

Targeting AURKA, nuclear factor erythroid-2-related factor 2 (Nrf2), and phosphoserine aminotransferase 1 (PSAT1) in KRAS G12C-mutant lung adenocarcinoma



Mengxin Zhou², Jordi Codony-Servat², Daniel Olmo¹, Yu Wang³, Kevin Valencia², Jessica Gonzalez², Jingya Zhang³, Fusheng Zhou³, Feng Yan³, Rafael Rosell¹



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1. Dr. Rosell Oncology Institute (IOR), Barcelona, Spain; 2. The Institute for Health Science Research Germans Trias i Pujol (IGTP), Badalona, Spain; 3. Genfleet Therapeutics, Shanghai, China

Introduction

* Drug resistance is one of the challenges in treating KRAS G12C-mutant lung adenocarcinoma. AURKA and PSAT1 elicit adaptive resistance to target therapy in lung cancer [1,2].

* Cetuximab, an EGFR-targeting drug, is proved to have antitumor effect via inhibiting NRF2 in KRAS mutant colon cancer cells [3].

* Concurrent treatment with cetuximab and MRTX1133 (KRAS G12D inhibitor) has been demonstrated strong synergism in KRASG12D-mutated colorectal cancer cell lines and cetuximab plus fulzerasib (KRAS G12C inhibitor) yields 80% response rate in KRAS G12C mutant lung cancer patients [4].

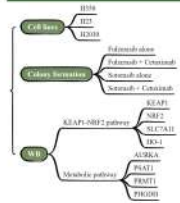
Objectives

* To compare the antitumor effect of fulzerasib or sotorasib in different lung adenocarcinoma cell lines with KRAS G12C mutation.

* To testify whether cetuximab would enhance the antitumor effect of KRAS G12C inhibitors.

* To explore the underlying mechanism of the synergism of KRAS G12C inhibitors and cetuximab.

Methods



The KRAS mutant NSCLC cell lines H358, H23 and H2030 were treated with Fulzerasib or Sotorasib in combination with Cetuximab.

Colony formation assays were used to check the inhibitory effect of these treatments.

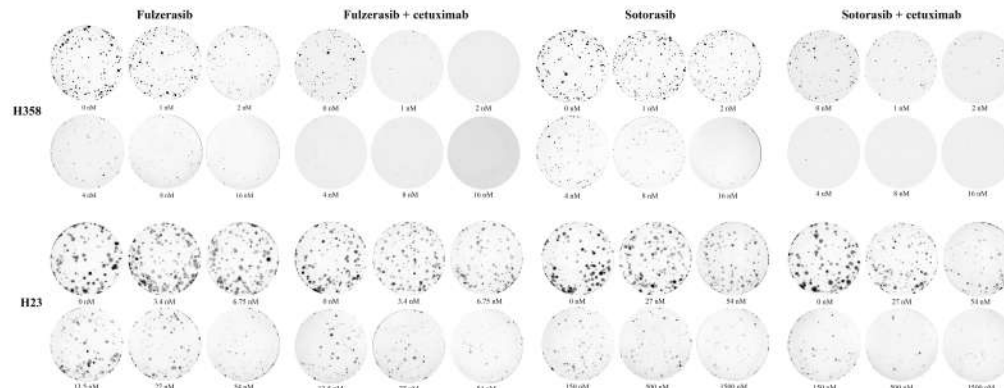
Western blotting experiments were carried out to analyze the expression or activation of the following proteins: NRF2, KEAP1, SLC7A11, AURKA, PSAT1, PRMT1 and PGDH.

References

1. Deng, B., et al., Cell Death Dis, 2024. 15(3): p. 233.
2. Luo, M.Y., et al., Cancer Res, 2022. 82(19): p. 3516-3531.
3. Yang, J., et al., Cell Death Dis, 2021. 12(11): p. 1079.
4. Zhou, Q., et al., Eur J Cancer, 2024. 212: p. 114337.

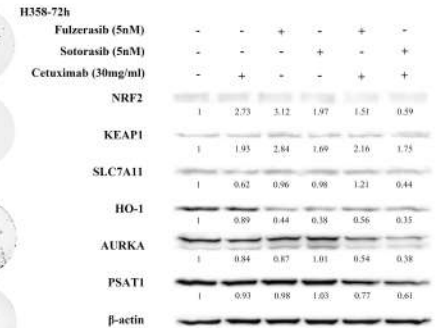
Results

Result 1: Fulzerasib has better effect than sotorasib in inhibiting colony formation, and cetuximab can enhance the effect of both fulzerasib and sotorasib



Note: The number under each well indicates the dose of fulzerasib or sotorasib. The dose of cetuximab was 45ug/ml in H358 and 66ug/ml in H23.

Result 2: Fulzerasib or sotorasib combined with cetuximab inhibited NRF2, SLC7A11, PSAT1 and AURKA expressions



Note: The number under each band indicates their multiples of the mean grey values to the negative control (the first sample of each band). All the grey values were normalized to the mean grey value of β-actin.

Conclusions

Fulzerasib inhibits formation of clones of tumor cells with a much lower dose of fulzerasib than sotorasib with or without cetuximab, even in H23, which is more resistant to fulzerasib and sotorasib.

Cetuximab improves the antitumor properties of fulzerasib as well as sotorasib.

mzhou@fundacionior.org
jcodony@fundacionior.org
rrosell@oncorosell.com

Contact