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Establishment of KRAS G12C mutant patient-derived xenograft (PDX) models for pre-clinical evaluation of KRAS G12C targeted anticancer therapy

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Background

KRAS is one of the most prevalent oncogenes in human cancers. The G12C mutation results in an amino acid substitution at position 12 in KRAS, from a glycine (G) to a cysteine (C), lead to accretion of GTP-bound activated state KRAS and activation of downstream signaling pathways. In non-small cell lung cancer (NSCLC), KRAS p.G12C is the most common mutation, comprising nearly half of all KRAS mutations. Recent breakthrough work led to the development of selective inhibitors targeting the KRAS G12C mutation, which have shown promise in early clinical trials. However, the therapeutic benefit of targeted therapies can be impaired by intrinsic or acquired resistance mechanisms, suggesting an urgent need of combinatorial strategies to overcome the resistance to drugs targeting KRAS G12C.

Method

Here we report on the establishment of a panel of KRAS G12C mutant PDX models, encompass non-small cell lung cancer, colorectal cancer and gastric cancer. The activity of AMG510, a selective KRAS G12C inhibitors in clinical trial, was characterized in these PDX models. Given that in clinic only 50% of NSCLC patients with KRAS G12C mutation would benefit from KRAS G12C targeted inhibitors, in order to provide an insights for clinical therapeutic strategy, we investigated the combinatorial strategies in NSCLC PDX models.

Results

Table 1. Summary of KRAS G12C mutant PDX models

Model ID	Cancer Type	Pathological diagnosis	Gender	Age	Tumor Grade	Tumor Stage
LU-01-0030	NSCLC	Adenocarcinoma	Male	49	G2/G3	T3N3M0
LU-01-0046	NSCLC	Adenocarcinoma	Male	74	G2/G3	T2N2M0
LU-01-0361	NSCLC	Squamous cell carcinoma	Male	60	G3	T2N0M0
LU-01-0462	NSCLC	Adenocarcinoma	Male	63	G3	T2N2M0
CO-04-0070	Colorectal cancer	Adenocarcinoma (Colon)	Female	78	NA	T4N0
CO-04-0307	Colorectal cancer	Tubular Adenocarcinoma (Rectum)	Female	82	G2	NA
CO-04-0310	Colorectal cancer	Tubular Adenocarcinoma (Rectum)	Female	82	G2	T4Nx
CO-04-0315	Colorectal cancer	Papillary/Tubular adenocarcinoma (Ileocecum)	Male	75	G2	NA
ST-02-0331	Gastric cancer	Adenocarcinoma	Male	47	G2/G3	NA

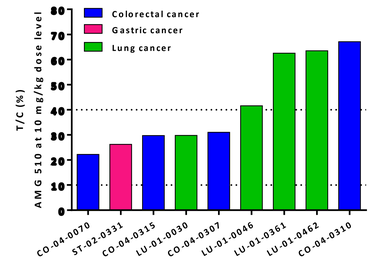

Fig 1. Establishment of a panel of KRAS G12C mutant PDX models
A. The activity of AMG510 was characterized in these PDX models. Data showed that the validated KRAS G12C mutant models display a range of sensitivity to single treatment of AMG510. **B.** Antitumor efficacy of AMG510 against 4 NSCLC PDX models bearing KRAS G12C mutation.

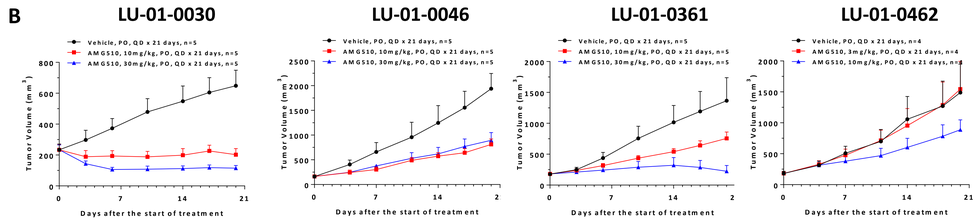

Table 2. Gene expression data of KRAS G12C mutant NSCLC PDX models

Model ID	AMG510, 10mg/kg, T/C (%)	EGFR		HER2		CD274		CCND1	
		CNV	RSQ	CNV	RSQ	CNV	RSQ	CNV	RSQ
LU-01-0030	29.8	**3.2837**	**120.3441**	2.1220	14.4007	1.0701	0.9979	**2.2945**	**85.5109**
LU-01-0046	41.6	**3.3861**	**122.4484**	1.9458	6.5251	2.1818	7.0787	**2.5946**	**110.8131**
LU-01-0361	62.5	1.9761	16.1726	**5.1223**	**86.9597**	**4.9948**	**19.1475**	1.7056	19.8712
LU-01-0462	63.5	1.9402	17.3014	2.3199	7.1606	**4.3256**	**21.8328**	2.0108	31.1344

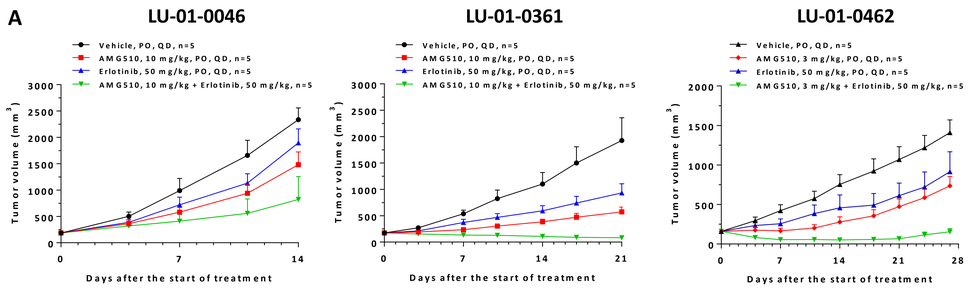

Fig 2. EGFR inhibitor is active in combination with AMG510 in several KRAS G12C mutant NSCLC PDX models.
Combinatorial efficacy of AMG510 and EGFR inhibitor **Erlotinib (A)** and **Cetuximab (B)** against three PDX models LU-01-0046, LU-01-0361 and LU-01-0462. **C.** Western blots in LU-01-0361 tumors showing effect of combination treatment of AMG510 and Erlotinib on phosphorylation of ERK 24 hr after 21 days treatment. *$P < 0.05$

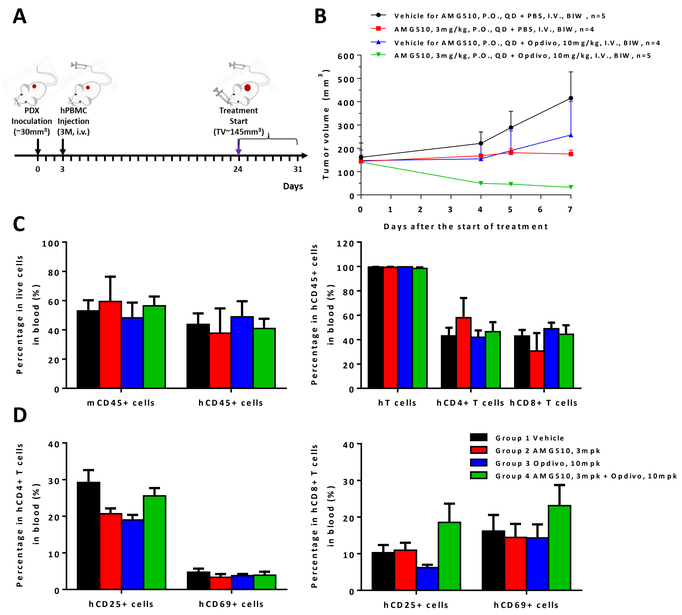

Fig 3. AMG510 and anti-hPD-1 (Opdivo) alone or in combination show antitumor activity against human PBMC humanized LU-01-0361 model.
A. NOG mice were inoculated with LU-01-0361 tumor fragment and injected with 3 x 10^6 human PBMCs i.v. to establish the hPBMC humanized model. Treatments were started 3 weeks after hPBMC injection and the tumor growth curves are shown in **(B)**. Peripheral blood from each treatment group were studied by flow cytometry. **C.** Percentage of hCD45+, hT, hCD4+ T and hCD8+ T cells in blood. **D.** Percentage of CD25+ and CD69+ activated T cells in blood.

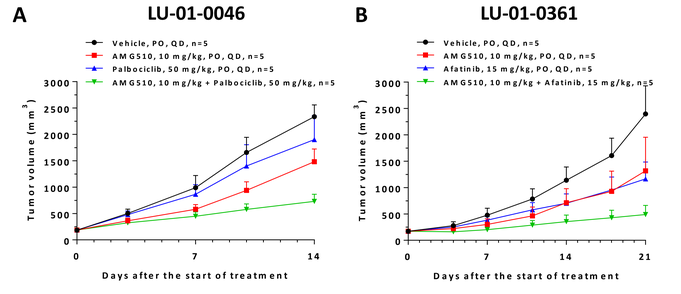

Fig 4. Other combinatorial strategies in KRAS G12C mutant NSCLC PDX models
A. Combinatorial efficacy of AMG510 and CDK4/6 inhibitor Palbociclib in LU-01-0046 model. **B.** Combinatorial efficacy of AMG510 and HER2 inhibitor Afatinib in LU-01-0361 model.

Summary

- We have established a panel of KRAS G12C mutant PDX models and validated the efficacy of AMG510 in there models.
- Based on the genomic profiling data, we tested several combinatorial strategies in KRAS G12C mutant NSCLC PDX models.
- The panel of PDX models are valuable for the pre-clinical evaluation of KRAS G12C targeted anti-cancer therapies.