Real-world survival outcomes in patients with different types of cancer managed with immune checkpoint inhibitors

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Abstract

Introduction: Immune checkpoint inhibitors (ICI) are now standard of care in systemic treatment for many types of metastatic cancer, often together with cytotoxic chemotherapy. Monitoring of treatment efficacy against clinical trial benchmarks in real-world populations and subgroups such as elderly patients is necessary. Based on the results of a previous study, we evaluated age-related survival differences in a larger cohort.

Methods: Retrospective analysis of 272 patients managed in a rural real-world setting, after exclusion of those who had received neoadjuvant, adjuvant or maintenance ICI treatment. We defined four different survival categories: death within 3 months of the first ICI dose, 3-6 months survival, 6-12 months survival, and >12 months survival. All surviving patients were followed for >12 months. Actuarial overall survival was assessed too. Age was stratified in 10-year increments.

Results: Non-small cell lung cancer (NSCLC) and malignant melanoma represented the most common tumor types. Median age was 70 years. Median actuarial overall survival was 13.6 months (5-year estimate 16%). The best survival was recorded in patients 61-70 years of age. The highest rate of early death within 3 months (29%) was seen in those aged >80 years. Long-term survival was not observed in this age-group, in contrast to all others.

Conclusion: Satisfactory survival was observed in this elderly patient cohort, but survival varied with tumor type and performance status. Age was not a major determinant of survival. However, the oldest patients were at higher risk of short survival.

Introduction

Sub-specialization into geriatric or adolescent/young adult oncology has been a development resulting from the increased awareness of the special needs of age-defined patient groups [1-4]. Both treatment efficacy and toxicity may vary by age group, with factors related to comorbidity, organ function, frailty and social support impacting on choice of treatment, especially in elderly patients [5]. Introduction of new treatments after successful development in clinical trials may or may not give identical results in the so-called real-world setting, where patients often are older and/or less healthy than carefully selected study participants [6-9].

Introduction of immune checkpoint inhibitors (ICI) can be regarded one of the major game changers in oncology during the last decade [10]. Both number of approved drugs and indications have evolved rapidly, now also including certain neoadjuvant, adjuvant and maintenance settings. Our group has monitored several outcomes of ICI treatment in our rural, mostly elderly patient population in the framework of long-standing research on patient safety [11, 12]. A previous analysis of 199 patients (July 1, 2018 through October 31, 2021) included also those managed with adjuvant or maintenance therapy [13]. There was no significant impact of age and gender on overall survival in this heterogeneous cohort. Nevertheless, a high proportion of patients aged ≥80 years (5 of 13, 38%) died within 3 months of their first ICI dose. We were therefore interested in continued evaluation of age-related survival differences in a larger study with improved age stratification, and with particular focus on different survival categories.

Methods

Patients and Materials

A previously employed institutional quality-of-care database [13], which includes all consecutive patients treated with ICI outside of clinical trials, was updated for survival outcomes in January 2024. Patients managed with neoadjuvant, adjuvant or maintenance treatment were excluded. We defined four different survival categories: death within 3 months of the first ICI dose, 3-6 months survival, 6-12 months survival, and >12 months survival. To ensure sufficient follow-up, inclusion was limited to July 1, 2018 through October 31, 2022. Data was abstracted from the regional electronic patient records. Age was stratified in 5 groups (up to 50, 51-60, 61-70, 71-80, >80 years). In the initial study period, approved treatment in Norway included monotherapy with atezolizumab, nivolumab or pembrolizumab for non-small cell lung cancer (NSCLC), malignant melanoma, renal cell carcinoma (RCC) and bladder cancer. In addition, ipilimumab/nivolumab was available for malignant melanoma and, later on, RCC. Consecutive other indications were added: head and neck cancer (first patient treated in July 2019), colorectal cancer [microsatellite instability (MSI) high; first patient treated in July 2020; pembrolizumab], hepatocellular carcinoma (HCC; first patient treated in February 2021; atezolizumab/bevacizumab), small cell lung cancer (SCLC; first patient treated in October 2021; carboplatin/etoposide/atezolizumab), upper gastrointestinal tract cancers and non-melanoma skin cancer (2022; cemiplimab for skin cancer). On a national level, regular price negotiations led to changes in the recommended first choice ICI in some indications during the study period. All treatment costs were covered by the national healthcare system.

Statistics

The Kaplan-Meier method was employed to calculate actuarial survival. Seventy-two patients (26%) with median follow-up of 28 months were alive in January 2024 and thus censored in the Kaplan-Meier analysis. Date of death was known in the remaining 200 patients. The study's median follow-up was 14.9 months. Two-sided chi-square tests were employed to compare baseline characteristics between groups. The log-rank test was employed to compare actuarial survival curves. Afterwards, a multivariable forward conditional Cox regression analysis of prognostic factors for actuarial overall survival was performed. The significance level was set to $p<0.05$.

Results

The study cohort was dominated by patients with NSCLC (51%), many of whom received first-line platinum-based doublet chemotherapy together with pembrolizumab. All other cancer types contributed relatively few patients, maximum 12% for malignant melanoma (Table 1). Many elderly patients were included, median age: 70 years.

Median actuarial overall survival was 13.6 months (95% confidence interval (CI) 11.6-15.6). As illustrated in Figure 1, actuarial overall survival was best in MSI high colorectal cancer (median not reached) and RCC (median 47.0 months). We observed 15.3 months in HCC, 15.0 months in malignant melanoma, and 13.5 months in NSCLC. Poorer outcomes were registered in SCLC (median 11.0 months) and a combined group of all remaining types (others; median 6.8 months; $p<0.001$ pooled over all strata).

Age-related overall survival is displayed in Table 2. The best results were obtained in the group 61-70 years of age. The highest rate of early death within 3 months was seen in those aged

>80 years (29%, p=0.09). As shown in Figure 2 (p=0.35 pooled over all strata), long-term survival was not observed in this age-group, in contrast to all others. The actuarial 5-year survival estimate was 16%. The multivariable analysis did not confirm age as significant prognostic factor for survival, in contrast to performance status and primary tumor type (Table 3).

In patients with RCC (n=18), survival differences emerged after stratification for age (≤70 versus >70 years), Figure 3. Median actuarial overall survival was 47.0 months (95% CI 25.3-68.7) in younger and 16.0 months (95% CI 3.8-28.2) in older patients, p=0.06. However, only a single patient in the higher-age-group had received ipilimumab/nivolumab (monotherapy with nivolumab in 5). Younger patients often received ipilimumab/nivolumab or TKI/nivolumab (7 of 12). Conversely, younger patients with NSCLC had shorter actuarial overall survival than their older counterparts. However, a different cut-off was required to demonstrate a difference: ≤60 versus >60 years. Median actuarial overall survival was 9.2 months (95% CI 7.5-10.9) in younger and 13.8 months (95% CI 11.9-15.7) in older patients, p=0.02, Figure 4. Treatment intensity was comparable. No age-related overall survival differences were observed in malignant melanoma, SCLC and HCC. The other groups were too small.

Discussion

This comprehensive single-institution study described real-world treatment concepts and survival outcomes after ICI/ICI combinations in a rural part of Norway. National guidelines and drug price negotiations result in coherent, nationwide patterns of care. Socioeconomic differences are less pronounced than in many other countries, however differences between

urban and rural populations still exist [14]. Many elderly patients were included in the present study and previous research with fewer patients and shorter follow-up suggested that those aged ≥80 years had a relatively high rate of death within 3 months of their first ICI dose [13]. This finding led us to embark on a larger study with extended follow-up beyond 5 years. Overall, age was not a statistically significant predictor of actuarial overall survival. Shorter survival was observed in elderly RCC patients, but treatment intensity was different from that in their younger peers. Results from the International mRCC Database Consortium (IMDC) were published with a ≥70-years cut-off defining older patients [15]. Of 1427 included patients, 397 (28%) were in the older age group. In univariable analysis, older patients had inferior survival compared to younger ones (25.1 versus 30.8 months, $p<0.01$). In multivariable analyses, older age was not independently associated with worse survival.

NSCLC behaved differently in our study, without explanation because the database does not include details about tumor burden or metastases location. A higher disease burden or prevalence of unfavorable metastatic sites or other differences in baseline characteristics may explain the surprisingly poor survival of patients ≤60 years of age. Further work is needed to fully elucidate the present observation. An analysis of the National Cancer Database included patients who were diagnosed with stage IV NSCLC between 2016 and 2018 [16]. ICIs were administered in the first-line setting. Different age groups (< 40, 40-49, 50-59, 60-69, 70-79, and ≥ 80 years) were analyzed. In univariate analysis, ICI treatment was not associated with a survival benefit in patients younger than 40 years relative to their ICI-naïve counterparts. Multivariate analysis confirmed that ICI use was not an independent predictor of survival in this age group. Interestingly, sequential improvement of the hazard ratio for survival was observed with increasing age.

In a multi-institutional, retrospective study of patients with advanced melanoma treated with monotherapy or ICI combination, survival was examined based on age, comparing those under 40 years of age with older patients (age 41-70 and ≥71 years) [17]. A total of 676 patients were included. Overall survival was inferior in patients ≥71 years, who had low response rates to combination therapy. Toxicity incidence was similar across age groups, though organs affected were substantially different.

In our study, the highest rate of early death within 3 months (29%) was seen in those aged >80 years. Long-term survival was not observed in this age-group, in contrast to all others. Previous studies have not analyzed the 3-month time period. Nebhan et al. reported a multicenter, international retrospective study of 928 geriatric patients with different tumors treated with single-agent ICI between 2010 to 2019 [18]. Median age was 83 years. The three most common tumors were NSCLC, malignant melanoma, and genitourinary tumors (GU). Median survival was 10.9 months (NSCLC), 30.0 months (melanoma), and 15.0 months (GU), i.e. consistently higher than the 10.3 months observed in our database. Within these three diagnoses, outcomes were similar across age subgroups (aged <85 vs ≥85 years). There was no significant difference in the rate of immune-related adverse events (irAEs) among patients aged younger than 85, 85 to 89, and 90 years or older. Most patients had performance status 0-1, while our study included a larger proportion of patients with performance status 2, especially in this age group.

Ninomiya et al. employed randomized controlled trials of ICIs across multiple cancer types stratified by patient age (cut-off 65 years) [19]. The primary objective of their study was to assess the difference in ICI efficacy between younger and older patients. Eventually, 24 eligible

trials, including a total of 8157 younger and 6104 older cancer patients, were analyzed. The survival benefit conferred by ICI was not age-dependent, amongst patients aged 65 years or younger. Afterwards, a different study included 17476 patients, comprising 10119 younger (<65 years old) and 7357 older (≥65 years old) patients [20]. The hazard ratio (HR) for survival was 0.77 (95% Ci 0.70-0.85) and 0.77 (95% CI 0.70-0.85) in the younger and elderly groups, respectively, suggesting similar efficacies of ICIs in these two age groups. Overall, the literature consistently suggested that older age should not be a contraindication for ICI treatment, regardless of age cut-off (65, 75 or 80 years).

Our rural real-world results are not clearly inferior to those from other real-world settings, as already discussed in a previous publication [13]. For patients with malignant melanoma, nation-wide Danish data suggested a median survival of 11.3 months (26% survived for more than 3 years) [9]. As already discussed and shown in Figure 1, our own data are slightly better. Clinical trials tend to report better survival than our study, as exemplified by the NSCLC pembrolizumab plus chemotherapy data. This regimen was commonly used in the present cohort. In the squamous NSCLC study, the 5-year survival rate was 18.4% [21], compared to 19.4% in nonsquamous NSCLC [22]. These results are 3-4% higher than in our database, but within our 95% CI. For SCLC, the pivotal trial reported median survival of 12.3 months, compared to 11.0 months in our study [23]. Limitations of our study include its size and consequently also statistical power. Several tumor types were uncommon (<20 patients), including but not limited to RCC and HCC. Endpoints other than survival were not analyzed, but a currently ongoing PhD project is collecting toxicity and electronic patient-reported outcome (ePRO) data. As outlined in our recent review [24], future studies could address real-

world patients' toxicity burden by integrating user-friendly ePRO systems in clinical care pathways.

Conclusions

Satisfactory survival was observed in this elderly, rural patient cohort, but survival varied with tumor type and performance status. Age was not a major determinant of survival. However, the oldest patients were at higher risk of short survival.

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Figure 1. Actuarial overall survival stratified by primary tumor type, p<0.001 (pooled over all strata).

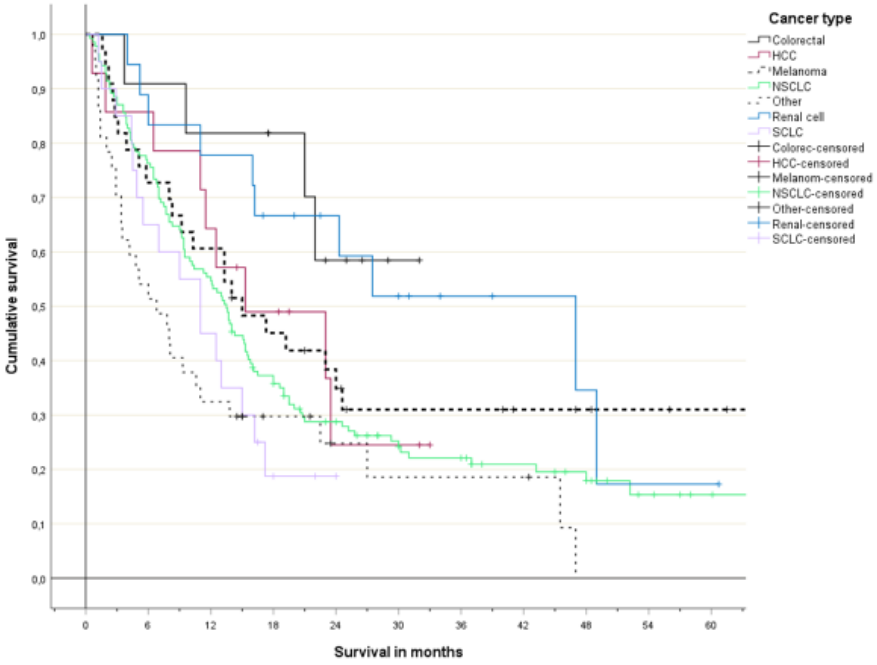

Figure 2. Actuarial overall survival stratified by age group, p=0.35 (pooled over all strata).

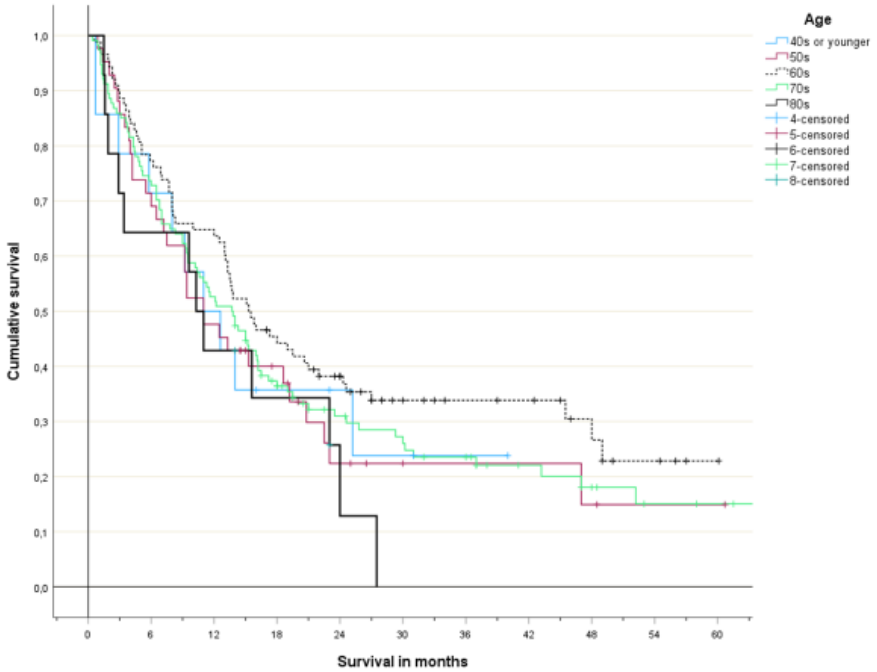

Figure 3. Actuarial overall survival stratified by age group (renal cell cancer only), p=0.06.

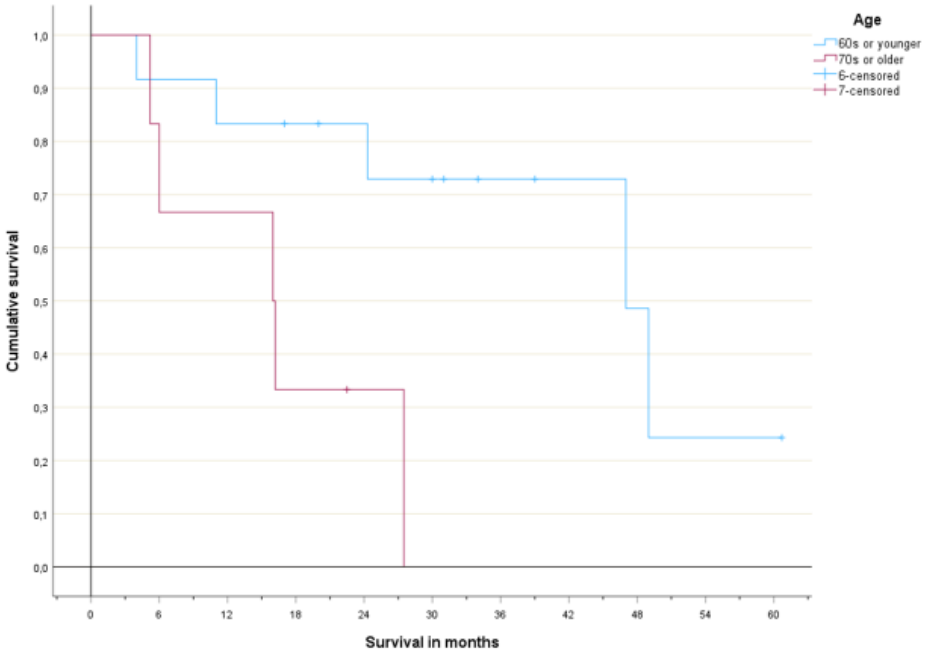

Figure 4. Actuarial overall survival stratified by age group (non-small cell lung cancer only), p=0.02.

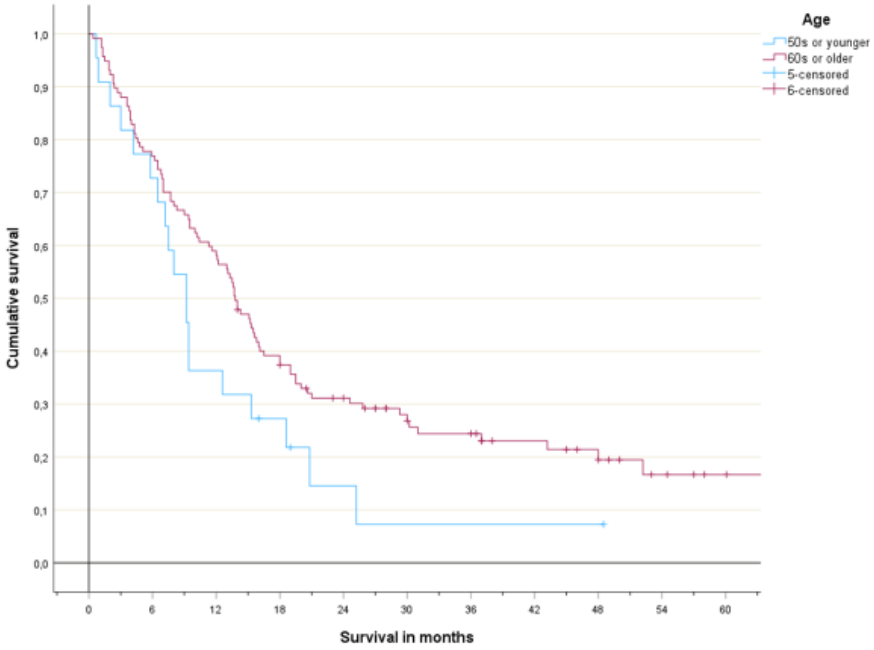

Table 1. Baseline characteristics in 272 patients (July 2018- October 2022)

Parameter	n	%
Cancer type		
Non-small cell lung cancer	139	51
Malignant melanoma	33	12
Small cell lung cancer	20	7
Renal cell cancer	18	7
Hepatocellular carcinoma	14	5
Head and neck cancer	12	4
Colorectal cancer	11	4
Bladder cancer	9	3
Others	16	6
Sex		
Female	116	43
Male	156	57
Drug type		
Ipilimumab/nivolumab	19	7
Nivolumab	44	16
Pembrolizumab	61	22
Atezolizumab	31	11
Cemiplimab	2	1
SCLC triple combination	20	7
Triple combination (ICI, chemotherapy)	79	29
Atezolizumab/Bevacizumab	14	5
TKI/ICI for RCC	2	1
Age		
Median, range (years)	70	22-87
ECOG performance status		
Median, range	1	0-4

SCLC: small cell lung cancer, ICI: immune checkpoint inhibitor, TKI: tyrosine kinase inhibitor, ECOG: Eastern Cooperative Oncology Group

Table 3. Multivariable forward conditional Cox regression analysis, endpoint: actuarial overall survival

Parameter	Hazard ratio	95% CI	p-value
ECOG PS 0-1			
ECOG PS >1	4.4	3-0-5.8	<0.001
Tumor type 1*			
Tumor type 2*	1.9	1.2-2.6	<0.001
Sex			>0.1
Age, continuous			>0.1
Age, by decade			>0.1
Age, >80 vs younger			>0.1

ECOG PS: Eastern Cooperative Oncology Group performance status, CI: confidence interval

*Tumor type 1: colorectal, renal cell, non-small cell lung, melanoma, hepatocellular

*tumor type 2: small cell lung, bladder, head and neck, and all others

Table 2. Overview of survival outcomes by age group, percentages

Age group (n)	≤3 months	3.1-6 months	6.1-12 months	>12 months	Actuarial median
≤50 years (14)	21	7	21	50	11.0 months
51-60 (40)	13	18	20	50	11.0 months
61-70 (88)	11	11	13	65	15.3 months
71-80 (116)	13	15	21	52	13.7 months
>80 years (14)	29	7	21	43	10.3 months