CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER

AMG-319

PHASE I/IIA SMALL MOLECULE PI3K DELTA-SELECTIVE INHIBITOR

NON-CONFIDENTIAL OVERVIEW

March 2023

AMG-319 PHASE I/IIA READY

A HIGHLY SELECTIVE, POTENT SMALL MOLECULE PI3K DELTA INHIBITOR FOR USE IN SOLID TUMOURS

PROJECT SUMMARY

Clinical hypothesis

PI3Kδ blockade as immunotherapy for solid tumours

- PI3Kδ has a preferential modulatory effect on regulatory cells (Treg) vs. other T cell subtypes
- The primary hypothesis is that exposure of an immunologically sensitive solid tumour to a PI3Kδi inhibitor will result in an anti-tumour effect by releasing Treg suppression of CD8+ T cells

AMG-319 status

Phase IIa asset for evaluation at amended dosing +/- as a combination therapy

- Phase IIa trial: AMG-319 monotherapy in head and neck squamous cell carcinoma (HPV+/-) patients
- Reduced tumour Treg cell count and heightened intratumoural CD8+ T cell cytotoxicity observed providing evidence to support proof of mechanism
- Recent evidence to support intermittent dosing as a method to address toxicity

License package

Full data package, two active patents, pre-existing API supply

- License to develop in all solid tumours and full clinical data package including the CSR
- Covered by 2 active patents with the latest filed in 2012
- Pre-existing drug supply ready for follow-on trials

BACKGROUND

AMGEN LICENSED AMG-319 TO CRUK'S CENTRE FOR DRUG DEVELOPMENT (CDD)

CONTEXT

Amgen

- Amgen is the AMG-319 originator who developed the drug and conducted a First-in-Human Phase I trial in relapsed or refractory lymphoid malignancies
- Subsequently licensed AMG-319 to:

Aspire Therapeutics (Acerta Pharma subsidiary)

- License to develop in haematology indications
- Ongoing Ph I/II trials testing AMG-319 in combination with BTK inhibitor ACP-196 (acalabrutinib, Calquence)
  - Chronic Lymphocytic Leukaemia
  - B cell malignancies (Non-Hodgkin's Lymphoma, Multiple Myeloma, B-ALL)

CRUK CDD

- Clinical Development Partnership between Amgen and CRUK where CRUK was granted a license to AMG-319 to run a Ph IIa trial for AMG-319 in HNSCC patients at the charity's cost
- Following CRUK's study, Amgen declined to further develop AMG-319. CRUK now has an option to obtain exclusive rights to the program and related IP

CRUK are currently seeking a new partner to license AMG-319 for further development in solid tumours

USE OF PI3KδI AS AN IMMUNOTHERAPEUTIC HAS BEEN VALIDATED IN VIVO AND IN PATIENTS

CLINICAL VALIDATION

- Various PI3Kδ inhibitors have been approved for treatment of B-cell malignancies, where inhibition targets intrinsic cancer cell dependency on BCR signalling
- A large body of preclinical and clinical evidence [1][2][3] has been gathered to demonstrate its distinct effect in preferentially inhibiting Treg cells vs. other T cell subsets
- AMG-319's Phase IIa trial was the first in-depth study of the immunotherapeutic effect of PI3Kδi in solid tumours
- The trial was closed before efficacy endpoints could be assessed due to difficulties around dosing and a protocol limitations however PI3Kδ inhibition was found to displace Treg cells from tissues including tumour tissue whilst inducing expansion and greater cytotoxic effects of intratumoural CD4+ and CD8+ T cells

Further details on subsequent slides

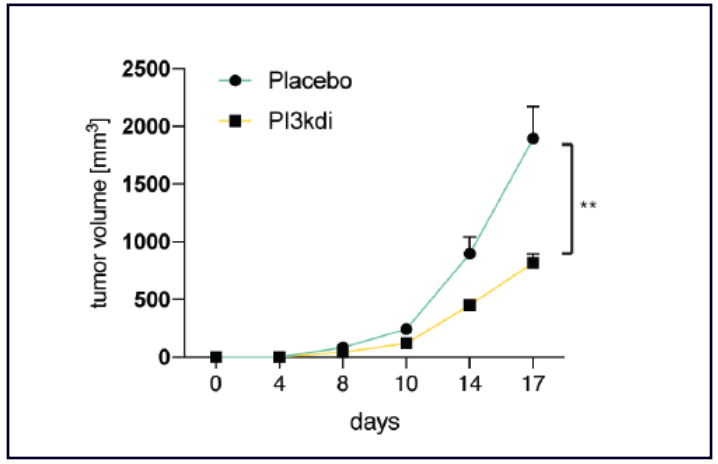
[1] Ali, K. et al. (2014); [2] Chellappa, S. et al. (2016); [3] Lim, E.L. & Okkenhaug, K (2019)

PI3Kδ PRECLINICAL DATA

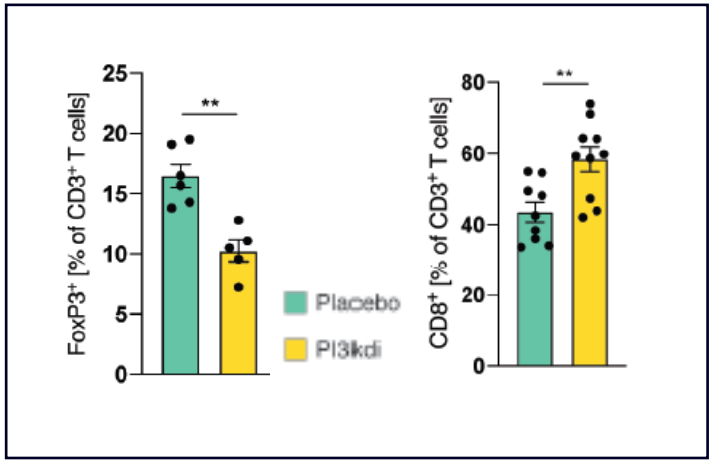
PI3Kδi REDUCES TUMOUR VOLUME AND PROMOTES ANTI-TUMOUR IMMUNE ACTIVITY IN MICE

PRECLINICAL DATA

PI3Kδi significantly reduces tumour volume in preclinical melanoma models



Greater intratumoural CD8+ T cell:Treg ratio observed following treatment



Increase in cytotoxicity markers in tumour infiltrating CD8+ T cells

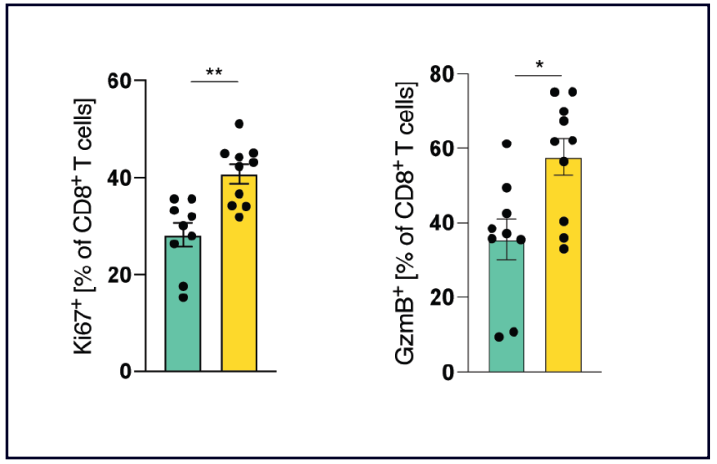


Figure 1: Mice were inoculated subcutaneously with B16F10-OVA cells and fed either a control diet or a diet containing the PI-3065 PI3Kδ inhibitor for the indicated treatment period. n=9-10 mice/group. Data are mean +/- S.E.M. Significance for comparisons were computed using Mann-Whitney test are the data are representative of two independent experiments. (a) Tumour volume of PI3kdi vs. placebo-treated mice (b-c) flow-cytometric analyses of T-cell frequencies

Eschweiler, S. et al. (2022)

AMG-319 CLINICAL DATA

AMGEN CONDUCTED A FIRST-IN-HUMAN PHASE I STUDY IN PRETREATED CLL/NHL

FIH PHASE I

PHASE I FIRST-IN-HUMAN DOSE ESCALATION TRIAL

Study sponsor	AMGEN	
Study size	• 28 participants	
Patient population	• Relapsed or refractory CLL and NHL patients	
Study design	**Part I Dose Exploration** • 25, 50, 100, 200, 300 and 400 mg daily • Continuous reassessment model used to guide dose escalation and to define the maximally-tolerated dose (MTD)	**Part II Dose Expansion** • Use dose no higher than the MTD • Further explore the safety, PK, and clinical activity of AMG 319
Key findings	• 400 mg per day administered without reaching a maximally-tolerated dose • This dosage led to near complete target inhibition and >50% nodal regression while immune related adverse events (irAE) at grade 3 or above did not occur till after days 40 and 60	

Lanasa, M. C. et al. (2013)

CRUK CDD SUBSEQUENTLY CONDUCTED A PHASE IIA TRIAL IN HNSCC PATIENTS

PHASE IIa TRIAL

PHASE IIA TRIAL IN NEOADJUVANT HNSCC (HPV+/-) PATIENTS

Study sponsor	CANCER RESEARCH UK | CENTRE FOR DRUG DEVELOPMENT
Study size	• 30 participants (9 placebo, 21 treated with AMG-319)
Patient population	• Head and neck small cell carcinoma patients (neoadjuvant setting)
Study design	• Patients received between 20 and 28 days of oral dosing with AMG 319 or placebo immediately before resection surgery • Dosing set at 400mg/day based on the rationale that high grade irAE would be unlikely given the shorter treatment duration as compared to the Phase I study (28 days vs up to 60 days)
Key findings	• Analysis shows that PI3K inhibition reduced tumour Tregs and heightened CD8+ cell toxicity • Dose requires amendment (this was reduced to 300mg/day in the trial however protocol design did not allow changes to dose scheduling to further explore safety in this patient population. CDD decided to close the study.) • Toxicity likely owed to greater immunocompetency of solid tumour patients in the neoadjuvant setting. Scientific advice that intermittent dosing addresses toxicity, opening a path for safe use

Lanasa, M. C. et al. (2013); Eschweiler, S. et al. (2022)

AMG-319 WAS FOUND TO DISPLACE TREG CELLS AND HEIGHTENED CD8+ CYTOTOXICITY

CLINICAL DATA

Steady state plasma concentrations comparable to previous Phase I trial

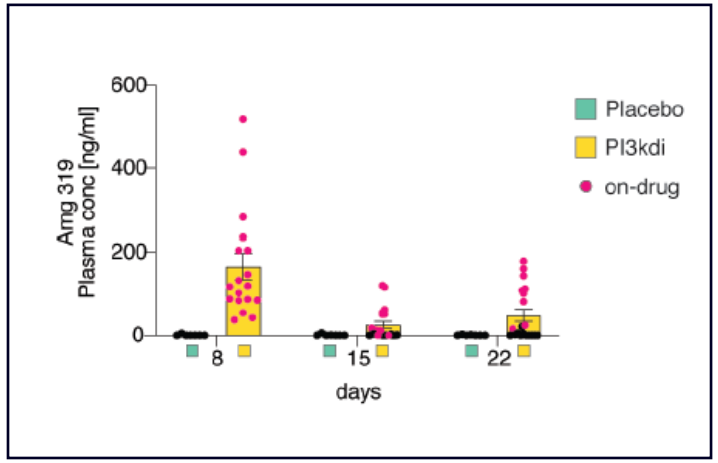


Figure 1: AMG-319 plasma concentration over time in placebo- and AMG-31- treated patients

8 patients discontinued treatment between day 7-9 resulting in loss of detectable drug in PK analysis on day 15

Reduced Treg in tumour samples from AMG-319-treated patients

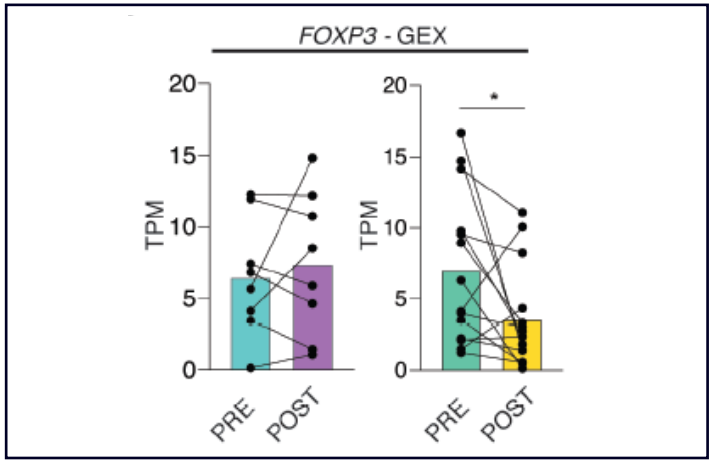


Figure 2: FoxP3 levels in tumour samples from patients treated with AMG-319 as assessed by gene set enrichment analysis. Placebo (LHS), AMG-319 treated (RHS)

Increased CD8+ T cell cytotoxicity in AMG-319 treated vs. placebo patients

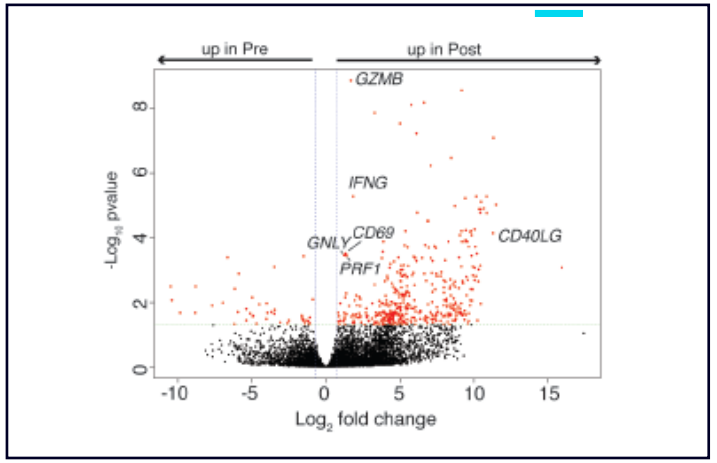


Figure 3: Bulk RNA-seq analysis of CD8+ T cells comparing AMG-319 to placebo treated patients. Differentially expressed genes between pre- and post-treatment samples are highlighted in red

Eschweiler, S. et al. (2022)

FUTURE DIRECTION

RATIONALE TO SUPPORT FURTHER EVALUATION WITH INTERMITTENT DOSING AND IN COMBINATION

NEXT STEPS

MONOTHERAPY

- **Intermittent, lower dosing:** PI's recent Nature paper demonstrates that intermittent dosing can abrogate toxicity of PI3Kδ inhibitors without impacting antitumour response [1]
- **Use in more established settings:** current toxicity likely owed to immunocompetency of neoadjuvant patients

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ANTI-PD-1/PD-L1 COMBO

- In a recent Nature paper, Professor Simon Eschweiler demonstrated that intratumoural regulatory T cells can impede the efficacy of anti-PD-1 therapy
- Depletion of Tregs prior to anti-PD-1 treatment was associated with a better survival outcome [2]
- Given the Treg displacement seen in AMG-319-treated patients, PIs are keen to explore the anti-PD-1 combo

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ANTI-LAG-3 COMBO

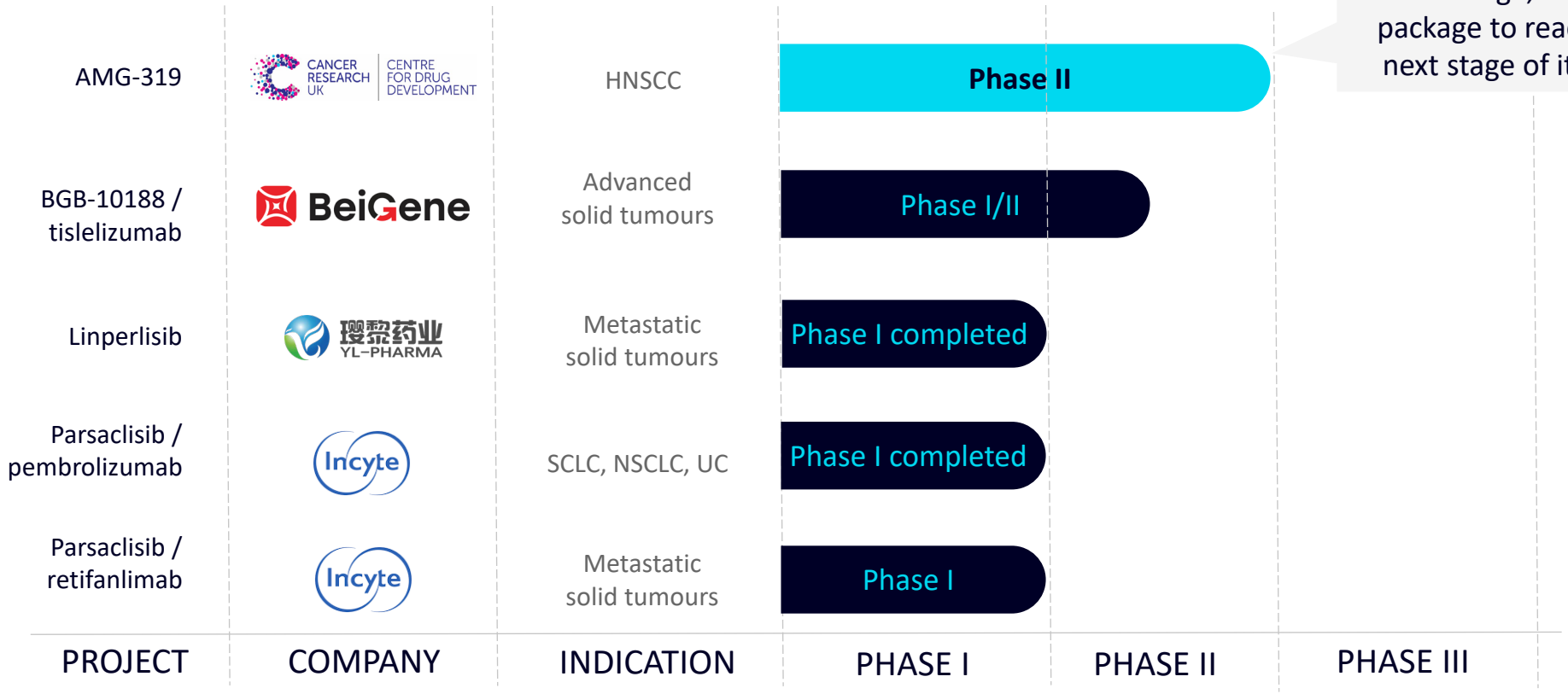
- LAG3 expression on Tregs is necessary for their suppressive function
- Professor Sarah Lauder demonstrated anti-LAG3 potentiated PI3Kδ based immunotherapy, resulting in successful tumour control in all treated mice [3]
- There are no trials currently investigating an anti-LAG3 in combination with a PI3Kδ inhibitor

[1] Eschweiler, S et al (2022) [2] Eschweiler, S et al (2021); [3] Lauder, S.N. et al (2021)

AMG-319 IS THE MOST ADVANCED PI3Kδ-SELECTIVE INHIBITOR IN DEVELOPMENT FOR SOLID TUMOURS

MARKET LANDSCAPE

PI3Kδ-SELECTIVE INHIBITORS – SOLID TUMOURS*



AMG-319 is an advanced asset with a large, accumulated data package to readily support the next stage of its development

* As of June 2022. Excludes trials for dual or pan selective PI3K inhibitors, excludes PI3Kδi trials for haematological malignancies
ClinicalTrials.gov; PharmaProjects

A COMPREHENSIVE IP AND DATA PACKAGE IS AVAILABLE FOR FURTHER DEVELOPMENT

IP / DATA PACKAGE

Patents

PATENT #1: WO2008118468
Priority date: March 2007

PATENT #2: WO2013152150
Priority date: April 2012

Data packages

Phase I Trial	Phase IIa Trial	
Regulatory documentation: IMPD, IB (includes AMG-319 preclinical data)	Clinical Study Report	All regulatory documentation: IMPD, IB

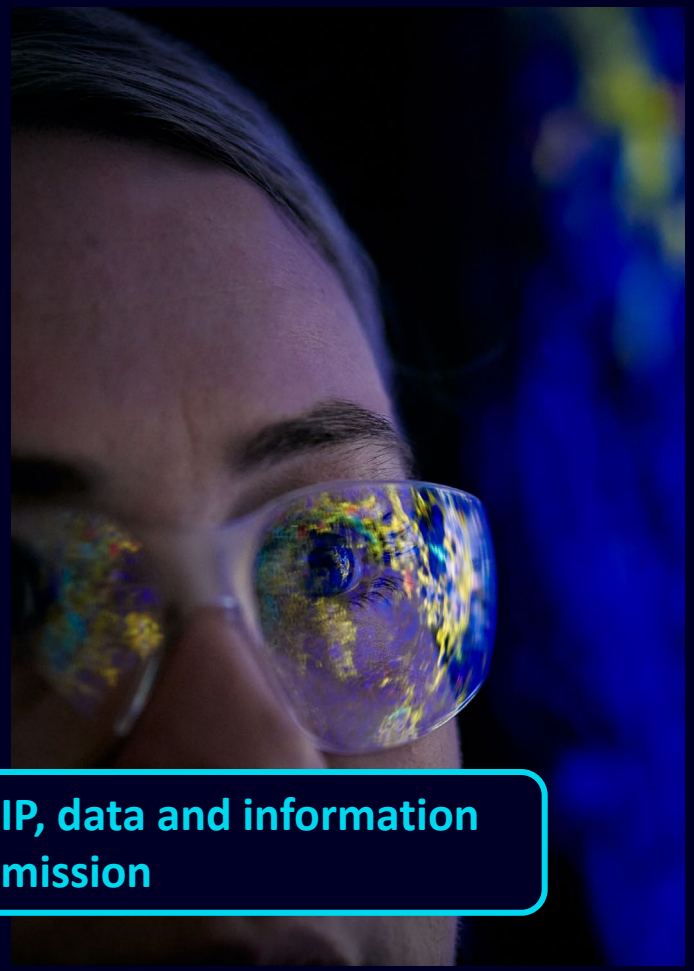
API supply

API supply available in sufficient quantities for a follow-on trial

SUMMARY

AMG-319 is a Phase I/IIa ready, highly selective PI3Kδ inhibitor

- Most advanced PI3Kδ-selective inhibitor in development for solid tumours
- Phase IIa proof of mechanism evidence, with Treg displacement and increased intratumoural CD8+ T cell cytotoxicity observed
- Potential routes for development in oncology through dose optimisation, more-established solid tumour setting and combinations
- Comprehensive data package (preclinical and clinical) and patent life to support further development
- Pre-existing API supply sufficient for follow-on trial



CRUK are seeking a new partner to license AMG-319 and have a full IP, data and information package available for evaluation and regulatory submission

CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER

THANK YOU

Please contact Laura.Huynh@cancer.org.uk or Claire.Hyder@cancer.org.uk for further information