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CURRENT OPINION

Cancer Immunotherapies: Are They as Effective in the Elderly?

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Abstract Almost two-thirds of all new cancer diagnoses are made in persons over the age of 65 years, yet it is unclear if age affects patient responsiveness to immunotherapy, which is increasingly becoming first-line therapy in advanced stages of different tumor types. Preclinical animal studies may be difficult to translate into humans since they frequently use young mice (2–3 months of age) equivalent to adolescent human subjects. Nevertheless, ex vivo studies from humans are concordant with mice tissue findings—older patients have an increased density of circulating regulatory immune cells and a decreased ratio of naïve-to-memory T cells. A review of different immunotherapy trials reveals that contrary to expectations, advanced age generally does not hinder safety and clinical response to different treatment modalities. A growing number of immune checkpoint inhibitor immunotherapy trials have been published with basic safety and clinical response data stratified by age. We present the clinical response data from 21 phase II/III clinical trials based on age stratification into young and old subgroups. Data from these trials indicate that these agents have an overall low toxicity profile and that they are similarly well-tolerated in young and old patient subgroups. However, drug-specific differences exist for immune checkpoint inhibition in elderly subjects when comparing overall survival and progression-free survival hazard ratios with those of young subjects. Additional work is needed to better stratify 'responders' and 'nonresponders' within the elderly age group in order to optimize immunotherapy use in a heterogeneous patient population.

Key Points

Preclinical and clinical ex vivo data demonstrate that advanced age is associated with decreasing antitumor immune responses, including a reduction in T-cell receptor diversity and a drive towards pro-inflammatory and -angiogenic pathways

In spite of these findings, clinical trials from different immunotherapeutic agents have demonstrated that patients at least 65 years of age treated with the checkpoint inhibitors pembrolizumab and ipilimumab have comparable positive clinical responses to patients <65 years of age

Advanced age (at least 75 years) may represent a tipping point in clinical antitumor immunity, as reflected by decreased clinical responses in this age group treated with nivolumab

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1 Introduction

For the first time in history, we are embarking on a paradigm shift in clinical cancer management: immunotherapy is becoming first-line treatment for advanced stage cancer patients [1–4]. As almost two-thirds of all new cancer diagnoses are made in persons over the age of 65 [5], it is of extreme importance to understand how immunotherapy agents perform in elderly patients. Over the past 4 years, the number of clinical trials utilizing immunotherapeutic agents—mainly immune checkpoint inhibitors—has sharply increased. With lower toxicity profiles compared with conventional chemotherapies, these are especially attractive agents for elderly patients.

Preclinical and clinical data indicate that aging is associated with a waning in immunity, which raises the concern that extremes in age could impair the response to immunotherapies.

Preclinical mouse models indicate that aged mice mount a less effective antitumor immune response compared with younger mice. However, most preclinical drug development data are from young mice that are 2–3 months of age (roughly equivalent in age to a young adult), which is not representative of the demographics of tumor development in human subjects. Further compounding the issue is the fact that scientific data in human models are scant, likely a reflection of the fact that elderly subjects are underrepresented, often comprising at most a quarter of all trial participants [6]. This underrepresentation is likely due to comorbidities making these subjects ineligible for inclusion in these trials.

To better understand the clinical response of elderly subjects to immunotherapy, we performed a review of the literature of the different types of immunotherapies in elderly subjects, including immune checkpoint inhibitors, immune-modulating monoclonal antibodies (mAbs), adoptive cellular therapies, cancer vaccines, chimeric antigen receptor (CAR) T cells, and oncolytic immunotherapies. With emphasis on immune checkpoint inhibitors, we performed a meta-analysis of published clinical trials with available results for elderly age subgroups for five different immune checkpoint inhibitors spanning several solid tumor types.

2 Age-Associated Immune Alterations in Antitumor Response and Preclinical Data

Aging results in both quantitative and qualitative changes in both innate and adaptive immune responses, causing elderly subjects to be more susceptible to infections and cancer [7, 8]. As the thymus begins to involute with age, there is a general reduction in global T-cell receptor (TCR) repertoire diversity as well as the output of phenotypically naïve T cells [9–11]. Corresponding with this decrease in circulating naïve T cells is an increase in memory T-cell populations, resulting in a reduced naïve-to- memory T-cell ratio [12–14]. In murine breast cancer models, older mice were found to rely on an innate immune antitumor response and had reduced $CD8^+$ T-cell antitumor activity [15, 16]. Aging is also associated with altered murine memory $CD8^+$ T-cell phenotypes, including decreased expression of the co-stimulatory molecule CD28 and CD27 [17–19]. The effector T cells from older mice have been shown to be more functionally impaired and produce fewer cytokines compared with those of younger mice. This overall imbalance and reduction in T-cell diversity and proliferation capacities are part of a process termed immunosenescence.

Accompanying immunosenescence is low-grade inflammation and subsequent activation of pro-inflammatory signaling pathways as a result of aberrant secretion of the cytokines interleukin (IL)-1α, IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) [5, 20, 21]. Elderly patients with cancer have been shown to have higher serum levels of pro-angiogenic proteins such as vascular endothelial growth factor (VEGF) [22]. Additionally, age-related increases in tumor-resident antigen-presenting cell subsets, specifically pro-inflammatory macrophages, have been found in both murine and human subjects [19, 23]. In spite of these changes, elderly subjects with a higher presence of tumor-infiltrating lymphocytes (TILs) have a better prognosis than those who have lower TIL levels, suggesting that in the setting of tumor, compensatory responses might be able to counter immunoinhibitory effects [24].

Effector T cells are thought to be impaired in older mice due to the increase in the number of T-regulatory (Treg) cells and expression of exhaustion markers. Research in murine models has demonstrated a positive correlation of age with the quantity of Treg cells in lymphoid tissues [25, 26]. When compared with 2-month-old mice, mice over 18 months of age have been shown to have increased expression of programmed death receptor 1 (PD-1) and T cell immunoglobulin and mucin domain 3 (TIM-3) on $CD4^+$ and $CD8^+$ T cells [27]. However, similar findings have not yet been demonstrated in human subjects with cancer—in a study of patients with non-small-cell lung cancer (NSCLC) (median age 67 years), PD-1, programmed death receptor ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene expression did not positively correlate with increased age [28].

Additionally, preclinical and clinical research have demonstrated the negative effect of aging on response to immunotherapeutic agents [29]. For example, upon stimulation with lipopolysaccharide (LPS), bone marrow- and peripheral blood mononuclear cell (PBMC)-derived macrophages of older, but not younger mice or human subjects,

respectively, produced substantially elevated levels of pro-inflammatory molecules IL-6 and TNF-α [30]. Young mice also differ from old mice on the basis of their ability to mount a stronger antitumor T-cell response to immune-stimulating agents; when challenged with CPG, only young mice were observed to generate an antitumor response [16]. Similarly, only young mice with renal cell carcinoma (RCC) were responsive to combined IL-2 and anti-CD40 mAb administration [31]. Other attempts to overcome age-related suppressed T-cell responses in aged mice have proven unsuccessful; when treated with OX40-agonists, young mice, but not middle-aged and elderly mice, demonstrated impaired tumor growth [32]. In other settings, immunotherapies have had better success in the setting of advanced age, as it was shown that tumor regression occurred after blocking $CD4^+FoxP3^+$ Treg cells in older mice with colon cancer and BM-185-EGFP tumor types, although the same finding was not observed in B16 melanoma or Her2/neu tumor models [16, 33, 34].

Preclinical data also suggest that aging is associated with an increased toxicity profile to immunotherapies, which is a finding that remains less clear in human subjects. For example, older mice treated with combination therapy with IL-2 and anti-CD40 mAbs had an increase in mortality and multi-organ pathology as well as elevations in pro-inflammatory cytokines such as IL-6 [30]. Such cytokines, including granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF), result in the stimulation of inhibitory myeloid-derived suppressor cells (MDSC) [35]. As potent inhibitors of T-cell proliferation and a source of reactive oxygen species, MDSC have been found to increase in total numbers in the bone marrow, blood, and secondary lymphoid organs in both aged murine and human models [23, 33, 36–39]. When stratified by age, human subjects >67 years of age ($n = 131$) have been shown to have significantly higher levels of circulating $HLA\text{-}DR^+CD33^+$ MDSC, particularly the myeloid subset ($CD11b^+CD15^+$), compared with subjects <60 years of age ($n = 41$) [37]. The frequency of MDSC was even more significantly elevated in elderly subjects with a history of cancer. Additionally, in vivo depletion of MDSC has been selectively advantageous for older mice versus younger mice, resulting in the induction of a larger quantity of interferon (IFN)-γ-producing $CD8^+$ T cells and subsequent reduction in tumor growth [33].

3 Review of Clinical Trials in Human Cancer Patients

In contrast to mouse data, our knowledge of the effects of aging on the immune system of human subjects is often only in the absence of cancer. The median age of most large immunotherapy clinical trials is frequently at least 60 years, and treatment responses measured in different age subgroups from phase II/III clinical trials are often reported, allowing for extrapolation of an age cutoff for treatment efficacy. In the following section, we will discuss data available from clinical trials of older subjects (generally at least 65 years of age) spanning several different categories of immunotherapies. Particular focus will be on immune checkpoint inhibitors, which includes a meta-analysis of current published clinical trial data involving elderly subjects.

3.1 Immune Checkpoint Inhibitors

Precision medicine has ushered in immune checkpoint inhibitors as an exciting new treatment option for advanced stage cancer patients. These agents are an appealing alternative in elderly patients to conventional cytotoxic chemotherapeutic agents, which have significant toxicities. Humanized mAb inhibitors of CTLA-4, PD-1, and its ligand PD-L1 are examples of checkpoint inhibitors that have received Food and Drug Administration (FDA) approval for treatment of different solid tumors. Numerous clinical trials have demonstrated that these agents are as well-tolerated in older patients as they are in younger patients. Numerous phase I–III studies utilizing checkpoint blockade with agents such as pembrolizumab (anti-PD-1) have a median age greater than 60 years of age, such as those for NSCLC, gastric cancer, head and neck squamous cell carcinoma (HNSCC), and urothelial cancer [40–45]. The number of checkpoint blockade immunotherapies available for treating advanced stage tumors is rapidly growing. To date, ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1), and pembrolizumab have been approved as first-line therapy for patients with non-BRAF mutated unresectable or distant metastatic melanoma; pembrolizumab has been approved as first-line therapy for metastatic NSCLC and as second-line therapy for recurrent or metastatic head and neck cancer; nivolumab has been approved as second-line therapy for renal cell cancer; and atezolizumab (anti-PD-L1) has been approved for platinum-resistant advanced or metastatic bladder cancer [46–48].

In general, most immune checkpoint immunotherapy trials have age subgroup analysis typically stratified on the basis of an age cutoff of 65 years and less frequently on the basis of an age cutoff of 75 years. Nine randomized control trials with age subgroup analysis published through 2015 were identified in a meta-analysis of anti-PD-1/CTLA-4 immunotherapies (ipilimumab/tremelimumab/nivolumab/pembrolizumab) [46]. The combined results of all these trials demonstrated a significantly improved overall survival (OS) for both younger (<65 years old) and older (≥65 years old) study subgroups receiving anti-PD-1 and

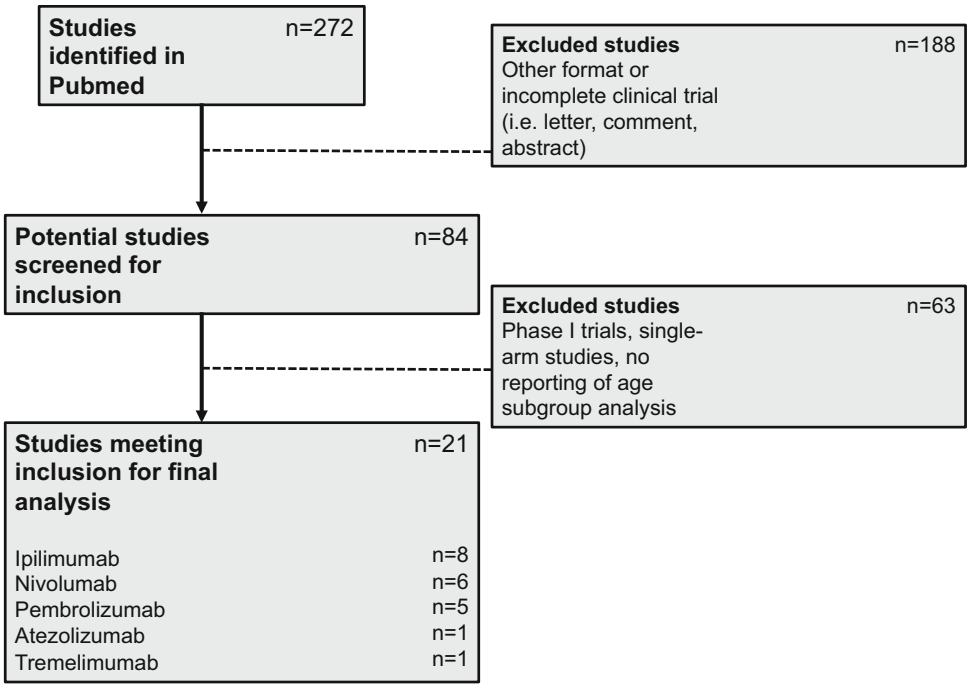

Fig. 1 Flow chart demonstrating the search methodology for clinical trials of different checkpoint blockade agents

anti-CTLA-4 immunotherapies [46]. Importantly, the analysis of four clinical trials using anti-PD-1 agents demonstrated no improved OS in patients ≥75 years of age when compared with subjects <75 years of age. Another meta-analysis of elderly subjects on checkpoint blockade agents found these agents had an overall positive impact, albeit drug class-specific responses were not performed in this study. It has also been shown that both older and younger patients taking anti-PD-1/PD-L1 agents had similarly reduced hazard ratios (HRs) for OS and that patients at least 65 years of age had an improved overall progression-free survival (PFS) [49]. Pooled analysis from three randomized controlled trials of patients with NSCLC or renal cell cancer treated with nivolumab showed that patients aged 65–75 years of age had a survival benefit that was not observed in patients over 75 years of age [50].

To provide an up-to-date assessment of the current state of performance of elderly subjects in the ever-growing checkpoint immunotherapy clinical trial landscape, we performed a comprehensive search of all randomized clinical trials testing a checkpoint immunotherapy agent by searching PubMed from January 1, 1996 to April 20, 2017 using the following keywords: "immunotherapy", "checkpoint immunotherapy", "cancer", "clinical trial", and "subgroup analysis". Our search yielded a total of 272 studies, of which we reviewed 84 clinical trials for potential inclusion (see Fig. 1). Among these studies, we identified a total of 21 publications that met the criteria for final inclusion (randomized phase II/III trials with age-based subgroup analysis). From each study, we extracted the following information: tumor site, immunotherapeutic agent tested, number of subjects, and HRs and 95% confidence intervals (CIs) for OS and PFS. Prism 7 (GraphPad Software) was used to generate forest plots. R (R Development Core Team 2010) was used to calculate pooled HR by running a random effects model.

In our meta-analysis of published clinical trials, we identified 21 studies published on 19 different phase II/III clinical trials (see Table 1) that tested five different checkpoint blockade agents—ipilimumab ($n = 8$), nivolumab ($n = 6$), pembrolizumab ($n = 5$), atezolizumab ($n = 1$), and tremelimumab ($n = 1$)—for seven different solid tumor types: melanoma, NSCLC, small-cell lung cancer (SCLC), prostate cancer, HNSCC, urothelial cancer, and RCC [44, 51–70]. For ipilimumab, nivolumab, and pembrolizumab, we constructed forest plots to compare the OS and PFS for younger and older patient subgroups. Among the 21 studies, 19 provided HR values for OS (95% CI), seven provided HR values for PFS (95% CI), and five studies provided HR for both OS and PFS.

In general, both younger and older subgroups for all trial patients had similar pooled OS and PFS, with the exception of a few notable drug-specific differences. The overall pooled effect size for all groups on all drugs was 0.79 (95% CI 0.73–0.85), with high heterogeneity scores ($I^2 = 43\%$, $p < 0.001$; Cochran's $Q = 57$, $p = 0.0015$). Whereas both older and younger patients taking pembrolizumab and ipilimumab had similar OS HR, age-related differences were present for patient responses to nivolumab (see Fig. 2a, b). The pooled OS HR for the older patient

Table 1 Summary of checkpoint inhibitor immunotherapy clinical trials included in the meta-analysis

References	Tumor site	Trial phase	Immunotherapy agent	Age	*N*	PFS HR (95% CI)	OS HR (95% CI)
Hodi et al. [51]	Melanoma	III	Ipilimumab + gp100 vs. gp100	<65	291	NR	0.70 (0.54–0.90)
				≥65	112		0.69 (0.47–1.01)
Robert et al. [52]	Melanoma	III	Ipilimumab + dacarbazine vs. dacarbazine	<65	165	NR	0.70 (0.56–0.88)
				≥65	85		0.91 (0.647–1.29)
Ribas et al. [53]	Melanoma	III	Tremelimumab vs. temozolomide or dacarbazine	<65	218	NR	0.88 (0.72–1.07)
				≥65	110		0.87 (0.64–1.19)
Kwon et al. [54]	Prostate cancer	III	Ipilimumab vs. placebo	<70	125	NR	0.81 (0.64–1.01)
				≥70	131		0.88 (0.69–1.13)
Robert et al. [55]	Melanoma	III	Nivolumab vs. dacarbazine	<65	200	NR	0.52 (0.32–0.85)
				65–74	151		0.44 (0.24–0.81)
				≥75	67		0.25 (0.10–0.62)
Robert et al. [56]	Melanoma	III	Pembrolizumab vs. ipilimumab	<65	319	0.55 (0.41–0.73)	0.65 (0.44–0.95)
				≥65	238	0.61 (0.41–0.81)	0.56 (0.36–0.87)
Ribas et al. [57]	Melanoma	III	Pembrolizumab vs. chemotherapy	<65	200	0.47 (0.34–0.66)	NR
				≥65	159	0.70 (0.48–1.01)	
Motzer et al. [58]; Escudier et al. [59]	RCC	III	Nivolumab vs. everolimus	<65	257	NR	0.78 (0.60–1.01)
				65–74	119		0.64 (0.45–0.91)
				≥75	34		1.23 (0.66–2.31)
Borghaei et al. [60]			Nonsquamous NSCLC	III		Nivolumab vs. docetaxel	<65
							339
							0.89 (0.70–1.13)
0.81 (0.62–1.04)							
65–74	200	0.94	(0.69–1.27)	0.63		(0.45–0.89)	
≥75	43	0.97	(0.49–1.95)	0.90		(0.43–1.87)	
Brahmer et al. [61]	Squamous NSCLC	III	Nivolumab vs. docetaxel	<65	152	0.62 (0.44–0.89)	0.52 (0.36–0.75)
				65–74	91	0.510 (0.32–0.82)	0.56 (0.34–0.91)
				≥75	29	1.76 (0.77–4.05)	1.85 (0.76–4.51)
Hodi et al. [62]	Melanoma	II	Nivolumab + ipilimumab vs. ipilimumab	<65	68	0.29 (0.14–0.60)	0.52 (0.24–1.12)
				≥65	74	0.43 (0.24–0.79)	0.95 (0.45–2.02)
Herbst et al. [63]	NSCLC (PD-L1+)	II/III	Pembrolizumab vs. docetaxel	<65	466, 317	0.84 (0.69–1.02)	0.63 (0.5–0.79)
				≥65	312, 204	0.93 (0.72–1.19)	0.76 (0.57–1.02)
Fehrenbacher et al. [64]; Rittmeyer et al. [70]	NSCLC	II/III	Atezolizumab vs. docetaxel	<65	453	NR	0.80 (0.64–1.0)
				≥65	397		0.66 (0.52–0.83)
Reck et al. [65]	SCLC	III	Ipilimumab + etoposide + platinum vs. etoposide + platinum	<65	299	NR	1.08 (0.90–1.31)
				65–74	147		1.14 (0.87–1.49)
				≥75	32		0.70 (0.40–1.20)
Beer et al. [66]	Prostate cancer (chemo-naïve)	III	Ipilimumab vs. placebo	<70	200	NR	1.16 (0.85–1.57)
				≥70	200		1.02 (0.75–1.37)
Ferris et al. [67]	HNSCC	III	Nivolumab vs. standard therapy	<65	172	NR	0.64 (0.45–0.89)
				65–74	56		0.93 (0.56–1.54)
				≥75	12		N/A
Reck et al. [44]	NSCLC	III	Pembrolizumab vs. platinum-based chemotherapy	<65	141	0.61 (0.4–0.92)	NR
				≥65	164	0.45 (0.29–0.72)	
Bellmunt et al. [68]	Urothelial cancer	III	Pembrolizumab vs. chemotherapy	<65	230	NR	0.75 (0.53–1.05)
				≥65	312		0.76 (0.56–1.02)

Table 1 continued

References	Tumor site	Trial phase	Immunotherapy agent	Age	*N*	PFS HR (95% CI)	OS HR (95% CI)
Ascierto et al. [69]	Melanoma	III	Ipilimumab (10 mg/kg) vs. ipilimumab (3 mg/kg)	<65	224	NR	0.78 (0.62–0.97)
				≥65	141		0.99 (0.77–1.28)

CI confidence interval, *HNSCC* head and neck squamous cell carcinoma, *HR* hazard ratio, *NR* not reported, *NSCLC* non-small-cell lung cancer, *RCC* renal cell carcinoma; *OS* overall survival, *PD-L1* programmed death receptor ligand 1, *PFS* progression-free survival, *SCLC* small-cell lung cancer

subgroup on pembrolizumab was 0.72 (95% CI 0.60–0.87) compared with 0.66 (95% CI 0.56–0.78) for the younger subgroup. For ipilimumab, this was 0.90 (95% CI 0.79–1.02) compared with 0.85 (95% CI 0.72–1.01) for the older and younger subgroups, respectively (see the electronic supplementary material, online resource 1, Supplementary Figure 1). Pooled OS HR for older patients on nivolumab was 0.91 (95% CI 0.62–1.33) compared with 0.67 (95% CI 0.56–0.80) for younger patients. Similar trends were present for PFS HRs for pembrolizumab and nivolumab trials (see Fig. 3a, b).

Elderly patients on nivolumab had a much higher OS HR compared with the age groups less than 75 years of age. Four of the six nivolumab trials included >75 years of age subgroups, and the HRs were higher in value compared with pembrolizumab and ipilimumab trials, which only provided data for the older age subgroup at 65 years of age or older. It is important to note that our pooled subgroup analysis of the older subgroup receiving nivolumab was for patients >75 years of age, which likely explains the more pronounced difference in HR for OS and PFS between the old and young age groups compared with the other checkpoint immunotherapies. Unexpectedly and importantly, patients in nivolumab trials in the 65–75 years age group for all tumor types mainly had HR for OS and PFS that were in fact lower than those for the <65 years age subgroup for the same trials (see Table 1). This could likely be the result of the tumor-dependent poor performance status of patients >75 years of age, as only nivolumab-administered patients >75 years of age with NSCLC and RCC, but not those with melanoma, had an OS HR of >1. In fact, in the nivolumab melanoma clinical trial [55], patients > 75 years of age ($n = 67$) actually had the lowest OS HR (0.25 95% CI 0.10–0.62) when compared with the other two younger age groups (see Table 1).

In contrast, in the nivolumab trial of patients with squamous NSCLC [61], patients >75 years ($n = 29$) with squamous cell NSCLC had the highest HR for OS (1.85, 95% CI 0.76–4.51) amongst any of the examined 21 clinical trials in this analysis, whereas those patients 65–75 years of age in this study had an OS HR that was low and similar to patients in the <65 years age group (see Table 1). In a phase II nivolumab trial of NSCLC—of which 42% ($n = 54$) of patients had squamous NSCLC—patients at least 70 years of age had a comparable overall response rates (ORR) to patients less than 70 years of age [71]. Thus, it remains unclear if elderly subjects >75 years of age with squamous NSCLC are a high-risk group that does not benefit from nivolumab, and findings from future trials should further elucidate the benefit of checkpoint immunotherapy in this elderly age group.

Patients at least 75 years old have been shown to perform well in other checkpoint blockade trials. In one of two trials with a median patient age of at least 75 years, patients with Merkel cell carcinoma treated with pembrolizumab (polyoma virus-positive subset median age 76 years), there was a 56% ORR in this treatment group, with a relatively low frequency (15%) of grade 3/4 adverse events [42]. Similar findings were observed for a recent urothelial cancer trial, Keynote-052 (median age 75 years) [45]. In two separate phase II trials of cisplatin-ineligible patients with advanced or metastatic urothelial cancer treated with atezolizumab (anti-PD-L1), patients ≥65 [72] and ≥80 years old [73] actually had a better ORR than younger patients. Similarly, another anti-PD-L1 agent, avelumab, has been shown to have comparable median OS for patients both younger and older than 65 years of age, albeit the PFS was lower in the older age group [74]. Amongst all immune checkpoint inhibitors, avelumab is the only agent to demonstrate natural killer (NK) cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro in preclinical studies [75].

Data correlating age with immunotherapy toxicity have demonstrated that these agents are well-tolerated in the elderly. For instance, in a phase III trial of nivolumab versus everolimus for metastatic RCC, patients ≥65 years of age actually had similarly low rates of any grade adverse event, including grade 3/4 events, when compared with patients <65 years of age [59]. Additionally patients at least 65 years of age treated with nivolumab had a rate of grade 3/4 adverse events that was less than half that of that for patients treated with everolimus [59]. Similar findings have been demonstrated in retrospective analyses of older subjects with melanoma treated with anti-PD-1 blockade [76, 77]. In another study, Johnpulle et al. [78] presented the outcomes of three consecutive nonagenarians

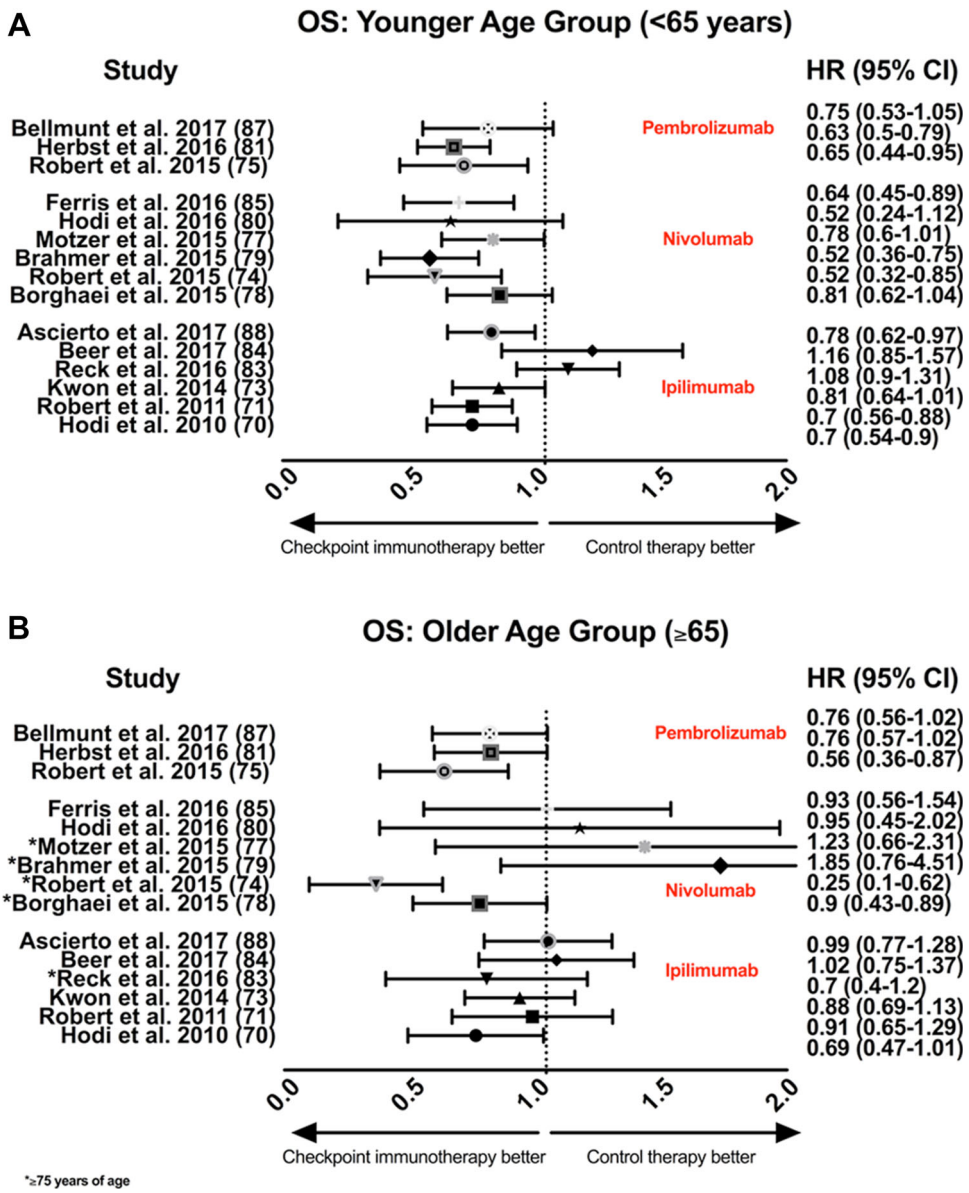

Fig. 2 **a** Forest plot for OS HR (95% CI) for younger (<65 years) subjects in 15 different phase II/III clinical trials using pembrolizumab, nivolumab and ipilimumab. **b** Forest plot for OS HR (95% CI) for older patients (at least 65 years of age). Studies reporting subjects at least 75 years of age are denoted. Six of the eight trials testing ipilimumab and three of the five trials testing pembrolizumab are displayed. *CI* confidence interval, *HR* hazard ratio, *OS* overall survival

(≥90 years old) with metastatic melanoma, treated with single-agent or combination immune checkpoint inhibitors. Two patients experienced objective response with acceptable safety profiles, and one other tolerated therapy well without an objective response. While anecdotal, this established the feasibility of giving these drugs in the very elderly with efficacy, but not overwhelming toxicity. Finally, with respect to CTLA-4 blockade in elderly subjects with metastatic melanoma, the toxicity profile does not appear to be heightened in this patient cohort; in one of the largest trials of elderly subjects (>70 years) ($n = 193$), ipilimumab was as well-tolerated among these subjects as it was for subjects <70 years [79].

While collectively these findings demonstrate that age does not appear to impact a patient's toxicity profile to different checkpoint immunotherapies, it is important to keep in mind that while serious side effects are rare, checkpoint immunotherapies should not be considered completely devoid of severe and even potentially fatal side effects. As a recent meta-analysis has found, checkpoint blockade is responsible for an incidence of fatal immune-related adverse events of <1% and is associated with a small but significant increase in risk of high-grade gastrointestinal and liver toxicities [80].

Thus, the findings in this meta-analysis together with previously published analyses reveal that cancer patients over 65 years of age tolerate checkpoint inhibitors as well as younger patients based on our pooled HR for OS and PFS from 21 different clinical trials. Furthermore, our findings demonstrate that there is no evidence to show that

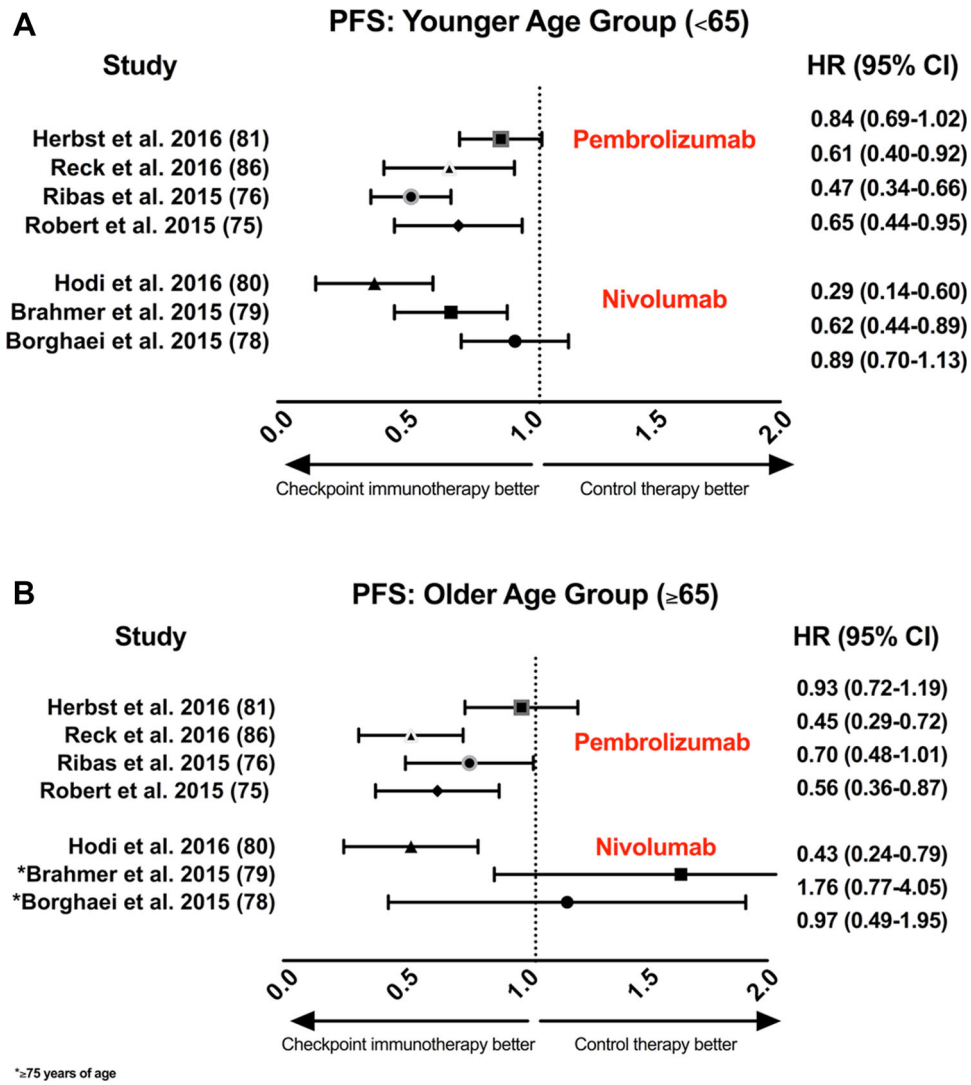

Fig. 3 **a** Forest plot for PFS HR (95% CI) for younger (<65 years) subjects in seven different phase II/III clinical trials using pembrolizumab and nivolumab. **b** Forest plot for OS HR (95% CI) for older patients (at least 65 years of age). Studies reporting subjects at least 75 years of age are denoted. *CI* confidence interval, *HR* hazard ratio, *PFS* progression-free survival

pembrolizumab is less effective in elderly patients. Caution should be used in patients >75 years of age with RCC and NSCLC, particularly when treated with nivolumab. The latter is a finding that needs to be tested in elderly subjects suffering from other cancer types and receiving other checkpoint blockade agents.

3.2 Immune-Modulating Monoclonal Antibodies/ Inhibitors

In this section we will discuss the non-checkpoint mAbs/ inhibitors, focusing on those used for treating B-cell neoplasias. The myelosuppressive effects of chemotherapeutic agents like bendamustine present clinical challenges for treating elderly patients afflicted with hematopoietic malignancies such as chronic lymphocytic leukemia (CLL), a disease largely of the elderly and in whom many cannot withstand the multiple toxicities of multi-agent chemotherapy. mAbs targeting receptors involved in B-cell neoplasias are a more precise means of treating elderly subjects while minimizing side effects. Of interest are those that have been shown in vitro and in vivo to induce ADCC. The use of anti-CD20 mAbs for the treatment of B-cell lymphomas/leukemias, and more recently mAbs directed against CD37, CD19, and CD22, have provided highly targeted therapies for elderly patients with B-cell neoplasms like CLL. Rituximab, a chimeric mAb with high binding affinity and specificity for CD20, utilizes ADCC for tumor killing [81, 82]. Adding rituximab to bendamustine as combination chemo-immunotherapy has been shown to be an effective, less toxic alternative to single-agent chemotherapy for elderly patients with CLL [83]. This is of particular importance because single-agent, standard-dose rituximab has limited activity in relapsed/ refractory CLL [84–86]. The same effect has been observed in elderly patients receiving combined therapies for mantle cell lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma [87–90].

Alemtuzumab, a humanized IgG1 mAb that targets the human pan-lymphocyte antigen CD52, which is expressed in a variety of lymphoid neoplasms, was approved for treatment of fludaribine-refractory CLL in 2001 [91]. Using its IgG Fc region, it utilizes both complement-mediated cytotoxicity and ADCC [92–95]. An Italian retrospective review found that among patients (median age 68 years) with CLL treated with alemtuzumab, patients under the age of 70 years had comparable rates of complete remission and ORR to those at least 70 years of age [96]. Unfortunately, as larger trials have found that alemtuzumab is associated with an increased risk for reactivated herpes and cytomegalovirus, in 2012 it was no longer commercially available [97].

In recent years, newer generation anti-CD20 mAbs have been approved for use in CLL therapy, including ofatumumab, a second-generation CD20 mAb that has been shown to be more effective at complement-dependent cytotoxicity compared with rituximab [97]. In a large phase II clinical trial, it was found to have a good clinical response in elderly patients over the age of 80 years with diffuse large B-cell lymphoma [98, 99]. When given in combination with immunomodulatory agents that induce T-cell and NK-cell activation, such as lenalidomide, ofatumumab was shown in a phase II clinical trial (subject median age 63 years) to be well-tolerated in relapsed and refractory patients with CLL [100]. A study of patients with relapsed and refractory CLL found that weekly infusions of ofatumumab resulted in a comparable ORR in patients at least 70 years of age when compared with those younger than 70 years [101].

Afucosylated antibodies improve ADCC via their ability to activate NK cells. In 2013, the FDA approved the humanized afucosylated third-generation anti-CD20 mAb obinutuzumab for treatment of CLL in combination with chemotherapy. Obinutuzumab induces greater direct tumor cell killing and ADCC over rituximab and is considered a safer alternative for elderly subjects with comorbidities—it has been shown to eradicate minimal residual disease more effectively than rituximab in these patients [97, 102].

3.3 Adoptive Cellular Therapies

Adoptive immunization of cancer patients with T cells represents one of the earliest efforts to treat cancer patients with immunotherapy. In pioneering work that paved the way for future immunotherapy endeavors, TIL administered with IL-2 to patients with melanoma and other solid tumors such as colorectal carcinoma and NSCLC resulted in a clinical response in some patients and in up to 50% of patients with melanoma who were treated with TIL following non-myeloablative chemotherapy [103–105]. One of the earliest applications of adoptive immunotherapy was in the form of IL-2 and lymphokine-activated killer (LAK) cells used to treat tumors such as melanoma, RCC, non-Hodgkin's lymphoma and colorectal cancer [106–109]. While complete or partial responses were frequently only observed in a small fraction of all trial subjects with age ranges spanning 25–70 years, up to one-third of responders were in patients over the age of 60 years, and in some cases, the mean ages of responders were older than non-responders [107–109].

In several cases, adoptive immunotherapy trials were in smaller patient cohorts and published results infrequently provided patient age data, making it difficult to correlate age with response to such therapy. When subject age was made available, the data revealed that advanced age (>60 years) did not hinder TIL efficacy in these subjects compared with chemotherapy [110, 111]. For instance, in a trial of patients with gastric cancer (median age 66 years), two of 22 treated subjects—both of whom were of advanced age (76 and 79 years, respectively)—had a clinical response as measured by a reduction in tumor-related ascites with in vitro production of IFN-α by $CD8^+$ T cells co-cultured with autologous tumor [110]. Among all subjects, three harbored $CD8^+$ TILs that were reactive to autologous tumor in in vitro assays; two of these subjects were younger (49 and 50 years, respectively), but interestingly only the third patient (76 years of age) had a positive clinical response [110].

Data from clinical trials utilizing adoptive transfer of in vitro generated cytotoxic T lymphocytes (CTLs) show clinical responses in some patients over 60 years of age. For instance, in a phase I trial of 11 HLA-$A2^+$ patients (age range 35–68 years) with metastatic melanoma treated with melan-A-specific CTLs, clinical and immunologic responses were observed in three of 11 patients, two of whom were over the age of 60 years [112].

Sequence analysis of the TCR beta chain in patients administered adoptive TIL transfer has revealed that tumor regression directly correlates to the persistence of the adoptively transferred T-cell clonotype in peripheral blood [113, 114]. Telomere length is one way in which the replicative capacity of transferred T cells may be understood—shortening inevitably occurs during T-cell clonal expansion, and stabilization of T-cell telomere length is key for maintenance of T-cell replicative capacity. In a study of patients with metastatic melanoma who were administered autologous TIL infusion therapy, TIL telomere lengths did not correlate to patient age, but to a patient's clinical response to immunotherapy [115].

In all, it is difficult to draw conclusions regarding the efficacy of adoptive immunotherapies in elderly subjects, as these trials are confined to small study cohorts, and larger studies are needed to better establish the role of adoptive T-cell transfer in aged subjects.

3.4 Cancer Vaccines

Tumor-associated antigens from different cancer types are used in peptide-based tumor vaccines with low success rates. While murine models overwhelmingly demonstrate a negative effect of aging on clinical response to tumor vaccines, it is unclear if the same is true in human subjects.

In a small phase I pancreatic cancer vaccine trial of nine patients using peptide KIF20A, four patients achieved stable disease, among whom three patients were at least 60 years of age and had at least moderate levels of induction of antigen-specific CTL responses [116]. However, among the five patients with progressive disease, three were at least 60 years of age, including two patients with weak antigen-specific CTL responses. In another application of tumor vaccination, Sipuleucel-T, an FDA-approved tumor vaccine for high-stage prostate cancer, is an autologous cellular vaccine that uses a patient's dendritic cells cultured with prostate antigens to treat metastatic, hormone-resistant prostate cancer. The phase III IMPACT trial showed a significant reduction in risk of death in a large cohort of patients ($n = 1254$) who received the therapy. Subjects in this trial older than 80 years of age ($n = 278$) had median cumulative antigen-presenting cell counts and activation parameters comparable to their younger counterpart [117]. Further work is needed to elucidate the correlations of OS with these immune parameters and age.

While these trials have demonstrated adequate safety and tolerance, the overall efficacy of tumor vaccines is marginal at best, and no benefit in OS has been demonstrated, irrespective of age [118, 119]. It appears that while tumor vaccines may be safe, their efficacy is questionable and will almost certainly have to be administered with other active immune agents such as immune checkpoint inhibitors in order to achieve clinical responses.

3.5 CAR T cells

CARs are fusion proteins expressed on adoptively transferred T cells that recognize specific antigens and kill malignant cells. While the most promising results were first shown in children and young adults with CD19-expressing acute lymphoblastic leukemia (ALL), the therapy is expanding to other B-cell neoplasms that typically affect older adults. While preclinical studies indicate young patients are likely a better source of high-affinity TCRs that would be needed for autologous adoptive therapy [18], it remains unclear how age affects antitumor response in older CAR T-cell recipients. In fact, results thus far have demonstrated positive response rates in older subjects.

For instance, in a trial of 15 patients (median age 56 years) with non-Hodgkin lymphoma, complete or partial responses were observed in all four study subjects who were over the age of 60 years, including two who received high-dosage infusions of CAR T cells [120]. One of these four subjects experienced severe neurologic toxicities, but completely recovered over the study duration. CAR T-cell infusion showed great efficacy in some of the older subjects, including a 68-year-old man with CLL with bulky lymphadenopathy that dramatically regressed after treatment, with a third of all infiltrating T cells showing an anti-CD19 CAR T-cell phenotype. In another study of patients with CLL ($n = 7$), administration of CAR T cells was generally well-tolerated, although mild and self-limiting cytokine release syndrome (CRS) was observed in three patients, which was positively correlated to CAR T-cell persistence [121]. In its most severe form, CRS can be potentially fatal by inducing cerebral edema [122]. In a phase I trial of patients with refractory aggressive diffuse large B-cell lymphoma ($n = 7$) treated with anti-CD19 CAR T cells, three of the patients were over the age of 65, including one patient with a complete response and one patient who underwent disease progression and ultimately died [123]. Persisting $CD19^+$ CAR T cells were detectable in all patients 4 weeks following infusion, and co-culture experiments demonstrated that the older patients produced comparable and in some cases higher levels of IFN-γ compared with their younger counterparts.

Further work is needed to elucidate the effect of age on in vitro expansion of T cells from elderly patients receiving CAR T-cell therapy, and much can be learned from data from pediatric patients with ALL; in those pediatric patients responding to CAR T-cell therapy, their pre-infusion T cells were found to be enriched in early lineage markers, with overall improved T-cell rates of expansion, which was directly correlated to in vitro IL-7 and IL-15 supplementation [124]. As it is known that elderly patients have an overall reduced amount of circulating naïve T cells, treatment of their T cells with these cytokines could enhance in vivo efficacy of CAR T-cell therapy.

3.6 Oncolytic Immunotherapies

Oncolytic viruses are novel immunotherapies that replicate and kill cancer cells in a tumor-specific fashion by activating T cells to recognize viral and tumor-specific antigens exposed during oncolysis [125]. Talimogene laherparepvec (T-VEC), an attenuated herpes simian virus (HSV) type 1 intralesional oncolytic immunotherapy with insertion of the gene encoding GM-CSF, was the first oncolytic immunotherapy to be approved by the FDA following positive clinical responses in the phase III OPTiM trial [126, 127]. Among patients with high-stage melanoma, T-VEC ($n = 163$, median age 63 years) was well-tolerated and resulted in a CR in 17% and a PR in 24% of all patients

[128]. However, age subgroup analysis was not performed. Safety data from other phase I trials of small patient cohorts receiving oncolytic immunotherapies reveal that advanced age does not preclude patient responsiveness. For instance, in a trial using pexastimogene devacirepvec (Pexa-Vec)—a thymidine kinase gene-inactivated oncolytic vaccinia virus that expresses transgenes encoding GM-CSF and β-galactosidase—biweekly intravenous infusions were administered to refractory, metastatic colorectal cancer patients ($n = 15$, median age 58 years) [129]. Intravenous infusions of Pexa-Vec were well-tolerated, without adverse events; however, four patients (27%) did not complete treatment, because of disease progression that occurred in two patients who were 60 years of age and two who were below 40 years of age, indicating that disease progression was likely independent of age [129]. In a trial of metastatic pancreatic cancer (median age 64 years) using Reolysin, a reovirus-based oncolytic immunotherapy that preferentially replicates and induces cell death in cells expressing activated Ras, multivariate analysis of OS and PFS revealed that younger and older subgroups had similar HRs and responses to therapy [130].

4 Discussion

In this review, we find that the preclinical data demonstrating impaired tumor killing in aged mice treated with different types of immunotherapies does not appear to be also evident in elderly human subjects. However, it is important that future clinical trials include age subgroup analysis for older patients, and age cutoffs of 75 or 80 years of age may provide better insights regarding the toxicity and efficacy of different immunotherapies. Here, we identified 21 checkpoint immunotherapy clinical trials with available age subgroup analysis, and our meta-analysis of the pooled HRs for OS and PFS demonstrates no clear differences in these values for older patients when compared with younger patients, with the exception of nivolumab treatment in patients over 75 years of age with RCC and squamous NSCLC. Based on the pooled data, pembrolizumab has the lowest HR for OS and PFS for patients at least 65 years of age, although it is unclear if the same is true for patients who are over 75 years of age receiving pembrolizumab. Similarly, patients >65 years of age with melanoma receiving either anti-CTLA-4 or anti-PD-1 therapies have comparable HR for OS and PFS to younger subgroups.

Immunotherapy is becoming an increasingly favored treatment modality in many cancers, and age-dependent patient responses are largely based on the type and efficacy of immunotherapy administered. While the argument can be made that empirically, immunosenescence and baseline low-level inflammation sets the stage for impaired tumor killing in aged subjects, in actuality, this is definitely not precluding patient responsiveness to immune checkpoint blockade. In fact, in the rare instances when quantitative biomarkers of cellular immunity are obtained, such as the grade of antigen-specific CTL response following tumor vaccination or the penetrance of tumor tissue by CD19-reactive CAR T cells, older subjects are not performing any worse than younger subjects.

Among the different modalities discussed, checkpoint immune blockade with mAbs is the most promising treatment type for older subjects as well as younger patients, which mirrors the general trend currently underway in the field of immunotherapy. Infrequently, immunotherapeutic agents present a major health risk to older subjects, and in most cases, no differences in toxicities are present between young and old study subjects. This is in stark contrast to immunotherapies utilizing specific cytokines where age is critical, as older patients over 75 years of age can have severe neurotoxicities. The use of interleukins is largely out of the question for patients over 70 years of age because of its propensity to induce vascular leak syndrome [131].

In summary, 'second-generation' immunotherapies developed in recent years have been demonstrated to be safe and effective in all patient age groups, providing exciting results that help assuage concerns that have arisen from 'first-generation' immunotherapies such as IFN and IL-2 cytokine therapies in humans and mouse models. Immune checkpoint inhibitors can be given in challenging settings, including to patients of increased age with comorbidities. Further research is needed to determine ways to better optimize patient responses to immunotherapies, including the use of biomarker screening and adoptive cellular therapy with in vitro expansion techniques.

Compliance with Ethical Standards

Conflict of interest Jeffery Sosman has received consulting fees or honorarium from Genentech, BMS, and Merck. All other authors declare no conflict of interest.

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