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Original Research

Older and younger patients treated with immune checkpoint inhibitors have similar outcomes in real-life setting

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Abstract ***Background:*** Age-related immune dysfunction might impair the efficacy of immune checkpoint inhibitors (ICIs) in older patients. We aimed to evaluate the impact of age on clinical outcomes and tolerance of ICIs in a real-life setting.
Methods: All patients receiving a single-agent ICI (cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] or programmed death(ligand)1 [PD(L)-1] inhibitors) for the standard treatment of a locally advanced or metastatic cancer were included in this retrospective multicentric series. The primary end-point was overall survival (OS). Progression-free survival (PFS) and

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immune-related adverse events (irAEs) were secondary end-points. The impact of age was assessed using the threshold of 70 years.

Results: A total of 410 patients were included, for 435 lines of treatment, including 150 lines (34%) given to patients aged 70 years or older. The primary tumour types were lung cancer (n = 304, 74%), melanoma (n = 79, 19%) and urologic cancer (n = 27, 7%). Most of the administered treatments were PD(L)-1 inhibitors (n = 356, 82%). Median follow-up reached 46 months in the CTLA-4 cohort, and 20 months in the PD(L)-1 cohort. In both treatment cohorts, age did not impact OS (respectively, HR = 0.82, 95% CI 0.5–1.4; log-rank P = 0.49 and HR = 0.9, 95% CI 0.7–1.1; log-rank P = 0.27) or PFS (HR = 0.7, 95% CI 0.4–1.1; log-rank P = 0.13 and HR = 0.9, 95% CI 0.7–1.1; log-rank P = 0.19). Grade 3–4 irAEs rates were not statistically different between older and younger patients (11% vs 12%, P = 0.87).

Conclusion: In a large real-world series of patients treated by ICI monotherapy, the long-term clinical outcomes were not statistically different between older or younger patients, with no increased immune-related toxicity.

1. Introduction

Immune checkpoint inhibitors (ICIs) such as anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti–programmed death(ligand)1 [PD(L)1] inhibitors have dramatically modified the therapeutic strategies in a variety of solid malignancies [1]. However, only a subset of patients derives a long-term benefit from these treatments. Apart from PD-L1 expression in lung cancer [2], we lack predictive biomarkers that could help to identify a subgroup of patients likely to benefit from ICIs and unlikely to experience immune toxicities. The safety profile of ICIs compares favourably to cytotoxic chemotherapies, with no known cumulative toxicity. ICIs therefore represent an attractive option for older patients. "Immunosenescence, defined as gradual remodelling and decline of immune functions associated not only with ageing but also with chronic inflammation and cancer, raises the concern of the efficacy and safety of ICIs in older patients. In the preclinical setting, age-related immune dysfunction has been shown to alter ICIs efficacy [3]. Our understanding of ICIs clinical activity in the elderly is limited by their underrepresentation in clinical trials and by the selection of fit older patients in these trials [4]. Available data from meta-analyses of randomized clinical trials did not identify an impact of age on ICIs efficacy nor tolerance [5–9]. A few real-life setting retrospective studies were also in favour of similar [10–14] or even better outcomes among older patients treated with ICIs [15,16].

We therefore conducted a large real-world retrospective analysis including patients from three French units who have received ICIs as a single agent in standard practice. We aimed to explore if age affected long-term outcomes (overall survival [OS] and progression-free survival [PFS]) and toxicity profile of ICIs.

2. Materials and methods

2.1. Setting and participants

Patients eligible in this series were adults aged ≥18 years with an advanced or metastatic malignant tumour who started a treatment with ICIs as single agent (CTLA-4 inhibitors [ipilimumab] or PD(L)-1 inhibitors [nivolumab, pembrolizumab, or atezolizumab]) administered in standard clinical practice in one of the sites of the University Hospital of Lyon, France. 'At the time of patients' treatment initiation, single-agent ICIs were approved in France for use in advanced-stage tumours. No ICI had been approved for use in adjuvant setting.' The study was authorized by the ethical review board of the Hospices Civils de Lyon. Patients did not receive any compensation for their participation.

2.2. Data collection

Data collection was performed retrospectively using a standardized data collection by two dermatologists (A.B. and M.P.M) and one medical oncologist (P.C.). Data collected included the following patient characteristics: age at treatment initiation, gender, history of autoimmune disease, Eastern Cooperative Oncology Group performance status, body mass index (BMI) and smoking habits (active smoker, never smoker or former smoker since at least one year) before treatment with ICIs. Disease characteristics included the following: tumour type and number of metastatic sites at treatment initiation. Treatment characteristics included the number of prior systemic treatments, type of ICI and concomitant use of systemic corticosteroids. The concomitant use of systemic corticosteroids was defined by a prescription of ≥20 mg of oral prednisone or

equivalent for more than 10 consecutive days within the period of ICI treatment.

The date of disease progression was determined by treating physicians according to standard practice. The progression had to be either clinical or radiological, and RECIST criteria 1.1 were used. iRECIST criteria were not considered in this study as they were not routinely used for all patients at the time they were treated with an ICI.

Immune adverse events (irAEs) included diarrhoea and colitis during ICI treatment, pneumonitis, cutaneous eruption, vitiligo, thyroid modifications, hepatitis, hypophysitis and other adverse events considered at least possibly immune related by the treating physician. We collected the date of onset of the adverse events and their severity according to National Cancer Institutes–Common Terminology Criteria for Adverse Events, version 4.0.

Clinical follow-up was scheduled every two or three weeks during treatment. Imaging follow-up was scheduled every two to three months, depending on tumour type and according to standard clinical practice.

2.3. Statistical analysis

The characteristics of patients in the two age groups were compared using two-tailed univariate analyses. Fisher exact test was used to compare binary or qualitative variables including the rates of irAEs according to age. Mann–Whitney test was used to compare quantitative variables.

Primary end-point was overall survival (OS). Secondary end-points were PFS and irAEs rate. OS was defined as the time from treatment initiation to death from any cause. PFS was defined as the time from treatment initiation to progressive disease or death from any cause, whichever came first. Survival probabilities were estimated using Kaplan–Meier method and compared between groups using two-tailed log-rank tests. Covariates, including age, were considered statistically associated with PFS or OS if the associated P value was less than 0.05. To assess the adjusted effect of age on OS and PFS, we used multivariate Cox proportional hazard models. All variables with a statistically significant impact on OS or PFS in univariate analysis plus age were included in the multivariate models.

All analyses were performed using R statistical software (R Foundation for Statistical Computing). Database follow-up was closed in July 2018. Data were rarely missing, and no data imputation was performed through the analyses.

3. Results

3.1. Patients and treatment baseline characteristics

Between January 2007 and October 2017, we included 410 patients in the study for a total of 435 lines of treatment, 285 (66%) in the "69 years or younger" cohort and 150 (34%) in the "70 years or older" cohort. The treatment was more frequently a PD(L)-1 inhibitor (n = 356, 82%), and less frequently a CTLA-4 inhibitor (n = 79, 18%). Three-hundred and four (74%) patients were treated for a non-small cell lung cancer (NSCLC) with only one ICI line per patient, 79 (19%) for a melanoma for a total of 104 lines of ICI. The remaining 27 patients (7%) were treated for a urologic cancer (Table 1).

Older patients were less likely to be active smokers and less likely to receive concomitant systemic corticosteroids (Table 1).

Median follow-up duration after the initiation of the ICI was 46 months (95% CI: 41-NA) among patients treated with a CTLA-4 inhibitor, and 20 months (95% CI: 17–23) among those treated with a PD(L)-1 inhibitor, with no significant impact of age on the length of follow-up.

3.2. Patients' outcomes according to age

Patients older than 70 years and receiving a CTLA-4 inhibitor had a 2-year OS rate of 30% (95% CI, 16–59) compared to 22% (95% CI, 13–37) if they were aged 69 years or younger (hazard ratio [HR] = 0.82, 95% CI: 0.5–1.4; log-rank P = 0.49, Table 2, Fig. 1A). The 6-month PFS rate reached 35% for older patients versus 10% for younger patients, but the overall difference in terms of PFS was not statistically significant (HR = 0.7, 95% CI: 0.4–1.1; log-rank P = 0.13, Table 2, Fig. 1B). The absence of statistically significant impact of age on OS and PFS was confirmed after adjustment on prognosis covariates (Table 2). Older patients treated with PD(L)-1 inhibitors had a 2-year OS rate of 29% versus 27% among younger patients (HR = 0.9, 95% CI: 0.7–1.1; log-rank P = 0.27, Table 3, Fig. 1C). The 6-month PFS rate reached 40% among older patients and 29% among younger patients (HR = 0.9, 95% CI: 0.7–1.1; log-rank P = 0.19, Table 3, Fig. 1D). Again, the OS and PFS differences according to age groups were not statistically significant in both unadjusted and adjusted analyses (Table 3).

3.3. Immune-related adverse events

The rate of irAEs was not statistically different between older and younger patients, reported, respectively, in 15 (71%) and 35 (60%) (P = 0.52) patients treated with CTLA-4 inhibitors, and in, respectively, 59 (46%) and 98 (43%) (P = 0.66) patients under PD(L)-1 inhibitors. Same results were observed when only grade $\geq$3 irAEs were considered, reported in 4 (19%) older patients and 16 (28%) younger patients treated with CTLA-4 inhibitors (P = 0.64), and in 12 (9%) older patients and 17 (7%) younger patients treated with PD(L)-1 inhibitors (P = 0.55). There was no significant difference in the

Table 1
Patient characteristics according to tumour type and age.

Variable	All tumours			Melanoma			Lung cancer			Urologic cancer		
	≤69 years (n = 285)	≥70 years (n = 150)	P	≤69 years (n = 71)	≥70 years (n = 33)	P	≤69 years (n = 201)	≥70 years (n = 103)	P	≤69 years (n = 13)	≥70 years (n = 14)	P
Age, years, median (25th-75th) *NA = 0*	61 (53–66)	75 (72–75)	<0.001	53 (46–64)	76 (74–80)	<0.001	62 (57–66)	75 (72–79)	<0.001	59 (57–65)	76 (73–80)	<0.001
Gender male (%) NA = 0	186 (65%)	109 (73%)	0.14	38 (53%)	23 (70%)	0.18	138 (69%)	79 (77%)	0.18	10 (77%)	7 (50%)	0.24
Treatment type (%) NA = 0												
CTLA-4 inhibitor	58 (20%)	21 (14%)	0.13	58 (82%)	21 (64%)	0.081	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0
PD(L)1-inhibitor	227 (80%)	129 (86%)		13 (18%)	12 (36%)		201 (100%)	103 (100%)		13 (100%)	14 (100%)	
Treatment start ≥ 01/01/2016 (%) NA = 0	163 (57%)	94 (63%)	0.32	0 (0%)	1 (3%)	0.69	151 (75%)	80 (78%)	0.72	12 (92%)	13 (93%)	1.0
PS ≥ 2 (%) NA = 0	73 (26%)	34 (23%)	0.56	12 (17%)	2 (6%)	0.22	58 (29%)	30 (29%)	1.0	3 (23%)	2 (14%)	0.65
BMI (%) NA = 0												
< 18	24 (8%)	6 (4%)	0.22	3 (4%)	0 (0%)	0.083	21 (10%)	3 (3%)	0.030	0 (0%)	3 (21%)	0.037
18–30	227 (80%)	127 (85%)		60 (85%)	24 (73%)		159 (79%)	93 (90%)		8 (62%)	10 (71%)	
>30	34 (12%)	17 (11%)		8 (11%)	9 (27%)		21 (10%)	7 (7%)		5 (38%)	1 (7%)	
≥ 3 metastatic sites (%) NA = 0	125 (44%)	51 (34%)	0.051	42 (59%)	13 (39%)	0.091	79 (39%)	33 (32%)	0.26	4 (31%)	5 (36%)	1.0
≥ 3rd line in metastatic setting (%) NA = 0	115 (40%)	46 (37%)	0.61	16 (23%)	10 (30%)	0.54	95 (47%)	40 (39%)	0.20	4 (31%)	6 (43%)	0.69
Known brain metastases (%) NA = 0	84 (29%)	33 (22%)	0.12	20 (28%)	4 (12%)	0.12	64 (32%)	28 (27%)	0.48	0 (0%)	1 (7%)	1.0
Bone metastases (%) NA = 0	111 (39%)	48 (32%)	0.19	10 (14%)	3 (10%)	0.69	94 (47%)	39 (38%)	0.17	7 (54%)	6 (43%)	0.71
Visceral metastases (%) NA = 0	235 (82%)	126 (84%)	0.78	48 (82%)	28 (85%)	0.91	167 (83%)	86 (83%)	1.0	10 (77%)	12 (86%)	0.65
Smoking habits (%) NA = 1												
Active	90 (32%)	17 (11%)	<0.001	13 (18%)	2 (6%)	0.035	75 (38%)	15 (15%)	<0.001	2 (15%)	0 (0%)	0.31
Stopped > 1 year	125 (44%)	91 (61%)		11 (15%)	12 (36%)		110 (55%)	73 (71%)		3 (23%)	6 (43%)	
Never	69 (24%)	42 (28%)		47 (66%)	19 (58%)		14 (7%)	15 (15%)		8 (62%)	8 (57%)	
Corticosteroid use (%) NA = 0	81 (28%)	25 (17%)	0.0069	33 (46%)	5 (15%)	0.0021	48 (24%)	18 (17%)	0.24	0 (0%)	2 (14%)	0.48
Any history of autoimmune disorder (%) NA = 6	24 (9%)	13 (9%)	1.0	9 (13%)	3 (9%)	0.75	15 (8%)	8 (8%)	1.0	0 (0%)	2 (14%)	0.48
Any immune-related AE (%) NA = 0	133 (47%)	74 (49%)	0.62	44 (62%)	24 (73%)	0.38	81 (40%)	45 (44%)	0.62	9 (62%)	5 (36%)	0.26
Grade ≥ 3 immune-related AE (%) NA = 0	33 (12%)	16 (11%)	0.87	18 (25%)	6 (18%)	0.47	14 (7%)	9 (9%)	0.65	1 (8%)	1 (7%)	1.0

Abbreviations: AE = adverse event; BMI = body mass index; CTLA4 = cytotoxic T-lymphocyte-associated protein 4; NA=not available data; PD(L)1 = programmed death(ligand)1; PS = performance status.

Table 2
Prognostic factors of overall survival and progression-free survival among patients treated with a CTLA-4 inhibitor in univariate and multivariate analysis (Cox model).

Patient characteristics	Cox proportional hazards regression for overall survival										
		Overall survival					Progression-free survival				
			Unadjusted analysis		Adjusted Analysis			Unadjusted analysis		Adjusted Analysis	
	N (%)	2-years OS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P	6-months PFS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P
Age NA = 0											
≤69 years	58 (73%)	22 (13–37)	REF	0.49	REF	0.90	10 (5–22)	REF	0.13	REF	0.27
≥70 years	21 (27%)	30 (16–59)	0.82 (0.5–1.4)		1.0 (0.6–1.9)		35 (20–64)	0.7 (0.4–1.1)		0.7 (0.4–1.3)	
Gender NA = 0											
Female	33 (42%)	16 (7–36)	REF	0.15	NI	NI	12 (5–30)	REF	0.48	NI	NI
Male	46 (58%)	31 (19–48)	0.67 (0.4–1.1)				21 (11–37)	0.8 (0.5–1.3)			
PS NA = 0											
0–1	67 (85%)	27 (18–41)	REF	0.00013	REF	0.0015	19 (11–31)	REF	0.0012	REF	0.00012
≥2	12 (15%)	8 (2–54)	3.3 (1.7–6.2)		3.0 (1.5–5.8)		8 (1–5)	2.8 (1.5–5.2)		4.2 (2.0–8.8)	
BMI NA = 0											
<18	3 (4%)	33 (7–100)	1.8 (0.6–5.7)	0.60	NI	NI	33 (7–100)	0.9 (0.3–2.8)	0.92	NI	NI
18–30	64 (81%)	24 (15–38)	REF				16 (9–29)	REF			
>30	12 (15%)	21 (6–68)	0.95 (0.5–1.9)				17 (5–59)	1.1 (0.6–2.0)			
Number of metastatic sites NA = 0											
<3	38 (48%)	32 (19–52)	REF	0.078	REF	0.32	20 (10–38)	REF	0.31	NI	NI
≥3	41 (52%)	18 (9–35)	1.55 (0.9–2.5)		1.3 (0.8–2.3)		15 (7–31)	1.3 (0.8–2.0)			
Previous treatment NA = 0											
<2	63 (80%)	21 (13–34)	REF	0.54	NI	NI	13 (7–24)	REF	0.054	REF	0.0035
≥2	16 (20%)	39 (20–74)	0.83 (0.4–1.5)				34 (15–68)	0.6 (0.3–1.0)		0.4 (0.2–0.7)	
Smoking habits NA = 1											
Active	12 (15%)	8 (1–54)	REF	0.12	NI	NI	25 (9–67)	REF	0.71	NI	NI
Stopped > 1 year	16 (20%)	33 (16–70)	0.42 (0.2–1.0)				25 (11–58)	1.1 (0.5–2.4)			
Never	51 (65%)	25 (16–41)	0.71 (0.4–1.4)				12 (6–26)	1.3 (0.5–2.4)			
Corticosteroid use NA = 0											
No	49 (62%)	26 (16–43)	REF	0.75	NI	NI	19 (11–34)	REF	0.94	NI	NI
Yes	30 (38%)	21 (10–42)	1.1 (0.7–1.8)				14 (6–34)	1.0 (0.6–1.6)			

Abbreviations: HR = hazard ratio; CI = confidence interval; CTLA4 = cytotoxic T-lymphocyte-associated protein 4; OS = overall survival; PFS = progression-free survival; NA = not available data; BMI = body mass index; REF = reference; NI = not included.

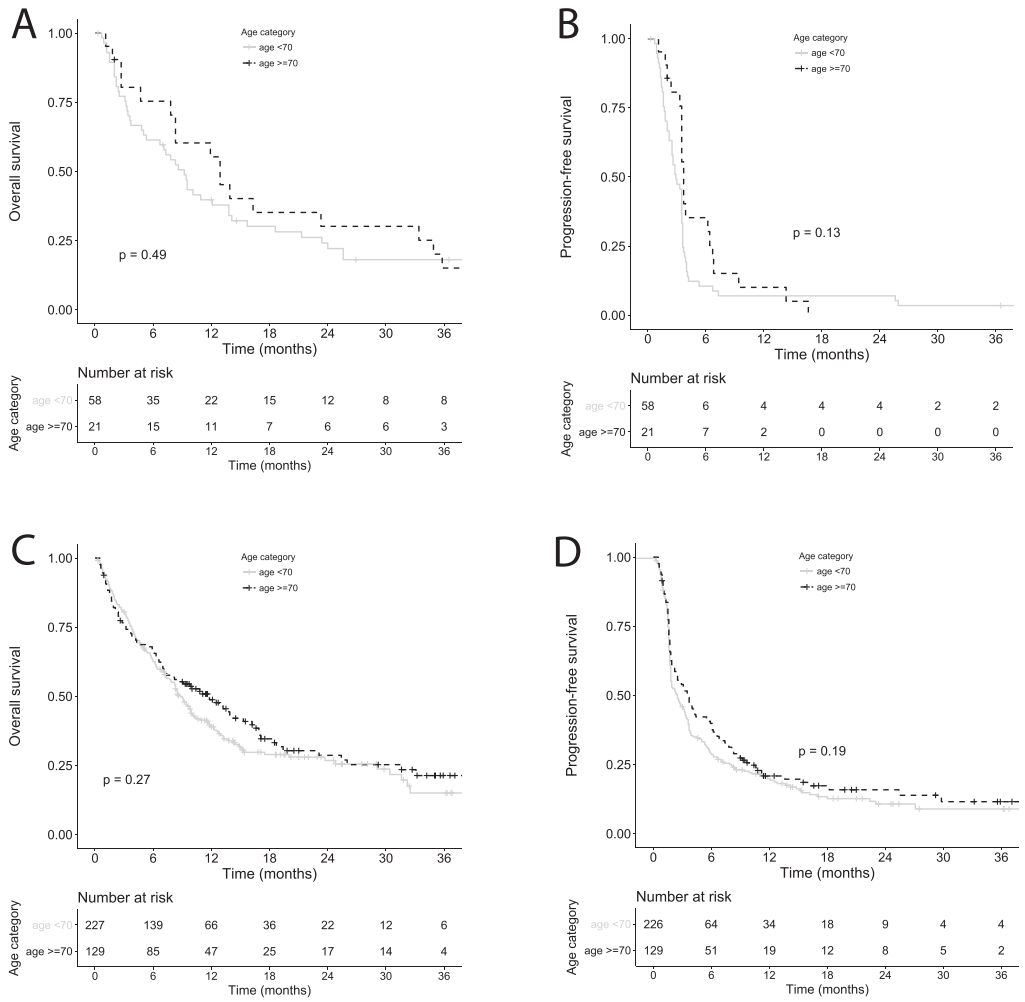

Fig. 1. Kaplan–Meier estimates according to age for patients treated with a cytotoxic T-lymphocyte-associated protein 4 inhibitor for (A) overall survival and (B) progression-free survival. Kaplan–Meier estimates according to age for patients treated with a programmed death(ligand)1 inhibitor for (C) overall survival and (D) progression-free survival.

occurrence of any type of toxicity between the two age cohorts (Table 4).

3.4. Prognostic factors of efficacy other than age

3.4.1. CTLA-4 inhibitors

Performance status (PS) ≥ 2 was an independent predictor for a shorter OS (adjusted HR = 3.0, 95% CI, 1.5–5.8, P = 0.0015) and for a shorter PFS (adjusted HR = 2.8, 95% CI, 1.5–5.2, P = 0.0012). A number of previous treatment lines in metastatic setting of 2 or greater was an independent predictor for a longer PFS (adjusted HR = 0.4, 95% CI, 0.2–0.7, P = 0.0035). Gender, active smoking, BMI, corticosteroid use and number of metastatic sites at the time of ipilimumab initiation had no significant impact on OS or PFS (Table 2).

3.4.2. PD(L)-1 inhibitors

PS ≥ 2 was an independent predictor for a shorter OS (adjusted HR = 2.3, 95% CI, 1.7–3.1, P < 0.0001) and for a shorter PFS (adjusted HR = 1.8, 95% CI, 1.4–2.4, P < 0.0001). The number of metastatic sites was also independently associated with OS (adjusted HR = 1.4, 95% CI, 1.0–1.8, P = 0.028) and PFS (adjusted HR = 1.3, 95% CI, 1.0–1.7, P = 0.023). The number of previous treatment lines in metastasis setting was independently associated with OS (adjusted HR = 0.8, 95% CI, 0.6–1.0, P = 0.042). Gender, BMI and corticosteroid use had no significant impact on survival outcomes (Table 3). Smoking habits had no statistically significant impact on PFS or OS of patients overall nor in the subgroup of patients with lung cancer.

4. Discussion

In this real-life retrospective series, patients treated with single-agent ICIs for various cancer types had comparable efficacy and safety outcomes if they were older or younger than 70 years. There was even a trend towards better long-term outcomes in the older cohort. The

Table 3
Prognostic factors of overall survival and progression-free survival among patients treated with a PD(L)-1 inhibitor in univariate and multivariate analysis (Cox model).

Patient characteristics	N (%)	Cox proportional hazards regression for overall survival									
		Overall survival					Progression-free survival				
			Unadjusted analysis		Adjusted analysis			Unadjusted analysis		Adjusted analysis	
		2-year OS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P	6-month PFS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P
Age NA = 0											
≤69 years	227 (64%)	27 (21–35)	REF	0.27	REF	0.84	29 (23–35)	REF	0.19	REF	0.51
≥70 years	129 (36%)	29 (21–40)	0.9 (0.7–1.1)		1.0 (0.7–1.3)		40 (32–49)	0.9 (0.7–1.1)		0.9 (0.7–1.2)	
Tumour type NA = 0											
Lung cancer	304 (85%)	25 (20–32)	REF	0.044	REF	0.15	31 (26–37)	REF	0.018	REF	0.039
Melanoma	25 (7%)	40 (25–65)	0.6 (0.4–1.0)		0.8 (0.4–1.4)		44 (28–69)	0.6 (0.3–0.9)		0.6 (0.4–0.9)	
Urologic cancer	27 (8%)	NA (NA–NA)	0.6 (0.4–1.2)		0.6 (0.4–1.1)		41 (9–64)	0.7 (0.4–1.1)		0.8 (0.5–1.3)	
Gender NA = 0											
Female	107 (30%)	24 (16–36)	REF	0.26	NI	NI	26 (19–36)	REF	0.15	NI	NI
Male	249 (70%)	29 (23–36)	0.9 (0.7–1.1)				36 (30–42)	0.8 (0.7–1.1)			
PS NA = 0											
0–1	261 (73%)	33 (27–41)	REF	<0.0001	REF	<0.0001	39 (33–45)	REF	<0.0001	REF	<0.0001
≥2	95 (27%)	11 (5–22)	2.7 (2.0–3.5)		2.3 (1.7–3.1)		16 (10–25)	2.0 (1.6–2.6)		1.8 (1.4–2.4)	
BMI NA = 0											
<18	27 (8%)	11 (3–36)	1.8 (1.2–2.8)	0.0047	1.4 (0.9–2.2)	0.29	30 (17–53)	1.2 (0.8–1.8)	0.10	NI	NI
18–30	290 (81%)	28 (23–35)	REF		REF		31 (26–37)	REF			
>30	39 (11%)	35 (21–58)	0.7 (0.5–1.1)		0.9 (0.6–1.4)		46 (33–65)	0.7 (0.5–1.0)			
Number of metastatic sites NA = 0											
<3	221 (62%)	30 (23–38)	REF	0.0087	REF	0.028	38 (31–45)	REF	0.017	REF	0.023
≥3	135 (38%)	23 (17–33)	1.4 (1.1–1.8)		1.4 (1.0–1.8)		25 (18–33)	1.3 (1.1–1.7)		1.3 (1.0–1.7)	
Previous treatment NA = 0											
<2	201 (56%)	23 (17–31)	REF	0.097	REF	0.042	31 (26–39)	REF	0.83	NI	NI
≥2	155 (44%)	33 (26–43)	0.8 (0.6–1.0)		0.8 (0.6–1.0)		34 (28–43)	1.0 (0.8–1.2)			
Smoking habits NA=1											
Active	95 (27%)	24 (16–38)	REF	0.12	NI	NI	27 (19–37)	REF	0.47	NI	NI
Stopped > 1 year	199 (56%)	28 (22–37)	0.7 (0.6–1.0)				36 (30–43)	0.8 (0.6–1.1)			
Never	60 (17%)	31 (19–50)	0.7 (0.4–1.0)				32 (22–46)	0.8 (0.6–1.1)			
Corticosteroid use NA = 0											
No	280 (79%)	29 (23–36)	REF	0.13	NI	NI	32 (27–38)	REF	0.87	NI	NI
Yes	76 (21%)	23 (14–37)	1.3 (0.9–1.7)				36 (27–49)	1.0 (0.7–1.3)			

Abbreviations: HR = hazard ratio; CI = confidence interval; OS = overall survival; PFS = progression-free survival; NA = not available data; BMI = body mass index; REF = reference; NI = not included.

Table 4
Immune-related adverse events rates.

Variable	CTLA4-inhibitors			PD(L)1-inhibitors		
	≤69 years (n = 58)	≥70 years (n = 21)	P	≤69 years (n = 227)	≥70 years (n = 129)	P
Immune AE, any grade (%) NA = 0	35 (60%)	15 (71%)	0.52	98 (43%)	59 (46%)	0.66
Immune AE, grade ≥ 3 (%) NA = 0	16 (28%)	4 (19%)	0.63	17 (7%)	12 (9%)	0.55
Immune colitis, any grade (%) NA = 0	13 (22%)	7 (33%)	0.38	26 (11%)	18 (14%)	0.51
Immune colitis, grade ≥ 3 (%) NA = 0	7 (12%)	2 (10%)	1.0	3 (1%)	1 (1%)	1.0
Immune rash, any grade (%) NA = 0	10 (17%)	6 (29%)	0.34	31 (14%)	19 (15%)	0.87
Immune rash, grade ≥ 3 (%) NA = 0	2 (3%)	1 (5%)	1.0	7 (3%)	2 (2%)	0.50
Thyroiditis, any grade (%) NA = 0	8 (14%)	3 (14%)	1.0	37 (16%)	20 (16%)	0.88
Thyroiditis, grade ≥ 3 (%) NA = 0	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Hypophysitis, any grade (%) NA = 0	4 (7%)	0 (0%)	0.57	2 (1%)	0 (0%)	0.54
Hypophysitis, grade ≥ 3 (%) NA = 0	3 (5%)	0 (0%)	0.56	1 (0%)	0 (0%)	1.0
Immune hepatitis, any grade (%) NA = 0	12 (21%)	6 (29%)	0.55	10 (4%)	8 (6%)	0.46
Immune hepatitis, grade ≥ 3 (%) NA = 0	6 (10%)	2 (10%)	1.0	1 (0%)	2 (2%)	0.30
Other immune AE, any grade (%) NA = 0	15 (26%)	5 (24%)	1.0	41 (18%)	24 (19%)	0.89
Other immune AE, grade ≥ 3 (%) NA = 0	3 (5%)	0 (0%)	0.56	8 (4%)	7 (5%)	0.42

Abbreviations: AE = adverse events; CTLA4 = cytotoxic T-lymphocyte-associated protein 4; NA = not available data; PD(L)1 = programmed death(ligand)1.

present study is the first to report, in real-life conditions, long-term efficacy and security of ICIs among more than 400 patients with various solid malignancies. These results are in line with several meta-analyses of phase II and phase III clinical trials that suggested single-agent ICIs had similar efficacy in older and younger patients [5–9]. However, it is well known that older patients included in pivotal clinical trials are highly selected [17]. As older patients treated in standard clinical practice are likely to be frailer, it was important to assess the activity and toxicity of ICIs among older patients in a real-life setting. We chose a cutoff age of 70 years for its better relevance considering the higher prevalence of age-related changes over 70 years [18]. Between 1980 and 2012 in France, 45% of newly diagnosed cancers occurred in patients older than 70 years [19]. However, only 10% of patients enrolled in ICI clinical trials were ≥75 years [5]. In our study including unselected patients receiving an ICI monotherapy, patients aged ≥70 years represented 34% of the total population, a clearly increased percentage compared to what is usually seen in immune-oncology clinical trials. Therefore, older patients included in this series appear to be representative of a real-life older population.

Several retrospective series have explored the relative efficacy of ICIs according to age. For patients with melanoma, Chiarion and colleagues first suggested in an Italian multicentric study that efficacy and safety data from 188 patients aged >70 years treated with ipilimumab were consistent with the outcomes observed in a younger population, with a safety profile also consistent with that observed in the general population [10]. Betof and colleagues found similar efficacy and safety results for 254 patients with melanoma treated with PD(L)-1 inhibitors [11]. The Italian nivolumab multicentric expand access program recently provided data for 1588 patients with nonsquamous and 371 patients with squamous NSCLC patients, showing comparable results [13,12], as well as the French nivolumab expand access program with, respectively, 370 and 230 patients [20]. Another retrospective series of 78 patients in a real-world population suggested that patients aged ≥75 years were able to gain as much benefit from CTLA-4 and PDL-1 inhibitors administered for advanced melanoma, NSCLC or renal cell carcinoma as younger patients [14]. Furthermore, Herin *et al.* found that patients older than 70 years enrolled in phase I trials experienced similar efficacy than younger patients, with no significant difference between the two groups in grade III and IV irAEs [21]. On the other hand, two retrospective studies of 538 and 92 patients with melanoma even suggested that older patients might benefit more of ICIs than younger patients [15,16]. The patients included in the second study came from the same institution as the current series. The favourable outcomes that have been reported in the older subgroup could not be reproduced, likely because of longer follow-up.

Most of the anticancer systemic treatments (cytotoxic chemotherapy, molecular targeted therapies) have increased toxicity among older and frail patients leading to suboptimal treatment and worse prognosis [22,23]. ICIs administered as single agent might then be particularly appealing for the treatment of older and frail patients. However, the emerging combinations of ICIs with other ICIs, targeted therapies or cytotoxic chemotherapies are likely to be less tolerated by older patients with the risk of toxicity and undertreatment of this patient population. Nevertheless, these efficacy and safety data suggest that ICIs as a single agent could be safely used and monitored in the elderly in the same conditions as in younger patients.

We did not find any statistically significant association between outcomes and clinical factors such as smoking habits, BMI or concomitant use of corticosteroids. A better efficacy of ICIs has been suggested among patients with NSCLC exposed to tobacco in subgroup analyses of randomized trials [24,25], while the concomitant administration of corticosteroids has been suggested *by Arbour et al.* to decrease the efficacy of PD(L)1-inhibitors in NSCLC [26]. Moreover, a negative impact of malnutrition on ICIs efficacy has also been suggested [27]. Our study might have been underpowered for some of these factors, and its retrospective nature should prevent any strong conclusion. Neither the timing between the start of the use of corticosteroid and the ICI initiation nor the reason for the corticosteroid administration was collected in this study. A specific impact on patient outcomes according to the timing, dose and reason of administration of the corticosteroid then cannot be ruled out. However, this study does not support a strong prognosis or predictive value of these clinicobiologic markers.

Preclinical and clinical ex vivo data suggest that older patients undergo age-related immune changes, grouped under the term "Age Related Immune Dysfunction" (ARID), as part of the immunosenescence process [28]. ARID leads to a decline in the production of naïve CD8+ T cells [29], reducing the antigenic diversity of immune cells which could make the immune response to newly encountered antigens less effective [30]. If memory T lymphocyte regulators increase with ageing [31], they have reduced functionality with less ability to traffic to the tumour [32]. Some publications have described a chronic state of low-grade inflammation with ageing, known as "inflammaging" [33]. Older individuals have high concentrations of inflammatory cytokines and autoantibodies, suggesting an increased risk of immune-related AEs. It was hypothesized that immunosenescence might undermine ICIs efficacy and might increase the risk of immune-related side effects. Ferrara *et al.* determined a senescent immune phenotype in patients with advanced NSCLC that was associated with lower disease control rate upon ICI therapy [34].

Our study was obviously limited by its retrospective design, especially for the assessment of adverse event rates. Low-grade adverse events are likely to be underreported in real-life setting. However, it is unlikely that severe adverse events, impairing patient functioning and with potential threatening to patient life have been underreported. Although this study represents a large cohort, the number of older patients was relatively small, with a limited number of event occurrence, especially for severe irAEs, preventing us from drawing definitive conclusion without further investigations. A standardized assessment of patients' frailty was not available for most of the patients. As all patients received an ICI in standard practice, older patients included in this series are likely to represent a cohort of relatively fit patients. Our conclusions should not be generalized to a population of frail older patients. Moreover, biological mechanisms that might underlie ICIs outcomes, such as PD-L1 staining of tumour samples or biomarkers exploring cellular immunological senescence, were not explored in this study. These biological measurements were not performed routinely at the time of ICIs initiation for most included patients.

5. Conclusions

Older and younger patients treated in real-life setting with single-agent ICIs had similar long-term oncological outcomes and a similar risk of irAEs. These findings were consistent after adjustment on important prognosis factors such as tumour type and general status. These results suggest that ICIs could be safely used in older patients following the same indications and the same monitoring plan as in younger patients.

Conflict of interest statement

None declared.

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