‘565 (MALT1)

CTA submission expected in 2024

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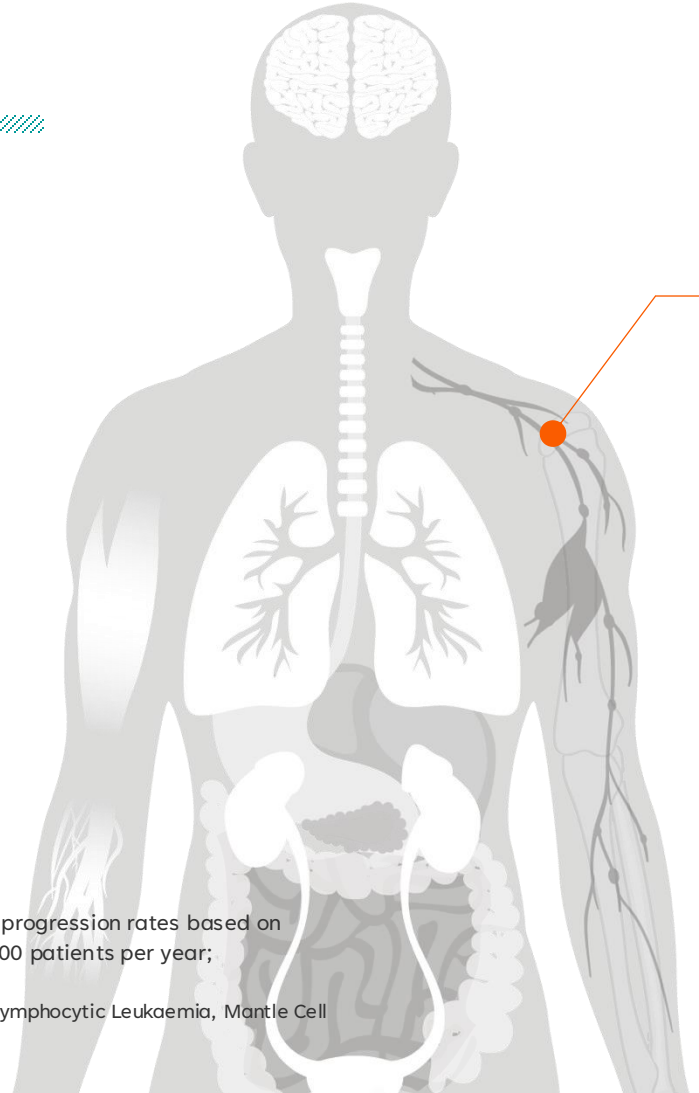
MALT1: ‘565 focusing on B-cell malignancies (including CLL)

United States incidence for planned patient population

Key Updates:

- CTA submission expected in 2H 2024
- Clinical development laying foundation for combination approaches in practice
  - Currently exploring current standard of care combination opportunities
- Expect to commence clinical study for B-cell malignancies in 2025
  - Will target CLL combination therapy as primary opportunity



20K

R/R B-cell Malignancies

Including Chronic Lymphocytic Leukaemia (CLL)

Covers all indications currently being prioritised for IND/CTA-enabling studies. Treatment rate and progression rates based on Cerner Enviza Treatment Architecture Reports 2023; Numbers have been rounded to the nearest 1000 patients per year;

B-cell malignancies include but not limited to: Diffuse Large B-cell Lymphoma, Follicular Lymphoma, Chronic Lymphocytic Leukaemia, Mantle Cell Lymphoma, Marginal Zone Lymphoma, Burkitt Lymphoma

MALT1 inhibitor designed to enable combination therapy

Precision design – developing a differentiated and selective inhibitor

Made for combination therapy

Selectivity over UGT1A1 creates better combination profile with drugs that have known liver tox issues (BTK & BCL2)

Strong *in vivo* performance

Preclinical efficacy demonstrated as a monotherapy and in combination

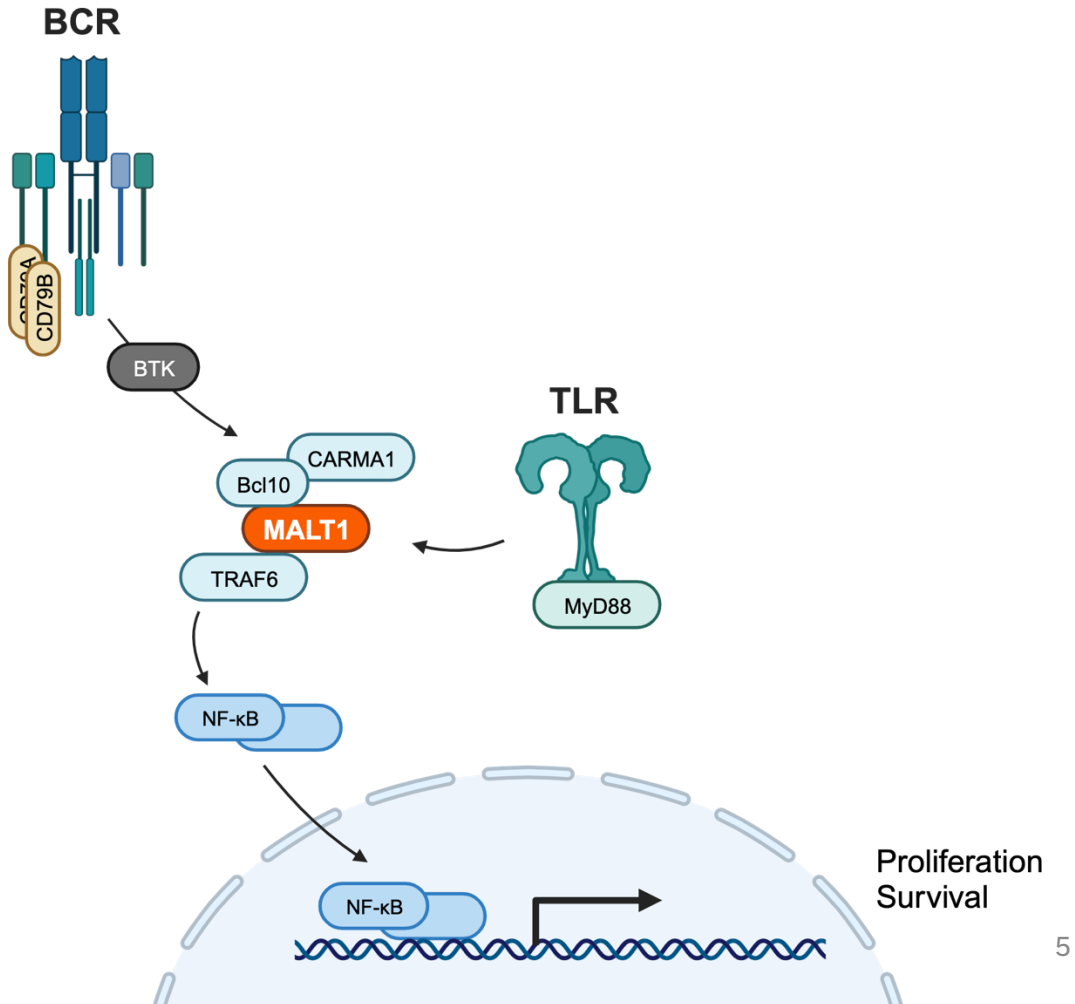
Well balanced molecular properties

Potentially enabling daily dosing for orally administered drug

MALT1: Inhibiting malignant cell signaling in B-cell lymphomas

Important mechanism in haematologic malignancies

- Chronic activation of the B-cell receptor (BCR) in malignant B-cells can lead to inappropriate NF-κB signalling, driving uncontrolled tumour cell proliferation and survival
- MALT1 functions downstream of the BCR and also the therapeutic target, BTK, and is a critical component of tumourogenic signalling pathways in these tumour cells
- Inhibition of MALT1 protease activity blocks the pathogenic signals from the BCR and, in a subset of NF-κB-addicted tumours, inhibits tumour cell proliferation
- Combining MALT1 and BTK inhibitors could provide additional efficacy in these lymphomas by stronger inhibition of the pathway and by maintaining activity in tumours with target-mediated BTK inhibitor resistance



Avoiding uridine glucuronyl transferase (UGT1A1)

‘565 offers potential competitive differentiation

- Bilirubin is made during the natural degradation of red blood cells. It is rapidly cleared from the body, mainly through liver metabolism and subsequent biliary elimination
  - Uptake of unconjugated bilirubin into the liver occurs in part *via* OATP transport
  - Once in the liver, bilirubin is exclusively glucuronidated by UGT1A1, and then effluxed into the bile by MRP2

- UGT1A1 inhibition can cause elevated bilirubin (hyperbilirubinaemia) and can lead to metabolic disorder
  - Jaundice, nausea, vomiting and potentially encephalopathy can occur

- UGT1A1 pathway has an active role in triggering potential drug-drug interactions in the clinic
  - This is particularly relevant to BTKi given the many reports of drug-induced liver injury with these agents

MALT1 allosteric competitor profiles

Most competitor compounds have a high UGT1A1 inhibition risk

Parameter	Phase 1/2 (Large pharma)	Phase 1 (Large pharma, patent examples)	Phase 1 (Mid-size pharma, patent examples)	Phase 1 (Biotech)	Exscientia Candidate '565
Biochemical pIC_{50} >7	Minor deviation	Meets or exceeds criteria	Meets or exceeds criteria	Meets or exceeds criteria	Meets or exceeds criteria
OCI-Ly3 IL-10 pIC_{50} >7	Meets or exceeds criteria	Meets or exceeds criteria	Not tested	Not tested	Meets or exceeds criteria
OCI-Ly3 proliferation IC_{50} (<400 nM)	Minor deviation	Meets or exceeds criteria	Meets or exceeds criteria	Meets or exceeds criteria	Meets or exceeds criteria
TMD8 IL-10 IC_{50} (<200 nM)	Minor deviation	Meets or exceeds criteria	Meets or exceeds criteria	Not tested	Meets or exceeds criteria
TMD8 proliferation IC_{50} (<300 nM)	Minor deviation	Meets or exceeds criteria	Not tested	Not tested	Meets or exceeds criteria
UGT1A1 IC_{50} (>10 µM)	Major deviation	Minor deviation	Major deviation	Major deviation	Meets or exceeds criteria
Hu heps Clu calc (ml/min/kg) <20	Meets or exceeds criteria	Not tested	Meets or exceeds criteria	Meets or exceeds criteria	Meets or exceeds criteria
Caco-2 A-B (ER) 10^{-6} cm/s [>5(<3)]	Meets or exceeds criteria	Major deviation	Major deviation	Minor deviation	Meets or exceeds criteria
Solubility pH 7.4 (>250 µg/mL)	Minor deviation	Major deviation	Major deviation	Major deviation	Minor deviation
Cerep / full kinase panel	Meets or exceeds criteria	Meets or exceeds criteria	Not tested	Not tested	Meets or exceeds criteria

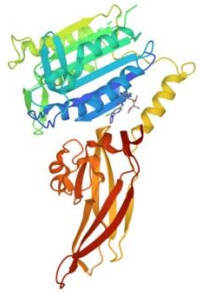
Meets or exceeds criteria Minor deviation Major deviation Not tested

Technology in action: Precision design of ‘565

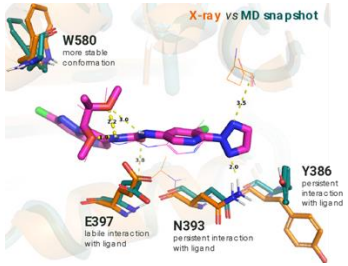
Designing and selecting the right molecules to synthesise

Generative Design | Machine Learning | Structure

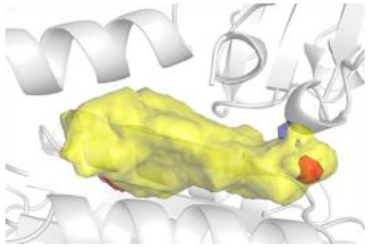
Initiate



Use of MD to define dynamic pocket



Analyse



Hotspot analysis to find key interactions and drive generative algorithms

Evolve

Evolutionary Algorithm

Automated structural informatics

Evolve in 3D directed towards Hotspot interaction (Gambit)

Hybridisations

2D Models

2D Models **ML Models**

Good physchem properties

MPO

Good predictions against models

3D Models

Interaction Filter

Compatibility with key Hotspots

Active Learning

10-20 for Synthesis

Coverage Score

Active Learning Exploitation

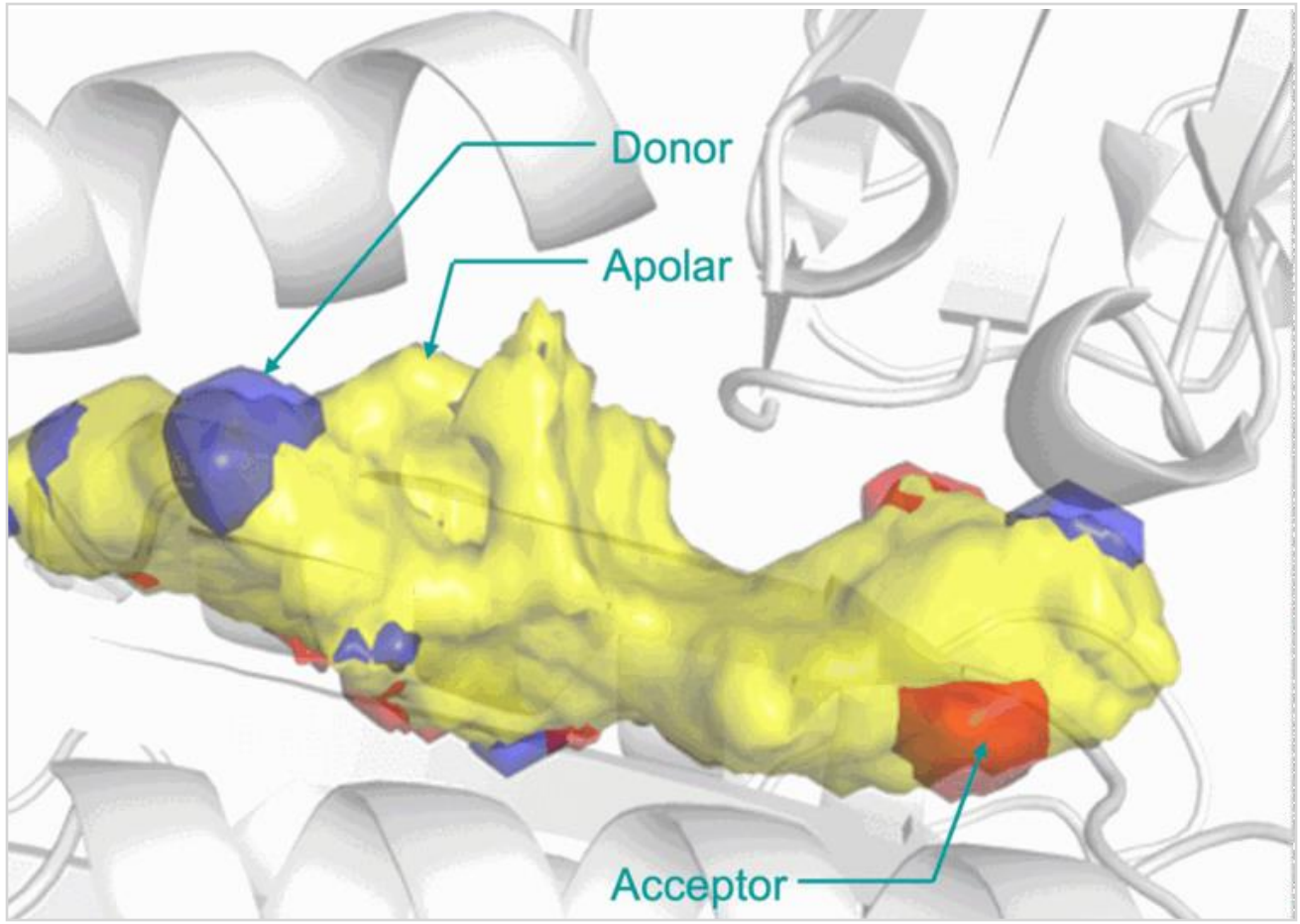
Solubility Potency

AL pushes design into novel chemical space

Proof of concept to use MD with our end-to-end AI-driven platform

‘565 leveraged physics-based predictive modelling

Understanding protein flexibility using molecular dynamics

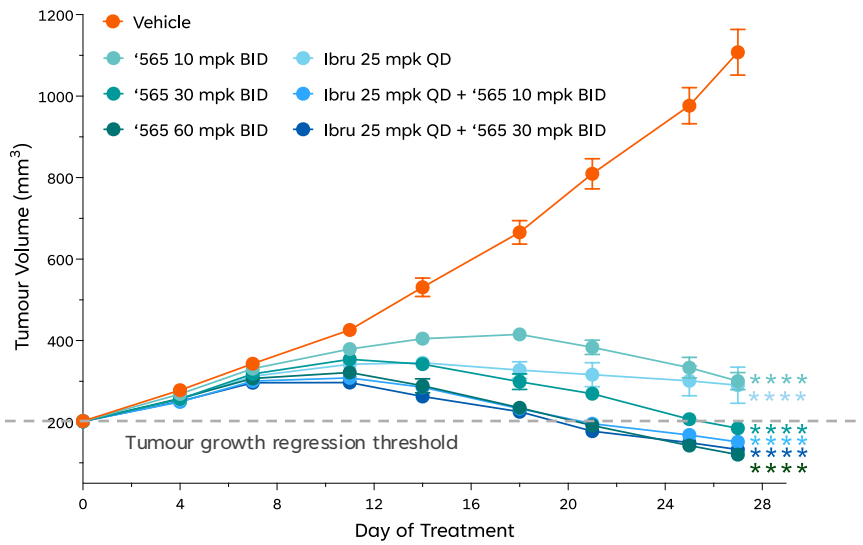


- Simulated binding site movements and integrated with Hotspots for automated definition
- Design of ‘565 expanded our approach onto complex dynamic targets and into novel chemical space
- Drove our generate constraints towards delivering improvement in permeability
- ‘565 candidate delivered using physics-based constraints in allosteric site

‘565 inhibits DLBCL tumour model growth *in vivo*

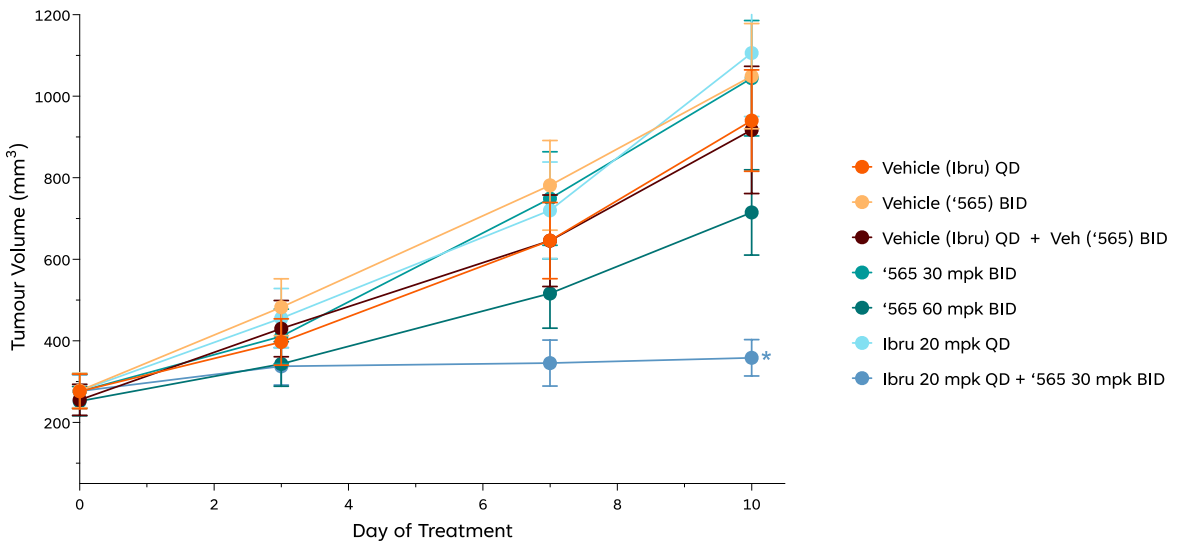
Single agent and synergistic effects seen in DLBCL xenograft models

‘565 ± Ibrutinib in OCI-Ly10 Xenograft Model



- OCI-Ly10 cells are sensitive to both MALT1i and ibrutinib *in vitro*
- Administration of ‘565 as a single agent showed tumour growth regression
- Synergistic tumour growth regression observed when 10 mpk ‘565 was combined with ibrutinib

‘565 ± Ibrutinib in TMD8 Xenograft Model

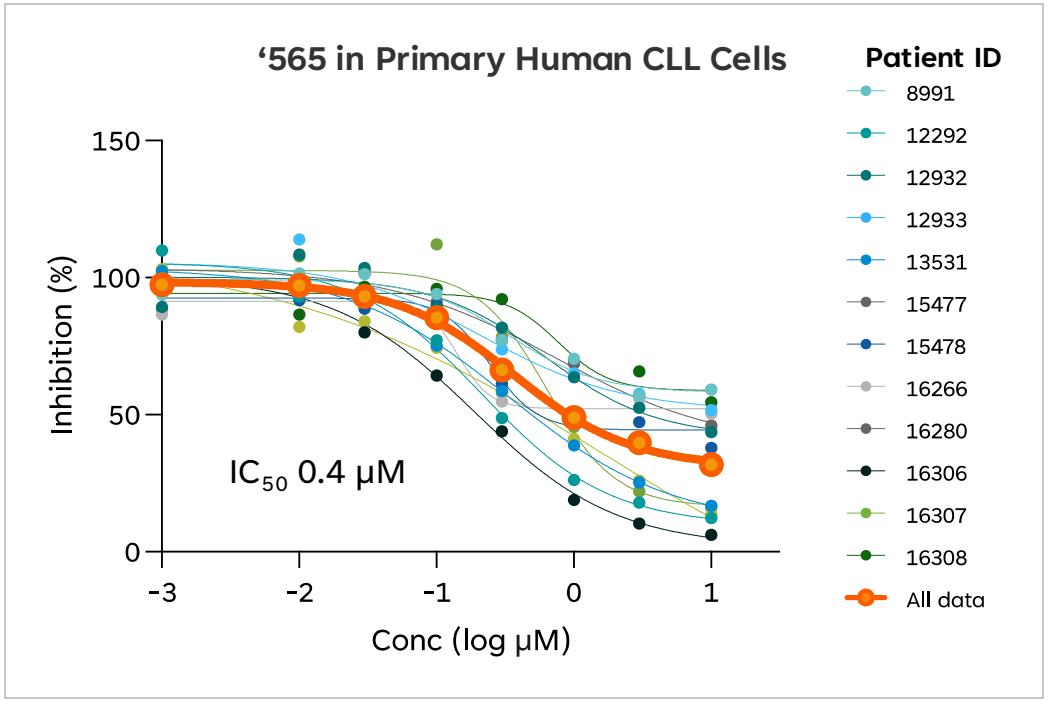


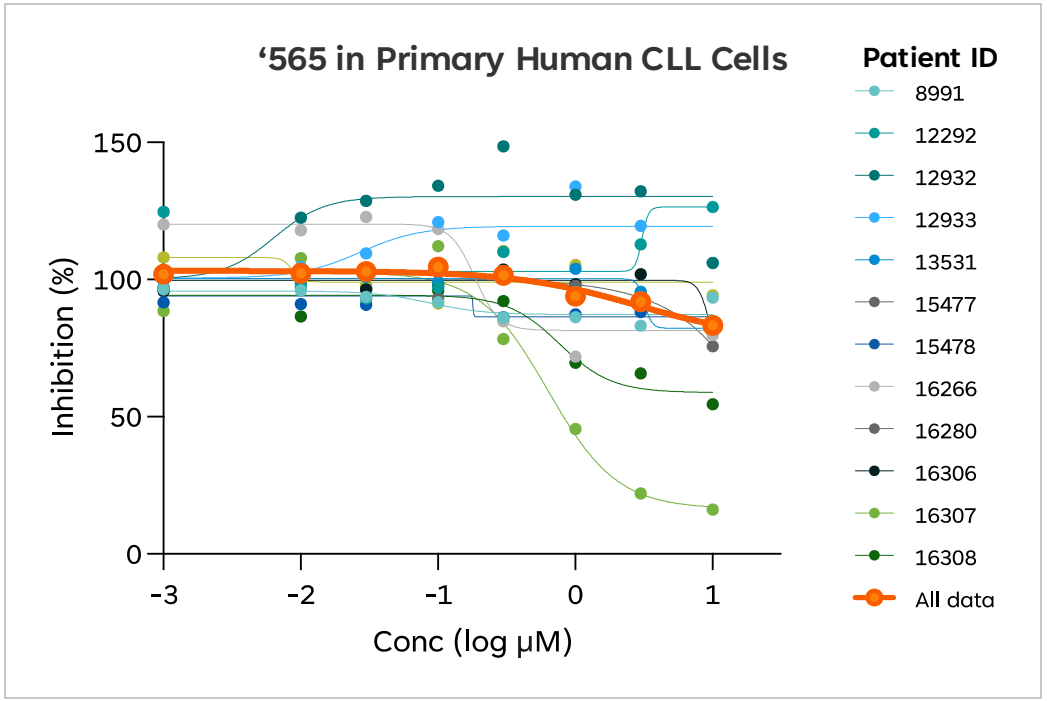
- TMD8 DLBCL cells are sensitive to both MALT1i and ibrutinib *in vitro,* however, standalone administration of ibrutinib showed no activity *in vivo*
- Significant synergistic efficacy was observed when ‘565 was combined with ibrutinib in the study
- ‘565 was well tolerated with body weight maintained in both monotherapy and combination groups

Payne et al. ESMO, 2023; OCI-Ly10 xenograft model: CD79A mutant; TMD8 xenograft model: CD79B mutant

‘565 inhibits primary human CLL cell proliferation

Efficacy in primary human tissues without impacting T-cell viability





- CLL samples from both treatment naïve patients and patients exposed to previous lines of therapy
- ‘565 selectively inhibited the proliferation of primary human CLL cells
- Limited impact of ‘565 observed on T-cell viability

Payne et al. ESMO, 2023

‘565 has a low predicted risk of hyperbilirubinaemia

Potential safety benefit compared with clinical MALT1i in development

- We predict that selectivity over UGT1A1 could be an issue for some clinical stage MALT1 inhibitors
- Inhibition of UGT1A1 mediates bilirubin glucuronidation, potentially leading to hyperbilirubinaemia
- ‘565 has a low risk of potential DDI/ hyperbilirubinaemia at predicted human efficacious doses
- Potential for safer dose escalation for ‘565 to reach the level of target engagement necessary to achieve clinical efficacy

			UGT1A1					
Compound	**Best-estimate Scenario**	**$C_{max,u}$ ($I_{max,u,inlet}$)**	**IC_{50} (μM)**	**$IC_{50}/I_{max,u,inlet}$**	**R_{free}**	**$R_{in,free}$**	**F_i**	**Prediction**
Pharma Phase 1b[1]	$t_{½}$: 127 hr (230 mg QD)	0.28 (0.32) μM	0.76	2.4	1.37	1.42	0.27	Hyperbilirubinaemia Risk
‘565	$t_{½}$: 39 hr	0.30 (0.42) μM	>10	34	1.02	1.03	0.02	Low Risk

Payne et al. ESMO, 2023. 1) Hertzberg et al. *Hematol Oncol*, 2023; Cmax,u: Predicted maximum free plasma; Imax,u,inlet: free liver inlet concentration

MALT1: ‘565 preclinical profile

Favourable PK, toxicology & safety pharm in preclinical species

Pharmacokinetics (PK)

- Excellent PK across preclinical species
- Low predicted human clearance and high oral bioavailability
- Human clearance data suggests a half-life consistent with QD dosing
- Low UGT1A1-mediated DDI risk (differentiated vs other compounds) leading to potentially better safety (hyperbilirubinaemia) profile

Toxicology & Safety Pharmacology

- No unexpected *in vitro* or *in vivo* safety concerns identified for a patient trial
- Well tolerated in rat/dog dose range finding (DRF) studies
- GLP toxicology studies completed and identified a suitable NOAEL enabling clinical trials

‘565: Summary

- GLP-tox studies completed
- CMC work continuing
- CTA submission expected in 2024

Programme Highlights:

- Potent and highly selective MALT1 allosteric inhibitor with low UGT1A1 inhibition risk
- Suitable therapeutic index established
- Potential in broad range of haematologic malignancies
- Potential in combination with BTKi for the prevention and treatment of BTKi-resistant disease
- Potent activity on primary human B-cell lymphoma patient cells; ongoing studies in other indications

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