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Targeting Immunocheckpoint In The Tumor Microenvironment And Cancer Immunotherapy

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ABSTRACT

The immune system can detect and eliminate the cancer immune editingand immune surveillance inhibits the growth and development of tumor by the recognition and rejection of abnormal cells. Variety of cancers are observed, immunotherapy (isanov, 2018) has emerged as an effective and most promising treatment that are designed to target the immune system itself by triggering an effective immune attack against the cancer cells. Immune checkpoints inhibitors (ICIs) targets the co-inhibitory signals that block effective cytotoxic T lymphocyte activation. The co-inhibitory receptor has come forefront in cancer. Antigen presenting cells (APCs) in the tumor include B cells, dendritic cells (DCs) and macrophages, the DCs express major histocompatibility complex (MHC) 1&2 for the activation and differentiation of CD8 and CD4 T cells which produces the co-stimulatory molecule. The tumor microenvironment (TME) (Ahmed, 2014) is the route for immune escape which is considered one of the hallmark of cancerthe tumor cells interact with the surrounding cells through the lymphatic and circulating system to influence the progression and development of cancer and it also plays a critical role by facilitating and stimulating uncontrolled cell proliferation.

1. Introduction

Immune checkpoints or co-inhibitory receptors (menzel, 2020) plays a critical role in the maintenance of immune homeostasis their expression on regulatory T cells and effector T cells and they are important for maintaining self-tolerance and protect the tissue from damage. The expression of the immune checkpoint proteins can be dysregulated by the tumor which is an important mechanism of tumor resistance. The T cell receptor is regulated by the balance between co-stimulatory and co-inhibitory signals (i.e. immune checkpoints). ICIs (Centanni, 2019) have greatly improved the prognosis of melanoma they are the group of regulatory surface protein within the immune system that prevent autoimmune response, it's also prevents the inhibitory signals in T cells and restores the immune activity of the T cells. Immune regulation occurs locally within the tumor leading to the suppressed anti-tumor response. The anti-tumor activity within the TME can suppress variety of tumor infiltrating leucocytes which includes myeloid derived suppressor cell, regulatory T cells and macrophages etc. it also suppresses the effective immunity secretion of cytokines such as TGF-β, IL-10 and also the expression of inhibitory receptor (isanov, 2018) such as PD-1, CTLA-4. Monoclonal antibodies have drastically changed the clinical care of cancer. Anti CTLA4 antibody was approved by the FDA for anticancer treatment the advance development of immunotherapies based on the immune checkpoints inhibitors (ICIs) (boas, 2016)leads to the beginning of a new era in the cancer treatment.

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Immune checkpoint blockade (Topalian, 2015) is becoming recently one the most successful cancer immunotherapies. Emerging novel immune checkpoints is the recent hot topic. New research development and studies have identified several immune checkpoints like CTLA4, PD1, LAG3, TIM3, TIGIT, and VISTA and so on. Cancer therapy (shrager, 2020) has shown promise in various type of cancer. The clinical care of cancer have drastically changed by the immune checkpoint inhibitors ICIs). Majority of the immune checkpoints are initiated by the receptor ligand interaction that can be blocked by the antibodies. Tumor microenvironment (TME) plays a major role in the anti-cancer immunity, clinical findings with immune checkpoints and blockers have broad and diverse opportunities to increase anti-tumor activity.

IMMUNE CHECKPPOINTS

T cell activation regulated by the co-inhibitors and co-stimulators (attanasio, 2016)and the negative regulator of T cell immunity is called immune checkpoints (Sharma, 2015). The T cell activation depends on different signals i.e. the interaction between the major histocompatibility complexes (MHC) on the surface of the antigen presenting cells (APCs) which converts the extracellular binding events to the intracellular signaling leads to the T cell proliferation ,cytokine production and the cytolytic activities. The T cell receptor associated CD3 subunit gets phosphorylated and replenish and activate the kinase ZAP70 which is the membrane adaptor LAT which triggers the ca^{2+} signaling and MAPK signaling to activate the T cell transcriptional program. The T cell receptor also requires an antigen independent co-signaling molecule. If the MHC and T cell receptor binding is highly trained by the co-stimulatory receptor it will allow the proliferation of T cell towards specific antigen the binding occur by the engagement of the co-inhibitory receptors which suppresses the T cell activation (iwahori, 2019). The main aim of the co-inhibitors is to reduce damage to normal tissue and prevent no longer desired autoimmunity.

The immune checkpoints do not directly kill the tumor cells but they control the ability of the host immune system to heighten the antitumor activity. Some cancer generate inhibitory ligand which bind to co-inhibitory receptor molecule. Apart from CTLA4, PD1 (Bai, 2017) is the novel immune check point molecule on the T cells. These two checkpoints are widely recognized inhibitory checkpoint pathway these receptors (shi, 2020) negatively regulate the T cell activation. So far number of inhibitory immune receptor have been identified such as PD1, CTLA4, LAG3, TIM3, BTLA, TIGIT (Anderson, 2016) these are called as immune checkpoints which act as a controlling access from one point to another or gateway of immune response.The immune checkpoints including PD-1 and CTLA-4 expressed on the activated T cells which leads to the inhibition of the T cell activation their interactions are blocked by the release of the cytokine and cytotoxic granules through targeting tumor cell using the monoclonal antibodies. Monoclonal antibodies (al e. , 2019) blocks the immune checkpoints. The function of the immune checkpoint inhibitor is to prevent the T cell from the exhaustion. CTLA-4 is one of the major receptor involved in the immune checkpoint it shows the anti-cancer effect which leads to the development of the first immune checkpoint inhibitor called ipilimumab an anti-CTLA-4 monoclonal antibody which further leads to the development of more efficacious immune checkpoint inhibitors like nivolumab, pembrolizumab are the PD-1 inhibitors and atezolizumab PD-L1 inhibitor. Pembrolizumab and nivolumab have shown promising results in the melanoma

and non-small cell lung carcinoma (NSCLC) they are currently under the phase 4 trial and also for treating various malignancies. Various immune responses are created in the tumor microenvironment through the complex factor regulated by the antitumor immunity. There are various agent that act on the anti-tumor immune system which includes small molecule, tumor vaccine, monoclonal antibodies, viral or cellular therapies but the most frequently utilized immunotherapies are immune checkpoint inhibitors. Some of the United States food and drug administration (FDA) approved immune checkpoint inhibitors are nivolumab and pembrolizumab (inhibitor of PD-1), atezolizumab (hida, 2018), durvalumab, Avelumab (inhibitors of PD-L1), Ipilimumab (inhibitor of CTLA-4) (al s.-f. e., 2016) these checkpoints inhibitors have much clinical pharmacological features as well as the pharmacometric approaches which is used to support the clinical development and regulatory approval (Takehiro Otoshi, Cancers 2019, 11, 935). The link between the auto-immunity and anti-tumor effect is obtained by the immune checkpoint inhibitors.

MECHANISM OF IMMUNE CHECKPOINT SIGNALLING PATHWAY

PD1 signaling:

Programmed cell death protein 1 (PD1) is a polypeptide Trans membrane protein that include both intracellular and extracellular domain the interaction of PD1/PD-L1 is essential for the development of immune tolerance and preventing the immune cells that can lead to the tissue destruction and autoimmunity. PD-L1 is the first functionally characterized ligand of co-inhibitory programmed death receptor it is otherwise called as B7-H11 or CD274. The function of PD-L1 depends on binding with PD1 (CD 279),PD-L1 induces the inhibitory signal and expressed on T cells. PD1 signaling trigger the PD-L1 and PD-L2 ligand they are expressed on the surface of the antigen presenting cells (APCs). (sasikumar, 2018)

PD-L1 can help tumor cell evade the immune system when it is expressed in abundance this occurs when the activated T cells releases interferon gamma which leading to the expression of PD-L1 on both tumor infiltrating immune cell and tumor cell. PD-L1 interfere the anticancer immune response by binding to its receptor. B7-1 and PD1 on the surface of the activated T cell which further deactivating the T cells cytotoxic activity. T cells also become deactivated when PD-L1 (zatloukalova, 2016) expressed on tumor infiltrating immune cells bind to PD1 or B7-1. T cell have receptor that allow them to recognize tumor. Cancer cells can prevent the elimination by turning on PD-1 and B7-1 blocking PD-L1 from binding PD-1 and B7-1 which prevents PD-L1 from communicating with them through this process T cell able to responds and kill cancer cells. PD-1 becomes phosphorylated to deliver inhibitory function. The cytoplasmic domain of PD-1 contain immune receptor tyrosine based inhibition motif (ITIM) and immune receptor tyrosine based switch motif (ITSM) they contribute PD-1 mediated T cell inhibition.
PD-1 becomes phosphorylated at ITIM and ITSM then binds to the Src homology 2(SH2) domain of SH2 containing phosphatase 2 (SHP2) initiating T cell activation. Mutation of tyrosine ITSM but not ITIM evades the inhibitory function of PD-1 phosphorylation and also ITSM recruits the SHP2 to dephosphorylate the key signaling molecule and decrease the activation level (al Q. e., 2019). Recent studies suggested that ITIM also plays an important role in converting SHP2 from inactive to active form. SAP (signaling lymphatic activation molecule associated protein) block the SHP2 interaction and inhibits PD-1 signaling. (Kurzrock, 2015)

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CTLA-4 signaling:
Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is the inhibitory receptor and the homologue of CD28 expressed on thymic Tregs. The cell activation occurs through the binding of the peptide major histocompatibility complex (MHC) and CD80/86 on the antigen presenting cells (APCs) with the TCR and CD28 on the T cells which leads to the T cell activation.

When the CD28 and CTLA-4 binds to the ligand CD80/86 resulting in the inhibitory signal that are the basic inhibition. Now the CTLA-4 compete CD28 to bind with CD80/86 which resulting in the no CD28 co-stimulation this is known as intrinsic pathway of CTLA-4 signaling. (al Q. e., 2019)

CTLA-4 binds to the CD80/86 using indoleamine 2,dioxygenase (IDO) production in the antigen presenting cells (APCs) that leads to the activation of naïve T cells by the tryptophan starvation further the induction of cytokine occur through CTLA-4 (lambertini, 2019) where it binds to the CD80/86 which stimulates the T cell to produce TGF-β which binds with the receptor on the antigen presenting cells(APCs) and T cells leading to the inhibition.CTLA-4 reduces the availability of CD80/86 which restrict the ligand availability. CTLA-4 captures the ligand from APCs by binding CD80/86 ligand and breaks it off in the APCs the complex tended is consumed by the T cell hence leaving no CD80/86 for CD 28 to bind to it is known as the extrinsic pathway of CTLA-4 signaling.

LAG-3 signaling:
Lymphocyte activation gene-3 (LAG-3) (Solinas, 2019)structurally resembles the CD4 co-receptor and it is identified as the ligand of MHC-2 with high affinity than CD4,it is up regulated on activation of CD4+ and CD8+ T cells and the subset of natural killer cells(NK cells). LSECtin a member of DC-SIGN family is another ligand for LAG-3 which is expressed in the liver and on many tumors. LSECtin and galectin-3 are the carbohydrate binding protein they bind to LAG-3 and suppress T cell function in the tumor microenvironment (TME). LAG-3 expressed on the CD4+ T cells have the regulatory function and it is expressed on both induces CD4+, FOXP3+, Treg(iTreg) cells and activated natural Treg(n Treg). The inhibitory function of LAG-3 in CD8+ T cells does not involve MHC-2 but other ligand might exist.

LAG-3 signaling plays (Anderson, 2016) an important role in Tcells where Tcells are associated with CD3, hence the crosslinking of LAG-3 with CD3 inhibits the T cell proliferation and cytokine production. Fibrinogen like protein (FGL1) was identified as the new ligand for LAG-3 which is released into blood at low level from the liver blocking the interaction between FGL1 and LAG-3 enhance the anti-tumor function of the T cell. The LAG-3 cytoplasmic tail is unique among all the immune receptor it contain 3 region conserved between human and mouse they are serine-phosphorylation site, unique KIEELE motif and glutamic acid proline EP repeats. KIEELE contain the essential inhibitory function of LAG-3 (al Q. e., 2019) in effector CD4+ T cells. Through the Trans membrane metalloprotease i.e. Disintegrin and metalloproteinase domain containing protein ADAM10 and ADAM 17 by TCR signaling up regulate the cleavage activity of ADAM 10&17 protein by separate mechanism which in turns cleaves LAG-3 and allow the efficient function and proliferation of T cells.

TIM-3 signaling:

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T cell immunoglobulin-3 (TIM-3) (Anderson, 2016) are the cell surface molecule expressed on IFN-gamma producing CD4+ t helper 1(TH1) and CD8+ T cytotoxic 1 (TC1) T cells. The C type lectin galectin-9 is the ligand of TIM-3. The inhibitory function of the galectin-9 triggering TIM-3 which induces cell death in TIM3+ T helper 1 cells which induces cell death in TIM-3+ T helper 1 cell and it consists other 3 ligand namely high mobility group box 1(HMGB1), carcinoembryonic antigen cell adhesion molecule (CEACAM1) and non-protein ligand phosphatidyl-serine(PS). Similar to LAG-3, TIM-3 does not have signaling motif in its cytoplasmic tail but it contains five conserved tyrosine residue in which Y256 and Y263 are involved in the binding of BAT3 and can be phosphorylated by either Src kinase or ITK and P13K, P85, FYN and LCK to the c- terminal tail of TIM-3.
BAT3 bound to TIM-3 and block SH2 domain binding site in TIM-3 tail in the absence of ligand mediated TIM-3 signaling. The catalytic active form of LCK is recruited by the BAT-3 forming the intracellular molecular complex with TIM-3 which promotes the T-cell signaling. The release of BAT-3 from the TIM-3 tail occurs when the galectin-9 (soluble protein with 2 carbohydrate recognition domain) and CEACAM-1 bind to TIM-3 which leads to the phosphorylation of Y263 and Y256, the binding of SH2 domain containing Src kinase and subsequent regulation of TCR signaling promoting the TIM-3 mediated T cell inhibition. (al Q. e., 2019)

FYN is the key kinase to activate the phosphoprotein associated with glycospingolipid micro domain (PAG) recruit CSK to suppress Lck function there is a possibility of switch between TIM3-BAT3 and TIM3-FYN which leads to the inhibition of upstream TCR signaling and being permissive to TCR signaling by triggering the switch of TIM-3 function. Since both FYN and BAT-3 bind to the same domain in the TIM-3 cytoplasmic tail. The balance between FYN and BAT-3 bound to the TIM-3 intercellular tail is the key factor of TIM-3 function. Cytoplasmic tail of TIM-3 has potential interaction with multiple component of TCR complex. TIM-3 has many different ligand it is important to determine the different effects of ligand binding of BAT-3 versus FYN to TIM-3 tail which determines the effector T cell response to the function of TIM-3.

TIGIT signaling:
T cell immune receptor with Ig and ITIM domain (TIGIT) (al Q. e., 2019) is expressed on the activated memory T cells, NK cells and Treg cells. TIGIT is the receptor of Ig superfamily particularly expressed on the immune cell where it function as a co-inhibitory receptor. TIGIT has two ligand CD155 (PVR) and CD112 (PVRL2, NECTIN-2) expressed on T cells, antigen presenting cells and various hematopoietic cell type including tumor cells.

TIGIT binds to the ligand CD155, CD112 with high affinity. The recruitment of SHIP1 (SH2 domain containing inositol 5 phosphatase1) through the cytosolic adaptor GRB2 (growth factor receptor bound protein 2) by the process of phosphorylation induced by TIGIT through CD155 through LCK and FYN. Which blocks the signal transduction through P13K (phosphoinositide 3-kinase) and MAPK (mitogen-activated protein kinase) pathway results in the cell inhibition. TIGIT also binds with β-arrestin 2 which recruits SHP1 to limit NF-kβ (nuclear factor kβ) signaling the combined effect of these pathway leads to reduction of granule polarization, Nk cytotoxicity and cytokine secretin in NK cells.

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TIGIT blocks the activation of T cells, acquisition and proliferation function by targeting molecule in the TCR signaling pathway and also down regulate the component of TCR complex it also up regulate the receptor for IL-2, IL-7 and IL-15 which promote the survival of T cells. It also ensures the T cell are functionally inhibited but not deleted. (Anderson, 2016)

Similarities and differences between CTLA-4 and PD-1:
Both expressed by the activated T cells
Both are belong to B7 receptor family
The cytokine production, T cell proliferation and glucose metabolism are reduces by both and they also regulate the overlapping set of intracellular T cell signaling protein.

CTLA-4 (cytotoxic T lymphocyte associated protein- 4)	PD-1 (programmed cell death-1)
It is expressed by the T cell	It is expressed by the T cell and by the other immune cells
It affects the Treg functioning	The PD1 role on the Treg is unclear
It limits the T cell response early in an immune response and also in the lymphoid tissue	It limits T cell response later in an immune response in peripheral tissue
Ligands are expressed by the antigen presenting cells (APCs)	The ligands are expressed by the APCs and other immune cells and also expressed on non-immune cells and also including tumor cells.
It interfere less with T cell signaling pathway	It interfere more with T cell signaling pathway

Comparison of LAG-3, TIM-3, and TIGIT: (Anderson, 2016)

LAG-3 (lymphocyte activation gene-3)	TIM-3 (T cell immunoglobulin -3)	TIGIT (T cell immunoglobulin and ITIM domain)
The ligands are MHC-2 LSECtin	The ligands are HMGB1,galectin9, ceacam-1,phosphatidyl serine	The ligands are CD155 and CD 112
It is expressed on CD8+ dysfunctional T cells	Expression on cd8+ TC1 and dysfunctional T cells	Expressed on CD8+ and dysfunctional T cells
It is also expressed in CD4, Tr1, nTreg, iTreg	It is also expressed in CD8+,TH1,Tr1 and nTreg	It is also expressed in CD4, Tr1, n Treg

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The signaling motif KIEELE	The signaling motif tyrosine.	The signaling motif are IITL, ITLM.

MULTIPLE IMMUNE CHECKPOINT BLOCKADE:

The inhibition of lymphocyte activity and the induction of lymphocyte anergy have been associated with the inhibitory receptor (isanov, 2018)with including LAG-3 (also known as CD223), BTLA (also known as CD272), and TIM-3 (also known as HAVCr2) (Anderson, 2016). Most of these receptors are induced on T cell activation and highly expressed on the Treg cells. CTLA-4 and PD1 (al Q. e., 2019) have multiple potential mechanism of action these receptor have dual role in inhibitory effector immune response and blocking the effector immune response of the antibodies. The treatment with the combination based on the PD-1 pathway blockade including anti-CTLA-4 and with the other checkpoint inhibitors tyrosine kinase inhibitors, cancer vaccines etc. are undergoing clinical development in diverse types of cancer.PD1 and LAG-3 are co-expressed on the exhausted T cells and causes dual blockade of PD1 and LAG-3 leads to virus specific CD8+ T cells and tumor specific CD8+ T cells setting of chronic infection.TIM3 ligand I.e.galectin-9 (Anderson, 2016) is up regulated in various type of cancer which inhibits T helper cell response. TIM3 antibodies enhance the anti-tumor immunity. TIM3 and PD1 co-expressed the tumor specific CD8+ T cells leads to the dual blockade (Tang, 2021)of cytokine production and proliferation of T cell.BTLA is an inhibitory receptor on T cells herpes virus entry mediator (HVEM also known as TNFRSF14) expressed on certain tumor and also on tumor associated endothelial cell which is shown by the BTLA ligand. BTLA cells are inhibited by the ligand HVEM, the dual blockade of PD1and BTLA enhance antitumor immunity. The multiple checkpoints are co-expressed with the PD-1/PD-L1 in tumor. The PD-L1 expression in the TME its expression by the infiltrating immune cells and the presence of the CD8+ tumor-infiltrating lymphocytes and other factors in combination are more specific predictors for the clinical outcome. Anti-CTLA-4 mAb paved the way for the development of other drugs with efficacy evolution and toxicity management. Immune related adverse event (irAEs) a new category of side effects were characterized and recognized leading the development of early detection and management. IrAEs are associated with the inflammation in normal tissues. The checkpoint blockade guide us to incorporate the approach of more successful therapeutic combinations based on the direct anti-tumor effect which leads to the reduction of tumor burden and indirect immune-mediated anti-tumor effect were increases of the tumor immunogenicity, the complete understanding and characterization of the checkpoint blockade leads to the designing of more powerful immuno therapeutics and its related combinations (al Q. e., 2019).

TARGETING DRUGS AND ITS CLINICAL DEVELOPMENT OF CANCER IMMUNOTHERAPIES: (Sharma, 2015)

TARGET	DRUG	PHASE	CLINICAL DEVELOPMENT

TIGIT (Anderson, 2016) (TROPHY, 2017)	Nivolumab Atezolizumab pembrolizumab	1 and 2	Advance solid tumor

2. BIOMARKERS IN CANCER IMMUNOTHERAPY

The targetable availability of tumor specific antigen (TSA) is otherwise called as “neoantigen” (Schumacher, 2015) which is expressed on the tumor cells is the major limitation of cancer therapy (al e. , 2019). The clinical biomarker have relating pharmacogenomics, diagnostic and predictive value which will provide the greatest benefit from a treatment. The biomarker are solely depends upon the biological role of the tumor progression and transformation to malignant tumor. Neoantigens are the useful biomarker (Brennick, 2017) in response to cancer immunotherapies. It is considered that the neoantigens that exist in all type of tumor cells is called clonal neoantigen and the neoantigen which exist only in some tumor cell is called sub clonal neoantigen (Schumacher, 2015). The high degree of foreignness to cell which helps the immune cells to attack and eliminate the tumor cells is major and primary function of the neoantigen and the mutation in the protein coding region of the DNA is called neoantigen.

The tumor mutational burden (TMB) (al g. e., 2017) affects the immunogenic neoantigen that brings the specific T cells in response. TMB influences the response of cancer to the treatment it is one of the most important emerging biomarker in cancer immunotherapy. It has come with the better outcome in patients in the cancer immunotherapy with 21 different types of cancer. It is also a potential biomarker (menzel, 2020) for combination therapies (e.g. ipilimumab plus nivolumab) TMB is independent of PD-L1 expression (Kurzrock, 2015). TMB is calculated based on the next generation sequencing (NGS) technologies using whole exome sequencing by number of mutation per mega base. It is also an important biomarker for predicting the efficacy of the immune checkpoints inhibitor (ICIs). High TMB indicates that new neoantigens can be produced by the tumor cells to activate the T cells suppressed by the immune checkpoints (vinay, 2018). Another recent studies has suggested that the immune checkpoint ligand such as PD-1, PD-L1 and CTLA-4 (al a. e., 2018) are strongly expressed in the tumor microenvironment of mismatch pair-deficient malignancies, blockade of these checkpoints may be effective in the cancer with mismatch pair deficiency. The indoleamine 2, 3-dioxygenase (IOD_1) is an immune checkpoint protein which inhibits the T cells by promoting the catabolism of tryptophan it is related to T cell infiltration. The anti-tumor T cells can be suppressed by the myeloid derived suppressor cell (MDSCs) and Treg cells via IDO_1 promoting tumor immune evasion. IOD_1 causes the immune suppression and decreases the efficacy of the anti-PD-1 therapy, it also determines the predictive value in some tumor and used to arrange and define some cancers.it is considered as a good predictive biomarker (al Y. e., 2016) for the treatment of cancer and a new approach in the cancer immunotherapy (maciejko, 2017)

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TARGET	DRUG	CLINICAL DEVELOPMENT
PD-1/PD-L1 (maciejko, 2017) (Kurzrock, 2015) (Centanni, 2019) (hida, 2018)	Atezolimab	Phase3-bladder and lung cancer Phase2-kidney cancer
	Durvalumab	Phase2-glioblastoma, colorectal cancer Phase3-lung, head and neck cancer.
	pembrolizumab	Phase2-pancreatic, colorectal cancer and glioblastoma Phase3- lung, head and neck, gastric, and urothelial cancer. It is FDA approved for the treatment of melanoma Phase2-kidney cancer and hematologic malignancies
	pidilizumab	Phase3-kidney,lung, head and neck, gastric cancer and glioblastoma Phase2-cervical, colorectal and pancreatic cancer
	Nivolumab	Merkel cell & urothelial carcinoma
	Avelumab (PD-L1)	Phase 1 trial in multiple cancer.
	Inhibitory receptors Mk 3475 CT-011, AMP-224	

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TARGET	DRUG	CLINICAL DEVELOPMENT
CTLA-4 (Sharma, 2015) (al Q. e., 2019) (lambertini, 2019)	Ipilimumab Tremelimumab Inhibitory receptor Ipilimumab tremelimumab	Phase2- cervical, colorectal, pancreatic, ovarian, and urothelial cancer Phase3- kidney, prostrate and lung cancer Phase2- lung cancer Phase 2 and phase 3 trials of multiple cancer and it is FDA approved for melanoma Phase3- melanoma

TARGET	DRUG	CLINICAL DEVELOPMENT
TIM-3 (Anderson, 2016) (al e. , 2019)	Bevacizumab Camrelizumab Ramvcirumab Nivolumab TSR-040 Spartalizumab Inhibitory receptor	Phase1- advanced solid tumor Phase2-liver cancer Phase1-GBM Preclinical development

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TARGET	DRUG	CLINICAL DEVELOPMENT
LAG-3 (Anderson, 2016) (Solinas, 2019)	IMP321/Eftigimod	Phase1- metastatic RCC
	BMS-986016/ Relatlimab	Phase1&2-advanced solid tumor
	B1754111	Early neoplasm
	REGN3767	Phase1- advanced cancer
	MK-4280 Pembrolizumab Oxaliplatin, Irinotecan	Phase1- advanced solid tumor

Various processes such as activation, differentiation, recognition, chemo taxis are required for the T cell immune function the disruption of these process leads to T cell dysfunction and tumor immune escape. T cells play an important role in determining the efficacy of the immune checkpoint inhibitor (ICIs) the cytotoxic activity of the T cells is closely associated with the peripheral blood T cells which may predict the immune response at the tumor site.CD8+ tumor infiltrating lymphocytes (TILs) are specific for tumor antigen.CD39 is the possible biomarker (fukumura, 2018) for the CD8+ T cells and the CD39+ and CD8+ determine the efficacy of the ICIs.

Biomarker (iwahori, 2019) for PD1/PD-L1 blockade (zatloukalova, 2016), the patients are better when treated. The PD-1 blockade results in the up regulation of the PD-1 expression. The JAK/STAT is critical for the PD-1 expression and drug resistance it also up regulates the PD-L1 expression (Bai, 2017) and also plays an important role in the tumor antigen expression. PD-L1 has the direct effect on tumor it promotes the tumor growth and metastasis via ITGB4/SNAI$_1$/SIRT3 signaling which is the main cause for the resistance of PD-L1 and the suggested that targeting PD-1 and PD-L1 (mouw, 2018) in the combination with downstream factor like ITGB4 can enhance the immunological efficacy of PD1/PD-L1. Tumor with high mutational load are more immunogenic which stimulate the CD4+ and CD8+ T cell neoantigen specific activation. Interferon (IF) based transcriptomic are the most potential predictive marker for the PD-1 /PD-L 1 (Bai, 2017) immune checkpoint blockade (ICB) treatment it is also beneficial for the other types of tumor and it represents tumor immunogenicity (mutational burden) or anti-tumor immunity (tumor infiltrating lymphocyte).The inhibitory signals in the T

cells are prevented by the immune checkpoint inhibitors and restore by the T cell immune activity. The PD-1 expressed on the tumor cell plays a very important role in suppressing the immune activity of Tcell. The relationship between the CD8+ T infiltrates and response to the blockade of PD-1 in the melanoma and the cytotoxic T cell activity appears to the central role in the cancer immunotherapy. The basic principle of the anti PD-1/PD-L1 therapy is inhibiting the immune suppression mediated by the PD-1 pathway. The PD-1/PD-L1 (Kurzrock, 2015)efficacy is detected by the cytokine, the cytokine plays an important role in the mutation, differentiation and migration of various immune cells, other cytokine and interferon involve in inhibiting the tumor cells. The major histocompatibility complex (MHC) isup regulated by the IFN-gamma (gao, 2016) in the antigen presenting cell (APCs) which enhance the production of CTLs and up regulates the expressions of PD-L1 in tumor cell. The IFN-signaling causes the tumor cells to resist other immune checkpoints.

For CTLA-4 immune checkpoint blockade (Ni, 2017) such as soluble CD125, vascular endothelial growth factor, C- reactive protein etc. have come up with the advance treatment for melanoma. Non-small cell lung cancer (NSCLC) (al l. e., 2018) with high mutational load are treated with PD-1 ICB. Biomarker for CTLA-4 ICB such as co-stimulator positive T cell in bladder, breast cancer and mesothelioma and lymphocyte count in solid tumors and melanoma,CD4+ and CD8+ antigen specific T cell response in ovarian and prostate cancer and IFN gamma response gene in other melanoma. FDA approved ipilimumab anti-CTLA4 mAb against the metastatic melanoma has launched the new era of cancer immune therapy (lopez, 2018). The tumor microenvironment (TME) (Tang, 2021) contains immune system regulation which controls the immune checkpoints located on the T cell membrane their interactions with the ligands present on the surface of the tumor cell or antigen presenting cells (APCs) between two cells provide either stimulatory or inhibitory signals. Further there are co-stimulatory and co-inhibitory markers (attanasio, 2016) which holds T lymphocyte marker, macrophage marker and the natural killer cell (NK cell) marker, the co-inhibitory

LAG-3 blockade in cancer is associated with PD-1 or anti-PD-1 the important consequence of dual inhibition are promoting DC maturation (Anderson, 2016), CD4+ThTIL and CD8+CTL TIL dysfunctional rescuing and the inhibition of Treg activities. LAG-3 is also a promising approach for the development of cancer immunotherapy in response to multiple cancer. Therefore the LAG-3, PD-1/PD-L1, CTLA-4, TIM-3 are the tending to produce combination in cancer immunotherapies targeting multiple tumor microenvironment immunesuppressive pathway that hold promises for the drugs and treatment that are more feasible and tolerable . Personalized drug based on the specific biomarker or pathways are expected to produce different drug combinations and promising for the treatment of various cancer in cancer immunotherapy. (Takehiro Otoshi, Cancers 2019, 11, 935)

3. CONCLUSION

CTLA-4 and PD-1 are considered to be first co-inhibitory receptor which is primarily responsible for the restricting T cells and maintaining self-tolerance. In the lymphoid organ namely LAG3,TIM3, TIGIT (Anderson, 2016) are the second co- inhibitory receptor molecule which plays specific role in regulating immune response especially at the site of inflammation. The FDA approved immune checkpoints blockade for cancer immunotherapy is used to treat advanced melanoma, however immunotherapy is the key component for the treatment, control

and cure for cancer. The interaction between the tumor cell and immune system in the TME is the significant cause for the immune status of every individual. Immunotherapy of cancer (yuan, 2016) can induce the anti-tumor response are often not complete the immuno regulatory nature of the tumor microenvironmentcan inhibit the effective immune response against cancer and its modulation can enhance the efficacy of immunotherapy to destroy the tumor. Biomarker based research and recent advances in technology helps to understand the extrinsic and intrinsic mechanism and also have provided tool which will facilitate with great attention to detail understanding of mechanism and development of future personalized cancer immunotherapies (lopez, 2018). Therefore the recent clinical studies have brought cancer immunotherapy into main stream of oncology. Immune checkpoint inhibitors can provide long lasting and durable response in the cancer patient. Currently available biomarkers (Takehiro Otoshi, Cancers 2019, 11, 935) have stronger predictive abilities, single biomarkers is insufficient cannot respond and to cancer immunotherapy because of the complexity of the immune system. The cancer immunity T cell cycle checkpoint blockade (Ni, 2017) will provide the information about the interaction of tumor and immune system. The immunosuppressive and the immunosupportive balance within the tumor can be influenced by the cytokine content of the microenvironment various strategies have been used to render the TME less suppressive using immunotherapies but with the use of combinational therapies it is becoming possible, the immunotherapy of the cancer can induce the anti-tumor response the immunoregulatory nature of the TME (Devaud, 2013) inhibit the effective response against the cancer and the modulation of the TME enhance the efficacy of the cancer immunotherapy to destruct the tumor. The blockade of the T cell checkpoints include CTLA-4 and PD-1/PD-L1 (al Q. e., 2019) in both mono and combination therapies is the current standard treatment for the various type of cancer treatment. Therefore immune checkpoints inhibitors (ICIs) are approved for the treatment of various types of cancer with much less side effects and researches have been focusing on the PD-1, neoantigen, and mismatch repair as a potential biomarker for the cancer immunotherapy and also identifying the potential biomarker for the prediction of immune check point inhibitor efficacy. Although PD-1 may not be the ideal biomarker future (lambertini, 2019) for treatment combination that is combination of ICIs or the chemotherapy plus ICIs are becoming option for the cancer treatment therefore researches are in the process identification of new biomarker with combination therapy for the treatment of cancer. Neoantigen specific T cell reactivity is a major reactive ingredient for the cancer immunotherapy. Personalized cancer immunotherapies (yuan, 2016) offers the promise of high specificity and safety neoantigen (Schumacher, 2015) specific T cell reactivity with the personalized immunotherapies will increase the respond to the treatment of cancer in cancer immunotherapies.

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