Appropriate treatment for older patients with cancer: the importance of geriatric assessment and blood biomarkers for patient-related outcomes

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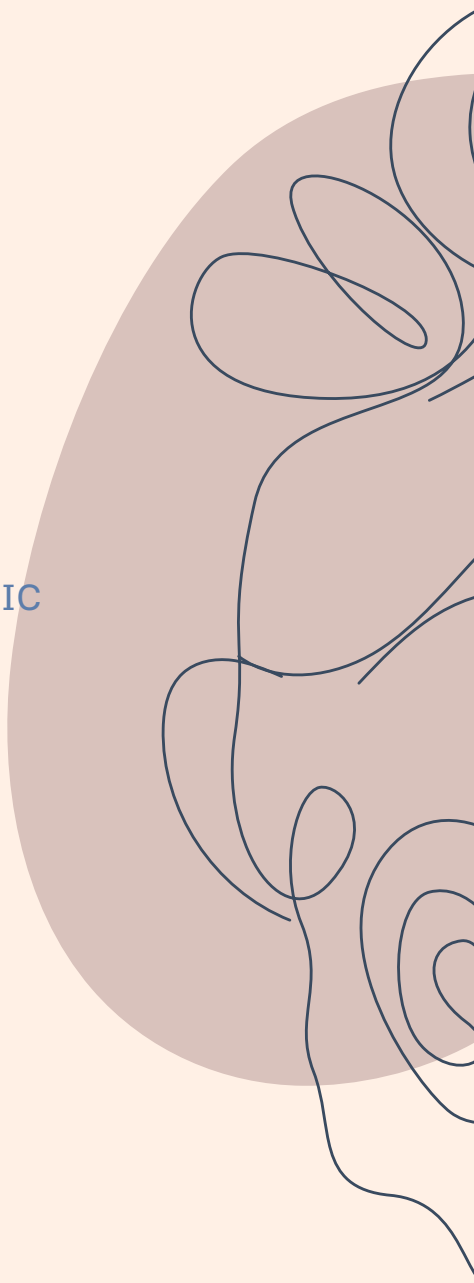
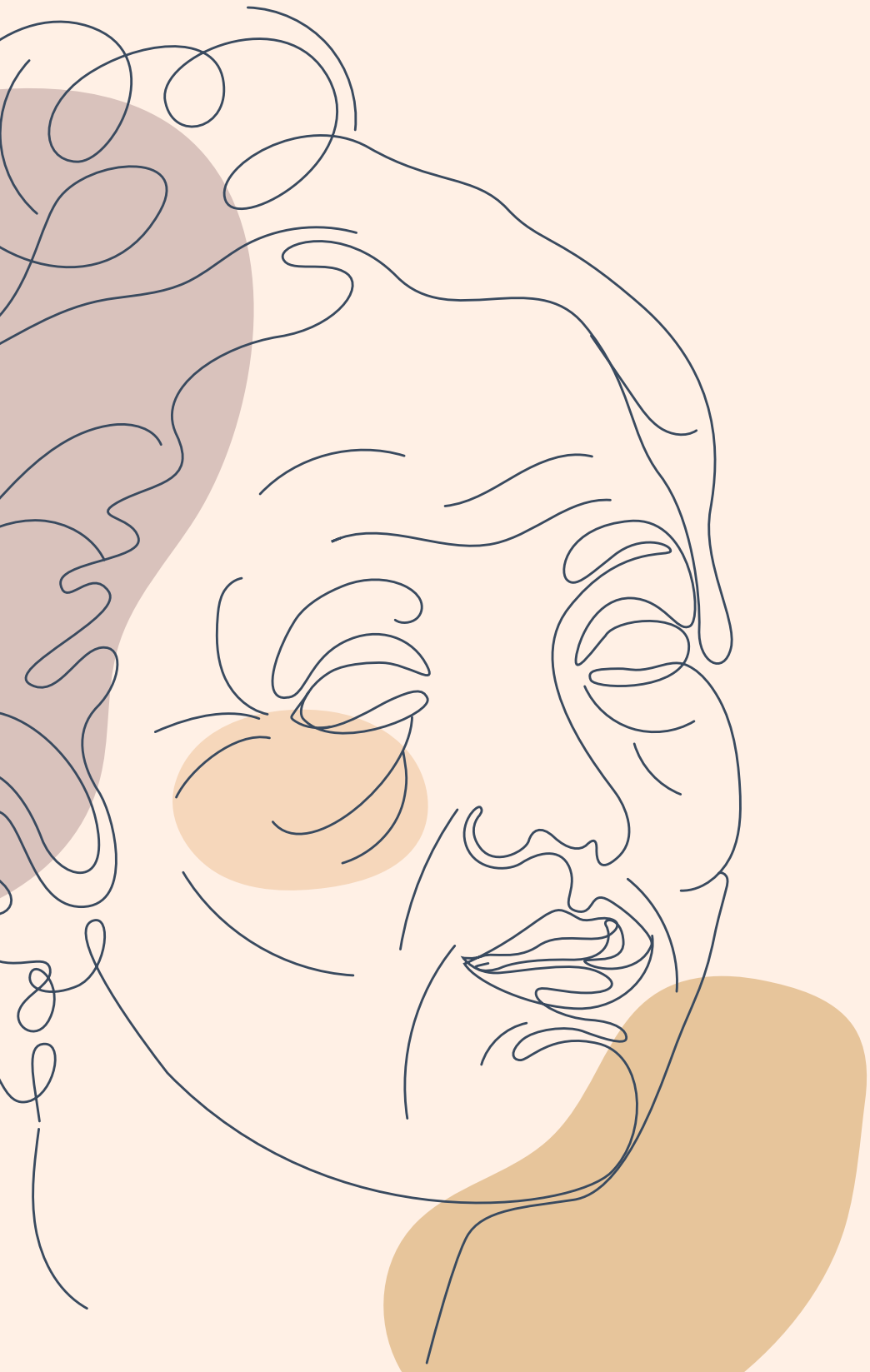
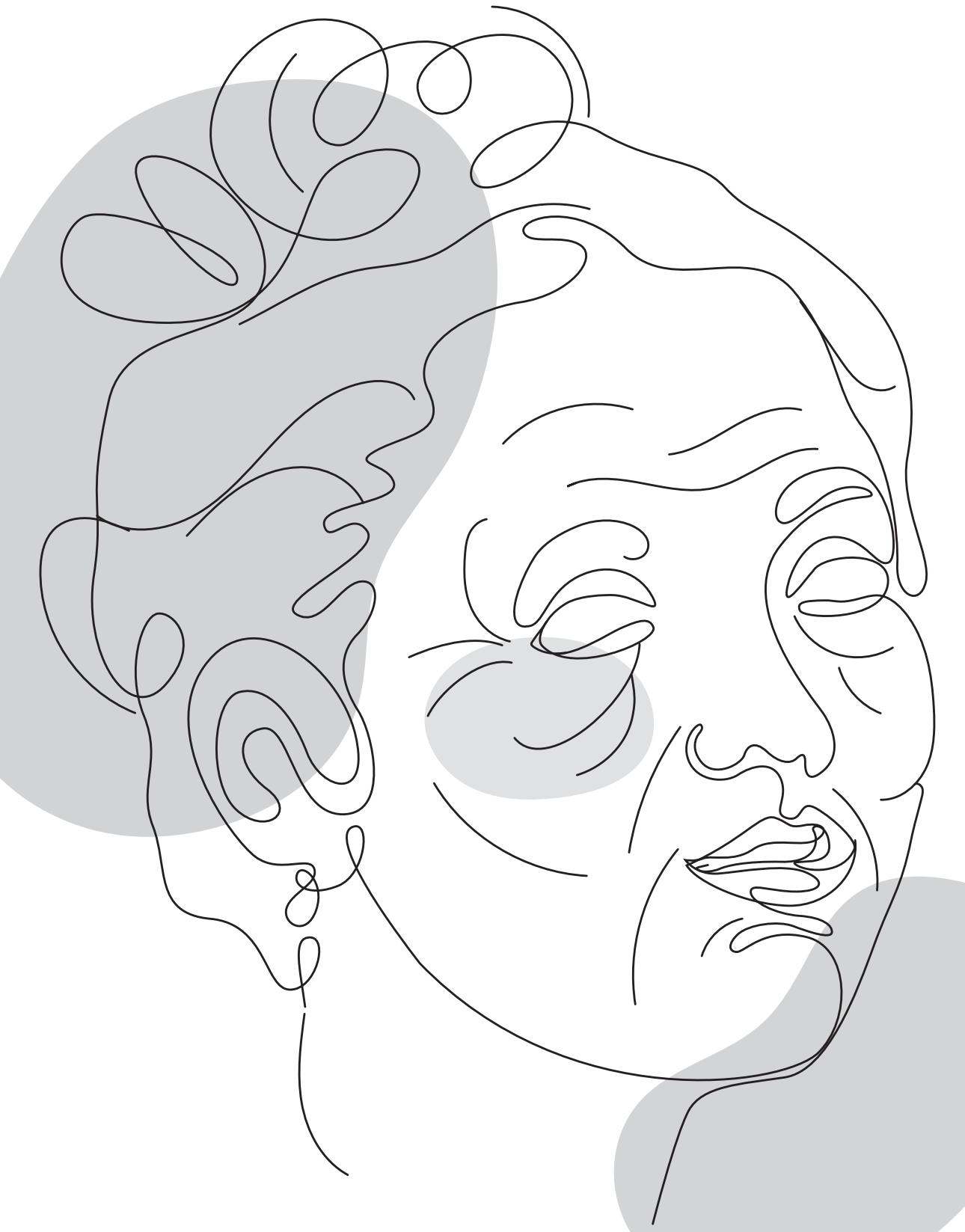
PART I

CURRENT EVIDENCE AND GERIATRIC ASSESSMENT IN OLDER PATIENTS WITH CANCER







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Chapter

Efficacy and adverse events of immunotherapy with checkpoint inhibitors in older patients with cancer

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Abstract

The number of older patients with cancer is increasing due to aging of Western societies. Immune checkpoint inhibitors have improved the treatment accompanied with less treatment related toxicity compared to chemotherapy in the general population. Nonetheless, immune checkpoint inhibitors have potentially serious immune-related adverse events (irAEs), which might have a greater impact on older and more vulnerable patients and potentially influence treatment efficacy and quality of life. Previous clinical trials show no major increase in irAEs, however older patients are underrepresented and relatively healthy in these trials. Observational studies suggest that older and more vulnerable patients may be at higher risk of irAEs and early treatment discontinuation. Geriatric assessment could help identify older patients that will benefit from immune checkpoint inhibitors.

Introduction

In recent years, the number of older patients with cancer is strongly increasing due to ageing of Western societies. In the Netherlands 45% of patients with melanoma, 68% of patients with lung cancer and 69% of patients with urinary tract cancer is older than 65 years [1]. Cancer in older patients frequently appears in the context of comorbid diseases, frailty and geriatric problems such as physical or cognitive impairment [2], which has shown to affect the ability to endure toxic cancer treatments [3]. Previous studies have shown that older patients are at increased risk of chemotherapy toxicity [3]. Also, the risk of dying from other causes increases with age [4,5], which means that some patients may not have the remaining life expectancy to benefit from anti-cancer therapy. Therefore, it is important to weigh benefits and risks of anti-cancer treatment in older patients.

In recent years, immunotherapy targeting checkpoint inhibition has improved the treatment of different types of cancer. Immunological checkpoint molecules suppress the attack of tumour-specific T cells which reinforces anti-tumour immunity [6,7]. Some checkpoint inhibitors block the interaction between PD-1 (programmed cell death-1) on T-cells and its ligand PD-L1 on cancer cells and myeloid cells [6,8]. Others target CTLA-4 (cytotoxic T-lymphocyte antigen-4), which blocks negative signals during T-cell interaction with antigen presenting cells and depletes regulatory T cells, thereby restoring and enhancing T-cell reactivity [9,10]. These drugs are used in an expanding group of tumour types but are most successful in advanced and metastasized melanoma, where progression-free and overall survival have strongly improved [11-14].

However, it is possible that checkpoint inhibitors may be less efficient in older patients due to ageing of the immune system (immunosenescence) [6,7]. The numbers of dendritic cells and CD4+ naive T cells decline while the pool of terminally-differentiated CD8+ T-cells increases [7,15]. In addition, the number of circulating and intratumoural myeloid derived suppressor cells (MDSC's) increases. Hence, T-cell function may decrease and lead to impaired responsiveness to therapies aiming to boost tumour immunity [6,16]. Treatment with checkpoint inhibitors is expensive, since they cost around 50.000-80.000 euros per treatment [17]. Because checkpoint inhibitors potentially have serious adverse events and are costly, it is essential to determine which patients truly benefit from therapy and at what risk.

The aim of this review is to provide a summary of available efficacy data and to provide an overview of the occurrence of adverse events of checkpoint inhibitors in older patients, and to evaluate the available evidence on treatment of these adverse events. We performed an explorative search on PubMed using the following keywords: "Elderly", "Older", "Immune Checkpoint Inihibitors", "Immunotherapy", "Toxicity" and "Immune-related adverse events". We additionally searched through the references of the publications found and we searched abstracts presented at recent Oncology conferences.

Treatment efficacy of immune checkpoint inhibitors in older patients

Melanoma

Several studies have shown the effectiveness of immune checkpoint inhibitors in melanoma for patients of all ages. In 2018 an update of the Cochrane review was performed with respect to systemic treatments for metastatic cutaneous melanoma [18], which showed that with regard to immune checkpoint inhibitors, anti-PD-1 improved overall survival (OS) compared to chemotherapy, and probably improved progression-free survival (PFS). Anti-PD-1 was associated with a better OS and PFS compared with anti-CTLA-4. Anti-CTLA-4 plus chemotherapy probably increased PFS compared to chemotherapy alone, but was not significantly associated with OS gain. Lastly, the combination of anti-CTLA-4 plus anti-PD-1, as compared to anti-CTLA-4 alone, was associated with better PFS. Patients in this Cochrane review had a mean age of 57.5 years at the time of treatment randomization, representing a younger population than the general melanoma patients (Table 1).

Table 1 Overview of systemic treatments for metastatic cutaneous melanoma, Cochrane 2018

Cochrane review	Relative effect (95%CI)	No of patients (studies)	Quality evidence (GRADE)
Anti-PD-1 compared with chemotherapy			
Overall survival	HR 0.42 (0.37-0.48)	418 (1)	High
Progression-free survival	HR 0.49 (0.39-0.61)	957 (2)	Moderate
Tumour response	RR 3.42 (2.38-4.92)	1367 (3)	High
Toxicity (≥G3)	RR 0.55 (0.31-0.97)	1360 (9)	Low
Anti-PD-1 compared with anti-CTLA-4			
Overall survival	HR 0.63 (0.60-0.66)	764 (1)	High
Progression-free survival	HR 0.54 (0.50-0.60)	1465 (2)	High
Tumour response	RR 2.47 (2.01-3.04)	1465 (2)	High
Toxicity (≥G3)	RR 0.70 (0.54-0.91)	1465 (2)	Low
Anti-CTLA-4 + chemotherapy compared with chemotherapy			
Overall survival	HR 0.81 (0.65-1.01)	1157 (2)	Low
Progression-free survival	HR 0.76 (0.69-0.92)	502 (1)	Moderate
Tumour response	RR 1.28 (0.92-1.77)	1157 (2)(	Moderate
Toxicity (≥G3)	RR 1.69 (1.19-2.42)	1142 (2)	Moderate
Anti-CTLA-4 + anti-PD-1 compared with anti-CTLA-4 (Overall survival not measured)			
Progression-free survival	HR 0.40 (0.35-0.46)	738 (2)	High
Tumour response	RR 3.50 (2.07-5.92)	738 (2)	High
Toxicity (≥G3)	RR 1.57 (0.85-2.92)	764 (2)	Low

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; G3, Grade 3.

In the general older patient population evidence with regard to efficacy and toxicity of CTLA-4 inhibitors is lacking. A meta-analysis including melanoma, lung and renal cell cancer patients suggested that the older patients benefit from anti-CTLA-4 therapy in terms of OS with a HR of 0.73 (95% CI 0.62–0.87; p < 0.001) in comparison with the control regimen [8]. In anti-PD-1 treatment, a retrospective study of Betof et al showed no difference in OS or PFS in patients with metastatic melanoma, comparing patients aged ≥75 with younger patients [19]. However, only 20-40% of patients included in these trials are aged >65 years [20], as 45% of the general melanoma population is aged >65 years [1].The older patients included in these trials are probably not representative for the general population of cancer patients due to selective inclusion criteria, such as a good performance status, normal hepatic and renal function and no autoimmune disease. Also, studies have shown that older patients discontinue their treatment more often than younger patient, possibly decreasing effectiveness [21].

Non-Small Cell Lung Cancer (NSCLC)

Khan et al performed a meta-analysis of the available evidence from RCTs in 2018 comparing anti-PD-1 or PD-L1 therapies and chemotherapy in the treatment of advanced NSCLC [22]. A total of 7 RCTs were selected for inclusion; anti-PD-1 or PD-L1 therapies resulted in a better OS, PFS, and objective response rate in comparison to chemotherapy with pooled HRs of 0.72 (95%CI 0.63-0.82; p<0.00001), 0.84 (95%CI 0.72-0.97; p<0.02) and OR 1.52 (95%CI 1.08-2.14; p<0.02), respectively. In subgroup analyses for OS, a significant HR was found in patients above 65 years (HR 0.71 (95%CI 0.56-0.91; p=0.006), however there was no benefit for patients above 75 years (HR 1.23 (0.61-2.48; p=0.56). For PFS, no significant association was found in subgroup analyses, with a HR of 0.78 (95%CI 0.57-1.09; p=0.14 for patient over the age of 65 years and HR 1.25 (0.70-2.22; p=0.45) for patients over the age of 75 years, respectively. A systematic review and meta-analysis of Peng et al showed that immune checkpoint inhibitor combination therapy was significantly associated with prolonged OS in NSCLC (HR 0.80 (0.73-0.88; p<0.00001), but not in SCLC (HR 0.94 (0.82-1.08; p=0.40)). Besides, the data suggested a higher efficacy for PD-1 inhibitors than PD-L1 or CTLA-4 inhibitors; however no specific data for older patients was reported [23].

Bladder and renal cell cancer

The first breakthrough in cancer therapy for metastatic bladder cancer was in 2016 with the approval of atezolizumab for patients who have disease progression during or following chemotherapy, or have disease progression within 12 months of (neo)adjuvant treatment with chemotherapy [24]. Since then, four additional checkpoint inhibitors have been approved [25]: durvalumab and avelumab (PD-L1 blockade) as well as nivolumab and pembrolizumab (PD-1 blockade). From the 5 available inhibitors, pembrolizumab is the

only drug with level I evidence from a phase III trial in specifically urothelial cancer. An improved OS was seen in the KEYNOTE-045 study [26] with a median OS of 10.3 months as compared to 7.4 months in the chemotherapy arm. There are several ongoing trials in patients with urothelial cancer with immune checkpoint inhibitors; however specific data for older patients is not yet available [27].

A recent meta-analysis with respect to metastatic renal cell cancer showed an improved survival with a HR of 0.75 (95%CI 0.66-0.85; p<0.001) for immunotherapy as first or second line therapy compared to standard of care and an improved PFS with an HR of 0.88 (95%CI 0.80-0.97; p=0.009) [28]. Unfortunately, no specific data for older patients was presented and those included in the trials are usually not representative of the general older population.

Immune-related adverse events in older patients

It has been shown that chemotherapy toxicity occurs more frequently in older patients than younger patients [3]. We hypothesize that, due to ageing of the immune system, age-related comorbidity and decreased functional reserve, older patients might also experience more immune-related toxicities with greater impact due to hospitalization. Immune checkpoint inhibitors are responsible for specific inflammatory toxicities by increasing the activity of the immune system. These adverse events are referred to as immune-related adverse events (irAEs). The precise underlying mechanism is unknown. Translational studies in patients with irAEs have shown that T-cell response, antibodies and cytokine responses may be involved [29]. The majority of the irAEs occur within the first 4 months of treatment, but can occur at any time during treatment or several months after discontinuation [29,30].

Nearly all organs can be affected: the skin, gastrointestinal tract, endocrine glands, lung, nervous system, liver, kidney, hematological cells, musculo-articular system, heart and eyes. The spectrum of toxicities seen in CTLA-4 inhibitors or PD-1/PD-L1 inhibitors is similar, but frequencies differ. In general, CTLA-4 inhibitors have shown more grade 3-4 irAEs than PD-1/PD-L1 inhibitors [20,30]. In addition, the combination of anti-CTLA-4 and PD-1/PD-L1 blockade for metastatic melanoma can cause treatment-related adverse events in 95% of patients, with grade 3 or higher events in 55% of patients [31].

With regard to toxicity in older patients, previous randomized trial have rarely studied these outcomes in relation to age. Most evidence is derived from subgroup analyses and cross trial meta-analyses of larger clinical trials. Table 2 summarizes the data from trial subgroup analyses, when published.

Table 2 Overview of trial data regarding immune-related adverse events in elderly

Study	Number of patients	Tumor type	Checkpoint inhibitor	Relevant outcome	Results
Friedman 2016	Patients aged ≥80 years N = 98	Melanoma	Ipilimumab Nivolumab Pembrolizumab Combination ipilimumab + nivolumab	irAEs	Any grade irAEs Ipi (n=74) 87.8% Anti-PD-1 (n=24) 87.5% Nivo+Ipi (n=8) 87.5% Grade 3 or 4 irAEs Ipi (n=74) 29.7% Anti-PD-1 (n=24) 20.8% Nivo+Ipi (n=8) 62.5%
Nosaki 2019	Patients aged ≥75 years Pooled analysis Pembrolizumab N = 149 Chemotherapy N = 105	NSCLC	Pembrolizumab	irAEs	Any treatment-related AE Pembro: ≥75 68%, <75 65% Chemo: ≥75 94%, <75 87% Grade 3-5 treatment-related AE Pembro: ≥75 24%, <75 17% Chemo: ≥75 61%, <75 39% irAEs and infusion reactions Pembro: ≥75 25%, <75 25% Chemo: ≥75 7%, <75 6%
Spigel 2017	N = 1,308 Age ≥70 years N = 520 ECOG PS 2 N = 108	NSCLC	Nivolumab	TRAEs	Any grade TRAE Age ≥70 62%, age <70 59% ECOG PS 2 46%, ECOG PS 0-1 61% Grade 3-4 TRAE Age ≥70 12%, age <70 11% ECOG PS 2 10%, ECOG PS 0-1 12% Grade 5 TRAE Age ≥70 <1%, age <70 <1% ECOG PS 2 2%, ECOG PS 0-1 <1%

Study	Number of patients	Tumor type	Checkpoint inhibitor	Relevant outcome	Results
Herin 2018	N = 220 Age ≥70 years N = 46	Bladder carcinoma NSCLC Gastrointestinal cancer Gynaecological cancer Head and neck carcinoma Breast cancer Renal cell carcinoma	Anti-PD-1/PD-L1 monotherapy Anti-PD-1/PD-L1 + other immuno-modulatory monoclonal antibodies Anti-PD-1 + targeted therapy	irAEs	Grade 1 irAE Age ≥70 72% Age <70 48% Grade 2 irAE Age ≥70 41% Age <70 20% Grade 3-4 irAE Age ≥70 22% Age <70 13% Median time before first event Age ≥70 16d Age <70 36d

Abbreviations: N, number of included patients; NSCLC, Non-small cell lung cancer; irAE, Immune-related adverse event; TRAE, Treatment-related adverse event; ECOG PS, ECOG performance status; d, days.

CTLA-4 inhibitors – trial data

Previous studies have reported irAEs in 60-86% of patients of all ages using ipilimumab (CTLA-4 inhibitor). Around 20-41.6% of patients develop grade 3 and 4 toxicities, depending on dose [20,30,32]. The most frequent observed toxicities (>10%) are diarrhea, rash, pruritus, fatigue, nausea, vomiting, anorexia and abdominal pain [20,30]. Friedman et al. reported toxicity analysis of published phase III data in a small group of patients older than 80 years old treated with different immune checkpoint inhibitors for melanoma. The rate of irAEs and early treatment discontinuation was was modestly higher in older patients compared to a younger population. This effect was especially seen in combination therapy [7,21].

PD-1 / PD-L1 inhibitors – trial data

For nivolumab 58-85% of patients of all ages reported irAEs, of which 7-20% being grade 3 and 4 toxicities, depending on tumour localization. For pembrolizumab 57-80% of patients reported irAEs, of which 10-26% grade 3 and 4 toxicities, depending on dose [20,30,32]. The most common observed toxicities (>10%) are fatigue, rash, pruritus, diarrhea, nausea and arthralgia [20,30].

The KEYNOTE trials have investigated the efficacy of pembrolizumab in 3991 patients with melanoma, NSCLC, head and neck cancers, urothelial carcinoma and Hodgkin's lymphoma. 46% of the patients were age ≥65 years and 16% were age ≥75 years. No overall differences in safety were observed between older and younger patients [33,34]. This was recently confirmed in an update that was presented at the European Lung Cancer Congress 2019, in which was shown that there was no difference in irAEs between patients aged <75 and >75 years [35].

The Checkmate trials assessed treatment with nivolumab for NSCLC, melanoma and renal carcinoma. In total 1359 patients were treated with nivolumab, of which 39% were age ≥65 years and 9% were age ≥75 years. No overall differences in safety were observed between older and younger patients [33,36]. Spigel et al presented a pooled analysis of 520 patients aged ≥70 years and 108 patients with a baseline ECOG performance status 2, receiving nivolumab for metastatic NSCLC in the Checkmate 153 trial. There was no difference in incidence of treatment-related adverse events, any grade and grade 3-5, between the older and younger patients and between the patients with ECOG performance status 2 and 0-1 [37].

The FDA published a subset analysis of the safety of nivolumab in elderly patients. They reviewed 1030 patients in registration trials of lung cancer, renal cancer and melanoma. The data show more reported grade 3-5 adverse events in patients aged ≥ 70 years and a trend of higher incidence of irAEs requiring treatment with immune modulating medication in this group. The indication for immune modulating medication was mostly rash or colitis [33,38].

Herin et al analyzed patients with advanced solid tumour enrolled in 14 immunotherapy phase I/II trials, comparing all included patients ≥ 70 years with control patients < 70 years. Median age in the older patients group was 75 years with an ECOG performance status 0-1. Cumulative incidence of grade 1-2 irAEs was significantly higher in older patients compared to younger patients. The data show a trend of higher incidence of grade 3-4 irAEs, occurring in 22% of older patients versus 13% in younger patients. However, the difference was not statistically significant. Median time before the occurrence of first event was shorter in older patients [39].

The clinical immunotherapy trials included only 20-40% patients aged >65 years [20]. Therefore, it must be noted that the data are derived from trials including primarily patients below the age of 75 and with an ECOG performance status of 0-1 or Karnofsky performance status of 80-100, while the general population of older patients with cancer is generally older and has a lower performance status [9,14,31,32,40-43]. It is conceivable that more vulnerable older patients with a decreased functional reserve experience more adverse events with a greater impact on quality of life.

Population-based data

There have been some previous observational studies in older patients who received immunotherapy that included a population-based sample of older patients, which is more likely to resemble daily clinical practice. Table 3 summarizes these studies.

For example, Sattar et al performed a retrospective study on efficacy and toxicity of ipilimumab, pembrolizumab and nivolumab including 23 patients aged ≥ 75 years with a median Charlson comorbidity score of 6.8. They found no statistically significant differences in irAEs, severity of grade 3 or higher, multiple irAEs, need for steroid treatment and types of adverse events when comparing different age groups. However, the data showed a trend of more irAEs of any severity and irAEs grade ≥3 occurring in the age ≥75 year group. The most frequently reported irAEs were skin toxicity, gastrointestinal toxicity and endocrinopathy [44].

Chiarion Sileni et al reported that melanoma patients over 70 years old using ipilimumab had similar rates of adverse events compared to patients ≤ 70 years old, 50% vs. 46% of any grade and 6% grade 3-4. The most frequently reported irAEs in patients over 70 years were pruritus, rash, diarrhea, nausea and liver toxicity. The median age in patients aged > 70 years was 75 years, but the ECOG performance status was 0 and 1 in 97% of the patients [45], which was not a representative population in daily practice.

Table 3 Overview of observational studies regarding immune-related adverse events in elderly

Study	Number of patients	Tumor type	Checkpoint inhibitor	Relevant outcome	Results
Sattar 2018	N = 78 26 (33%) age 65-74, 23 (30%) age ≥75	Melanoma NSCLC Renal cell carcinoma	Ipilimumab Nivolumab Pembrolizumab	irAEs	41 (53%) patients with irAEs, 12 (15%) multiple irAEs Any grade irAEs Age <65 (n=29) 41% Age 65-74 (n=26) 58% Age ≥75 (n=23) 61% Grade ≥3 irAEs Age <65 (n=17) 29% Age 65-74 (n=12) 25% Age ≥75 (n=11) 36%
Chiarion Sileni 2014	N = 855, 193 patients age >70	Melanoma	Ipilimumab	irAEs	Any irAE: Age >70 50%, age <70 46% Grade 3-4 irAE: Age >70 6%, age <70 no data.
Leroy 2019	N = 52, 23 patients age ≥80	Melanoma	Ipilimumab	irAEs Treatment irAEs Hospitalization due to irAEs	Any irAE: Age ≥80 65%, age ≤80 52% Grade ≥3 irAE: Age ≥80 22%, age ≤80 19% Steroid treatment: Age ≥80 22%, age ≤80 19% Additive immunosuppressive therapy: Age ≥80 9%, age ≤80 4% Hospitalization: Age ≥80 22%, age ≤80 9%
Freeman 2015	N = 148, 52 (35%) age ≥65	Melanoma	Nivolumab	irAEs	Most common irAEs: Rash: Age ≥65 40.4%, age <65 38.5% Diarrhea: Age ≥65 21.2%, age <65 30.2% Vitiligo: Age ≥65 7.7%, age <65 10.4%
Betof 2017	N = 254, 65 (25.6%) age 65-74, 47 (18.5%) ≥75	Melanoma	Anti-PD-1 Anti-PD-L1	irAEs	110 (43.3%) irAEs in all patients Age 65-74: more arthritis (10.8%, p=.02) Age ≥75 trend to more endocrine toxicity

Study	Number of patients	Tumor type	Checkpoint inhibitor	Relevant outcome	Results
Wong 2017	N = 91, 64% ECOG PS 0-1, 18% ECOG PS 2, 9% ECOG PS 3	Melanoma	Anti-PD-1	irAEs	Treatment related AEs grade ≥3: ECOG PS 0-1 5% ECOG PS 2 13% ECOG PS 3 0% irAEs grade ≥3: ECOG PS 0-1 15% ECOG PS 2 0% ECOG PS 3 0%
Horvat 2015	N = 298	Melanoma	Ipilimumab	Number of irAEs Treatment irAEs	254 (85%) irAE 56 (19%) treatment discontinuation 103 (35%) steroid treatment 29 (10%) anti-TNFα treatment
Luciani 2018	Patients aged ≥75 years N = 72	NSCLC	Nivolumab Pembrolizumab	irAEs	9 (14%) irAEs 4 (40%) grade 3-4 irAEs
Corral de la Fuente 2019	N = 98 27 age ≥70 years	NSCLC	Anti-PD-1 Anti-PD-L1	irAEs	30.6% irAEs No statistically significant differences between elder and younger patients
Verzoni 2019	N = 389 70 age ≥75 years N = 70	Renal cell carcinoma	Nivolumab	drAEs irAEs Treatment discontinuation	32% any drAE 7% grade ≥3 drAE 20% any grade irAE 2% grade 3 irAE <1% grade 4 irAE 7.9% treatment discontinuation, of which 45% due to irAEs

Study	Number of patients	Tumor type	Checkpoint inhibitor	Relevant outcome	Results
Muchnik 2019	Patients aged ≥70 years N = 75 53% CCI ≥3 49% ECOG PS ≥2	NSCLC	Nivolumab Pembrolizumab "Other"	irAEs Treatment irAEs Hospitalization	37% of any grade irAE 8% grade ≥3 irAE 64 patients treatment discontinuation, 15% due to irAEs 64% of patients with irAEs glucocorticoid treatment 72% hospitalization during treatment
Silva 2018	Patients aged ≥65 years N = 106	Lung cancer Melanoma Urological cancer Colorectal cancer	Nivolumab Pembrolizumab Ipilimumab Atezolizumab	irAEs	21 irAEs 5 severe irAEs Frailty predicted risk to AE: OR 3.03 (95%CI 1.36-6.74m p 0.006)

Abbreviations: N, number of included patients; CCI, Charlson Comorbidity Index; irAE, Immune-related adverse event; drAE, Drug-related adverse event; ECOG PS, ECOG performance status.

Leroy et al analyzed a retrospective cohort of patients over 80 years treated with ipilimumab for melanoma. Only 23 elderly patients were included, with a median age of 82 years. They had Charlson comorbidity scores of 0-3 and 96% of the patients had an ECOG performance status 0-1. In this study, 65% of elderly patients reported adverse events, with 22% grade 3 and there was 1 grade 5 adverse event. Of these patients, 22% of patients needed corticosteroid treatment, 2 patients needed additive immunosuppressive therapy, 4 were hospitalized and 3 had to discontinue ipilimumab. The grade 3 adverse events reported were hepatitis, colitis, hypophysitis and pneumopathy. The authors conclude that irAEs occur at the same rate in older patients compared to younger patients in this study and compared to previously reported studies [46].

Freeman et al performed a retrospective analysis of irAEs in a cohort melanoma patients <65 years compared to >65 years treated with nivolumab. This analysis showed no significant difference in incidence of irAEs or irAE profile between the two age groups. The most common reported irAEs were diarrhea/colitis, rash and vitiligo. However, no data about the ECOG performance status and severity of irAEs was provided [47].

In addition, Betof et al analyzed retrospectively 254 patients receiving anti-PD-1 and/or PD-L1 for metastatic melanoma, including 65 patients aged 65-74 years and 47 patients aged ≥75 years. The incidence of arthritis was significantly higher among patients aged 65-74 years. Patients aged ≥75 years had a higher incidence of thyroiditis or endocrine-related toxicity, however this was not statistically significant. No significant differences in dermatitis, colitis, hepatitis or pneumonitis were reported between the different age groups. The grade of severity of the adverse events was not reported [19].

Wong et al conducted a retrospective analysis of 91 patients with advanced melanoma treated by anti-PD-1, including patients with an ECOG performance status of 2 and 3. Median age in the different groups was 54 – 73 years. They showed no statistically significant difference in irAEs between the groups with a low versus high ECOG performance status. They did show that 81% of patients in the ECOG 2-3 group received anti-PD-1 therapy in the last month of life, compared to 46% in the ECOG 0-1 group (RR 1.75, 95% CI 1.04-2.56, P = 0.019). Ninety percent of the patients in the ECOG 2-3 group were admitted to the hospital in the last month of life, compared to 52% in the ECOG 0-1 group (RR 1.73, 95% CI 1.10-2.16, P = 0.009). The ECOG 2-3 group were also more likely to die in an acute hospital setting (62% versus 23% respectively; RR 2.68, 95% CI 1.17-6.51; P = 0.016) [48].

Horvat et al performed a retrospective study in 298 patients with metastatic melanoma treated with ipilimumab, with a median age of 65 years and an ECOG performance status of 0-1. Discontinuation of treatment because of an irAE was reported in 19% of patients, most commonly due to diarrhea and hepatotoxicity. Thirty

five percent of patients required systemic corticosteroid treatment for an irAE and 10% of all patients required additional systemic immunosuppressive therapy, mostly infliximab [49].

Luciani et al performed a multicenter retrospective analysis on patients aged ≥75 years with advanced NSCLC treated with anti-PD-1 therapy and showed in 72 patients with a median age of 77 years that irAEs grade 3-4 occurred in 14% of patients, but the majority of patients had an ECOG status of 0-1 (63%) [50].

Corral de la Fuente et al retrospectively analyzed 98 patients with advanced NSCLC treated with anti-PD-1 or anti-PD-L1 therapy. The mean age was 62 years and 27 patients (27.5%) were aged ≥70 years. They reported 30.6% irAEs, with no statistically significant difference between the older and younger patients. The grade of severity of the adverse events was not reported [51].

Verzoni et al conducted a retrospective analysis of 389 patients with previously treated advanced or metastatic renal cell carcinoma treated with nivolumab, including 70 patients (18%) with age ≥75 years with an ECOG performance status of 0-1 in 93.6% of patients. IrAEs occurred in 20% of patients, but no age-stratified analyses were performed [52].

Muchnik et al performed a retrospective study in older patients receiving PD-1 inhibitors for advanced-stage NSCLC. They included 75 patients, with a median age of 74 years and 17 (22.7%) of the patients being ≥80 years old. The Charlson Comorbidity Index was ≥3 in 40 (53.3%) patients and 37 (49.3%) patients had an ECOG performance status of ≥2. Overall, 37% of the patients experienced irAEs of any grade and 8% were grade ≥3 irAEs. Of these patients, 64% required treatment with glucocorticoids. The most common irAEs were pneumonitis, thyroiditis (both 12%), colitis and dermatitis (both 9%). Moreover, they showed that 64 patients discontinued treatment, of which 15% were caused by to irAEs. During treatment 54 (72%) patients were hospitalized, of which 7 patients due to irAEs. The authors found no significant difference in irAEs rates between different age, Charlson Comorbidity Index of ECOG performance status groups [53].

Finally, Silva et al performed a retrospective study in 106 elderly patients treated with immune checkpoint inhibitors for solid malignancies, with a mean age of 74.4 years. They found a similar irAE profile as found in literature. Remarkably, they reported that frailty was the only statistically significant variable associated with the development of adverse events [54].

Treatment of irAEs in older patients

Since irAEs are caused by an excessive immune response, most of them are treated by withholding the immune checkpoint inhibitor or inducing temporary immunosuppression with oral glucocorticoids or additional immunosuppressants [29]. Most irAEs are mild and can be treated symptomatically [30]. To our knowledge, there are no studies on how to treat irAEs specifically in older patients.

According to the ESMO guidelines grade 1 and some grade 2 toxicities are mostly treated by withholding immune checkpoint inhibitor while monitoring symptoms and starting symptomatic or local treatment. Grade 3 and 4 toxicities, and some grade 2, are mostly primarily treated with corticosteroid therapy. In case of no improvement, other immunosuppressive drugs such as mycophenolate mofetil (MMF), infliximab (anti-TNFα), tacrolimus, cyclophosphamide or anti-thymocyte globulin are recommended as additional therapy [32].

The use of some symptomatic treatments as antihistamine for pruritus or corticosteroids can be considered, but these may induce more extra adverse events in elderly, such as mental status disturbance, delirium, sodium and fluid retention, hypertension and diabetes worsening [30]. Patients with comorbidities such as diabetes mellitus, congestive heart failure or underlying mood disorders may be at higher risk for adverse events.

Discussion

In summary, the current available data show no difference in OS and PFS in older patients compared to younger patients and no major increase in irAE incidence in older patients. These data are mainly based on clinical trials, in which the elderly, especially aged ≥75 years, are underrepresented. There are no studies on how to treat irAEs specifically in older patients.

Most of the previously published immunotherapy trials did not perform any subanalyses in the different age groups. Moreover, due to strict inclusion criteria, only patients with a relatively good performance status and few comorbidities were enrolled in these trials. Hence, older patients with reduced functional reserve, age-related comorbidity including autoimmune diseases and impaired organ function were excluded. The patients included are therefore not representative for the general older population of patients with cancer, which limits the evidence for treatment with immunotherapy in this population.

Interestingly, some of the subgroup analysis of trial data showed a higher incidence of irAEs and a trend of early treatment discontinuation and higher incidence of irAEs requiring treatment with immune modulating medication in older patients[21,38]. Moreover, Herin et al showed increased incidence of grade 1-2 irAEs and early occurrence of irAEs

in older patients. This can be of consequence for older patients. For example, immune-related diarrhea may lead to higher incidence of dehydration, decline in renal function and hospitalization. Hospitalization may have a different impact on older patients compared to younger patients. In addition, occurrence of multiple grade 1-2 irAEs may be a reason to discontinue therapy which thereby hampers the efficacy of treatment.

We highlighted twelve observational studies in more real life older patients than included in clinical trials, but still mainly patients with a good performance status. Previous clinical trials comparing chemotherapy with immune checkpoint inhibitors showed a higher incidence of chemotherapy related grade 3-4 adverse events [42,55], implicating that immune checkpoint inhibitors might be well tolerated by elderly patients. The observational studies we cited overall did not show an increased incidence of irAEs. However, some of the included studies showed a trend of higher incidence of irAEs in older patients. As these studies were performed retrospectively and included a small number of patient, differences in number of irAEs might not have been detected due to bias or lack of power. Furthermore, Muchnik et al showed that a large proportion of the patients required treatment with glucocorticoids, discontinued treatment and were hospitalized. Moreover, the study of Wong et al did show an increase in patients discontinuing therapy and more hospital admissions with increasing performance status. This suggests that the incidence of adverse events could be higher in patients with impaired physical functioning. Besides, they also showed that more patients with a decreased performance status received immune checkpoint blockade therapy in the last month of life and were more likely to die in an acute hospital setting, which emphasizes the importance of a more precise selection of patients receiving therapy.

It must be noted that the impact of irAEs in elderly may be greater than in younger patients, due to age-related comorbidities and reduced functional reserve. For example, thyroiditis can result in either hypothyroidism or hyperthyroidism which might worsen the symptoms of an undiagnosed neurocognitive disorder [33]. Interaction of adverse events and comorbidity may be problematic. For example, anticoagulants or anti-aggregants may increase the risk of gastrointestinal hemorrhage in colitis or autoimmune thrombocytopenia [20,30].

There are minimal data on the safety in patients with renal of hepatic insufficiency. In contrast to chemotherapy, efficacy and safety of immune checkpoint inhibitors are thought to be similar in patients with renal or hepatic insufficiency, because they are not cleared by the kidneys or liver [29]. Therefore, at the moment no dose adjustment is recommended [30]. In addition, adverse events are mostly not dose dependent, besides the development of irAEs in patients receiving CTLA-4 inhibitors [56].

In treatment of irAEs, the additional adverse events of corticosteroids, infliximab and the effect of hospitalization on elderly patients must be taken into consideration. Although long-term glucocorticoid therapy is not frequently needed, it may lead to

additional complications, such as osteoporosis, glaucoma, cushingoid phenotype, opportunistic infections and proximal muscle weakness [29,57]. Del Castillo et al. performed a retrospective study in 790 patients with advanced melanoma treated with immune checkpoint blockade, assessing the risk of serious infections. They showed that the major risk factor for development of a serious infection was the use of immunosuppressive agents, including corticosteroids and infliximab (13.5% risk of serious infection vs. 2%) [58]. Therefore, duration of steroid usage should be limited, especially in older patients.

Furthermore, in case of high dose corticosteroid treatment, elderly patients are at increased risk of skin atrophy. Extra caution should also be taken when using high dose corticosteroid treatment in elderly with underlying gastritis or undiagnosed peptic ulcer disease [33].

Frail patients are at increased risk of chemotherapy intolerance, postoperative complications and mortality [59]. Selecting frail patients using a geriatric assessment can help personalize treatment decisions. Remarkably, only one of the highlighted studies showed that frailty was associated with the development of adverse events. None of the other studies provided data about comprehensive geriatric assessments and measures of frailty. The Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status generally overestimate physical functioning of older patients and as a result, these measurements are not valid to predict treatment toxicity [3]. The International Society of Geriatric Oncology (SIOG) therefore states that geriatric assessment can be valuable in clinical practice for detection of impairments that were not identified in routine history or physical examination. Furthermore, it has been shown to predict severe treatment-related toxicity [3], and has been associated with survival outcomes [60-62]. Previous studies have shown that when a geriatric assessment is performed, it affects treatment choice and intensity [60]. The SIOG recommendation is to evaluate the following domains: functional status, comorbidity, cognition, mental health status, fatigue, social status and support, nutrition, and presence of geriatric syndromes. However, the expert panel could not recommend one tool over another [2]. The G8 screening tool can help identify frail older cancer patients requiring geriatric assessment and tailoring of cancer treatment [63,64]. On the other hand, undertreatment of fit older patients might also be prevented this way. The ELDERS study is now comparing elderly patients to non-elderly patients receiving immunotherapy for lung cancer or melanoma, also gathering information about the comorbidity score and a geriatric screening assessment. Gomes et al presented preliminary results of 32 patients with a minimum of 3 months follow-up. They found no statistically significant correlation between higher comorbidity score or abnormal geriatric assessment and the incidence of irAEs and found no significant negative impact on the global health-related quality of life [65]. Unfortunately, these finding are in a small group of patients with a limited follow-

up and the final data are not presented yet. To our knowledge, to date this is the only study evaluating the role of geriatric assessment in older patients receiving immune checkpoint inhibitors, highlighting the importance of future studies in this field.

Furthermore, traditional therapeutic studies rarely include functionality or quality of life as an endpoint, despite the fact that many older adults prioritize it as an important factor in the decision-making process [66]. The effect of immunotherapy on functional status can be critical for older adults, especially if it affects their ability to live independently. Therefore, more real-life based data on adverse events and the effects on quality of life or effects on functional status can help in shared treatment decision making [67].

In conclusion, the clinical trials showed no age-dependent efficacy of immune checkpoint inhibitors. Overall, the incidence of treatment toxicity in older patients is higher in chemotherapy than immune therapy and clinical trials showed no major increase in irAE incidence with increasing age. However studies, in particular in real life data in older and more vulnerable patients showed a higher incidence of irAEs, a trend of early treatment discontinuation and more patients requiring treatment with immune modulating medication. The available observational data are limited. Since the enrolled elderly patients are not representative, further prospective studies should include more older patients in a representative real-life population. Furthermore, future studies should include a geriatric assessment to identify which patients will benefit from immune checkpoint inhibitors and which patients are at higher risk of irAEs, hospitalization and functional decline, and therefore might not benefit from immune checkpoint inhibitors.

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