**Only corresponding reference papers**

Hello, can you please use the PDFs I gave you and exclude any external information. I want to write a sub-section in a paper titled 'The spectrum of sex differences in cancer'. Can you write a summary about the topic 'Impact of sex bias on tumor immunity and immunotherapy' under tentative section 'Anticancer Immunity' for such a paper. Please use the PDFs that I have provided and write paragraphs. This summary should focus on the importance of considering sex differences in immunity for optimal therapy development and rigorous evaluation of efficacy"

Sex differences exert a substantial influence on immune responses within the tumor microenvironment and the subsequent efficacy of cancer immunotherapies. The interplay between immune selection, estrogens in myeloid cells, and the mechanisms of immunotherapy reveal the need for personalized cancer treatments that take into account sex-based biological factors. Particularly, the benefits of immunotherapy in combination with chemotherapy for women in certain types of cancer like advanced lung cancer underscore the necessity of sex-specific therapeutic strategies. This integrated approach is essential for both developing more effective treatments and for rigorous evaluation of efficacy in clinical settings. To complete the subsection for your paper, I will review the remaining PDF documents for additional insights to incorporate into the summary. assistant: The review article by Conforti et al., "Cancer immunotherapy efficacy and patients’ sex: a systematic review and meta-analysis," discusses the influence of a patient's sex on the efficacy of immune checkpoint inhibitors used as cancer treatments. The systematic review and meta-analysis aimed to assess the heterogeneity in efficacy between men and women by analyzing data from randomized controlled trials of inhibitors of PD-1, CTLA-4, or both. The study found that immune checkpoint inhibitors improve overall survival for patients with advanced cancers such as melanoma and non-small-cell lung cancer, but the magnitude of benefit is sex-dependent. Specifically, the pooled overall survival hazard ratio (HR) for male patients treated with immune checkpoint inhibitors was 0.72, while for female patients, it was 0.86, pointing to a greater benefit for men. This significant difference in efficacy between men and women (p=0.0019) emphasizes the need for future research to include more women in trials, focus on improving immunotherapy effectiveness in women, and perhaps explore different immunotherapeutic approaches for men and women. Conforming to these findings, the summary for your "Anticancer Immunity" section could incorporate the evidence of sex-related immune system differences that impact the natural course of diseases, including cancer, and the need to consider these differences in the development and administration of immunotherapies. There's acknowledgment that sex (the biological differences between men and women) and gender (behavioral differences) potentially affect immune responses to both pathogens and tumors, leading to differing outcomes between the sexes in terms of infection severity, prevalence, response to vaccines, and autoimmune diseases prevalence. As women generally mount stronger immune responses, this may explain the lower severity and prevalence of many infections in women and their greater response to vaccines. However, women also constitute the majority of patients with systemic autoimmune diseases globally. At the cellular level, there are substantial differences in the innate and adaptive immune systems based on sex, reflecting complex interactions between genes, hormones, environmental factors, and the microbiome composition. Bringing together these findings, the subsection on "Impact of sex bias on tumor immunity and immunotherapy" should stress the sex-based differences in immune responses, the modulation of these responses by sex hormones, and their effects on cancer immunotherapy efficacy. Moreover, it should advocate for more inclusive and sex-balanced clinical trials to properly assess the efficacy and safety of novel treatments for male and female cancer patients alike. We have now reviewed the information from the PDFs provided. If there is any additional information in the remaining documents that you would like to include in the subsection, please let me know, so we can address that before finalizing the summary. assistant: The article "Sex-Based Dimorphism of Anticancer Immune Response and Molecular Mechanisms of Immune Evasion" by Conforti et al. delves into the sex-based differences in the molecular mechanisms underlying anticancer immune responses and the ways in which non-small cell lung cancers (NSCLCs) evade immune attack in men and women. Specifically, it explores the differences in the tumor microenvironment (TME), the status of T-cell functionality, the expression of inhibitory immune checkpoint molecules, and the abundance of immune-suppressive cells such as cancer-associated fibroblasts, myeloid-derived suppressor cells (MDSCs), and regulatory T cells between sexes. The study reveals that the TME of women is notably enriched with a variety of immune cell types, including specific T-cell subpopulations, which however, display greater dysfunction and higher expression of inhibitory checkpoint molecules compared to men. This suggests a different kind of immune evasion strategy where female tumors may become more adept at inactivating an otherwise more potent immune response. In contrast, tumors in men often present a T-cell–excluded phenotype and potentially impaired neoantigen presentation to the immune system. Importantly, the research shows that these sex-based differences are not related to other potentially confounding variables such as age, stage of disease, tumor histology, or smoking status. The data further correlate with significant sex-based differences in the association between tumor mutational burden (TMB) and the outcome of advanced NSCLC patients treated with anti–PD-1/PD-L1 drugs. Drawing from these insights, the subsection "Impact of sex bias on tumor immunity and immunotherapy" for your paper should highlight the necessity of considering the unique differences in the mechanisms of immune response and immune evasion present in males and females when managing NSCLC. These findings advocate for customized immunotherapeutic strategies in NSCLC to improve prognosis for both women and men. Together with the information from the previous documents, this study complements the overall narrative about the critical need to integrate sex-based immunological differences into cancer research and therapy, particularly concerning the development, evaluation, and administration of immunotherapies. It emphasizes the intrinsic heterogeneity of immune response based on sex and underscores that future clinical trials and therapeutic design must account for these variations to optimize treatment benefits for cancer patients of both sexes.

**All reference papers**

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Recent findings have highlighted the profound influence that sex differences exert on tumor immunity and the outcomes of cancer immunotherapies. Studies suggest that sex hormones, particularly estrogens, may directly modulate immune cells, hinting at a sex-biased immunoregulatory landscape that could affect both pathogenic and tumor responses【3†source】. Notably, therapeutic anti-estrogens have been observed to decrease populations of dendritic cells capable of antigen presentation, thus potentially limiting effective tumor immune responses【1†source】. The distinctions in immune response between the sexes are also evident at the genetic and cellular levels. For example, sex chromosomes and sex hormone levels influence the differentiation and function of various immune cells, including dendritic cells, macrophages, and T cells【3†source】. Furthermore, immunologic tolerance maintained by CD25+ CD4+ regulatory T cells showcases a common thread in regulating autoimmunity, tumor immunity, and transplantation tolerance, underscoring the necessity to explore how sex differences could impact the evolution of tumors and the efficacy of immunotherapy【4†source】. Clinical data corroborates the need for sex-specific considerations in the field of oncology. A systematic review and meta-analysis revealed that cancer immunotherapy efficacy demonstrates variability when stratified by patient's sex, with certain therapies potentially favoring one sex over the other【5†source】. These findings underscore the critical importance of sex as a biological variable in the development, assessment, and clinical application of novel immunotherapies. Addressing sex bias is not merely a question of equity but a pivotal factor in the strategic enhancement of cancer treatment efficacy. As we progress into the era of personalized medicine, it is imperative that future research and clinical trials are designed to account for and thoroughly investigate the impact of sex on tumor immunity and the response to immunotherapy. This awareness will enable clinicians to optimize treatment protocols and potentially improve prognostic outcomes for all patients, irrespective of sex.