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Evaluation of the next-generation selective RET inhibitor EP0031/A400 (lunbotinib) +/- standard of care NSCLC chemotherapy regimens in preclinical models of RET-aberrated cancers

Tao Shen[1], Shriya Pandey[1], Geoff Fisher[2], Hendrik-Tobias Arkenau[2], Jie Wu[1], Sital Patel[2]

1. University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; 2. Ellipses Pharma, London, UK

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BACKGROUND

- Despite advances in the treatment of RET fusion-positive non-small cell lung cancer (NSCLC) with first-generation selective RET inhibitors (SRIs), tumour heterogeneity and diverse bypass mechanisms are challenges that currently limit the depth and duration of responses
- Combining an SRI with chemotherapy may address these challenges
- EP0031 (lunbotinib, A400) is a next-generation SRI with broad potency against common RET alterations (including resistance mutations) with greater potency, antitumour activity, and central nervous system activity, compared with first-generation SRIs in xenograft models[1]
- Here, we characterise the activity of EP0031 ± standard of care (SoC) chemotherapy in human cancer cell lines with pathogenic RET alterations

METHODS

- Inhibition of RET kinase activity was assessed by immunoblot in:
  - *CCDC6-RET* fusion-positive LC-2/ad and TPC1 cells
  - RET(C634W)-mutant TT human cancer cells
- LC-2/ad and TPC1 cells were used to evaluate the activity of EP0031 ± SoC NSCLC chemotherapy regimens in cell viability and colony growth assays
- Cell viability was measured by CellTiter-Glo luminescent cell viability assay
- Synergy was calculated using the Bliss model of independence

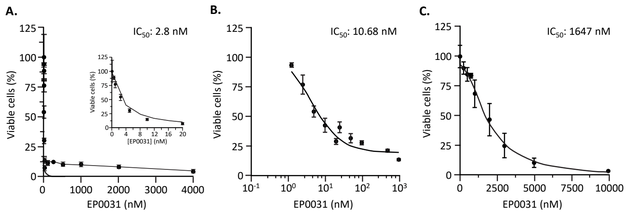
CONCLUSIONS

- Preclinical data confirms that there is strong synergy between EP0031 (a next-generation selective RET inhibitor) and SoC chemotherapy regimens in human cancer cell lines with pathogenic RET alterations
- The unexpected synergy and the challenge of tumour heterogeneity provides a strong rationale for evaluating the combination of EP0031 + SoC chemotherapy in the clinic
- A trial of EP0031 + platinum/pemetrexed is ongoing in patients with RET-fusion positive NSCLC, who are naïve to, or have been previously treated with a first-generation SRI (NCT05443126; presented at European Lung Cancer Congress [ELCC] 2026 in Copenhagen, Denmark, poster number: 142TiP)

RESULTS

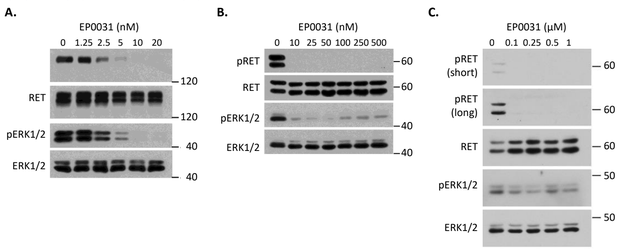
- **Figure 1** shows cell viability and measurement of half maximal inhibitory concentration (IC_{50}) following 5 days of exposure to varying doses of EP0031 in TT, TPC1, and LC-2/ad RET-aberrated cells
  - TT and TPC1 cells were more sensitive to EP0031 than LC-2/ad cells
  - The IC_{50} was in the range of 2.8–1647 nM
- In the colony growth assay (data not shown), whilst colony formation of the cells tested was significantly inhibited by EP0031, a small proportion of cells were tolerant even at doses ≥1 µM
- **Figure 2** shows immunoblot analysis of RET kinase inhibition in TT, TPC1 and LC-2/ad cells, each treated with increasing doses of EP0031 for 24 hours
- Maximal inhibition of phosphorylated-RET could be obtained at 10 nM EP0031 in TPC1 and TT cells and at 100nM in LC-2/ad cells
- **Figure 3** shows cell viability following 5 days of exposure to varying doses of EP0031 in combination with platinum and pemetrexed regimens in LC-2/ad RET-aberrated cells
  - Synergistic killing of LC-2/ad cells was primarily driven by the combination of EP0031 and pemetrexed

Figure 1. Effect of EP0031 on cell viability in human thyroid and lung cancer cell lines, (**A**) TT, (**B**) TPC1, and (**C**) LC-2/ad RET-aberrated cells



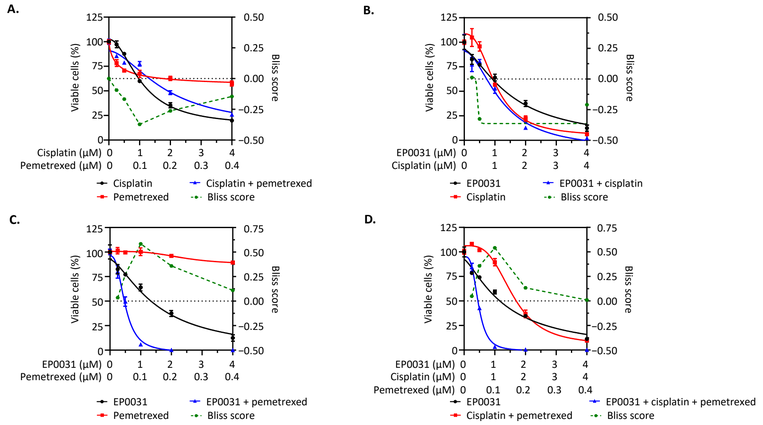
IC_{50}, half maximal inhibitory concentration; nM, nanomolar.

Figure 2. Immunoblots showing inhibition of RET kinase activity in (**A**) TT, (**B**) TPC1, and (**C**) LC-2/ad cells



pRET (short), exposed to film for a shorter time; pRET (long), exposed to film for a longer time. µM, micromolar; ERK1/2, extracellular signal-regulated kinase 1/2; nM, nanomolar; p, phosphorylated.

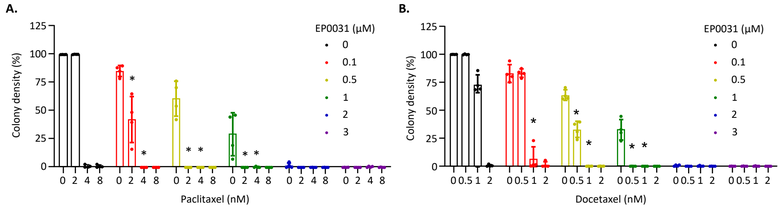
Figure 3. Synergistic killing of LC-2/ad cells treated with (**A**) platinum + pemetrexed, (**B**) EP0031 + platinum, (**C**) EP0031 + pemetrexed, and (**D**) EP0031+ platinum + pemetrexed



Bliss score value: >0, synergy; 0, additive; <0, antagonistic. µM, micromolar.

- Bliss scores indicated that pemetrexed ± cisplatin displayed the strongest synergy when combined with EP0031 in LC-2/ad cells (**Figure 3D**)
- **Figure 4** shows cell viability following 5 days of exposure to varying doses of EP0031 in combination with SoC taxane regimens in TPC1 RET-aberrated cells
  - Synergistic killing of TPC1 cells was observed with both paclitaxel and docetaxel

Figure 4. Synergistic killing of TPC1 cells as shown by colony density following treatment with (**A**) EP0031 + paclitaxel and (**B**) EP0031 + docetaxel



*Synergy. Bliss score value interpretation: >0, synergy; 0, additive; <0, antagonistic. µM, micromolar, nM, nanomolar.

Acknowledgements

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References

1. Zhou Q, et al. J Clin Oncol 2023:41:16_suppl, 3007

For further information please contact: Jie Wu, Jie-Wu@ou.edu and Sital Patel, sital@ellipses.life