Safety and efficacy of immunotherapy according to the age threshold of 80 years

Soraya Mebarki, Frédéric Pamoukdjian, Monica Pierro, Johanne Poisson, Capucine Baldini, Widad Lahlou, Julien Taieb, Elizabeth Fabre, Florence Canoui-Poitrine, Stéphane Oudard, et al.

Safety and efficacy of immunotherapy according to the age threshold of 80 years

Authors:

Soraya Mebarki[1, *], Frédéric Pamoukdjian[2, 3, *], Monica Pierro[1], Johanne Poisson[1, 4], Capucine Baldini[5], Widad Lahlou[5], Julien Taieb[6], Elizabeth Fabre[7], Florence Canoui-Poitrine[8,9,], Stéphane Oudard [7], Elena Paillaud[1, 9]

Affiliations:

1. AP-HP, Paris Cancer Institute CARPEM, Europeen Hospital Georges Pompidou, Department of geriatrics, F-75015 Paris, France

2 APHP, Hôpital Avicenne, Service de médecine gériatrique, Bobigny 93000, France.

3 Université Sorbonne Paris Nord, Inserm UMR_S942, Cardiovascular Markers in Stressed Conditions, MASCOT, Bobigny 93000, France.

4 Centre de recherche sur l'inflammation, Inserm UMR 1149, 46 rue Henri-Huchard, 75018 Paris, France.

5 Drug Development Department, Gustave Roussy, Villejuif 94800, France

6 APHP, Paris Cancer Institute CARPEM, European Hospital Georges Pompidou, Digestive Oncology Department, F-75015, Paris, France.

7 APHP, Paris Cancer Institute CARPEM, European Hospital Georges Pompidou, Department of Oncology, F-75015, Paris, France.

8 AP-HP, Henri-Mondor Hospital, Public Health and Clinical Research Unit (URC-Mondor), F-94010, Creteil, France.

9 Université Paris-Est Creteil, IMRB, Inserm U955, Clinical, Epidemiology and Ageing, F-94000, Creteil, France

* These authors contributed equally to this work

Correspondence:

Frédéric Pamoukdjian, M.D., Ph.D.

APHP, Hôpital Avicenne, Service de médecine gériatrique, 125 rue de Stalingrad, 93000 Bobigny, France.

Tel: +33 (0)1 48 95 70 35

Abstract (350 words):

Background: safety of immune-checkpoint inhibitors (ICIs) remains unclear among ~~older~~ patients with advanced cancer aged 80 years and over. We aimed to assess safety and efficacy of ICIs among patients with advanced cancer and to compare them among those < 80 and those ≥ 80 years old.

Methods: A single-centre retrospective observational cohort study comparing patients < 80 and ≥ 80 years old, with matching on the cancer site (lung *vs* others) and the participation in a clinical trial. Primary endpoint: grade ≥ 2 toxicity during the first three months of ICIs. Secondary endpoints: efficacy of ICIs including RECIST 1.1 criteria, progression free survival (PFS) and overall survival (OS).

Results: 210 consecutive patients, mean age: 66.5 ± 16.8; 20% aged ≥ 80 years; 75% male; 97% ECOG-PS ≤ 2; 78% G8-index ≤ 14/17; 80% lung or kidney cancer; and 97% metastatic cancer. Distribution of ICIs (Nivolumab 81%, Pembrolizumab 18% or Atezolizumab 1%) did not differ significantly between the two groups. The grade ≥ 2 toxicity rate was of 68%.

Compared to patients < 80 years old, patients ≥ 80 years old had a more significant ($P < 0.05$) proportion of grade ≥ 2 non-hematological toxicities (64% *vs* 45%): rash (14% *vs* 4%), arthralgia (7.1% *vs* 0.6%), colitis (4.7% *vs* 0.6%), cytolysis (7.1% *vs* 1.2%), gastrointestinal bleeding (2.4% *vs* 0%), onycholysis (2.4% *vs* 0%), oral mucositis (2.4% *vs* 0%), psoriasis (2.4% *vs* 0%) or other skin toxicities (25% *vs* 3%). Efficacy among patients ≥ 80 and < 80 years old was comparable: Complete response rate (2.5% *vs* 2.0%); Partial response rate (10.5% *vs* 10.0%); Stable disease rate (21.0% *vs* 23.0%); Progression disease rate (66.0% *vs* 65.0%); median PFS (5.70 [3.70-10.7] *vs* 4.20 [3.12-8.21]; $P = 0.69$); and median OS (13.0 [7.60-20.8] *vs* 16.4 [11.5-24.0]; $P = 0.13$).

Conclusion: Except for non-hematological toxicities, safety and efficacy were comparable among patients ≥ 80 and < 80 years old with advanced cancer and treated with ICIs. Additional studies using a standardized geriatric assessment are needed to assess safety and efficacy of ICIs among the oldest patients with advanced cancer.

Key word:

Immune checkpoint inhibitors; Immune-related adverse events; Efficacy; Metastatic cancer; Aged, 80 and over; Sex-specific differences

INTRODUCTION

In recent years, immunotherapies including immune checkpoint inhibitors (ICI) targeting PD-1/PD-L1, alone or in combination with chemotherapy have drastically changed the landscape of cancer treatment and the prognosis for many solid and hematological malignancies [1–3]. While older adults aged 65 and over account for two-thirds of newly diagnosed cancer, they are often excluded from clinical trials [4,5], and immunotherapy is no exception. Data from evidence-based-medicine are thus lacking in older adults with cancer, especially for the oldest ones.

Interestingly, in a recent meta-analysis of RCTs including 5458 patients with advanced cancer (lung, kidney, head and neck or melanoma) treated with ICIs and with 42% aged 65 and over, the authors found no significant differences in terms of overall survival (OS) and progression free survival (PFS) according to the age: pooled hazard ratios for OS and PFS was of 0.64/0.68 and 0.74/0.73 for adults < 65 years and ≥ 65 years respectively [6]. The pooled results from RCTs regarding the benefit of ICIs on OS in cancer patients aged 75 and over were also confirmed in another meta-analysis with no significant differences with younger patients [7]. In terms of safety, the ICI-related toxicity was estimated in a meta-analysis of RCTs including 15370 participants with various advanced cancers. Overall, the pooled incidence of any grade 1-5 toxicity ranged between 54% and 76% [8]. More recently, a meta-analysis of observational studies including specifically 5524 older patients aged 65 and over, with various advanced cancers and treated with ICIs, the authors found that the pooled rates of any grade 1-5 toxicity ranged between 5.3% (cytolysis) and 7.6% (diarrhea) [9].

To date, in terms of safety, we lack of sufficient data regarding specifically the oldest patients aged 80 and over with advanced cancers and treated with ICIs. For example, in a recent multicenter retrospective study including 928 older patients with a mean age of 80.3 years and

with various advanced cancers treated with single-agent ICIs, the authors reported a rate of any grade 1-5 toxicity of 41.3% and a rate of grade ≥ 3 toxicity of 12.2% [10]. In this study, there were no significant differences in the rate of any grade toxicity among the age groups < 85; 85-89; and ≥ 90 years.

Here, we aimed to assess safety and efficacy of the use of ICIs in older patients with various advanced cancers and to compare them among those < 80 years and those ≥ 80 years.

METHODS

We followed the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology method (STROBE) for the reporting of observational epidemiological studies [11].

Study design and patients

The IM-AGE ("IMmunothérapie chez le sujet AGE") was a single-centre retrospective observational cohort study comparing patients < 80 and ≥ 80 years old, with matching of on the type of cancer site (lung *vs* other sites) and participation in a randomized clinical trial (RCT).

All patients with a diagnosis of cancer confirmed histologically and treated (≥ 1 cycle) with an immune therapy by immune checkpoint inhibitor (ICI) regardless nivolumab, atezolizumab, or pembrolizumab, were consecutively included between April 1 2015 and April 1 2019 in the Georges Pompidou European Hospital.

Oral informed consent was obtained from the patients before inclusion.

The inclusion date was the date of the first perfusion of ICI.

The study was approved by the local ethics committee (CERAPHP; reference: 2021-07-10).

Data collection

At the time of the first inclusion, demographic and lifestyle data including age, sex, and smoking status (active, former or never) were recorded.

Cancer-related data was: site (lung *vs* other sites: kidney, bladder, head and neck, mesothelioma, colon, or anus), extension (locally advanced or metastatic), the presence of brain metastases, inclusion in a RCT, the Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and the PDL-1 expression (0, < 1, 1-10, 11-50 or > 50%).

Immune checkpoint inhibitor therapy data included single-agent therapy (yes/no), the regimens (atezolizumab, nivolumab or pembrolizumab), the line of treatment, and the number of perfusions.

Covariates were retrospectively retrieved from medical records as follows: the G8-index frailty screening tool which is considered as abnormal if ≤ 14/17 [12]; the Charlson's comorbidity index as continuous variable [13]; polymedication defined as ≥ 5 drugs a day [14]; the use of antibiotics or proton pomp inhibitors during the study follow-up; and nutrition parameters as continuous variables (albumin level (g/L), neutrophil cell count (G/L), lymphocyte cell count (G/L), and the neutrophil to lymphocyte ratio).

Endpoints

The primary endpoint was the occurrence of grade ≥ 2 toxicity (CTCAE V.4) during the first three months of immune therapy. Patients were followed every 2-3 weeks depending on the type of tumor up to the end of treatment or up to death.

Secondary enpoints were 1) the immune therapy efficacy compared to baseline using RECIST 1.1 criteria with the last CT-scan during or before stopping immune therapy (complete response: CR, partial response: PR, stable disease: SD, progression disease: PD). According to the RECIST criteria, overall response (OR) was defined as the number of complete response + partial response; and disease control (DC) was defined as the number of CR + SD + PR; 2) the progression free survival (PFS); and 3) the overall survival (OS). Vital status was determined by calling patients or their families, or from medical records

Statistical analysis

Assuming a grade ≥ 2 toxicity rate of 50% in patients ≥ 80 years old and of 25% in patients < 80 years old, we included the patients according to a ratio of 1/4 to detect a significant difference as follows: 42 patients ≥ 80 years old, and 166 patients < 80 years old. Patients

were matched for cancer site (lung vs others) and for inclusion in a RCT to take into account their potential random effect.

Categorical variables were described as numbers (%) and quantitative variables were described as a median ± interquartile range (IQR) (min-max).

Patients ≥ 80 and < 80 years old were compared using a univariate mixed logistic regression with “cancer site” and “inclusion in a RCT” variables as random effect. Due to a significant difference regarding grade ≥ 2 non-hematological toxicities between the two groups, we then compared patients according to the grade ≥ 2 non-hematological status using a univariate mixed logistic regression with the same variables as random effect.

Median progression free survival (PFS) and median overall survival (OS) were compared between the two groups using the log-rank test.

Graphically, all grade ≥ 2 non-hematological toxicities were plotted according to the age group (≥ 80 or < 80 years old) using a pyramid plot. Median PFS and OS curves according to the age group were determined using the Kaplan-Meier method.

All the tests were two-sided, and the threshold for statistical significance was set at a *P* value of less than 5%. The data was analysed using R statistical software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

By April 1 2019, 210 consecutive patients with a locally advanced or metastatic cancer and treated with at least 1 cycle of immune checkpoint inhibitor were selected in this study. Overall, the median time of follow-up was 28.4 months [Q1-Q3: 9.0-77.0].

The median age ± IQR was 66.5 ± 16.8 years. The study population included 20% (42/210) of patients ≥ 80 years old. Most patients were male (75%, 157/210) with a lung (45%, 95/210) or kidney cancer (35%, 74/210) at a metastatic stage (97%, 204/210), with a PDL-1 expression > 50% (57%, 21/37), an ECOG-PS ≤ 2 (97%, 201/208), and were former smoking (47%, 61/120). Abnormal G8-index (≤ 14/17) concerned 78% (164/210) of the patients. Immune checkpoint inhibitors were mainly used in single-agent therapy (98.5%, 207/210), and were distributed as follows: Nivolumab (81%, 170/210), Pembrolizumab (18%, 37/210), and Atezolizumab (1%, 3/210). Whether in the ≥ 80 or < 80 years old group, the distribution of ICIs according to the cancer site (lung *vs* other sites) was not significantly different ($P \geq 0.05$).

Comparison of patients according to exposure to age group

Compared to patients < 80 years old and taking into account the random effect of "lung cancer" and "RCT" variables, patients ≥ 80 years old were more significantly treated with pembrolizumab or atezolizumab, with a more significant proportion of abnormal G8-index and polymedication, a significant higher Charlson's comorbidity index, and a significant lower value of lymphocyte cell count (Table 1).

Immune therapy-related toxicity

All grade ≥ 2 toxicity rate was 68% (143/210). There were no significant differences among all grade ≥ 2 toxicities between patients ≥ 80 and < 80 years old (Table 2). In stratified analysis, patients ≥ 80 years old had a more significant ($P < 0.05$) proportion of grade ≥ 2

non-hematological toxicities (64% *vs* 45%). Grade ≥ 2 non-hematological toxicity rates ranged between 1% (alopecia or cholestasis) and 43% (asthenia) (see supplementary Table 1). Exposed patients had a more significant proportion of grade ≥ 2 rash (14% *vs* 4%), arthralgia (7.1% *vs* 0.6%), colitis (4.7% *vs* 0.6%), cytolysis (7.1% *vs* 1.2%), gastrointestinal bleeding (2.4% *vs* 0%), onycholysis (2.4% *vs* 0%), oral mucositis (2.4% *vs* 0%), psoriasis (2.4% *vs* 0%) or other skin toxicities (25% *vs* 3%) (Figure 1). Compared to grade < 2 non-hematological toxicities, patients with grade ≥ 2 non-hematological toxicities were significantly older men, and were exclusively metastatic (Table 1). Supplementary Figure 1 shows a comparison of grade ≥ 2 non-hematological toxicities among men and women. While men exhibited more significantly rash than women, women exhibited more significantly alopecia.

Immune therapy efficacy and survivals

According to the RECIST 1.1 criteria, there were no significant differences between patients ≥ 80 and patients < 80 years old among CR, PR, SD, PD, OR and DS (Table 2). There were also no significant differences according to the median PFS (≥ 80 years: 5.70 [3.70-10.7]; < 80 years: 4.20 [3.12-8.21]; $P = 0.69$) and median OS (≥ 80 years: 13.0 [7.60-20.8]; < 80 years: 16.4 [11.5-24.0]; $P = 0.13$) during the study follow-up (Figure 2).

DISCUSSION

In this observational study of 210 consecutive patients with cancer mainly lung or kidney at a metastatic stage and treated by immune check point inhibitors (Nivolumab, Pembrolizumab or Atezolizumab) mainly in first line of single-agent, grade ≥ 2 toxicity rate was not significantly different among patients ≥ 80 and patients < 80 years old. However, in subgroup analysis, while hematological toxicities did not differ between both groups, compared to patients < 80 years, patients ≥ 80 years experienced a more frequently grade ≥ 2 non-hematological toxicity, especially skin and appendages, arthralgia, colitis, cytolysis or gastrointestinal bleeding. Progression free survival (PFS) and overall survival (OS) were not significantly different among patients ≥ 80 and < 80 years old.

Despite the retrospective design, the main strength is the methodology used which did make possible a stringent comparison between the oldest and younger patients receiving ICIs. Particularly, accounting for the random effect of cancer site and the inclusion of patients in a RCT, patients with grade ≥ 2 non-hematological toxicity were not only and significantly the oldest (≥ 80 years) but also were significantly men with an exclusively metastatic cancer. Here, we found that the grade ≥ 2 non-hematological toxicity rate was greater than previous studies [10]. A hypothesis could be that in spite of the absence of a significant difference, these patients were more frequently drawn from clinical trials with a closer monitoring. Contrary to a recent meta-analysis, regarding non-hematological toxicities, we found a significant sex difference [15]. However, this sex dimorphism in toxicity was recently highlighted for anticancer immunotherapy including complex interactions between immune functions, hormones and genes [16]. Biologically, sex differences concern both innate and adaptative immune responses, and among immunotherapies, women seem to have a better response to those that stimulate immunity (e.g., vaccines), while men seem to have a better response to those that repress immunity (e.g., ICIs) [17]. Genomic expression and/or

circulating hormones (sex steroids) in both sex contribute to these differences [18]. Regarding ICIs, while some studies found that men exhibited more frequently any grade ICI-related toxicity [19], others found the opposite [20]. This discrepancy could be explained by the nature of toxicity observed, typically autoimmune *vs* non autoimmune adverse events. Thus, interacting with PD1/PDL1 pathways, it was shown that circulating estrogens levels could lead to greater autoimmune adverse events in women than in men [21]. Moreover, a recent study showed an inverse association between the longitudinal changes of the LH/FSH ratio and PFS during immunotherapy in 22 patients (men and women) with metastatic renal cell cancer [22]. As such in our study, among non-hematological toxicities, women were significantly more affected by alopecia (a typical autoimmune adverse event), while men exhibited significantly more skin rash (a typical non autoimmune adverse event) [23]. Another finding of our study is that comparing with locally-advanced extension, the metastatic extension was significantly associated with non-hematological toxicities. This study result could be explained by the balanced interaction between cancer growing and anti-tumor immunity [24]. Indeed, with cancer growing, this interaction relies on tumor-intrinsic factors (e.g., release of PDL-1+ extracellular vesticles or recruitment of immune cells) and tumor-extrinsic factors (e.g., systemic inflammation) [24]. By dysregulating this homeostasis, ICIs could lead to a loss of self-tolerance and a circulating auto-immunity, leading to immune-related adverse events, especially since the tumor mass is important [24].

Also, as previously reported in the literature, we confirm the efficacy of ICIs among patients $\geq$ 80 years which resulted in no significant differences in terms of response rates, disease control rates, PFS or OS as compared for patients < 80 years during the study follow-up [7,10].

Although our older patients were selected, based on our study, except for non-hematological toxicities which resulted in no fatal issue, we confirm the safety and efficacy of

ICIs which were comparable among patients aged ≥ 80 years and < 80 years with advanced cancer. To date, there are still few studies using geriatric assessment among older adults with cancer and treated with ICIs [25]. Additional studies using a standardized geriatric assessment designed for older cancer patients are thus needed to provide a deep analysis of the use of ICIs in this vulnerable population [26].

CONCLUSION

Except for non-hematological toxicities, safety and efficacy were comparable among patients aged ≥ 80 years and < 80 years with advanced cancer and treated with ICIs. Additional studies using a standardized geriatric assessment are needed to assess safety and efficacy of ICIs among the oldest patients with advanced cancer.

REFERENCES

1. Duan J, Cui L, Zhao X, Bai H, Cai S, Wang G, et al. Use of Immunotherapy With Programmed Cell Death 1 vs Programmed Cell Death Ligand 1 Inhibitors in Patients With Cancer: A Systematic Review and Meta-analysis. JAMA Oncology. 1 mars 2020;6(3):375‑84.

2. Wang C, Qiao W, Jiang Y, Zhu M, Shao J, Wang T, et al. The landscape of immune checkpoint inhibitor plus chemotherapy versus immunotherapy for advanced non-small-cell lung cancer: A systematic review and meta-analysis. Journal of Cellular Physiology. 2020;235(5):4913‑27.

3. Kapoor S, Champion G, Basu A, Mariampillai A, Olnes MJ. Immune Therapies for Myelodysplastic Syndromes and Acute Myeloid Leukemia. Cancers. janv 2021;13(19):5026.

4. Pilleron S, Sarfati D, Janssen-Heijnen M, Vignat J, Ferlay J, Bray F, et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. Int J Cancer. 1 janv 2019;144(1):49‑58.

5. Canouï‐Poitrine F, Lièvre 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. The Oncologist. 2019;24(12):e1351‑9.

6. 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. 4 avr 2018;6:26.

7. Kasherman L, Siu DHW, Lee KWC, Lord S, Marschner I, Lewis CR, et al. Efficacy of immune checkpoint inhibitors in older adults with advanced stage cancers: A meta-analysis. Journal of Geriatric Oncology. avr 2020;11(3):508‑14.

8. Xu C, Chen Y-P, Du X-J, Liu J-Q, Huang C-L, Chen L, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ. 8 nov 2018;k4226.

9. Luciani A, Ghidini A, Dottorini L, Petrelli F. Safety and Effectiveness of Immune Checkpoint Inhibitors in Older Patients with Cancer: A Systematic Review of 48 Real-World Studies. Drugs Aging. déc 2021;38(12):1055‑65.

10. Nebhan CA, Cortellini A, Ma W, Ganta T, Song H, Ye F, et al. Clinical Outcomes and Toxic Effects of Single-Agent Immune Checkpoint Inhibitors Among Patients Aged 80 Years or Older With Cancer: A Multicenter International Cohort Study. JAMA Oncol. 1 déc 2021;7(12):1856‑61.

11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 16 oct 2007;4(10):e296.

12. Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for Vulnerability in Older Cancer Patients: The ONCODAGE Prospective Multicenter Cohort Study. PLOS ONE. 11 déc 2014;9(12):e115060.

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373‑83.

14. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. Journal of Clinical Epidemiology. sept 2012;65(9):989‑95.

15. Jing Y, Zhang Y, Wang J, Li K, Chen X, Heng J, et al. Association Between Sex and Immune-Related Adverse Events During Immune Checkpoint Inhibitor Therapy. J Natl Cancer Inst. 1 oct 2021;113(10):1396‑404.

16. Pala L, Conforti F. The effect of patient sex on the efficacy and safety of anticancer immunotherapy. Expert Opin Drug Saf. déc 2021;20(12):1535‑44.

17. Klein SL, Morgan R. The impact of sex and gender on immunotherapy outcomes. Biol Sex Differ. déc 2020;11(1):24.

18. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. oct 2016;16(10):626‑38.

19. Tsiouda T, Sardeli C, Porpodis K, Pilikidou M, Apostolidis G, Kyrka K, et al. Sex Differences and Adverse Effects between Chemotherapy and Immunotherapy for Non-Small Cell Lung Cancer. J Cancer. 5 mars 2020;11(11):3407‑15.

20. Duma N, Abdel-Ghani A, Yadav S, Hoversten KP, Reed CT, Sitek AN, et al. Sex Differences in Tolerability to Anti-Programmed Cell Death Protein 1 Therapy in Patients with Metastatic Melanoma and Non-Small Cell Lung Cancer: Are We All Equal? Oncologist. nov 2019;24(11):e1148‑55.

21. Wang C, Dehghani B, Li Y, Kaler LJ, Proctor T, Vandenbark AA, et al. Membrane Estrogen Receptor Regulates EAE Through Upregulation of Programmed Death 1,. J Immunol. 1 mars 2009;182(5):3294‑303.

22. Tulchiner G, Pichler R, Ulmer H, Staudacher N, Lindner AK, Brunner A, et al. Sex-specific hormone changes during immunotherapy and its influence on survival in metastatic renal cell carcinoma. Cancer Immunol Immunother. 2021;70(10):2805‑17.

23. Malviya N, Tattersall IW, Leventhal J, Alloo A. Cutaneous immune-related adverse events to checkpoint inhibitors. Clinics in Dermatology. nov 2020;38(6):660‑78.

24. Morad G, Helmink BA, Sharma P, Wargo JA. Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. Cell. 14 oct 2021;184(21):5309‑37.

25. Welaya K, Loh KP, Messing S, Szuba E, Magnuson A, Mohile SG, et al. Geriatric assessment and treatment outcomes in older adults with cancer receiving immune checkpoint inhibitors. J Geriatr Oncol. avr 2020;11(3):523‑8.

26. Paillaud E, Caillet P, Cudennec T, Pamoukdjian F, Fossey-Diaz V, Liuu E, et al.

DIALOG task force for definition of a geriatric minimum data set for clinical oncology research. European Journal of Cancer. 1 févr 2017;72:S114.

Tables

Table 1. Comparison of patients treated with immune checkpoint inhibitor therapy according to age group (≥ 80 years and < 80 years) and to grade ≥ 2 non-hematological toxicities

Table 2. Toxicity and efficacy of immune checkpoint inhibitor therapy

Figure legends

Figure 1. Comparison of grade ≥ 2 non-hematological toxicities (%) according to age group (≥ 80 years and < 80 years). * Significant *P* value at the threshold of 0.05

Figure 2. Progression free survival (A) and overall survival (B) in patients with immune checkpoint inhibitor therapy according to age group (≥ 80 years and < 80 years).

Table 1.

Variables	Available data	≥ 80 years	< 80 years	*P**	Grade ≥ 2 non-hematological toxicities	Grade < 2 non-hematological toxicities	*P**
		N=42 (%)	N=168 (%)		N = 103 (%)	N = 107 (%)	
Age (y)	210			**<0.0001**			
Median ± IQR (min-max)		82.0 ± 4.0 (80.0-93.0)	64.0 ± 12.0 (22.0-78.0)		68.0 ± 21.5 (33.0-91.0)	66.0 ± 12.5 (22.0-93.0)	0.19
≥ 80		-	-		27 (26)	15 (14)	**0.03**
Sex ratio (M/F)	210	32 (76)/10 (24)	125 (74)/43 (26)	0.81	85 (82.5)/18 (17.5)	72 (67)/35 (33)	**0.005**
Matched data (random effect):							
Lung cancer (yes)**	210	19 (45)	77 (46)	0.94	53 (51.5)	43 (40)	0.06
Inclusion in a RCT (yes)	210	5 (12)	20 (12)	1.00	16 (15.5)	9 (8)	0.05
Cancer extension	210			0.08			**0.01**
Locally-advanced		3 (7)	3 (2)		0 (0)	6 (6)	
Metastatic		39 (93)	165 (98)		103 (100)	101 (94)	
Brain metastases (yes)	116	0 (0)	30 (26)	0.40	18 (18)	12 (11)	0.17
PDL-1 expression (%)	37			0.09			0.30
0		0 (0)	2 (7)		0 (0)	2 (9.5)	
< 1		2 (22.5)	7 (25)		3 (19)	6 (28.5)	
1-10		2 (22.5)	0 (0)		2 (12.5)	0 (0)	
11-50		0 (0)	3 (11)		1 (6)	2 (9.5)	
> 50		5 (55.5)	16 (57)		10 (62.5)	11 (52.5)	
Immune checkpoint inhibitor therapy	210						
Single therapy (yes)		41 (98)	166 (99)	0.56	100 (97)	107 (100)	0.99
Regimens				**0.001**			0.28
Atezolizumab (yes)		3 (7)	0 (0)		2 (2)	1 (1)	
Nivolumab (yes)		29 (69)	141 (84)		87 (84.5)	83 (78)	
Pembrolizumab (yes)		10 (24)	27 (16)		14 (13.5)	23 (21)	
Line of treatment > 2 (yes)		15 (36)	39 (23)	0.10	30 (29)	24 (22)	0.08
N° of perfusion, median ± IQR (min-max)		7.0 ± 10.0 (1.0-37.0)	7.0 ± 12.0 (1.0-96.0)	0.47	8.0 ± 13.5 [5.0-18.5]	6.0 ± 11.0 [2.0-13.0]	0.07
Smoking status	130			0.87			0.08
Active		1 (25)	31 (25)		17 (16.5)	15 (14)	
Former		2 (50)	59 (47)		33 (32)	28 (26)	
Never		1 (25)	36 (28)		13 (13)	24 (22)	
G8 index ≤ 14/17 (yes)	210	39 (93)	125 (74)	**0.01**	82 ()	82 ()	0.61
ECOG-PS > 2 (yes)	208	2 (5)	5 (3)	0.56	1 (1)	6 (6)	0.08
Charlson's index, median ± IQR (min-max)	209	10.5 ± 2.0 (6.0-15.0)	8.0 ± 2.0 (2.0-13.0)	**<0.0001**	9.0 ± 3.0 (2.0-15.0)	8.0 ± 3.0 (2.0-14.0)	0.22

Medications							
Polymedication ≥ 5 drugs a day	210	29 (69)	64 (38)	**<0.001**	46 (45)	47 (44)	0.89
Antibiotics (yes)	210	9 (21)	48 (28.5)	0.35	31 (30)	26 (24)	0.36
Proton pomp inhibitors (yes)	208	23 (55)	74 (44.5)	0.24	49 (47.5)	48 (45)	0.67
Albumin level (g/L), median ± IQR (min-max)	195	36.0 ± 5.6 (22.0-44.0)	36.4 ± 10.0 (15.0-50.0)	0.48	36.0 ± 7.0 (16.0-50.0)	36.0 ± 11.1 (15.0-48.0)	0.36
Neutrophil (G/L), median ± IQR (min-max)	210	4.3 ± 2.4 (1.6-13.3)	4.6 ± 3.3 (0.8-15.5)	0.31	4.2 ± 3.3 (1.4-13.2)	4.6 ± 3.2 (0.8-15.5)	0.73
Lymphocyte (G/L), median ± IQR (min-max)	208	1.1 ± 0.5 (0.4-2.8)	1.4 ± 0.8 (0.3-4.7)	**0.005**	1.4 ± 0.7 (0.4-4.7)	1.3 ± 0.8 (0.3-3.9)	0.17
NLR, median ± IQR (min-max)	208	3.7 ± 2.4 (1.4-16.2)	3.2 ± 3.0 (0.8-22.0)	0.52	3.1 ± 2.6 (0.98-16.2)	3.6 ± 3.1 (0.80-22.0)	0.26

* *P* value for mixed logistic regression with “lung cancer” and “RCT” variables as random effect

** other cancer site: Kidney = 75; Bladder = 19; head and neck = 14; mesothelioma = 4; Colon = 1; anus = 1

Bold = significant *P* value at the threshold of 0.05

Table 2.

Outcomes	**≥ 80 years**	**< 80 years**	***P****
	N = 42	**N = 168**	
Grade ≥ 2 toxicity (n=210)	33 (78.5)	110 (65.5)	0.10
Hematological toxicity	6 (14)	34 (20)	0.38
Non-hematological toxicity	27 (64)	76 (45)	**0.03**
RECIST 1.1 criteria (n=159)			0.95
Complete response rate	1 (2.5)	2 (2.0)	
Partial response rate	4 (10.5)	12 (10.0)	
Stable disease rate	8 (21.0)	28 (23.0)	
Progression disease rate	25 (66.0)	79 (65.0)	
Overall response rate (n=159)	5 (13.0)	14 (11.5)	0.79
- First line of treatment (n=20)	2 (33.0)	5 (36.0)	0.91
Disease control rate (n=159)	13 (34.0)	42 (35.0)	0.96
- First line of treatment (n=20)	2 (33.0)	10 (71.0)	0.11

* *P* value for mixed logistic regression with lung cancer and RCTs variables as random effect.

Figure 1.

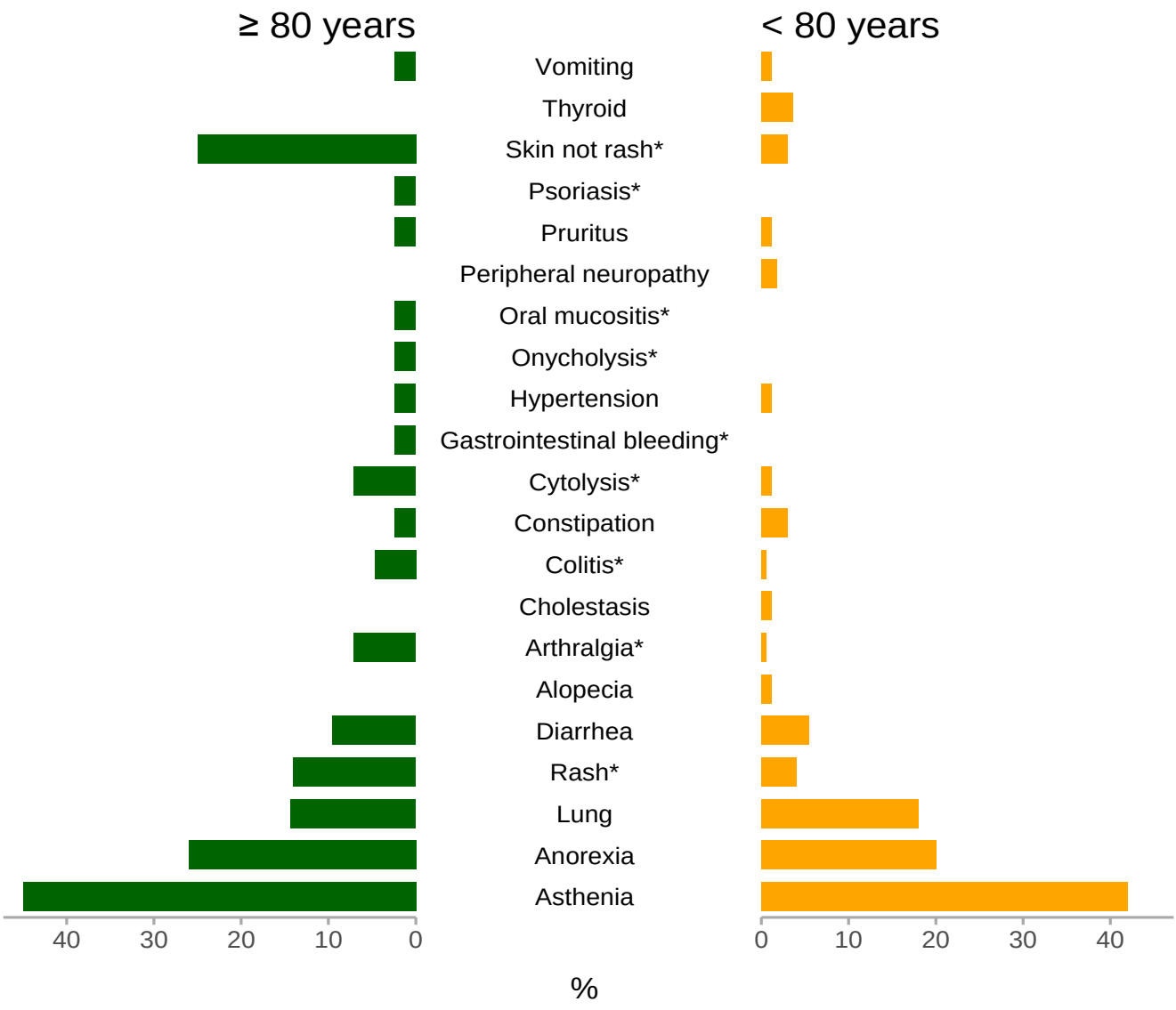
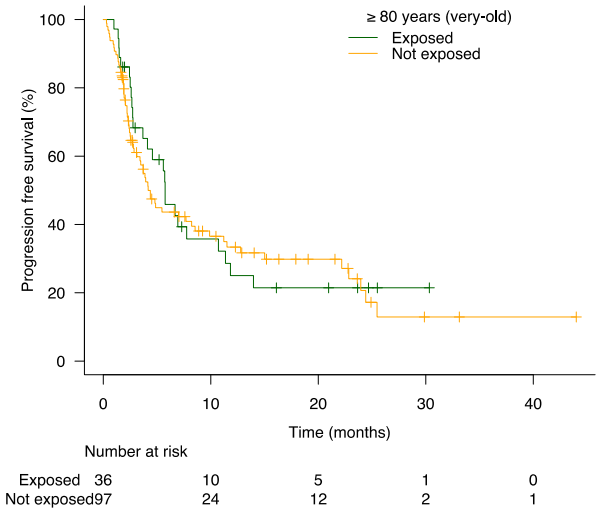
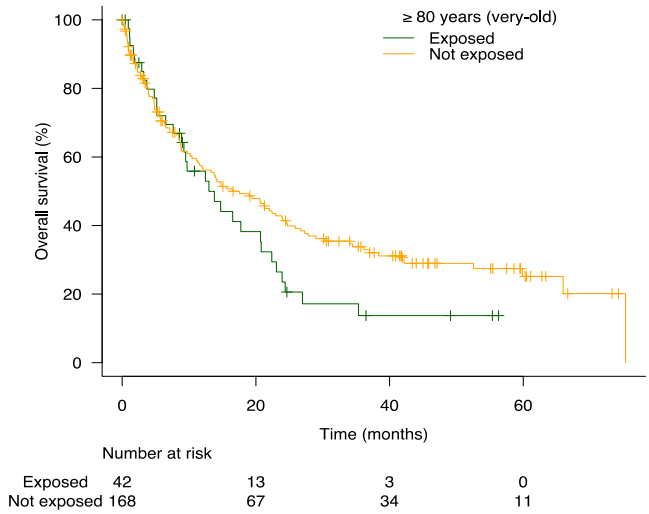

≥ 80 years
< 80 years
Vomiting
Thyroid
Skin not rash*
Psoriasis*
Pruritus
Peripheral neuropathy
Oral mucositis*
Onycholysis*
Hypertension
Gastrointestinal bleeding*
Cytolysis*
Constipation
Colitis*
Cholestasis
Arthralgia*
Alopecia
Diarrhea
Rash*
Lung
Anorexia
Asthenia
40
30
20
10
0
0
10
20
30
40
%

Figure 2.

A


≥ 80 years (very-old)
Exposed
Not exposed
Progression free survival (%)
100
80
60
40
20
0
0
10
20
30
40
Time (months)
Number at risk
Exposed 36 10 5 1 0
Not exposed 97 24 12 2 1

B


≥ 80 years (very-old)
Exposed
Not exposed
Overall survival (%)
100
80
60
40
20
0
0
20
40
60
Time (months)
Number at risk
Exposed 42 13 3 0
Not exposed 168 67 34 11

Supplementary table

Table S1. Number (%) of adverse events during immune checkpoint inhibitor therapy

Toxicity	G1	G2	G3	G4	≥ G2/total patient	(%)
Hematological						
Anemia	37	29	7	2	38/206	(18)
Thrombopenia	6	1	1	0	2/207	(1)
Non hematological						
Alopecia	3	2	0	0	2/207	(1)
Adrenal insufficiency	2	0	0	0	0/123	(0)
Anorexia	51	35	9	0	44/207	(21)
Arthralgia	10	4	0	0	4/207	(2)
Asthenia	88	67	21	1	89/207	(43)
Cholestasis	31	1	1	0	2/207	(1)
Colitis	1	0	3	0	3/207	(1.5)
Constipation	34	6	0	0	6/207	(3)
Cytolysis	17	2	3	0	5/207	(2.5)
Diabetes	1	0	0	0	0/102	(0)
Diarrhea	25	9	4	0	13/207	(6)
Epigastralgia	9	0	0	0	0/207	(0)
Epistaxis	7	0	0	0	0/207	(0)
Gastrointestinal bleeding	2	0	3	0	3/207	(1.5)
Hypertension	4	2	1	0	3/207	(1.5)
Hypocalcemia	6	0	0	0	0/165	(0)
Lung	45	31	5	0	36/209	(17)
Onycholysis	2	1	0	0	1/207	(0.5)
Oral mucositis	11	1	0	0	1/206	(0.5)
Pericarditis	3	0	0	0	0/165	(0)
Peripheral neuropathy	19	3	0	0	3/165	(2)
Proteinuria	1	0	0	0	0/206	(0)
Pruritus	13	3	0	0	3/207	(1.5)
Psoriasis	0	1	0	0	1/207	(0.5)
Rash	28	7	4	1	12/207	(6)
Skin not rash	23	6	0	0	6/165	(4)
Sub-occlusion	1	0	0	0	0/144	(0)
Thyroid	26	6	0	0	6/209	(3)
Vomiting	26	3	0	0	3/207	(1.5)
Weight gain	2	0	0	0	0/140	(0)

Supplementary Figure

Figure S1. Comparison of grade ≥ 2 non-hematological toxicities (%) according to sex.
*** Significant *P* value at the threshold of 0.05**