PD-1/PD-L1-Based Immunotherapy for Metastatic Triple-Negative Breast Cancer

Subjects: Oncology

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Triple-negative breast cancer (TNBC) refers to a type of breast cancer in which the immunohistochemistry of the cancer tissue is negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2), and it accounts for 15–20% of all breast cancer patients. Because of its rapid progression, most patients with TNBC have progressed to the more malignant and aggressive metastatic TNBC (mTNBC), with a shorter survival period by the time they seek medical attention. The majority of breast cancer deaths are caused by mTNBC. According to pathological characteristics, it lacks specific therapeutic targets, and it cannot be completely removed surgically due to unclear distant micro-metastases. Therefore, treatment of mTNBC is usually based on chemotherapy. However, according to clinical statistics, the overall response rate (ORR‘) of mTNBC with single-agent chemotherapy is only 10–30%, and with the best multi-drug combination chemotherapy regimen it is only 63%. The average pathologically complete response (pCR) to mTNBC with multi-drug combination chemotherapy regimen is about 30–40%. In summary, the benefit of chemotherapy for patients with mTNBC is not promising. The search for treatments with high clearance, good targeting, and few side effects has become a major focus of medical research.

Keywords: cancer therapy ; metastatic triple-negative breast cancer ; immunotherapy ; immune checkpoint blockade therapy ; PD-1/PD-L1

1. Immune Checkpoint and Immune Checkpoint Blockade Therapy

Under normal circumstances, the human immune system functions in immune surveillance and elimination, but as the tumor grows, the tumor cells develop immune-suppressive responses, such as weakened antigenicity of the tumor cells, reduced responsiveness to the immune killing mechanism, and expression of immunosuppressive molecules. Under these circumstances, the immune system develops immune tolerance to tumor cells, known as immune editing (**Figure 1**) [1][2]. Immunotherapy for tumors is based on immune editing, applying immunological principles and methods to reactivate immune cells, enhance the anti-tumor immune response, break the immune tolerance, and inhibit tumor growth by enhancing the antigenicity of tumor cells and the killing ability of immune cells, and inhibiting the effect of immunosuppressive molecules. It mainly includes immune checkpoint blocking therapy [3], therapeutic antibodies [4], cancer vaccines [5], adoptive cellular immunotherapy [6], small-molecule inhibitors [7], and other methods.

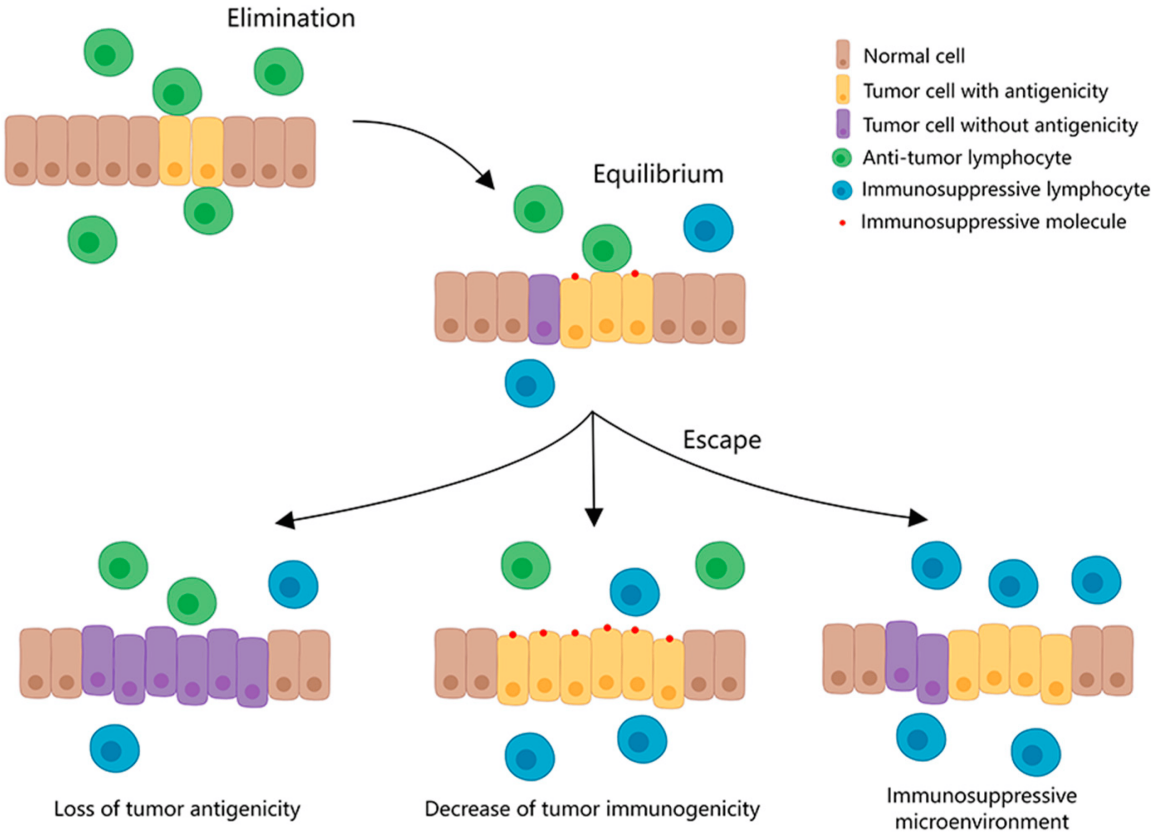

Figure 1. Immune escape mechanism of tumors. Along with tumor growth, the immune system develops immune tolerance to tumor cells due to weakened antigenicity of tumor cells, reduced responsiveness to immune killing mechanisms, and expression of immunosuppressive molecules.

Immune checkpoint therapy (ICT) blocks the action of immune checkpoints by artificially administering inhibitors of immune checkpoints or their ligands, thereby upregulating T cells activity and improving the anti-tumor immune response. The Food and Drug Administration (FDA) has approved multiple immune-checkpoint-blocking drugs for cancer treatment because of the advantages of this method, such as being highly targeted and not prone to tumor resistance [8]. Currently, PD-1/PD-L1 and CTLA-4/B7-1 are the primary targets of immune checkpoint blockade therapies. In addition, molecules such as lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin domain 3 (TIM-3), and T-cell immunoglobulin and ITIM domains (TIGIT) have also been extensively investigated as targets.

PD-1, also known as CD279, is a 55 kDa transmembrane protein. It is mainly expressed by activated T cells, B cells, and natural killer cells and is significantly highly expressed by tumor-specific T cells. PD-L1, also known as CD274 or B7-H1, belongs to the B7 family and is a 33 kDa transmembrane glycoprotein. This protein is normally expressed by macrophages, activated T cells, and B cells, and its expression in tumor cells increases with the progression of the disease and/or with the degree of heterogeneity of tumor cells. When PD-1 is combined with PD-L1, it can inhibit the activation and proliferation of T cells in peripheral tumor tissues and attenuate the cell-killing effect of T cells by regulating the PI3K-AKT-mTOR [9] and Ras-EMK-ERK pathways [10]. In addition, tumor cells can be stimulated to grow and invade, causing immunosuppression, inhibiting the secretion of pro-inflammatory factors, and weakening the antigen-presenting ability of dendritic cells, which leads to the immune escape of tumors [3].

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), also known as CD152, is a leukocyte differentiation antigen that functions primarily in the T cell activation phase of lymphoid organs. As a transmembrane receptor on the surface of T cells, CTLA-4 inhibits T cell hyperactivation by competitively binding ligand B7-1/2 (CD80/86) to CD28, the activating receptor of T cells [11].

PD-1/PD-L1 therapies are more specific and act faster because PD-1 acts mainly in peripheral tumor sites and works in the T cell effector phase, while CTLA-4 acts mainly in lymphoid organs and works in the T cell activation phase [12]. Several studies have compared the adverse effects of treatment with CTLA-4 and PD-1/PD-L1 inhibitors and found that CTLA4 inhibitors have more side effects than PD-1/PD-L1 inhibitors [13]. Therefore, immunotherapy with PD-1/PD-L1 inhibitors can enhance anti-tumor immunity, which is more suitable for patients in poor condition and with aggressive tumors and is important for the treatment of rapidly progressing mTNBC (**Figure 2**).

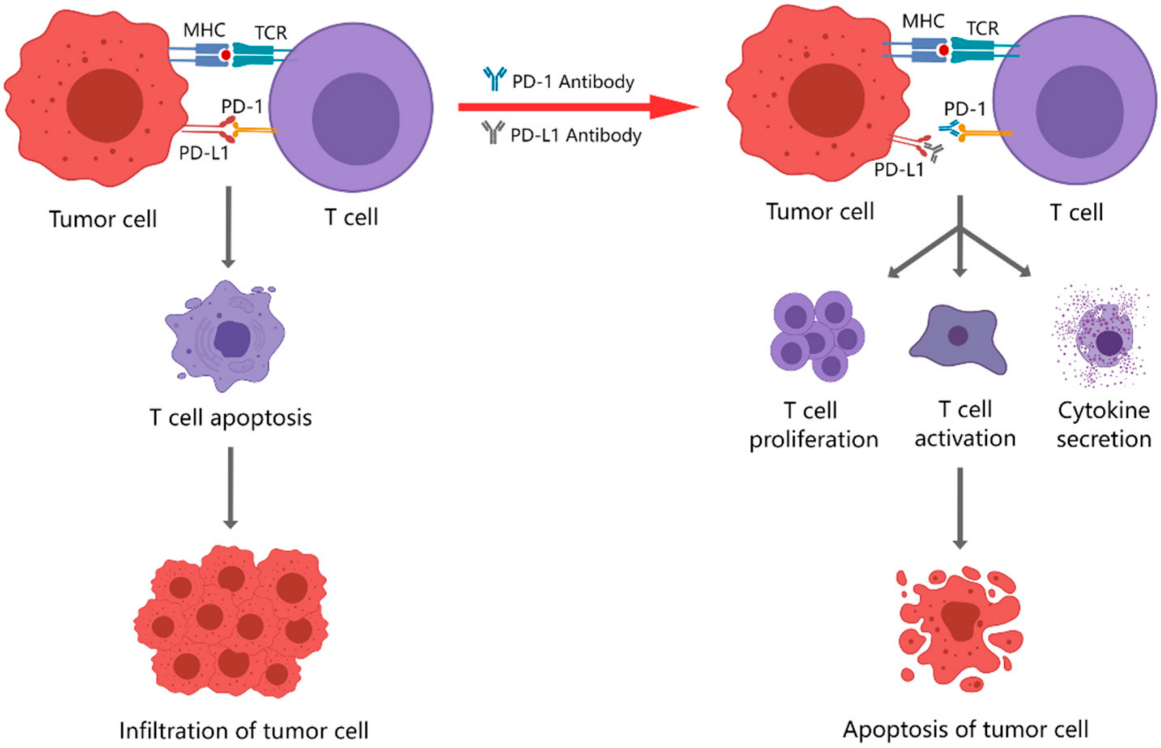

Figure 2. Effect of PD-1 and PD-L1 inhibitors. The combination of PD-1 and PD-L1 induces T-cell apoptosis, so the tumor cells will infiltrate; the use of PD-1 or PD-L1 inhibitors promotes T-cell proliferation, activation and secretion of cytokines, and enhances the tumor-killing effect of T cells.

2. PD-1/PD-L1 Inhibitors Currently Used for Clinical Treatment

2.1. PD-1 Inhibitors

PD-1 inhibitors are monoclonal antibodies that bind to the PD-1 on T cells, effectively inhibiting the binding of PD-1 to PD-L1 and PD-L2 receptors on cancer cells, allowing the immune escape of tumor cells to be recognized by T cells and exert anti-tumor effects. Studies have shown that PD-1 monoclonal antibodies do not bind Fc or activate complements during the blockade of PD-1; therefore, they are not cytotoxic [14].

2.2. PD-L1 Inhibitors

PD-L1 inhibitors are monoclonal antibodies engineered from human PD-L1 that target PD-L1 on tumor cells and inhibit the PD-1/PD-L1 pathway, thereby reactivating anti-tumor immunity. The durable safety and long-term clinical benefits of monoclonal antibodies against PD-L1 have led the FDA to approve them for use in the treatment of many types of cancers [15][16][17].

3. Monotherapy with PD-1/PD-L1 Inhibitors

Atezolizumab monotherapy was evaluated in the clinical phase I trial PCD4989g for anti-tumor efficacy and safety in advanced or metastatic solid and hematological tumors. The results showed that among 116 evaluable patients, treatment-related adverse events (trAEs) occurred in 73 (63%), and most of them (79%) were grade 1 to 2, which was similar to the other antineoplastic drugs. Patients with mTNBC treated with atezolizumab as a first-line therapy had an objective response rate (ORR) of 24%, and a median overall survival (mOS) of 17.6 months (95% CI:10.2–N/A), and the incidence of trAEs was 62%. In contrast, women treated with atezolizumab as second- or third-line therapy had an ORR of 6% and an mOS of 7.3 months (95% CI: 6.1–10.8). In addition, the study showed that atezolizumab monotherapy had a higher ORR, mOS, and median progression-free survival (mPFS) in patients with mTNBC with higher levels of TILs. It is leaded to the preliminary conclusion that first-line treatment with atezolizumab monotherapy is well tolerated and beneficial in patients with advanced TNBC or mTNBC, especially in those with higher levels of TILs [18].

A small-sample phase Ib clinical trial, KEYNOTE-012, is being conducted to determine the safety and anti-tumor activity of pembrolizumab monotherapy in advanced PD-L1-positive mTNBC. All patients included in the study received other prior therapies (i.e., pembrolizumab monotherapy was not used as the first-line therapy). The results showed that among the 27 study subjects with evaluable efficacy, ORR was 18.5% (95% CI: 6.3%–38.1%), including one complete remission and

four partial remissions, with a disease-control rate of 25.9% (95% CI: 11.1–46.3%), and mPFS and mOS were 1.9 (95% CI: 1.3–4.3) and 10.2 (95% CI: 5.3–N/A) months. The most common trAEs were arthralgia, fatigue, myalgia, and nausea, with only 15.6% of grade 3–5 trAEs occurring. This result is comparable to the treatment effect of pembrolizumab in other high-grade malignancies [19][20][21]. In addition, this result is similar to the results of second- and third-line treatments in PCD4989g, further demonstrating the authenticity and reliability of both trials.

Pembrolizumab monotherapy in mTNBC was also studied in a clinical phase II trial (KEYNOTE-086). The results showed that patients with PD-L1-positive mTNBC treated with first-line pembrolizumab monotherapy had an mPFS of 2.1 months (95% CI: 1.9–2.0), an mOS of 18 months (95% CI: 12.9–23.0), and an ORR of 21.4%. In contrast, patients with mTNBC who had received prior chemotherapy (i.e., pembrolizumab alone, not as first-line therapy) had an mPFS of 2.0 months (95% CI: 1.9–2.0), an mOS of 9 months (95% CI: 7.6–11.2), and an ORR of only 5.3%. The incidence of trAEs was 63.1% for the first-line treatment population and 60.6% for those who had received other prior treatments, both of which were comparable. It is concluded that pembrolizumab monotherapy has durable anti-tumor activity in patients with PD-L1-positive mTNBC [22]. It further confirmed the effectiveness of PD-1 inhibitors in the treatment of TNBC.

A phase III randomized controlled trial, KEYNOTE-119, compared the efficacy of pembrolizumab monotherapy as non-first-line therapy with chemotherapy for the treatment of mTNBC. The study showed an ORR of 26% for pembrolizumab monotherapy and 12% for chemotherapy in patients with PD-L1 positive tumors and combined positive score (cps) ≥20. Among patients with cps ≥ 10, the mOS was 12.7 months (95% CI: 9.9–16.3), and ORR was 18% for pembrolizumab monotherapy; mOS was 11.6 months (95% CI: 8.3–13.7), and ORR was 9% for chemotherapy. Among patients with cps ≥1, mOS was 10.7 months (95% CI: 9.3–12.5) and ORR was 12% for pembrolizumab monotherapy; the mOS was 10.2 months (95% CI: 7.9–12.6), and ORR was 9% for chemotherapy. Overall, the mOS was 9.9 months (95% CI: 8.3–11.4) for pembrolizumab monotherapy and 10.8 months (95% CI: 9.1–12.6) for chemotherapy. In addition, the incidence of adverse events was comparable between the trAEs of both therapies, except for a statistically significant difference in the incidence of immune-related adverse events [23]. It is evident that pembrolizumab monotherapy did not significantly improve ORR or OS in patients with mTNBC who had previously received other treatments compared to monotherapy. However, as PD-L1 increased in the tumor microenvironment, pembrolizumab monotherapy was more effective, while there was little difference in the efficacy of chemotherapy, suggesting that the degree of clinical benefit of pembrolizumab treatment in patients with mTNBC may be correlated with tumor PD-L1 expression.

In addition, the efficacy of avelumab in monotherapy of locally advanced or metastatic breast cancer was studied in a phase 1 JAVELIN Solid Tumor trial (NCT01772004) [24], demonstrating an acceptable safety profile and clinical activity. However, in-depth studies for Avelumab, such as NCT04360941, NCT03971409, and NCT03971409, are still in progress.

By analyzing the results of these trials, it could be preliminarily concluded that the application of PD-1/PD-L1 inhibitors for the treatment of locally advanced TNBC or mTNBC has a certain clinical efficacy. Comparing the clinical efficacy with treatment-related adverse reactions shows that the safety of this regimen is guaranteed. Therefore, this regimen could be clinically useful. However, further research is needed to clarify the conditions under which PD-1/PD-L1 inhibitor therapy is indicated and to determine whether there is any clinical benefit compared to chemotherapy, which was the gold-standard treatment in the past. From these trials, it can be seen that the more positive PD-L1 and high cps, the earlier the application of the treatment, and the better the treatment outcome for patients with advanced TNBC or mTNBC. In addition, the study subjects of the above trial had strict inclusion criteria, their general condition was good, and the actual situation, such as patients′ willingness and economic status, was not considered, so their representativeness was poor. In summary, single-agent immunotherapy has major clinical limitations, and the treatment of mTNBC remains unclear. Therefore, the combination of immune checkpoint inhibitors with other therapies is a noteworthy treatment strategy.

References

1. Van Parijs, L.; Abbas, A.K. Homeostasis and self-tolerance in the immune system: Turning lymphocytes off. Science 1998, 280, 243–248.
2. O’Donnell, J.S.; Teng, M.W.L.; Smyth, M.J. Cancer immunoediting and resistance to T cell-based immunotherapy. Nat. Rev. Clin. Oncol. 2019, 16, 151–167.
3. Han, Y.; Liu, D.; Li, L. PD-1/PD-L1 pathway: Current researches in cancer. Am. J. Cancer Res. 2020, 10, 727–742.
4. Klein, C.; Jamois, C.; Nielsen, T. Anti-CD20 treatment for B-cell malignancies: Current status and future directions. Expert Opin. Biol. Ther. 2021, 21, 161–181.

5. Zhu, F.-C.; Hu, S.-Y.; Hong, Y.; Hu, Y.-M.; Zhang, X.; Zhang, Y.-J.; Pan, Q.-J.; Zhang, W.-H.; Zhao, F.-H.; Zhang, C.-F.; et al. Efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine in Chinese women aged 18–25 years: Event-triggered analysis of a randomized controlled trial. Cancer Med. 2017, 6, 12–25.
6. June, C.H.; O'Connor, R.S.; Kawalekar, O.U.; Ghassemi, S.; Milone, M.C. CAR T cell immunotherapy for human cancer. Science 2018, 359, 1361–1365.
7. Terness, P.; Chuang, J.J.; Bauer, T.; Jiga, L.; Opelz, G. Regulation of human auto- and alloreactive T cells by indoleamine 2,3-dioxygenase (IDO)-producing dendritic cells: Too much ado about IDO? Blood 2005, 105, 2480–2486.
8. Jiang, W.J.; Deng, X.-Y.; Li, X.-L.; Li, X.-Y.; Zeng, Z.-Y.; Xiong, W.; Li, G.-Y.; Xiong, F.; Guo, C. Immunotherapy targeted to immune checkpoint—A revolutionary breakthrough in cancer therapy written on the occasion of the 2018 Nobel Prize in Physiology or Medicine. Prog. Biochem. Biophys. 2018, 45, 1178–1186.
9. Boussiotis, V.A. Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway. N. Engl. J. Med. 2016, 375, 1767–1778.
10. Qiu, X.Y.; Hu, D.X.; Chen, W.-Q.; Chen, R.Q.; Qian, S.R.; Li, C.Y.; Li, Y.J.; Xiong, X.X.; Liu, D.; Pan, F.; et al. PD-L1 confers glioblastoma multiforme malignancy via Ras binding and Ras/Erk/EMT activation. Biochim. Biophys. Acta Mol. Basis Dis. 2018, 1864, 1754–1769.
11. Sharma, P.; Allison, J.P. Immune checkpoint targeting in cancer therapy: Toward combination strategies with curative potential. Cell 2015, 161, 205–214.
12. Topalian, S.L.; Taube, J.M.; Anders, R.A.; Pardoll, D.M. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat. Reviews. Cancer 2016, 16, 275.
13. Puzanov, I.; Diab, A.; Abdallah, K.; Bingham, C.; Brogdon, C.; Dadu, R.; Hamad, L.; Kim, S.; Lacouture, M.; LeBoeuf, N.; et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J. Immun.Therapy. Cancer 2017, 5, 95.
14. Kwok, G.; Yau, T.C.C.; Chiu, J.W.; Tse, E.; Kwong, Y.L. Pembrolizumab (Keytruda). Hum. Vaccines 2016, 12, 2777–2789.
15. Rittmeyer, A.; Barlesi, F.; Waterkamp, D.; Park, K.; Ciardiello, F.; von Pawel, J.; Gadgeel, S.M.; Hida, T.; Kowalski, D.M.; Dols, M.C.; et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. Lancet 2017, 389, 255–265.
16. Balar, A.V.; Galsky, M.D.; Rosenberg, J.E.; Powles, T.; Petrylak, D.P.; Bellmunt, J.; Loriot, Y.; Necchi, A.; Hoffman-Censits, J.; Perez-Gracia, J.L.; et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: A single-arm, multicentre, phase 2 trial. Lancet 2017, 389, 67–76.
17. McDermott, D.F.; Sosman, J.A.; Sznol, M.; Massard, C.; Gordon, M.S.; Hamid, O.; Powderly, J.D.; Infante, J.R.; Fassò, M.; Wang, Y.V.; et al. Atezolizumab, an Anti-Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates From a Phase Ia Study. J. Clin. Oncol. 2016, 34, 833–842.
18. Emens, L.A.; Cruz, C.; Eder, J.P.; Braiteh, F.; Chung, C.; Tolaney, S.M.; Kuter, I.; Nanda, R.; Cassier, P.A.; Delord, J.-P.; 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.
19. Seiwert, T.Y.; Burtness, B.; Weiss, J. A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV-associated head and neck (H/N) cancer. Mccarthy 2014, 32, 6011.
20. Muro, K.; Bang, Y.; Shankaran, V.; Geva, R.; Catenacci, D.V.T.; Eder, S.G.P.; Berger, R.; Gonzalez, E.J.; Ray, A.; Dolled-Filhart, M. Relationship between PD-L1 expression and clinical outcomes in patients (Pts) with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (Pembro; MK-3475) in KEYNOTE-012. J. Clin. Oncol. 2015, 33, 3.
21. Chow, L.Q.; Burtness, B.; Weiss, J.; Berger, R.; Eder, J.P.; Gonzalez, E.J.; Pulini, J.; Johnson, J.; Dolled-Filhart, M.; Emancipator, K. A phase Ib study of pembrolizumab (Pembro; MK-3475) in patients (Pts) with human papiilloma virus (HPV)-positive and negative head and neck cancer. Ann. Oncol. 2014, 25 (Suppl. S4), 1–41.
22. Adams, S.; Schmid, P.; Rugo, H.S.; Winer, E.P.; Loirat, D.; Awada, A.; Cescon, D.W.; Iwata, H.; Campone, M.; Nanda, R.; et al. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: Cohort A of the phase II KEYNOTE-086 study. Ann. Oncol. 2019, 30, 397–404.
23. Winer, E.P.; Lipatov, O.; Im, S.-A.; Goncalves, A.; Muñoz-Couselo, E.; Lee, K.S.; Schmid, P.; Tamura, K.; Testa, L.; Witzel, I.; 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.

24. Dirix, L.Y.; Takacs, I.; Jerusalem, G.; Nikolinakos, P.; Arkenau, H.T.; Forero-Torres, A.; Boccia, R.; Lippman, M.E.; Somer, R.; Smakal, M.; 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, 671–686.