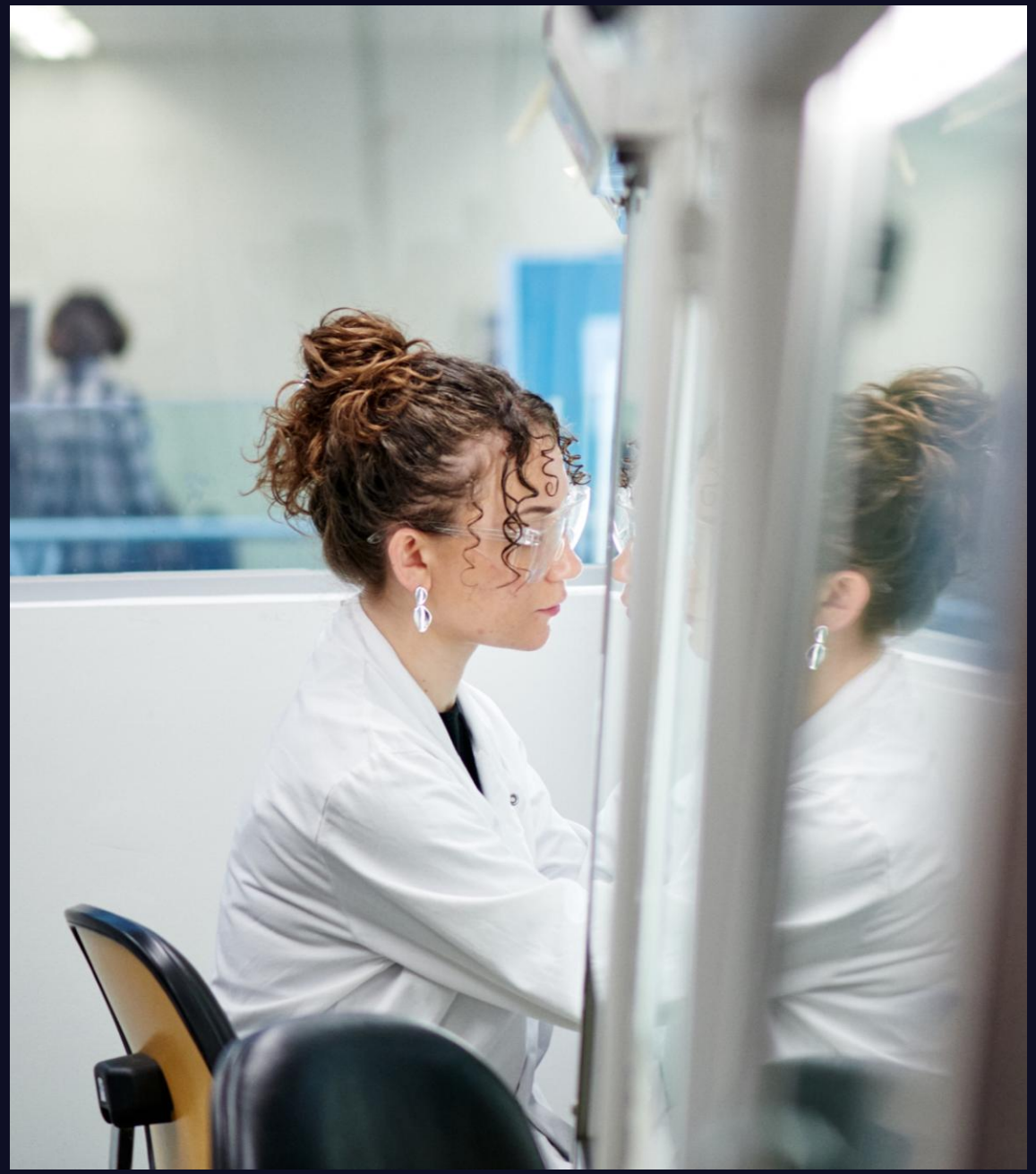


CANCER RESEARCH HORIZONS

RET Kinase Inhibitors

Licensing opportunity

Non-confidential deck

FURTHER FASTER TOGETHER
We are beating cancer

Asset summary

CANCER RESEARCH HORIZONS

Available for licensing

Asset: RET kinase inhibitor pre-clinical candidate. Potent biochemical (<10nM IC50) activity and cellular (~50nM IC50) activity against breadth of mutational backgrounds, including emerging resistance RET mutations. Significant tumour growth inhibition in relevant NSCLC, RET driver mutation-bearing PDX models.

Landscape: Clinically validated target with marketed drugs for NSCLC. Emergence of resistance to first in class RET kinase inhibitors agents selpercatinib (Retevmo) and pralsetinib (Gavreto) through RET 'solvent front mutations.

Commercial: 3 granted patent families with broad coverage, distinct chemical series including preclinical candidate (priority 2016/17). Sales for marketed RET inhibitors forecast to rise to $1B by 2030, next generation RET kinase inhibitors have potential to succeed these.

Key qualities:

- Clear path to patients with high unmet need
- Validated market opportunity
- Active against resistance mechanism to Pralsetinib and Selpercatinib
- Full PK and toxicology studies in rat and dog complete
- Robust tumour growth inhibition/regression demonstrated in RET fusion and RET-mutant tumour models
- Drug substance and drug product available



Potential to replace first in class RET inhibitors in NSCLC, as resistance emerges in clinic

Clinical need

Resistance emerging to 1st-generation selective RET inhibitors creates an opportunity for development of next-gen inhibitors

Clinically validated target

RET fusion proteins drive oncogenesis, and occur in 1-2% of NSCLC. Selective RET inhibitors (SRIs) have been very successful clinically.

RET fusions result in ligand-independent hyperactive RET signalling, establishing RET as a highly actionable therapeutic target.

1st generation SRIs selpercatinib (Retevmo) and pralsetinib (Gavreto) have demonstrated ~80% ORR

Emerging challenge

RET G810 solvent-front mutations have emerged as the predominant mechanism of resistance to 1st generation SRIs.

As solvent front mutations emerge, there are an increasing number of treatment resistant or naïve patients.

Opportunity

Preclinical data demonstrate PDD00031746 as a potent RET inhibitor across both WT RET and clinically relevant G810 solvent-front mutants

PDD00031746 is a RET receptor tyrosine kinase inhibitor directed toward the treatment of 1st-generation SRI treatment resistant or naïve patients.

Patent portfolio at a glance

- **Three global patent families** protecting the core technology
- **Granted** patents covering **broad medicinal chemistry space including multiple series and chemotypes of RET inhibitors**
- **25+ granted patents** worldwide across **12 jurisdictions**
- Patent **protection secured across key markets** in Europe, North America, and Asia-Pacific

- **First patent family WO/2017/178844**
  - PCT filing date: 18.04.2017 (GB priority application no. 1606631.8 and 1619277.5)
  - Publication date: 19.10.2017

- **Second patent family WO/2017/178845**
  - PCT filing date: 18.04.2017 (GB priority application no. 1606635.9)
  - Publication date: 19.10.2017

- **Third patent family WO/2018/189553**
  - PCT filing date: 13.04.2018 (GB priority application no 1705971.8)
  - Publication date: 18.10.2018

Inhibition of emerging RET resistance mutations

CANCER RESEARCH HORIZONS

PDD00031746 retains potent inhibition of solvent-front mutant RET

Biochemical Activity Against Wild-Type and Resistance-Mutant RET Kinases

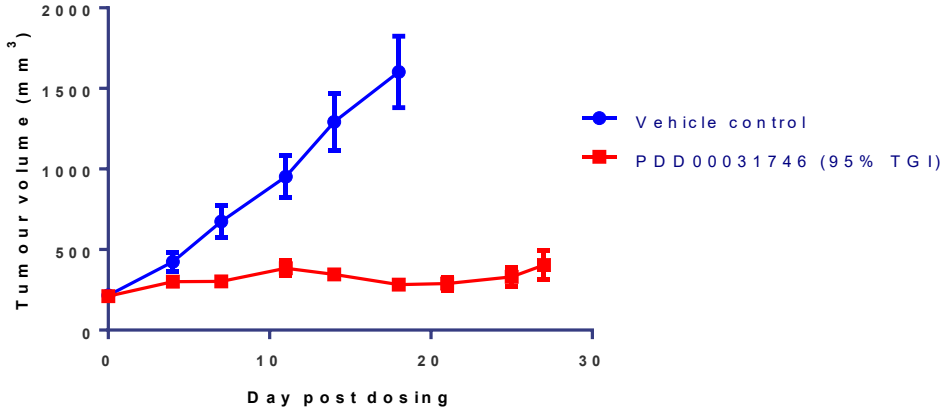
	Compound IC50 (and potency shift vs WT RET)		
	PDD00031746	Selpercatinib	Pralsetinib
RET WT	25.3 nM	8.8 nM	15.0 nM
RET G810C	40.8 nM (1.6x)	672 nM (76x)	271 nM (18.1x)
RET G810R	80.9 nM (3.2x)	977 nM (110.5x)	1320 nM (88x)
RET G810S	33.6 nM (1.3x)	125 nM (14.1x)	59.8 nM (4x)

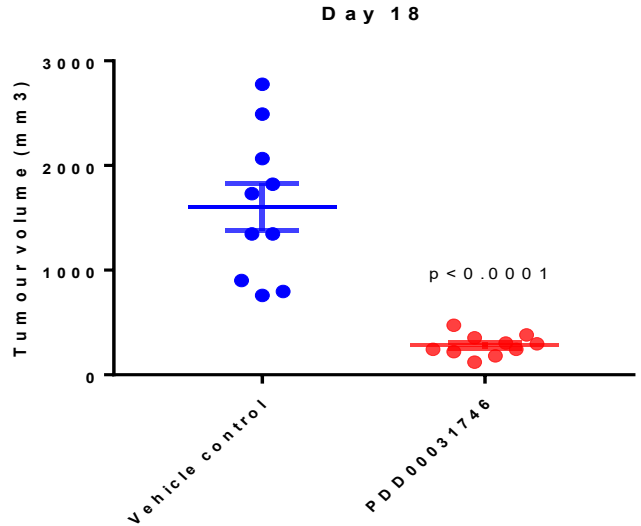
Source: *WO2023/064843 A1, Inhibitors of Mutant RET Kinases for Use in Treating Cancer, Table 3. Biochemical RET kinase inhibition assay.*

Demonstrated in vivo potency

PDD00031746 induces tumour regression at highest doses

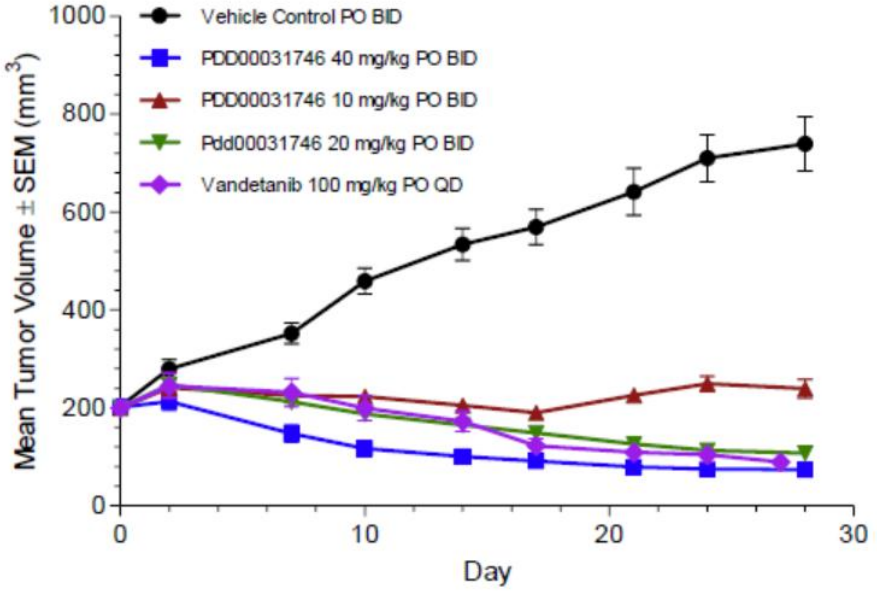
*KIF5B-RET PDX model (LAD)





KIF5B-RET PDX model (CTG0838) dose escalation

Dose	TGI (%)
40mg/kg	124
20mg/kg	117
10mg/kg	92
Vandetanib	121



KIF5B-RET is the most prevalent RET fusion in NSCLC

Key compound data - PK/ADMET

CANCER RESEARCH HORIZONS

Property	PDD00031746
Solubility (µM)	65
Thermo Solubility pH 7.4	ND
LogD pH 7.4	3.68
pKa (Base / Acid)	3.86 / 11.32
Microsomal CLint (h/r/m/d)	~0 / 16.7 / 5.5 / 1.5
Hepatocyte CLint (h/r/m/d)	2.0 / 15.2 / 16.5 / 16.1
CYP Inhibition IC50 (µM)	1A >25; 2C9 >25; 2C19 8.4; 2D6 >25; 3A4 >25
Time-Dependent CYP Inhibition	None
PXR Activation (max fold)	2.55
AhR Activation (max fold)	3.52

Property	PDD00031746
Caco-2 Papp A→B	20.5 $\times 10^{-6}$ cm/s
Efflux Ratio	1.83
hERG IC50 (µM)	>25
Plasma fu % (h/r/m/d)	9.5 / 6.0 / 6.7 / 6.7
Blood fu % (h/r/m/d)	3.6 / 6.1 / 2.9 / 2.2
P-gp IC50 (uM)	3.02
BCRP IC50 (uM)	0.80
OATP1B1 IC50 (uM)	1.70

Additional data

Further data packages are available under CDA, including:

Target Engagement:

- Direct RET target enagement demonstrated (BLI)
- RET pathway inhibition confirmed in KIF5B-RET NSCLC PDX tumour tissue (Western blot analysis of pRET, pSHC, pAKT and pERK)

In Vivo Efficacy:

- Anti-tumour activity demonstrated in RET fusion and RET-mutant models, including: KIF5B-RET NSCLC PDX (95% TGI), BaF3 BCR-RET (V804M) allograft (83% TGI)

PK & Tolerability:

- IV and oral PK characterised across in mouse, rat and dog species
- Dose-ranging, repeat-dose and tolerability studies
- First-in-man dose range predictions

PK/PD Relationship:

- PK/PD study in Ba/F3 KIF5B-RET allograft (70-100% reduction in pRET levels following dosing, compound levels ~160× cellular IC50)

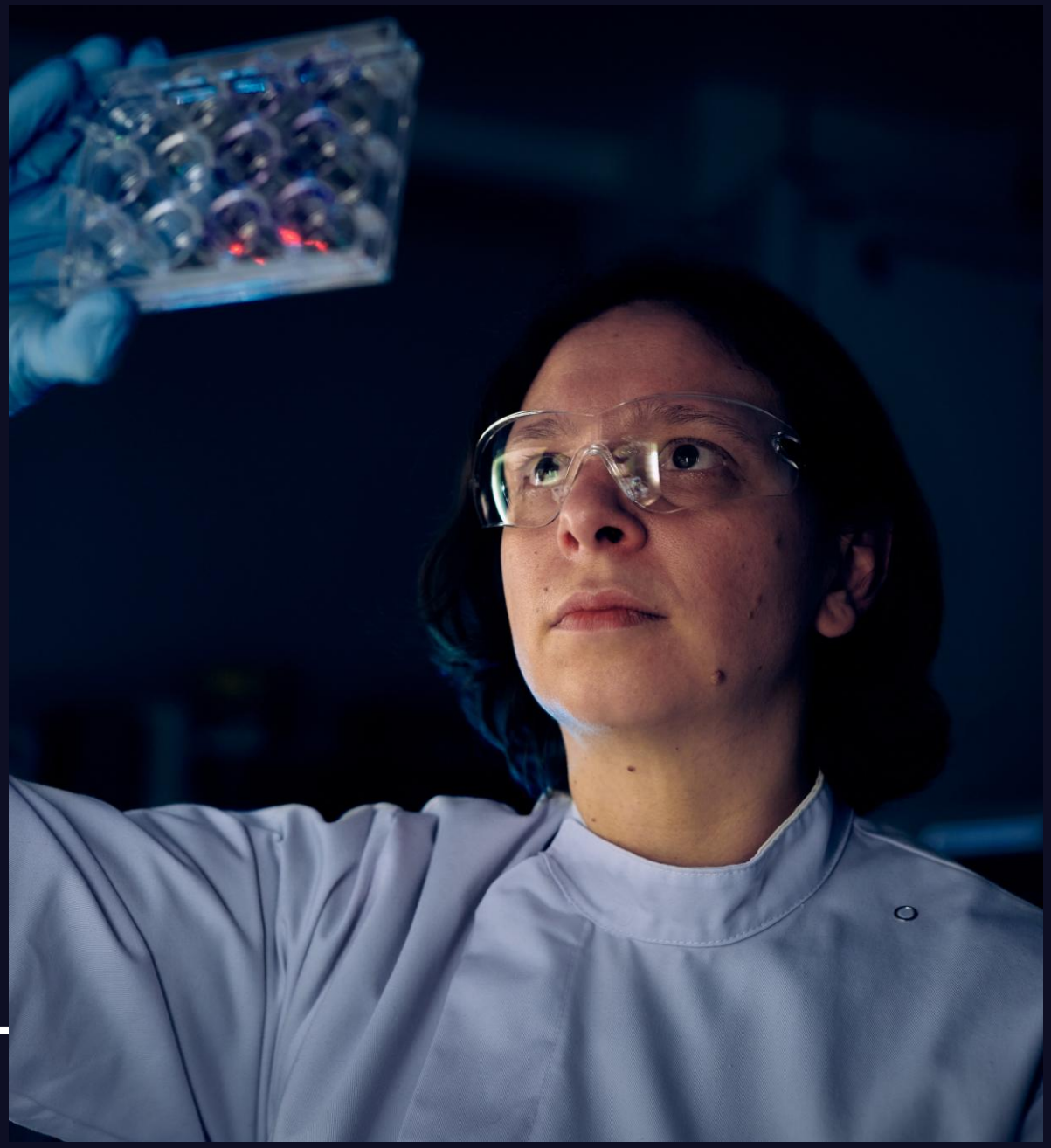
Thank you

For further information please contact

Dom Pollard

Business Development Executive (Therapeutics)

dominic.pollard@cancer.org.uk



CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER
We are beating cancer