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Preclinical evaluation of CM-272 and palbociclib in murine high-grade neuroendocrine lung cancer cell lines and allograft models

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Background

Lung Cancer is a serious health issue, being the leading cause of cancer-related death worldwide. High-grade neuroendocrine carcinoma of the lung which comprises small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) are particularly aggressive malignant phenotypes accounting for 15-20 % of the cases. Since clinical benefit has not been improved for these tumours over recent decades, there is an urgent need of new therapeutic approaches. Lung cancer animal models are essential tools to reach this purpose. Therefore, we have generated a *p107, Rb1, Tp53 and Pten* quadruple KO animal model that renders high-grade lung neuroendocrine tumours. These tumours share morphological and anatomopathological features with their human counterparts.

The molecular profile of these tumours has identified multiple alterations that could be actionable through molecularly targeted therapies. Based on the identification of G9a as a potential target in lung cancer, we decided to test the effect of a recently described dual inhibitor against G9a/DNMTs, CM-272 (developed in CIMA, Pamplona, Spain). In addition, palbociclib (Pfizer), a CDK4/6 inhibitor, has been assayed in our high-grade lung neuroendrocrine cancer models.

Objectives

Preclinical evaluation of two compounds, CM-272 and palbociclib, using murine neuroendocrine lung cancer cell lines generated from quadruple KO mice and allograft models generated after subcutaneous injection of tumour cells in immunodeficient mice.

Methods

LCNEC and SCLC tumours were developed in *Rb1*$^{F/F}$; p107$^{-/-}$; *Trp53*$^{F/F}$; Pten$^{F/F}$mice. SCLC and LCNEC primary cell lines were isolated from these tumours and were tested for *in vitro* sensitivity to CM272 and palbociclib. Cell viability was evaluated by XTT Cell proliferation kit II. Allograft tumours were generated by subcutaneous injection of SCLC and LCNEC cell lines in immunocompromised nude (nu/nu) mice. When tumour volume reached 150-350 mm^3, mice were randomized in 3 groups to receive daily treatments: vehicle (PBS) (n=4 in LCNEC, n=4 in SCLC), CM-272 (5mg/kg,i.p.) (n=4 in LCNEC, n=5 in SCLC), palbociclib (75mg/kg, i.p. (n=5 in LCNEC, n=4 in SCLC). Fourteen days after the start of the treatment, mice were sacrificed and tumours were collected and processed for immunohistological analysis.

Results and Conclusions

The *in vitro* viability assays showed that the IC50 of CM-272 ranges between 2-6 µM, whereas the IC50 of palbociclib ranges between 3-7 µM depending on the tumour type.

In vivo studies in LCNEC allograft models confirmed that CM-272 exerted a significant inhibition of tumour growth. CM-272 treatment also resulted in a significant decrease of the relative tumour volume. Besides, tumour weight after sacrifice was significantly lower in this group. In SCLC allograft models, no effect of CM-272 was observed with regard to the reduction of tumour volume or tumour weight

After palbociclib treatment, we observed a significant decrease of the relative tumour volume in the LCNEC allograft, whereas no effect was observed in the SCLC allograft model. Changes in proliferation and/or apoptosis as a consequence of both treatments are being analyzed by immunohistological analysis.

CM-272 exerts anti-tumour effects *in vitro* and *in vivo* in LCNEC allografts. Thus, CM-272 may emerge as a candidate to be tested alone or in combination with other therapies in immunocompetent models of LCNEC.

Preliminary data indicate an effect of palbociclib in the reduction of tumour volume in LCNEC allografts.

In SCLC, the anti-tumour effects of both compounds are only observed *in vitro*.

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