Activity of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in patients with NSCLC with uncommon *EGFR* mutations: a real-world cohort study (UpSwinG)

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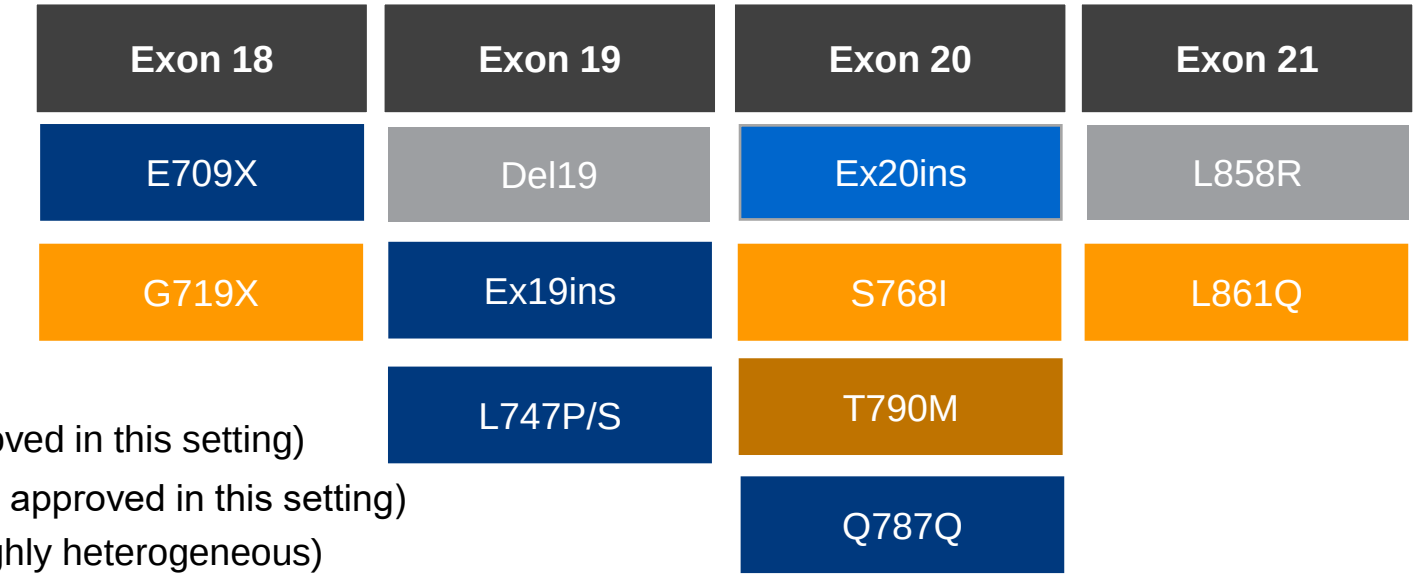
Introduction

- 7–23% of *EGFR* mutations are ‘uncommon’ mutations (not Del19 or L858R)[1]
- Around a quarter to a third of *EGFR*m+ tumors harbour compound mutations[1]
- Increased use of sensitive sequencing-based detection methods and liquid biopsy will increase the frequency of uncommon mutations detected in real-world clinical practice[2]

Frequency of *EGFR* mutations in lung cancer according to recent large studies are shown below (illustrative examples)



- Common (sensitive to all TKIs; afatinib approved in this setting)
- ‘Major’ uncommon (sensitive to TKIs: afatinib approved in this setting)
- Ex20ins (considered resistant to TKIs but highly heterogeneous)
- Others (little data on TKI sensitivity; highly heterogeneous)
- T790M (resistant to 1st- and 2nd-gen TKIs)

*EGFR*m+, *EGFR* mutation-positive; gen, generation; TKI, tyrosine kinase inhibitor.

1. Yang JC, et al. J Thorac Oncol 2020;15:803–15; 2. Kobayashi Y & Mitsudomi T. Cancer Sci 2016;107:1179–86

Objectives and methods

Aims (uncommon mutations cohort)

1) Investigate the treatment of patients with uncommon *EGFR* mutations

2) Assess the efficacy of EGFR TKIs in each uncommon mutation category

3) Assess how *EGFR* mutations are detected in real-world practice

Patients (n=246)

- All had at least one uncommon mutation
- All received an EGFR TKI (afatinib, gefitinib, erlotinib or osimertinib) in 1st- or 2nd-line

Key exclusion criteria

- Treated in a clinical trial
- Active brain metastases
- Patients with acquired T790M only and treated with osimertinib

Primary objective

TTF

Secondary objectives

ORR, OS, DoR

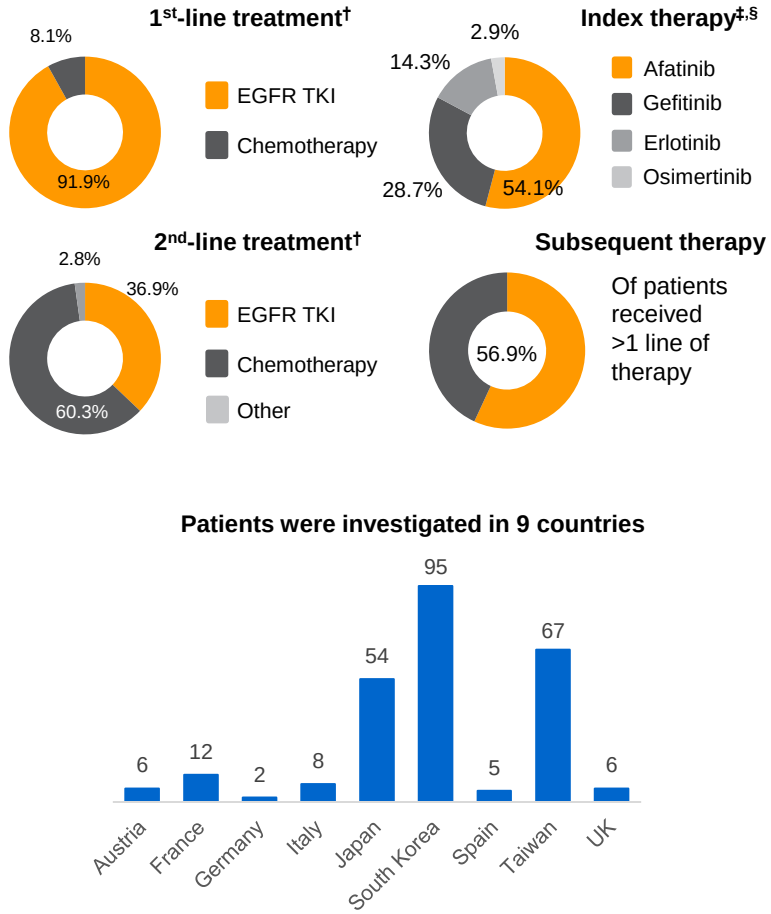
DoR, duration of response; ORR, overall response rate; OS, overall survival; TTF, time-to-treatment failure

Results

Patient characteristics were similar regardless of EGFR TKI received as index therapy

	All (n=246)	1st-gen TKIs (n=106†)	Afatinib (n=132)	Osimertinib (n=7)
Median age, years (range)	69.5 (27.0–93.0)	70.5 (42.0–91.0)	68.5 (27.0–93.0)	71.0 (56.0–85.0)
Female, n (%)	138 (56.1)	66 (62.3)	67 (50.8)	5 (71.4)
Asian, n (%)	206 (83.7)	87 (82.1)	114 (86.4)	5 (71.4)
Brain metastases, n (%)	17 (6.9)	6 (5.7)	13 (9.8)	0
ECOG PS ≥2, n (%)	31 (12.6)	15 (14.2)	16 (12.1)	0
Mutation status, n (%)				
Major uncommon	179 (72.8)	80 (75.5)	94 (71.2)	4 (57.1)
Exon 20 insertion	29 (11.8)	10 (9.4)	18 (13.6)	1 (14.3)
T790M	17 (6.9)	4 (3.8)	11 (8.3)	2 (28.6)
Other	21 (8.5)	12 (11.3)	9 (6.8)	0
Compound	82 (33.3)	32 (30.2)	46 (34.8)	4 (57.1)

EGFR TKIs were generally the first-line treatment of choice for uncommon mutations



†An additional patient was treated with chemotherapy plus bevacizumab; ‡Includes one patient treated with gefitinib/erlotinib; §Includes one patient treated with afatinib/gefitinib

Results (cont'd)

EGFR TKIs maintained patients' fitness

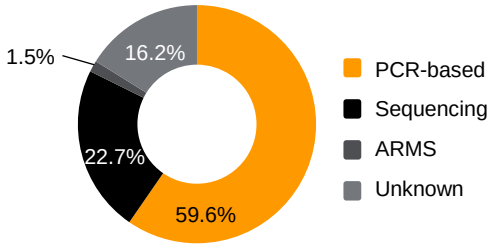
ECOG PS at start of 1st-line treatment (n=246)

ECOG PS at start of 2nd-line treatment (n=140)

0 1 ≥2 Unknown

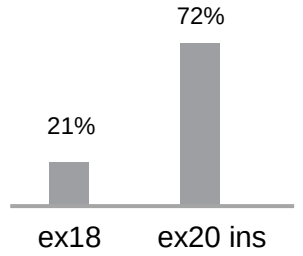
Pathology reports on uncommon *EGFR* mutations are sub-optimal in real-world practice

Mutation testing methodology (1st-line; n=246)



- Mutations were mainly detected from tissue biopsy (85%), liquid biopsies were uncommon (1%)
- Pathology reports varied in quality with many mutations (e.g. ex18 and ex20ins) undefined

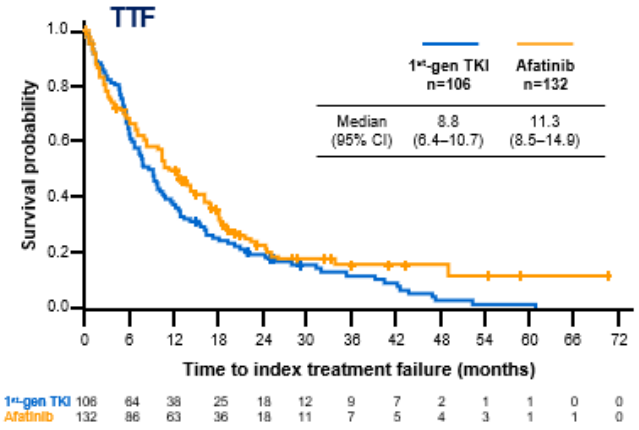
Undefined mutations

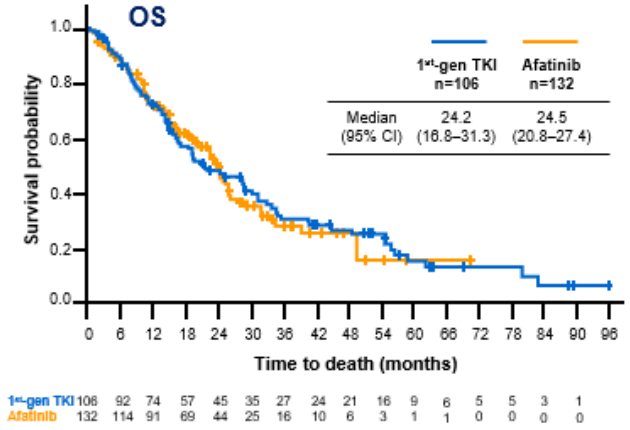


ARMS, amplification refractory mutation system; ECOG PS, Eastern Cooperative Oncology Group performance status

Results (cont'd)

EGFR TKIs conferred encouraging TTF, OS and ORR

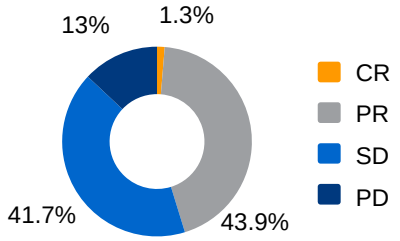




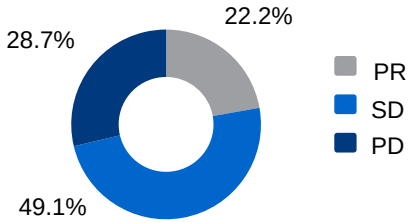
Clinical outcomes varied according to mutation category¶

	Any TKI (n=246)				1st-gen EGFR TKIs (n=106)				Afatinib (n=132)			
	TTF, mos	OS, mos	ORR**, %	DoR**, mos	TTF, mos	OS, mos	ORR**, %	DoR**, mos	TTF, mos	OS, mos	ORR**, %	DoR**, mos
All patients	9.9	24.4	43.4	10.0	8.8	24.2	44.1	6.0	11.3	24.5	43.8	12.0
Major uncommon	11.3	25.7	49.1	10.0	9.8	28.5	47.3	6.5	14.3	24.5	50.6	12.0
Exon 20 insertion	5.5	22.5	17.4	19.3	5.2	21.0	16.7	33.0	8.3	22.5	18.8	5.5
T790M	2.8	32.7	20.0	6.0	2.1	14.2	0	-	5.7	-	33.3	6.0
Other	7.4	13.4	43.8	7.5	7.3	12.8	55.6	4.5	10.8	20.2	28.6	10.5
Compound	12.3	28.7	48.6	10.0	12.4	31.3	43.8	6.0	12.6	23.4	52.5	10.0

Response to 1st-line treatment**



Response to 2nd-line treatment**



CR, complete response; Mos, months; PR, partial response; SD stable disease; PD, progressive disease. ¶Results from patients treated with osimertinib not shown due to small sample size; **Evaluable patients

Key findings and conclusions

Real-world study (NCT04179890) in patients with *EGFR*m+ NSCLC (uncommon mutations)

- EGFR TKIs are 1st-line treatment of choice for uncommon mutations in everyday clinical practice
- Afatinib was the most commonly used EGFR TKI
- Strongest outcomes were seen in major uncommon and compound mutations
- Optimal treatment requires improvements in pathology reports
- Treatment with an EGFR TKI should be considered for most patients with uncommon mutations