NEW HOPE IN TRIPLE NEGATIVE BREAST CANCER TREATMENT: ROLE OF IMMUNOTHERAPY

Noorwati Sutandyo[*,1]
[*]Department of Hematology and Medical Oncology, Dharmais National Cancer Centre Hospital, Jakarta, Indonesia.

ABSTRACT Breast cancer is one of the most common types of solid cancer, with an incidence rate of 16.7% of all cancer cases in Indonesia. There are several molecular subtypes in breast cancer. Among these molecular subtypes, basal-like breast cancer, commonly known as triple-negative breast cancer, has a more aggressive clinical course than other subtypes. Most of the previous studies showed that triple negative breast cancer showed worse prognosis compared to hormonal positive breast cancer. Triple negative breast cancer has a higher number of tumour-infiltrating lymphocytes and Programmed Death-Ligand 1 expression compared to other subtypes. Before the era of immunotherapy, triple negative breast cancer patients were treated using chemotherapy either as neoadjuvant or adjuvant chemotherapy. However, treatment of metastatic triple negative breast cancer using chemotherapy has limited effectiveness and also associated with unexpected toxicity profile. Therefore, other therapeutic agent options to improve the outcomes of treatment in triple negative breast cancer were developed. New treatments in triple negative breast cancer have different target of pathways or molecules. Immunotherapy, based on specific biomarkers, is new hope in the management of triple negative breast cancer.

KEYWORDS triple negative breast cancer, treatment, immunotherapy

Introduction

According to Global Cancer Observatory (Globocan) 2018 data, breast cancer is the most common type of solid tumor diagnosed in women and one of the leading cause of cancer deaths in women throughout the world.[1] In Indonesia, breast cancer is also the most common type of cancer with an incidence rate of 16.7% of all cancer cases.[2] Breast cancer is a heterogeneous disease with different genetic, histological and clinical characteristics. Molecular classification of breast cancer is divided into five groups (luminal A, luminal B, HER-2, normal breast-like, and basal-like) which are determined based on examination of the gene expression profile.[3,4] Among these molecular subtypes, basal-like breast cancer, commonly known as triple-negative breast cancer (TNBC), has a more aggressive clinical course than other subtypes. About 10-15% of all diagnosis of breast cancer is TNBC, which is clinically defined as the absence of an estrogen receptor (ER / estrogen receptor), progesterone receptor (PR / progesterone receptor),[5] and receptor human epidermal growth factor 2 (HER2).[6,7]

Most of the previous studies showed that TNBC showed worse prognosis compared to hormonal positive breast cancer. TNBC has a more aggressive course of disease than other types of breast cancer.[5,8] It is more common in younger and obese women with an average onset at 53 years.[8-12] Triple negative breast cancer has special characteristics like high mitosis index, area of central necrosis, significant-high degree pleomorphic, few stromal components, large average tumor size, higher tumor grade, and commonly involving lymph nodes. The absence of hormonal receptors in TNBC patients leads to difficulties in managing TNBC. Chemotherapy is the backbone of treatment in TNBC since it does not respond to hormonal treatment or target therapy.[13-15] Population-based studies by Bauer et al. showed that TNBC is 1.5 times more common in women younger than 40

DOI:10.5455/IJMRCR.triple-negative-breast-cancer-immunotherapy
First Received: February 18, 2020
Accepted: March 05, 2020
Manuscript Associate Editor: Ivan Inkov (BG)

[1]Dr. Noorwati Sutandyo, SpPD-KHOM; Department of Hematology-Medical Oncology, Dharmais National Cancer Centre Hospital Jl. Letjen. S. ParmanKav. 84-86, Slipi, Jakarta 11420, Indonesia; Tel: +62 21-568 1570 ext. 2356;
E-mail:noorwatis3@yahoo.com

years with a 5-year survival of 14%.[16] As many as 50% of early-stage TNBC patients (stage I to III) experience disease recurrence, and 37% die within the first five years after surgery.[17-18]

Triple negative breast cancer has a strong correlation with BRCA1/2 mutation status, and nearly 20% of patients are mutation carriers.[19] Patients are usually diagnosed at T2 or T3, with lymphovascular invasion, and already metastasized to the lymph nodes.[9] Brain, lungs and bones are the most common target organ in metastatic TNBC.[8]

A cohort study in Brazil about survival in TNBC patients found that most patients presented with stage III, high p53 expression, lymphocytic infiltration, multifocal and previously treated with radical surgery and chemotherapy. It was reported that overall survival (OS) and disease-free survival (DFS) for five years of TNBC patients was 62.1% and 57.5%, whereas in non-TNBC patients were 80.8% and 75.3%, p <0.001.[20] Therefore, this review is made to learn more about TNBC, 'the very dangerous breast cancer' along with immunotherapy as a new hope in TNBC treatment.

Expression of PD-1/PD-L1 in Triple Negative Breast Cancer

Among breast cancer subtypes, TNBC has a high mutation burden, which can result in a higher frequency of immunogenic mutations.[21-22] Programmed cell death protein 1 (PD-1) is a negative regulator of T cell activity that limits T cell activity at various stages of the immune response when interacting with two ligands, namely PD-L1 and PD-L2. PD-1 is expressed on the surface of lymphocytes and antigen-presenting cells. When PD-1 binds to a ligand, through phosphorylase activity, it will inhibit the signalling kinase pathway, which generally leads to activation of T cell receptors.[23] In other words, the presence of PD-1 in the tumor microenvironment prevents the occurrence of a comprehensive antitumor immune response.[24] PD-L1 expression is found in 20-50% of all breast cancer subtypes and is associated with higher histological grade, larger tumors, and the absence of hormone receptors.[25] PD-L1 expression is expected to be higher in TNBC compared to non-TNBC.[26-29]

TNBC has a higher number of tumour-infiltrating lymphocytes (TIL) than other subtypes. In the earlier stage, the amount of TIL is associated with better survival, decreased risk of recurrence, and an increased response to neoadjuvant chemotherapy. Besides, TNBC which has higher PD-L1 expression than other breast cancer subtypes, thus making anti-PD-1 and PD-L1 as potential therapeutic targets.[28-29] These characteristics will make TNBC more responsive to immunotherapy.

Therapeutic agents targeting PD-1 and PD-L1 are the focus of the blockade of immune checks in various tumors. Some anti-PD-1 agents such as pembrolizumab and nivolumab, anti-PD-L1 such as atezolizumab, avelumab, and durvalumab are effective in the treatment of various malignancies and have been approved as treatments for melanoma, non-small cell lung cancer, Hodgkin's lymphoma, bladder cancer, cell lymphoma B, cervical cancer, kidney cancer, and head and neck cancer.[30]

Treatment of TNBC in Pre-Immunotherapy Era

Before the era of immunotherapy, TNBC patients were treated using chemotherapy either as neoadjuvant or adjuvant chemotherapy. Neoadjuvant chemotherapy is given as the treatment of local early-stage breast cancer patients who are contraindicated in surgery or breast-conserving therapy.[31-32] The platinum-based regimen is recommended because it might work better on TNBC.[33-34]

Studies on metastatic TNBC patients who received cisplatin or carboplatin as first-line or second-line obtained an ORR of 26% with a median PFS of 2.9 months, where the ORR was better in the first-line group.[35] In phase II randomized study, metastatic TNBC treated with iniparib compared with gemcitabine combined with carboplatin showed a median of PFS 3.6 months and median of OS of 7.7 months.[36]

Complete pathological response in breast cancer have a strong association with better long-term outcomes [37-39]. Neoadjuvant chemotherapy in TNBC results in a higher complete pathologic response rate compared to hormonal positive and negative HER2 breast cancer (28-30% vs 6.7%). However, TNBC patients showed lower progression-free survival (PFS) and 3-years OS.37-38 The 5-year OS of TNBC treated with adjuvant chemotherapy was 66.5% (95% CI 55.5-75.3).[40]

Based on a systematic review by Li CH et al., treatment of metastatic TNBC using chemotherapy has limited effectiveness and also associated with unexpected toxicity profile. Therefore, other therapeutic agent options to improve the outcomes of treatment in TNBC were developed.[41] New treatments in TNBC have different target of pathways or molecules. Targeted therapies in TNBC have been developed such as Poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor, and some are still in research such as targeted therapy in epidermal growth factor receptor (EGFR) receptors, FGFR2, VEGF, and mammalian target of rapamycin (mTOR).[42]

Immunotherapy as A New Hope in Management of TNBC

In the last decade, some evidences highlighted the leading role of the immune system in the course of TNBC disease. The presence of tumour-infiltrating lymphocytes (TIL) in the immunohistochemical examination is widely recognized as a good predictor of TNBC prognosis.[43-46] In addition, the presence of a high cytotoxic TIL (CD8+), or high CD8 + / FOXP3 + ratio, indicates that TNBC patients will have a better prognosis with neoadjuvant chemotherapy treatment.[47]

Along with the presence of TIL, the expression of immune inhibitor antitumor molecules in tumor microenvironment, such as programmed death-ligand 1 (PD-L1), has also been shown to affect the prognosis of TNBC.[28,29,48] The presence of lymphocyte infiltration or immune response is associated with a better TNBC prognosis.[49] These findings showed that utilizing the immune system might provide good benefits in fighting breast cancer. The development of new therapeutic agents aimed at competing for immune checkpoint molecules, such as anti-PD-L1 and anti-PD-L monoclonal antibodies, provide a rational approach to use immunotherapy as a treatment in TNBC patients. At present, several clinical trials regarding the role of immunotherapy in the treatment of TNBC have been carried out, although some are still under investigation. Several studies use immune checkpoint inhibitors against TNBC, both monotherapy or a combination with chemotherapy.

In the IM Passion 130 study, Schmid et al. demonstrated the benefits in OS of metastatic or advanced local TNBC patients who were inoperable with PD-L1 positive through the addition of an anti-PD-L1 agent, atezolizumab, to the first-line chemotherapy regimen with Nab-paclitaxel. About 60% of patients in the study experienced a relapse after previous adjuvant/neoadjuvant treatment, of which 37% were in stage IV. In

12.9 months observation, the median PFS of the patient was significantly increased in patients given additional atezolizumab compared to chemotherapy alone (7.2 vs. 5.5 months), subsequently, in the TNBC population with PD-L1 + the benefit in PFS was better (7.5 vs. 5.0 months). Median OS statistically increased 9.5 months with the addition of atezolizumab in the PD-L1 + population (25.0 vs. 15.5 months). In addition, the objective response rate (ORR) and complete response are higher in populations treated with atezolimumab.[50] The results of IMpassion130 study lead breast cancer treatment into the era of immunotherapy.[51]

The KEYNOTE-150 study assessed a combination of chemotherapy with immunotherapy, namely eribulin and pembrolizumab. Of 107 metastatic TNBC patients, 65 patients were treatment-naive, and 42 patients received first or second-line treatment. Half of the population in this study is PD-L1 positive TNBC (45.8%). The ORR of this combined treatment in the overall population was 26.4% and 30.6% in patients with PD-L1 positive. The median PFS in this study population was 4.2 months, with a median OS of 17.7 months.[52]

Several studies used immunotherapy as a single agent, such as KEYNOTE-012, KEYNOTE-086, JAVELIN, and NCT01375842. In the KEYNOTE-012 study, phase 1B of pembrolizumab study included 111 advanced TNBC patients. This study assessed the safety profile and antitumor activity. Reported toxicity that occurred mostly mild and similar to the observation in other cohort studies such as arthralgia, fatigue, myalgia, and nausea. Only 15.6% of patients experienced toxicity more than grade 3 and one experienced death due to treatment. A total of 27 patients that could be evaluated for antitumor activity, only 18.5% of patients achieved a complete or partial response, with a median duration of treatment response of 17.9 weeks (range 7.3 to 32.4 weeks). In this study, PFS was 1.9 months, with a median OS of 11.2 months. In other words, this phase 1B study described the evidence of clinical activity and the potential safety profile in TNBC treatment using 14-days cycles pembrolizumab.[53]

KEYNOTE-086 study demonstrated that administration of pembrolizumab monotherapy has a good antitumor activity and safety profile in metastatic TNBC patients who have received prior treatment. In addition, TIL levels can identify metastatic TNBC patients with a higher likelihood of achieving good response to pembrolizumab monotherapy, especially if given as first-line.[54,55]

In phase 1 JAVELIN Study, the anti-PD-L1 agent, avelumab, produced an ORR of 5.2% in treatment-naïve metastatic TNBC patients. As many as 68.8% of the population have positive PD-L1. Avelumab shows an acceptable safety profile and clinical activity in metastatic breast cancer patients. PD-L1 expression may be related to the possibility of a better clinical response to avelumab in metastatic breast cancer patients.[56] In NCT01375842 study, which included 116 advanced TNBC patients without differentiating PD-L1 status, atezolizumab was used as monotherapy. The study showed ORR of 10%, median PFS 1.4-1.9 months, with a median OS of 8.9 months. A total of 65.7% of patients had positive PD-L1 with an ORR of 12.7%. Of the 116 patients that could be evaluated, adverse events were reported due to treatment in 73 patients (63%), which 79% of them were grade 1 and 2. Most side effects appear in the first year of treatment. In other words, the sole agent atezolizumab is well tolerated and provides good clinical benefits in metastatic TNBC patients with stable or responsive disease and as the first-line treatment.[57]

Conclusion

Immunotherapy is new hope in the management of TNBC. The immunotherapy that currently available is pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab. Before deciding treatment for advanced TNBC patients, it is better to identify the patients based on specific biomarkers. Immune checkpoint inhibitors are better to be combined with other agents to increase treatment efficacy. The combination of atezolizumab and nab-paclitaxel provides the best treatment outcomes in TNBC. Immunotherapy should also be given as first-line treatment in metastatic TNBC to improve treatment response. Also, immunotherapy has a tolerable good safety profile and good clinical activity in TNBC.

Disclosure Statement

There were no financial support or relationships between the authors and any organization or professional bodies that could pose conflict of interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394 - 424.

2. Global Cancer Statistic, 2018. Indonesian Fact sheet. 2018. [cited 20 January, 2020]. Available from:https://gco.iarc.fr/today/data/factsheets/populations/60-indonesia-fact-sheets.pdf

3. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollackk JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. Nature. 2000;406:747–52.

4. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Eystein Lonning P, Borresen-Dale AL. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001;98:10869–74.

5. Dawson SJ, Provenzano E, Caldas C. Triple negative breast cancers: clinical and prognostic implications. Eur J Cancer 2009;45:27–40.

6. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784–95.

7. Wolff AC, Hammond ME, Hicks DG, et al. on behalf of the American Society of Clinical Oncology and the College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997–4013.

8. Lin NU, Vanderplas A, Hughes ME, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer, 2012;118:5463–72.

9. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429–34.

10. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-likee breast cancer. Breast Cancer Res Treat, 2008;109:123–39. [Erratum in Breast Cancer Res Treat 2008;109:141]

11. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA, 2006;295:2492–502.

12. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysiss. Breast Cancer Res Treat, 2013;137:307–14.

13. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121:2750–67.

14. Masuda H, Baggerly KA, Wang Y, Zhang Y, Gonzalez-Angulo AM, Meric- Bernstam F, Valero V, Lehmann BD, Pietenpol JA, Hortobagyi GN, Symmans WF, Ueno NT. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res. 2013;19:5533–40.

15. Prat A, Adamo B, Cheang MC, Anders CK, Carey LA, Perou CM. Molecular characterization of basal-like and non-basal-like triple-negative breast cancer. Oncologist. 2013;18:123–33.

16. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007 May 1;109(9):1721-8.

17. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26: 1275-81.

18. Guarneri V, Broglio K, Kau SW, et al: Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. J Clin Oncol 24:1037-1044, 2006.

19. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor–negative breast cancer. Clin Cancer Res 2011;17:1082–9.

20. Gonçalves Jr H, Guerra MR, Duarte Cintra JR, Fayer VA, Brum IV, Bustamante Teixeira MT. Survival study of triple-negative and non–triple-negative breast cancer in a Brazilian cohort. Clinical Medicine Insights: Oncology. 2018 Jul 26;12:1179554918790563.

21. Budczies J, Bockmayr M, Denkert C, Klauschen F, Lennerz JK, Györffy B, et al. Classical pathology and mutational load of breast cancer - integration of two worlds. J Pathol Clin Res. 2015;1(4): 225–38. https://doi.org/10.1002/cjp2.25.

22. Luen S, Virassamy B, Savas P, Salgado R, Loi S. The genomic landscape of breast cancer and its interaction with host immunity. Breast. 2016;29:241–50. https://doi.org/10.1016/j.breast.2016.07.015.

23. Postow, MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. Journal of clinical oncology. 2015 Jun 10;33(17):1974.

24. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–264.

25. Ghebeh H, Mohammed S, Al-Omair A, et al. The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. Neoplasia. 2006;8(3):190–198

26. Muenst S, Soysal SD, Gao F, Obermann EC, Oertli D, Gillanders WE. The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat. 2013;139(3):667–676.

27. Muenst S, Schaerli AR, Gao F, et al. Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat. 2014;146(1):15–24.

28. Mittendorf EA, Philips AV, Meric-Bernstam F, et al. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res. 2014;2(4):361–370.

29. Beckers RK, Selinger CI, Vilain R, Madore J, Wilmott JS, Harvey K, et al. Programmed death ligand 1 expression in triple-negative breast cancer is associated with tumour-infiltrating lymphocytes and improved outcome. Histopathology. 2016;69(1):25–34. https://doi.org/10.1200/JCO.2018.36.15_suppl.1010. 1

30. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol. 2018;62:29–39.

31. Senkus E, Kyriakides S, Ohno S, et al. on behalf of the European Society for Medical Oncology (esmo) Guidelines Committee. Primary breast cancer: esmo clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(suppl 5):v8–30.

32. Brackstone M, Fletcher GG, Dayes IS, Madarnas Y, Sen-Gupta SK, Verma S on behalf of the members of the Breast Cancer Disease Site Group. Locoregional therapy of locally advanced breast cancer: a clinical practice guideline. Curr Oncol 2015;22:S54–66.

33. Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. J Clin Oncol 2010;28:1145–53.

34. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once- per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage ii to iii triple-negative breast cancer: calgb 40603 (Alliance). J Clin Oncol 2014;33:13–21.

35. Isakoff SJ, Mayer EL, He L, Traina TA, Carey LA, Krag KJ, et al. TBCRC009: a multicenter phase II clinical trial of platinum monotherapy with biomarker assessment in metastatic triple-negative breast cancer. J Clin Oncol. 2015;33(17):1902–9.

36. O'Shaughnessy J, Osborne C, Pippen JE, Yoffe M, Patt D, Rocha C, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med. 2011;364(3):205–14.

37. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30:1796–804.

38. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26:1275–81.

39. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the ctneobc pooled analysis. Lancet, 2014;384:164–72.

40. Steponaviciene L, Lachej-Mikeroviene N, Smailyte G, Aleknavicius E, Meskauskas R, Didziapetriene J. Triple negative breast cancer: adjuvant chemotherapy effect on survival. Advances in medical sciences. 2011 Dec 1;56(2):285-90.

41. Li CH, Karantza V, Aktan G, Lala M. Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: a systematic literature review. Breast Cancer Research. 2019 Dec 1;21(1):143.

42. Wahba HA, El-Hadaad HA. Current approaches in treatment of triple-negative breast cancer. Cancer biology & medicine. 2015 Jun;12(2):106.

43. Criscitiello C, Esposito A, Trapani D, Curigliano G. Prognostic and predictive value of tumor infiltrating lymphocytes in early breast cancer. Cancer Treat Rev. 2016;50:205–7.

44. Loi S, Sirtaine N, Piette F, et al. Prognostic and predictive value of tumor- infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol. 2013;31:860–7.

45. Dieci MV, Mathieu MC, Guarneri V, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in two phase III randomized adjuvant breast cancer trials. Ann Oncol. 2015;26:1698–704.

46. Loi S, Drubay D, Adams S, et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. J Clin Oncol. 2019;37(7):559–69.

47. Miyashita M, Sasano H, Tamaki K, et al. Prognostic significance of tumor- infiltrating CD8+ and FOXP3+ lymphocytes in residual tumors and alterations in these parameters after neoadjuvant chemotherapy in triple-negativee breast cancer: a retrospective multicenter study. Breast Cancer Res. 2015;17:124.

48. Li X, Li M, Lian Z, et al. Prognostic role of programmed death ligand-1 expression in breast cancer: a systematic review and meta-analysis. Target Oncol. 2016;11:753–61.

49. Adams S, Gray RJ, Demaria S, et al. Prognostic value of tumor- infiltrating lymphocytes in triple-negative breast cancers from two phase iii randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol 2014;32:2959–66.

50. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379:2108–21.

51. Marra A, Viale G, Curigliano G. Recent advances in triple negative breast cancer: the immunotherapy era. BMC medicine. 2019 Dec;17(1):90.

52. Tolaney S, Kalinsky K, Kaklamani V, et al. Phase 1b/2 study to evaluate eribulin mesylate in combination with pembrolizumab in patients with metastatic triple-negative breast cancer. Cancer Res. 2018;78(abstr):PD6–PD13.

53. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. J Clin Oncol. 2016;34:2460–7.

54. Loi S, Adams S, Schmid P, et al. LBA13 relationship between tumor infiltrating lymphocyte (TIL) levels and response to pembrolizumab (pembro) in metastatic triple-negative breast cancer (mTNBC): results from KEYNOTE-086. Ann Oncol. 2017;28(Suppl 5):mdx440.005.

55. Adams S, Schmid P, Rugo HS, et al. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort a of the phase 2 KEYNOTE-086 study. Ann Oncol. 2019;30):397–404.

56. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN solid tumor study. Breast Cancer Res Treat. 2018;167:671–86.

57. Emens LA, Cruz C, Eder JP, et al. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. JAMA Oncol. 2019;5(1):74–82.