‘539 (LSD1)

IND submission expected in 2024

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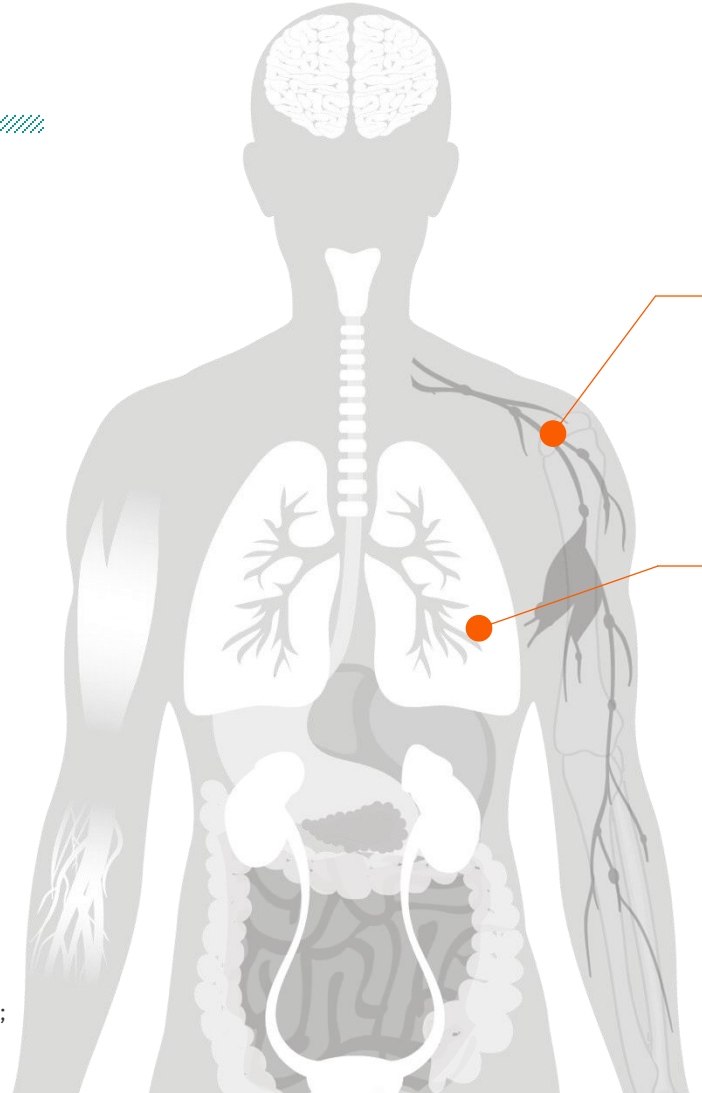
LSD1: ‘539 opportunity in SCLC and AML

United States incidence for planned patient population

Key Updates:

- IND submission expected in 2H 2024
- Expect to commence Phase 1/2 study in early 2025
- Patient selection work ongoing



17K

Acute Myeloid Leukaemia

28K

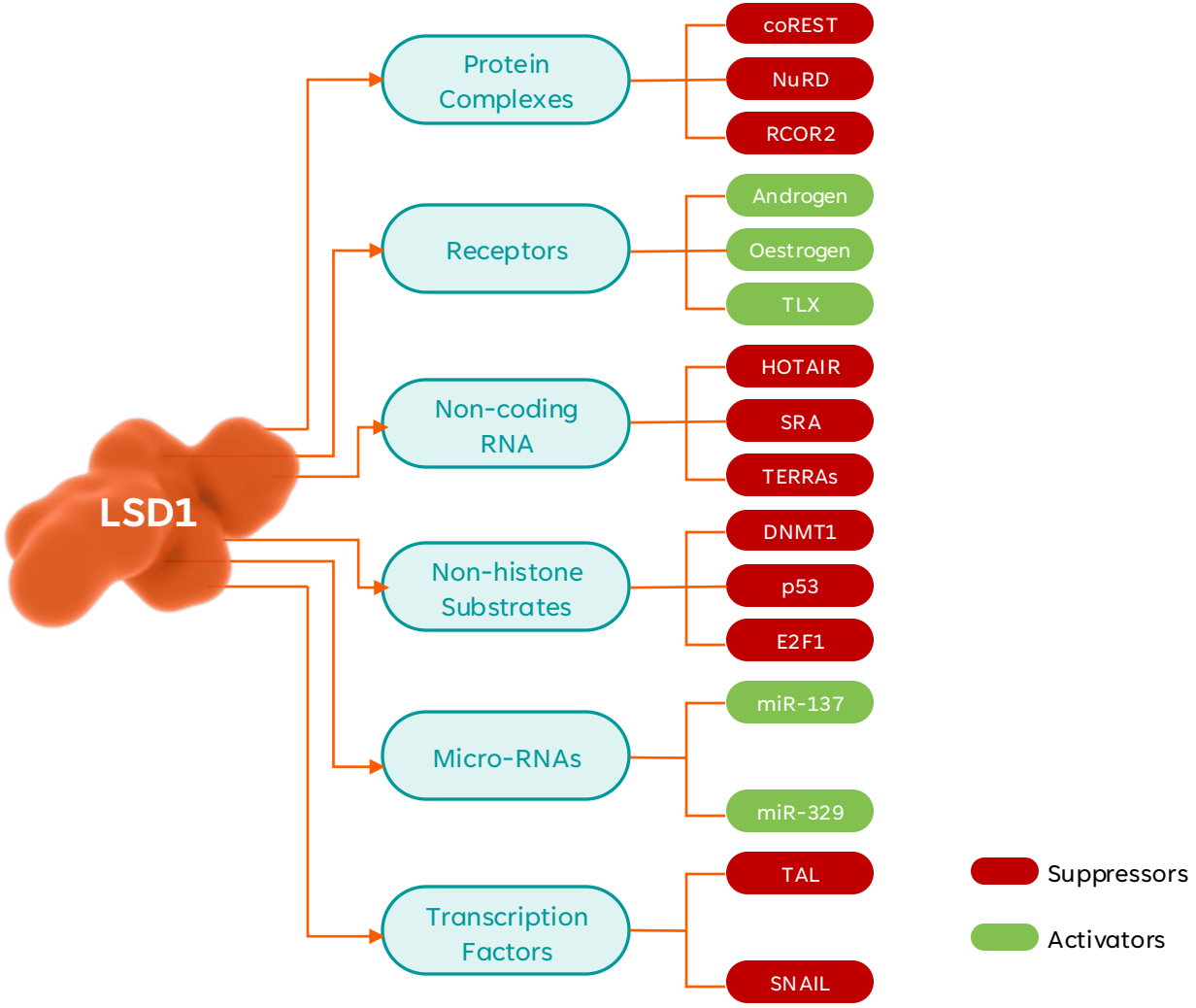
Small-cell Lung Cancer

Extensive Disease (Stage III/IV)

Treatment rate and progression rates based on Cerner Enviza Treatment Architecture Reports 2022;
Numbers have been rounded to the nearest 1000 patients per year;

LSD1 inhibition leads to differentiation of tumour cells

Sensitising stem-cell like tumour cells to combination therapies



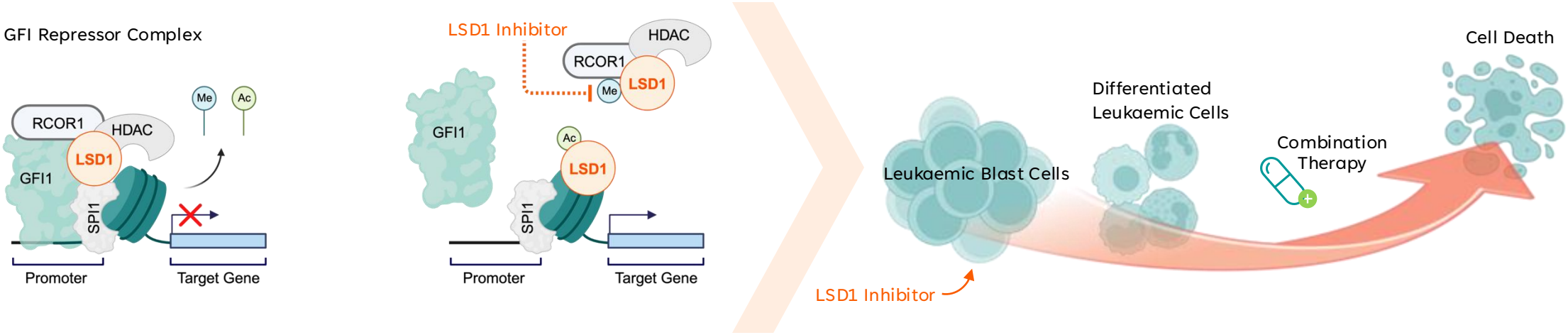
- LSD1 is not only an epigenetic modifier but also forms a variety of complexes with transcription factors, promoters, activators, corepressors and non-coding RNAs
- This variety of functions can drive tumourigenesis and modify the tumour microenvironment to enable enhanced cancer cell proliferation
- LSD1 is overexpressed in many cancer types across haematological and solid tumours and correlates with poor patient survival[1]
  - Literature has shown potential benefit of LSD1 inhibition in indications including AML[2], and neuroendocrine-like cancer types including SCLC[3], pancreatic[4] and prostate[5] cancer

Graphic adapted from Ismail et al. *Epigenetics Chromatin*, 2018.

1) Kim et al. *J Biomed Sci*, 2021; 2) Maes et al. *Cancer Cell*, 2018; 3) Mohammad et al. *Cancer Cell*, 2015; 4) Qin et al. *Cancer Lett*, 2014; 5) Kumaraswamy et al. *JCI Insight*, 2023.

LSD1 inhibition promotes cell differentiation in AML

‘539 reversibility and dosing schedule may provide safety benefits



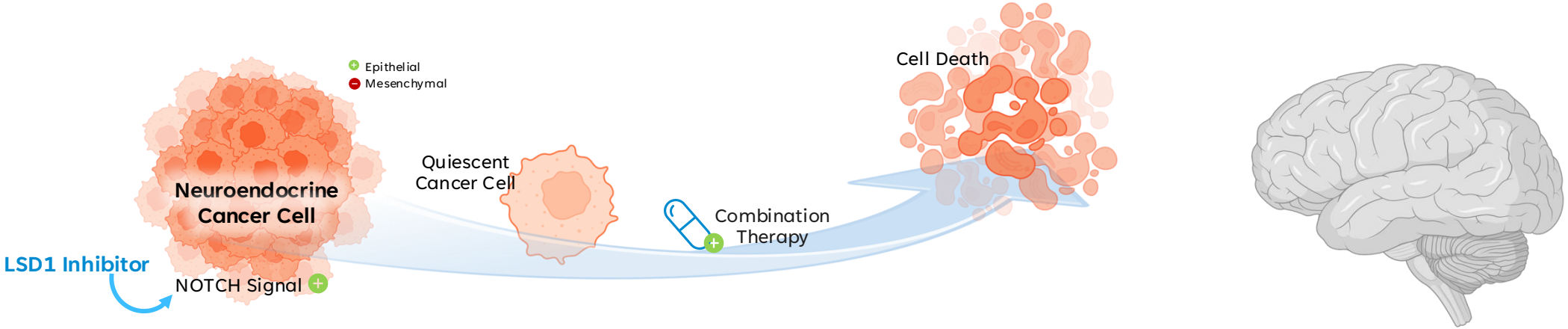
- LSD1 has key scaffolding function in GFI repressor complex that blocks differentiation
- Inhibiting LSD1 blocks the repressor complex and leads to increased acetylation of key promoters
- Results in the induction of leukaemic blast differentiation, which in turn stops cancer cell proliferation

- LSD1 inhibition has shown reduction of tumour growth in AML xenograft models[1]
- ‘539’s reversibility coupled with planned intermittent dosing is expected to reduce on target toxicity in AML

1) Maes et al. *Cancer Cell*, 2018

LSD1 inhibition drives neuroendocrine SCLC to quiescence

‘539 CNS penetrance may provide competitive differentiation



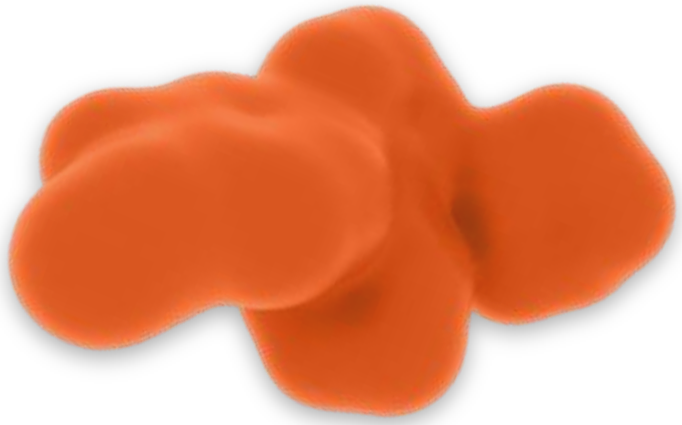
NE to Quiescence	LSD1i + Cytotoxic	‘539 Brain Penetrance
Inhibiting LSD1 upregulates NOTCH signalling which promotes differentiation of neuroendocrine cancer cells into quiescent cancer cells	Quiescent cells treated with an LSD1 inhibitor and cytotoxic agent combination undergo apoptosis	Brain metastases develop in ~50% of SCLC patients[1] ‘539, a brain penetrant molecule, may target brain metastases as well as peripheral disease

Patient selection strategies underway to identify patients most likely to respond

1) Li et al. *Int J Gen Med*, 2021

First LSD1i designed to be reversible and brain penetrant

Precision design – highly differentiated LSD1 inhibitor



Reversible & appropriate half-life to reflect MoA

Potential improved therapeutic index through better management of on-target toxicity – reduced impact on platelets

Highly selective

Potential improved therapeutic index from reduced off-target toxicity

CNS penetrant

Increased potential for patients with brain metastases

LSD1: Delivering quality candidate against a novel TPP

EXS74539 offers potential best-in-class asset with unique property profile

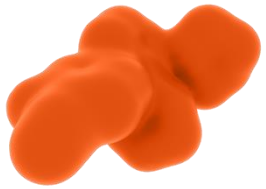
	Assay	Candidate Properties	Competing Irreversible Ph 1/2 Candidate	Competing Reversible Candidate	Exscientia Candidate '539
CNS penetration	Brain:plasma ratio	>0.5			
Target affinity and mechanism	LSD1 IC_{50} (nM)	<10			
	Surface plasmon resonance	Reversible			
Cell potency and *in vivo* efficacy	SCLC cell line proliferation (nM)	<100			
	Efficacy in 2x SCLC models *in vivo*	TVR >65%			
Safety and metabolism	CV safety margin				
	Human microsome Clint µL/min/mg	<15			
	Human hep Clint µLmin/10^6 cells	<15			
Permeability / transporter liability	MDCK-MDR1 efflux ratio (Pgp inhibition)	<2			
	Solubility pH 7.4 µg/ml	>50			
PK properties	F % (p.o.)	>30%			
	Half-life	Suitable for QD administration			

- CNS penetrant
- Potent and reversible
- Highly selective (including related amine oxidases)
- Efficacious *in vivo*
- Excellent metabolic stability, bioavailability and efflux
- Shorter predicted half-life than competitors

Meets or exceeds criteria | Minor deviation | Major deviation | Not tested

Technology in action: Precision design of ‘539

Designing and selecting the right molecules to synthesise



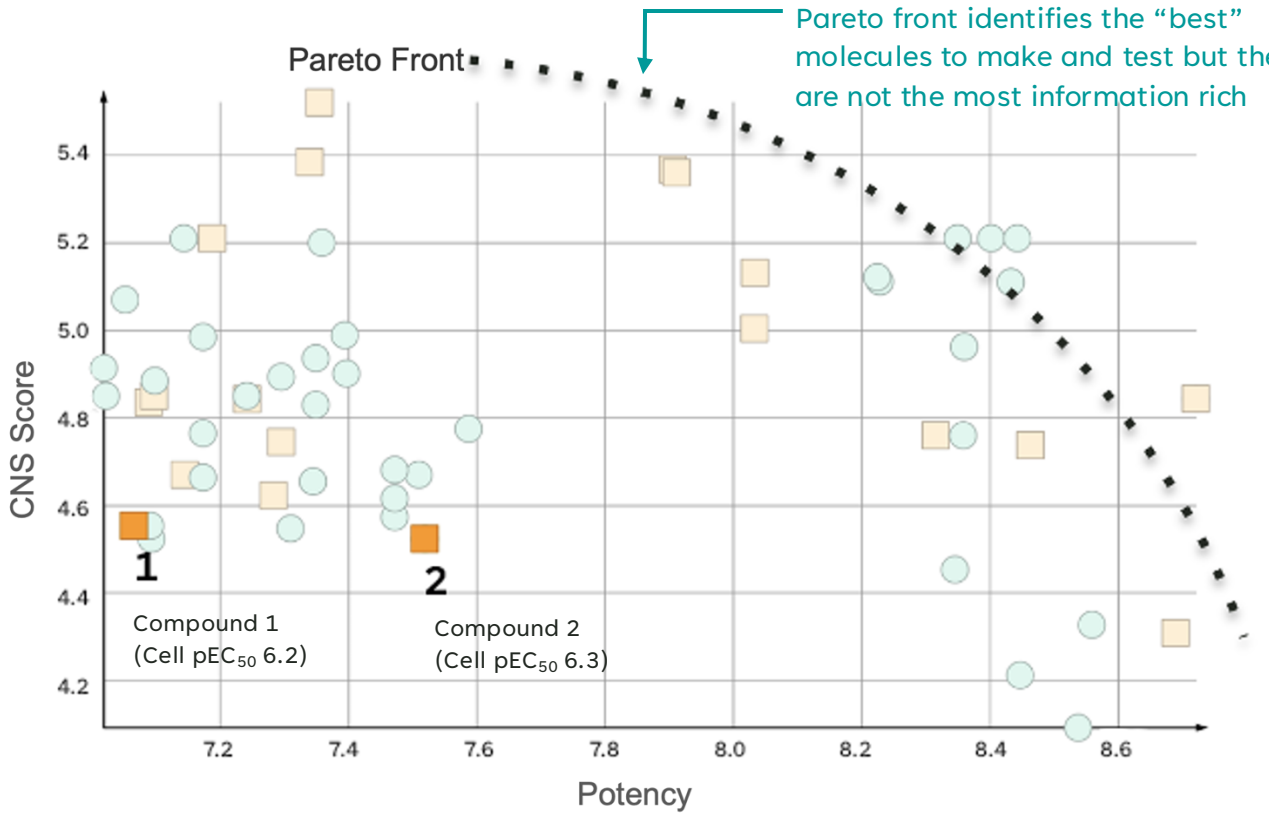
Generative Design → Machine Learning → Structure → Selection Criteria → Active Learning

Initiate	Evolve	2D Models	3D Models	Prioritise	Synthesis
Knowledge-based Evolutions Using 2D and 3D Data	**Evolutionary Algorithm**	**2D Models** **ML Models**	**Interaction Filter**	**Coverage Score** **Active Learning Exploitation**	**10-20 for Synthesis**
Improve properties of compounds from knowledge-based starting points	**Gambit** Evolve into 3D binding pocket and shape of known ligands 2D generative approaches	Use known LSD1 amine groups Good physchem properties CNS MPO Good predictions against models	Prioritise on key interactions with the protein	hERG and CNS constraints	AL pushes design into novel chemical space

Key example of active learning exploring chemical space

Active learning enabled breakthrough for ‘539

Counterintuitive selection went against preconceptions to break dogma

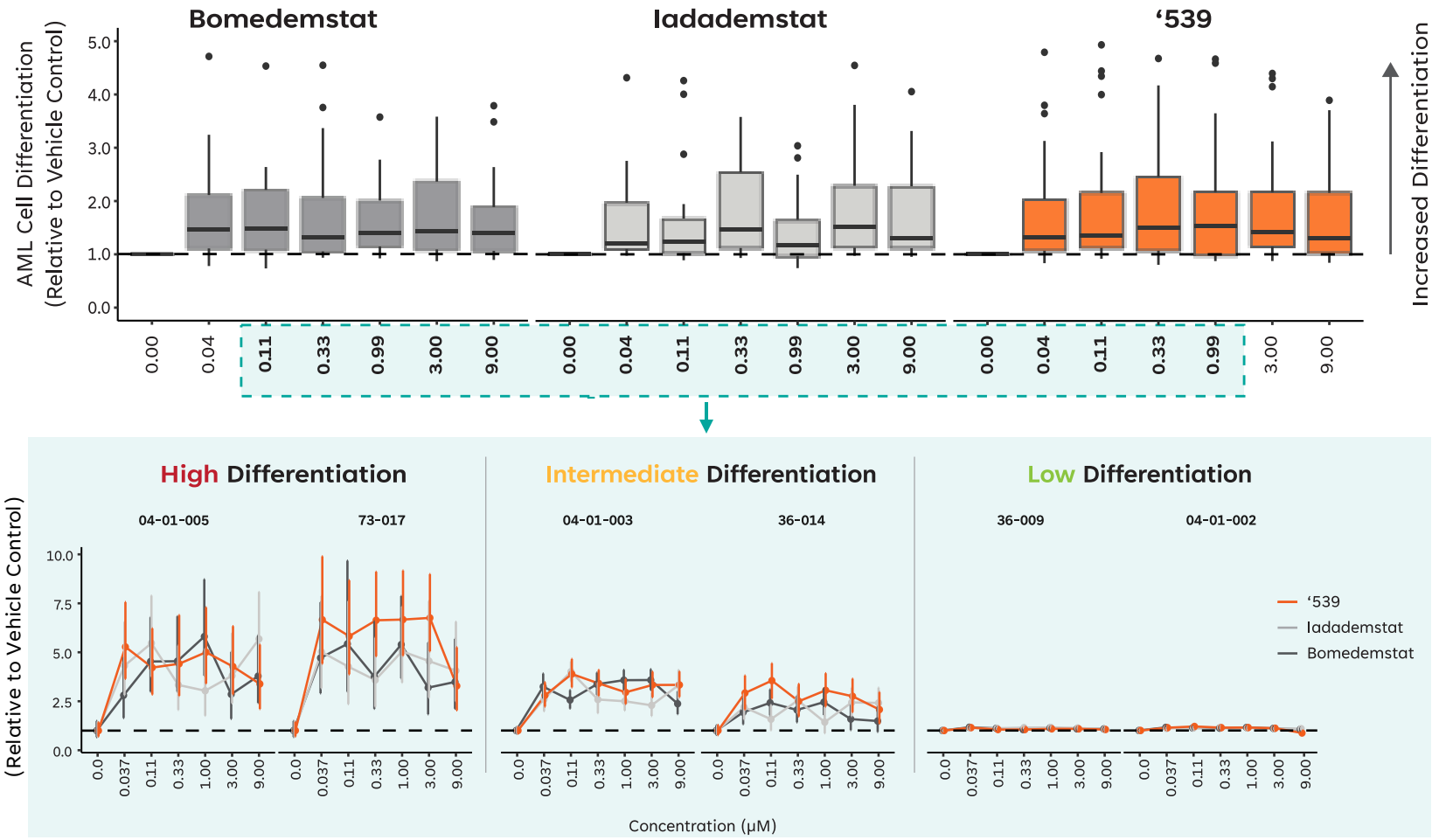


20 compounds (square) are selected by active learning chemical coverage; other compounds (circles) were not selected

- Our active learning approach selected compounds both close to and away from the pareto front (dotted arch) using a combination of MPO and coverage score
- “Seemingly unattractive” compounds, 1&2, were identified, away from the pareto front
- 1&2 were non-optimal on any predicted property but were structurally different
- Structures were synthesised and tested – this new scaffold providing a better starting point to achieve the TPP
- Further cycles of design refined hits to produce ‘539

‘539 induces *ex vivo* myeloid differentiation

Preclinical activity comparable to irreversible LSD1 inhibitors



Okumura et al. ESMO, 2023; Differentiation measured by CD86 marker expression induction

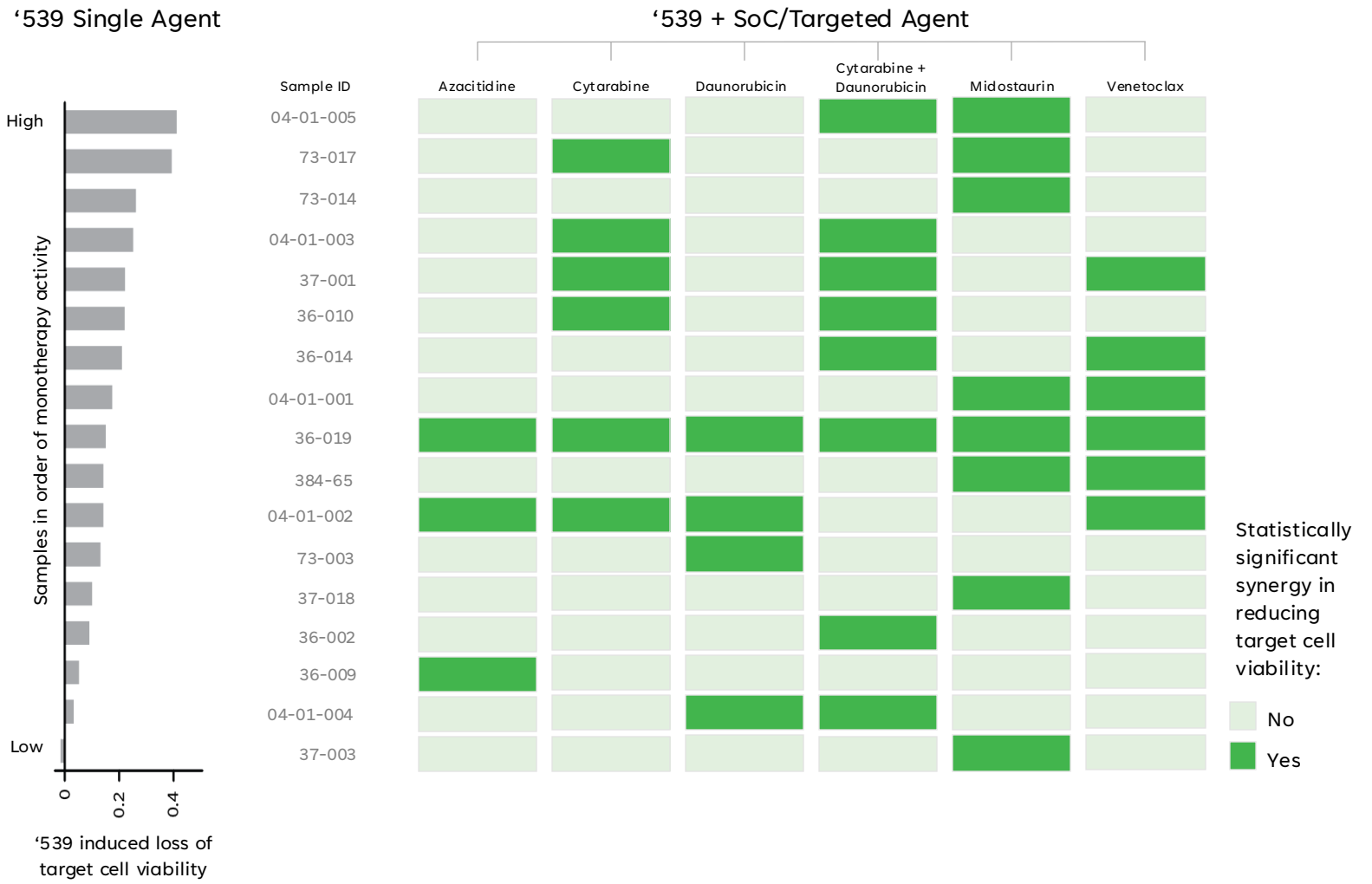
‘539 has potent *ex vivo* activity against primary human AML samples

‘539, a reversible inhibitor, has comparable *ex vivo* efficacy to clinical stage irreversible inhibitors

Heterogeneity of response supports further exploration of patient selection strategies in the clinic

‘539 synergises with first line SoC and targeted therapies

Combination potential established preclinically in primary AML samples



Azacitidine + ‘539
SoC nucleoside analogue
Synergy in 3/17 patients

Cytarabine + ‘539
SoC nucleoside analogue
Synergy in 6/17 patients

Daunorubicin + ‘539
SoC anthracycline/DNA intercalating agent
Synergy in 4/17 patients

Cyta + Dauno + ‘539
Combination SoC
Synergy in 8/17 patients

Midostaurin + ‘539
FLT3 inhibitor
Synergy in 8/17 patients

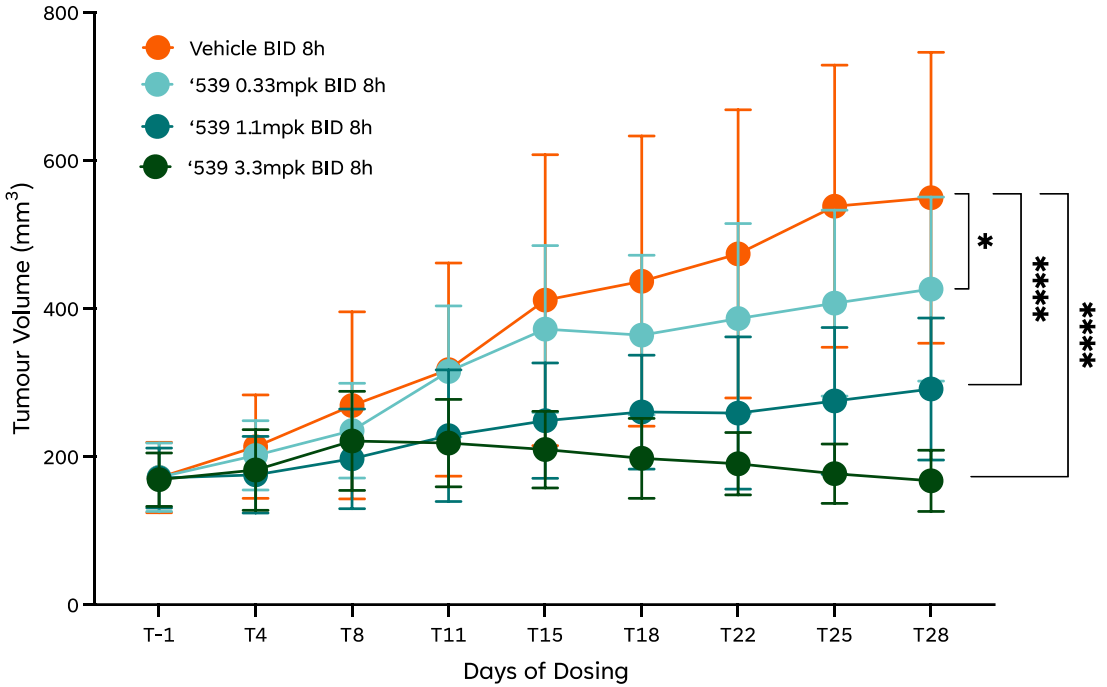
Venetoclax + ‘539
Bcl-2 inhibitor
Synergy in 6/17 patients

Okumura et al. ESMO, 2023; synergy calculated using highest single agent (HSA) index. Significant synergy = p<0.05, (tested with multiple hypothesis correction); SoC = standard of care

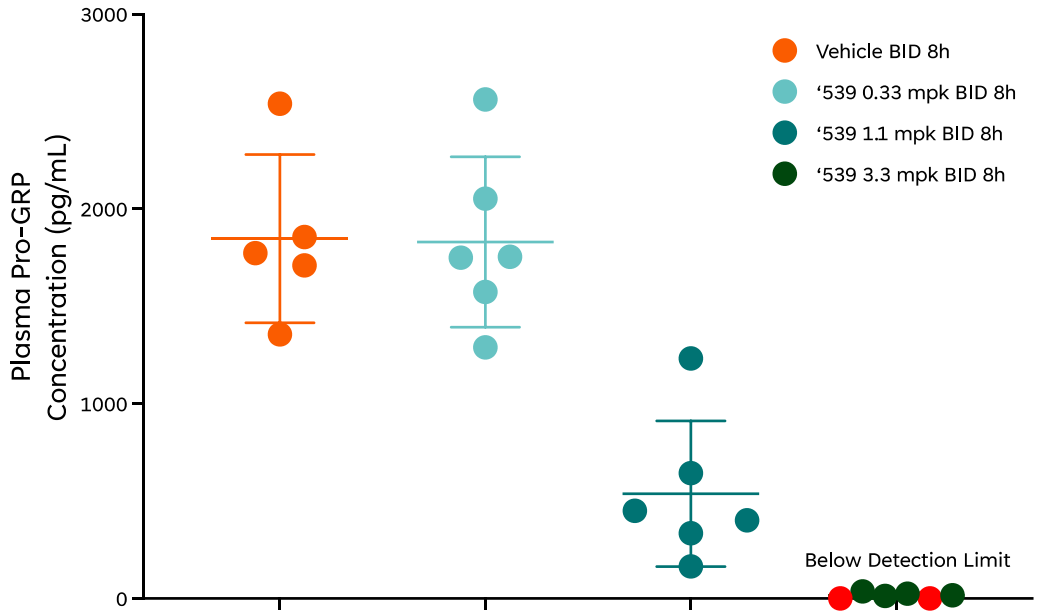
‘539 inhibits tumour growth *in vivo*

Dose-dependent tumour growth inhibition in SCLC xenograft model

Tumour Volume (mean +/- SD) Data From Dose Response BID Study



Dose-dependent Reduction in Plasma Pro-GRP



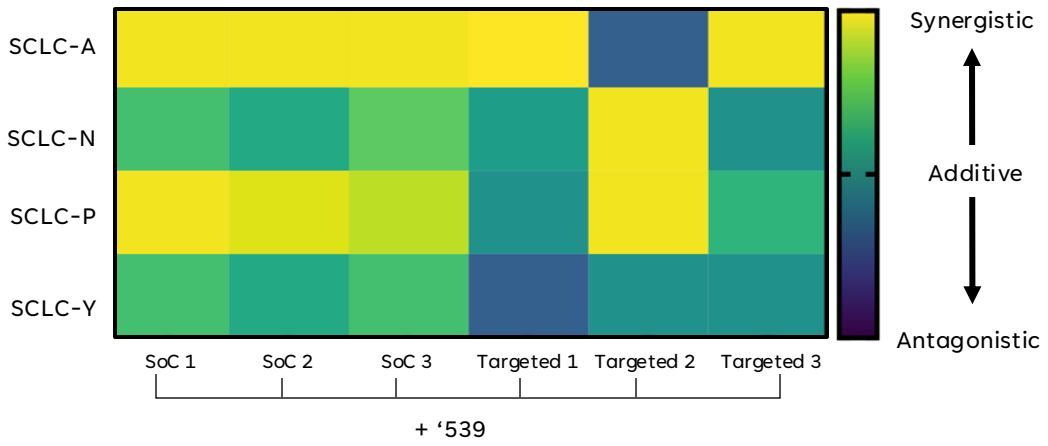
‘539 was well tolerated with body weight maintained in our studies

NCI-H1417 xenograft (SCLC); Pro-GRP: Progastrin-releasing peptide is a commonly used biomarker for SCLC malignancies

‘539 synergises with approved SoC and targeted therapies

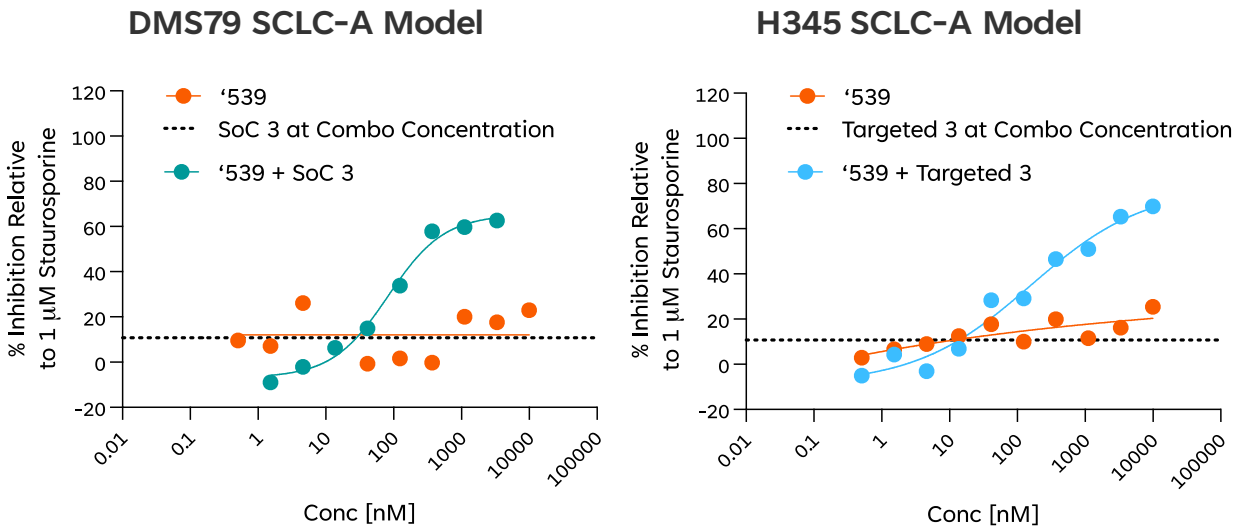
Combinations enhance anti-proliferative effects in ‘539 unresponsive SCLC cell lines

‘539 Combination Synergy (Calculated Using Bliss Independence Model)



SCLC molecular subtypes[1]	SCLC-A	SCLC-N	SCLC-P	SCLC-Y
Percentage (%)	70	11	17	2

‘539 + SoC/targeted Agent in SCLC-A Cell Lines Non-responsive to ‘539

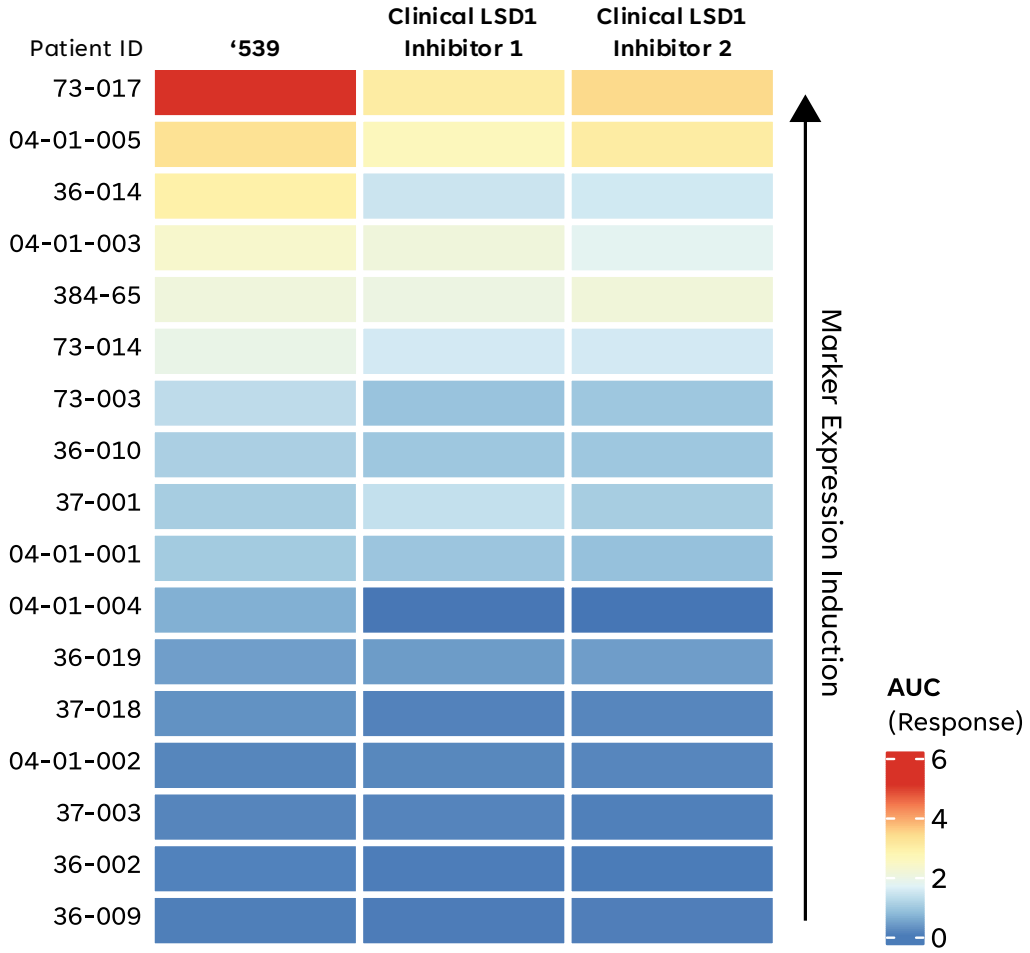


‘539 in combination with SoC has potential in most common SCLC patient sub-types even for those that are not responsive to LSD1i as a single agent

1) Rudin et al. *Nat Rev Cancer*, 2019

Variability observed in ‘539-induced AML cell differentiation

Patient enrichment is critical to clinical success



- High patient-to-patient variability in LSD1-induced myeloid cell differentiation *ex vivo* in primary AML patient samples
- Crucial to identify AML patients more likely to respond to ‘539 in the clinic
- Currently generating patient enrichment hypotheses leveraging our single cell omics capabilities to detail ‘539-induced gene expression on AML cell subpopulations

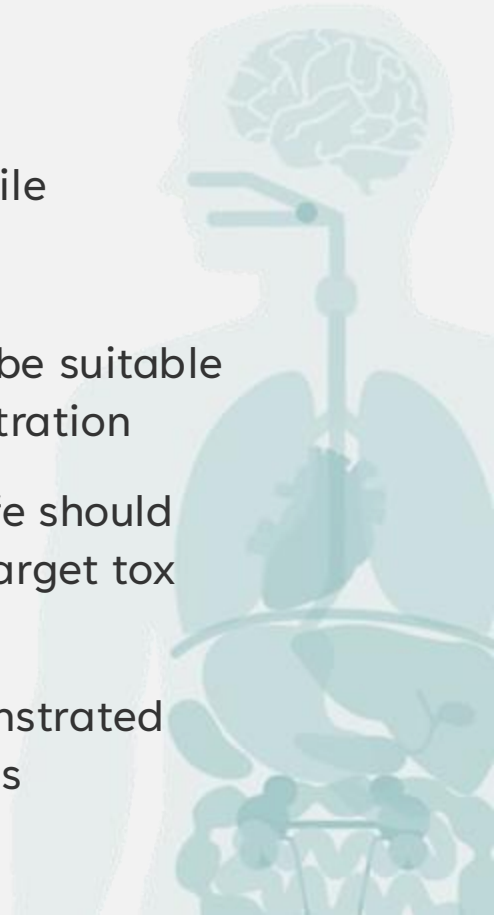
Okumura et al. ESMO, 2023; Variability observed across all diagnoses, age groups and subtypes

LSD1: ‘539 preclinical profile

Favourable PK, tox and safety profile supports ongoing development

Pharmacokinetics (PK)

- Good preclinical PK profile
- High oral bioavailability
- Human PK predicted to be suitable for once-a-day administration
- Predicted human half-life should provide benefits to on-target tox management
- Brain penetration demonstrated across preclinical species

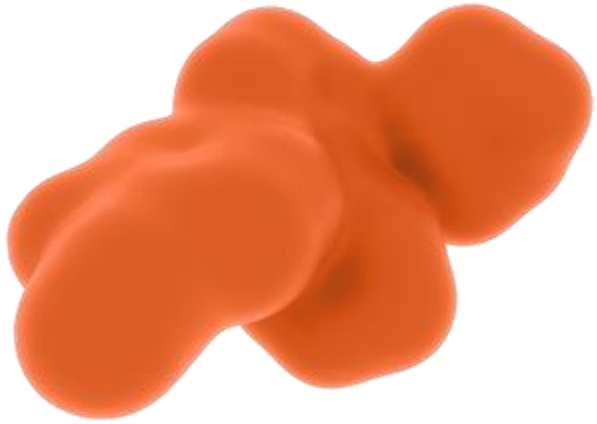


Toxicology & Safety Pharmacology

- No unexpected *in vitro* or *in vivo* safety concerns identified
- No changes recorded in dog CV telemetry study
- Tolerated in rat/dog 28-day GLP tox studies with expected effects on haematology parameters
- Margins suitable for progression to clinical trial

‘539: Summary

- GLP-tox studies completed
- MIDD to define best dose and dosing regimen
- Patient study expected to start in early 2025



MIDD = Model-informed Drug Development

Programme Highlights:

- Potent, highly selective, reversible and brain penetrant LSD1 inhibitor
- Suitable therapeutic index established with no unexpected toxicity in GLP tox studies
- Potential in broad range of haematologic and oncologic diseases
- Potential as monotherapy or combination therapy
- Translational work ongoing to define optimal patient populations and validation of PD biomarkers

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