Abstract LB362

P65-047, a novel TEAD degrader, overcomes KRAS inhibitor resistance through Hippo pathway disruption in NSCLC

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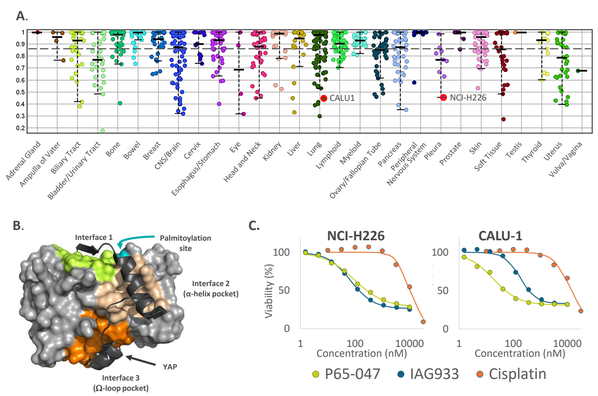
Abstract

Background: Allele-specific KRAS inhibitors (e.g. MRTX849, MRTX1133) show clinical benefit in KRAS-mutant NSCLC but face rapid development of resistance mediated by adaptive YAP–TEAD axis activation. TEAD degraders represent a rational mechanistic partner to intercept this bypass pathway and restore KRAS inhibitor sensitivity.
Methods: P65-047, a cereblon-recruiting TEAD degrader, was evaluated in: (1) *in vivo* subcutaneous CDX models using NCI-H226 ($NF2^{-/-}$ mesothelioma, Hippo-dysregulated) and CALU-1 ($KRAS^{G12C}$/$TP53^{-/-}$ NSCLC); and (2) *in vitro* parental and KRASi-resistant NSCLC human cell models H23 $KRAS^{G12C}$ and A427 $KRAS^{G12D}$. TEAD protein degradation and target gene suppression were assessed by Western blot and qPCR.
Results: P65-047 monotherapy induced dose-dependent tumour regression in both xenograft models (vehicle-treated tumours progressed). In resistant cell models *in vitro*, P65-047 exhibited minimal single-agent activity but produced marked restoration of KRAS inhibitor-dependent growth suppression in combination settings: P65-047 + MRTX1133 resensitized MRTX1133-resistant A427 $KRAS^{G12D}$ cells, and P65-047 + MRTX849 resensitized MRTX849-resistant H23 $KRAS^{G12C}$ cells in cell viability assays. Mechanistic studies confirmed on-target TEAD degradation and suppression of TEAD-regulated transcripts in resistant cells.
Conclusions: P65-047 displays high efficacy, delivering robust *in vivo* tumour regression and strong resensitisation *in vitro*, establishing TEAD degradation as a mechanistically validated strategy to overcome acquired resistance in KRAS-mutant NSCLC. These data support clinical advancement of TEAD degrader P65-047 in patients with allele-specific KRAS inhibitor-refractory disease.

P65-047 lineage coverage and CDX cell line selection

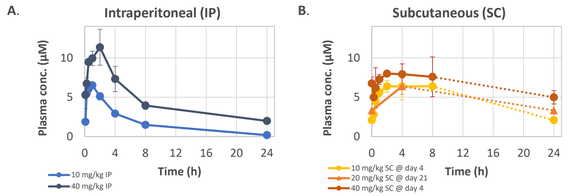
A previous PRISM screen confirmed a broad lineage coverage for P65-047 and revealed that cell lines from pleura (mesothelioma), bladder/urinary tract and uterus are particularly sensitive.[1] Two cell lines were selected for a proof-of-concept study in mice: NCI-H226 ($NF2^{-/-}$) representing pleural epithelioid mesothelioma and CALU-1 ($KRAS^{G12C}$/$TP53^{-/-}$) representing non-small cell lung cancer (NSCLC). Confirmatory dose-response data showed that P65-047 is potent in both cell lines with EC50s of 94 and 18 nM, respectively. As a reference compound, IAG933 was selected, showing EC50s of 68 nM and 183 nM, respectively.



A) Lineage enrichment analysis of the PRISM data. B) Interface 3 binding site used by P65-047. C) Cell viability data from CALU-1 and NCI-H226 cell lines confirming the PRISM results and comparing P65-047 with IAG933.

P65-047 pharmacokinetics

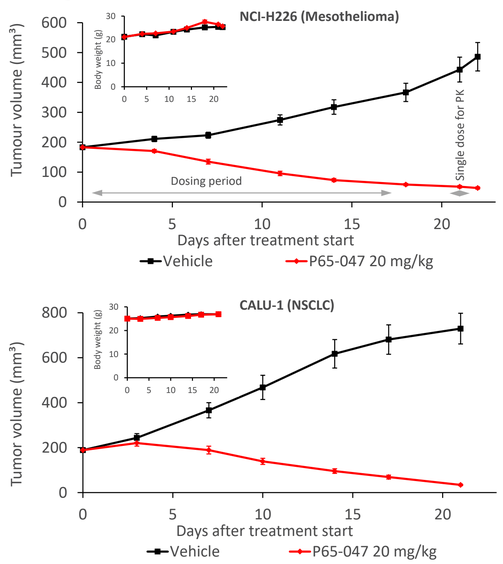
Plasma pharmacokinetics of P65-047 was characterized in mice following intraperitoneal (IP) and subcutaneous (SC) administration across multiple dose levels and dosing regimens. Single-dose IP exposure was assessed at 10 and 40 mg/kg to establish baseline systemic exposure. To relate exposure to safety, once-daily SC dosing at 10 and 40 mg/kg was evaluated with plasma sampling on day 14 of a tolerability study, capturing repeat-dose kinetics at the end of the dosing period. In addition, once-daily SC dosing at 20 mg/kg was investigated in a 21-day CDX efficacy study, with plasma sampling on the final day to link exposure to antitumour activity.



Plasma exposure of P65-047 in mice following A) IP and B) SC administration across acute and repeat-dose regimens. Dashed line extrapolations to 24 h assuming steady state.

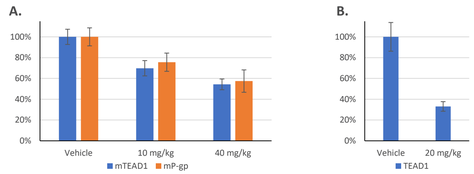
In vivo efficacy

In vivo, the *in vitro* potency translated into strong antitumour activity in both thoracic CDX models. P65-047 treatment with 20 mg/kg once-daily SC dosing resulted in clear tumour regression rather than simple growth delay. Across both models, mean body weights were similar between treated and vehicle groups, supporting that these efficacious regimens were well tolerated in mice.



TEAD1 degradation *in vivo* and reduction of drug efflux transporter in mouse lung

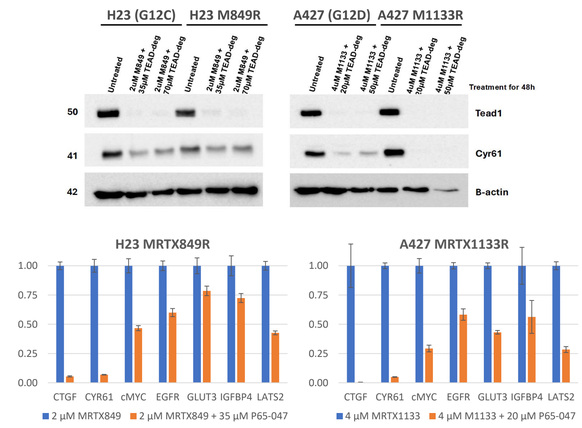
TEAD1 protein levels were quantified in mouse lung after 14 days of once-daily subcutaneous dosing with P65-047 in a tolerability study. In addition, the drug-efflux transporter P-glycoprotein (P-gp/MDR1) was quantified as an exploratory pharmacodynamic marker because TEAD–YAP/TAZ signaling has been linked to ABC transporter regulation, and changes in P-gp/MDR1 abundance may influence tissue exposure to the degrader and co-administered agents. It is clear from this study that TEAD1 degradation correlates with mouse P-gp/MDR1 levels. Further, TEAD1 protein levels were quantified in remaining human CALU-1 xenograft tumours at the end of the 21-day efficacy study.



A. Dose-dependent reduction of mouse TEAD1 and P-gp/MDR1 protein in mouse lung after 14 days of once-daily subcutaneous dosing with P65-047. B. *In vivo* degradation of human TEAD1 in remaining CALU-1 tumours after 21 days of once-daily subcutaneous dosing with P65-047.

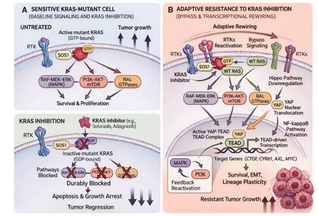
Expression of TEAD1 and TEAD target genes in KRAS-mutant human NSCLC cells

Western blot analysis confirmed complete loss of TEAD1 protein following degrader treatment *in vitro*, validating efficient target engagement. Co-treatment with a TEAD degrader and KRAS inhibitor almost completely suppressed canonical YAP–TEAD targets CTGF and CYR61 in MRTX849- and MRTX1133-resistant cells, confirming on-target pathway blockade. Expression of key resistance-associated effectors, including cMYC, EGFR, GLUT3, and IGFBP4, was markedly reduced, indicating that TEAD degradation constrains the transcriptional rewiring that drives adaptive escape from KRAS inhibition and supports vertical co-targeting of the Hippo–YAP axis.



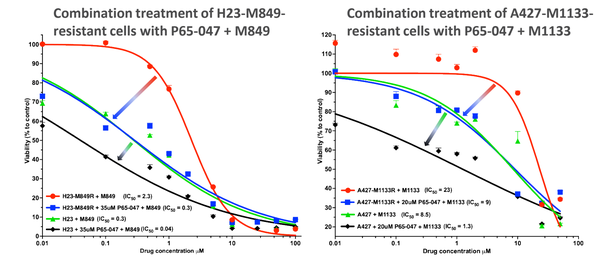
Hippo-mediated adaptive resistance to KRAS inhibition and TEAD co-targeting

In vitro, KRAS inhibitors initially suppress growth of KRAS-mutant NSCLC cells, but adaptive resistance invariably emerges. Resistance to these agents involves activation of PI3K–PDK1 and Hippo pathway signalling, suggesting that co-targeting the YAP–TEAD axis could re-sensitize KRAS inhibitor-resistant cells.[2]



Sensitisation of parental KRAS-mutant cells and resensitisation of KRASi-resistant cells

Parental and KRASi-resistant NSCLC human cell models – H23 ($KRAS^{G12C}$) and A427 ($KRAS^{G12D}$), were treated *in vitro* with the TEAD degrader P65-047 in combination with MRTX849 or MRTX1133, respectively. Growth inhibition assays were performed to measure the % viability. The combination treatment with P65-047 completely reversed the resistance of the KRASi-resistant human cell models and restored their sensitivity to the respective KRAS inhibitors (as indicated by reduction in IC50 of resistant cells). This outcome is consistent with prior reports that YAP1/TAZ–TEAD activation underlies resistance to KRAS-targeted therapy and indicates that selective degradation of TEAD effectively abrogates the Hippo/YAP1 bypass pathway, resensitising KRAS-mutant lung cancer cells to G12C or G12D inhibition.[3]



Summary

- P65-047 degrades TEAD1 *in vivo* and drives tumour regression in $KRAS^{G12C}$ NSCLC and $NF2^{-/-}$ mesothelioma CDX models, with a PK profile supporting once-daily dosing.
- TEAD degradation resensitises KRASi-resistant $KRAS^{G12C}$ and $KRAS^{G12D}$ NSCLC cells to their respective KRAS inhibitors, confirmed by TEAD1 protein loss and YAP–TEAD target gene suppression.
- P65-047-mediated reduction of P-gp/MDR1 may enhance tumour sensitivity to co-administered P-gp substrate agents, suggesting potential for combinations beyond KRAS inhibitors.

References
1) Sawant R, *et al.* AACR Annual Meeting 2025; Cancer Res. 85(Suppl 2):LB238.
2) Barua A, *et al*. bioRxiv 2025.12.22.696060.
3) Edwards AC, *et al*. Cancer Res. 2023; 83(24):4112-4129.

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