TPX-0005 with an EGFR tyrosine kinase inhibitor (TKI) overcomes innate resistance in EGFR mutant NSCLC

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Background

Overexpression of several RTKs substitutes EGFR signaling in EGFR mutant NSCLC, including MET, CDCP1 or AX. SHP2, a non-receptor protein tyrosine phosphatase is central in signal transduction downstream of RTK signaling and in Src activation. We previously demonstrated that STAT3 and Src-YAP1 signaling limits EGFR TKI efficacy. We are now exploring the possibility of multiple RTK activation through a Src-YAP1-mediated transcriptional program. We are evaluating whether combined EGFR inhibition with **TPX-0005**, a novel orally available multikinase inhibitor and potent Src/FAK and JAK2 inhibitor, can be more efficient than EGFR inhibition alone in EGFR-mutant NSCLC cells.

Methods: We studied the mRNA expression levels of stromal HGF and tumor RTKs, AXL, CDCP1, MET, EphA2 and SHP2, and clinical outcome in baseline samples of 64 EGFR-mutantNSCLC patients treated with first-line EGFR TKI. We combined in vitro and in vivo approaches to explore whether gefitinib or osimertinib combined with TPX-0005 can abolish STAT3 and Src-YAP1 and downregulate the expression of RTKs.

RESULTS

Figure 1: PFS according to the expression levels of AXL, CDCP1 and SHP2

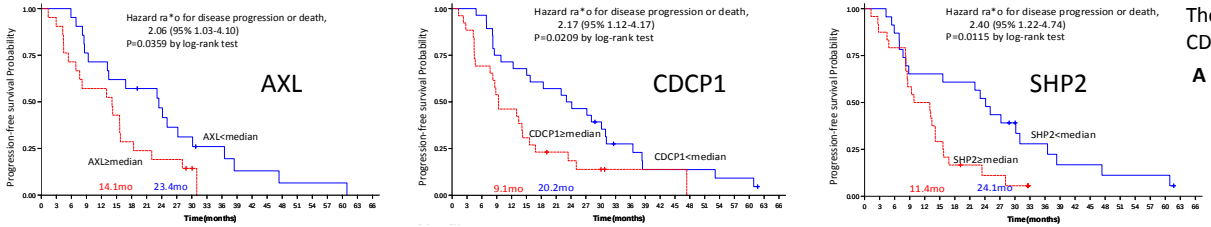


Figure 2: **A).** TPX-0005 in combination with an EGFR TKI in EGFR-mutant NSCLC in vitro and in vivo **B).** TPX-0005 and the combination inversed the gefitinib-induced STAT3 activation and translocation into the nucleus

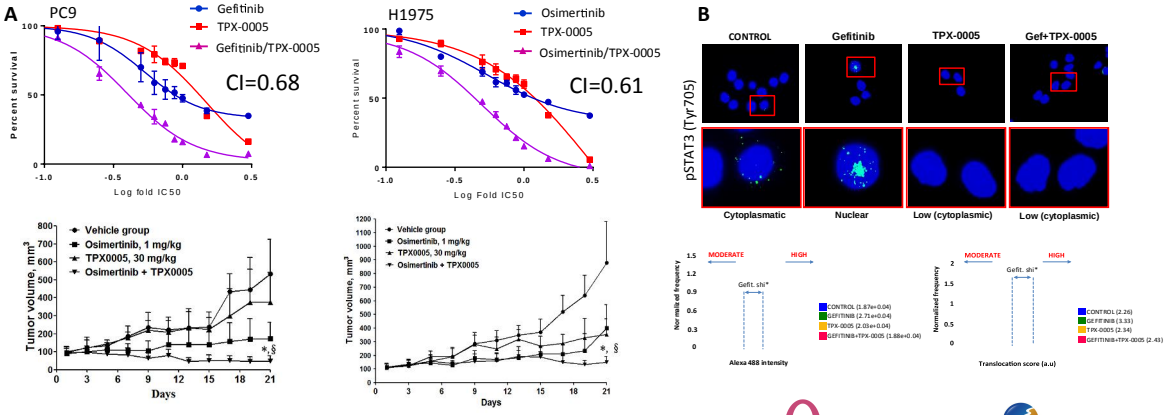
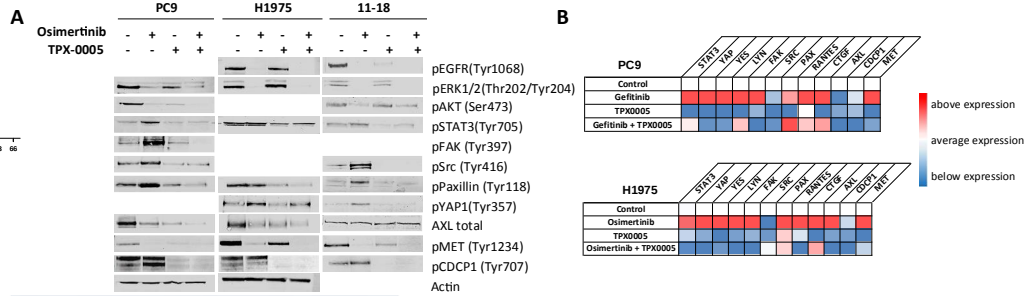


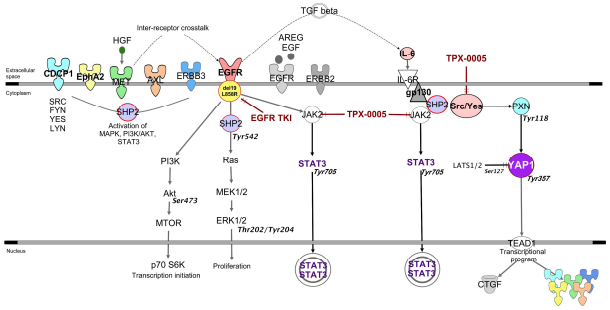
Figure 3: **A).** TPX-0005 in combination with an EGFR TKI in EGFR-mutant NSCLC cell lines abolished the EGFR inhibition-induced STAT3 and YAP1 phosphorylation, as well as the activation of SFKs, FAK and the RTKs. **B).** The EGFR TKI-induced mRNA expression of STAT3, YAP1 and target genes as well as SFKs FAK, AXL, MET and CDCP1 mRNA expression was decreased with the combination of gefitinib or osimertinib with TPX-0005



CONCLUSIONS

AXL and CDCP1 are adverse predictive markers of PFS in EGFR-mutant NSCLC patients. STAT3 and Src-YAP1 signaling limits the efficacy EGFR TKI. **Combined EGFR inhibition with TPX-0005 (currently in phase I clinical testing) is a particularly attractive strategy.**

Figure 4: Our model



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