



Immune Checkpoint Inhibitors in Geriatric Oncology

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Abstract

Purpose of Review This manuscript will update prior reviews of immune checkpoint inhibitors (ICIs) in light of basic science, translational, and clinical discoveries in the field of cancer immunology and aging.

Recent Findings ICIs have led to significant advancements in the treatment of cancer. Landmark trials of ICIs have cited the efficacy and toxicity experienced by older patients, but most trials are not specifically designed to address outcomes in older patients. Underlying mechanisms of aging, like cellular senescence, affect the immune system and may ultimately alter the host's response to ICIs. Validated tools are currently used to identify older adults who may be at greater risk of developing complications from their cancer treatment.

Summary We review changes in the aging immune system that may alter responses to ICIs, report outcomes and toxicities in older adults from recent ICI clinical trials, and discuss clinical tools specific to older patients with cancer.

Keywords Immune checkpoint inhibitors · Geriatric oncology · Immunosenescence · Immunotherapy

Introduction

Cancer is widely considered a disease of aging. The care of older adults with cancer is complicated by factors such as frailty, multiple comorbidities, and age-related organ dysfunction [1]. These issues pose specific challenges to optimal treatment approaches in older patients with cancer. Currently, in the United States, 50% of cancers are diagnosed in people who are 65 years of age or older [2], and cancer incidence in older adults is increasing worldwide [3].

The discovery that cancer cells use immune escape mechanisms, including the upregulation of immune checkpoints in the tumor microenvironment, has led to dramatic

therapeutic breakthroughs in cancer treatment in the form of immune checkpoint inhibitors (ICIs) [4]. Programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA4) are both expressed on the surface of activated T cells and act as important immune checkpoints in normal T cell activation in order to maintain immune tolerance. CTLA4 is a T cell coreceptor that inhibits T cell activation through outcompeting CD28, the activation receptor, to binding of its ligands CD80/CD86. Similarly, PD-1 is expressed during T cell activation and, upon binding to its ligand (PD-L1), suppresses T cell receptor (TCR) transduction and CD28 co-stimulation. Tumor cells have co-opted this pathway by expressing high levels of PD-L1 in order to inhibit the anti-tumor response [5, 6]. Similarly, lymphocyte activation gene 3 (LAG3, also known as CD223) is expressed on multiple cell types, including activated CD4+ and CD8+ T cells.

ICIs have not just shown efficacy but have been transformative in the treatment of cancers with previously poor prognoses such as advanced melanoma [7]. Antibodies that target immune checkpoint proteins such as CTLA-4, PD-1, PD-L1, and LAG3 have been evaluated in most cancer types over the last two decades [5]. ICIs are part of everyday clinical oncology practice and have been used as monotherapy and/or in combination and along with cytotoxic, targeted, or other anticancer therapies. Although ICIs are generally

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considered to be better tolerated than traditional cytotoxic chemotherapy, they are associated with unique toxicities, termed immune-related adverse events (irAEs). Since ICIs indirectly target malignant cells through T cell activation, age-related changes to the immune system may impact the efficacy and toxicity of these drugs.

The purpose of our review is to update the 2019 review of immunotherapies in older patients with cancer, by covering recent advances in the understanding of basic, translational, and clinical discoveries in the field of cancer immunology and aging [8]. We outline the effects of aging on the immune system and implications for ICIs. Then, we provide a comprehensive inventory of prospective clinical trials for older cancer patients by disease type focusing on trials within the past 3 years. Finally, we describe treatment toxicities as they pertain to ICI use in older patients with cancer and advocate for the use of geriatric assessment (GA).

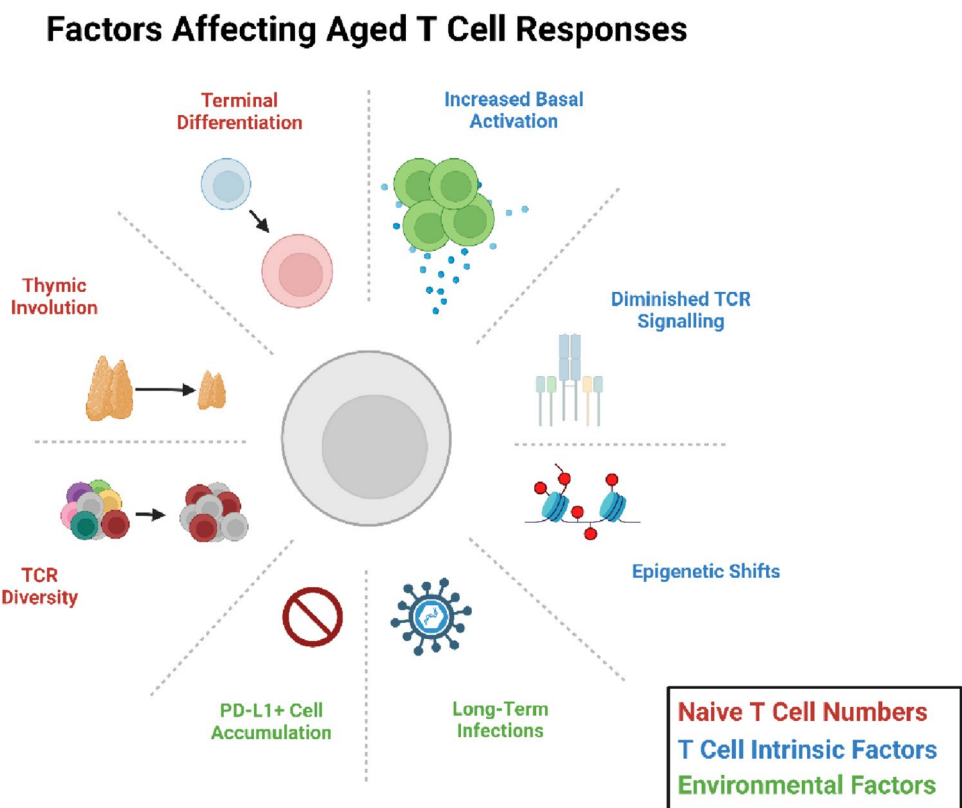
Effects of Aging on the Immune System and Implications for Immune Checkpoint Therapies

Cellular senescence is a cell state triggered by stressful insults, characterized by a prolonged and generally irreversible cell-cycle arrest with secretory features, macromolecular damage, and altered metabolism [9•]. Senescent

cells secrete a range of inflammatory factors, which allows the activation of immune response in order to eliminate the senescent cells. Senescent cells accumulate in aging, with mouse models showing the half-life of senescent cells more than quadruples as mice age from 3 to 22 months [10], and transplant of senescent cells from old to young mice can induce physical dysfunctions in the recipients [11]. This accumulation of senescent cells leads to chronic inflammation and contributes to the attenuation and exhaustion of the immune response, known as immunosenescence. Multiple studies have shown that these natural changes during the biological aging process can have profound effects on the efficacy of ICI therapy: anti-CTLA4 and PD-L1 ICI therapy administered to young mice bearing GL261 orthotopic gliomas can result in 67% long-term survival, yet in aged mice, this is reduced to 27% [12]; anti-PD-L1 therapy in aged mice does not slow the growth of melanoma [13] or breast [14] tumor cells unlike in young mice; and anti-CTLA4 therapy in aged mice has no effect on breast tumor growth, unlike in young mice [14].

Immunosenescence affects both innate and adaptive arms of the immune system but has a dramatic impact on the presence, phenotype, and function of T cells, the target of immune checkpoint therapies (Fig. 1). During the aging process, the numbers of naïve T cells decrease due to thymic involution, which corresponds with proportional shifts from naïve to memory or terminally differentiated phenotypes,

Fig. 1 Factors affecting aged T cell responses. Summary of T cell intrinsic and extrinsic factors that can affect the response of aging T cells to anti-tumor therapy. References in text. Created with Biorender.com



often fueled by persistent long-term viral infections, such as cytomegalovirus (CMV) [15, 16]. In order to maintain a naïve T cell pool, aged T cells can persist longer than young T cells, but this is not due to increased proliferation of the naïve cells, but rather a reduction in apoptosis [17, 18]. Phenotypic changes in T cell function occur at multiple levels; molecular and epigenetic studies reveal that during the aging process, T cell subsets shift to a more activated, effector-like basal state, with an increase in pro-inflammatory T regulatory cells [19]. This corresponds with chronic inflammation observed throughout the aging process. The T cells themselves undergo diminished T cell receptor (TCR) and co-stimulation signaling, as well as reduced proliferation, polyfunctionality, response to pro-inflammatory cytokines, and epigenetic changes resulting in different polarization [20, 21]. Although both cytotoxic CD8 and helper CD4 T cells are affected, the changes in CD8 numbers and phenotype are more dramatic, affecting the cytotoxic response to vaccination and pathogens.

A consequence of a reduced naïve T cell pool in the aging process is declining TCR diversity, and recent studies have shown this results in less recognition of peptide mutants, which can in turn affect the efficacy of vaccination strategies. Indeed, vaccine effectiveness against seasonal influenza has been shown to drop as low as 31% in the 60–69 age group [22], although it is controversial whether the reduction of the naïve T cell repertoire actually impacts the ability to make a successful immune response [23]. Consequently, therapies that improve T cell function in the presence of an immunosenescent environment could overcome the limitation of TCR diversity in an aging population. In fact, mouse T cells can survive, proliferate, and respond to vaccination even after 10 years of prime-boost vaccination challenges and transfers *in vivo* [24••], well beyond the lifetime of the organism. Furthermore, heterochronic parabiosis experiments, where an aged mouse is conjoined with a young mouse and they share a blood system for 3 months, result in the aged mice having epigenetic and transcriptomic changes resulting in both an extended lifespan and healthspan [25••]. Therefore, it is clear that in the right environment, aged cells can function effectively.

PD-L1-expressing senescent cells accumulate with age [26], and immune checkpoint therapy to PD-1 increases CD8 T cell-mediated killing of these cells. Furthermore, both mouse and human podocytes of the kidney have been shown to increase their expression of PD-1 during the aging process [27]. Although it is unclear which, if any, other cells throughout the body express these immune checkpoint targets during the natural aging process, it is plausible to hypothesize that expression of checkpoint-targeting proteins away from T cells and the tumor site could reduce the efficacy of systemic administration of ICI therapy in older patients, due to natural competition for antibody binding.

Therefore, targeting ICI therapy at the tumor site, instead of systemically, could have improved outcomes for older patients. Altogether, this research shows that ICI therapy administration to older patients should be rationally designed and administered and must overcome both the ineffectiveness of T cells and the inflammatory and exhaustion environment of the organism as a whole.

Overview of Prospective Clinical Trials Focused on Treatment of Older Patients with ICIs by Select Cancer Subtype

ICIs have brought new hope to the treatment of cancer. Compared to traditional chemotherapeutic agents, ICIs may in some instances have greater efficacy and less toxicity. Some recent landmark trials of ICIs have cited the efficacy and toxicity experienced by older patients enrolled in those trials (Table 1), but most trials are not designed to specifically address outcomes in older patients. It is also important to acknowledge that despite significant progress, ICIs may not be as effective or may lose efficacy in some patients, and lead to a spectrum of side effects, from minor to life-limiting irAEs. Here, we review clinical trials of ICIs that included older patients with cancer broken down by cancer subtype. We acknowledge that although we present a comprehensive overview, this is by no means an exhaustive list of cancer subtypes.

Non-small Cell Lung Cancer

Older adults with non-small cell lung cancer (NSCLC) represent the largest subset of older patients treated with ICIs. Yet, the proportion of older adults (≥ 65 years) in the pivotal phase III clinical trials accounted for only 41–55% of participants [28]. A recent large meta-analysis concluded that survival gains in the era of ICIs for treatment of advanced NSCLC were not as substantial for older patients compared to their younger counterparts [29••].

CheckMate 153 (NCT02066636), a phase IIIb/IV study of nivolumab monotherapy in previously treated patients with advanced NSCLC, allowed enrollment of patients of advanced age or diminished Eastern Cooperative Oncology Group performance status (ECOG PS). After 1 year of receiving treatment, patients were randomized to either stop or continue therapy. Among 1426 patients, 556 patients were aged 70 years or older (Table 1). The median overall survival (mOS) time was comparable between the overall population (9.1 months) and patients ≥ 70 years (10.3 months), and the incidence of high-grade (grade 3–5) select treatment-related adverse events (TRAEs) was also similar between the overall population (6%) and patients aged 70 years or older (6%) [30].

Checkmate 171, a phase II trial of 811 patients designed to assess response to nivolumab in those with previously

Table 1 Prospective clinical trials focused on treatment of older patients with ICIs by select cancer type (limited to last 5 years)

Trial name, first author et al., year	N, patient age range (median)	# older patients (age cutoff)	ICI(s)	Outcomes (all ages)	Toxicities (all ages) grade 3 or more	Outcomes in older patients (age cutoff)	Toxicities in older patients by age cutoff
NSCLC Checkmate 171; Felip et al., 2020	N = 811, 31–86 (66)	278 (≥ 70); 125 (≥ 75)	Nivolumab	mOS 10.0 months	Diarrhea (1%), increased alanine aminotransferase (ALT) 1%, pneumonitis (0.7%), colitis (0.6%), increased aspartate aminotransferase (AST) (0.5%)	mOS 10.0 months (≥ 70); 11.2 months (≥ 75)	Low-grade diarrhea more common in patients ≥ 70
Checkmate 153; Spigel et al., 2019	N = 1426, 34–92 (66)	556 (≥ 70)	Nivolumab	mOS 9.1 months	Fatigue (2%), diarrhea (1%), nausea (< 1%), hypothyroidism (< 1%), decreased appetite (< 1%), rash (< 1%)	mOS 10.3 months (≥ 70)	Fatigue (4%), diarrhea (1%), rash (< 1%), pruritus (1%) in patients ≥ 70
Spanish Lung Cancer Group; Bianco et al., 2023	N = 74, (78.1)	74 (> 70)	Pembrolizumab	—	—	mOS 19.2 months (> 70)	9.5% grade 3 (2 diarrhea, 2 pneumonitis, 1 hyperuricemia, 1 acute renal failure, and 1 thrombocytopenia plus infection) in patients > 70
Renal JAVELIN Renal 101; Tomita et al., 2022	N = 886, 29–88	266 (≥ 65 to < 75); 74 (≥ 75)	Avelumab	Improved PFS 13.8 months vs. 8.4 months	Grade ≥ 3 AE 309 (71.2%): hypertension 111 (25.6%), diarrhea 29 (6.7%), increased ALT 26 (6%), palmar plantar erythrodysesthesia syndrome 25 (5.8%)	PFS 13.8 months vs. 11.0 months (≥ 65 to 75), 13.8 months vs. 9.8 months (≥ 75)	Grade ≥ 3 AE 108 (81.2%) in patients ≥ 65–75: hypertension 39 (29.3%), ALT increased 11 (8.3%), hand foot syndrome 9 (6.8%), fatigue 9 (6.8%) Grade ≥ 3 AE 24 (72.7%) in patients ≥ 75: hypertension 10 (30.3%), hepatitis 2 (6.1%), dyspnea 2 (6.1%)

Table 1 (continued)

	Trial name, first author et al., year	N, patient age range (median)	# older patients (age cutoff)	ICI(s)	Outcomes (all ages)	Toxicities (all ages) grade 3 or more	Outcomes in older patients (age cutoff)	Toxicities in older patients by age cutoff
GI	RAMONA; Ebert et al., 2022	N=66, (70.5)	36 (≥ 70)	Nivolumab plus ipilimumab	–	–	Improved mOS	Grade 3–5 TRAEs 13 (20%): pneumonitis ($n=2$), colitis or diarrhea (2), general physical deterioration (2), and increased gamma glutamyltransferase (2)
Brain	NUTMEG, 2023; Sim et al., 2023	N=103, 65–88 (73)	103 (≥ 65)	Nivolumab	–	–	No improvement in OS	Grade 3 irAEs: pneumonitis ($n=1$), infection with possible pneumonitis (1), extraocular muscle paresis (1)

treated squamous non-small cell lung cancer, specifically included older populations ($n=278 \geq 70$ and $n=125 \geq 75$) (Table 1). The study found that mOS was 10.0 months for all patients, 10.0 months for patients aged ≥ 70 years, and 11.2 months for patients aged ≥ 75 years. In terms of toxicities, any grade AEs were reported in 57.3% of all treated patients, but more frequently among older patients (62.9% for ≥ 70 and 68.8% for ≥ 75). Subgroup analysis showed similar event types and rates with the exception of low-grade diarrhea, which was more common in patients aged ≥ 70 years and ≥ 75 years [31].

A single-arm, open-label, prospective, multicenter phase II trial carried out by the Spanish Lung Cancer Group explored the efficacy of pembrolizumab as first-line treatment for advanced NSCLC in older patients [32••] (Table 1). It included a total of 74 evaluable patients > 70 years (median age 78.1 years). The mOS was 19.2 months, and the estimated overall survival (OS) at 1 year and 2 years was 61.7% and 40.2%, respectively. The results were encouraging from a survival benefit, but importantly, this study was specifically designed to capture quality of life (QoL) as well as geriatric measures [32••]. Interestingly, patient-reported and geriatric parameters used in this study tended to improve or remain stable over the study period [32••].

The efficacy of durvalumab (vs. placebo) after chemoradiotherapy in patients with stage III NSCLC was tested in the PACIFIC trial [33]. Although this trial was not specifically designed for older patients, a post hoc analysis concluded that durvalumab was associated with treatment benefit, manageable safety, and no detrimental impact on patient-reported outcomes in those ≥ 70 years. However, serious adverse events (42.6% vs. 25.5%) were more common with durvalumab versus placebo among patients aged ≥ 70 [34].

There are several studies underway, including a phase III randomized trial, ELDERLY, that is designed to study the addition of atezolizumab in older patients with advanced NSCLC receiving carboplatin and paclitaxel chemotherapy (NCT03977194), as well as an ongoing phase II study, DURVALUNG, that is exploring the impact of durvalumab as a maintenance therapy after chemoradiotherapy in frail small cell lung cancer patients [35]. A phase III study, ACHIEVE, plans to assess the differences between older patients (≥ 70) with stage IIIB, IIIC, or IV NSCLC who receive combination of chemotherapy and pembrolizumab versus pembrolizumab alone [36].

Melanoma

Melanoma is a malignant neoplasm that arises from melanocytes in the skin (most common), eyes, genitalia, sinuses, and gastrointestinal tract. Melanoma represents the fifth most common cancer in the United States, accounting for 6% of all cancer cases, with approximately 99,780 cases

reported in 2022, and an increasing incidence with age [2]. Due to increased screening efforts and improvements in therapeutic agents, it carries a 5-year relative survival rate of 94% for all stages combined, with survival highly dependent on the disease stage at the time of diagnosis [37].

Advances in systemic therapy, namely ICIs, have dramatically improved outcomes for patients with advanced or metastatic melanoma. Prior to 2010, high dose interleukin-2 was the only FDA-approved treatment for advanced or metastatic melanoma. Since 2010, the FDA has approved numerous ICIs alone or in combination, including pembrolizumab, nivolumab, ipilimumab, and relatlimab [38]. With the introduction of newer treatments, a significant reduction in melanoma mortality was observed in the United States between 2013 and 2017, which likely reflects a benefit from the availability of more effective therapies [39]. Older patients are also living longer with melanoma, which suggests that these newer therapies are being used successfully among older populations [39].

Older patients (> 65 years) comprise 22–50% of patients enrolled in landmark melanoma studies [38, 40–49], though this certainly remains under-representative given the increased incidence of melanoma with age. Although most subgroup analyses show similar ICI efficacy regardless of age [38, 41–49], the SWOG S1801 study demonstrated a 35% improvement in 2-year event-free survival in older patients receiving neoadjuvant followed by adjuvant pembrolizumab when compared to adjuvant pembrolizumab alone for resectable stage III/IV melanoma [40]. This improvement in 2-year event-free survival was greater than that seen in the younger patient population (14%) and suggests potential differences in efficacy of ICI therapy in the perioperative setting in geriatric patients. ICI-related toxicity in older patients is not specifically reported in landmark melanoma studies; however, Bruijnen et al. [49] showed increased rates of hospitalization due to irAEs (despite no significant difference in rates of irAEs) in melanoma patients aged 70 years and older who were classified as frail by the independently validated Geriatric 8 Assessment (G8).

Renal Cell Cancer

In the JAVELIN renal 101 trial, avelumab plus axitinib was compared to sunitinib. There were 886 patients included in this study. A post hoc analysis of the study showed 266 and 74 recruited patients were aged ≥ 65 to < 75 and ≥ 75 , respectively. Avelumab plus axitinib demonstrated favorable efficacy in both progression-free survival (PFS) and OS compared to sunitinib across all age groups. The hazard ratios (HR) for both PFS and OS were higher in older

patients (aged ≥ 65 –75 and ≥ 75) compared to younger ones (aged < 65). Of patients who received avelumab plus axitinib, 206 (76.9%), 108 (81.2%), and 24 (72.7%) patients aged < 65 , ≥ 65 –75, and ≥ 75 , respectively, experienced grade 3 or higher AEs. Avelumab plus axitinib had a higher rate of discontinuation in patients ≥ 75 compared to younger groups (< 65 and ≥ 65 –75 years old), whereas no obvious difference of discontinuation rate was observed among each age group treated with sunitinib [50].

Atezolizumab was compared to placebo in patients with an increased risk of recurrence following resection in the IMmotion 010 trial (NCT03024996) [50]. Of 778 recruited patients, 282 patients were ≥ 65 . The study failed to show favorable efficacy of atezolizumab as an adjuvant therapy. Further subgroup analyses showed that in patients aged < 65 , the median disease-free survival (DFS) was 57.2 months and 52.9 months in atezolizumab and placebo groups, respectively. In patients aged ≥ 65 years, DFS was 42.5 and 47.9 months atezolizumab and placebo group, respectively [51]. No data related to age-specific, treatment-related adverse effects were reported.

The International mRCC Database Consortium evaluated patients (< 70 years vs. ≥ 70 years) with metastatic renal cell cancer (mRCC) receiving PD-L1-based therapy. The study failed to show any significant differences in OS, time to treatment failure, and time to next treatment between younger versus older patients. Lower overall response rates were reported in older patients compared to younger ones (24% vs. 31%, $p = 0.01$) where ICI was used as first-line therapy [52]. Finally, a recent meta-analysis demonstrated that pembrolizumab plus lenvatinib and pembrolizumab plus axitinib had better OS in older patients as a first-line therapy for advanced renal cell cancer and challenges the idea that combination therapies that include ICIs should be avoided in older adults [53].

Breast Cancer

ICIs have been studied in all subtypes of breast cancer, particularly in triple-negative breast cancer (TNBC), but also in human epidermal growth factor receptor 2 (HER2)-positive breast cancer, and, to a lesser extent, in hormone receptor (HR)-positive breast cancer [54].

In TNBC, ICIs in combination with chemotherapy have led to approvals for use in routine clinical practice [55], but ongoing trials are investigating combination immunotherapies involving ICI with other anticancer therapies. To the best of our knowledge, there are no reported clinical trial results of ICI specifically in older patients with breast cancer.

Gastrointestinal Cancers

Overall, the incidence and mortality rates of gastrointestinal cancer increase with age [56]. Checkmate 577, a phase III trial, demonstrated statistically significant improvement in median DFS in patients with esophageal or gastroesophageal junction cancer who received nivolumab as an adjuvant therapy. Among 794 patients, 287 were aged ≥ 65 . Subgroup analysis of the study showed median DFS in nivolumab and placebo was 17.0 months and 13.9 months, respectively, in patients aged ≥ 65 , whereas in the overall population, median DFS was 22.4 months and 11.0 months, respectively [57].

Nivolumab plus chemotherapy versus placebo plus chemotherapy was tested in patients with HER2-negative gastric or gastro-esophageal junction cancer in a phase III trial named ATTRACTION-4. Of 724 patients, 368 patients were aged ≥ 65 . Median PFS in the nivolumab plus chemotherapy and placebo plus chemotherapy was 9.89 months and 8.54 months, respectively, in the ≥ 65 age group. In patients aged < 65 years, median PFS in the nivolumab plus chemotherapy and placebo plus chemotherapy was 11.24 months and 6.93 months, respectively [58]. In terms of OS, the superiority of nivolumab plus chemotherapy was also maintained in checkmate 649 trial ($n = 1581$, 620 patients aged 65 or more) [59].

A phase II trial, RAMONA, was designed for older patients and showed promising effects of combination nivolumab and ipilimumab in patients with esophageal squamous carcinoma. Patients aged 65 years or more ($n = 66$) were included in the study, and the median age was 70.5 years (IQR 67.0–76.0). The study showed a higher median OS compared to an historical cohort receiving standard chemotherapy (7.2 months vs. 5.9 months, $p = 0.006$). In safety analyses, the study reported no difference in grade 3 or more treatment-related adverse events (TRAEs) in patients who received nivolumab monotherapy or nivolumab plus ipilimumab therapy [60].

Primary and Metastatic Cancer of the Central Nervous System

Efficacy of ICIs in brain metastases compared with extracranial metastases is limited, as most clinical trials with these new agents excluded patients with active brain metastases. However, promising intracranial responses have been reported in numerous clinical trials for patients with brain metastases, especially in trials of melanoma and NSCLC [61, 62]. In some trials, intracranial response rates were comparable with systemic responses [63].

The central nervous system (CNS) has an immune microenvironment with a unique immune surveillance and a complex role for myeloid cells and lymphatic system. Glioblastoma has a cancer-associated immunosuppressive

environment with few tumor-infiltrating lymphocytes that are present, but they often demonstrate increased fractions of CD4-positive T cells and FoxP3-positive regulatory T cells. Trials of ICIs, predominantly targeting PD-1/PD-L1 and/or CTLA-4, have reported negative results in glioblastoma [64, 65]. However, responses have been reported to anti-PD-1 inhibitors in patients with germline mismatch repair-deficient (dMMR) tumors (Lynch syndrome) or microsatellite instability (MSI)-high status [66]. Trials of adjuvant ICIs for treatment of glioblastoma have shown no survival advantage, including a trial with nivolumab in patients with glioblastoma who were 65 years or older (Table 1) [67].

Immune Checkpoint Inhibitor-Related Toxicities in Older Cancer Patients

Small retrospective studies have shown fairly equal rates of irAEs between older and younger cohorts receiving ICIs [68, 69]. This finding has been recapitulated in a larger international retrospective study that confirmed treatment with ICIs may be effective and generally well tolerated among older patients with cancer, but ICI discontinuation due to irAEs was more frequent with increasing age [70]. The “Elders” study, a prospective observational study designed to address the safety of single-agent ICIs in older patients with advanced/metastatic NSCLC or melanoma, found no significant difference in the incidence of grade 3–5 irAEs between older and younger patients [71]. However, Bruinen and colleagues demonstrated that although frailty did not influence the occurrence of an irAE in older patients with stage 4 melanoma, irAEs were more likely to lead to hospital admissions and could be more challenging to manage in frail patients [49]. Currently, the Cancer and Aging Research Group (GARG) has a validated, publicly available online tool for predicting chemo-related toxicities for older patients [72]. However, to the best of our knowledge, no specific toxicity nomograms for ICIs are available to date.

Role of Geriatric Assessment in Treating Older Patients with Immune Checkpoint Inhibitors

A challenge in the study and treatment of older patients is identifying an accurate definition of “older,” “elderly,” or “geriatric.” Most often an age cutoff of ≥ 65 is used in the literature, but on the individual patient level, there may be a discrepancy in chronological versus physiological age. Using chronological age alone does not always bring to light information regarding a patient’s ability to tolerate cancer-directed therapy. There is often a need to differentiate older patients who are likely to benefit from and tolerate

cancer-directed therapies from those who may be predisposed to developing side effects and/or require modified treatment plans. Therefore, screening tools and/or tailored clinical assessments may help identify older patients with regard to functional impairments and complex psychosocial issues.

The comprehensive geriatric assessment (CGA) addresses not only functional status, but comorbid conditions, cognitive function, psychological state, social support, nutritional status, and polypharmacy [73]. In 2023, the American Society of Clinical Oncology (ASCO) updated the clinical practice guidelines regarding the assessment and management of vulnerabilities in older patients receiving systemic cancer treatments [74]. Although recommendations are for the ongoing use of GA for all patients with cancer who are 65 years or older, and that GA-guided management be included in their care plan, the panel also included the option of a practical geriatric assessment (PGA). The PGA is a concise and validated tool designed with input from experts from ASCO and CARG that can be completed by the patient or caregiver before a visit or in the waiting area at the office [74]. The PGA may be more manageable and therefore lead to higher rates of compliance with the tool than the traditional CGA in a busy clinical oncology practice.

In the new era of ICI therapies, there are ongoing prospective trials underway. For example, in NSCLC (NCT05230888), the GA and its potential to identify functional predictors of ICI-related events in patients ≥ 70 are being evaluated [75]. Overall, the evidence and recommendations point toward utilizing, at a minimum, a validated screening tool like the G8 to identify patients in need of a CGA or completing a PGA prior to and during the treatment of older patients with ICIs [76, 77]. Performing these assessments is important, but ultimately, the goal is to use the results to guide and create a patient-centered and multi-disciplinary care plan.

Conclusions

Research on maladaptive cellular aging, immunosenescence, inflammation, and evasion of adaptive and innate immune responses and their implications for cancer immunotherapy in older patients is critical to moving the field of geriatric oncology forward. Since the underlying mechanisms of aging, like cellular senescence, affect the immune system and may ultimately alter the body's response to ICIs, advances in basic science are integral to understanding and improving clinical outcomes with ICIs in older adults. Current work in mouse models utilizes "older" mice to better understand how maladaptive changes of aging affect T cell function, but also the inflammatory and exhaustion environment of the organism as a whole. This

work may 1 day have translational significance with regard to ICIs in older patients with cancer.

With the current gaps in our understanding of how physiological changes of aging impact the response to and toxicity of ICIs, lack of standardization with regard to assessing a patient's physiological age versus chronological age, and absence of ICI-specific "toxicity calculators" like those created by CARG for cytotoxic drugs, we conclude that utilizing tools like the G8 and/or GAs is important to help guide treatment decisions for older adults with cancer who are receiving ICIs.

We found very few trials with ICIs specifically designed for older adults. For NSCLC, esophageal, and glioblastoma, we identified trials specifically devoted to older patients, whereas other trials, like Checkmate 153, at least had a planned older adult group (Table 1). It must be acknowledged that in the prospective therapeutic trials with ICIs as we described above, even when older patients are included, those that ultimately participated may be more likely to have fewer comorbidities and better performance status, which may not accurately represent the "real world" practice.

Interestingly, there may be variable responses among older patients by cancer subtype. For example, melanoma showed an age-associated improved response to ICIs in older adults whereas older patients with advanced NSCLC did not appear to experience the same benefit. Clearly, it is crucial that more work be done to understand these differences. Although a small number of prospective clinical trials are underway, we advocate for trial design to specifically recruit and enroll older patients with cancer to identify the most effective ICIs, tailor dosing and treatments, minimize ICI-related toxicities, and evaluate geriatric-specific tools to help guide care.

Author contributions SQ, MG, and MK conceived the paper. All authors contributed to the writing and final approval of the manuscript.

Declarations

Competing interests MK reports research funding from: BMS, AbbVie, Daiichi Sankyo, BioNTech, Immorna Therapeutics, Celldex, Astellas, CNS Pharmaceuticals. Honoraria: GSK, Novocure, JAX lab for genomic research, Johnson and Johnson, Voyager therapeutics and George Clinical. The other authors have no disclosures.

Conflict of Interest MK reports research funding from BMS, AbbVie, Daiichi Sankyo, BioNTech, Immorna Therapeutics, Celldex, Astellas, and CNS Pharmaceuticals. Honoraria: GSK, Novocure, JAX lab for genomic research, Johnson and Johnson, Voyager therapeutics, and George Clinical. The other authors have no disclosures.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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