15P: FGFR3-TACC3 fusion (F) as an acquired resistance mechanism following treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) and a suggested novel target in advanced non-small cell lung cancer (aNSCLC).

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On behalf of the Israel Lung Cancer Group

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BACKGROUND

- Fusion between *FGFR3* and *TACC3* represents a rare acquired resistance mechanism following treatment with EGFR TKIs.
- Data regarding its prevalence and therapeutic implication is limited (Ref. 1-3).

OBJECTIVES

- *FGFR1/2/3* fusion prevalence in aNSCLC de novo and
- *FGFR1/2/3* fusion prevalence in aNSCLC as a resistant mechanism following EGFR TKIs in *EGFR* mutant (*EGFR* M) aNSCLC;
- Activity of the EGFR TKI+FGFR TKI combination following progression of EGFR TKIs in *EGFR* M aNSCLC.

METHODS

- Retrospective analysis
- Guardant Health (GH) de-identified electronic database (ED) (11/2016-07/2021) - prevalence of *FGFR2/3* fusions with and without co-existing *EGFR* mutations (assuming co-existing mutations reflect the status of acquired *FGFR* fusion-driven resistance to EGFR TKIs in *EGFR M* aNSCLC);
- aNSCLC ED of TASMC (06/2020-06/2021) - prevalence of *de novo FGFR1/2/3* fusions;
- Case-series of patients with *EGFR* M aNSCLC progressing on EGFR TKIs and developing an *FGFR3-TACC3* fusion selected from Davidoff Cancer Center (DCC) and Oncology Department, Bnei-Zion hospital (BZ) ED (04/2014-04/2021, n=3) - clinico-pathological characteristics, systemic therapies and outcomes.

Figure 1. *FGFR2/3* fusion subtypes distribution in aNSCLC.

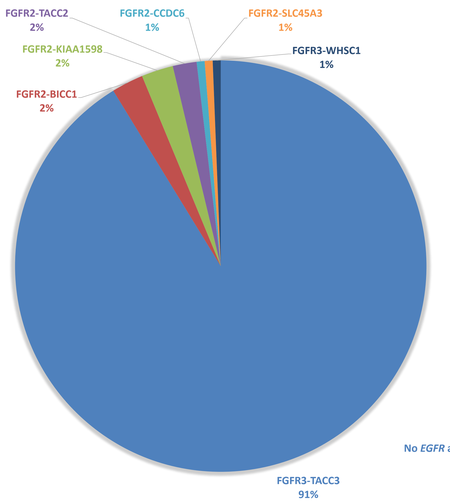
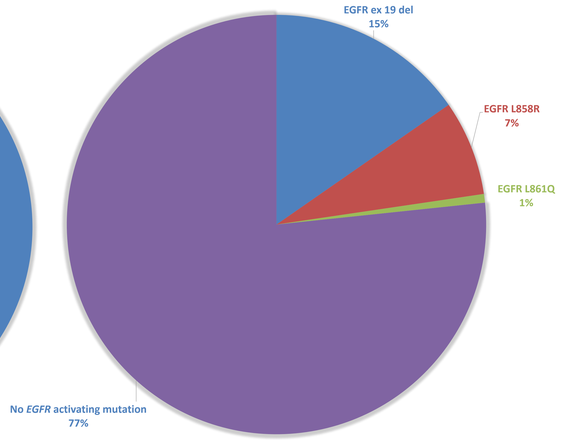


Figure 2. Prevalence of co-existing *EGFR* activating mutations in the patients with aNSCLC and *FGFR3-TACC3* fusions.



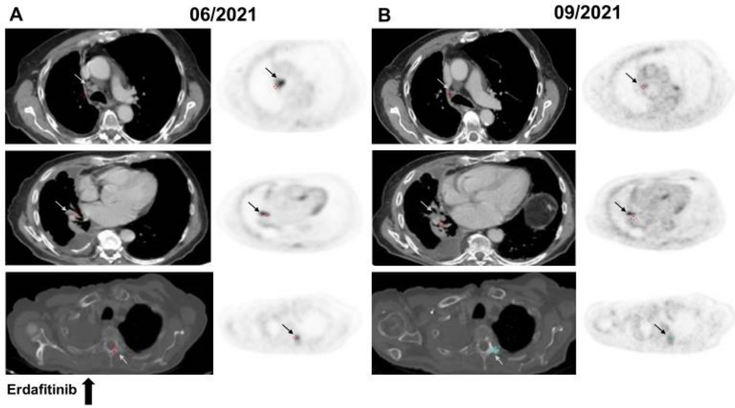
RESULTS

- In GH ED, the prevalence of *FGFR2* and *FGFR3* fusions were 0.02% and 0.26%, respectively.
- Of *FGFR3* fusions, 99.3% were *FGFR3-TACC3* (Figure 1).
- Of *FGFR3-TACC3* fusions, *EGFR* mutations co-existed in 23% (exon 19 del, 66%; L858R, 31%, L861Q, 3%) (Figure 2).
- In TASMC, 1 case of *de novo FGFR3-TACC3* fusion was detected (prevalence, 0.62%).
- Of 3 patients with *FGFR3-TACC3* fusions following progression on EGFR TKIs (2 females, age 59-84y, *EGFR* mutation type: E746_A750del, L858R, L747_A750delinsP) (Table 1), 2 patients received gefitinib/erdafitinib and osimertinib/erdafitinib combinations with a disease stabilization and a partial response for 4 and 2+ months, respectively (Figure 3).

Table 1. Demographic and clinico-pathological characteristics of patients with *EGFR* M aNSCLC progressing on EGFR TKIs and developing an *FGFR3-TACC3* fusion.

Case	Sex	Age, years	Tumor histology	Smoking history	*EGFR* M subtype	Treatment history: agent (PFS)	*FGFR3-TACC3* fusion MAF, %	Concurrent alterations, MAF/VAF, %
#1	F	59	Adenoca	Never-smoker	L858R	Gefitinib (7 mo), osimertinib (13 mo), carboplatin/pemetrexed (6 mo)	0.3	*EGFR* L858R, 33.4, *PIK3CA* E545K, 47.5, *CCND1* amplification, *CDK4* amplification, *KRAS* amplification, *MYC* amplification
#2	M	84	Adenoca	Never-smoker	E746_A750del	Osimertinib (11 mo)	0.04	*EGFR* E746_A750del, 1.3, *TP53* Y163C, 0.4
#3	F	63	Adenoca	Never-smoker	L747_A750delinsP	Gefitinib (52 mo), osimertinib (14 mo)	0.07	Gardant360: *EGFR* L747_A750delinsP, 0.5, *PIK3CA* V344G, 1.3 Tempus xT: *EGFR* L747_A750delinsP, 14.4, *EGFR* p. C797S, 3.6, *PIK3CA* V344G, 15.9

Figure 3. FDG-PET/CT images before (A) and during (B) therapy with osimertinib+erdafitinib in a patient with an *EGFR* M aNSCLC and *FGFR3-TACC3* fusion following progression on osimertinib. Shrinkage of a retro-caval lymph node with a reduction in FDG-avidity, stable lung metastasis with a reduction in FDG-avidity, sclerozation of a D3 lytic metastasis with a reduction in FDG-avidity.



CONCLUSIONS

- *FGFR3-TACC3* fusions are the most common *FGFR* fusion subtype in aNSCLC.
- Up to 23% of *FGFR3-TACC3* fusions in aNSCLC are associated with a co-existing *EGFR* M, possibly representing an acquired resistance following treatment with EGFR TKIs.
- In this clinical scenario, combination of EGFR TKIs and FGFR TKIs represents a promising treatment strategy.

References:

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