Cancer Vaccines

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Vaccines

- Are made from weakened or harmless versions of the disease
- Once administered it manufactures antibodies
- These antibodies can recognize the disease causing agent if the person come into contact with it in future

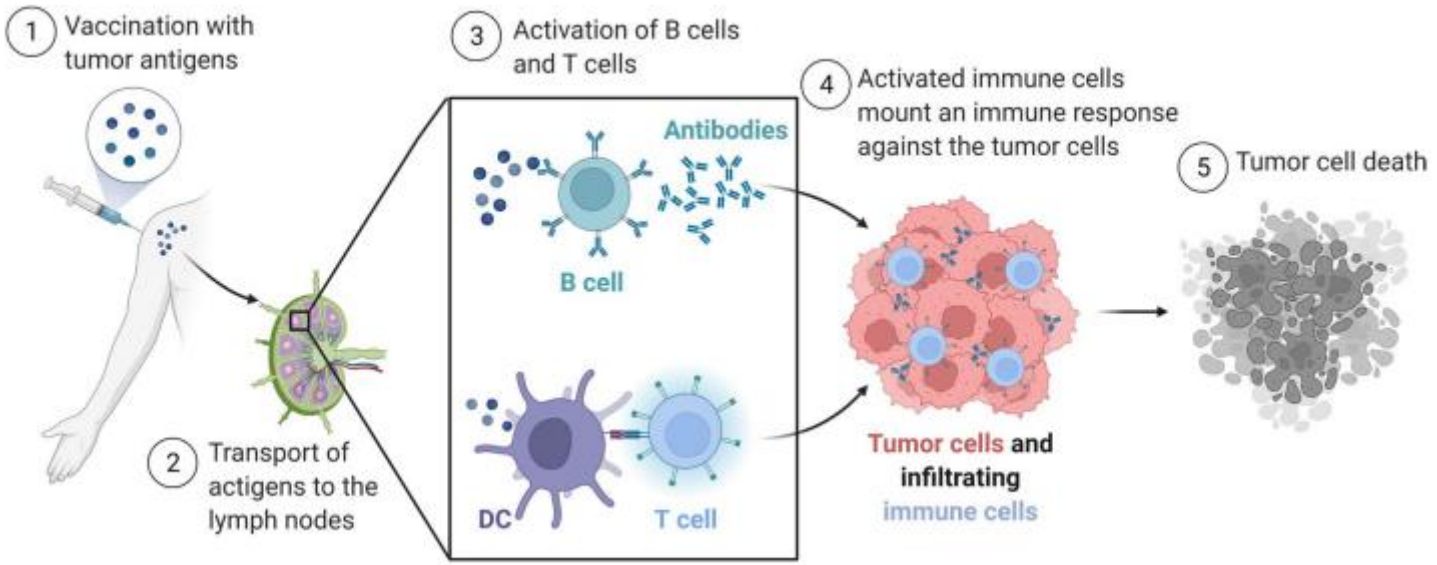
Vaccination Programme

- Vaccines - effective in preventing diseases caused by viruses and bacteria
- First vaccine was developed more than 200 years ago
- Vaccines have prevented some of the twentieth century's deadliest diseases and have helped save hundreds of millions of lives globally
  - Viruses (e.g., measles, polio, and smallpox) and
  - Bacteria (e.g., diphtheria, tetanus, and tuberculosis)
- WHO reports that licensed vaccines are currently available for 25 different preventable infections.
- The past few years have seen tremendous breakthrough in vaccine technology, including the most recent use of nucleic acid vaccines against COVID-19 infection
- Currently vaccines are available for 25 different preventable infections
- COVID-19 vaccine – a recent breakthrough

Cancer Vaccine – Mechanism of Action

- Antigens for tumor antigen vaccines are derived from cancer cells
- Vaccine containing tumor antigens train the immune system to target cancer cells not healthy cells
- Cancer-specific tumor antigens are activated in cancer cells or peptides containing cancer-specific mutations
- Antigen-presenting cells (APCs) such as dendritic cells take up antigens from the vaccine, process them into epitopes, and present the epitopes to T-cells via Major Histocompatibility Complex proteins.
- If T-cells recognize the epitope as foreign, the adaptive immune system is activated and target cells that express the antigens

Cancer Vaccine – Mechanism of Action



Types of Cancer Vaccine

1. Preventive Cancer Vaccines
   - Hepatitis B Vaccine
   - HPV vaccine

2. Therapeutic Cancer Vaccines
   - BCG Vaccine
   - Sipuleucel-T vaccine

Cancer Vaccine

Currently in use

Vaccine	Target antigen	Use	Cancer Type
Hepatitis B	Hepatitis B virus (HBV) surface antigen (HBsAg)	Preventative	Hepatocellular carcinoma caused by chronic HBV infection
Cervarix	L1 protein of Human papilloma virus (HPV) types 16 and 18	Preventative	HPV-associated cervical, oropharyngeal, anal, penile, and vulvovaginal cancers
Gardasil-4	L1 protein of HPV types 6, 11, 16, and 18	Preventative	HPV-associated cervical, oropharyngeal, anal, penile, and vulvovaginal cancers
Gardasil-9	L1 protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58	Preventative	HPV-associated cervical, oropharyngeal, anal, penile, and vulvovaginal cancers
Bacillus Calmette-Guerin (BCG)	Non-pathogenic *Mycobaterium bovis*	Therapeutic	high-risk non-muscle-invasive bladder cancer (NMIBC)
Sipuleucel-T (Provenge)	Prostate acid phosphatase (PAP) protein	Therapeutic	Castration-resistant prostatic cancer

Hepatitis B Vaccine

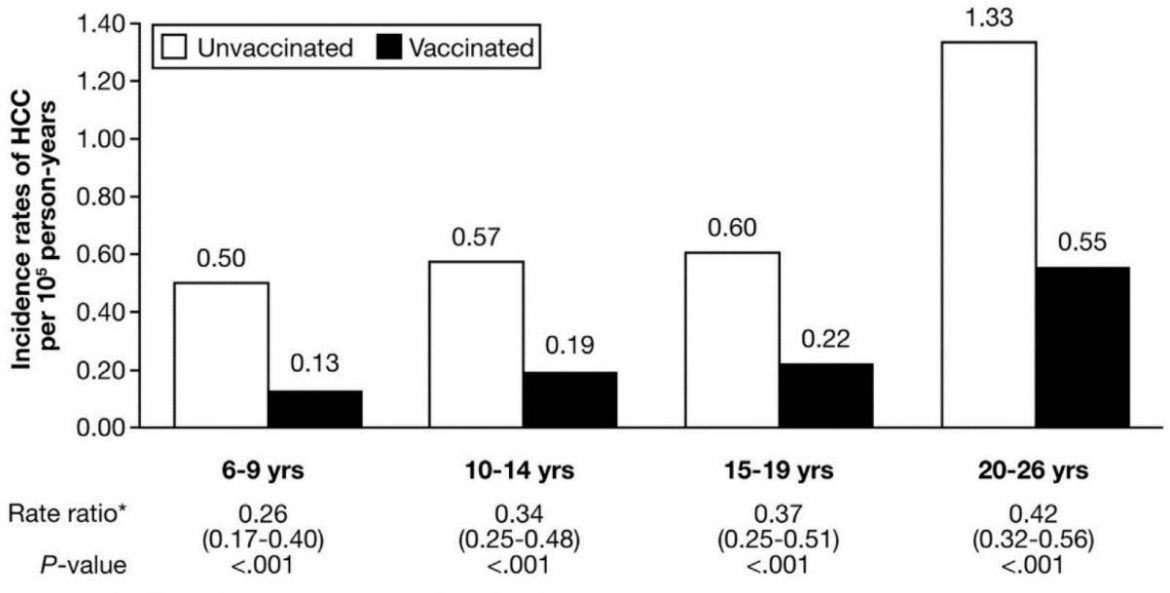
Hepatitis B Vaccine

- Hepatitis B – Can cause of liver cirrhosis and HCC
- An estimated 296 million people living with chronic hepatitis B infection, resulting in more than 820,000 deaths annually due to liver cirrhosis and HCC
- Hepatitis B is the cause of a third of all liver cancer deaths worldwide
- HCC risk is associated with persistent infection and there is typically a lag time of thirty to forty years between infection onset and HCC development

Hepatitis B Vaccine

- First developed in the 1970s
- The first ever cancer-preventing vaccine

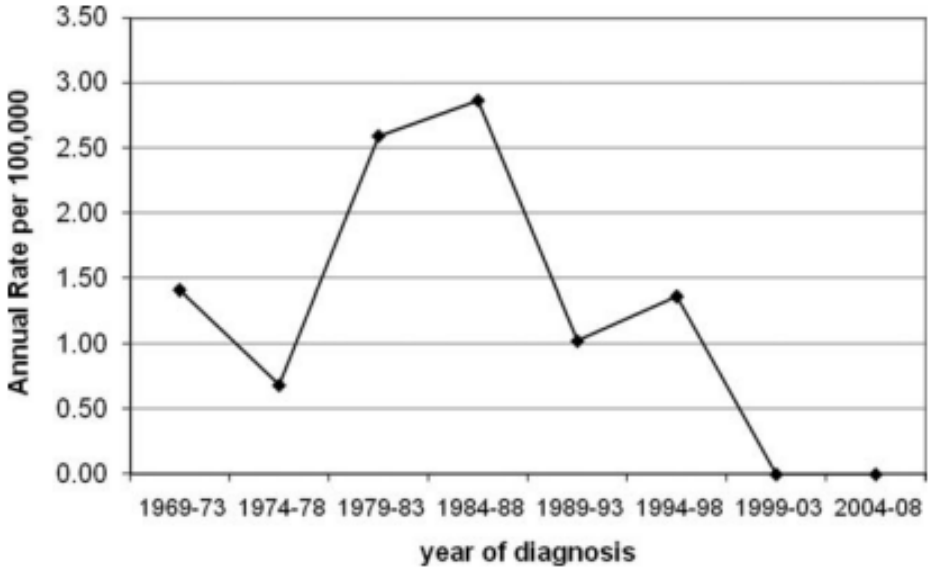
Impact of HBV vaccine on HCC incidence



Comparison of HCC incidence rate ratios (95% CI) by age group cohorts born before and after the commencement of the universal hepatitis B vaccination program in Taiwan

An impressive success story

Elimination of HCC under the age of 20 years in Alaska (USA)



HBV Vaccine – WHO Recommendation

- WHO recommends HBV vaccine for infants soon after birth
- 3 doses of the vaccine - highly affective in providing long-lasting immunity against chronic HBV infection

- Hepatitis B vaccination remains the cornerstone of public health policy to prevent HCC and a vital component of the global hepatitis B elimination response
  - The WHO has set a 90% vaccination target to achieve hepatitis B elimination by 2030

Cervical Cancer Vaccine

Magnitude of problem

- HPV types (16 and 18) are responsible for nearly 50% of high grade cervical pre-cancers
- HPV is mainly transmitted through sexual contact and most people are infected with HPV shortly after the onset of sexual activity
- More than 90% of them clear the infection eventually
- 95% of cervical cancer cases worldwide are caused by persistent infections with oncogenic strains of HPV (IARC data)
- 352,000 - new cases of cervical cancer in 2020 in Asia (GLOBOCAN)
- 200,000 women in Asia died from cervical cancer in 2020

Comprehensive cervical cancer control

Includes:

1. Primary prevention (vaccination against HPV)
2. Secondary prevention (screening and treatment of pre-cancerous lesions)
3. Tertiary prevention (diagnosis and treatment of invasive cervical cancer) and palliative care

Primary prevention	Secondary prevention	Tertiary prevention
Girls 9–14 years • HPV vaccination **Girls and boys should also be offered, as appropriate** • Health information and warnings about tobacco use • Sex education tailored to age and culture • Condom promotion and provision for those engaged in sexual activity • Male circumcision	**From 30 years of age for women from the general population and 25 years of age for women living with HIV** • Screening with a high-performance test equivalent or better than HPV test • Followed by immediate treatment or as quickly as possible after an HPV molecular positive test.	**All women as needed** Treatment of invasive cancer at any age • Surgery • Radiotherapy • Chemotherapy • Palliative care

Cervical Cancer Vaccine

HPV Vaccine – WHO Recommendation

- Currently 4 vaccines that have been prequalified by WHO, all protecting against HPV types 16 and 18, which are known to cause at least 70% of cervical cancers
- The 9-valent vaccine protects against 5 additional oncogenic HPV types, which cause a further 20% of cervical cancers
- Two of the vaccines also protect against HPV types 6 and 11, which cause anogenital warts
- Clinical trials and post-marketing surveillance have shown that HPV vaccines are
  - safe and effective in preventing infections with HPV infections, high grade precancerous lesions and invasive cancer
- HPV vaccines work best if administered prior to exposure to HPV
- Therefore, to prevent cervical cancer WHO recommends vaccinating girls aged 9 to 14 years, when most have not started sexual activity.
- Some countries have started to vaccinate boys as the vaccination prevents HPV related cancers in males as well as

HPV vaccination does not replace cervical cancer screening

Cervical Cancer Vaccine

Indications and age range – USA

- Advisory Committee on Immunization Practices (ACIP) in the United States recommend routine HPV vaccination for all females and males in the following age ranges:
  - Routine HPV vaccination is recommended at 11 to 12 years
    - It can be administered starting at 9 years of age.
  - For adolescents and adults aged 13 to 26 years who have not been previously vaccinated or who have not completed the vaccine series, catch-up vaccination is recommended
  - For adults 27 years and older, catch-up vaccination is not routinely recommended; the ACIP notes that the decision to vaccinate people in this age group should be made on an individual basis.

Gardasil 9

- In USA, the 9-valent vaccine (Gardasil 9) is specifically approved for prevention of:
  - Cervical
  - Vulvar
  - Vaginal
  - Anal
  - Oropharyngeal
  - Anogenital precancerous and dysplastic lesions, and genital warts
  - In males: for prevention of anal, oropharyngeal, and other head and neck cancers, anal precancerous and dysplastic lesions, and genital warts

Cervical Cancer Vaccine

Immunization schedule

- For immunocompetent individuals starting any HPV vaccine series when they are younger than 15 years old
  - A two- rather than a three-dose vaccine series
  - In such patients, the two doses are administered at least six months apart

- For individuals starting any HPV vaccine series at 15 years and older, the HPV vaccine is administered in three doses at 0, at 1 to 2 months, and at 6 months

- Immunocompromised patients, regardless of age, should also receive a three-dose series

Cervical Cancer Vaccine

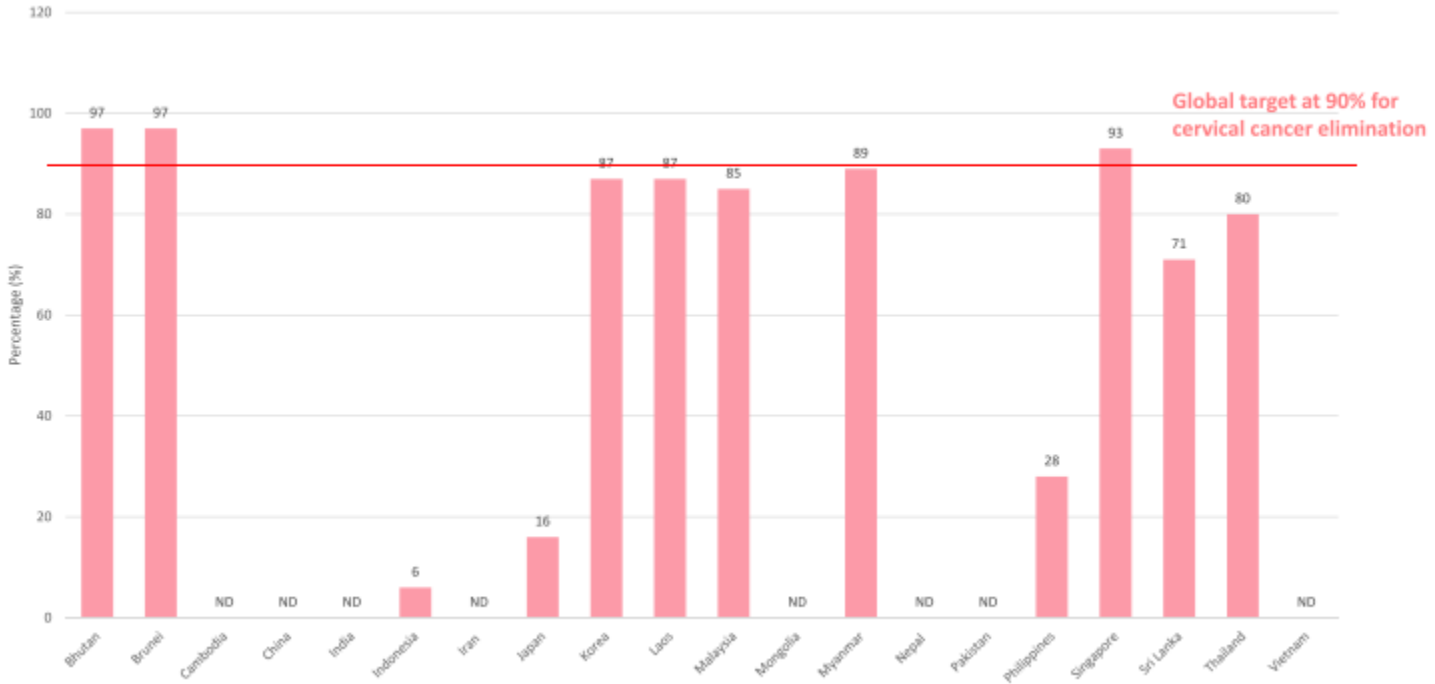
- **Immunogenicity** - Seroconversion rates of 93 to 100 percent in females and 99 to 100 percent in males

- **Vaccine safety** - Data from both registration trials and post-licensure safety surveillance systems demonstrate that the
  - Vaccine is safe and well tolerated apart from mild injection site reactions
  - Postvaccination syncopal events have emerged as a potential serious adverse effect, although it does not appear unique to HPV vaccination

Cervical cancer burden and HPV vaccination indicators

	Population (thousand)	ASIR	ASMR	HPV vac prog[a]	Year HPV vaccine introduced	Target age (school year)	HPV vac rate[b]	Population of girls aged 15 (thousand)
Bangladesh	166,427	10.6	6.7	O	2016	10–15	ND	1616
Bhutan	770	14.2	8.4	N	2010	12–18	97	7
Brunei Darussalam	440	20.8	5.7	N	2012	11–16	97	3
Cambodia	16,296	14	8.3	O	2017	9	ND	150
China	1,423,998	10.7	5.3	O	2016	ND	ND	7511
India	1,389,966	18	11.4	O	2008	9–14	ND	12 027
Indonesia	270,826	24.4	14.4	N	2017	11–16	6	2219
Iran	86,990	2.3	1.5	O	2019	9–14	ND	588
Japan	125,543	15.2	2.9	N	2013	12–16	16	530
Korea, Republic of	51,858	11.4	1.7	N	2016	11–12	87	211
Lao PDR	7266	12	6.7	N	2020	10–14	87	73
Malaysia	33,004	10.2	5.8	N	2010	13	85	442
Mongolia	3322	19.7	11.6	O	2012	11–15	ND	23
Myanmar	53,228	22.6	14.4	N	2020	9–10	89	442
Nepal	28,999	16.4	11.1	O	2016	11–13	ND	307
Pakistan	225,113	6.1	4.0	O	2019	ND	ND	2464
Philippines	111,288	15.2	7.9	P	2015	9–14	28	1072
Singapore	5894	6.7	1.8	N	2010	12–13	93	24
Sri Lanka	21,683	9.2	4.9	N	2017	10–11	71	178
Thailand	71,389	16.4	7.4	N	2017	11–12	80	396
Vietnam	96,204	6.6	3.4	P	2019	9–13	ND	668

HPV vaccination coverage of girls by age 15 years with at least 1 dose of the vaccine



BCG Vaccine

- BCG is a non-pathogenic bacterium derived from Mycobacterium bovis, which induces a protective immune response against tuberculosis caused by M. tuberculosis
- It remains the only commercially available vaccine against tuberculosis
- The use of BCG for treatment of high-risk non-muscle-invasive bladder cancer (NMIBC) was approved after it was shown in the mid-late 1970s that intravesical instillation of this bacterium could halt disease progression and recurrence of NMIBC
- BCG vaccine has since been routinely used for the treatment of NMIBC

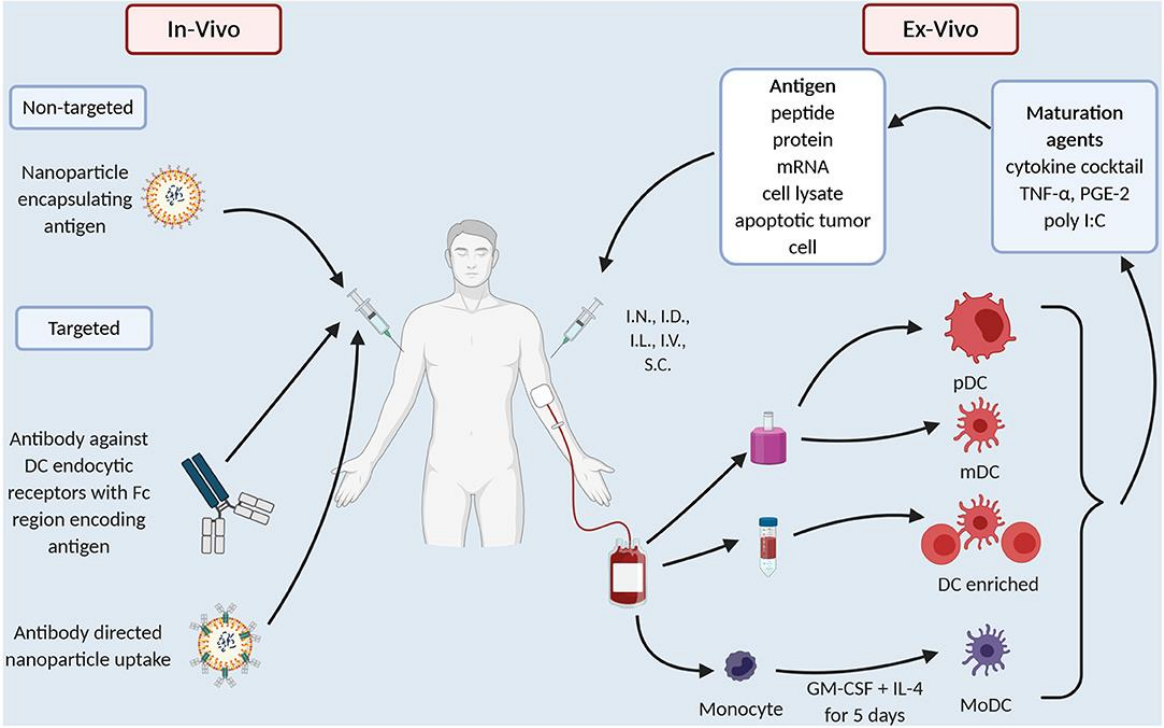
BCG Vaccine

- Treatment Schedule:
  - A weekly instillation of BCG into the bladder for 6 weeks after resection of the tumours
  - Patients can then enter a phase of maintenance treatment, which consists of weekly instillation of BCG vaccine into the bladder for 3–6 weeks every 3 months for 1–3 years

- BCG therapy is associated with some complications in the genitourinary tract, including cystitis, bladder ulceration, penile lesions, prostatitis, and kidney infection, as well as systemic complications, such as fever, disseminated infections, BCG sepsis, etc

Sipuleucel-T vaccine

Sipuleucel-T vaccine



Sipuleucel-T vaccine

- Sipuleucel-T vaccine is an DC-based vaccine, which uses autologous DC to stimulate cellular immune responses mediated by T cells against prostatic acid phosphatase (PAP) in CRPC

- DCs are antigen presenting cells that can efciently induce antigen-specifc priming and activation of T cell. They express class I and class II HLA molecules and present processed antigenic peptide: HLA complexes to T cells. Sipuleucel-T vaccine is prepared by incubating patient DCs with a fusion protein, consisting of PAP linked to granulocyte macrophage colony-stimulating factor (GM-CSF), to induce DC activation, processing of PAP antigenic epitopes, and expression of antigenic peptide: HLA complexes and costimulatory molecules. Activated DCs are then reinfused into the patient, which will present antigens and activate T cell responses against PAP protein

Sipuleucel-T vaccine

- Sipuleucel-T vaccine was approved for treatment of CRPC after phase III trails showed signifcantly improved median survival and decreased risk of death in patients receiving the vaccine compared to the placebo-treated group, most notable in patients with a Gleason score of 7 or less

- The treatment consists of 3 infusions of approximately 50 million autologous DCs given every two weeks

- Adverse reactions were found to be mild in most patients and included fu-like symptoms, back pain, joint pain, muscle aches, headache, vomiting, constipation, diarrhea, anemia, and dizziness

Cancer Vaccines

Future studies & Future direction

In situ vaccine candidates under clinical consideration as monotherapies or in combination

Receptor	Agonist	Clinical trial identifier	Route[a]	Treatment	Condition
TLR and STING agonists					
RIG-I/MDA5 and TLR3	Poly-ICLC	NCT02423863	IT + IM	Poly-ICLC + anti-PD1 or anti-PDL1	Melanoma, H&N cancer, sarcoma, non-melanoma skin cancers
		NCT02643303	IT + IM	Poly-ICLC + anti-CTLA-4 and anti-PDL1	Advanced, measurable, biopsy-accessible cancers
TLR4	Glucopyranosyl lipid A (G100)	NCT02501473	IT	G100 + pembrolizumab	Follicular low-grade NHL
		NCT03915678	IT	G100 + atezolizumab + radiotherapy	Multiple solid tumours
		NCT02406781	IT	G100 + pembrolizumab + cyclophosphamide	Sarcoma
TLR7/8	NKTR-262	NCT03435640	IT	NKTR-262 + NKTR-214 (CD122 agonist) + nivolumab	Multiple cancers
TLR9	CpG ODN SD-101	NCT02927964	IT	Radiotherapy + SD-101 + ibrutinib	Lymphoma
		NCT02521870	IT	SD-101 + pembrolizumab	Melanoma and H&N cancer
	(VLP) encapsulated-TLR9 agonist CMP-001	NCT03084640	SC	CMP-001 + pembrolizumab	Melanoma
		NCT03618641	SC + IT	CMP-001 + nivolumab	Melanoma
		NCT02680184	IT	CMP-001 ± pembrolizumab	Melanoma
		NCT03983668	IT	CMP-001 ± pembrolizumab	R/R lymphoma
		NCT03438318	SC + IT	CMP-001 + atezolizumab ± radiotherapy	NSCLC
		NCT03507699	SC + IT	CMP-001 + nivolumab + ipilimumab + radiotherapy	Metastatic CRC with liver metastases
STING	MK-1454	NCT03010176	IT	MK-1454 ± pembrolizumab	Solid tumours and lymphoma
	E7766	NCT04109092	IT	Monotherapy	Bladder cancer
	ADU-S100	NCT03937141	IV	ADU-S100 + pembrolizumab	H&N cancer
		NCT03172936	IT	ADU-S100 + anti-PD1	Solid tumours and lymphoma
		NCT02675439	IT	ADU-S100 + ipilimumab	Solid tumours and lymphoma
	BMS-986301	NCT03956680	ND	BMS-986301 + nivolumab + ipilimumab	Advanced solid cancers
	SB-11285	NCT04096638	IV	SB-11285 ± nivolumab	Advanced solid cancers

In situ vaccine candidates under clinical consideration as monotherapies or in combination

FLT3L and CD40 agonists					
rhFLT3L	CDX-301	NCT02129075	SC	Poly-ICLC + CDX-1401 ± CDX-301	Stage IIB–IV melanoma
		NCT03789097	ND	CDX-301 + poly-ICLC + pembrolizumab + radiotherapy	NHL, metastatic breast cancer, H&N squamous cell carcinoma
		NCT01976585	IT	CDX-301 + poly-ICLC	Low-grade BCL
		NCT02839265	SC	CDX-301 + SBRT	NSCLC
Agonistic anti-CD40 antibody	APX005M	NCT02482168	IV	Monotherapy	Multiple solid cancers
	CDX-1140	NCT03329950	ND	CDX-1140 ± CDX-301 (rhFLT3L) ± pembrolizumab	Multiple cancers
	SEA-CD40	NCT02376699	IV or SC	SEA-CD40 + pembrolizumab + chemotherapy	Solid tumours and Lymphoma
Oncolytic virus, TVec					
Modified HSV-1	TVec	NCT02263508	IT	Tvec ± pembrolizumab	Melanoma
		NCT03802604	IT	Tvec + atezolizumab	Breast cancer
		NCT03256344	IT	Tvec + atezolizumab	Breast cancer and CRC
		NCT02509507	IT	Tvec + pembrolizumab	Multiple cancers
		NCT04185311	IT	Tvec + nivolumab + ipilimumab	Breast cancer

In situ vaccine candidates under clinical consideration as monotherapies or in combination

Receptor	Agonist	Clinical trial identifier	Route[a]	Treatment	Condition
Stereotactic radiotherapy					
SRS	NA	NCT03483012	NA	SRS + atezolizumab	Metastatic breast cancer with metastasis to brain
	NA	NCT03807765	NA	SRS + nivolumab	Metastatic breast cancer with metastasis to brain
SBRT	NA	NCT01896271	NA	SBRT + IL-2	CCRCC

Cancer Vaccines

Futuristic View

A time may come when cancer vaccines will be part of the immunization history, and oncologists share the joy of a pediatrician knowing that immunized patients are protected not only against infectious pathogens but against specific types of cancers

Thank You