

Survival and Early Death Within Three Months from the Start of Immune Checkpoint Inhibitors in Patients With Different Types of Cancer

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Abstract. *Background/Aim: Implementation of new anti-cancer treatments in rural healthcare might not always result in identical survival outcomes as those seen in the randomized trials leading to approval. Therefore, the survival of patients treated with immune checkpoint inhibitors (ICI) in Nordland county was analyzed. Patients and Methods: Retrospective analysis of 199 patients, mainly treated in adjuvant or palliative settings, e.g., for non-small cell lung cancer (NSCLC) or malignant melanoma (from 2018 to 2021). Overall survival and death within 3 months from start of ICI were evaluated. Results: All patients who received (neo)adjuvant treatment were alive at the time of this analysis. Median survival was not reached for patients treated with consolidation durvalumab for NSCLC. Twenty-five patients died within 3 months [none after (neo)adjuvant or consolidation ICI]. Among these 25 patients, none had performance status (PS) 0 and only 7 had PS 1. Among 13 patients aged ≥ 80 years, 5 (38%) died within 3 months. Four of five patients treated on an individual basis outside of generally accepted indications died within 3 months. Conclusion: The overall survival outcomes observed after limited follow-up appear satisfactory. Death within 3 months was typically caused by cancer progression and mostly related to reduced PS (≥ 2) and/or advanced age (≥ 80 years).*

Outside of clinical trials, Norwegian cancer patients gained sequential access to immune checkpoint inhibitors (ICI), such as atezolizumab, durvalumab, ipilimumab, nivolumab and

pembrolizumab through the publicly-funded national healthcare system starting in 2016 (1). First, metastatic malignant melanoma (MM) and non-small cell lung cancer (NSCLC) became approved indications. Due to the fact that the authors' healthcare region, Nordland county in the northern part of Norway, is a sparsely populated, but geographically large rural area served by only one Department of Oncology (located in Bodø) that utilizes telemedicine to coordinate care provided by local chemotherapy units, our group has long been interested in avoiding potential barriers to different components of care, e.g., positron emission tomography (PET) or radiotherapy access (2, 3). Compared to the participants in pivotal randomized trials that led to drug approval, the cancer patient population in Nordland county is composed of many elderly patients, which also impacts on comorbidity and organ function, as illustrated in a previous analysis of trial eligibility and survival in patients with metastatic renal cell cancer (RCC) that included nivolumab (4). Interestingly, trial-eligible patients managed according to national guidelines had survival outcomes in line with published first-line trial results, a reassuring finding.

We were concerned about the safety of ICI administered in small, remote local hospitals, where the responsible oncologists at the Department of Oncology in Bodø might or might not receive information about adverse events and unplanned hospitalizations. This led us to investigate the patterns of care in deceased patients with NSCLC treated with ICI (5). The small study included 32 patients treated with first- or second-line ICI regimens. The cohort was compared with a matched contemporary group of patients who had received systemic treatment other than ICI. Death caused by toxicity was recorded in two patients (non-ICI) and one patient (ICI), respectively. More ICI patients (21 versus 14) received systemic therapy during the last three months of life ($p=0.13$). The treatment rates during the last four weeks were comparable, $p=0.8$. Within the framework

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of our comprehensive patient safety research (6), we performed a larger study of ICI treatment in Nordland county, also including several newly approved indications and the adjuvant or consolidation setting.

Patients and Methods

The healthcare region's electronic patient record system was utilized to create a retrospective database of all consecutive patients who received ICI for non-hematological malignancies between July 1, 2018, and October 31, 2021. Overall survival was evaluated as the main endpoint in February 2022. Primarily, we were interested in the proportion of patients who initiated ICI treatment in the terminal phase of the disease (last 3 months, thus inclusion was limited to those who received their first dose before October 31, 2021, meaning they were followed for at least 3 months) and to distinguish between death from cancer progression and ICI toxicity. Baseline characteristics, such as age and sex were compared between short-term survivors (3 months from the start of ICI) and those with longer survival. The Kaplan-Meier method was employed to calculate actuarial survival. Ninety-one patients (46%) were alive in February 2022 and thus censored in the Kaplan-Meier analysis. Their median follow-up was 14 months. Date of death was known in the remaining 108 patients. The log-rank test was employed to compare survival curves. Two-sided chi-square tests were employed to compare baseline characteristics between groups. The significance level was set to $p < 0.05$. New indications for ICI treatment were added by the national authorities after health-economic considerations several times during the study period. In addition, regular price negotiations led to changes in the recommended first choice ICI in a given indication. All treatment costs were covered by the national healthcare system. Only one patient participated in a clinical trial. All patients provided informed consent before treatment. Ethics approval for this retrospective non-interventional quality-of-care study was not required.

Results

The majority of patients were treated for NSCLC (n=113, 57%, consolidation durvalumab after chemoradiation for stage III disease, first-line pembrolizumab, first-line pembrolizumab with platinum-based doublet chemotherapy, second-line nivolumab or atezolizumab after previous chemotherapy). The second largest group included patients with MM (n=36, 18%, adjuvant nivolumab after resection, ipilimumab/nivolumab or nivolumab alone). New indications after June 2018 included head and neck cancer (first patient treated in July 2019), colorectal cancer [microsatellite instability (MSI) high; first patient treated in July 2020], hepatocellular carcinoma (HCC; first patient treated in February 2021) and small cell lung cancer (SCLC; first patient treated in October 2021). Further baseline characteristics are shown in Table I.

The Kaplan-Meier survival curves are displayed in Figure 1. All patients who received (neo)adjuvant treatment were alive at the time of this analysis. Median survival was not reached for patients treated with consolidation durvalumab for NSCLC. Median survival was 13.8 months for the main group (different

Table I. Baseline characteristics in 199 patients (July 2018-October 2021).

Parameter	n	%
Cancer type		
Non-small cell lung cancer	113	57
Malignant melanoma	36	18
Kidney cancer	13	7
Colorectal cancer	8	4
Bladder cancer	6	3
Head and neck cancer	5	3
Hepatocellular carcinoma	4	2
Others	14	7
Sex		
Female	90	45
Male	109	55
Drug type		
Ipilimumab/nivolumab	16	8
Nivolumab	47	24
Pembrolizumab	49	25
Atezolizumab	30	15
Triple combination (pembrolizumab, chemotherapy)	50	25
Durvalumab consolidation	7	4
Setting		
Adjuvant (malignant melanoma)	10	5
Neoadjuvant (clinical trial, breast cancer)	1	0.5
Age		
Median, range (years)	69	22-84
ECOG performance status		
Median, range	1	0-4

ECOG: Eastern Cooperative Oncology Group.

tumors and settings) and 3-year survival was 27%. Restricted to the only large subgroup (NSCLC), the corresponding figures were 13.8 months and 25%, respectively. There was no significant impact of age and sex on overall survival.

A total of 25 patients died within 3 months from their first dose of ICI [all from the main group, *i.e.*, not (neo)adjuvant or consolidation ICI]. They represented 14% of the patients in the main group. Table II shows detailed information about these 25 patients. Sex and median age were not significantly different between patients who died within 3 months and those with longer survival. Regarding the 4 most common diagnoses (excluding consolidation/adjuvant), 12% of the patients with NSCLC and 12% of those with MM died within 3 months (0% with kidney and colorectal cancer). Among these 25 patients, none had performance status (PS) 0 and only 7 had PS 1 (median PS was 2). Among 13 patients aged ≥ 80 years, 5 (38%) died within 3 months. Among 16 patients managed with ipilimumab/nivolumab, none died within 3 months. Four of five patients treated on an individual basis outside of generally accepted indications died within 3 months (cancer types: sarcoma, gastric cancer, breast cancer). With regard to all 25 patients, the median number of ICI cycles was 2 and almost all patients stopped

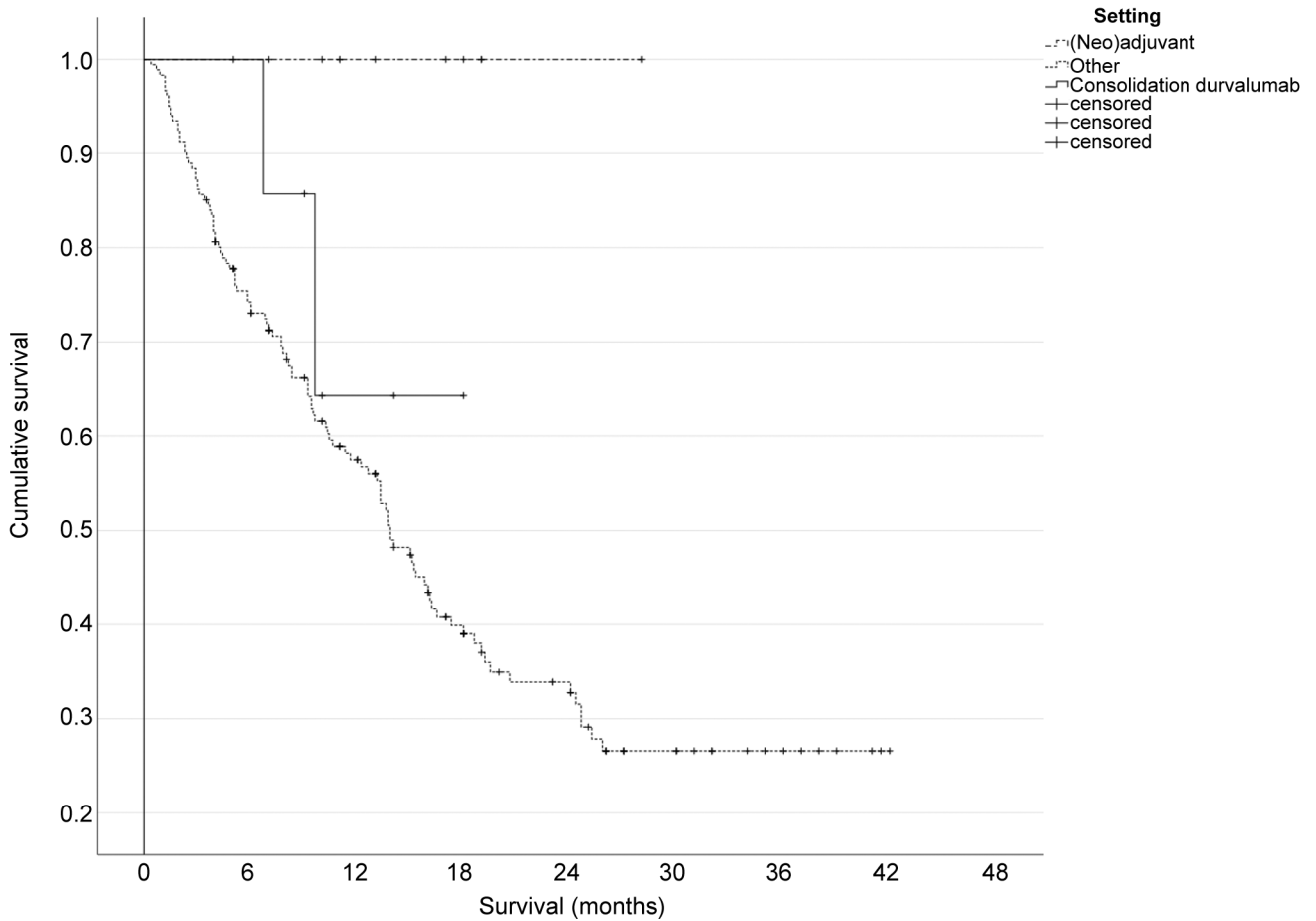


Figure 1. Actuarial overall survival for three different settings, $p=0.01$ (pooled over all strata).

treatment due to early disease progression. No adverse events leading to death within 3 months were observed.

Discussion

Prospective clinical trials often restrict inclusion to healthier patients with PS 0-1 (7). In addition, participating centers are mainly located in urban areas. Real-world utilization of newly approved anti-cancer drugs throughout a larger healthcare system might thus result in different toxicities and efficacy, and close monitoring after approval should be advocated (8). As reported by Thana *et al.*, real-world data of ICI treatment might actually resemble those generated in prospective trials (9), but one should be careful in extrapolating outcome data before comparative efficacy results become available. On the basis of these considerations, our group decided to evaluate survival after ICI treatment in our rural healthcare region. Both overall survival and death within 3 months from the start of treatment were selected as endpoints.

We included different tumor types, drugs, indications and settings. Basically, the survival curves shown in Figure 1 were in line with expected results. The largest subgroup in our study consisted of patients with NSCLC who received first- or second-line ICI monotherapy or first-line ICI with platinum-based doublet chemotherapy in a palliative setting ($n=106$). Median survival was 13.8 months and projected 3-year survival 25%. In the phase III OAK study of atezolizumab *versus* docetaxel for relapsed NSCLC, 28% of the patients treated with atezolizumab were alive after at least 24 months (10). The 5-year pooled survival rate was 13% in the nivolumab studies (11). First-line results, *e.g.*, with pembrolizumab or combined pembrolizumab/chemotherapy, were even better (12, 13). Also, durvalumab after chemoradiotherapy in stage III NSCLC gave promising results in the pivotal clinical trial (14), which might also be achievable in our healthcare setting, considering the present shape of the Kaplan-Meier curve. However, the current number of stage III patients is not sufficient to draw firm conclusions. Size of the subgroups, *e.g.*, with MM or RCC, and

Table II. Overview of 25 patients who died within 3 months from their first immune checkpoint inhibitors (ICI) treatment.

Cancer type	ECOG PS	Age (years)	Disease extent	Setting	Number of cycles, further details
NSCLC	2	76	Brain & pleura met.	2 nd line atezolizumab	1, rapid thoracic progression
NSCLC	2	78	Stage III	2 nd line atezolizumab	2, pulmonary failure (COPD, infection)
NSCLC	2	71	Bone & lung met.	2 nd line atezolizumab	2, disease progression
NSCLC	1	71	Bone met.	2 nd line atezolizumab	1, disease progression
NSCLC	1	57	Bone & adrenal met.	1 st line triple therapy	3, disease progression
NSCLC	2	71	Lung & pleura met.	1 st line triple therapy	1, rapid thoracic progression
NSCLC	2	62	Liver & bone met.	1 st line triple therapy	3, disease progression
NSCLC	2	67	Pleura met.	1 st line triple therapy	2, rapid thoracic progression
NSCLC	1	80	Lung met.	1 st line triple therapy	2, rapid thoracic progression
NSCLC	2	54	Bone met.	1 st line triple therapy	2, disease progression
NSCLC	3	62	Brain, adrenal, lymph.	1 st line triple therapy	2, disease progression
NSCLC	1	70	Adrenal & lymph. met.	1 st line pembrolizumab	1, ileus
NSCLC	3	83	Lung & skin met.	1 st line pembrolizumab	1, disease progression
SCLC	3	82	Extensive disease	1 st line triple therapy	1, disease progression
Melanoma	2	81	Liver, lung, bone met.	1 st line nivolumab	2, disease progression
Melanoma	1	80	Brain & subcut. met.	1 st line nivolumab	4, brain met. progression
Melanoma	1	77	Brain, liver, lymph. met.	1 st line nivolumab	1, bowel perforation
Non-MS	2	79	Liver & lymph met.	1 st line pembrolizumab	1, disease progression
Head & neck	2	66	Locoregional relapse	2 nd line pembrolizumab	3, disease progression
Bladder	2	73	Lung & bone met.	2 nd line atezolizumab	1, disease progression
Bladder	2	62	Lung, liver, lymph. met.	2 nd line atezolizumab	1, disease progression
STS	2	22	Lung met.	3 rd line pembrolizumab	1, rapid thoracic progression
AS	2	58	Lung met.	3 rd line nivolumab	2, rapid thoracic progression
Breast	1	56	Skin & lymph. met.	3 rd line CTx/atezoliz.	1, disease progression
Gastric	4	35	Bone & peritoneal met.	1 st line CTx/nivolumab	8, disease progression

ECOG PS: Eastern Cooperative Oncology Group performance status, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, non-MS: non-melanoma skin cancer, STS: soft tissue sarcoma, AS: angiosarcoma, Met.: metastases, subcut.: subcutaneous soft tissue, lymph.: lymph node (non-regional), COPD: chronic obstructive pulmonary disease, CTx: chemotherapy.

limited length of follow-up are also the main limitations of the study. In addition, we did not include response rates, progression-free survival and the complete range of toxicities observed in our heterogeneous cohort. Baseline comorbidity data were not collected.

Other authors have also generated data from their everyday clinical practice of NSCLC treatment. In a study of 190 patients who received pembrolizumab, 74% were treatment naïve (15). Median survival in the first-line and $\geq 2^{\text{nd}}$ line settings were 24.3 months and 13.4 months, respectively. Those with PS 2 or 3 had lower median survival than their counterparts with PS 0/1 (5.8 months vs. 16.7 months, $p < 0.0001$). Also, the odds of grade ≥ 3 immune-related adverse events (irAE) within 3 months were 6.3-fold higher if PS was 2 or 3 versus 0/1 ($p = 0.05$). Development of irAE did not result in improved survival. In a region in southern Norway ($n = 78$, $\geq 2^{\text{nd}}$ line), median survival was 12.6 months (16). In a larger Danish study ($n = 840$, $\geq 2^{\text{nd}}$ line), the corresponding result was 12.2 months (17). Patients with PS ≥ 2 had a median survival of 4.5 months.

For patients with metastatic MM, nation-wide Danish data suggest a median survival of 11.3 months (26% survived for more than 3 years) (18).

Besides overall survival, early death after ICI treatment initiation was evaluated in our study. A total of 25 patients died within 3 months from initiation (all from the main, palliative intention group; corresponding to 14% of these patients). Reduced PS and/or age ≥ 80 years were the main explanatory variables for early death. Among 16 patients managed with ipilimumab/nivolumab, none died within 3 months. It was also interesting to note that 4 of 5 patients who were treated on an individual basis outside of generally accepted indications died within 3 months, making these approaches of “salvage” after failed previous lines of standard treatment highly questionable. As illustrated in Table II, these patients were often young and in desperate search of an additional option. No adverse events leading to death within 3 months were observed in this study. In other words, early disease progression was the main cause of early death. As mentioned earlier, Ksienski *et al.* also found an association between PS 2/3 and reduced survival (15). In a different study of 98 Australian patients receiving ICI, 22.5% died within 30 days of commencement (19). Disease progression was the most common cause of death (79%). The lower rate of 14% in 3 months that is reported in our study, appears more satisfactory.

Finally, the issue of rurality has to be discussed. A study by Li *et al.* included 8078 patients with MM diagnosed in the pre-ICI (2005-2010) and post-ICI period (2011-2016) from the Surveillance, Epidemiology, and End Results (SEER) program (20). Patients in the post-ICI period had a significantly longer median overall survival than those in the pre-ICI period. However, significant differences in this endpoint for pre- and post-ICI were only observed in patients with medical insurance and those living in urban or low-poverty regions, but not uninsured and rural or high-poverty area patients. A study by Ray *et al.* included 6,259 American patients with NSCLC, 47% of whom resided in rural areas (21). Two of five participating institutions were rurally located and provided care for 20% of patients. Compared with rural residents at rural institutions, urban and rural residents attending urban institutions were more likely to receive stage-preferred treatment, after adjusting for insurance, age, and clinical stage. Urban and rural residents attending urban institutions had a lower hazard of death compared with rural residents attending rural institutions [hazard ratio (HR)=0.69 (0.64-0.75) and 0.61 (0.55-0.67), respectively]. When analyzed by stage, care for late-stage patients at urban institutions remained less hazardous. To overcome rurality-associated NSCLC survival disparity, the authors recommended that interventions should preferentially target the institution level, including expanding access to higher-quality guideline-concordant care. Due to major differences between cancer care in the US and Norway (insurance system, financial barriers reducing access, *etc.*) and the high adherence to national guidelines in our institution and region (22, 23), results are difficult to compare. In several of our own studies (4, 5, 22-24), including the present one, we have so far not identified areas of concern regarding treatment access and efficacy in the framework of the publicly-funded healthcare system.

Conflicts of Interest

SGA has received lecture fees from BMS, Astra Zeneca and Pfizer. Other authors: no competing interests.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Carsten Nieder. The first draft of the manuscript was written by Carsten Nieder and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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