Based on immune checkpoint inhibitor to improve cancer treatment

Yijin Chen

Department of Medical, Jiangsu University, Zhenjiang, 212000, China

Abstract. Different kinds of cancer normally have enormous prognosis according to its kind and different therapeutic methods. Sometimes use approprete treatment can get better prognosis, tradinional therapeutic such as chemotherapy, radiotherapy are notsuitable for some patients. Cancer cure is always a hot issue for scientists to think about, as growing population of cancer patients every year. Immune checkpoint therapy (ICT) has a significant advantage for its high accuracy. For patients with immune system related kind of cancer are most likely to benefit from its high precision. NSCLC patients, TNBC patients and people who got HER2-positive advanced gastric cancer thes specific types of have different reasons for bad result, but the basic factors are low response to chemotherapy. As treatment for some types of cancer has encountered with block, some types are hard to react to chemotherapy and some have lower mOS. Some patients have badly side effects compare with other, and the drug-fast problem is significant. For better result scientists believe ICT can activated immune system and keep its natural power in killing cancer cells. As more combination therapies of ICIs proposed in the future cancer patients are diffinatly have more chance. In conclution, ICT is a powerful way to heal cancer patients, and for many sevier patients this maybe their best chiose. ICT still need futher improvement to deal with more different kinds of cancer and reduce the side effects that it causes but its high efficiency is a good news for people who got cancer.

Keywords: cancer immune therapy, immune checkpoint inhibitor.

1. Introduction

Cancer is a kind of malignant tumor, with cell differentiation and proliferation disorders, and growing without control causes tissue infiltration and tumor metastasis more often. Most cases are because abnormal gene mutation or some infections from outside. Some specific types of cancers are even more serious for both patients and doctors. Lung cancer is always one of the most common types around the world, in 2020 world health organization announced that lung cancer still has the world's second infection rate 11.4%. In lung cancer patients over 80% are getting Non-Small-Cell Lung Cancer (NSCLC), NSCLC is a kind of lung cancer with a higher prevalence and lower cure rate, the proportion of NSCLC is 80% median survival time only 1 year with chemotherapy is a tricky thing. Most patients with unreplaceable lung cancer caused by gene mutation need targeted therapy. [1]. But scientists are still looking for new ways as fewer patients have the target gene. Breast cancer is another kind of cancer that many people are plagued by, one reason is the complicated typing, some kinds are hard to cure. Because lack the expression of both estrogen (ER) and progesterone (PgR) receptors, triple-negative breast cancer (TNBC) is hardly reacting to general treatments. And prognosis worse Same thing happens on gastric cancer which is one of most frequent cancer that occurs in China, every year about 4 million people are diagnosis and over 2 million patients die because of it. Gastric cancer has 4 kinds according to four molecular subtypes, every one of them has a specific genotype and this related to their prognosis condition. Almost 50% of the gastric cancer patients are having the chromosomally unstable tumors (CIN) subtype,the most common one for [2]. Although medication for gastric cancer are rich, some specific kinds remain unknown for doctors. For example, therapeutic methods are limited for HER2-positive advanced gastric cancer patients, and the prognosis for them is poor [3].

Cancer treatment used to use chemotherapy, radiotherapy and different kinds of enzyme depressors, but for some cancer cells developed the drug-fast, this is knotty for researchers. These years as immune escape mechanism clarified scientists began to look for immune checkpoint inhibitors especially for their high efficiency. Immune checkpoint is a mechanism that controls

immune response and stops damage of human tissue as soon as possible. Most times clinical block PD-1, PD-L1, CTLA-4 receptors which are common immune escape checkpoint receptors. This therapy helps to solve some cancers that chemotherapy is useless to. PD-1 expressed on T cells and primary B cells, PD-L1 and PD-L2 are the ligands of PD-1, PD-L1 expressed on APCs and other immune-privileged site of human bodies while PD-L2 is on activated macrophages and DC cells. PD-1 inhibitor block the combination between PD-1 and PD-L1 receptor on the T cells reactivated T cells to improve body immune response increase the number of NK cells B cells and release cytokines in the same time. CTLA-4 mainly expressed on activated T cells, act on ITAM on CD3 destroy the original biochemical signals works for T cell activation in order to suppress T cells activation essentially.

Except good news for cancer patient ICT has its side effects some mechanisms still remain unknown which makes it hard to put it in clinical trials for many patients. Scientists are facing three main problems for ICIs, the first one is severe immune-related adverse events (irAEs) affect most of our organs, irAEs are frequently seen in our gut and cutaneous also sometime with has hematologic toxicities, even neurologic diseases like myasthenia gravis, encephalitis/ meningitis, inflammatory polyradiculopathies such as Guillain-Barre syndrome, and peripheral neuropathy. Secondly, immune therapy only works on approximately 5-6% of patients because of gene mutation like JAK1, JAK2 gene mutated patients don't react to pembrolizumab, or some patients have metabolic imbalance which makes ICIs unable to take effects. This year researchers found that some patients even got new immunosuppressive cells in their bodies deactivated ICIs. Scientists want to find new therapies to solve the problems found by now, one of them is combined with some other molecules to improve the result. PD-1/PD-L1 therapy combine with mitogen-activated protein kinase (MAPK)-targeted therapy can upregulate immune therapies work and significantly improve the efficiency by multiaspect elevate immune system. Gut microbiota with ICIs is another new angle for improvement, commensal Bifidobacterium is commonly seen in our gastrointestinal tract and surprisingly enhance the treatment by improving tumor-specific immune responses. Using costimulate factors like CD137, OX40, CD40, ICOS, GITR and CD27 is also helpful. A specific type of CD137xPD-L1 bispecific antibody, MCLA-145 is proposed. Even under supressive conditions or sub-nanomolar concentrations, MCLA-145 still can activate T cells promote T cell priming, differentiation and immune memory recall [4]. Having a connection with CD8 T cells to increase in tumor microenvironment, also greatly reduced the side effects.

This review focused on three specific kinds of cancer which by using ICT has significantly improved the results of the patients, and problems that need to be solved with this one, some improvements made by scientists.

2. ICT for Non-Small-Cell Lung Cancer patients

2.1. The overview of Non-Small-Cell Lung Cancer

Lung cancer remains the deadliest form of cancer among males in the world, in 2020 11.4% of people around the world got it, and over 1.79 million of people died made it be the top one of malignant tumors. Non-Small-Cell Lung Cancer (NSCLC), is a kind of lung cancer with a higher prevalence and lower cure rate, it is the most common type of lung cancer, over 80% of all lung cancers. NSCLC can be divided into 5 groups, adenocarcinoma is the most common type starting from bronchial mucosa, Bronchial gland or alveolar epithelium most likely to grow outside of the bronchial then cause a 2-4 cm lump in the lung. Squamous cell carcinoma (SCC) is also frequently see in smokers' central airway end up with some significant obstructions caused dyspnea. The other 3 types are much hard to see in NSCLC patients. NSCLC usually happen because the interaction between environmental factors and Gene mutations almost 85-90% of patients had long term smoking history, others like air pollution, occupational carcinogenesis, ionizing radiation, lung disease recurrent infection even foods are more and more likely to see with NSCLC patients. Commonly

symptoms are repeatedly continuously coughing sometime with bloody sputum, dyspnea and some patients a fever. NSCLC metastasizing to other organs may cause serious problems.

2.2. The mechinism of PD-1/PD-L1 blockers

Physiologically, PD-1/PD-L1 pathway transmits negative messages to activated T cells in order to down-regulate the level of immune system response, as PD-L1 is a ligand normally expressed on APCs and other cells in the immune-privileged sites of human bodies. Pathologically, cancer cells also express it to invade the immune system causing immune escape and T cells incapacitation. Pembrolizumab works by blocking this pathway so that immune response can be theoretically unlimited and has more possibility to recognize and kill cancer cells.

2.3. ICT with NSCLC patients

According to different stages of this disease scientists drew up plans to help the patients, currently doctors have chemotherapy, radiotherapy, surgery, interventional therapy and traditional Chinese medicines. And for different kinds doctors have different solutions, for example for gene mutated patients with acute lung cancer targeted therapy is the best chance for them. But most patients don't have specific target genes for medicines to work,which drives researchers to find new ways like ICIs therapies for them. FDA has proved PD-1/PD-L1 therapies now for cancer patients, the first two ICIs for advanced NSCLC were approved in 2015 which were pembrolizumab and nivolumab. Patients who haven't receive treatment before or have advanced NSCLC, pembrolizumab extend the long-term OS, 5-year OS rates for them are improved to 23.2% and 15.5% [5]. As we can see in this graph ICI therapies have significantly changed the situation of NSCLC patients. This soon became the first-line for advanced and metastasis NSCLC.

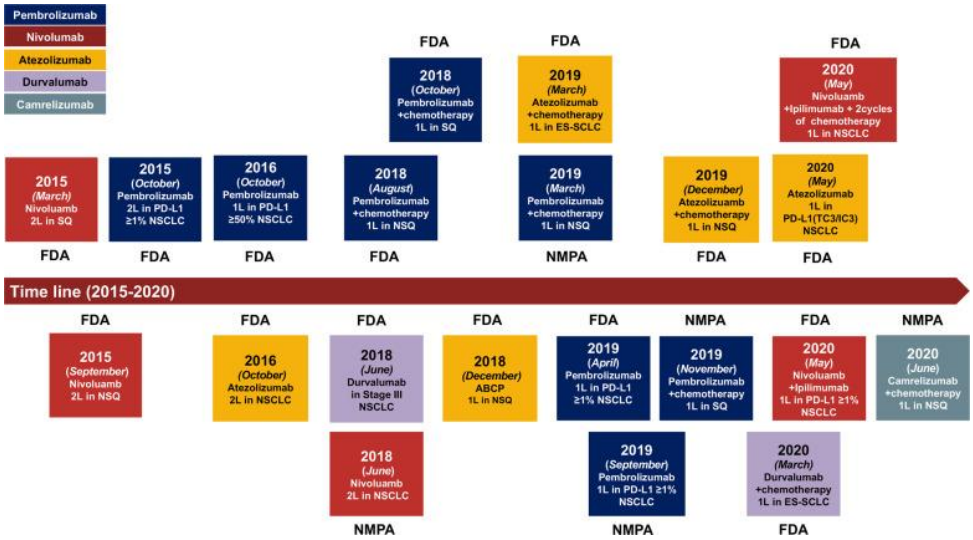

Figure 1. ICIs in Lung cancer treatment [5].

There still are some limitation because it works better only when patients have high expression of PD-L1 ligands, best choice is combined this therapy with chemotherapy and other medicine can highly improve the result of the patients.

In normal circumstances researchers believe that ICIs combined with each other may significantly improve the effects of therapies in the mean-time this may also lead to more side effects, by comparing every single one mOS, scientists want to make sure that combination therapy can help with advanced NSCLC patients. now ICT combine with some other therapies give patients more options, like single ICI; double ICIs (DICIs); ICI + chemotherapy (CT); DICIs+ CT [7]. In general, DICI+CT group has better mOS for almost any kind of patient whether man or woman, smoking or not. Researchers still need to find ways to induce the side effects of blocking CTLA-4, but DICI will be a good one for patients in the future as scientists can find new ways to control or eliminate the side effects.

In conclusion, by successfully introducing ICI therapies into NSCLC and other metastatic lung cancers had completely change the prospect of the patients with these refractory diseases, also this therapy has long-distance reactions and long-term survival in some cases.

3. Triple-negative breast cancer with ICIs

3.1. Basic knowledge of Triple-negative breast cancer

Breast cancer is another important kind of cancer, in 2020 world health organization confirmed that the number of people who had breast cancer had gone beyond the number of lung cancer patients, becoming the top morbidity cancer over all. According to GLOBO CAN 2020, new cases of breast cancer increased to 34,65,951 and deaths were reported[6].This leads more attention to it, breast cancer occurs because malignant proliferation of mammary epithelial cells cause breast lump, nipple discharge, and enlarged axillary nodes further issues contain metastasis and organ lesions. Breast cancer can be divided into many groups by different kinds of standards of classification. Triple-negative breast cancer (TNBC) is a peculiar one that pathological examination shows PR, ER, HER-2 are negative these characters makes it hard to react to endocrinotherapy and target therapy also prognosis is worse than other kinds of breast cancers. TNBC is likely to see in women under 50 years old. Histological features include significant lymphocyte infiltration, central necrosis, pushing tumor borders, and fibrosis [8]. TNBC is a special type easily metastasize at the early stage and spreading all over the patient bodies, because of this it is more likely to relapse over time.

3.2. Appropriate Triple-negative breast cancer therapies

Unexpectedly, the likelihood of TNBC patients to benefit from ICT is higher than other kinds of breast cancer because the high immunogenicity, abundant of TILs and more PD-L1 ligands are expressed [9]. Nowadays even though chemotherapy still is the first line treatment for TNBC patients, but now doctors also use chemotherapy as a mother therapy for patients and add more new helpful therapies to enhance the chance of saving patients [10]. Normal technological process is using chemotherapy first then doing surgery. But in some situation surgery is not allowed for some metastasis or in late-stage cancers. Scientists think ICI therapies maybe the best choice for many patients. Combining nanoparticle albumin-bound (nab)-paclitaxel with Atezolizumab (anti-PD-L1 antibody) was confirmed as a first-line therapy in 2019[10]. Atezolizumab plays a part in tumor microenvironment (TME), reduce the suppressor molecules cause anti-tumor T cells to increase. But this better result only found in patients with high expression of PD-L1 while others seem to be useless. ICIs generally have strong tolerance with TNBC patients, immune-related adverse events(irAEs) are less and normally milder.

Because off targets happen constantly, researchers try actionable biomarkers combine with ICIs in order to improve the therapy. Clinical trials based on combination findings of various targeting agents and anti-PD-1/PD-L1 mAbs for the propose of upmost the effectiveness of the treatment, for patients only response to ICIs(metastatic TNBC patients) this therapy can work as monotherapy[11]. An important factor for wound healing and tissue repair, inflammation and angiogenesis called Platelet-derived growth factor receptor β (PDGFRβ) combine with ICIs can restrain this therapy and suppress tumor growth. [12]. This new combination group result in a remarkably stronger reduction of cell growth (50% inhibition), in comparison to the single anti-PD-L1 antibody or anti-PDGFRβ aptamer [13].

Except for PD-L1 ligands researchers also identified that an anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) monoclonal antibody can improve cancer therapy by combine with RNA vaccines. In this figure anti-CTLA-4 block the combination between B7 and CTLA-4 let T cells sustainingly activate to enhance the ability in killing cancer cells.

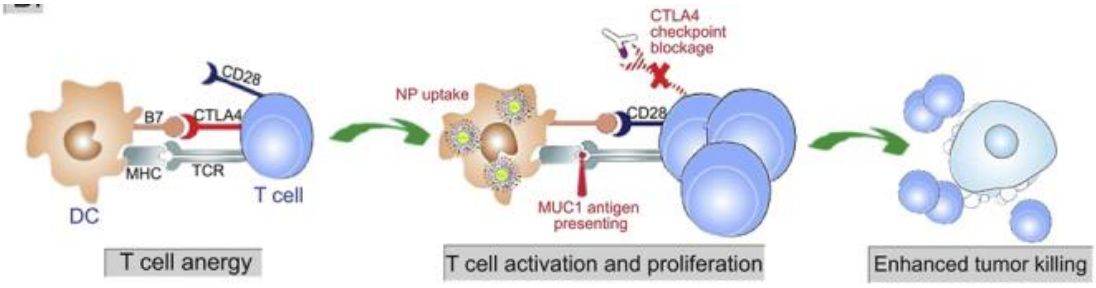

Figure 2. How CTLA-4 work [14].

In order to figue out how dose CTLA-4 enhance the work of RNA vaccine. Doctors inject the NP-based RNA vaccine containing MUC1 encoding RNA sequences, this MUC1 vaccine induce antigen-specific antitumor immunity. In the same time it also lead CTLA-4 over expressed, so by using ICIs this combination therapy can work much better. As this graph shows, MUC1 vaccine group and anti-CTLA-4 antibody group both have strong antitumor activity. By combining these two therapies together improve the ability of the MUC1 vaccine [14].

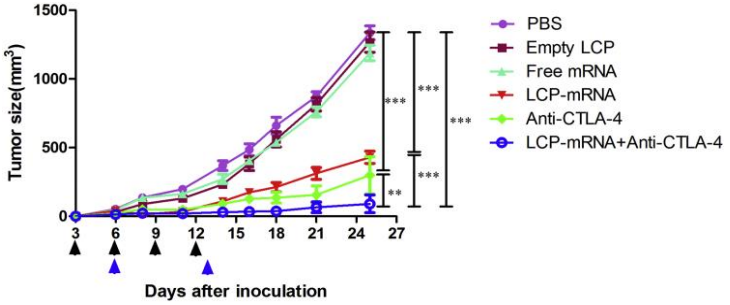

Figure 3. The result of combination therapy [14].

Anti-CTLA-4 antibodies strengthen the abilities of T cells and improve the effects of the vaccine. This big progress suggests that ICIs can not only work alone or combine with chemotherapy, it also other ways in killing cancer cells, that means this therapy didn't just change the situation of some cancer treatment it also help to change some therapies because it has high pertinence with some specific kinds of receptors help scientists to develop new treatments to cover the shortage or to amend some existing therapies.

Generally speaking, ICI therapies have changed the mOS and five-year survival rate of most TNBC patients, except some don't react to the therapy it has great effects for others, in the future researchers try to find more receptors or ligands in order to enlarge the range of cancer patients,it is important to see that ICI therapy is vital for some patients with unique kinds of cancers and for some of them this is the only useful way to do.

4. ICT and HER2-positive advanced gastric cancer

4.1. HER2-positive advanced gastric cancer

Gastric cancer is the fifth most common cancer in the world and the third-leading cause of cancer-related death [15]. Especially in Asian countries like China, Japan and Korea from 20 years ago the incidence rate and death rate have rosen steadily. Studies found that patients with gastric cancer early symtoms including regurgitation of gastric acid, heartburn and epigastric discomfort are quite same to the symptoms caused by gastritus orgastric ulcer, this leads to most patients only get to terminal stage of cancer then seek for medical advice. Gastric cancer can be divided into two diffirent groups the most common type for olds is intestinal type of gastric cancer, for this kind of person timely cure previous gastric diseases is important for them. Another type is more often see in yough people the diffuse gastric cancer this kind is high malignant and helluva. Except pathological classification, gastric cancer also can be divided into 4 subtypes, over 50% of gastric cancer patients are the

chromosomally unstable tumors (CIN) subtype. CIN often is connected with amplification of receptor tyrosine kinases, including HER2 [23,24] HER2-positive advanced gastric cancer patients are hard to find appropppriate therapy, and the prognosis for them is poor.

4.2. The ICT for HER2-positive advanced gastric cancer patients

However now, pembrolizumab has prospective antineoplastic activity for advanced gastric or gastroesophageal junction adenocarcinoma patients and this makes doctors more confident about HER2-positive advanced gastric cancer patients' future. Pembrolizumab Combine with trastuzumab and chemotherapy may have more advantage on advanced HER2-positive gastric cancer patients [16]. Scientists carried out experiments to explore whether pembrolizumab is the best choise for gastric cancer patients. They use contrast experiment to evaluate the efficiancy of pembrolizumab therapy with paclitaxel in patients with advanced gastric cancer, they concluded that although the mOS of the patients are almost the same but pembrolizumab shows longer reaction time than paclitaxel and has a greater survival benefit. These datas shows pembrolizumab maybe a better chiose for advanced gastric cancer patients. Although now pembrolizumab therapy is still in inspection, but combine with chemotherapy or trastuzumab can let the result become better.

5. Future developments of ICT

5.1. Shortcoming of ICT

Although ICIs seem to nice to cancer patients, still just like any other treatment it has its own problems. For example, now immune therapies still cann't carry out for many patients, because immune therapies need patients own immune system to work better, but for many of them their immune system are hard to response to the therapies, others may develop the drug resistance in short period of time.

5.2. Combination therapies to improve

To help with the drug-fast problem, researchers believe that co-treatment may reacts better, PD-1/PD-L1 therapy combine with mitogen-activated protein kinase (MAPK)-targeted therapy can upregulating ICIs work and significantly improve the efficiency by multiaspect elevate immune system. MAPKi can promote macrophage division and cause IFN-γ and abundant of inflammatory cytokines secretion. In the same time by increasing the number of $CD8^{+}$T cells can highly improve the whole function of the immune system. After combine with anti-PD-1/PD-L1 therapy this co-treatment can suppress therapeutic resistance.

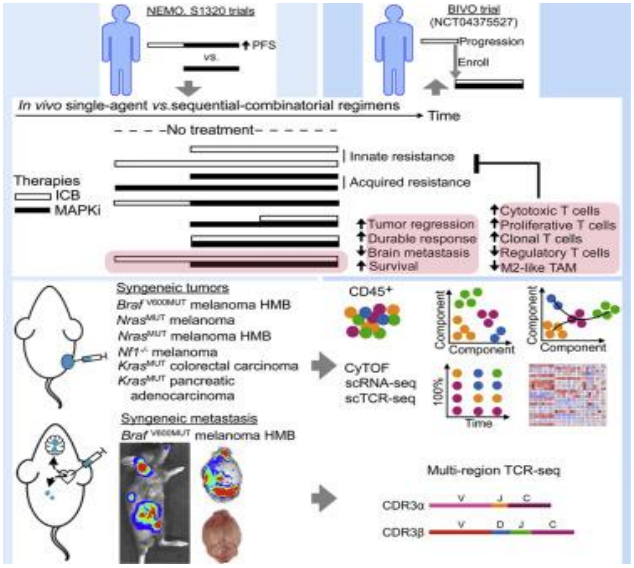

Figure 4. The mechinism ofMAPKi [17].

This combination therapy can highly reduce the drug resistance of ICIs, make progress for better achevments.

A new human CD137xPD-L1 bispecific antibody, MCLA-145 is identified recently, it can activate both CD137 and PD-L1 simultaneously. Because expande the range of reacting receptors, using CD137 receptors on activated T cells and NK cells scientists can provide a co-stimulate signal without CD28, this can enhance the production, proliferation, survival, effector function and immune memory module. CD137 plays an important role in the tumor microenvironment, act as tumor specific CTLs' marker and is co-expressed with PD-1[19,20]. As CD137 activated, the tumor-specific CTLs can be promoted and increased. CD137 ligands on the tumor cells increasing also has benefits on tumor elimination [21,18]. T cells are activated and increased sharply because of MCLA-145, it also leads to T cells differentiation and memory recall responses [18]

In daily life gut microbiota plays an important role in digestion and absorb, these bacteria also reinforce the work of ICIs. Except affect the whole immune system they also adjust local inflammation. Researchers concluded that in patients with higher response of ICI therapy there are some specific typies of gut microbiota like A. muciniphil and Ruminococcus spp. Doctors want to comfirm that whether have these bacteria have a connection with ICIs response, they inject the faeces of ICIs responsers into unresponsive patients and obviously it works. This gives researchers hope, in the future combine gut microbiota with ICIs to do moreclinical trials will change the unresponse situation.

6. Conclusions

In conclution, cancer is deadly even though thechnique has improved a lot for some specific type of cancer and for some specific patients, available therapies now are helpless for their living. Meanwhile, doctors emphasize the living quality of the cancer patients after their treatments now, so for study on cancer therapies scientists are not only focus on the result also cansider the side effects and living quality. Cancer treatment need to be more accurate only in this way can it be more useful but scientists need to focus on generalized in the same time. Nowadays ICT is a crucial therapy for some patients it change some cancer patients lives remarkablely, it has completely different mechanism with other therapies, activated peatients own immune system to rebuild the ability of killing cancer cells and even strengthen the immune system itself to deal with the unself parts. For patients with NSCLC, normal therapies have poor mOS and immune therapy works much better for them, and TNBC patients because lack of the expression of PR, ER, HER-2 troubles doctors a lot so by ICT they can reach a better result, and for HER2-positive advanced gastric cancer this therapy shows significant work. In these cancers normal therapies may have more limitation by ICT more problems can be solved. Although ICT has some defects that limit the range of application scientist are using more combination and other receptors to achieve a outstanding ending. Researchers hope to find more ICIs and other combination therapies in the future may achieve individual-baced treatment for every patient, this can enhance the ability of every therapy and get a better result for patients. For cancer therapy there still has a large scope for researchers to find out.

References

[1] E.L.Kwak,Y.-J.-J.Bang, D.R.Camidge, etal. Anaplasticlym phomakinase inhibitionin non–small-cell lung cancer N.Engl.J.Med., 363(2010), pp.1693-1703

[2] The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 513(7517), 202–209 (2014).

[3] Chung HC, Bang YJ, S Fuchs C, Qin SK, Satoh T, Shitara K, Tabernero J, Van Cutsem E, Alsina M, Cao ZA, Lu J, Bhagia P, Shih CS, Janjigian YY. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. Future Oncol. 2021 Feb; 17(5): 491-501.

[4] Geuijen C, Tacken P, Wang LC, Klooster R, van Loo PF, Zhou J, Mondal A, Liu YB, Kramer A, Condamine T, Volgina A, Hendriks LJA, van der Maaden H, Rovers E, Engels S, Fransen F, den Blanken-Smit R, Zondag-van der Zande V, Basmeleh A, Bartelink W, Kulkarni A, Marissen W, Huang CY, Hall L, Harvey S, Kim S, Martinez M, O'Brien S, Moon E, Albelda S, Kanellopoulou C, Stewart S, Nastri H, Bakker ABH, Scherle P, Logtenberg T, Hollis G, de Kruif J, Huber R, Mayes PA, Throsby M. A human CD137×PD-L1 bispecific antibody promotes anti-tumor immunity via context-dependent T cell costimulation and checkpoint blockade. Nat Commun. 2021 Jul 21;12(1):4445.

[5] Zhou F, Qiao M, Zhou C. The cutting-edge progress of immune-checkpoint blockade in lung cancer. Cellular & Molecular Immunology. 2021 Feb;18(2):279-293.

[6] Manjunath M, Choudhary B. Triple-negative breast cancer: A run-through of features, classification and current therapies. Oncology Letters. 2021 Jul;22(1):512.

[7] Xu Q, Zhang X, Huang M, et al. Comparison of Efficacy and Safety of Single and Double Immune Checkpoint Inhibitor-Based First-Line Treatments for Advanced Driver-Gene Wild-Type Non-Small Cell Lung Cancer: A Systematic Review and Network Meta-Analysis. Frontiers in Immunology. 2021;12:731546.

[8] Marotti JD, de Abreu FB, Wells WA, Tsongalis GJ. Triple-negative breast cancer: Next-generation sequencing for target identification. Am J Pathol. 2017; 187:2133–2138.

[9] Kwapisz D. Pembrolizumab and atezolizumab in triple-negative breast cancer. Cancer Immunol Immunother. 2021 Mar;70(3):607-617.

[10] Won KA, Spruck C. Triple-negative breast cancer therapy: Current and future perspectives (Review). International Journal of Oncology. 2020 Dec;57(6):1245-1261.

[11] Page DB, Bear H, Prabhakaran S, Gatti-Mays ME, Thomas A, Cobain E, et al. Two may be better than one: PD-1/PD-L1 blockade combination approaches in metastatic breast cancer. NPJ Breast Cancer. 2019; 5: 34.

[12] Fredriksson L, Li H, Eriksson U. The PDGF family: four gene products form five dimeric isoforms. Cytokine Growth Factor Rev. 2004; 15: 197–204.

[13] Camorani S, Passariello M, Agnello L, et al. Aptamer targeted therapy potentiates immune checkpoint blockade in triple-negative breast cancer. Journal of Experimental & Clinical Cancer Research: CR. 2020 Sep;39(1):180. DOI: 10.1186/s13046-020-01694-9.

[14] Liu L, Wang Y, Miao L, et al. Combination Immunotherapy of MUC1 mRNA Nano-vaccine and CTLA-4 Blockade Effectively Inhibits Growth of Triple Negative Breast Cancer. Molecular Therapy: The Journal of the American Society of Gene Therapy. 2018 Jan;26(1):45-55. DOI: 10.1016/j.ymthe.2017.10.020.

[15] BrayF, FerlayJ, SoerjomataramI, SiegelRL, TorreLA, JemalA. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J. Clin. 68(6), 394–424 (2018).

[16] Chung HC, Bang YJ, S Fuchs C, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. Future Oncology (London, England). 2021 Feb;17(5):491-501.

[17] Wang Y, Liu S, Yang Z, Algazi AP, Lomeli SH, Wang Y, Othus M, Hong A, Wang X, Randolph CE, Jones AM, Bosenberg MW, Byrum SD, Tackett AJ, Lopez H, Yates C, Solit DB, Ribas A, Piva M, Moriceau G, Lo RS. Anti-PD-1/L1 lead-in before MAPK inhibitor combination maximizes antitumor immunity and efficacy. Cancer Cell. 2021 Oct 11;39(10):1375-1387.e6.

[18] Geuijen C, Tacken P, Wang LC, et al. A human CD137×PD-L1 bispecific antibody promotes anti-tumor immunity via context-dependent T cell costimulation and checkpoint blockade. Nature Communications. 2021 Jul;12(1):4445.

[19] Gros A, et al. PD-1 identifies the patient-specific CD8+ tumor-reactive repertoire infiltrating human tumors. J. Clin. Invest. 2014; 124:2246–2259.

[20] Ye, Q. et al. CD137 accurately identifies and enriches for naturally occurring tumor-reactive T cells in tumor. Clin. Cancer Res.10.1158/1078-0432.CCR-13-0945 (2014).

[21] Melero I, et al. Amplification of tumor immunity by gene transfer of the co-stimulatory 4-1BB ligand: synergy with the CD28 co-stimulatory pathway. Eur. J. Immunol. 1998; 28: 1116–1121.

[22] Ye Z, et al. Gene therapy for cancer using single-chain Fv fragments specific for 4-1BB. Nat. Med. 2002.

[23] The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 513(7517), 202–209 (2014).

[24] Van Cutsem E, Bang YJ, Feng-Yi Fet al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 18(3), 476–484 (2015).