

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Immuno-Oncology, Imaging Biomarkers and Response to Chemotherapy in Cancer Treatment

Alireza Ziaei and Forough Kheiry

Abstract

Immuno-oncology is a young and growing field in cancer therapy. It stimulates immune system to target and attack the tumor or inhibiting the immune response. Recent findings in cancer immunotherapy has revealed that the immune system can control many cancers across various histologies, producing durable responses in a way which not seen with many small molecule drugs. Advances in understanding the role and molecular mechanisms of immunotherapy are revolutionizing clinical practice in cancer treatment. Immunotherapy is being intensively explored with the aim of improving primary response rates or prolonging overall survival. The purpose of this chapter is to review the different aspect of immunotherapy including blockade of immunological checkpoints, immuno-oncology and imaging biomarkers, immune response, therapeutic resistance and combination therapy, while several additional immuno-therapeutic strategies are also highlighted.

Keywords: immune response, immunotherapy, immuno-oncology, cancer

1. Introduction

Cancer plays a serious role in public health bother. Global demographic features increase the predicted incidence of cancer in the coming decades. Annually, cancer is expected to reach 420 million new cases by 2025. Female breast cancer, colorectal, prostate, and lung are often diagnostic cancers in Europe, while lung cancer is the leading explanation for cancer and death worldwide [1]. The increasing information of biology and tumors over the past 15 years has considerably modified the pattern of cancer. Throughout the past decades, immune therapy has been used as a promising approach to the treatment of a broad variety of human cancers. But these methods such as chemotherapy and radiotherapy seem to be effective enough due to the problems including low target property, drug resistance, severe side effects and immuno-therapies induce host immune system to promote a response against tumors [2]. An important feature of Immunotherapy is to kill malignant tumors whereas healthy tissues not damaged. The issue of immunotherapy is to expand strategies that effectively and securely enhance anti-tumor responses. A few current cancer immunotherapy methods tested for their effectiveness include cytokine

treatment, cell-receptor cell transfer, cancer vaccines and monoclonal antibodies (mAbs). The most encouraging of these approaches are those that are specific T-cell stimulants that are capable of long-term tumor immunity [3]. The activity and regulation of T-cell is vital for the development of the tumor, since T-cells have the ability to remove cancerous cells [4].

2. Checkpoint blockade in immuno-oncology therapy

Checkpoint inhibitors are immune synapses which decrease the function of T-lymphocyte [5]. They are against autoimmunity and systemic inflammations. These mechanisms help tumor to escape from immune detection [2, 5]. The most frequent useful checkpoint inhibitor is checkpoint inhibitor mAbs, anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) [6, 7]. Checkpoint inhibitors invigorate immune system and persuade tumors. However, stimulation of cancerous T-cell proliferation can provide non-Hodgkin lymphoma (NHL) [2, 8]. Complication of checkpoint inhibitors is an autoimmune disease. Due to PD-1 or CTLA-4 illustrates beneficial result on advanced-stage melanoma [2, 9]. So, cytotoxic T lymphocyte antigen-4 and B7.1 are the most frequent targets in Immunotherapy. They can manage the interaction between T-cell and dendritic cells [1, 10].

2.1 PD-1

PD-1 is a receptor which is increased by T-cells during peripheral activation. PD-1 blockade down regulates the activity of intramural T regulatory cells [10]. Tumors can evade from immune system by inhibiting PD-1. Also, PD-1 is expressed by other immune cells such as lymphocyte B, natural killer (NK) cells and dendritic cells [4, 11–13]. PD-L1 has two ligands including PD-L1 (B7-H1) and PD-L2 (B7-H2). These two ligands expressed by inflammation and tumors tissues [4, 14]. Also, these ligands are expressed on antigen presenting cell (APCs). In addition, tumor tissues express these ligands [13]. PD-1 reduces the activity of T-cells later than CTLA-4. So, PD-1 influences on immune response during the chronic inflammation. PD-1 is important for the monitoring of Tregs suppressor performance [4]. CD80 or B7-1 is linked to PD-L1. Bidirectional interactions can inhibit PD-L1 and B7-1. Evading of PD-1 from immune diagnosis is so important [13]. Overall, PD-L1 in cancer is related to poor prognosis and larger tumor size and reduction in cytotoxic activity [4, 15, 16]. But, PD-1 can stop NHL by diminishing the proliferation of cancerous T-cells [15]. PD-L2 only can regulate the responses of Th2. But, PD-L2 is not selected as a target in cancer. PD-L2 does not have strong relation with survival. However, PD-L1 has the most potent influence and anti-tumor Th1 responses [4, 9]. PD-L1 is a useful ligand to manage several cancers like melanoma, non-small cell lung cancer (NSCLC) and kidney cancer [9].

2.2 CTLA-4

Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a glycoprotein that exists on the surface of T cells [1]. When T-cells activation is regulated in its early stage, T-cells in central lymph nodes express CTLA-4. CTLA-4 which is expressed by regulatory T cells (Tregs) can control the activated lymphocyte's proliferation in the lymph nodes. CTLA-4 plays a role in joining to B7.1 and B7.2 and involves with CD28. So, CTLA-4 can discontinue the activation and production of T cells. Anti-CTLA-4 decreases the Tregs cell to promote the proliferation of T cells [2, 10].

2.3 CD73

The investigations on anti-CD73 or anti-adenosine phase 1 found that they could effectively provoke immune response and improve the functions of first generation immune checkpoint inhibitors [17]. CD73 in Triple-negative breast cancer have poor prognosis [18]. Estrogen receptor (ER) negative has poor prognosis as well. CD73 in ER positive has no prognostic value. Stages I–III have good prognosis [19]. CD73 in B-cell acute lymphoblastic leukemia is a marker of minimal residual disease. B-cell chronic lymphocytic leukemia expresses CD73 as a marker of aggressiveness. CD73 is associated with CD38 and ZAP70 expression; two markers of disease progression in B-cell chronic lymphocytic leukemia [18, 20, 21]. CD73 in glioblastoma multiform (GBM) has poor prognosis [17]. CD73 is associated with limited metastatic potential in melanoma [17]. High-grade serous CD73 expression shows poor prognosis in ovarian cancers. However, CD73 expression indicated good prognosis in Epithelial ovarian cancer [17].

3. First group of immunotherapy medication

3.1 Ipilimumab (Yervoy)

Ipilimumab is a fully human immunoglobulin G1 (IgG1) monoclonal. It up regulates T-cell activation by targeting CTLA-4 and is used in phase 2 data for tumor response and safety by logistic regression models. Ipilimumab dosage is about 0.3, 3, and 10 mg/kg every 3 weeks for maximum four doses. About 10 mg/kg doses of Ipilimumab are more effective than 3 mg/kg in metastatic melanoma. However, 10 mg/kg doses of Ipilimumab have more serious side effects [1, 22, 23]. Clinical efficacy of Ipilimumab shows strong improvement on survival. Its response rate is 9–18% in phase III clinical trial in patients with NSCLC. Also, treatment scenario for Ipilimumab is pretreated and its control arm is Docetaxel. Response rate in patient with melanoma in phase 3 trial is p100 10.9 mo vs. 1.5 mo. Treatment scenario for Ipilimumab is pretreated in management of melanoma [1].

3.2 Tremelimumab

Tremelimumab is fully humanized IgG2 antibody and its target cell is T lymphocyte. Tremelimumab affects T lymphocyte by targeting CTL-4 and is an immune checkpoint inhibitor in hepatocellular carcinoma (HCC) clinical trials [1]. The effect of Tremelimumab has recently been studied in combination with Durvalumab on HCC. The response rate of this combination on HCC was approximately 25%. In phase 3 on metastatic melanoma, Tremelimumab can increase overall survival in comparison to chemotherapy [10]. It is given every 3 weeks for the management of melanoma and has 10% response rate [1]. Another study on phase 1 clinical trial has shown that the combination of Tremelimumab and CP-893,870 (a CD40-agonist mAb) provides the 27% objective response rate and 26 months overall survival. Also this combination provides 8% complete response rate [2].

3.3 Pembrolizumab (Keytruda)

Pembrolizumab is a humanized IgG4 monoclonal antibody against PD-1. It has only influence on tumors express programmed death-ligand 1 (PD-L1) [4, 24]. Pembrolizumab is recommended for the management of advance melanoma along with Ipilimumab. The recommended dosage is 2 mg/kg each 3 weeks in phase 1

clinical trial in patient with metastatic melanoma [1, 4, 24]. Also, Pembrolizumab is suggested for the treatment of metastatic NSCLC [4]. This drug has been studied in various cancer including gastric/gastroesophageal junction cancer (phase III), NSCLC (phase III), squamous cell carcinoma of the head and neck (SCCHN) (phase III), urothelial cancer (phase III), colorectal carcinoma (phase II), gastric/gastroesophageal junction cancer (phase II), GBM Merkel cell carcinoma (phase II), Hodgkin lymphoma (HL) and NHL (phase II). Pembrolizumab is one of the most important immune checkpoint inhibitors in HCC clinical trials. Response rate of Pembrolizumab is about 25 vs. 4% in patients with melanoma in phase II clinical trial. Also its control arm is investigator's choice chemotherapy. Also, using Pembrolizumab, as first line in treatment of melanoma, has 33.7 vs. 11.9% response rate in phase 3 clinical trial [23]. A recent study shows the saturations of Pembrolizumab is reached to 95% by dosage of 1 mg/kg every 3 week. Some studies revealed that reaching to complete achievement of the goal is 64% by 1 mg/kg each 3 week. However, complete achievements ≥ 2 mg/kg (such as 10 mg/kg) is higher 90% [25]. Later study has found that Pembrolizumab illustrates equivalence in exposure at dosage body weight-based 2-mg/kg each 3 week. But, Nivolumab does not have equality in exposure at indefinite quantity of two hundred mg each 3 weeks [24, 26]. Pembrolizumab clearance decreases about 20% after first injection. But this clearance is not clinically important [24, 27]. Common side effects of Pembrolizumab are fatigue, pruritus, and decreased appetite. Recent study in lung cancer patients shows 50% of tumors cell has PD-L1 receptors. In addition, Pembrolizumab has 45.2% response rate in patients who has PD-L1 receptors. But, objective response rate is 19.4% through all patients with metastatic lung cancer [27].

3.4 Blinatumomab (connecting bi-specific antibodies)

Blinatumomab is approved for CD19+ B-cell malignancies and its pre-clinical finding has strong in-vitro cytolytic activity. Blinatumomab's pharmacokinetics has clear kinetics and can trigger T lymphocytes to reach tumors cell. One of the recent studies on Blinatumomab shows that its clinical efficacy has high response rates, and its safety has moderate to severe toxicity [23].

3.5 Nivolumab (Optivo)

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that targets PD-1. Nivolumab target cell is T lymphocyte and is accepted in cancer with expressing PD-L1 and also without expressing PD-L1 [4]. Nivolumab dosage is about 1–10 mg/kg. Also non-clinical data recommends 0.3 mg/kg as initial dose. Low-immunogenic tumor types needed higher Nivolumab dosage. For instance, beneficial dosage for melanoma and renal cell carcinoma (immunogenic tumors) is 1–10 mg/kg (1 mg/kg each 2 week) [26]. However, higher dosage (3 and 10 mg/kg each 2 week) needs for NSCLC. Thus, lower dose level can have longer progression-free survival in immunogenic tumor types. Nivolumab is approved for both PD-L1 expressers [24, 28]. Recent studies indicate that Nivolumab has increased the survival in patients with melanoma [28, 29]. Nivolumab has 25–40% response rate with long lasting response (2 years) in patients with melanoma. Another study in phase III trial has shown Nivolumab has increased survival in comparison with chemotherapy in patients with advance melanoma and advance NSCLC [4]. Nivolumab should be selected 3 mg/kg each 2 week as monotherapy dose for different type of tumors to improve survival [30]. The investigation exhibited that there was a linear relationship between Nivolumab pharmacokinetics and the dose range. For renal cell carcinoma, metastatic melanoma and NSCLC, suggested dosage is

240 mg IV every 2 week depends on population pharmacokinetics analyses and response analyses of dose and exposure [31]. Also, Nivolumab is prescribed for renal cell carcinoma due to second choice. Pharmacometrics has main role in changing body weight based on dosage to flat dosage. The advantages of using a flat dose include removing excess material waste, the convenience of health care providers, and reducing worries about the exact dose in patients with weight fluctuations. Combination of Nivolumab and Ipilimumab are used in the management of melanoma [28]. Nivolumab are investigated in different types of tumors including gastric cancer (phase III), GBM (phase III), acute myeloid leukemia (AML) (phase II), anal canal (phase II), cervical cancer (phase II), colon cancer (phase II), HL, NHL (phase II), nasopharyngeal carcinoma (phase II), pancreatic cancer (phase II) [4]. Nivolumab is one of important Immune checkpoint inhibitors in HCC clinical trials. Nivolumab's pre-clinical findings has moderate effect and its clinical efficacy has a strong influence on improvement of survival. It is used for the first line treatment of melanoma in phase 3 clinical trial. Nivolumab's control arm is Dacarbazine. Melanoma response rate of Nivolumab is approximately 40 vs. 13.9%. Nivolumab is used in treatment of NSCLC as pretreated with response rate about 32 vs. 11% in phase 3 clinical trial and the control arm is investigator's choice chemotherapy [1].

3.6 Atezolizumab

Atezolizumab is a humanized Fc-engineered IgG1 monoclonal and binds to PD-L1. Atezolizumab promote neither activate antibody-dependent cell-mediated cytotoxicity (ADCC) nor complement-dependent cytotoxicity (CDC). Also, Atezolizumab blocks the interaction with PD-1 and B7.1 receptors on tumor cells. Recent study shows that the best dosage for metastatic urothelial carcinoma and metastatic NSCLC is 1200 mg every 3 weeks. Also later study on dose-escalation in phase 1 indicates dosage of Atezolizumab is about 0.01–20 mg/kg based on body weights [32].

3.7 Durvalumab

Durvalumab is a humanized Fc-engineered IgG1 monoclonal and binds to PD-L1. Durvalumab promote neither ADCC nor CDC, and avoids the ability of toxicity caused by it does not have attraction to joining PD-L2. Recommended dosage of Durvalumab is 10 mg/kg each 2 weeks in carcinoma of urothelial. Proposed concentration in metastatic urothelial carcinoma is about 50 µg/mL. Recommended fixed dosage regimen of Durvalumab is 1500 mg every 4 week or 750 mg every 2 week. This regimen indicates similar overall pharmacokinetic exposure based on body weight [33].

3.8 Avelumab

Avelumab is a fully human IgG1 monoclonal antibody and has short half-life for about 3.9–4.1 days compare to Nivolumab which is about 12–20 days, Pembrolizumab with half-life of 14–22 days, and Atezolizumab with half-life of 21 days. Avelumab shows the reduction in clearance similar to Nivolumab and Pembrolizumab during long treatments. The investigation of avelumab on metastatic Merkel cell carcinoma after 1 year of follow up has shown that avelumab can be effective in treating advance Merkel cell carcinoma due to 33.0% overall response rate (ORR) and 11.4% to complete response rate. The dosage is used in that study was 10 mg/kg every 2 weeks. Also, studies in phase 1 have shown that this drug can also be effective in patients with platinum-refractory metastatic urothelial carcinoma cancer due to 17.3% ORR [24, 34–38].

4. Second group of immunotherapy medication

Next-generation of novel therapeutic target include VISTA, LAG-3, TIGIT, and TIM-3 inhibitors. Also, another potential checkpoint is p-selectin glycoprotein ligand-1 (PSGL-1) which regulates T-cell responses in tumor microenvironment (TME). CTLA-4 and PD-1 are co-target receptors which they are responsible for supporting overall immune self-tolerance. However, TIGIT, LAG-3, and TIM-3 receptors influence on NK and CD8⁺ T-cell. Treg cell suppressive influence and improving CD8⁺ and NK cell activity inside malignancy tissues is revoked by synergizing their corresponding blockade. Thus, synergizing of first- and second generation inhibitors provoke immune system to have beneficial response against malignancies [2, 39–41].

4.1 T-cell immunoglobulin-3 (Tim-3)

Tim-3 is expressed on IFN γ producing CD4⁺ T helper 1 (Th1) and CD8⁺ T cytotoxic 1 (Tc1) T-cells. Also, Tim-3 is expressed on Treg cells and on innate immune cells (DC, NK cells, and monocytes). Co-inhibition of Tim-3 and PD-1 is more beneficial than PD-1 alone inhibition in anti-tumor effector functions. Tim-3 shows the dysfunction of CD8⁺ T-cells in cancers. Co-inhibition in Tim-3 and PD-1 has greater effects in managing melanoma, NSCLC, and NHL [37].

4.2 T-cell immunoglobulin and ITIM domain (TIGIT)

T-cell immunoglobulin and ITIM domain (TIGIT) Ligand (CD155 and CD112) are expressed in tumors cells. Negative TIGIT up regulate anti-tumors activities. Dysfunctional phenotype among CD8⁺ TILs is produced by co-expression of CD8 plus TIGIT⁺ TILs with PD-1, Tim-3, and Lag3. Co-inhibition of TIGIT with PD-1 increased proliferation, cytokine production, and degranulation In CD8⁺ TILs from melanoma patients [37]. Moreover, TIGIT synergies with Tim-3 to improve anti-tumor responses. So, both co-inhibition of TIGIT with PD-1 or TIGIT with Tim-3 induce anti-tumor effects. In addition, TIGIT are expressed on tumor infiltrating Treg. Restrictive phenotype of Treg cell is provided by the TIGIT⁺ Treg in tissues with malignancy cells. Notably, CD8⁺ T-cell function (direct suppression) and promotion of Treg function (indirect suppression) can suppress anti-tumor immunity by TIGIT [37].

4.3 B-cell and T-cell lymphocyte attenuator (BLTA)

B-cell and T-cell lymphocyte attenuator (BTLA) is an immunoglobulin-like molecule expressed on different cells such as on B-cells, T-cells, NK cells, and APCs. BLTA is a section of CD28 family. BLTA plays a major role in early T-cell regulation and provides early T-cell response gene. Combination of BLTA and herpes virus entry mediator (HVEM) induces reduction of T-cell proliferation and cytokine production. Melanoma cells are expressed HVEM. The combination of BTLA and HVEM inhibits the expansion and IFN γ production. Also, BLTA is related to restricted T-cell expansion. Inhibition of BTLA, PD-1, and TIM3 together increase IL-2. Inhibition of BTLA, PD-1, and TIM3 can restore T-cell dysfunctions. After the BTLA and HVEM interconnections, T-cell activation and level of IFN γ decreases [13].

4.4 V-domain Ig suppressor of T-cell activation (VISTA)

V-domain Ig suppressor of T-cell activation (VISTA) is a powerful suppressor of T-cell [13] which is expressed by hematopoietic tissues and infiltrating leukocytes.

VISTA is predominantly found on leukocytes inside tumors and myeloid hematopoietic section 140. Like PD-L1, it promotes suppression of CD4 and CD8. VISTA also has long-lasting kinetics which can induce the reduction of cytokine production such as IL-10, TNF- α , and IFN γ . VISTA inhibition increase the frequency of tumor-infiltrating effector T-cells by combining to a specific antibody. Thus this combination inhibit tumor growth. VISTA can increase overall survival by combining to an agonistic CD40 antibody, TLR agonists, and tumor antigen peptides [13].

4.5 CD160

CD160 is a glycosyl-phosphatidyl-inositol (GPI) which is expressed on CD8 β T-cells, NK cells, and NK-T cells. CD160 inhibition induces T-cell proliferation and cytokine production 147. Also, CD160 is a ligand for HVEM. The combination of CD160 and HVEM promote the suppression of T-cells. So, CD160 is an inhibitory checkpoint for T-cells [13].

4.6 CD244

CD244 is a immunoglobulin which can regulate and activates the lymphocytes. In addition, CD244 can stimulate both T-cell and NK cells. NK cytotoxicity is inhibited opposed the expression of CD48 by CD244. CD244 can provide both suppression and activation of T-cell by cross linking, related to CD244 level of expression and adaptation of intracellular molecule. Recent study shows that CD244, LAG-3, and PD-1 is reduced in tumor-infiltrating antigen-specific CD8 β T-cells by herpes virus glycoprotein (GD) adjuvant vaccine [13].

5. Passive immuno-therapy

With the exception of immuno-suppressants, many other important therapies are developing immunization that can be divided into active or inactive Immunotherapy with respect to host immunity when detecting anti-tumor responses. Active immuno-therapies have correlation with capacity of anti-tumor attack of T-cell. However, passive Immunotherapy includes inherent anti-tumor properties of adaptive T-cell therapy [1, 41].

5.1 Tumor-targeting monoclonal antibodies (mAbs)

mAbs have different effects on immune cells. First, mAbs can change the receptor's signaling role which malignant cells expressed them. Second, they neutralize the signals which malignant cells or stromal components or neoplastic lesion provided them. mAbs identify cancer cells due to tumor associated antigen (TAA) expression which expressed by transformed cells [39, 42]. Another anti-cancer immuno-therapies against activatory checkpoint receptors include anti-CD137 or anti-CD40 which are being tested in clinical trials [1]. mAbs Cetuximab blocks signaling pathways which determine neoplastic cells' survival or progression. Also Cetuximab is approved for the treatment of head and neck cancer. In addition, it is used in managing colorectal carcinoma [9, 39, 43, 44]. Naked mAbs such as Tigatuzumab activates murderous receptors of malignant cells. Gemtuzumab ozogamicin is an anti-CD33 Calicheamicin. Gemtuzumab ozogamicin binds to a TAA-specific mAbs. It use for acute myeloid leukemia patients [38]. CD20-specific mAb Rituximab is complement-dependent cytotoxicity. Rituximab is activated by TAA-specific mAbs. Also, naked TAA-specific mAbs activates ADCC and

antibody-dependent cellular phagocytosis [39, 45, 46]. A recent study shows that Rituximab has beneficial influence on chronic lymphocytic leukemia, and NHL [39, 46, 47]. Blinatumomab is a CD19- and CD3 bispecific T-cell engagers (BiTE) which is chimeric proteins includes of two single-chain changeable fragments from mAbs. BiTE has two fragments, one of them target a TAA and another target T-cell surface antigen. Blinatumomab is approved for treatment of B-cell acute lymphoblastic leukemia. MAbs and BiTE should be considered active immuno-therapeutic or passive immun0-therapeutics. This implying depends on host immune responses. For example, Cituximab can block epidermal growth factor receptor (EGFR) signaling and also can induce ADCC. In addition, Cituximab can mediate the effects of immuno-stimulatory [39, 48]. Bevacizumab is approved for management of glioblastoma multiform, cervical carcinoma, renal cell carcinoma, and lung cancer due to anti-angiogenesis effects. But, Bevacizumab induces tumor infiltration via lymphocyte B and lymphocyte T. In addition, Bevacizumab blocks CD4+ CD25+ FOXP3+ regulatory T-cells [39, 48, 49].

5.2 Summary of anti mAbs indications

Alemtuzumab's indication is chronic lymphocytic leukemia. Bevacizumab's indications are colorectal carcinoma, lung carcinoma, renal cell carcinoma. Brentuximab vedotin indications are anaplastic large cell lymphoma and HL. Blinatumomab indication is acute lymphoblastic leukemia. Catumaxomab indications are malignant ascites in patients with epithelial cell adhesion molecule (EPCAM) + cancer. Cetuximab indications are head and neck cancer and colorectal carcinoma. Denosumab indications are breast carcinoma, prostate carcinoma, and bone giant cell tumors. Gemtuzumab ozogamicin indication is acute myeloid leukemia. Ibritumomab tiuxetan indication is NHL. Panitumumab indication is colorectal carcinoma. Pertuzumab indication is breast carcinoma. [38]. Obinutuzumab indication is chronic lymphocytic leukemia. Ofatumumab indication is chronic lymphocytic leukemia. Ramucirumab indications are gastric or gastroesophageal junction adenocarcinoma. Rituximab indications are chronic lymphocytic leukemia and NHL. Siltuximab indication is Multicentric Castleman's disease. Tositumomab indication is NHL, and Trastuzumab indications are breast carcinoma, gastric or gastroesophageal and junction adenocarcinoma [38].

5.3 Oncolytic viruses

Oncolytic viruses have potential anti-neoplastic effects and can inherent cytopathic effects. Productive viral infection up regulates the mortal overcharge of cellular metabolism. Oncolytic viruses are lethal for host cells due to endogenous or exogenous gene products, and are approved by US food and drug administration (FDA) [39, 50].

5.4 Oncorine H101

Oncorine H101 is oncolytic viruses. Oncorine indication is head and neck cancer. The mechanism of action is selective lysis of malignant cells [38].

6. Immune oncology biomarker and immune response

Biomarkers have different purpose and are seen as a pre-existing anti-tumor in certain developing tumors. Also, response to immune treatments can

provide specific biomarkers [48]. When blockade of the PD-1/PD-L1 checkpoint response increase, PD-L1 expression can be seen in the TME. The high level expression of PD-L1 is related with a higher response rate and its expression increases survival [48]. Immunotherapy can exacerbate tumor lymphocytes (TILs), which illustrates antitumor immune response [48]. CD8 T-cells are associated with tumor regression after stopping of PD-1/L1 in melanoma metastasis. Increased immunogenicity of a tumor shows an increasing of tumor mutational load and neoantigen [49]. High mutational burdens increase survival than low load. Mutational load and neoantigens have been shown in many type of advance tumors including melanoma, NSCLC, and colorectal carcinoma. The investigations on colorectal carcinoma illustrate higher tumor-infiltrating lymphocytes and smokers response which is better than nonsmokers (adenocarcinomas) [1]. Immuno-stimulatory or immune inhibitory cytokines existence in the microscopic environment of the tumor forecast susceptibility or resistance. There are several methods for research in the microscopic environment of the tumor including immuno-histochemistry, immuno-fluorescence, whole-exome sequencing, transcriptome analysis, proteomics, flow cytometry and others [48]. Type I interferon-based transcriptomic signatures has beneficial effect in metastatic melanoma. However, it may originally be used for other types of tumors [1]. Several investigations on PD-1/PD-L1 checkpoints indicate that TME PD-L1 (TME cell types express PD-L1) expression is significantly related with response [29]. Tumors with negative PD-L1 are resistance to therapy since tumor or immune cell must have PD-L1 for immune checkpoint therapy [29]. Alone PD-L1 (B7-H1) expression cannot adequately predict the Immunotherapy response. So, adding PD-L1 with another parameters (CD8+ T-cells or an IFN γ gene signature) improves predictive value [48].

6.1 Imaging biomarker

There are two main approaches for imaging in clinical oncology including anatomic and functional imaging. Anatomic change fluorescence and bioluminescence are the most useful imaging techniques. In addition, magnetic resonance imaging (MRI) improves contrast and increase resolution of anatomic images. Also, MRI can improve range of functional measure. Dynamic contrast-enhanced MRI can indicate tumor perfusion and permeability of cell membrane. Diffusion-weighted MRI demonstrates the access of drug by parameters such as rate and distance of water molecule. Recent study evaluates immunotherapy by using cells labeled with either super paramagnetic iron oxide particles or perfluorocarbon nanoemulsions in MRI-based cell follow [51, 52]. Detecting biochemical markers in tumors is possible by single-photon emission computed tomography (SPECT) and PET. These two mature imaging techniques has beneficial effects such as high-resolution images, the potential to quantify metabolic activity for corrects attraction of therapeutic influences [52]. The investigations on lymphoma and solid tumors shows that ^{18}F -FDG-PET imaging which is oncologic nuclear imaging is very useful for disease response evaluations. But, there are few important problem with ^{18}F -FDG-PET such as the distinction between neoplasm and infectious or inflammatory processes. SPECT provide high resolution similar to PET. However, beneficial advantage of SPECT in comparison with PET is ubiquity of SPECT cameras, reduced cost structure, increased logistics for imaging caused by longer half-lives of the radionuclides, and a greater number of radionuclides available for labeling. $^{99\text{m}}\text{Tc}$ -methyldiphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) is the most useful SPECT agents in imaging of advance osteoblastic bone cancer. Real metastases are not detected by bone scan, while the reaction of the skeleton

to metastases can be found [52, 53]. Also, another SPECT agents which they are useful for different cancers including using ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) in neuroblastoma, using ¹¹¹In-pentetreotide in patients with neuro-endocrine tumors, and ¹²³I-sodium iodide (NaI) for thyroid distinction between expected post immuno-therapeutic results. The most frequent use of PET agent is ¹⁸F-fluorothymidine (¹⁸F-FLT) which is a marker for proliferation of the cells. ¹⁸F-fluorothymidine (¹⁸F-FLT) improves the differentiation between tumors and false positive rate associated to infections and inflammations [52]. ¹⁸F-FLT has some limitations in comparison with ¹⁸F-FDG-PET such as reduction in signal to background ration. Also, ¹⁸F-FLT shows background structures such as bone marrow, which cannot show the activity of the tumors and reduces the identification of tumors. Furthermore, ¹⁸F-FIT gathers in area of infection and inflammation lesser than ¹⁸F-FDG [54].

7. Immune response

Genomic factors play an important role in responding to Immunotherapy. Across several mechanisms, viral proteins have influence on intercommunication alongside T-cells and malignancy. For example anti-tumor cytotoxic activity of the NK cells is increased by hidden cytomegalovirus [55]. In addition, PD-L1 expression is provoked by EBV in NHL and other EBV+ cancers [53]. one of the most responsive cancer to checkpoints inhibitor is HL. Also, HL has high level of PD-L1 expression. PD-L1 expression is reduced in HPV+ tumors; But, T-cell infiltration is increased in HPV+ tumors. Therefore, an important biological biomarkers for Immunotherapy is the presence of viral proteins [56]. Recent study shows that Merkel-cell polyomavirus positive tumors have higher PD-L1 expression (71 vs. 25%). Response rate in virus positive tumor is about 65 vs. 44% higher than virus negatives tumors [48].

8. Combination therapy

Combination therapy can increase response rate, efficacy and improve multiple components of T-cell anti-tumor responses. It has been reported that, Nivolumab + Ipilimumab are beneficial against melanoma. But, this combinations may have many serious side effects such as hepatitis, colitis, pneumonia. Bevacizumab combine with interferon-alpha to manage renal cancer. The combination of Elotuzumab and Dexamethasone and Lenalidomide is useful to control multiple myeloma [7, 59]. Combination of Nivolumab and Pembrolizumab is prescribed for managing squamous and non-squamous NSCLC [4, 33].

8.1 Binary checkpoint inhibition

Combination of Nivolumab (anti-PD-1) and Ipilimumab (anti-CTLA-4) provide total two-year survival in 79% of cases in metastatic melanoma. Also this combination has 53% objective response rate in metastatic melanoma. Recent study shows combinations of Nivolumab and Ipilimumab has 61% objective response rate. However, Ipilimumab alone has 11% objective response rate. Totally, recent study shows 22% remission [2]. Also, later investigations shows that the combination of anti-PD-1 and CTLA-4 stimulate T-cell more than anti-CTLA-4 alone. In combination of PD-1, CTLA-4 and VISTA blockade checkpoint is demonstrated the stimulation of T-cell [2].

8.2 Checkpoint inhibitor and mAbs

Combination of Tremelimumab (anti-PD-1) and a CD40-agonist mAb has 27% objective response rate, 26 months overall survival. T-cell antigen 4-1BB is targeted by mAb's, and improves T-cell stimulation [57]. Combination of 4-1BB agonists with PD-1 blockade has notable results in rejection in murine model with colon adenocarcinoma. This combination therapy led to increase the level of IFN γ -producing CD8+ and CD4+ T-cells in comparison with monotherapies. Efficacy of OX40 agonist is decreased by PD-1 inhibitions. Also, PD-1 blockade causes reduction of CD4+ and CD8+ lymphocyte infiltration and causes 30% breast tumors remissions [58].

8.3 Epigenome regulator

Epigenome regulator is coupled with checkpoint inhibitor, and includes an inhibitor of histone deacetylases (HDAC) or DNA methyl-transferase (DNMT). HDAC typically associated with the cancer process [59]. Immune checkpoint management mechanisms contain covalent modifications, microRNAs (miRNAs), and long noncoding RNAs (lncRNAs), and histone modifications. DNA methylation and histone acetylation have the most effects in management of growth and activation of T lymphocyte. Inhibition of HDAC promotes tumor death. Inhibition of HDAC provokes tumor death by different pathway such as reactive oxygen species (ROS) and apoptosis. HDAC inhibitor is prescribed for different type of malignancies including leukemia, gastric carcinoma, NSCLC. HDAC inhibitors have several complications including lymphopenia, leukopenia, neutropenia, and thrombocytopenia. Combination therapy of HDAC and DNMT inhibitors with other immunological agents is used for more efficacy. For example, Entinostat is combined with Nivolumab and Ipilimumab for managing metastatic breast cancer. Also, Entinostat with Pembrolizumab is used for solid tumors, metastatic uveal melanoma and NSCLC. Mocetinostat and Durvalumab are used for managing solid tumors [60–62].

8.4 Selective therapy with checkpoint inhibitor

Checkpoint blockers coupled with receptor and non-receptor tyrosine kinases (TK) play major roles in tumorigenesis. The angiogenesis provides growth factor VEGF and restricts T-cell infiltration through the tumor endothelium. In addition, angiogenesis promotes myeloid-derived suppressor cells (MDSCs) and Treg cells inside tumors. Combination of Bevacizumab (a VEGF inhibitor) with Ipilimumab can control 67% in metastatic melanoma. In addition, this combination can induce T-cell activation inside tumors with approving toleration level. It is currently attempting to coordinate anti-PD-1/PD-L1 MABs with VEGF inhibitor for even greater effectiveness [60]. Imatinib (TKI) with an anti-CTLA-4 mAb decrease Treg cell. Tumor volume is decreased 50% by CTLA-4 and Indoleamine 2,3-dioxygenase (IDO) blockade combination during 80 days [60]. Tumor volume is decreased 50% by CTLA-4 and IDO blockade combination during 80 days [60]. Combination of PD-1 and IDO blockades has favorable effects on advanced melanoma [2].

8.5 Adaptive T-cell therapy (ACT) with checkpoint inhibitor

Adaptive T-cell therapy induces anti-tumor stimulation. CD19-specific chimeric antigen receptor (CAR) T-cell therapies provide 90% revocation of which 67% of them have response following 6 months in acute lymphoblastic leukemia patients. In addition, more than 53% complete response rate has shown in B-cell lymphoma [61].

8.6 Nanoscale coordination polymer (NCP) with checkpoint inhibitor

Combination of anti-PD-l1 (Pembrolizumab) and nanoscale coordination polymer (NCP) combination increase CD8⁺ T-cells in tumors. Survival rate is increased by antiPD-1 checkpoint inhibitors and agonistic anti-OX40 antibodies. Anti-OX40 antibodies encourage the stimulation of elevated T-cell due to increased release of IFN γ and increased CD8⁺/Treg cell ratio [59]. It has recently been shown that presentation of antigen is increased by synthetic polymeric nanoparticle PC7A. Also, flexible nanovaccin platform carry antigens to lymph nodes. The combination of PD-L1 inhibitor and laser light and gold nanostars, which they are called photo-thermal nanotherapy, can manage advance metastatic bladder malignancy [2].

9. Conclusion

Immunology has changed the way of cancer treatments and control. Primitive immunotherapy with checkpoint inhibitors provides beneficial results. However, the combination of checkpoint inhibitor with other immune target agents provide new generation of immune-oncology treatments. Knowledge about immunological checkpoints, immuno-oncology biomarkers, immune response, therapeutic resistance and combination therapy helps us in the process of cancer diagnosis/follow-up, and imaging during immunotherapy helps to better understand the patients' immune response.

Author details

Alireza Ziaei^{1,2*} and Forough Kheiry

1 Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

2 Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

*Address all correspondence to: alireza.ziaei@childrens.harvard.edu

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Ares L. Current challenges in cancer treatment. *Clinical Therapeutics*. 2016;**38**(7):1551-1566
- [2] Marshall HT, Djamgoz MB. Immuno-oncology: Emerging targets and combination therapies. *Frontiers in Oncology*. 2018;**8**:1-29
- [3] Robinson TO, Schluns KS. The potential and promise of IL-15 in immuno-oncogenic therapies. *Immunology Letters*. 2017;**190**:159-168
- [4] Medina PJ, Adams VR. PD-1 pathway inhibitors: Immuno-oncology agents for restoring antitumor immune responses. *Pharmacotherapy*. 2016;**36**(3):317-334
- [5] Baumeister SH, Freeman GJ, Dranoff G, Sharpe AH. Coinhibitory pathways in immunotherapy for cancer. *Annual Review of Immunology*. 2016;**34**(1):539-573
- [6] Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. *Nature Reviews Drug Discovery*. 2016;**13**(20):1796-1803
- [7] Azoury CS, Straughan MD, Shukla V. Immune checkpoint inhibitors for cancer therapy: Clinical efficacy and safety. *Current Cancer Drug Targets*. 2015;**15**(6):452-462
- [8] Ludin A, Zon LI, Tchekmedyian N, Gray JE, Creelan BC, Chiappori AA, et al. Propelling immunotherapy combinations into the clinic. *Oncology*. 2015;**29**:990-1002
- [9] Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: A common denominator approach to cancer therapy. *Cancer Cell*. 2015;**27**(4):451-461
- [10] Russi AE, Brown MA. The meninges: New therapeutic targets for multiple sclerosis. *Translational Research*. 2015;**165**(2):255-269
- [11] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews. Cancer*. 2012;**12**:252-264
- [12] Taube JM, Taube JM, Klein AP, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clinical Cancer Research*. 2014;**20**:5064-5074
- [13] Baksh K, Weber J. Immune checkpoint protein inhibition for cancer: Preclinical justification for CTLA-4 and PD-1 blockade and new combinations. *Seminars in Oncology*. 2015;**42**(3):363-377
- [14] Rozali EN, Hato SV, Robinson BW, Lake RA, Lesterhuis WJ. Programmed death ligand 2 in cancer-induced immune suppression. *Clinical & Developmental Immunology*. 2012;**2012**:656340
- [15] Couzin-Frankel J. Autoimmune diseases surface after cancer treatment. *Science*. 2017;**358**(6365):852-852
- [16] Peng W, Liu C, Xu C, Lou Y, Chen J, Yang Y, et al. PD-1 blockade enhances T-cell migration to tumors by elevating IFN- γ inducible chemokines. *Cancer Research*. 2012;**72**(20):5209-5218
- [17] Allard D, Allard B, Gaudreau PO, Chrobak P, Stagg J. CD73–adenosine: A next-generation target in immuno-oncology. *Immunotherapy*. 2016;**8**(2):145-163
- [18] Leclerc BG, Charlebois R, Chouinard G, Allard B, Pommey S, Saad F, et al. CD73 expression is an independent prognostic factor

in prostate cancer. *Clinical Cancer Research*. 2016;**22**(1):158-166

[19] Long JS, Schoonen PM, Graczyk D, O'Prey J, Ryan KM. p73 engages A2B receptor signalling to prime cancer cells to chemotherapy-induced death. *Oncogene*. 2015;**34**(40):5152-5162

[20] Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA. Pattern of metastatic spread in triple-negative breast cancer. *Breast Cancer Research and Treatment*. 2009;**115**(2):423-428

[21] Morgensztern D, Campo MJ, Dahlberg SE, Doebele RC, Garon E, Gerber DE, et al. Molecularly targeted therapies in non-small-cell lung cancer annual update 2014. *Journal of Thoracic Oncology*. 2015;**10**(1):S1-S63

[22] Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *Journal of the American Medical Association*. 2014;**311**(19):1998

[23] Diao L, Meibohm B. Pharmacometric applications and challenges in the development of therapeutic antibodies in immuno-oncology. *Current Pharmacology Reports*. 2018;**4**(4):285-291

[24] Elassaiss-Schaap J, Rossenu S, Lindauer A, Kang S, De Greef R, Sachs J, et al. Using model-based "learn and confirm" to reveal the pharmacokinetics-pharmacodynamics relationship of Pembrolizumab in the KEYNOTE-001 trial. *CPT: Pharmacometrics & Systems Pharmacology*. 2017;**6**(1):21-28

[25] Freshwater T, Kondic A, Ahamadi M, Li CH, de Greef R, de Alwis D, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. *Journal for Immuno Therapy of Cancer*. 2017;**5**(1):1-9

[26] Li H, Yu J, Liu C, Liu J, Subramaniam S, Zhao H, et al. Time dependent pharmacokinetics of pembrolizumab in patients with solid tumor and its correlation with best overall response. *Journal of Pharmacokinetics and Pharmacodynamics*. 2017;**44**(5):403-414

[27] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *The New England Journal of Medicine*. 2015;**372**(21):2018-2028

[28] Morrissey K, Yuraszeck T, Li C-C, Zhang Y, Kasichayanula S. Immunotherapy and novel combinations in oncology: Current landscape, challenges, and opportunities. *Clinical and Translational Science*. 2016;**9**(2):89-104

[29] Agrawal S, Feng Y, Roy A, Kollia G, Lestini B. Nivolumab dose selection: Challenges, opportunities, and lessons learned for cancer immunotherapy. *Journal for ImmunoTherapy of Cancer*. 2016;**4**(1):72

[30] Bajaj G, Wang X, Agrawal S, Gupta M, Roy A, Feng Y. Model-based population pharmacokinetic analysis of Nivolumab in patients with solid tumors. *CPT: Pharmacometrics & Systems Pharmacology*. 2017;**6**(1):58-66

[31] Zhao X, Suryawanshi S, Hruska M, Feng Y, Wang X, Shen J, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. *Annals of Oncology*. 2017;**28**(8):2002-2008

[32] Stroh M, Winter H, Marchand M, Claret L, Eppler S, Ruppel J, et al. Clinical pharmacokinetics and pharmacodynamics of atezolizumab

in metastatic urothelial carcinoma. *Clinical Pharmacology and Therapeutics*. 2017;**102**(2):305-312

[33] Baverel P, Dubois V, Jin C, Song X, Jin X, Mukhopadhyay P, et al. Population pharmacokinetics of durvalumab and fixed dosing regimens in patients with advanced solid tumors. *Journal of Clinical Oncology*. 2017;**35**(15 suppl):2566-2566

[34] Wilkins JJ, Brockhaus B, Dai H, Vugmeyster Y, White JT, Brar S, et al. Time-varying clearance and impact of disease state on the pharmacokinetics of avelumab in Merkel cell carcinoma and urothelial carcinoma. *CPT: Pharmacometrics & Systems Pharmacology*. 13 Apr 2019

[35] Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN solid tumor): A phase 1a, multicohort, dose-escalation trial. *The Lancet Oncology*. 2017;**18**(5):587-598

[36] Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: Co-inhibitory receptors with specialized functions in immune regulation. *Immunity*. 2016;**44**(5):989-1004

[37] Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: Co-inhibitory receptors with specialized functions in immune regulation. *Immunity*. 2016;**44**(5):989-1004

[38] Galluzzi L, Vacchelli E, Bravo-San Pedro JM, Buqué A, Senovilla L, Baracco EE, et al. Classification of current anticancer immunotherapies. *Oncotarget*. 2014;**5**(24):12472

[39] Coulie PG, Van den Eynde BJ, van der Bruggen P, Boon T. Tumour antigens recognized by T lymphocytes: At the core of cancer immunotherapy. *Nature Reviews Cancer*. 2014;**14**(2):135-146

[40] De T, Rouge LM, Galluzzi L, Olaussen KA, Zermati Y, Tasdemir E, et al. A novel epidermal growth factor receptor inhibitor promotes apoptosis in non-small cell lung cancer cells resistant to Erlotinib. *Cancer Research*. 2007;**67**(13):6253-6262

[41] Lim CM, Stephenson R, Salazar AM, Ferris RL. Tlr3 agonists improve the immunostimulatory potential of cetuximab against egfr+ head and neck cancer cells. *Oncoimmunology*. 2013;**2**(6):1-10

[42] Forero-Torres A, Infante JR, Waterhouse D, Wong L, Vickers S, Arrowsmith E, et al. Phase 2, multicenter, open-label study of tigatuzumab (CS-1008), a humanized monoclonal antibody targeting death receptor 5, in combination with gemcitabine in chemotherapy-naïve patients with unresectable or metastatic pancreatic cancer. *Cancer Medicine*. 2013;**2**(6):925-932

[43] Battella S, Cox MC, Santoni A, Palmieri G. Natural killer (NK) cells and anti-tumor therapeutic mAb: Unexplored interactions. *Journal of Leukocyte Biology*. 2016;**99**(1):87-96

[44] van Oers MHJ, Klasa R, Marcus RE, Wolf M, Kimby E, Gascoyne RD, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial. *Blood*. 2006;**108**(10):3295-3301

[45] Manzoni M, Rovati B, Ronzoni M, Loupakakis F, Mariucci S, Ricci V, et al. Immunological effects of bevacizumab-based treatment in metastatic colorectal cancer. *Oncology*. 2010;**79**(3-4):187-196

[46] Terme M, Pernot S, Marcheteau E, Sandoval F, Benhamouda N, Colussi O, et al. VEGFA-VEGFR pathway blockade

inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. *Cancer Research*. 2013;**73**(2):539-549

[47] Linette GP, Carreno BM. Dendritic cell-based vaccines. *Oncoimmunology*. 2013;**2**(11):e26512

[48] Janice MM, Monjazeb AM, Beerthuijzen JMT, Collyar D, Rubinstein L, Harris LN. The challenge for development of valuable immuno-oncology biomarkers. 2017:4970-4979

[49] Wilson FH, Johannessen CM, Piccioni F, Tamayo P, Kim JW, Van Allen EM, et al. A functional landscape of resistance to ALK inhibition in lung cancer. *Cancer Cell*. 2015;**27**(3):397-408

[50] Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: Recommendations by an international TILs working group 2014. *Annals of Oncology*. 2015;**26**(2):259-271

[51] Hegde PS, Karanikas V, Evers S. The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. *Clinical Cancer Research*. 2016;**22**(8):1865-1874

[52] Juergens RA, Zukotynski KA, Singnurkar A, Snider DP, Valliant JF, Gulenchyn KY. Imaging biomarkers in immunotherapy. *Biomarkers in Cancer*. 2016;**8**s2(II):BIC.S31805

[53] Sartor O, Eisenberger M, Kattan MW, Tombal B, Lecouvet F. Unmet needs in the prediction and detection of metastases in prostate cancer. *The Oncologist*. 2013;**18**(5):549-557

[54] Tan YY, Liang J, Liu DF, Zhu F, Wang GM, Ding XM, et al. 18F-FLT PET/CT imaging in a wister rabbit inflammation model. *Experimental and Therapeutic Medicine*. 2014;**8**(1):69-72

[55] Bigley AB, Rezvani K, Shah N, Sekine T, Balneger N, Pistillo M, et al. Latent cytomegalovirus infection enhances anti-tumour cytotoxicity through accumulation of NKG2C+ NK cells in healthy humans. *Clinical and Experimental Immunology*. 2016;**185**(2):239-251

[56] Huehls AM, Coupet TA, Sentman CL. Bispecific T-cell engagers for cancer immunotherapy. *Immunology and Cell Biology*. 2015;**93**(3):290-296

[57] Gao J, Ward JF, Pettaway CA, Shi LZ, Subudhi SK, Vence LM, et al. VISTA is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. *Nature Medicine*. 2017;**23**(5):551-555

[58] Messenheimer DJ, Jensen SM, Afentoulis ME, Wegmann KW, Feng Z, Friedman DJ, et al. Cancer therapy: Preclinical timing of PD-1 blockade is critical to effective combination immunotherapy with anti-OX40. *Clinical Cancer Research*. 2017;**23**(20)

[59] Weintraub K. Take two: Combining immunotherapy with epigenetic drugs to tackle cancer. *Nature Medicine*. 2016;**22**(1):8-10

[60] Steinsaltz A. What does rabbi Steinsaltz say? There are no final answers. *Parabola*. 2006;**31**(4):56-58

[61] Kochenderfer JN, Dudley ME, Kassim SH, Somerville RPT, Carpenter RO, Maryalice SS, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *Journal of Clinical Oncology*. 2015;**33**(6):540-549

[62] Mazzone R, Zwergel C, Mai A, Valente S. Epi-drugs in combination with immunotherapy: A new avenue to improve anticancer efficacy. *Clinical Epigenetics*. 2017;**9**(1):1-15