ACTA ONCOLOGICA
2020, VOL. 59, NO. 3, 249–256
https://doi.org/10.1080/0284186X.2019.1695062

Taylor & Francis
Taylor & Francis Group

REVIEW

Influence of age on the efficacy of immune checkpoint inhibitors in advanced cancers: a systematic review and meta-analysis

Kiichiro Ninomiya[a], Isao Oze[b], Yuka Kato[c], Toshio Kubo[d], Eiki Ichihara[e], Kammei Rai[e], Kadoaki Ohashi[e], Toshiyuki Kozuki[f], Masahiro Tabata[d], Yoshinobu Maeda[a], Katsuyuki Kiura[e] and Katsuyuki Hotta[c]

[a]Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [b]Division of Cancer Epidemiology and Prevention, Aichi Cancer Center, Nagoya, Japan; [c]Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan; [d]Center for Clinical Oncology, Okayama University Hospital, Okayama, Japan; [e]Department of Allergy and Respiratory Medicine, Okayama University Hospital, Okayama, Japan; [f]Department of Thoracic Oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) represent a paradigm shift in the development of cancer treatment. However, it remains to be clarified whether the benefits that they confer differ according to patient age. We conducted a systematic review and meta-analysis to assess age differences in the benefits of ICI treatment.

Methods: We systematically searched the PubMed database for randomised controlled trials of ICIs, including PD-1, PD-L1 and CTLA-4 inhibitors across multiple cancer types, such as melanoma, lung cancer and gastric cancer. We extracted trials including hazard ratios (HRs) for death stratified by patient age (cut-off age, 65 years). The primary objective of this study was to assess the difference in ICI efficacy between younger and older patients. We calculated pooled HRs and 95% confidence intervals (CIs) for younger and older cancer patients, and assessed data heterogeneity.

Results: We identified 3999 studies in our search. Of these, 24 eligible randomised trials, including a total of 8157 (57%) younger and 6104 (43%) older cancer patients, fulfilled the criteria for our study and were thus further analysed. The pooled HRs of the younger and older patients were 0.76 (95% CI: 0.69–0.84) and 0.80 (95% CI: 0.71–0.86), respectively; the difference in ICI efficacy between younger and older cancer patients was not significant ($p = .82$). Regarding the PD-1 and PD-L1 inhibitors, the survival benefit was similar in both age groups (HR: 0.74; $p = .96$), whereas for the CTLA-4 inhibitors, there tended to be less survival benefit for older versus younger patients (HR: 0.90 and 0.77, respectively; $p = .26$).

Conclusions: The survival benefit conferred by ICI was not age-dependent, amongst patients aged 65 years or younger. However, age-dependent benefits may vary amongst different types of ICIs.

ARTICLE HISTORY
Received 3 August 2019
Accepted 15 November 2019

Introduction

Immune checkpoint inhibitors (ICIs) have dramatic effects in patients with various carcinomas, and have been described as a paradigm shift in the development of cancer treatment [1]. The considerable survival benefits of ICIs were first observed following the development of ipilimumab, a CTLA-4 inhibitor, for patients with advanced melanoma [2]. Subsequently, PD-1 inhibitors, namely nivolumab, and pembrolizumab, were approved after demonstrating anti-tumour activity, particularly against tumours with a high mutation burden, such as melanoma and non-small cell lung cancer (NSCLC) [3,4]. Similarly promising results have been reported extensively in several clinical trials investigating the efficacy of PD-L1 inhibitors, such as atezolizumab and avelumab [5–7].

Generally, clinical trials of novel anti-tumour agents mainly target younger populations, resulting in a paucity of data describing the effects of these agents in elderly patients [8–11]. Therefore, in clinical practice, elderly patients are rarely considered suitable candidates for anticancer therapies. Several reports have also shown that cytotoxic chemotherapy treatments are less effective in elderly patients than in younger patients [12,13]. As a result, treatment strategies for advanced cancer in elderly patients remain controversial.

In older people, immune function is generally low compared to that of younger people [14,15], such that elderly patients may benefit little from ICIs. However, ICIs have been reported to extend survival regardless of age [16,17] amongst patients with certain types of cancers (e.g. melanoma and NSCLC). One study also suggested that ICIs may be more

CONTACT Katsuyuki Hotta khotta@okayama-u.ac.jp Center for Innovative Clinical Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama 700-8558, Japan

Supplemental data for this article can be accessed here.

effective in the elderly, reporting different mechanisms of action of ICIs amongst age groups [18,19]. Therefore, the true efficacy of ICIs in elderly patients remains to be established.

In the context of these findings, we conducted a meta-analysis of survival outcomes of younger and older patients with various types of cancers treated using ICIs.

Methods

Database search strategy

The analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Supplementary Table S1) [20]. We independently searched the PubMed database for phase 2 and 3 randomised controlled trials (RCTs) published between January 2010 and September 2018. We also reviewed abstracts and presentations from the proceedings of all relevant major conferences, including those held by the American Society of Clinical Oncology and European Society for Medical Oncology, published between January 2010 and June 2018. The database search terms used were 'CTLA-4', 'cytotoxic T-lymphocyte-associated protein 4', 'PD-1', 'programmed death receptor 1', 'PD-L1', 'programmed death receptor ligand 1', 'immune checkpoint inhibitor', 'ipilimumab', 'tremelimumab', 'nivolumab', 'pembrolizumab', 'atezolizumab', 'durvalumab' and 'avelumab'. When duplicate publications were found, only the most recent complete report was included.

Study selection

We focussed on trials including patients with advanced or recurrent cancer and evaluated the efficacy of ICIs, including PD-1, PD-L1 and CTLA-4 inhibitors, or combinations thereof. Phase 2 and 3 RCTs evaluating the efficacy of these ICIs in patients with advanced or recurrent cancer were included in this study. Trials without a non-ICI arm were excluded. Hazard ratios (HRs) for death, with 95% confidence intervals (CIs) or standard error (SE) and stratified by age (younger vs. older patients), were extracted from the retrieved publications. Typically, older patients were defined as those aged $\geq$65 years. Trials in which older patients were defined as those aged $\geq$70 years were excluded. We included trials that compared individual or combination ICI treatment with non-immunotherapy, including cytotoxic chemotherapy.

Two investigators (KN, and KH who held the board certificate of Japanese Society of Medical Oncology) searched the databases independently and took part in the trial selection process. The quality of the included trials was assessed according to the reportage of randomisation and blinding methods, as well as withdrawals and dropouts, using the five-point Jadad scale [21].

Statistical analysis

The primary objective of this study was to examine the difference in ICI treatment efficacy between younger and older cancer patients. We derived HRs for death with 95% CIs for both age groups, based on the data from all included studies. We calculated summary HRs using a random effects model. We also extracted HRs for death and their 95% CIs from eligible studies that examined ICI treatment efficacy in younger and older patients. The HR and CI values were combined using the random effects model.

We evaluated the heterogeneity of the summary HRs using the I^2 statistic, which yields the percentage of variability in the effect estimate due to heterogeneity rather than sampling error [22]. Publication bias was assessed using funnel plots and Egger's test [23]. All reported p values are two-sided. All statistical analyses were conducted using STATA/SE software (ver. 11.0; StataCorp, College Station, TX, USA).

Results

Trial selection

During our database search, we examined 3999 publications (excluding review articles), and identified 55 relevant RCTs following abstract or full-text review. Despite containing survival data, some trials were excluded for the following reasons: two randomised trials with subgroup analysis had an age cut-off of 70 years [24,25], and three trials compared ICIs to each other, rather than to non-immunotherapy [26–28]. The review process (Figure 1) yielded 24 trials, including 14,261 advanced or metastatic cancer patients, which fulfilled the criteria for inclusion in our analysis (Table 1). Because one trial had three arms, we decided to consider it as two separate RCTs, giving a final total of 25 trials [2].

Characteristics of the 25 included trials

The 25 trials included 7 on CTLA-4 inhibitors (ipilimumab, $n=5$; tremelimumab, $n=2$), 13 on PD-1 inhibitors (nivolumab, $n=8$; pembrolizumab, $n=5$), 4 on PD-L1 inhibitors (atezolizumab and avelumab, both $n=2$) and 1 on CTLA-4 and PD-1 inhibitors used in combination (ipilimumab plus nivolumab). Most of the 25 trials targeted patients with NSCLC (9 trials including 5729 patients) or melanoma (6 trials including 2792 patients); the remaining trials targeted patients with gastric cancer ($n=3$), SCLC ($n=2$), renal cell carcinoma (RCC; $n=2$), mesothelioma ($n=1$), head and neck cancer ($n=1$), and urothelial carcinoma ($n=1$). Of the 25 trials, 10 (40%) were in a first-line setting; 16 trials (64%) were designed to compare ICI with standard treatment (head-to-head design) and 9 (36%) evaluated the efficacy of adding ICI to standard therapy (add-on design).

Amongst all 14,261 patients, 8157 (57%) were aged $<$65 years, and 6104 (43%) were aged $\geq$65 years. The median age of the patients ranged from 55 to 67 years amongst all studies, which was consistent with the tumour types. Eight trials evaluated combination therapy of ICIs involving 2931 patients, 41.8% of whom were elderly. This proportion was equivalent to that in the whole 25 trials evaluated in this current meta-analysis (42.4%). Randomised treatment allocation was performed properly in all trials. A double-blind

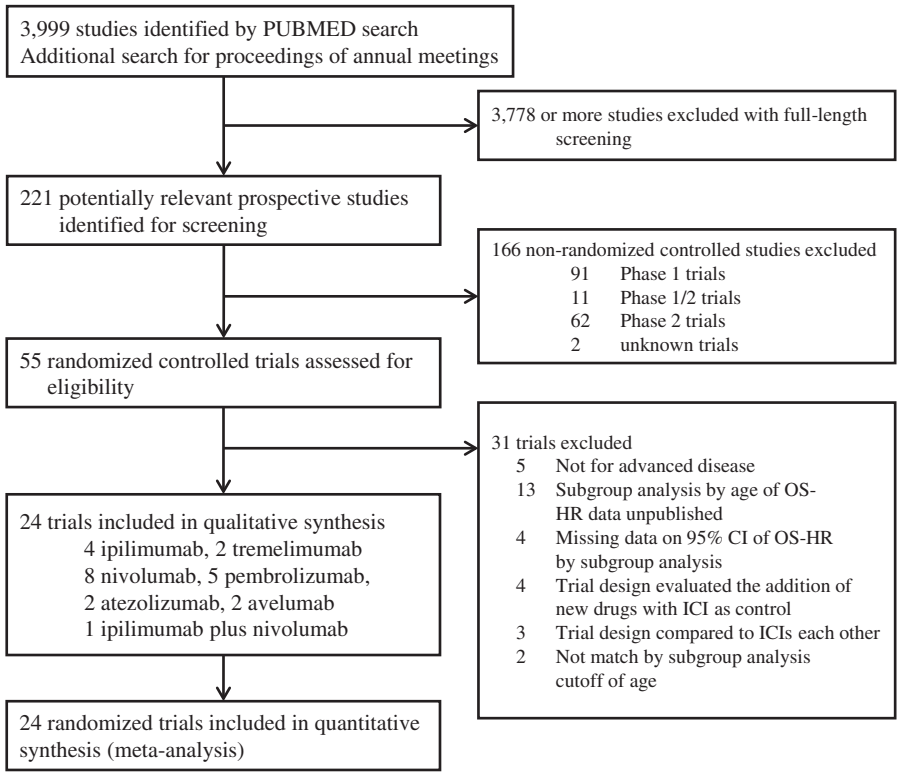

Figure 1. Flowchart of study selection. HR: hazard ratio; ICI: immune checkpoint inhibitor; OS: overall survival.

design was used by 11 trials. Jadad scores for each trial are listed in Supplementary Table S2; the mean score was 4 (range: 3–5). No trial had a Jadad score indicative of low quality (i.e. 1–2). Funnel plots of the whole population and each of the young and older populations, shown in Supplementary Figure S1, suggested potential existence of publication bias.

Meta-analysis of ICI efficacy in younger and older patients

In younger patients, ICI use was associated with a lower risk of death compared to control treatment (pooled HR: 0.76, 95% CI: 0.69–0.84). Elderly patients also exhibited lower risk of death following ICI treatment (pooled HR: 0.80, 95% CI: 0.71–0.86). The difference in ICI treatment efficacy between younger and older patients was not substantial ($p_{\text{heterogeneity}} = .82$; Figure 2).

We detected substantial inter-study heterogeneity in risk estimates in both younger patients ($I^2 = 66\%$) and older patients ($I^2 = 43\%$). This result indicated potential differences in ICI efficacy amongst the trials included in our analysis. Therefore, we conducted a subset analysis stratified by ICI type (anti-CTLA-4 antibody or anti-PD-1/PD-L1 antibody), type of carcinoma, line of treatment and trial design (Figure 3). Notably, the sub-analysis of CTLA-4 inhibitor treatment showed that its survival advantage in younger patients was similar to that in the whole population (pooled HR: 0.77, 95% CI: 0.66–0.91); however, this effect was weaker in older patients (pooled HR: 0.90, 95% CI: 0.80–1.01), although the difference was not statistically substantial ($p_{\text{heterogeneity}} = .258$). In contrast, the efficacy of PD-1/PD-L1 inhibitors was similar between younger and older groups (HR: 0.74, 95% CI: 0.65–0.84; and HR: 0.74, 95% CI: 0.66–0.83, respectively; $p_{\text{heterogeneity}} = .963$). The other three sub-analyses (carcinoma type, line of treatment and trial design) indicated that ICI yielded the same substantial survival benefit in both age groups (Figure 3).

Discussion

In this analysis, the pooled HRs for death of the younger and older patient groups were almost identical, at 0.76 (95% CI: 0.69–0.84) and 0.80 (95% CI: 0.71–0.86), respectively. This age-independent survival benefit of ICIs was also reproduced in sub-groups stratified by carcinoma type, line of treatment and trial design. Despite no substantial difference, this effect appeared to vary across the type of ICI, being weaker in elderly patients in trials of CTLA-4 inhibitor treatment (pooled HR: 0.90, 95% CI: 0.80–1.01).

In general, the healthy young will live longer than elderly. On the other hands, it has hardly been clear as to whether the survival effects of anticancer agents including ICIs in are similar in the young and elderly patients, although ICIs have shown a log-tail survival effect in cancers patients without any age-restriction [52,53]. Here, our analysis showed that the survival benefit of ICI for elderly was substantially equal to that of young.

Several reports have examined the effects of age on ICI treatment efficacy. Nishijima et al. [16] reported that ICIs prolonged overall survival similarly in both younger and older patient groups (HR: 0.747 and 0.734, respectively); however, the different age cut-offs were applied and only one trial was assessed for the efficacy of CTLA-4 inhibitor in their

Table 1. Characteristics of studies included in the meta-analysis.

Reference	Phase	Cancer type	Line	Treatment	No.	Median age (years)	Median follow-up (months)	Overall survival HR (95% CI)
Hodi et al. (2010)[1]	3	Melanoma	≥2	A: Ipilimumab (a) vs. gp100 (c) B: Ipilimumab plus gp100 (b) vs. gp100 (c) (plus placebo in each other group)	676	a: 56.8† (NA) b: 55.6† (NA) c: 57.4† (NA)	a: 27.8 b: 21.0 c: 17.2	A: 0.64 (0.49–0.84) B: 0.69 (0.56–0.85)
Robert et al. (2011)[29]	3	Melanoma	1	Ipilimumab plus dacarbazine vs. placebo plus dacarbazine	502	57.5† (NA) 56.4† (NA)	36.6#	0.72 (0.59–0.87)
Ribas et al. (2013)[30]	3	Melanoma	1	Tremelimumab vs. chemotherapy*	655	57 (22–90) 56 (22–90)	NA	0.88 (NA) $p = .1267$
Robert et al. (2015)[31]	3	Melanoma	1	Nivolumab vs. dacarbazine	418	64 (18–86) 66 (26–87)	8.9 6.8	0.42 (0.30–0.59)
Larkin et al. (2018)[32]	3	Melanoma	≥2	Nivolumab vs. chemotherapy*	405	59 (23–88) 62 (29–85)	2‡	0.92 (0.71–1.18)
Brahmer et al. (2015)[33]	3	NSCLC	≥2	Nivolumab vs. docetaxel	272	62 (39–85) 64 (42–84)	11§	0.59 (0.44–0.78)
Borghaei et al. (2015)[34]	3	NSCLC	≥2	Nivolumab vs. docetaxel	580	61 (37–84) 64 (21–85)	13.2§	0.75 (0.62–0.91)
Herbst et al. (2016)[35]	2/3	NSCLC	≥2	Pembrolizumab (2 mg/kg or 10 mg/kg) vs. docetaxel	1033	63 (56–69) 62 (56–69)	13.1	0.67 (0.56–0.80)
Carbone et al. (2017)[36]	3	NSCLC	1	Nivolumab vs. chemotherapy*	541	63 (32–89) 65 (29–87)	13.5	1.08 (0.87–1.34)
Rittmeyer et al. (2017)[37]	3	NSCLC	≥2	Atezolizumab vs. docetaxel	850	63 (33–82) 64 (34–85)	21	0.73 (0.62–0.87)
Govindan et al. (2017)[38]	3	NSCLC	1	Ipilimumab plus carboplatin/paclitaxel vs. placebo plus carboplatin/paclitaxel	749	64 (28–84) 64 (28–85)	12.5 11.8	0.91 (0.77–1.07)
Gandhi et al. (2018)[39]	3	NSCLC	1	Pembrolizumab plus platinum/pemetrexed vs. placebo plus platinum/pemetrexed	616	65 (34–84) 63.5 (34–84)	10.5	0.49 (0.38–0.64)
Paz-Ares et al. (2018)[40]	3	NSCLC	1	Pembrolizumab plus carboplatin/(nab)paclitaxel vs. placebo plus carboplatin/(nab)paclitaxel	559	65 (29–87) 65 (36–88)	7.8	0.64 (0.49–0.85)
Barlesi et al. (2018)[41]	3	NSCLC	≥2	Avelumab vs. docetaxel	529	64 (59–70) 63 (56–69)	18.9 17.8	0.90 (0.73–1.12)
Reck et al. (2016)[42]	3	SCLC	1	Ipilimumab plus platinum/etoposide vs. placebo plus platinum/etoposide	954	62 (39–85) 63 (36–81)	10.5 10.2	0.94 (0.81–1.09)
Horn et al. (2018)[43]	3	SCLC	1	Atezolizumab plus carboplatin/etoposide vs. placebo plus carboplatin/etoposide	403	64 (28–90) 64 (26–87)	13.9	0.70 (0.54–0.91)
Maio et al. (2017)[44]	2b	Mesothelioma	≥2	Tremelimumab vs. placebo	571	66 (60–72) 67 (61–73)	NA	0.92 (0.76–1.12)
Motzer et al. (2015)[45]	3	Renal cell carcinoma	≥2	Nivolumab vs. everolimus	821	62 (23–88) 62 (18–86)	14.0§	0.76 (0.62–0.92)
Motzer et al. (2018)[46]	3	Renal cell carcinoma	1	Nivolumab plus ipilimumab vs. sunitinib	847	62 (26–85) 61 (21–85)	25.2	0.66 (0.53–0.82)
Ferris et al. (2016)[47]	3	Head and neck squamous-cell carcinoma	≥2	Nivolumab vs. chemotherapy*	361	59 (29–83) 61 (28–78)	5.1	0.69 (0.53–0.91)
Bellmunt et al. (2017)[48]	3	Urothelial carcinoma	≥2	Pembrolizumab vs. chemotherapy*	542	67 (29–88) 65 (26–84)	14.1	0.73 (0.59–0.91)
Kang et al. (2017)[49]	3	Gastric or gastroesophageal junction cancer	≥2	Nivolumab vs. placebo	493	62 (54–69) 61 (53–68)	8.87 8.59	0.65 (0.53–0.80)
Shitara et al. (2018)[50]	3	Gastric or gastroesophageal junction cancer	≥2	Pembrolizumab vs. paclitaxel	395	62.5 (54–70) 60 (53–68)	7.9	0.82 (0.66–1.03)
Bang et al. (2018)[51]	3	Gastric or gastroesophageal junction cancer	≥2	Avelumab vs. chemotherapy*	371	59 (29–86) 61 (18–82)	10.6	1.1 (0.9–1.4)

NA, not applicable; *investigator's choice of regimen; †mean; ‡approximate duration of follow-up; §minimum follow-up time; #time between the last patient undergoing randomisation (first visit of last patient) and the end of the study.

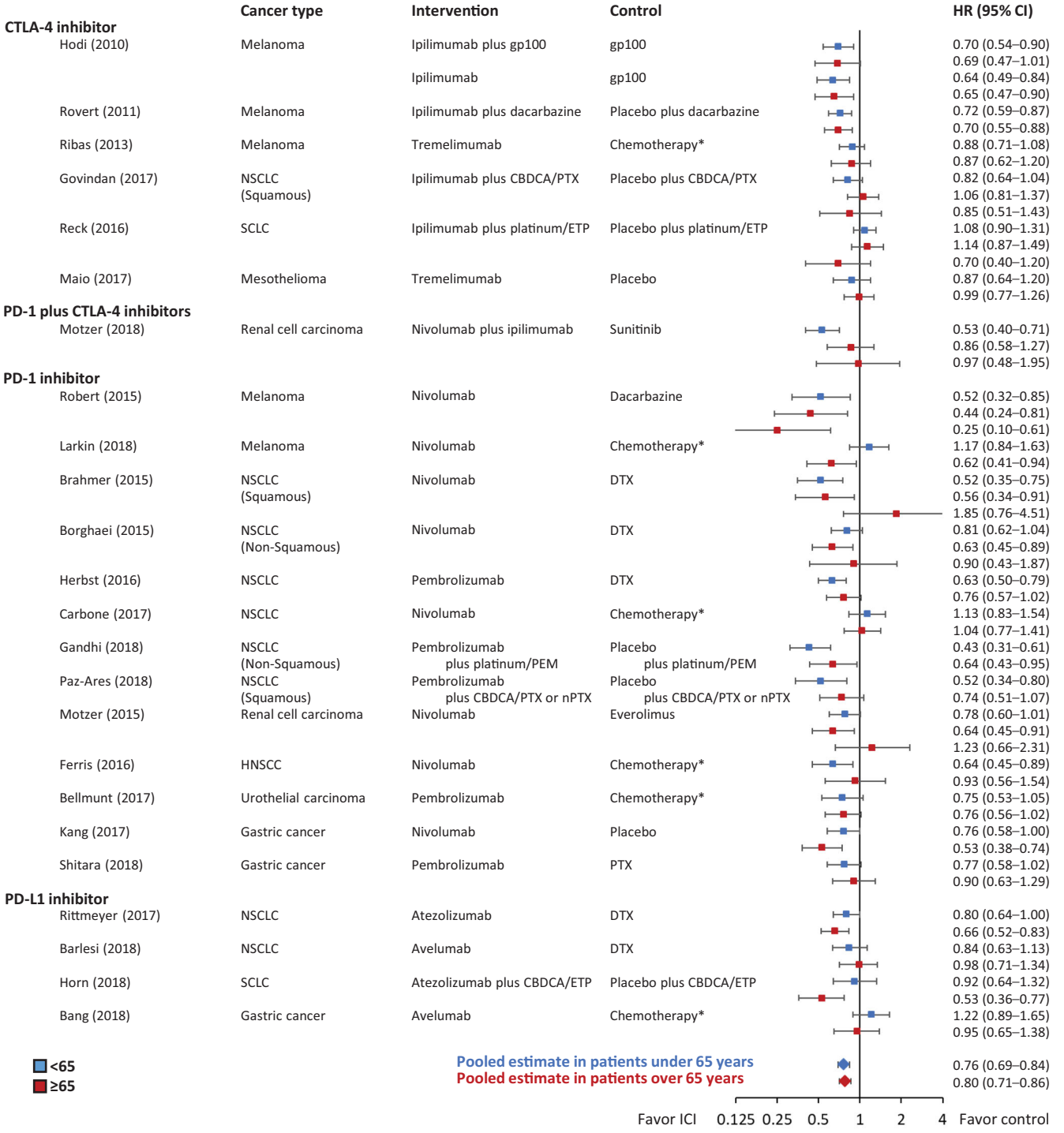

Figure 2. Results of meta-analysis of immune checkpoint inhibitor (ICI) efficacy: HRs for death in younger and older patients. NSCLC: non-small-cell lung cancer; SCLC: small-cell lung cancer. *investigator's choice of regimen.

meta-analysis. Elias et al. [17] also showed significant efficacy of PD-1 and PD-L1 inhibitor treatment in the elderly; however, agent assessed as PD-L1 inhibitor amongst ICIs was limited to atezolizumab, and most of the trials included in their study concerned only NSCLC. In contrast to our main results (Figure 2), Wu et al. [19] showed that patients aged 65 or over benefited better from ICI as compared with younger patients did; it might be partly because of increased cancer-related somatic mutations by aging [54]. However, tumor mutational burden but not age could influence the effect of ICI on OS in other reports [55]. Thus, the potential causal relationship of aging, high tumor mutational burden and treatment outcome remains unresolved, which warrants further investigations. Our study included more types of carcinomas and ICIs, which might better reflect the true nature of the variation in ICI efficacy by age.

This study also revealed a potential age difference in the efficacy of CTLA-4 inhibitor treatment between two subpopulations (Figure 3). Inhibition of the CTLA-4 pathway in the priming phase of immunity increases naïve T cells in the

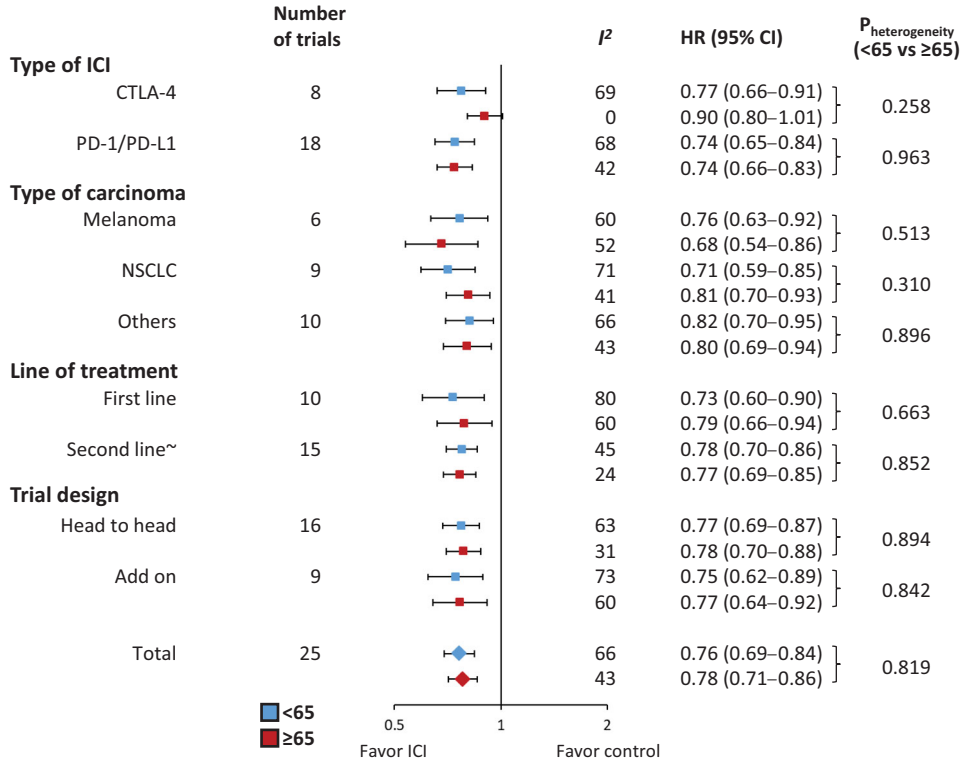

Figure 3. Subgroup analysis of the effects of ICI and cancer type on HRs for death.

peripheral blood [56]. Furthermore, CTLA-4 inhibitor treatment can deplete the levels of regulatory T cells via antibody-dependent cellular cytotoxicity [57,58]. In the elderly, (1) the naïve T cells produced from the thymus are depleted [59], so it is difficult to increase the levels of immature lymphocytes [60,61], and (2) intratumoral infiltration of regulatory T cells is poor [18]. These characteristics may explain the relatively weak survival effect of CTLA-4 inhibitor treatment seen in elderly patients. Furthermore, CTLA-4 inhibitors are more toxic than PD-1 inhibitors [62], suggesting that it may have been poorly tolerated for elderly patients with comorbidities. In our data-set, unfortunately, toxicity assessment by age sub-groups is not available, and further study will be required.

This meta-analysis had some limitations. First, as shown in Figure 2, there was a large degree of heterogeneity. Patient age distribution, type of treatment used as standard, and ICI efficacy vary inherently depending on the cancer type. We attempted to address this variation by performing subgroup analyses (Figure 3), and detected an age-independent survival effect of ICI that was consistent with that observed in the whole cohort, suggesting that the influence of age on ICI efficacy was small. Furthermore, this meta-analysis revealed a publication bias, as demonstrated by funnel plots (Supplementary Figure S1), which implies the presence of unreported negative trials on ICI treatments. Therefore, our results should be interpreted cautiously, and highlight the need to review published studies for concealed unfavourable results.

In conclusion, we detected no difference in the impact of ICIs on overall survival between elderly and young patients in this meta-analysis. However, treatment efficacy may differ by ICI type. Individual or combination ICI therapy with existing chemotherapy is currently recognised as a standard treatment; future studies should clarify whether and how the efficacy of such combination therapies is influenced by patient age.

Acknowledgements

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/IMDvHF.

Disclosure statement

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organisation or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

KN has received honoraria outside the current work from AstraZeneca, BMS, Chugai Pharmaceutical, Ono Pharmaceutical and MSD. KH has received honoraria outside the current work from AstraZeneca, Ono Pharmaceutical, BMS, MSD, Boehringer-Ingelheim and Chugai Pharmaceutical. KH has received grants and personal fees from AstraZeneca, grants and personal fees from Eli Lilly, grants and personal fees from Bristol-Myers Squibb, personal fees from MSD, personal fees from Ono Pharmaceutical, personal fees from Nippon Kayaku, personal fees from Taiho pharmaceutical, personal fees from Novartis, personal fees from Daiichi-Sankyo, personal fees from Kyorin, personal fees from Kyowa-Kirin, personal fees from Boehringer Ingelheim, grants from Astellas, and grants and personal fees from Chugai pharmaceutical outside the submitted work. EI has recieved honoraria outside the current work from AstraZeneca, Eli Lilly Japan, Boehringer-Ingelheim and Chugai Pharmaceutical. EI also has received additional research funding outside the current work from Eli Lilly Japan and MSD. KK has received honoraria

outside the current work from AstraZeneca and Chugai Pharmaceutical. All the other authors declare no conflicts of interest regarding this study.

References

[1] Ninomiya K, Hotta K. Pembrolizumab for the first-line treatment of non-small cell lung cancer. Expert Opin Biol Ther. 2018;18(10): 1015–1021.

[2] Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–723.

[3] Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature. 2013;499(7457):214–218.

[4] Martincorena I, Campbell PJ. Somatic mutation in cancer and normal cells. Science. 2015;349(6255):1483–1489.

[5] Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288–2301.

[6] Kelly K, Infante JR, Taylor MH, et al. Safety profile of avelumab in patients with advanced solid tumors: a pooled analysis of data from the phase 1 JAVELIN solid tumor and phase 2 JAVELIN Merkel 200 clinical trials. Cancer. 2018;124(9):2010–2017.

[7] D'Angelo SP, Russell J, Lebbé C, et al. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic Merkel cell carcinoma: a preplanned interim analysis of a clinical trial. JAMA Oncol. 2018; 4:e180077.

[8] Hotta K, Ueoka H, Kiura K, et al. An overview of forty-eight elderly-specific clinical trials of systemic chemotherapy for advanced non-small cell lung cancer. Lung Cancer. 2004;46(1):61–76.

[9] Kubo T, Fujiwara K, Hotta K, et al. A phase II study of topotecan and cisplatin with sequential thoracic radiotherapy in elderly patients with small-cell lung cancer: Okayama Lung Cancer Study Group 0102. Cancer Chemother Pharmacol. 2016;78(4):769–774.

[10] Aoe K, Takigawa N, Hotta K, et al. A phase II study of S-1 chemotherapy with concurrent thoracic radiotherapy in elderly patients with locally advanced non-small-cell lung cancer: the Okayama Lung Cancer Study Group Trial 0801. Eur J Cancer. 2014;50(16): 2783–2790.

[11] Hotta K, Ueoka H, Kiura K, et al. Safety and efficacy of gefitinib treatment in elderly patients with non-small-cell lung cancer: Okayama Lung Cancer Study Group experience. Acta Oncol. 2005;44(7):717–722.

[12] Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9(3):215–221.

[13] Abe T, Takeda K, Ohe Y, et al. Randomized phase III trial comparing weekly docetaxel plus cisplatin versus docetaxel monotherapy every 3 weeks in elderly patients with advanced non-small-cell lung cancer: the intergroup trial JCOG0803/WJOG4307L. J Clin Oncol. 2015;33(6):575–581.

[14] Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. J Pathol. 2007;211(2):144–156.

[15] Castelo-Branco C, Soveral I. The immune system and aging: a review. Gynecol Endocrinol. 2014;30(1):16–22.

[16] Nishijima TF, Muss HB, Shachar SS, et al. Comparison of efficacy of immune checkpoint inhibitors (ICIs) between younger and older patients: a systematic review and meta-analysis. Cancer Treat Rev. 2016;45:30–37.

[17] Elias R, Giobbie-Hurder A, McCleary NJ, et al. Efficacy of PD-1 & PD-L1 inhibitors in older adults: a meta-analysis. J Immunother Cancer. 2018;6(1):26.

[18] Kugel CH, 3rd, Douglass SM, Webster MR, et al. Age correlates with response to anti-PD1, reflecting age-related differences in intratumoral effector and regulatory T-cell populations. Clin Cancer Res. 2018;24(21):5347–5356.

[19] Wu Q, Wang Q, Tang X, et al. Correlation between patients' age and cancer immunotherapy efficacy. Oncoimmunology. 2019;8(4): e1568810.

[20] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–1012.

[21] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.

[22] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–560.

[23] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–1101.

[24] Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(7):700–712.

[25] Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer. J Clin Oncol. 2017; 35(1):40–47.

[26] Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26): 2521–2532.

[27] Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;17(11): 1558–1568.

[28] Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377(14):1345–1356.

[29] Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364(26):2517–2526.

[30] Ribas A, Kefford R, Marshall MA, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol. 2013; 31(5):616–622.

[31] Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320–330.

[32] Larkin J, Minor D, D'Angelo S, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: a randomized, controlled, open-label phase III trial. J Clin Oncol. 2018;36(4): 383–390.

[33] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–135.

[34] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–1639.

[35] Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–1550.

[36] Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med. 2017;376(25):2415–2426.

[37] Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–265.

[38] Govindan R, Szczesna A, Ahn MJ, et al. Phase III trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer. J Clin Oncol. 2017;35(30): 3449–3457.

[39] Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378(22):2078–2092.
[40] Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379(21):2040–2051.
[41] Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol. 2018;19(11):1468–1479.
[42] Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. J Clin Oncol. 2016;34(31):3740–3748.
[43] Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–2229.
[44] Maio M, Scherpereel A, Calabrò L, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Lancet Oncol. 2017;18(9):1261–1273.
[45] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373(19):1803–1813.
[46] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277–1290.
[47] Ferris RL, Blumenschein G, Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–1867.
[48] Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376(11):1015–1026.
[49] Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10111):2461–2471.
[50] Shitara K, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018;392(10142):123–133.
[51] Bang YJ, Ruiz EY, Van Cutsem E, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol. 2018;29(10):2052–2060.
[52] Gettinger S, Horn L, Jackman D, et al. Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study. J Clin Oncol. 2018;36(17):1675–1684.
[53] Garon EB, Hellmann MD, Costa EC, et al. Five-year long-term overall survival for patients with advanced NSCLC treated with pembrolizumab: results from KEYNOTE-001. J Clin Oncol. 2019;37(28):2518–2527.
[54] Risques RA, Kennedy SR. Aging and the rise of somatic cancer-associated mutations in normal tissues. PLoS Genet. 2018;14(1):e1007108.
[55] Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019;51(2):202–206.
[56] Pedicord VA, Montalvo W, Leiner IM, et al. Single dose of anti-CTLA-4 enhances CD8+ T-cell memory formation, function, and maintenance. Proc Natl Acad Sci USA. 2011;108(1):266–271.
[57] Selby MJ, Engelhardt JJ, Quigley M, et al. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res. 2013;1(1):32–42.
[58] Bulliard Y, Jolicoeur R, Windman M, et al. Activating Fc γ receptors contribute to the antitumor activities of immunoregulatory receptor-targeting antibodies. J Exp Med. 2013;210(9):1685–1693.
[59] Naylor K, Li G, Vallejo AN, et al. The influence of age on T cell generation and TCR diversity. J Immunol. 2005;174(11):7446–7452.
[60] Haynes L, Eaton SM, Burns EM, et al. CD4 T cell memory derived from young naive cells functions well into old age, but memory generated from aged naive cells functions poorly. Proc Natl Acad Sci USA. 2003;100(25):15053–15058.
[61] Saule P, Trauet J, Dutriez V, et al. Accumulation of memory T cells from childhood to old age: central and effector memory cells in CD4(+) versus effector memory and terminally differentiated memory cells in CD8(+) compartment. Mech Ageing Dev. 2006;127(3):274–281.
[62] Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017;377(19):1824–1835.