Patterns of progression on osimertinib in EGFR T790M positive NSCLC: A Swiss cohort study

S. Schmid[a,*], D. Klingbiel[b,1], S. Aeppli[a], C. Britschgi[c], O. Gautschi[d], M. Pless[e], S. Rothschild[f], L. Wannesson[g], W. Janthur[h], D. Foerbs[i], I. Demmer[i], W. Jochum[i], M. Früh[a]

[a] Department of Oncology/Haematology, Cantonal Hospital St. Gallen, University of Bern Switzerland, Switzerland
[b] SAKK, Swiss Group for Clinical Cancer Research Coordinating Center, Bern, Switzerland
[c] Department of Hematology and Oncology, University Hospital Zürich, Switzerland
[d] Department of Oncology, Cantonal Hospital Lucerne, Switzerland
[e] Department of Oncology, Cantonal Hospital Winterthur, Switzerland
[f] Department of Oncology, University Hospital Basel, Switzerland
[g] Istituto Oncologico della Svizzera Italiana, Ospedale Regionale di Bellinzona e Valli, Switzerland
[h] Department of Oncology, Cantonal Hospital Aarau, Switzerland
[i] Institute of Pathology, Cantonal Hospital St. Gallen, Switzerland

ARTICLE INFO

ABSTRACT

Introduction: Osimertinib is an EGFR tyrosine kinase inhibitor (TKI) with antitumor activity in non-small cell lung cancer (NSCLC) with EGFR T790 M mutations. The incidence of oligo-progression (PD) on osimertinib is unknown.

Methods: We retrospectively analyzed 50 pre-treated EGFR T790M-positive NSCLC patients treated with osimertinib at seven Swiss centers. Oligo-PD was defined as PD in ≤ 5 lesions. Mutational profiling of pre- and post-osimertinib tumor samples was performed.

Results: Median age was 62 years (37–89), 64% were females, 86% had a PS ≤ 1, 54%/13% were never/current smokers. Median follow-up was 15.3 (IQR: 8.6–21.6) months. Overall response rate was 80%, median progression-free survival 12.1 months (95% CI 8.3–18.3), median overall survival 28 months (95% CI 20.2-not reached [NR]) and median treatment duration 18.8 months (95%CI 16-8-NR). PD occurred in 36 patients (72%). 73% had oligo-PD. Median osimertinib treatment duration in patients with oligo-PD was 19.6 vs. 7 months if systemic PD (p = 0.007). The number of progressive lesions in patients with oligo-PD was 1 (27%), 2 (35%) and 3–5 (39%). Sites of PD included lungs (56%), bones (44%), and brain (17%). Sixteen patients with oligo-PD continued treatment with osimertinib for a median of 6.7 months beyond PD. Thirteen received local ablative treatment (LAT). In pre- and post-PD tumor tissue multiple molecular alterations were detected.

Conclusion: In patients with acquired resistance to osimertinib, we observed a high rate (73%) of oligo-PD. Outcomes of patients receiving LAT were favorable, supporting the concept of osimertinib treatment beyond progression in combination with LAT of progressing lesions.

1. Introduction

In recent years, multiple actionable oncogenic drivers and corresponding targeted agents have been identified in non-small-cell lung cancer (NSCLC) patients. In patients with activating epidermal growth factor receptor (EGFR) mutations improved outcomes with respect to response rate (ORR), progression-free survival (PFS), and quality of life were demonstrated with first- or second-generation EGFR tyrosine

kinase inhibitors (TKIs) in comparison to standard first line platinum-based chemotherapy [1–6]. More than half of the patients with EGFR mutations progressing on EGFR TKIs develop a T790 M resistance mutation [7]. Osimertinib is an irreversible third generation EGFR-TKI selective for both EGFR-TKI sensitizing mutations and the T790 M resistance mutation in exon 20. The phase II non-randomised AURA II trial in patients with T790M-resistance mutation after first-line TKI treatment showed a high RR of 70% [8] and led to approval of

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* Corresponding author at: Rorschacherstrasse 95, 9007, St.Gallen, Switzerland.
  E-mail address: Sabine.schmid@kssg.ch (S. Schmid).
1 Now at Roche.

osimertinib by health authorities. The confirmatory randomized AURA III trial assessed osimertinib versus platinum-pemetrexed chemotherapy demonstrated superiority of the osimertinib versus platinum/pemetrexed in the second-line setting [9]. Patients in the osimertinib arm had improved PFS (11.0 months versus 4.2 months) and a higher ORR (71% versus 31%) [9]. In treatment-naïve patients with an activating EGFR mutation the randomised phase III FLAURA trial compared osimertinib with a first-generation EGFR-TKI and demonstrated superiority of osimertinib with respect to PFS and duration of response [10]. OS results are currently immature. Osimertinib has been approved as second-line treatment after failure of a first or second-generation TKI and presence of a T790M-mutation and as first-line treatment in all EGFR-mutated NSCLC patients by the by FDA and EMEA.

Unfortunately, all patients on osimertinib eventually progress after a median of 11 months in the second line setting [9]. Therefore, patterns of recurrence are clinically relevant, as they can direct surveillance strategies and may identify situations of oligoprogression (oligo-PD), in which continuation of targeted treatment after an ablative local therapy may be beneficial, as has been shown for first-generation EGFR- and ALK-TKIs [11]. To the best of our knowledge, the incidence of oligo-PD on osimertinib and the role of local treatment strategies in this situation are unknown as are outcomes with systemic therapy after osimertinib failure.

Next-generation sequencing (NGS) analysis of cell-free plasma DNA (cfDNA) of 15 *T790M*-positive patients treated with osimertinib in the phase I AURA study revealed an additional *C797S* mutation concurrently with persistent T790 M mutation in 40% of cases at progression, whereas loss of *T790M* mutation occurred in 27% [12]. in vitro, the *C797S* mutation which is located within the EGFR kinase-binding site, conferred resistance to all current EGFR TKIs in the presence of EGFR *T790 M* mutation, but the subset of cells with *L858R/T790M* and *C797S* remained partially sensitive to cetuximab [13]. Recently a first non-competitive allosteric inhibitor-EAI045-was presented, exhibiting dramatic synergistic activity with cetuximab in overcoming resistance in *L858R + /T790M + /C797S +* cell lines [14]. In addition, EGFR-independent mechanisms of osimertinib resistance have been identified including *HER2* and *MET* gene amplification, in both cases with concurrent loss of the *T790M* mutation [15]. Oxnard and colleagues presented molecular analyses from cfDNA progressing on osimertinib and found no *T790 M* mutation in 46%, *C797* in 27% (deletion exon 19 only and all with T790 M) and one patient each with *BRAF V600E* mutation, *PIK3CA* mutation, *MET* amplification, *HER2* amplification (all with no *T790M*) [16]. Most recently, the same group demonstrated that 32% of the patients maintained *T790M* mutation, of which the majority had a *C797S* mutation as resistance mechanism [17]. On the other hand, of the 68% with loss of *T790 M* mutation a wide range of resistance mechanisms occurred resulting in a shorter time to treatment discontinuation, likely due to emergence of pre-existing resistant clones [17].

The main aims of our study were to analyze recurrence patterns in patients with *EGFR T790M*-positive NSCLC receiving osimertinib and to evaluate the potential value of local and systemic treatment strategies during oligo-PD. Molecular analyses of NSCLC samples were performed to identify novel mechanisms of osimertinib resistance.

2. Methods

Eligible patients with T790M-positive NSCLC treated with osimertinib between January 2015 and December 2017 at seven oncology centres in Switzerland were included in this analysis. Clinical, radiological and pathological data were collected by local investigators. The primary objectives of the study were to assess progression patterns on treatment with osimertinib, to analyse the outcome of patients with oligo-PD in comparison to patients with systemic progression, and to evaluate a potential added benefit of local ablative therapy (LAT) in patients with oligo-PD.

Oligo-PD was defined as progression of ≤ 5 lesions and being overall PD according to RECIST 1.1. There is no universally accepted definition of oligometastatic disease however we based our definition on the most frequently applied definition of ≤ 5 metastases for solid tumors [18,19]. Secondary endpoints were site of progression on osimertinib treatment, OS, PFS, RR with osimertinib, RR to subsequent systemic therapy. Patients must have received adequate follow-up including documented radiological evaluation of tumor manifestations generally with computed tomography (CT) every two to three months. Anonymized data were documented and analyzed in a central electronic database at the Group for Clinical Cancer Research (SAKK) Coordinating Center. Data on patient and tumor characteristics, treatment and treatment outcome were collected. Responses were defined according to the Response Evaluation Criteria in the Solid Tumors guidelines, version 1.1. Tumor assessments were performed by local radiologists.

PFS was defined as time from osimertinib treatment start to progression; OS was defined as time from start of osimertinib treatment to death or last contact. Patients not experiencing an event were censored at the time of data cut-off (Aug 21, 2018) or at the last contact of lost to follow-up. The first patient started treatment in August 2014, the last patient in December 2017. Treatment over progression was defined as treatment which was continued for at least two months after progression. The interval of two months was chosen since this represents the mostly applied minimum imaging frequency in everyday clinical practice and thus patients receiving osimertinib for a minimum of two months over PD represent patients who were treated over PD with an adequate imaging assessment. Time-to-event end points were analyzed by the Kaplan-Meier method.

To identify molecular mechanism of osimertinib resistance, mutational profiling of paired tumor samples obtained prior to osimertinib treatment and after progression was performed using a next-generation sequencing (NGS)-based assay (Oncomine Focus Assay; ThermoFisher), which enables the detection of genomic variants in 52 cancer-associated genes (see Supplementary Table 1 for details).

Approval from the ethics committee of St. Gallen (Lead Ethics), Ticino, Zürich and Central Switzerland was obtained before starting data collection.

3. Results

3.1. Patient and tumor characteristics

Fifty patients were included in this analysis. The median age was 62 (range: 37–89), the majority were females (64%) and never (54%) or former smokers (25%) with good ECOG performance status (PS ≤ 1) (86%). Patient and tumor characteristics are summarized in Table 1.

The main molecular baseline characteristics at diagnosis were *EGFR exon 19 deletion* (74%) and *EGFR L858R exon 21 mutation* (24%). 12% of patients (2 with *exon 19 deletion* and 4 with *L858R* mutation) had initial concomitant alterations (*exon 18/ exon 20* mutation [n = 1], *TP53* mutation [n = 1], *E709 K EGFR*-mutation in Exon 18 [n = 1], *ALK* rearrangement [n = 2], *K757 N EGFR*-mutation in Exon 19 [n = 1] and de novo *T790M*-mutation [n = 1]). The initial *EGFR* mutation persisted in 96% of pre-osimertinib tumor samples with *T790M* mutation; in four patients additional alterations were found, namely *E746_A750 Exon 19 deletion*, *K757 N exon 19* mutation, *CTNNB1 S33F* mutation with concomitant *FGFR1* Fusion and one patient with *EGFR, MET* and F*GFR4*-amplification.

3.2. Outcomes

The median follow-up of the cohort was 18 (IQR: 8.6–28) months. ORR was 80%, including 4 patients with a complete remission (CR). Disease-control-rate (DCR) was 92%, median PFS 12.1 months (95% CI

Table 1
Patient Characteristics.

Baseline Characteristics before start of osimertinib	
Median Age	62
Gender	Male: 18 (36%)
	Female: 32 (64%)
PS	0: 25 (50%)
	1: 18 (36%)
	2:5 (10%)
	3: 2 (4%)
Smoking history	Current: 6 (12%)
	Former: 16 (32%)
	Never: 26 (52%)
Brain metastasis at start of osimertinib treatment	Present and treated: 15 (30%)
	Present and untreated: 7 (14%)
	Not present: 28 (56%)
Stage at initial diagnosis	II: 1 (2%)
	IIIA: 2 (4%)
	IVA: 5 (10%)
	IVB:42 (84%)
Previous treatment lines	1: 22 (44%)
	2: 17 (34%)
	3: 4 (8%)
	4: 4 (8%)
	6: 1 (2%)
	7: 2 (4%)
Initial type of EGFR mutation	Deletion Exon 19: 37 (74%)
	L858R Mutation Exon 21: 12 (24%)
	Other : 1 (2%)
Type of material for T790 M assessment	Liquid biopsy: 14 (28%)
	Tumor tissue: 36 (72%)
New mutation other than T790 M before osimertinib start(name them)	Yes: 4 (8%)
	- p.E746_A750 Exon 19 deletion,
	- p.K757 N exon 19 mutation,
	- CTNNB1 p.Ser33Phe mutation and concomitant FGFR1 Fusion
	- EGFR, MET and FGFR4-amplification.
	No: 46 (92%)

Table 2
Patient Characteristics depending on PD Type.

	Oligo-PD (n = 26)	Systemic-PD (n = 10)
Median Age	61	69
Gender		
Female	15 (58%)	7 (70%)
Male	11 (42%)	3 (30%
PS		
≤1:	24 (92%)	6 (60%)
> 1:	2 (8%)	4 (40%)
Smoking history		
Current	3 (12%)	1 (10%)
Former	10 (28%)	3 (30%)
Never	13 (50%)	5 (50%)
Missing	0	1 (10%)
Brain Metastasis		
Yes:	14 (54%)	3 (30%)
No:	12 (46%)	7 (70%)
Previous Treatment lines		
1	9 (35%)	6 (60%)
2	9 (35%)	3 (30%)
> 2	8 (30%)	1 (10%)
Initial Type of EGFR mutation	21 (81%)	7 (70%)
Deletion Exon 19	4 (15%)	3 (30%)
L858R Mutation Exon 21	1 (4%)	0 (0%)
Other		
Concomitant Genetic alterations at initial diagnosis	2 (8%)	2 (20%)
Yes:	24 (92%)	8 (80%)
No:		
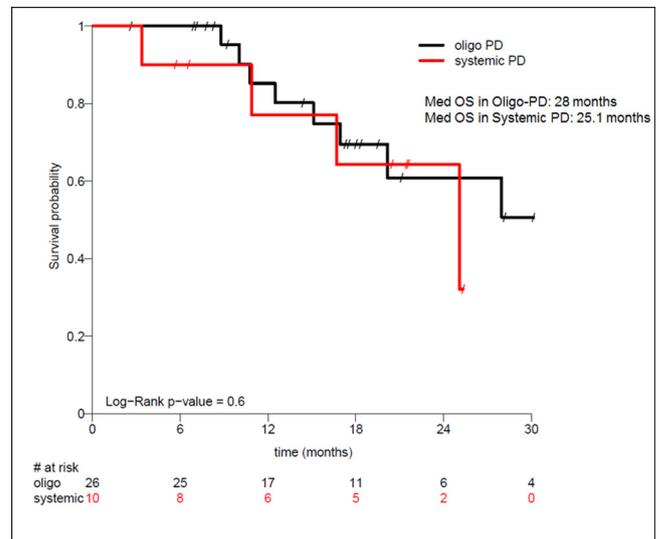
Fig. 1. OS Oligo versus systemic PD.

8.3–18.3) and median OS 28.0 months (95%CI 20.2-not reached [NR]) with a median treatment duration of 18.8 months (95%CI 16.8-NR). At data cut off, progressive disease (PD) had occurred in 36 patients (72%). There were 72% patients with oligo-PD and 28% patients had systemic PD (Table 2).

Main sites of PD were lung (56%), bone (44%), lymph nodes (22%), liver (14%), pleura (19%) and brain (17%). The majority of patients who had PD in the brain (n = 6) had oligo-PD. Four of these patients already had brain metastases at the beginning of osimertinib treatment and only one of these patients had received local treatment prior to treatment start.

Median treatment duration in patients with oligo-PD was 19.6 vs. 7 months if systemic PD (p = 0.007), and median OS was 28.0 months versus 25.1 months, respectively (p = 0.6) (see Fig. 1). The number of progressive lesions in oligo-PD patients was 1 (27%), 2 (35%), 3 (23%), 4 (8) and 5 (8%). OS decreased for every additional lesion (not reached for patients with one lesion, 22.4 months with 2 lesions, 17.6 for three and 10.8 for five lesions). Thirteen patients with oligo-PD received local treatment. These patients had an improved OS compared to patients with oligo-PD without local treatment (med. OS not reached versus 20.2 months, see Fig. 2).

Sixteen of 26 patients with oligo-PD (61%) continued treatment with osimertinib beyond progression, eleven of them after local ablative therapy (LAT) was applied (9x radiotherapy, 2 x surgeries). Median time of osimertinib treatment beyond PD was 6.7 months in patients with oligo-PD (IQR: 5.4-NR). Only three of ten patients with systemic PD were treated beyond PD for 3, 4 and 9 months respectively.

3.3. Treatment patterns after osimertinib failure

To date 15 of 36 (42%) patients with PD on osimertinib have already received subsequent treatment lines. The majority has received only one further line (range 1–4 lines). According to the guidelines, 73% were treated with chemotherapy. A limited number of patients received subsequent TKI (n = 2) or immunotherapy (n = 2). Due to a short median follow-up of 4.6 months (IQR 1.6–13 months), outcome data on these subsequent lines are not yet mature.

Please see also Fig. 3 for detailed treatment patterns.

3.4. Osimertinib resistance mechanisms

Paired pre- and post-osimertinib tumor samples were available for 9 patients. For one additional patient, only a post-osimertinib sample was available. Sites of pre-osimertinib biopsy were lymph nodes (n = 5),
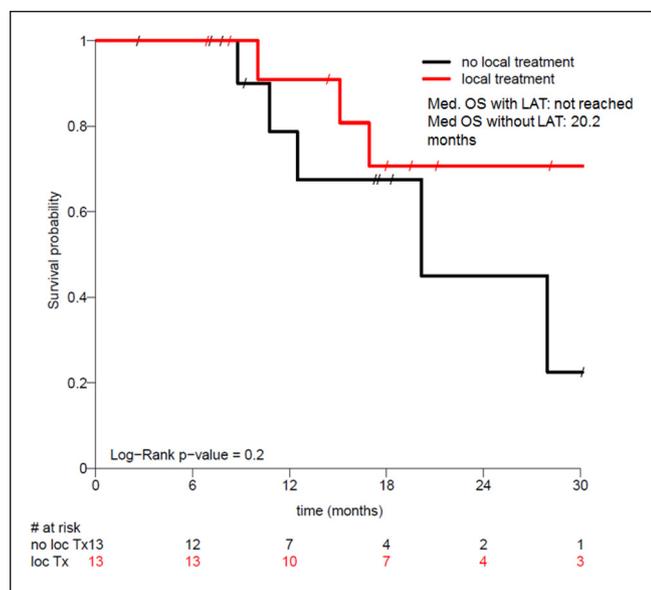
Fig. 2. OS in oligo-PD with/without LAT.

osimertinib significantly longer compared to patients with systemic progression (19.6 months vs. 7 months), possibly due to overall lower tumor volume and potentially biologically more indolent behavior. However median overall survival was comparable between subgroups (28.0 months vs. 25.1 months, respectively). Patients who were treated with LAT had an improved OS compared those who had no LAT (not reached vs. 22.0 months)

A possible explanation for the similar OS of patients with oligo- versus systemic PD may be that molecular resistance mechanisms are potentially more relevant in this setting than patterns of recurrence. On the other hand, we demonstrated that patients with oligo-PD who received LAT had more favourable outcomes. The retrospective nature of our study with the lack of a control group does not allow us to conclude whether improved outcomes of these patients actually resulted from LAT or from a more favourable patient group which was able to receive LAT. In addition to stay comparable with existing data and be congruent with RECIST no lesion-specific response after LAT was assessed and therefore we do not have any information on direct benefit of LAT on a specific lesion. Nonetheless, our findings are in line with previous reports that studied first- generation EGFR-TKI and ALK-TKIs demonstrating that the continuation of targeted treatment after LAT leads to favourable outcomes, indicating that this strategy is reasonable also in the setting of oligo-PD patients on osimertinib [11]. In the series of Weickhardt et al with 65 patients with an ALK-translocation or EGFR-mutation who received crizotinib or erlotininb were evaluated for oligoprogression defined as either non-leptomeningeal CNS-progression and/or ≤ 4 sites of extracranial progression [11]. Twenty-five oligo-PD patients (15 ALK, 10 EGFR) were treated with a LAT and then resumed their previous TKI-treatment; PFS after LAT was 6.2 months, suggesting relevant prolongation of disease control with the same TKI-treatment in oligoprogressive patients after LAT. Of note, our definition for oligo-PD was slightly different including patients with ≤ 5 progressive lesions irrespective of organ thus excluding patients with > 5 cerebral lesions needing WBRT. A more recent study by Xu et al analysed the benefit of local treatment in patients treated with an EGFR-TKI (gefitinib, erlotinib or icotinib) [20]. In their retrospective analysis local treatment to all lesions in oligometastatic patients (maximum of five lesions) resulted in significant PFS and OS-benefit compared to TKI-treatment alone or TKI-treatment in combination to local treatment to some of the lesions [20]. At ASCO 2018 another study focusing on treatment strategies after osimertinib failure was presented [21]. Of 71 patients progressing on osimertinib 62% continued treatment over progression,
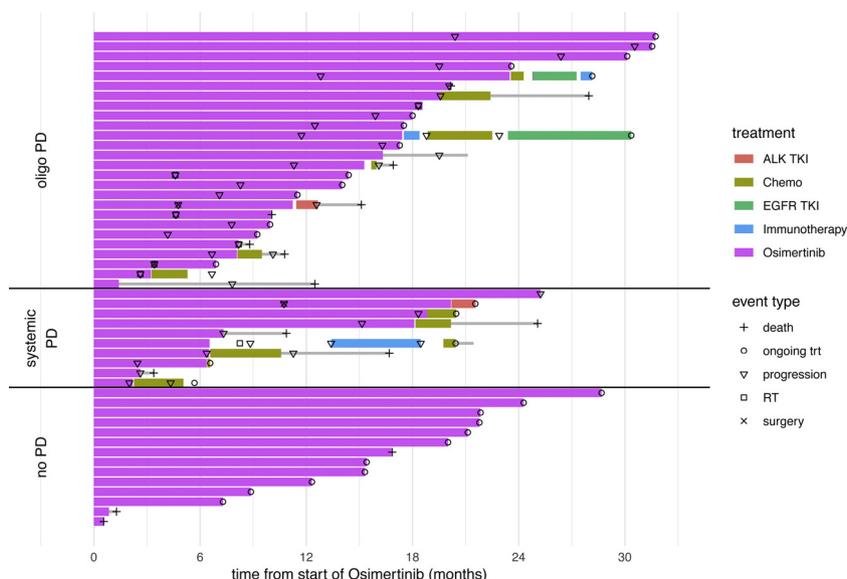
bone, brain, pleura and pleural effusion (one each) for the post-osimertiib samples lymph nodes (n = 2), liver (n = 3), primary tumor (n = 2), pleura effusion, thoracic wall and adrenal gland (one each). Results of mutational profiling with a targeted sequencing approach using a panel of 52 genes including EGFR are summarized in Table 3. *EGFR C797S* and loss of *T790M* were detected in 3/10 (30%) and 5/10 (50%) of post-osimertinib samples, respectively. In addition, the following genomic alterations were found in post-osimertinib, but absent in pre-osimertinib samples: *EGFR* amplification (n = 1), *CCND1* amplification (n = 1), *CDK4* amplification (n = 1), *MET* amplification (n = 1), *MET N375S* (n = 1), *AR* amplification (n = 1), and *PIK3CA K111N* (n = 1).

4. Discussion

In this analysis of patients with *T790M*-positive metastatic adenocarcinoma of the lung treated with osimertinib we found an unexpectedly high rate (73%) of oligo-PD, which mainly occurred outside of the central nervous system. Patients with oligo-PD received

Fig. 3. Swimmers plot: Treatment patterns.

Table 3
Mutational profiling results.

UPN	Type of PD	PFS on osimertinib (months)	OS on osimertinib (months)	Best response to osimertinib	Pre-osimertinib			Post-osimertinib		
					Site of biopsy	EGFR	Other genes	Site of re-biopsy	EGFR	Other genes
0018	Systemic	15.1	25.1	CR	Lymph node	p.E746_A750del p.T790M	FGFR3 p.G697S MTOR p.S2215F	Pleural effusion	p.E746_A750del p.T790M p.C797Samplification (CN: 9.02)	
0016	Oligo	12.8	28.2	PR	Lymph node	p.E746_A750del p.T790M		Adrenal gland	p.E746_A750del loss of p.T790M	CCND1 amplification (CN: 7.3) CDK4 amplification (CN: 5.95)
0021	Oligo	4.8	15.1	PR	Pleura	p.E746_A750del p.T790M amplification (CN: 6.45)	CCND1 amplification (CN: 5.37) CDK4 amplification (CN: 11.47)	Thoracic wall	p.E746_A750del loss of p.T790M amplification (CN: 13.28)	CCND1 amplification (CN: 13.97) CDK4 amplification (CN: 17.88) MET amplification(CN: 8.02)
0011	Oligo	11.7	30.4	PR	n.a.	n.a.	n.a.	Liver	p.E746_A750del p.T790M p.C797Samplification (CN: 6.46)	
0047	Systemic	10.7	2.6	PR	Pleural effusion	p.E746_T751delinsF p.T790M		Primary tumor	p.E746_T751delinsF p.T790M p.C797S	MET p.N375S
0030	Oligo	4.6	10.1	PR	Bone (os ileum)	p.L858R p.T790M		Liver	p.L858R p.T790M	
0032	Systemic	2.5	6.6	PD	Lymph node	p.E746_A750del p.T790M	HER2 amplification (CN: 9.49)	Lymph node	p.E746_A750del loss of p.T790M	HER2 amplification (CN: 30.24)
0033	Oligo	30.6	31.5	CR	Brain	p.E746_A750del p.T790M amplification (CN: 6.51)	GNAQ p.Q209K	Lymph node	p.E746_A750del p.T790M	AR amplification (CN: 5.53)
0036	Oligo	11.3	16.9	PR	Lymph node	p.L747_P753delinsQ p.T790M amplification (CN: 9.83)		Liver	p.L747_P753delinsQ loss of p.T790M	PIK3CA p.K111N
0042	Oligo	19.5	19.8	PR	Lymph node	p.E746_A750del p.T790M		Primary tumor	p.E746_A750del loss of p.T790M	

Not available: n.a. CN: copy number.

in 21 patients after local consolidation radiotherapy was applied. Patients receiving treatment over progression had a longer second PFS then the patients that discontinued treatment. However no information on type of progression and site of treatment failure was given. At ASTRO 2018 another prospective study assessing LAT in oligometastatic NSCLC not progressing after front-line systemic therapy was presented, including patients with EGFR-mutations treated at least for three months with an EGFR-TKI. In this trial an OS benefit was shown for LAT of all oligometastatic lesions (≤3) [22].

To the best of our knowledge, our study is the first to show that LAT in oligo-PD patients on osimertinib may be beneficial in *T790M* positive NSCLC patients progressing in a limited number of metastatic lesions on osimertinib. The true benefit of continuing osimertinib after LAT versus switching to an alternative systemic treatment however has to be further evaluated in prospective randomized trials such as the currently ongoing ETOP HALT trial (ISRCTN53398136).

CNS metastases are common in EGFR-mutated NSCLC patients and the brain is a common site of treatment failure in patients treated with first and second-generation EGFR TKIs. In a pooled analysis of two phase II trials (AURA expansion, AURA II) osimertinib was associated with ORR of 54% and DCR of 92% in the brain in 50 evaluable patients with at least one measurable CNS metastasis at baseline, irrespective of prior local treatment to the brain [23]. In addition, in the recently published FLAURA first line trial brain relapses were significantly lower with osimertinib then with first-generation TKIs in the first-line setting (19% versus 43%) [10]. In patients with known brain metastases prior to osimertinib start median CNS-PFS was not reached with osimertinib and 13.9 months with first generation-TKIs and CNS response rates were significantly higher with osimertinib (91% versus 68%) in patients with measurable lesions [24]. We observed 6 patients (17%) with progressive disease in the brain. Of note, the majority (83%) of these patients had oligo-PD and 4 out of 6 had previous brain metastases (only one of which has received prior local therapy). We conclude that radiological surveillance on osimertinib may therefore be beneficial, particularly in those with previous brain metastases.

Overall, efficacy results in our cohort of *T790M* positive, mainly EGFR TKI pretreated patients receiving osimertinib outside of a clinical trial are in line with trial data reported in the literature and the recently presented real-life cohort ASTRIS [25], although we observed slightly higher response rates compared to the phase III AURA 3 trial [9].

In a subset of patients we were able to perform mutational profiling of tumor cells at progression to identify potential mechanisms of osimertinib resistance. In concordance with previous reports of molecular resistance mechanisms after second-line osimertinib [12,17,26] as well as the recently presented data of the FLAURA-study with *MET*-amplification in 15% of resistant patients [27] we observed additional *EGFR* alterations (loss of *T790M, C797S*), *EGFR* amplifications and *MET* amplifications in post-osimertinib samples. In addition, we found missense mutations and gene amplifications in other genes not previously described (e.g *AR*-amplification). The biological and clinical significance of these genetic alterations is unclear and requires further functional studies.

Our study has several limitations. The analysis had a retrospective design and included only a limited number of patients. In addition due to the retrospective nature of our analysis follow-up imaging in our series was not standardized and therefore oligo-PD may just be a result of close CT-intervals. However, our collaborative multicentre effort in a Swiss population is the first study that specifically addressed the prevalence of oligo-PD and outcome in *T790M*-positive NSCLC on osimertinib treatment. Due to the relatively short follow-up time, data on response to further treatment lines after osimertinib failure are not mature yet and thus purely descriptive at this point. As proposed by guidelines, most patients received chemotherapy and there is at least preclinical evidence, that osimertinib-resistant cells remain sensitive to paclitaxel [28]. Also with emerging data from the FLAURA trial, osimertinib is likely to move into first line and our findings may not be

extrapolated to this setting. It will be interesting to study whether similar progression patterns emerge when osimertinib is used as first line treatment.

5. Conclusion

In patients with acquired osimertinib resistance, we observed a high rate (73%) of oligo-PD. Although OS of patients with oligo- versus systemic PD were similar, outcomes of patients with oligo-PD who received local ablative therapy were favorable with the majority continuing osimertinib for an extended period of time in addition to local therapy, supporting the concept of continuing osimertinib beyond progression in combination with LAT of progressing lesions. Prospective trials to confirm the role of LAT in patients with oligo-PD on osimertinib are warranted and currently ongoing (ETOP HALT). Patients with previous CNS metastases may benefit from regular radiological monitoring for progression.

Funding

Conflict of interest

On behalf of the co-authors of this manuscript we declare the following conflicts of interest for this manuscript.

- Oliver Gautschi: Honorarium for Advisory Board for Astra Zeneca (institutional)
- Christian Britschgi: Honorarium for Advisory Board for Astra Zeneca
- Miklos Pless: Honorarium for Advisory Board for Astra Zeneca
- Martin Früh: Honorarium for Advisory Board for Astra Zeneca (institutional)
- Sacha Rothschild: Honorarium for Advisory Board for Astra Zeneca (institutional)
- Dirk Klingbiel: Roche employee disclosure

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.02.020.

References

[1] T.S. Mok, Y.L. Wu, S. Thongprasert, C.H. Yang, D.T. Chu, N. Saijo, P. Sunpaweravong, B. Han, B. Margono, Y. Ichinose, Y. Nishiwaki, Y. Ohe, J.J. Yang, B. Chewaskulyong, H. Jiang, E.L. Duffield, C.L. Watkins, A.A. Armour, M. Fukuoka, Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma, N. Engl. J. Med. 361 (2009) 947–957.
[2] R. Rosell, E. Carcereny, R. Gervais, A. Vergnenegre, B. Massuti, E. Felip, R. Palmero, R. Garcia-Gomez, C. Pallares, J.M. Sanchez, R. Porta, M. Cobo, P. Garrido, F. Longo, T. Moran, A. Insa, F. De Marinis, R. Corre, I. Bover, A. Illiano, E. Dansin, J. de Castro, M. Milella, N. Reguart, G. Altavilla, U. Jimenez, M. Provencio, M.A. Moreno, J. Terrasa, J. Munoz-Langa, J. Valdivia, D. Isla, M. Domine, O. Molinier, J. Mazieres, N. Baize, R. Garcia-Campelo, G. Robinet, D. Rodriguez-Abreu, G. Lopez-Vivanco, V. Gebbia, L. Ferrera-Delgado, P. Bombaron, R. Bernabe, A. Bearz, A. Artal, E. Cortesi, C. Rolfo, M. Sanchez-Ronco, A. Drozdowskyj, C. Queralt, I. de Aguirre, J.L. Ramírez, J.J. Sanchez, M.A. Molina, M. Taron, L. Paz-Ares, Spanish Lung Cancer Group in collaboration with Groupe Francais de P-C, Associazione Italiana Oncologia T. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial, Lancet Oncol. 13 (2012) 239–246.
[3] L.V. Sequist, J.C. Yang, N. Yamamoto, K. O'Byrne, V. Hirsh, T. Mok, S.L. Geater, S. Orlov, C.M. Tsai, M. Boyer, W.C. Su, J. Bennouna, T. Kato, V. Gorbunova, K.H. Lee, R. Shah, D. Massey, V. Zazulina, M. Shahidi, M. Schuler, Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations, J. Clin. Oncol. 31 (2013) 3327–3334.
[4] Y.L. Wu, C. Zhou, C.P. Hu, J. Feng, S. Lu, Y. Huang, W. Li, M. Hou, J.H. Shi, K.Y. Lee, C.R. Xu, D. Massey, M. Kim, Y. Shi, S.L. Geater, Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-

cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial, Lancet Oncol. 15 (2014) 213–222.

[5] K. Park, E.H. Tan, K. O'Byrne, L. Zhang, M. Boyer, T. Mok, V. Hirsh, J.C. Yang, K.H. Lee, S. Lu, Y. Shi, S.W. Kim, J. Laskin, D.W. Kim, C.D. Arvis, K. Kolbeck, S.A. Laurie, C.M. Tsai, M. Shahidi, M. Kim, D. Massey, V. Zazulina, L. Paz-Ares, Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial, Lancet Oncol. 17 (2016) 577–589.

[6] Y.L. Wu, C. Zhou, C.K. Liam, G. Wu, X. Liu, Z. Zhong, S. Lu, Y. Cheng, B. Han, L. Chen, C. Huang, S. Qin, Y. Zhu, H. Pan, H. Liang, E. Li, G. Jiang, S.H. How, M.C. Fernando, Y. Zhang, F. Xia, Y. Zuo, First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study, Ann. Oncol. 26 (2015) 1883–1889.

[7] J. Remon, D. Planchard, AZD9291 in EGFR-mutant advanced non-small-cell lung cancer patients, Future Oncol. 11 (2015) 3069–3081.

[8] G. Goss, C.M. Tsai, F.A. Shepherd, L. Bazhenova, J.S. Lee, G.C. Chang, L. Crino, M. Satouchi, Q. Chu, T. Hida, J.Y. Han, O. Juan, F. Dunphy, M. Nishio, J.H. Kang, M. Majem, H. Mann, M. Cantarini, S. Ghiorghiu, T. Mitsudomi, Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study, Lancet Oncol. 17 (2016) 1643–1652.

[9] T.S. Mok, Y.L. Wu, M.J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, V.A. Papadimitrakopoulou, A. Investigators, Osimertinib or platinum-pemetrexed in EGFR T790M-Positive lung Cancer, N. Engl. J. Med. 375 (26) (2016) 2519–2529, https://doi.org/10.1056/NEJMoa1611593 Epub 2016 Nov 13.

[10] J.C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.C. Su, J.E. Gray, S.M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, S.S. Ramalingam, F. Investigators, Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer, N. Engl. J. Med. 378 (2018) 113–125.

[11] A.J. Weickhardt, B. Scheier, J.M. Burke, G. Gan, X. Lu, P.A. Bunn Jr, D.L. Aisner, L.E. Gaspar, B.D. Kavanagh, R.C. Doebele, D.R. Camidge, Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer, J. Thorac. Oncol. 7 (2012) 1807–1814.

[12] K.S. Thress, C.P. Paweletz, E. Felip, B.C. Cho, D. Stetson, B. Dougherty, Z. Lai, A. Markovets, A. Vivancos, Y. Kuang, D. Ercan, S.E. Matthews, M. Cantarini, J.C. Barrett, P.A. Janne, G.R. Oxnard, Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M, Nat. Med. 21 (2015) 560–562.

[13] D. Ercan, H.G. Choi, C.H. Yun, M. Capelletti, T. Xie, M.J. Eck, N.S. Gray, P.A. Janne, EGFR mutations and resistance to irreversible pyrimidine-based EGFR inhibitors, Clin. Cancer Res. 21 (2015) 3913–3923.

[14] Y. Jia, C.H. Yun, E. Park, D. Ercan, M. Manuia, J. Juarez, C. Xu, K. Rhee, T. Chen, H. Zhang, S. Palakurthi, J. Jang, G. Lelais, M. DiDonato, B. Bursulaya, P.Y. Michellys, R. Epple, T.H. Marsilje, M. McNeill, W. Lu, J. Harris, S. Bender, K.K. Wong, P.A. Janne, M.J. Eck, Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors, Nature 534 (2016) 129–132.

[15] D. Planchard, Y. Loriot, F. Andre, A. Gobert, N. Auger, L. Lacroix, J.C. Soria, EGFR-independent mechanisms of acquired resistance to AZD9291 in EGFR T790M-positive NSCLC patients, Ann. Oncol. 26 (2015) 2073–2078.

[16] G.R. Oxnard, Mechanisms of acquired resistance to AZD9291 in EGFR T790M positive lung cancer, ORAL 17.01 WCLC 2015, J. Thorac. Oncol. 10 (Suppl. 2) (2015) 2015.

[17] G.R. Oxnard, Y. Hu, K.F. Mileham, H. Husain, D.B. Costa, P. Tracy, N. Feeney, L.M. Sholl, S.E. Dahlberg, A.J. Redig, D.J. Kwiatkowski, M.S. Rabin, C.P. Paweletz, K.S. Thress, P.A. Janne, Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M-positive lung cancer and acquired resistance to osimertinib, JAMA Oncol. (2018).

[18] S. Hellman, R.R. Weichselbaum, Oligometastases, J. Clin. Oncol. 13 (1995) 8–10.

[19] R.R. Weichselbaum, S. Hellman, Oligometastases revisited, Nat. Rev. Clin. Oncol. 8 (2011) 378–382.

[20] Q. Xu, F. Zhou, H. Liu, T. Jiang, X. Li, Y. Xu, C. Zhou, Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs, J. Thorac. Oncol. 13 (9) (2018) 1383–1392, https://doi.org/10.1016/j.jtho.2018.05.019 Epub 2018 May 29.

[21] X. Le, S. Puri, M. Negrao, M. Nilsson, J. Robichaux, T. Boyle, J. Hicks, E. Roarty, W. Rinsurongkawong, B. Glisson, J. Zhang, V. Papadimitrakopoulou, J. Gray, J. Heymach, Landscape of EGFR-dependent and independent mechanisms of osimertinib resistance in EGFR-mutant NSCLC patients, ASCO 24 (24) (2018) 6195–6203, https://doi.org/10.1158/1078-0432.CCR-18-1542 Epub 2018 Sep 18.

[22] D. Gomez, C. Tang, J. Zhang, G.R. Blumenschein, M. Hernandez, J. Lee, R. Ye, D. Camidge, F. Skoulidis, R.C. Doebele, L.E. Gaspar, D. Gibbons, J. Karam, B.D. Kavanagh, D. Palma, A. Louie, A. Tsao, B. Sepesi, S. Swisher, J. Heymach, LBA3: Local Consolidative Therapy (LCT) Improves Overall Survival (OS) Compared to Maintenance Therapy/Observation in Oligometastatic Non-Small Cell Lung Cancer (NSCLC): Final Results of a Multicenter, Randomized, Controlled Phase 2 Trial. ASTRO2018, (2018).

[23] G. Goss, C.M. Tsai, F.A. Shepherd, M.J. Ahn, L. Bazhenova, L. Crino, F. de Marinis, E. Felip, A. Morabito, R. Hodge, M. Cantarini, M. Johnson, T. Mitsudomi, P.A. Janne, J.C. Yang, CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials, Ann. Oncol. 29 (2018) 687–693.

[24] T. Reungwetwattana, K. Nakagawa, B.C. Cho, M. Cobo, E.K. Cho, A. Bertolini, S. Bohnet, C. Zhou, K.H. Lee, N. Nogami, I. Okamoto, N. Leighl, R. Hodge, A. McKeown, A.P. Brown, Y. Rukazenkov, S.S. Ramalingam, J. Vansteenkiste, CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer, J. Clin. Oncol. (2018) JCO2018783118.

[25] Y. Wu, B. Cho, Q. Zhou, G. Chang, L. Jiang, G. Metro, C. Martin, G. de Castro, J. Vansteenkiste, D. Vicente, A. Milner, J. Rigas, Y. Chen, M. Provencio, ASTRIS: A Real World Treatment Study of Osimertinib in Patients With EGFR T790M-Positive NSCLC, ESMO, 2018.

[26] V. Papadimitrakopoulou, Y. Wu, J. Han, M. Ahn, S. Ramalingam, T. John, I. Okamoto, J. Yang, K. Bulusu, G. Laus, B. Collins, J.C. Barrett, J. Chmielecki, T. Mok, Analysis of Resistance Mechanisms to OSIMERTINIB in Patients with Egfr T790M Advanced NSCLC From the AURA3 STUDY, ESMO, 2018.

[27] S. Ramalingam, Y. Cheng, C. Zhou, Y. Ohe, F. Imamura, B. Cho, M. Lin, M. Majem, R. Shah, Y. Rukazenkov, A. Todd, A. Markovets, C. Barrett, J. Chmielecki, J. Gray, Mechanisms of Acquired Resistance to First-Line Osimertinib: Preliminary Data From the Phase III Flaura Study, ESMO, 2018.

[28] Z.H. Tang, X.M. Jiang, X. Guo, C.M. Fong, X. Chen, J.J. Lu, Characterization of osimertinib (AZD9291)-resistant non-small cell lung cancer NCI-H1975/OSIR cell line, Oncotarget 7 (49) (2016) 81598–81610, https://doi.org/10.18632/oncotarget.13150.