**Review Article**

# CAR-T Cell Therapy: Hope and Healing in the Battle Against Cancer


## ABSTRACT

With numerous forms and a myriad of genetic and environmental factors, cancer continues to be a leading cause of morbidity and mortality worldwide. Advances in cancer research have led to a deeper understanding of the molecular mechanisms driving cancer progression, facilitating the development of targeted therapies and immunotherapies. Chimeric Antigen Receptor T-cell therapy, commonly known as CAR-T cell therapy, represents a groundbreaking approach in the field of cancer immunotherapy. This innovative treatment involves genetically engineering a patient's T cells to express chimeric antigen receptors (CARs) that target specific cancer cells. CAR-T therapy has demonstrated remarkable success in the treatment of certain hematologic malignancies, particularly B-cell malignancies like acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and non-Hodgkin lymphoma (NHL). CAR-T cell therapy also has challenges, such as managing side effects like cytokine release syndrome and neurotoxicity, high treatment costs, and the need for further research to broaden its applicability to solid tumors. CAR T-cell therapies, such as Kymriah and Yescarta, have demonstrated impressive clinical outcomes in patients with relapsed or refractory cancers, offering hope for those with limited treatment options.Additionally, the long-term durability of responses requires continuous monitoring and research.



*Keywords:CAR-T cell, Neurotoxicity, Autologous Therapy, Adoptive Cell Therapy, Immunotherapy, Leukaemia, Cytokine Release Syndrome (CRS).*




## 1. INTRODUCTION

The term malignant growth envelops a wide assortment of illnesses, recognizable by organ or tissue of beginning and cell type and morphology Top of the Document (1) (Carbone, 2020). Cancer is the world's subsequent driving reason for death after a coronary episode. Regardless of advances in standard treatments, including a medical procedure, radiation, and chemotherapy (Guedan*et al.,* 2019), cancer patients' general endurance has not improved (Muhammad *et al.,* 2017). Furthermore, it is predicted to overtake ischemic heart disorders as the primary cause of fatalities in the coming decades (Mattiuzzi and Lippi, 2019). The human guard framework can effectively distinguish self and non-selfparticles, including microbes, infections and strange disease cells. The recognition of cancer cells depends on their procured antigenicity and immunogenicity through the presence of unfamiliar antigens (Galluzzi and Martin, 2017). Be that as it may, disease cells can undermine the safe framework for their potential benefit, bringing about lacking antitumor invulnerability, and growth endurance and movement (Perales *et al.,* 2018). The capacity of T-cells to target and kill cancer cells is essential for the cancer immune cycle (Jogalekar*et al.,* 2022). Lymphocytes are a basic part of the adaptive immune system as they coordinate cytotoxic impacts, yet additionally give long cell 'memory' of explicit antigens (Pennock *et al.,* 2013). Immunotherapy has been perceived as another age of an antitumor weapons and will be the main power in future disease treatment. Immunotherapy is a sort of

treatment that objectives the human defense system rather than focusing on cancers. By turning on a patient's defences, it can fend off and kill tumour cells (Emens *et al.,* 2017). One of the freshest and most encouraging cancer therapies, chimeric antigen receptor (CAR) T-cell treatment, supports the body's resistant framework to battle disease. The progression of CAR T treatment has been made conceivable by the combination of quality sequencing, developing hereditary information, new strategies for genome manipulation, and the improvement of novel gene exchange advancements (Huang *et al.,* 2023). Antigen recognition and T-cell signalling domains combine to form the fusion protein known as CAR. (Brudno and Kochenderfer, 2019). CAR-T cells are autologous lymphocytes produced through the laboratory process of leukapheresis, which is the process of separating white blood cells from a sample of blood. and genetically altered to express a CAR (often via lentiviral or retroviral transduction; Roex *et al.,* 2020). With CD19 and CD20 as its primary targets, CAR T cell therapy has revolutionised the treatment of haematological malignancies. The patient's existing T lymphocytes are modified in CAR T cell treatment so that they can identify and eradicate cancer cells (Mazinani and Rahbarizadeh, 2022). For many years, biomarkers have been a crucial part of understanding cancer, and with the development of CAR T cell therapy, a new class of therapeutic biomarkers has emerged. CAR T cells can be directed to cancerous target cells using these markers (Townsend *et al.,* 2018). A powerful cytotoxic immune response is combined with tumour selectivity when the CAR is expressed on the T cell (Porter *et al.,* 2018). CAR-T cells get stimulated to multiply and release cytokines when certain antigens are recognised. According to Maoet al. (2004) and Louis et al. (2011), CAR-T cells can aid in the destruction of cancer and have showed promise for the immunotherapy of several human malignancies. Patients who receive CAR T cell therapy can have tremendous efficacy, but there is a chance of serious side effects as well. Patients have experienced brain toxicity and the cytokine release syndrome, which serve as examples of the negative effects of powerful immune detection of antigenic sites and the ensuing vigorous immune response (Akce*et al.,* 2018).

## 2. CAR STRUCTURE

CARs are engineered receptors with rational structure on T-Cells that target exterior antigens of the target malignant cell. The restriction typically imposed by the major histocompatibility complex (MHC) can be avoided by T cells that have been genetically modified to express CAR (Zhao *et al.,* 2018). Therefore, it is essential to build CARs with the proper affinity to distinguish between cancerous and healthy cells without causing any toxicity (Caruso *et al.,* 2015). Chimeric antigen receptors (CARs) are synthetic receptors that typically include the transmembrane domain of the T cell receptor, the cytoplasmic signalling domain of the CD3 zeta chain, and the antigen-binding portion of a monoclonal antibody (mAb).

### 2.1 Antigen Binding Region

The antigen recognition domain is derived from the variable region of monoclonal antibodies (Lam *et al.,* 2020). This area interacts with the target antigen and is constantly revealed to the outside of the cell (Zhang *et al.,* 2017; Rafiq *et al.,* 2020). The variable heavy (VH) and light (VL) chains of monoclonal antibodies are what give rise to single-chain variable fragments (scFv), a component of CARs. These scFvs often target membrane-bound cancer cell surface receptors and trigger T cell activation independent of the MHC. Although the sequences of linkers vary greatly, those frequently utilised in CARs contain repeats of the amino acids glycine and serine to give antigen-binding sites the flexibility they need to change orientation and remain stable (Yan and Sun, 1997). The presence of Gly and Ser residues also inhibits secondary structure development and lessens the possibility that the linker may obstruct the folding and functionality of the scFv (Van Rosmalen*et al.,* 2017). In the external domain, a hinge or spacer region is also present. This region serves to link the scFv to the transmembrane domain and to provide flexibility to overcome steric hindrance (Jayaraman *et al.,* 2020). It also adds to the length to enable the antigen-binding domain to access the targeted epitope (sterner and sterner, 2021).Thisenhances antigen binding and synapse

formation between the CAR T cells and target cancer cells (Hudecek *et al.,* 2015) as increasing epitope-paratope distance can also result in decreased delivery of granzymes and perforins to the target cell, limiting lytic efficacy (Woodsworth *et al.,* 2015).

### 2.2 Transmembrane Domain

The ectodomain and endodomain are joined by the transmembrane domain, which also acts as the cell membrane's anchor (Huang *et al.,* 2020). The transmembrane's primary role is to hook the CAR to the T cell membrane. The transmembrane domain of the CAR is perhaps the least well-studied part of the structure, consisting of a hydrophobic helix that traverses the cell membrane (Guedan*et al.,* 2019). In a study by Morin et al. (2015), CD28's extracellular and transmembrane domains can substantially activate T cells. It has been demonstrated that transmembrane domains control other crucial processes associated with CAR asembly, activation and aggregation. Furthermore, it is known that this domain influences the release of cytokines, which, if it is excessive, can result in significant non-specific toxicity. Most of these domains come from CD3ζ, CD4, CD8α, or CD28each, giving CAR-T cells radically distinct features (Harris and Kranz, 2016).

### 2.3 Intracellular Signalling Domain

The endodomain of the receptor is located within the cell and contains an internal T cell signalling domain (Chandran and Klebanoff, 2019). CD3ζendodomain present in initially designed car has a conserved amino acid sequence known as immunoreceptor tyrosine based activaing motifs which upon phosphorylation creates binding site for zap70, a signalling kinase (Courtney *et al.,* 2018). But relying solely on these patterns for signalling cannot result in efficient T cell responses (Pan et al., 2022). The generation of a co-stimulatory domain in series with the CD3 intracellular signalling domain increased IL-2 production and proliferation under repeated antigen exposure (Maher *et al.,* 2002).The release of proinflammatory cytokines such IL-17A, IL-17F, IL-22, and IFN- is increased when inducible co-stimulatory is used, which improves CAR T cell persistence (Guedan*et al.,* 2014). High response rates in patients have been linked to CAR T cells with the CD28 and 4-1BB domains. In preclinical trials, new costimulation domains like ICOS and CD27 have effectively eliminated tumour cells (Guedan*et al.,* 2014; Song *et al.,* 2012). Co-stimulatory receptors 4-1BB, ICOS, and OX40 influence metabolic cycles, apoptosis, and activation-induced cell death in addition to T-cell differentiation processes (Weinkove*et al.,* 2019).

## 3. MANUFACTURING CAR T-CELL

CAR T-cells are the immune cells that have been genetically modified to identify target antigens on the surface of targets and destroy them after adoptive transfer. The process includes the following steps (Fig 1).

### 3.1 Leukapheresis

Blood from the patient is drawn, and the lymphocytes are separated using apheresis (also known as leukapheresis), which is the first step in the creation of CAR T cell. Clinicians arrange collection based on the treatment regimen being used by the patient to guarantee that there are enough T cells present (Wang and Rivière, 2016). The operation is carried out at an approved clinic or infusion facility under the direction of the patient's medical professional (Batlevi*et al.,* 2016).

### 3.2 Engineering T cell with CAR gene

Eshhar and colleagues developed CARs (formerly known as T-bodies) in 1989 as fusions of antibody and TCR subunits which, when produced on T cells, facilitated MHC-independent T-cell activation. The scFv generated from phage display or the mAbs produced against cell-

surface antigens are typically used to impart CAR specificity (Stastny *et al.,* 2007).CAR, a protein made from the gene, binds to cancer cells and either permanently or temporarily expresses a therapeutic gene. The optimal target for CAR T cells is expressed on the surface of all cancer cells but is not present on the surface of any normal cells. Based on its cell-surface expression and function in the majority of leukaemias and lymphomas, CD19 has been identified as a viable target (Sadelain*et al.,* 2017). The effective transport of the coding DNA is necessary for CAR T cell gene editing operations (Benmebarek*et al.,* 2019). There are currently two methods for incorporating genes into vectors: viral systems and non-viral systems (Zhang *et al.,* 2017). Adenovirus, adeno-associated virus, and retroviruses (including lentivirus) are some of the virus vectors. The most widely used of them for delivering genes are genetically modified retroviruses (Lundstorm, 2018). High gene transfer efficiency and consistent CAR expression are two benefits of these vectors (Ruella *et al.,* 2018). Naked DNA, liposomes, polymerizers, and molecular conjugates are examples of non-viral vectors. Minicircle DNA vectors, which are unique non-viral vectors developed in bacteria from a parental plasmid and can persistently express transgene at high levels in vivo (Kay *et al.,* 2010), are free of plasmid bacterial DNA sequences. The anti-CD20 antibody vector that contains a CD3-signaling cassette is used to clone single-chain variable segments to create the CD19 CAR construct (Kimman *et al.,* 2023). Finally, new strategies involving in situ T cell modification are being investigated as a way to streamline and lower the cost of CAR T cell manufacture. Pre-clinical models of B cell malignancies have demonstrated the safety and efficacy of in situ T cell programming utilizing DNA nanocarriers (Smith *et al.,* 2017) or lentiviral vectors selectively targeting human CD8+ T cells (Pfeiffer *et al.,* 2018). The immune cells have been altered to selectively combat cancer cells. The viral vector attaches to the patient's cells using viral machinery, and after entering the cells, the vector delivers genetic material in the form of RNA. As the patient cells proliferate and become more numerous in the bioreactor, the RNA is reverse-transcribed into DNA and permanently incorporated into their genomes. As a result, CAR expression is preserved. The patient's cells then translate and express the CAR, which is expressed on the cell surface (Levine *et al.,* 2016).

### 3.3 Grow and expand CAR T cells

The ideal culture mixing and gas exchange conditions required to produce a large amount of cells for clinical usage are provided by bioreactor culture systems. The CD19-targeted CAR T cell has been expanded using the WAVE Bioreactor, which includes a rocking platform (Somerville, 2012). The cell culture, which may have a volume of up to 5 L when the cell growth procedure is complete, needs to be condensed to a volume that can be infused into the patient. After product release, the cleaned and purified cells are cryopreserved in infusible media and transferred to and thawed at the facility where the patient is to be treated (Levine, 2015).

### 3.4 Infusion

CAR T cells will be returned to the patient once there are enough of them. The patient might get chemotherapy a few days before to the CAR T-cell infusion to assist reduce the amount of other immune cells. This increases the likelihood that the CAR T cells will become activated to fight the tumour. Because CAR T cells function best while there are still cancer cells to assault, this chemotherapy is typically not very potent. The CAR T cells begin to multiply and potentially aid in the destruction of additional cancer cells once they begin binding with malignant cells.

## 4. KILLING MECHANISM OF CAR T CELL

Through their T cell receptor, T cells identify and kill their target, which are mostly infections. The T cell receptor notifies the T cell to kill the invader when it detects a particular chemical on a bacterium

or virus. Engineered T cells' ability to move to cancer sites, multiply, and mediate effector functions that eradicate numerically greater tumour loads is the basis for their anti-tumor actions (Gattinoni*et al.,* 2012). When a target antigen is recognised and bound to by a CAR T cell's antigen binding domain, the CAR T cell is activated. Following this engagement, CAR molecules on the surface of T cells group together, which causes the CAR molecule to become immobile and creates an immunological synapse (Liu *et al.,* 2020). With enhanced tumour cell targeting and persistence for long-term tumour control, CAR T cells have been engineered to precisely identify and lyse target cells on their own while also stimulating T cell growth and differentiation—two critical processes for CAR T cell efficacy. According to Korell et al. (2022) immunological synapses, target antigen density, CAR affinity for the target, and signal transduction strength all affect how much CAR T cells are activated. For effective signal transduction and activation, CARs need noticeably greater antigen concentrations (Harris *et al.,* 2018). Different cytokines promote T cell differentiation into effector cells and boost T cell proliferation. The signal transduction is begun by CD3, with co-stimulatory molecules providing signal amplification (Fraietta*et al.,* 2018). Due to rapid degranulation and perforin release compared to natural T cells, CAR T cells destroy tumour cells more quickly (Davenport *et al.,* 2015). Additionally, given that CAR T cells can kill antigen-negative tumour cells through this mechanism and that Fas-negative tumour cells are resistant to the apoptosis produced by CAR T cells, they may be more dependent on Fas/FasL for the destruction of tumour cells. IFN- is a protein that CAR T cells also secrete to help kill tumour cells. Currently, leukaemia and lymphoma are the most common blood malignancies treated with car-t cell therapy in India. Many other types of car-t cell therapy have received FDA approval, and many more are awaiting approval (Ravindranath *et al.,* 2022). A few of these are listed in table 1.

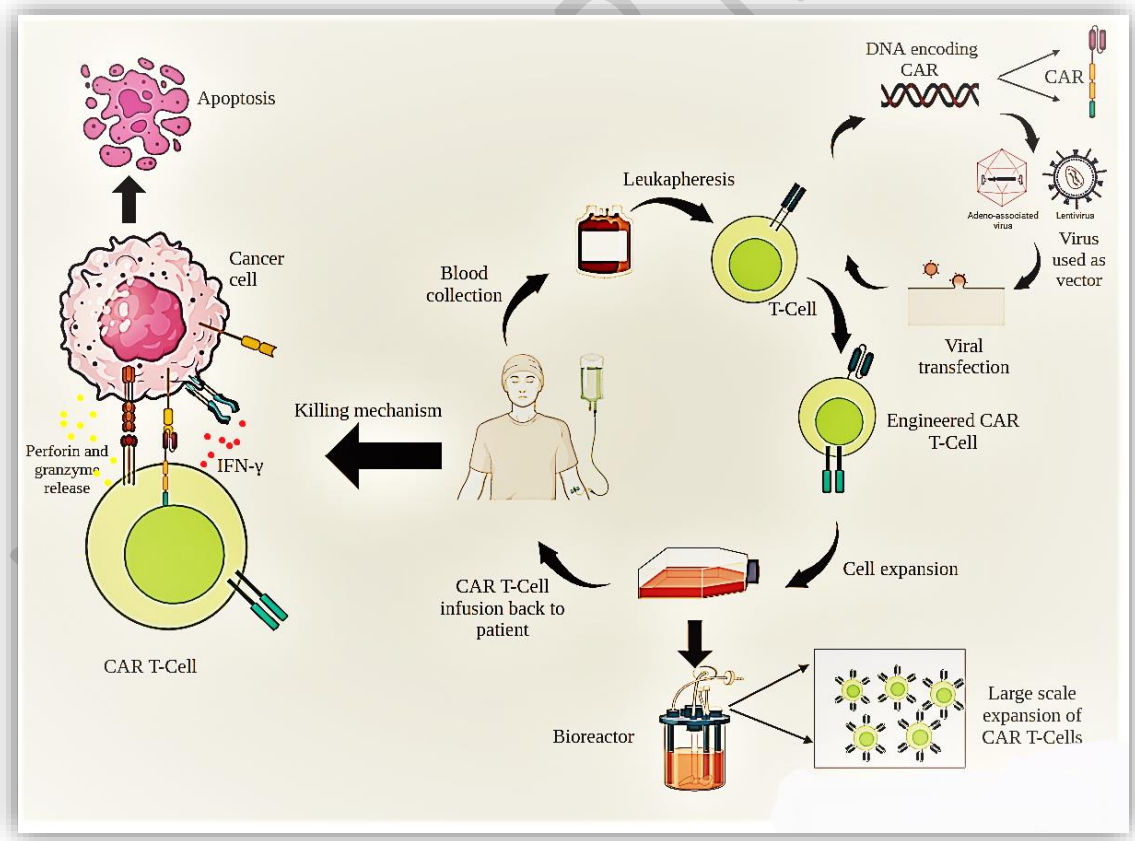


**Fig 1. CAR T-Cell Therapy and its Mechanism of Action.**

## 5. PROS & CONS ASSOCIATED WITH THERAPY

The advantages of CAR T-cell therapy, which is also a "living drug," can last for many years. Since the cells can survive in the body for a long time, if and when a recurrence occurs, they could be able to identify and combat cancer cells. The cost of and the amount of modification needed for the CAR T cells are significantly higher. Although CAR T cells have been effective in treating liquid (blood) cancers, they have not been as effective in treating solid tumours, and they are linked to toxicities that pose a serious risk to human life (Kandra *et al.,* 2022). Tumour resistance to single antigen targeting CAR constructions is one of the most difficult limitations of CAR-T cell treatment. Antigen escape is the term used to describe this process (Majzner and Mackall, 2018). It may be beneficial to use human or humanised antibody fragments instead of murine-derived CARs to minimise CAR immunogenicity because the host immune system's detection of CAR constructions may be a factor in cytokine-related toxicities (Sommermeyer*et al.,* 2017). The effectiveness of CAR-T cell therapy in solid tumours, such as lung cancer, is constrained in part by CAR-T cell depletion (Kasakovski*et al.,* 2018). Aphasia, tremor, ataxia, myoclonus, and CRS are among the neurological toxicities associated with the use of CAR-T cell treatment. Organ damage could conceivably result in CAR-T cells when they react with an antigen expressed in normal tissue that is identical to the target antigen expressed by cancer (Brudno and Kochenderfer, 2016) as without the assistance of HLA expression, CAR-T cells are capable of recognising cell surface chemicals (Zhao *et al.,* 2018).CAR T-Cell Therapy is a targeted cancer treatment that targets cancer cells, minimizing damage to healthy tissues. It has the potential for long-term remission in some cases, particularly in blood cancers like leukemia and lymphoma. CAR T-cell therapy is personalized, reducing immune rejection. It has shown promise in treating refractory cancers and is an innovative breakthrough in personalized medicine and immune system-based therapies. However, it has serious side effects, is expensive and resource-intensive, and is limited to certain blood cancers. The complex and time-consuming process can be time-consuming for patients with aggressive cancers. Additionally, there is a risk of relapse.

## 6. CONCLUSION

In conclusion, CAR-T cell therapy stands as a transformative advancement in the realm of cancer treatment, holding the potential to reshape the prognosis for patients with certain blood cancers. One may predict similar results with additional leukemia targets and haematological cancers given the success of CD19 CARs. The way is being prepared for CAR T cell treatment to be used more widely and with greater success. CAR T cells' functionality, selectivity, and effectiveness are constantly being enhanced. CAR T cells hold potential for cancer treatment that has not yet been fully realized when combined with developments in cell engineering and gene editing. The recent approval of two CAR T cell therapies heralds the beginning of a new age in cell therapy, where it will be necessary to show that such methods are broadly applicable. On-target off-tumor effects can happen even with proper antigen targeting and result in related toxicity. Getting CAR-T cells to make their way to and infiltrate solid tumors is difficult. Future CAR T-cell therapy solutions will specifically target two, three, or even more different molecules on a given tumor. As a result, CAR T-cells would be able to identify malignancy even if one of their targets was missed. It is anticipated that the toxicity and adverse effects of this new CAR T cell therapy would be reduced. The ultimate goal is to replace chemotherapy and stem cell transplantation with CAR T-cell therapy. However, it is not a panacea, and further research is needed to extend its benefits to a wider range of cancer types and to address safety and accessibility concerns. Ongoing research and clinical trials continue to refine and expand the application of CAR-T therapy, offering hope for more widespread use and improvements in safety and affordability.

### Consent for publication

Not applicable.

Disclaimer (Artificial intelligence)

Author hereby declares that generative AI technologies such as Chat Gpt,Quillbot and Biorender etc. have been used during the writing or editing of manuscripts.

Details of the AI usage are given below:

1.OpenAI.ChatGPT. Version 4.0.

2.Quillbot.Version v15.485.7

3.BioRender. Version2024.

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**Table 1. CAR-T Cell Therapies in Cancer.**

| S.No. | Trade Name | Drug | Target Disease | References |
|---|---|---|---|---|
| 1 | ABECMA | IdecabtageneVicleucel | Multiple Myeloma | **Hansen *et al.,* 2023** |
| 2 | BREYANZI | LisocabtageneMaraleucel | B-Cell Non-Hodgkin Lymphoma (NHL) | **Jaklevic, 2021** |
| 3 | CARVYKTI | CiltacabtageneAutoleucel | Multiple Myeloma | **Martin *et al.,* 2023** |
| 4 | KYMRIAH | Tisagenlecleucel | Acute Lymphoblastic Leukemia, B-Cell Lymphoma, and Follicular Lymphoma. | **Awasthi *et al.,* 2023** |
| 5 | TECARTUS | BrexucabtageneAutoleucel | Mantle Cell Lymphoma (MCL) | **Mian and Hill, 2021** |
| 6 | YESCARTA | AxicabtageneCiloleucel | B-Cell Non-Hodgkin Lymphoma (NHL) | **Papadouli*et al.,*2020** |
| 7 | BAVENCIO | Avelumab | Metastatic Merkel Cell Carcinoma (MCC) | **Gaiser *et al.,* 2018** |
| 8 | TECENTRIQ | Atezolizumab | Non–Small-Cell Lung Cancer (NSCLC) | **Dhillon and Syed, 2019** |
| 9 | KEYTRUDA | Pembrolizumab | Metastatic Gastric Cancer | **Kamath *et al.,*2018** |
| 10 | IMFINZI | Durvalumab | Non–Small-Cell Lung Cancer (NSCLC) | **Antonia *et al.,*2018** |
| 11 | OPDIVO | Nivolumab | Melanoma, Non-Small Cell Lung Cancer (NSCLC), Urothelial Cancer, and Renal Cell Cancer. | **Prasad and Kaestner, 2017** |

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|---|---|---|---|---|
| 12 | PROVENGE | Sipuleucel- T | Prostate Cancer | **Cheever and Higano, 2011** |
| 13 | YERVOY | Iplimumab | Metastatic Melanoma | **Graziani *et al.,* 2012** |
| 14 | BLINCYTO | Blinatumomab | Acute Lymphoblastic Leukaemia | **Sanford, 2015** |
| 15 | JEMPERLI | Dostarlimab | Colorectal Cancer | **ul Hussain *et al.,*2022** |
| 16 | LYNPARZA | Olaparib | Ovarian Cancer | **Gunderson and Moore, 2015** |
| 17 | ZEJULA | Niraparib | Ovarian Cancer | **Heo *et al.,*2018** |