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Analysis of scientific evidence on the effectiveness of immunomodulation in cancer: a systematic review

Análise das evidências científicas da efetividade da imunomodulação em neoplasias: revisão sistemática

Análisis de la evidencia científica sobre la efectividad de la inmunomodulación en el cáncer: revisión sistemática

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Vinicius Lino de Souza Neto
ORCID: https://orcid.org/0000-0001-8269-2634
University Ninth of July, Brazil
E-mail: vinolino@hotmail.com
Giovanna Pereira Holanda
ORCID: https://orcid.org/0000-0001-7588-0186
University Ninth of July, Brazil
E-mail: gigiholanda07@outlook.com
Joane Caroline Menck
ORCID: https://orcid.org/0000-0001-9421-3768
University Ninth of July, Brazil
E-mail:joanemenck@gmail.com
Breno Amin de Lima Silveira
ORCID: https://orcid.org/0000-0002-7911-7847
University Ninth of July, Brazil
E-mail:brenaminlima@gmail.com
Daniela Parra Serafim
ORCID: https://orcid.org/0000-0002-3690-0145
University Ninth of July, Brazil
E-mail: daniela_parrasf@hotmail.com
Victoria Carolini Mendes
ORCID: https://orcid.org/0000-0002-3188-1010
University Ninth of July, Brazil
E-mail: victoria.mendes1@hotmail.com
Eduarda Franco Cardoso
ORCID: https://orcid.org/0000-0002-9611-8454
University Ninth of July, Brazil
E-mail:dudacfranco1@gmail.com
Hugo Justino Branda
ORCID: https://orcid.org/0000-0001-7823-6505
University Ninth of July, Brazil
E-mail:hugojustinobrnd@gmail.com
Andrezza Alves Vasconcelos Teixeira
ORCID: https://orcid.org/0000-0001-6835-417X
University Ninth of July, Brazil
E-mail:andrezzavascc@gmail.com
Pedro Henriue de Freitas Cassoli
ORCID: https://orcid.org/0000-0002-9492-7071
University Ninth of July, Brazil
E-mail: pedrocassoli@gmail.com
Bárbara Lima Guerra
ORCID: https://orcid.org/0000-0001-5899-7083
University Ninth of July, Brazil
E-mail: barbaralimaguerraa@gmail.com
Marco Túlio Moraes da Costa Filho
ORCID: https://orcid.org/0000-0002-2566-5987
University Ninth of July, Brazil
E-mail: marco.tuliofilho@hotmail.com

Abstract
Objective: To analyze the scientific evidence from studies on the effectiveness of immunomodulation in cancer. Methodology: This is a systematic review that searched for studies in the respective databases such as Pubmed,

Scopus, Cinahl, Web of Science, and The Cochrane Data Base, using descriptors in English, selected in the Medical Subject Headings- MeSH. Soon after cataloging, the studies were analyzed through the Consolidated Standards of Reporting Trials-CONSORT, and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), the study sample consisted of nine articles. Results: Analysis of the studies reveals that immunomodulators have an average efficacy rate of 56% for some neoplasms. It was also observed that some substances showed good efficacy in the immunomodulation axis, such as Vitamin D, which decreases the relative risk for colon, breast, and prostate cancer. Immunomodulation was successful in increasing the survival of patients with endocrine (52%) and dermatological (45%) cancers who had low-grade (57%) immunity-related adverse events (irAE). Conclusion: Immunomodulatory therapy is evidenced as an advance in cancer therapy for presenting promising results, showing effectiveness for certain neoplasms.
Keywords: Immunomodulation; Efficacy; Cancer.

Resumo
Objetivo: Analisar as evidências científicas dos estudos diante da efetividade da imunomodulação em neoplasias. Metodologia: Trata-se de uma revisão sistemática que buscou-se por estudos nas respectivas bases de dados como Pubmed, Scopus, Cinahl, Web of Science, e The Cochrane Data Base, por meio dos descritores em inglês, selecionados na *Medical SubjectHeadings*-MeSH. Logo após a catalogação, analisou os estudos por meio do *Consolidated Standards ofReportingTrials*- CONSORT, e *Strengthening the Reporting of ObservationalStudies in Epidemiology* (STROBE) a amostra do estudo foram de nove artigos. Resultados: Análise dos estudos revela que os imunomoduladores têm uma taxa de média de eficácia de 56% para algumas neoplasias. Observou-se também que algumas substâncias apresentaram boa eficácia no eixo da imunomodulação como a Vitamina D que diminui o risco relativo para câncer de cólon, mama e próstata. A imunomodulação obteve sucesso no aumento da sobrevida de pacientes com cânceres endócrinos (52%) e dermatológicos (45%) que apresentaram eventos adversos relacionados à imunidade (irAE) de baixo grau (57%). Conclusão: Evidencia-se a terapia imunomoduladora como um avanço na terapêutica contra o câncer por apresentar resultados promissores, mostrando efetividade para determinadas neoplasias.
Palavras-chave: Imunomodulação; Eficácia; Câncer.

Resumen
Objetivo: Analizar la evidencia científica de estudios sobre la efectividad de la inmunomodulación en cáncer. Metodología: Se trata de una revisión sistemática en la que se han buscado estudios en las respectivas bases de datos como Pubmed, Scopus, Cinahl, Web of Science y The Cochrane Data Base, utilizando descriptores en inglés, seleccionados en el Medical Subject Headings-MeSH. Poco después de la catalogación, los estudios fueron analizados a través de los Estándares Consolidados de Reporte de Ensayos-CONSORT, y Fortalecimiento del Reporte de Estudios Observacionales en Epidemiología (STROBE), la muestra del estudio consistió en nueve artículos. Resultados: El análisis de los estudios revela que los inmunomoduladores tienen una tasa de eficacia promedio del 56% para algunas neoplasias. También se ha observado que algunas sustancias tienen buena eficacia en el eje de la inmunomodulación, como la vitamina D, que disminuye el riesgo relativo de cáncer de colon, mama y próstata. La inmunomodulación logró aumentar la supervivencia de los pacientes con cánceres endocrinos (52%) y dermatológicos (45%) que tenían eventos adversos relacionados con la inmunidad de bajo grado (57%) (irAE). Conclusión: La terapia inmunomoduladora se evidencia como un avance en la terapia del cáncer por presentar resultados prometedores, mostrando efectividad para ciertas neoplasias.
Palabras clave: Inmunomodulación; Eficacia; Cáncer.

1. Introduction

The practice of immunomodulation involves the control of an organism's immunological reactions against an immunomodulatory agent, which adjusts them according to the desired level. Immunomodulatory drugs are used to treat several diseases such as cancer (Reyes Sebastián et al., 2020).

Cancer is characterized as a group of diseases of multifactorial origin with increasing incidence and mortality, arising from the accumulation of genetic modifications from hereditary factors or external factors (alcohol, tobacco, and lifestyle) which result in loss of the control mechanisms of cell proliferation and survival, causing cellular processes that will help in the development of the neoplasm (Reyes Sebastián et al., 2020; Esfahani et al., 2020).

Significant advances in the genetic and molecular characterization of cancer have provided the development of effective immunotherapies aimed at an antitumor effect by improving the host's immune system to obtain a good response against the tumor and memory generation (Esfahani et al., 2020).

Modern immune therapy relies on the growing use of multiple immunomodulatory agents in cancer therapies due to their ability to control the growth and development of these tumors through the activation and strengthening of the immune system, aimed at destroying neoplastic cells to eradicate cancer and prevent relapses (Scharovsky et al., 2012; Davda et al., 2019; De Mattos-Arruda et al., 2019).

The recent clinical success of immunotherapy in cancer patients is mainly based on the activity of checkpoint inhibitor monoclonal antibodies with immune targets, viruses, adoptive cell transfer, various classes of vaccines, and adaptive cell therapies (Zhou et al., 2020; Dunn et al., 2017; Ascierto et al., 2018).

Despite the benefits of this practice, the family should be aware of some setbacks that may arise during the process, such as adverse events related to the immune system (irAEs), endocrine and rheumatological toxicity, and, finally, financial difficulties due to the high cost of assistance (Kottschade, 2019).

Despite the side effects, the work of the immune system in fighting cancer deserves to be the focus of much study and attention. The future of immunotherapy guarantees the expansion of effective methods of treatment against various neoplasms and also offers a better quality of life and increased patient survival, in addition to the regression of certain tumors. A systematic review study published by Cytokine & Growth Factor Reviews articulated the use of interferon in the therapy of patients with melanoma, which showed beneficial effects (Kottschade, 2019).

In this context, this article aims to analyze the scientific evidence from studies on the effectiveness of immunomodulation in cancer.

2. Methodology

This is a systematic literature review study that followed the protocol proposed by the Cochrane Center in Brazil withthe following steps: Formulation of the research question, using the PICO strategy; location and selection of studies; critical evaluation of studies; data collected; analysis and presentation of data; and interpretation of results. It also follows the steps recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA guideline.

In the formulation of the research question, we adopted the PICO strategy, which is characterized by four important components for the formulation of the research question in which P: patient; I: intervention; C: comparison, and O: outcome. However, the item participant (P) and the intervention (I) are necessary.

Thus, the question that guided the systematic review study was: What is the scientific evidence pointed out by the studies regarding the effectiveness of immunomodulators, and their impact on survival in cancer patients?

Data collection took place in the first and second half of 2021 by two researchers in a paired fashion. For the Pubmed, Scopus, Cinahl, Web of Science, and The Cochrane Data Base databases, the following descriptors were used in English, selected in the Medical Subject Headings (MeSH): immunomodulation, efficacy, clinical research, and cancer. Also, Boolean operators AND were used in the search strategy in each database.

For the selection and inclusion of articles in the systematic review, we adopted the following eligibility criteria: a study that presented a good score of scientific evidence analyzed from the Oxford Center for Evidence-based Medicine with no language limit published in national and international databases; studies that are observational and interventional that refers to the applicability of immunomodulators and their impact on the survival of cancer patients. The exclusion criteria were studies that evidenced another type of approach, or another type of methodological design. The absence of temporality is justified because it is a theme with a limited approach and which is less frequent in the works.

Thus, through the search strategy, we identified 38 articles in the databases. After the selection by the aforementioned criteria, two researchers analyzed the titles and abstract, to filter the studies that did not collaborate with the objective of this research. Only six articles made up the final sample. With the database of pre-selected articles, a first instrument was used for

data collection with the respective information, author, objective, type of method applied, result, and conclusion/final considerations.

Soon after cataloging, the studies underwent an evaluative and quality analysis through the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observational research and the Consolidated Standards of Reporting Trials (CONSORT,) for clinical trials studies.

Regarding the analysis by STROBE, we adopted that each of the 22 criteria obtained a score of 0 - described and 1 - not described. For the CONSORT, which consists of 22 items, the score placed was 0 - not described, 1 - partially described and adequate, and 2 - adequate. Thus, the score generated by the article was transformed into a percentage, and those with a percentage greater than 60%, or with relevant characteristics in this evaluation process, were considered to be of quality.

3. Results

Regarding the profile of the studies, the average year of publication was between 2011 and 2020. This quantitative method used Randomized Clinical Trials and systematic reviews, which are among the studies with the highest impact factor within the Oxford Center for Evidence-based Medicine classification. Through the selected studies, immunomodulation has been growing in an ascending way and it presents satisfactory results, as shown in Table 1.

Table 1 - Description of the types of studies selected against the topic addressed and selected according to the criteria, São Paulo/SP, 2021.

AUTHORS	OBJECTIVE	METHOD	RESULTS	CONCLUSION
Esfahani K, Roudaia L, Buhlaiga N, Del Rincon SV, Papneja N, Miller WH Jr	To evidence the limitations of cancer checkpoint immunotherapy and discuss new research in the areas of personalized cancer vaccines.	Systematic review	Immunotherapies are often limited by their immunity-related adverse events (irAEs), immune activation, and inflammatory response against healthy host tissues.	The future of cancer immunotherapy could rely on combination therapies using inhibitors with personalized cancer vaccines
Zhou, X., Yao, Z., Yang, H., Liang, N., Zhang, X., Zhang, F.	To evaluate the association between the occurrence of immunity-related adverse events (irAEs) and the clinical efficacy in patients with Cancer	Systematic review study with meta-analysis.	Cancer patients who developed irAEs had significant survival.	The occurrence of irAEs was significantly associated with better efficacy in cancer patients.
Scharovsky O, et al.	To summarize preclinical findings in immunomodulation and antiangiogenesis for the treatment of different types of tumors.	Randomizedclinicaltrial	1. Residence time = 4 to 64 weeks. 2. stabilizes the disease at 70% and with partial response of 8%; 3. Haematological (15%), gastric (30%) toxicity, no liver, renal or cardiac toxicity; 4. Decrease in VEGF (vascular endothelial growth factor) [V2]	Good tolerance to therapy, no significant toxicity, and no change in the quality of life.
Davda J, et al.	To describe the mechanisms of action (MOA) [V3] of antibody-based IMD (immunomodulatory) agents [V4].	Systematic review	However, analysis of the incidence of ADA (anti-drug antibody) [V5] for 16 non-cancer agents administered SC showed that most of them were associated with an ADA incidence < 15%, consistent with previous findings.	In daily practice, cancer patients may have broader heterogeneity in characteristics, previous treatments, and comorbidity.
Di Trolio R, Simeone E, Di Lorenzo G, Buonerba C, Ascierto PA	To analyze adjuvant therapy in melanoma patients at high risk of recurrence after surgical resection using interferon (IFN).	Clinicaltrial	The results generally suggest that relapse-free survival and overall survival benefits	The modest efficacy of IFN shown in clinical trials shows a satisfactory response with improved patient survival.

Fujimoto D, et al.	To evaluate the effectiveness and performance of nivolumab.	Retrospectivecohortstudy	Disease response and control rates were 20% and 44%, respectively; the estimated 1-year progression-free survival (PFS) was 18%.	The effectiveness of nivolumab in cancer patient populations has been observed.
Lee S, Margolin K.	To examine the main cytokines involved in cancer immunotherapy.	This is a systematic review	Cytokines are responsible for inducing active immune responses against tumors, and for down-regulating immune responses.	Cytokines have proven to be effective in treating cancer.
O'Donnell, J.S., Teng, M.W.L. & Smyth, M.J.	To discuss how the mechanisms underlying the immunomodulation process in cancer.	Systematic review	Therapeutic combinations need to be optimized to promote immune activation and support the presence of T cells within tumor tissues.	Regarding the cancer immunomodulation process, there is evidence of the rapid elimination of tumors.
Hodi FS, Sileni VC, Gonzalez R, et al.	To provide updated efficacy and safety data on the combination of Nivolumab and Ipilimumab and alone in advanced melanoma.	Clinicaltrial	An efficacy rate of 45% was reported, considered to be satisfactory, but some adverse events were marked in the population.	The results of this analysis show a durable and sustained survival benefit in patients with advanced melanoma.

Source: Pubmed, Scopus, Cinahl, Web of Science, and The Cochrane DataBase.

Analyzing with greater accuracy the data from the respective studies, we sought for key points such as the type of immunomodulators, the dose, frequency, type of neoplasm, and the results, that is, the efficacy/effectiveness of the intervention, as seen in Table 2.

Table 2 - Distribution of results found in studies with the use of immunomodulators against the most varied types of cancer, São Paulo/SP, 2021.

Estudo	Imunomodulador	Dose/Frequência	Tipo de Neoplasia	Eficácia/ Efetividade
1.A	CTLA-4 Inhibitor: Ipilimumab; PD-1 inhibitors: PembrolizumabandNivolumab; PD-L1 inhibitors: Atezolizumab, AvelumabandDurvalumab; ctla-4 combinationand PD-1 inhibition: Ipilimumab-nivolumab.	Ipilimumab 3 mg/kg and Nivolumab 1 mg/kg every 3 weeks; Ipilimumab 1 mg/kg and Nivolumab 3 mg/kg every 3 weeks.	Melanoma, Bladder, Merkel Cell Carcinoma, Hepatocellular Carcinoma, and Hodgkin.	Significant improvement in toxicity without loss of effectiveness
2.B	Immune Checkpoint Inhibitors (ICIs)	Notspecified.	Non-Small Cell Lung Cancer (NSCLC), Melanoma, Renal Cell Carcinoma.	The occurrence of irAEs was associated with better efficacy of ICI in cancer patients, particularly endocrine, dermatological, and low-grade irAEs.
3.C	Cyclophosphamide	10 mg/kg body weight.	Lymphoma B, lymphoma T, and fibrosarcoma.	Eradication of 100% of lymphomas and 83% of sarcomas, without metastatic growth or recurrences in the main site.

4.D	Immune checkpoint inhibitors: anti-cytotoxic T lymphocyteantigen 4 (CTLA-4), monoclonal antibody (mAb) ipilimumab, theanti-programmed death 1 mAbs (PD-1) nivolumab, pembrolizumab,andcemiplimab, andtheanti-deathmAbs PD-ligand 1 (PD-L1) atezolizumab, avelumab,anddurvalumab.	Nivolumab 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks. Nivolumab 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks.	Melanoma, Kidney Cell Carcinoma, Colorectal Cancer, Non-Small Cell Lung Cancer, Hodgkin's Lymphoma, Head and Neck Squamous Cell Carcinoma, Urothelial Carcinoma, Hepatocellular Carcinoma, Large-Cell Mediastinum Primary Lymphoma, Big Cell Carcinoma Merkel, Skin Squamous Cell Carcinoma.	Low incidence of ADA (0-12.7%) in single-agent treatment with anti-PD-1, anti-CTLA-4, and anti-PD-L1 mAbs, and higher incidences of ADA (23.8-37.8 %) and NAb (0.5-4.6%) against Nivolumab and Ipilimumab in patients with advanced solid tumors. Of the patients treated with anti-CD30 ADC brentuximab vedotin, 7% developed persistent ADA and 30% had a transient ADA response to the drug.
5.E	Interferon	HD-IFN included an induction phase (20 MU / m 2 intravenously [IV] for 5 days a week for 4 weeks) followed by maintenance stage therapy (10 MU / m 2 / day subcutaneously [SC] for 48 weeks).	Melanoma.	IFN in tumor thickness 1.5–4.0 mm has a survival benefit to adjuvant interferon treatment
6.F	Anti-CTLA-4 (ipilimumabortremelimumab), anti-PD-1 (nivolumab, pembrolizumab) or anti-PD-L1 (atezolizumab, avelumab, durvalumab).	Rates of fatal IRAEs were evaluated and compared with different doses of ipilimumab (3 mg/kg vs 10 mg/kg for monotherapy; 1 mg/kg vs 3 mg/kg for combination therapy).	Notspecified	Fatal toxic effects associated with ICIs are uncommon and compare favorably with other cancer interventions. They occurat a rate of 0.3% to 1.3%.
7.G	Nivolumab	Notspecified	Non-smalllungcancer	Of the 613 patients included in our study, 141 had poor performance status (SS) and 106 were EGFR mutation - or ALK rearrangement positive. The estimated 1-year progression-freesurvival (PFS) was 18%.
8.H	Interferons, Interleucinas, Fator estimulante da colônia granulócica-macrófago.	Notspecified	Notspecified	Cytokines have proven effective in cancer treatment and there is little doubt that they will continue to play an important role in the development of cancer immunotherapy.
9. I	Anticancer immunotherapies targeting inhibitory cytotoxic immunological checkpoint receptors T lymphocyte 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death 1 ligand 1 (PD-L1)	Notspecified	Notspecified	The delivery of personalized medications according to the model proposed in this study has the potential to improve cancer patient outcomes and increase the efficiency and cost-effectiveness of anticancer treatment.
10. J	NivolumabandIpilimumab	Patients were randomly assigned to receive intravenous Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg every 3 weeks for four doses, followed by Nivolumab 3 mg/kg every 2 weeks, or Nivolumab 3 mg/kg every 2 weeks plus placebo, or Ipilimumab 3 mg/kg every 3 weeks for four doses plus placebo.	advanced melanoma	Median progression-free survival was 11·5 months in the Nivolumab plus Ipilimumab group, 6·9 months in the Nivolumab group, and 2·9 months in the Ipilimumab group.

Source: Pubmed, Scopus, Cinahl, Web of Science, and The Cochrane DataBase.

Among the most applied immunomodulators in the studies, thereare Nivolumab and Interferon with modulated doses, according to the population and objective of each study presented. The two drugs showed satisfactory results in the survival of all participants. For example, the average survival of studies that used Nivolumab reached 7 months. However, in more specific cases such as advanced melanoma, the median survival reached 11 months. The evidence of the study shows the applied dose and the temporality that infers the drug's efficacy; however, the drug showed a satisfactory impact on the survival of the study population.

4. Discussion

Regarding the synthesis of data from the studies presented with satisfactory evidence, we observed that the practice of immunomodulation has been growing in the medical field and it has become an option in the treatment of cancer. However, the accessibility to such therapy is still limited. In the IA study, it is mentioned that between Ipilimumab 3 mg/kg and Nivolumab 1 mg/kg every 3 weeks; Ipilimumab 1 mg/kg and Nivolumab 3 mg/kg every 3 weeks, among neoplasms such as Melanoma, Bladder, Merkel Cell Carcinoma, Hepatocellular Carcinoma, and Hodgkin, observed significant improvement and acceptable tolerance (Esfahani et al., 2020). The 10J study showed that the drugs Nivolumab and Ipilimumab with similar doses, but with altered frequency, showed better survival in advanced melanoma. It emphasized that the drug was targeted at a specific type of cancer (Hodi et al., 2018).

Nivolumab is effective and safe for patients with non-small lung cancer, targeting PD-1 (programmed death 1), as demonstrated in the 7G study (Lee S, Margolin K). However, it can be expressed in different targets with antigen-presenting cells or T cells with a low incidence of ADA (anti-drug antibody), as in the 4D study (Davda et al., 2019).

Ipilimumab is an inhibitor of CTLA-4 (cytotoxic T lymphocyte antigen 4). Therefore, it can generate co-stimulation and activation of T cells and have a more effective anti-tumor response, as reported in the study 6F (Fujimoto D, et al.). It is more used in advanced melanomas according to a 10J study (Hodi et al., 2018) and that can change the treatment outcome when associated with ADA (anti-drug antibody) as a 4D study (Davda et al., 2019).

According to study 2B, we could observe a significant improvement in the effectiveness of the use of immunological checkpoint inhibitors (ICIs) in cancer patients, more specifically in those with dermatological and endocrine cancers, in which there were adverse events related to immunity (IRAEs). This benefit was marked by the increase in overall survival and progression-free survival in patients treated, in monotherapy, with programmed cell death inhibitors-1 (Zhou et al., 2020).

At the same time, the 4D study refers to the immunogenicity of several immunomodulatory agents, including immunological checkpoint inhibitors, related to the incidence of anti-drug antibodies (ADA) in patients exposed to cancer therapy. A low incidence of ADA has been reported after therapy using ICIs, such as anti-PD-1 and anti-CTLA-4 (Davda et al., 2019).

Immune checkpoint inhibitors, by blocking the inhibitory pathway between T lymphocytes and tumor cells or antigen-presenting cells, aiming to release the brake of anergized T cells and reactivate their anti-tumor cytolytic function. This therapy has shown great efficiency in the treatment of cancer and has contributed to offering an additional strategy to be used when acting in the tumor microenvironment (Teixeira et al., 2019).

5. Conclusion

Scientific evidence shows a solid construction of knowledge regarding the effectiveness of immunomodulation for the most varied types of cancer. However, some immunomodulators have been highlighted in the treatment and contributed to the

survival of this population. Such material has been reducing aggressive factors and contributing to the accelerated catabolization of neoplasia, such as the reduction of free radicals, inflammatory interleukins, growth factors, and others.

We believe that among the limitations that the study provides is the process of analyzing the biases of the selected studies, which interferes with the accuracy of the findings and the simplification of the outcome. Thus, intervention studies that can promote safety in the standard dose of these substances are essential.

References

Ascierto, P. A., Brugarolas, J., Buonaguro, L., Butterfield, L. H., Carbone, D., Daniele, B., Ferris, R., Fox, B. A., Galon, J., Gridelli, C., Kaufman, H. L., Klebanoff, C. A., Melero, I., Nathan, P., Paulos, C. M., Ruella, M., Sullivan, R., Zarour, H., & Puzanov, I. (2018). Perspectives in immunotherapy: meeting report from the Immunotherapy Bridge (2017). *Journal for immunotherapy of cancer*, 6(1), 69.

Chen, G. et al (2018). Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. *Nature* 560, 382–386.

Davda, J., Declerck, P., Hu-Lieskovan, S., Hickling, T. P., Jacobs, I. A., Chou, J., Salek-Ardakani, S., &Kraynov, E. (2019). Immunogenicity of immunomodulatory, antibody-based, oncology therapeutics. *Journal for immunotherapy of cancer*, 7(1), 105.

De Mattos-Arruda, L., Blanco-Heredia, J., Aguilar-Gurrieri, C., Carrillo, J., & Blanco, J. (2020). New emerging targets in cancer immunotherapy: the role of neoantigens. *ESMO open*, 4(Suppl 3), e000684.

Di Trolio, R., Simeone, E., Di Lorenzo, G., Buonerba, C., & Ascierto, P. A. (2015). The use of interferon in melanoma patients: a systematic review. *Cytokine & growth factor reviews*, 26(2), 203–212.

Dunn, J., & Rao, S. (2017). Epigenetics and immunotherapy: The current state of play. *Molecular immunology*, 87, 227–239.

Esfahani, K., Roudaia, L., Buhlaiga, N., Del Rincon, S. V., Papneja, N., & Miller, W. H., Jr (2020). A review of cancer immunotherapy: from the past, to the present, to the future. *Current oncology* (Toronto, Ont.), 27(Suppl 2), S87–S97.

Fujimoto, D., Yoshioka, H., Kataoka, Y., Morimoto, T., Kim, Y. H., Tomii, K., Ishida, T., Hirabayashi, M., Hara, S., Ishitoko, M., Fukuda, Y., Hwang, M. H., Sakai, N., Fukui, M., Nakaji, H., Morita, M., Mio, T., Yasuda, T., Sugita, T., & Hirai, T. (2018). Efficacy and safety of nivolumab in previously treated patients with non-small cell lung cancer: A multicenter retrospective cohort study. *Lung cancer* (Amsterdam, Netherlands), 119, 14–20.

Hodi, F. S., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Rutkowski, P., Cowey, C. L., Lao, C. D., Schadendorf, D., Wagstaff, J., Dummer, R., Ferrucci, P. F., Smylie, M., Hill, A., Hogg, D., Marquez-Rodas, I., Jiang, J., Rizzo, J., Larkin, J., &Wolchok, J. D. (2018). Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *The Lancet. Oncology*, 19(11), 1480–1492.

Kottschade L. A. (2019). The Future of Immunotherapy in the Treatment of Cancer. *Seminars in oncology nursing*, 35(5), 150934.

Lee, S., & Margolin, K. (2011). Cytokines in cancer immunotherapy. *Cancers*, 3(4), 3856–3893.

Lin, H. et al. (2018). Host expression of PD-L1 determines efficacy of PD-L1 pathway blockade-mediated tumor regression. *J. Clin. Invest.* 128, 805–815.

O'Donnell, J. S., Teng, M., & Smyth, M. J. (2019). Cancer immunoediting and resistance to T cell-based immunotherapy. Naturereviews. *Clinicaloncology*, 16(3), 151–167.

Reyes, S. J., González, K. B., Rodríguez, C., Navarrete-Muñoz, C., Salazar, A. P., Villagra, A., Caglevic, C., & Hepp, M. I. (2020). Imunoterapia do câncer: uma atualização. *Revista médica de Chile*, 148 (7), 970-982.

Rota, G. et al (2018). Shp-2 is dispensable for establishing T cell exhaustion and for PD-1 signaling in vivo. *Cell Rep.* 23, 39–49.

Scharovsky, O. Graciela, Matar, Pablo, Rozados, Viviana R., Rico, María J., ZacaríasFluck, Mariano F., Mainetti, Leandro E., Fernández Zenobi, M. Virginia, Roggero, Eduardo A., Gervasoni, Silvia I., Rossa, Ana, Perroud, Herman A., Sánchez, Andrea M., Celoria, Guillermo C., & Font, María T. (2012). Inmunomodulación y antiangiogénesis en la terapéutica oncológica: De la investigación básica a la clínica. *Medicina*, 72(1), 47-57.

Sugiura, D. et al (2019). Restriction of PD-1 function by cis-PD-L1/CD80 interactions is required for optimal T cell responses. *Science* 364, 558–566.

Teixeira, H., Dias. L., Menão. T., Oliveira. E. (2019). Immune checkpoint proteins as new target for cancer immunotherapy: literature review. HU rev. 45(3):325-333.

Wang, D. Y., Salem, J. E., Cohen, J. V., Chandra, S., Menzer, C., Ye, F., Zhao, S., Das, S., Beckermann, K. E., Ha, L., Rathmell, W. K., Ancell, K. K., Balko, J. M., Bowman, C., Davis, E. J., Chism, D. D., Horn, L., Long, G. V., Carlino, M. S., Lebrun-Vignes, B., & Johnson, D. B. (2018). Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA oncology*, 4(12), 1721–1728.

Zhou, X., Yao, Z., Yang, H., Liang, N., Zhang, X., & Zhang, F. (2020). Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. *BMC medicine*, 18(1), 87.