

## Mini Review

## Latest Results from Immunotherapy Clinical Trials in Triple Negative Breast Cancer

Alexios Strimpakos, MD, PhD, MRCP<sup>1\*</sup>; Konstantinos Tsigaridas, MD<sup>1</sup>; Maria Avgoustidou, MD<sup>2</sup><sup>1</sup>5<sup>th</sup> Department Medical Oncology, Hygeia Hospital, Marousi, Athens 151 23, Greece<sup>2</sup>St. Lukas Klinik Solingen, Germany

## \*Corresponding author

Alexios Strimpakos, MD, PhD, MRCP

Medical Oncologist, Head, 5<sup>th</sup> Department Medical Oncology, Hygeia Hospital, Marousi, Athens 151 23, Greece; Tel. +302106867656; Fax. +302103007122;

E-mail: alexstrimp@gmail.com

## Article information

Received: June 12<sup>th</sup>, 2019; Revised: July 4<sup>th</sup>, 2019; Accepted: July 10<sup>th</sup>, 2019; Published: July 23<sup>rd</sup>, 2019

## Cite this article

Strimpakos A, Tsigaridas K, Avgoustidou M. Latest results from immunotherapy clinical trials in triple negative breast cancer. *Clin Trial Pract Open J.* 2019; 2(1): 10-13. doi: 10.17140/CTPOJ-2-105

## ABSTRACT

Cancer immunotherapy has evolved enormously in the recent years with better understanding of immune reactions, immune microenvironment and immunosurveillance. Breast cancer is characterized by large heterogeneity, a fact which rather complicated the development and the approval of novel therapeutic options in comparison to the majority of other solid tumors since each subtype has required a unique scientific approach and different targets and goals. Triple negative breast cancer (TNBC) is considered the most aggressive of the breast cancer subtypes with limited treatment options and worse outcome compared to others. This article summarizes some of the early clinical studies and the recently presented phase III clinical study of immunotherapy checkpoint inhibitors in this difficult setting.

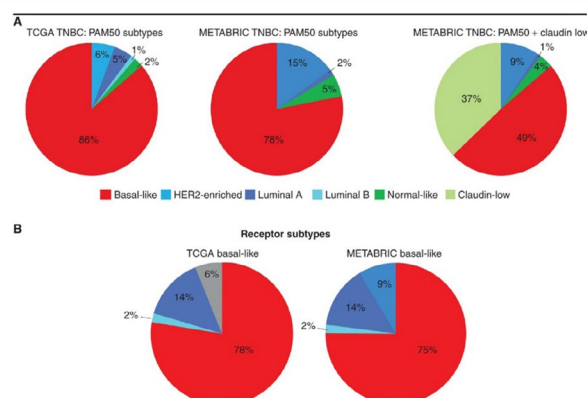
## Keywords

Cancer; Immunotherapy; Triple negative breast cancer (TNBC); Breast cancer.

## INTRODUCTION

Breast cancer is the commonest solid tumor affecting females worldwide and the second leading cause of cancer relating mortality.<sup>1</sup> The impact on women and their families, the morbidity and the change of millions of lives remains enormous. Cytotoxic drugs or hormonal agents have remained for decades the backbone of treatment. Fortunately, with the recognition of distinct subtypes of breast adenocarcinoma with variable natural course and prognosis, the therapeutic options have broadened with the addition of biological agents, targeted therapies, monoclonal antibodies and recently immunotherapy drugs. The latest have changed the outcome of many solid tumors once seemed fatal, such as melanoma, lung cancer, renal cancer, etc.

We have now data that some of these drugs work in specific cases of breast cancer. In this mini review we will try to put the current knowledge and data of immunotherapy in triple negative breast cancer (TNBC) (Figure 1).

Figure 1. Molecular Subtypes of Breast Cancer in pivotal Genomic Studies<sup>2</sup>

## CONCEPT OF IMMUNOTHERAPY IN BREAST CANCER

One of the recognized hallmarks of cancer growth and progres-

sion is its escape from destruction by immune cells. We now know that this might happen due to overexpression of molecules that halt the activity of immune reaction, in other words that work as immune breaks. Such molecules are the PD1 (Programmed Death 1), PD-L1 (Programmed Death-Ligand 1) and CTLA-4 (Cytotoxic T-Lymphocyte Antigen-4) proteins. When the PD-1 receptor protein or its ligand is upregulated in the T-cells or the cancer cells we observe both innate and adaptive immunity inhibition. Likewise, overexpression of the inhibitory CTLA-4 protein in the T-lymphocytes leads to inactivity of immune system allowing further progression of cancer cells.

TNBC represents around 15% of advanced breast cancer patients.<sup>2</sup> It is associated with poor prognosis compared to the other forms and its management remains an oncological challenge.

Initially, breast cancer was deemed to be a non-immunogenic cancer with low tumor burden but recent research has suggested that TNBC yields immunogenic features subjective to targeting with the novel immunotherapy agents. HER2 positive and TNBC express higher levels of PD-L1 protein.<sup>3</sup> Triple-negative breast cancers (TNBC) as well as the HER2-positive breast cancer are also more likely than the luminal subtypes to harbor higher stromal-infiltrating immune cells (TILs) at diagnosis. There are data showing a linear relationship between stromal TILs and better clinical outcomes.<sup>4</sup>

## EARLY CLINICAL DATA

Early phase clinical studies (Ia/Ib) in metastatic breast cancer patients showed that there is some response from immunotherapy treatment with avelumab (the ZAVELIN Ia/Ib study, ORR 8.6% but 44% in TNBC PD-L1+patients),<sup>5</sup> pembrolizumab (KEYNOTE-012 Ib study, ORR 18.5%)<sup>6</sup> or atezolizumab (ORR 13% in PD-L1+ TNBC).<sup>7</sup> Though numerically the benefit was small, it was somehow encouraging given the fact that immunotherapy in these studies was used as monotherapy in an already heavily pretreated population.

Following those early data, combination of these checkpoint inhibitors with chemotherapy agents was next tested.

Atezolizumab (840 mg every 2-weeks) was combined with nab-paclitaxel (125 mg/m<sup>2</sup> on days 1, 8, and 15 every 28-days) in a phase Ib study in 32 metastatic TNBC patients of any PD-L1 status. After a median follow-up over 5-months, the ORR was 38% (1 CR, 11 PRs).<sup>8</sup>

Pembrolizumab (200 mg i.v. every 3-weeks) was tested with eribulin (1.4 mg/m<sup>2</sup> on days 1 and 8 every 21-days) in a phase II trial designed to enroll 107 patients with metastatic TNBC of any PD-L1 status treated with ≤2 prior lines of chemotherapy. The ORR for the combination was 26.4% (3 CRs, 25 PRs in 106 out of 107 evaluable patients). The mOS was 17.7-months and the duration of response (DoR) 8.3-months for the 28 patients with objective response.<sup>9</sup>

## LATE PHASE STUDIES

Following the above encouraging results researchers and industry moved to larger phase III studies.

The KEYNOTE-355 phase III trial is evaluating pembrolizumab with chemotherapy relative to various chemotherapy regimens alone as first-line therapy for incurable TNBC. The study is expected to complete accrual in December 2019.<sup>10</sup>

Very recently, results from the IMpassion130 phase III study were presented at both the ESMO 2018 Congress and the ASCO 2019 Annual Meeting (31<sup>st</sup> May-4<sup>th</sup> June, 2019).<sup>11</sup>

The IMpassion 130 was a phase III trial that enrolled 902 patients with metastatic triple-negative breast cancer treatment naïved for metastatic disease.<sup>12</sup> Patients were randomized between the standard chemotherapy (nab-paclitaxel 125 mg/m<sup>2</sup> on days 1, 8, and 15 every 28-days) plus atezolizumab (840 mg every 2-weeks) and the standard chemotherapy plus placebo. The primary endpoints were progression-free survival (PFS) and overall survival (OS). The patients were followed for a median follow-up time of 12.9-months. The two arms were quite balanced in terms of demographic details and the results of the study are the following.

The chemotherapy/immunotherapy combination arm reduced the risk of disease progression and death by 20% in all patients and 38% in the subgroup overexpressing PD-L1. In the whole study population, the median PFS was 7.2-months with the immunotherapy combination and 5.5-months with chemotherapy/placebo (hazard ratio [HR]=0.80, *p*=0.0025). Of interest, the PD-L1-positive group showed a median progression-free survival of 7.5-months with the combination and 5-months with chemotherapy alone (HR=0.62, *p*<0.0001).

Though the PFS data supported the use of immunotherapy in TNBC, the updated overall survival results presented at the 2019 American Society clinical oncology meeting showed that in the whole study population there is no significant clinical benefit in the atezolizumab arm (median OS=21.0 *vs* 18.7 months; HR=0.86, 95% CI: 0.72-1.02, *p*=0.078) although the selected PD-L1 positive TILs cohort did get survival benefit (median OS=25.0 *vs* 18.0 months; HR=0.71, 95% CI: 0.54-0.93). Another important observation was that after two years follow-up, over 50% (43-59%) of PD-L1-positive metastatic TNBC patients in the atezolizumab arm were alive, compared to 37% (29-45%) in the control arm.

The objective response rate (a secondary endpoint) was higher in the combination group compared to the standard chemotherapy/placebo group for the whole patients cohort (56% *vs* 46%) and especially those with PD-L1-positive tumors (59% *vs* 43%) (Figures 2 and 3).

Figure 2. Updated Survival Data Within the IMpassion 130 study<sup>11</sup>

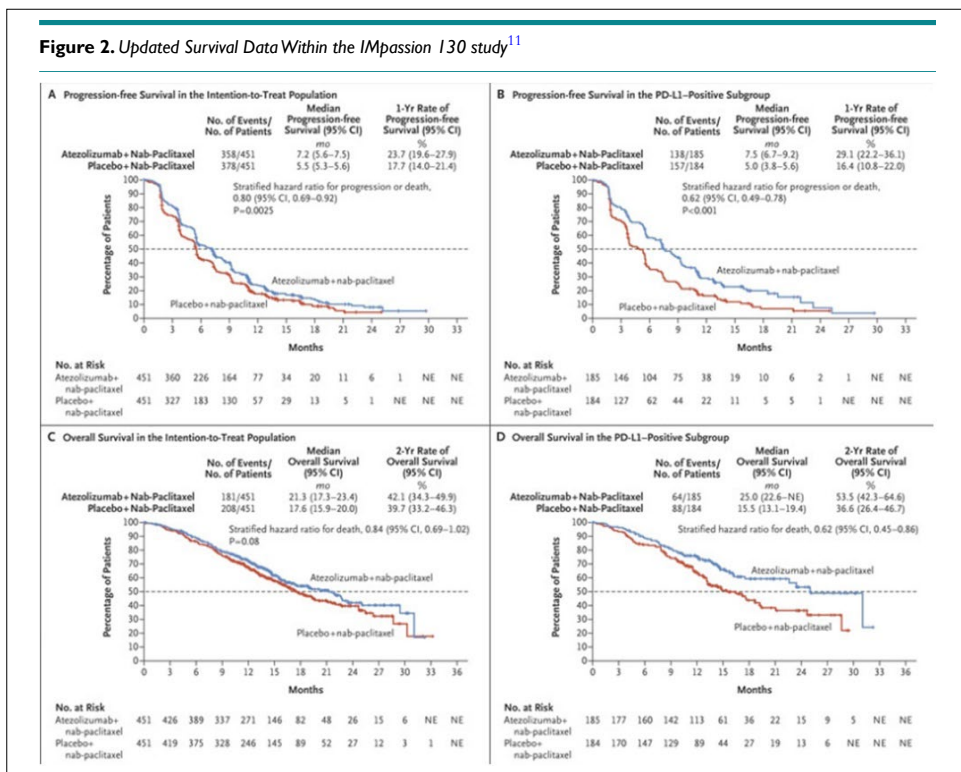
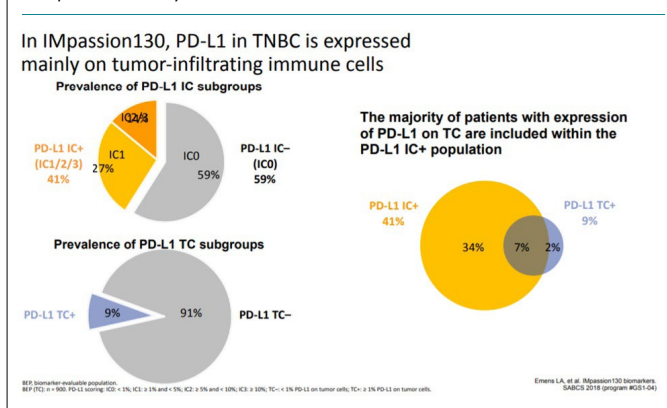


Figure 3. PD-L1 Expression on Tumor Cells (TC) and Tumor-Infiltrating Immune Cells (IC) in IMpassion130 Study<sup>8</sup>



Regarding safety no particular concerns were noted and the side effects related to immune therapy were rare, the most common being hypothyroidism, that occurred in 17.3% of patients receiving immunotherapy and 4.3% receiving chemotherapy alone. Most side effects were due to chemotherapy and occurred at a similar rate in both treatment groups, although there was a minor increase in nausea and cough in the combination group. Similarly, the quality of life was satisfactory in both groups.<sup>11</sup>

## CONCLUSION

This mini review shows that the field of immunotherapy in breast cancer is still evolving. There is no outstanding benefit in the whole breast cancer patients, even in the TNBC subtype. Biomarkers such as PD-L1 expression or TILs seem to play some role but more data is needed. There is no doubt that the much expected

results from the ongoing phase III studies and exploratory studies will shed more light to the many questions we still have. But we feel confidence that with more research will find the settings where immunotherapy benefits breast cancer patients similarly to other solid tumors.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017; 67: 7-30. doi: 10.3322/caac.21387
2. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. *Nat Rev Clin Oncol.* 2016; 13: 674-690. doi: 10.1038/nrclinonc.2016.66
3. Cimino-Mathews A, Foote JB, Emens LA. Immune targeting in breast cancer. *Oncology (Williston Park).* 2015; 29: 375-385.
4. Savas P, Salgado R, Denkert C, et al. Clinical relevance of host immunity in breast cancer: From TILs to clinic. *Nat Rev Clin Oncol.* 2016; 13: 228-241. doi: 10.1038/nrclinonc.2015.215
5. Dirix L, Takacs I, Nikolinakos P, et al. Avelumab (MSB0010718C), and an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A phase 1b JAVELIN solid tumor study. Paper presented at: 38<sup>th</sup> Annual CTRC-AACR annual meeting

cancer symposium; December 8-12, 2016; San Antonio, TX. Philadelphia (PA), USA.

6. Nanda R, Specht J, Dees EC, et al. KEYNOTE-012: long-lasting responses in a phase 1b study of pembrolizumab for metastatic triple-negative breast cancer (mTNBC). Paper presented at: 38<sup>th</sup> Annual CTRC-AACR San Antonio breast cancer symposium; December 6-10, 2016; San Antonio, TX. Philadelphia (PA), USA.

7. Schmid P, Cruz C, Braiteh FS, et al. Atezolizumab in metastatic triple-negative breast cancer: Long-term clinical outcomes and biomarker analyses. Paper presented at: American Association for Cancer Research Annual Meeting 2017; April 1-5, 2017; Washington, DC. Philadelphia (PA), USA. doi: [10.1158/1538-7445.AM2017-2986](https://doi.org/10.1158/1538-7445.AM2017-2986)

8. Adams S, Dieras V, Barrios CH, et al. Patient-reported outcomes (PROs) from the phase III IMpassion130 trial of atezolizumab (atezo) plus nab-paclitaxel (nP) in metastatic triple-negative breast cancer (mTNBC). Paper presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL, USA. doi: [10.1200/JCO.2019.37.15\\_suppl.1067](https://doi.org/10.1200/JCO.2019.37.15_suppl.1067)

9. Tolaney S, Savulsky C, Aktan G, et al. Phase 1b/2 study to evaluate eribulin mesylate in combination with pembrolizumab in pa-

tients with metastatic triple-negative breast cancer. Paper presented at: San Antonio Breast Cancer Symposium; December 6-10, 2016; San Antonio, TX. Philadelphia (PA), USA.

10. US National Library of Medicine. Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs. Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (MK-3475-355/KEYNOTE-355). Web site. <https://clinicaltrials.gov/ct2/show/NCT02819518>. Accessed June 11, 2019.

11. Schneeweiss A, et al. IMpassion130: expanded safety analysis from a P3 study of atezolizumab (A) + nab-paclitaxel (nP) in patients (pts) with treatment (tx)-naïve, locally advanced or metastatic triple-negative breast cancer (mTNBC). Paper presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL, USA. doi: [10.1200/JCO.2019.37.15\\_suppl.1068](https://doi.org/10.1200/JCO.2019.37.15_suppl.1068)

12. Schmid P, Adams S, Rugo HS, et al. IMpassion130: Updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, phase III study of atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC). Paper presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL, USA. doi: [10.1200/JCO.2019.37.15\\_suppl.1003](https://doi.org/10.1200/JCO.2019.37.15_suppl.1003)