International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

# Immunotherapy in Older Patients with Cancer: A Narrative Review

Alexandra Smith[1,*], Jeffrey Mathew Boby[2,*], Steve Joseph Benny[3,*], Nadia Ghazali[4,*], Elke Vermeulen[1], Mathew George[1]

[1]Tamworth Hospital, Hunter New England Local Health District (NSW Health), Tamworth, NSW, Australia; [2]Government Medical College, Kozhikode, Kerala, India; [3]Government Medical College, Thrissur, Kerala, India; [4]Calvary Mater Newcastle, Newcastle, NSW, Australia

*These authors contributed equally to this work

Correspondence: Alexandra Smith, North West Cancer Centre, Tamworth Hospital, Dean Street, Tamworth, NSW, 2340, Australia, Email Alexandra.smith2@health.nsw.gov.au



**Purpose:** Immunotherapies have revolutionized cancer treatment; however, relatively little is known about their efficacy and toxicity in the elderly, a cohort accounting for more than half of total cancer cases. In this review, we aim to provide insight into the current knowledge base regarding the clinical utility and side effects of immunotherapies in the geriatric population as well as identify key gaps in the literature where further research is essential.

**Methods:** We conducted a rapid critical review of available literature, focusing on studies reporting on use of immunotherapy in cancer patients aged ≥65 years. The review assessed studies that included different types of cancer, were of multiple study types (although predominantly retrospective), had different study duration, and reported different outcomes of interest. Owing to this heterogeneity, meta-analysis and a direct comparison between studies were not feasible.

**Results:** Overall, the review findings indicate that certain malignancies have shown comparable survival rates in younger and older age groups when managed with immunotherapeutic drugs, the incidence of immunotherapy-related side effects varies only slightly by age groups, and in general there is a lack of studies on the determinants of the clinical outcomes of immunotherapy in or including geriatric patients.

**Conclusion:** Enhanced clinical benefits along with better tolerability associated with immunotherapies make it an attractive alternative to conventional chemotherapeutic drugs, especially in elderly patients. There is currently a limited number of studies assessing the clinical outcomes of immunotherapies, particularly in the elderly. Overall, our findings reflect a need for further prospective studies focussing on geriatric patients representative of the real-life population, in order to derive a more precise understanding of the clinical utility, toxicity profile, and cost-effectiveness of immune checkpoint inhibitors in older patients with cancer.

**Keywords:** cancer treatment, immunotherapies, geriatric oncology, toxicities

## Introduction

Immunotherapies stimulate the host's immune system to mount a response against tumor cells. The advent of immunotherapies has ushered in a new era in cancer care. When compared to conventional chemotherapies for certain types of cancer, immunotherapies are associated with decreased mortality, longer progression-free survival, enhanced selectivity, and better tolerability.[1] This is especially true in certain cancers like metastatic Non Small Cell Lung Carcinoma (NSCLC), melanoma, and renal cell carcinoma, where immunotherapies are currently the first-line agents.[2] Improved clinical outcomes and better tolerability associated with immunotherapies can make it a suitable choice in the elderly with poor response or decreased tolerability to conventional chemotherapies.

The incidence of cancer increases markedly with older age, with a median age of diagnosis at 66 years in the United States.[3] In the year 2020, around 9.95 million new cases of cancer and 5.9 million deaths were estimated to have occurred globally in patients aged greater than 65 years.[4] This incidence is projected to increase by around 36% in the coming decade.[5] In spite of the fact that

Received: 7 September 2023
Accepted: 9 January 2024
Published: 30 January 2024

almost 50% of new cancer cases occur in adults aged 65 years or above, the older population remains largely underrepresented in oncology clinical trials assessing the clinical efficacy of immunotherapies.[6–9] A study analyzing the enrollment of older patients in cancer drug clinical trials between 2005 and 2015 reported that only 12% of the total patients were above 75 years of age.[10] The exclusion of the geriatric population could be attributed to multiple causes including safety concerns, age limit in enrollment, coexisting comorbidities, and deteriorating health status.[6,7] The older population is functionally distinct from the younger age group owing to immunosenescence, old age onset organ dysfunction, poorer baseline health status, and presence of comorbidities.[6,7] Cancer care in the geriatric population is further complicated by polypharmacy, greater risk of adverse events like depression and falls and altered immune status.[7] While the authors acknowledge the limitations of RCTs and their translation to "real world" contexts, these aforementioned factors could impact determinations of the efficacy, tolerance, toxicity, and clinical outcome of immunotherapies in the geriatric population. The elderly population are normally under-represented in clinical trials, and physicians are often required to extrapolate findings from clinical trials on the non-elderly population in their clinical practice with older patients. This is likely to be of limited utility, in part owing to heterogeneity between the two groups. Hence, there is an imperative to address the age-related disparities in cancer research and the underrepresentation of older cancer patients in clinical trials participant cohorts. Given the escalating utilization of immunotherapies in the elderly, data regarding the outcomes and toxicity profile specific to this subgroup become more crucial. Hence, in our review, we aim to provide insight into the current knowledge base regarding the clinical utility and side effects of immunotherapies in the geriatric population as well as to identify key gaps in the literature where further research is essential.

# Review Scope & Limitations

## Scope of Review: Summary

Immunotherapies have emerged as a promising advancement in cancer care and to date have changed the face of cancer treatment. Various clinical trials are being conducted across the globe to assess its clinical efficacy in various cancer and stages. However, it has been observed that older patients with cancer are not being included in many of the trials, although they constitute the majority of newly diagnosed cancer cases. Though a similar efficacy of immunotherapeutic drugs across all age groups, they are limited by the inadequate representation of elderly patients in them. Ongoing debates among research communities highlight the need for comprehensive studies addressing the efficacy and potential adverse effects of immunotherapy in geriatric populations. Research should encompass short- and long-term outcomes, assessing not only treatment effectiveness but also the impact on the quality of life for elderly individuals. Incorporating immunotherapy into routine clinical practice for the elderly should be grounded in robust evidence to ensure both safety and efficacy in this specific demographic. The aim of the review is to evaluate and discuss the efficacy and safety of immunotherapy in older patients with cancer. The following review is presented according to the narrative review reporting checklist.

## Methods

A literature search was conducted on PubMed, encompassing English-language articles available until December 2021. The primary focus of our investigation was on meta-analyses and randomized clinical trials that assessed the use of immunotherapy in solid organ tumors. Additionally, we included studies that provided real-world analyses of immunotherapy specifically in the elderly population.

## Limitations

The studies included in our review assessed various cancer types, employed diverse methodologies, varied in duration, and reported different outcomes. Despite conducting a thorough literature search, the scarcity of studies on our topic resulted in insufficient data to offer a comprehensive insight. The predominance of retrospective cohort-designed studies raises concerns about potential recall bias. However, these limitations highlight key recommendations and suggest areas for future research.

## Findings

Even though more than half of the newly diagnosed cancer cases are in adults older than 65 years of age, it has been elicited from various research articles that this group has not been given adequate representation in clinical trials to determine the scope of immunotherapeutic agents in cancer care.[6,8,9,11] Overall, the review findings indicate that certain malignancies have shown comparable survival rates in younger and older age groups when managed with immunotherapeutic drugs[12,13], the incidence of immunotherapy-related side effects varies only slightly by age groups,[14] and in general there is a lack of studies on the determinants of the clinical outcomes of immunotherapy in geriatric patients.

### Clinical Efficacy of Immune Checkpoint Inhibitors in Older Cancer Patients

The efficacy of any therapy must be assessed in depth with high-quality clinical trials which are representative of the target population before its clinical value can be ascertained. Hence, a dearth of studies on the geriatric population means that our current knowledge of the clinical efficacy of immunotherapies in the elderly is limited. Here, we provide a review of the existing literature on the topic as well as compare the efficacies between the younger and elderly populations.

A meta-analysis by Sun et al in 2020 evaluated the clinical efficacy of first-line immune checkpoint inhibitor against chemotherapy in the geriatric population with metastatic NSCLC. A total of 10 studies were included in the meta-analysis with a sample population of 4633 (1971 patients ≥ 65 years and 2662 patients below 65). This study reported similar clinical efficacy of immune checkpoint inhibitors among NSCLC patients aged above and below 65 years with overall survival [HR 0.75 95% CI (0.64–0.88) vs 0.76 95% CI (0.66–0.87); $p < 0.001$].[15] A similar study done in geriatric patients with pretreated NSCLC also showed no significant differences in the clinical effectiveness of immune checkpoint inhibitor nivolumab in the older population.[16]

Lichtenstein et al evaluated the clinical efficacy of immunotherapy in the elderly with NSCLC. In contrast to other studies, here the study population was split into 4 age cohorts, less than 60, 60–69, 70–79, and 80 years and above.[17] Progression-free survival when evaluated showed an increasing trend with age with a peak at 70–79 age cohort. The 70–79 age group had progression-free survival of 3.75 months compared to 1.81 months in the younger population.[17] Overall survival was similar among patients aged <60, 60–69, and 70–79. All of them had an OS of 12–15 months.[17] However, both progression-free survival and overall survival were shortest among the above 80 age group amounting to 1.64 months and 3.63 months, respectively. Patients aged above 80 also had a significantly greater hazard for death as per multiple Cox regression compared to the younger subset.[17] 201 patients (44.8% ≥65 years) with metastatic small cell cancers who were managed with first-line atezolizumab therapy were included in the study of Impower133 and revealed a median overall survival and progression-free survival of 12.3 months and 5.2 months, respectively.[18]

The impact of immunotherapy in the treatment of melanoma was also assessed by several studies. Perier-Muzet et al conducted a retrospective analysis of 92 patients comparing between the below and above 65-year-old population (n = 54 ≤65 years; and n = 38 aged >65 years) with metastatic melanoma who were treated with immune checkpoint inhibitors. The study reported better progression-free survival and overall survival in patients aged ≥65 compared to the younger population.[19] Wolchok et al studied patients with advanced melanoma who received nivolumab therapy (37.3% of the study population were aged 65 years and above) and reported the median overall survival of patients as 37.6 months and the median progression-free survival as 6.9 months in the study population.[20] Recent studies have reported promising results in elderly patients with melanomas, non-small cell lung cancers, and clear cell kidney cancer, who were treated with immunotherapeutic drugs.[13]

Cheson et al studied the effects of the combined administration of two immunological drugs, brentuximab vedotin and nivolumab, in patients with classic Hodgkin's lymphoma, who were considered incompatible with standard chemotherapeutic drugs. Brentuximab vedotin administration alone has proved to be effective in younger patients, with an overall response rate of 75%, as recorded in a previous study.[21] Similarly, there is evidence for nivolumab monotherapy to have produced an overall response in 69% of patients enrolled in a study, the median age of participants being 37 years.[22] However, the study by Cheson et al reported an overall response rate of 64% for the combination therapy, including both these drugs, which was lower than expected.[23] The most likely cause attributed to this finding was the weaker immune system of the participants, compared to those enrolled in studies conducted among younger individuals.[23]

Efficacy of immunotherapy in the geriatric population with metastatic renal carcinoma showed no significant difference in clinical outcome with similar overall survival of 15.8 months (≥75 years), 12.2 months (65–74 years), and 14.4 months (≤65 years). Progression-free survival also showed no statistically significant difference among the three age cohorts.[12]

Atezolizumab is currently the first-line treatment for urothelial cancer where chemotherapy with platinum agents is either contraindicated or unresponsive.[24] Nivolumab, durvalumab, avelumab, and pembrolizumab are four other FDA-approved immunotherapy agents against urothelial carcinoma.[24] Nishiyama et al used propensity score matching to assess the clinical utility of pembrolizumab among the elderly and reported an overall survival of 7.8 months (95% CI = 5.2–10.4) in patients aged less than 75 years and 10.4 months (95% CI = 7.3–13.5) in the ≥75 age cohort.[25]

## Toxic Effects of Immunotherapies in Older Cancer Patients

The immune system and the human body as a whole undergo a multitude of changes as individuals age. Immunosenescence, fall in naïve T cell population, and worsening of functional activity of T and B cell results in a characteristically different toxic profile of the elderly compared to younger counterparts.[13] For this reason, the literature referenced here on the adverse effects of immunotherapies in younger patients cannot be readily extrapolated to the geriatric population. A retrospective cohort study analyzing the toxic effects of immunotherapy in the geriatric population reported that immune checkpoint inhibitors were essentially safe among the older cancer patient cohort and found no significant relationship between age of patient and toxicity of immunotherapies.[26] Here, the sample population of 448 patients was divided into 3 age cohorts <65 years, 65–74 years, and ≥75 years of which 18.9%, 16.2%, and 11%, respectively, experienced ≥ Grade 3 toxicity. Moreover, the older cohort also had a lower ICI discontinuation rate. Toxicity-related treatment discontinuation rates were 20.5%, 10.1%, and 7.4% in age cohort <65 years, 65–74 years, and ≥75 years, respectively. As per this study, treatment type was the sole significant determinant of toxicity and the overall grade of toxicity was similar among the different age groups. Similar results were reported by Ron et al, which found comparable immune-related adverse events (irAE) in patients aged below and above 70 years who were treated with immune checkpoint inhibitor nivolumab.[16] Another study done in 2018 with a sample population of 245 patients also found no relation between the incidence of irAE and age and reported similar rates of immunotherapy-related hospitalization and steroid use across different age groups.[17]

In melanoma patients too, results were reported with similar grades and incidence of commonly reported irAE like diarrhea, enterocolitis, vitiligo, skin eruptions, and endocrinopathies among the different age groups.[19] However, certain rarer adverse effects like immunologic nephritis and meningitis were reported among the older population, while no such cases were seen in the younger subset.[19] Phase I trials by Herin et al evaluated the clinical efficacy and toxic profile of immunotherapy in patients older than 70 years with advanced solid carcinoma. In total 220 patients were enrolled in the trial of which 46 were ≥70 years and 174 were <70 years. The older population experienced a significantly higher incidence of grade 1 and 2 adverse events compared to younger patients.[27] The time of onset of grade 1 toxicity was also earlier in older patients compared to younger ones (0.67 months vs 2.67 months).[27] However, no such significant difference could be found in the incidence and onset of grade 3 and 4 toxicity.[27]

The FDA recently approved the use of nivolumab plus ipilimumab combination therapy as first-line treatment of various malignancies like unresectable malignant pleural mesothelioma and metastatic non-small cell lung cancer (NSCLC).[28] Several studies that evaluated the toxicity levels of anti-PD(L)-1 and anti-CTLA-4 combination therapies in patients aged above 80 years have shown relatively higher toxicities in that age cohort.[29,30] The study by Friedman et al reported that 37.5% of the patients on ipilimumab plus nivolumab combination therapy had to be administered infliximab for diarrhea and 50% of the patients had an asymptomatic increase in lipase levels.[30] Toxicities of grade 3 or 4 were observed in 62.5% of the study population with a mean age of 82 years.[30] However, the Checkmate 817 study by Paz-Ares et al demonstrated comparatively lower side effects for a younger population who were managed with ipilimumab plus nivolumab combination therapy as first-line treatment for advanced NSCLC. The median age of the patients enrolled in the study was 65 years, and grade 3–4 treatment-related adverse effects were seen in only 27.6% of the patients.[31] Elderly patients treated with anti-PD-1/PD-L1 is also at increased risk for hyper progression of disease as reported by Champiat et al.[32] Moreover, the impact of toxic effects of immunotherapies is usually more pronounced in the elderly despite similar rates of adverse events as that of the younger population. This can be attributed to coexisting co-morbidities and poor functional reserve in patients as age advances.[13]

Hermansen and Donskov evaluated the toxic profile of immunotherapies when used against metastatic renal cell carcinoma and reported that the elderly population was associated with a significantly higher risk of toxicity.[12] Interruption or dose reduction of immunotherapy drugs were seen in around 76% of patients aged above 75 years.[12] Nishiyama et al studied the toxicity of immunotherapy agent pembrolizumab in patients with urothelial carcinoma. When adverse events of all grades were considered, the incidence was significantly higher in the elderly population (55.3% in ≥75 years and 41.9% in <75 years with a p-value of 0.007).[25] However, the incidence of grade ≥3 AEs was similar among the two age cohorts.[25]

## Discussion

More than half of all cancer patients are over the age of 65 years, and more than 26% fall into the age group of 75–84 years.[33,34] Cancer care has undergone various reforms in recent years, the most striking being the emergence of immunotherapeutic drugs in the treatment of various solid tumor malignancies.

Understanding how aging influences immune response and considering interactions with comorbidities and medications is crucial. Studies have reported changes in the functioning of the immune system with ageing.[35] Declining levels of B-cell and T-cell replication and their worsening functional levels, alterations in antigen-presenting cells (APCs) and an increase in the number of regulatory cells have been observed in the elderly.[36–46] Some of the most remarkable changes associated with ageing have been linked with the adaptive immune system.[47] The naive T-cell population gradually shrinks, while the number of memory T-cells continues to rise, both these changes ultimately resulting in a vulnerable immune system combined with poor memory of prior antigen exposure.[35] CTLA-4 and PD-1 are two main inhibitory receptors physiologically expressed by T cells following activation in order to control their proliferation.[13] There is an increased expression of these receptors in certain conditions like cancer.[48] In the present era of cancer treatment, immunotherapies, especially PD-1 and its ligand PD-L1 checkpoint inhibitors, have gained much significance owing to their impressive clinical response.[49] This could be largely attributed to higher efficacy in certain types of cancer as compared to chemotherapy with comparatively lesser side effects.[13]

The second generation of immunotherapy is centered on the combined administration of multiple immunomodulators (anti- PDL-1 and anti-CTLA-4) or combining anti-PDL-1 with conventional treatments (chemotherapy, radiotherapy, etc.). These combination therapies have recently gained FDA approval for being used as first-line treatment to manage various malignancies.[28] The combined use of ipilimumab plus nivolumab combination therapy has been shown to result in better outcomes and survival rates than nivolumab/ipilimumab monotherapy.[50] Despite their high clinical utility, this combination therapy is known to increase the risk of treatment-related adverse effects, which can greatly affect the quality of life of the patient if not addressed properly.[50] They include hepatitis, skin rash, pneumonitis and colitis.[51] These toxicities tend to be more pronounced in elderly patients, mostly above the age of 80 years.[29,30] Moreover, grade 3–4 toxicities associated with combination therapies are also seen to be more prevalent in elderly patients.[30,31] Hence, combination therapies are less preferred in geriatric patients, though they have excellent outcomes in younger patients.

The above findings incorporate studies that have shown that there is a substantial increment in the overall survival of patients managed with immunotherapies for melanomas, non-small cell lung cancer, and clear cell renal carcinoma.[13,52] The efficacy of pembrolizumab therapy for melanoma, NSCLC, head and neck cancers, urothelial carcinoma, and Hodgkin's lymphoma had been assessed by several randomized controlled trials, and no notable differences were observed between older and younger patients.[53–56] However, only 16% of the patients included in the KEYNOTE trials in particular were aged ≥75 years.[57] There are also varied reports suggesting the possibility of a decreased response to immunotherapeutic drugs in older patients due to an aging immune system.[29,57] The study by Pasquali et al published in 2020 has documented the effectiveness of anti-PD-1 therapy for melanoma patients across all ages.[58] However, the mean age of the participants was 57.5 years, which is not representative of the geriatric population. Since then, very few studies have been conducted to assess the clinical efficacy of immune checkpoint inhibitors in elderly patients. Even though the proportion of elderly patients with cancer continues to rise, the number of clinical trials assessing the efficacy of immunotherapy in the management

of cancer in this cohort is still relatively low.[59] Ailments associated with ageing, physiological changes in the body and other comorbidities have a significant impact on deciding the treatment modality and may also influence patient outcomes.[60]

One of the major concerns of oncologists is deciding on the intensity of cancer therapy best suited for each patient in the geriatric category, as there can be significant variations in health status across individuals.[13] Hence, the risk versus benefit ratio must be well evaluated before initiating management for each patient.[60] Many authors recommend a comprehensive geriatric assessment (CGA) to be done before framing cancer treatment guidelines for the elderly since it helps to analyse various health conditions that can potentially affect patient outcomes.[61] This helps oncologists adequately evaluate the comorbidities and health status of the elderly and better design individualised treatment regimens.[60]

Treatment-related toxicities have been reported to be more prevalent in the elderly compared to younger patients.[62] Similar studies were conducted to analyze immune-related adverse events (irAEs), the toxicities caused by immune checkpoint inhibitors. They can affect nearly all organ systems, and while most of them manifest within the first 4 months of treatment, others show up later during the course of treatment.[63–65] The incidence of fatal toxicities is observed to occur more frequently in elderly patients.[66] Moreover, studies suggest that the ability of older patients to recover from the adverse effects of immunotherapy is less compared to the younger population, though the incidence of many of these events is fairly similar across all age groups.[14] Another retrospective study conducted by Sattar et al which includes 23 patients aged ≥75 years also showed no statistically significant increase in irAEs as age advances.[53]

## Conclusion

Immunotherapies are widely regarded as a promising development in oncology with the potential to alter the landscape of cancer care in the coming years. Enhanced clinical benefits along with better tolerability associated with immunotherapies make it an attractive alternative to conventional chemotherapeutic drugs, especially in elderly patients. Even though the geriatric population account for more than 50% of the total cancer patient population, their representation in landmark trials of these clinical agents continues to remain minimal. Additionally, while immunosenescence and co-existing comorbidities make the elderly functionally distinct from the younger population, there is currently a limited number of studies assessing the clinical outcomes of immunotherapies, particularly in the elderly. As noted in our review, many of these studies report no significant difference in the clinical efficacy and toxic events between the elderly and their younger counterparts. Recent findings suggest comparable outcomes for elderly patients with good functional status, yet knowledge gaps persist on the impact of immunosenescence, comorbidities, and declining health. Despite this, comprehensive data on hospitalization, health resource use, patient-reported outcomes, cost-effectiveness, and functional outcomes for older adults receiving immunotherapies remain lacking. Future research should explore the role of immunosenescence in these outcomes, how to incorporate it into the geriatric assessment framework, and leverage these insights to guide the development of prospective studies for older adults with cancer undergoing immunotherapy.

## Funding

The authors received funding from Tamworth Rural Referral Hospital, Hunter New England Local Health District, to support publication costs.

## Disclosure

The authors have no conflicts of interest in this work.

## References

1. D'Errico G, Machado HL, Sainz B. A current perspective on cancer immune therapy: step-by-step approach to constructing the magic bullet. *Clin Transl Med*. 2017;6(1). doi:10.1186/s40169-016-0130-5
2. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540–1550. doi:10.1016/S0140-6736(15)01281-7

3. Cancer of any site - cancer stat facts. SEER. Available from: https://seer.cancer.gov/statfacts/html/all.html. Accessed November 26, 2021.
4. Cancer today. Estimated number of new cases in 2020, World, Both sexes, ages 65+. Available from: https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=13&ages_group%5B%5D=17&group_cancer=1&include_nmsc=0&include_nmsc_other=1. Accessed November 26, 2021.
5. Cancer Tomorrow. Changes of new cases from 2020 to 2030, Both sexes, age (65-85+). Available from: https://gco.iarc.fr/tomorrow/en/dataviz/bars?mode=population&years=2030&age_start=13&key=percent&show_bar_mode_prop=0. Accessed November 26, 2021.
6. Elkrief A, Richard C, Malo J, et al. Efficacy of immune checkpoint inhibitors in older patients with non-small cell lung cancer: real-world data from multicentric cohorts in Canada and France. *J Geriatr Oncol*. 2020;11(5):802–806. doi:10.1016/j.jgo.2020.01.002
7. Abraham G, Jobanputra K, Noronha V, et al. Immune checkpoint inhibitors in older patients with solid tumors: real-world experience from India. *Cancer Res Stat Treat*. 2021;4(2):270–276. doi:10.4103/crst.crst_86_21
8. Betof AS, Nipp RD, Giobbie-Hurder A, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. *oncologist*. 2017;22(8):963–971. doi:10.1634/theoncologist.2016-0450
9. Elias R, Giobbie-Hurder A, McCleary NJ, Ott P, Hodi FS, Rahma O. Efficacy of PD-1 & PD-L1 inhibitors in older adults: a meta-analysis. *J Immunother Cancer*. 2018;6(1):26. doi:10.1186/s40425-018-0336-8
10. Singh H, Kanapuru B, Smith C, et al.; Food and Drug Administration. FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: a 10-year experience by the U.S. *J Clin Oncol*. 2017;35(15_suppl):10009. doi:10.1200/JCO.2017.35.15_suppl.10009
11. Abraham G, Jobanputra KN, Noronha V, et al. Immune checkpoint inhibitors in older patients with solid tumors: real-world experience from India. *Cancer Res Stat Treat*. 2021;4(2):270. doi:10.4103/crst.crst_86_21
12. Hermansen CK, Donskov F. Outcomes based on age in patients with metastatic renal cell carcinoma treated with first line targeted therapy or checkpoint immunotherapy: older patients more prone to toxicity. *J Geriatr Oncol*. 2021;12(5):827–833. doi:10.1016/j.jgo.2020.12.008
13. Granier C, Gey A, Roncelin S, Weiss L, Paillaud E, Tartour E. Immunotherapy in older patients with cancer. *Biomed J*. 2021;44(3):260–271. doi:10.1016/j.bj.2020.07.009
14. Godby RC, Johnson DB, Williams GR. Immunotherapy in Older Adults with Cancer. *Curr Oncol Rep*. 2019;21(7):56. doi:10.1007/s11912-019-0806-2
15. Sun YM, Wang Y, Sun XX, Chen J, Gong ZP, Meng HY. Clinical efficacy of immune checkpoint inhibitors in older non-small-cell lung cancer patients: a meta-analysis. *Front Oncol*. 2020;10:558454. doi:10.3389/fonc.2020.558454
16. Ron DA, Manrique MAA, Martínez JM, et al. Efficacy and safety of Nivolumab in older patients with pretreated lung cancer: a subgroup analysis of the Galician lung cancer group. *J Geriatr Oncol*. 2020. doi:10.1016/j.jgo.2020.11.010
17. Lichtenstein MRL, Nipp RD, Muzikansky A, et al. Impact of age on outcomes with immunotherapy in patients with non–small cell lung cancer. *J Thorac Oncol*. 2019;14(3):547–552. doi:10.1016/j.jtho.2018.11.011
18. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379(23):2220–2229. doi:10.1056/NEJMoa1809064
19. Perier-Muzet M, Gatt E, Péron J, et al. Association of immunotherapy with overall survival in elderly patients with melanoma. *JAMA Dermatol*. 2018;154(1):82. doi:10.1001/jamadermatol.2017.4584
20. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345–1356. doi:10.1056/NEJMoa1709684
21. Cheson BD, Bartlett NL, LaPlant B et al. Brentuximab vedotin plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with Hodgkin lymphoma (ACCRU): a multicentre, single-arm, phase 2 trial. *The Lancet: Haematology*. 2020;7(11):e808–e815 . doi:10.1016/S2352-3026(20)30275-1
22. Ramchandren R, Domingo-Domènech E, Rueda A, et al. Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the Phase II CHECKMATE 205 study. *J Clin Oncol off J Am Soc Clin Oncol*. 2019;37(23):1997–2007. doi:10.1200/JCO.19.00315
23. Connors JM. Immunotherapy for older patients with classic Hodgkin lymphoma. *Lancet Haematol*. 2020;7(11):e776. doi:10.1016/S2352-3026(20)30321-5
24. Jodon G, Fischer S, Kessler ER. Treatment of urothelial cancer in elderly patients: focus on immune checkpoint inhibitors. *Drugs Aging*. 2018;35(5):409–421. doi:10.1007/s40266-018-0540-8
25. Nishiyama N, Kobayashi T, Narita S, et al. Efficacy and safety of pembrolizumab for older patients with chemoresistant urothelial carcinoma assessed using propensity score matching. *J Geriatr Oncol*. 2022;13(1):88–93. doi:10.1016/j.jgo.2021.07.002
26. Samani A, Zhang S, Spiers L, et al. Impact of age on the toxicity of immune checkpoint inhibition. *J Immunother Cancer*. 2020;8(2):e000871. doi:10.1136/jitc-2020-000871
27. Herin H, Castanon E, Dyevre V, et al. Immunotherapy phase I trials in patients over 70 years with advanced solid tumours: the Gustave Roussy experience. *Ann Oncol*. 2017;28:v413. doi:10.1093/annonc/mdx376.028
28. US Food and Drug Administration (FDA) . Oncology (Cancer) / Hematologic malignancies approval notifications. FDA; 2021. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications. Accessed January 5, 2022.
29. Elias R, Karantanos T, Sira E, Hartshorn KL. Immunotherapy comes of age: immune aging & checkpoint inhibitors. *J Geriatr Oncol*. 2017;8(3):229–235. doi:10.1016/j.jgo.2017.02.001
30. Friedman CF, Horvat TZ, Minehart J, et al. Efficacy and safety of checkpoint blockade for treatment of advanced melanoma (mel) in patients (pts) age 80 and older (80+). *J Clin Oncol*. 2016;34(15_suppl):10009. doi:10.1200/JCO.2016.34.15_suppl.10009
31. Paz-Ares L, Urban L, Audigier-Valette C, et al. P1.01-79 CheckMate 817: safety of flat-dose nivolumab plus weight-based ipilimumab for the first-line (1L) treatment of advanced NSCLC. *J Thorac Oncol*. 2018;13(10):S493. doi:10.1016/j.jtho.2018.08.635
32. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. *Clin Cancer Res*. 2017;23(8):1920–1928. PMID: 27827313. doi:10.1158/1078-0432.CCR-16-1741
33. Yancik R. Cancer in older persons: an international issue in an aging world. *Semin Oncol*. 2004;31(2):128–136. doi:10.1053/j.seminoncol.2003.12.024
34. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29. doi:10.3322/caac.20138

35. Marrone KA, Forde PM. Cancer immunotherapy in older patients. *Cancer J Sudbury Mass*. 2017;23(4):219–222. doi:10.1097/PPO.0000000000000268
36. Paganelli R, Quinti I, Fagiolo U, et al. Changes in circulating B cells and immunoglobulin classes and subclasses in a healthy aged population. *Clin Exp Immunol*. 1992;90(2):351–354. doi:10.1111/j.1365-2249.1992.tb07954.x
37. Apoil PA, Puissant-Lubrano B, Congy-Jolivet N, et al. Influence of age, sex and HCMV-serostatus on blood lymphocyte subpopulations in healthy adults. *Cell Immunol*. 2017;314:42–53. doi:10.1016/j.cellimm.2017.02.001
38. Krichevsky S, Pawelec G, Gural A, et al. Age related microsatellite instability in T cells from healthy individuals. *Exp Gerontol*. 2004;39(4):507–515. doi:10.1016/j.exger.2003.12.016
39. Globerson A, Effros RB. Ageing of lymphocytes and lymphocytes in the aged. *Immunol Today*. 2000;21(10):515–521. doi:10.1016/s0167-5699(00)01714-x
40. Shurin MR, Shurin GV, Chatta GS. Aging and the Dendritic cell system: implications for cancer. *Crit Rev Oncol Hematol*. 2007;64(2):90–105. doi:10.1016/j.critrevonc.2007.03.002
41. Hazeldine J, Lord JM. The impact of ageing on natural killer cell function and potential consequences for health in older adults. *Ageing Res Rev*. 2013;12(4):1069–1078. doi:10.1016/j.arr.2013.04.003
42. Facchini A, Mariani E, Mariani AR, Papa S, Vitale M, Manzoli FA. Increased number of circulating Leu 11+ (CD 16) large granular lymphocytes and decreased NK activity during human ageing. *Clin Exp Immunol*. 1987;68(2):340–347.
43. Rukavina D, Laskarin G, Rubesa G, et al. Age-related decline of perforin expression in human cytotoxic T lymphocytes and natural killer cells. *Blood*. 1998;92(7):2410–2420. doi:10.1182/blood.V92.7.2410
44. Plackett TP, Boehmer ED, Faunce DE, Kovacs EJ. Aging and innate immune cells. *J Leukoc Biol*. 2004;76(2):291–299. doi:10.1189/jlb.1103592
45. Nishioka T, Shimizu J, Iida R, Yamazaki S, Sakaguchi S. CD4+CD25+Foxp3+ T cells and CD4+CD25-Foxp3+ T cells in aged mice. *J Immunol*. 2006;176(11):6586–6593. doi:10.4049/jimmunol.176.11.6586
46. Grizzle WE, Xu X, Zhang S, et al. Age-related increase of tumor susceptibility is associated with myeloid-derived suppressor cell mediated suppression of T cell cytotoxicity in recombinant inbred BXD12 mice. *Mech Ageing Dev*. 2007;128(11–12):672–680. doi:10.1016/j.mad.2007.10.003
47. Fülöp T, Dupuis G, Witkowski JM, Larbi A. The role of immunosenescence in the development of age-related diseases. *Rev Investig Clin Organo Hosp Enfermedades Nutr*. 2016;68(2):84–91.
48. Baitsch L, Baumgaertner P, Devêvre E, et al. Exhaustion of tumor-specific CD8+ T cells in metastases from melanoma patients. *J Clin Invest*. 2011;121(6):2350–2360. doi:10.1172/JCI46102
49. Yildiz B, Acar R. Immunotherapy in geriatric patients with advanced cancer. *Eurasian J Med Oncol*. 2020;4(3):209–214. doi:10.14744/ejmo.2020.44446
50. Yang Y, Jin G, Pang Y, et al. Comparative efficacy and safety of nivolumab and nivolumab plus ipilimumab in advanced cancer: a systematic review and meta-analysis. *Front Pharmacol*. 2020;11:40. doi:10.3389/fphar.2020.00040
51. Zhou S, Khanal S, Zhang H. Risk of immune-related adverse events associated with ipilimumab-plus-nivolumab and nivolumab therapy in cancer patients. *Ther Clin Risk Manag*. 2019;15:211–221. doi:10.2147/TCRM.S193338
52. Garon EB, Hellmann MD, Rizvi NA, et al. Five-year overall survival for patients with advanced non–small-cell lung cancer treated with pembrolizumab: results from the Phase I KEYNOTE-001 study. *J Clin Oncol*. 2019;37(28):2518–2527. doi:10.1200/JCO.19.00934
53. Sattar J, Kartolo A, Hopman WM, Lakoff JM, Baetz T. The efficacy and toxicity of immune checkpoint inhibitors in a real-world older patient population. *J Geriatr Oncol*. 2019;10(3):411–414. doi:10.1016/j.jgo.2018.07.015
54. Kanesvaran R, Cordoba R, Maggiore R. Immunotherapy in older adults with advanced cancers: implications for clinical decision-making and future research. *Am Soc Clin Oncol Educ Book*. 2018;38. doi:10.1200/EDBK_201435
55. Khan M, Lin J, Liao G, et al. Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer. *Medicine*. 2018;97(33):e11936. doi:10.1097/MD.0000000000011936
56. Alkharabsheh O, Kannarkatt P, Kannarkatt J, Karapetyan L, Laird-Fick HS, Al-Janadi A. An overview of the toxicities of checkpoint inhibitors in older patients with cancer. *J Geriatr Oncol*. 2018;9(5):451–458. doi:10.1016/j.jgo.2018.02.002
57. Elias R, Morales J, Rehman Y, Khurshid H. Immune Checkpoint Inhibitors in Older Adults. *Curr Oncol Rep*. 2016;18(8):47. doi:10.1007/s11912-016-0534-9
58. Pasquali S, Hadjinicolaou AV, Chiarion Sileni V, Rossi CR, Mocellin S. Systemic treatments for metastatic cutaneous melanoma. *Cochrane Database Syst Rev*. 2018;2018(2):CD011123. doi:10.1002/14651858.CD011123.pub2
59. Canouï-Poitrine F, Lièvre A, Dayde F, et al. Inclusion of older patients with cancer in clinical trials: the SAGE prospective multicenter cohort survey. *oncologist*. 2019;24(12):e1351–e1359. doi:10.1634/theoncologist.2019-0166
60. Hamaker ME, Vos AG, Smorenburg CH, de Rooij SE, van Munster BC. The value of geriatric assessments in predicting treatment tolerance and all-cause mortality in older patients with cancer. *oncologist*. 2012;17(11):1439–1449. doi:10.1634/theoncologist.2012-0186
61. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol off J Am Soc Clin Oncol*. 2014;32(24):2595–2603. doi:10.1200/JCO.2013.54.8347
62. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol*. 2011;29(25):3457–3465. doi:10.1200/JCO.2011.34.7625
63. Van holstein Y, Kapiteijn E, Bastiaannet E, van den Bos F, Portielje J, de Glas NA. Efficacy and adverse events of immunotherapy with checkpoint inhibitors in older patients with cancer. *Drugs Aging*. 2019;36(10):927–938. doi:10.1007/s40266-019-00697-2
64. Postow MA, Sidlow R, Hellmann MD, Longo DL. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158–168. doi:10.1056/NEJMra1703481
65. Helissey C, Vicier C, Champiat S. The development of immunotherapy in older adults: new treatments, new toxicities? *J Geriatr Oncol*. 2016;7(5):325–333. doi:10.1016/j.jgo.2016.05.007
66. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(12):1721–1728. doi:10.1001/jamaoncol.2018.3923