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Characteristics and survival of patients with cancer with intended off-label use—a cohort study

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ABSTRACT

Objective To describe the characteristics and the survival of patients with cancer with intended off-label use (OLU) cancer treatment and reimbursement request.

Design Cohort study using medical record data.

Setting Three major cancer centres in Switzerland.

Participants 519 patients with cancer and a reimbursement request for OLU between January 2015 and July 2018.

Main outcomes Characteristics of patients with cancer with and without access to intended OLU. Characteristics included the Glasgow prognostic score (GPS) which includes C reactive protein and albumin and discriminates prognostic groups.

Results OLU was intended for 519 (17%) of 3046 patients with cancer, as first-line treatment in 51% (n=264) and second-line in 31% (n=162). Of the 519 patients, 63% (n=328) were male, 63% (n=329) had solid cancer and 21% (n=111) had a haematological malignancy. Their median overall survival was 23.6 months (95% CI: 19.0 to 32.5). Access to OLU had 389 (75%) patients who were compared with patients without access on average 4.9 years younger (mean; 95% CI: 1.9 to 7.9 years), had a better overall prognosis according to the GPS (51% with GPS of 0 vs 39%; OR: 1.62 (95% CI: 1.01 to 2.59)), had less frequently solid cancer (62% vs 71%; OR: 0.66 (95% CI: 0.41 to 1.05)) and advanced stage cancer (53% vs 70%; OR: 0.48 (95% CI: 0.30 to 0.75)), were more frequently treatment-naive (53% vs 43%; OR: 1.55 (95% CI 1.01 to 2.39)) and were more frequently in an adjuvant/neoadjuvant treatment setting (14% vs 5%; OR: 3.39 (95% CI: 1.45 to 9.93)). Patients with access to OLU had a median OS of 31.1 months versus 8.7 months for patients without access (unadjusted HR: 0.54; (95% CI: 0.41 to 0.70)).

Conclusion Contrary to the common assumption, OLU in oncology is typically not primarily intended for patients with exhausted treatment options. Patient characteristics largely differ between patients with and without access to intended OLU. More systematic evaluations of the benefits and harms of OLU in cancer care and the regulation of its access is warranted.

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ Representative sample of Swiss patients with cancer from three major Swiss cancer centres.
⇒ Detailed picture of off-label use in oncology by reporting characteristics of patients with cancer with intended off-label use treatment and not just patients with access to off-label use treatments.
⇒ The study design does not allow making causal conclusions regarding the impact of access to off-label use treatment on patient's survival

INTRODUCTION

Off-label drug use (OLU) is common in oncology.[1 2] OLU is the use of drugs outside their approved label, and can be further subdivided (eg, use in a different disease entity, use of an unapproved route of administration or an unapproved dose).[2] Whether the use of a drug is off-label may vary across different countries and can change over time.[3] In Switzerland, about 20% of patients with cancer are treated at least once with OLU.[4] Situations in which OLU is intended include those when heavily pretreated patients do not have any further approved treatment option,[5] or when randomised evidence for new and beneficial treatment options becomes available but formal approval is pending,[6 7] or when treatment strategies from other cancer types are extrapolated to the specific case.[8] Typically, OLU is perceived as last option in situations when approved therapies are exhausted.[9–11] However, we have recently shown that 45% of all reimbursement requests for OLU in Switzerland were for first-line therapies.[4]

Access to OLU is commonly regulated through reimbursement restrictions, given the frequently high costs of these drugs.[12] In Switzerland, reimbursement of OLU is individually determined by the health insurers. An upfront reimbursement request is issued by the treating physician and the reimbursement decision is made on a case-by-case basis. While most patients in Switzerland get reimbursement and therefore access to OLU, the decisions seem arbitrary and were

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not associated with the underlying evidence on treatment benefits in a systematic analysis of the supporting evidence.[4]

Previous studies explored widely the prevalence of OLU,[1 2] but did not focus on the actual clinical situations when patients and physicians aim to get access to OLU. Characteristics and prognostic factors of such patients have not been investigated so far, and it is unclear whether the individual risk profile is associated with access to OLU. Furthermore, previous studies have investigated patients who were treated with OLU but not all patients for whom OLU was initially intended.

We aimed to describe the characteristics of patients with cancer with intended OLU, their survival and differences between patients with or without access to OLU.

METHODS

This retrospective cohort study is part of the CEIT-OLU project (Comparative Effectiveness of Innovative Treatments in Cancer—Off Label Use) described elsewhere.[13] In brief, we screened medical records of patients with a first consultation at three major Swiss oncology/haematology centres (Basel, Bern and St. Gallen) between January 2015 and July 2018. From one centre (Basel), we included all eligible patients, and we randomly sampled 1000 patients from all eligible patients in each of the two other centres for feasibility reasons. We used routinely collected data from medical records to investigate the prevalence of intended OLU in patients with cancer, their characteristics, the access to OLU and the overall survival (OS) of patients with cancer with intended OLU. We also compared patient, disease and treatment characteristics between patients who had access to the requested OLU and received the treatment (labelled as 'access to OLU' throughout the script) compared with patients without access to OLU who received another or no treatment (labelled 'no access to OLU' throughout the script).

Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology and RECORD guidelines.[14 15]

Inclusion and exclusion criteria

We identified all patients with a malignant disease with at least one reimbursement request for OLU. We defined OLU as any drug use that did not agree with the official approval of the Swiss drug regulator (Swissmedic) described in the drug label regarding the malignancy, treatment setting or line of treatment at the time of the reimbursement request.[13] We excluded reimbursement requests for supportive treatments (eg, zoledronic acid for patients receiving aromatase inhibitors). Reimbursement requests solely for the change of treatment interval (eg, nivolumab 480 mg every 4 weeks instead of nivolumab 240 mg every 2 weeks), requests for different application of the same drug (eg, subcutaneous rituximab instead of intravenous application) were excluded as they do not change the overall management of the anticancer treatment. We also excluded requests if the treatment situation changed after the request was issued (ie, reimbursement request for new treatment line because disease progression or relapse was suspected but was not confirmed in due course). Patients who died after the date of the reimbursement request but prior to the reimbursement decision would have been excluded (also this was not the case in our sample).

Data collection

Between August 2018 and October 2020, we extracted from medical records the baseline information at the time point of the reimbursement request, and the follow-up information up to 16 November 2020. We chose the date of the request as the beginning of the follow-up period, reflecting the time point when the treatment decision for OLU was made. The extracted baseline information was data on patient characteristics (age, sex), disease (cancer type, stage) and previous and intended treatments (drug type, line of treatment, treatment setting). Cancer type was categorised according to organ systems and histological subtypes. Biomarkers were only extracted if mandatory for the drug treatment intended (ie, PD-L1 expression for treatment of lung cancer with immune checkpoint inhibitors). Drug types were categorised as antihormonal (eg, aromatase inhibitors), cytotoxic chemotherapy, checkpoint inhibitor (drugs targeting PD-1, PD-L1 or CTLA4), immunomodulating drugs (eg, lenalidomide), monoclonal antibodies, monoclonal antibody–drug conjugates, targeted treatments (small molecules, eg, BRAF inhibitors) and other (including Alitretinoin, Lu-177-PSMA, Nelfinavir, Novo-TTF). We extracted C reactive protein (CRP) and albumin values to calculate the Glasgow prognostic score (GPS).[16 17] The GPS discriminates three prognostic groups: 0 (CRP within normal range; albumin normal or decreased); 1 (CRP elevated; albumin normal); 2 (CRP elevated; albumin decreased). GPS is correlated with mortality in patients with various types of cancer; with higher mortality for patients with GPS 1 versus patients with GPS 0, or GPS 2 versus GPS 1.[16] The extracted follow-up information included the occurrence death and date of last contact.

OLU indications

OLU indications were defined based on the drug, disease entity (eg, non-small cell lung cancer, adenocarcinoma), treatment setting (adjuvant/neoadjuvant, induction, maintenance therapy, palliative/advanced) and line of treatment (first line, second line or third line and beyond). On 9 May 2021, we examined Swissmedic labels for all OLU drugs requested at least four times, to assess how many had been then approved by the Swissmedic and included in the label.

Statistical analysis

We used descriptive statistics to summarise patient, treatment and disease characteristics. We calculated ORs for associations of binary patient, disease and treatment

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characteristics between patients with and without access to the requested OLU, p values were derived using the Wald test.[18] OS was defined as the time between the date of request and death due to any cause. We used the Kaplan-Meier method to estimate and visualise OS with 95% CIs. We used the inverse Kaplan-Meier estimator to estimate the follow-up time for the entire cohort, and we also report the median (range) follow-up for all patients alive.[19] Patients were censored at the date of last contact when the event of interest did not occur during follow-up. All analyses are explorative.

We conducted two subgroup analyses. First, we described the patients with solid cancer in the advanced setting. Their survival was expected to differ substantially from other patients with cancer with earlier disease stages.[20] Second, we investigated patients with solid cancer in the advanced setting with intended OLU as a first systemic treatment, as we expect their survival to differ substantially from patients treated in later lines. We used R for data cleaning and analyses (The R Project for Statistical Computing, https://www.r-project.org/).[21]

Patient and public involvement statement

Patients and public were not directly involved in this cohort study.

RESULTS

We identified 3046 patients with a malignant disease who were treated with systemic anticancer treatment and had a first consultation between January 2015 and July 2018. Forty-seven patients were excluded (for details see online supplemental figure S1). For 519 (17%) of the 3046 patients, OLU was intended and a request for reimbursement was issued. Of the 519 patients, 389 (75%) patients had access to the intended OLU drug due to reimbursement by the health insurer or other sources, while 108 (21%) did not. Of those 108 patients, 61 received another treatment and 47 did not receive any further active cancer treatment at all. For 22 (4%) patients, information on access to OLU was missing.

Characteristics of patients and intended OLU

Patients with intended OLU had a median age of 65 and 63% were men (n=328; table 1). Most patients had a solid cancer (63%, n=329), 21% (n=111) had a haematological malignancy and 15% (n=79) had lymphoma.

OLU was most frequently requested for the treatment of non-small cell lung cancer (9%, n=48), multiple myeloma (8%, n=44) and acute myeloid leukaemia (6%, n=29). Treatment with a checkpoint-inhibitor was requested for 21% (n=109), a targeted therapy for 12% of the patients (n=63). OLU was mostly intended as a first-line (51%, n=264) or second-line treatment (31%, n=162). Most patients were in an advanced or palliative treatment setting (56%, n=291). Forty-one OLU indications were requested at least four times, covering 283 of all 519 OLU requests (55%, online supplemental table S1). Swissmedic approved 41% (17 of 41) of these most frequently requested indications subsequently (ie, by 9 May 2021).

Patients with access to OLU were on average 4.9 years younger (95% CI: 1.9 to 7.9 years, p=0.002, table 1) had a better overall prognosis according to the GPS (51% with GPS of 0 vs 39%; OR: 1.62 (1.01 to 2.59)), had less likely solid cancer (62% vs 71%; OR: 0.48 (0.30 to 0.75)), less likely advanced stage cancer (53% vs 70%; OR: 0.48 (0.30 to 0.75)), had less likely thoracic cancers (11% vs 24%; OR: 0.39 (0.23 to 0.68)), were more likely treatment naive (53% vs 43%; OR: 1.55 (1.01 to 2.39)) and were more likely in an adjuvant/neoadjuvant setting (14% vs 5%; OR: 3.39 (1.45 to 9.93)). Data were limited for assessing differences among other types of cancers or drugs, but CIs were compatible with substantial differences between patients who received access or not.

Survival

Complete survival data were available for 488 (94%) of the 519 patients, for 11 the date of request was missing and for 20 data on access to OLU were missing (online supplemental figure S1). After an estimated median follow-up of 35 months, 279 of the 488 patients with intended OLU died (57%). The median OS was 23.6 months (95% CI: 19.0 to 32.5; table 2).

Patients with access to OLU (n=381) had a median OS of 31.1 months (95% CI: 21.6 to 41.4) versus 8.7 months (95% CI: 5.1 to 22.3) for patients without access (n=107; figure 1).

Subgroup analyses

Patients with metastatic solid cancer and a palliative treatment setting (n=258) had a median age of 66 years and 67% were men (n=174; Online supplemental table S2). They had a median OS of 10.6 months (95% CI: 8.4 to 14.0).

Patients with access to OLU were on average 5.9 years younger (95% CI: 2.3 to 9.4, p=0.001) than patients without access, and numerically more patients with better overall prognosis according to the GPS (41% with GPS of 0 vs 33%; OR: 1.47 (95% CI: 0.82 to 2.69)) had access to OLU. The proportion of treatment-naive patients (first-line treatment 41% vs 40%; OR: 1.05 (0.60 to 1.83); online supplemental table S2) was similar in both groups. Patients with access to OLU (n=186) had a median OS of 13.8 months (95% CI: 10.8 to 16.2) compared with 4.2 months (95% CI: 2.5 to 7.4) for patients without access (n=72; figure 2A, table 2).

Patients with solid cancer with intended OLU as a first systemic treatment in the advanced treatment setting (n=106) had a median age of 71 years and 75% were men (n=106; Online supplemental table S3). They had a median OS of 17.9 months (95% CI: 14.9 to 33.8). Patients with access to OLU were on average 9 years younger (95% CI: 3.9 to 14.1, p=0.001) than patients without access and had numerically more often a better overall prognosis according to the GPS (45% with GPS of

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Table 1 Characteristics of patients with intended OLU in Switzerland

	All patients*	Access to OLU	No access to OLU		
	n=519	n=389	n=108	OR (95% CI)	P value
Age, median (IQR)	65 (55, 73)	64 (54, 72)	70 (59, 77)	–	<0.01
Sex—male, no (%)	328 (63)	248 (64)	68 (63)	1.03 (0.66 to 1.60)	0.88
Glasgow prognostic score, no (%)				1.62 (1.01 to 2.59)†	0.04†
0	243 (47)	198 (51)	42 (39)		
1	150 (29)	104 (27)	40 (37)		
2	44 (8)	36 (9)	8 (7)		
Missing	82 (16)	51 (13)	18 (17)		
Time period					
2015	38 (7)	28 (7)	9 (8)	0.86 (0.41 to 1.99)	0.71
2016	125 (24)	89 (23)	28 (26)	0.86 (0.53 to 1.42)	0.54
2017	225 (43)	171 (44)	48 (44)	1.00 (0.65 to 1.54)	0.99
2018	121 (23)	94 (24)	22 (20)	1.26 (0.76 to 2.17)	0.39
Unknown	10 (2)	7 (2)	1 (1)	–	–
Tumour type, no (%)					
Haematological	111 (21)	84 (22)	18 (17)	1.38 (0.80 to 2.47)	0.26
Haematological other	3 (1)	2 (1)	0	–	
Leukaemia	44 (8)	32 (8)	7 (6)	1.58 (0.69 to 4.27)	0.32
MDS and MPN	19 (4)	14 (4)	4 (4)	0.97 (0.34 to 3.48)	0.96
Multiple myeloma	49 (9)	39 (10)	7 (6)	1.61 (0.74 to 4.02)	0.27
Lymphoma	79 (15)	63 (16)	13 (12)	1.41 (0.77 to 2.78)	0.29
Aggressive lymphoma	42 (8)	30 (8)	10 (9)	0.82 (0.40 to 1.82)	0.60
Indolent lymphoma	33 (6)	30 (8)	3 (3)	2.92 (1.02 to 12.37)	0.08
Solid tumour	329 (63)	242 (62)	77 (71)	0.66 (0.41 to 1.05)	0.08
Brain	41 (8)	32 (8)	8 (7)	1.12 (0.52 to 2.68)	0.78
Breast	22 (4)	17 (4)	3 (3)	1.60 (0.52 to 6.94)	0.46
Endocrine	8 (2)	8 (2)	0	–	
Gastrointestinal	69 (13)	59 (15)	10 (9)	1.75 (0.90 to 3.76)	0.12
Gynaecological	21 (4)	12 (3)	7 (6)	0.46 (0.18 to 1.26)	0.11
Head and neck	14 (3)	12 (3)	2 (2)	1.69 (0.45 to 10.95)	0.50
Skin	34 (7)	25 (6)	8 (7)	0.86 (0.39 to 2.09)	0.72
Sarcoma and gist	23 (4)	15 (4)	7 (6)	0.58 (0.24 to 1.55)	0.25
Thoracic	72 (14)	43 (11)	26 (24)	0.39 (0.23 to 0.68)	0.001
Urogenital	24 (5)	18 (5)	6 (6)	0.82 (0.34 to 2.32)	0.69
Treatment setting					
Adjuvant/neoadjuvant	64 (12)	55 (14)	5 (5)	3.39 (1.45 to 9.93)	0.01
Induction	83 (17)	70 (18)	11 (10)	1.94 (1.02 to 3.99)	0.06
Maintenance	81 (16)	57 (15)	16 (15)	1.01 (0.56 to 1.89)	0.98
Advanced/palliative	291 (56)	207 (53)	76 (70)	0.48 (0.30 to 0.75)	0.002
Line of treatment‡				1.55 (1.01 to 2.39)§	0.05
First	264 (51)	208 (53)	46 (43)		
Second	162 (31)	114 (29)	40 (38)		
Third and beyond	93 (18)	67 (17)	22 (20)		
Drug type					
Antihormonal	22 (4)	18 (5)	3 (3)	1.70 (0.56 to 7.35)	0.40
Cytotoxic agents	157 (30)	123 (32)	28 (26)	1.32 (0.83 to 2.16)	0.26

Continued

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Table 1 Continued

	All patients*	Access to OLU	No access to OLU		
	n=519	n=389	n=108	OR (95% CI)	P value
Checkpoint Inhibitor	109 (21)	68 (17)	38 (35)	0.39 (0.24 to 0.63)	<0.001
Immunomodulator	35 (7)	23 (6)	9 (8)	0.69 (0.32 to 1.62)	0.37
Monoclonal antibody	106 (20)	90 (23)	11 (10)	2.65 (1.42 to 5.44)	<0.001
Antibody drug conjugate	3 (1)	1 (0)	2 (2)	0.14 (0.01 to 1.44)	0.11
Other¶	24 (5)	21 (5)	3 (3)	2.00 (0.67 to 8.57)	0.27
Targeted therapy	63 (12)	45 (12)	14 (13)	0.88 (0.47 to 1.72)	0.69

Patient characteristics, stratified by patients with access to OLU, patients without access to OLU. An OR greater than 1 indicates higher prevalence of the characteristic in patients with access to OLU.
*For 22 patients information regarding access to OLU was missing.
†OR for GPS 0 vs GPS>0.
‡Description of line of treatments includes all patients and treatment settings (eg, neoadjuvant/adjuvant treatment setting).
§OR for having first-line treatment vs second-line treatment or beyond.
¶Including Alitretinoin, Lu-177-PSMA, Nelfinavir, Novo-TTF.
GPS, Glasgow prognostic score; MDS, myelodysplastic syndrome; MPS, myeloproliferative neoplasia; OLU, off-label use.

0 vs 31%; 2.07 (0.82 to 5.47); online supplemental table S3). Patients with access to OLU (n=77) had a median OS of 25.2 months (95% CI: 15.7 to 38.5) compared with 4.5 months (95% CI: 2.7 to 22.9) for patients without access (n=29; figure 2B, table 2).

DISCUSSION

This cohort study based on routinely collected data from 519 patients in Switzerland shows that OLU is common in various cancer treatment settings across the entire spectrum of malignancies. In contrast to frequent assumptions, many patients with intended OLU do not have a critically limited survival prognosis or exhausted approved treatment options. While patients with intended OLU had overall a median survival of 2 years, those with access to OLU lived longer than those without.

While it may be tempting to conclude that this observed survival difference (31.1 vs 8.7 months) is caused by the OLU drug treatment, this interpretation is unlikely to be valid. Our study was not designed to explore causal effects. We report crude, unadjusted estimates to describe the survival that are not valid to measure causal effects. Patients who had access to OLU were on average younger, were more frequently treated within an adjuvant or maintenance setting and had a better prognosis according to the GPS. Patients with and without access received different drug types and had different types of cancer. In addition to such known and measured critical

Table 2 Overall survival among all patients and subgroups

	No of patients	Median OS months (95% CI)	1-year survival in % (95% CI)	2-year survival in % (95% CI)	3-year survival in % (95% CI)	4-year survival in % (95% CI)
Main analysis including all patients						
All patients	488	23.6 (19.0 to 32.5)	66 (62 to 70)	50 (45 to 54)	43 (38 to 48)	35 (29 to 41)
Access to OLU	381	31.1 (21.6 to 41.4)	72 (68 to 77)	53 (49 to 59)	46 (41 to 52)	37 (31 to 45)
No access to OLU	107	8.7 (5.1 to 22.3)	45 (36 to 55)	36 (28 to 46)	30 (22 to 39)	25 (16 to 36)
Patients with solid cancer in advanced or palliative treatment setting						
All patients	258	10.6 (8.4 to 14.0)	48 (42 to 55)	27 (22 to 33)	20 (15 to 26)	11 (7 to 19)
Access to OLU	186	13.8 (10.8 to 16.2)	56 (49 to 63)	30 (24 to 38)	22 (17 to 30)	13 (7 to 23)
No access to OLU	72	4.2 (2.5 to 7.4)	28 (19 to 42)	16 (10 to 29)	13 (7 to 25)	7 (2 to 22)
Patients with OLU as first systemic treatment						
All patients	106	17.9 (14.9 to 33.8)	64 (55 to 74)	45 (36 to 56)	35 (26 to 47)	25 (15 to 41)
Access to OLU	77	25.2 (15.7 to 38.5)	72 (63 to 83)	53 (42 to 65)	39 (28 to 53)	25 (13 to 46)
No access to OLU	29	4.5 (2.73 to 22.9)	40 (25 to 64)	22 (11 to 47)	22 (11 to 47)	22 (11 to 47)

Patient survival for the main analyses and subgroups, stratified by patients with access to OLU vs patients without.
OLU, off-label use; OS, overall survival.

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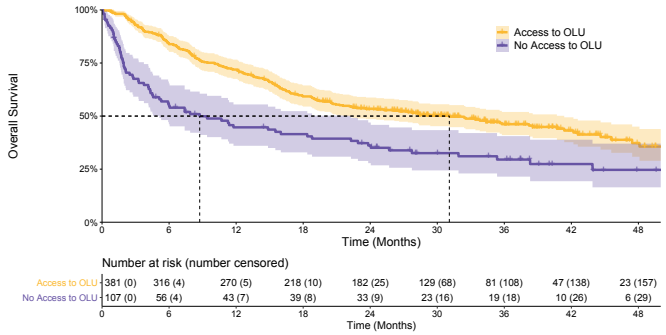

Figure 1 Overall survival of patients with intended OLU. OLU, off-label use.

confounding factors, there are numerous known but unmeasured potential confounders that are relevant for survival prognosis that are not considered in our analyses. One of them is the clinical performance status, which was not systematically documented in the health records available to us. Beyond this, the observed survival difference is substantially larger than the small impact on OS of 2.4 months that new cancer drugs showed in randomised trials on average within their first approved indication.[22 23]

When restricting the analysis to patients in a palliative treatment situation or patients receiving their first systemic treatment, survival differences remained. Almost half of the patients without access to intended OLU received no other treatment after their reimbursement request was rejected, and for almost half of them, OLU was intended as a first-line therapy. This means that 9% of all 519 patients received no treatment at all due to the

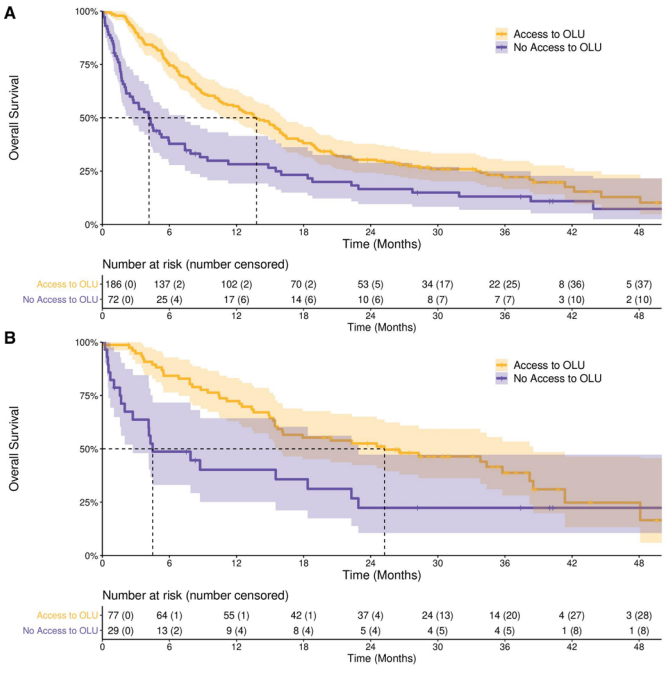

Figure 2 Overall survival among patient subgroups. (A) Overall survival among patients with metastatic solid cancer. (B) Overall survival among patients with metastatic solid cancer and intended OLU as first-line treatment. OLU, off-label use.

reimbursement decision. This frequent disagreement of the health insurer's decision with the individual clinical decision suggests an impact of health insurer's decisions on treatment strategies but it remains unclear how this impacts patient outcome.

In contrast to previous studies investigating OLU in oncology, we did not screen for the actual treatment with off-label drugs but for reimbursement requests for OLU by the treating physician.[2 12] This allowed us to capture all situations in which the treating oncologist/haematologist sought treatment with OLU and not just the actual prescribed OLU treatments[1 2] and therefore have more detailed insights into the role of OLU in oncological care. This approach also allowed us to describe the differences in the cohort of patients who ultimately did or did not receive access to intended OLU.

Our cohort includes intended OLU in a variety of settings. While it was for most patients the first treatment, others were heavily pretreated. For one patient with multiple myeloma, the requested OLU treatment was for the 10th line. But overall, those indications reflecting the common assumption that OLU is for patients with exhausted treatment options were a minority.

In our cohort, OLU was often intended in scenarios when new evidence for treatment benefits emerged (eg, publication of trial results in peer-reviewed journals or at expert conferences) but formal approval was pending. In our study, 41% of the most frequently requested OLU indications were approved by Swissmedic in the following 3 years. For example, in September 2017, the first randomised controlled trial indicating clinical benefit of adjuvant nivolumab for localised melanoma was published.[7] Swissmedic approved nivolumab for this indication 1 year later in August 2018. Within this year, nivolumab was requested 14 times as OLU for the adjuvant treatment of localised melanoma in our cohort (see also Herbrand *et al*[4]). Another example is pembrolizumab, which was requested nine times as first-line treatment for metastatic non-small lung cancer. First evidence for an OS benefit in this indication was published in October of 2016,[6] which led to formal approval by Swissmedic 6 months later. Overall, this highlights that OLU is frequently intended not when approved standard treatments are exhausted or have failed, but when promising evidence emerges that sometimes may result in formal approval.

This study has some limitations: first, OLU status of cancer drugs may change over time, also during our study period. However, there have been no changes in the OLU reimbursement process or in the approval process of new cancer drugs in Switzerland during our study period. Additionally, current estimates of approval times for new cancer drugs range from 6 months in the USA to 12 months in Europe.[24] We therefore think that OLU with its current challenges for physicians and patients will remain an issue in oncology. Second, our study investigated OLU in Switzerland only. Characteristics of patients with intended OLU may vary across different

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countries and healthcare systems with different regulations. However, OLU in oncology is common in many western healthcare systems.[2] Therefore, we assume that the use of and access to OLU has a substantial impact on the treatment strategies of patients with cancer in other healthcare systems as well. Nevertheless, we think similar investigations conducted in other healthcare systems will be needed to complement the picture of the role of OLU in oncology. Third, while our sample of more than 500 patients represents a birds-eye view on a pan cancer population, this heterogeneity of different patients, diseases and treatment characteristics is reflected in estimates with sometimes wide CIs precluding more in-depth analyses. Because patients may die after the request for OLU but before the decision and access to OLU, the definition of the timepoints for survival time analyses requires careful attention to avoid immortal time bias. While in our study no patient died between request and reimbursement decision, future studies need to carefully consider this aspect. One option would be a landmark analysis with a plausible fixed time point since the request (eg, the median time from request to decision).

Our study shows that OLU is an integral part of current clinical routine in oncology. OLU is often applied for patients in early and sometimes curative treatment settings and not only in situations of exhausted treatment options. Patient characteristics and survival largely differ between patients with and without access to intended OLU. An in-depth and systematic evaluation of the benefits and harms of OLU in cancer care including transparent regulation of access to OLU for patients with cancer is urgently needed.

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Contributors AMS, BK and LH were involved in concept and design. Collection of data was done by AKH, AMS and MW. AMS analysed the data with input from GM, LH and BK. Drafting of the manuscript was done by AMS, MWC, LH and BK. Critical revision of the manuscript for important intellectual content was performed by AMS, MW, AKH, MJ, GM, UN, LH and BK. LH and BK obtained funding for this study. AMS, MW, AKH, MJ, GM, UN, LH and BK read and approved the final manuscript. AMS is responsible for the overall content as guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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