

Inactivation of TSC1/2 attenuates the response to osimertinib in EGFRm NSCLC and can be reversed by mTORC1/2 inhibition P3.195

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Introduction

- Osimertinib is a 3rd generation EGFR tyrosine kinase inhibitor (TKI) with demonstrated efficacy in the first- and second-line advanced or metastatic EGFR-mutant (EGFRm) NSCLC setting. Despite clinical benefit, most patients develop resistance to treatment, highlighting the need for combination strategies in both the front-line and post-progression settings, to maximize duration of response.
- Tumour Suppressor genes (TSGs) are often co-mutated in NSCLC, and their loss can potentially alter the response to treatment, including TKIs.
- Previous work (1) has established that loss of specific TSGs, including *PTEN* and *KEAP1* lead to a diminished response to osimertinib.
- This study aimed to evaluate the consequence of mutating up to 58 putative TSGs in a transgenic mode of EGFR-L858R driven NSCLC on tumour number, tumour size and response to osimertinib.

Results

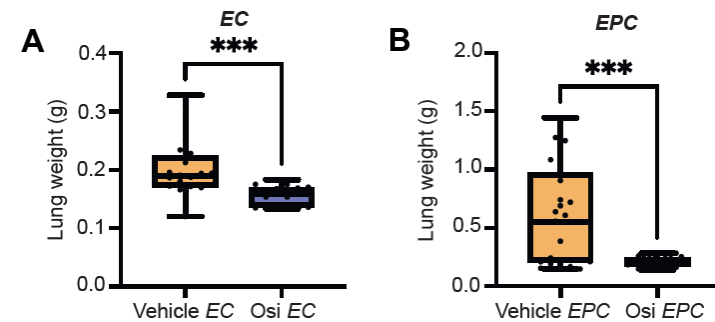


Fig. 1 EGFR-L858R tumour growth is enhanced by loss of TP53 but maintains sensitivity to osimertinib. Lung weights of vehicle and osimertinib-treated EGFR-Cre (EC; A) and EGFR-TP3-Cre (EPC; B) mice at the time of collection.

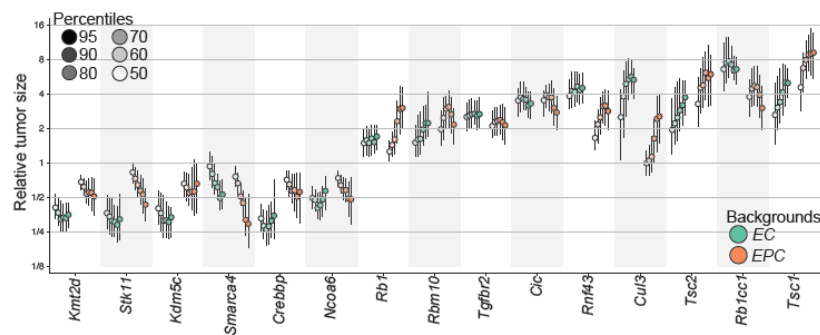


Fig. 2 TSC1 and TSC2 loss enhances tumour size in EGFR-L858R-expressing lung tumours. Genes that when inactivated have consistent detrimental or positive tumour growth promoting effects in EC and EPC tumours at the 95th percentile (50th-95th percentiles shown).

Experimental Design

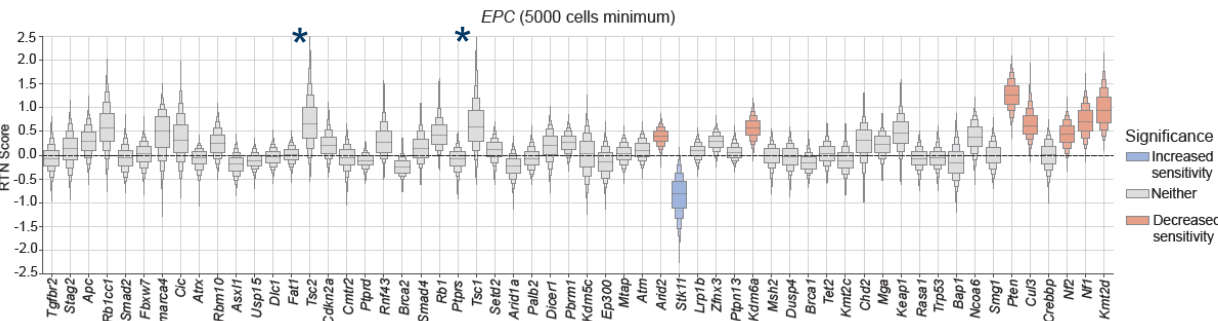
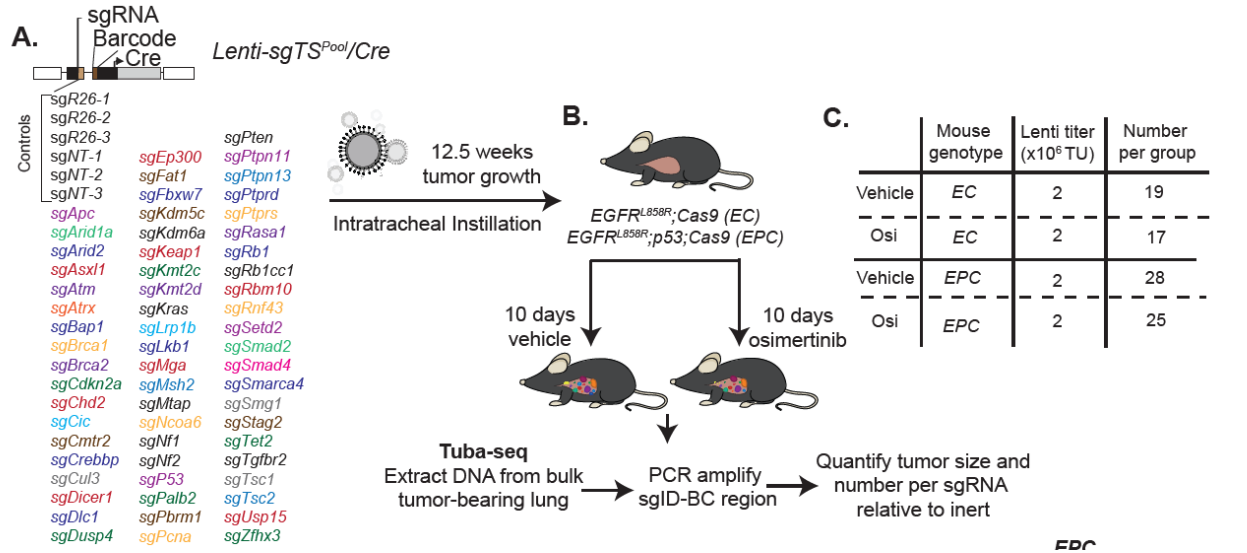


Fig. 3 TSC1 and TSC2 loss diminishes antitumour response of osimertinib in EGFR-L858R-expressing lung tumours with TP53 loss. Plots showing the relative tumour number (RTN) score as a measure of the genotype-specific response to osimertinib for EPC-driven tumours at a minimum tumour size cutoff of 5000 cells. (*) Indicates statistical significance when TSC1 and TSC2 knockout data is pooled.

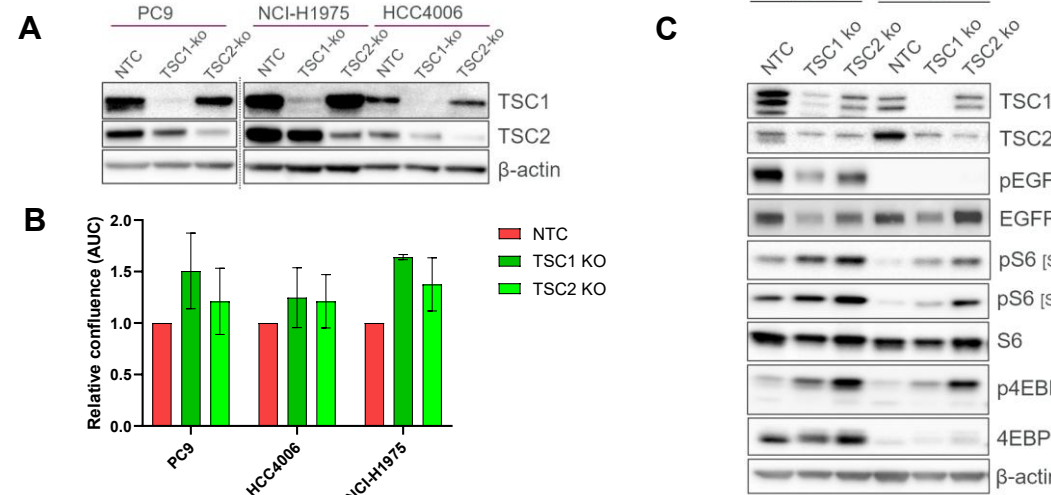


Fig. 4 Knockout of TSC1 or TSC2 leads to diminished antitumour response to osimertinib in EGFRm cell lines, via sustained signaling via the S6 kinase pathway. (A) Western blot confirmation of decreased TSC1 or TSC2 protein levels in CRISPR engineered cell lines, compared to non-targeting control (NTC). (B) Summary of cell confluence over 10 day osimertinib (100 nM) treatment (AUC), as measured on the Incucyte imaging platform (C) Western blot of key S6 kinase pathway biomarkers in NCI-H1975 TSC1/2 knockout cells compared to NTC.

Results (Ctd.)

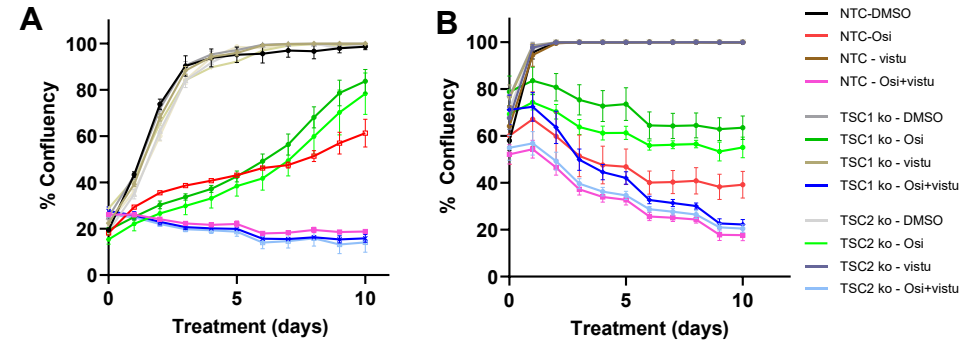


Fig. 5 mTORC1/2 inhibitor vistusertib reverses enhanced growth of osimertinib-treated TSC1/2 knockout cells. HCC4006 (A) and PC9 (B) cells, with TSC1ko, TSC2ko or were treated with osimertinib (100 nM), vistusertib (100 nM) alone or in combination for 10 days. Cell confluence was monitored every 24h using the Incucyte imaging platform.

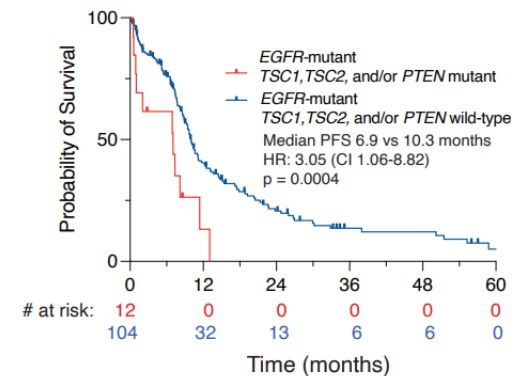


Fig. 6 Patients with PTEN/TSC pathway genetic loss show diminished clinical response to osimertinib. Kaplan-Meier curve showing progression free survival (PFS) for patients in the AACR Project GENIE NSCLC database (2) with advanced EGFR-mutant lung cancer with or without concurrent oncogenic mutations in PTEN/TSC1/TSC2 treated with first-line EGFR TKI therapy.

Conclusions

- Lung-specific expression of EGFR-L858R drives NSCLC in transgenic mice, with tumour growth enhanced by concurrent loss of TP53.
- In both the EC and EPC background, deletion of TSC1 or TSC2 results in significantly larger tumours.
- In the EPC background PTEN loss shows a significant decrease in the response to osimertinib, as does pooled data from TSC1/TSC2 loss.
- CRISPR-mediated knockout of TSC1 or TSC2 in EGFRm cell lines validates the diminished response to osimertinib, both in terms of cell growth and oncogenic signaling.
- The growth advantage of TSC1/2 knockout cells in the presence of osimertinib is reversed by mTOR inhibitor co-treatment.
- Real-world clinical data shows that PTEN, TSC1 or TSC2 loss leads to a significantly shorter PFS for relevant patients treated with EGFR TKIs.

References

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- AACR Project GENIE Consortium. Cancer Discov. 2017 Aug;7(8):818-831.

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Disclaimer: Artificial Intelligence (AI) was not used to analyse data or prepare this presentation.