TAK-788: PURSUING A FAST-TO-PATIENT STRATEGY FOR NSCLC PATIENTS WITH EGFR EXON 20 INSERTIONS

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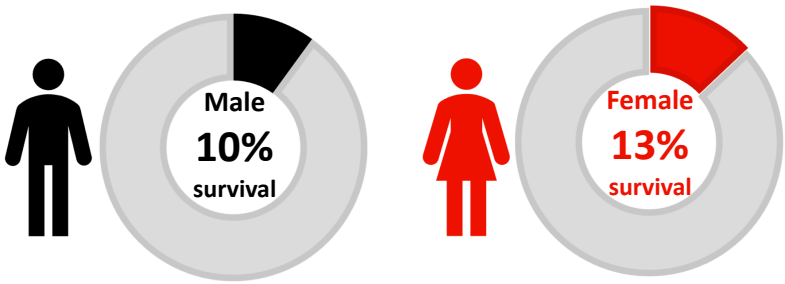
THE SIZE OF THE LUNG CANCER CHALLENGE IS VAST

228,000[1]
New Lung cancer cases / year

143,000[1]
Lung cancer deaths/ yr
More than breast, colon, and prostate cancer combined

Survival of Lung cancer is amongst the lowest of all cancers

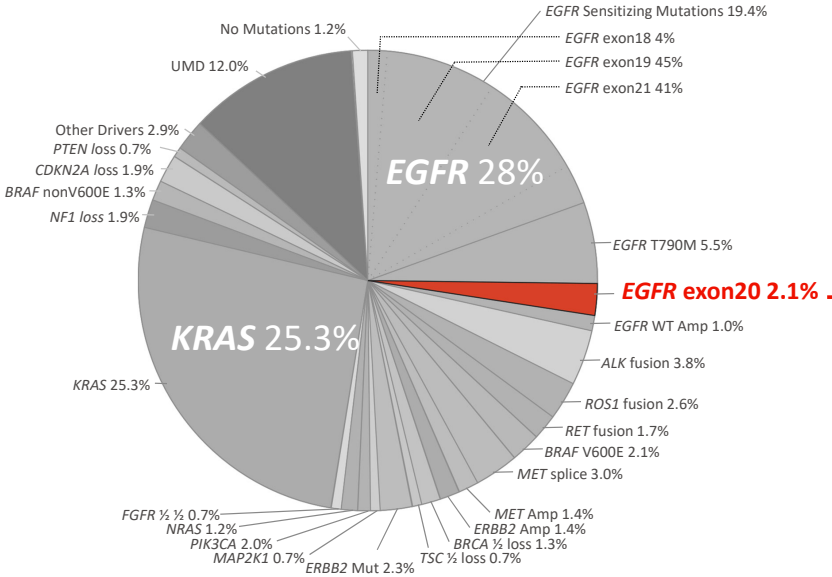


5 yr survival estimates among adults diagnosed with lung cancer between 2007-2011[2]

1. American Cancer Society; Cancer facts and figures 2019
2. Office for National Statistics UK (www.ons.gov.uk)

EXON 20 INSERTIONS ARE A RARE SUBSET OF EGFR MUTANT NSCLC

Non-Sq NSCLC
200,000 pts/yr[1]



EGFR Exon 20 insertions
2,000 pts/yr[2]

Insertion variants

1.	V769_D770insASV	(≈20%)
2.	D770_N771insSVD	(≈19%)
3.	H773_V774insH	(≈8%)
4.	A763_Y764insFQEA	(≈7%)
5.	H773_v774insPH	(≈5%)
6.	H773_V774insNPH	(≈4%)
7.	N771_P772insN	(≈3%)
8.	H773_V774insAH	(≈3%)
9.	Other	(≈31%)

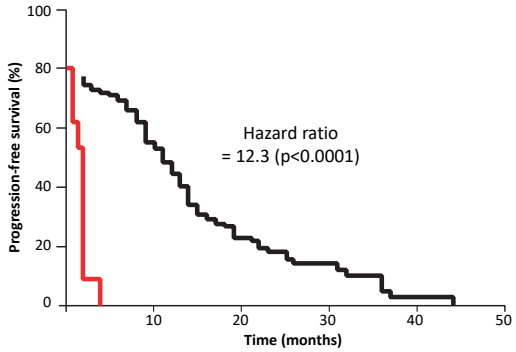
Sources: Leduc C et al., Ann Oncol 2017; Jorge S et al. Braz J Med Biol Res 2014; Kobayashi Y & Mitsudomi T. Cancer Sci 2016; Arcila M et al. Mol Cancer Ther 2013; Oxnard G et al. J Thorac Oncol 2013

1. Estimated US annual incidence of non-squamous NSCLC
2. Represents annual incidence of the US addressable patient population

PATIENTS WITH EGFR EXON 20 INSERTIONS HAVE NO EFFECTIVE THERAPY

POOR RESPONSE TO EXISTING TKIs [1]

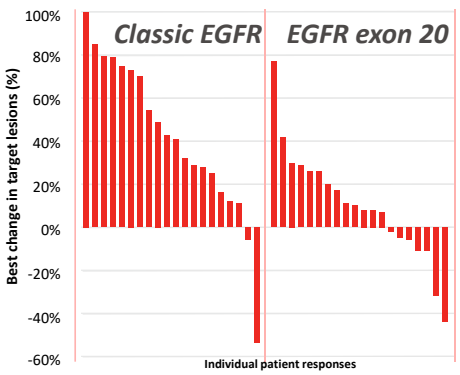
EGFR exon 20 insertions do not demonstrate significant PFS benefit with 1st and 2nd gen EGFR TKIs



Group	Median PFS (months)
EGFR exon 20 ins (n=9)	2.0
Classical EGFR mut (n=129)	12.0

POOR RESPONSE TO ANTI PD-1/PDL-1 THERAPY [2]

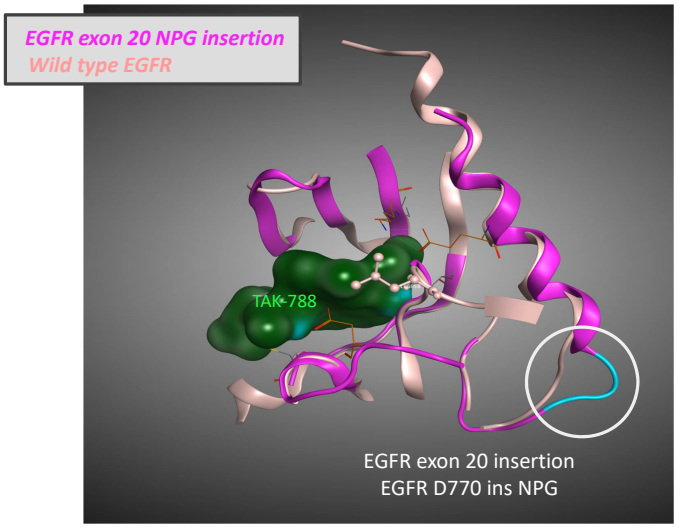
EGFR exon 20 ins patients demonstrate limited benefit to anti PD-1 directed therapy



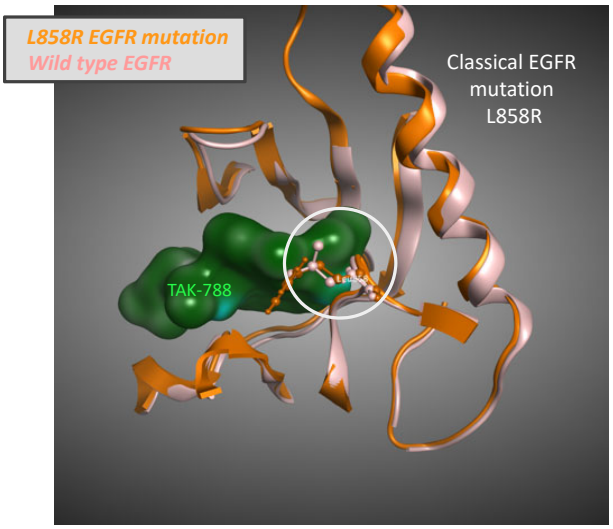
Group	Median PFS (months)	PDL-1 expression ≥1%
EGFR exon 20 ins (n=20)	2.7 (1.7-3.8)	40%
Classical EGFR mut (n=22)	1.8 (1.2-2.4)	25%

1. Robichaux et al., WCLC 2016.
2. Adapted from Negrao et al., WCLC 2019

OVERCOMING THE DRUG DEVELOPMENT CHALLENGE IN EXON 20 INSERTIONS



EGFR exon 20 insertion mutations have a similar structure and similar affinity for ATP to wild type EGFR



Classical EGFR mutations Significantly alter both structure and affinity for ATP compared to wild type EGFR

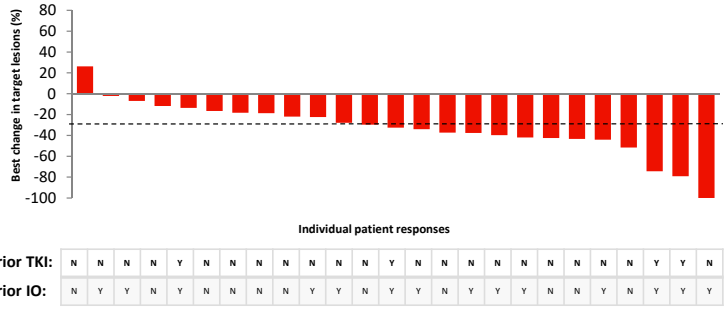
Source. TAK-788 bound to EGFR kinase domain containing D770 ins NPG, crystal structure (data on file)

TAK-788 PROOF OF CONCEPT DATA IN EGFR EXON 20 INSERTIONS

2019 ASCO ANNUAL MEETING

• Confirmed ORR: 12/28 patients: 43% (24.5-62.8%) • Median PFS: 7.3 months (4.4 mo - NR)

ANTITUMOR ACTIVITY IN EGFR EXON 20 INS AT 160 MG DAILY



SAFETY SUMMARY IN PATIENTS TREATED WITH TAK-788

N (%)	All Patients 160 mg qd (n=72)
Treatment-related AE	
Any grade	68 (94)
Grade ≥3	29 (40)
Dose reduction due to AE	18 (25)
Dose interruption due to AE	36 (50)
Discontinuation due to treatment-related AE	10 (14)

TAK-788 has not been approved for the use or indications under investigation in the clinical trials (and there is no guarantee it will be approved for such use or indication). Claims of safety and effectiveness can only be made after regulatory review of the data and approval of the labeled claims.
Adapted from Riley et al. ASCO. 2019

ENCOURAGING EFFICACY AND SAFETY HAS BEEN OBSERVED WITH TAK-788

Select signs of efficacy				
Clinical feature	**TAK-788 [1] n=28**	**Poziotinib [2] n=50**	**Afatinib [3] n=23**	**Osimertinib [4] n=15**
ITT confirmed ORR (%)	43%	NR	8.7%	0%
Evaluable confirmed ORR (%)	NR	43%	NR	NR
ITT median PFS (months)	7.3	5.5	2.7	3.5
Select treatment related adverse events attributable to wild type EGFR inhibition				
Grade ≥ 3 Adverse event	**TAK-788 [1] n=72**	**Poziotinib [2] n=63**	**Afatinib [5] n=229**	**Osimertinib [6] n=279**
Diarrhea ≥ Gr3	18%	17.5%	14%	1%
Rash ≥ Gr3	1%	35%	16%	1%
Paronychia ≥ Gr3	0%	9.5%	11%	0%
Total dose reduction rates				
AE related dose reductions (%)	25%	60%	52%	2.9%

Direct cross-trial comparison can not be made between TAK-788 and other treatments due to different studies with different designs
ITT = Intention to treat, ORR = Overall response rate, PFS = progression free survival, NR = Not reported.
Sources: 1. Riley et al. ASCO. 2019; 2. Haymach et al. WCLC 2018; 3. Yang et al., Lancet. 2016.; 4. Kim et al., ESMO 2019; 5. Yang et al., Lancet. 2012; 6. Mok et at., NEJM 2017

STRONGER DIARRHEA MANAGEMENT SHOULD = ENHANCED EFFICACY

June 2016
FIRST IN HUMAN
Diarrhea management very late - medicate when at Grade 2

Average time on TAK-788 7.9 months

Diarrhea	Time on Treatment (Mo)
Grade 3	4.6
Grade 2	9.8
Grade 1	12.7
No diarrhea	12.1

Feb 2019 new trial
Exclaim
Comprehensive diarrhea management guidelines implemented earlier

WE HAVE MODIFIED OUR APPROACH TO GI ADVERSE EVENT MANAGEMENT WITH THE AIM TO IMPROVE EFFICACY

Source. TAK-788 Clinical trial database (data on file)

2021: EXPECTED FIRST APPROVAL IN EGFR EXON 20 INSERTIONS

· Single arm Phase 2 trial
· Refractory EGFR Exon 20 insertion patients

- Previously treated, ≤2 systemic anticancer chemotherapy
- Locally advanced or metastatic
- NSCLC harboring *EGFR* exon 20 insertion

Exclaim

TAK-788 at 160 mg qd

1. Overall Response Rate
2. Duration of Response
3. Median Progression Free Survival
4. Overall survival

· ACTIVELY ENROLLING US, EU, AND ASIA
· POTENTIAL APPROVAL MID 2021

· Supporting data generation
· Real world evidence (RWE) data collection

RWE will be used to assess the benefit of conventional standard of care (SOC) agents in patients with EGFR Exon 20 insertions

EMR claims databases and Medical Chart Review

Chemo +/- VEGFR | **Immunotherapy** | **Other**

1. Overall Response Rate
2. Time to treatment failure
3. Median progression free survival
4. Duration of Response
5. Overall survival

· US (FLAT IRON HEALTH) · JP (SCRUM-JAPAN)
· EU AND CHINA CHART REVIEW

Source. https://clinicaltrials.gov/ct2/show/NCT02716116, https://www.exclaimstudy.com/

NEW ACTIVATION: A TRIAL FOR NEWLY DIAGNOSED PATIENTS

Exclaim -2

2 year enrollment
Anticipated approval 2023

· Randomized, controlled, Phase 3 trial
· Treatment-naïve EGFR exon 20 insertion patients

- Advanced or metastatic
- Treatment-naïve patients diagnosed with NSCLC harboring EGFR exon 20 insertion mutations

R
1:1

TAK-788 at 160 mg qd | **Platinum doublet**

1. Median Progression Free Survival
2. Overall Response Rate
3. Duration of Response
4. Overall survival

Electronic patient reported outcomes

· ACTIVELY ENROLLING
· US, EU, LATIN AMERICA AND ASIA-PACIFIC

Source. https://clinicaltrials.gov/ct2/show/NCT04129502

SUMMARY

1

NSCLC patients with EGFR Exon 20 insertions are underserved with the current available therapies

2

TAK-788 is the first purposely designed inhibitor and clinical proof-of-concept has demonstrated efficacy

3

The EXCLAIM trial in refractory patients could lead to the first approval of TAK-788 by 2021