Bemcentinib, a selective AXL kinase inhibitor: potential application in treatment of COVID-19

SACHS - DIGITAL NOVEL CORONAVIRUS INVESTMENT FORUM

Dr. Akil Jackson MBBS MRCP PhD

Medical Director, Non-Oncology Clinical Development

BerGenBio ASA

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BerGenBio corporate overview

World leaders in understanding AXL biology

AXL tyrosine kinase mediates aggressive disease:
immune evasion, therapy resistance & metastatic cancer, fibrosis and viral infection

Selective AXL inhibitors have the potential to treat many serious unmet medical needs

Pipeline opportunities in multiple aggressive diseases

2 selective AXL inhibitors in clinical development

Bemcentinib (oral *once-a-day* pill)
Tilvestamab (mAb)

Bemcentinib broad Phase II program
Monotherapy and combos with CPI, targeted & chemo

Biomarker correlation, parallel CDx development

Bemcentinib clinical data points 2020:
AML (chemo-combo)
NSCLC (KEYTRUDA combo) **COVID19** (mono)

Resourced to deliver milestones

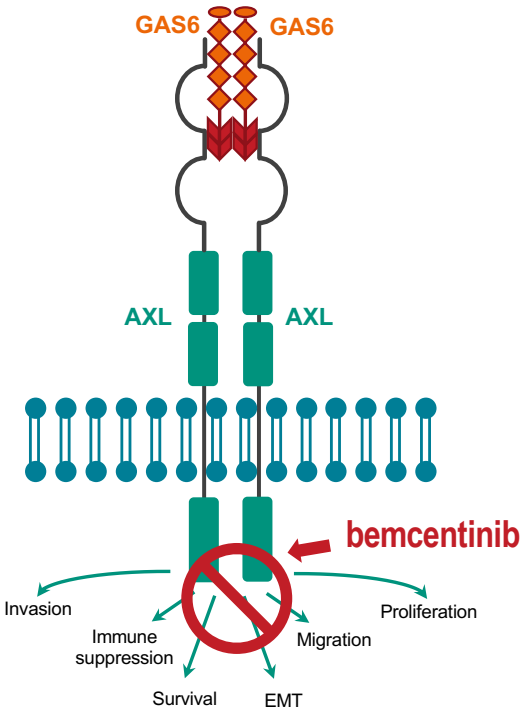
Listed on Oslo Børs: BGBIO

Clinical trial collaborations
Merck, UKRI, and leading academic centres EU & USA

40 staff at two locations:
HQ & R&D in Bergen, Norway;
Clinical Development in Oxford, UK

Cash Q1'20 NOK419m,
(+ PIPE NOK500m May'20)

AXL Biology



- AXL mediates multiple survival mechanisms used by cancers:
  - Chemo drug resistance, immune evasion, metastasis
- AXL mediates viral entry to host cells and reduces anti-viral immunity

- AXL is a member of the Tyro3, AXL, Mer (TAM) family of receptor tyrosine kinases, activated by Growth Arrest Specific Factor (Gas6) - involved in phagocytosis of apoptotic cells
- AXL a receptor tyrosine kinase that is important for regulating innate immune cells.[1]
- AXL levels are elevated by cellular stress and is strongly associated with inflammatory diseases including cancer and fibrosis.[2]
- It functions as a homeostatic regulator in adult tissues and organ systems that are subject to continuous challenge and renewal throughout life – immune, nervous, vascular and reproductive
- AXL drives cancer progression, immune evasion, and resistance to targeted therapies.[3]
- AXL is a key suppressor of the type I interferon response and is targeted by viruses to block the anti-viral immunity.[4]
- AXL is used by several different enveloped viruses (e.g. Ebola, Zika) to enter cells.[5]

Very low expression under healthy physiological conditions	Elevated AXL signaling strongly associated with cancer progression, immune evasion, drug resistance and metastasis	AXL mediates viral entry to cells and dampening of viral immune response

[1]Lemke Cold Spring Harb Perspect Biol 2013; [2]Zagórska Nat Immunol 2014, Ludwig Cancer Res 2018, Espindola, Am J Respir Crit Care Med. 2018;[3]Gay, Br J Cancer 2013; [4]Chen Nat Microbiol 2018; [5]Moller-Tank Virology 2014;

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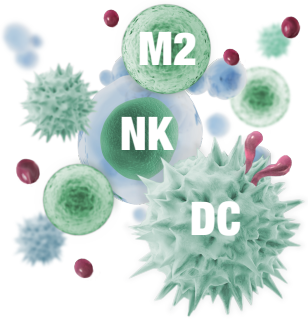
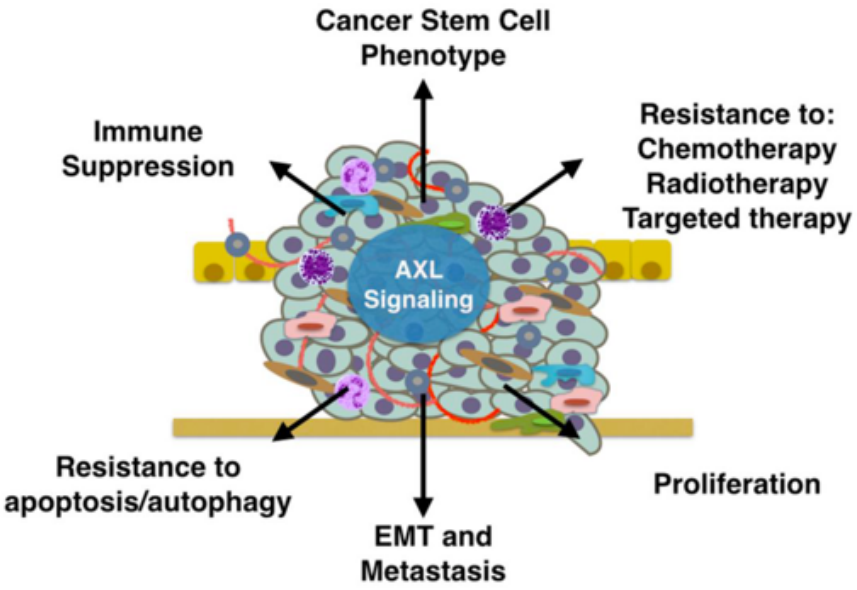
AXL is a key survival mechanism 'hijacked' by aggressive cancers and drives drug resistance, immune-suppression & metastasis

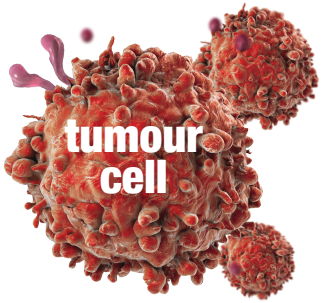
very low expression under healthy physiological conditions → overexpressed in response to hypoxia, inflammation, cellular stress & drug treatment → overexpression correlates with worse prognosis in most cancers



AXL increases on immune cells and suppresses the innate immune response

- M1 to M2 macrophage polarisation[1]
- Decreased antigen presentation by DCs[2]
- Prevent CD8+ T cell mediated cell death[3]
- Activates Treg cells





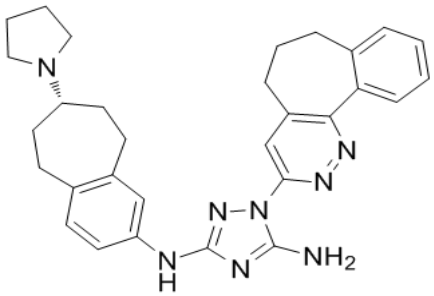
AXL increases on the tumor cell and causes cancer escape and survival

- AXL is a unique type I interferon (IFN) response checkpoint
- Acquired drug resistance
- Immune cell death resistant
- Metastasis

DC- dendritic cells Treg – Regulatory T Cell

1.Ludvig et al Can Res, 2018; Davidsen et al., submitted 2.Kurowska-Stolarska et al Nature Comm 2017; Rothlin et al Cell 2007 3.Ludvig et al Can Res, 2018; Davidsen et al., submitted

Bemcentinib, a first-in-class, potent, oral, highly selective AXL inhibitor



- ✓ Nanomolar in vitro potency (IC_{50} = 150 nM)
- ✓ Uniquely selective for AXL
  - ✓ 50-100 fold selective *cf.* TAM kinases

- ✓ Manufacturing at increased scale for late stage regulatory filing
- ✓ Size 0 100mg HPMC capsules
- ✓ 3 years stability confirmed

- ✓ Once daily oral dosing
- ✓ Extensive Phase I & II experience
  - ✓ >280 patients
- ✓ Safety and tolerability profile supports use in combination with other drugs
- ✓ MOA is synergistic with other therapies, enhancing response

BerGenBio pipeline of sponsored clinical trials and near term news flow

Candidate	Targeted Indication	Discovery	Preclinical	Phase I	Phase II	Registrational	Next expected news**
Bemcentinib monotherapy	>2L AML	Ph II safety and POC efficacy demonstrated in 39 patient trial					
Bemcentinib combination with LDAC	2L AML	Ph IIb Safety demonstrated, efficacy POC expansion study- 20 pts.					Q4'20 Update clinical & translational data[1]
Bemcentinib combination with Keytruda MERCK	2L NSCLC chemo refractory	Ph II POC efficacy demonstrated in 50 patient trial, end points met					Q2'20 Updated Survival data[2]
	2L NSCLC CPI refractory	Ph II stage 1, 13 pts. met ORR proof of concept end point			Expansion 16 pts.		Q2'20 Stage 1 clinical and translational data[2]
	2L NSCLC CPI+chemo refractory	Ph II POC study ongoing 29 pts					Q4'20 Stage 1 preliminary interim clinical and translational data[3/4]
Tilvestamab (BGB149)	TBA	Ph Ia HV complete		Ph Ib in set up			
*BGB601**		Ph I Terminated (change in clinical plan and drug supply)					*Update by collaborators*

*Development Out licensed to ADCT
** Increased uncertainty due to COVID crisis
CPI – checkpoint inhibitor
mOS – median overall survival

1 ASH – American Society of Heamatology (Dec 5-8)
2 Next Gen Immuno Oncology (25th June)
3 SITC – Society of Immunotherapy of Cancer (Nov10-15)
4 WCLC – World Congress of Lung Cancer (Jan 26-29 2021)

BGB Sponsored Studies Only

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BerGenBio pipeline of Investigator Sponsored Trials (ISTs)

Candidate	Sponsor	Targeted Indication	Dimensions	Phase I	Phase II	Registrational	Next expected news*
Bemcentinib	**Uni. Hospital Southampton / UKRI funded**	**COVID19**	**Monotherapy**	Randomised Phase II – 15 day treatment			**Stage 1 IA Q3**
	European MDS Cooperative Group	2L AML	Monotherapy	open-label, single-arm , phase II study.			Fully recruited. Q4'20 ASH
		2L MDS	Monotherapy	open-label, single-arm , phase II study			
	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Recurrent Glioblastoma	Monotherapy	Set up			FPI Q2 [recruitment of hold due to COVID-19]
	University of Leicester MERCK	Relapse Mesothelioma	+ pembrolizumab	Set up			FPI Q2 [recruitment of hold due to COVID-19]
	Haukeland University Hospital	1L Metastatic Melanoma	+ pembrolizumab or +Dabrafenib/Trametinib	Randomised Phase II			Biomarker Analysis Q3
	UT Southwestern Medical Center	2-4L Stage 4 NSCLC	+ docetaxel	Ph I safety study			RP2D Q3 [recruitment of hold due to COVID-19]
	UT Southwestern Medical Center	1L metastatic or recurrent PDAC	+ Nab-paclitaxel+ Gemcitabine+ Cisplatin	Ph I safety study			[recruitment of hold due to COVID-19]

* Increased uncertainty due to COVID crisis

Bemcentinib

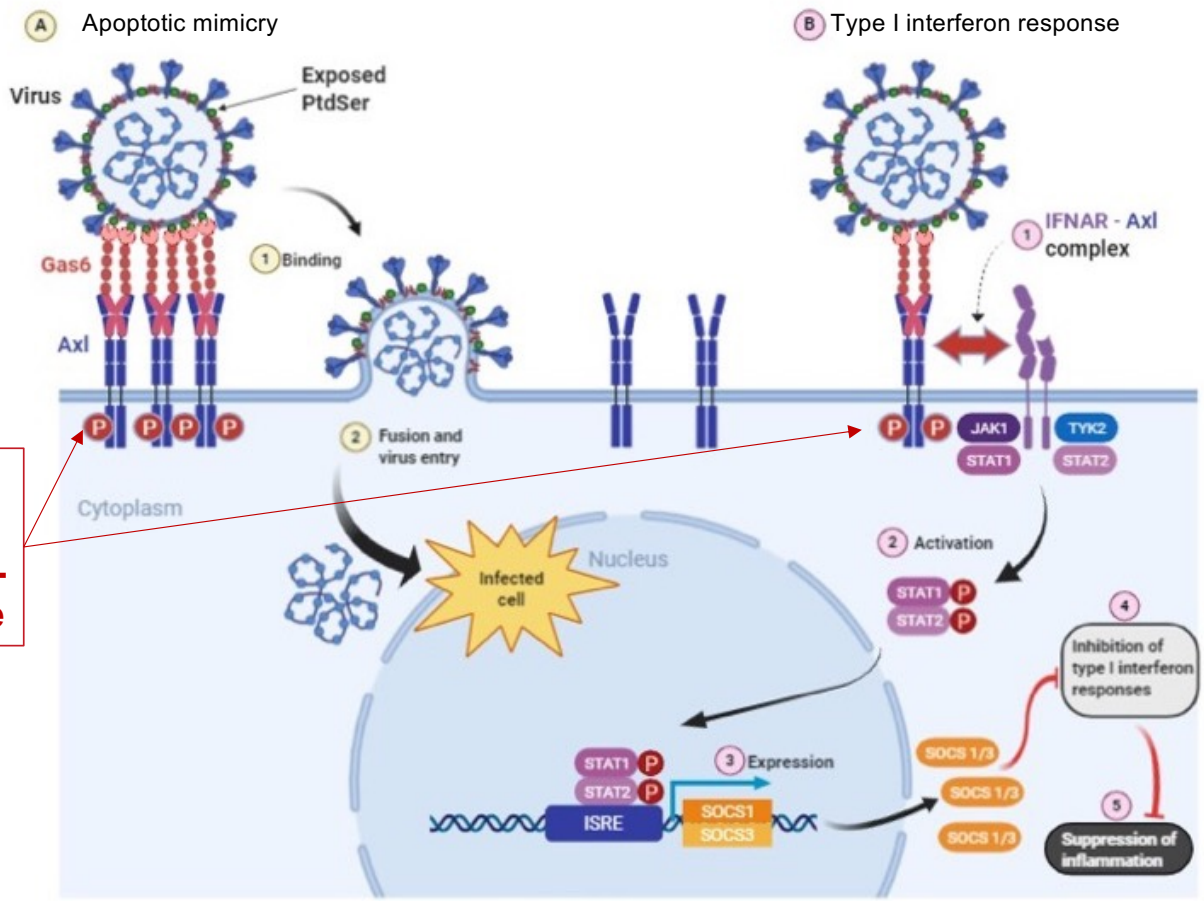
A potential therapy for enveloped viruses, including SARS-CoV2

AXL is targeted by enveloped viruses to enter cells and dampen the viral immune response

Enveloped viruses display phosphatidylserine that is recognized by GAS6, the AXL receptor ligand, that mediates viral entry through “apoptotic mimicry”.

bemcentinib blocks AXL-dependent viral entry and enhances anti-viral interferon response

Bemcentinib potently inhibits SARS-CoV-2 infection of cells.[1]



Viral-mediated AXL receptor activation dampens type I interferon responses, a key anti-viral defence mechanism for all cells

[1] Maury IOWA unpublished / Meertens L *et al. Cell Host & Microbe* 2012, *12*:544 / Chen J *et al. Nat Microbiol* 2018 *3*:302

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Bemcentinib showed effect against lethal EBOV infection in animal models conducted by PHE

viruses

MDPI

Article

Antiviral Screening of Multiple Compounds against Ebola Virus

Stuart D. Dowall [1,6,*], Kevin Bewley [1], Robert J. Watson [1], Seshadri S. Vasan [1,2], Chandradhish Ghosh [3], Mohini M. Konai [3], Gro Gausdal [4], James B. Lorens [4], Jason Long [5], Wendy Barclay [5], Isabel Garcia-Dorival [6], Julian Hiscox [6,7], Andrew Bosworth [1,7], Irene Taylor [1], Linda Easterbrook [1], James Pitman [1], Sian Summers [1], Jenny Chan-Pensley [1], Simon Funnell [1], Julia Vipond [1], Sue Charlton [1], Jayanta Haldar [3], Roger Hewson [1,7] and Miles W. Carroll [1,7]

[1] Public Health England, Porton Down, Salisbury, Wiltshire SP4 0JG, UK; kevin.bewley@phe.gov.uk (K.B.); robert.watson@phe.gov.uk (R.J.W.); seshadri.vasan@phe.gov.uk (S.S.V.); andrew.bosworth@phe.gov.uk (A.B.); irene.taylor@phe.gov.uk (I.T.); linda.easterbrook@phe.gov.uk (L.E.); james.pitman@phe.gov.uk (J.P.); sian.summers@phe.gov.uk (S.S.); jenny.chan-pensley@phe.gov.uk (J.C.-P.); simon.funnell@phe.gov.uk (S.F.); julia.vipond@phe.gov.uk (J.V.); sue.charlton@phe.gov.uk (S.C.); roger.hewson@phe.gov.uk (R.H.); miles.carroll@phe.gov.uk (M.W.C.)

Abstract: In light of the recent outbreak of Ebola virus (EBOV) disease in West Africa, there have been renewed efforts to search for effective antiviral countermeasures. A range of compounds currently available with broad antimicrobial activity have been tested for activity against EBOV. Using live EBOV, eighteen candidate compounds were screened for antiviral activity in vitro. The compounds were selected on a rational basis because their mechanisms of action suggested that they had the potential to disrupt EBOV entry, replication or exit from cells or because they had displayed some antiviral activity against EBOV in previous tests. Nine compounds caused no reduction in viral replication despite cells remaining healthy, so they were excluded from further analysis (zidovudine; didanosine; stavudine; abacavir sulphate; entecavir; JB1a; Aimspro; celgosivir; and castanospermine). A second screen of the remaining compounds and the feasibility of appropriateness for in vivo testing removed six further compounds (ouabain; omeprazole; esomeprazole; Gleevec; D-LANA-14; and Tasigna). The three most promising compounds (17-DMAG; BGB324; and NCK-8) were further screened for in vivo activity in the guinea pig model of EBOV disease. Two of the compounds, BGB324 and NCK-8, showed some effect against lethal infection in vivo at the concentrations tested, which warrants further investigation. Further, these data add to the body of knowledge on the antiviral activities of multiple compounds against EBOV and indicate that the scientific community should invest more effort into the development of novel and specific antiviral compounds to treat Ebola virus disease.

ACCORD2 platform study

BerGenBio's bemcentinib selected to be fast-tracked as a potential treatment for COVID-19

- Preclinical data suggest that bemcentinib is potentially useful for the treatment of early SARS-CoV-2 infection, as it selectively inhibits AXL kinase activity

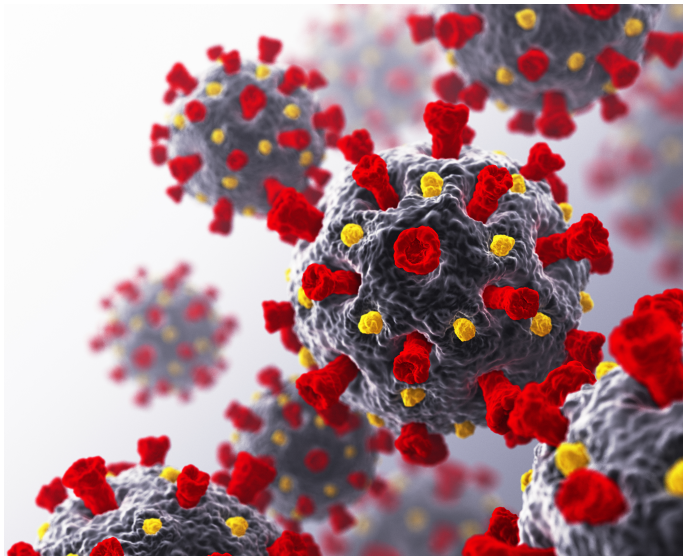
- Bemcentinib selected as first candidate in first wave of new and existing medicines fast-tracked into a new Phase 2 clinical trial initiative to investigate potential treatments for hospitalised COVID-19 patients

- ACCORD-2 (**AC**celerating **C**OVID-19 **R**esearch & **D**evelopment: Phase 2 platform) study is funded by the UK Department of Health and Social Care and UK Research and Innovation

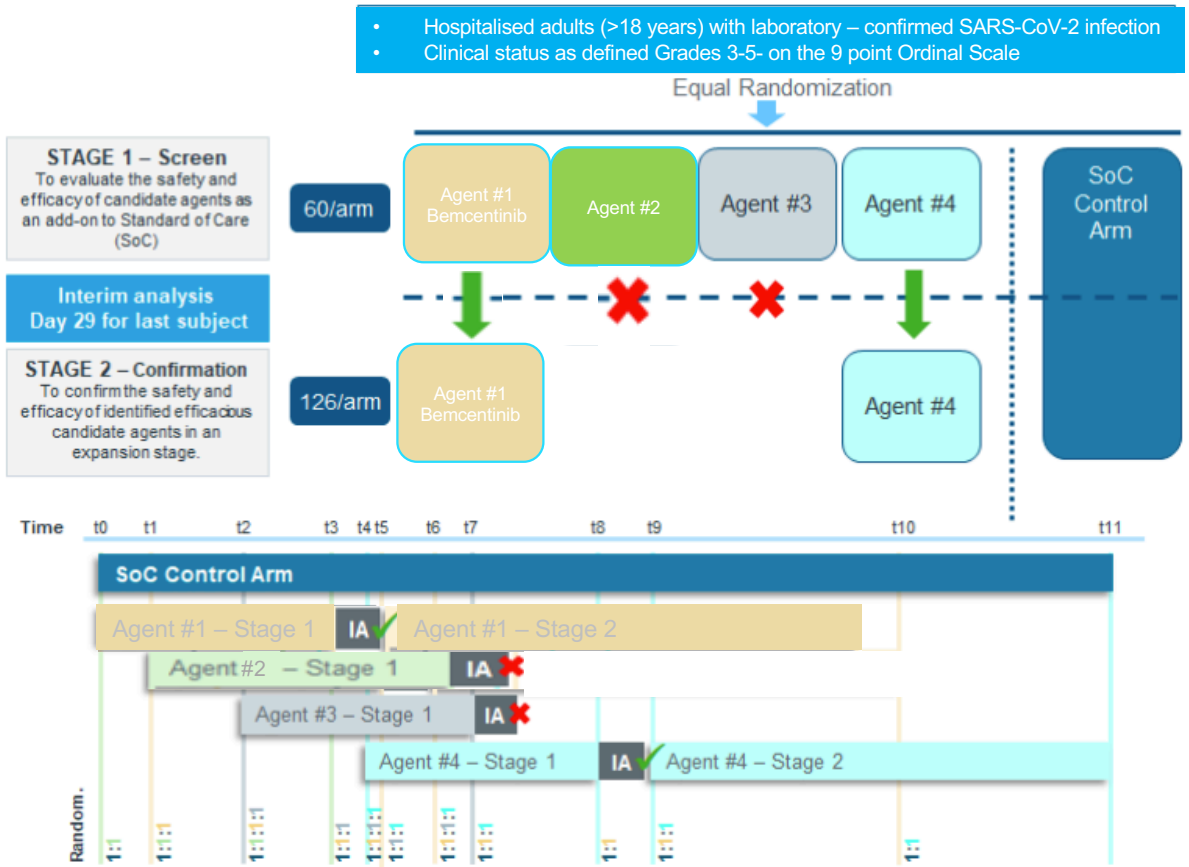
- Study is a collaboration between the UK Government Scientific Office, the NIHR's Biomedical Research centres and clinical research company IQVIA

- Professor Tom Wilkinson is the academic lead of ACCORD-2, based at the National Institute for Health Research (NIHR) Southampton Biomedical Research Centre

- The study will test 120 patients across 11 UK NHS hospital sites.



ACCORD-2 Platform Study overview



IA=interim analysis; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SoC=standard of care.
Note: This figure shows a hypothetical situation, where in Stage 1 of the study there are 4 candidate agents being compared with the SoC, of which 2 candidate agents progress to Stage 2.

SPONSOR: University Hospitals Southampton
Funded by UK Research & Innovation (UKRI)

- ❑ adaptive platform study – selected repurposed agents
  - Randomised, open label
  - Phase 2
  - Comparison with standard of care (SoC) N = 60:60
  - 2-stage design

- 10 NHS sites across UK
- Standard bemcentinib dosing
- Up to 15-day duration
- Independent Data monitoring Committee
- Seamless transition to confirmatory second stage - subject to compelling data

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Protocol title: A Multicentre, Seamless, Phase 2 Adaptive Randomisation Study to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalised Patients

Rationale:

There are currently only two approved therapeutic agents available to treat coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19 disease, and there is an urgent public health need for rapid development of other such interventions. This adaptive platform study is designed to rapidly assess multiple candidate agents as treatments for COVID-19. Candidate drugs that are initially assessed as being efficacious will be moved from an evaluation (pilot) stage to a confirmatory stage, with candidate agents being added to and removed from the study on an ongoing basis, depending on the results of their evaluation. Patients to be included in the study will be hospitalised and may require either supplemental oxygen, noninvasive ventilation or high flow oxygen devices, or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Objectives:

Stage 1: To evaluate the efficacy of candidate agents as add-on therapies to standard of care (SoC) in patients hospitalised with COVID-19 in a screening stage.

Stage 2: To confirm the efficacy of identified efficacious candidate agents in patients hospitalised with COVID-19 in an expansion stage.

Endpoints:

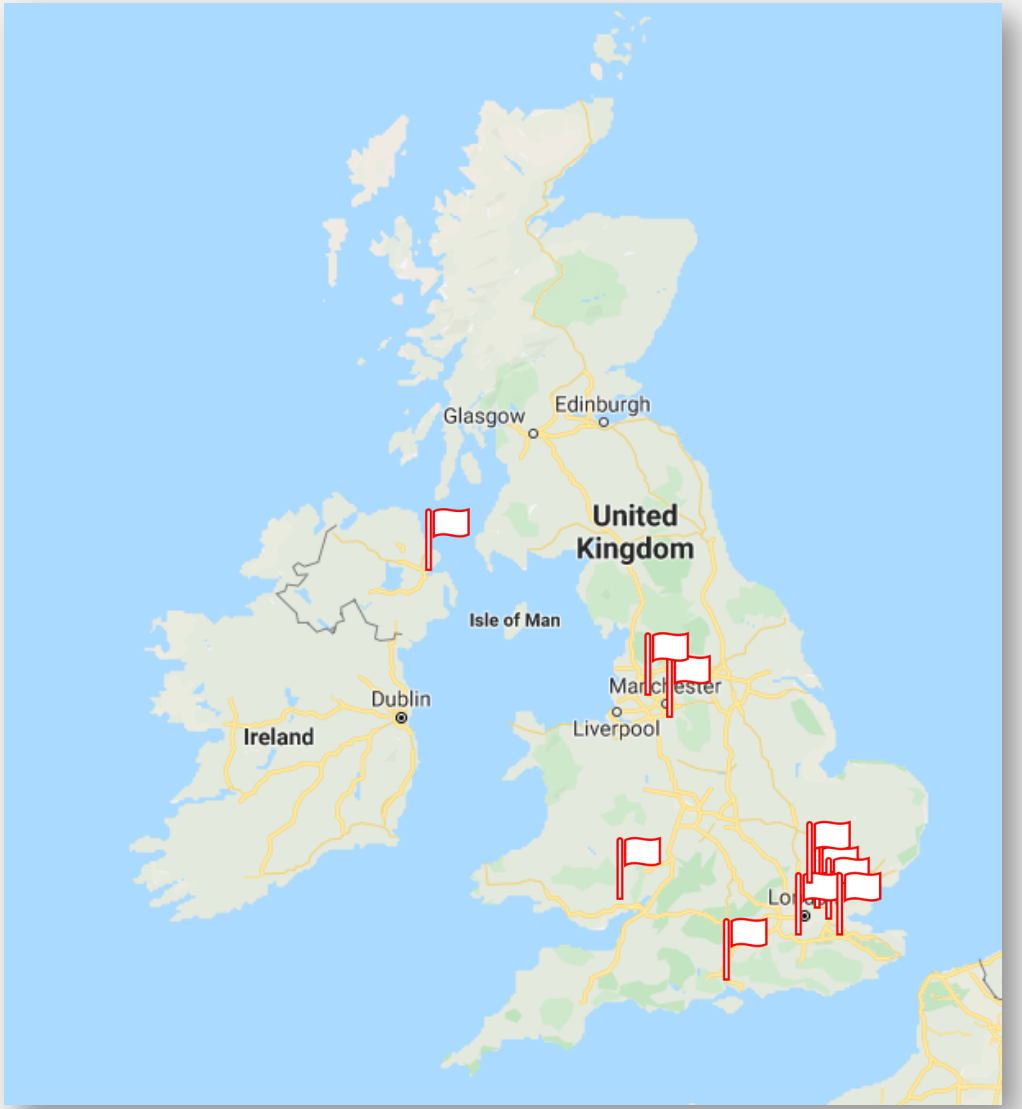
- Time to clinical improvement of at least 2 points (from randomisation) of patients stage 3, 4 or 5 on a 9-point category ordinal scale, or live discharge from the hospital, whichever comes first

9-Point Category Ordinal Scale:

0. Uninfected, no clinical or virological evidence of infection
1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. **Hospitalised – mild disease, no oxygen therapy**
4. **Hospitalised – mild disease, oxygen by mask or nasal prongs**
5. **Hospitalised – severe disease, noninvasive ventilation or high flow oxygen**
6. Hospitalised – severe disease, intubation and mechanical ventilation
7. Hospitalised – severe disease, ventilation and additional organ support – pressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)
8. Death

WHO COVID19: 9-point category ordinal scale

	Setting	Severity	Supportive intervention	ACCORD 2 platform	Dexamethasone	Remdesivir	Community study	High risk post-exposure prophylaxis
0	Uninfected	no clinical or virological evidence of infection						
1	Ambulatory	no limitation of activities						
2		limitation of activities						
3	Hospitalised	mild	no oxygen therapy					
4			oxygen by mask or nasal prongs					
5		severe	noninvasive ventilation or high-flow oxygen					
6			intubation and mechanical ventilation					
7			ventilation and additional organ support – - vasopressors - renal replacement therapy (RRT) - extracorporeal membrane oxygenation (ECMO)					
8		Death						

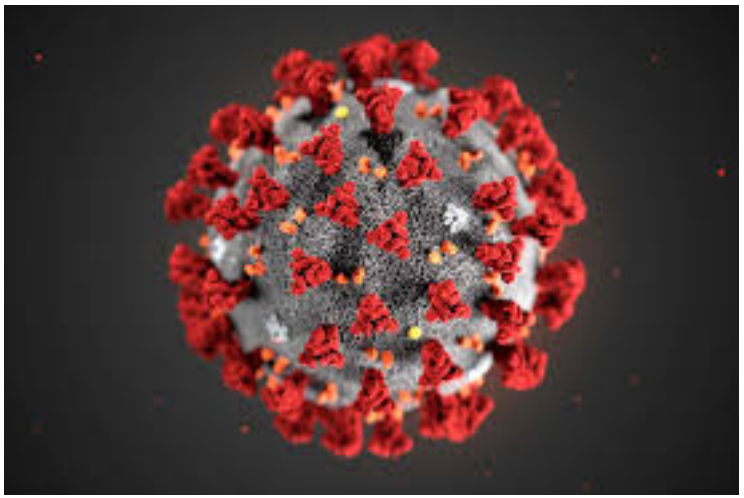


ACCORD-2 bemcentinib Trial Sites

#	Hospital	City
1	Barts Hospital and the Royal London	London
2	Whipps Cross hospital	London
3	University Hospitals Southampton	Southampton
4	Manchester Royal Infirmary	Manchester
5	Wythenshawe Hospital	Manchester
6	Royal Victoria Hospital	Belfast
7	Guy's Hospital	London
8	St Thomas' Hospital	London
9	Royal Gwent Hospital	Newport
10	Kings College Hospital NHS	London

Summary & next steps

- Mechanistic and preclinical research supports rationale to treat COVID19 with selective AXL inhibition - BEMCENTINIB
- ACCORD-2 study aims to get an early indication of whether potential drug treatments could save the lives and improve the outcomes of the most vulnerable patients with COVID-19
- Top line data from the Phase 2 study will read out over ensuing months
- If results are positive, bemcentinib will advance rapidly into the phase III trials currently in progress across the UK
- If successful, bemcentinib would ease pressures on hospital intensive care units, and ultimately treat thousands of patients



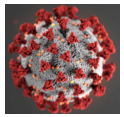
Expected Newsflow 2020

Next-Gen
25th June
NSCLC
Bem + KEYTRUDA

SITC
10-15 Nov
NSCLC
Bem + KEYTRUDA

WCLC
26-29 Jan
NSCLC
Bem + KEYTRUDA

2020 MAY JUN JUL AUG SEP OCT NOV DEC 2021



ACCORD-2

ASH
5-8 Dec
AML
Bem + LDAC
update

ASCO-SITC: Clinical Immuno-Oncology symposium, San Francisco
ASCO: American Society of Clinical Oncology, Chicago
WCLC: World Conference of Lung Cancer, Toronto
ESMO: European Society of Medical Oncology, Munich
AACR: American Association for Cancer Research, Chicago
EHA: European Hematology Association, Stockholm
SITC: Society for Immunotherapy of Cancer, DC
ASH: American Society for Hematology, San Diego