ELSEVIER

Blood 142 (2023) 5795–5796

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Preclinical and Early Clinical Results Indicate a Role for the Oral p300/CBP Inhibitor Inobrodib (CCS1477) in T-Cell Lymphoma

Victoria Campbell, MD PhD[1], Harriet Walter[2], Adam Gibb[3], Andrew S. Davies, BSc (Hons) BM (Hons) PhDFRCP[4], Nagah Elmusharaf[5], Neil Pegg[6], Will Henry West, PhD MSc, MBA[6], Tomasz Knurowski, MD[6], Kris Frese, PhD[6], Debbie Haynes, BSc[6], Karen Clegg, PhD[6], Tim Somervaille[7,3]

[1] Department of Hematology, Western General Hospital, Edinburgh, United Kingdom
[2] University of Leicester and University Hospitals Leicester, Leicester, GBR
[3] The Christie NHS Foundation Trust, Manchester, United Kingdom
[4] University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
[5] University Hospital of Wales, Cardiff, GBR
[6] CellCentric Ltd, Cambridge, United Kingdom
[7] Cancer Research UK Manchester Institute, Manchester, United Kingdom

Inobrodib (CCS1477) is a potent, selective, and orally bioavailable inhibitor of the bromodomains of CBP and EP300, two homologous histone acetyltransferases with critical roles in cellular growth and differentiation. Lymphomas can harbor multiple putative predictive biomarkers for inobrodib, including deleterious mutations in CBP/EP300 that convey synthetic lethality and expression of the lineage transcription factors IRF4 and GATA3.

The preclinical efficacy of inobrodib was assessed in a range of solid cancer and hematological cancer cell lines. Select models, including multiple myeloma, acute myeloid leukaemia, and lymphoma cell lines were sensitive to submicromolar concentrations of inobrodib. These in vitro results were extended to xenograft models in which inobrodib demonstrated dose-dependent efficacy.

Based on these results, we initiated a clinical trial to test the safety and efficacy of inobrodib in advanced hematological malignancies (NCT04068597). Dose escalation was conducted in multiple myeloma patients and select B and T-cell lymphomas. The safety profile was similar to other hematological and solid tumour indications with readily manageable and reversible thrombocytopenia as the main toxicity. The recommended phase 2 dose was established at 35mg bidaily on a 4 days on/3 days off intermittent schedule.

Initial data in peripheral T cell lymphoma - not otherwise specified (PTCL-NOS) shows a potential benefit with objective responses in 3 of 4 patients as of data cut-off date (20 Jul 2023). These included a complete metabolic response in a patient (with previously refractory disease) continuing on treatment for over 1.5 yrs and 2 patients with minor responses. Translational investigations indicate that responders all express IRF4 and GATA3, but do not harbour CBP/EP300 mutations.

Together these data support the further development of inobrodib for the treatment of peripheral T cell lymphoma. Expansion continues with a focus on T-cell lymphomas, which may be driven by IRF4 and GATA3.

Disclosures Walter: *Pfizer, Gilead, Roche:* Research Funding; *Astrazeneca:* Other: Conference attendance. **Davies:** *BMS:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Cellcentric:* Research Funding; *Kite/Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sobi:* Consultancy; *AstraZeneca:* Consultancy, Honoraria, Research Funding; *Incyte:* Consultancy; *Abbvie:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel grant, Research Funding; *MSD:* Research Funding; *Genmab:* Consultancy, Honoraria. **Pegg:** *CellCentric Ltd:* Current Employment, Current equity holder in private company; *Phoremost:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **West:** *CellCentric Ltd:* Current Employment, Current equity holder in private company. **Knurowski:** *CellCentric Ltd:* Current Employment, Current equity holder in private company. **Frese:** *CellCentric Ltd:* Current Employment, Current equity holder in private company. **Haynes:** *CellCentric Ltd:* Current Employment, Current equity holder in private company. **Clegg:** *CellCentric Ltd:* Current Employment, Current equity holder in private company. **Somervaille:** *AbbVie:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Imago Biosciences:* Research Funding; *Glaxo Smith Kline:* Consultancy,

Membership on an entity's Board of Directors or advisory committees; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *CellCentric:* Research Funding; *Rain Oncology:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees.

https://doi.org/10.1182/blood-2023-187378