity
- Control of antigen presentation

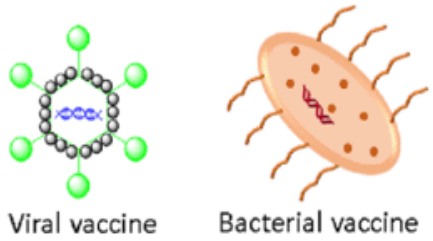
Cons (-):
- Expensive and difficult to produce
- Risk of leukapheresis (vascular injury, electrolyte imbalance)

Protein/peptide-based vaccines

Pros (+):
- Low toxicity
- Easy to produce

Cons (-):
- Low/moderate immunogenicity
- Peptide vaccines: restricted to the HLA subtype
- Protein vaccines: expensive to produce

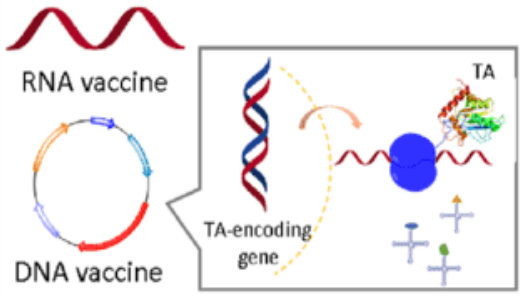
Viral/bacterial-based vaccines



Pros (+):
- High immunogenicity
- Easy to produce on large scale

Cons (-):
- Potential high toxicity
- Risk of undesired infections
- Immune response against the vector

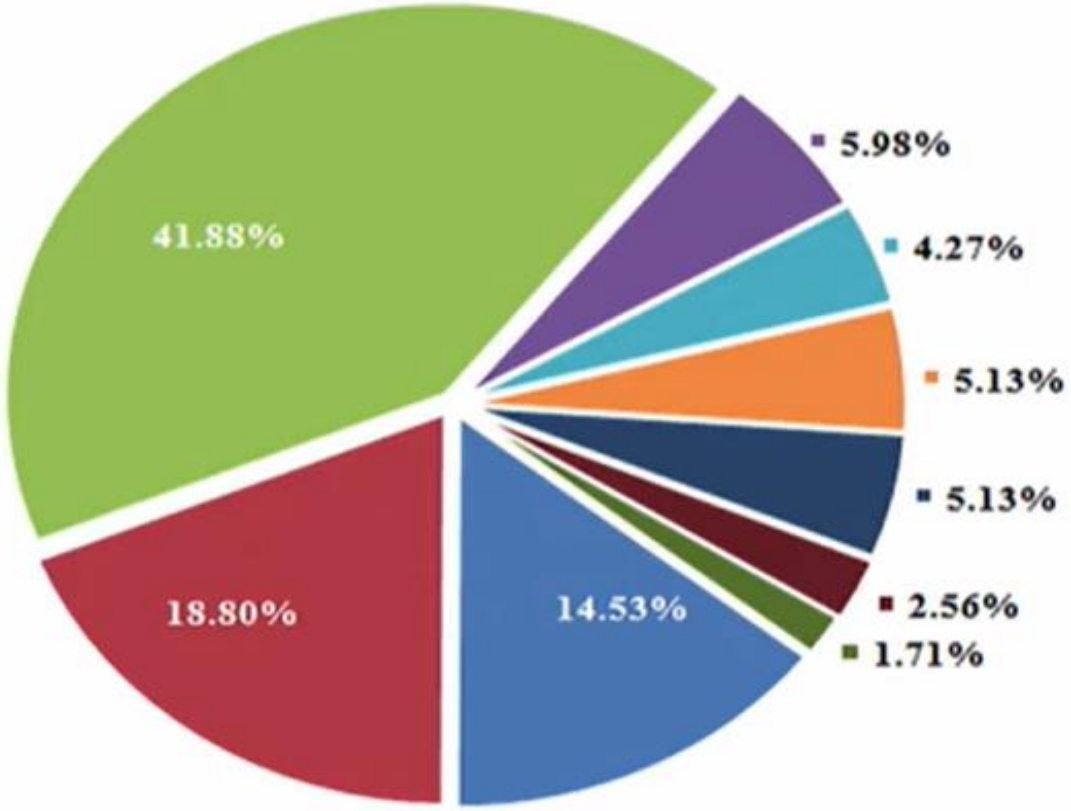
Gene-based vaccines

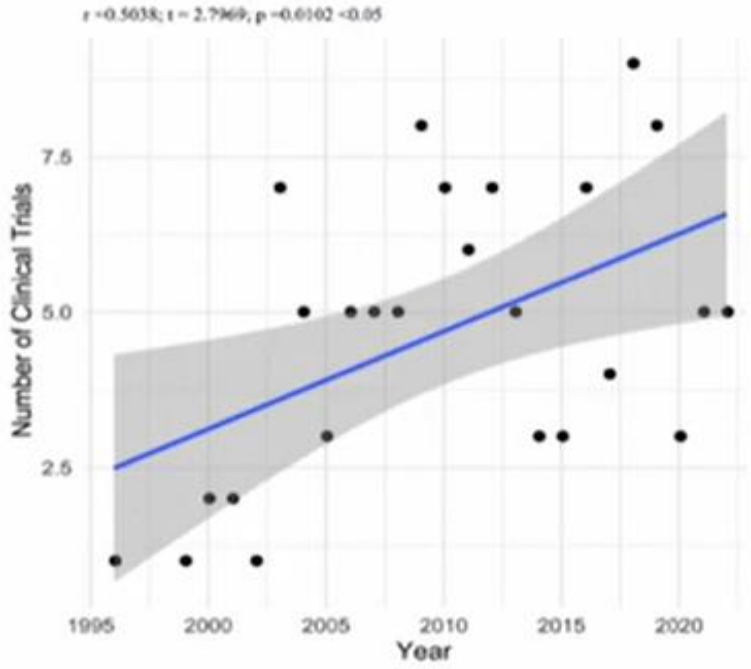


Pros (+):
- Easy delivery of multiple antigens
- Induction of cellular and humoral immunity
- Not restricted to HLA-patient type

Cons (-):
- RNA vaccines require specific transportation/storage conditions
- DNA and RNA vaccines: poorly immunogenic in humans

NSCLC Terapötik kanser aşı çalışmaları (2022 sonuna kadar) N:117) Clinicaltrials.org

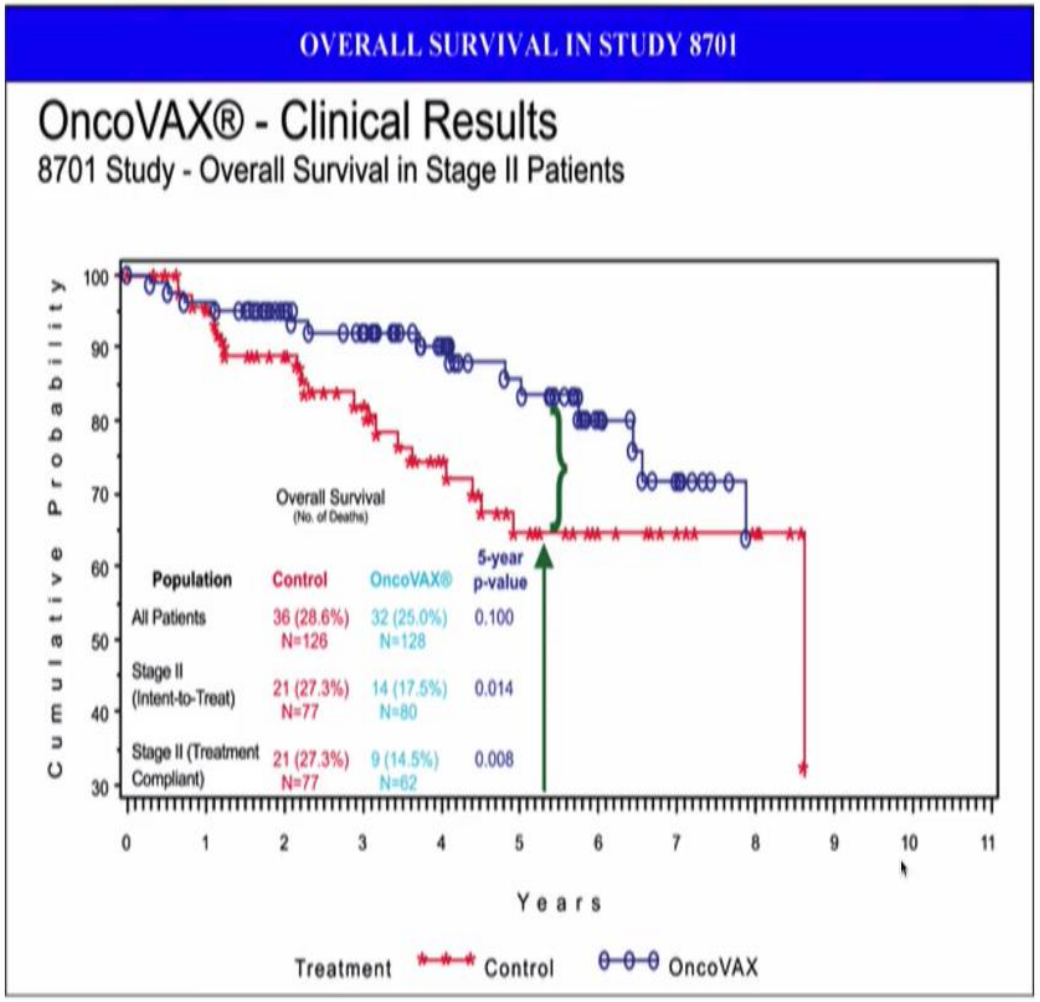




- Tumor Cell Vaccines
- Dendritic Cell Vaccines
- Protein/peptide Vaccines
- RNA Vaccines
- DNA Vaccines
- T Cell Vaccines
- Viral Vector Vaccines
- Autophagosome Vaccine
- Telomerase Vaccine

Frontiers in Immunology 2022

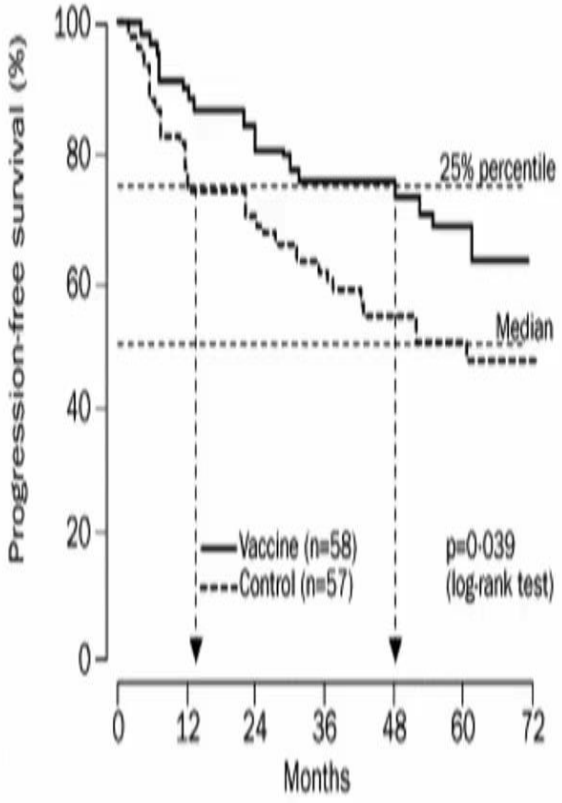
Tümör hücre tabanlı aşılar



Kolorektal
- otolog tümör hücre aşısı + BCG (OncoVAX).

Evre II hastalarda yararlı.
- 5-yılık sağkalım avantajı : %25.

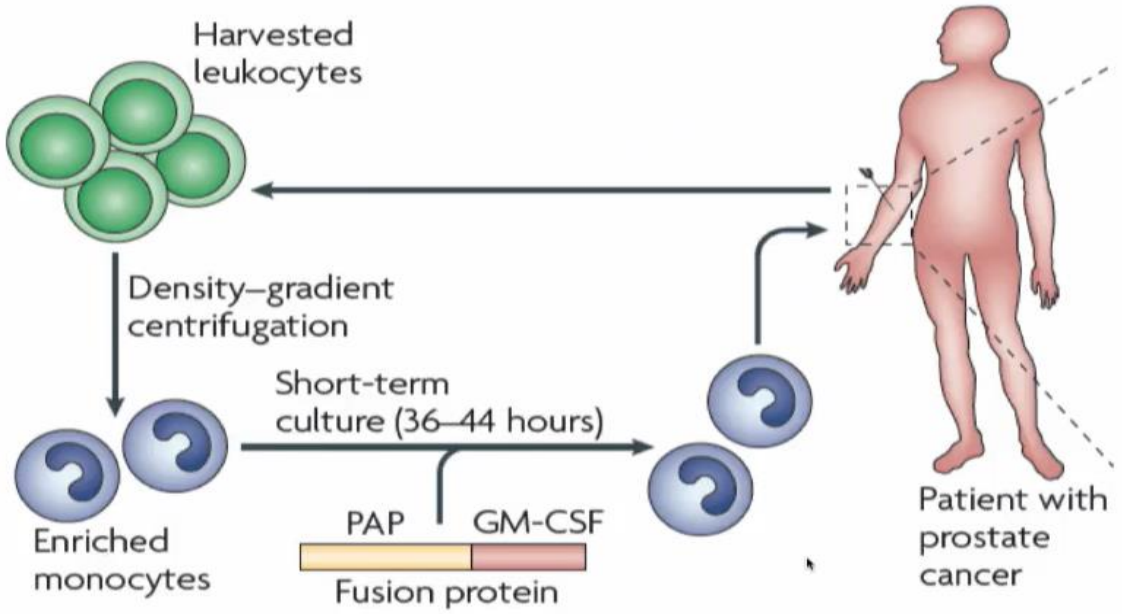
RCC de Liponova



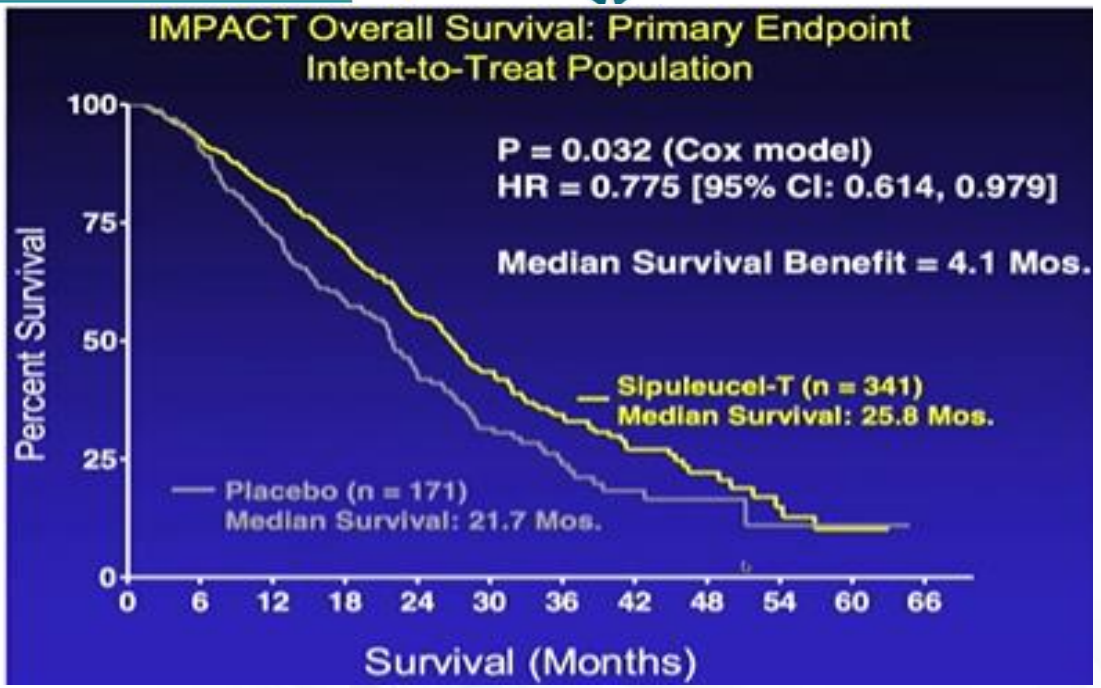
RCC
- Liponova; IFN-gama ile muamele edilmiş tümör hücre lizatı (reniale)
- Evre II and III RCC , adjuvan
- Yarar:
- 5 yıllık PFS: Aşı kolunda: %77.4, cerrahi kolunda %67,8
- Evre III; %67.5 vs %49.7

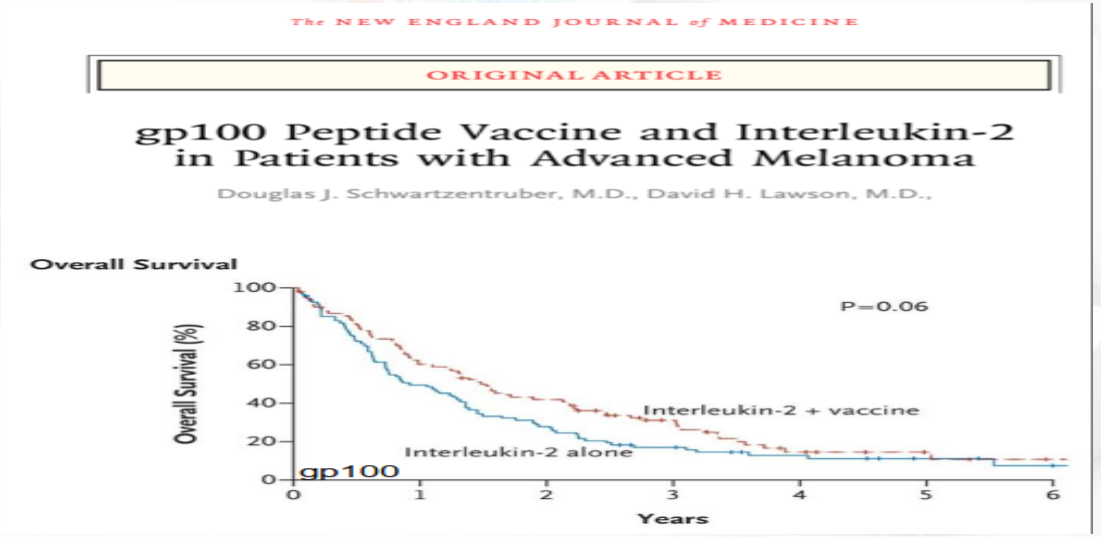
Immun hücre tabanlı aşılar

Dendritik hücre aşısı: Sipuleucel T



Nat Rev Immunol. 2010



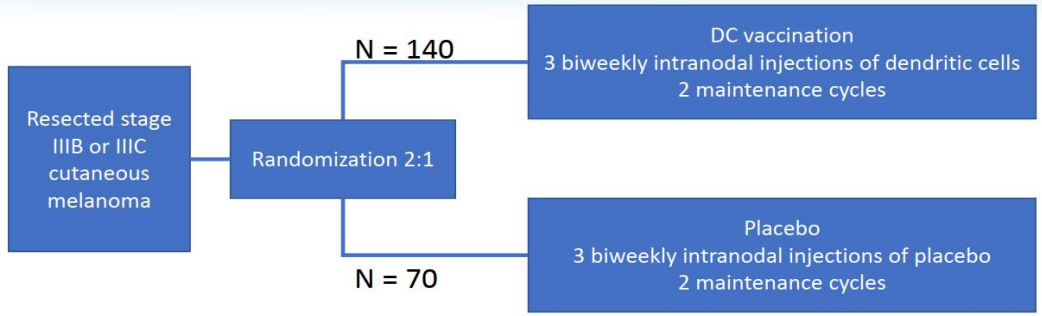


MIND-DC: preplanned interim analysis

A randomized phase III trial to assess the efficacy of adjuvant dendritic cell vaccination in comparison to placebo in stage IIIB and IIIC melanoma patients

Kalijn F. Bol, Martine Bloemendal*, Wouter W. van Willigen*, Gerty Schreibelt*, Simone Hins-de Bree, Anna de Goede, Astrid A. van der Veldt, Carl G. Figdor, Jan Willem B. de Groot, Johannes H.W. de Wilt, Johannes Textor, Winald R. Gerritsen, I. Jolanda M. de Vries

TRIAL DESIGN



accrual was stopped prematurely after inclusion of 151 patients as adjuvant treatment with anti-PD1 antibodies became available in the Netherlands (November 2018)

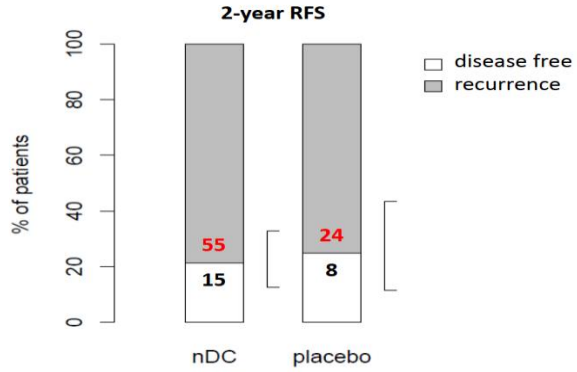
autologous natural dendritic cells (myeloid and plasmacytoid)
matured with protamine/mRNA
loaded with gp100, tyrosinase, MAGE-C2, MAGE-A3 and NY-ESO-1

VIRTUAL 2020 ESMO congress

Institute for Molecular Life Sciences
Radboudumc

2-YEAR RECURRENCE-FREE SURVIVAL: no survival benefit

2-year RFS: 21.4% versus 25.0% (HR 1.05; 95% CI: 0.47-3.23; p=0.67)
in 102 patients who reached the primary endpoint (2-year recurrence-free or recurrence)



percentage of RFS will increase with longer follow-up

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Institute for Molecular Life Sciences
Radboudumc

CONCLUSIONS OF INTERIM ANALYSIS

ADJUVANT DENDRITIC CELL VACCINATION IN STAGE IIIB/IIIC MELANOMA PATIENTS:

- showed no benefit over placebo in terms of 2-year recurrence-free survival
- effectively induces tumor-specific T cells
- gives mild toxicity

VIRTUAL 2020 ESMO congress

Institute for Molecular Life Sciences
Radboudumc

Neeha Zaidi
Johns Hopkins School of Medicine

Harnessing the power of DCs

Dendritic cells (DCs) are known for their efficiency in presenting antigens to T cells—a key component of the immune system's fight against cancer. DCs are thus an ideal cell type to harness therapeutically in order to elicit anti-tumor $CD4^+$ and $CD8^+$ T cell responses against specific cancer epitopes. Multiple studies have pulsed DCs *in vitro* with tumor antigens from dying tumor cells, or RNA or peptides corresponding to specific tumor epitopes. Although such studies have shown variable outcomes, the only therapeutic cancer vaccine that has been FDA approved to date is a prostate cancer DC vaccine, Sipuleucel-T, for use against asymptomatic or minimally symptomatic castration-resistant prostate cancer. Methods to generate mature and effective DCs *in vitro*, optimize DC maturation stimuli, and load antigens, as well as algorithms to select immunogenic tumor antigens, will continue to advance DC-based vaccines in the clinic. A second related set of strategies involve coaxing DCs to pick up tumor antigens *in vivo*—for example, GVAX is an irradiated, autologous vaccine consisting of tumor cells modified to secrete GM-CSF. These irradiated tumor cells allow for antigens to be picked up by DCs and then get presented to T cells. GVAX in combination with immune checkpoint blockade has yielded clinical responses in advanced pancreatic cancer, among other immunologically cold cancers. Areas of promise include combining DC vaccines and other immunotherapy strategies, such as immune checkpoint blockade; the use of personalized neoepitopes enabled by the rapidity, efficiency, and low cost of next-generation sequencing; and the deployment of mRNA technology to encode multiple epitopes more rapidly and efficiently in DC-based vaccines as well as for co-encoding of DC maturation

Peptid tabanlı aşılar

Kanser aşılarında kullanılan mutant antijenler

Tümör antijeni	Kanser türü
Aşırı ifade olan antijenler	
HER2/NEU	Meme kanseri
Human TERT	Çeşitli kanserler
p53 WT	Çeşitli kanserler
Survivin	Çeşitli kanserler
TPD52	Çeşitli kanserler
CD19	Hematolojik maliyniteler
Folate reseptor-α	Over kanseri
MAGE-A3	Melanoma
Translasyon sonrası modifye olanlar	
MUC1	Çeşitli kanserler
Vimentin	Çeşitli kanserler
ENO1	Hepatoma
BCAR3	Meme kanseri ve melanoma
ISR2	Melanoma
Mutasyona uğrayan antijenler	
AIM2	KRK
HT001	KRK
TAF1B	KRK
Micoryx	KRK
TGFbRII mutant	KRK
ERVE-4	Renal hücreli kanser
Mutant p53	Çeşitli kanserler
Mutant Ras	Çeşitli kanserler

Kanser aşılarında kullanılan viral antijenler

Tümör antijeni	Köken aldığı virüs	Kanser türü
LMP1	EBV	Nazofarenks kanseri, B hücreli lenfoma, Hodgkin hastalığı
LMP2	EBV	Nazofarenks kanseri, B hücreli lenfoma, Hodgkin hastalığı
Tax protein	HTLV1	Erişkin T hücreli lösemi
HBV proteinleri	HBV	Hepatoma
HCV proteinleri	HCV	Hepatoma
E6	HPV	Anogenital kanserler, baş-boyun kanseleri
E7	HPV	Anogenital kanserler, baş-boyun kanseleri
Large T protein	Merkel hücresi Polyoma virüsü	Cilt kanseri
Small T protein	Merkel hücresi Polyoma virüsü	Cilt kanseri

Peptid tabanlı aşılar

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Phase I/II Multicenter Trial of a Novel Therapeutic Cancer Vaccine, HepaVac-101, for Hepatocellular Carcinoma

Markus W. Löffler[1,2,3,4,5], Stefania Gori[6], Francesco Izzo[7], Andrea Mayer-Mokler[8], Paolo A. Ascierto[9], Alfred Königsrainer[1,3,4], Yuk Ting Ma[10], Bruno Sangro[11], Sven Francque[12], Luisa Vonghia[12], Alessandro Inno[6], Antonio Avallone[13], Jörg Ludwig[8], Diego Duarte Alcoba[8], Christian Flohr[8], Katrin Aslan[8], Regina Mendrzyk[8], Heiko Schuster[8], Marco Borrelli[13], Danila Valmori[14], Tanguy Chaumette[14], Regina Heidenreich[15], Cécile Gouttefangeas[2,3], Greta Forlani[16], Maria Tagliamonte[17], Caterina Fusco[18], Roberta Penta[18], Mercedes Iñarrairaegui[11], Ulrike Gnad-Vogt[15], Carsten Reinhardt[8], Toni Weinschenk[8], Roberto S. Accolla[16], Harpreet Singh-Jasuja[8], Hans-Georg Rammensee[2,3,4], and Luigi Buonaguro[17]

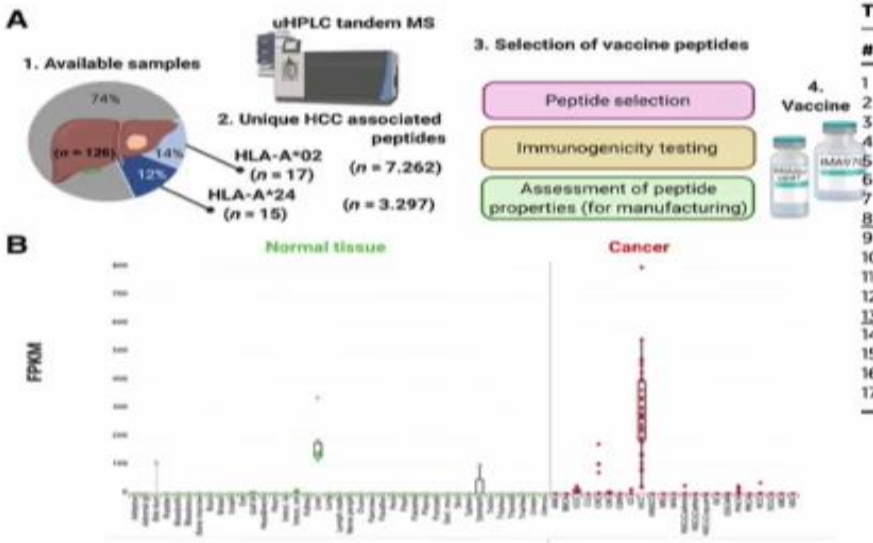

Table 1. IMA970A multipeptide antigen composition.

#	Source protein	HLA	Length (aa)	Sequence
1	ACSS3 (acyl-CoA synthetase short-chain family member 3)	A*02:01	9	ILDDNMQKL
2	ALDH1L1 (aldehyde dehydrogenase 1 family member L1)	A*02:01	9	KLQAGTVFV
3	APOB (apolipoprotein B)	A*02:01	9	VMAPFTMTI
4	AXIN2 (axin-related protein 2)	A*02:01	9	KLSPTVVGL
5	C1QTNF3 (C1q and tumor necrosis factor-related protein 3)	A*02:01	9	VLADFGARV
6	IGF2BP3 (insulin-like growth factor 2 mRNA-binding protein 3)	A*02:01	9	KIQEILTQV
7	QAR (glutaminyl-tRNA synthetase)	A*02:01	9	KMDPVAYRV
8	HBV Control peptide (hepatitis B virus)	A*02:01	10	FLPSDFFPSV
9	AFIM2 (acyl-CoA synthetase short-chain family member 3)	A*24:02	9	AYKPGALTF
10	APOB (apolipoprotein B)	A*24:02	9	DYIPYVFKL
11	DAP3 (death-associated protein 3)	A*24:02	9	AYPAIRYLL
12	MANE (mannosidase)	A*24:02	9	SYTKPEKW
13	SLC35B1 (solute carrier family 35 member B1)	A*24:02	9	VYGILQEKI
14	IGF2BP3 (insulin-like growth factor 2 mRNA-binding protein 3)	DR	14	KLYIGNLSENAAPS
15	MET (hepatocyte growth factor receptor)	DR	17	TFSYVDPVITSISPKYG
16	MTT (mitochondrial tricarboxylate transporter)	DR	18	LKMENKEVLPQLVAVTS
17	SLC25A13 (calcium-binding mitochondrial carrier protein Aralar2)	DR	21	GLYLPLFKPSVSTSKAIGGGP

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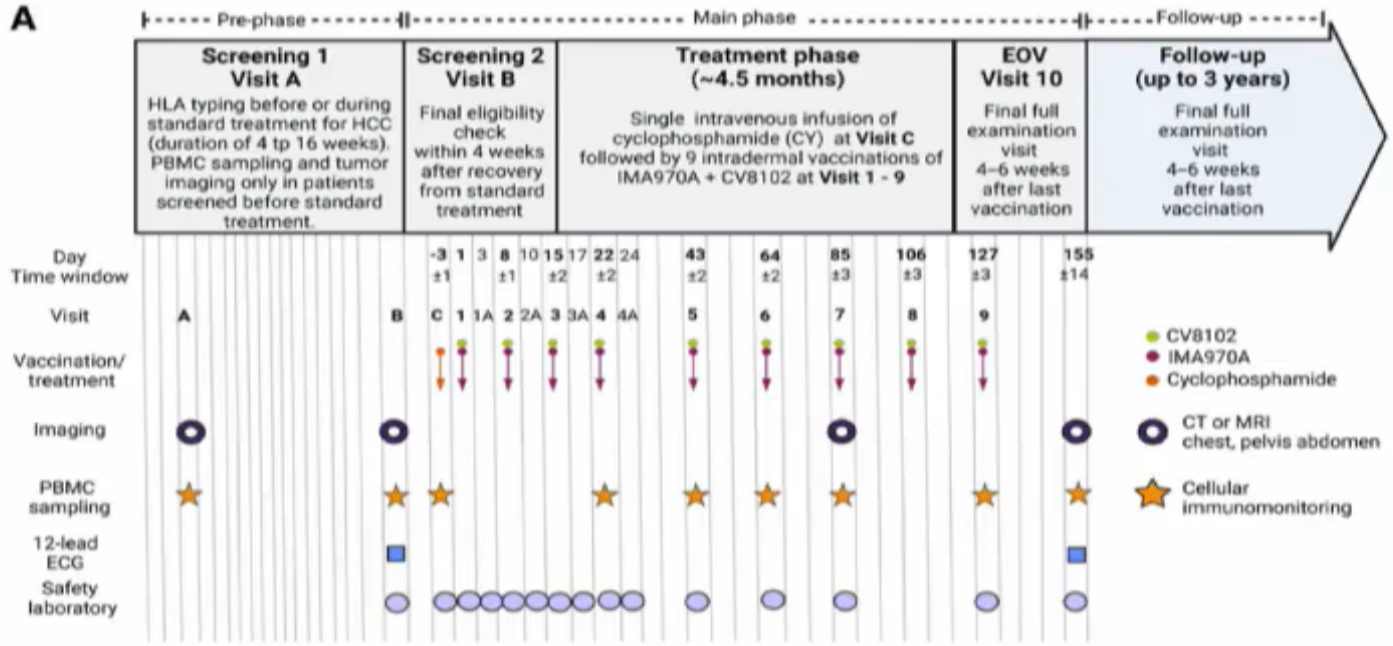
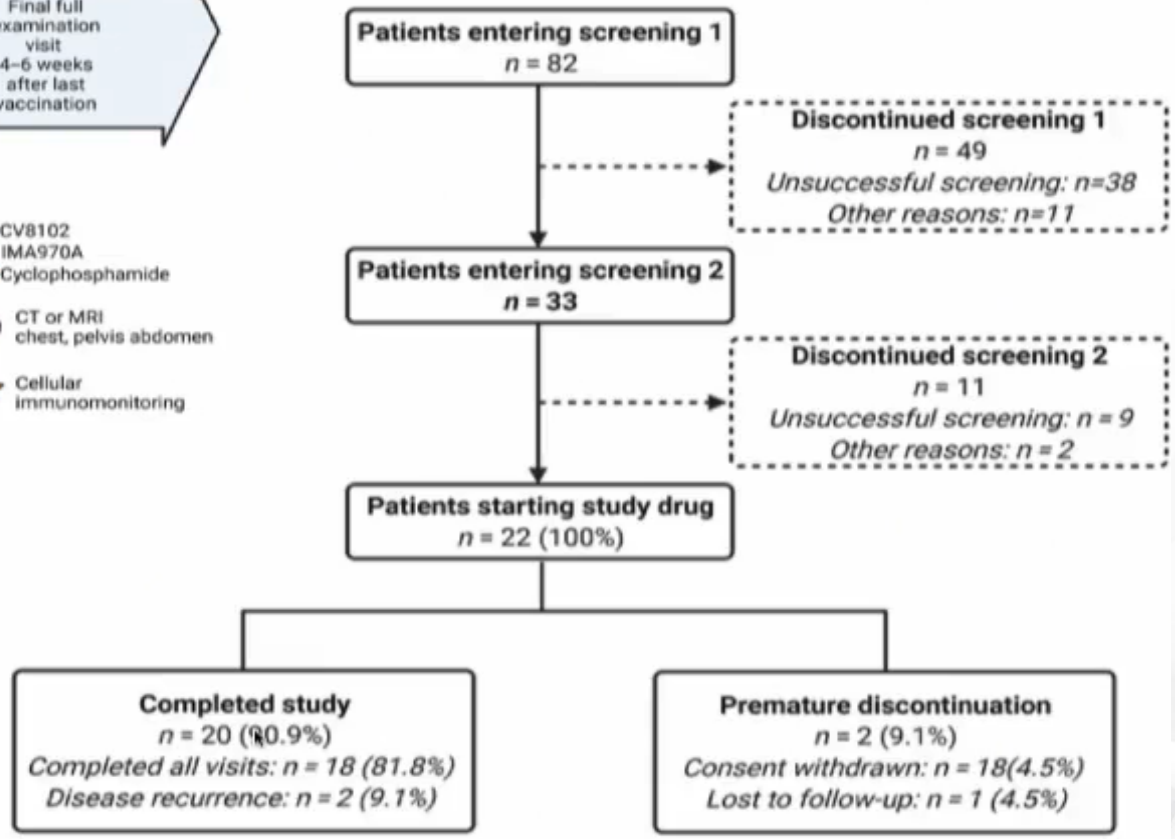
Peptid tabanlı aşılar





Cevap oranı İmmün yanıt olanlarda yaklaşık %50.

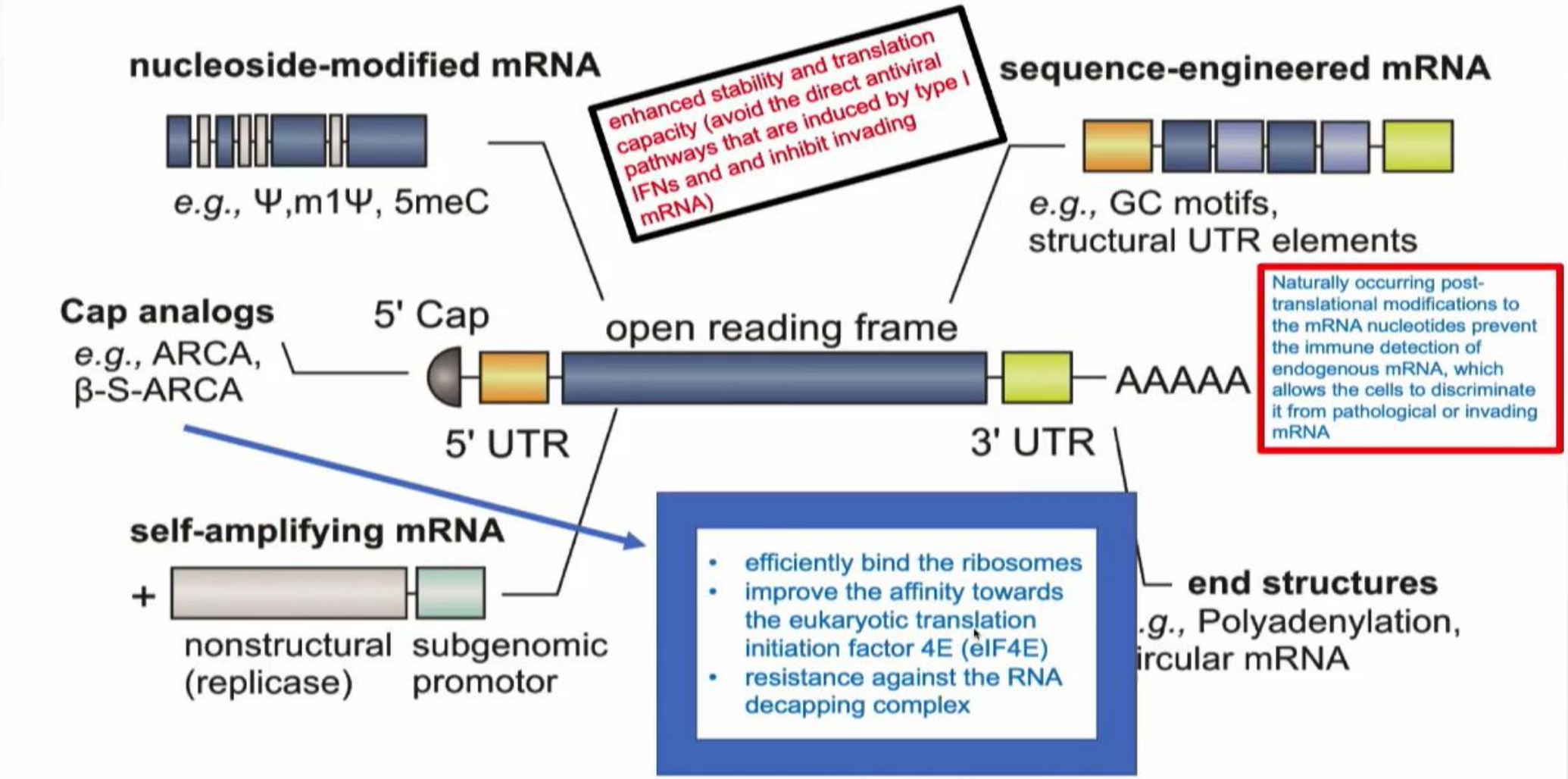
Clin Can Res 2022

Eduardo Vilar
The University of Texas MD Anderson Cancer Center

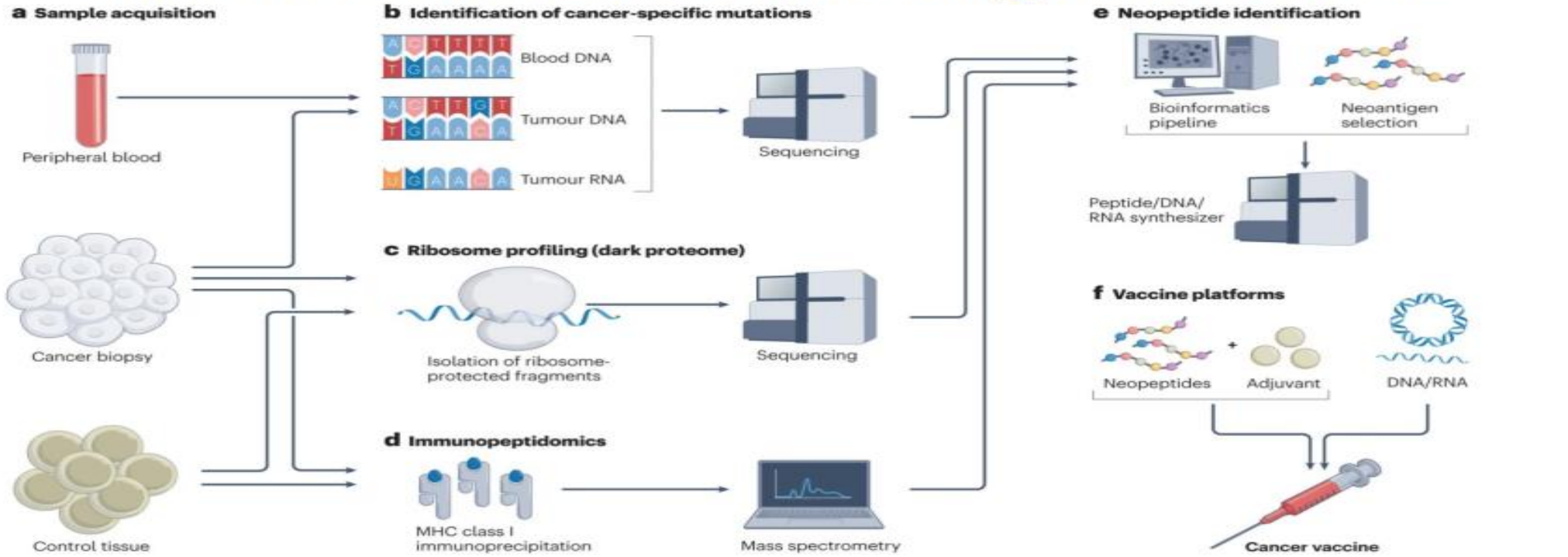
Cancer interception in Lynch syndrome

Lynch syndrome (LS) affects >1 million Americans, imparting significantly increased risks of several malignancies, especially colorectal and endometrial cancers. LS results from a heterozygous germline mutation in one of four DNA mismatch repair (MMR) genes. When LS cells harboring the germline defect acquire a somatic "second hit" in one of the MMR genes, they lose the ability to maintain genomic integrity, thereby accumulating hundreds to thousands of small insertion/deletions (indels) in microsatellite regions. When these indels occur in coding regions, they result in the expression of mutated neoantigens (frameshift peptides) that are presented on the cell surface via the major histocompatibility complexes (MHC-I/II). Extensive inter-individual variability in both the set of expressed neoantigens and MHC I/II responses has previously challenged the development of a neoantigen-based vaccines for LS patients. However, recent improvements in bioinformatic approaches now allow us to more accurately catalog and identify the most frequently recurring and shared neoantigens in LS-associated tumors. We can now combine sophisticated bioinformatic pipelines with state-of-the art immunology assessments to determine the most immunogenic neoantigens for inclusion in population-based vaccines. Using this approach, the Vilar Lab has worked with Nouscom, s.r.l., and the National Cancer Institute to develop a phase I clinical trial (NCT05078866) using a viral-based vaccine encoding 209 distinct mutated neoantigens present in LS tumors. The primary endpoint is the safety and assessment of immunogenicity. Forty-five participants will be enrolled to receive a prime and boost vaccine, based on a Great Apes and Modified Vaccina Ankara Virus, respectively. Going forward, it will be important to study the ability of NSAIDs to synergize with a vaccine, as preclinical work in an LS mouse model suggests that the combination of peptide vaccination with either aspirin or naproxen prolongs survival and reduces tumor burden significantly more than vaccination alone. A phase Ib trial in 80 LS patients provides further support for the ability of naproxen to activate different types of immune cells resident in the intestine.

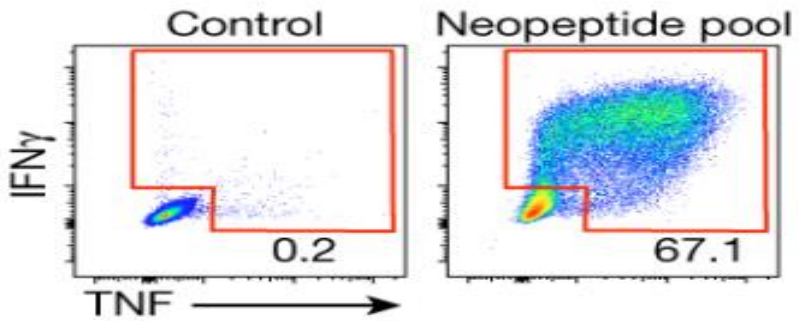
Nükleik asit tabanlı aşılar



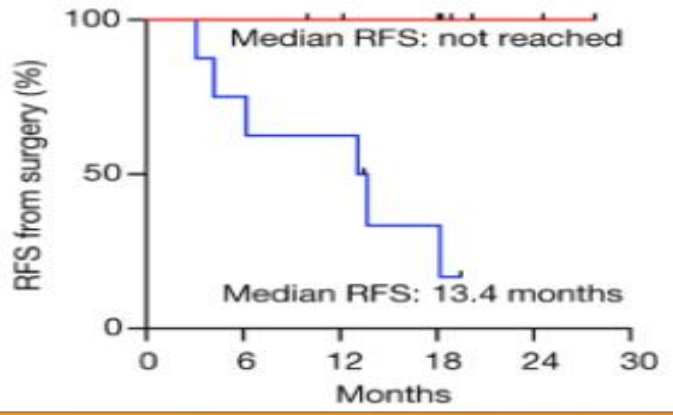
Cancer vaccines: Pre-defined Ag, Personalized



autogene cevumeran
BNT122/RO7198457



Responders (n = 8)
Non-responders (n = 8)
P = 0.003
HR: 0.08 (0.01–0.4)
Median follow-up: 18.0 months



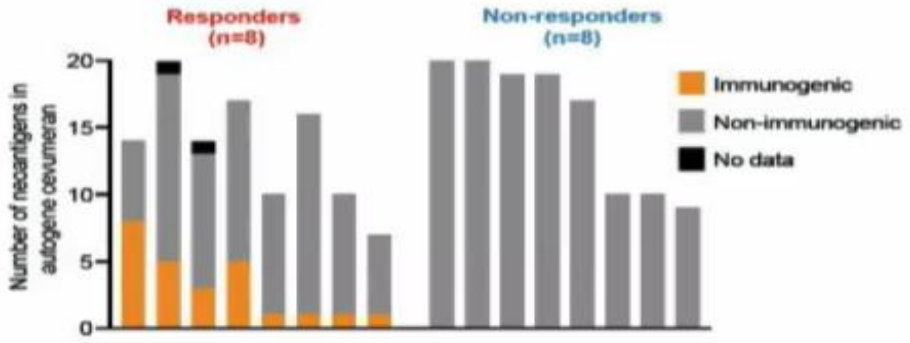
Balachandran VP et al, *Nature* 2023

Nükleik asit tabanlı aşılar

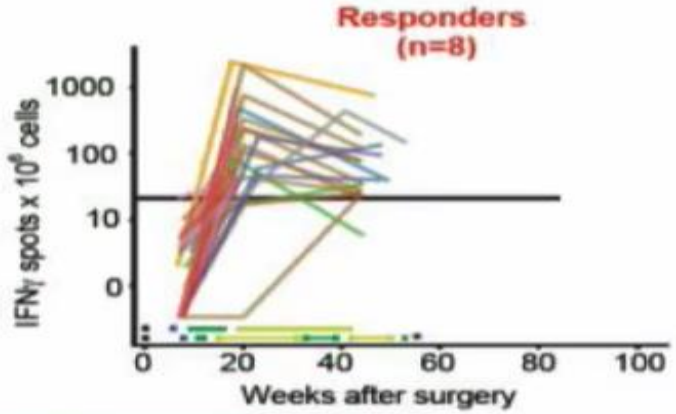
Phase I trial of adjuvant autogene cevumeran, an individualized mRNA neoantigen vaccine, for pancreatic ductal adenocarcinoma.

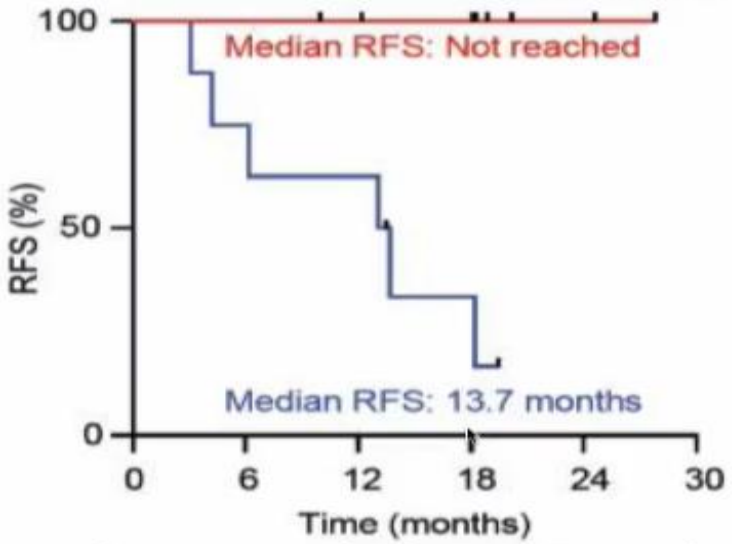
Vinod P. Balachandran, Luis A. Rojas, Zachary Sethna, Kevin Soares, Evelyna Derhovanessian, Felicitas Mueller, Mahesh Yadav, Olca Basturk, Mithat Gonen, Alice Chia-chi Wei, Michael Ian D'Angelica, T. Peter Kingham, Benjamin Greenbaum, Taha Merghoub, William R. Jarnagin, Jeffrey A. Drebin, Ugur Sahin, Oezlem Tuereci, Jedd D. Wolchok, Eileen Mary O'Reilly; Memorial Sloan Kettering Cancer Center, New York, NY; BioNTech SE, Mainz, Germany; Genentech, Inc., San Francisco, CA

ASCO 2022



Vaccine-induced T cells.			
	Median % of all blood T cells (95% CI)		
	Pre-vaccine	*Post-vaccine*	*P* value
Non-responders (n=8)	0 (0-0)	0 (0-0.6)	0.001
Responders (n=8)	0 (0-0)	2.9 (0.2-10.4)	





median not reached vs. 13.7 months, HR 0.08, 95% CI 0.01-0.5, $P = 0.007$

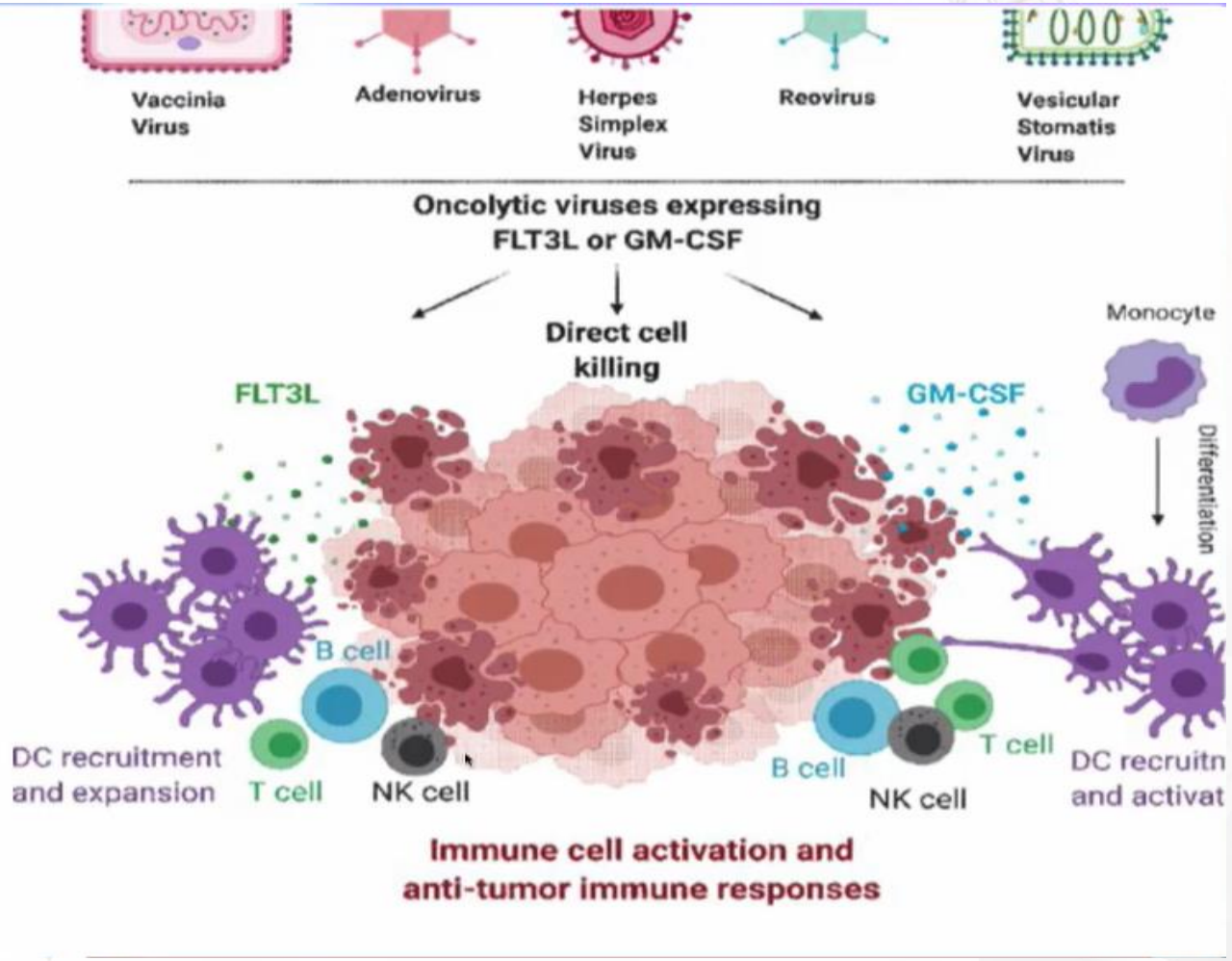
Patrick A. Ott
Dana Farber Cancer Institute

Personalized cancer vaccines

Cancer vaccines aim to eliminate tumor cells by stimulating and broadening T cell responses specific for those cells. The lack of a foreign invader to target against and the diversity and complexity of tumors are key obstacles and explain at least in part why it has been difficult to achieve successes similar to vaccines against infectious pathogens. The availability of powerful genomic sequencing technologies has enabled the targeting of neoantigens encoded by tumor mutations, which is conceptually attractive, as cancer is a disease driven and characterized by mutations. Because most mutations are specific to individual tumors (i.e., not shared) and the restriction of neoantigen epitopes to specific MHC molecules, vaccines directed at neoantigens ideally should be customized for each individual patient. Initial forays in the clinic have demonstrated that such personalized vaccines are feasible and immunogenic in patients with cancer. While signals for vaccine-mediated anti-tumor activity have been detected in these early trials, more definitive efficacy data from ongoing randomized studies are awaited. Key opportunities for further progress lie broadly in three arenas: (1) vaccine technology, (2) neoantigen discovery, and (3) co-therapies. Improved vaccine technology includes the development of optimal vaccine formulations, delivery vehicles, and immune adjuvants including most effective dosing and scheduling, as well as timely and cost-effective manufacturing processes. Innovation in the neoantigen discovery field can be achieved by further optimizing current neoantigen prediction tools including the development of new discovery tools that will allow tapping into new classes of neoantigens. Co-therapies will be critical to maximize priming of vaccine-induced T cells and to counteract

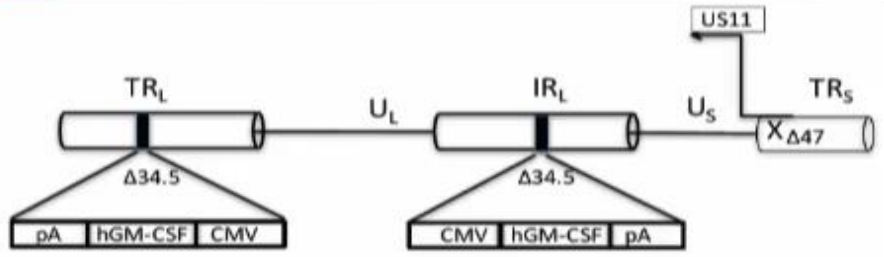
Virus tabanlı aşılar

ONKOLİTİK VİRÜSLER



VOLUME 33 · NUMBER 25 · SEPTEMBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Figure Modifications made to the JS1 backbone of herpes simplex virus type 1 (HSV-1) to generate talimogene laherparepvec.

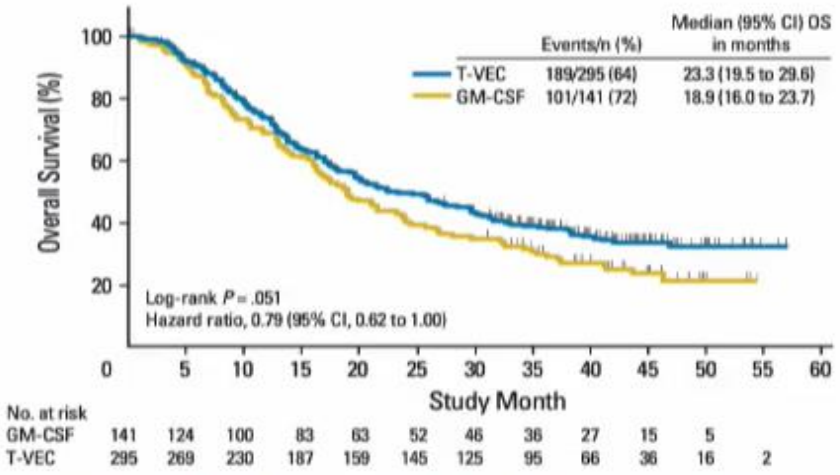


JS1 is an isolated strain of HSV-1 and has been modified by deletion of the 2 copies of the viral-infected cell protein 34.5 (ICP34.5) and ICP47 genes. These deletions result in a vector with improved tumor cell–selective replication, reduced pathogenicity, and enhanced immunogenicity. In place of the 2 viral ICP34.5 genes, 2 copies of the human gene-encoding granulocyte-macrophage colony-stimulating factor (GM-CSF) have been inserted to further augment host immunity.

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

Robert H.I. Andtbacka, Howard L. Kaufman, Frances Collichio, Thomas Amatruda, Neil Senzer, ...

Response	T-VEC (n = 295)	GM-CSF (n = 141)	P
DRR			< .001
Patients with durable response, No.	48	3	
DRR, %*	16.3	2.1	
95% CI	12.1 to 20.5	0 to 4.5	
Unadjusted odds ratio	8.9		
95% CI	2.7 to 29.2		
ORR			< .001†
CR			
No.	32	1	
%	10.8	< 1	
PR			
No.	46	7	
%	15.6	5.0	
ORR, %*	26.4	5.7	
95% CI	21.4 to 31.5	1.9 to 9.5	



UpToDate®

Evidence-based approach to prevention

PREVENTIVE ACTIVITIES IN CLINICAL SETTINGS

Immunization — Childhood immunizations to prevent 15 different diseases largely determine visit schedules to the pediatrician in the early months of life. Human papillomavirus (HPV) and meningococcal vaccinations are recommended for adolescents. Adult immunizations include diphtheria, pertussis, and tetanus (DPT) boosters as well as vaccinations to prevent influenza, pneumococcal pneumonia, and hepatitis A and B. COVID-19 vaccinations are recommended for children, adolescents, and adults. (See "Standard immunizations for children and adolescents:

Adult immunization schedule by age - Recommendations for ages 19 years or older, United States, 2024

+ 75% −

Vaccine	Age group (years)			
	19 through 26 years	27 through 49 years	50 through 64 years	≥65 years
COVID-19*	1 or more doses of updated (2023-2024 formula) (refer to footnotes)			
Influenza inactivated (IIV4)¶ or Influenza recombinant (RIV4)¶	1 dose annually			
or	or			
Influenza live, attenuated (LAIV4)¶	1 dose annually			
Respiratory syncytial virus (RSV)Δ	Seasonal administration during pregnancy. (Refer to footnotes.)			≥60 years
Tetanus, diphtheria, pertussis (Tdap or Td)◇	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (refer to footnotes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)§	1 or 2 doses depending on indication (if born in 1957 or later)			For health care personnel, (refer to footnotes)
Varicella (VAR)¥	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)‡	2 doses for immunocompromising conditions (refer to footnotes)		2 doses	
Human papillomavirus (HPV)†	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23)**				Refer to footnotes
				Refer to footnotes
Hepatitis A (HepA)¶¶	2, 3, or 4 doses depending on vaccine			
Hepatitis B (HepB)ΔΔ	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W, Y (MenACWY)◇◇	1 or 2 doses depending on indication, refer to footnotes for booster recommendations			
Meningococcal B (MenB)◇◇	2 or 3 doses depending on vaccine and indication, refer to footnotes for booster recommendations			
	19 through 23 years			
Haemophilus influenzae type b (Hib)§§	1 or 3 doses depending on indication			
Mpox¥¥				

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 73 / No. 1
January 11, 2024

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

- **HepB:** In the "Routine vaccination" section, additional context and details were added to the bullets describing the risk-based vaccination recommendation for persons aged ≥60 years. In addition, a note was added at the end of the "Routine vaccination" section describing the shared clinical decision-making recommendation for persons aged ≥60 years with diabetes.

UpToDate®

Hepatitis B vaccine — All unvaccinated patients with cancer aged 19 to 59 years and those ≥60 years old with risk factors (eg, diabetes mellitus, chronic liver disease, hepatitis C, hemodialysis, and other risk factors) should receive the hepatitis B vaccine [32]. As with other vaccines, cancer patients may have suboptimal response to the hepatitis B vaccine. Regimens that include doubling the standard antigen dose or administering additional doses may increase response rates but, given the limited data with these alternative regimens, this approach cannot be routinely recommended.

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 73 / No. 1
January 11, 2024

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

- **HPV:** In the "Routine vaccination" section, the recommendation for interrupted schedules was removed because that information is also presented on the Cover Page and applicable to all vaccines. In addition, to improve clarity, the words, "of any valency" were added to the bullet, "No additional dose recommended when any HPV vaccine series *of any valency* has been completed using the recommended dosing intervals."

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Human papillomavirus vaccine — Cancer patients through age 26 (and some adults aged 27 to 45 years) with an indication for human papillomavirus (HPV) vaccination should be immunized [33]. However, cancer patients may have a suboptimal antibody response and lower vaccine efficacy. Patients with thrombocytopenia are at risk of developing a hematoma after the intramuscular injection of the vaccine. Indications for HPV vaccination are discussed separately. (See "Human papillomavirus vaccination".)

Efficacy of Gardasil-4 in prevention of disease related to HPV 6, 11, 16, 18 at 36 months (PP)

CIN 2/3 or AIS	98%	(95% CI: 86.0 -100.0)
CIN 1	100%	(95% CI: 92.0 -100.0)
VIN 2/3 or VaIN 2/3	100%	(95% CI: 72.0 -100.0)
Genital warts	100%	(95% CI: 94.0 -100.0)

Joura et al. Lancet 2007; 369: 1693-702 , Garland et al. NEJM 2007; 356: 1928-43 *Koutsky et al. NEJM 2007; 356: 1915-27*

Vaccine Efficacy (Cervarix) against CIN2+ associated with HPV-16/18 (ATP- E)

HPV DNA type in the lesion	n cases (HPV)	n cases (Control)	VE (95% CI)
HPV-16/18	**1**	**97**	**99.0** (94.2, 100)
HPV-16	**1**	**83**	**98.8** (93.2, 100)
HPV-18	**0**	**20**	**100** (79.9, 100)

Paavonen J et al.Lancet 2009, Lehtinen M. et al. Lancet Oncol 2012

Vaccine efficacy against non-vaccine types (TVC-naïve)

	6-month persistent infection		CIN2+	
HPV type	n cases HPV/Control	VE % (95% CI)	n cases HPV/Control	VE % (95% CI)
HPV-31	38/163	**77.1** (67.2, 84.4)	3/28	**89.4** (65.5, 97.9)
HPV-33	53/92	**43.1** (19.3, 60.2)	5/28	**82.3** (53.4, 94.7)
HPV-45	13/61	**79.0** (61.3, 89.4)	0/8	**100** (41.7, 100)
12 non-vaccine HPV types**			45/102	**56.2** (37.2, 69.9)
Any oncogenic type***			46/151	**69.8** (57.8, 78.8)

*Efficacy against CIN2+ do not correct for HPV-16/18 co-infections in the lesions
TVC-naïve cohort = total vaccinated cohort of HPV-naïve women. At Month 0: Normal cytology; HPV DNA negative for 14 oncogenic types; Seronegative for HPV 16 and 18.N = 11,641; ≥ 1 dose; Case counting ≥ 1 day post-Dose 1.
n = number of evaluable women reporting at least one event in each group

Romanowski B on behalf of the PATRICIA study group. 26th International Papillomavirus Conference. 2010; Abstract

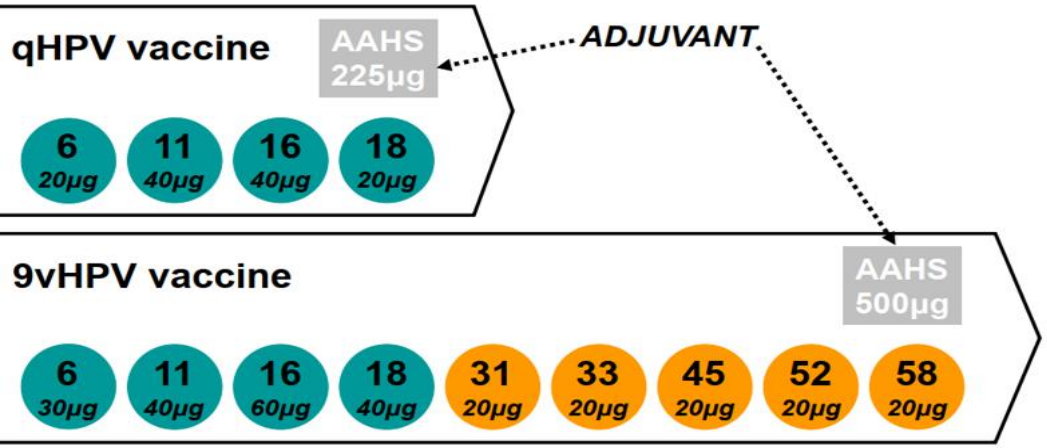
* HPV-31/33/35/39/45/51/52/56/58/59/66/68

PATRICIA – Final Analysis Irrespective of Type - Cervarix

		TVC – naïve				TVC			
Endpoint	Group	n	No. of cases	Rate	Efficacy (96.1% CI)	n	No. of cases	Rate	Efficacy (96.1% CI)
CIN1+	Vaccine	5,449	106	0.67	**50.1 (35.9,61.4)**	8,667	451	1.85	21.7 (10.7, 31.4)
	Control	5,436	211	1.35		8,682	577	2.37	
CIN2+	Vaccine	5,449	33	0.21	**70.2 (54.7,80.9)**	8,667	224	0.91	30.4 (16.4, 42.1)
	Control	5,436	110	0.70		8,682	322	1.31	
CIN3+	Vaccine	5,449	3	0.02	**87.0 (54.9, 97.7)**	8,667	77	0.31	33.4 (9.1, 51.5)
	Control	5,436	23	0.15		8,682	116	0.47	

Apter et al 2015

Comparison of 9vHPV Vaccine and qHPV Vaccine



Efficacy of Gardasil 9 Against HPV 31/33/45/52/58

Cervical/Vulvar/Vaginal Disease, Persistent Infection)

Per Protocol Efficacy Population

Endpoint	9vHPV Vaccine No. of cases/n	qHPV Vaccine No. of cases/n	Efficacy (95% CI)
CIN2+, VIN2/3, VaIN2/3	**1** / 6016	**30** / 6017	**96.7% (80.9, 99.8)**
All CIN, VIN, VaIN	**3** / 6016	**103** / 6017	**97.1% (91.8, 99.2)**
6-month persistent infection	**35** / 5939	**810** / 5953	**96.0% (94.4, 97.2)**

Joura *et al* NEJM 2015

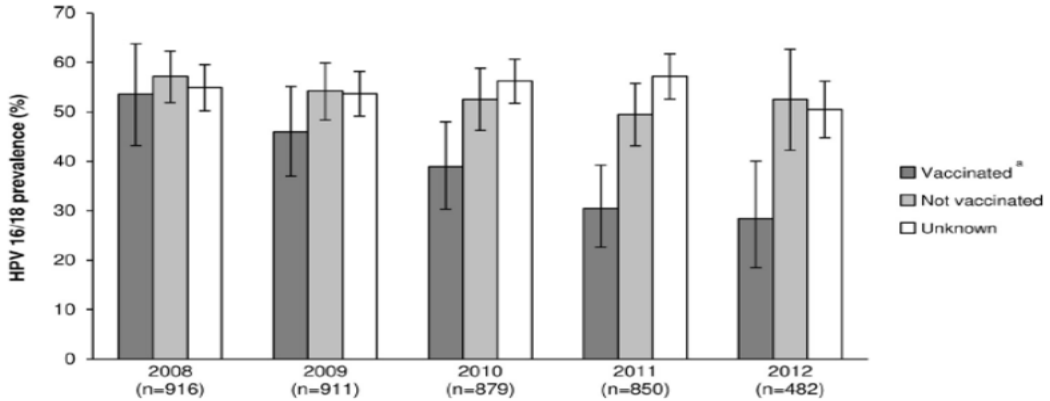
9-Valent Vaccine

- Potential 90 % protection again cervix cancer
- 50% protection against CIN2/3
- No serious toxicity
  - Some increase in injection site reactions

Current HPV Vaccine Programmes

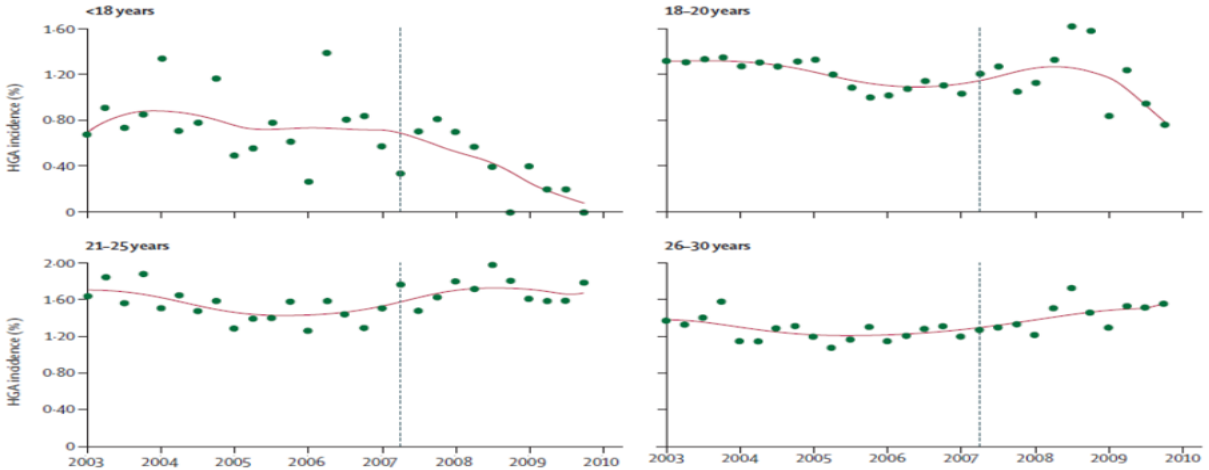
- Focussed on Girls aged 12-14y
- Virtually 100% effective for vaccine types if given before infection
- Long period before vaccinated girls will benefit

Impact of Vaccination on CIN2+ in the USA



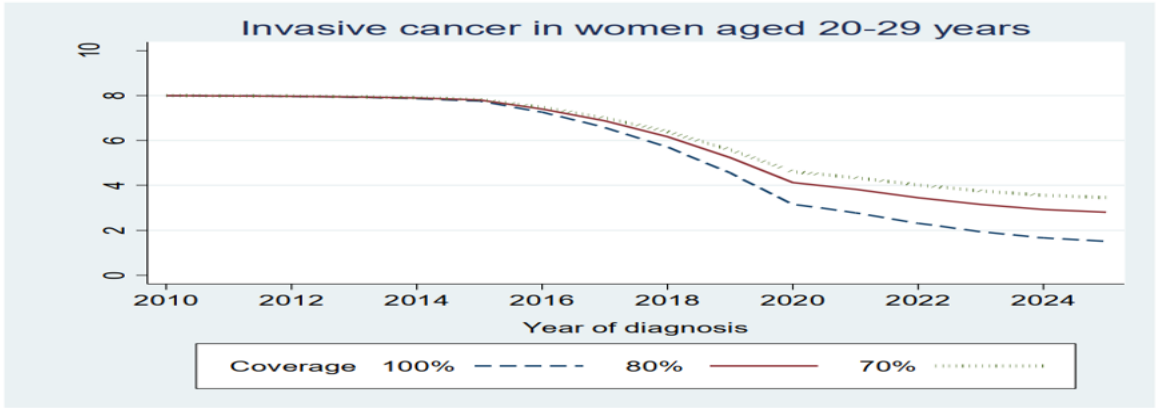
Hariri *et al*, Vaccine 2015

Incidence of High Grade CIN by Age after Vaccine Introduction
Victoria, Australia



Brotherton *et al* 2011

Effect of HPV Vaccine over Time
Invasive Cancer

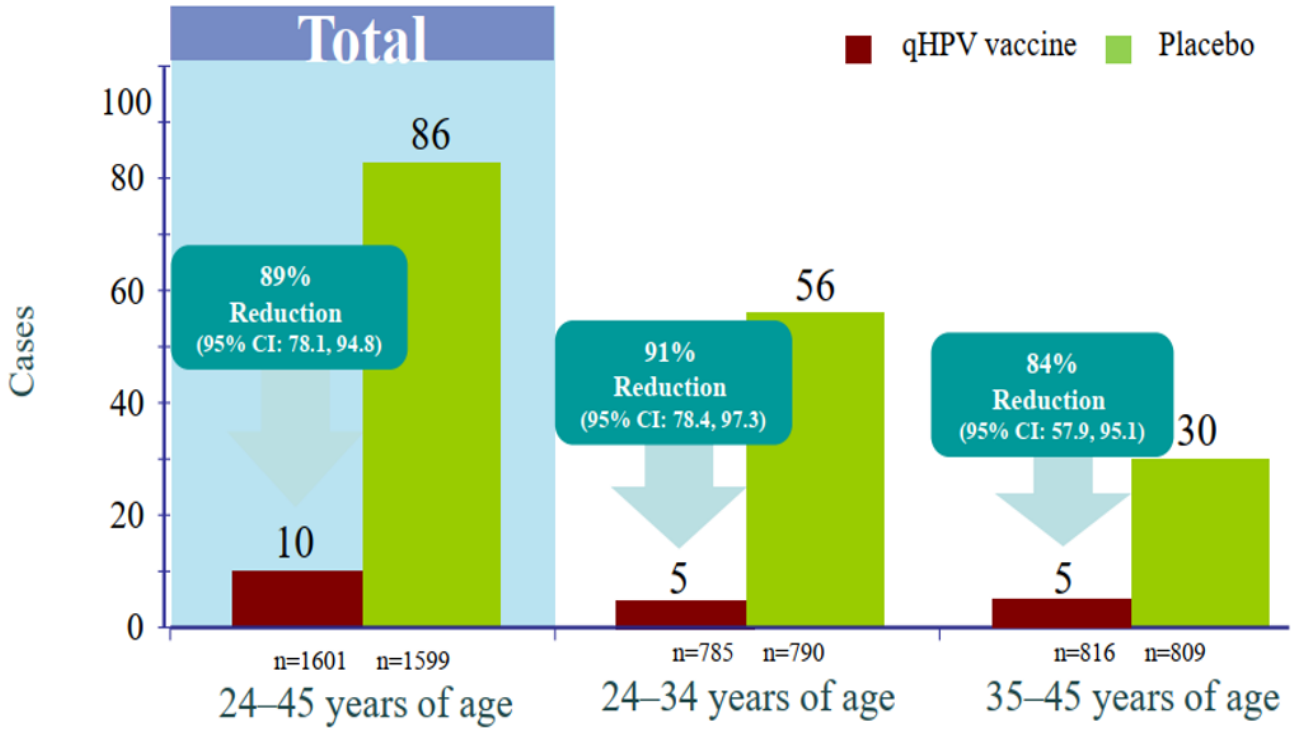


Cuzick et al Br J Cancer 2010

Adult Women (Age 24-45y, N = 3819)

Per protocol population End-of-Study Results (Gardasil)

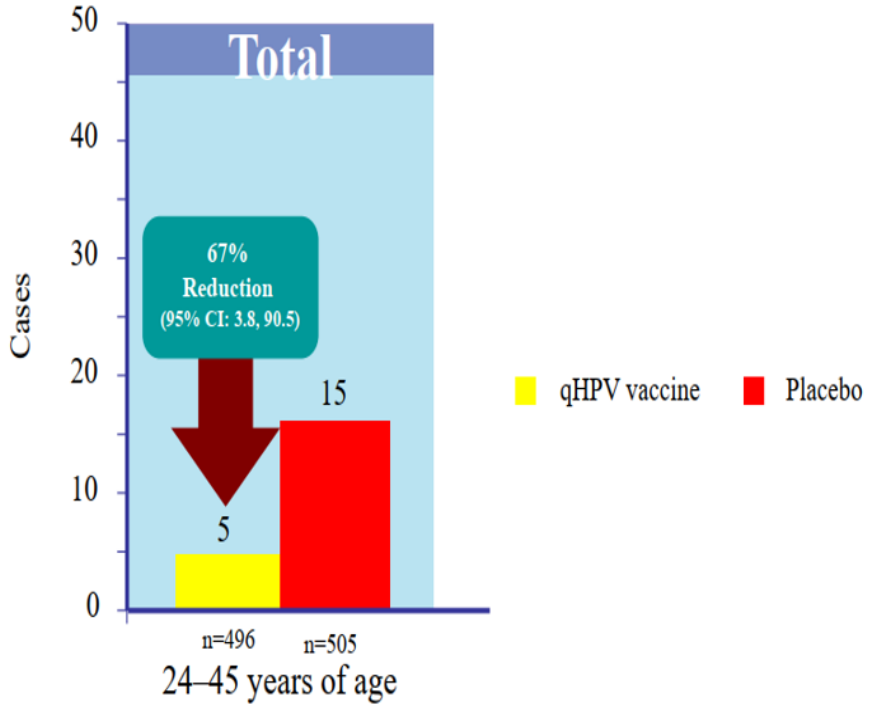
Efficacy against combined incidence of HPV 6/11/16/18–Related Persistent Infection, CIN (any grade), and EGLs



Castellsagué X et al. *Br J Cancer*. 2011

Adult Women (Age 24-45y)

Efficacy against persistent infection in subjects with **previously cleared vaccine HPV type infection** (seropositive/DNA negative)



Castellsagué X et al. *Br J Cancer*. 2011

VIVIANNE - Women aged 26- 45y
According to Protocol – 4y follow up

	Vaccine group*			Control group			Efficacy (97·7% CI)	Number cases prevented per 100 000 woman-years (97·7% CI)
	n	Cases	Rate	n	Cases	Rate		
According-to-protocol cohort for efficacy								
Combined primary endpoint (6-month persistent infection or CIN1+)								
All	1898	7	0·11	1854	36	0·58	81·1% (52·1 to 94·0)	474 (252 to 751)
26–35 years	857	4	0·14	819	23	0·86	83·5% (45·0 to 96·8)	720 (320 to 1247)
36–45 years	827	3	0·11	822	13	0·47	77·2% (2·8 to 96·9)	364 (44 to 779)
≥46 years	214	0	0·00	213	0	0·00	..	0 (-705 to 706)
6-month persistent infection								
All	1859	6	0·09	1822	34	0·55	82·9% (53·8 to 95·1)	459 (245 to 730)
26–35 years	834	3	0·11	800	22	0·83	87·1% (50·4 to 98·2)	721 (341 to 1239)
36–45 years	816	3	0·11	809	12	0·44	75·4% (-7·5 to 96·7)	329 (14 to 734)
≥46 years	209	0	0·00	213	0	0·00	..	0 (-708 to 706)
CIN1+								
All	1898	1	0·02	1854	7	0·11	86·1% (-35·4 to 99·9)	98 (-8 to 248)
CIN2+								
All	1898	0	0·00	1854	4	0·06	100% (-100·7 to 100·0)	65 (-17 to 192)

Skinner et al , Lancet 2014

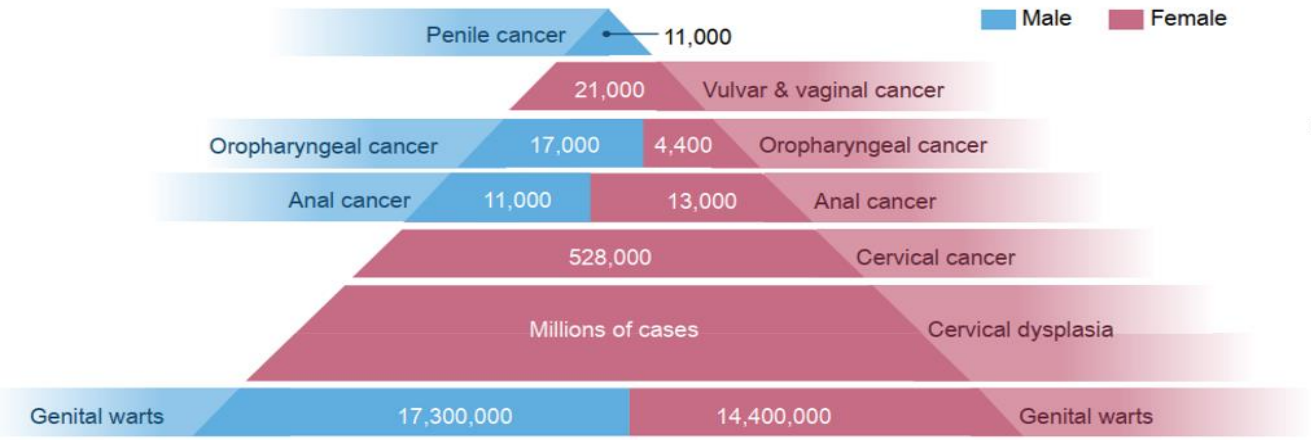
VIVIANNE - Women aged 26- 45y
Total Vaccinated Cohort – 4y follow up

	Vaccine group*			Control group			Efficacy (97·7% CI)	Number cases prevented per 100 000 woman-years (97·7% CI)
	n	Cases	Rate	n	Cases	Rate		
Total vaccinated cohort								
Combined primary endpoint (6-month persistent infection and CIN1+)								
All	2772	90	0·89	2779	158	1·59	43·9% (23·9 to 59·0)	698 (346 to 1065)
26–35 years	1225	63	1·46	1243	97	2·26	35·4% (5·8 to 56·1)	800 (140 to 1482)
36–45 years	1245	23	0·50	1229	48	1·07	53·4% (15·7 to 75·2)	569 (156 to 1022)
46+ years	300	4	0·35	307	13	1·14	69·3% (-15·6 to 94·3)	792 (-33 to 1801)
6-month persistent infection								
All	2767	71	0·70	2776	132	1·32	47·0% (25·4 to 62·7)	620 (303 to 952)
26–35 years	1221	48	1·10	1242	78	1·80	38·7% (5·9 to 60·6)	695 (115 to 1301)
36–45 years	1244	19	0·41	1228	43	0·95	57·0% (18·2 to 78·5)	543 (159 to 971)
≥46 years	300	4	0·35	306	11	0·96	63·6% (-44·4 to 93·4)	613 (-186 to 1566)
CIN1+								
All	2740	35	0·34	2737	56	0·55	37·8% (-3·2 to 63·1)	209 (-5 to 433)
CIN2+								
All	2740	32	0·31	2737	45	0·44	29·1% (-22·5 to 59·6)	129 (-69 to 335)

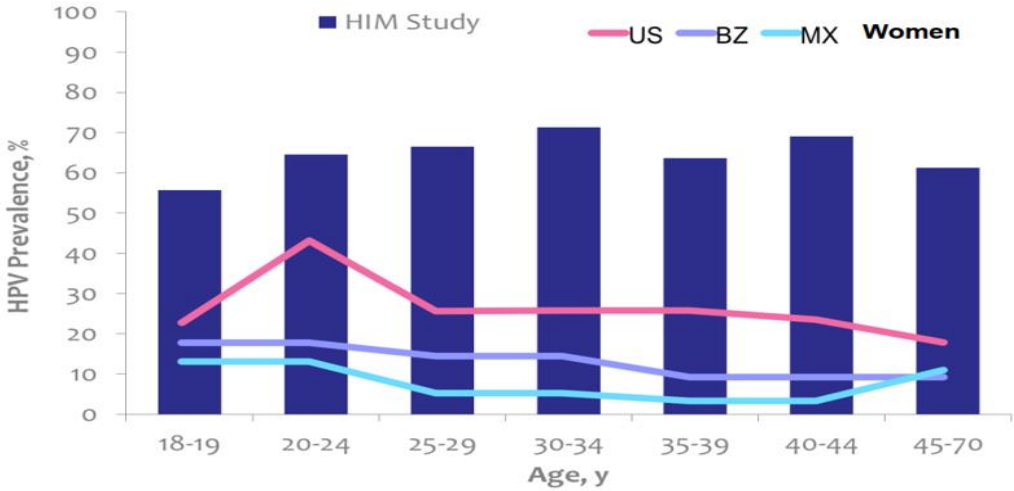
Skinner et al , Lancet 2014

HPV Disease Burden Among Males

Global Estimated Annual New HPV-Related Disease Cases in Males and Females



Genital HPV Prevalence is Higher in Men than Women and Does Not Vary with Age



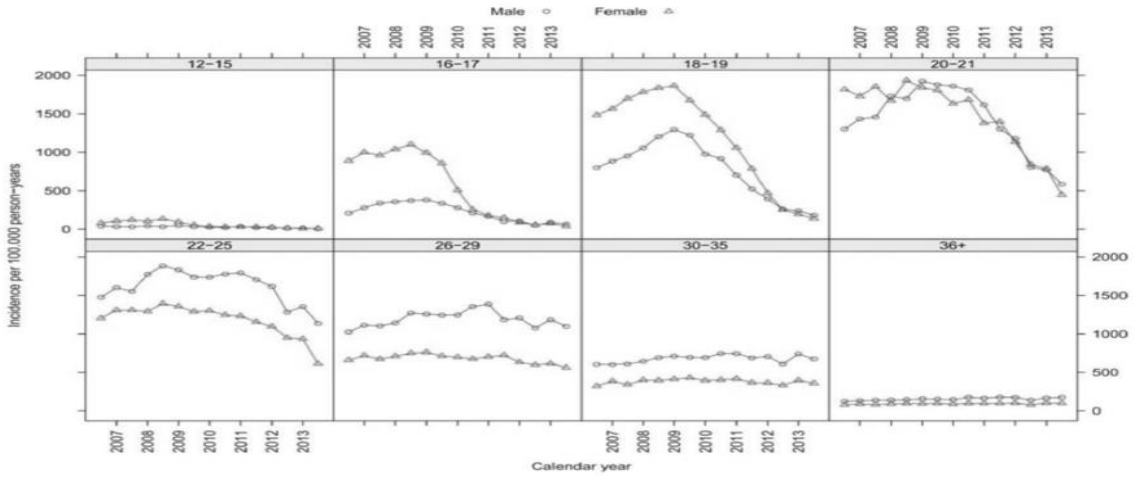
Giuliano AR et al., *CEBP* 2008; Dunne E et al., *JAMA* 2007.

Efficacy Against HPV 6/11/16/18 Related Genital Warts in Males aged 16-26y

	qVaccine		Placebo			
population	Cases	Inc. per 100 PY	Cases	Inc. per 100 PY	Efficacy (%)	95% CI
Per protocol (N = 2805)	3	0.11	28	1.00	89.4	65.5, 97.9
ITT (N = 4055)	24	0.52	72	1.58	67.2	47.3, 80.3

Giuliano AR, Palefsky J, et al. *N Engl J Med* 2011

Genital Warts in Denmark 2006-2013



Bollerup et al , Sex Trans Dis 2016

Global burden of HPV HNSCC, 2012

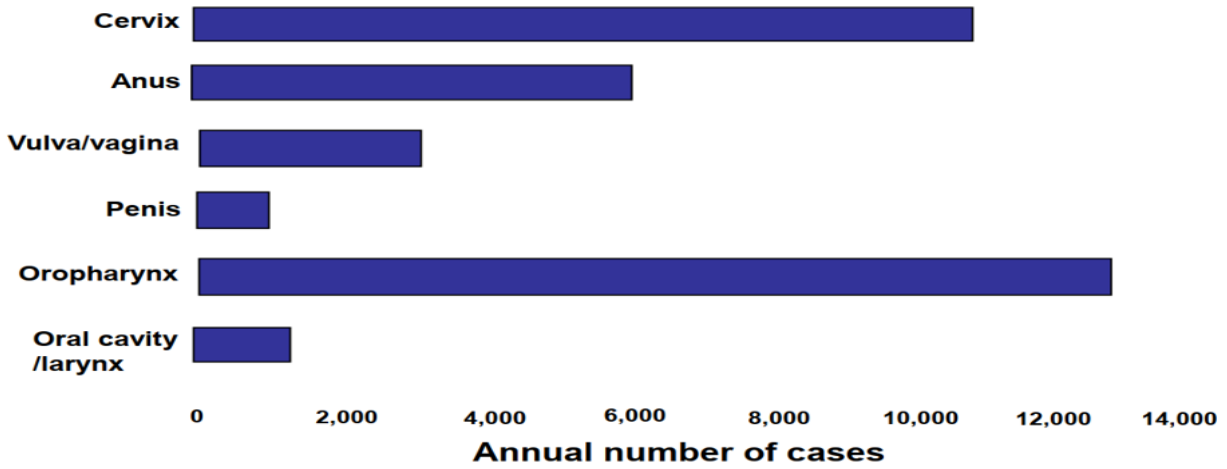
Site	Cases	HPV AF(%)	Burden
Oropharynx	96,000	30.8	29,000
Oral cavity	200,000	3.9	4,400
Larynx	160,000	2.4	3,800
Total	--	--	37,200*

32,768 (88.1%) attributable to HPV16/18/31/33/45/52/58/6/11

Castellsague, J Natl Cancer Inst 2016;
De Sanjose S, JNCI Cancer Spectrum 2019; De Martel C, Int J Cancer 2017

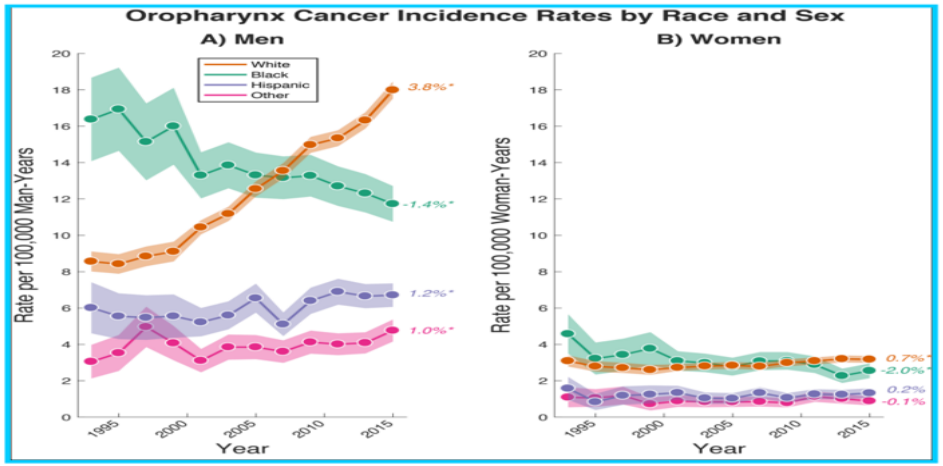
Incidence and Distribution of Cancers Attributable to HPV

United States



Modified from CDC MMWR 2018

OPC Incidence Trends, US 1990-2015



Tota J J Clin Oncol 2019

Recommended number of doses and intervals for human papillomavirus (HPV) vaccine United States, 2016

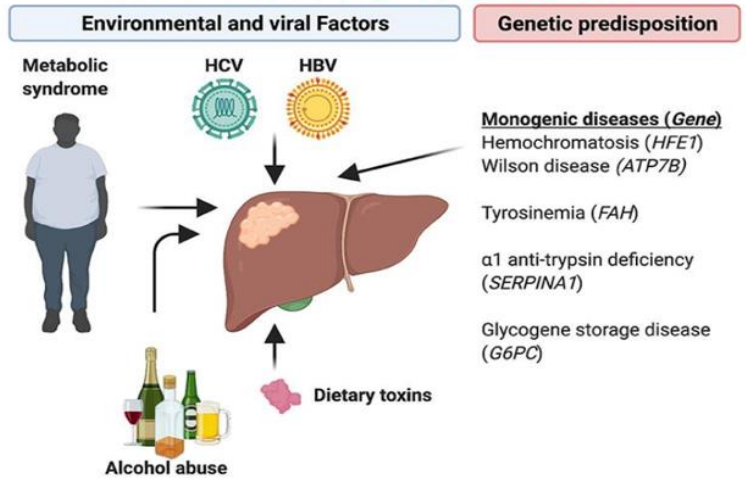
Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Population	Recommended number of HPV vaccine doses	Recommended interval between doses
Persons initiating HPV vaccination at ages 9 through 14 years,* except immunocompromised persons	2	0, 6–12 months
Persons initiating HPV vaccination at ages 15 through 26 years and immunocompromised persons initiating HPV vaccination at ages 9 through 26 years	3	0, 1–2, 6 months

Deites et al, MMWR Morb Mortal Wkly Rep 2016;65:1405–1408. DOI: http://dx.doi.org/10.15585/mmwr.mm6549a5external

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

LIVER CANCER

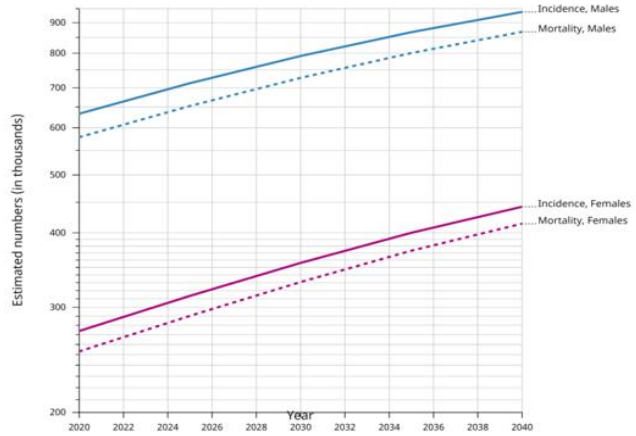


ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Risk factors for HCC and geographical variability.

Estimated numbers from 2020 to 2040, Males and Females, age [0-85+]
Liver and intrahepatic bile ducts
WHO Africa (AFRO) + WHO Americas (PAHO) + WHO East Mediterranean (EMRO) + WHO Europe (EURO) + WHO South-East Asia (SEARO) + WHO Western Pacific (WPRO)

GLOBAL CANCER OBSERVATORY



Cancer Vaccine Clinical Trial Targets

Vaccine targets under evaluation in clinical trials include:

- **5T4:** an antigen often expressed by several different types of cancers
- **CEA:** a protein involved in cellular adhesion normally produced only before birth; often abnormally expressed in cancer and may contribute to metastasis
- **Cytomegalovirus (CMV)-related antigens:** foreign viral proteins expressed by CMV-infected cancer cells
- **Folate-related proteins:** proteins in this pathway are commonly overexpressed in cancer
- **EGFR:** a pathway that controls cell growth and is often mutated in cancer
- **HER2:** a pathway that controls cell growth and is commonly overexpressed in breast cancer and is associated with metastasis, or disease spread
- **Human Papilloma Virus (HPV)-related antigens:** foreign viral proteins expressed by HPV-infected cancer cells
- **MAGE antigens:** the genes that produce these proteins are normally turned off in adult cells, but cancer cells often reactivate their expression
- **Mesothelin:** a protein that is commonly overexpressed in cancer and may aid metastasis
- **MUC-1:** a sugar-coated protein that is commonly overexpressed in cancer
- **NY-ESO-1:** a protein that is normally produced only before birth but is often abnormally expressed in cancer
- **P53:** a tumor suppressor protein that is often mutated, nonfunctional, and overexpressed in cancer
- **PAP and PSA:** enzymes made by prostate cells that is often overproduced by prostate tumors
- **Personalized neoantigens:** these abnormal markers arise from mutations and are expressed exclusively by tumor cells
- **Ras:** a central signaling protein that is commonly mutated in cancer and has been linked to abnormal growth and cell division
- **Survivin:** a protein that can prevent cellular death and is overexpressed by a number of cancer cell types
- **Telomerase:** an enzyme that helps maintain the health of cellular DNA; exploited by cancer cells to achieve immortality
- **Tumor-associated antigens:** antigens often expressed at abnormally high levels on tumor cells and can be used to target them; also found on normal cells at lower levels
- **WT1:** a protein that is often mutated and abnormally expressed in patients with cancer, especially Wilms' tumor

- TEŞEKKÜRLER…