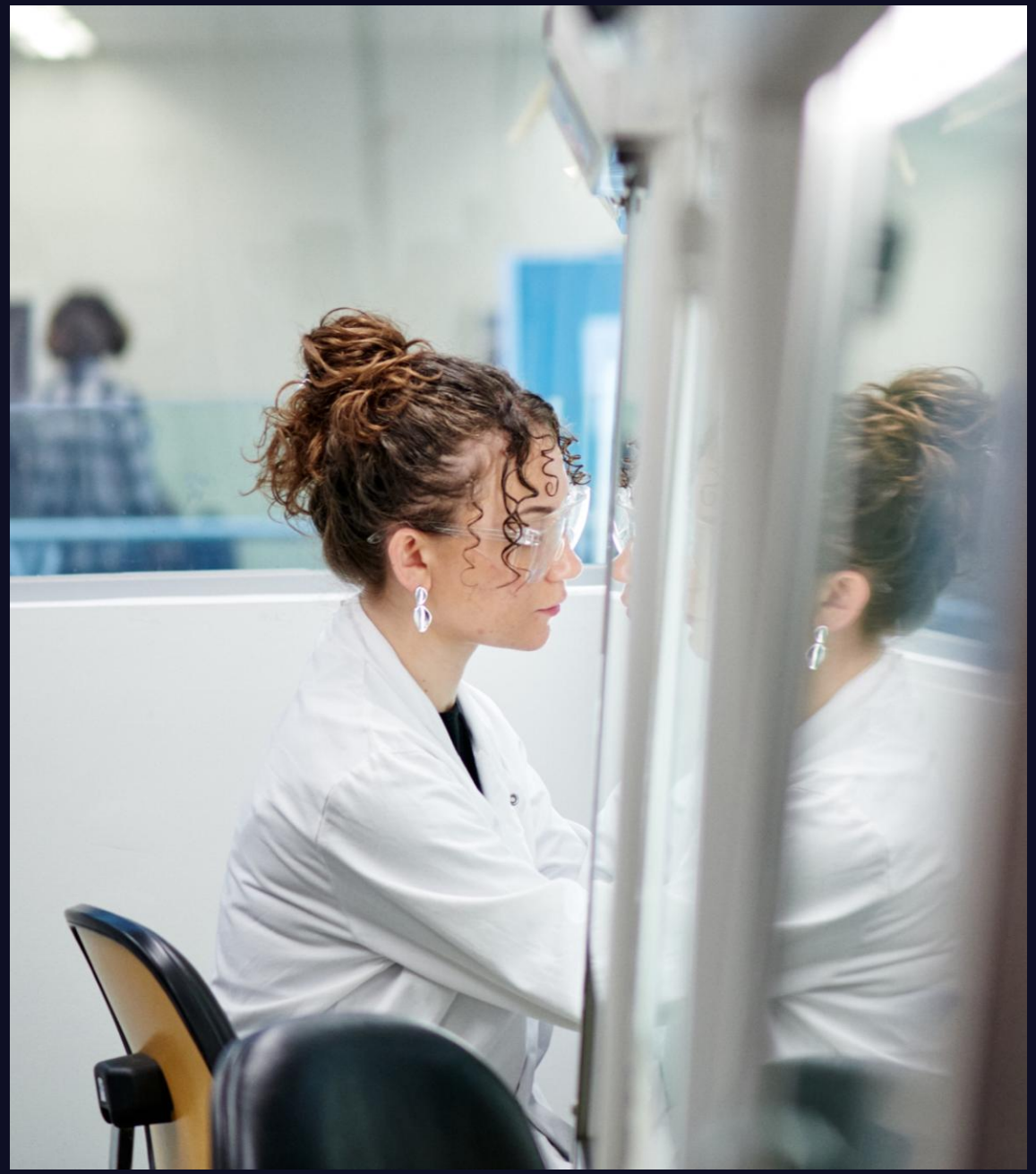


CANCER RESEARCH HORIZONS

Glutaminase Inhibitors

Licensing opportunity

Non-confidential deck

FURTHER FASTER TOGETHER
We are beating cancer

GLS-1 inhibitors executive summary

Target statement

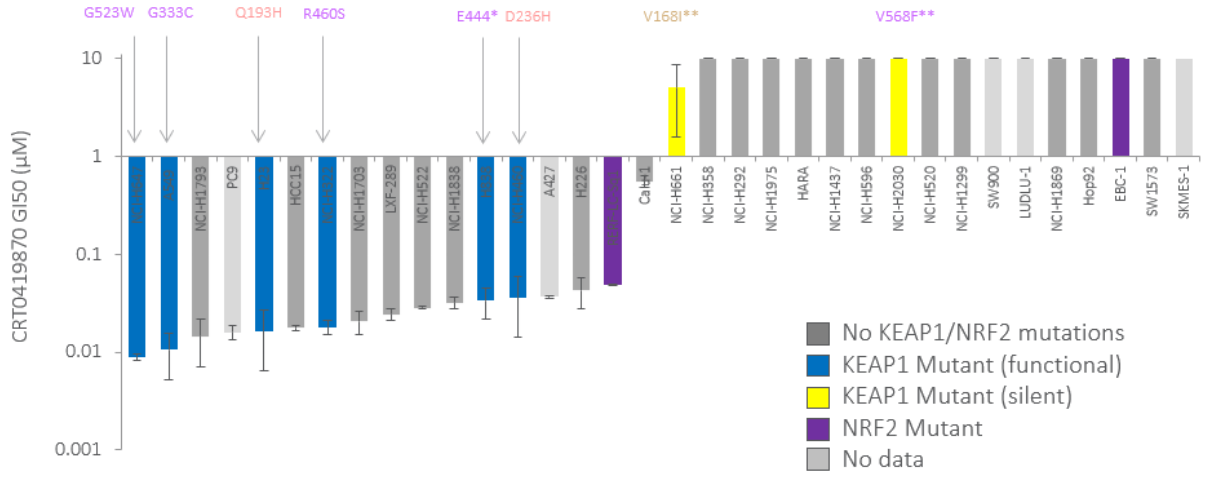
- Best in class small molecule inhibitor as a single agent or combination treatment for NRF2/KEAP1m lung cancers & ASNS low cancers
- Status: Pre-candidate nomination profiling

Overall summary

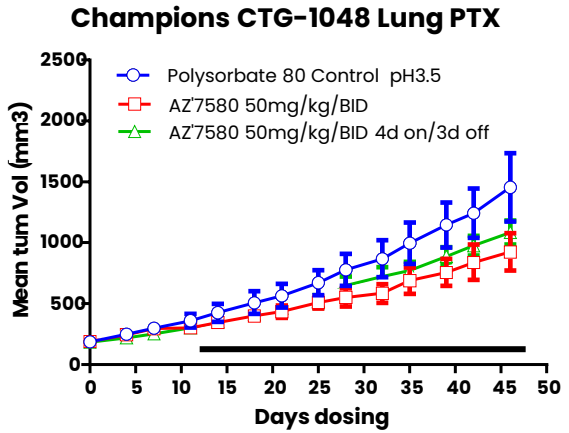
- Early lead molecules first developed as part of metabolism alliance between CRH and AstraZeneca
- CRH have since identified high quality candidate molecules with improved PK and significantly lower dose to human than historical competitor from Calithera
- Strong IP position with four granted patent families across global territories

Glutaminase inhibitor overview

- Potent (<10 nM cells), selective and orally bioavailable allosteric inhibitors of GLS1
- Early lead shows similar in vivo efficacy to Calithera candidate CB-839
- 7 day rat toxicity showed early lead was well tolerated up to 250 mg/kg
- Advanced leads show dose to man projections 22-48 mg qd (CB-839 is dosed 600 mg bid)
- Patents covering the initial and advanced leads have been published and are owned by CRUK
- Gln levels increase in vivo in plasma and tumour Glu levels unchanged after multiple doses

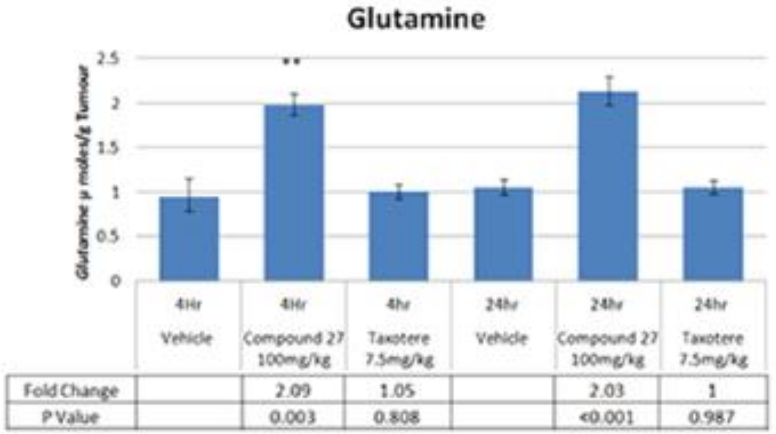


Cellular potency of CRT0419870 in a lung cancer panel

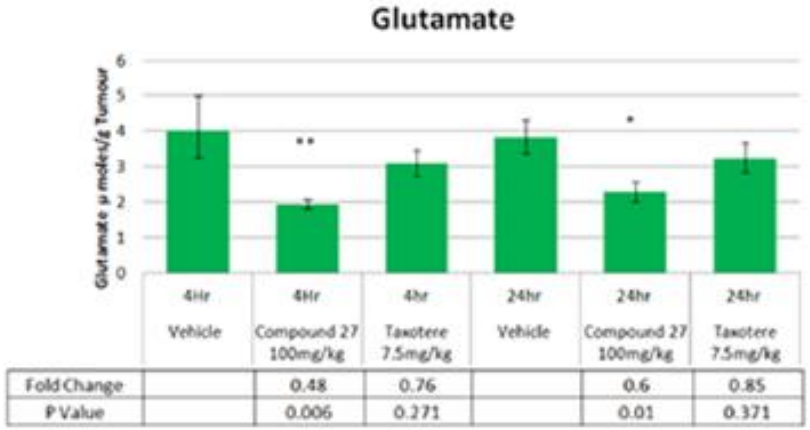


KEAP1m lung PDX data for CRT0419870

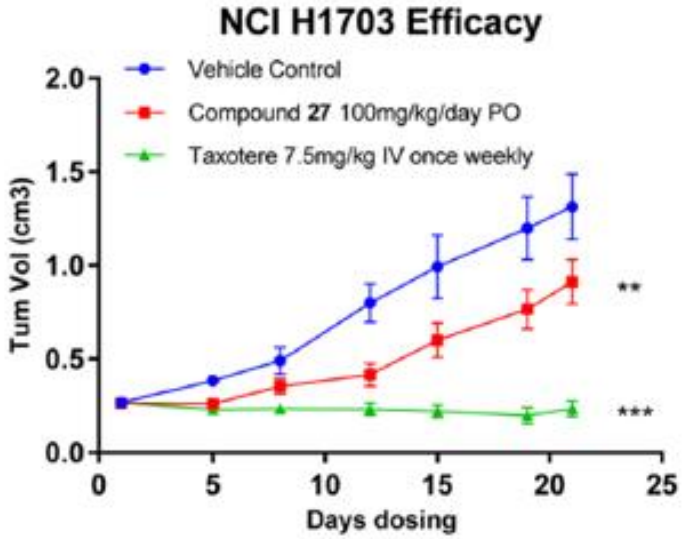
In vivo efficacy and PD modulation in keap1 mutant NSCLC model



Fold Change		2.09	1.05		2.03	1
P Value		0.003	0.808		<0.001	0.987



Fold Change		0.48	0.76		0.6	0.85
P Value		0.006	0.271		0.01	0.371



Time after PO dosing (h)	Mean concentration of **27** (µM)	Mean free concentration of **27** (µM)	Fold free cover over cell GI_{50}
4	3.57	0.582	53
24	3.63	0.592	54

J Med Chem; 2019; 62, 6540-6560

Key compound data table

	Early lead (CRT0419870)	Advanced lead 1 (CRT0510351)	Advanced lead 2 (CRT0510352)	CB-839 Calithera (CRT042914)
Cell biomarker (PC3) IC50 (nM)	0.3	0.9	7	7
Cell proliferation (H-1703) IC50 (nM)	11	2	6	7
LogD pH 7.4	1.7	2.6	2.6	3.9
Solubility (µM)	59	337	558	0.4
PPB % free (r, d, h)	19.4 / 6.8 / 9.2	17.1 / 5.9 / 4.4	4.82 / 1.46 /3.6	nd/1.6/0.9
Heps Clint µl/min/million cells (r, d, h)	2.2 / 2.53 / <1	4.11 / <1 / <1	3.1 / <1 / 1.4	30.2, 54.8, 8.25
CACO2 Papp Int / MDCK Efflux Ratio	6.9 / 22	14 / 34	11 / 38	3.8 / 50.5
Rat PK (CLp mL/min/kg), Vss (L/Kg), t1/2 (h), F%) discrete 1 mpk iv 3 mpk po	13.6, 0.48, 0.88, 24.6	14.5, 1.80, 4.6, 30	3.51, 0.43, 2.83, 45	14, 3.0, 4.6, 32
Predicted HED mg/day (in vitro/in vivo scaling)	>1/983 bid	20/328 qd	22/48 qd	nd/285 bid*

*CB-839 RP2D 600-800mg bid

Thank you

For further information please contact

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