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Role of Immunotherapy in the Treatment of Triple-Negative Breast Cancer: A Literature Review

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Abstract

Numerous malignancies, including metastatic triple-negative breast cancer (TNBC), which has long been associated with a poor prognosis, have been transformed by the widespread use of immunotherapy. Immune checkpoint inhibitors (ICIs) that target and block programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) have demonstrated encouraging outcomes in the treatment of patients with metastatic TNBC. The PD-1 inhibitor pembrolizumab is the first-line treatment of metastatic PD-L1+ TNBC in combination with chemotherapy, and the PD-L1 inhibitor atezolizumab has also shown clinical activity. The median progression-free survival for pembrolizumab or atezolizumab combined with chemotherapy increased by 4.1 months and 2.5 months, respectively, with the addition of immunotherapy. Despite this progress, there is still more to be desired. The addition of immunotherapy to chemotherapy improved the pathological complete response (PCR) rate compared to chemotherapy with placebo in landmark phase III trials in the early-stage neoadjuvant context, whereas others reported no meaningful improvement in PCR. There are various ongoing trials that show that more research and studies are needed for components in the TNBC microenvironment and to further explore its importance in the treatment of TNBC.

Categories: Internal Medicine, Obstetrics/Gynecology, Oncology

Keywords: immune checkpoint inhibitor, tumor immune microenvironment, breast cancer, metastatic triple-negative breast cancer, cancer-immunotherapy

Introduction And Background

A total of 6,85,000 people worldwide died in 2020 and 2.3 million women were diagnosed with breast cancer. Breast cancer is the most common cancer worldwide and in the United States with 29.6 percent of all diagnoses as of the end of 2020 when there were 7.8 million women still alive who had received a diagnosis during the previous five years [1,2]. Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer that lacks the estrogen and progesterone hormone receptors and the human skin growth factor 2 (Her2) amplification. It makes up approximately 15-20 percent of all breast cancers [3-5]. It is made up of an immunological tumor microenvironment (TME) with high production of vascular endothelial growth factors (VEGF), tumor-infiltrating lymphocytes (TILs), tumor-associated macrophages (TAMs), extracellular matrix (ECM), connective tissue, stromal fibroblasts, and cytokines that stimulate the growth and migration of tumor cells, this TME plays a dual function in the development, progression, and metastasis of tumor [6-9].

The ECM is a key element of the TME. It is characterized by a network of different macromolecules that, in both healthy and sick states, forms the structural environment that determines the mechanical properties of the tissue [10]. Fibular collagen, fibronectin, elastin, and laminins are the predominant ECM molecules seen in solid tumors such as breast cancer [11,12]. Increased ECM deposition in breast and other solid cancers has been linked to poor survival in patients [13-19]. Tumor-associated collagen signatures (TACS) and alterations in collagen fiber architecture are suggestive of poor patient outcomes across all subtypes of breast cancer, including TNBC [14,18,20]. TILs are crucial in the killing and removal of tumor cells, but high expression of immune checkpoints inhibits immune cell function and promotes tumor immune escape [21-25], which excludes immune cell infiltration and also promotes immunosuppression and resistance to immune checkpoint inhibitors (ICI) [26-28]. These alterations in fibrotic ECM lead to cell behavior towards tumor progression [7,29,30], and the increase in tumor antigen expression provides the basis for immune system recognition and tumor removal. In order to diagnose and treat TNBC, it is crucial to comprehend the immunological microenvironment of the disease [31].

Chemotherapy is the backbone of treatment for both early-stage and metastatic TNBC because this tumor lacks hormone receptors and Her2 amplification, making endocrine therapy or Her2-directed therapy inefficient as targeted therapy [3]. Chemotherapy also lowers the risk of recurrence and death and is now

frequently advised as preoperative (neoadjuvant) therapy [3]. Some patients experience a pathological complete response (PCR), while others do not, and their five-year overall survival rates (OS) range from 50 to 62 percent [32,33]. To improve patient survival, new immunotherapies, antibody-drug conjugates (ADCs), and other tumor- and stromal-targeted medicines must be developed for TNBC patients [34].

The immune system is involved in tumor development and progression and cancer cell detection and destruction. The antitumor immune response slows tumor formation and progression through tumor-directed immune responses involving cytolytic T cells [35,36]. Tumors must dodge the cytotoxic antitumor response through a variety of methods to progress. Immune evasion can take many different forms, including chronic activation of humoral immunity, invasion by T helper 2 (Th2) cells, innate inflammatory cells that are protumor-polarized, varying levels of tumor-specific antigens, negative immune checkpoints on tumor cells, and the absence of major histocompatibility complexes (MHC) on the surface of tumor cells [35,36]. Finally, these pathways work together to modulate anticancer responses while promoting tumor growth and disease progression. Early TNBC is still typically treated with a combination of several chemotherapeutic medications, most frequently given preoperatively to evaluate tumor sensitivity and modify postoperative systemic therapy as necessary [37]. In fact, individuals who have untreated residual illness after neoadjuvant chemotherapy are most at risk for recurrence [32] and benefit greatly from adjuvant capecitabine [38].

In this review, we will discuss the various modes of treatment for TNBC such as immunotherapy which includes ICI, the role of poly (ADP-ribose) polymerase inhibitors (PARPi), various clinical trials which are ongoing, completed, and active, not recruiting, etc., also see in a brief about role of vaccines in immunity to get a clear picture of what mode of treatment is followed and what is beneficial for patients in improving their prognosis.

Review

Discussion

Immunotherapy

Immunotherapy is stimulation of the one's immune system by either active immunization with cancer vaccines or passive immunization through tumor-specific antibodies and immune modulators, like immune-checkpoint inhibitors.

Immune checkpoint inhibitors: Immune checkpoints are a broad group of adaptive immune system regulatory points that play roles in self-tolerance and antitumor immunity. Physiologically, these checkpoints regulate the immune response negatively or positively, coordinating the intensity and type of reaction. Antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein 1 pathway (PD-1/PD-L1) have been the focus of many clinical trials using immunecheckpoint blockade. CTLA-4 and PD-1 in the tumor microenvironment act as negative regulators of immune activation, preventing anticancer immune response. Monoclonal antibodies work by eliminating suppression of the antitumor immune response [39]. Tumor antigens cause overexpression of several inhibitory receptors by T cells when a person develops a malignancy, which can lead to poor tumor identification [40]. Tumor cells secrete PD-L1, which interacts with PD-1 receptors on T cells and hinders the immune system's ability to recognize developing tumor cells [41]. Drugs like pembrolizumab, $Nivolumab, and\ Atezolizumab\ target\ PD-1\ receptors\ present\ in\ T\ cells\ or\ in\ tumor\ cells, which\ boosts$ antitumor immunity [42]. The PD-1/PD-L1 axis is activated when PD-1 binds to its ligand (PD-L1), inhibiting the immune response [43]. T cells, B cells, natural killer cells, dendritic cells, and macrophages are among the immune cells that are inhibited by PD-L1 expression in the innate and adaptive immune systems [44]. This high degree of PD-L1 expression in TNBC makes ICIs, such as anti-PD-1 treatments, easy targets [43-45].

PD-1 Inhibitors

Pembrolizumab: In the phase Ib KEYNOTE-012 trial, it was initially studied as a monotherapy in 32 patients, including those who had received chemotherapy prior to treatment and those without treatment PD-L1-positive TNBC [46]. This showed a positive overall response rate (ORR) of 18.5 percent, so it was given the first ICI approval in TNBC. The ORR in another phase II KEYNOTE-086 study was not as good, showing only 5.3 percent in 170 patients with a PD-L1-unselected pre-treated cancer. In the same study, the ORR was 21.4 percent in 84 without treatment patients, indicating that ICIs are more effective in the first-line metastatic scenario [47]. The KEYNOTE-119 trial, which compared single-agent pembrolizumab to single-agent chemotherapy in pre-treatment metastatic TNBC, found similar results to KEYNOTE-086 in terms of progression-free survival (PFS) and overall survival (OS) [48].

PD-L1 Inhibitors

Atezolizumab/Avelumab: It reverses T cell suppression by directly attacking PD-L1 to inhibit association with the PD-1 and B7-1 receptors [49]. In a phase 1 trial, atezolizumab produced a 10 percent ORR in 115 pre-treated patients, in contrast, patients with PD-L1 negative showed no improvement [50]. In 58 patients

who had received significant pre-treatment, the phase 1b JAVELIN trial that evaluated atezolizumab as a monotherapy reported that the ORR was only 5.2 percent [51]. These studies demonstrate the ineffectiveness of a single agent in treating metastatic TNBC, with especially low response rates in the metastatic disease groups that had already received treatment.

Chemotherapeutic Agents Used in Combination With Immunotherapy

Anthracyclines, taxanes, platinum compounds, and a combination of doxorubicin and cyclophosphamide or docetaxel and cyclophosphamide are most commonly used as chemotherapy agents. These agents have shown improved pathologic complete response rates when given along with conventional chemotherapy [52,53]. Chemotherapy in the neoadjuvant context for early-stage TNBC is recommended by several guidelines [54]. The most typical neoadjuvant method is to administer anthracycline and taxane-based chemotherapy sequentially, with the addition of carboplatin, which has been shown to improve the PCR rate [55]. ICI monotherapy was generally effective against metastatic TNBC when the illness was contained; however, in women with progressive disease and an increased metastatic tumor burden, there was little to no response. As a result, researchers began to focus on ICI combined with chemotherapy. Chemotherapy was thought to increase anticancer responses to ICI. Taxanes have the ability to activate toll-like receptors and increase dendritic-cell activity in particular [56]. In patients with TNBC expressing PD-L1, the KEYNOTE-355 study found that first-line treatment with pembrolizumab significantly improved progression-free survival compared to chemotherapy [57].

Patients with stage II/III cancer who received combined chemotherapy and pembrolizumab had a response rate approximately three times higher than those who received chemotherapy alone in the I-SPY 2 study [46]. Pembrolizumab with chemotherapy enhanced response rates (51.2 percent to 64.8 percent) and 18-month event-free survival (EFS) (85.3 percent to 91.3 percent) in both the neoadjuvant and adjuvant contexts in the KEYNOTE-522 study [58,59]. In contrast to the findings of the previous studies, the NeoTRIPaPDl1 research found that conventional chemotherapy in conjunction with atezolizumab did not affect response rates in patients with progressed TNBC [60].

Phase 3 Randomized Controlled Trials

- 1. KEYNOTE-119/NCT02555657 (completed): Pembrolizumab and chemotherapy were compared in this phase 3 trial of patients with metastatic TNBC. The 1098 patients who were enrolled in the experiment received either pembrolizumab or chemotherapy at random. The primary goals were OS in PD-L1 positive patients and in all patients. With pembrolizumab, the median OS for PD-L1 positive patients was 12.7 months, compared to 11.6 months with chemotherapy (0.057). In the entire population, the median OS for the pembrolizumab group was 9.9 months, while it was 10.8 months for the chemotherapy group (nonsignificant). The most frequent side effects were neutropenia and anemia [48].
- 2. KEYNOTE-355/NCT02819518 (active, not recruiting): In the study of Pembrolizumab (MK-3475) Plus Chemotherapy vs. Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer, 1372 patients were randomly assigned to one of two therapy groups. In patients with PD-L1 positivity, PFS was 9.7 months in the pembrolizumab group and 5.6 months in the placebo group (p = 0.0012). For all patients, the median PFS was 7.5 months, as opposed to 5.6 months for the control group. The effects of pembrolizumab treatment were enhanced by PD-L1 enrichment. Sixtyeight percent of pembrolizumab patients and 67 percent of placebo individuals [61] reported adverse events.
- 3. KEYNOTE-522/NCT03036488 (active, not recruiting): The trial enrolled 602 patients who were randomly assigned to one of two therapy groups, that is, pembrolizumab (MK-3475) with chemotherapy versus placebo with chemotherapy as neoadjuvant therapy and pembrolizumab versus placebo as adjuvant therapy and received the primary PCR at the time of surgery as well as EFS. The pembrolizumab group had a 64.8 percent PCR compared to 51.2 percent in the placebo group. The two groups had similar adverse effects. Unlike metastatic trials, the PCR rate improved when compared to chemotherapy alone, regardless of PD-L1 levels; nevertheless, the PD-L1+ group had the highest absolute PCR of 81.7 percent [62].
- 4. KEYNOTE-242/NCT02954874 (active, not recruiting): This is a phase 3 trial that evaluates pembrolizumab versus a placebo in patients with 1 cm of residual invasive carcinoma and positive lymph nodes after receiving adjuvant neoadjuvant therapy for a year. OS and disease-free survival (DFS) are the most crucial results [62].
- 5. Impassion130/NCT02425891 (completed): In individuals with untreated metastatic TNBC, a phase 3 trial examined atezolizumab in combination with nab-paclitaxel or a placebo. The trial was randomized and had 451 patients in each group. The treatment was continued until the disease progressed or harmful effects reached an unacceptable level. PFS and OS were the main objectives. Within the two groups, the PFS with atezolizumab was 7.2 months compared to 5.5 months with placebo, and the median OS was 21.3 months compared to 17.6 months. Overall, 15.9 percent of patients who got atezolizumab and 8.2 percent of those who received a placebo experienced adverse events that caused them to stop taking the drug [59].

- 6. Impassion030/NCT03498716 (recruiting): In *A Study Comparing Atezolizumab (Anti PD-L1 Antibody) in Combination with Adjuvant Anthracycline/Taxane-Based Chemotherapy Versus Chemotherapy Alone in Patients with Operable Triple-Negative Breast Cancer,* another phase 3 trial is now recruiting 2300 people with operable stage II or III TNBC. They were divided into two groups based on surgery type, lymph node status, and PD-L1 status. The major endpoint is DFS [63]. This trial is still recruiting participants, and no findings have been disclosed.
- 7. Impassion031/NCT03197935 (active, not recruiting): It is a phase 3 trial, with the main goals being PCR in all patients and PD-L1 positive patients. Three hundred and thirty-three patients were randomly randomized to receive atezolizumab with chemotherapy or placebo plus chemotherapy. When compared to the placebo group, the PCR with atezolizumab was 58 percent in all patients as opposed to 41 percent. When it came to PD-L1 positive patients, the difference was even more pronounced, with 69 percent of atezolizumab patients attaining a PCR as opposed to 49 percent in the placebo group [64].
- 8. NSABP B-59/GBG 96-GeparDouze/NCT03281954 (active, not recruiting): In the study *Clinical Trial of Neoadjuvant Chemotherapy with Atezolizumab or Placebo in Patients with Triple-Negative Breast Cancer Followed After Surgery by Atezolizumab or Placebo,* the NSABP B-59 trial compares neoadjuvant chemotherapy with atezolizumab or placebo to adjuvant mepolizumab or placebo in individuals with early-stage TNBC. The main goals are EFS and PCR in the breast and lymph nodes. No results have been released yet [65].
- 9. NCT01042379 (recruiting): In the study *I-SPY TRIAL*: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer, the effectiveness of traditional chemotherapy alone and new medications combined with it are compared. The objective is to find better treatment plans for subsets depending on the molecular features (biomarker signatures) of the tumor. It is a multicenter, open-label, randomized phase 2 platform experiment that is still running. The trial is still actively recruiting participants, and no findings have been made public [66].

Other Immunotherapy Strategies

Breast cancer (BRCA) gene-positive tumors have DNA repair deficiencies and so this PARP (poly (ADP-ribose) polymerase) is a nuclear enzyme that aids in the repair of DNA single-strand breaks and is found in over 90 percent of TNBC [67]. PARPi, which target these recombination repair mechanisms and are beneficial in the treatment of breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2) mutation carriers with TNBC, are being combined with immune checkpoint inhibition to elicit a stronger antitumor immune response. The release of tumor antigens by PARPi-induced cell death activates invading T cells (NCT03281954) [66,68]. Ongoing trials are investigating the use of PARPi in the treatment of TNBC that are currently recruiting participants.

Another cutting-edge approach in cancer immunotherapy is the use of cancer vaccines, which may trigger an immune response against tumor-specific and tumor-associated antigens. Additionally, it is acknowledged that using immunotherapy as the initial line of metastatic treatment will increase OS rates [69].

Limitations

This study may have some limitations, as the quality of this review depends on available studies and published systematic and literature reviews. Several unpublished study trials are ongoing, recruiting patients for in-depth research on therapeutic strategies and it is not yet known if they will be used in the population. In addition, there may be bias due to study heterogeneity. With these drawbacks, we have made an effort to increase the validity of literature reviews by combining the findings of the many research that have been conducted so far. On the other hand, a thorough investigation would probably result in a stronger connection, a more conclusive result, improved patient treatment, and increased awareness.

Conclusions

Studies show that PD-1 inhibitors like pembrolizumab used as monotherapy with prior chemotherapy showed an ORR of 18.5 percent and proved to be one of the most effective therapy. On the contrary, using atezolizumab as monotherapy was not very effective in subsequent trials. Also, taxane-based chemotherapy is proven to be the most efficient in terms of PCR rate. Antibodies targeting PD-1/PD-L1/CTLA-4 are mainly focused in combination with chemotherapy to suppress tumor progression. A combination of pembrolizumab and chemotherapy showed a response rate three times higher than using chemotherapy alone. Various phase 3 randomized control trials also depict a combination of PD-1/PD-L1 inhibitors with chemotherapy drugs showing effective response against TNBC. The tumor microenvironment is responsible for the progression, development, and metastasis of tumors, and hence, in-depth research studies of TME and various other drug combinations have to keep going for knowing advancements in treating TNBC. The nature of TNBC is heterogenous and so the combination of various drugs should be continuously tried, and its efficacy should be known through various clinical trials.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

- Breast cancer. (2021). Accessed: March 26: https://www.who.int/news-room/fact-sheets/detail/breast-cancer.
- Sherman R, Firth R, Charlton M, et al.: Cancer in North America: 2014-2018. Volume One: Combined Cancer Incidence for the United States, Canada and North America. North American Association of Central Cancer Registries, Inc., Springfield, IL; May 2021.
- 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. 10.1200/JCO.2007.14.4147
- Rakha EA, Reis-Filho JS, Ellis IO: Basal-like breast cancer: a critical review. J Clin Oncol. 2008, 26:2568-81. 10.1200/ICO.2007.13.1748
- Irshad S, Ellis P, Tutt A: Molecular heterogeneity of triple-negative breast cancer and its clinical implications. Curr Opin Oncol. 2011, 23:566-77. 10.1097/CCO.0b013e32834bf8ae
- Fan Y, He S: The characteristics of tumor microenvironment in triple negative breast cancer. Cancer Manag Res. 2022, 14:1-17. 10.2147/CMAR.S316700
- Kai F, Drain AP, Weaver VM: The extracellular matrix modulates the metastatic journey. Dev Cell. 2019, 49:332-46. 10.1016/j.devcel.2019.03.026
- Chen Y, McAndrews KM, Kalluri R: Clinical and therapeutic relevance of cancer-associated fibroblasts. Nat Rev Clin Oncol. 2021. 18:792-804. 10.1038/s41571-021-00546-5
- Deligne C, Midwood KS: Macrophages and extracellular matrix in breast cancer: partners in crime or protective allies?. Front Oncol. 2021. 11:620773. 10.3389/fonc.2021.620773
- Yue B: Biology of the extracellular matrix: an overview . J Glaucoma. 2014, 23:S20-3. 10.1097/IG.0000000000000108
- Naba A, Clauser KR, Hoersch S, Liu H, Carr SA, Hynes RO: The matrisome: in silico definition and in vivo characterization by proteomics of normal and tumor extracellular matrices. Mol Cell Proteomics. 2012, 11:M111.014647. 10.1074/mcp.M111.014647
- Henke E, Nandigama R, Ergün S: Extracellular matrix in the tumor microenvironment and its impact on cancer therapy. Front Mol Biosci. 2019. 6:160. 10.3389/fmolb.2019.00160
- Armstrong T, Packham G, Murphy LB, et al.: Type I collagen promotes the malignant phenotype of pancreatic ductal adenocarcinoma. Clin Cancer Res. 2004, 10:7427-37. 10.1158/1078-0432.CCR-03-0825
- Conklin MW, Eickhoff JC, Riching KM, et al.: Aligned collagen is a prognostic signature for survival in human breast carcinoma. Am J Pathol. 2011, 178:1221-32. 10.1016/j.ajpath.2010.11.076
- Acerbi I, Cassereau L, Dean I, et al.: Human breast cancer invasion and aggression correlates with ECM stiffening and immune cell infiltration. Integr Biol (Camb). 2015, 7:1120-34. 10.1039/c5ib00040h
- Čunderlíková B: Clinical significance of immunohistochemically detected extracellular matrix proteins and their spatial distribution in primary cancer. Crit Rev Oncol Hematol. 2016, 105:127-44. 10.1016/j.critrevonc.2016.04.017
- Hanley CJ, Noble F, Ward M, et al.: A subset of myofibroblastic cancer-associated fibroblasts regulate collagen fiber elongation, which is prognostic in multiple cancers. Oncotarget. 2016, 7:6159-74.
 10.18632/oncotarget.6740
- Esbona K, Yi Y, Saha S, et al.: The presence of cyclooxygenase 2, tumor-associated macrophages, and collagen alignment as prognostic markers for invasive breast carcinoma patients. Am J Pathol. 2018, 188:559-73. 10.1016/j.ajpath.2017.10.025
- Tomko LA, Hill RC, Barrett A, et al.: Targeted matrisome analysis identifies thrombospondin-2 and tenascin-C in aligned collagen stroma from invasive breast carcinoma. Sci Rep. 2018, 8:12941. 10.1038/s41598-018-31126-w
- Provenzano PP, Eliceiri KW, Campbell JM, Inman DR, White JG, Keely PJ: Collagen reorganization at the tumor-stromal interface facilitates local invasion. BMC Med. 2006, 4:38. 10.1186/1741-7015-4-38
- Denkert C, Loibl S, Noske A, et al.: Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol. 2010, 28:105-13. 10.1200/JCO.2009.23.7370
- Santoni M, Romagnoli E, Saladino T, et al.: Triple negative breast cancer: key role of tumor-associated macrophages in regulating the activity of anti-PD-1/PD-L1 agents. Biochim Biophys Acta Rev Cancer. 2018, 1869:78-84. 10.1016/j.bbcan.2017.10.007
- Lotfinejad P, Asghari Jafarabadi M, Abdoli Shadbad M, et al.: Prognostic role and clinical significance of tumor-infiltrating lymphocyte (TIL) and programmed death ligand 1 (PD-L1) expression in triple-negative breast cancer (TNBC): a systematic review and meta-analysis study. Diagnostics (Basel). 2020, 10:704. 10.3390/diagnostics10090704
- 24. Sahin Ozkan H, Ugurlu MU, Yumuk PF, Kaya H: Prognostic role of immune markers in triple negative breast carcinoma. Pathol Oncol Res. 2020, 26:2733-45. 10.1007/s12253-020-00874-4
- Deepak KG, Vempati R, Nagaraju GP, Dasari VR, Nagini S, Rao DN, Malla RR: Tumor microenvironment: challenges and opportunities in targeting metastasis of triple negative breast cancer. Pharmacol Res. 2020, 153:104683. 10.1016/j.phrs.2020.104683
- 26. Jain RK: Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers . J Clin Oncol.

- 2013, 31:2205-18. 10.1200/JCO.2012.46.3653
- Chen IX, Chauhan VP, Posada J, et al.: Blocking CXCR4 alleviates desmoplasia, increases T-lymphocyte infiltration, and improves immunotherapy in metastatic breast cancer. Proc Natl Acad Sci U S A. 2019, 116:4558-66. 10.1073/pnas.1815515116
- Bates AM, O'Leary KA, Emma S, Nystuen E, Sumiec EG, Schuler LA, Morris ZS: Enhancing immunogenicity in immunologically cold ER+ breast cancer using estrogen receptor blockade and radiation therapy. Cancer Res. 2020. 80:2255. 10.1158/1538-7445.AM2020-2255
- Hastings JF, Skhinas JN, Fey D, Croucher DR, Cox TR: The extracellular matrix as a key regulator of intracellular signalling networks. Br J Pharmacol. 2019, 176:82-92. 10.1111/bph.14195
- Winkler J, Abisoye-Ogunniyan A, Metcalf KJ, Werb Z: Concepts of extracellular matrix remodelling in tumour progression and metastasis. Nat Commun. 2020, 11:5120. 10.1038/s41467-020-18794-x
- Primeau AJ, Rendon A, Hedley D, Lilge L, Tannock IF: The distribution of the anticancer drug doxorubicin in relation to blood vessels in solid tumors. Clin Cancer Res. 2005, 11:8782-8. 10.1158/1078-0432.CCR-05-1664
- 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. 10.1016/S0140-6736(13)62422-8
- Bagegni NA, Tao Y, Ademuyiwa FO: Clinical outcomes with neoadjuvant versus adjuvant chemotherapy for triple negative breast cancer: a report from the National Cancer Database. PLoS One. 2019, 14:e0222358.
 10.1371/journal.pone.0222358
- Fertal SA, Poterala JE, Ponik SM, Wisinski KB: Stromal characteristics and impact on new therapies for metastatic triple-negative breast cancer. Cancers (Basel). 2022, 14:1238. 10.3390/cancers14051238
- Hanahan D, Weinberg RA: Hallmarks of cancer: the next generation. Cell. 2011, 144:646-74.
 10.1016/i.cell.2011.02.013
- de Visser KE, Coussens LM: The inflammatory tumor microenvironment and its impact on cancer development. Contrib Microbiol. 2006, 13:118-37. 10.1159/000092969
- Cardoso F, Paluch-Shimon S, Senkus E, et al.: 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020, 31:1623-49. 10.1016/j.annonc.2020.09.010
- Masuda N, Lee SJ, Ohtani S, et al.: Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017, 376:2147-59, 10.1056/NEJMoa1612645
- Pardoll DM: The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012, 12:252-64. 10.1038/nrc3239
- Wherry EJ, Kurachi M: Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol. 2015, 15:486-99. 10.1038/nri3862
- 41. Paulsen EE, Kilvaer TK, Khanehkenari MR, et al.: Assessing PDL-1 and PD-1 in non-small cell lung cancer: a novel Immunoscore approach. Clin Lung Cancer. 2017, 18:220-33.e8. 10.1016/j.cllc.2016.09.009
- Turnis ME, Andrews LP, Vignali DA: Inhibitory receptors as targets for cancer immunotherapy. Eur J Immunol. 2015, 45:1892-905. 10.1002/eji.201344413
- 43. Mittendorf EA, Philips AV, Meric-Bernstam F, et al.: PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res. 2014, 2:361-70. 10.1158/2326-6066.CIR-13-0127
- 44. 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-negative breast cancer: a retrospective multicenter study. Breast Cancer Res. 2015, 17:124. 10.1186/s13058-015-0632-x
- Topalian SL, Hodi FS, Brahmer JR, et al.: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012, 366:2443-54. 10.1056/NEJMoa1200690
- Nanda R, Liu MC, Yau C, et al.: Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. JAMA Oncol. 2020, 6:676-84. 10.1001/jamaoncol.2019.6650
- Adams S, Loi S, Toppmeyer D, et al.: Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study. Ann Oncol. 2019, 30:405-11. 10.1093/annonc/mdy518
- 48. Winer EP, Lipatov O, Im SA, et al.: Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE- 119): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021, 22:499-511. 10.1016/S1470-2045(20)30754-3
- O'Sullivan H, Collins D, O'Reilly S: Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2019, 380:985-88. 10.1056/NEJMc1900150
- 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, 5:74-82. 10.1001/jamaoncol.2018.4224
- 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. 10.1007/s10549-017-4537-5
- Masuda H, Baggerly KA, Wang Y, et al.: Differential response to neoadjuvant chemotherapy among 7 triplenegative breast cancer molecular subtypes. Clin Cancer Res. 2013, 19:5533-40. 10.1158/1078-0432.CCR-13-0700
- 53. Petrelli F, Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Barni S: The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014, 144:223-32. 10.1007/s10549-014-2876-z
- Wood DE: National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. Thorac Surg Clin. 2015, 25:185-97. 10.1016/j.thorsurg.2014.12.003
- 55. von Minckwitz G, Schneeweiss A, Loibl S, et al.: Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol. 2014. 15:747-56. 10.1016/S1470-2045(14)70160-3
- Emens LA, Middleton G: The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res. 2015, 3:436-43. 10.1158/2326-6066.CIR-15-0064

- 57. Kulangara K, Zhang N, Corigliano E, et al.: Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. Arch Pathol Lab Med. 2019, 143:330-7. 10.5858/arpa.2018-0043-OA
- Keenan TE, Tolaney SM: Role of immunotherapy in triple-negative breast cancer. J Natl Compr Canc Netw. 2020, 18:479-89. 10.6004/jnccn.2020.7554
- Schmid P, Cortes J, Pusztai L, et al.: Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020, 382:810-21, 10.1056/NEIMoa1910549
- Suppan C, Balic M: Treatment options in early triple-negative breast cancer. Memo Mag Eur Med Oncol. 2020. 13:346-48. 10.1007/s12254-020-00609-w
- Cortes J, Cescon DW, Rugo HS, et al.: Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020, 396:1817-28.
 10.1016/S0140-6736(20)32531-9
- Berger ER, Park T, Saridakis A, Golshan M, Greenup RA, Ahuja N: Immunotherapy treatment for triple negative breast cancer. Pharmaceuticals (Basel). 2021, 14:763. 10.3390/ph14080763
- McArthur HL, Ignatiadis M, Guillaume S, et al.: ALEXANDRA/IMpassion030: a phase III study of standard adjuvant chemotherapy with or without atezolizumab in early-stage triple-negative breast cancer. J Clin Oncol. 2019, 37:598. 10.1200/JCO.2019.37.15_suppl.TPS598
- 64. Mittendorf EA, Zhang H, Barrios CH, et al.: Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020, 396:P1090-100. 10.1016/S0140-6736(20)31953-X
- 65. Geyer CE, Loibl S, Rastogi P, et al.: NSABP B-59/GBG 96-GeparDouze: a randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. J Clin Oncol. 2018, 36:603. 10.1200/JCO.2018.36.15_suppl.TPS603
- Thomas R, Al-Khadairi G, Decock J: Immune checkpoint inhibitors in triple negative breast cancer treatment: promising future prospects. Front Oncol. 2020, 10:600573. 10.3389/fonc.2020.600573
- Li Z, Qiu Y, Lu W, Jiang Y, Wang J: Immunotherapeutic interventions of triple negative breast cancer. J Transl Med. 2018, 16:147. 10.1186/s12967-018-1514-7
- Jiao S, Xia W, Yamaguchi H, et al.: PARP inhibitor upregulates PD-L1 expression and enhances cancerassociated immunosuppression. Clin Cancer Res. 2017, 23:3711-20. 10.1158/1078-0432.CCR-16-3215
- 69. Marra A, Viale G, Curigliano G: Recent advances in triple negative breast cancer: the immunotherapy era . BMC Med. 2019, 17:90. 10.1186/s12916-019-1326-5