Afatinib for the treatment of NSCLC with uncommon *EGFR* mutations: an updated database of 1023 cases

#1212P

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Introduction

- Around 7–23% of patients with *EGFR*m+ NSCLC have tumours harbouring uncommon mutations (non-Del19/L858R); up to 25% of *EGFR*m+ tumours harbour compound mutations (>1 *EGFR* mutation)[1]
- There is a lack of clinical data assessing the activity of EGFR TKIs in patients with NSCLC harbouring uncommon *EGFR* mutations
- Increased use of NGS for mutation detection and plasma-based assays will increase identification of uncommon *EGFR* mutations in everyday clinical practice[2]
- Previously, we developed a database of 693 patients with NSCLC and uncommon *EGFR* mutations treated with afatinib in RCTs and real-world practice (https://www.uncommonegfrmutations.com). Here we provide an update of >1000 patients, with more data on specific mutations

*EGFR*m+, epidermal growth factor receptor mutation positive; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; RCTs, randomised controlled trials; TKI, tyrosine kinase inhibitor

Methods

Aims

1) Investigate afatinib as a treatment for patients with uncommon *EGFR* mutations

2) Update the uncommon mutations database with new findings, with a focus on individual ex20ins and 'other' uncommon mutations

Patients categorised into four groups

T790M+ | ex20ins | 'Other'* | G719X, L861Q, S768I

Patients with compound mutations were also analysed†

Key endpoints

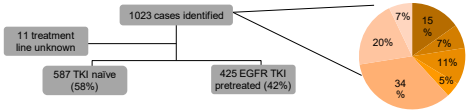
TTF

ORR

*Any mutation not represented in the other groups; †Defined as ≥2 mutations with at least one uncommon mutation.
ex20ins, exon 20 insertions; ORR, objective response rate; TTF, time to treatment failure

Results

1023 patient were identified, with most patients treated in clinical studies/compassionate use programmes



	TKI naïve (N=587)	TKI pretreated (N=425)
Asian / non-Asian, %	62.8 / 37.2	46.2 / 53.8
<75 / ≥75 years, %	79.6 / 20.4	89.1 / 10.9
Male / female, %	46.7 / 53.3	35.6 / 64.4
Ever-smoker / never smoker, %	46.4 / 53.6	34.2 / 65.8
Confirmed brain mets, %	11.9	5.6

mets, metastases

Key findings and conclusions

- Data are in line with previously published data
- Afatinib demonstrated strong activity against major uncommon, compound, and 'other' uncommon mutations
- Afatinib showed excellent activity against E709X and L747X mutations in TKI-naïve patients
- Afatinib demonstrated activity against certain exon 20 insertions at residues A763, M766, N771, and V769
- Afatinib showed activity against the osimertinib resistance mutations G724S, L718Q, L718V, and C797S

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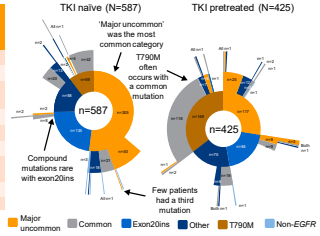
Results (cont'd)

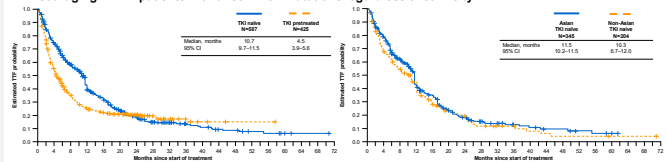
Incidence and composition of uncommon mutation categories

	TKI naïve (N=587)	TKI pretreated (N=425)
T790M	10.1%	35.1%
Exon20ins	23.0%	19.8%
Major uncommon	52.0%	27.5%
Others	15.0%	17.6%
E709X	2.6%	2.6%
L747X	3.1%	0.9%
Compound mutations	31.5%	50.4%
≥3 mutations	1.7%	4.0%
≥4 mutations	0.5%	0.5%



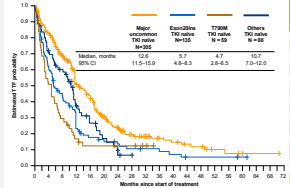
Results (cont'd)

Encouraging TTF in patients with uncommon mutations regardless of ethnicity



- TTF was also encouraging in patients with uncommon mutations, regardless of presence of brain metastasis: 8.2 months (95% CI: 5.5–12.6)

Strong TTF and ORRs against major uncommon, compound and 'other' uncommon mutations (including E790X and L747X)



Median TTF

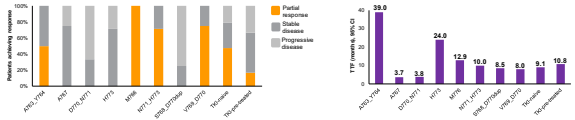
Mutation category, pts (N)	TKI naïve (N=587) N	TKI naïve (N=587) Median TTF, mos (95% CI)	TKI pretreated (N=425) N	TKI pretreated (N=425) Median TTF, mos (95% CI)
T790M	59	4.7 (2.8–6.5)	149	4.0 (3.4–5.6)
Exon20ins	135	5.7 (4.8–8.3)	84	4.4 (2.8–7.5)
Major uncommon	305	12.6 (11.5–15.9)	117	5.3 (3.6–8.4)
G719X	194	14.2 (11.5–17.0)	81	4.7 (3.0–8.9)
L861Q	109	11.5 (10.5–13.8)	45	4.4 (2.5–8.1)
S768I	61	15.9 (11.5–20.5)	34	3.0 (3.0–5.7)
Others	88	10.7 (7.0–12.0)	75	4.5 (3.0–6.1)
E709X	15	11.4 (3.8–19.3)	11	12.2 (7.0–NR)
L747X	18	14.7 (9.0–19.8)	0	NR (0.5–NR)
Compound	182	11.5 (9.5–13.8)	210	4.4 (3.5–5.6)
With major	90	16.0 (14.2–20.5)	38	6.0 (3.0–9.9)
With exon20ins	11	12.5 (3.8–13.1)	19	4.2 (2.0–7.5)
With T790M	48	4.7 (3.0–6.5)	131	3.8 (3.0–5.7)
With others	33	11.5 (9.5–13.8)	22	4.5 (2.7–15.0)

ORR

Mutation category, pts (N)	TKI naïve (N=587) N	TKI naïve (N=587) ORR, %	TKI pretreated (N=425) N	TKI pretreated (N=425) ORR, %
T790M	42	26.2	73	17.8
Exon20ins	114	27.2	31	12.9
Major uncommon	278	59.0	54	29.6
G719X	181	61.3	39	12.8
L861Q	97	57.7	23	39.1
S768I	56	71.4	16	18.8
Others	72	63.9	47	46.8
E709X	13	84.6	7	85.7
L747X	15	80.0	3	66.7
Compound	155	63.9	110	21.8
With major	83	73.5	20	25.0
With exon20ins	9	55.6	10	0.0
With T790M	35	31.4	62	19.4
With others	28	78.6	18	38.9

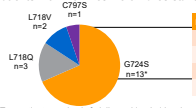
CI, confidence interval; pts, patients; NR, not reached

Evidence of activity against certain Exon 20 insertions at residues A763, M766, N771, and V769



Evidence of activity against osimertinib resistance mechanisms

Patients with known osimertinib resistance mutations



Resistance mutation	ORR, %	DCR, %
G724S	25	100
L718Q	66	100
L718V	50	100
C797S	0	100

*Two patients received afatinib combined with osimertinib.
ORR, overall response rate; DCR, disease control rate

Evidence of activity of afatinib after osimertinib

- In the 15 pts who received afatinib after osimertinib, ORR was 36% and DCR was 100%

References

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

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