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ORIGINAL ARTICLE

Population-level effect of molecular testing and targeted therapy in patients with advanced pulmonary adenocarcinoma: a prospective cohort study

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Abstract Large cancer centres in the USA demonstrated that molecular diagnosis and targeted therapy improved overall survival of patients with advanced pulmonary adenocarcinoma. We validated this finding in a rural area of Switzerland, served by private practices, community hospitals and a tertiary referral centre. We conducted a prospective cohort study with the Cancer Registry of Central Switzerland, covering 4 cantons and 517,000 inhabitants. All residents newly diagnosed with stage IV pulmonary adenocarcinoma from 2010 to 2014 were enrolled. We obtained information on patients, tumour, molecular testing, therapy and survival. Three hundred forty-eight patients were included in the study. Molecular testing was performed in 279 (80%); 132 (38%) had oncogenic driver mutations: Kirsten rat sarcoma (KRAS, 16%), epidermal growth factor receptor (EGFR, 11%), anaplastic lymphoma kinase (ALK, 5%), human epidermal growth factor receptor 2 (HER2, 2%), B rapidly accelerated fibrosarcoma (BRAF, 1%), rearranged during transfection (RET, 0.5%), MET proto-oncogene (0.5%) and multiple mutations (2%). Fifty-six patients with an oncogenic driver mutation, mostly epidermal growth factor receptor (34) and anaplastic lymphoma kinase (12), received genotype-matched targeted therapy, at least 25 (45%) of whom in a clinical trial or named patient programme. Median overall survival was 18 months for patients with driver mutations and targeted therapy, 8 months for patients with driver mutations and conventional therapy and 10 months for patients with no driver mutation and conventional therapy. For patients with driver mutations and targeted therapy, overall survival was significantly better than that for patients with driver mutations and conventional therapy (HR 0.64, $p = 0.04$). Rigorous testing combined with optimal access to targeted therapy in clinical trials improved the prognosis of patients with advanced pulmonary adenocarcinoma in Central Switzerland. This effect was mainly driven by therapies targeting epidermal growth factor receptor and anaplastic lymphoma kinase.

Keywords Molecular diagnosis · Chemotherapy · Targeted therapy · Population study

Introduction

Every year, approximately 2500 men and 1500 women are diagnosed with lung cancer in Switzerland. Mortality is very high and on average, 2000 men and 1100 women die from lung cancer per year. It is the most common cause of cancer-related death among men in Switzerland, and the second most common among women [1]. Adenocarcinoma (AD) is the predominant subtype, and AD rates are increasing among both sexes [2]. Most patients (70–80%) with pulmonary AD have advanced/metastatic disease at the time of initial diagnosis and require palliative therapy. Chemotherapy can prolong survival and improve quality of life, and is a standard of care since several decades [3]. In 2004, the activity of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in AD with

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activating EGFR mutations was discovered, and in 2007, anaplastic lymphoma kinase (ALK) rearrangement was described as a drug target in a subset of AD predominantly found in non-smokers [4]. These and other discoveries led to the advent of molecular-targeted therapy in lung cancer in the following years.

At our institution, molecular testing and targeted therapy for pulmonary AD was introduced in the year 2010. In the same year, the Cancer Registry of Central Switzerland was established, providing an opportunity to study the impact of molecular testing and targeted therapy in our population in a prospective way. We therefore conducted a prospective cohort study with the Cancer Registry of Central Switzerland, covering the 4 cantons of Lucerne, Nidwalden, Obwalden and Uri, with a total of 517,000 inhabitants. Health care in Central Switzerland is provided by a network of private practices, community hospitals and a tertiary referral hospital offering all services required for the management of patients with thoracic cancers, including pathology, radiology, pneumology, thoracic surgery, radio-oncology, medical oncology, a clinical trial unit and palliative care. The Cancer Registry of Central Switzerland registers data of all residents of the canton of Lucerne (400,000 residents) newly diagnosed in 2010 or later, respectively, of all residents of the cantons of Nidwalden, Obwalden and Uri newly diagnosed in 2011 or later. The objective of our study was to describe the rate of molecular testing, the use of targeted therapies, and the survival outcome for residents in Central Switzerland who were newly diagnosed with pulmonary AD in the years 2010 to 2014.

Methods

Patients and data collection Our main study hypothesis was that targeted therapy correlates with improved survival compared with conventional chemotherapy. For the study, we enrolled all residents newly diagnosed with stage IV pulmonary AD from 2010 to 2014 (citizens of the canton of Lucerne), respectively, from 2011 to 2014 (citizens of the cantons of Nidwalden, Obwalden and Uri). From the cancer registry, the central pathology and the residents' offices, we obtained information on the date of diagnosis, the date of death, gender, smoking history (never, current or former smoker), tumour histology, TNM stage (as defined by the International Union Against Cancer, TNM classification, 7th edition [5]), molecular testing and type of treatment (type of chemotherapy or targeted therapy, participation in clinical trials, surgery and chest radiotherapy). The cutoff date for data collection was 19 February 2016.

The Cancer Registry of Central Switzerland is approved by the Federal Department of Home Affairs. The approval gives permission to the registry to collect data on cancer patients without a written informed consent of each patient, yet patients have to be informed about the activities of the Cancer Registry by their physician and all patients have the right of veto. Our study was approved by the Ethics Committee of Northwestern and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz EKNZ).

Histological diagnosis and molecular analysis The histological diagnosis and molecular analysis were mostly carried out in the central pathology. The methods used for histological diagnosis of lung AD were light microscopy and immunohistochemistry (TTF1, napsin), according to the WHO classification [6]. Ordering of additional molecular testing was the responsibility of the treating physician, no reflex testing was carried out directly by the pathologist. The fluorescence in situ hybridization (FISH) technique was used for testing of ALK, ROS proto-oncogene 1 (ROS1) and rearranged during transfection (RET) (all probes purchased from Zytovision, Germany). In addition, immunohistochemistry for ALK (clone D5F3, Roche-Ventana, USA) and ROS1 (clone D4D6, Cell Signaling, USA) was performed on a Benchmark automated stainer (Roche-Ventana). Sanger sequencing was used for mutation analysis of EGFR, Kirsten rat sarcoma (KRAS), neuroblastoma rat sarcoma (NRAS), B rapidly accelerated fibrosarcoma (BRAF), human epidermal growth factor receptor 2 (HER2) and MET proto-oncogene (MET). The success rate of molecular testing in the Institute of Pathology of Lucerne is > 95%.

Statistical analysis The Kaplan-Meier method is used for computing survival curves of our groups of interest. Overall survival (OS) time is determined by time of diagnosis of stage IV (time when cancer has spread to distant parts of the body) to time of death. We used right censoring for patients without event or which were lost to follow-up. The Kaplan-Meier curves show the survival probability for up to 5 years. The log-rank test [7] was used for comparing the OS of two or more groups. The hazard ratio is defined as the ratio of the relative death rates in the groups. p values less than .05 were considered to indicate statistical significance. A Cox proportional hazards model was used for association with age, gender, smoking and brain metastasis. We tested the proportional hazard assumption of the Cox regression model [8]. For statistical analysis, we used R version 3.2.2 and the survival package version 2.38-3. No adjustment was made for multiple testing.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results

Patient selection In the Cancer Registry of Central Switzerland, 424 patients were registered with pure pulmonary AD (excluding mixed histology) diagnosed between 2010 and 2014. After review, 73 patients were excluded

because no stage IV disease was reported, and 3 patients were excluded because diagnosis occurred at autopsy. Ultimately, 348 patients with advanced pulmonary AD were included in the study. In 132 (38%) patients, at least one oncogenic driver mutation (ODM) was found by molecular analysis. After review of the administered therapies, patients were assigned to four therapy groups, as shown in Fig. 1: Of the 132 patients with an ODM, 59 (45%) received conventional therapy (group 1: surgery, chest radiotherapy or chemotherapy), and 56 (42%) received genotype-matched targeted therapy (group 2) as first-line or second-line treatment. One hundred fifty-three patients with no known ODM received conventional therapy (group 3), and the remaining 80 patients (group 4: 63 with no known ODM and 17 with an ODM) were treated with best supportive care (BSC) only.

Patient characteristics Table 1 shows the patient characteristics of the total study population, and of the four therapy groups. In the study population, 190 (55%) patients were men, median age at diagnosis of stage IV was 66 years (range, 30–94) and at least 197 (57%) were current or former smokers. At the time of the initial diagnosis, 294 (84%) had stage IV disease and 54 (16%) had stages I to III, but developed stage IV during the course of the disease. Patient characteristics were as expected. We used Pearson's chi-squared test and Fisher's exact test to check for independence of patient sex, smoking history and tumour stage with respect to the assigned therapy group. The test does not provide any evidence against the independence of sex and the assigned therapy group, but there is evidence for associations between tumour stage as well as smoking history and the assignment to a therapy group.

Molecular testing In relation to the year of diagnosis of the disease, the testing rate increased each year from 59% for patients diagnosed in 2010 to 94% for patients diagnosed in 2014 (2010 59%, 2011 79%, 2012 84%, 2013 85%, 2014 94%). These percentages are identical with EGFR testing. Details on the frequency of gene testing in relation to the year of diagnosis of the disease are shown in Online Resource 4. Overall, molecular testing (PCR, IHC and FISH) of at least one gene was performed in 279 (80%) of the patients. One hundred thirty-two (38%) patients had positive molecular analyses: 125 patients had one ODM, 6 had two ODMs and 1 had three ODMs reported. The distribution of ODMs is shown in Fig. 2: 56 KRAS (16%), 39 EGFR (11%), 16 ALK (5%), 6 HER2 (2%), 4 BRAF (1%), 1 RET (0.5%), 1 MET (0.5%), 1 phosphatase and tensin homolog (PTEN) (0.5%), 1 FGFR1 (0.5%) and 7 with multiple ODMs (2%). In 147 (42%) patients, molecular testing was negative by current standard methods. The percentages earlier refer to the overall study population of 348 patients. Referring the percentages to the number of tested patients only (279), 47% had positive molecular analyses and the distribution of ODMs is as follows: 20% KRAS, 14% EGFR, 6% ALK, 2% HER2, 1% BRAF, 0.5% RET, 0.5% MET, 0.5% PTEN, 0.5% FGFR1, 3% multiple ODMs. Combinations in patients with multiple ODMs were 1 EGFR and MET, 1 EGFR and HER2, 1 EGFR and ALK, 1 KRAS and ALK, 1 KRAS and EGFR, 1 NRAS and ALK, 1 KRAS and HER2 and ALK.

Cancer therapy In the group of patients who received genotype-matched targeted therapy, 34 of 56 (61%) had an activating EGFR mutation and 12 (21%) had an ALK rearrangement. Other mutations in this group were 1 BRAF, 4 HER2, 1 KRAS, 1 RET and 3 multiple ODMs (1 EGFR and MET, 1 EGFR and HER2, 1 EGFR and ALK). At least 25 of 56 (45%) patients in this group took part in a clinical trial or named patient programme providing access to new targeted therapies. In the group of the 59 patients with an ODM who received conventional therapy, 44 (75%) had tumours with KRAS mutations. Other mutations in this group were 4

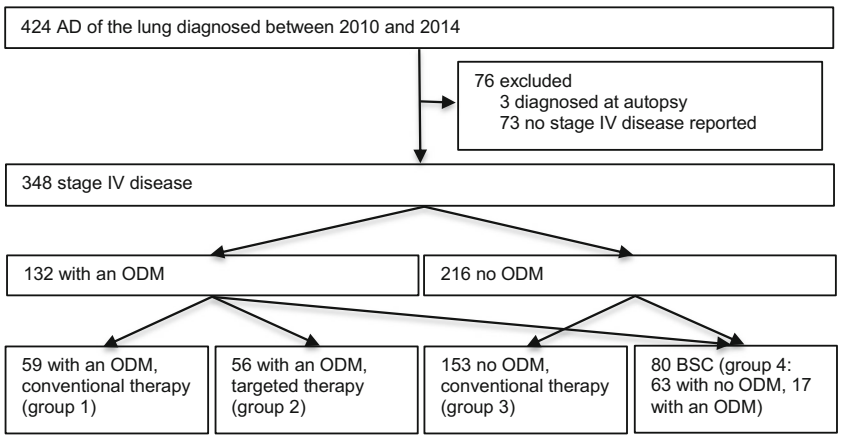


Fig. 1 Study flow chart with therapy groups. *AD* adenocarcinoma, *ODM* oncogenic driver mutation, *BSC* best supportive care

Table 1 Patient characteristics of the study population and the therapy groups

	Study population	ODM, conventional therapy	ODM, targeted therapy	No ODM, conventional therapy	BSC[a]	*p* value
No. (%)	*n* = 348	*n* = 59	*n* = 56	*n* = 153	*n* = 80	
Sex						0.09
Men	190 (55)	27 (46)	25 (45)	93 (61)	45 (56)	
Women	158 (45)	32 (54)	31 (55)	60 (39)	35 (44)	
Age at diagnosis of disease, median (range), years	65 (30–94)	60 (42–78)	65 (30–81)	65 (37–85)	75 (39–94)	
Age at diagnosis of stage IV[b], median (range), years	66 (30–94)	60 (42–78)	66 (30–81)	65 (37–85)	75 (39–94)	
Smoking history						< 10E−6*
Never	30 (9)	3 (5)	16 (29)	9 (6)	2 (3)	
Current	159 (46)	35 (59)	9 (16)	83 (54)	32 (40)	
Former	38 (11)	6 (10)	5 (9)	20 (13)	7 (9)	
Missing	121 (35)	15 (25)	26 (46)	41 (27)	39 (49)	
Stage[b] at diagnosis of disease						0.01*
Stage I	12 (3)	2 (4)	1 (2)	8 (5)	1 (1)	
Stage II	10 (3)	1 (2)	1 (2)	5 (3)	3 (4)	
Stage III	32 (9)	10 (17)	4 (7)	18 (12)	0 (0)	
Stage IV	294 (84)	46 (78)	50 (89)	122 (80)	76 (95)	
Brain metastasis at diagnosis of disease	72 (21)	17 (29)	10 (18)	27 (18)	18 (23)	

ODM oncogenic driver mutation, *BSC* best supportive care

[a] 63 patients with no ODM and 17 patients with an ODM

[b] TNM Classification of Malignant Tumours, 7th edition

EGFR, 2 ALK, 1 BRAF, 1 HER2, 1 FGFR1, 1 MET, 1 PTEN and 4 with multiple ODMs (1 KRAS and ALK, 1 KRAS and EGFR, 1 NRAS and ALK, 1 KRAS and HER2 and ALK). The 17 patients with an ODM in the BSC population had the following mutations: 11 KRAS, 2 ALK, 2 BRAF, 1 EGFR, 1 HER2. Detailed therapies are shown in Table 2 and in Online Resource 1.

Clinical outcome Survival data were available from the registry for all 348 patients, including 289 deaths and 59 censored patients (49 alive at the cutoff date, and 10 lost to follow-up). Figure 3 shows the median OS of the different therapy groups. The plot in Fig. 3a compares the survival of the genotype-matched targeted therapy group to conventional therapy and BSC populations. The OS was 18 months for patients with an ODM who received targeted therapy, 8 months for patients with an ODM who received conventional therapy, 10 months for patients with no ODM who received conventional therapy and 1 month for patients who received BSC only. For patients

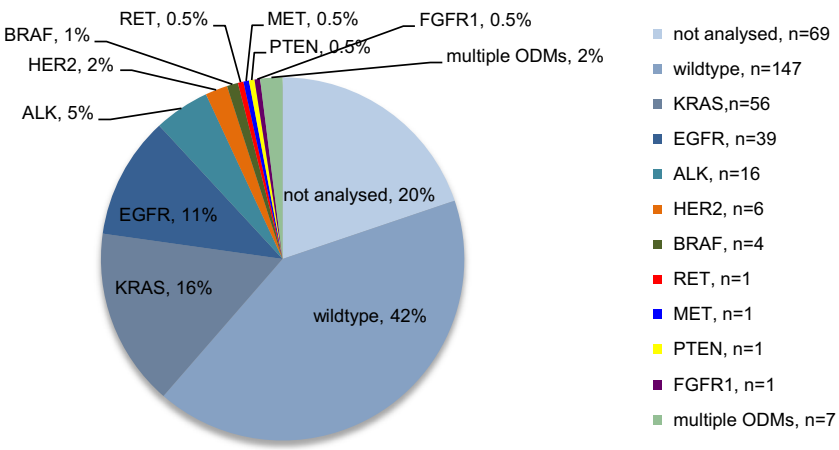


Fig. 2 Frequency of oncogenic driver mutations in our study population. *KRAS* Kirsten rat sarcoma, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase, *HER2* human epidermal growth factor receptor 2, *BRAF* B rapidly accelerated fibrosarcoma, *RET* rearranged during transfection, *MET* MET proto-oncogene, *PTEN* phosphatase and tensin homolog, *FGFR1* fibroblast growth factor receptor 1, *ODMs* oncogenic driver mutations

Table 2 Assigned therapies in the overall study population and in the therapy groups

	Study population	ODM, conventional therapy	ODM, targeted therapy	No ODM, conventional therapy
No. (%)	$n = 348$	$n = 59$	$n = 56$	$n = 153$
Surgery	55 (16)	17 (29)	8 (14)	30 (20)
Chest radiotherapy	44 (13)	10 (17)	10 (18)	24 (16)
Chemotherapy	233 (67)	54 (92)	40 (71)	139 (91)
EGFR TKI				
Erlotinib	58 (17)	4[e] (7)	27 (48)	27 (18)
Gefitinib	8 (2)	0 (0)	8 (14)	0 (0)
Afatinib	11 (3)	0 (0)	11 (20)	0 (0)
Osimertinib	2 (1)	0 (0)	2 (4)	0 (0)
ALK TKI				
Crizotinib	14 (4)	2[f] (3)	12 (21)	0 (0)
Alectinib	2 (1)	0 (0)	2 (4)	0 (0)
Ceritinib	3 (1)	0 (0)	3 (5)	0 (0)
Other targeted therapies				
Lapatinib	1[a] (0.5)	0 (0)	1[a] (2)	0 (0)
Trastuzumab	4[a] (1)	0 (0)	4[a] (7)	0 (0)
Ponatinib	1[b] (0.5)	0 (0)	1[b] (2)	0 (0)
Vemurafenib	1[c] (0.5)	0 (0)	1[c] (2)	0 (0)
Buparlisib-trametinib	1[d] (0.5)	0 (0)	1[d] (2)	0 (0)

ODM oncogenic driver mutation, *EGFR* epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor, *ALK* anaplastic lymphoma kinase

[a] Patients with HER2 mutation

[b] Patient with fusion of RET-KIF5B

[c] Patient with BRAF mutation

[d] Patient with KRAS mutation

[e] All four patients with KRAS mutation

[f] One patient with KRAS mutation and ALK amplification, the other patient with KRAS mutation, HER2 mutation and ALK amplification

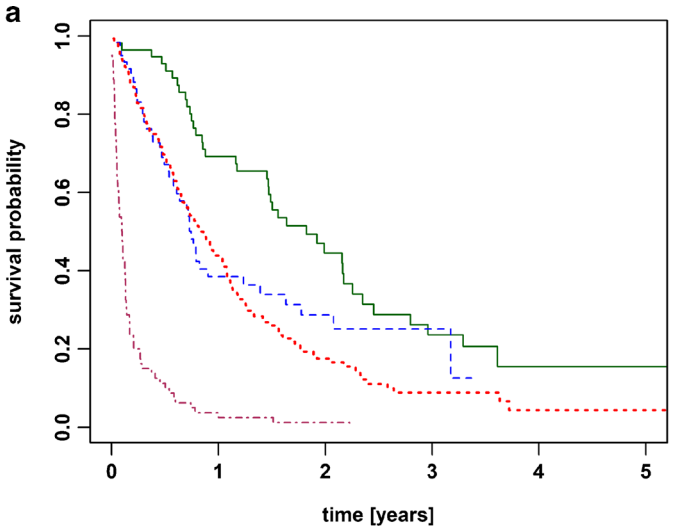
with an ODM and targeted therapy, the OS was significantly better than that for patients with an ODM and conventional therapy (HR 0.64, $p = 0.04$). A Cox proportional hazards model was used for association with age, gender, smoking and brain metastasis. No influence of these confounders on OS was found.

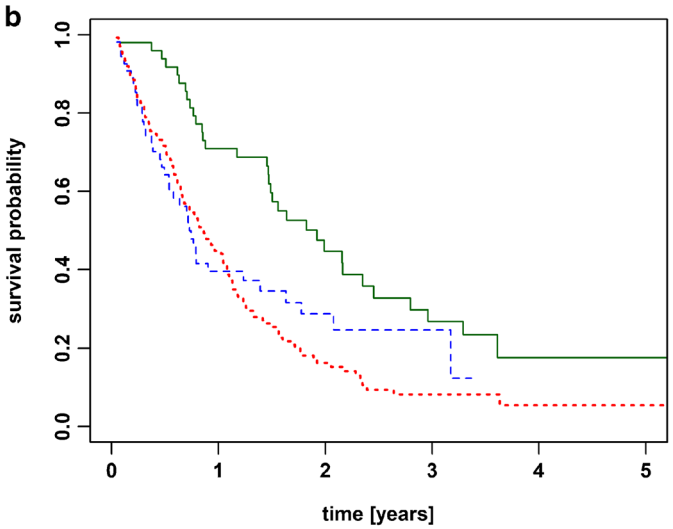
The plot in Fig. 3b equally shows the median OS of the different therapy groups, yet here, the therapy group populations were restricted to patients who received at least one chemotherapy (therefore excluding patients who received surgery and/or chest radiotherapy only) and the therapy group that received genotype-matched targeted therapy is restricted to patients with EGFR mutations and ALK rearrangements. See Online Resource 2 for the patient characteristics of these subgroups. The OS of the EGFR and ALK subgroups was 19 months and was significantly better than that for patients with ODM and chemotherapy (HR 0.6, $p = 0.03$).

The plot in Fig. 3c shows OS for the ALK subgroup compared with that of EGFR and KRAS subgroups. ALK rearrangements and EGFR mutations (and subsequent targeted therapies) were associated with favourable prognosis, with an OS of 24 months in the ALK subgroup and 19 months in the EGFR subgroup. KRAS patients had a significantly poorer outcome, with an OS of 11 months ($p = 0.01$). See Online Resource 3 for patient characteristics of these subgroups.

Discussion

We evaluated the impact of molecular testing and targeted therapy for patients in our region, newly diagnosed with advanced pulmonary AD in the time period from 2010 to 2014. The main advantages of our study were that it was relatively large, had a duration of 5 years and that it was prospective and based on a population registry rather than a single-institution database, thereby excluding selection bias. Stage migration was not a problem in our study, because whole-body FDG-PET/CT and brain MRI were





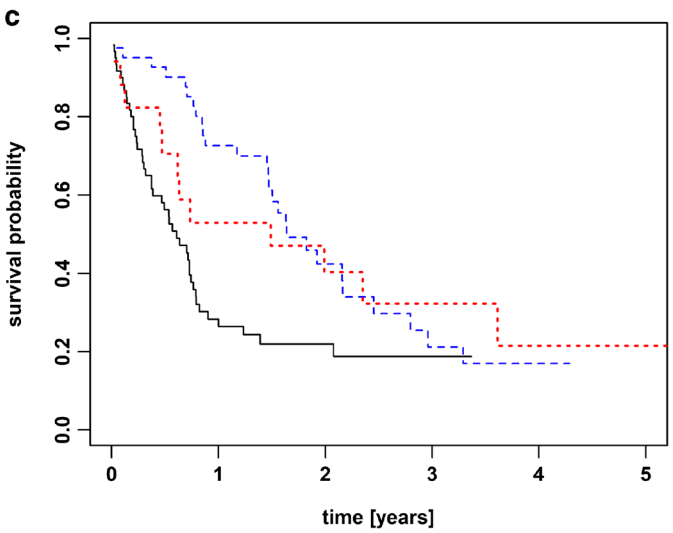


Fig. 3 Survival curves. **a** Survival for genotype-matched targeted therapy group compared with conventional therapy and BSC populations. **b** Survival for EGFR and ALK genotype-matched targeted therapy subgroup compared with chemotherapy populations. **c** Survival for ALK subgroup compared with EGFR and KRAS subgroups. *BSC* best supportive care, *ODM* oncogenic driver mutation, *HR* hazard ratio, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase, *KRAS* Kirsten rat sarcoma

routinely used for tumour staging from 2010 onward. Potential limitations of the study were incompleteness of smoking status in some cases and individual molecular testing based on the decision of the responsible clinician. Nevertheless, the rate of molecular testing increased over the study period and overall was 80% of our study population. This is comparable to the recently reported test rate in another hospital in Eastern Switzerland [9], and higher than the rates reported in some areas of Germany and the USA [10, 11]. The increase in the testing rate represents testing of the EGFR and ALK genes only. The increase for the other genes was less consistent. The 20% patients without testing in our study were mainly elderly patients (median age at diagnosis of stage IV was 71 years, compared to 66 years in the overall study population) or unfit for systemic therapy (52% received BSC only, compared to 23% in the overall study population). These data support our current practice, in that costly molecular diagnostics such as next gene sequencing (NGS) or FISH are ordered by clinicians on-demand, rather than reflex-based by pathology institutes, unless testing can be provided to patients for free. In France, molecular testing is offered through a national research programme to enhance drug development in oncology [12]. On behalf of the Federal Government, the Swiss Academy of Medical Sciences is currently launching a similar initiative, the Swiss Personalized Health Network (SPHN) [13].

In our study, molecular testing showed at least one molecular alteration in 38% of the tumours and enabled the detection of a potentially actionable molecular alteration in 20% of the patients. The prevalence of detected ODMs was consistent with that of the literature [12]. EGFR and ALK were the most frequent actionable ODMs and add up to 88% of the therapy group who received genotype-matched targeted therapy. In this therapy group, at least 25 (45%) patients took part in a clinical trial or named patient programme, showing the importance of tertiary referral centres with an active clinical trial unit and access to emerging new drugs. Our study confirms that molecular oncology is a highly dynamic field. At the start of our study in 2010, the only drug approved in Switzerland for targeted therapy was erlotinib (EGFR), however, it was not yet reimbursed by health insurance. In the course of the study, our centre enrolled patients into clinical trials, including SAKK19/09 [14], PROFILE1014 [15], REVEL [16] and ASCEND-5 [17]. Today, several new drugs are approved in Switzerland for targeting EGFR (erlotinib, gefitinib, afatinib, osimertinib), ALK (crizotinib, ceritinib, alectinib), ROS1 (crizotinib) and BRAF V600E (dabrafenib and trametinib) in pulmonary AD. Further drugs are commercially available for off-label use, including trastuzumab-emtansine (for HER2 exon 20 insertions), vandetanib (for RET rearrangements) and crizotinib (for MET exon 14 mutations).

Most importantly, our prospective study confirmed our hypothesis that targeted therapy was correlated with significantly improved survival in our region, compared with conventional chemotherapy. This finding is consistent with a large study conducted by the US LCMC, but to the best of our knowledge was not yet reproduced by many centres outside of the USA [18]. Patient characteristics between the chemotherapy and the targeted therapy groups were comparable. Of note, patients receiving best supportive care only were more likely to be older and to have comorbidities. Expected from the prevalence of some mutations and the speed of drug development in different fields, we found that EGFR and ALK were the main ODMs associated with measurable clinical benefit in our population. This finding was consistent with a recent study by the Network Genomic Medicine (NGM) in Germany, established in 2010 [19].

In the group of patients with a known ODM, who received conventional therapy, most (81%) had KRAS mutations. As expected from the literature, KRAS-mutant pulmonary AD remains a prevalent subtype with unmet medical need. Previous clinical trials with MEK inhibitors in this subgroup failed, including a recent phase III study with selumetinib [20]. Immune checkpoint inhibitors offer new hope for those patients. Between 2015 and 2017, programmed death (PD1)-immune checkpoint inhibitors were approved in Switzerland for the treatment of patients with advanced lung cancer, irrespective of tumour histology or mutation type. To study the prognostic impact of immunotherapy in our region, we are planning a follow-on project for patients diagnosed with advanced lung cancer between 2015 and 2017. Moreover, we participate in an international project (IMMUNOTARGET) to study potential correlations between tumour mutations and immunotherapy activity. Immune checkpoint inhibitors (nivolumab, pembrolizumab and atezolizumab) are predominantly active in current or former smokers, because smokers develop lung cancers with a high tumour mutation burden (TMB) [21]. In contrast, patients with pulmonary AD and EGFR mutations do not appear to benefit from immune checkpoint inhibitors [22]. IMMUNOTARGET and other studies are expected to lead to improved personalisation of systemic therapy for patients with advanced lung cancer in the near future.

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Compliance with ethical standards This study was reviewed and approved by the Ethics Committee of Northwestern and Central Switzerland, Basel, Switzerland (2016-00925).

Conflict of interest The authors declare that they have no conflict of interest.

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