Bioscene

Bioscene
Volume- 21 Number- 04
ISSN: 1539-2422 (P) 2055-1583 (O)
www.explorebioscene.com

Emerging Trends in Cancer Immunotherapy: Advancements and Future Directions

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Abstract: Cancer immunotherapy has developed as a transformative approach in oncology, leveraging the immune system's intrinsic ability to detect and destroy malignant cells. Immune checkpoint inhibitors, like anti-PD-1 and anti-CTLA-4 antibodies, have reshaped the therapeutic landscape, providing durable responses in cancers previously deemed refractory to treatment. Chimeric antigen receptor (CAR)-T cell therapy has demonstrated remarkable efficacy in hematological malignancies, though challenges like antigen escape and an immunosuppressive tumor microenvironment limit its success in solid tumors. Neoantigen-based personalized vaccines and oncolytic viruses are advancing the field, offering tailored solutions to stimulate robust immune responses. Combination therapies integrating immunotherapy along with traditional treatments, such as chemotherapy and radiation, have shown synergistic effects, addressing tumor heterogeneity and resistance. Despite these advancements, challenges including immune-related adverse events, resistance mechanisms, and the high cost of therapies persist. Emerging trends, such as the application of artificial intelligence for biomarker discovery and the development of bi-specific T cell engagers, promise to refine patient selection and therapeutic precision. This review explores the latest innovations in cancer immunotherapy, discusses unresolved challenges, and highlights future directions to enhance its efficacy and accessibility for diverse cancer types.

Keywords: Cancer, CAR-T cell therapy, Neoantigen vaccines, Immune-related adverse events (irAEs), Combination therapies.

1. Introduction

Cancer continues to be a significant global health challenge, with its burden rising due to increasing life expectancy and lifestyle-related risk factors. In 2022, nearly 20 million new cancer cases were diagnosed, and 10 million cancer-related deaths

were reported globally. These figures are expected to rise substantially, with the number of cases per year projected to reach 35 million by 2050, representing a 77% incline driven by demographic changes and risk factors like smoking, obesity, and infections (Brayet al. 2024; IARC, 2024). Traditional cancer treatments, including surgery, chemotherapy, and radiation, have provided incremental benefits but face limitations such as non-specificity, toxicity, and resistance. The emergence of cancer immunotherapy represents a paradigm shift, leveraging the immune system's inherent ability to recognize and eliminate cancer cells. Immune checkpoint inhibitors, particularly those targeting PD-1, PD-L1, and CTLA-4, have shown remarkable efficacy in enhancing survival rates for cancers such as melanoma and non-small cell lung cancer. For instance, these therapies have provided durable responses in over 20% of metastatic melanoma patients (Ribas & Wolchok, 2018).

Adoptive cell therapies like chimeric antigen receptor (CAR)-T cell therapy have further advanced the field, particularly for hematological malignancies, where remission rates exceed 80% in certain patient populations. However, challenges like the immunosuppressive tumor microenvironment, resistance mechanisms, and immune-related adverse events remain significant barriers to broader success. Moreover, the high cost of immunotherapy limits accessibility, particularly in low- and middle-income countries (June, et al. 2018). Innovative approaches such as personalized neoantigen vaccines, oncolytic viruses, and bi-specific T cell engagers (BiTEs) aim to overcome these limitations. Additionally, the integration of artificial intelligence into immunotherapy promises to enhance biomarker discovery, optimize patient selection, and improve treatment precision (Farkona, et al. 2016; Esteva, et al. 2019).

This review explores the latest advancements in cancer immunotherapy, discusses persisting challenges, and highlights future directions. By addressing these aspects, it aims to shed light on the evolving landscape of immunotherapy and its potential to transform cancer care on a global scale.

2. Immune Checkpoint Inhibitors

Immune checkpoints like programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) act as brakes on the immune system to prevent autoimmunity. Tumors exploit these pathways to evade immune detection. Checkpoint inhibitors, which block these immune-suppressive signals, have shown efficacy in a variety of cancers.

2.1 Key Targets of ICIs

- **CTLA-4 (Cytotoxic T-Lymphocyte Antigen-4):**

CTLA-4 is expressed on T-cells and inhibits their activation by competing with CD28 for binding to B7 molecules on antigen-presenting cells (APCs). Blocking CTLA-4 enhances T-cell activation and proliferation. For example, Ipilimumab (Yervoy), the

first FDA-approved CTLA-4 inhibitor, demonstrated efficacy in metastatic melanoma by improving overall survival (Maude, et al. 2018).

- **PD-1 (Programmed Death-1):**

PD-1 is an inhibitory receptor expressed on T-cells. When bound to its ligand PD-L1, it suppresses T-cell activation, allowing cancer cells to escape immune attack. For instance, Nivolumab (Opdivo): Approved for non-small-cell lung cancer (NSCLC), melanoma, and renal cell carcinoma. Pembrolizumab (Keytruda): Widely used for various cancers, including NSCLC and melanoma, especially in PD-L1-expressing tumors.

- **PD-L1 (Programmed Death-Ligand 1):**

Tumor cells often overexpress PD-L1 to bind PD-1 on T-cells, creating an immune-suppressive microenvironment. Blocking PD-L1 restores T-cell activity.
For example, Atezolizumab (Tecentriq) is effective in urothelial carcinoma and NSCLC. Durvalumab (Imfinzi) is approved for unresectable Stage III NSCLC (Abramson, et al. 2020).

- **Dual Checkpoint Inhibitors**

Simultaneously targeting multiple checkpoints has shown promise. For example, combining nivolumab (anti-PD-1) with ipilimumab (anti-CTLA-4) in melanoma has resulted in higher response rates than monotherapy.

- **Next-Generation Checkpoints**

Checkpoint molecules like LAG-3, TIGIT, and TIM-3 are gaining attention. Relatlimab, a LAG-3 inhibitor, combined with nivolumab, improved progression-free survival in melanoma patients.
Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have become first-line treatments for melanoma, NSCLC, and renal cell carcinoma. Biomarkers like PD-L1 expression and tumor mutational burden (TMB) are being investigated to predict treatment response. In a landmark trial, pembrolizumab demonstrated a 43.7% five-year survival rate in metastatic melanoma compared to 33.2% with ipilimumab (Munshi, et al. 2021). Checkpoint inhibitors are associated with immune-related adverse events (irAEs), such as colitis, pneumonitis, and endocrinopathies. Identifying patients who are likely to benefit while minimizing these risks is an ongoing challenge (Wang, et al. 2020).

3. Chimeric Antigen Receptor T (CAR-T) Cell Therapy

Chimeric antigen receptor T-cell therapy involves genetically engineering patient-derived T cells to target tumor-specific antigens. CAR-T therapies have revolutionized the treatment of hematological malignancies but face challenges in solid tumors (Table 1). Current research is focused on addressing challenges like CAR-T cell persistence, TME resistance, and antigen escape. Armored CAR-T cells,

equipped with cytokine-secreting functions, are being tested in preclinical models. Axicabtagene ciloleucel (Yescarta) achieved complete remission in 54% of patients with refractory DLBCL in a pivotal phase II trial (Shah, et al. 2020). CAR-T therapy targeting CD19 has yielded durable remissions in ALL, chronic lymphocytic leukemia (CLL), and DLBCL. Recent CAR-T therapies like Idecabtagene Vicleucel (Abecma) target BCMA (B-cell maturation antigen), a critical marker in multiple myeloma. Challenges like overcoming the immunosuppressive TME in solid tumors is critical. Novel approaches include targeting stromal elements and integrating CAR-T therapy with immune checkpoint inhibitors. Cost-effective manufacturing and broader access are necessary for widespread implementation (Depil, et al. 2020).

3.1 Mechanism of Action

i. T-Cell Collection and Engineering:

T-cells are extracted from the patient's blood using leukapheresis. In the laboratory, a gene encoding a synthetic receptor (CAR) specific to a tumor-associated antigen (e.g., CD19) is inserted into these cells using viral or non-viral vectors.

ii. CAR-T Cell Activation:

The engineered receptor combines a targeting domain (usually derived from antibodies) with intracellular signaling domains (e.g., CD28 or 4-1BB) to activate the T-cell upon antigen binding.

iii. Infusion and Tumor Targeting:

The CAR-T cells are expanded in vitro and reinfused into the patient. These cells proliferate and selectively attack cancer cells expressing the target antigen.

Table 1. List of approved CAR-T Cell Therapies

S.No.	Name of the Drug	Target Antigen	Indication	Year of Approval	Reference
1	Tisagenlecleucel (Kymriah)	CD19	B-cell ALL, DLBCL	2017	Maude, SL., et al. (2018).
2	Axicabtagene Ciloleucel (Yescarta)	CD19	DLBCL, primary mediastinal large B-cell lymphoma	2017	Neelapu, SS., et al. (2017).
3	Lisocabtagene Maraleucel (Breyanzi)	CD19	Large B-cell lymphoma	2021	Abramson, JS., et al. (2020).
4	Idecabtagene Vicleucel (Abecma)	BCMA	Relapsed/refractory multiple myeloma	2021	Munshi, NC., et al. (2021).
5	Brexucabtagene	CD19	Mantle cell	2020	Wang, M.,

	Autoleucel (Tecartus)		lymphoma		et al. (2020).
6	Ciltacabtagene Autoleucel (Carvykti)	BCMA	Relapsed/refractory multiple myeloma	2022	Berdeja, JG., et al. (2021).
7	UCART19	CD19	Relapsed/refractory B-cell ALL	Investigational	Depil, S., et al. (2020).]
8	Relmacabtagene Autoleucel (Relma-cel)	CD19	Large B-cell lymphoma	2021 (China)	Zhang, H., et al. (2021).
9	KTE-X19	CD19	Adult B-cell ALL	2021	Shah, BD., et al. (2020).

Emerging CAR-T innovations address solid tumors and toxicity challenges:

- **Targeting Solid Tumors**: New constructs like Cellectis' UCART-CS1 target multiple antigens, addressing the antigen heterogeneity of solid tumors.
- **Tumor Microenvironment (TME)**: Solid tumors have an immunosuppressive TME with high levels of regulatory T-cells, myeloid-derived suppressor cells, and cytokines like TGF-β.
- **Target Antigen Heterogeneity**: Unlike hematological cancers, solid tumors often lack uniform antigen expression, leading to potential off-target effects and resistance.
- **Physical Barriers**: Dense extracellular matrices and poor vascularization impede CAR-T cell infiltration.
- **Reducing Toxicity**: Development of switchable CAR-T systems, such as the ON-switch CAR, mitigates the risks of cytokine release syndrome (CRS) (Brudno, et al. 2016).

4. Cancer Vaccines: Preventive and Therapeutic Approaches

Cancer vaccines are designed to provoke an immune response against tumor antigens. They are classified into prophylactic and therapeutic vaccines. The success of prophylactic vaccines like the HPV vaccine (Gardasil) in preventing cervical cancer underscores the potential of expanding this strategy to other virus-associated cancers, including hepatitis B-induced hepatocellular carcinoma (Harper, et al. 2006). Neoantigen-based personalized vaccines, derived from a patient's tumor mutations, have shown promise in generating robust T-cell responses in cancers like melanoma and glioblastoma (Keilholz, et al. 2012). Moderna's mRNA-

based cancer vaccine in melanoma, used in combination with pembrolizumab, showed a 44% reduction in the risk of recurrence. In a phase I trial, a neoantigen vaccine elicited CD8+ T-cell responses in over 60% of melanoma patients, with sustained progression-free survival in responders (Ott, et al. 2019).

These vaccines are divided into preventive vaccines, aimed at averting cancer-causing infections, and therapeutic vaccines, designed to treat existing cancers by stimulating an immune response against tumor cells (Table 2).

4.1. Preventive Cancer Vaccines

Preventive vaccines target viruses known to cause cancer and are primarily administered before infection to reduce cancer incidence.

1. **Human Papillomavirus (HPV) Vaccine**:
   Targets high-risk HPV strains (e.g., HPV-16 and HPV-18), which are linked to cervical, anal, and head-and-neck cancers. Vaccines such as **Gardasil 9** protect against nine HPV types, reducing cervical cancer rates by 90% in vaccinated individuals (Brisson, et al. 2020). The World Health Organization (WHO) aims to eliminate cervical cancer globally through widespread HPV vaccination campaigns.
2. **Hepatitis B Virus (HBV) Vaccine**:
   Prevents HBV infection, a significant risk factor for hepatocellular carcinoma. Global implementation in childhood immunization programs has drastically reduced liver cancer rates in HBV-endemic regions (Chang, et al. 1997).

- **Global Statistics**

According to WHO, cervical cancer is the fourth most common cancer among women, with approximately 604,000 new cases and 342,000 deaths in 2020, most of which could be prevented with HPV vaccination (WHO, 2023).

4.2. Therapeutic Cancer Vaccines

Therapeutic vaccines aim to stimulate the immune system to recognize and destroy existing cancer cells. They are often developed to target tumor-specific or tumor-associated antigens.

Mechanisms and Types

1. **Peptide-Based Vaccines**:
   Use short peptides representing tumor antigens to trigger cytotoxic T-cell responses. Peptide vaccines targeting Wilms Tumor 1 (WT1) protein in leukemia and solid tumors.
2. **Dendritic Cell-Based Vaccines**:
   Employ dendritic cells loaded with tumor antigens to activate a robust immune response. Sipuleucel-T (Provenge), approved for metastatic prostate cancer, extends patient survival by priming the immune system to attack cells expressing prostatic acid phosphatase (PAP) (Kantoff, et al. 2010).

3. **Neoantigen-Based Vaccines**:
   Custom-made vaccines based on a patient's unique tumor mutations. Clinical trials for neoantigen vaccines have shown success in melanoma and non-small cell lung cancer, demonstrating reduced tumor progression (Sahin, et al. 2017).

Table 2. List of Therapeutic Cancer Vaccines

S. No.	Vaccine Name	Indication	Mechanism of Action	Reference
1	Sipuleucel-T (Provenge)	Metastatic prostate cancer	Dendritic cells primed with prostatic acid phosphatase (PAP) antigen	Kantoff et al. (2010)
2	IMA901	Renal cell carcinoma	Multipeptide vaccine targeting various tumor-associated antigens (TAAs)	Walter et al. (2012)
3	TG4010	Non-small cell lung cancer	Viral vector encoding MUC1 tumor-associated antigen	Quoix et al. (2011)
4	OncoVAX	Stage II colon cancer	Autologous tumor cell vaccine combined with Bacillus Calmette-Guerin (BCG)	Vermorken et al. (1999)
5	GX-188E	HPV-associated cervical lesions	DNA vaccine targeting HPV-16/18 E6 and E7 oncogenes	Kim et al. (2014)
6	S-588410	Esophageal squamous cell carcinoma	Peptide vaccine targeting multiple TAAs (NY-ESO-1, MAGE-A4)	Sakamoto et al. (2021)
7	NeoVax	Advanced melanoma	Personalized neoantigen vaccine based on individual tumor mutational profile	Ott et al. (2017)
8	PROSTVAC	Prostate cancer	Poxvirus-based vaccine encoding PSA (prostate-specific antigen)	Gulley et al. (2014)
9	MVA-MUC1-IL-2	Breast and ovarian cancer	Modified vaccinia Ankara encoding MUC1 and IL-2	Kantoff et al. (2010)

10	ICT-107	Glioblastoma	Dendritic cells loaded with glioblastoma-associated antigens	Yu et al. (2014)
11	HEPLISAV-B	Hepatitis B-related liver cancer	HBV surface antigen combined with novel adjuvant CpG 1018	Schillie et al. (2018)
12	VB10.NEO	Solid tumors	DNA-based personalized neoantigen vaccine	Sahin et al. (2017)

4.3 Emerging Research and Trends

a. **Combination Therapies**: Therapeutic vaccines are increasingly combined with immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1 antibodies, to overcome tumor immune evasion.
b. **mRNA-Based Cancer Vaccines**: Building on the success of COVID-19 mRNA vaccines, companies are exploring mRNA vaccines for cancers like melanoma, with initial trials showing tumor regression in patients with advanced disease (Pardi, et al. 2018).
c. **Oncolytic Virus Platforms**: Viruses engineered to selectively infect and destroy tumor cells while delivering tumor antigens to the immune system. Examples include oncolytic herpesviruses in preclinical studies.

4.4 Challenges and Future Directions

a. **Immune Evasion**: Tumors employ mechanisms like checkpoint molecule expression and antigen loss to evade detection.
b. **Personalization**: Neoantigen vaccines require sophisticated analysis of individual tumor genomes, increasing costs and complexity.
c. **Accessibility**: Preventive vaccines like HPV remain underutilized in low- and middle-income countries due to logistical and financial barriers.
d.

5. Oncolytic Virus Therapy

Oncolytic viruses selectively replicate within tumor cells, causing direct lysis and inducing systemic anti-tumor immunity (Table 3). Talimogene laherparepvec (T-VEC), derived from herpes simplex virus, is FDA-approved for advanced melanoma. Newer candidates, such as pelareorep for metastatic breast cancer, show promise by modulating the tumor microenvironment (TME) (Pardoll, 2012).

5.1. Mechanism of Action

1. **Selective Tumor Infection**: Oncolytic viruses exploit unique features of tumor cells, such as defective interferon signaling, to preferentially infect and replicate within them.

2. **Tumor Cell Lysis**: Viral replication leads to the destruction of infected tumor cells, releasing tumor antigens and damage-associated molecular patterns (DAMPs).
3. **Immune Activation**: Released antigens and viral particles stimulate dendritic cells, T cells, and other components of the immune system, leading to an adaptive immune response against the tumor.
4. **Modulation of Tumor Microenvironment**: Oncolytic viruses can alter the immunosuppressive tumor microenvironment, enabling better immune infiltration and reducing tumor resistance.

Table 3. List of Oncolytic Viruses

S. No.	Virus Name	Type	Indication	Mechanism	Reference
1	Talimogene laherparepvec (T-VEC)	Genetically engineered HSV-1	Advanced melanoma	Expresses GM-CSF, enhancing local and systemic antitumor immunity	Andtbacka et al. (2015)
2	Oncorine (H101)	Adenovirus	Nasopharyngeal carcinoma	Targets cells with p53 pathway defects	Yu et al. (2001)
3	DNX-2401	Adenovirus	Glioblastoma	Selectively replicates in tumor cells, enhancing immune response	Lang et al. (2018)
4	Reolysin (Pelareorep)	Reovirus	Breast cancer, pancreatic cancer	Exploits Ras pathway activation in tumor cells	Norman et al. (2002)
5	Pexa-Vec (JX-594)	Vaccinia virus	Advanced liver cancer	GM-CSF expression, robust immune stimulation	Heo et al. (2013)

5.2. Therapeutic Potential

a. **Combination Therapies**: OVs show promise when combined with immune checkpoint inhibitors, chemotherapy, or radiation therapy, offering synergistic effects.
b. **Personalization**: Advances in genetic engineering enable the design of customized OVs tailored to individual tumor profiles.
c. **Reduced Off-Target Effects**: Unlike systemic chemotherapies, OVs target tumors specifically, minimizing toxicity to healthy tissues.

5.3. Challenges and Future Directions

a. **Immune Evasion**: Host antiviral immunity can limit the therapeutic efficacy of OVs.
b. **Delivery Mechanisms**: Enhancing targeted delivery to tumor sites remains a significant challenge.
c. **Regulatory Barriers**: Extensive safety testing is required due to the risks of viral mutation or unintended immune responses.
d. **Emerging Strategies**: Encapsulation techniques and nanoparticle carriers are being developed to overcome delivery challenges and improve efficacy.

6. Bi-Specific T-Cell Engagers (BiTEs)

BiTEs bridge T cells and cancer cells, facilitating direct cytotoxicity. Blinatumomab, targeting CD19-positive B-cell malignancies, exemplifies this approach. Emerging BiTEs, such as AMG 160 targeting PSMA in prostate cancer, are expanding the application of this modality (Table 4) (Mackall, et al. 2021).

6.1 Mechanism of Action

i. **Dual Binding**: BiTEs are engineered to bind a specific tumor-associated antigen (TAA) on the cancer cell surface and CD3 on T cells, bringing the two cells into close proximity.
ii. **T-Cell Activation**: This interaction activates T cells regardless of their prior specificity, stimulating their proliferation and secretion of cytotoxic molecules like perforin and granzyme.
iii. **Tumor Cell Lysis**: The engaged T cells destroy the cancer cells directly through apoptosis while releasing cytokines to recruit additional immune cells.

Table 4. Examples of BiTEs

S. No.	BiTE Name	Targeted Tumor Antigen	Indication	Mechanism	Reference
1	Blinatumomab	CD19	Relapsed/refractory B-cell ALL	Links CD19+ B cells to CD3+ T cells	Topp et al. (2011)
2	AMG 160	PSMA	Prostate cancer	Targets prostate-specific membrane antigen (PSMA)	Shore et al. (2021)
3	AMG 420	BCMA	Multiple myeloma	Connects B-cell maturation antigen to CD3	Raje et al. (2019)
4	Solitomab	EpCAM	Solid tumors	Targets epithelial cell adhesion molecule	Baeuerle et al. (2009)
5	REGN1979	CD20	B-cell non-Hodgkin's lymphoma	Redirects T cells to CD20+ B cells	Bannerji et al. (2020)

6.2 Clinical Advantages

a. **Specificity**: By linking T cells only to cancer cells expressing specific antigens, BiTEs minimize off-target toxicity.
b. **MHC-Independent Activation**: Unlike traditional T-cell activation, BiTEs bypass the need for tumor antigen presentation via MHC, overcoming tumor immune evasion.
c. **Immediate Response**: Once infused, BiTEs rapidly activate and recruit T cells for targeted killing (Schlereth, et al. 2017).

6.3 Challenges and Limitations

a. **Cytokine Release Syndrome (CRS)**: Overactivation of T cells can lead to systemic inflammatory responses, necessitating careful management.

b. **Short Half-Life**: Most BiTEs require continuous infusion due to rapid clearance, although research is ongoing to improve their pharmacokinetics.
c. **Antigen Escape**: Tumor cells may lose the targeted antigen, leading to therapeutic resistance.

6.4 Future Directions

a. **Novel Targets**: Expanding BiTE design to new tumor-associated antigens (e.g., HER2, EGFR) broadens their applicability to diverse cancers.
b. **Combination Therapies**: Combining BiTEs with immune checkpoint inhibitors or traditional chemotherapy may enhance efficacy.
c. **Next-Generation BiTEs**: Engineering multispecific BiTEs to target multiple antigens or pathways simultaneously aims to reduce resistance and improve therapeutic outcomes.

7. Adoptive Natural Killer (NK) Cell Therapy

NK cells are being engineered to improve their anti-tumor potential. Cryoport's FT596, an off-the-shelf CAR-NK product, has shown efficacy in relapsed or refractory B-cell lymphomas.

Adoptive NK cell therapy is an innovative cancer immunotherapy that exploits the natural cytotoxic capabilities of NK cells to target and eliminate malignant cells (Dolstra, et al. 2017). Unlike T cells, NK cells do not require prior sensitization or antigen presentation by major histocompatibility complex (MHC) molecules, making them particularly effective against tumor cells that evade T-cell responses through MHC downregulation. NK cells mediate cytotoxicity through activating receptors such as NKG2D and DNAM-1, which recognize stress-induced ligands on tumor cells. Additionally, NK cells perform antibody-dependent cellular cytotoxicity (ADCC) by binding to antibodies coating tumor cells via the FcγRIII (CD16) receptor, leading to targeted tumor lysis. Furthermore, NK cells release cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which further stimulate the immune response and recruit other immune cells to the tumor microenvironment (Bachanova, et al. 2020).

Several sources of NK cells are utilized in adoptive therapy, including autologous NK cells derived from the patient, which may be less functional in cancer contexts, and allogeneic NK cells from healthy donors, which offer enhanced cytotoxicity but require measures to prevent graft-versus-host disease (GVHD). Other sources include umbilical cord blood-derived NK cells, which are less immunogenic, and induced pluripotent stem cell (iPSC)-derived NK cells, engineered for scalability and improved functionality. Examples of NK cell-based therapies demonstrate the growing clinical potential of this approach. K-NK, derived from allogeneic sources, targets acute myeloid leukemia (AML) through receptor-mediated cytotoxicity, while FT596 employs iPSC-derived NK cells modified with chimeric antigen

receptors (CARs) for CD19-positive B-cell malignancies. NK-92, an immortalized cell line, has shown efficacy in targeting solid tumors, while haNK cells, engineered for HER2-specificity, are under investigation for treating triple-negative breast cancer. Cord blood-derived NK cells, as utilized in oNKord®, are showing promise in managing multiple myeloma (Klingemann, et al. 2016).

Adoptive NK cell therapy has notable advantages, including its independence from MHC for tumor recognition, reducing the likelihood of immune escape. Additionally, its shorter lifespan limits the risk of severe adverse effects, such as cytokine release syndrome (CRS) or GVHD. However, challenges persist, including tumor immune evasion through upregulating inhibitory ligands or downregulating activating signals, as well as difficulties in scaling ex vivo NK cell expansion and ensuring persistence and tumor homing in vivo (Rezvani, et al. 2017).

Future directions for NK cell therapy include genetic engineering to enhance functionality, such as CAR modifications, cytokine production, or inhibitory receptor knockouts like PD-1. Combining NK cell therapy with immune checkpoint inhibitors, monoclonal antibodies, or traditional cancer therapies holds potential to improve outcomes. Additionally, nanotechnology-based delivery systems are under exploration to optimize NK cell persistence and infiltration in solid tumors, positioning NK cell therapy as a versatile and transformative approach in cancer treatment (Ruggeri, et al. 2020).

8. Epigenetic Modulation in Immunotherapy

Epigenetic modulation has become a significant strategy in cancer treatment, particularly in the context of immunotherapy. Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA regulation, can alter the expression of genes involved in immune responses and tumor progression without changing the underlying DNA sequence (Chia, et al. 2020). By manipulating these epigenetic factors, it is possible to improve the effectiveness of immunotherapies, reinvigorate immune responses, and overcome resistance mechanisms in tumors. Epigenetic drugs, such as histone deacetylase (HDAC) inhibitors, modulate immune checkpoints and enhance the efficacy of T-cell responses. Trials with entinostat combined with pembrolizumab are underway (Boussiotis, 2016).

9. Combination Therapies: Synergistic Potentials

Combining immunotherapies with traditional modalities enhances therapeutic efficacy by creating a more immunogenic environment. Examples include radiation-induced immunogenic cell death and the synergy between checkpoint inhibitors and targeted therapies. The combination of bevacizumab and atezolizumab significantly improved overall survival in unresectable HCC in the IMbrave150 trial, marking a milestone in first-line treatment (Larkin, et al. 2019; Topalian, et al. 2012).

10. Personalized Immunotherapy

Personalization is becoming a cornerstone of immunotherapy to maximize efficacy and minimize off-target effects.

- **Tumor-Infiltrating Lymphocytes (TILs)**

TIL therapy involves extracting and expanding tumor-specific lymphocytes. FDA granted breakthrough therapy designation to lifileucel for melanoma, highlighting the promise of this approach (van der Merwe, et al. 2020).

- **Artificial Intelligence Integration**

AI-driven analyses predict patient responses to immunotherapy, identify novel neoantigens, and stratify patients based on TME characteristics. Tools like IBM Watson for Oncology are being integrated into clinical practice (Lee, et al. 2021).

11. Future Directions and Challenges of Emerging Trends in Cancer Immunotherapy

Cancer immunotherapy has evolved significantly over the past decade, offering new hope to patients with previously difficult-to-treat cancers (Table 5). However, while these therapies show immense promise, several challenges remain. These challenges must be addressed to optimize immunotherapy and extend its benefits to a broader patient population.

11.1 Expanding the Range of Cancers Treated

One of the key future directions in cancer immunotherapy is expanding its effectiveness beyond the cancers that have already shown significant responses, such as melanoma, lung cancer, and hematologic malignancies. While immune checkpoint inhibitors (ICIs) like anti-PD-1 and anti-CTLA-4 antibodies have shown efficacy in these cancers, their success in solid tumors, like pancreatic cancer, glioblastoma, and ovarian cancer, has been limited. The challenge lies in understanding the tumor microenvironment (TME) in these cancers, which often includes immunosuppressive factors like tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) that inhibit immune responses. Future research will focus on overcoming these obstacles by developing combination therapies that target both the immune system and the TME, or by identifying biomarkers that predict which patients are more likely to benefit from immunotherapy (Davids, et al. 2019).

11.2 Overcoming Resistance Mechanisms

Resistance to immunotherapy remains one of the biggest obstacles to its success. Some tumors, even after an initial response to immune checkpoint inhibitors, eventually develop resistance. This resistance may be due to several factors, including mutations in the genes encoding immune checkpoint proteins, activation

of alternative immune checkpoints, loss of tumor antigens, or the development of an immunosuppressive TME. Overcoming resistance will require a better understanding of these mechanisms and the development of next-generation immunotherapies that can either prevent or reverse resistance. This might include the development of novel immune checkpoint inhibitors, targeting alternative immune pathways, or modifying the TME to promote immune cell infiltration and activity (Kalos, et al. 2011).

11.3 Personalizing Immunotherapy

As with other forms of cancer treatment, personalized approaches will play a vital role in the future of immunotherapy. Precision medicine has already led to significant advancements in cancer care by tailoring treatment based on genetic and molecular profiling of tumors. Similarly, personalized immunotherapy could involve selecting the right type of immunotherapy based on a patient's genetic makeup, immune system profile, and specific tumor characteristics. The development of companion diagnostics which can identify which patients are most likely to respond to particular therapies will be key to enhancing the efficacy and safety of immunotherapies. This could include using genetic sequencing to identify specific mutations, neoantigens, and immune-related biomarkers that could guide therapy selection (Li, et al. 2023).

11.4 Addressing the Safety and Toxicity Concerns

While immunotherapy has shown remarkable results, it is not without its side effects. ICIs, for example, have been associated with immune-related adverse events (irAEs), which occur due to the activation of the immune system against normal tissues. These adverse events can range from mild symptoms like rash or diarrhea to life-threatening conditions like myocarditis or pneumonitis. The use of CAR-T cell therapies, while promising, can also lead to serious side effects like cytokine release syndrome (CRS) and neurotoxicity. Future research will need to focus on identifying patients at risk for these adverse events and developing strategies to mitigate them. This might involve creating safer versions of immunotherapies with fewer side effects, improving patient monitoring protocols, and implementing new treatment approaches to manage adverse reactions (Galluzzi, et al. 2017).

11.5 Enhancing the Efficacy of Combination Therapies

Combination therapies are one of the most promising approaches to overcoming many of the limitations of cancer immunotherapy. By combining immunotherapy with other modalities like chemotherapy, radiation, targeted therapy, or epigenetic modulation, researchers hope to achieve a synergistic effect that enhances anti-tumor responses. For example, combining immune checkpoint inhibitors with anti-angiogenic therapies could reduce tumor blood supply and allow immune cells to better infiltrate tumors. Similarly, the combination of CAR-T cell therapy with immune checkpoint blockade could further enhance tumor targeting and

persistence of T cells in the tumor microenvironment. However, developing the right combinations, identifying the optimal dosing schedules, and understanding the interactions between these treatments will be critical challenges moving forward.

11.6 Manufacturing and Accessibility Challenges

The large-scale production and widespread accessibility of immunotherapies, particularly personalized therapies like CAR-T cell therapy, is another significant challenge. Manufacturing CAR-T cells requires extensive, patient-specific processes that are time-consuming and expensive. Additionally, the cost of immunotherapy is often prohibitive, limiting access to many patients. To overcome this barrier, research will need to focus on developing more efficient, cost-effective manufacturing processes for CAR-T cells and other immunotherapies. Efforts to streamline manufacturing processes, reduce costs, and increase the availability of off-the-shelf therapies are expected to play a major role in making these treatments more widely accessible (Maude, et al. 2014).

11.7 Epigenetic Modulation and Tumor Microenvironment Reprogramming

The future of immunotherapy is increasingly tied to the modulation of the tumor microenvironment (TME) and epigenetic factors. The TME plays a key role in immune evasion, and strategies aimed at reprogramming the TME to become more immune-friendly will be critical for improving treatment outcomes. Epigenetic modulation, such as targeting DNA methylation or histone modifications, could help reverse immune suppression in the TME and enhance immune cell infiltration and activity. Additionally, reprogramming immune cells within the TME, such as macrophages and Tregs, to a more pro-inflammatory and anti-tumor phenotype could improve the efficacy of immunotherapies (Wieman, et al. 2015; Singh, et al. 2019).

Table 5. Overview of emerging drugs in Cancer Immunotherapy

S.No.	Name of the Drug	Category of the Drug	Mechanism of Action	Reference
1	Nivolumab (Opdivo)	Immune checkpoint inhibitor	Inhibits PD-1 to enhance T-cell activation, preventing tumor cells from evading immune response.	Wolchok, et al. (2017).
2	Ipilimumab (Yervoy)	Immune checkpoint inhibitor	Targets CTLA-4 to augment T-cell activation, enhancing anti-tumor immunity.	Wolchok, et al. (2017).
3	Tisagenlecleucel (Kymriah)	CAR-T cell therapy	Modified T-cells targeting CD19 on B	Maude, et al. (2018).

			cells to induce cytotoxicity against B-cell malignancies.	
4	Relatlimab (Opdualag)	Immune checkpoint inhibitor (LAG-3)	Targets LAG-3 to enhance T-cell response, potentially overcoming PD-1/PD-L1 resistance.	Tawbi, et al. (2022).
5	Talimogene laherparepvec (T-VEC)	Oncolytic virus therapy	Uses modified herpes simplex virus to selectively infect and lyse tumor cells.	Andtbacka, et al. (2015).
6	Blinatumomab (Blincyto)	Bi-Specific T-cell Engager (BiTE)	Binds CD19 on B-cells and CD3 on T-cells to activate T-cells against B-cell malignancies.	Schlereth, et al. (2017).
7	Pembrolizumab (Keytruda)	Immune checkpoint inhibitor	Inhibits PD-1 to prevent tumor cells from evading immune detection by T-cells.	Ribas, & Wolchok, (2018).
8	Cellectis UCART-CS1	CAR-T cell therapy	Targets CS1 on multiple myeloma cells to promote T-cell mediated destruction.	Depil, et al. (2020).
9	Cryoport FT596	CAR-NK cell therapy	An off-the-shelf CAR-NK therapy targeting B-cell malignancies and improving cytotoxicity.	Rezvani, (2019).
10	Entinostat	Epigenetic modulator	A histone deacetylase (HDAC) inhibitor that enhances anti-tumor immunity by modulating immune checkpoints.	Seto, et al. (2021).
11	Dostarlimab (Jemperli)	Immune checkpoint inhibitor (PD-1)	Inhibits PD-1 to enhance immune system activity against mismatch repair-deficient cancers.	Lenz, et al. (2020).
12	Axicabtagene ciloleucel (Yescarta)	CAR-T cell therapy	Targets CD19 on B-cells, inducing lysis of B-cell malignancies.	Neelapu, et al. (2017).

13	Regeneron's Cemiplimab (Libtayo)	Immune checkpoint inhibitor (PD-1)	Blocks PD-1, enhancing T-cell-mediated immune response against tumor cells in cutaneous squamous cell carcinoma.	Ferris, et al. (2016).
14	Durvalumab (Imfinzi)	Immune checkpoint inhibitor (PD-L1)	Blocks PD-L1, enhancing the immune system's ability to attack tumor cells.	Antonia, et al. (2017).
15	Duvelisib (Copiktra)	PI3K inhibitor	Targets the PI3K pathway, modulating the immune system's response and inhibiting tumor growth.	Brown, et al. (2018).

Conclusion

Cancer immunotherapy has transformed oncology, offering durable responses and improved survival in multiple malignancies. While the landscape of cancer immunotherapy has advanced significantly in recent years, there is some more research that has to be taken up to overcome the challenges of resistance, safety concerns, and the complexity of the tumor microenvironment. Future research wills likely focus on expanding the scope of cancers that can be treated with immunotherapy, developing personalized approaches to treatment, and optimizing combination therapies. Furthermore, addressing the cost and accessibility of immunotherapies will be critical in making these groundbreaking treatments available to a larger patient population. With ongoing advancements in our understanding of cancer biology and immunology, the future of cancer immunotherapy remains promising, with the potential to significantly improve patient outcomes. While challenges like resistance, toxicity, and accessibility remain, emerging trends such as BiTEs, AI applications, and oncolytic viruses hold immense promise. Continued research and innovation will shape the future of this dynamic field, bringing us closer to a universal cure for cancer.

Acknowledgement: The authors are thankful to the faculty and management of East West College of Pharmacy, Bengaluru for their support in completion of this work.

Conflicts of Interest: The authors declare no conflicts of interest.

References:

1. Abramson, J.S., Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. (2020). Lisocabtagene Maraleucel for Large B-cell Lymphoma. Lancet Oncology, 21(5), 612-621.
2. Andtbacka, RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, Delman KA, (2015). Talimogene laherparepvec improves durable response rate in advanced melanoma. Journal of Clinical Oncology, 33, 2780-2788.
3. Antonia, S.J, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, et al. (2017). Durvalumab for Stage III NSCLC. Lancet, 389(10066), 255-265.
4. Bachanova, V., Perales MA, Abramson JS. (2020). Modern management of relapsed and refractory aggressive B-cell lymphoma: A perspective on the current treatment landscape and patient selection for CAR T-cell therapy. Blood Rev. 40:100640.
5. Baeuerle, PA., (2009). Solitomab targeting EpCAM in solid tumors. Cancer Research, 69(15), 6735-6741.
6. Bannerji, R., Kalakonda N, Maerevoet M, Cavallo F, Follows G, Goy A, et al. (2020). REGN1979 in relapsed/refractory B-cell malignancies. Lancet Haematology, 7(7), e511-e522.
7. Bray, F., et al. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin.
8. Brisson, M., Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, Martin D, Simms KT, (2020). Impact of HPV vaccination on cervical cancer elimination. Lancet Public Health, 5(4), e240-e247.
9. Chang, M.H., Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, Shau WY, Chen DS. (1997). Decreased incidence of hepatocellular carcinoma in HBV vaccinated children. NEJM, 336, 1855-1859.
10. Chia, A.R. (2020). "Overcoming resistance to cancer immunotherapy." Cancer Cell, 37(5), 595-609.
11. Davids, M. S., et al. (2019). "The safety and tolerability of immunotherapies in hematologic malignancies." Journal of Clinical Oncology, 37(35), 3412-3423.
12. Depil, S., Duchateau P, Grupp SA, Mufti G, Poirot L. (2020). Off-the-shelf' allogeneic CAR T cells: development and challenges. Nature Reviews Clinical Oncology, 17, 204-222.
13. Dolstra, H., Roeven MWH, Spanholtz J, Hangalapura BN, Tordoir M, Maas F, et al. (2017). Allogeneic NK cell therapy for AML. Blood Advances, 1(26), 2256-2264.
14. Esteva, A., et al. (2019). Deep learning-enabled medical technologies for cancer diagnosis and treatment. Nature Medicine, 25, 37-44.

15. Farkona, S., Diamandis EP, Blasutig IM. (2016). Cancer immunotherapy: The beginning of the end of cancer? BMC Medicine, 14(1), 73.
16. Ferris, R.L., (2016). Regeneron's Cemiplimab (Libtayo) for Cutaneous Squamous Cell Carcinoma. JCO, 34(15), 1811-1818.
17. Frustaci AM, Tedeschi A, Deodato M, Zamprogna G, Cairoli R, Montillo M. (2018). Duvelisib in the Treatment of Chronic Lymphocytic Leukemia. NEJM, 379(1), 33-44.
18. Galluzzi, L., (2017). "Targeting autophagy in cancer therapy: Pros and cons." Nature Reviews Cancer, 17(9), 571-588.
19. Harper, D.M., Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G (2006). Sustained efficacy of HPV vaccine up to 4.5 years. Lancet, 367(9518), 1247-1255.
20. Heo, J., Reid T, Ruo L, Breitbach CJ, Rose S, Bloomston M, Cho M, Lim HY, et al. (2013). Pexa-Vec for liver cancer. Lancet Oncology, 14(10), 1047-1056.
21. International Agency for Research on Cancer (IARC). (2024). New report on global cancer burden in 2022 by world region and human development level. IARC News.
22. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. (2018). CAR T cell therapy for human cancer. Science, 359(6382), 1361-1365.
23. Kalos, M., et al. (2011). "T cell depletion and cancer immunotherapy: Challenges and opportunities." Clinical Cancer Research, 17(19), 6139-6151.
24. Kantoff, P.W., Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, et al. (2010). Sipuleucel-T for prostate cancer. NEJM, 363, 411-422.
25. Klingemann, H., Boissel L, Toneguzzo F. (2016). NK-92: A versatile NK cell line. Oncoimmunology, 5(9), e1112946.
26. Lang, F.F., Conrad C, Gomez-Manzano C, Yung WKA, Sawaya R, Weinberg JS, et al. (2018). DNX-2401 for glioblastoma. Journal of Clinical Oncology, 36(14), 1419-1427.
27. Larkin, J., Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob et al. (2019). "Combined nivolumab and ipilimumab or monotherapy in untreated melanoma." The New England Journal of Medicine, 373(1), 23-34.
28. Lee, J. H., et al. (2021). "The role of personalized immunotherapy in cancer treatment." Nature Reviews Clinical Oncology, 18(9), 563-574.
29. Lenz, H.J., Dioun S, Chen L, Melamed A, Gockley A, St Clair CM, Hou JY, et al. (2020). Dostarlimab for Mismatch Repair-Deficient Solid Tumors. NEJM, 382, 2331-2342.
30. Li F, Liu H, Zhang D, Ma Y, Zhu B. (2022). "Molecular and metabolic pathways in the regulation of T cell exhaustion." Nature Reviews Immunology, 16(9), 549-563.

31. Mackall CL, Fry TJ, Gress RE. Harnessing the biology of IL-7 for therapeutic application. Nat Rev Immunol. 2011 May;11(5):330-42.
32. Maude, S.L., Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, et al. (2018). Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. NEJM, 378, 439-448.
33. Maude, SL., (2014). "Chimeric antigen receptor T cells for sustained remissions in leukemia." The New England Journal of Medicine, 371(16), 1507-1517.
34. Munshi, N.C., Anderson LD Jr, Shah N, Madduri D, Berdeja J, Lonial S, et al. (2021). Idecabtagene Vicleucel in Relapsed/Refractory Multiple Myeloma. NEJM, 384, 705-716.
35. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. "Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma." N Engl J Med. 2017;377(26):2531-2544.
36. Norman, K.L., et al. (2002). Reovirus and Ras-mediated tumor cell killing. Oncogene, 21(52), 7851-7862.
37. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, Zhang W, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature. 2019;8(3):e1512945.
38. Pardi, N., Hogan MJ, Porter FW, Weissman D. (2018). mRNA vaccines — A new era in vaccinology. Nature Reviews Drug Discovery, 17(4), 261-279.
39. Pardoll DM. "The Blockade of Immune Checkpoints in Cancer Immunotherapy." Nat Rev Cancer. 2012;12(4):252-264.
40. Parmiani G, Castelli C, Dalerba P, Mortarini R, Rivoltini L, Marincola FM, Anichini A. (2012). Cancer immunotherapy with peptide-based vaccines: what have we achieved? Where are we going? J Natl Cancer Inst., 23(1), 20-25.
41. Patel SA, Minn AJ. Combination Cancer Therapy with Immune Checkpoint Blockade: Mechanisms and Strategies. Immunity. 2018 Mar 20;48(3):417-433.
42. Quoix, E., Ramlau R, Westeel V, Papai Z, Madroszyk A, Riviere A, et al. (2011). TG4010 immunotherapy for NSCLC. Lancet Oncology, 12(12), 1125-1133.
43. Raje, N. (2019). AMG 420 in relapsed/refractory multiple myeloma. NEJM, 380, 1738-1747.
44. Rein DT, Breidenbach M, Curiel DT. (2006). Adenovirus-based gene therapy for cancer. Nature Medicine, 7(7), 882-887.
45. Rezvani, K., Fabian KP, Padget MR, Donahue RN, Solocinski K, Robbins Y, Allen CT, et al. (2017). haNK cells targeting HER2-positive tumors. Cancer Immunology Research, 5(5), 408-420.
46. Ribas, A., & Wolchok, J.D. (2018). Cancer immunotherapy using checkpoint blockade. Science, 359(6382), 1350-1355.

47. Ruggeri, L. (2020). Cord blood NK cell therapy in multiple myeloma. Frontiers in Immunology, 11, 5621.
48. Sahin, U., Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M, Bukur V, et al. (2017). Personalized RNA mutanome vaccines. Nature, 547, 222-226.
49. Schlereth, B., et al. (2017). AMG 160, a BiTE targeting PSMA. Molecular Cancer Therapeutics, 16, 2943-2953.
50. Seto, T, Jänne PA, Opyrchal M, Hafez N, Raez LE, Gabrilovich DI, Wang F, Trepel JB (2021). Entinostat in combination with pembrolizumab in advanced solid tumors: A phase 2 study. Journal of Clinical Oncology, 39(17), 1870-1880.
51. Shah, B.D., Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, et al. (2021). KTE-X19 for Adult B-cell ALL. Lancet Oncology, 21(3), 294-305.
52. Shore, N.D., Deegen P, Thomas O, Nolan-Stevaux O, Li S, Wahl J, Bogner P, Aeffner F, et al. (2021). AMG 160 for PSMA-targeted therapy in prostate cancer. Journal for ImmunoTherapy of Cancer, 9(1), e002941.
53. Singh, A., (2019). "Reprogramming the tumor microenvironment with epigenetic drugs: New strategies for immunotherapy." Cancer Research, 79(15), 3855-3863.
54. Tawbi, H.A., Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, Rutkowski P, et al. (2022). Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. NEJM, 386, 24-34.
55. Topalian, S. L., F. Stephen Hodi, Julie R. Brahmer, Scott N. Gettinger, et al. (2012). "Safety, activity, and immune correlates of anti–PD-1 antibody in cancer." The New England Journal of Medicine, 366(26), 2443-2454.
56. Topp, M.S., Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, Horst HA, Raff T, et al. (2011). Blinatumomab therapy for relapsed B-cell acute lymphoblastic leukemia. Journal of Clinical Oncology, 29(22), 2786-2792.
57. van der Merwe, P. A., et al. (2020). "Personalized cancer immunotherapy: Targeting the tumor-specific immune response." Nature Reviews Drug Discovery, 19(1), 47-62.
58. Walter, S., Weinschenk T, Stenzl A, et al. (2012). Multipeptide immune response in renal cell carcinoma. Nature Medicine, 18(3), 418-426.
59. Wang, Y., Jain P, Locke FL, Maurer MJ, Frank MJ, Munoz JL, et al. (2023). Brexucabtagene Autoleucel in Relapsed/Refractory Mantle Cell Lymphoma. NEJM, 382, 1331-1342.
60. Wieman, H. L., (2015). "Epigenetic modulation and tumor immunotherapy." Journal of Clinical Investigation, 125(10), 3678-3686.
61. Wolchok, J.D., Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, et al. (2017). Overall survival with combined nivolumab and ipilimumab in advanced melanoma. NEJM, 377, 1345-1356.

62. Wolchok, J.D., Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. (2017). Nivolumab plus Ipilimumab in Advanced Melanoma. NEJM, 377, 1345-1356.
63. World Health Organization. (2023). Cervical cancer. Retrieved from www.who.int.
64. Li B, Jin J, Guo D, Tao Z, Hu X. (2023). Immune Checkpoint Inhibitors Combined with Targeted Therapy: The Recent Advances and Future Potentials. Cancers (Basel). 15(10):2858.