Preclinical characterization of LY3537982, a novel, highly selective and potent KRAS-G12C inhibitor

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Preclinical characterization of LY3537982, a novel, highly selective and potent KRAS-G12C inhibitor

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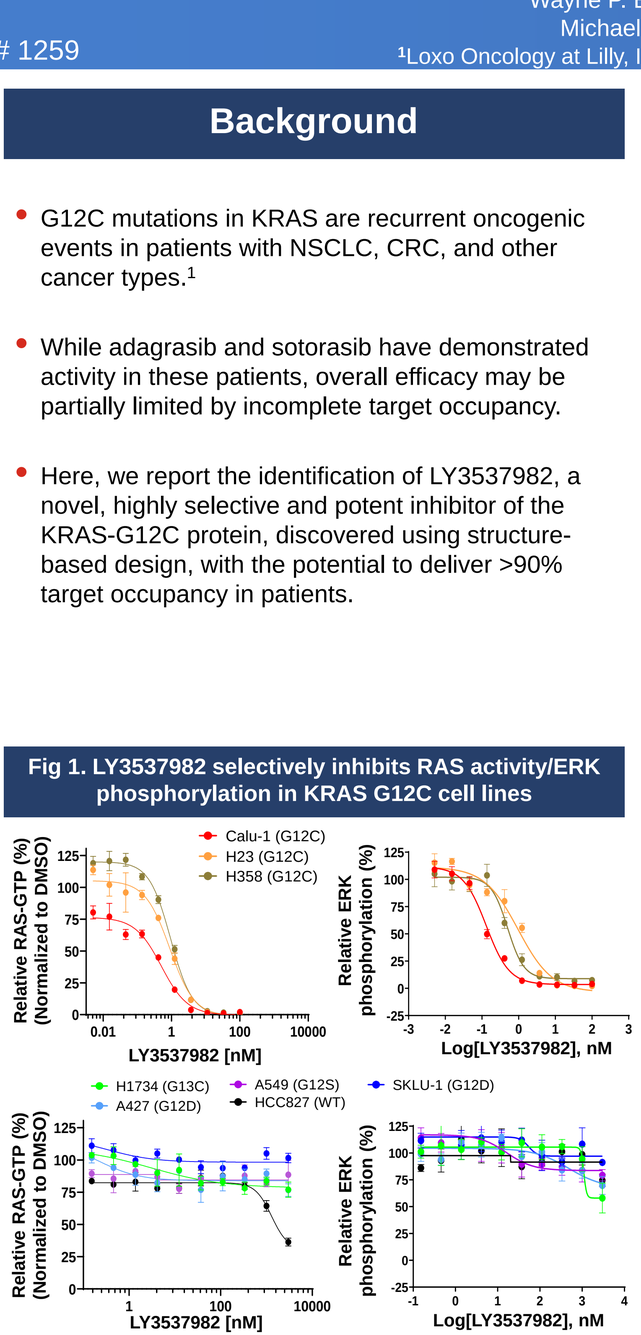
Background

- G12C mutations in KRAS are recurrent oncogenic events in patients with NSCLC, CRC, and other cancer types.[1]
- While adagrasib and sotorasib have demonstrated activity in these patients, overall efficacy may be partially limited by incomplete target occupancy.
- Here, we report the identification of LY3537982, a novel, highly selective and potent inhibitor of the KRAS-G12C protein, discovered using structure-based design, with the potential to deliver >90% target occupancy in patients.

Fig 1. LY3537982 selectively inhibits RAS activity/ERK phosphorylation in KRAS G12C cell lines



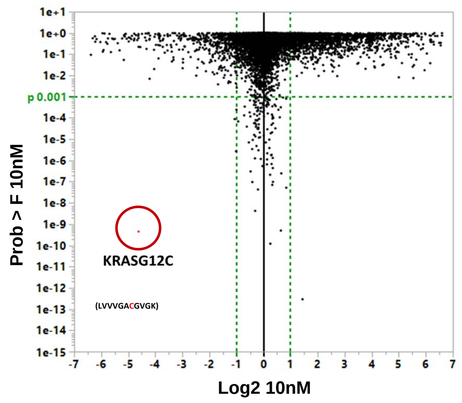
Lung cancer cell lines were treated with LY3537982 at various doses for 4 hours. Cellular RAS-GTP levels were measured using active-RAS ELISA assays (n=3). Data are mean ± SD.

Table 1. LY3537982 selectively inhibits growth of KRAS G12C mutant cells

Cell Line	KRAS Mutation	IC_{50} (nM)
H23	G12C	1.04
H358	G12C	1.16
H2122	G12C	11.38
Calu-1	G12C	59.56
H1734	G13C	>10,000
A549	G12S	>10,000
SK-LU-1	G12D	>10,000
HCC827	WT	>10,000

4-day cell growth assays were performed in cell lines with KRAS G12C or KRAS non-G12C mutations, and KRAS WT using 0 – 10,000 nM of LY3537982. The IC_{50} values were determined by fitting the relative cell viability data at each drug concentration using a sigmoidal dose-response (variable slope) equation (n=6).

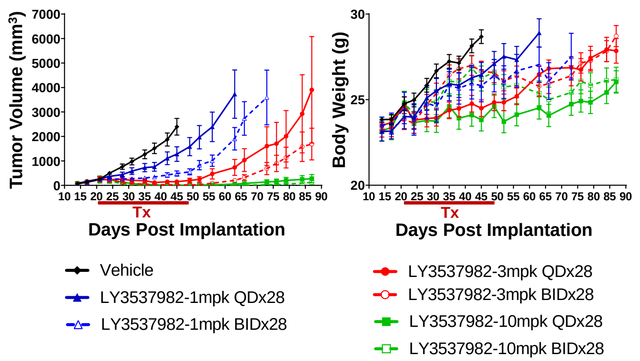
Fig 2. H358 proteome cysteine selectivity with 10 nM LY3537982 (4h treatment)



LY3537982 selectivity for proteome-wide cysteine residues was evaluated using competitive chemical proteomics.

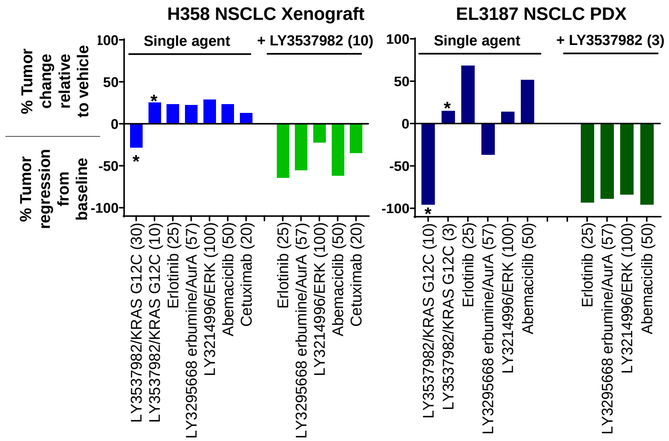
Among 8866 peptides, only one – KRAS G12C (LVVVGACGVGK) – showed a statistically significant reduction in LY3537982/DMSO ratio with 10 nM – 100 nM LY3537982 treatment for 4 h.

Fig 3. *In vivo* efficacy of LY3537982 in EL3187 KRAS G12C NSCLC PDX model



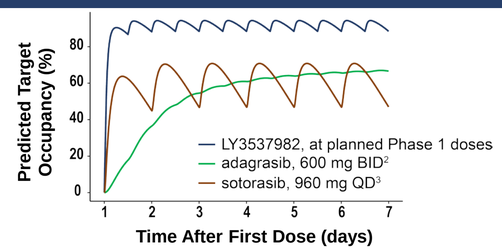
LY3537982 inhibits the growth of subcutaneous EL3187 NSCLC PDX tumors in nude mice (n=5) in a dose dependent manner. The red line under the X axis indicates the compound treatment period; Tx = Treatment Duration (day 21-49). Data are mean ± SEM.

Fig 4. *In vivo* efficacy of LY3537982 combination regimens in KRAS G12C sensitive NSCLC models



*Single agent LY3537982 activity was determined at 30 mpk BID and 10 mpk QD (H358) or 10 mpk QD and 3 mpk QD (EL3187). Combination studies used suboptimal LY3537982 doses (10 mpk for H358; 3 mpk for EL3287).
Treatment: 28 days PO QD at the indicated mpk doses within parentheses; LY3295668 erbumine was BID; cetuximab was IP BIDx4weeks. n=5/group.

Fig 5. LY3537982 is a highly potent covalent inhibitor, with potential for >90% clinical target occupancy



	LY3537982	Adagrasib	Sotorasib
pERK H358 IC_{50} (nM)	0.65 (2h, n=5)	14 (3h)[4]	13.5 (2h, n=2)
Active RAS H358 IC_{50} (2h, nM)	3.35 (n=6)	89.9 (n=1)	47.9 (n=3)
Kinact/Ki ($M^{-1}s^{-1}$)	522,000	35,000[4]	9,900[5]
Predicted Target Occupancy Range	**>90% trough***	**60%***	**45–70%***

*Target Occupancy (TO) predicted by a mechanistic PK/PD model using mouse xenograft and cell-based studies that account for KRAS turnover, KRAS-GTP hydrolysis, GDP to GTP exchange, and KRAS-GDP binding to drug and inactivation, relative to human free exposures. For adagrasib and sotorasib, PK of the RP2D and relative Koff values were used to predict TO.

Conclusions

- LY3537982:
  - Is a potent, highly selective covalent inhibitor of KRAS G12C with cellular IC_{50} of 3.35 nM.
  - Demonstrates robust tumor growth inhibition as single agent in KRAS G12C *in vivo* models.
  - Demonstrates robust tumor regression in combination with other agents in KRAS G12C *in vivo* models.
  - Is a promising KRAS G12C inhibitor predicted to deliver >90% KRAS G12C target occupancy in the clinic.
- A first-in-human trial is planned for 2021.

Acknowledgements

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References

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