Efficacy of immune checkpoint inhibitors and age in cancer patients

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Aim: To evaluate the impact of age on the efficacy of immune checkpoint inhibitors (ICI) in cancer patients.

Materials & methods: The primary outcomes included overall survival (OS) and progression-free survival (PFS). Subgroup, meta-regression analysis and within-trial interaction HR were conducted. **Results:** A total of 34 studies containing 20,511 cancer patients were included. ICI could improve the OS and PFS in patient aged <65 and ≥65 years. Patients aged <75 years treated with ICI also had favorable OS and PFS compared with the control groups. **Conclusion:** ICI has comparable efficacy in cancer patients aged <65 and ≥65 years. Cancer patients aged ≥75 years need more attention in the future clinical trials.

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Keywords: age • immune checkpoint inhibitors • immunotherapy • overall survival • progression-free survival

Programmed cell death protein-1 (PD-1), programmed cell death-ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are the predominant and most well-studied immune checkpoints associated with immune escape by tumor cells [1,2]. The immune checkpoint inhibitors (ICI) against PD-1, PD-L1 and CTLA-4 have been shown to exhibit improved efficacy, lower toxicity and higher safety profiles compared with traditional cytotoxic agents for cancer treatment [3]. Thus, immunotherapies based on ICI have become an attractive treatment option and changed the therapeutic landscape for several advanced malignancies.

Cancer is predominantly a disease affecting older adults, with a significantly higher incidence in patients aged ≥65 years [4]. Although older adults comprise the majority of patients diagnosed with cancer in the ‘real world’, older adults continue to be under-represented in clinical studies evaluating ICI immunotherapies since older patients tend to exhibit a higher number of comorbidities and less favorable performance status; therefore, these patients are frequently excluded from clinical studies [5]. In addition, the age-related decline in immune function leads to immune dysregulation in both cellular and humoral responses, which may be an important reason for a higher incidence of cancer with age [6–8]. Moreover, the phenomenon of gradual aging and deterioration of immune function with age is termed immunosenescence [6,7]. Age-related alterations in the immune system primarily occur with regards T cell-mediated immune function, which is a crucial aspect of immunosenescence [6]. Importantly, T cells are the major antitumor effector cells for ICI immunotherapies and some researchers consider ICI immunotherapies to have reduced efficacy in older cancer patients due to the negative effect induced by immunosenescence. Therefore, it is inappropriate to manage older cancer patients simply using the clinical evidence extrapolated from studies of younger cancer patients.

A previous meta-analysis by Wu *et al.* only found that ICI immunotherapies significantly improved survival in both patient groups of <65 and ≥65 years, but did not evaluate the patient population aged ≥75 years [9]. Li *et al.* reported that ICI immunotherapies had comparable benefit in both of the younger (<65 years) and older cancer patients (≥65 years) but did not prolong survival in patients aged ≥75 years [10]. Interestingly, a melanoma-specific meta-analysis showed that melanoma patients aged ≥75 years would benefit more from ICI immunotherapies compared with younger patients, which was opposite with the possible negative impact of immunosenescence on

ICI efficacy [11]. Nevertheless, the number of included studies in these meta-analyses was limited. Thus, the result regarding the efficacy of ICI immunotherapies in older cancer patients still remains controversial.

The purpose of this study was to explore the efficacy of ICI immunotherapies in both younger and older cancer patients (<65 vs ≥65 years and <75 vs ≥75 years).

Materials & methods

Literature search

The PubMed and Embase databases were searched for Phase II and III randomized controlled trials (RCT) that evaluated the efficacy of ICI immunotherapies in younger and older cancer patients (up to February 2019). We also performed a literature search through the American Society of Clinical Oncology and European Society of Medical Oncology conference databases. The search terms consisted of 'nivolumab', 'pembrolizumab', 'avelumab', 'atezolizumab', 'lambrolizumab', 'pidilizumab', 'durvalumab', 'ipilimumab', 'tremelimumab', 'PD-1', 'PD-L1', 'programmed death protein 1', 'programmed death ligand 1', 'CTLA-4', 'cytotoxic T-lymphocyte associated protein 4', 'cytotoxic T-lymphocyte associated antigen 4', 'immune checkpoint inhibitor', 'randomised trial', 'randomized trial', 'randomised study' and 'randomized study'. Furthermore, we manually searched the reference lists of the relevant studies and reviews for other potential studies.

Inclusion criteria

The eligibility criteria for the Phase II or III RCTs to be included in this meta-analysis were as follows: participants: patients who were diagnosed with solid cancer and aged 18 years or older; intervention: ICIs (PD-1, PD-L1 or CTLA-4 inhibitors) were administered alone or in combination with another ICIs/chemotherapeutic agents, irrespective of the duration and dosage; comparison: the control group was treated with either a placebo or other non-ICI agents; outcome: the two primary outcomes consisted of the overall survival (OS) and progression-free survival (PFS) according to different age groups (i.e., <65, ≥65, <75 and ≥75 years) and the hazard ratio (HR) and corresponding 95% CI could be extracted. Moreover, we included the most recent study if several duplicated studies were identified based on the use of the same patient population.

Exclusion criteria

The exclusion criteria consisted of: animal or *in vitro* studies; cohort, case-control studies or Phase I trials; the outcome measures could not be extracted from the published data; the therapeutic regimen of the control group contained ICI or other nonspecific immunological agents; and duplicate studies based on the same population.

Data extraction & quality assessment

Two authors (X Huang and P Gao) reviewed the eligible studies and independently extracted the data. For each study, the following data were extracted: first author, publication year, trial name, trial phase, study design, cancer type, therapy line, ICI drug, treatment regimens, sample size, age, follow-up time and outcome measures. The quality of the included studies was evaluated using the Jadad scale, which was based on three aspects of the study: randomization; blinding; and withdrawals/dropouts [12]. Any disagreements regarding the data extraction and quality assessment were resolved by discussion.

Statistical analysis

The primary outcomes consisted of the clinical efficacy (OS and PFS) of ICI immunotherapies between different age groups (i.e., <65, ≥65, <75 and ≥75 years), measured by HR with 95% CI. We used a random-effect model to pool the HRs because the random-effect model could obtain more conservative results than the fixed-effect model, considering the heterogeneity among multicenter clinical studies [13]. The overall analysis was performed by including all eligible studies and a subgroup analysis was performed by stratifying the data by cancer type (non-small-cell lung cancer, melanoma, renal-cell carcinoma, small-cell lung cancer, gastric cancer/gastro-esophageal junction cancer and head-and-neck squamous cell carcinoma), therapy line (line 1 and line ≥2) and ICI drug (PD-1/PD-L1, CTLA-4, PD-1 and ICI plus chemotherapy). The heterogeneity among the studies was evaluated using a Cochran Q test and I^2 statistics [14]. Publication bias was evaluated using Begg's and Egger's tests [15,16].

We used a meta-regression analysis to assess the impact of age on the efficacy of ICI immunotherapies in cancer patients. Furthermore, we used the within-trial interaction HR (ratio of the HR in patients aged <65 and ≥65 years;

Figure 1. Literature search and study selection.

and <75 and ≥ 75 years) to evaluate the differences in the efficacy of ICI immunotherapies between different age groups (<65 vs ≥ 65 years and <75 vs ≥ 75 years) [17].

All statistical analyses were performed using Stata software version 12.0 (Stata Corporation, TX, USA). A two-sided p-value of <0.05 was considered statistically significant.

Results

Study selection & associated characteristics

A total of 4853 studies were identified from our literature search, of which 409 studies were excluded due to duplications. A total of 3383 studies were excluded after reviewing the titles and abstracts and 1061 full-text studies were further assessed for eligibility. There were 1027 studies that were excluded based on the inclusion and exclusion criteria. Finally, 34 eligible studies were included in the quantitative analysis [18–51]. **Figure 1** shows a detailed flowchart of the study selection.

The 34 included studies were published between 2010 and 2018, of which 21 (62%) studies were published in 2017 and 2018. A total of 20,511 patients (mean: 603; median with range: 565 [272–1033]) were included in this meta-analysis. There were 32 Phase III RCTs [18–32,34–40,42–51] and one of each Phase IIb and II/III RCTs [33,41]. Of the eligible studies, 13 studies involved patients with non-small-cell lung cancer [18,21,25,26,29,31,32,35,36,39,41,46,47]; seven studies of patients with melanoma [23,27,43,44,49–51]; three studies of patients with gastric or gastro-esophageal junction cancer [19,30,34]; two studies each for patients with renal-cell cancer [22,45], small-cell lung cancer [24,40]; prostate cancer [38,48] and head-and-neck squamous cell carcinoma [28,42]; and one study each for breast cancer [20], malignant mesothelioma [33] and urothelial carcinoma [37] patients. Of the 20,511 patients, 7740 (38%) patients had non-small-cell lung cancer and 4215 (21%) had melanoma. In terms of the ICI drug, 24 studies used anti-PD-1/PD-L1 inhibitors [18–21,23,24,26–32,34,36,37,39,41–47], eight studies used anti-CTLA-4 inhibitors [33,35,38,40,48–51] and two studies used anti-PD-1/PD-L1 inhibitors plus anti-CTLA-4 inhibitors [22,25]. There were 17 studies each

evaluating the efficacy of ICI as a first-line therapy [18,20–22,24–27,31,35,36,38–40,43,49,50] and second or more line therapies [19,23,28–30,32–34,37,41,42,44–48,51], respectively. A total of 11,162 patients were aged <65 years and 7865 patients were aged ≥65 years. There were 13 studies that reported an age group of ≥75 years with a total of 630 patients [18,22,25,28–30,35,40,42,43,45–47]. The baseline characteristics of the included studies are summarized in Table 1.

Overall survival & cut-off age of 65 years

Our results indicated that ICI immunotherapies significantly improved the OS in patient groups of <65 and ≥65 years compared with the control groups (<65 years: HR = 0.76; 95% CI = 0.70–0.84; $p < 0.001$; ≥65 years: HR = 0.79; 95% CI = 0.73–0.86; $p < 0.001$; Figure 2). Subgroup analysis of the cancer type revealed a OS improvement of ICI immunotherapies in patients with non-small-cell lung cancer (<65 years: HR = 0.71; 95% CI = 0.59–0.85; $p < 0.001$; ≥65 years: HR = 0.81; 95% CI = 0.70–0.94; $p = 0.005$), melanoma (<65 years: HR = 0.76; 95% CI = 0.64–0.92; $p = 0.004$; ≥65 years: HR = 0.66; 95% CI = 0.52–0.84; $p = 0.001$) and renal-cell carcinoma (<65 years: HR = 0.65; 95% CI = 0.44–0.94; $p = 0.024$; ≥65 years: HR = 0.80; 95% CI = 0.64–1.01; $p = 0.055$), but not in patients with small-cell lung cancer, gastric cancer/gastro-esophageal junction cancer and head-and-neck squamous cell carcinoma (Table 2). Subgroup analysis based on ICI drug also indicated that anti-PD-1/PD-L1 inhibitors (<65 years: HR = 0.76; 95% CI = 0.68–0.86; $p < 0.001$; ≥65 years: HR = 0.72; 95% CI = 0.65–0.81; $p < 0.001$), anti-PD-1 inhibitors (<65 years: HR = 0.73; 95% CI = 0.63–0.84; $p < 0.001$; ≥65 years: HR = 0.71; 95% CI = 0.63–0.81; $p < 0.001$) and ICI plus chemotherapy (<65 years: HR = 0.72; 95% CI = 0.58–0.88; $p = 0.001$; ≥65 years: HR = 0.79; 95% CI = 0.66–0.94; $p = 0.008$) could improve OS in patient groups of <65 and ≥65 years. Stratifying by therapy line of 1 and ≥2, our results also indicated an improved OS in both patients aged <65 and ≥65 years (Table 2).

Furthermore, our results found no significant differences in the OS improvement of ICI immunotherapies between patients aged <65 and ≥65 years in comparison with the controls for each age group (p for interaction = 0.656). The pooled within-trial interaction HRs confirmed that patients aged <65 and ≥65 years were associated with a comparable benefit from ICI immunotherapies (HR = 1.01; 95% CI = 0.91–1.12; $p = 0.796$; Supplementary Figure 1). Moreover, the pooled analysis of within-trial interaction HRs based on cancer type (Supplementary Figure 1), ICI drug and therapy line also obtained similar results.

Overall survival & cut-off age of 75 years

Our results indicated that ICI immunotherapies significantly improved the OS in patients aged <75 years (HR = 0.78; 95% CI = 0.68–0.89; $p < 0.001$; Figure 3), but patients aged ≥75 years experienced less OS benefit from ICI immunotherapies (HR = 0.88; 95% CI = 0.67–1.16; $p = 0.377$; Figure 3). Moreover, after stratifying by cancer type (non-small-cell lung cancer and renal-cell carcinoma), therapy line (line 1 and line ≥2) and ICI drug (anti-PD-1/PD-L1 inhibitors and anti-PD-1 inhibitors), the subgroup analyses yielded similar results (Table 2), indicating differences in the OS improvement of ICI immunotherapies between patients aged <75 and ≥75 years compared with the controls for each age group. However, we observed that the number of patients in groups of ≥75 years was limited and several in-depth subgroup analyses could not be performed owing to limited number of eligible studies.

Progression-free survival & cut-off age of 65 years

Our results indicated that patients aged <65 years treated with ICI immunotherapies had a favorable PFS compared with the control groups (HR = 0.69; 95% CI = 0.58–0.82; $p < 0.001$; Figure 4). Similarly, for patients aged ≥65 years, ICI immunotherapies could significantly improve the PFS compared with the control groups (HR = 0.77; 95% CI = 0.67–0.88; $p < 0.001$; Figure 4). We observed similar results in the subgroup analyses stratified by non-small-cell lung cancer, melanoma, anti-PD-1/PD-L1 inhibitors, ICI plus chemotherapy, anti-PD-1 inhibitors and first line therapy; however, the ICI immunotherapies did not improve the PFS when ICI immunotherapies were treated as a second line therapy (Table 2).

Moreover, there was no differences in the PFS between patients aged <65 and ≥65 years when the ICI immunotherapies were compared with the control group for each age group (p for interaction = 0.369), confirmed by the pooled within-trial interaction HRs (HR = 1.12; 95% CI = 0.98–1.28; $p = 0.106$; Supplementary Figure 2). Similar results were obtained when we performed subgroup analysis based on cancer type (Supplementary Figure 2), ICI drug and therapy line.

Table 1. The baseline characteristics of included studies.

Study and year	Study name	Phase	Cancer type	Line	Treatment group vs control group	Sample	Age (ICI vs ICC) median (range)	Age group	Jada score
Cohen 2019	KEYNOTE-040	III	Head-and-neck carcinoma	≥2	Pembrolizumab vs methotrexate or docetaxel or cetuximab	495	60 (55–66) vs 60 (54–66)	<65 y: 332; 65–74 y: 132; ≥75 y: 31	3
Socinski 2018	IMpower150	III	Nonsquamous NSCLC	1	Atezolizumab plus bevacizumab plus carboplatin plus paclitaxel vs bevacizumab plus carboplatin plus paclitaxel	692	63 (31–89) vs 63 (41–87)	<65 y: 375; 65–74 y: 248; 75–84 y: 64	3
Antonia 2018	PACIFIC	III	NSCLC	1	Durvalumab vs placebo	713	64 (31–84) vs 64 (23–90)	<65 y: 391; ≥65 y: 322	5
Shitara 2018	KEYNOTE-061	III	GC/GEJC	2	Pembrolizumab vs paclitaxel	395	64 (IQR57–70.5) vs 61 (IQR54–68)	≤65 y: 232; ≥65 y: 163	3
Schmid 2018	IMpassion130	3	Breast cancer	1	Atezolizumab plus nab-paclitaxel vs placebo plus nab-paclitaxel	902	55 (20–82) vs 56 (26–86)	18–40 y: 114; 41–64 y: 569; ≥65 y: 219	5
Paz-Ares 2018	KEYNOTE-407	III	Squamous NSCLC	1	Pembrolizumab plus carboplatin plus paclitaxel/nab-paclitaxel vs placebo plus carboplatin plus paclitaxel/nab-paclitaxel	559	65 (29–87) vs 65 (36–88)	<65 y: 254; ≥65 y: 305	5
Motzer 2018	CheckMate 214	III	Renal-cell carcinoma	1	Nivolumab plus ipilimumab vs sunitinib	847	62 (26–85) vs 61 (21–85)	<65 y: 524; 65–74 y: 258; ≥75 y: 65	3
Larkin 2018	CheckMate 037	III	Melanoma	≥2	Nivolumab vs dacarbazine or carboplatin plus paclitaxel	405	59 (23–88) vs 62 (29–85)	<65 y: 257; ≥65 y: 148	3
Horn 2018	IMpower133	III	Small-cell lung cancer	1	Atezolizumab plus carboplatin plus etoposide vs placebo plus carboplatin plus etoposide	403	64 (28–90) vs 64 (26–87)	<65 y: 217; ≥65 y: 186	5
Hellmann 2018	CheckMate 227	III	NSCLC	1	Nivolumab plus ipilimumab vs platinum doublet chemotherapy	299	64 (41–87) vs 64 (29–80)	<65 y: 156; ≥65 y: 143; ≥75 y: 27	3
Gandhi 2018	KEYNOTE-189	III	Nonsquamous NSCLC	1	Pembrolizumab plus pemetrexed plus platinum-based drug vs placebo plus pemetrexed plus platinum-based drug	616	65 (34–84) vs 63.5 (34–84)	<65 y: 312; ≥65 y: 304	5
Eggermont 2018	KEYNOTE-054	III	Melanoma	1	Pembrolizumab vs placebo	1019	54 (19–88) vs 54 (19–83)	<65 y: 768; ≥65 y: 251	5
Barlesi 2018	JAVELIN Lung 200	III	NSCLC	≥2	Avelumab vs docetaxel	529	64 (59–70) vs 60 (54–66)	<65 y: 279; ≥65 y: 250; <75 y: 479; ≥75 y: 50	3
Bang 2018	JAVELIN Gastric 300	III	GC/GEJC	3	Avelumab vs paclitaxel or irinotecan	371	59 (29–86) vs 61 (18–82)	<65 y: 230; ≥65 y: 141; <75 y: 334; ≥75 y: 37	3
Rittmeyer 2017	OAK	III	NSCLC	≥2	Atezolizumab vs docetaxel	850	63 (33–82) vs 64 (34–85)	<65 y: 453; ≥65 y: 397	3
Maio 2017	DETERMINE	IIb	Malignant mesothelioma	≥2	Tremelimumab vs placebo	571	66 (60–72) vs 67 (61–73)	<65 y: 237; ≥65 y: 334	5
Kang 2017	ATTRACTION-2	III	GC/GEJC	≥3	Nivolumab vs placebo	493	62 (54–69) vs 61 (53–68)	<65 y: 284; ≥65 y: 209	5

ICC: investigator's choice chemotherapy; ICI: Immune checkpoint inhibitor; GC/GEJC: Gastric cancer or gastro-esophageal junction cancer; IQR: Interquartile range; NR: Not reported; NSCLC: Non-small-cell lung cancer.

Table 1. The baseline characteristics of included studies (cont.).

Study and year	Study name	Phase	Cancer type	Line	Treatment group vs control group	Sample	Age (ICI vs ICC) median (range)	Age group	Jada score
Govindan 2017	Study 104	III	Squamous NSCLC	1	Ipilimumab plus paclitaxel plus carboplatin vs placebo plus paclitaxel plus carboplatin	749	64 (28–84) vs 64 (28–85)	<65 y: 380; 65–74 y: 298; ≥75 y: 71	5
Carbone 2017	CheckMate 026	III	NSCLC	1	Nivolumab vs platinum-based chemotherapy	541	63 (32–89) vs 65 (29–87)	<65 y: 281; ≥65 y: 260	3
Bellmunt 2017	KEYNOTE-045	III	Urothelial cancer	2	Pembrolizumab vs paclitaxel or docetaxel or vinflunine	542	67 (29–88) vs 65 (26–84)	<65 y: 230; ≥65 y: 312	3
Beer 2017	CA184-095	III	Prostate cancer	1	Ipilimumab vs placebo	602	70 (44–91) vs 69 (42–92)	<70 y: 304; ≥70 y: 298	5
Reck 2016	KEYNOTE-024	III	NSCLC	1	Pembrolizumab vs platinum-based chemotherapy	305	64.5 (33–90) vs 66 (38–85)	<65 y: 141; ≥65 y: 164	3
Reck 2016	CA184-156	III	Small-cell lung cancer	1	Ipilimumab plus etoposide plus platinum vs placebo plus etoposide plus platinum	954	62 (39–85) vs 63 (36–81)	<65 y: 435; 65–74 y: 218; ≥75 y: 54	5
Herbst 2016	KEYNOTE-010	II/III	NSCLC	≥2	Pembrolizumab vs docetaxel	1033	63 (56–69) vs 62 (56–69)	<65 y: 604; ≥65 y: 429	3
Ferris 2016	CheckMate 141	III	Head-and-neck carcinoma	≥2	Nivolumab vs methotrexate or docetaxel or cetuximab	361	59 (29–83) vs 61 (28–78)	<65 y: 248; 65–74 y: 95; ≥75 y: 18	3
Robert 2015	CheckMate 066	III	Melanoma	1	Nivolumab plus dacarbazine-matched placebo vs dacarbazine plus nivolumab-matched placebo	418	64 (18–86) vs 66 (26–87)	<65 y: 200; 65–74 y: 151; ≥75 y: 67	5
Ribas 2015	KEYNOTE-002	II	Melanoma	≥2	Pembrolizumab vs paclitaxel plus carboplatin or paclitaxel or carboplatin or dacarbazine or oral temozolomide	540	(15–89) vs 63 (27–87)	2 mg/kg: <65 y: 200; ≥65 y: 159; 10 mg/kg: <65 y: 204; ≥65 y: 156	3
Motzer 2015	CheckMate 025	III	Renal-cell carcinoma	≥2	Nivolumab vs everolimus	821	62 (23–88) vs 62 (18–86)	<65 y: 497; 65–74 y: 250; ≥75 y: 74	3
Brahmer 2015	CheckMate 017	III	Squamous NSCLC	2	Nivolumab vs docetaxel	272	62 (39–85) vs 64 (42–84)	<65 y: 152; 65–74 y: 91; ≥75 y: 29	3
Borghaei 2015	CheckMate 057	III	Nonsquamous NSCLC	2	Nivolumab vs docetaxel	582	61 (37–84) vs 64 (21–85)	<65 y: 339; 65–74 y: 200; ≥75 y: 43	3
Kwon 2014	CA184-043	III	Prostate cancer	≥2	Ipilimumab vs placebo	799	69 (47–86) vs 67.5 (45–86)	<70 y: 449; ≥70 y: 350	5
Ribas 2013	NR	III	Melanoma	1	Tremelimumab vs temozolomide or dacarbazine	655	57 (22–90) vs 56 (22–90)	<65 y: 455; ≥65 y: 200	3
Robert 2011	NR	III	Melanoma	1	Ipilimumab plus dacarbazine vs dacarbazine plus placebo	502	Mean: 57.5 vs 56.4	<65 y: 342; ≥65 y: 160	5
Hodi 2010	NR	III	Melanoma	≥2	Ipilimumab plus gp100 vs ipilimumab plus gp100 placebo vs gp100 plus ipilimumab placebo	676	Mean: 55.6 vs 56.8 vs 57.4	<65 y: 480; ≥65 y: 196	5

ICC: Investigator's choice chemotherapy; ICI: Immune checkpoint inhibitor; GC/GEIC: Gastric cancer or gastro-esophageal junction cancer; IQR: Interquartile range; NR: Not reported; NSCLC: Non-small-cell lung cancer.

Figure 2. Hazard ratio of overall survival for patients aged <65 and ≥ 65 years treated with immune checkpoint inhibitors when compared with those in control group. (A) Overall survival (OS) for patients aged < 65 years; (B) OS for patients aged ≥ 65 years.

Table 2. The results of subgroup analyses for efficacy of immune checkpoint inhibitors in different age groups.

	HR	95% CI	p for HR
Overall survival			
<65 years	0.76	0.70–0.84	<0.001
≥65 years	0.79	0.73–0.86	<0.001
<75 years	0.78	0.68–0.89	<0.001
≥75 years	0.88	0.67–1.16	0.377
Cancer type			
NSCLC			
<65 years	0.71	0.59–0.85	<0.001
≥65 years	0.81	0.70–0.94	0.005
<75 years	0.77	0.65–0.91	0.003
≥75 years	1.03	0.73–1.44	0.88
Melanoma			
<65 years	0.76	0.64–0.92	0.004
≥65 years	0.66	0.52–0.84	0.001
SCLC			
<65 years	0.85	0.59–1.23	0.400
≥65 years	0.77	0.55–1.09	0.136
GC/GEJC			
<65 years	0.89	0.66–1.19	0.425
≥65 years	0.76	0.52–1.11	0.157
RCC			
<65 years	0.65	0.44–0.94	0.024
≥65 years	0.80	0.64–1.01	0.055
<75 years	0.68	0.55–0.85	<0.001
≥75 years	1.11	0.69–1.77	0.670
HNSCC			
<65 years	0.79	0.54–1.15	0.218
≥65 years	0.76	0.51–1.13	0.049
Therapy line			
Line 1			
<65 years	0.72	0.60–0.87	0.001
≥65 years	0.82	0.71–0.94	0.005
<75 years	0.80	0.64–1.01	0.059
≥75 years	0.67	0.42–1.07	0.095
Line ≥2			
<65 years	0.79	0.71–0.87	<0.001
≥65 years	0.76	0.69–0.84	<0.001
<75 years	0.76	0.65–0.89	0.001
≥75 years	1.11	0.81–1.53	0.521
ICI drug			
PD-1/PD-L1			
<65 years	0.76	0.68–0.86	<0.001
≥65 years	0.72	0.65–0.81	<0.001
<75 years	0.72	0.62–0.84	<0.001
≥75 years	0.92	0.60–1.41	0.7

CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4; GC/GEJC: Gastric cancer/gastro-esophageal junction cancer; HNSCC: Head-and-neck squamous cell carcinoma; HR: Hazard ratio; I2: Degree of heterogeneity; ICC: Investigator's choice chemotherapy; ICI: Immune checkpoint inhibitor; NSCLC: Non-small-cell lung cancer; p: p for the HR; PD-1: Programmed cell death protein-1; PD-L1: Programmed cell death-ligand 1; RCC: Renal-cell carcinoma; SCLC: Small-cell lung cancer.

Table 2. The results of subgroup analyses for efficacy of immune checkpoint inhibitors in different age groups (cont.).

	HR	95% CI	p for HR
PD-1			
<65 years	0.73	0.63–0.84	<0.001
≥65 years	0.71	0.63–0.81	<0.001
<75 years	0.7	0.63–0.78	<0.001
≥75 years	0.91	0.49–1.68	0.761
CTLA-4			
<65 years	0.82	0.71–0.94	0.005
≥65 years	0.93	0.84–1.02	0.129
ICI + ICC			
<65 years	0.72	0.58–0.88	0.001
≥65 years	0.79	0.66–0.94	0.008
Progression-free survival			
Overall			
<65 years	0.69	0.58–0.82	<0.001
≥65 years	0.77	0.67–0.88	<0.001
<75 years	0.77	0.58–1.03	0.081
≥75 years	0.85	0.61–1.19	0.354
Cancer type			
NSCLC			
<65 years	0.64	0.51–0.80	<0.001
≥65 years	0.76	0.63–0.92	0.004
<75 years	0.70	0.57–0.85	<0.001
≥75 years	0.91	0.64–1.30	0.597
Melanoma			
<65 years	0.48	0.40–0.59	<0.001
≥65 years	0.63	0.49–0.80	<0.001
SCLC			
<65 years	0.81	0.69–0.96	0.012
≥65 years	0.86	0.71–1.04	0.119
Therapy line			
Line 1			
<65 years	0.63	0.52–0.76	<0.001
≥65 years	0.69	0.59–0.81	<0.001
<75 years	0.57	0.49–0.67	<0.001
≥75 years	0.69	0.42–1.13	0.142
Line ≥2			
<65 years	0.78	0.56–1.10	0.157
≥65 years	0.89	0.72–1.09	0.264
<75 years	0.92	0.65–1.28	0.61
≥75 years	0.98	0.63–1.51	0.921
ICI drug			
PD-1/PD-L1			
<65 years	0.70	0.58–0.84	<0.001
≥65 years	0.77	0.67–0.89	<0.001
<75 years	0.82	0.60–1.10	0.183
≥75 years	0.91	0.66–1.25	0.402

CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4; GC/GEJC: Gastric cancer/gastro-esophageal junction cancer; HNSCC: Head-and-neck squamous cell carcinoma; HR: Hazard ratio; I2: Degree of heterogeneity; ICC: Investigator's choice chemotherapy; ICI: Immune checkpoint inhibitor; NSCLC: Non-small-cell lung cancer; p: p for the HR; PD-1: Programmed cell death protein-1; PD-L1: Programmed cell death-ligand 1; RCC: Renal-cell carcinoma; SCLC: Small-cell lung cancer.

Table 2. The results of subgroup analyses for efficacy of immune checkpoint inhibitors in different age groups (cont.).

	HR	95% CI	p for HR
PD-1			
<65 years	0.6	0.48–0.75	<0.001
≥65 years	0.75	0.64–0.89	0.001
<75 years	0.75	0.58–0.97	0.029
≥75 years	1.24	0.73–2.10	0.431
ICI + ICC			
<65 years	0.64	0.52–0.81	<0.001
≥65 years	0.67	0.59–0.77	<0.001

CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4; GC/GEJC: Gastric cancer/gastro-esophageal junction cancer; HNSCC: Head-and-neck squamous cell carcinoma; HR: Hazard ratio; I2: Degree of heterogeneity; ICC: Investigator's choice chemotherapy; ICI: Immune checkpoint inhibitor; NSCLC: Non-small-cell lung cancer; p: p for the HR; PD-1: Programmed cell death protein-1; PD-L1: Programmed cell death-ligand 1; RCC: Renal-cell carcinoma; SCLC: Small-cell lung cancer.

Figure 3. Hazard ratio of overall survival and progression-free survival for patients aged <75 and ≥75 years treated with immune checkpoint inhibitors when compared with those in control group. (A) Overall survival (OS) for patients aged <75 years; (B) OS for patients aged ≥75 years; (C) progression-free survival (PFS) for patients aged <75 years; (D) PFS for patients aged ≥75 years.

Figure 4. Hazard ratio of progression-free survival for patients aged <65 and ≥65 years treated with immune checkpoint inhibitors when compared with those in control group. (A) Progression-free survival (PFS) for patients aged < 65 years; (B) PFS for patients aged ≥ 65 years.

Progression-free survival & cut-off age of 75 years

ICI immunotherapies tended toward a favorable PFS in patients aged <75 years, although statistical significance was not reached (HR = 0.77; 95% CI = 0.58–1.03; **Figure 3**); however, we observed less PFS benefit from ICI immunotherapies in patients aged ≥75 years (HR = 0.85; 95% CI = 0.61–1.19; $p = 0.354$; **Figure 3**). Similar results were observed in the subgroup analysis of non-small-cell lung cancer and first line therapy. ICI immunotherapies treated as a second line therapy did not significantly improve the PFS in patients aged both <75 and ≥75 years compared with the control groups.

Discussion

ICI immunotherapies have changed the landscape of cancer treatment for several advanced solid tumors [52]. New cancer cases and deaths due to cancer which primarily occur in older patients aged ≥65 years [4]. However, the evidence regarding the efficacy of ICI immunotherapies in older adults with cancer are limited because such older patients continue to be under-represented in cancer clinical trials considering the safety profile of ICI drugs. ICI immunotherapies can re-activate host immune function and subsequently enhance the antitumor response through inhibiting the PD-1 or CTLA-4 pathways; therefore, host immune function is critically important for the efficacy of ICI drugs [53,54]. Theoretically, the age-related immunosenescence of older patients may negatively impact the clinical efficacy of ICI immunotherapies; however, no studies have drawn definitive conclusions specific to older patients.

We included 34 Phase II or III studies containing a total of 20,511 patients to evaluate the clinical efficacy of ICI immunotherapies among different age groups (<65 vs ≥65 years and <75 vs ≥75 years). Our results indicated that ICI immunotherapies could prolong the OS and PFS in the patient groups of <65 and ≥65 years compared with the control groups, which was not significantly different when compared with the controls for each age group. In addition, our results indicated that ICI immunotherapies improved the OS and PFS in patients aged <75 years, while patients aged ≥75 years experienced less survival benefit from ICI immunotherapies. However, there may not be enough power to definitively make a conclusion about the effectiveness of ICI immunotherapies in patients aged ≥75 years due to limited patients in groups of ≥75 years (~3%, 630 patients). Further large-scale studies are needed to explore the impact of age on ICI efficacy in cancer patients.

As a revolutionary cancer treatment, ICI immunotherapies combined with or without chemotherapy have become an alternative first-line or subsequent treatment for several cancers [21,22,24,26,39,50]. The pooled results indicated an improved OS and PFS for ICI immunotherapies in patients aged <65 and ≥65 years; however, the magnitude of the benefit observed in the ≥65 years group was slightly lower than that observed in the <65 year age group, although not statistically significant, particularly for non-small-cell lung cancer. We also observed less survival benefit from ICI immunotherapies in patients aged ≥75 years, but the limited number of included patients may affect the reliability of our results. Currently, although it was unclear how the patients' age affected the antitumor response and clinical efficacy of ICI immunotherapies, several studies have reported that the number and functional diversity of T cells decreased with age due to thymic involution and the conversion of naive T cells into memory T cells [8,55]. Thus, it was hypothesized that immunosenescence, which mainly occurred with regards to T cell-mediated immunity, was an important contributing factor to the limited efficacy of ICI immunotherapies in older patients [6,7]. Surprisingly, however, we found that melanoma patients aged ≥65 years could benefit more from immunotherapy than younger patients. The potential explanation was that age-related differences in intratumoral immune microenvironment were different in different tumor. Indeed, a melanoma clinical and animal study by Kugel *et al.* found that the likelihood of response to anti-PD-1 immunotherapies increased with age in melanoma patients and the melanoma animal models showed that older mice had a lower Tregs level and higher CD8⁺: Treg ratio, confirmed by the human melanoma biopsies [56]. Thus, age-dependent ICI efficacy may be different between cancer diseases, which need further studies to explore the correlation. Among the eligible trials, there were ten that evaluated the efficacy of ICI immunotherapies among cancer patients aged ≥75 years [22,28–30,35,40,43,45–47], nine of which consistently showed that ICI immunotherapies did not improve the OS in cancer patients aged ≥75 years, regardless of the type of cancer and ICI drug. CheckMate 017 by Brahmer *et al.* assessed the efficacy of nivolumab versus chemotherapy in previously treated, advanced squamous-cell non-small-cell lung cancer; the results showed that nivolumab could prolong the OS in patients aged <65 (HR = 0.52; 95% CI = 0.35–0.75) and 65–74 years (HR = 0.56; 95% CI = 0.34–0.91), but not in patients aged ≥75 years (HR = 1.85; 95% CI = 0.74–4.51) [46]. CheckMate 057 was a Phase III study comparing nivolumab with docetaxel in patients previously treated with advanced nonsquamous non-small-cell lung cancer, which reported that OS was longer in the nivolumab group

compared with the chemotherapy group in the overall cohort. Moreover, the subgroup analysis based on age showed that the HR for the OS was 0.81 (95% CI = 0.62–1.04) in patients aged <65 years, 0.63 (95% CI = 0.45–0.89) in patients aged 65–74 years and 0.90 (95% CI = 0.43–1.87) in patients aged ≥75 years [47]. Moreover, in CheckMate 025, the nivolumab group was associated with a favorable OS compared with everolimus in advanced renal-cell carcinoma patients aged <65 (HR = 0.78; 95% CI = 0.60–1.01) and 65–74 years (HR = 0.64; 95% CI = 0.45–0.91); however, nivolumab did not prolong the OS in patients aged ≥75 years (HR = 1.23; 95% CI = 0.66–2.31) [45]. Further studies are required to explore the underlying mechanism of the impact of age on the efficacy of ICI immunotherapies in cancer patients.

Most trials have assessed the impact of age on the efficacy of ICI immunotherapies using a numerical cut-off age of 65 years. An accurate definition of a cut-off age for ‘older patients’ remains controversial in clinical practice when considering the difference between chronological and physiological age. While the included studies used chronological age, the aging of the organs and functional status of an individual was a physiological process; thus, the chronological age could not comprehensively reflect the physiological age status of the patients [57]. In general, ‘older patients’ represented a heterogeneous population and the incidence of comorbidities and poor performance status typically increased with age [57,58]. However, the older patients included in clinical trials were more likely to have a low number of comorbidities and good performance status when considering the drug safety profile, which did not represent the ‘real world’ situation of older patients. Therefore, the definition of ‘older patients’ in studies involving ICI immunotherapies should include an evaluation of the functional status, comorbidities, cognition, nutritional status, social support and psychological status of the patients [57]. Therefore, further studies are required to precisely define ‘older patients’ for ICI immunotherapies when considering the efficacy, safety and cost, as well as to evaluate the efficacy of ICI immunotherapies in “older patients”.

Preclinical evidence has shown that chemotherapy could activate and enhance the T cell-mediated antitumor immune response via killing tumor cells, promote tumor-associated antigen release and stimulate dendritic cell maturation [59,60]. Indeed, emerging clinical trials have reported that treatment with immunotherapies in combination with chemotherapy displayed a synergistic antitumor effect and combination therapies could improve the prognosis of cancer patients [18,20,21,26]. However, it was unclear whether age has an effect on the efficacy between the use of combination therapies and ICI immunotherapies alone. Therefore, we further evaluated the impact of age on the efficacy of ICI immunotherapy in combination with chemotherapy and the results showed a similar result with the overall analysis. Further studies are required to explore which chemotherapeutic drug is suitable for being combined with ICI immunotherapies, as well as the optimum dose of the chemotherapeutic drug.

There were several limitations associated with the present study. First, the age cut-off (65 and 75 years) in this study was predefined by the included trials and we could not explore the optimal age cut-off for ICI efficacy in cancer patients. Meanwhile, the pre-defined age cut-off lead to limited patients aged >75 years (a total of 630 patients [~3%]) and limited cancer diseases being included in our study. Thus, potential patients with more survival benefit from ICI such as melanoma were not included in the subgroup analysis of patient aged ≥75 years, which may underestimate the ICI efficacy and affect the reliability of our results. Further large-scale multicenter studies are required to evaluate the efficacy of ICI immunotherapies in older patients and to explore the optimal age cut-off for ICI immunotherapies according different cancer diseases. Second, although our study have performed subgroup analysis based on cancer type, therapy line and ICI drug, we could not control for or avoid any potentially confounding factors and relevant bias (e.g., smoking status, comorbidities). For example, lung cancer patients and head and neck cancer patients are more likely to be current or former smokers and have comorbidities. Several studies reported that smokers were associated with higher ICI efficacy for lung cancer, but not for head and neck cancer [61,62] and we could not assess comorbidities because patients with numerous comorbidities were frequently excluded from clinical studies. Furthermore, there may be an important difference in comorbidities between some patients groups. For example, chronic obstructive pulmonary disease and coronary artery disease are common smoker-related comorbidities in non-small-cell lung cancer patients and would be more problematic in patients aged ≥75 years than in patients aged ≥65 years, which may limit the potential ICI efficacy in that patient group. Oppositely, this situation does not apply to the older patients with melanoma because melanoma patients are much less likely to have smoker-related comorbidities. Thus, further studies are needed to determine whether and how these different confounding factors among various cancers affect ICI efficacy. Third, we could not assess the immune-related adverse events of ICI immunotherapies stratified by age and it was unclear as to whether the benefit of ICI immunotherapies in older patients (particularly in patients aged ≥65 years) outweighed the associated adverse events.

Conclusion

Our results indicate that ICI immunotherapies can prolong the OS and PFS in patient groups aged <65 and ≥65 years without significant differences when compared with the controls for each age group. However, our results cannot definitively conclude that ICI immunotherapies are ineffective for patients aged ≥75 years due to limited patients in this group. Further large-scale multicenter studies are required to explore the impact of age on ICI efficacy and the optimal age cut-off for ICI immunotherapies according different cancer diseases.

Future perspective

Immunotherapies based on ICI have become an attractive treatment option and changed the therapeutic landscape for several advanced malignancies. However, older adults are under-represented in clinical studies evaluating ICI immunotherapies and age-related immunosenescence may negatively impact the efficacy of ICI. We included two or three randomized controlled trials to evaluate the clinical efficacy of ICI immunotherapies among different age groups. Our results indicate that ICI immunotherapies can prolong the OS and PFS in patient groups aged <65 and ≥65 years without significant differences. Moreover, ICI can improve the survival in patients aged <75 years, but less survival benefit were observed in patients aged ≥75 years. However, there may not be enough power to definitively make a conclusion about the effectiveness of ICI immunotherapies in patients aged ≥75 years due to limited patients in groups. Further studies are required to explore the underlying mechanism of the impact of age on the efficacy of ICI immunotherapies and to precisely define 'older patients' for ICI immunotherapies when considering the efficacy, safety and cost, as well as to evaluate the efficacy of ICI immunotherapies in 'older patients'.

Summary points

Background

- Immunotherapies based on immune checkpoint inhibitors (ICI) have become an attractive treatment option and changed the therapeutic landscape for several advanced malignancies.
- Older adults comprise the majority of patients diagnosed with cancer in the 'real world', but older adults are under-represented in clinical studies evaluating ICI immunotherapies.
- The age-related immunosenescence may negatively impact the efficacy of ICI.
- It is inappropriate to manage older cancer patients simply using the clinical evidence extrapolated from studies of younger cancer patients.

Materials & methods

- PubMed, Embase and conference databases were systematically searched for studies that reported the efficacy of ICI according to patient age.
- The inclusion criteria consisted of eligible patients diagnosed with solid cancer, ICI immunotherapies as interventions and overall survival (OS) and progression-free survival (PFS) as outcomes.
- Subgroup, metaregression analysis and within-trial interaction hazard ratio were used to assess the impact of age on the efficacy of ICI.

Results

- A total of 34 studies containing 20,511 cancer patients were included. ICI could improve the OS and PFS in both patient groups of <65 and ≥65 years compared with the control groups, without significant differences when compared with the controls for each age group.
- ICI immunotherapies improved the OS and PFS in patients aged <75 years, while patients aged ≥75 years experienced less survival benefit from ICI immunotherapies when the cut-off age was set to 75 years.
- The age-related immunosenescence could negatively impact the efficacy of ICI.

Conclusion

- ICI has comparable efficacy in cancer patients aged <65 and ≥65 years. Cancer patients aged ≥75 years need more attention in the future clinical trials.
- Further studies are required to explore the underlying mechanism of the impact of age on the efficacy of ICI immunotherapies.

Supplementary data

To view the supplementary data that accompany this article please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2019-0124

Author contributions

X Huang, P Gao and Z Wang were responsible for conception and design of the study. All authors contributed to the acquisition, analysis, interpretation of data, manuscript drafting and revising, final approval of the version to be submitted and published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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