

**University of Mosul**  
**College of Medicine**



# **Expression of PD-L1 in HER2- neu positive breast cancer**

A Thesis

Submitted to Council of the College of Medicine at the  
University of Mosul

In Partial Fulfillment of The Requirement for The Degree of  
The Master of Science in Pathology

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**1444 A.H**

**2023 A.D**

## **Abstract**

### **Background:**

Breast cancer is the most frequent cancer and the main cause of cancer death in women worldwide. Some subtypes of breast cancers escape the immune system response by overexpressing programmed death-ligand 1 (PD-L1) on their cell surfaces. PD-L1 is expressed on cancer cells, and its interaction with programmed death-1-(PD-1) on the T-cell surface results in suppressing the immune system activation and decreases T-cell proliferation.

Clinical research has demonstrated that the immune checkpoint inhibitor programmed death (PD)- 1-PD-ligand 1 (PD-L1) axis is a promising therapeutic target in variable malignancies. This route has recently received a lot of attention. Different detecting antibodies confound the value of PD-L1 detection by immunohistochemistry as a valuable marker in breast cancer.

### **Aims of the Study:**

To identify the expression of PD-L1 in HER2-neu positive breast cancer cases using an immunohistochemical method. To investigate the association between the expression of PD-L1 and several clinicopathological parameters including age, grade, laterality, tumor-infiltrating lymphocytes, lymphovascular invasion, necrosis, Ki67, estrogen & progesterone receptors expression.

### **Materials and Methods:**

This is a case series study (retrospective and prospective) that was performed on 50 tru-cut samples of HER2-neu positive breast cancers, which were collected from some private clinics & private laboratories in

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the North of Iraq over a period of 7 months extending from November 2021 through May 2022.

Hematoxylin and eosin-stained glass slides were processed from Formalin-fixed and paraffin-embedded blocks and were revised regarding diagnosis and other histopathological parameters including histological type, grade, vascular invasion, tumor-infiltrating lymphocytes, and necrosis. Medical information including age and laterality were taken from the patient's medical records. Also, results of HER-2 neu status, estrogen & progesterone receptors expression, and Ki67 were previously prepared, and information is taken from medical records.

PD-L1 immunohistochemical stain was conducted for all cases on formalin-fixed paraffin-embedded tissues of the tumor, in the Vajeen medical laboratory (histopathology department)/ Duhok city / Iraq, using PD-L1 IHC 22C3 pharmDx (Dako) monoclonal mouse anti-PD-L1, clone 22C3 anticipated for the detection of PD-L1 protein in Formalin-fixed and paraffin-embedded blocks using EnVision FLEX visualization system on Autostainer Link 48.

The assessment of immunohistochemical expression of PD-L1 is done using a combined positive score, in which both tumor cells and tumor-infiltrating immune cells are evaluated in relation to total viable tumor cells with a cutoff value of 10% and its association with various histopathological parameters.

### **Results:**

The patients ranged in age from 27 to 81 years with a mean age of (48.46+-13.35SD) years, most of them were in the 4<sup>th</sup> and 5<sup>th</sup> decade. Histologically, all of the cases were of invasive ductal carcinoma type.

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Regarding the grade of the tumor, less than two third of tumors were of moderate grade at 62%. The tumor laterality was on the Left side in 52% of cases. Estrogen receptor, progesterone receptor status was positive in 70% of cases, regarding Ki67, Ki67 status was high in 82% of cases.

Tumor-infiltrating lymphocytes were in the moderate grade in 56% of cases. Vascular invasion was observed in 34% of cases, while necrosis was presented in 48% of cases.

Immunohistochemical expression of PD-L1 in the sampled cases, PD-L1 is found to be expressed in 34% of HER2-neu positive cases with a combined positive score equal to or more than 10, whereas 66% of cases have a negative expression with a combined positive score less than 10.

PD-L1 has statistically no significant relation with age with a p-value of 0.717. The highest proportion of PD-L1-positive tumors occurred in patients aged 31-50 years.

The grade and the laterality of the tumors showed no significant relation to the PD-L1 state with a p-value of 0.345, and 0.644 respectively.

Statistically, a significant association was found between TIL% and PDL1 state with a p-value of 0.020, forty-three percent of the moderate grade of TIL% and seventy-five percent of high grade were PD-L1 positive.

There was no significant relationship with a p-value of 0.392 between estrogen & progesterone receptor and PD-L1 states, and also no statistically significant association was found between PD-L1 and Ki67 with a p-value of = 0.358.

PD-L1 has a statistically significant relationship with vascular invasion with a p-value of 0.035, 42% of cases without vascular invasion

have positive PD-L1 expression, compared to 17% in cases with vascular invasion.

PD-L1 status failed to show a statistically significant association with tumor necrosis with a p-value of 0.081.

### **Conclusions:**

- The study demonstrated that PD-L1 is expressed in a third of HER2-neu positive breast cancer, and this may potentially be useful in therapy prediction for a patient who does not benefit from Trastuzumab treatment.
- This study found that PD-L1 is positively associated with tumor-infiltrating lymphocytes in which PD-L1 expression increased proportionally to increased tumor-infiltrating lymphocytes and negatively associated with lymphovascular invasion.
- The highest proportion of PD-L1-positive tumors occurred in the patients in the 4th and 5th decades.
- High PD-L1 expression detected in the moderate grade of the tumor.
- High expression of PD-L1 found in negative estrogen and progesterone receptors.
- There was an approximate expression of PD-L1 in the right and left sided tumors.
- High PD-L1 expression observed in tumor with low Ki67, and in tumors with necrosis.

**Keywords:** Breast cancer, HER2-neu, PD-L1, Tumor-infiltrating lymphocyte.