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 AKT. SHP2, a non-receptor protein tyrosine phosphatase, is central in signal transduction downstream of RTK signaling and 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.

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 reversed 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 combined 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.

REFERENCES


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