

**Emerging role of the immunotherapy in treatment of breast cancer****Nagwa A. Ahmed<sup>a</sup>, Maisa H. Mohammed<sup>a</sup>**<sup>a</sup>Pathology Department, Faculty of Medicine, Sohag University, Sohag, Egypt**Abstract**

**Background:** Breast cancer is a life-threatening malignant tumor that ranks the most frequent cancer in females worldwide. Emerging studies suggest the important role of the immunotherapy in breast cancer. Triple negative breast cancer (TNBC) is associated with the worst prognosis and is resistant to the conventional therapeutic agents. Recently, the immunotherapy has achieved satisfactory results in the treatment of breast cancer in general and in TNBC in particular. The immune checkpoints are targeted in many clinical trials. The checkpoint inhibitors results in advances in treatment of breast cancer, especially refractory molecular subtypes. This review is aimed to highlight the current knowledge on the immunotherapy and the advances in its implications in treatment of breast cancer with emphasis on newly approved therapeutic approaches in this field.

**Conclusion:** The immunotherapy is considered as an emerging therapeutic strategy for treatment of breast cancer, particularly TNBC. Several clinical trials focusing on the potential role of immunotherapy in breast cancer are still under research.

**Keywords:** breast cancer, TNBC, immunotherapy, Programmed Death 1, Programmed Death Ligand 1

**Introduction:**

Breast cancer is characterized by high incidence and mortality rates, so it represents a major public health problem. It represents the most common diagnosed cancer and the most common leading cause of cancer-related deaths among women worldwide comprising 11.6% on average of all cancers (Bray et al., 2018).

The immune system plays a key role in carcinogenesis process; it recognizes, destroys and finally eliminates the genetic mutations. The immune cells act in concert to protect against the neoplastic transformation and prevent the tumor development. The interactions between the immune system and tumor cells are conflicting and complex. Such interactions in breast cancer constitute an active research focus and are considered a challenge for the scientific research for several years (Makhoul et al., 2018).

To date, few studies have addressed the potential role of immunotherapy in breast cancer, so knowledge about its implications in treatment of breast cancer needs further elucidation.

**Anti-tumor Immunity:**

The immune system is the first line of defense that protects against the risk of tumor development. Therefore, the efficiency of the immune system is a critical factor in controlling the tumor growth. It has the ability to recognize and eliminate the genetic mutations. The immune system also can influence the fate and outcome of tumors by activation of innate and adaptive immune responses. The interactions between the immune system and tumor cells divided into three main phases that include: the elimination phase, equilibrium phase and escape phase (Mittal et al., 2014).

**Evasion and Escape from Immune Surveillance:**

Resistant or non-immunogenic tumor cells don't recognize by the immune cells and so have the ability to evade the

immune surveillance. Variable mechanisms can be involved in evasion and escape phase which include; absence of antigens, release of immunosuppressive factors by cancer cells, resistance to the immune cells, expression of immune inhibitory co-stimulatory receptors, reduced or absence of major histocompatibility complex (MHC) expression, immunological tolerance and defective T-cell function (Steven and Seliger, 2018).

Immune evasion in breast cancer is mediated by different mechanisms according to the molecular subtype. Hormone receptor positive (HR+ve) tumors, is low immunogenic tumors due to the immunosuppressive action of estrogen, reduced MHC-I expression and absence of tumor antigens. Human epidermal receptor negative (HER2-ve) tumors are characterized by reduced levels of tumor antigens expression compared to HER2+ve tumors. TNBC molecular subtype has immunosuppressive tumor microenvironment and prominent tumor infiltrating lymphocytes (TILs) that result in escape from the immune surveillance. The use of immunotherapy has yielded significant advances in different molecular subtypes of breast cancer, particularly in TNBC (Wang et al., 2017).

#### **Prognostic Roles of TILs in Breast Cancer:**

TILs are indicators for host immune reactions against the tumor cells. The extent of lymphocytic infiltration also reflects the responsiveness of the tumor to anti-cancer therapy. TILs have an important prognostic and predictive role in various neoplasms, however, this role in breast cancer remains controversial. Different molecular subtypes of breast cancer have different patterns of lymphocytic infiltration. TNBC and HER2+ve tumors demonstrate more prominent TILs than other molecular subtype that is associated with more

favorable prognosis. TILs are proved as a reliable biomarker to predict the outcome and the response to immunotherapy that is applied for all molecular subtypes of breast cancer, especially for TNBC and HER2+ve subtypes (Denkert et al., 2018).

Each subset of lymphocytes has different prognostic role; tumors with increased level of CD8+ T cells infiltrate have favorable prognosis, while the prognostic value of increased CD4+ T cells is controversial; CD4+ T helper cells have good prognosis (Liu et al., 2011).

#### **Function of Programmed Death 1 (PD1) and Its Ligand (PDL1):**

PDL1 is a type I trans-membrane glycoprotein. It acts as a ligand for PD1 and has an important prognostic and predictive value in various types of neoplasms. It is over-expressed in several neoplasms such as bronchogenic carcinoma, hepatocellular carcinoma and breast cancer. PD1 and PDL1 are immune checkpoints and members of cytotoxic T lymphocyte antigen-4 family. They are responsible for immunosuppression and decreased antitumor cytokines. They are expressed by tumor cells to escape immune surveillance. Moreover, PD1/PDL1 pathway activates the intercellular signals that inhibit apoptosis and enhance survival of tumor cells. PD1 and PDL1 are targeted in many clinical trials (Pascolutti et al., 2016).

#### **Checkpoint Inhibitors:**

Immunoregulatory pathways have a key role in immune regulation; these pathways act as checkpoints in the immune reactions. PD1 and its ligand PDL1 act as immune checkpoints. In recent years, the use of checkpoint inhibitors to target the PD1/PDL1 pathway results in breakthrough in the immunotherapy field. Anti-PD1 and anti-PDL1 therapeutic agents were approved by the FDA for treatment of TNBC with more favorable results (Havel et al., 2019).

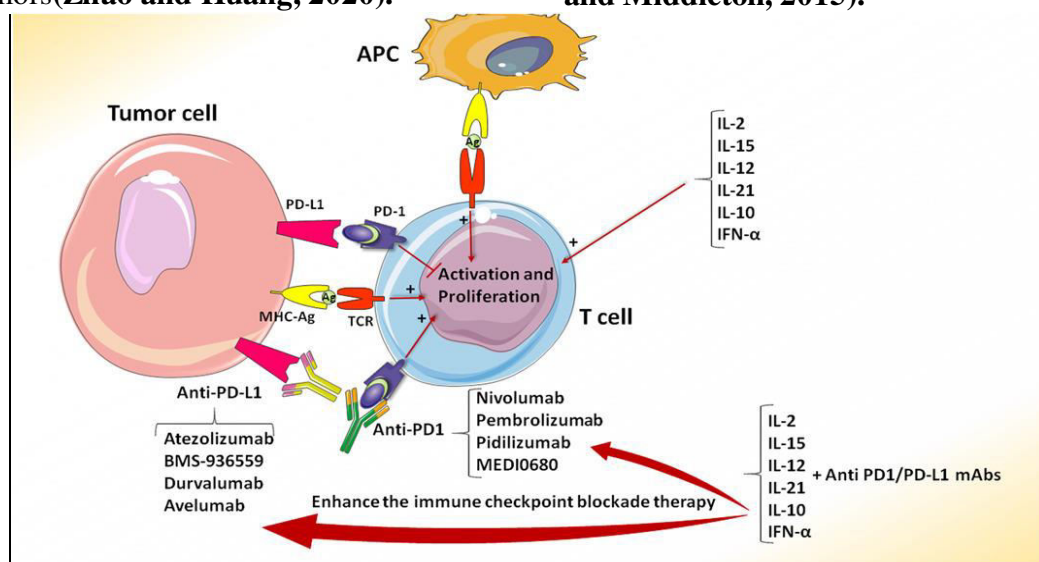
### Role of Anti-PD1/PDL1 Agents in Treatment of Breast Cancer:

Targeting the PDL1/PD1 pathway is a promising therapeutic strategy, which based on inhibition of the interaction between PD1 and its ligand. Recent studies have shown that inhibition of the interaction between PDL-1 and PD-1 with monoclonal antibodies is a promising therapeutic approach in treatment of breast cancer (Lipson et al., 2015).

Checkpoint inhibition can activate the T cell function, stimulate the cytokines release and enhance the antitumor activity (Figure 1). The immunotherapy achieves more favorable outcomes in breast cancer; especially by using the combination strategy included PD-1/PD-L1 inhibitors. Many clinical trials are arising; pembrolizumab that is anti-PD1 inhibitor demonstrate satisfactory results and an effective antitumor activity in TNBC. Atezolizumab and avelumab are anti-PDL1 inhibitors which are associated with enhanced survival rates in TNBC patients. No effective results were obtained in HR+/HER2-tumors (Zhao and Huang, 2020).

### Anti-PD1/PDL1 in Combination with Other Therapeutic Agents:

The use of anti-PD1/PDL1 agents alone doesn't show effective results in treatment of breast cancer due to low immunogenic potential of this tumor. Several studies have revealed that the combination therapy in which the anti-PD1/PDL1 inhibitors are combined with other therapeutic agents result in enhancement of their efficacy. The chemotherapy stimulates the release of antigens and initiates signals that recruit antigen-presenting cells (APCs) stimulating the immune system to elicit an immune reactions against the tumor cells. Several chemotherapeutics commonly used in breast cancer can promote immunogenic cell death resulting in release of tumor antigens. Immunotherapy in combination with other therapeutic strategies has achieved more effective results in the treatment of breast cancer; immunotherapy in combination with chemotherapy results in more promising outcomes in breast cancer, particularly in TNBC (Emens and Middleton, 2015).



**Figure 1:** Role of the PD1/PDL1 and cytokines in T cell function in the tumor microenvironment (Rahimi et al., 2020).

### Challenges That Hinder the Use of Immunotherapy:

Although immunotherapy has achieved effective responses in different types of neoplasms, many challenges for its clinical implications are still reported. The side effects of immunotherapy still limit its use. Immunotherapy may cause a rare variety of toxicity called immune-related adverse events (IRAEs) due to hyper-activation of the immune system. Another challenge is the wide variety of atypical clinical response patterns even within the same tumor subtype (Sambiet al., 2019).

### Conclusion

Immunotherapy has achieved promising results in the treatment of breast cancer, especially by using it in combination with other therapeutic strategies.

### List of Abbreviations

**APCs:**antigen-presenting cells,  
**HER2:**human epidermal receptor 2,  
**HR:**hormone receptor, **MHC:** major histocompatibility complex, **IRAEs:** immune-related adverse events **PD1:** Programmed death-1, **PDL1:** programmed death ligand, **TNBC:**triple negative breast cancer,**Th1:**T helper, **TILs:**Tumor-infiltrating Lymphocyte.

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