International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1544-1550 www.ijprajournal.com ISSN: 2249-7781

Immune Check point Inhibitors: A review

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Submitted: 01-02-2023 Accepted: 10-02-2023

INTRODUCTION:

The development of immune checkpoint inhibitors (ICIs) is a revolutionary milestone in the field of immuno-oncology. Tumor cells evade immunosurveillance and progress through different mechanisms, including activation of immune checkpoint pathways that suppress antitumor immune responses.[1]

Cancer growth and progression are associated with immune suppression. Cancer cells have the ability to activate different immune checkpoint pathways that harbor immunosuppressive functions.

Tumor recognition followed by tumor antigen presentation to T cells and T-cell activation leads to tumor cell kill. T-cell-mediated immune response is modulated by stimulatory and inhibitory signals. These immune checkpoints exist in a normal physiological state to protect against autoimmunity and inflammation. In a neoplastic state, dysfunction of these immune checkpoint proteins can lead to tumor tolerance and eventually allow for tumor 'escape' from the immune system.[2]

Immune checkpoint inhibitors (ICIs), work by blocking checkpoint proteins from binding with their partner proteins. The two main pathways that are specifically targeted in clinical practice are cytotoxic T-lymphocyte antigen-4 (CTLA- 4) and programmed cell death protein 1 (PD-1) that showed potent immune-modulatory effects through their function as negative regulators of T cell activation.[3]

Cytotoxic T-lymphocyte- associated antigen 4 (CTLA-4, also known as CD152), with its ligands CD80 and CD86, an inhibitory receptor as a global immune checkpoint engaged in priming immune responses via downmodulating the initial stages of T-cell activation, was the first clinically validated checkpoint pathway target.[4]

Programmed death-1 (PD-1), an inhibitory receptor expressed on activated T cells, can reverse immune suppression and release T cell activation. Anti-PD1/PDL1 antibodies have become some of the most widely prescribed anticancer therapies.[5]

It is in a favorable position to regulate T cell function in dendritic cells and other antigen-presenting cells (APCs). T cells recognize tumor cells in the human body and kill them, but when tumor cells recognize PD1 protein on T cells, the tumor cells will upregulate the PDL1 protein and PD1 binds to PDL1 leading to apoptosis of the T cells.[6]

T-cell-targeted immunomodulators are now used as single agents or in combination with chemotherapies as first or second lines of treatment for various cancer.[7] In this review, we discuss different predictive biomarkers for anti-PD-1/PD-L1 and anti-CTLA-4 inhibitors.

Nivolumab: is a genetically engineered anti-PD-1 mAb, developed by immunizing transgenic mice for human immunoglobulin loci with recombinant Chinese hamster ovary cells expressing human PD-1 and PD-1/human IgG1 Fc fusion protein.[8]

The ligands PD-L1 and PD-L2 bind to the PD-1 receptor on T-cells, inhibiting the action of these cells. Tumor cells express PD-L1 and PD-L2. Nivolumab binds to PD-1, preventing PD-L1 and PD-L2 from inhibiting the action of T-cells, restoring a patient's tumor-specific T-cell response.[9]It has a long duration of action as it is administered every 2-4 weeks.

Common side effects:Fatigue, Lymphocytopenia, Musculoskeletal pain, Decreased appetite, Cough.

less common side effects(occurring in about 10-29%):Nausea, Anemia, Constipation, Rash, Abdominal pain, Thrombocytopenia

A rare but severe side effects include: Immune-mediated: Pneumonitis, Colitis, Hepatitis, Nephritis and Renal Dysfunction, Hypothyroidism and Hyperthyroidism

Indications: to treat unresectable or metastatic melanoma, melanoma as adjuvant treatment, resectable or metastatic non-small cell lung cancer, small cell lung cancer, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1544-1550 www.ijprajournal.com ISSN: 2249-7781

urothelial carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, hepatocellular carcinoma, and esophageal cancer.
Nivolumab is also approved for the treatment of HER2-negative advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma when used in combination with a fluoropyrimidine- and platinum-containing chemotherapy regimen.[10, 11]

Pembrolizumab: is a highly selective IgG4-kappa humanized monoclonal antibody directed against human cell surface PD-1 (programmed death receptor-1) on lymphocytes.It was generated by grafting the variable sequences of a very high-affinity mouse antihuman PD-1 antibody onto a human IgG4-kappa isotype. The PD-1 receptor provides an important "immune checkpoint," which helps prevent the immune system from attacking itself. Certain types of tumors have a high expression of PD-L1(programmed death receptor ligand-1).Other tumor types use adaptive immune resistance where they take the natural physiology of PD-L1 induction (protection of immune-mediated damage from infections) and adapt it towards anti-tumor responses.When PD-L1 engages with PD-1, the T-cell function becomes inhibited; pembrolizumab blocks the PD-1: PDL-1 complex formation allowing improved T-cell mediated killing.[12, 13]
Common side effects:Fatigue, Anemia, Cough, Itching, Rash, Decreased appetite, Constipation, Diarrhea, Abdominal pain.Less common side effects: Immune-mediated: pneumonitis, nephritis, colitis, hepatitis, hyperthyroidism, hypothyroidism.

Indications:[14,15,16]

- Melanoma: Unresectable or metastatic melanoma
- Non-Small Cell Lung Cancer: First-line metastatic non-squamous NSCLC without EGFR/ALK tumor abnormality in combination with platinum chemotherapy and pemetrexed.
- Head and Neck Squamous Cell Carcinoma: First-line metastatic or unresectable/recurrent HNSCC in combination with FU and platinum.
- Renal Cell Carcinoma:First-line advanced RCC in combination with axitinib
- Classical Hodgkin Lymphoma
- Primary Mediastinal Large B-Cell Lymphoma
- Urothelial Carcinoma:Locally advanced or metastatic urothelial carcinoma not eligible for any platinum-based chemotherapy
- Microsatellite Instability-High (MSI-H) Cancer
- Gastric Cancer: Locally advanced, metastatic gastric or gastroesophageal junction adenocarcinoma with tumor PD-L1 expression greater than 1% with disease progression after at least two lines of therapy, including platinum or fluoropyrimidine chemotherapy.
- Cervical Cancer Metastatic or recurrent cervical cancer, following chemotherapy, with tumor expression of PD-L1 greater than 1%.
- Hepatocellular Carcinoma: HCC patients previously treated with sorafenib
- Merkel Cell Carcinoma: Pediatric and adult recurrent or locally advanced MCC.
- Small Cell Lung Cancer: Metastatic SCLC following platinum-based chemotherapy and at least one other therapy.

Ipilimumab:is a fully humanized IgG1 monoclonal antibody, which targets cytotoxic T-lymphocyte antigen-4 (CTLA-4), was the first approved (25 March 2011) immune checkpoint inhibitor for treating patients with advanced melanoma.[17]

Cancer cells produce antigens, which the immune system can use to identify and destroy them. These antigens are recognized by dendritic cells, which present the antigens to CTLs in the lymph nodes. The CTLs can then recognize the cancer cells by those antigens and destroy them. However, dendritic cells also present the antigens to CTLs along with an inhibitory signal, which binds to a receptor, CTLA-4 (cytotoxic T lymphocyte-associated antigen 4), on the CTL and turns off the cytotoxic reaction. This allows the cancer cells to survive. Ipilimumab blocks the CTLA-4 inhibitory signal, and allows the CTLs to destroy the cancer cells.[18]It has a long duration of action as it is given every 3 to 4 weeks.

Indications:[19,20,21,22,23]

- Melanoma: Treatment of unresectable or metastatic melanoma, in combination with nivolumab, in adult patients.
- Renal Cell Carcinoma (RCC): Ipilimumab is used with nivolumab in some patients with intermediate- or poor-risk advancedrenal cell carcinoma as the first treatment.
- Colorectal Cancer: In adults and children aged 12 years and older. Ipilimumab is used with nivolumab to
  treat metastatic microsatellite instability-high (MSI-H) or mismatch repair

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1544-1550 www.ijprajournal.com ISSN: 2249-7781

deficient (dMMR) cancer that got worse after treatment with a fluoropyrimidine,oxaliplatin, and irinotecan hydrochloride.

- Hepatocellular Carcinoma : Ipilimumab is used with nivolumab in patients who have already been treated with sorafenib.
- Non-Small Cell Lung Cancer (NSCLC) : Ipilimumab is used with nivolumab as the first treatment in adults withmetastatic non-small cell lung cancer expressing PD-L1, but does not have a mutation in the EGFR or ALK gene.

a. metastatic or recurrent non-small cell lung cancer, and does not have a mutation in the EGFR or ALK gene. It is used with platinum chemotherapy.
b. Malignant Pleural Mesothelioma: Ipilimumab is used with nivolumab as the first-line treatment ofadult patients with unresectable malignant pleural mesothelioma.

- Esophageal Cancer - Ipilimumab is used with nivolumab as the first treatment in adults with squamous cell carcinoma of the esophagus.

Ipilimumab causes increased activation of T-cells, and thus its adverse effects generally result from excess T-cell activation.

Common side effects: pruritic rash, diarrhea, or colitis. Less common adverse effects include conjunctivitis, uveitis, inflammatory hepatitis, liver failure, hypothyroidism, hypopituitarism, adrenal insufficiency, hypogonadism, intestinal perforation, severe enterocolitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Tremelimumab: also known as ticilimumab, is a fully human IgG2 monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). It binds to cytotoxic T-lymphocyte-associated protein (CTLA)-4 and results in inhibition of B7-CTLA-4-mediated downregulation of T cell activation.[24] Tremelimumab enhances T cell-mediated killing of tumours and reduces tumour growth

In synergistic mouse tumor models, blocking CTLA-4 activity resulted in decreased tumor growth and increased proliferation of T cells in tumors. Tremelimumab was first approved in October 2022.[25]

Indications:[26]

- used to treat unresectable hepatocellular carcinoma in combination with durvalumab.
- in combination with durvalumab and platinum-based chemotherapy for adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

Durvalumab:is a selective, high-affinity human immunoglobulin G1 monoclonal antibody and a novel immune-checkpoint inhibitor for cancer treatment.[2] Produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell suspension

Culture. Durvalumab is a programmed death-ligand 1 (PD-L1) blocking antibody that works to promote normal immune responses that attack tumour cells.

PD-L1 expression on tumor cells and tumor-associated immune cells in the tumor microenvironment can be induced by inflammatory signals and cytokines. PD-L1 blocks T-cell function and activation by interacting with PD-1 and CD80 (B7.1), and reduces cytotoxic T-cell activity, proliferation, and cytokine production.Durvalumab blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) and exerts its anticancer effects by increasing T-cell activation, enhancing detection and ablation of tumour cells.[27]

Indications:[28,29,30]

- unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumour aberrations, in combination with tremelimumab and platinum-based chemotherapy.
- extensive-stage small cell lung cancer (ES-SCLC) in combination with etoposide and either carboplatin or cisplatin as first-line therapy.
- locally advanced or metastatic biliary tract cancer (BTC) in combination with gemcitabine and cisplatin.unresectable hepatocellular carcinoma (uHCC) in combination with tremelimumab.

Cemiplimab:is a recombinant human immunoglobulin G4 monoclonal antibody that targets and blocks the PD-1 pathway, thus helping

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1544-1550 www.ijprajournal.com ISSN: 2249-7781

the immune system to fight cancer cells.Cemiplimab binds to the PD-1 receptor found on T-cells, blocking its interaction with PD ligand 1 (PD-L1) and PD-L2, thereby inhibiting T-cell proliferation and cytokine production.[31]

Indications:[32]

- Locally advanced or metastatic cutaneous squamous cell carcinoma in patients who are not candidates for curative surgery or curative radiation.
- Metastatic basal cell carcinoma
- Locally advanced non-small cell lung cancerin combination with platinum- based chemotherapy for the first- line treatment of adults with no EGFR, ALK or ROS1 aberrations, who are not candidates for surgical resection or definitive chemoradiation.
- Recurrent or metastatic cervical cancer in adults with disease progression on or after platinum-based chemotherapy.

Atezolimumab:

Atezolizumab is a humanized monoclonal antibody,binds selectively to PD-L1 and prevents the binding of PD-L1 to PD-1 and B7-1, which enhances the magnitude and quality of the tumor-specific T-cell responses, resulting in improved antitumor activity.[33]

In this way, T-cell activation is enabled and tumor cell death is ultimately induced.

As a biologic agent, atezolizumab can cause a number of immune-mediated complications.

Side effects: Adrenal insufficiency has been reported with the drug both alone and in combination with other antineoplastic agents.[34]Pulmonary toxicity in the form of immune-mediated pneumonitis and insterstitial lung disease. Ocular toxicity in the form of uveitis and iritis have been reported in the literature. Hypothyroidism, hyperthyroidism, and rarely, acute thyroiditis can arise secondary to the administration of atezolizumab.[35]Hepatotoxicity. Most common adverse reactions (≥ 20% of patients) included: fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation.

Atezolizumab is given as an intravenous injection through a vein (IV) over 60 minutes for the first infusion, and if no infusion reaction, over 30 minutes for each infusion thereafter. Treatment cycles are every 3 weeks (21 days). Medications can be given before the infusion to reduce allergic reactions.

Indications:[36,37,38]

- Metastatic Non-small-cell Lung Cancer (NSCLC):

a. Atezolizumab, as a single agent, in patients with metastatic NSCLC.
b. Atezolizumab, in combination with bevacizumab plus chemotherapy (paclitaxel and carboplatin), in adult patients with metastatic non-squamous NSCLC.

- Unresectable or Metastatic Hepatocellular Carcinoma**:** Atezolizumab, in combination with bevacizumab.
- Unresectable or Metastatic Melanoma:Atezolizumab, in combination with vemurafenib and cobimetinib.
- Locally Advanced or Metastatic Urothelial Carcinoma:Atezolizumab, as a single agent, is indicated in patients with locally advanced or metastatic urothelial carcinoma.
- Extensive-stage Small Cell Lung Cancer:Atezolizumab, in combination with carboplatin and etoposide.

Avelumab: is a human recombinant monoclonal IgG1 antibody to the programmed cell death ligand-1 (PD-L1), which has distinctive immunomodulatory activity and is used as a checkpoint inhibitor in cancer immunotherapy.

It specifically bind to PD-L1, preventing the interaction between PD-L1 and the inhibitory T-cell receptor PD-1. PD-L1 blockade removes the suppression of T-cell activity, resulting in T-cell-mediated, adaptive antitumour immune responses.[39]In addition, avelumab inhibits the interaction of PD-L1 with a second inhibitory receptor, B7.1, which may be expressed on APCs and T cells. Thus, avelumab may also potentiate T-cell reactivation and cytokine production by inhibiting the interaction with PD-1 and B7.1 on T cells with PD-L1 on APCs.[40] Unlike other anti-PD-L1 or anti-PD-1 antibodies, avelumab has a (Fc) region, which enables avelumab to engage with Fc-γ receptors on natural killer cells and induce tumour-directed antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.

Side effects are fatigue, headache, musculosketetal pain, arthralgia, abdominal pain, diarrhea, nausea, vomiting, decreased appetite, weight loss, fever, cough, dyspnea, pruritus, and rash. As a result of the immune enhancement, between 15% and 30% of avelumab treated patients

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1544-1550 www.ijprajournal.com ISSN: 2249-7781

develop immune related side effects, including enterocolitis, dermatitis, endocrinopathy, pneumonitis, neuropathy, nephritis and hepatitis.[41] The recommended dose is 800 mg as an intravenous infusion every 2 weeks. Premedication with acetaminophen and antihistamines is recommended for the first 4 infusions.

Indications:[42,43]

- In adult and pediatric patients ≥12 years of age with metastatic Merkel cell carcinoma (MCC).
- locally advanced or metastatic urothelial carcinoma
- Advanced renal cell carcinoma (RCC): in combination with axitinib.

Dostarlimab:is an IgG_4 humanized monoclonal antibody targeted against the human programmed death receptor-1 (PD-1).It inhibits programmed cell death receptor-1 (PD-
1) and blocks the interaction of receptors with PD-L1 and PD-L2, which in turn activates T-cells and enhances overall immunity. Dostarlimab works as a functional antagonist, resulting in increased IL-2 production.[44]
The dose of dostarlimab that is generally recommended is 500 mg every 3 weeks (for the first four doses), after the fourth dose, 1000 mg every 6 weeks is administered until disease progression or any unacceptable toxicity is noticed.

Indications:[45,46]

- for adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer that has progressed despite ongoing or prior treatment with a platinum-containing chemotherapy regimen.
- Dostarlimab has also shown promising results in endometrial cancer, ovarian cancer, melanoma, head and neck cancer, and breast cancer therapy.

REFERENCES:

[1]. Darvin, P., Toor, S.M., Sasidharan Nair, V. et al. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med **50**, 1–11 (2018). https://doi.org/10.1038/s12276-018-0191-1

[2]. Sundar R, Cho BC, Brahmer JR, Soo RA. Nivolumab in NSCLC: latest evidence and clinical potential. Ther Adv Med Oncol. 2015 Mar;7(2):85-96. doi: 10.1177/1758834014567470. PMID: 25755681; PMCID: PMC4346216.

[3]. Zam W, Ali L. Immune Checkpoint Inhibitors in the Treatment of Cancer. Curr Rev Clin Exp Pharmacol. 2022;17(2):103-113. doi: 10.2174/1574884716666210325095022. PMID: 33823768.

[4]. Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer. 2016;16(5):275–87.

[5]. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH. et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer. 2016;60:12–25. [PMC free article] [PubMed] [Google Scholar]

[6]. Li Y., Fang M., Zhang J., Wang J., Song Y., Shi J., et al. (2015). Hydrogel Dual Delivered Celecoxib and Anti-PD-1 Synergistically Improve Antitumor Immunity. Oncoimmunology 5 (2), e1074374. 10.1080/2162402X.2015.1074374

[7]. Darvin, P., Toor, S.M., Sasidharan Nair, V. et al. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med **50**, 1–11 (2018). https://doi.org/10.1038/s12276-018-0191-1

[8]. Brahmer JR, Hammers H, Lipson EJ. Nivolumab: targeting PD-1 to bolster antitumor immunity. Future Oncol. 2015;11(9):1307–
26. [PubMed] [Google Scholar]

[9]. Lee KW, Lee DH, Kang JH, Park JO, Kim SH, Hong YS, Kim ST, Oh DY, Bang YJ: Phase I Pharmacokinetic Study of Nivolumab in Korean Patients with Advanced Solid Tumors. Oncologist. 2018 Feb;23(2):155-e17. doi: 10.1634/theoncologist.2017-0528. Epub 2017 Nov 20.

[10]. Solimando DA Jr, Waddell JA: Nivolumab and Olaparib. Hosp Pharm. 2015 May;50(5):356-66. doi: 10.1310/hpj5005-356

[11]. Mashima E, Inoue A, Sakuragi Y, Yamaguchi T, Sasaki N, Hara Y, Omoto D, Ohmori S, Haruyama S, Sawada Y, Yoshioka M, Nishio D, Nakamura M:

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1544-1550 www.ijprajournal.com ISSN: 2249-7781

Nivolumab in the treatment of malignant melanoma: review of the literature. Onco Targets Ther. 2015 Aug 6;8:2045-51. doi: 10.2147/OTT.S62102. eCollection 2015.

[12]. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010 Jul;236:219-42

[13]. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Mar 22;12(4):252-64

[14]. Zhang T, Xie J, Arai S, et al. The efficacy and safety of anti-PD-1/PD-L1 antibodies for treatment of advanced or refractory cancers: a meta-analysis. Oncotarget. 2016;**7**(45):73068–73079.

[15]. Oliveira AF, Bretes L, Furtado I. Review of PD-1/PD-L1 Inhibitors in Metastatic dMMR/MSI-H Colorectal Cancer. Front Oncol. 2019;9:396

[16]. Nan X, Gold KA, Cohen E. Immunotherapeutic Approaches to the Management of Head and Neck Cancer. Oncology (Williston Park). 2018 Dec 17;32(12):617-9, 625-6.

[17]. Passiglia F, Novello S. Immunotherapy in first line for extensive-stage small-cell lung cancer: another piece is going to fill the puzzle? Ann Transl Med. 2018 Dec;6(Suppl 2):S120.

[18]. Robert, C. et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N. Engl. J. Med. 364, 2517–2526.

[19]. Thumar JR, Kluger HM: Ipilimumab: a promising immunotherapy for melanoma. Oncology (Williston Park). 2010 Dec;24(14):1280-8.

[20]. Farolfi A., Ridolfi L., Guidoboni M., Nicoletti S. V., Piciucchi S., Valmorri L., et al. (2012). Ipilimumab in Advanced Melanoma: Reports of Long-Lasting Responses. Melanoma Res. 22 (3), 263–270. 10.1097/CMR.0b013e328353e65c [PubMed] [CrossRef] [Google Scholar

[21]. Yang JC, Hughes M, Kammula U, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother2007;30:825-30.

[22]. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol. 2018;36(8):773-779. doi:10.1200/JCO.2017.76.9901

[23]. Yau, T. et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040 [abstract]. J. Clin. Oncol. **37** (Suppl. 15), 4012 (2019).

[24]. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non–small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31-41. doi:10.1016/S1470-2045(16)30624-6

[25]. Duffy AG, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol. 2017 Mar;66(3):545-551. doi: 10.1016/j.jhep.2016.10.029. Epub 2016 Nov 2. PMID: 27816492; PMCID: PMC5316490.

[26]. Cho BC, Reinmuth N, et al. Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020 May 1;6(5):661-674. doi: 10.1001/jamaoncol.2020.0237.

[27]. Syed YY:Durvalumab: First Global Approval. Drugs. 2017 Aug;77(12):1369-1376. doi: 10.1007/s40265-017-0782-5.

[28]. Antonia SJ, Villegas A, Daniel D, et al; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. NEngl J Med. 2017;377(20):1919-1929. doi:10.1056/NEJMoa1709937

[29]. Al-Salama ZT. Durvalumab: A Review in Extensive-Stage SCLC. Target Oncol. 2021 Nov;16(6):857-864. doi: 10.1007/s11523-021-00843-0. Epub 2021 Nov 3. Erratum in: Target Oncol. 2022 Jan;17(1):91. PMID: 34731446; PMCID: PMC8648650.

[30]. Do-Youn Oh et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract CancerNEJM Evid 2022; 1 (8)DOI:https://doi.org/10.1056/EVIDoa2200015

[31]. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018;379:341-351.

[32]. Migden MR, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. Lancet Oncol. 2020 Feb;21(2):294-305. doi: 10.1016/S1470-2045(19)30728-4. Epub 2020 Jan 14. PMID: 31952975; PMCID: PMC7771329.

[33]. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy – inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res. 2012;**18**(24):6580–6587.

[34]. Drug Monograph taken from Accessmedicine. Available at: https://accessmedicine-mhmedical-comm.proxygw.wrlc.org/drugs.aspx?gbosID=423740#monoNumber=423740&sectionID=222845233&tab=tab0.

[35]. U.S. Food and Drug Administration. FDA approves atezolizumab for extensive-stage small cell lung cancer. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-extensive-stage-small-cell-lung-cancer. Accessed July 28, 2019.

[36]. Herbst RS, Giaccone G, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. N Engl J Med. 2020 Oct 01;383(14):1328-1339. [PubMed]

[37]. Socinski MA, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med. 2018 Jun 14;378(24):2288-2301. [PubMed]

[38]. Schmid P, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Jan;21(1):44-59.

[39]. Grenga I, Donahue RN, Lepone LM. et al. A fully human IgG1 anti-PD-L1 MAb in an in vitro assay enhances antigen-specific T-cell responses. Clin Transl Immunol 2016; 5(5): e83

[40]. Brown JA, Dorfman DM, Ma FR. et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003; 170(3): 1257–1266.

[41]. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Avelumab. [Updated 2022 Jun 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548530/

[42]. Uekawa A, Kurahashi R, Motoshima T, Murakami Y, Yatsuda J, Kamba T. Efficacy of avelumab plus axitinib for advanced renal cell carcinoma as late-line therapy: A case report. Urol Case Rep. 2022 Aug 24;45:102198. doi: 10.1016/j.eucr.2022.102198. PMID: 36072283; PMCID: PMC9441301.

[43]. Apolo AB, Ellerton JA, Infante JR, et al. Avelumab as second-line therapy for metastatic, platinum-treated urothelial carcinoma in the phase Ib JAVELIN Solid Tumor study: 2-year updated efficacy and safety analysis. Journal for ImmunoTherapy of Cancer 2020;8:e001246. doi:10.1136/ jitc-2020-00124

[44]. Costa B, Vale N. Dostarlimab: A Review. Biomolecules. 2022 Jul 26;12(8):1031. doi: 10.3390/biom12081031. PMID: 35892341; PMCID: PMC9331682.

[45]. Alkholifi, F.K.; Alsaffar, R.M. Dostarlimab an Inhibitor of PD-1/PD-L1: A New Paradigm for the Treatment of Cancer. Medicina 2022, 58, 1572. https://doi.org/ 10.3390/medicina58111572

[46]. Singh V, Sheikh A. Dostarlimab as a Miracle Drug: Rising Hope against Cancer Treatment. Biosensors (Basel). 2022 Aug 8;12(8):617. doi: 10.3390/bios12080617. PMID: 36005013; PMCID: PMC9406030.