ASX Announcement

AZD0466 active in small cell lung cancer patient models

Melbourne, Australia; 20 April 2023: Starpharma (ASX: SPL, OTCQX: SPHRY) today announces AZD0466 results from a preclinical study in small cell lung cancer (SCLC) patient-derived xenograft (PDX) models. Starpharma's partner, AstraZeneca, presented these results overnight at the American Association for Cancer Research (AACR) Annual Meeting.

AZD0466 is a highly optimised dendrimer nanoparticle formulation of AstraZeneca's dual Bcl-2/xL inhibitor, AZD4320, which utilises Starpharma's DEP® technology and is being developed by AstraZeneca under their multi-product DEP® license with Starpharma. AZD0466 is the first candidate under Starpharma's multi-product license with AstraZeneca whereby Starpharma is eligible to receive development, launch and sales milestones, in addition to royalties.

The AACR Annual Meeting is one of the world's largest cancer research conferences, bringing together thousands of investigators, scientists, and clinical researchers to discuss new and significant observations.

SCLC is an aggressive form of lung cancer with relatively few treatment options and a 5-year survival rate of only ~7%[1]. The results from this latest research in SCLC presented by AstraZeneca at the AACR Annual Meeting showed that Bcl-2/xL inhibition has therapeutic potential in SCLC:

- AZD0466 was active in 50% of SCLC models, resulting in tumour regression in 33% of models.
- Dual Bcl-2/xL inhibitor AZD0466 outperformed marketed Bcl-2 inhibitor venetoclax[2] in 60% of SCLC models.
- Notably, AZD0466 was also active in models *resistant* to the current standard-of-care treatment for SCLC: platinum/etoposide chemotherapy.

In addition to the preclinical data in SCLC, the poster presented by AstraZeneca at the AACR Annual Meeting also included newly released clinical trial data from AstraZeneca's first-in-human study of AZD0466 in patients with advanced solid tumours (NCT04214093). In this clinical trial (NCT04214093), 9 patients with adrenal carcinoma, anal cancer, bile duct cancer, bladder/urethral cancer, colorectal cancer, lung cancer, pancreatic cancer, and sarcoma were treated with AZD0466. Of the 9 patients treated with AZD0466 in this trial, efficacy signals were observed in 33% of these patients who achieved stable disease for periods of up to 5.5 months.

AZD0466 is also currently being evaluated in patients with advanced haematological malignancies (NCT04865419) and non-Hodgkin lymphoma (NCT05205161). 33[3] patients have been treated with AZD0466 across the advanced solid tumour and advanced haematological malignancy trials.

The AstraZeneca poster included updated clinical data from the ongoing global Phase 1/2 clinical trial in patients with advanced haematological malignancies (NCT04865419). This trial has now treated 24[4] patients at doses up to 3600mg, with patient treatment ongoing and

[1] Gazdar A et al. Nat Rev Cancer 2017
[2] Venetoclax is an oral medication, sold under the brand names Venclexta and Venclyxto, used to treat adults with chronic lymphocytic leukemia, small lymphocytic lymphoma, or acute myeloid leukemia.
[3] Anderson C L et al. AZD0466, a dual BCL-2/XL targeting nanomedicine, is active in small cell lung cancer models [abstract]. In: Proceedings of the 114th Annual Meeting of the American Association for Cancer Research; 2023 April 14-19; Orlando, FL. Philadelphia (PA): AACR; 2023. Abstract nr 6150/12
[4] Patient data as at 24 January 2023

further dose escalations planned. This trial continues to progress well, with no dose-limiting toxicities reported to date and with initial clinical activity observed through reduction of bone marrow blasts following AZD0466 treatment and a mean treatment duration of 4.4 months. This Phase 1/2 trial in patients with acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) continues to enroll at 18 sites across the United States, Europe, Asia and Australia, with additional sites planned.

These new preclinical and clinical results for AZD0466 were presented in a poster presentation by AstraZeneca at the AACR Annual Meeting overnight. The poster and corresponding abstract are appended and will be available on Starpharma's website: www.starpharma.com. In addition to the poster presentation, AZD0466 featured at AstraZeneca's booth at the AACR Annual Meeting, as part of their haematology development portfolio, through an interactive display highlighting AstraZeneca's clinical pipeline and portfolio.

Starpharma's dendrimer drug delivery technology, known as DEP®, is used to enhance the therapeutic properties of drugs to improve solubility, efficacy, pharmacokinetics, targeting, and to reduce certain toxicities. Starpharma has established partnerships with three of the world's largest pharmaceutical companies – AstraZeneca, MSD, and Genentech – and has also developed three clinical-stage anticancer products based on its DEP® technology, with others in preclinical development.

Dr Jackie Fairley, Starpharma CEO, commented: "It is exciting to see AstraZeneca continue to invest in the preclinical and clinical development of their licensed DEP® product, AZD0466. This AZD0466 poster presentation in Small Cell Lung Cancer at one of the world's largest cancer research conferences – the American Association for Cancer Research – adds to the growing body of preclinical and clinical data AstraZeneca is generating for this innovative anti-cancer product, which was developed using Starpharma's DEP® technology.

"AZD0466 is already being trialed globally in patients with advanced leukaemias and non-Hodgkin lymphoma. The preclinical and clinical results presented at AACR are encouraging and the positive data in SCLC may lead to an expanded market opportunity for AZD0466 and, importantly, bring a potentially more efficacious product to patients in need. We look forward to seeing further data and clinical progress for AZD0466."

About AZD0466 and Starpharma's multi-product DEP® license with AstraZeneca

AZD0466 is a highly optimised dendrimer nanoparticle formulation of AstraZeneca's dual Bcl-2/xL inhibitor, AZD4320, which utilises Starpharma's DEP® technology and is being developed by AstraZeneca under their multi-product DEP® license with Starpharma. AZD0466 is in a novel class of oncology drugs called dual Bcl-2/xL inhibitors which seek to overcome drug resistance which occurs in treatment with BcL-2-specific inhibitors including venetoclax. AZD0466 allows for efficient delivery of AstraZeneca's dual Bcl-2/xL inhibitor, with an optimised release profile also designed to reduce the potential for toxicities associated with dual Bcl-2/xL inhibition. Dual Bcl-2/xL inhibition with AZD0466 also has the potential for broader activity than the marketed Bcl-2-specific inhibitor, venetoclax (Venclexta®).

AZD0466 is the first candidate under Starpharma's multi-product license with AstraZeneca. Starpharma is eligible to receive development, launch and sales milestones, in addition to royalties. To date, Starpharma has received US$7M in milestones for AZD0466, with the potential to receive milestones of up to US$124M, plus royalties.

About Starpharma

Starpharma Holdings Limited (ASX:SPL, OTCQX:SPHRY) is a biopharmaceutical company, focussed on the development of pharmaceutical and medical products for unmet patient needs, including in the areas of oncology and infectious diseases.

Starpharma's innovative technology is based on proprietary polymers called dendrimers, which are precise, synthetically manufactured, nanoscale molecules. The unique properties of dendrimers – including their size, structure, high degree of branching, polyvalency, and water solubility – are advantageous in medical and pharmaceutical applications.

Starpharma uses its dendrimer technology to develop novel therapeutics and to improve the performance of existing pharmaceuticals. Starpharma's portfolio includes multiple clinical stage oncology products, which utilise its Dendrimer Enhanced Product ('DEP®') drug delivery technology; and marketed products, including VIRALEZE™ and VivaGel® BV, which utilise SPL7013, a proprietary dendrimer with antimicrobial properties.

Starpharma's DEP® drug delivery platform is being used to enhance the effectiveness of existing and novel therapies and to reduce drug-related toxicities through controlled and specified drug delivery.

In addition to Starpharma's internal DEP® programs, Starpharma has multiple DEP® partnerships with international biopharmaceutical companies including AstraZeneca (oncology); MSD (antibody drug conjugates); Chase Sun (anti-infectives); and other world leading pharmaceutical companies. Due to the broad applicability and optionality of Starpharma's DEP® platform, partnered DEP® programs have the potential to generate significant future milestones and royalties.

Starpharma's topical antiviral nasal spray, VIRALEZE™, is now registered in more than 30 countries*, including in Europe, in the UK, and in Southeast Asia. Starpharma's novel non-antibiotic vaginal gel, VivaGel® BV, for treatment of bacterial vaginosis (BV) and prevention of recurrent BV, is registered in more than 45 countries, including in the UK, in Europe, in Southeast Asia, South Africa, Australia and New Zealand.

* Note: VIRALEZE™ is not approved for use or supply in Australia.

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Disclosure
This ASX Announcement was authorised for release by the Chairman, Mr Rob Thomas.

Forward Looking Statements

This document contains certain forward-looking statements, relating to Starpharma's business, which can be identified by the use of forward-looking terminology such as "promising", "plans", "anticipated", "will", "project", "believe", "forecast", "expected", "estimated", "targeting", "aiming", "set to", "potential", "seeking to", "goal", "could provide", "intends", "is being developed", "could be", "on track", or similar expressions, or by express or implied discussions regarding potential filings or marketing approvals, or potential future sales of product candidates. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no assurance that any existing or future regulatory filings will satisfy the FDA's and other authorities' requirements regarding any one or more product candidates nor can there be any assurance that such product candidates will be approved by any authorities for sale in any market or that they will reach any particular level of sales. In particular, management's expectations regarding the approval and commercialization of the product candidates could be affected by, among other things, unexpected trial results, including additional analysis of existing data, and new data; unexpected regulatory actions or delays, or government regulation generally; our ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry, and general public pricing pressures; and additional factors that involve significant risks and uncertainties about our products, product candidates, financial results and business prospects. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected. Starpharma is providing this information as of the date of this document and does not assume any obligation to update any forward-looking statements contained in this document as a result of new information, future events or developments or otherwise. Clinical case studies and other clinical information given in this document are given for illustrative purposes only and are not necessarily a guide to product performance and no representation or warranty is made by any person as to the likelihood of achievement or reasonableness of future results. Nothing contained in this document nor any information made available to you is, or shall be relied upon as, a promise, representation, warranty or guarantee as to the past, present or the future performance of any Starpharma product.

AZD0466, a dual BCL-2/XL targeting nanomedicine, is active in small cell lung cancer models

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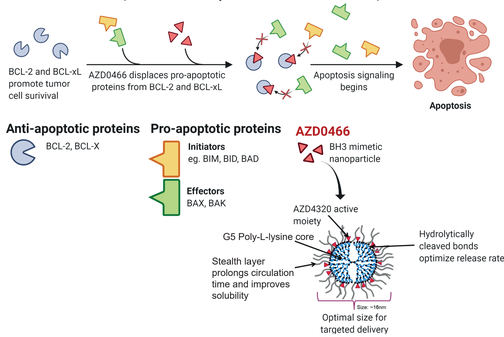
Small cell lung cancer (SCLC)

- Small cell lung cancer is an aggressive, heterogenous malignancy
  - Accounts for ~15% of all lung cancer cases in the US[1]
  - Five (5)-year survival is <7%[1]
- Currently all patients receive same upfront chemotherapy (platinum/etoposide)
- SCLC is comprised of distinct transcriptional subtypes requiring unique targeted therapeutic approaches[2,3]
  - ASCL1 (A), POU2F3 (P), NEUROD1 (N), and YAP (Y)
- BCL-2 is highly expressed in A- and P- subtypes
  - Subtypes represent ~51% (A) and ~7% (P) of SCLC patients[2]
- We evaluated the potential of AZD0466, a dual BCL-2/XL inhibitor, in SCLC models

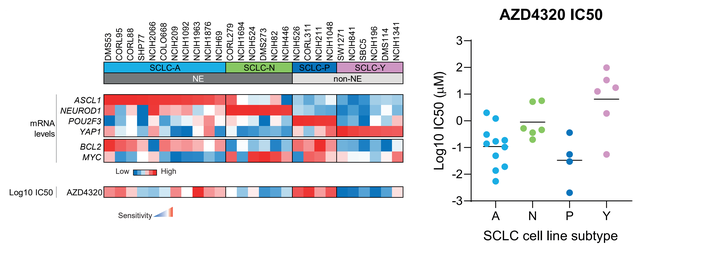
AZD0466: a dual BCL-2/XL inhibitor

AZD0466 is a novel drug-dendrimer conjugate, where the active moiety, AZD4320, is chemically conjugated to Starpharma's clinically validated DEP® dendrimer platform



AZD0466 dosed intermittently to deliver efficacy while maximizing therapeutic index

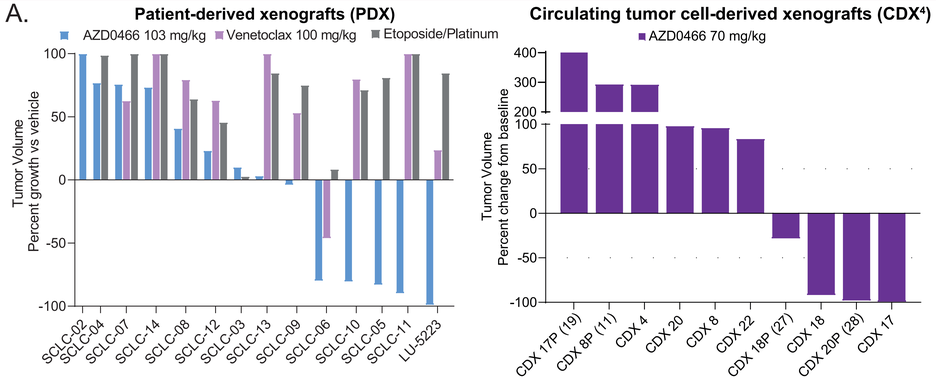
AZD4320 is active in SCLC cell lines



A- and P-subtype SCLC cell lines have higher BCL-2 and are more sensitive to AZD4320

AZD0466 drives regressions in SCLC patient-derived models

A.



-Response in 12 / 24 models (PDX + CDX)
-Regression in 8 / 24
-Dual BCL-2/XL inhibition more active than selective BCL-2 inhibition with venetoclax
-AZD0466 active in models resistant to Platnium/Etoposide (SOC)

B.

*Post-chemotherapy relapsed model

AZD0466 can produce prolonged CRs in SCLC models

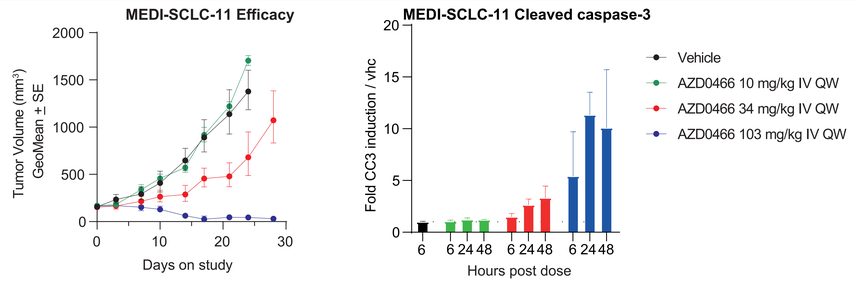
AZD0466 efficacy is enriched in subtype-A patient-derived models

N/D: no data on subtype
*CDX22 and CDX4 also have high YAP1 expression
**ATOH1 represents recently reported subtype*

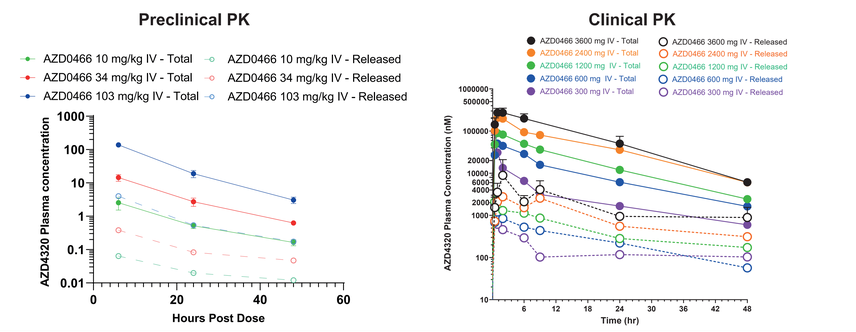
Tumor volume reduction correlates with BCL2 mRNA and protein expression

Preclinical SCLC efficacy observed at clinically achievable doses

A.



B.



AZD0466 is under clinical investigation

	Advanced solid tumors[a]	Advanced hematologic malignancies[b,5]
Number of patients treated	9 patients	24 patients
Doses administered (range)	50 mg to 200 mg	300 mg to 3600 mg
Disease indication (number of patients)	Adrenal carcinoma (1), anal cancer (1), bile duct cancer (1), bladder/urethral cancer (1), colorectal cancer (1), lung cancer (1), pancreatic cancer (1), sarcoma (2)	AML (20), ALL (4), MDS (0)
Mean treatment duration	3.4 months	4.4 months
Adverse events ≥ Grade 3 related to AZD0466* (number of patients)	Aspartate aminotransferase increased (2), alanine aminotransferase increased (1)	Febrile neutropenia (3), thrombocytopenia (1), diarrhea (1), gamma-glutamyl transferase increased (1), platelet count decreased (1)

AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndrome
* Reasonable possibility adverse event was caused by AZD0466, as assessed by the investigator. Graded per CTCAE v5.
a. A study of AZD0466 in patients with advanced hematologic or solid tumors (NCT04214093). Data as of 20-Dec-2021.
b. A study of AZD0466 monotherapy or combination in patients with advanced hematologic malignancies (NCT04865419)[5]. Patient treatment is ongoing and only data up to 24-Jan-2023 are captured.

Summary

- BCL-2/XL inhibition with AZD4320 and AZD0466 is active in SCLC models
- Efficacy is enriched in models representing A and P subtypes of SCLC
- AZD0466 is currently under clinical investigation and has been well-tolerated in doses up to 3600 mg
- Preclinical efficacy is observed at clinically achievable exposures

Acknowledgements: Emily Rowe, Kaitlyn Beyfuss

References: 1. Gazdar A et al. Nat REv Cancer 2017, 2. Gay CM et al. Cancer Cell 2021, 3. Rudin CM et al. Nat Rev Cancer 2019. 4. Simpson KL et al. Nat Cancer 2020. 5. Arslan et al. Abstract #4094 ASH Annual Meeting 2022.

Add to My Itinerary

Session PO.ET06.05 - Cell Death Pathways and Treatment / Molecular Classification of Tumors for Diagnostics, Prognostics, and Therapeutic Outcomes

6150 / 12 - AZD0466, a dual BCL-2/XL targeting nanomedicine, is active in small cell lung cancer models

April 19, 2023, 9:00 AM - 12:30 PM | Section 16

Presenter/Authors

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Disclosures

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K. Simpson, None.
C. Dive,
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Takeda-Millenium, GalxoSmithKline, Taiho, Roche Pharmaceuticals, Hummingbird, Yingli Other, Clinical research (to institution).
European Society for Medical Oncology Travel.
Vall d'Hebron Institute of Oncology/Ministero De Empleo Y Seguridad Social, Chinese University of Hong Kong, Boxer Capital, LLC, Tang Advisors, LLC Other.
Bycicle Therapeutics, Merus, Curis, Bayer, AadiBioscience, Nuvation, ForeBio, BioMed Valley Discoveries, Loxo Oncology, Hutchinson MediPharma Other, Clinical research (to institution).
Cellestia, Deciphera, Ideaya, Amgen, Tango Therapeutics, Mirati Linnaeus Therapeutics Other, Clinical research (to institution).
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AstraZeneca Employment, Stock.

Abstract

Small cell lung cancer (SCLC) is an aggressive malignancy with critical need for new therapies. While currently treated as a single disease, SCLC is heterogenous, comprised of several transcriptional subtypes. Each of these subtypes has distinct drivers and may warrant unique therapeutic targets. Two potential therapeutic targets for SCLC are the pro-survival proteins BCL-2 and BCL-XL. BCL-2 is overexpressed in ASCL1 (A) and POUF3 (P) subtypes of SCLC. We therefore sought to evaluate efficacy of the dual BCL-2/XL inhibitor AZD0466 in SCLC models and to determine whether transcriptional subtype would predict response. AZD0466 is a novel drug-dendrimer conjugate. The active moiety, AZD4320, is a potent dual inhibitor of BCL-2 and BCL-XL. AZD4320 is covalently conjugated to a 5^{th}-generation PEGylated poly-lysine dendrimer through a hydrolytically labile linker to make AZD0466. AZD0466 has been optimized to deliver efficacy while mitigating potential Cmax-driven on-target toxicities of AZD4320. AZD4320 was active (IC50 ≤0.1 μM) in 9/27 SCLC cell lines. AZD4320 in vitro sensitivity was enriched in cell lines that represented A and P subtypes of SCLC compared to NEUROD1 and YAP1 subtypes. We next profiled AZD0466 in a panel of SCLC patient-derived models: 14 patient-derived xenografts and 10 circulating tumor cell-derived xenografts. AZD0466 monotherapy dosed weekly IV was active in 12/24 SCLC xenografts, driving regressions in 8 models. AZD0466 drove efficacy and cleaved caspase-3 induction in a dose-dependent manner. Similar to in vitro, AZD0466 in vivo efficacy was enriched in subtype-A, driving responses in 10/14 ASCL1 models (7 regression, 3 stable disease). AZD0466 response also correlated strongly with BCL-2 mRNA expression ($P<0.0001$). AZD0466 outperformed the selective BCL-2 inhibitor venetoclax in 6/10 models. Notably, AZD0466 was active in models resistant to platinum/etoposide chemotherapy, the standard-of-care for SCLC. Together, these data suggest BCL-2/XL inhibition has therapeutic potential in SCLC. AZD0466 is in clinical development. The first-in-human study treated 9 patients with advanced solid tumors (NCT04214093) at doses from 50-200mg, all of which were well-tolerated. The BOR was SD observed in 3 patients (100mg) with 1 patient receiving treatment for 5.5 months. AZD0466 is now under evaluation in patients with hematologic malignancies (NCT04865419 and NCT05205161). AZD0466 has been dosed in 33 patients up to 2400mg. No DLTs have been reported to date. Initial clinical activity has been observed through reduction of bone marrow blasts following AZD0466 treatment. AZD0466 exhibits linear PK, consistent across solid tumor and leukemia patients. The doses tested are in line with preclinical studies in SCLC.