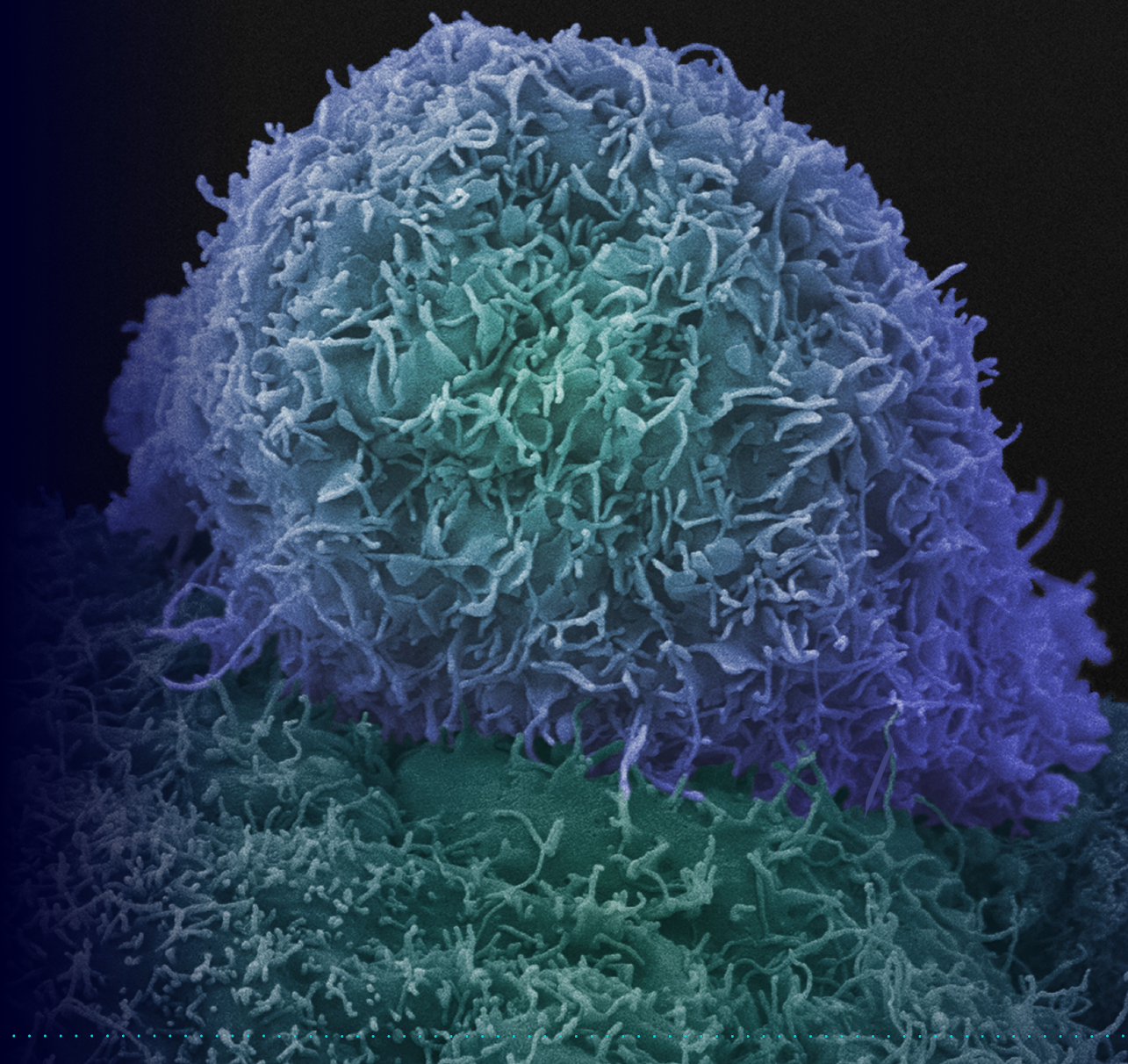
CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER

LICENSING OPPORTUNITY: MCT-1 INHIBITOR AZD3965

Autumn 2023



OPPORTUNITY OVERVIEW

LICENSING OPPORUNUTY

AZD3965 is a first-in-class, potent and selective inhibitor of monocarboxylase transporter 1 (MCT-1)

- ✓ Demonstrated anti-proliferative activity in MCT-1 high MCT4 low cell lines
- ✓ Demonstrated efficacy in DLBCL & Burkitt's Lymphoma xenograft models

Phase I Study Completed

- ✓ Phase II recommended dose established
- ✓ 1 prolonged stable disease and 1 complete response observed – promising signs of efficacy.

US patent protection from granted composition of matter patent

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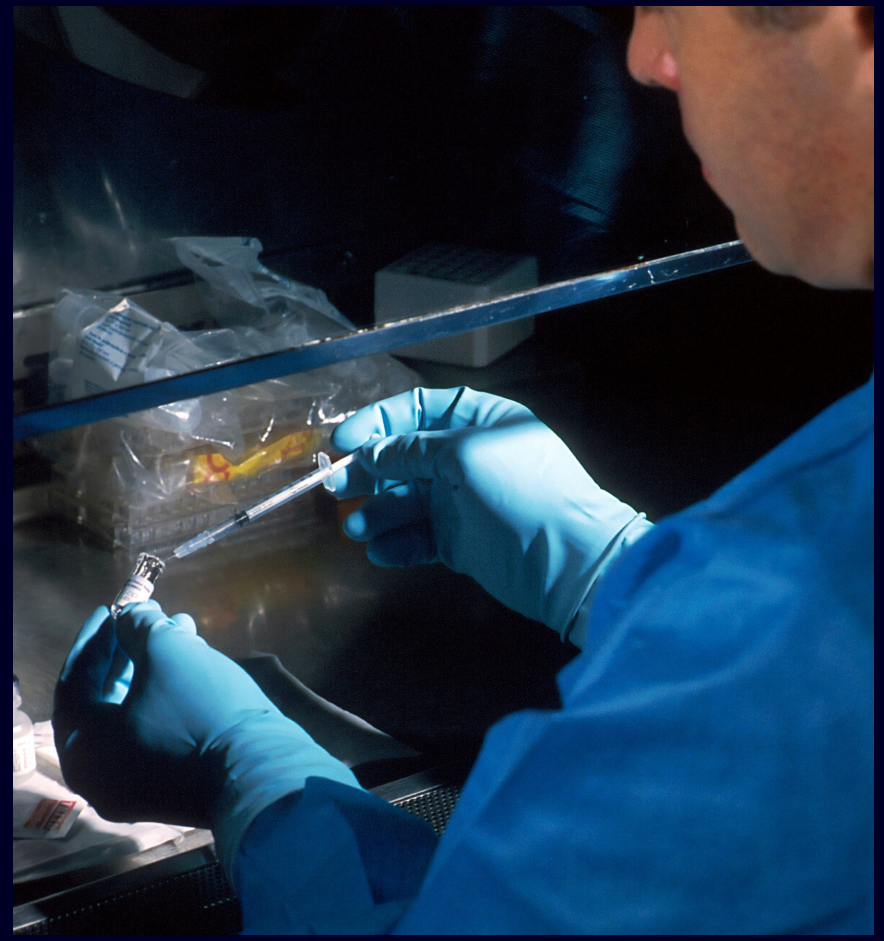
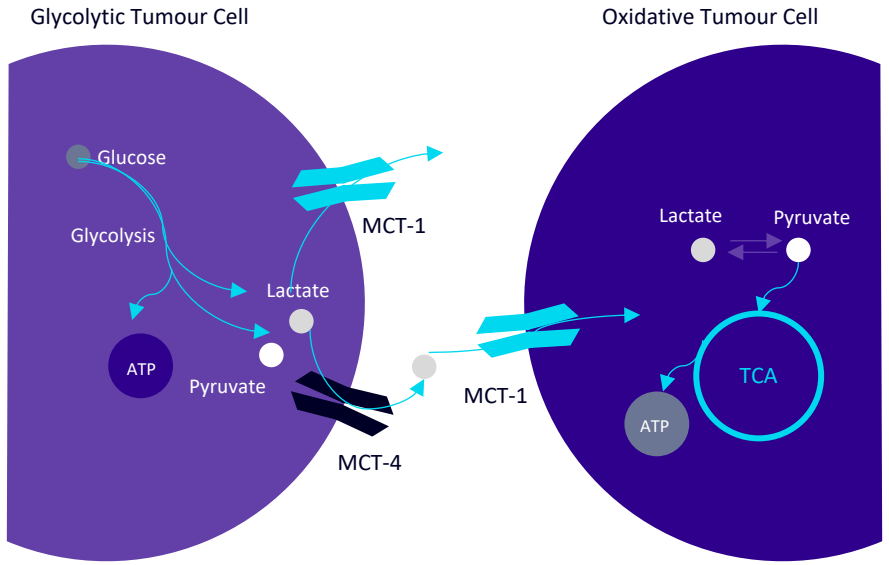
SCIENTIFIC DEVELOPMENT & BACKGROUND



AZD3965 – MECHANISM OF ACTION

A lactate symporter, action of MCT1 and its role in lactate influx or efflux varies depending on the level of oxygen and glucose in the tumour microenvironment

- Tumours have an increased dependency on the glycolytic pathway for ATP generation
- Intracellular lactate produced by glycolysis is transported out of cells by the MCTs 1, 2, 3 and 4
- Lactate conveyance avoids the access accumulation of lactate and the subsequent acidification of the cells.
- The excreted lactate from the glycolytic cells to the extracellular tumour milieu has been reported to enhance tumour growth and metastasis, angiogenesis, amino acid metabolism, histone deacetylases, GPR81 signalling, and suppression of anti-tumour immunity.
- AZD3965 has the potential to inhibit the export of lactate from tumour cells, leading to an accumulation of lactate and subsequent acidosis, inhibition of glycolysis and possible cell death



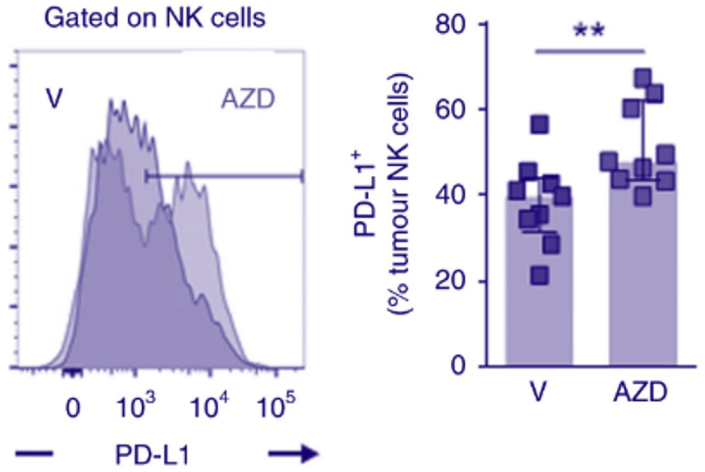
While glycolytic cancer cells rely on anaerobic glycolysis to adapt to the hypoxic environment, oxidative cancer cells take in lactate secreted from glycolytic cancer cells for energy supply, a hypothesis known as the ‘‘metabolic symbiosis”. Diagram adapted from Yan et al

AZD3965 – IO COMBINATION

Preliminary pre-clinical work is investigating the hypothesis that MCT-1 inhibition will enhance anti-tumour responses to immunotherapy via:

1. Impacting the highly acidic microenvironment that blunts the effectiveness of antitumour immunity. Husain et al. 2013
2. Minimising the fuel available from oxidative stromal cell supporting immune evasion and tumour development. Fischer et al. 2007
3. Decreased immuno-suppressive function of T-reg cells involved in upregulating pathways involved in lactic acid metabolism Watson et al. 2021

AZD3965-mediated inhibition of MCT1 in the Raji B cell lymphoma cells (MCT4-/MCT1+) increased the abundance of dendritic cells (DC) and natural killer (NK) cells in the tumour. Those cells upregulated PD-L1, further suggesting that the combination of MCT1 with immune-modulating agents is worth testing in the clinic.

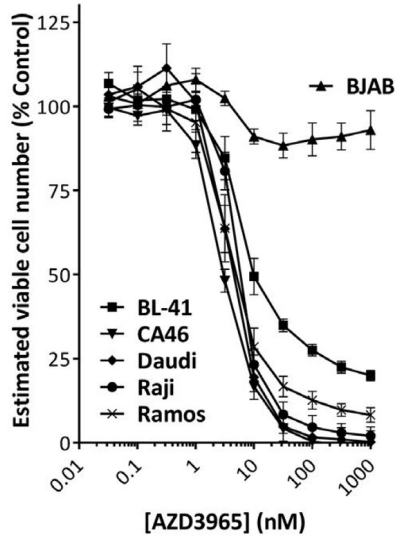


The percentage of tumour NK cells that were PD-L1⁺ (Beloueche-Babari et al. 2020).

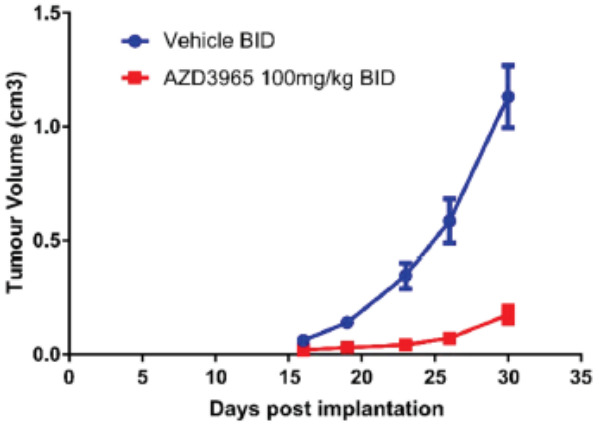
PRECLINICAL DATA

Extensive pre-clinical data showing efficacy in several tumour models

- Has demonstrated low nanomolar inhibition of MCT-1 and no inhibition of MCT-4 activity at 10qM
- In vitro and in vivo inhibition of lactate transport has been shown
- Demonstrates anti-proliferative activity in NHL, DLBCL and Burkitt lymphoma cell lines
- Exhibits activity in NHL tumour xenograft data
- Additive effect seen with standard of care agents & potential synergy observed with other metabolic agents
- Additional research performed by CRUK, and through AstraZeneca Open Innovation scheme



Noble RA et al., *Haematologica*, 102: 1247-57, 2017



Curtis et al., *Oncotarget*, 2017 Vol 8 (41) 69219-69236

CLINICAL TRIAL PART 1 RESULTS

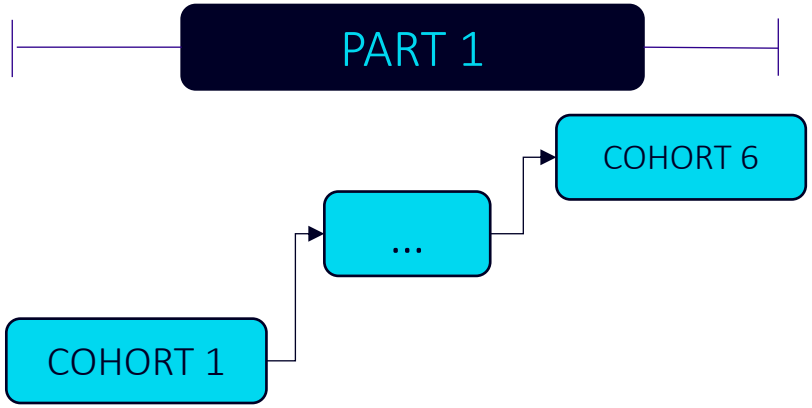
AZD3965 can be safely given to patients at doses which engage with drug target.

DOSE ESCALATION - DESIGN

Rolling 6 design

Daily dosing in 28 day cycle

Open to all comers – 40 patients recruited



DOSE ESCALATION – RESULTS

40 patients with solid cancers treated (trial open to all comers)

- DLTs primarily on-target dose-dependent, **reversible and asymptomatic alterations in retinal function** seen on ERG and comprehensive monitoring protocol designed to track changes
- Pharmacokinetic (PK) showed exposure estimated to produce a minimum MCT1 occupancy of 90% (based on modelling)
- **Anaemia not observed** despite high MCT1 expression on blood cells
- Metabolomic changes in **urinary lactate** and urinary ketones correlate with on-target activity
- Oral recommended phase 2 dose (RP2D) of 10mg twice-daily (bd)

CLINICAL TRIAL PART 2 RESULTS

AZD3965 has shown promising signs of efficacy.

DOSE EXPANSION - DESIGN

Recruited Expansion cohort enrolled 11 patients with relapsed/refractory DLBCL and BL. Expression of MCT1/MCT4 was assessed by immunohistochemistry

Trial & CSR completed

Promising efficacy demonstrated

PD data collected:

- Assessment of MCT1/MCT4 status
- FDG-PET
- Metabolomics
- Genetic information

DOSE EXPANSION – RESULTS

11 heavily pre-treated late stage DLBCL patients treated

- 1 prolonged stable disease of 5 evaluable (20%)
- **1 complete response** with progression-free survival > 15 months (17 cycles)
- FDG-PET confirms response providing evidence indicative of proof of mechanism
- cfDNA collected for further genetic analysis

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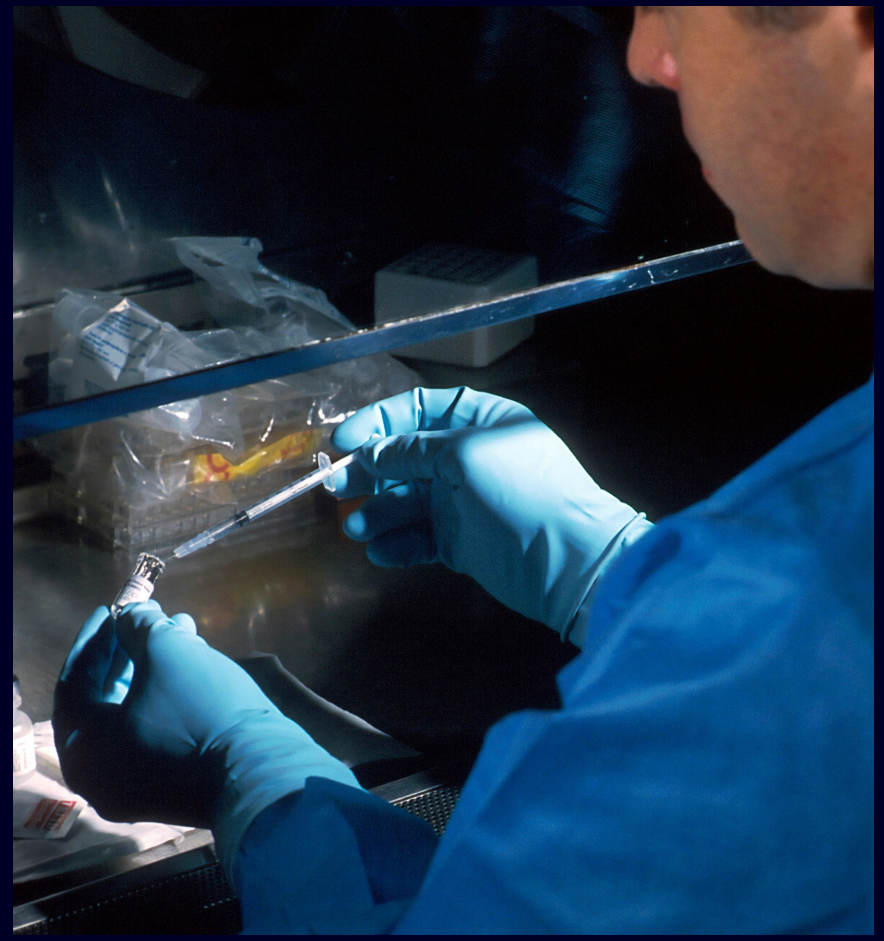
COMMERCIAL & CLINICAL DEVELOPMENT



INTELLECTUAL PROPERTY

Composition of matter patents covering US territory only

- Priority date: 17 Jan 2003
- Patent family stemming from WO 2004/065394
- No method of use or formulation patents at present
- Know-how from AZ open innovation scheme (non-exclusive)

Pre-Clinical Data

Phase 1 Trial Data

Clinical Study Report

All regulatory documentation: IMPD, IB

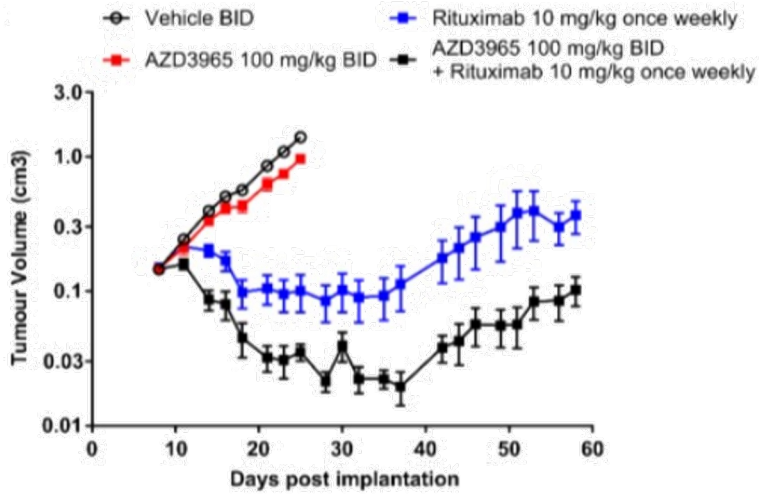
Advice on Orphan Drug Designation Documentation

FUTURE CLINICAL DIRECTION

There are several opportunities to develop life cycle IP and extend data exclusivity

1. Combinations

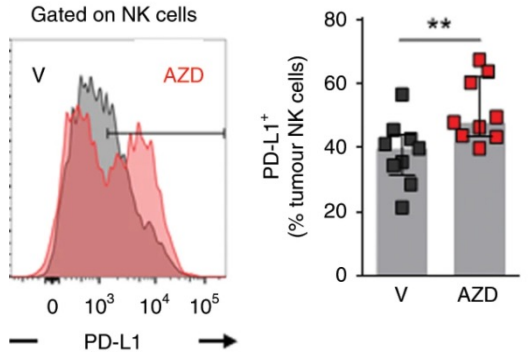
Ultimately viewed as a drug that will be given in combination. It has show efficacy with standard of care Rituximab.



Enhanced efficacy observed when combining AZD3965 with rituximab in the Raji xenograft model

Additionally, there is a strong scientific rationale to combine with

- Other metabolic inhibitors
- Mitochondrial Inhibitors
- **Immune Checkpoint Blockade (see slide)**



Percentage of tumour NK cells that were PD-L1+ with AZD

FUTURE CLINICAL DIRECTION

There are several opportunities to develop life cycle IP and extend data exclusivity

2. Orphan Drug Designation

AZD3965 clearly targets a well described rare disease (Diffuse Large B-Cell Lymphoma) that meets the population criteria. e.g. Designation Database

- ✓ AZD3965 has proven activity in a Phase I clinical trial
- ✓ AZD3965 has a well studied mechanism of action with extensive pre-clinical data.

Major ongoing benefits to obtaining ODD status (see here)

- ✓ Waivers and reductions in fees
- ✓ Access to grants
- ✓ Boost credibility and value of small biotech's.

FUTURE CLINICAL DIRECTION

There are several opportunities to develop life cycle IP and extend data exclusivity

3. Patient Stratification

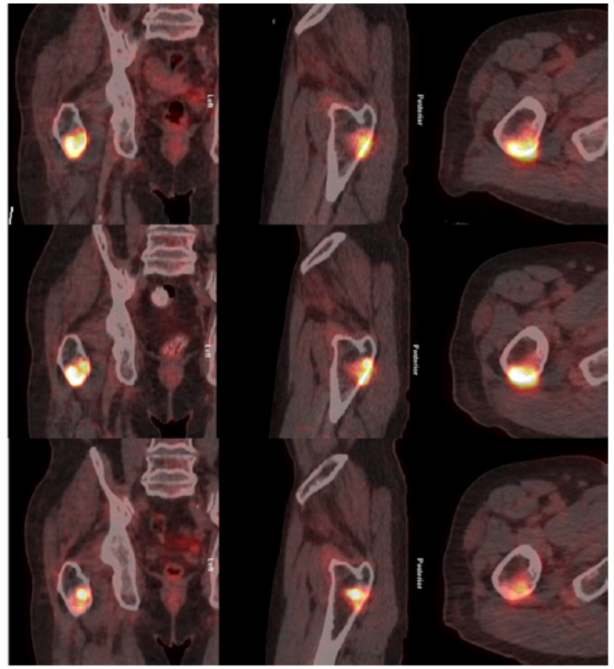
Some early work has begun to identify patient populations that will benefit most from AZD3965. Clearly low MCT-4 status is important.

- In CR patient changes in FDG-PET providing evidence indicative of proof of mechanism
- Changes in FDG uptake on day 3 in the responding patient warrant further investigation of FDG-PET as biomarker predictive of clinical response
- Further biomarker analysis and preclinical studies are ongoing to understand the biology and explore effective combinations with other agents targeting tumour cell metabolism.

Baseline

Day 3 cycle 1 ΔTLG -21%

Day 17 cycle 1 ΔTLG -40%



Fused FDG PET-CT images of right femoral tumour focus in patient 21/210 scaled the same (SUV max 0-10) demonstrating altered morphology on PET and reduced FDG uptake at part of the lesion

IP STRATEGY & TIMELINE

AstraZeneca

CANCER RESEARCH UK | CENTRE FOR DRUG DEVELOPMENT

DRUG DISCOVERY

PHASE I

PHASE II

PHASE III

GENERICS ENTER THE MARKET

RESEARCH → PRODUCT DEVELOPMENT → PRODUCT AVAILABLE FOR PATIENTS

PATENT 20 YEARS

NEW IP FILED - PATENT EXCLUSIVITY

PATENTS FILED **2003**

CDP AGEEMENT SIGNED **2010**

AZ ASSIGNMENT **2020**

COM PATENT EXPIRES **2023**

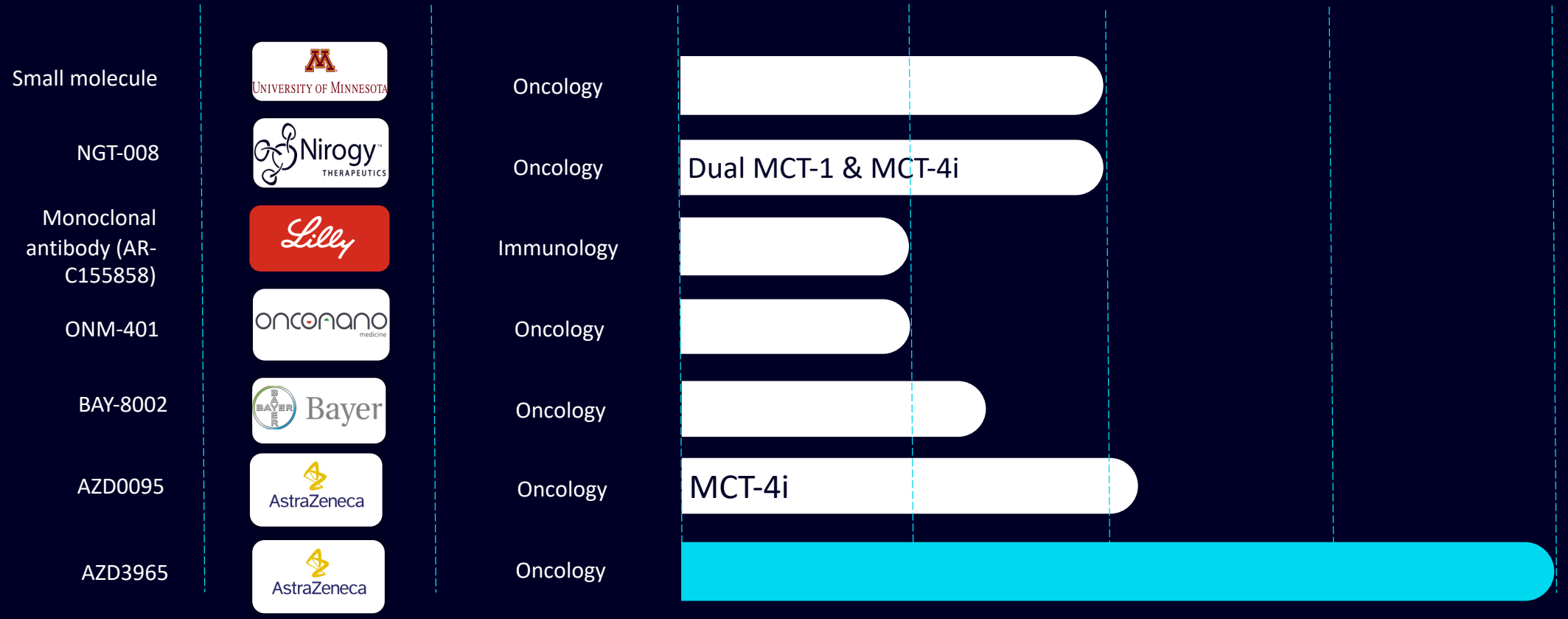
CURRENT STATUS

NEW CHEMICAL ENITITY 5 YEARS

ORPHAN EXLUSIVITY 7 YEARS

COMMERCIAL ANALYSIS

AZD3965 is Phase II ready and the only clinical MCT-1 inhibitor.



SUMMARY AND NEXT STEPS

AZD3965 is a first-in-class, potent and selective inhibitor of MCT1

- ✓ Phase II ready, selective, first-in-class MCT1 inhibitor
- ✓ Most advanced MCT-1 inhibitor in development
- ✓ Phase I showed signs of clinical efficacy with a Complete Response and prolonged stable disease in heavily pre-treated patient population
- ✓ Extensive supporting pre-clinical work
- ✓ Potential routes for development in oncology through patient selection and combinations
- ✓ US patent with potential to explore Orphan Drug Designation

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THANK YOU

Please contact Thomas.Edwards@cancer.org.uk for further information