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ORIGINAL RESEARCH

Systemic anticancer therapy near the end of life: an analysis of factors influencing treatment in advanced tumor disease

N.-S. Le[1,2], A. Zeybek[3], K. Hackner[1,4], S. Gottsauner-Wolf[5], I. Groissenberger[1], F. Jutz[1], L. Tschurlovich[1], J. Schediwy[1], J. Singer[1,2] & G. Kreye[1,2*]

[1]Karl Landsteiner University of Health Sciences, Krems; [2]Division of Palliative Care, Department of Internal Medicine 2, University Hospital Krems, Karl Landsteiner University of Health Sciences, Krems, Austria; [3]Department of Internal Medicine, Kantonsspital Zug, Zug, Switzerland; [4]Division of Pneumology, University Hospital Krems, Karl Landsteiner University of Health Sciences, Krems; [5]Strategy and Quality Medicine Medical Strategy and Development, Landesgesundheitsagentur Niederösterreich, St. Pölten, Austria

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Background: Systemic anticancer treatment (SACT) for advanced cancer patients with limited prognosis before death is associated with high toxicity and reduced quality of life. Guidelines discourage this approach as low-value care. However, a significant number of patients continue to receive SACT in the last 30 days of life.

Materials and methods: A retrospective study was carried out at the University Hospital Krems, encompassing the analysis of patients who were diagnosed with a solid tumor and died between 2017 and 2021, with a particular focus on the use of end-of-life (EOL) SACT.

Results: A total of 685 patients were included in the study. SACT was applied in 342 (49.9%) patients, of whom 143 (41.8%, total population: 20.9%) patients received SACT within the last 30 days of life. Median time from last SACT to death was 44.5 days. The analysis of potential factors impacting the administration of EOL SACT revealed the following significant findings: type of SACT [$P < 0.001$, targeted therapy odds ratio (OR) 5.09, 95% confidence interval (CI) 2.26-11.48; chemotherapy/targeted therapy OR 3.60, 95% CI 1.47-8.82; immune checkpoint inhibitor OR 2.32, 95% CI 1.37-3.92], no referral to palliative care (PC) ($P = 0.009$, OR 1.86, 95% CI 1.16-2.96), no admission to PC ward ($P < 0.001$, OR 2.70, 95% CI 1.67-4.35), and poor Eastern Cooperative Oncology Group (ECOG) performance status (≥ 2, $P < 0.001$, OR 3.35, 95% CI 1.93-5.83).

Conclusion: The timing of SACT near the EOL is significantly influenced by several factors, including the type of SACT, referral to PC services, admission to PC unit, and ECOG performance status. These findings underscore the complexity of treatment decisions in advanced cancer care and highlight the need for personalized, patient-centered approaches that consider both clinical and patient-related factors to optimize care at the EOL.

Key words: systemic anticancer treatment, end of life, palliative care

INTRODUCTION

In the realm of oncology, the landscape of systemic anticancer therapy (SACT) has evolved significantly, offering new avenues for extending survival and improving outcomes for patients with advanced malignancies.[1,2] However, as patients approach the end of life (EOL), the appropriateness and efficacy of continuing SACT become subjects of intense debate and ethical consideration while the primary goal remains improvement of patients' quality of life (QOL).[3,4]

According to the guidelines of the European Society of Medical Oncology (ESMO), SACT should be avoided during the final weeks of a patient's life, as EOL SACT is associated with poor quality of care, increased acute care use, resuscitation attempts, and death occurring in an intensive care unit.[5] The American Society of Clinical Oncology (ASCO) also endorses this strategy, stating that SACT should be stopped in patients with poor performance status (PS), no observed benefit from prior therapies, ineligibility for clinical trials, or low anticipated success rates, as further antitumor therapy offers limited benefit.[6]

Despite guidelines discouraging the approach of SACT in the last weeks of life,[5,6] a substantial portion (20%-50%) of advanced cancer patients still receive SACT within this critical timeframe.[3,4] Several institutions have examined the

*Correspondence to: Priv. Doz. Dr Gudrun Kreye, Division of Palliative Care, Department of Internal Medicine 2, University Hospital Krems, Mitterweg 10, 3500 Krems an der Donau, Austria. Tel: +43-2732-9004-0; Fax: +43-2732-9004-5555

E-mail: gudrun.kreye@krems.lknoe.at (G. Kreye).

administration of SACT within 30 days before death, but comparisons are challenging due to differences in patient characteristics, treatment intent, and outcome measures.[7-15] Although various validated prognostic tools exist, physicians tend to overestimate survival in patients with advanced cancer, resulting in patients receiving more aggressive tumor therapy at the EOL.[16-18] Furthermore, the advent of novel treatment modalities such as targeted therapy and immune checkpoint inhibitors has added complexity to treatment decision making.[6] Particularly, orally administered therapies are known for improved tolerability and diminished adverse events, which could lead to prolonged administration.[2] Despite limited evidence and guidelines advising against antitumor therapy beyond the third line, such therapy is frequently administered, even in the last weeks of life.[6,19] For patients with metastatic tumors, the chance of treatment success after unsuccessful third-line therapy is minimal, but toxicity risk remains high.[6] Best supportive care and specialized palliative care (SPC) can be a more suitable alternative for many patients.[20]

It is crucial to minimize futile treatments in cancer care to improve patient outcomes and QOL. Therefore, there is an urgent necessity to develop and implement tools that effectively prevent the administration of unnecessary treatments to this vulnerable group of cancer patients. Such tools would not only align with best practice guidelines but also ensure a more patient-centered approach to cancer treatment.[6]

The aim of this study was to investigate the use of SACT at the EOL and to provide insight into potential factors influencing the administration of EOL SACT. In particular, the study focused on the role of SPC in treatment decisions of patients with advanced tumor disease.

MATERIALS AND METHODS

Study population

This single-center retrospective study was conducted at the middle-sized University Hospital Krems, Austria, where an average of ∼1000 patients per year are newly diagnosed with a malignant disease (ICD-Code C00-C97). Of these cancer patients, 814 patients died with a diagnosis of a malignant neoplasm between 1 January 2017 and 30 June 2021.

Our inclusion criteria were as follows:

- All patients with a solid tumor disease (ICD-Code C00-C80, C97) who died between 1 January 2017 and 30 June 2021.
- Completion of oncological treatment at our hospital.

Our exclusion criteria were as follows:

- Individuals under the age of 18.
- Patients with hematological tumors (ICD-Code C81-C96).
- Patients diagnosed with neurologic, ophthalmologic or dermatologic tumors were treated at affiliate hospitals and, therefore, excluded from the study.
- Patients who changed the oncological center during the disease.

There is a limitation in the presence of patients with breast cancer, as our hospital is not specialized in treatment of breast tumors, and a portion of those patients are treated at a specialized partner facility. Similarly, prostate carcinomas are underrepresented, as patients with early stages of the disease are increasingly managed by outpatient urologists following primary therapy at the hospital and thus have been excluded. In total, 685 (84.2%) patients could be included in the analysis.

Data collection

A review of patient records was conducted via the access-limited computer system. Any access to patient records was personalized and monitored. Study-relevant data were pseudonymously compiled and evaluated. Only authorized people had access to the original data. All patients participating in the study were assigned a sequential number. The evaluation was carried out using only this pseudonymization number.

This retrospective study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the local ethics committee (EK Nr: 1012/2020, https://ecs.kl.ac.at/core/submission/form/1387/#status_tab).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software, version 28 (SPSS Inc., Armonk, NY) was used for the statistical analyses. Logistic regression (univariate and multivariate), chi-square test, and Fisher's exact test were used to determine the association of study variables [gender, tumor entity, type of SACT, SPC referral, PC admission, Union for International Cancer Control (UICC) stage, age $\leq$65 years versus $>$65 years, and Eastern Cooperative Oncology Group (ECOG) PS] on SACT at the EOL and PC referral, respectively. Variables that demonstrated statistical significance in univariate analyses were subsequently scrutinized through multivariate analyses. Forest plots were created using SPSS to visually represent the odds ratio (OR) of logistic regression. In the event of missing data, an examination was conducted to determine whether the proportion of absent data was linked to a distinct test outcome. Two-sided tests provided all P values. P values ≤ 0.05 were considered as statistically significant.

RESULTS

Patient and tumor characteristics

The median age at diagnosis was 72.0 years (range 39-98 years, standard deviation = 10.6). The male-to-female ratio was 1.6 : 1, and 261 (38.1%) patients were female.

The distribution of tumor entities was as follows: 311 (45.4%) were lung cancers, 177 (25.8%) gastrointestinal tumors, 69 (10.1%) urogenital tumors, 57 (8.3%) head and

neck tumors, 52 (7.6%) gynecologic cancers, and 19 (2.8%) cancer of unknown primary (CUP).

The histological examination revealed moderate to poor differentiation (G2-3) in 479 (96.2%, excluding missing data) patients. At the time of diagnosis, 54 (9.0%, excluding missing data) patients were classified as stage I, 50 (8.4%) patients as stage II, 116 (19.4%) patients as stage III, and 378 (63.2%) patients as stage IV according to the UICC TNM (tumor—node—metastasis) staging system.

Further details can be seen in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103683.

Tumor therapy

In our patient cohort, 211 (30.8%) patients underwent surgery during their oncologic course of disease. The distribution of the intention of surgery was as follows: 65.4% ($n = 138$) curative, 14.2% ($n = 30$) palliative, 15.1% ($n = 32$) diagnostic, and in 5.2% ($n = 11$) of cases as emergency surgery. In 1.5% ($n = 10$) and 0.1% ($n = 1$) of cases, patients underwent a second and third surgery, respectively.

Radiotherapy during the oncologic course of disease was carried out in 261 (38.1%) patients. While 110 (16.1%) patients received curative radiotherapy, palliative-intended radiotherapy was applied in 166 (24.2%) patients. Furthermore, 15 (2.2%) patients received both curative and palliative radiotherapy. Simultaneous radio-chemotherapy was administered in 46 (6.7%) patients.

SACT alone ($n = 231$, 67.5%), or as part of multimodality treatment ($n = 111$, 32.5%), was applied in 342 (49.9%) patients. The distribution of SACT was as follows: 241 (35.2%) patients received at least one line of chemotherapy, 114 (16.6%) immune checkpoint inhibitors, 37 (5.4%) chemotherapy plus targeted therapy, 33 (4.8%) targeted therapy (small molecule), 31 (4.5%) chemotherapy plus immune checkpoint inhibitors, 18 (2.6%) targeted therapy (monoclonal antibodies), and 1 (0.1%) immune checkpoint inhibitor plus targeted therapy. Endocrine therapy was given to a total of 22 (3.2%) patients in the study cohort.

Further details of the applied SACT can be seen in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103683.

Overview of the last administered SACT

Patients received the last dose of the SACT 44.5 days (median time) before death. In 179 (52.3%) patients, chemotherapy was administered as the last SACT, followed by immune checkpoint inhibitor ($n = 88$, 25.7%), targeted therapy ($n = 32$, 9.4%), combined chemotherapy plus targeted therapy ($n = 23$, 6.7%), and combined chemotherapy plus immune checkpoint inhibitor ($n = 20$, 5.8%). Further details of the type of SACT can be seen in Table 1.

On average, chemotherapy or immune checkpoint inhibitor was administered for 3.2 cycles (median 2.0). SACT was terminated in 80.7% ($n = 276$) of the cases for the following reasons: most frequently due to death in 31.9% ($n = 88$) of the cases, followed by side-effects ($n = 58$, 21.0%), tumor progression ($n = 46$, 16.7%), and complications ($n = 15$, 5.4%). In 19.3% ($n = 66$) of patients, the therapy was ended according to the predefined plan after a specified number of cycles.

Table 1. Overview of the last administered systemic anticancer therapy ($n = 342$)

Type of SACT	Number of patients (% of patients receiving SACT)
CTx	179 (52.3%)
Immune checkpoint inhibitor	88 (25.7%)
Targeted therapy	32 (9.4%)
Small molecule	26 (7.6%)
Monoclonal antibody	6 (1.8%)
CTx plus targeted therapy	23 (6.7%)
CTx plus targeted therapy (small molecule)	8 (4.4%)
CTx plus targeted therapy (monoclonal antibody)	15 (2.3%)
CTx plus immune checkpoint inhibitor	20 (5.8%)
ECOG performance status	
0	133 (38.9%)
1	140 (40.9%)
2	60 (17.5%)
3	9 (2.6%)
No SACT	343 (50.1%)
Discontinuation of last administered SACT	276 (80.7%)
Reason for discontinuation of last administered SACT	
Death	88 (31.9%)
Side-effects	58 (21.0%)
Tumor progression	46 (16.7%)
Complications	15 (5.4%)
Multimorbidity	11 (4.0%)
Patient's request	9 (3.3%)
Side-effects and tumor progression	4 (1.4%)
Unknown/missing	41 (16.3%)
Time from last SACT to death (days, median, range)	44.5 (0-989)
SACT at the end of life (≤30 days before death)	
Yes (total population/patients with SACT)	143 (20.9%/41.8%)
No (total population/patients with SACT)	540 (79.1%/58.2%)

CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; SACT, systemic anticancer treatment.

Most commonly, patients had an ECOG score of 1 ($n = 140$, 40.9%) at the time of the final applied SACT, followed in descending order by ECOG 0 ($n = 133$, 38.9%), ECOG 2 ($n = 60$, 17.5%), and ECOG 3 ($n = 9$, 2.6%).

Analysis of SACT at the end of life. According to the literature, patients were divided into groups based on administration of SACT within the last 30 days.[14,21] Within the patient cohort who received systemic therapy, SACT was administered to 41.8% ($n = 143$) of the patients within the last 30 days before death. Endocrine therapy was not included in the EOL analysis.

SACT at the EOL (≤30 days before death) was most commonly administered to patients with CUP ($n = 6$, 54.5%; OR 3.12) and gastrointestinal tumors ($n = 32$, 45.1%; OR 2.13), followed by urogenital tumors ($n = 8$, 44.4%; OR 2.08), lung tumors ($n = 84$, 42.6%; OR 1.93), head and neck tumors ($n = 8$, 29.6%; OR 1.09), and gynecological tumors ($n = 5$, 27.7%; OR 1.00). A statistically significant difference between tumor entities could not be observed. Similarly, no significant

difference could be observed when histologically separating lung cancer into small-cell and non-small-cell cancer, and comparing them to other tumor types and within lung cancer subgroups (see Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103683).

In contrast, the study revealed a highly significant difference when comparing the influence of SPC on EOL SACT solely within the patient cohort that received SACT ($P = 0.009$). SACT within the last 30 days of life was administered in 37.2% ($n = 89$) of SPC-referred patients, compared to 52.4% ($n = 54$; OR 1.86, 95% CI 1.16-2.96) of patients without SPC referral. Patients who were admitted to a PC unit significantly less frequently (27% versus 50%) received EOL SACT ($P < 0.001$, OR 2.70, 95% CI 1.67-4.35). Furthermore, there was a significant association between timely SPC referral and reduced administration of EOL SACT ($P < 0.001$). Patients who were referred to SPC ≥130 days ($n = 14$, 20.6%, OR 0.23, 95% CI 0.11-0.49) before death received less EOL SACT compared to those referred 60-129 days ($n = 13$, 26.5%, OR 0.32, 95% CI 0.14-0.71), 30-59 days ($n = 24$, 50.0%, OR 0.89, 95% CI 0.42-1.86), and <30 days ($n = 35$, 53.0%) before death.

The study revealed a statistically significant difference regarding the type of SACT given at the EOL ($P < 0.001$). As mentioned in the preceding text, chemotherapy was numerically the most frequently ($n = 179$) administered last SACT. However, mono-chemotherapy was significantly less frequently administered compared to other treatment options in the last 30 days of life ($P < 0.001$, OR 0.36, 95% CI 0.23-0.56). Chemotherapy was given within the 30-day cutoff only in 30.2% ($n = 54$; OR 1.00) of cases, whereas targeted therapy was most frequently continued until ≤30 days before death, accounting for 68.7% ($n = 22$; OR 5.09, 95% CI 2.26-11.48), followed by chemotherapy plus targeted therapy ($n = 14$, 60.9%; OR 3.60, 95% CI 1.47-8.82), immune checkpoint inhibitor ($n = 44$, 50.0%; OR 2.32, 95% CI 1.37-3.92), and chemotherapy plus immune checkpoint inhibitor ($n = 9$, 45.0%; OR 1.89, 95% CI 0.74-4.83). Furthermore, there is a highly significant association between EOL SACT and cessation of the systemic therapy ($P < 0.001$). EOL SACT was terminated in 92.3% of cases ($n = 132$; OR 4.58, 95% CI 2.30-9.13), while therapy in patients receiving SACT >30 days before EOL was discontinued in 72.4% ($n = 144$). The main reason for termination of EOL SACT was death ($n = 80$, 60.6%), followed by side-effects ($n = 16$, 12.1%), unknown reason ($n = 12$, 9.1%), tumor progression ($n = 10$, 7.6%), complications ($n = 7$, 5.3%), patient's request ($n = 3$, 2.3%), multimorbidity ($n = 3$, 2.3%), and side-effects and tumor progression ($n = 1$, 0.8%). Comparatively, therapy in patients with SACT >30 days before the EOL was mainly discontinued due to side-effects ($n = 42$, 29.2%) and tumor progression ($n = 36$, 25.0%), while death was the reason in only 5.6% ($n = 8$) of patients ($P < 0.001$).

Patients with a poor ECOG PS ≥2 at the beginning of the last applied line of SACT had higher odds ($P < 0.001$, OR 3.35, 95% CI 1.93-5.83) of receiving SACT within 30 days before death compared to those with an ECOG PS of <2. Moreover, a distinct trend was observed in favor of implementing SACT towards EOL in patients aged ≤65 years (OR 1.53, 95% CI 0.99-2.36, $P = 0.055$) and in those with UICC stage IV (versus stage I-III, OR 1.71, 95% CI 0.99-2.94, $P = 0.053$). The ECOG PS did not influence the type of last administered SACT (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.103683).

Statistically significant variables (type of SACT, SPC referral, PC admission, ECOG PS 0-1 versus ≥2) were included in the multivariate analysis. Statistical significance was evident for type of SACT ($P < 0.001$, OR 2.84, 95% CI 1.76-4.58), PC admission ($P = 0.007$, OR 2.22, 95% CI 1.23-3.97), and ECOG PS 0-1 versus ≥2 ($P < 0.001$, OR 4.49, 95% CI 2.44-8.27). Further details can be found in Table 2 and Figure 1.

Impact of study variables on SPC referral. In total, 436 (63.6%) patients were referred to SPC. The median time from the first contact with SPC to death was 43.0 days. Poor ECOG PS (2-4 versus 0-1) at the first tumor board ($P = 0.001$, OR 1.86, 95% CI 1.26-2.75) and advanced UICC stage (IV versus I-III) at time of diagnosis ($P < 0.001$, OR 3.01, 95% CI 2.12-4.26) had a significant impact on the incidence of receiving SPC. Patients with CUP (89.5%), gastrointestinal (75.1%), and gynecological tumor (65.4%) were most frequently referred to SPC compared to head and neck (61.4%), lung (58.8%), and urogenital tumors (49.3%) ($P < 0.001$). Patients with lung cancer had a significantly lower likelihood of being referred to PC compared to other tumor entities ($P = 0.017$, OR 1.462, 95% CI 1.07-2.00). Moreover, there was a discernible trend indicating an increasing referral to PC among patients ≤65 years ($P = 0.058$) and women ($P = 0.074$).

Multivariate analysis of statistically significant variables in univariate analyses revealed significance for poor ECOG PS (≥2 versus 0-1, $P = 0.006$, OR 1.86, 95% CI 1.19-2.92) and advanced UICC stage (IV versus III, $P < 0.001$, 95% CI 2.09-4.32) (Table 3, Figure 2).

DISCUSSION

The present study provides valuable insights into the complexity of treatment decisions in advanced cancer care, particularly regarding the timing of SACT near EOL. The substantial proportion (up to 50%) of patients receiving SACT in the last 30 days, despite guidelines discouraging this practice, underscores the need for a closer examination of decision-making processes.[3,4,6,22] In line with the literature, 20.9% of our patients received SACT within this critical timeframe. Among the patient group who have undergone systemic therapy, the percentage amounts to 41.8%. In a recent retrospective study, Golob et al. revealed that 14% of their patients even received anticancer treatments in the last 2 weeks of life, with an increasing trend in the use of novel therapies such as targeted therapy and immunotherapy.[1] Understanding the factors influencing EOL SACT is pivotal for optimizing treatment decisions in advanced cancer care. An American study by Canavan et al. described the significant role of race and insurance. Caucasian

Table 2. Association between study variables and odds of receiving systemic anticancer treatment within the end of life (i.e. SACT within the last 30 days of life) in patients who received SACT ($n = 342$)

	SACT ≤30 days before death		Unadjusted		
	No	Yes	OR	95% CI	*P* value
Age at diagnosis					
>65 years	121 (62.7%)	72 (37.3%)	1.00	Referent	0.055[a]
≤65 years	78 (52.4%)	71 (47.6%)	1.53	0.99-2.36	
Age at last applied SACT					
>65 years	121 (61.7%)	75 (38.3%)	1.00	Referent	0.124[a]
≤65 years	78 (53.4%)	68 (46.6%)	1.41	0.91-2.17	
Gender					
Female	72 (55.8%)	57 (44.2%)	1.00	Referent	0.489[a]
Male	127 (59.6%)	86 (40.4%)	0.85	0.55-1.33	
Tumor entity					
Gynecologic	13 (72.3%)	5 (27.7%)	1.00	Referent	0.521[b]
Lung	113 (57.4%)	84 (42.6%)	1.93	0.66-5.63	
Gastrointestinal	39 (54.9%)	32 (45.1%)	2.13	0.68-6.62	
Head and neck	19 (70.4%)	8 (29.6%)	1.09	0.29-4.10	
Urogenital	10 (55.6%)	8 (44.4%)	2.08	0.52-8.34	
CUP	5 (45.5%)	6 (54.5%)	3.12	0.64-15.03	
Type of SACT					
Chemotherapy	125 (69.2%)	54 (30.2%)	1.00	Referent	<0.001[b]
Immune checkpoint inhibitor	44 (50.0%)	44 (50.0%)	2.32	1.37-3.92	
Targeted therapy	10 (31.3%)	22 (68.7%)	5.09	2.26-11.48	
CTx plus ICI	11 (55.0%)	9 (45.0%)	1.89	0.74-4.83	
CTx plus targeted therapy	9 (39.1%)	14 (60.9%)	3.60	1.47-8.82	
Type of SACT					
Mono-chemotherapy	125 (69.8%)	54 (30.2%)	1.00	Referent	<0.001[a]
Others[c]	74 (45.4%)	89 (54.6%)	2.78	1.79-4.34	
SPC referral					
Yes	150 (62.8%)	89 (37.2%)	1.00	Referent	0.009[a]
No	49 (47.6%)	54 (52.4%)	1.86	1.16-2.96	
Timing of SPC referral among patients referred to SPC					
<30 days before death	31 (47.0%)	35 (53.0%)	1.00	Referent	<0.001[a]
30-59 days before death	24 (50.0%)	24 (50.0%)	0.89	0.42-1.86	
60-129 days before death	36 (73.5%)	13 (26.5%)	0.32	0.14-0.71	
≥130 days before death	54 (79.4%)	14 (20.6%)	0.23	0.11-0.49	
Palliative care admission					
Yes	89 (73.0%)	33 (27.0%)	1.00	Referent	<0.001[a]
No	110 (50.0%)	110 (50.0%)	2.70	1.67-4.35	
ECOG PS (last applied SACT)					
0	88 (66.2%)	45 (33.8%)	1.00	Referent	<0.001[b]
1	87 (62.1%)	53 (37.9%)	1.19	0.73-1.96	
2	22 (36.7%)	38 (63.3%)	3.38	1.79-6.38	
3	2 (22.2%)	7 (77.8%)	6.84	1.37-34.31	
ECOG PS (last applied SACT)					
0-1	175 (64.1%)	98 (35.9%)	1.00	Referent	<0.001[a]
2-4	24 (34.8%)	45 (65.2%)	3.35	1.93-5.83	
UICC stage (last applied SACT)					
I-III	51 (68.0%)	24 (32.0%)	1.00	Referent	0.053[a]
IV	148 (55.4%)	119 (44.6%)	1.71	0.99-2.94	
Lines of SACT					
≤3 lines	182 (58.5%)	129 (41.5%)	1.00	Referent	0.692[a]
>3 lines	17 (54.8%)	14 (45.2%)	1.16	0.55-2.44	
Multivariate analysis					
Mono-chemotherapy versus others[c]	—	—	2.84	1.76-4.58	<0.001
Palliative referral	—	—	1.59	0.89-2.81	0.114
Palliative care admission	—	—	2.22	1.23-3.97	0.007
ECOG PS 0-1 versus 2-4	—	—	4.49	2.44-8.27	<0.001

CI, confidence interval; CTx, chemotherapy; CUP, cancer of unknown primary; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; OR, odds ratio; PS, performance status; SACT, systemic anticancer treatment; SPC, specialized palliative care; UICC, Union for International Cancer Control.
[a]Chi-square test.
[b]Fisher's exact test.
[c]immune checkpoint inhibitor, targeted therapy, CTx/ICI, CTx/targeted therapy.

patients (compared to Black patients) and those with commercial insurance (compared to Medicaid) were more likely to receive EOL SACT. In this context, differences in treatment decisions were revealed which should not be relevant at this stage of a tumor disease, as the focus should be on the well-being of the patient.[22] As the Austrian insurance system is on a social security basis, economic factors were not investigated in this study.

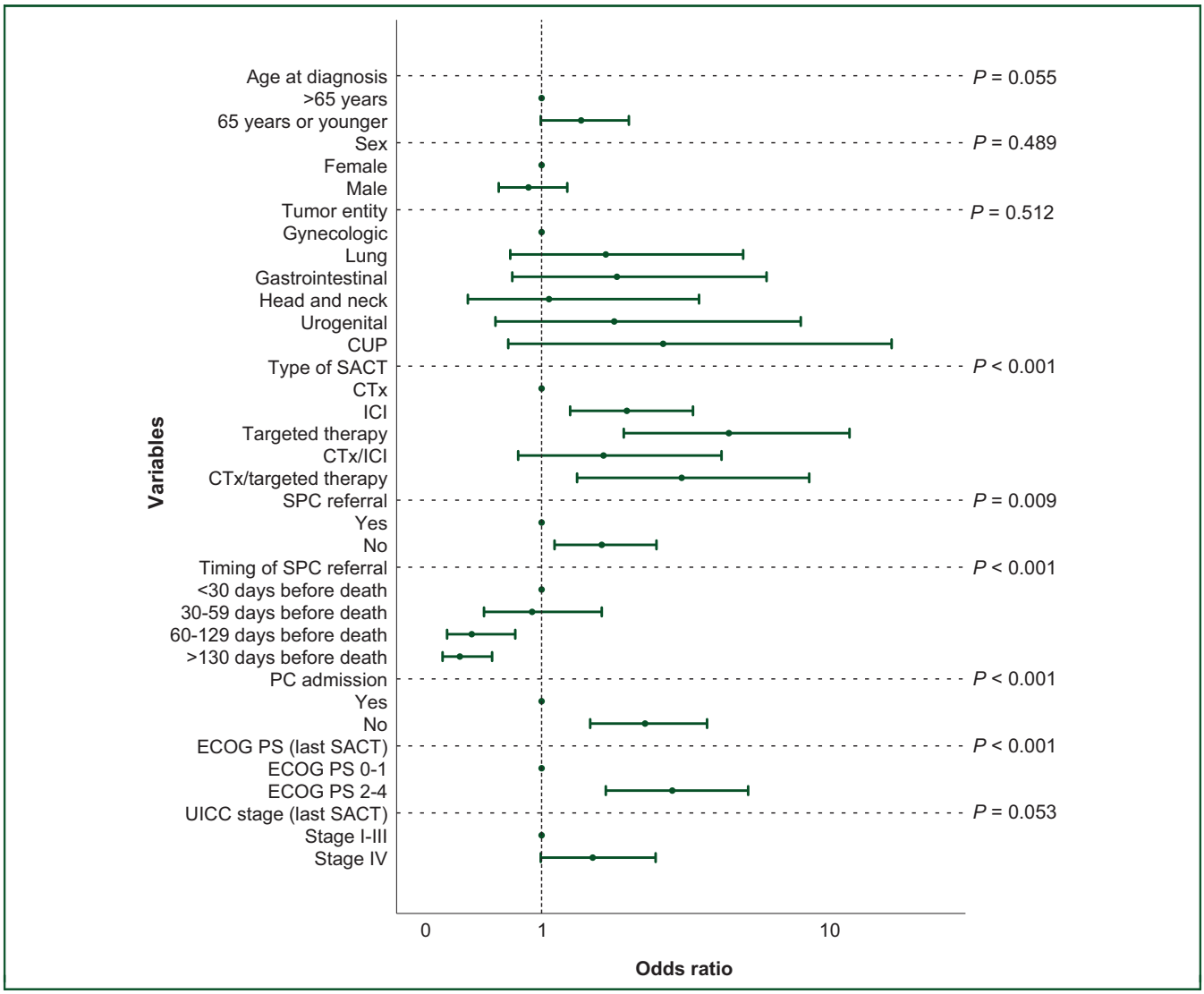

Figure 1. Association between study variables and odds of receiving systemic anticancer treatment (SACT) within the last 30 days of life in patients who received SACT ($n = 342$).

CTx, chemotherapy; CUP, cancer of unknown primary; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; PC, palliative care; PS, performance status; SPC, specialized palliative care; UICC, Union for International Cancer Control.

In advanced tumor disease, the main goal of SACT is to achieve tumor response, extend survival, and to alleviate symptoms.[3,4] However, timely cessation of systemic therapy and transition to best supportive care pose challenges for physicians. The dilemma is highlighted in our study, as the therapy was terminated solely due to death in 60.6% of patients undergoing EOL SACT. In contrast, this occurred in 5.6% of cases for patients with SACT administered >30 days before the EOL. These patients predominantly concluded their final systemic therapy due to side-effects (29.2%) or tumor progression (25.0%). These findings could be related to modern, particularly orally administered, therapy options, which are associated with better tolerability and typically taken until death.[2] Pacetti et al. observed that the majority of their included patients died due to disease progression, affirming that EOL chemotherapy does not alter the natural evolution of the disease. Nearly half of their patients (46%) faced mortality during first-line chemotherapy. The authors raised the question of whether initiating chemotherapy was the optimal choice, suggesting a potential preference for the timely introduction of PC.[14]

Large-scale registry studies demonstrated a higher likelihood of chemotherapy/SACT at the EOL in the absence of a PC unit.[1,23,24] Furthermore, EOL SACT is associated with diminished and delayed access to PC, elevated rates of hospital admission and emergency department visits, higher in-hospital mortality, and a shorter median survival.[25,26] In our study, the significant difference observed in the influence of SPC on EOL SACT within the patient cohort of solid tumors receiving SACT introduces a crucial aspect. Among patients referred to SPC, 37.2% received SACT near the EOL contrasting with a higher percentage of 52.4% observed in those without SPC referral. Furthermore, the timing of SPC referral was essential, as patients were more likely to receive EOL SACT the closer they were referred to SPC before death. A parallel observation indicates that patients admitted to a PC unit also significantly less frequently

Table 3. Association between study variables and odds of specialized palliative care referral (n = 685)

	Referral to SPC		Unadjusted		
	No	Yes	OR	95% CI	*P* value
Age at diagnosis					
≤65 years	64 (31.1%)	142 (68.9%)	1.00	Referent	0.058[a]
>65 years	185 (38.6%)	294 (61.4%)	0.71	0.51-1.01	
Gender					
Female	84 (32.2%)	177 (67.8%)	1.34	0.97-1.86	0.074[a]
Male	165 (38.9%)	259 (61.1%)	1.00	Referent	
Type of SACT					
Chemotherapy	51 (28.5%)	128 (71.5%)	1.00	Referent	0.511[a]
Immune checkpoint inhibitor	27 (30.7%)	61 (69.3%)	0.90	0.52-1.57	
Targeted therapy	11 (34.4%)	21 (65.6%)	0.76	0.34-1.69	
CTx plus ICI	9 (45.0%)	11 (55.0%)	0.49	0.19-1.25	
CTx plus targeted therapy	5 (21.7%)	18 (78.3%)	1.43	0.51-4.07	
ECOG PS at first tumor board					
0	114 (40.7%)	166 (59.3%)	1.00	Referent	0.024[b]
1	71 (38.4%)	114 (61.6%)	1.10	0.75-1.61	
2	24 (26.4%)	67 (73.6%)	1.92	1.14-3.24	
3	16 (29.6%)	38 (70.4%)	1.63	0.87-3.07	
4	4 (17.4%)	19 (82.6%)	3.26	1.08-9.84	
ECOG PS at first tumor board					
0-1	185 (39.8%)	280 (60.2%)	1.00	Referent	0.001[a]
2-4	44 (26.2%)	124 (73.8%)	1.86	1.26-2.75	
UICC stage at diagnosis					
Stage I	32 (59.3%)	22 (40.7%)	1.00	Referent	<0.001[a]
Stage II	32 (64.0%)	18 (36.0%)	0.82	0.37-1.81	
Stage III	54 (46.6%)	62 (53.4%)	1.67	0.87-3.21	
Stage IV	105 (27.8%)	273 (72.2%)	3.78	2.10-6.81	
Unknown/missing	26 (29.9%)	61 (70.1%)	3.41	1.68-6.95	
Tumor entity					
Lung	128 (41.2%)	183 (58.8%)	1.00	Referent	<0.001[a]
Gynecologic	18 (34.6%)	34 (65.4%)	1.32	0.72-2.44	
Gastrointestinal	44 (24.9%)	133 (75.1%)	2.11	1.41-3.18	
Head and neck	22 (38.6%)	35 (61.4%)	1.11	0.62-1.98	
Urogenital	35 (50.7%)	34 (49.3%)	0.67	0.40-1.15	
CUP	2 (10.5%)	17 (89.5%)	5.94	1.35-26.18	
Lines of SACT					
≤3 lines	98 (31.5%)	213 (68.5%)	1.00	Referent	0.099[b]
>3 lines	5 (16.1%)	26 (83.9%)	2.39	0.89-6.42	
Multivariate analysis					
ECOG PS 0-1 versus 2-4	—	—	1.86	1.19-2.92	0.006
UICC stage I-III versus IV	—	—	3.00	2.09-4.32	<0.001
Lung cancer versus other tumors	—	—	1.17	0.81-1.68	0.403

CI, confidence interval; CTx, chemotherapy; CUP, cancer of unknown primary; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; OR, odds ratio; PS, performance status; SACT, systemic anticancer treatment; SPC, specialized palliative care; UICC, Union for International Cancer Control.
[a]Chi-square test.
[b]Fisher's exact test.

received EOL SACT. These discrepancies suggest a complex interplay between the involvement of SPC and the decision to administer SACT near the EOL, highlighting the potential role of PC in shaping treatment decisions. Chiaruttini et al. showed the comprehensive impact of PC on health care utilization patterns and EOL interventions. This underlines the argument for timely integration of PC into the overall care plan for individuals with life-limiting illnesses, given that patients referred to SPC had fewer diagnostic/therapeutic procedures, less use of chemotherapy in the last 30 days, and fewer hospital visits (both outpatient and inpatient).[27,28]

The present study identified significant factors influencing the likelihood of receiving SPC. As expected and similar to other studies,[29] poor ECOG PS at the first tumor board and an advanced UICC stage at the time of diagnosis emerged as strong predictors. These findings emphasize the need for timely integration of PC to facilitate informed decision making aligned with patients' values and preferences. Furthermore, the study provides insight into the distribution of SPC referrals across different tumor types. Patients with CUP had the highest rate of referral to SPC, followed by gastrointestinal tumors and gynecological tumors. Conversely, head and neck, lung, and urogenital tumors had comparatively lower rates of referral. This discrepancy in referral rates among different tumor types could be attributed to variations in disease trajectories, treatment options, and associated symptom burdens. However, the literature reflects disagreement regarding tumor entity and referral to SPC, as lung tumors have been associated with both the highest and lowest odds for SPC referral.[29,30]

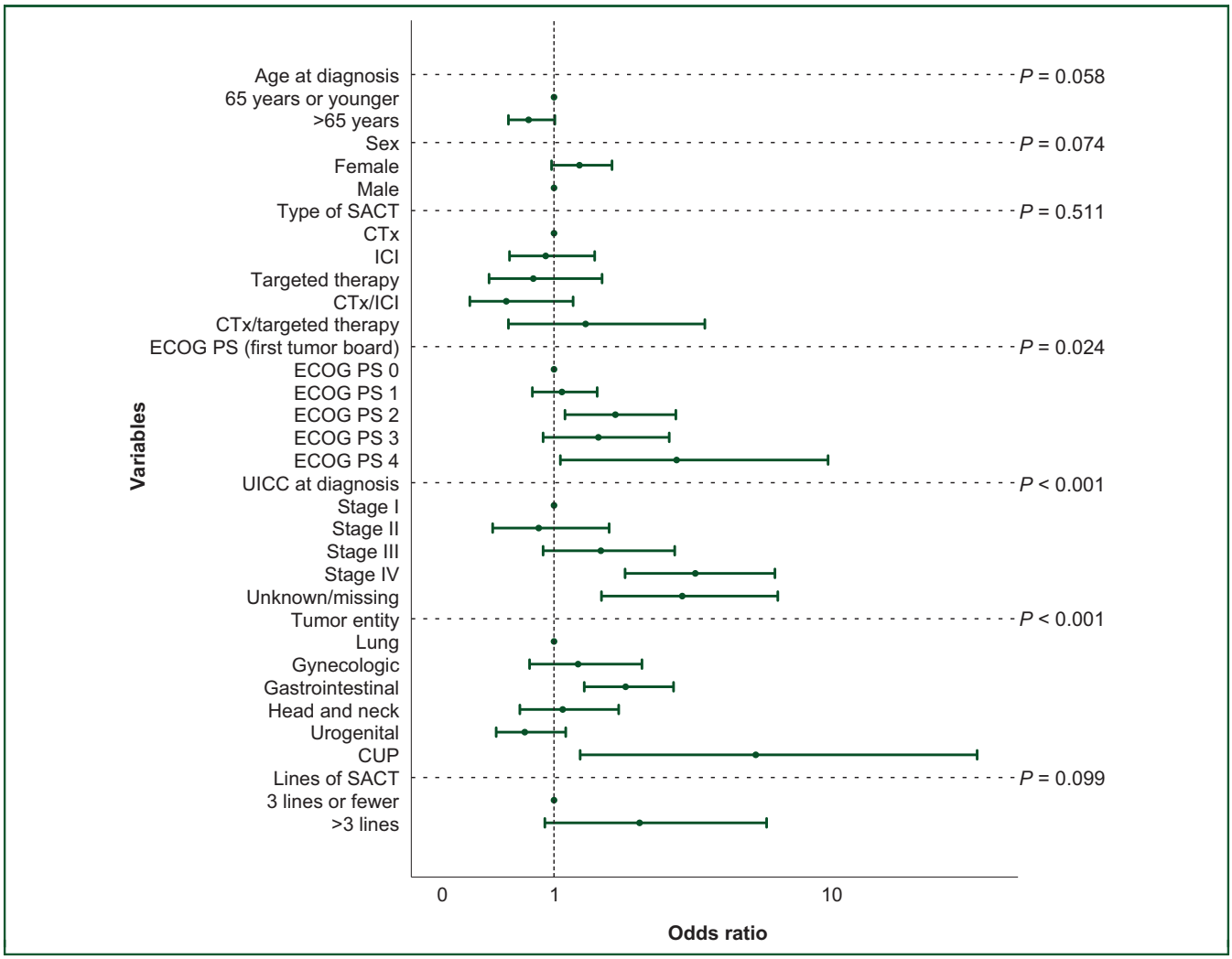

Figure 2. Association between study variables and odds of specialized palliative care referral ($n = 685$).
CTx, chemotherapy; CUP, cancer of unknown primary; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; PC, palliative care; SPC, specialized palliative care.

Recent developments in cancer treatment have introduced a multitude of therapeutic options, including chemotherapy, endocrine or hormonal agents, targeted or biologic agents, and immune checkpoint inhibitors. Non-chemotherapy treatments are frequently linked to simpler administration methods, a diminished but still noteworthy occurrence of adverse effects, and the possibility of significant and enduring clinical response.[2] In literature, the use of immunotherapy at EOL is associated with an increased risk of in-hospital death and can lead to substantial financial burden; thus, ESMO does not recommend the administration of immune checkpoint inhibitors during the final period.[5] Our study reveals significant differences in the types of SACT administered at the EOL, with targeted therapy, combined targeted therapy/chemotherapy, and immune checkpoint inhibitor showing a higher likelihood of being continued until $\leq$30 days before death. However, a systematic literature review of Clarke et al. revealed the absence of a consistent recommendation for timely discontinuation of oral anticancer therapy at the EOL.[31] Although the ASCO guidelines explicitly acknowledge 'cancer-directed therapies', encompassing antitumor treatments beyond exclusively chemotherapy, recommendations are predominantly based on studies focused almost exclusively on chemotherapy.[2,6] In accordance with our study, we were able to emphasize the urgent need for guidelines regarding the cessation of SACT for newer therapeutic options (i.e. targeted therapy), as their application at the EOL is carried out with a significantly higher probability compared to mono-chemotherapy. The recent study by Golob et al. also demonstrated younger age as a significant predictor for SACT in the final days of life.[1] In our study, we also observed a clear trend where patients $\leq$65 years of age were more likely to receive EOL SACT.

Additionally, present data further encourage the urgency of new guidelines, as EOL SACT is currently administered notably frequently to individuals with a poor ECOG PS. The increased utilization of SACT near the EOL among patients with a poor ECOG PS may be associated with the implementation of novel therapeutic modalities and its attribution to perceived tolerability and advantageous risk-benefit profile compared to traditional chemotherapy.[7,32] Glisch et al. and Bloom et al.

demonstrated the association of immune checkpoint inhibitor at the EOL with a poor ECOG PS (>2) at the time of their last immune checkpoint inhibitor dose, and considered poor ECOG PS as an important prognostic factor,[7,32] similarly to chemotherapy.[10] In our study, we also found an association between EOL SACT and poor ECOG PS (≥2), but ECOG PS did not influence the type of last administered SACT. The discrepancy between guidelines recommending against EOL SACT in patients with poor ECOG PS and its continued frequent administration might be further attributed to several factors, including real-world settings as observed in our study, treatment decision influenced by patient or family wishes, and clinical judgment. The ECOG scale assesses functional impairment but not specific organ function.[33] Moreover, ECOG PS is considered as a subjective tool,[34] relying on both patient self-reporting and clinician interpretation, which can vary based on individual perceptions and biases.[34] This lack of objective measures can lead to inconsistencies in assessments, affecting clinical decisions and research outcomes. Observer agreement is higher for patients with good PS, but both the ECOG and Karnofsky PS struggle with sensitivity in patients with poor PS, potentially leading to inaccuracies.[34-36] Identifying frailty and underlying geriatric conditions at the time of cancer diagnosis is crucial for optimizing cancer treatment in older patients. Therefore, the literature recommends using the G8 geriatric screening tool to promptly assess overall health status, identify patients needing further assessment, and pinpoint those at risk of increased health care utilization in the short and long term.[37-39] Especially in advanced cancer disease, the G8 screening tool assists in identifying frail elderly patients who may be more susceptible to adverse outcomes from aggressive cancer treatments, potentially affecting treatment tolerance and QOL in EOL care.[38,39]

In current oncology, patients with advanced disease often encounter uncertainty and may hold inaccurate perceptions of their prognosis and treatment objectives.[40,41] Patients may struggle to balance the risks of treatment toxicity with the benefits for symptom control and QOL, which can undermine informed decision making and lead to aggressive EOL care.[40,41] Personalized decision making is essential to address PC aspects such as symptom burden, illness and prognosis understanding, spirituality, life closure, and family involvement.[42] However, there is limited guidance for oncologists on making decisions about SACT for palliative intent.[1,40,43] Moreover, oncologists may face emotional challenges when ceasing treatment, as they frequently form bonds with their patients, experiencing sorrow when no reasonable treatment options remain.[44,45] The ESMO-Magnitude of Clinical Benefit Scale standardizes the evaluation of cancer treatment benefits, focusing on metrics like overall survival, progression-free survival, and QOL.[46] By systematically evaluating therapies, it can reduce unnecessary EOL SACT, ensuring interventions that truly enhance well-being in final stages.[46] This approach optimizes health care resource use and aligns treatment strategies with PC goals.[46]

Overall, this insight into the patterns of SACT utilization and SPC referral provides valuable information for physicians and contributes to the ongoing discourse on optimizing treatment modalities in advanced cancer care.

Limitations

The presented study has certain limitations that should be considered when interpreting the results. The study design is retrospective, allowing both biases or inaccuracies in the data collection process and instances of missing data. Furthermore, the single-center study is conducted in an above-average affluent country, potentially limiting the generalizability of the findings to a broader population due to sociodemographic disparity. Different health care settings and practices could influence the results. The uneven distribution of tumor entities, with lung tumors constituting nearly half of all patients, reflects real data from a medium-sized oncological center. However, as mentioned in the preceding text, certain tumor entities (neurological, dermatological, and ophthalmological tumors) treated in partner hospitals were excluded. Moreover, hematological tumors were not included and therefore the results may not be directly applicable to this specific patient population. Furthermore, as the study focused on EOL SACT, only patients who died were included. This results in the inclusion of a small, specific subgroup of patients, mostly in advanced tumor stages, and consequently, with significantly limited prognosis.

Conclusions

This study illustrates the significant impact of PC on the administration of SACT. The absence of PC referral and PC unit admission were associated with more frequent SACT during the critical period of the last 30 days of life. Furthermore, poor ECOG PS and newer therapeutic modalities such as targeted therapy and immune checkpoint inhibitors had a significant impact on EOL SACT. These findings emphasize, on the one hand, the complexity of treatment decisions in advanced cancer care and highlight the need for personalized, patient-centered approaches that consider both clinical and patient-related factors to optimize care at the EOL. On the other hand, prospective studies are urgently needed to screen patients before palliative SACT is provided to reduce the risk of futile treatment at the EOL and to provide evidence-based recommendations for the optimal timing of discontinuing targeted therapies and immune checkpoint inhibitors. Finally, we conclude that in accordance with the current literature, the application of SACT in the last month of life should be absolutely avoided.

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DISCLOSURE

KH declares that he received honoraria from AstraZeneca, Roche, Amgen, Novartis, Boehringer Ingelheim, and Exscientia and had consulting or advisory roles for Amgen, Novartis, and Boehringer Ingelheim. JS declares honorarium payments from Abbvie, Amgen, Exscientia, Gilead, Janssen, Kite, Merck, Merck Sharp & Dohme, Miltenyi, Novartis, Pfizer, Roche, and Servier as an invited speaker or expert consulting. GK declares that she received honoraria as a speaker at the Salzburger Palliativlehrgang, Onconovum Academy OEGHO, Ärztediplomlehrgang Palliativ, and Palliativdiplomlehrgang SFU. All other authors have declared no conflicts of interest.

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