

Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Review Article

Immunotherapy in older patients with cancer



C. Granier ^{a,b,c,*}, A. Gey ^{a,b,c}, S. Roncelin ^a, L. Weiss ^{d,e,f}, E. Paillaud ^{g,h},
E. Tartour ^{a,b,c}

^a Biological Immunology Department, APHP, Georges Pompidou European Hospital, Paris, France

^b University of Paris, PARCC, INSERM, APHP, Paris, France

^c Ligue Contre le Cancer Labeled Team, France

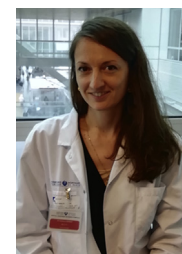
^d Clinical Immunology Department, APHP, Paris, France

^e INSERM U976 HIPI, Paris, France

^f Paris Descartes Medical School, University of Paris, Paris, France

^g Department of Geriatric, APHP, Paris Cancer Institute CARPEM, European Georges Pompidou Hospital, Paris, France

^h Paris Est Creteil University, INSERM, IMRB, Creteil, France



Dr. C. Granier

ARTICLE INFO

Article history:

Received 12 March 2020

Accepted 22 July 2020

Available online 26 July 2020

Keywords:

Immunosenescence

Ageing

Immunotherapy

Oncogeriatry

Cancer

Old people

Elderly

ABSTRACT

Ageing implicates a remodeling of our immune system, which is a consequence of the physiological senescence of our cells and tissues coupled with environmental factors and chronic antigen exposure. An immune system that senesces includes more differentiated cells with accumulation of highly differentiated CD4 and CD8 T cells. The pool of naive T cells decreases with the exponential thymic involution induced by age. Differentiated T cells have similar, if not higher, functional capacities but scarce studies are looking at the impact of senescence among specific T cells. After a stimulation, other immune cells (monocytes, dendritic cells and NK) are functionally altered during ageing. It is as if the immune system was more efficient at the basal level, but less efficient after a stimulation in the old compared to young people, likely due to less reserve. Concerning the clinical impact, older people are more prone to certain pathogens and their clinical manifestations differ from the younger people. Severe flu and VZV reactivation are more frequent with an altered cellular response to vaccination. Vaccination failure can have detrimental consequences in people presenting frailty criteria. Old people frailty is majored by their comorbidities and diseases like cancer. Thus, chemotherapies are employed with circumspection in older patients. The use of anti-PD-1/PD-L1 immunotherapies is therefore attractive, because of less side effects with a better response compared to chemotherapy. Old persons inclusion is lacking in current studies and clinical trials. Some subgroups or pooled analyses confirm the gain in response without increased toxicities in older patients but their inclusion criteria differ from the real-life practice. Specific studies focusing on this population are needed because of the increasing cancer incidence with age and the overall ageing of the population.

* Corresponding author. Biological Immunology Department, APHP, Georges Pompidou European Hospital, 20 rue Leblanc, 75015 Paris, France.

E-mail address: clemence.granier@aphp.fr (C. Granier).

Peer review under responsibility of Chang Gung University.

<https://doi.org/10.1016/j.bj.2020.07.009>

2319-4170/© 2020 Chang Gung University. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Getting older implies several changes. Particularly, ageing is accompanied by biological senescence. The process of cellular senescence was first described on fibroblasts by L. Hayflick in the early 1960s. Indeed, he reported a maximum proliferative lifespan of *in vitro* primary human fibroblasts [1]. This process characterizes the replicative senescence. One of the processes leading to replicative senescence is the telomere shortening when the cell enters in division. Telomeres are repeated hexameric DNA sequences located at the end of the chromosomes that are unable to replicate. This results in the telomere shortening from 11 kb at birth to 4 kb in the old age [2,3].

The senescence mechanism implies tissue ageing, but is useful to avoid malignant transformation of cells. Senescent cells can be cleared by the immune system; however, senescent cells accumulate with age. The immune system itself undergoes senescence. The overall process of immune and non-immune senescence is thought to induce several pathologies linked with ageing.

The cancer incidence increases with age [4]. Chemotherapies are used cautiously in the elderly, because of high risk of side effects in patients with several criteria of frailty. Immunotherapies targeting immune checkpoints, as PD-1 and PD-L1, have emerged recently as a new therapeutic class in the field of cancer with a good response rate and less side effects in average compared to chemotherapies. Immunotherapies constitute an excellent alternative option in the elderly. Focusing in the elderly population treated by this immunotherapy is necessary in our world with increasing lifespan.

Immunity, ageing and cancer

Variation of immune parameters with age

During life, the immune system is shaped by several environmental factors, sex and age.

The naïve T cells are released by the bone marrow and mature into the thymus from birth. They protect against all the encountered pathogens during the childhood. The progressive thymus involution and loss of T cell repertoire occurs during ageing and are well characterized in older people. In the thymus, the epithelial space that nurtures developing thymocytes is reduced with age, benefiting to the perivascular space that contain adipocytes. In the thymus microenvironment, the stromal cell functions are diverted as well. This leads to decrease in IL-7 secretion that plays an important role for T cell ontogenesis into the thymus [5,6].

Hematopoietic stem cells loss progressively their repopulation capacities and homing abilities [7]. The hematopoiesis is reoriented toward myeloid versus lymphoid lineage. Increase of IL-6 during ageing could play a role in this differentiation bias as shown in murine models. Myeloid phagocytic cells have higher capacities to secrete pro-inflammatory cytokines but are less able to exert their activity against pathogens [8].

The whole cytokine network progresses with a 'secretory associated senescence phenotype' or SASP. Proinflammatory cytokines (IL-6, TNF α , IL-8, TGF β , IL-10) are one of the SASP components involved in the chronic progressive increase in the proinflammatory status [9]. This basal inflammatory state

could be involved in inflammatory disease development that occurs during ageing [10]. This phenomenon, theorized and named inflamm-aging is provoked by a continuous antigenic load and stress and is accompanied by slightly higher levels of CRP in older people [5,11].

The basal level of cytokines production by monocytes and dendritic cells (DC) is sometimes increased in the elderly. However, in many contexts, the monocyte and DC functionality after Toll-like receptor (TLR) stimulation were found to be altered. This suggests that the TLR-mediated immunity is impaired. Interestingly, the increasing oxidative stress during ageing could be responsible for the subsequent impaired type I IFN response. Plasmacytoid DC, involved in the antiviral rapid response via IFN type I secretion, has reduce capacity to secrete type I IFN in response to TLR or CMV and herpes virus stimulation, probably preventing herpes virus clearance [12–14].

The proportion of individuals seropositive for CMV increases with age. It was suggested that the CMV repertoire takes more and more space in the whole repertoire during ageing. Even if the CMV serological status has been reported to affect various aspects of the immune response, the idea of its implication in the reduction of T cell repertoire has been recently challenged. Highly differentiated CMV specific T cells accumulate and resist to apoptosis [15].

Immune and lympho-senescence

Independently of their specificity, highly differentiated T cells accumulate during ageing. At the cellular level, during T cell differentiation into memory phenotype CD28 and CD27 expressions progressively decrease. At the individual level, the proportion of CD28⁺/CD27⁺ in the whole CD4 and CD8 subsets decreases during ageing. The naïve pool of T cells (CD28⁺ CD27⁺) has been estimated to reduce of 3% per year. In parallel, specific memory T cells accumulate.

CD45RA is lost during the naïve to effector transition and can be reacquired at the very late stages of T cell differentiation. The CD28-/CD45RA⁺ subset called EMRA is the more differentiated. These cells also lack CCR7 homing markers that is lost when the T cell becomes an effector.

CD57 expression frequently accompanied T cell differentiation.

The proliferation capacity of EMRA had been shown to decrease and EMRA T cells harbor shorter telomere length, which are characteristics of cellular senescence [16,17].

Physiologically, the cell proliferation is induced by mitogenic stimuli (growth factors, hormones, nutrients and cytokines) that activate MAPK and mTOR signaling. These pathways induce cyclin D1 and the cell cycle. This drives cell growth that is balanced by cell division. When the cell cycle is arrested by p21 or p16 cell cycle inhibitors, the MAPK and mTOR growth promoting pathway are activated in turn to overcome this block. This induces cell growth in size and without cell division, leading to hypertrophy and hypersecretory phenotype. When the mitogenic stimuli are strong, the geroconversion happens and the senescence becomes irreversible.

A cell that senesces is characterized by a cell cycle arrest with an upstream activation of mitogenic stimulation. Thus, MAP-Kinases increase in T cells during ageing. Particularly, in

highly differentiated T cells a complex of Erk, Jnk and p38 accumulates. This complex is coupled together with stress sensing proteins named sestrins. The sMAC (sestrin MAP-Kinase complex) is another intracytoplasmic marker of senescence that has been well characterized in CD4⁺ T cells [18].

During cell differentiation, the metabolism is reoriented. The mitochondria and their functions decline in the EMRA-T cells compare to early differentiation stages. In EMRAs, anaerobic glycolysis becomes predominant and fatty acid oxidation is altered leading to glucose dependence and lipid accumulation [16].

Finally, it seems like late differentiated T cells acquire an NK-like behavior. They recognize cells via non-MHC mediated interaction, harbor narrow TCR β gene expression and express KIR (that regulate the cell in case of non-self MHC recognition). Highly differentiated T cell can express other NK receptors KLRG1, NKG2D and NKG2A [19,20].

T cell senescence and exhaustion are two different processes to distinguish. Highly differentiated T cells loss proliferative capacities (Ki-67, CFSE), but conserve their functional capacities. They secrete perforin/granzyme cytotoxic granules and cytokines. Even if it is clear that EMRA express more granzyme B and perforin in peripheral blood, they are less prone to secrete two or three cytokines at the same time (IL-2 and TNF α \pm IFN γ) [16,21]. When compared between young and old people, T cell polyfunctionality after a superantigen stimulation is the same (effector memory or effector) or sometimes increase (for naïve T cell subset) for both CD4 and CD8 T cells. This suggests that the immune system adapts from the loss of the T cell pool regeneration and loss of naïve T cells. It has been shown that such CD4⁺ T cells were significantly more functional and cytotoxic in people over 110 years of age in a Japanese cohort [22]. These results were observed independently of any TCR specificity. One study reports that melanoma specific T cells secrete less granzyme B in older people so it might be possible that the effect of ageing could impact T cells when they are specific [23].

Conversely, highly dysfunctional T cells named 'exhausted' T cells loss their functionality. Multiple inhibitory receptor (PD-1, TIM-3, LAG-3 and CTLA-4) expression occurs in chronic antigen exposure leading to a chronic stimulation and progressively to exhaustion. In many studies, people use these markers to identify exhausted T cells. But these are indirect markers: they are expressed also just after T cell stimulation (to progressively turn off the T cell activation) and can in this case reflect activation [24]. An exhaustive characterization of functional testing (abolition of cytotoxicity/cytokine secretion/death receptor apoptosis induction) should be the best way to identify them [25]. Exhausted T cells are thought to be involved in chronic antigen persistence in certain situations (cancer, HIV, HCV) in which senescence is not involved so far.

Infection and vaccination in the elderly

A couple of studies reported an immune risk profile in patients suffering of healthcare-associated infections. Their rate of naïve subset among CD8 T cells was decreased compared to the patients without healthcare-associated infection. Their CD4/CD8 ratio was lower. In addition, they harbor a higher count of more differentiated and memory CD28⁻ CD8⁺ T cells [26].

Globally viral and bacterial infections have different clinical manifestations and certain are more severe in older compared to younger people. The higher prevalence of infections in the elderly varies according to the pathogen and strain involved. Fever is infrequent in the older patients. Hospitalization rate and institutionalization favor respectively nosocomial and community infections. Pneumonia and urinary tract infections seem to be the more prevalent. Influenza and shingles (VZV reactivation) are of major concern in the elderly as their clinical manifestations are more frequent and/or severe.

The majority of the seasonal influenza related mortality occurs in individual over age 65. However, the majority of the deaths linked with the H1N1 pandemic influenza virus in 2009 touch age 20–49 people. This suggests the presence of antibodies generated after H1N1 strain exposure in the 1950s that could induce cross-protection in the elderly [27]. In anti-influenza immunity, CD8-T cell functionality (IFN γ secretion and cytotoxicity) as well as T cell expansion decreases with age [28].

Vaccination represents the main tool today to protect people from flu epidemy, but its efficacy can be limited. In particular, vaccination is thought to be less effective generally in the elderly. This loss of efficacy against flu vaccine in older people was accompanied with lower levels of vaccine-specific antibodies [29]. Clinical data reported that older people vaccinated for the flu can undergo more severe complications compared to younger people. For the H3N2 but not for the H1N1pdm09 strain, the vaccination efficacy is lower in the older population [30].

A link between telomere shortening of immune cells and vaccine decreased efficacy had been suggested. Najarro et al. reported that not only antibodies titer, but also specific CD8-T cell expansion *in vitro* were higher in influenza vaccinated older people with increased B-lymphocytes count and CD8 telomere length [31]. This reflects the impact of cellular senescence on B and T cellular specific responses with potential clinical consequences.

The frequency and severity of VZV increase with age. This increase seems to correlate with the age decline of VZV-specific cell mediated immunity, while specific antibodies remain stable with aging [32]. In another hand, VZV reactivation occurs in patients with a cellular immune deficiency. These arguments support the role of lymphocyte immunity in the control of VZV reactivation. CD4-T cells seem to be particularly involved, as after VZV challenge with live attenuated antigens, functional and specific CD4-T cell responses significantly decrease with age. This was correlated with a lower clinical score in older people [33]. Among VZV vaccinated people, after 70 years old the efficacy tumble (half efficacy compared to under 70 years) [34]. This loss of vaccine response to live attenuated vaccine seems not to be observed with recombinant VZV vaccine (at least 90% of efficacy against zona in all age groups) [35].

The efficacy depends also on the viral strain, the adjuvant composition or the vaccine formulation.

Immune age defects and pathology

Considering epidemiological data in the elderly leads to the suggestion that an abolished immunity in the elderly favors

cardiovascular disease and cancer. Scientific proofs are scarce in the literature.

Cardiovascular morbidities had been correlated with the leukocyte telomere length. The shorter leukocyte telomere length was related with cardiovascular disease events [36,37].

During lifespan, the immune system is less able to differentiate the self from the non-self, leading to increased autoimmunity. Increased risk of auto-immune disease arises during ageing particularly for thyroiditis and arthritis [38,39]. This occurs in parallel with senescent T cells accumulation. These two observations could be linked [40]. Because highly differentiated T cells adopt a non-specific way to recognize their target, it could be that they are becoming sensitive toward self-antigen positive cells. Regarding the fact that immunotherapy targeting PD-1 and PD-L1 awakes autoimmunity with possible severe adverse effects, these considerations are meaningful.

The increase in cancer incidence with age could be an indirect suggestion that the immunosurveillance is weakened by senescence but it does not constitute a scientific proof. CD4 regulatory T cells (T-REG) as well as other immunosuppressive cells like MDSC levels are found to be higher in the elderly [8,41]. A report had shown that less naïve (CD28⁺) and more differentiated (CD28⁻ CD57⁺) percentages among CD8-T cells in PBMCs of lung cancer patients *versus* controls. Surprisingly some CD57⁺ CD8-T cells were found to express CD28 [42]. In line with the importance of CD28 expression by T cells in the cancer treatment, after anti-PD-1/PD-L1 treatment of lung cancer patients, CD28⁺ CD8-T cells were found to be highly proliferative (Ki67⁺). They also expressed less frequently the TIM-3 inhibitory receptor compared with CD28⁻ cells [43].

Biology: senescent cell elimination by the immune system

Cellular senescence is characterized by a cell cycle arrest, which is an advantageous mechanism to avoid the tumor cell transformation. However, during ageing senescent cells accumulate in tissue, responsible for tissue ageing. They are metabolically active and secrete inflammatory mediators that constitute together the SASP (cytokines (see upper)), chemokines, metalloproteases, growth factors and also the reactive oxygen species. The fate of the senescent cell is to undergo apoptosis or to be recognized and eliminated by the immune system. This should at the end protect from cancer development.

Senescent cells can be recognized by NK cells via the MICA/MICB expression and ligation to NKG2D [44].

An *in vitro*, irradiation-induced senescence on primary fibroblasts leads to non-classical MHC class I MICA/MICB and HLA-E expression. HLA-E can engage NKG2A leading to NK inhibition. In addition, highly differentiated T cells, that are overrepresented in older people, can express NKG2A as well. Therefore the HLA-E expression by senescent cells allows the immune-escape from not only NK but also CD8⁺ T cell mediated cytotoxicity. HLA-E expression was (i) induced by the IL-6 and other SASP components and (ii) regulated by p38 MAPK that accumulates in the highly differentiated cells. Interestingly *in vivo* exploration shows that in the old compared to young skins HLA-E was overexpressed in senescent fibroblasts. Finally, HLA-E overexpression in melanocytic nevi may

explain their persistence for decades in the tissues despite the CD8⁺ T cell infiltrate [45].

Tumor cell develops more easily in an immunosuppressive microenvironment. In a mouse model it has been proven that the senescent stromal cells drive immunosuppressive myeloid cell accumulation via interleukin-6. In humans, this cytokine is overexpressed in invasive forms of cervical carcinomas [46] and the implication of the intratumor IL-6 in tumorigenesis, aggressiveness and drug resistance was demonstrated. IL-6 and CRP levels (that are both increasing with age) correlated with IL-2 resistance and prognosis in melanoma treated patients [47].

Globally the chronic inflammation, commonly designated as inflamm-aging, could initiate under certain conditions a favorable niche for tumor cell induction.

T cell dysfunction and cancer

The antitumor immunity is also abolished by inhibitory molecules expression on intratumor T cells. Inhibitory receptors are physiologically expressed by T cells after T cell activation in order to stop T cell activation and proliferation. Under certain circumstances with chronic antigen exposure like cancer and chronic infection, these inhibitory receptors can accumulate on T cells. They counteract intracellular TCR kinases signaling. This effect is exerted by dephosphorylation of the TCR-CD3 directly or via CD28, a costimulatory molecule essential for T cells to be activated [48]. CTLA-4 and PD-1 are the two mainly described inhibitory receptors. CTLA-4 appears rapidly after T cell activation and PD-1 accumulates mainly in peripheral T cells after activation. In cancer patients, PD-1 and other inhibitory receptors (TIM-3, LAG-3) are overexpressed by lymphocytes within the tumor compared to peripheral blood [49]. PD-1 is the most famous one, as monoclonal antibodies targeting PD-1 and its ligand PD-L1 are successful in many indications of cancer treatment.

Cancer immunotherapy and cancer management in the elderly

Cancer immunotherapy: a brief overview

Since the first demonstrations of the clinical efficacy of the PD-1/PD-L1 and CTLA-4/CD80-CD86 axis inhibitors, the success of these treatments has continued to be confirmed and expanded. Objective clinical responses to these treatments have been observed in more than 20 types of cancer and marketing approval has been granted for 19 clinical indications (melanoma, NSCLC, renal cell carcinoma, bladder cancer, breast cancer, Hodgkin lymphoma, Merkel carcinoma, MSI-H or dMMR cancer, gastric cancer, hepatocellular carcinoma, cervical cancer, PMBCL, SCLC, cutaneous squamous cell carcinoma, endometrial carcinoma esophagus cancer, colorectal cancer) by the FDA. Anti-PD-1 and anti-PD-L1 represent the immunomodulatory antibodies with the most clinical indications and whose development remains the most important with 2975 clinical trials evaluating these molecules alone or in combination with other treatments at the end of 2019. Seven anti-PD-1 antibodies (Pembrolizumab,

nivolumab, cemiplimab, sintilimab, camrelizumab, toripalimab, tislelizumab) and three anti-PD-L1 antibodies (durvalumab, Atezolizumab, avelumab) are currently available worldwide. The 2nd generation of immunotherapy is based on the combination of several immunomodulators (i.e. anti-PD-(L)1 and anti-CTLA-4) or the association of anti-PD(L)-1 with conventional treatments (chemotherapy, radiotherapy, anti-angiogenic, targeted therapies). These treatments, initially given as 2nd or 3rd line therapy, are currently being evaluated as 1st line therapy or as neoadjuvant therapy and have already obtained FDA approval in patients without prior treatment [50–53].

Recent data obtained with more than 3–4 years of follow-up show that many patients treated with these immunotherapies remain long responders in patients with melanomas, non-small cell lung cancer or clear cell kidney cancer. The overall survival of these patients has significantly increased over the last 5 years with these treatments and some of them could be considered as cured [54]. The expression of PD-L1 or the microsatellite instability status allow in some indications to select patients for these treatments, but these biomarkers remain imperfect and the identification of novel one remains an important medical challenge [55]. Many biomarkers are currently being evaluated (mutational load, IFN signature, expression of checkpoint inhibitors in the tumor microenvironment, microbiota, infiltration by CD8⁺ T cells, etc.) [52,56,57]. Regarding the toxicity of these products, it is now established that PD-1/PD-L1 axis inhibitors as monotherapy are globally well tolerated with grade 3 and 4 side effects less frequent than chemotherapy. Anti-CTLA-4 antibodies alone or in combination appear more toxic [58,59]. This therapeutic revolution led to the awarding of the Nobel Prize to two researchers, Tasuku Honjo and JP Allison, who identified and/or validated the PD-1, PD-L1 and CTLA-4 targets.

Chemotherapy risk/benefit in the elderly

The median age of cancer diagnostic is mainly around 65 according to the National cancer statistic institute: 70 for lung cancer, 63 for melanoma and 64 for kidney [83]. Despite the rapid growth of the older patients with cancer in the real-life setting, they are underrepresented in the clinical trials that set the standards of care in oncology [60]. As a result, there is a lack of evidence on the risk/benefit ratio of cancer treatments in older patients. Comorbidities, organ-specific physiologic changes, disabilities and geriatric syndromes become increasingly prevalent with advancing age and are associated with treatment-related side effects and poorer outcomes [61]. Thus, a major issue for oncologists is determination of the intensity of cancer treatment best suited to each older patient. There is considerable heterogeneity among older patients of the same age, so that chronologic age alone provides little information regarding an individual's tolerance to cancer treatments.

Identifying comorbid conditions and geriatric health domains that increase the risk of toxicities may allow oncologists to better assess the risk/benefit ratio in individual patients, to develop customized treatment adjustments, and to implement interventions designed to decrease the risk of toxicity [61]. Scientific societies recommend a comprehensive

geriatric assessment (CGA) to detect multi-domain health problems potentially associated with adverse outcomes, to guide decision making about cancer treatments [62]. The assessment is based on validated tools to systematically assess functional, nutritional, cognitive, emotional, and social status as well as comorbidities. Geriatric assessment can help oncologists identify older patients with cancer who could benefit from optimal anticancer treatment and those likely to benefit from adapted treatment [63]. Moreover, CGA allows for organizing early medico-psycho-social follow-up and supportive care, before and during the anticancer treatment, to improve treatment safety and to maintain the quality of life of older patients.

Clinical response to immunotherapy in elderly

Because of the immunosenescence and the data in the literature showing a poorer vaccine response in the elderly, it was expected that the elderly would have a poorer clinical response to treatment with molecules that block the interaction of checkpoint inhibitors with their ligands (anti-PD-1/PD-L1, anti-CTLA-4) [52].

In fact, in the majority of published studies and meta-analyses, people with different types of cancer (non-small cell lung cancer, clear cell renal cancer, melanoma, head and neck cancer), aged between 65 and 75 years, respond as well as the subjects under 65 years. This conclusion was true whatever the response criteria (overall survival, recurrence-free survival, RECIST response) and regardless the location of the cancer. Results from these analysis included both molecules inhibiting the PD-1/PD-L1 axis and anti-CTLA-4 antibodies [64–70].

However, in patients over 75 years of age, some controversies still exist. Indeed, resistance to anti-PD-1/PD-L1 therapy has been observed, particularly in Phase 3 pivotal clinical trials in patients with squamous cell carcinoma or adenocarcinoma of the lung, metastatic clear cell renal cancer and squamous cell carcinoma of the upper aerodigestive tract [71–75]. Nevertheless, in NSCLC, other studies show a benefit of anti-PD-1 treatment in patients over 70 or 75 years of age [76–78].

On the contrary, in patients with metastatic melanoma or advanced bladder cancer, no age limit for response to these treatments has been recorded. In both cancer types, clinical responses in subjects over 70 or 75 years of age have been observed in a comparable manner to younger subjects [79–84]. Anecdotally, in patients with metastatic melanoma, clinical responses have been reported after treatment with anti-PD-1 or a combination of anti-PD-1 and anti-CTLA-4 in patients over 90 years of age [85]. These results and publications are summarized in Table 1.

It therefore appears that there may be a difference in sensitivity to immunotherapy in people over 75 years of age depending on the location of the tumour, although these results deserve to be validated on larger series of patients. In addition, older adults are often underrepresented in clinical trials because of selective inclusion criteria, such as a good performance status, normal hepatic and renal function, and no autoimmune disease.

More recent studies in patients with metastatic melanoma suggest that anti-PD-1 treatments may be more effective in elderly patients with a threshold of 60–80 years of age to define this group of patients [86,87]. In order to explain this paradoxical effect, the authors showed in both elderly mice and melanoma patients treated with anti-PD-1, an increased ratio of the number of CD8⁺ T cells to regulatory T cells [86]. Another hypothesis to explain this better response of elderly subjects to immunotherapy would be that the tumour of these patients would present more mutations or neoantigens because of a longer exposure to environmental carcinogens. It is interesting to note that in another form of immunotherapy based on the administration of T cell with a receptor composed of antibodies fragment (scFv) directed against the CD19 molecule (CAR T cells) in patients with large cell lymphomas, the elderly have the same response rate as younger subjects, but more complete clinical responses (62% vs. 46%) [88].

Immunotherapy toxicity

Due to preclinical data in mice showing that immunotherapy resulted in often rapid and sometimes lethal toxicity in older mice compared to younger mice [89], the follow-up of side effects in patients treated with immunotherapy was particularly well analysed. Overall, no more general or severe (particularly for grade 3 or 4) adverse events were observed in elderly patients treated with immunotherapy compared to the general population or younger patients [Table 1]. This lack of increase in adverse events was reported for both anti-PD-1/PD-L1 or anti-CTLA-4 monotherapies and anti-PD-1 and anti-CTLA-4 combination therapies [69,78,82,90,91]. Although the thresholds varied from one study to another to define the elderly, these cohorts included patients between 70 and 80 years of age, which seems to rule out a threshold effect.

A few studies have reported a slight increase in toxicity with anti-PD(L)-1 and anti-CTLA-4 combination therapies in people over 80 years of age [92,93].

Different studies have reported a risk of hyperprogression under anti-PD-1/PD-L1 immunotherapies with variable frequency depending on the authors and the tumour location [94,95]. Although the studies reported conflicting results, it should be mentioned that in one publication, age has been associated with a risk of hyperprogression under immunotherapy [94].

Although the frequency of side effects of immunotherapy does not appear to be significantly higher in the elderly, the impact of these effects may be more pronounced in the elderly due to co-morbidity and lack of functional reserve.

Finally, there is clear evidence that immunotherapy by blocking the PD-1-PD-L1 axis is less toxic than chemotherapy in the elderly [96].

Recommendations and concluding remarks

Initial studies are quite reassuring about the use of immunotherapy in the elderly. The risk of toxicity does not seem to increase significantly and reproducibly with the age of the patients. Clinical efficacy in patients under 75 is well demonstrated. Beyond 75 years of age, the studies are more

contradictory. Differences in response depending on tumor location may exist in the elderly. Nevertheless, the limitations and potential biases of these studies must be considered. Indeed, in the majority of cases, the influence of age is sought from retrospective studies, where the number of elderly patients is not very large. The threshold for defining an elderly person is variable across studies (between 65 and 75 years of age) often making meta-analyses difficult. In the protocols, elderly patients are selected on the basis of fairly strict criteria (performance status: 0–1), which probably eliminates patients with significant comorbidities. No in-depth Geriatric Evaluation (functional status and mobility, number of drugs, comorbidities, mood and cognitive disorders, nutritional status ...) has been performed during these different protocols. A global assessment of frailty could improve the future studies.

Perspective in immunotherapy management in older patients

The immune system is challenged from the birth and during lifelong. As all the cells in our body, it undergoes several changes, more or less characterized so far. Its remodeling induced by ageing varies among people according to their environment, sex and age leading to immunosenescence. There are several studies linking telomere length with several pathologies. The telomere length attrition had been linked with many comorbidities factors in the elderly, while it seems to be improved by favorable social context and sport activity [97]. It might be therefore possible that some immunosenescence patterns are linked with frailty degree of the older patients. The elderly whom health support is delicate rightly because of their weakness would benefit from a scoring of these criteria. The geriatric assessment already includes an evaluation of the frailty with scoring like GCA. Immunosenescence markers are known, but does not benefit to the clinical practice so far. In cancer patients, few studies exist. Anti-melanoma T cells are less functional in the old versus young people [23]. However, at the basal level, the functionality of the ageing T cells, but also DC, NK cells and monocytes is preserved if not enhanced. B and T cells senescence seem to also impair vaccination against VZV and influenza that induce severe infections in the elderly. In another hand, in the HIV-infected individuals, persistent replication of HIV leads to antigen specific and non-specific differentiation and proliferation of T cell subsets and ultimately, to accumulation of highly differentiated immunosenescent cells characterized by a lack of CD28 expression, an increase in the expression of CD57 and a decrease in leucocyte telomere length compared to HIV negative people [98]. These are arguments to reinforce the studies of the immune system differentiation in the contexts like cancer. Finding the contexts in which the immune-age is more important for the treatment strategy than the chronological age is challenging. In the future, it will be ideal to find a way to score or stratify immunosenescence. This score could be used to monitor anti-cancer immunotherapy and vaccination in the elderly.

Concerning the use of immunotherapies in the elderly, the subgroup or pooled analysis are reassuring regarding the safety and the clinical response. But the criteria to fit inclusion

Table 1 Outcomes in cancer patients treated by immunotherapy: studies including age group comparisons.

Publication (author, journal, year and study type)	Reference number	Immunotherapy (ies) used	Tumor localisation(s)	Immunotherapy arm	Elderly population		ORR
					n=	Age groups	
Elkrief A, J Geriatr Oncol, 2020, retrospective, real life and multicentric cohort	70	Anti-PD-1 and anti-PD-L1 nivolumab, pembrolizum and others	NSCLC	381	<70	257	
					≥70	124	
Borghaei H, NEJM, 2015, clinal trial versus docetaxel, subgroup analysis	72	Nivolumab	NSCLC	582	<65	339	
					65–75	200	
					≥75	43	
Brahmer J, NEJM, 2015, clinal trial versus docetaxel, subgroup analysis	73	Nivolumab	NSCLC	135	<65	79	
					65–75	45	
					>75	11	
Gettinger SN, JCO, 2015, phase 1	76	Nivolumab	NSCLC	129	<70	90	16.7%
					≥70	39	17.9%
Spigel D, J Thor oncol, 2019, phase 3 –4b	77	Nivolumab	NSCLC	1426	<70	870	
					≥70	556	
Grossi F, Eur J Cancer 2018, multicentric real-world study	78	Nivolumab	NSCLC	371	whole	1426	18%
					<65	126	
					65–75	175	
					≥75	70	
					whole	371	
Landre T, JCO, 2016, sub-group analysis of pooled published randomized control trials versus standard therapy	71	Nivolumab	NSCLC & RCC	687	65–75	541	
					≥75	146	
					<65	257	
Motzer RJ, NEJM, 2015, phase 3 versus everolimus	74	Nivolumab	RCC	410	65–75	119	
					≥75	34	
					<65	265	
Motzer RJ, NEJM, 2018, phase 3 versus sunitinib	74	Nivolumab + ipilimumab	RCC	425	65–75	125	
					≥75	35	
					<65	172	
Ferris RL, NEJM, 2007, phase 3 versus standard chemotherapy	75	Nivolumab	Head and neck	228	65–75	56	
					<65	57	
Balar AV, lancet oncol, 2017, multicentre phase 2, subgroup analysis	83	Pembrolizumab	Bladder	370	≥65	25	30%
					<65	25	26%
Bellmunt J, NEJM, 2017, phase 3 versus chemotherapy, subgroup analysis	84	Pembrolizumab	Bladder	270	<65	105	
					≥65	165	
Betof AS, the oncologist, 2017, retrospective, 2 centers	79	Anti-PD-1 and anti-PD-L1	Melanoma	254	<50	57	
					50–64	85	
					65–74	65	
					>75	47	
Rai R, annal oncol, 2016, retrospective and multicentric analysis	80	Pembrolizumab and nivolumab	Melanoma	283	≤75	256	34%
					>75	35	48%

Robert C, NEJM, 2015, phase 3 versus dacarbazine, subgroup analysis	81	Nivolumab	Melanoma	210	<65 65–75 >75	106 77 27
Chiarion Sileni V, J Exp Clin Cancer Res, 2014, multicentric pooled analysis	82	Ipilimumab	Melanoma	833	≤70 >70	645 188
Kugel CH, clin cancer research, 2018, retrospective multicentric + preclinical model	88	Pembrolizumab	Melanoma	538	<62 ≥62	238 300

Abbreviations: HR: hazard ratio; ns: non significant; NSCLC: non small cell lung cancer; OS: overall survival; ORR: overall response rate; RCC: renal cell carcinoma.

Overall survival (patients receiving immunotherapy)		Progression free or recurrence free survival		Toxicity (grade 3-4 adverse events unless specified any grades)		Statistical effect on clinical outcome	Conclusion
Median or HR	Statistical difference	Median or HR	Statistical difference	Median or HR	Statistical difference		
13,7 months 11,6 months HR = 0,81 HR = 0,63 HR = 0,9 HR = 0,52 HR = 0,56 HR = 1,85	$p = 0,23$	3,2 months 4,3 months	$p = 0,92$	6% 5%		no age interaction with the clinical outcome	No difference according to age groups OS comparable in the 65-75 but less better in the ≥ 75 years old group OS worse in the ≥75 years old group Similar ORR in age groups
10,3 months 9,1 months		60% 62%		12% 14%	$p = ns$	ECOG PS = 2 had shorter OS	No difference according to age groups ECOG geriatric score impacts OS No difference in <65 and 65–75 years of age
8,6 months 8 months 5,8 months 7,9 months HR = 0.6 HR = 1.22 HR = 0,78 HR = 0,64 HR = 1,23 HR = 0,53 HR = 0,86 HR = 0,97 HR = 0,64 HR = 0,93	$p < 0.0001$ $p = 0.36$	4 months 4,5 months 3,2 months 4,2 months HR = 0.78 HR = 1.24	ns $p = 0.06$ $p = 0.43$	3% 9% 3% 6%		age effect depending on the age group	OS/PFS worse in the ≥ 75 years old group Immunotherapy better than standard therapy in 67–75 but not if ≥ 75 years old OS comparable in the 65–75 but worse in the ≥75 years old group OS better in the 65–75 but worse in the ≥ 75 years old group compare to sunitinib OS worse in the 65–75 years old group

					in PD-L1 >10%, worse ORR in elderly	Similar ORR in age groups
HR = 0,75						Similar ORR in age groups
HR = 0,76						Similar ORR in age groups
22,9 months	ns HR = 0,93	4,1 months	ns HR = 0,98	any 38,6%		No difference according to age groups
25,3 months	ns HR = 0,88	6,5 months	ns HR = 0,82	43,50%		
22 months	ns HR = 0,83	5,4 months	ns HR = 0,85	49,20%		
24,3 months	HR = 1	7,9 months	HR = 1	40,40%		
48,1 months	p = ns	4,6 months	p = ns	any 37%	p = ns	No difference according to age groups
33,5 months		8,7 months		40%		OS similar in the 65–75 and better in the ≥75 years old group compare to sunitinib
HR = 0,52						No difference according to age groups
HR = 0,44						Probability of progression significantly decreases with age
HR = 0,25						
3,7 months	p = 0,17	7 months	p = 0,33	any 36%	p = ns	
4 months		8,9 months		any 33%		
		progression 48%	p = 0,02			
		37%				

in industrial trials are often drastic leading to potential risk of inclusion bias in favor to the healthier older people that could be over-represented in these studies. Real-life clinical data are thereby very informative. A retrospective study in lung cancer patients treated by immunotherapy in real-life practice suggests that patients over 70 years old may have a shorter overall survival than younger. This is regarding the fact that in the whole population the elderly also have shorter survival. The progression free survival was shorter as well, but at a lesser extend ($p = 0.012$). Finally, the toxicity was identical between the 2 sub-groups [99]. Furthermore, the age comparison results of immunotherapies could be organ and molecule-dependent. A geriatric evaluation of the frailty criteria is lacking in the existing studies. Whatever the case, even if these data has to be confirmed, the practitioners should be aware. Other larger studies conducted in a geriatric population with an evaluation of their frailty are needed to draw a more precise conclusion.

Conflicts of interest

The authors have no conflict of interest to declare.

Acknowledgements

This work is supported by cancerpole IDF, Fondation de France, Siric Carpem, Labex Immuno-oncologie, Fondation ARC, Institut National Du Cancer and FONCER.

REFERENCES

- [1] Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res* 1961;25:585–621.
- [2] von Zglinicki T, Martin-Ruiz CM. Telomeres as biomarkers for ageing and age-related diseases. *Curr Mol Med* 2005;5:197–203.
- [3] Bekaert S, De Meyer T, Van Oostveldt P. Telomere attrition as ageing biomarker. *Anticancer Res* 2005;25:3011–21.
- [4] Thakkar JP, McCarthy BJ, Villano JL. Age-specific cancer incidence rates increase through the oldest age groups. *Am J Med Sci* 2014;348:65–70.
- [5] Pawelec G. Does patient age influence anti-cancer immunity? *Semin Immunopathol* 2019;41:125–31.
- [6] Lynch HE, Goldberg GL, Chidgey A, Van den Brink MR, Boyd R, Sempowski GD. Thymic involution and immune reconstitution. *Trends Immunol* 2009;30:366–73.
- [7] Lee J, Yoon SR, Choi I, Jung H. Causes and mechanisms of hematopoietic stem cell aging. *Int J Mol Sci* 2019;20:1272.
- [8] Verschoor CP, Johnstone J, Millar J, Dorrington MG, Habibagahi M, Lelic A, et al. Blood CD33(+)-HLA-DR(-) myeloid-derived suppressor cells are increased with age and a history of cancer. *J Leukoc Biol* 2013;93:633–7.
- [9] Xia S, Zhang X, Zheng S, Khanabdali R, Kalionis B, Wu J, et al. An update on inflamm-aging: mechanisms, prevention, and treatment. *J Immunol Res* 2016;2016:8426874.
- [10] Fulop T, Witkowski JM, Pawelec G, Alan C, Larbi A. On the immunological theory of aging. *Interdiscip Top Gerontol* 2014;39:163–76.

- [11] Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 2000;908:244–54.
- [12] Metcalf TU, Wilkinson PA, Cameron MJ, Ghneim K, Chiang C, Wertheimer AM, et al. Human monocyte subsets are transcriptionally and functionally altered in aging in response to pattern recognition receptor agonists. *J Immunol* 2017;199:1405–17.
- [13] Panda A, Qian F, Mohanty S, van Duin D, Newman FK, Zhang L, et al. Age-associated decrease in TLR function in primary human dendritic cells predicts influenza vaccine response. *J Immunol* 2010;184:2518–27.
- [14] Agrawal A, Gupta S. Impact of aging on dendritic cell functions in humans. *Ageing Res Rev* 2011;10:336–45.
- [15] Lindau P, Mukherjee R, Gutschow MV, Vignali M, Warren EH, Riddell SR, et al. Cytomegalovirus exposure in the elderly does not reduce CD8 T cell repertoire diversity. *J Immunol* 2019;202:476–83.
- [16] Henson SM, Lanna A, Riddell NE, Franzese O, Macaulay R, Griffiths SJ, et al. p38 signaling inhibits mTORC1-independent autophagy in senescent human CD8(+) T cells. *J Clin Invest* 2014;124:4004–16.
- [17] Fali T, Papagno L, Bayard C, Mouloud Y, Boddaert J, Sauce D, et al. New insights into lymphocyte differentiation and aging from telomere length and telomerase activity measurements. *J Immunol* 2019;202:1962–9.
- [18] Lanna A, Gomes DC, Muller-Durovic B, McDonnell T, Escors D, Gilroy DW, et al. A sestrin-dependent Erk-Jnk-p38 MAPK activation complex inhibits immunity during aging. *Nat Immunol* 2017;18:354–63.
- [19] Bjorkstrom NK, Beziat V, Cichocki F, Liu LL, Levine J, Larsson S, et al. CD8 T cells express randomly selected KIRs with distinct specificities compared with NK cells. *Blood* 2012;120:3455–65.
- [20] Voehringer D, Koschella M, Pircher H. Lack of proliferative capacity of human effector and memory T cells expressing killer cell lectinlike receptor G1 (KLRG1). *Blood* 2002;100:3698–702.
- [21] Seidel JA, Vukmanovic-Stejic M, Muller-Durovic B, Patel N, Fuentes-Duculan J, Henson SM, et al. Skin resident memory CD8(+) T cells are phenotypically and functionally distinct from circulating populations and lack immediate cytotoxic function. *Clin Exp Immunol* 2018;194:79–92.
- [22] Hashimoto K, Kouno T, Ikawa T, Hayatsu N, Miyajima Y, Yabukami H, et al. Single-cell transcriptomics reveals expansion of cytotoxic CD4 T cells in supercentenarians. *Proc Natl Acad Sci U S A* 2019;116:24242–51.
- [23] Briceno O, Lissina A, Wanke K, Afonso G, von Braun A, Ragon K, et al. Reduced naive CD8(+) T-cell priming efficacy in elderly adults. *Ageing Cell* 2016;15:14–21.
- [24] Hailemichael Y, Dai Z, Jaffarizad N, Ye Y, Medina MA, Huang XF, et al. Persistent antigen at vaccination sites induces tumor-specific CD8(+) T cell sequestration, dysfunction and deletion. *Nat Med* 2013;19:465–72.
- [25] Apetoh L, Smyth MJ, Drake CG, Abastado JP, Apte RN, Ayyoub M, et al. Consensus nomenclature for CD8(+) T cell phenotypes in cancer. *OncoImmunology* 2015;4:e998538.
- [26] Laurent M, Bastuji-Garin S, Plonquet A, Bories PN, Le Thuaut A, Audureau E, et al. Interrelations of immunological parameters, nutrition, and healthcare-associated infections: prospective study in elderly in-patients. *Clin Nutr* 2015;34:79–85.
- [27] Leng J, Goldstein DR. Impact of aging on viral infections. *Microb Infect* 2010;12:1120–4.
- [28] Jiang J, Bennett AJ, Fisher E, Williams-Bey Y, Shen H, Murasko DM. Limited expansion of virus-specific CD8 T cells in the aged environment. *Mech Ageing Dev* 2009;130:713–21.
- [29] Sasaki S, Sullivan M, Narvaez CF, Holmes TH, Furman D, Zheng NY, et al. Limited efficacy of inactivated influenza vaccine in elderly individuals is associated with decreased production of vaccine-specific antibodies. *J Clin Invest* 2011;121:3109–19.
- [30] Belongia EA, Simpson MD, King JP, Sundaram ME, Kelley NS, Osterholm MT, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis* 2016;16:942–51.
- [31] Najjarro K, Nguyen H, Chen G, Xu M, Alcorta S, Yao X, et al. Telomere length as an indicator of the robustness of B- and T-cell response to influenza in older adults. *J Infect Dis* 2015;212:1261–9.
- [32] Levin MJ, Smith JG, Kaufhold RM, Barber D, Hayward AR, Chan CY, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. *J Infect Dis* 2003;188:1336–44.
- [33] Patel NP, Vukmanovic-Stejic M, Suarez-Farinas M, Chambers ES, Sandhu D, Fuentes-Duculan J, et al. Impact of zostavax vaccination on T-cell accumulation and cutaneous gene expression in the skin of older humans after varicella zoster virus antigen-specific challenge. *J Infect Dis* 2018;218:S88–98.
- [34] Schmader KE, Levin MJ, Gnann Jr JW, McNeil SA, Vesikari T, Betts RF, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clin Infect Dis* 2012;54:922–8.
- [35] Willer DO, Oostvogels L, Cunningham AL, Gervais P, Gorfinkel I, Hyung Kim J, et al. Efficacy of the adjuvanted recombinant zoster vaccine (RZV) by sex, geographic region, and geographic ancestry/ethnicity: a post-hoc analysis of the ZOE-50 and ZOE-70 randomized trials. *Vaccine* 2019;37:6262–7.
- [36] Xu C, Wang Z, Su X, Da M, Yang Z, Duan W, et al. Association between leucocyte telomere length and cardiovascular disease in a large general population in the United States. *Sci Rep* 2020;10:80.
- [37] Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 2014;349:g4227.
- [38] Zgibor JC, Ye L, Boudreau RM, Conroy MB, Vander Bilt J, Rodgers EA, et al. Community-based healthy aging interventions for older adults with arthritis and multimorbidity. *J Community Health* 2017;42:390–9.
- [39] Dilas LT, Icin T, Paro JN, Bajkin I. [Autoimmune thyroid disease and other non-endocrine autoimmune diseases]. *Med Pregl* 2011;64:183–7.
- [40] Lindstrom TM, Robinson WH. Rheumatoid arthritis: a role for immunosenescence? *J Am Geriatr Soc* 2010;58:1565–75.
- [41] Jagger A, Shimojima Y, Goronzy JJ, Weyand CM. Regulatory T cells and the immune aging process: a mini-review. *Gerontology* 2014;60:130–7.
- [42] Onyema OO, Decoster L, Njemini R, Forti LN, Bautmans I, De Waele M, et al. Shifts in subsets of CD8+ T-cells as evidence of immunosenescence in patients with cancers affecting the lungs: an observational case-control study. *BMC Canc* 2015;15:1016.
- [43] Kamphorst AO, Wieland A, Nasti T, Yang S, Zhang R, Barber DL, et al. Rescue of exhausted CD8 T cells by PD-1-targeted therapies is CD28-dependent. *Science* 2017;355:1423–7.
- [44] Sagiv A, Burton DG, Moshayev Z, Vadai E, Wensveen F, Bendor S, et al. NKG2D ligands mediate immunosurveillance of senescent cells. *Ageing* 2016;8:328–44.
- [45] Pereira BI, Devine OP, Vukmanovic-Stejic M, Chambers ES, Subramanian P, Patel N, et al. Senescent cells evade immune clearance via HLA-E-mediated NK and CD8(+) T cell inhibition. *Nat Commun* 2019;10:2387.

- [46] Tartour E, Gey A, Sastre-Garau X, Pannetier C, Mosseri V, Kourilsky P, et al. Analysis of interleukin 6 gene expression in cervical neoplasia using a quantitative polymerase chain reaction assay: evidence for enhanced interleukin 6 gene expression in invasive carcinoma. *Cancer Res* 1994;54:6243–8.
- [47] Tartour E, Dorval T, Mosseri V, Deneux L, Mathiot C, Brailly H, et al. Serum interleukin 6 and C-reactive protein levels correlate with resistance to IL-2 therapy and poor survival in melanoma patients. *Br J Cancer* 1994;69:911–3.
- [48] Hui E, Cheung J, Zhu J, Su X, Taylor MJ, Wallweber HA, et al. T cell costimulatory receptor CD28 is a primary target for PD-1-mediated inhibition. *Science* 2017;355:1428–33.
- [49] Baitsch L, Baumgaertner P, Devevre E, Raghav SK, Legat A, Barba L, et al. Exhaustion of tumor-specific CD8(+) T cells in metastases from melanoma patients. *J Clin Invest* 2011;121:2350–60.
- [50] FDA. Hematology/oncology (cancer) approvals & safety notifications. <https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications/>; 2020. [accessed 10 February 2020].
- [51] Xin Yu J, Hodge JP, Oliva C, Neftelinov ST, Hubbard-Lucey VM, Tang J. Trends in clinical development for PD-1/PD-L1 inhibitors. *Nat Rev Drug Discov* 2020;19:163–4.
- [52] Granier C, De Guillebon E, Blanc C, Roussel H, Badoual C, Colin E, et al. Mechanisms of action and rationale for the use of checkpoint inhibitors in cancer. *ESMO Open* 2017;2:e000213.
- [53] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1116–27.
- [54] Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leigh NB, Ahn MJ, et al. Five-year overall survival for patients with advanced NonSmall-cell lung cancer treated with pembrolizumab: results from the phase I KEYNOTE-001 study. *J Clin Oncol* 2019;37:2518–27.
- [55] De Guillebon E, Dardenne A, Saldmann A, Segulier S, Tran T, Paolini L, et al. Beyond the concept of cold and hot tumors for the development of novel predictive biomarkers and the rational design of immunotherapy combination. *Int J Cancer* 2020;147:1509–18.
- [56] Granier C, Dariane C, Combe P, Verkarre V, Urien S, Badoual C, et al. Tim-3 expression on tumor-infiltrating PD-1(+)CD8(+) T cells correlates with poor clinical outcome in renal cell carcinoma. *Cancer Res* 2017;77:1075–82.
- [57] Nizard M, Roussel H, Diniz MO, Karaki S, Tran T, Voron T, et al. Induction of resident memory T cells enhances the efficacy of cancer vaccine. *Nat Commun* 2017;8:15221.
- [58] Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin* 2020;70:86–104.
- [59] Urwyler P, Earnshaw I, Bermudez M, Perucha E, Wu W, Ryan S, et al. Mechanisms of checkpoint inhibition induced adverse events. *Clin Exp Immunol* 2020;200:141–54.
- [60] Canoui-Poitrine F, Lievre A, Dayde F, Lopez-Trabada-Ataz D, Baumgaertner I, Dubreuil O, et al. Inclusion of older patients with cancer in clinical trials: the SAGE prospective multicenter cohort survey. *Oncologist* 2019;24:e1351–9.
- [61] Hamaker ME, Vos AG, Smorenburg CH, de Rooij SE, van Munster BC. The value of geriatric assessments in predicting treatment tolerance and all-cause mortality in older patients with cancer. *Oncologist* 2012;17:1439–49.
- [62] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32:2595–603.
- [63] Pamoukdjian F, Liuu E, Caillet P, Herbaud S, Gisselbrecht M, Poisson J, et al. How to optimize cancer treatment in older patients: an overview of available geriatric tools. *Am J Clin Oncol* 2019;42:109–16.
- [64] Nishijima TF, Muss HB, Shachar SS, Moschos SJ. Comparison of efficacy of immune checkpoint inhibitors (ICIs) between younger and older patients: a systematic review and meta-analysis. *Cancer Treat Rev* 2016;45:30–7.
- [65] Daste A, Domblides C, Gross-Goupil M, Chakiba C, Quivy A, Cochin V, et al. Immune checkpoint inhibitors and elderly people: a review. *Eur J Cancer* 2017;82:155–66.
- [66] Elias R, Giobbie-Hurder A, McCleary NJ, Ott P, Hodi FS, Rahma O. Efficacy of PD-1 & PD-L1 inhibitors in older adults: a meta-analysis. *J Immunother Cancer* 2018;6:26.
- [67] Ferrara R, Mezquita L, Auclin E, Chaput N, Besse B. Immunosenescence and immunecheckpoint inhibitors in non-small cell lung cancer patients: does age really matter? *Cancer Treat Rev* 2017;60:60–8.
- [68] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
- [69] Herin H, Aspeslagh S, Castanon E, Dyeve V, Marabelle A, Varga A, et al. Immunotherapy phase I trials in patients Older than 70 years with advanced solid tumours. *Eur J Cancer* 2018;95:68–74.
- [70] Elkrief A, Richard C, Malo J, Cvetkovic L, Florescu M, Blais N, et al. Efficacy of immune checkpoint inhibitors in older patients with non-small cell lung cancer: real-world data from multicentric cohorts in Canada and France. *J Geriatr Oncol* 2020;11:802–6.
- [71] Landre T, Taleb C, Nicolas P, Des Guetz G. Is there a clinical benefit of anti-PD-1 in patients older than 75 years with previously treated solid tumour. *J Clin Oncol* 2016;34:3070.
- [72] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–39.
- [73] Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123–35.
- [74] Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378:1277–90.
- [75] Ferris RL, Blumenschein Jr G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;375:1856–67.
- [76] Gettinger S, Rizvi NA, Chow LQ, Borghaei H, Brahmer J, Ready N, et al. Nivolumab monotherapy for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2016;34:2980–7.
- [77] Spigel DR, McCleod M, Jotte RM, Einhorn L, Horn L, Waterhouse DM, et al. Safety, efficacy, and patient-reported health-related quality of life and symptom burden with nivolumab in patients with advanced non-small cell lung cancer, including patients aged 70 Years or older or with poor performance status (CheckMate 153). *J Thorac Oncol* 2019;14:1628–39.
- [78] Grossi F, Crino L, Logroscino A, Canova S, Delmonte A, Melotti B, et al. Use of nivolumab in elderly patients with advanced squamous non-small-cell lung cancer: results from the Italian cohort of an expanded access programme. *Eur J Cancer* 2018;100:126–34.
- [79] Betof AS, Nipp RD, Giobbie-Hurder A, Johnpulle RAN, Rubin K, Rubinstein SM, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. *Oncol* 2017;22:963–71.

- [80] Rai R, McQuade J, Wang D, Park J, Nahar K, Sosman J, et al. Safety and efficacy of anti-PD-1 antibodies in elderly patients with metastatic melanoma. *Ann Oncol* 2016;27:vi379–400.
- [81] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–30.
- [82] Chiarion Sileni V, Pigozzo J, Ascierto PA, Grimaldi AM, Maio M, Di Guardo L, et al. Efficacy and safety of ipilimumab in elderly patients with pretreated advanced melanoma treated at Italian centres through the expanded access programme. *J Exp Clin Cancer Res* 2014;33:30.
- [83] Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2017;18:1483–92.
- [84] Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017;376:1015–26.
- [85] Johnpulle RA, Conry RM, Sosman JA, Puzanov I, Johnson DB. Responses to immune checkpoint inhibitors in nonagenarians. *Oncol Immunology* 2016;5:e1234572.
- [86] Kugel 3rd CH, Douglass SM, Webster MR, Kaur A, Liu Q, Yin X, 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;24:5347–56.
- [87] Ibrahim T, Mateus C, Baz M, Robert C. Older melanoma patients aged 75 and above retain responsiveness to anti-PD1 therapy: results of a retrospective single-institution cohort study. *Cancer Immunol Immunother* 2018;67:1571–8.
- [88] Pasquini M, Locke F, Herrera A, Siddiqi T, Ghobadi A, Komanduri K, et al. Post-marketing use Outcomes of an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, axicabtagene ciloleucel (Axi-Cel), for the treatment of large B cell lymphoma (LBCL) in the United States (US). *Blood* 2019;134:764.
- [89] Bouchlaka MN, Murphy WJ. Impact of aging in cancer immunotherapy: the importance of using accurate preclinical models. *Oncol Immunology* 2013;2:e27186.
- [90] Friedman C, Horvat T, Minehart J, Panageas KS, Callahan M, Chapman P. Efficacy and safety of checkpoint blockade for treatment of advanced melanoma (mel) in patients (pts) age 80 and older (80+). *J Clin Oncol* 2016;34:10009.
- [91] Spigel D, Schwartzberg L, Waterhouse D, Chandler J, Hussein M, Jotte R, et al. Is nivolumab safe and effective in elderly and PS3 patients with non-small cell lung cancer (NSCLC)? Results of CheckMate 153. *J Thorac Oncol* 2017;12:S1287–8.
- [92] Elias R, Karantanos T, Sira E, Hartshorn KL. Immunotherapy comes of age: immune aging & checkpoint inhibitors. *J Geriatr Oncol* 2017;8:229–35.
- [93] Friedmann C, Horvat T, Minehart J, Panageas K, Callahan M, Chapman P, et al. Efficacy and safety of checkpoint blockade for treatment of advanced melanoma (mel) in patients (pts) age 80 and older (80+). in ASCO. *J Clin Oncol* 2016;34:10009.
- [94] Champiat S, Derclé L, Ammari S, Massard C, Hollebecque A, Postel-Vinay S, et al. Hyperprogressive disease (HPD) is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. *Clin Cancer Res* 2017;23:1920–8.
- [95] Ratner L, Waldmann TA, Janakiram M, Brammer JE. Rapid progression of adult T-cell leukemia-lymphoma after PD-1 inhibitor therapy. *N Engl J Med* 2018;378:1947–8.
- [96] van Holstein Y, Kapiteijn E, Bastiaannet E, van den Bos F, Portielje J, de Glas NA. Efficacy and adverse events of immunotherapy with checkpoint inhibitors in older patients with cancer. *Drugs Aging* 2019;36:927–38.
- [97] Duggal NA, Niemiro G, Harridge SDR, Simpson RJ, Lord JM. Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity? *Nat Rev Immunol* 2019;19:563–72.
- [98] Babu H, Ambikan AT, Gabriel EE, Svensson Akusjarvi S, Palaniappan AN, Sundaraj V, et al. Systemic inflammation and the increased risk of inflamm-aging and age-associated diseases in people living with HIV on long term suppressive antiretroviral therapy. *Front Immunol* 2019;10:1965.
- [99] Corral de la Fuente EEABG, Saavedra Serrano C, Olmedo García ME, Martín Huertas R, Serrano Domingo JJ, Albarrán Artahona V, et al. Benefit of immunotherapy (IT) in advanced non-small cell lung cancer (NSCLC) in elderly patients (EP). *Ann Oncol* 2019;30:1161–2.