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REVIEW Article

Immune checkpoint inhibitors and predictive biomarkers in checkpoint inhibition therapy

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ABSTRACT

Cancer is one of the leading causes of death at a global scale. Many malignancies prove very hard to manage and current treatment methods, although effective to some extent, need improvement. Recently, Immune Checkpoints such as Programmed death receptor 1 (PD-1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) have been a subject of great interest in cancer treatment. Blocking these receptors and their ligands enables the T-cells to recognize and destroy cancer cells easier, although this may not always be the case.

Many studies have shown benefits of using immune checkpoint inhibitors (ICIs) over conventional chemotherapy, although there are some treatment-related adverse effects that are also to be taken into calculation. Most adverse reactions are autoimmune, given the fact that ICIs make the T-cells more reactive and block their co-inhibitory signals when activated.

As with every treatment, predictive biomarkers for survival rate and response rate are very important, as such there has been a lot of research in order to find reliable markers that would allow an accurate estimate for the RR and OS of the patient. The most commonly used as of now are Tumor Mutation

Burden, a marker that represents how many mutations cancer cells have suffered, as more of them would make the chances of immunogenic neoantigens being produced higher, Mismatch Repair Deficiency/ Microsatellite Instability, which is a marker that shows a tumor phenotype characterized by the production of immunogenic neoantigen, PD-L1 expression, which is a biomarker that has been linked with better response to ICI therapy, and Neutrophil to Lymphocyte Ratio, a value that expresses the balance between cancer induced inflammation and anti-tumor response of the body.

In this review, I present FDA-approved checkpoint inhibitors and their applications, benefits and limitations of immune checkpoint blockade and predictive biomarkers and their accuracy and reliability. This manuscript offers insight into the uses and safety of checkpoint inhibitors as a cancer therapy, as well as the advantages and drawbacks of their most used biomarkers, thus allowing for a conclusive view on the topic.

As such, Immune Checkpoint Inhibitors show great potential for cancer treatment. Predictive biomarkers for this new medicine are also promising and have proven reliable across many malignancies, although their ability to predict the response to ICI therapy can come under question in a number of scenarios.

Keywords

Immune checkpoint inhibitors, Predictive biomarkers, FDA approved, Tumor mutation burden, dMMR/MSI-H, Neutrophil to lymphocyte ratio, PD-L1 expression.

Abbreviations

Immune checkpoint inhibitors (ICIs); Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4); Programmed death receptor 1 (PD-1); Programmed death receptor ligand 1 (PD-L1); Programmed death receptor ligand 2 (PD-L2); Tumor mutation burden (TMB); Mismatch repair deficiency (dMMR); Microsatellite instability (MSI); Neutrophil to Lymphocyte ratio (NLR); Food and Drug Administration (FDA).

SUMMARY

1. Introduction

In 2021 alone the American Cancer Society estimates a total of 1,898,160 new cases of cancer and 608,570 cancer deaths. It is worth noting that due to advancements in diagnostic methods and treatments cancer death rates have dropped by 31% between 1991 and 2018. This means that in 2018 there were 3.2 million deaths less than in 1991 in the US[1]. Even with better overall survival rates cancer is still one of the leading causes of death, therefore it is very important to develop efficient treatments.

T cells are able to target tumor cells by recognizing the non-self antigens present on the surface of tumor cells. The T cell response depends on two types of signals. The antigen-specific signals via T-cell receptors (TCR) and the antigen-unspecific costimulatory and coinhibitory pathways. As such, CD28 is a prominent costimulatory pathway activation receptor whereas CTLA-4 and PD-1 receptors activate coinhibitory pathways[2] (See Figure 1).

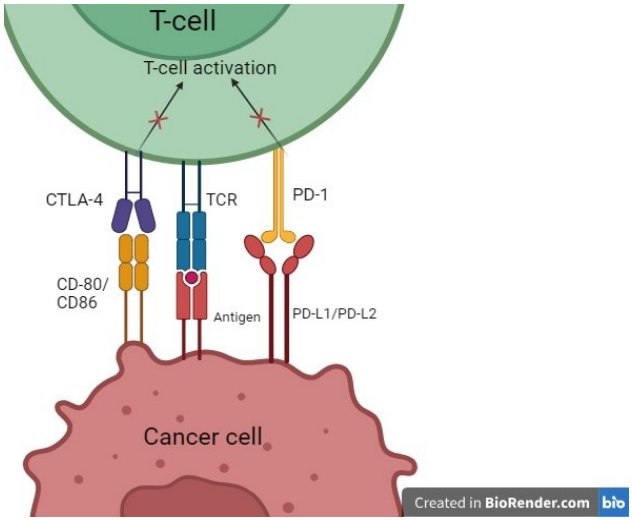

Figure 1. *Immune Checkpoints and their ligands*
It can be seen that the interaction between CTLA-4 and PD-1 present on the surface of the T-cells with their ligands on the cancer cell can lead to the inhibition of T-cell activation, thus allowing the cancer cell to evade immune detection.

A new approach to cancer treatment are immune checkpoint inhibitors. These antibodies target cellular receptors such as PD-1 and CTLA-4 that activate intracellular pathways that inhibit the T-cell response. The first approved immune checkpoint inhibitor was Ipilimumab, which received FDA approval in 2011 for treatment of melanoma. More checkpoint inhibitors have been approved by the FDA over the next years for a variety of malignancies[3].

However, as with every new drug, it is important to be able to measure the benefits and risks of using immune checkpoint inhibitors as cancer treatment. It is very important to establish predictive biomarkers to maximize therapeutic benefit. Such biomarkers need high positive and negative predictive values in order to be a reliable tool. A positive predictive value is the number of correctly predicted receivers or survivors out of the total of patients with the positive biomarker

result, and negative predictive value is the number of correctly predicted non-receivers or non-survivors out of the total number of patients with a negative biomarker result[4].

2. Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are monoclonal antibodies that are able to block PD-1, PD-L1 and CTLA-4. They have demonstrated impressive clinical activities against various malignancies, however durable benefits have been observed only in a small fraction of patients[2].

2.1 CTLA-4 inhibitors

Cancer cells make use of CTLA-4 in order to inhibit the activation of T-cells (See Figure 1) Ipilimumab, a monoclonal antibody that targets CTLA-4 was the first ever approved immune checkpoint inhibitor. It received approval under the commercial name of Yervoy for treatment of advanced melanoma. By binding to CTLA-4, ipilimumab prevents the co-stimulatory pathway of CD28, thus rendering the t-cell unable to completely activate and proliferate[5].

Ipilimumab (Yervoy) is the only approved CTLA-4 inhibitor. It is a human IgG1 monoclonal antibody directed at CTLA-4. The structure of the antibody is composed of two heavy chains and two kappa light chains, the light and heavy chains being linked by interchain disulfide chains[6].

2.2 PD-1 and PD-L1 inhibitors

Tumor cells usually overexpress PD-L1 (see Figure 1), thus being able to inhibit the activation of CD8+ T-cells that come into contact with them. The ending result of this is the evasion of the immune response by the cancer cells. By blocking PD1 and PD-L1, such inhibition will not take place, and the Cytotoxic T-cell will be able to properly activate upon contact with the tumor cells[7].

2.2.1 Approved PD-1 inhibitors

Nivolumab (OPDIVO) is a human IgG4 monoclonal antibody directed at PD-1 originally approved for. It consists of two heavy polypeptide chains and two light kappa chains binded by interchain disulfide chains. The method used to obtain nivolumab recombinant DNA technology[6]. Nivolumab blocks the PD-1 receptor, thus preventing it from binding to it's two ligands, PD-L1 and PD-L2. Such action will stop the inhibitory signaling cascade that would have normally been initiated by PD-1 upon contact with PD-L1 or PD-L2[7].

Pembrolizumab (Keytruda) is a human IgG4 monoclonal antibody directed at PD-1. It is composed of 2 heavy polypeptide chains and two kappa light chains bound together by interchain disulfide chains[8]. Pembrolizumab can bind to PD-1 receptor and block the inhibitory pathway associated with it, thus increasing immune reactivity and allowing T-cells to take anti-tumor action[7].

Cemiplimab (Libtayo), is a human IgG4 monoclonal antibody with high affinity for PD-1, it consists of two heavy polypeptide chains and two light kappa chains[9]. Cemiplimab up-regulates cytotoxic T-cells by binding to PD-1 receptor and preventing it's interaction with PD-L1 and PD-L2[7].

Dostarlimab (Jemperli) is a newly approved immune checkpoint inhibitor that targets PD-1, and has been approved in the treatment of endometrial cancer[10]. The new checkpoint inhibitor has been particularly effective in microsatellite instability and mismatch repair deficient endometrial cancer[11] (See Table 1).

2.2.2 Approved PD-L1 inhibitors

Durvalumab (Imfinzi) is a human monoclonal antibody with affinity for PD-L1. Blocking this ligand leads to increased immune reactivity and thus enables anti-tumor activity, making it a reliable immunotherapy option for cancer[12] (See Table 1).

Avelumab (Bavencio) is a human monoclonal antibody that binds to PD-L1, thus modulating T-cell immune reactivity to tumor cells[13].

Atezolizumab (Tecentriq) is a human monoclonal antibody that stops interaction between PD-L1 and both PD-1 and B7.1[14].

2.3 Benefits and limitations of using immune checkpoint inhibitors

2.3.1 Benefits

Given recent research results, it has been demonstrated that treatment with Immune Checkpoint Inhibitors improved the outcome in patients with solid tumors, as per RECIST criteria evaluation, increasing the progression free survival

and overall survival. Some of the cancers that have proven to respond to such treatments are melanoma, NSCLC, urothelial cancer, renal cell cancer and other malignancies[23].

A good example can be the overall response rate (ORR) achieved with pembrolizumab in triple negative breast cancer patients, which during the phase 1b of the KEYNOTE-012 study has been measured at 18,5%, which is double than that of capecitabine (9%), which was one of the common treatment options at the time of ICI introduction. Similar results have been achieved in other types of cancer, such as gastric (ORR 22,2%), head and neck cancer (ORR 21,4%) and even in urothelial cancer (ORR 27,6%)[24].

Table 1. *FDA approved checkpoint inhibitors and their indications*.

Drug Name	Inhibitor type	Indications
Ipilimumab[15]	CTLA-4 Inhibitor	• Unresectable or Metastatic Melanoma • Adjuvant Treatment of Melanoma • Advanced Renal Cell Carcinoma • Microsatellite Instability-High or Mismatch Repair • Deficient Metastatic Colorectal Cancer • Hepatocellular Carcinoma • Metastatic Non-Small Cell Lung Cancer • Malignant Pleural Mesothelioma
Nivolumab[16]	PD1 Inhibitor	• Unresectable or Metastatic Melanoma • Adjuvant Treatment of Melanoma • Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer • Metastatic Non-Small Cell Lung Cancer • Malignant Pleural Mesothelioma • Advanced Renal Cell Carcinoma • Classical Hodgkin Lymphoma • Squamous Cell Carcinoma of the Head and Neck • Urothelial Carcinoma • Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer • Hepatocellular Carcinoma • Esophageal Cancer • Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
Pembrolizumab[17]	PD1 Inhibitor	• Melanoma • Non-Small Cell Lung Cancer • Small Cell Lung Cancer • Head and Neck Squamous Cell Cancer • Classical Hodgkin Lymphoma 1.1 Melanoma • Primary Mediastinal Large B-Cell Lymphoma • Urothelial Carcinoma • Microsatellite Instability-High or Mismatch Repair Deficient Cancer • Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer • Gastric Cancer • Esophageal Cancer • Cervical Cancer • Hepatocellular Carcinoma • Merkel Cell Carcinoma • Renal Cell Carcinoma • Endometrial Carcinoma • Tumor Mutational Burden-High Cancer • Cutaneous Squamous Cell Carcinoma • Triple-Negative Breast Cancer

Cemiplimab[18]	PD1 Inhibitor	• Cutaneous Squamous Cell Carcinoma • Basal Cell Carcinoma • Non-Small Cell Lung Cancer
Dostarlimab[19]	PD-1 Inhibitor	• Endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen • Solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
Durvalumab[20]	PD-L1 Inhibitor	• Non-Small Cell Lung Cancer • Small Cell Lung Cancer • Biliary Tract Cancers • Hepatocellular Carcinoma
Avelumab[21]	PD-L1 Inhibitor	• Metastatic Merkel Cell Carcinoma • Locally Advanced or Metastatic Urothelial Carcinoma • Advanced Renal Cell Carcinoma
Atezolizumab[22]	PD-L1 Inhibitor	• Urothelial Carcinoma • Non-Small Cell Lung Cancer • Small Cell Lung Cancer • Hepatocellular Carcinoma • Melanoma

2.3.2 Limitations

One important limitation of ICI is the non-tumor-specific action of the treatment. A patient that receives ICI will indeed have a better cellular response to the tumor by blocking PD-1 and CTLA-4, however this activation will not be inhibited at contact with normal, healthy cells either, thus it can lead to autoimmune events. Immune toxicities can affect the skin, colon, thyroid gland, pancreas, liver, lung and central nervous system[25].

Activated T-cells are capable of causing inflammation and/or destruction of normal tissues, thus leading to autoimmune diseases or symptoms. ICI treatment can lead to toxicities in any organ but the most frequently afflicted ones have been the skin and gastro-intestinal tract[26].

More and more evidence suggest that B-cells are also responsible for the immune-related toxicities. By producing auto-antibodies due to ICI treatment, the activated B-cells can cause diabetes, thyroiditis, myasthenia gravis and even encephalitis[26].

3. Predictors of Response in Immune Checkpoint Inhibitors

Ever since ICIs have been introduced in the treatment of cancer, there has been a need for a reliable biomarker capable of determining whether or not the patient would respond to immunotherapy or if the treatment is progressing well.

3.1 Tumor mutation burden

Tumor Mutation Burden represents the mutations induced by the environmental and intracellular factors. There is a strong connection between TMB and mutational signatures that would allow the immune system to identify cancer cells.

Mutations in the cancer cells lead to the production of abnormal proteins, some of them being immunogenic. As such, the more mutations a cell has the higher the chance of immunogenic neoantigens being produced and recognized by the immune cells, thus allowing them to detect, activate and destroy the mutated cell[27]. These abnormal proteins that can be recognized by the immune system are called neoantigens. These neoantigens can be targeted by the immune system, especially after treatments including T-cell activating drugs. It is important to note that not all mutations generate neoantigens, as many of the abnormal proteins might not be presented on the cell's MHC complexes, and some of them might not even be recognized by the T-cells[28].

Tumor mutation burden has been correlated to the level of neoantigens present in a tumor. As such, there have been many studies that have shown that a high tumor mutation burden can be correlated with a better response to immune checkpoint blockade. As such it has been proven that high TMB correlates with improved response and a greater progression free survival in non-small-cell lung cancer (NSCLC)[29]. TMB-high cervical and endometrial tumors from the KEYNOTE 158 trial have demonstrated a better

response to immune checkpoint blockade than TMB low tumors. TMB high colorectal cancer has also shown increased response in a cohort of patients. Melanoma tumors with high TMB have also shown increased response rates, and a similar trend has been observed in TMB high bladder cancer and NSCLC adenocarcinoma. Overall survival has been analyzed as well, as such a better prognosis has been observed in TMB high colorectal cancer and melanoma, and trends for improved prognosis have been observed in TMB high NSCLC adenocarcinomas and bladder tumors[30]. Other studies have further confirmed TMB as a reliable predictive biomarker as it has been correlated with benefit from immune checkpoint blockade therapy. It is however worth noting, that disease specific TMB thresholds are a necessity for effective ICI therapy, and such thresholds have yet to have been established[28]. In contrast with these findings, some studies have shown that TMB high tumors in breast cancer, prostate cancer and glioma did not achieve a satisfactory overall response rate improvement[31].

3.2 Microsatellite instability/ mismatch repair deficiency

Microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) are markers of frequent frameshift mutations in solid tumors which lead to the creation of highly immunogenic neoantigens[32]. Studies have been made to see whether MSI can be used as a biomarker for response to immune checkpoint blockade therapy. One of the more intensively researched types of cancer has been colorectal cancer. In this malignancy, studies have shown that MSI-high colorectal cancer responded better to ICI therapy[33], while colorectal cancers that have shown microsatellite stability or low instability proved resistant to ICIs[34]. Furthermore, even regardless of the tissue of origin, dMMR tumors have shown increased levels of neoantigens, making them sensitive to ICI therapy[35]. MSI has proven itself to be a very important predictor of response, as FDA has recently approved checkpoint inhibitors for the treatment of adult and pediatric tumors based on the presence of dMMR or MSI-High biomarkers[36]. It has also been noticed that tumors that exhibit MSI-H/dMMR are also correlated with PD-L1 expression[37]. which is another predictive biomarker that will be further described in the next section.

3.3 PD-L1 expression

PD-L1 expression represents an important tumor characterisitc to be considered when administering ICI therapy. Studies have been made to test if PD-L1 expression in tumors can be linked to better response to ICB therapy. Some studies have linked PD-1 expression with improved metastatic-free survival and overall survival[37,38]. However, emerging data shows that patients with low expressions of PD-L1 have also had robust responses to treatment, thus imposing the problem of whether PD-L1 expression's reliability as an exclusionary predictive biomarker[39]. The use of immunohistochemistry as a detection method for PD-L1 expression has not proven sufficient for determining if a tumor might or might not respond well to ICI immunotherapy[4]. In other instances, PD-L1 expression might not be so relevant when anti-PD-1 and anti-CTLA-4 ICIs are used as a combination therapy[28].

3.4 Neutrophil to lymphocyte ratio

The neutrophil to lymphocyte ratio represents the balance between pro-tumoral inflammation and anti-tumoral response. NLR can show a disbalance regarding the evolution of the tumor, as a higher neutrophil count suggests a pro-tumoral inflammation status, denoting a progressive disease[40]. Studies have shown that a high NLR is associated with poorer outcomes for the patients, thus proving it's value as a predictive biomarker[41,42]. NLR has proven reliable as a predictive biomarker even when taken into consideration independent of other prognostic factors[43]. Furthermore, lower NLR has shown to predict better efficacy of ICI therapy[44].

4. Conclusion

In conclusion, immune checkpoint blockade has proven to be a groundbreaking therapy option in many malignancies. Furthermore, biomarkers such as TMB, dMMR/MSI-H, PD-L1 expression and NLR have all shown great promise as predictors of response for immune checkpoint inhibitors therapies. However, although the previously discussed biomarkers have proven reliable across many malignancies, there are still different scenarios where their accuracy can come into question. As such, further study is required in order to fully adapt each biomarker and their role in the clinical practice.

Conflict of Interest

There are no conflicts of interests.

Aknowledgements

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: A Cancer Journal for Clinicians. 2022 72(1), 7–33. doi: 10.3322/CAAC.21708
2. Hui E. Immune checkpoint inhibitors. J Cell Biol. 2019 Mar 4;218(3):740-741 Epub 2019 Feb 13. PMID: 30760493; PMCID: PMC6400575, doi: 10.1083/jcb.201810035.
3. Wakeley ME, Gray CC, Monaghan SF, Heffernan DS, Ayala A. Check Point Inhibitors and Their Role in Immunosuppression in Sepsis. Crit Care Clin. 2020 Jan;36(1):69-88. Epub 2019 Oct 21. PMID: 31733683; PMCID: PMC6863093. doi: 10.1016/j.ccc.2019.08.006
4. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol. 2016 Dec;17(12):e542-e551. PMID: 27924752; PMCID: PMC5702534. doi: 10.1016/S1470-2045(16)30406-5.
5. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med. 2018 Dec 13;50(12):1-11 PMID: 30546008; PMCID: PMC6292890. doi: 10.1038/s12276-018-0191-1.
6. Gao X, McDermott DF. Ipilimumab in combination with nivolumab for the treatment of renal cell carcinoma. Expert Opin Biol Ther. 2018 Sep;18(9):947-957. Epub 2018 Aug 30. PMID: 30124333; PMCID: PMC6289271. doi: 10.1080/14712598.2018.1513485.
7. Ai L, Chen J, Yan H, He Q, Luo P, Xu Z, Yang X. Research Status and Outlook of PD-1/PD-L1 Inhibitors for Cancer Therapy. Drug Des Devel Ther. 2020 Sep 8;14:3625-3649. PMID: 32982171; PMCID: PMC7490077. doi: 10.2147/DDDT.S267433.
8. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). Hum Vaccin Immunother. 2016 Nov;12(11):2777-2789. Epub 2016 Jul 11. PMID: 27398650; PMCID: PMC5137544. doi: 10.1080/21645515.2016.1199310.
9. Rischin D, Migden MR, Lim AM, Schmults CD, Khushalani NI, Hughes BGM. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. J Immunother Cancer. 2020 Jun;8(1):e000775. PMID: 32554615; PMCID: PMC7304829. doi: 10.1136/jitc-2020-000775
10. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145-2158. Epub 2023 Mar 27. PMID: 36972026. doi: 10.1056/NEJMoa2216334.
11. Kasherman L, Ahrari S, Lheureux S. Dostarlimab in the treatment of recurrent or primary advanced endometrial cancer. Future Oncol. 2021 Mar;17(8):877-892. Epub 2020 Nov 30. PMID: 33251877. doi: 10.2217/fon-2020-0655.
12. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. Durvalumab. 2022 Jun 23. PMID: 31643480.
13. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. Avelumab. 2022 Jun 23. PMID: 31643848.
14. Inman BA, Longo TA, Ramalingam S, Harrison MR. Atezolizumab: A PD-L1-Blocking Antibody for Bladder Cancer. Clin Cancer Res. 2017 Apr 15;23(8):1886-1890. Epub 2016 Nov 30. PMID: 27903674. doi: 10.1158/1078-0432.CCR-16-1417
15. U.S. Food and Drug Administration, accessed on 29.12.2023, also available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s115lbl.pdf
16. U.S. Food and Drug Administration, accessed on 29.12.2023, also available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125554s112lbl.pdf
17. U.S. Food and Drug Administration, accessed on 29.12.2023, also available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf
18. U.S. Food and Drug Administration, accessed on 29.12.2023, also available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761097s014lbl.pdf

19. U.S. Food and Drug Administration, accessed on 29.12.2023, also available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761174s002lbl.pdf

20. U.S. Food and Drug Administration, accessed on 29.12.2023, also available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761069s033lbl.pdf

21. U.S. Food and Drug Administration, accessed on 29.12.2023, also available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761049s009lbl.pdf

22. U.S. Food and Drug Administration, accessed on 29.12.2023, also available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761034s043lbl.pdf

23. Franzin R, Netti GS, Spadaccino F, Porta C, Gesualdo L, Stallone G. The Use of Immune Checkpoint Inhibitors in Oncology and the Occurrence of AKI: Where Do We Stand? Front Immunol. 2020 Oct 8;11:574271. PMID: 33162990; PMCID: PMC7580288. doi: 10.3389/fimmu.2020.574271.

24. Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. J Clin Oncol. 2016 Jul 20;34(21):2460-7. Epub 2016 May 2. PMID: 27138582; PMCID: PMC6816000. doi: 10.1200/JCO.2015.64.8931.

25. Heeke AL, Tan AR. Checkpoint inhibitor therapy for metastatic triple-negative breast cancer. Cancer Metastasis Rev. 2021 Jun;40(2):537-547. Epub 2021 Jun 8. PMID: 34101053; PMCID: PMC8184866. doi: 10.1007/s10555-021-09972-4.

26. Haugh AM, Probasco JC, Johnson DB. Neurologic complications of immune checkpoint inhibitors. Expert Opin Drug Saf. 2020 Apr;19(4):479-488. Epub 2020 Mar 11. PMID: 32126176; PMCID: PMC7192781. doi: 10.1080/14740338.2020.1738382.

27. ..Jardim DL, Goodman A, de Melo Gagliato D, Kurzrock R. The Challenges of Tumor Mutational Burden as an Immunotherapy Biomarker. Cancer Cell. 2021 Feb 8;39(2):154-173. Epub 2020 Oct 29. PMID: 33125859; PMCID: PMC7878292. doi: 10.1016/j.ccell.2020.10.001.

28. Chan TA, Yarchoan M, Jaffee E, Swanton C, Quezada SA, Stenzinger A, Peters S. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. Ann Oncol. 2019 Jan 1;30(1):44-56. PMID: 30395155; PMCID: PMC6336005. doi: 10.1093/annonc/mdy495.

29. Hellmann MD, Nathanson T, Rizvi H, Creelan BC, Sanchez-Vega F, Ahuja A. Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer. Cancer Cell. 2018 May 14;33(5):843-852.e4. Epub 2018 Apr 12. PMID: 29657128; PMCID: PMC5953836. doi: 10.1016/j.ccell.2018.03.018.

30. Pender A, Titmuss E, Pleasance ED, Fan KY, Pearson H, Brown SD. Genome and Transcriptome Biomarkers of Response to Immune Checkpoint Inhibitors in Advanced Solid Tumors. Clin Cancer Res. 2021 Jan 1;27(1):202-212. Epub 2020 Oct 5. PMID: 33020056. doi: 10.1158/1078-0432.CCR-20-1163.

31. McGrail DJ, Pilié PG, Rashid NU, Voorwerk L, Slagter M, Kok M et al. High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types. Ann Oncol. 2021 May;32(5):661-672 Epub 2021 Mar 15. PMID: 33736924; PMCID: PMC8053682. doi: 10.1016/j.annonc.2021.02.006.

32. Bhamidipati D, Subbiah V. Tumor-agnostic drug development in dMMR/MSI-H solid tumors. Trends Cancer. 2023 Oct;9(10):828-839. Epub 2023 Jul 28. PMID: 37517955. doi: 10.1016/j.trecan.2023.07.002.

33. André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med. 2020 Dec 3;383(23):2207-2218. PMID: 33264544. doi: 10.1056/NEJMoa2017699.

34. San-Román-Gil M, Torres-Jiménez J, Pozas J, Esteban-Villarrubia J, Albarrán-Fernández V, Álvarez-Ballesteros P, Current Landscape and Potential Challenges of Immune Checkpoint Inhibitors in Microsatellite Stable Metastatic Colorectal Carcinoma. Cancers (Basel). 2023 Jan 30;15(3):863. PMID: 36765821; PMCID: PMC9913409. doi: 10.3390/cancers15030863.

35. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science.

2017 Jul 28;357(6349):409-413. Epub 2017 Jun 8. PMID: 28596308; PMCID: PMC5576142. doi: 10.1126/science.aan6733.

36. Baretti M, Le DT. DNA mismatch repair in cancer. Pharmacol Ther. 2018 Sep;189:45-62.. Epub 2018 Apr 15. PMID: 29669262. doi: 10.1016/j.pharmthera.2018.04.004

37. Sukumar J, Gast K, Quiroga D, Lustberg M, Williams N. Triple-negative breast cancer: promising prognostic biomarkers currently in development. Expert Rev Anticancer Ther. 2021 Feb;21(2):135-148. PMID: 33198517; PMCID: PMC8174647. doi: 10.1080/14737140.2021.1840984.

38. Aguiar PN Jr, De Mello RA, Hall P, Tadokoro H, Lima Lopes G. PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: updated survival data. Immunotherapy. 2017 May;9(6):499-506 PMID: 28472902. doi: 10.2217/imt-2016-0150.

39. Patel SP, Kurzrock R. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. Mol Cancer Ther. 2015 Apr;14(4):847-56. Epub 2015 Feb 18. PMID: 25695955. doi: 10.1158/1535-7163.MCT-14-0983.

40. Li Y, Meng Y, Sun H, Ye L, Zeng F, Chen X. The Prognostic Significance of Baseline Neutrophil-to-Lymphocyte Ratio in Melanoma Patients Receiving Immunotherapy. J Immunother. 2022 Jan 1;45(1):43-50. PMID: 34510106; PMCID: PMC8654256. doi: 10.1097/CJI.0000000000000392.

41. Sacdalan DB, Lucero JA, Sacdalan DL. Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: a review and meta-analysis. Onco Targets Ther. 2018 Feb 23;11:955-965. PMID: 29503570; PMCID: PMC5827677. doi: 10.2147/OTT.S153290.

42. Takenaka Y, Oya R, Takemoto N, Inohara H. Neutrophil-to-lymphocyte ratio as a prognostic marker for head and neck squamous cell carcinoma treated with immune checkpoint inhibitors: Meta-analysis. Head Neck. 2022 May;44(5):1237-1245. Epub 2022 Feb 10. PMID: 35146824. doi: 10.1002/hed.26997

43. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer. 2017 Sep;111:176-181. Epub 2017 Jul 24. PMID: 28838390. doi: 10.1016/j.lungcan.2017.07.024.

44. Booka E, Kikuchi H, Haneda R, Soneda W, Kawata S, Murakami T. Neutrophil-to-Lymphocyte Ratio to Predict the Efficacy of Immune Checkpoint Inhibitor in Upper Gastrointestinal Cancer. Anticancer Res. 2022 Jun;42(6):2977-2987. PMID: 35641297. doi: 10.21873/anticanres.15781.