Cancer Immunotherapy

Dr Pranshul Chauhan,
Oncology Registrar & RCSI StAR MD Scholar
Beacon Hospital

Beacon Hospital
This is Modern Medicine

Overview

- History and evolution of Immunotherapy
- How Cancer Immunotherapy works?
- Biomarkers
- Current Indications for Immunotherapies
- Common and Uncommon Toxicities
- Future of Cancer Immunotherapies

Evolution of Immunotherapy

circa 1000 years BC
- first anecdotal reports about spontaneously disappearing tumours (ancient Egypt)

2nd century AD
- cancer might evolve from inflammatory lesions (Galen)

1765
- report about the effectiveness of inoculation (John Fewster)

1866
- significant tumour regression after erysipelas infection was noted (Fehleisen and Busch)

1890
- the discovery of antibodies (Ehrlich, von Behring and Shibasaburo)

1893
- "Coley's toxins" is now available commercially

1899
- Ehrlich confirmed Coley's observations

1908
- a genetic explanation for the rejection of transplanted tumours in animal models (Clarence Little)

1914
- the first report on histocompatibility antigens being involved in transplant rejection (Gorer and Snell)

1948
- the anti-tumour effects of the BCG bacteria in mice with bladder cancer (Old)

1957
- the theory of cancer immunosurveillance (Thomas and Burnet)

1959
- dendritic cells were discovered (Steinman)

1973
- monoclonal antibodies used to achieve the first biochemical identification and description of tumour-specific antigen in a mouse model of T-cell lymphoma (Allison)

1975
- the first description of NK cells activity (Klein)

1976
- The US FDA approved the use of BCG as a way of treating bladder cancer (Morales)

1982
- The first use of genetically engineered T cells derived and modified in this way to target cancer cells was reported in 1989 (Gross and Eshhar)

1986
- The world's first recombinant vaccine, HBV, vaccine was created (Valenzuela)

1989
- The US FDA approved the use of IL-2 as an immunotherapeutic treatment for metastatic melanoma

1991
- The US FDA approved the use of IL-2 as an immunotherapeutic treatment in metastatic kidney cancer

1998
- proof; the first human tumour antigen to be recognised by T lymphocytes (van der Bruggen)

2004
- T cells were able to provide anti-tumour surveillance (Schreiber, Dunn, Old)

2011
- The first checkpoint inhibitor, ipilimumab, approved by the FDA

2015
- The first oncolytic virus, T-VEC, approved by the FDA for the treatment of metastatic melanoma

2017
- relapsed B-cell acute lymphoblastic leukaemia in children as the first disease to be FDA approved for CAR T-cells therapy

2018
- The Nobel Prize for their discovery of cancer therapy by inhibition of negative immune regulation (James P. Allison and Tasuku Honjo)

3rd century BC
- purposeful inoculation with variola minor virus in order to prevent smallpox disease (China's Qin dynasty period)

1718
- first attempts to popularise inoculation in England (Lady Mary Wortley Montague)

1796
- immunity against smallpox through inoculation with common cowpox virus demonstrated for the first time (Edward Jenner)

1883
- identification of the bacterial strain responsible for the erysipelas and tumour shrinkage as Streptococcus pyogenes (Fehleisen)

1891
- first attempt to harness the immune system for treating bone cancer (William Bradley Coley)

1896
- The first description of the spontaneous tumour remission after severe influenza infection (Dock)

1902
- the first attempts to create cancer vaccine (Blumenthal and E. von Leyden)

1908
- Ehrlich confirmed Coley's observations

1915
- nonspecific stimulation of immune cells can provide a treatment for cancer (Murphy and Morton)

1957
- the discovery of interferon (Isaacs and Lindenmann)

1959
- the first ever cancer vaccine (Ruth and John Grahams)

1967
- the existence of T cells and their crucial role in immunity (Jacques Miller)

1974
- Immune surveillance theory re-emerged (Stutman)

1975
- the first production of monoclonal antibodies in the laboratory (Milstein and Köhler)

1976
- IL-2, the T-cell growth factor interleukin 2 (Morgan)

1983
- IL-2 was cloned (Devos)

1987
- The first immune checkpoint molecule was discovered CTLA-4 (Brunet)

1991
- proof; the first human tumour antigen to be recognised by T lymphocytes (van der Bruggen)

1997
- Rituximab became the first monoclonal antibody approved by the FDA for the treatment of cancer (Nadler)

4-1BB (CD137) molecule as the first evidence for T cell anti-tumour immune response (Melero)

2000
- the first ipilimumab clinical trial was launched

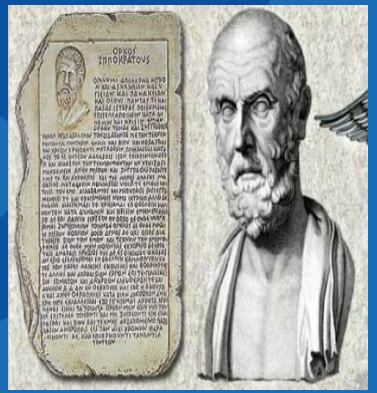
2010
- the FDA approved sipuleucel-T for treatment of castration-resistant prostate cancer

2014
- nivolumab, the first PD-1 molecule inhibitor, approved by the FDA

2016
- Atezolizumab, another checkpoint inhibitor of the PD-L1 protein, approved by the FDA

2018
- FDA approval of CAR T cells therapy for diffuse large B-cell lymphoma and certain other types of lymphoma

2019
- Atezolizumab, the checkpoint inhibitor of the PD-L1 protein, approved by the FDA for triple-negative breast cancer treatment



Beacon Hospital

1890
YES
William Coley toxin induces tumor regression in some patients

1900-1950
NO
Difficult to reproduce tumor regression with Coley toxin and transplantable tumors
BUT
Paul Ehrlich (1909) suggested that immune system may control cancer

1950
NO
Burnet's acquired immunological tolerance theory, experimentally verified by Medawar, suggests that tumor cells are self and they are not rejected

1959
YES
Lloyd J. Old "Father of Modern Tumor Immunology" showed that BCG could confer protection against tumors and prolong survival in experimental mouse models.

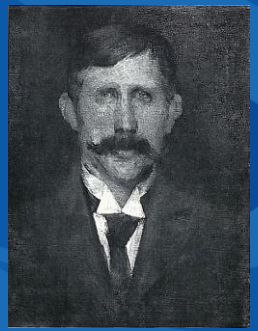
1960
YES
Evidence that animals can be immunized against syngeneic transplantable tumor;
Tumor surveillance proposed by Burnet, a modified version of Thomas views;
Search for tumor associated antigens (TAA)

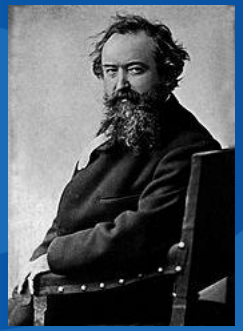
1970-85
NO
Hard to believe that immune system evolved to combat tumors;
Thymic selection deletes all auto-reactive T cells;
Anti-tumor immune response are artefactual as they are directed against endogenous viruses in tumors.

1985-1995
YES (potentially)
Auto-reactive T cells can escape from thymic depletion;
Many TAA identified
BUT
Tumor cells lack co-stimulatory molecules

1995-2002
YES
Dendritic cells can present TAA to adaptive immune system;
Many immunodeficient mice have a high tumor incidence (RAG$^{-/-}$, STAT$^{-/-}$ and perforin $^{-/-}$);
Study emergence of the innate immune system as an important mediator of antitumor immunity

2000 to the present
YES
Several immunotherapy strategies;
Tumor microenvironment studies;
Neoantigens;

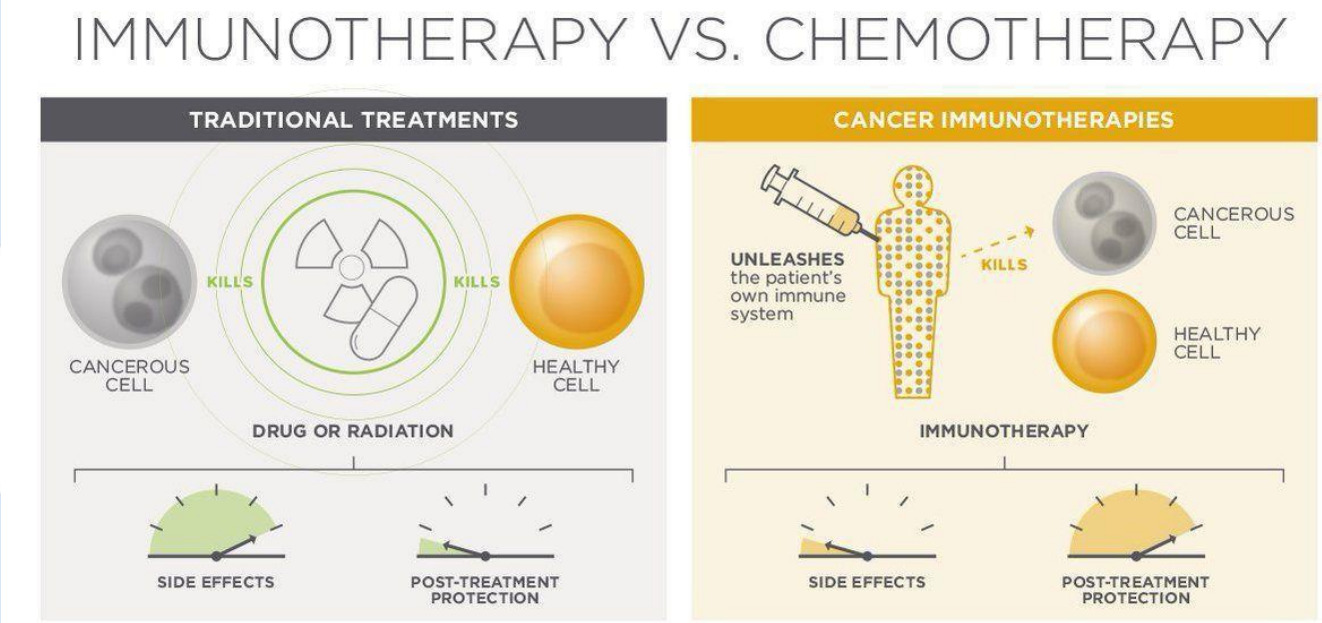

Friedrich Fehleisen


Wilhelm Busch


William Coley


James Allison and Tasuku Honjo

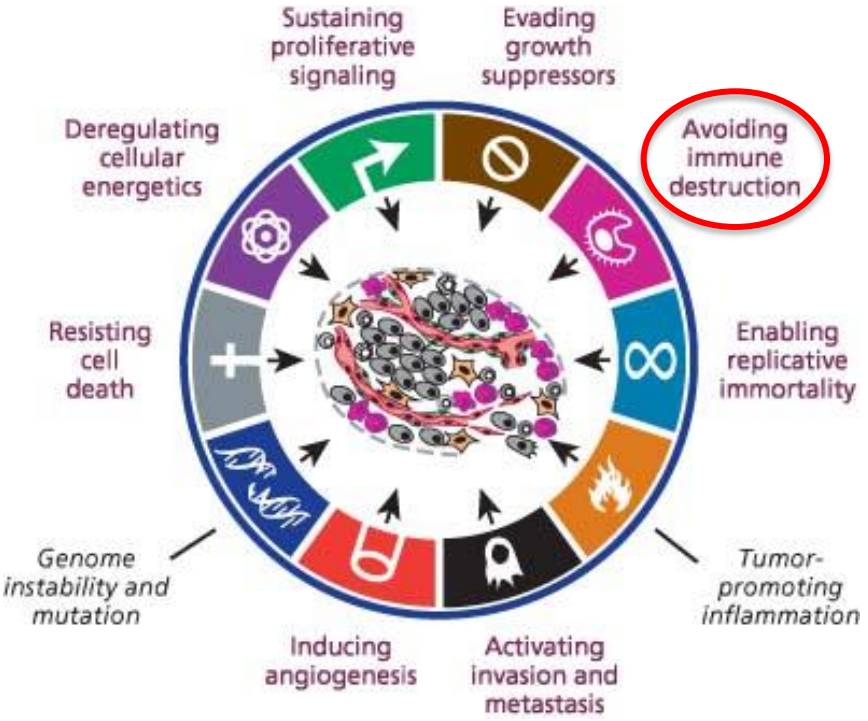
How does Immunotherapy Work?



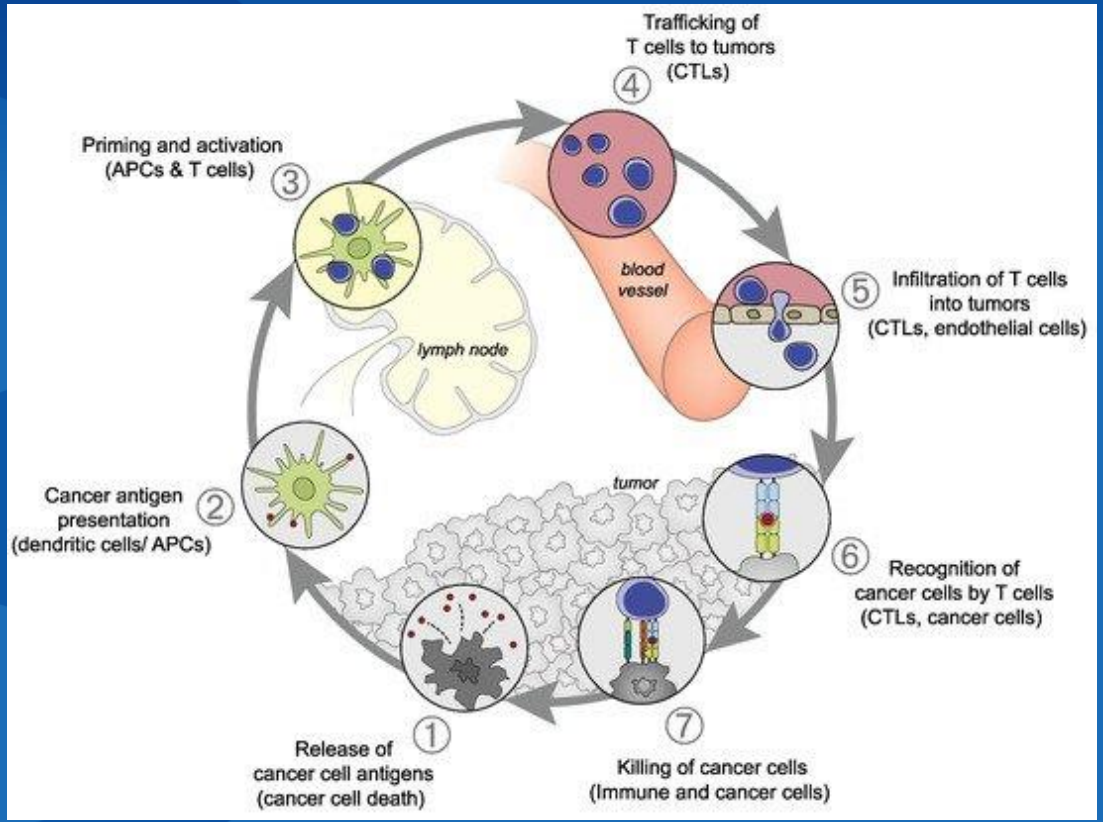
Beacon Hospital

Hallmarks of Cancer

An Emerging Hallmark: Evading Immune Destruction



Beacon Hospital

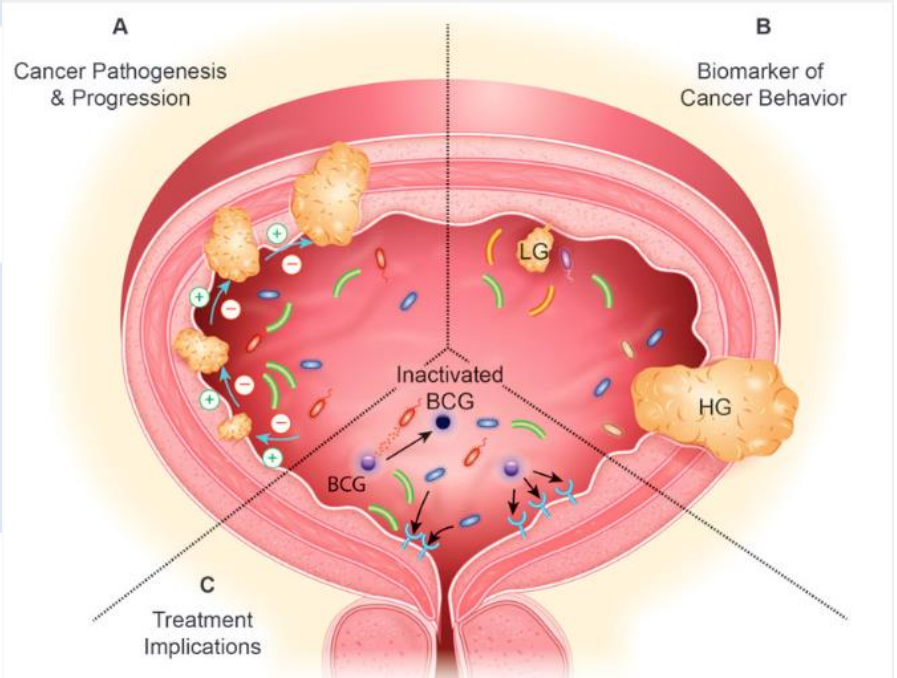


Beacon Hospital

Types of Immunotherapy

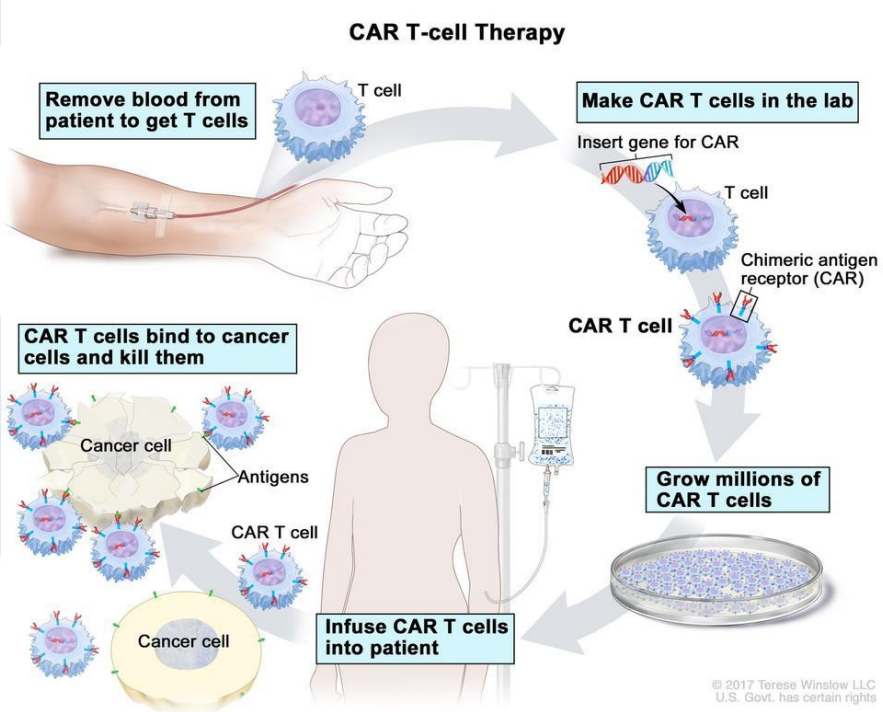
- Non Specific Immune Stimulation
- T Cell Transfer Therapy
- Immune Checkpoint Inhibition

Non Specific Immune Stimulation



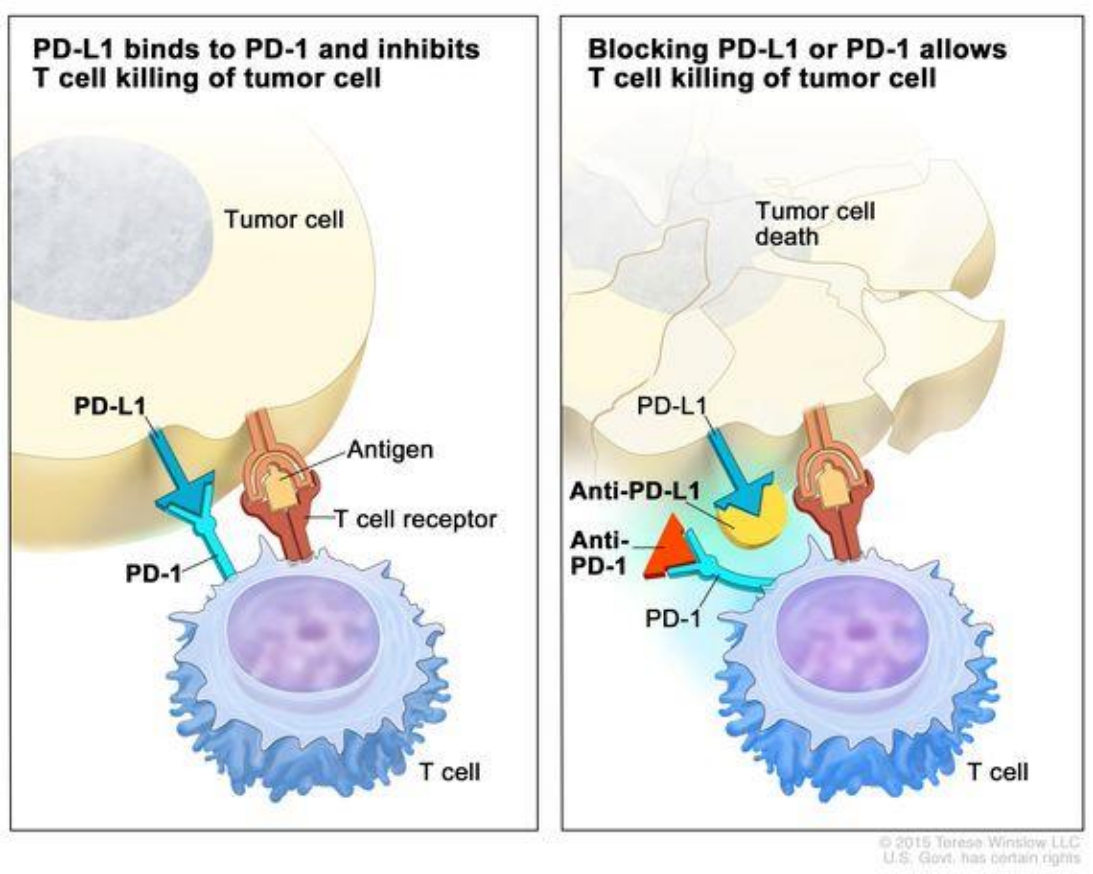
Beacon Hospital

T Cell Transfer Therapy



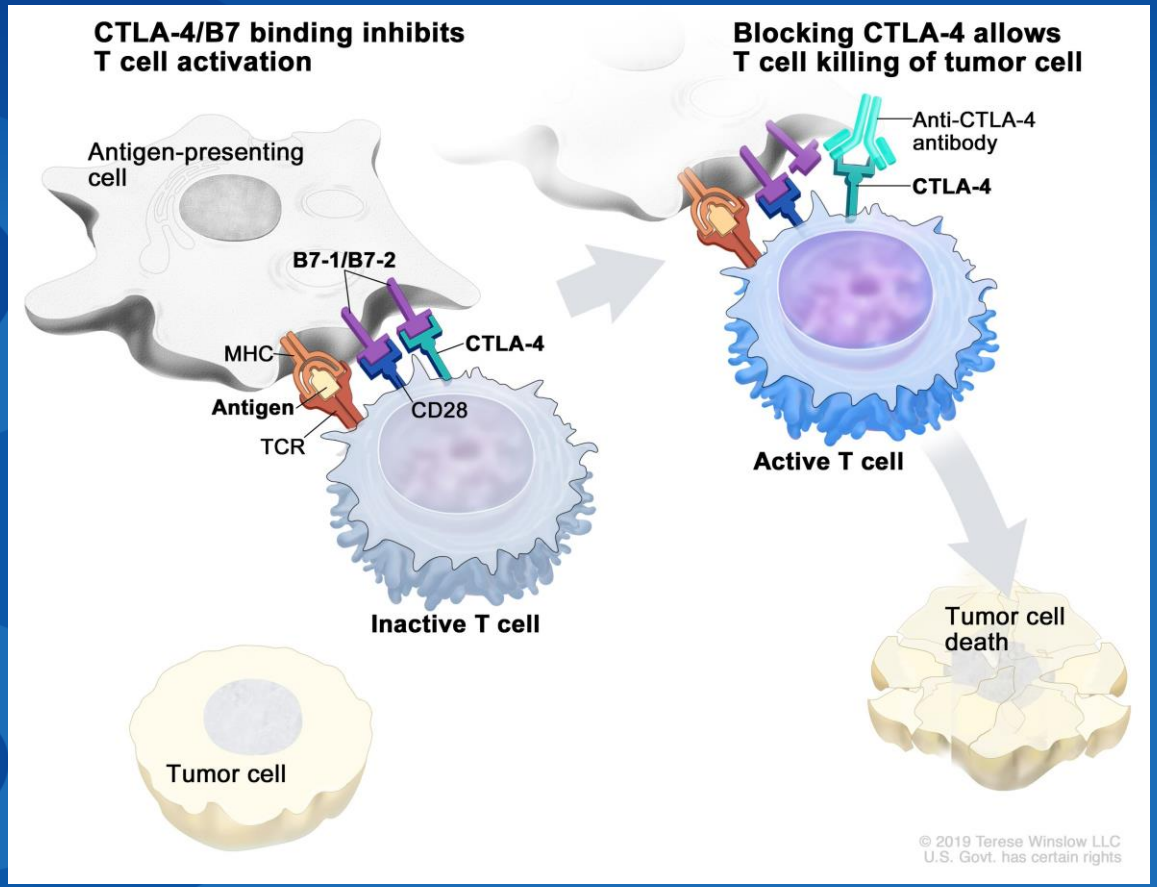
Beacon Hospital

Immune Checkpoint Inhibition



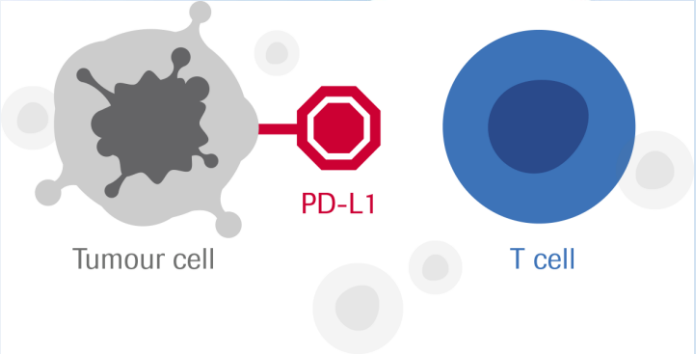
Beacon Hospital

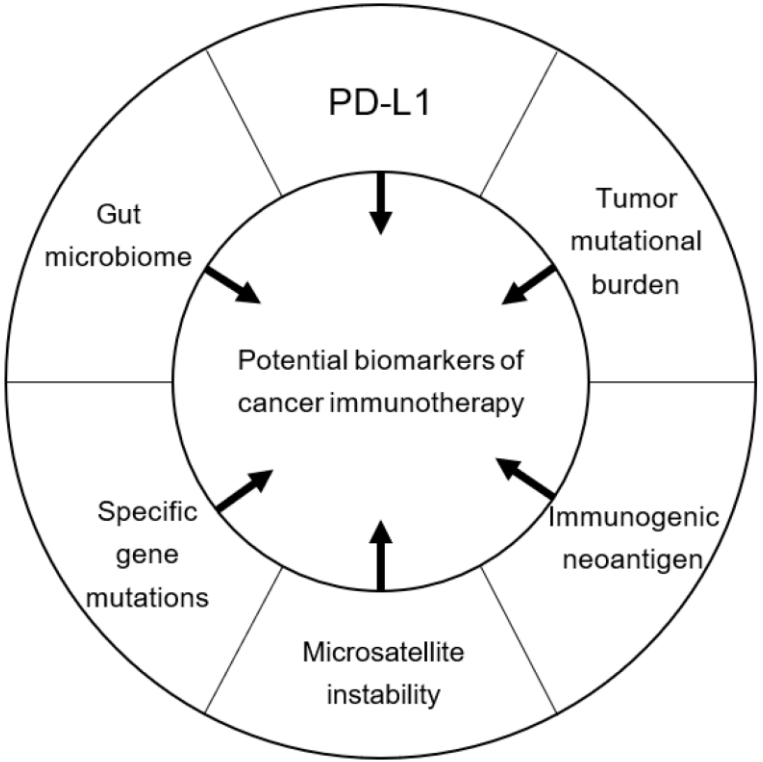
Immune Checkpoint Inhibition



Beacon Hospital

Biomarkers





Beacon Hospital

Currently Approved Immunotherapies

Name	Company	Target	Indications	Details
Nivolumab (Opdivo®)[1]	**Bristol-Myers Squibb**	**PD-1**	· 1L Inoperable or Metastatic Melanoma	· Single Agent for BRAF-WT and BRAF-MU *or* in Combination with Yervoy®
			· 2L Metastatic Non-Small Cell Lung Cancer	· Failure on Platinum-Doublet Chemotherapy · Failure on Targeted Agent (if Applicable)
			· 2L Advanced Renal Cell Carcinoma	· After Prior Treatment with Anti-Angiogenic Treatment
			· 4L Classical Hodgkin Lymphoma	· After Prior Auto-HSCT and Brentuximab Vendotin Treatment
			· 2L Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma	· Disease progression on *or* after Platinum-Based Chemotherapy
			· 1L/2L Locally Advanced or Metastatic Urothelial Carcinoma	· Failure on Prior Platinum-Based Chemotherapy · PD<12 Months after (Neo)Adjuvant Platinum-Based Chemotherapy
			· Microsatellite Instability-High (MSI-H) or Mismatch-Repair Deficient (dMMR) Metastatic Colorectal Cancer	· Adult and Paediatric Patients (≧12 years) · PD following FOLFOXIRI
Pembrolizumab (Keytruda®)[2]	**Merck (MSD)**	**PD-1**	· 1L Inoperable or Metastatic Melanoma	· Single Agent
			· 2L Metastatic Non-Small Cell Lung Cancer with PD-L1 Expression	· Failure on Platinum-Doublet Chemotherapy · Failure on Targeted Agent (if Applicable) · Tumour Proportion Score (TPS) ≧1%
			· 1L Metastatic *Non-Squamous* Non-Small Cell Lung Cancer	· In combination with Carboplatin and Pemetrexed · Regardless of Tumour Proportion Score (TPS)
			· 1L Metastatic Non-Small Cell Lung Cancer with high PD-L1 Expression	· No Prior Systemic Treatments · No Known Tumour-Driver Mutations · Tumour Proportion Score (TPS) ≧50%
			· 2L Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma	· Disease Progression on *or* after Platinum-Based Chemotherapy
			· 4L Refractory Classical Hodgkin Lymphoma	· Adult and Paediatric Patients · Disease Relapse after 3 Prior Treatments
			· 1L/2L Locally Advanced or Metastatic Urothelial Carcinoma	· Ineligible for Cisplatin-based Chemotherapy · Failure on Prior Platinum-Based Chemotherapy · PD<12 Months after (Neo)Adjuvant Platinum-Based Chemotherapy
			· Microsatellite Instability-High (MSI-H) or Mismatch-Repair Deficient (dMMR) Cancers	· Adult and Paediatric Patients · Solid Tumours Progressed Following Prior Treatment and Without Satisfactory Alternative Treatment Options · Colorectal Cancer PD following FOLFOXIRI · **Limitation of Use**: Safety and Effectiveness of Pembrolizumab not Established in Paediatric Patients with MSI-H Central Nervous System (CNS) Cancers
Ipilimumab (Yervoy®)[3]	**Bristol-Myers Squibb**	**CTLA-4**	· 1L Inoperable or Metastatic Melanoma	· Adult and Paediatric Patients (≧12 years) · Single Agent *or* in Combination with Opdivo® (see Opdivo® USPI)
			· Adjuvant Treatment of Stage IIIa Melanoma	· At Least One Metastasis >1 mm, no In-Transit Metastasis · Undergone Complete Resection, Including Total Lymphadenectomy
Atezolizumab (Tecentriq®)[4]	**Roche Genentech**	**PD-L1**	· 1L/2L Locally Advanced or Metastatic Urothelial Carcinoma	· Ineligible for Cisplatin-based Chemotherapy · Failure on Prior Platinum-Based Chemotherapy · PD<12 Months after (Neo)Adjuvant Platinum-based Chemotherapy
			· 2/L Metastatic Non-Small Cell Lung Cancer	· Failure on Platinum-Doublet Chemotherapy · Failure on Targeted Agent (if Applicable)
Avelumab (Bavencio®)[5]	**Merck Serono Pfizer**	**PD-L1**	· 1L Metastatic Merkel Cell Carcinoma (MCC)	· Adult and Pediatric Patients (≧12 years)
			· 1L/2L Locally Advanced or Metastatic Urothelial Carcinoma	· Failure on Prior Platinum-Based Chemotherapy · PD<12 Months after (Neo)Adjuvant Platinum-based Chemotherapy
Durvalumab (Imfinzi®)[6]	**AstraZeneca**	**PD-L1**	· 1L/2L Locally Advanced or Metastatic Urothelial Carcinoma	· Failure on Prior Platinum-Based Chemotherapy · PD<12 Months after (Neo)Adjuvant Platinum-based Chemotherapy

Cancer types in which Immunotherapy is Currently Used Commonly

Melanoma

Lung Cancer

Renal Cell Cancer

Bladder Cancer

Colorectal Cancer

Head & Neck Cancer

Future Uses

Breast Cancer
Gynaecological Cancers

First-line settings

Adjuvant Settings

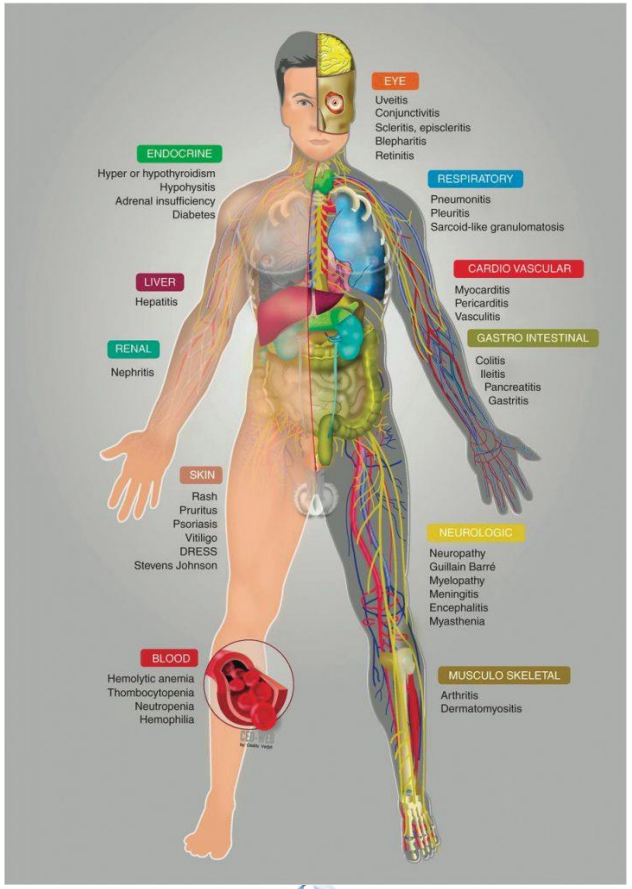
Neo-adjuvant settings

Combination with Chemotherapy

Toxicities associated with Immunotherapy

Immune-Related Adverse Events (irAEs)

Toxicity	Clinical Effects	All grades (grade 3/4)	Time Frame
Skin	Rash, vitiligo, pruritus	47-68% (0-4%)	2-3 weeks
Gastrointestinal (GI)	Diarrhea, colitis	31-46% (8-23%)	6-7 weeks
Liver	Elevated enzymes, bilirubin, hepatitis	3-9% (3-7%)	6-7 weeks
Endocrine	Hypophysitis, hypothyroidism	4-6% (1-5%)	After 9 weeks



Beacon Hospital

Summary

Immunotherapy is here to stay.

Generally well tolerated by patients of all ages.
We need to monitor for immune mediated side effects.

It will become more commonly used in various cancer types.
It will be used in combination with Immunotherapy in the future.

Thank you

Beacon Hospital