Targeting twin proteins p300 and CBP

A new approach to treating cancer

CCS1477

First-in-class p300/CBP bromodomain inhibitor in Phase I/II clinical trials

- Late stage, drug resistant prostate cancer
- Haematological malignancies
- Tumours with specific drivers

June 2020
• CCS1477, first-in-class inhibitor of key twin cancer activators p300 and CBP (oral capsule product)

• Exposures identified which can be safely administered, and associated with signs of biological and clinical activity: late stage prostate cancer, multiple myeloma, AML

• Recent regulatory approval to accelerate testing of patients with specific tumour drivers: p300 or CBP mutations, AR driven, or c-Myc over-expressors (wide range of tumour types)

• New patient identification and recruitment now re-starting following COVID-19 hiatus
p300/CBP: Critical co-regulators of transcriptional networks. Inhibition impacts AR, c-Myc, IRF4

Three strands of clinical application/clinical proof of concept

1. Castrate resistant prostate cancer, and resistance to current 2nd generation anti-hormonal drugs, driven by AR, AR-SV, AR-mutations and c-Myc

2. Multiple blood cancers exquisitely sensitive to p300/CBP inhibition

3. Certain tumours driven by AR or c-Myc

Certain tumours have a high prevalence of mutations in p300 or CBP: Sensitive to dual inhibitor. E.g. bladder, small cell lung
Targeting the p300/CBP bromodomain

p300/CBP can be targeted at different sites, causing different effects

- Targeting the conserved bromodomain of p300 and CBP impacts their ability to form gene co-activation complexes, and impacts selected acetylation functionality e.g. H3K27Ac, and not H3K18Ac
- Compounds binding to the CH1 domain (e.g. Inthera) and the HAT domain (e.g. AbbVie, A-485) have not advanced into the clinic

- **p300/CBP bromodomain inhibition is not generally cytotoxic**; it impacts discrete certain cancer types
- Clearly distinct from targeting the HAT catalytic domain which has a wider impact on acetylation functionality, and gene expression
- Differentiated from inhibiting other bromodomains;
  - CCS1477 >170x selective for p300/CBP bromodomain v’ BRD4
  - JQ1 resistant cell lines remain sensitive to CCS1477
Three strands of clinical investigation

Prostate cancer patients with tumours resistant (inherent/acquired) to 2nd generation anti-hormonal drugs

Late stage prostate cancer

- + abiraterone
- + enzalutamide

Haematological malignancies: relapsed, refractory disease

Multiple Myeloma, Lymphomas

- + pomalidomide (MM)

Acute Myeloid Leukaemia / MDS

Tumours with specific drivers

- AR dependent or c-Myc over-expressing tumours
- Loss of function p300 & CBP mutations

Mechanisms of Action

- AR, AR-SV
- c- (n-) Myc
- c- Myc
- IRF4

- AR, c-Myc
- mutations
Phase 1 PK and Safety

The first time a p300/CBP bromodomain inhibitor has been dosed to patients

- Oral exposure in efficacious range
- Little evidence of loss of exposure or drug accumulation over time
- Half life range: 8-11 hours
- But higher than expected inter-patient drug exposure; likely upper GI tract absorption driven (see later slide)

Patients heavily pre-treated, with few clinical intervention alternatives

- Reductions in platelets have been observed in some patients (including thrombocytopaenia). Reversible with a short drug holiday.
- Other adverse effects seen, but no overt, consistent tolerability issues at this point
- For prostate cancer, have investigated three capsule strengths (25mg, 50mg, 100mg), with different dosing schedule permutations (once or twice daily; intermittent e.g. 4d on/3d off)
Clear evidence of a therapeutic window:

Late stage prostate cancer
- Reductions and stabilisations in PSA, LDH, AlkP, CTC, tumour volume
- Multiple patients now on drug >6mths

Multiple Myeloma, Lymphomas
- MM: substantial urine protein decline
- AML: neutrophil recovery to normal range

Tumours with specific drivers
- Regulatory approval to accelerate targeted testing, gained April 2020
**Response biomarkers**

Protein expression in paired tumour biopsies
- AR full length; AR-V7
- c-Myc
- p300 and CBP
- Ki67

PSA in blood samples

Gene expression in blood samples (Paxgene)
- Cancer gene pathways and AR-splice variants by Nanostring
- Individual genes confirmed by qPCR (e.g. c-Myc)

Histone acetylation
- H3K27 in PBMCs

**Predictive of molecular markers of response**

Prospective and local identification
- P300/CBP loss of function mutations
- AR amplification
- c-Myc alterations/amplification

Retrospective identification
- Blood samples collected for cfDNA
- Paired biopsies
In the clinic

PROSTATE

Johann de Bono
Royal Marsden Hospital ICR, London

Active
- Johann de Bono RMH
- Ruth Plummer Newcastle
- Harriet Walter Leicester
- Vicky Coyle Belfast
- Louise Carter Christie

Multiple other centres soon to start

HAEM

Tim Somervaille
The Christie Hospital, Manchester

Active
- Tim Somervaille Christie
- Harriet Walter Leicester
- Steven Knapper Cardiff
- Paresh Vyas Oxford

Multiple other centres soon to start

In the US from Q3 2020

Karen Knudsen
William (Kevin) Kelly
TJU/Sidney Kimmel Cancer Center, PA

Perluigi Porcu
TJU/SKCC, PA

Leif Bergsagel
Mayo Clinic, AZ
• p300, CBP LoF mutations (e.g. bladder, lung..)
• c-Myc driven (e.g. SCLC)
• AR+ driven tumours (e.g. breast)

Encouraging signals in both MM and AML
Will explore paralogue lethality in lymphomas in particular

Sustained anti-tumour effects, whilst tolerated
Chronic exposure v’ harder with holidays
Cmax (or C>threshold) v’ AUC

Dose/exposure/schedule exploration

Monotherapy dose expansion
Combination +abi
Combination +enza

Monotherapy dose expansion
Combination +pom

Tumours with specific drivers

Estimated timelines

Q4 2019 Q1 2020 Q2 2020 Q3 2020 Q4 2020 Q1 2021 Q2 2021

Dose/exposure/schedule exploration

Formulation transition

PROSTATE

HAEM

GENETIC DRIVERS

UK Clinical Operations

US Clinical Operations coming on board
Drug discovery underpinned by world-class research and collaboration

Founded out of The Gurdon Institute, University of Cambridge with Prof Azim Surani, CellCentric has worked with >25 international laboratories at the cutting edge of epigenetics.

>50 Epigenetic-related targets investigated
7 Early discovery programs (one sold to Takeda)
1 Focused on paralogue HAT targets p300/CBP

ONGOING TRANSLATIONAL RESEARCH COLLABORATIONS

PROSTATE
• Johann De Bono ICR/Royal Marsden
• Karen Knudsen Kimmel Cancer Center, TJU
• Prostate Cancer Foundation
• Peter Nelson Seattle
• Luke Gaughan Newcastle
• Lisa Butler Adelaide

HAEMATOLOGICAL CANCERS
• Tim Somervaille Manchester/CRUK
• Laura Pasqualucci Columbia, New York
• Leif Bergsagel Mayo Clinic, Phoenix
Experienced leadership

**Will West**
CEO
Co-Founder with Azim Surani
PhD, Post-Doc (NIBSC), MBA
Ex-Clinical Operations, P&G Healthcare (UK, US, Asia)
Two other biotech Boards, Chair JIC

**Neil Pegg**
Research Director
Board Member
PhD, Post-Doc (Ohio State), medicinal chemistry
Ex-Piramed, headed PI3K discovery (acq’d by Roche)
Ex-Glaxo, OSI

**Nigel Brooks**
Director, Translational Research
PhD, Post-Doc (Uni Western Ontario)
Translational Res. Head, AZ; prostate/bladder cancers
Ex-Manchester Cancer Research Centre; Director of Research and Business Operations

**Thea Stanway**
Finance Director
FD & Company Secretary
Ex-PWC, qualified chartered accountant
Over 20 years finance experience
UK and international

**Tomasz Knurowski**
CMO
Medic, Krakow
Clinical research: solid tumours (prostate and haems)
Ex-Medical Director, Simbec-Orion (CRO)
Ex-Medical Monitor, Allergan

**Andrew Hughes**
Chief Development Advisor
Medic, Cambridge
Ex-Global VP, early clinical development, AZ
Multiple oncology drugs, from research to market
Tagrisso: First-in-Man to first registration in 2.5 years

**Karen Clegg**
Director, Clinical Operations
PhD (KCL)
Ex-Global Trials Leader, AZ (First-in-Man, Phase I/II)
Ex-Parexel, Napp Pharmaceuticals
Ex-Clinical Operations Director, Kesios

**Jason Dinges**
Investment Director
PhD (Iowa State), qualified patent attorney
Morningside Technology Advisory
Ex-Foley & Lardner
Multiple biotech Boards
Company at a glance...

Deep scientific foundation, epigenetics
- CellCentric was co-founded with one of the pioneers of epigenetics, Prof Azim Surani FRS CBE
- Collaborated with over 25 leading international labs

Opportunity triage
- Investigated >50 epigenetic-related targets
- Arginine methyl transferase program bought by Takeda
- CellCentric now focused on acetyltransferases p300/CBP

p300 and CBP
- Gene expression co-activator proteins assoc. with cancer
- Blocking the twin proteins causes sustained tumour growth inhibition

CCS1477
- First-in-class specific, potent small molecule inhibitor
- Potential for targeted, large cancer patient groups
- New Drug on the Horizon at AACR, Chicago 2019

Now in patients
- Drug resistant late stage prostate cancer
- Relapsed/refractory haematological malignancies
- Patients with specific tumour drivers to follow

Strong, long term financial support
- CellCentric’s lead investor is Boston based Morningside
- Committed to the long term development of CCS1477
Additional slides
p300/CBP bromodomain inhibition and the key drivers of late stage, drug resistant prostate cancer

Western analysis of AR-FL, AR-SV and c-Myc in 22Rv1 cells after incubation for 24h and 72h

qPCR of analysis of AR, c-Myc and AR-target genes after 72h incubation in 22Rv1 cells

KLK3 encodes PSA, which along with TMPRSS2 are downstream genes of AR signalling

Supports the MoA hypothesis that AR reduction is at the protein level (proteosomal degradation). This is reversed with MG132, a proteosomal inhibitor. Whereas c-Myc impact is at the gene level.
CCS1477 preferentially inhibits AR driven prostate cancer cells

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>AR status</th>
<th>Model</th>
<th>CCS1477 (Proliferation IC50 mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNCaP</td>
<td>AR-FL</td>
<td>Hormone responsive</td>
<td>0.230</td>
</tr>
<tr>
<td>LNCaP-AR</td>
<td>AR-FL over-expressed</td>
<td>CRPC</td>
<td>0.150</td>
</tr>
<tr>
<td>VCaP</td>
<td>AR-FL</td>
<td>CRPC</td>
<td>0.049</td>
</tr>
<tr>
<td></td>
<td>AR-SV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22Rv1</td>
<td>AR-FL</td>
<td>CRPC</td>
<td>0.096</td>
</tr>
<tr>
<td></td>
<td>AR-SV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DU145</td>
<td>AR negative</td>
<td>Hormone independent</td>
<td>1.280</td>
</tr>
<tr>
<td>PC3</td>
<td>AR negative</td>
<td>Hormone independent</td>
<td>1.490</td>
</tr>
</tbody>
</table>
In vivo efficacy in 22Rv1 xenograft

continued tumour growth block following drug withdrawal

Inhibition of plasma PSA

Drug treatment period

No drug treatment
CCS1477 is not generally cytotoxic, specific tumour types are particularly susceptible to p300/CBP inhibition

- 7 day proliferation assay (CTG)
- 277 cell lines
Xenograft model of multiple myeloma (OPM-2)

Tumour regression, then continued inhibition following drug withdrawal

CCS1477 given by oral gavage once daily to OPM-2 bearing athymic nude mice

IRF4 as well as c-Myc significantly impacted

Tumour cMYC and IRF4 gene expression by qPCR at day 6 of treatment
Consistent with other settings, continued tumour growth inhibition following CCS1477 withdrawal

- MOLM-16 tumour bearing NOD / SCID mice were treated with CCS1477 by oral gavage, once daily (5/10/20mg/kg)
- Vehicle (5% DMSO:95% methylcellulose [0.5%w/v]) was dosed once daily
Pre-clinical findings consistent with primary mode of action

- 28d toxicity studies in rodent (rat) and non-rodent (dog)
- Rat 28 day study – dose proportional weight reduction in male androgen-dependent organs
- No cardiac effects in an *in vivo* dog telemetry study
- Dose-proportional reduction on platelets in rodents
  - Fully reversible
  - Impact reduced by less frequent dosing
  - No greater effect on re-dosing

Patient receiving 100mg daily, as an example

Platelet recovery with breaks in dosing
Maintaining *in vivo* efficacy

**DURATION OF EFFECT POST DOSING CESSION**

**INTERMITTENT DOSING**

**Prostate cancer (22Rv1)**

- Drug treatment period
- No drug treatment

**Multiple myeloma (OPM2)**

- Drug treatment period
- No drug treatment

**Acute myeloid leukaemia (MOLM16)**

- Drug treatment period
- No drug treatment

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**Prostate cancer (22Rv1)**

- Vehicle
- **30mg/kg every 4th day**
- **30mg/kg every other day**

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**Multiple myeloma (OPM2)**

- Vehicle
- **CSS477 10mg/kg po-QD**

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**Acute myeloid leukaemia (MOLM16)**

- Vehicle
- **CSS477 5mg/kg po-QD**
- **CSS477 10mg/kg po-QD**
- **CSS477 20mg/kg po-QD**
Differentiation from BET inhibitors

**CCS1477 affects less/different genes than JQ1 in 22Rv1 cells**

Numbers of genes influenced

- JQ1
- CCS1477

**CCS1477 retains activity in a JQ1/BETi resistant 22Rv1 cell-line**

Proliferation was measured with a cell viability assay (CellTiter Glo) after compound treatment for 72h. Red line = Parental; Grey line = Resistant

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## CCS1477: highly potent, highly selective

**Crystal structure of the des-methyl analogue of CCS1477 bound to the bromodomain of hEP300 at 1.5Å resolution**

<table>
<thead>
<tr>
<th></th>
<th>CCS1477</th>
<th>(R)enantiomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>p300/CBP Kd (nM)</td>
<td>1.3 / 1.7</td>
<td>263 / -</td>
</tr>
<tr>
<td>BRD4 Kd (nM)</td>
<td>222</td>
<td>921</td>
</tr>
<tr>
<td>BRD4 Selectivity / Others</td>
<td>170 / &gt;1,000</td>
<td>3</td>
</tr>
<tr>
<td>Kinome scan @10uM; 97 kinases</td>
<td>No sig. activity</td>
<td>-</td>
</tr>
<tr>
<td>Cerep Safety Screen 44 @10uM</td>
<td>No sig. activity</td>
<td>-</td>
</tr>
<tr>
<td>22Rv1 cell proliferation GI50 (nM)</td>
<td>96</td>
<td>1892</td>
</tr>
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</table>

- 4-stage API synthesis
- Capsule formulated
- Orally administered
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