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Blood 142 (2023) 3093-3095

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

A First-in-Human Phase 1 Trial of NX-1607, a First-in-Class Oral CBL-B Inhibitor, in Patients with Advanced Malignancies Including DLBCL

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Introduction: Recurrent diffuse large B cell lymphoma (DLBCL) remains a high unmet medical need despite advances in treatment such as cell- and immune-mediated therapies. T cell dysfunction and emerging resistance to T cell-mediated therapies such as CAR-T and T cell engagers underscores the need for novel therapies that can enhance T cell function, counteract a suppressive tumor microenvironment (TME) and prevent tumor escape associated with low tumor antigen expression. Casitas B-lineage lymphoma proto-oncogene B (CBL-B) is an E3 ubiquitin ligase expressed in immune cells and is a master regulator of T, NK, and dendritic cell activation, collectively curtailing their anti-tumor functionality. Notably, it has been observed that, in the absence of CBL-B, T cell activation can occur even when antigen expression on tumor cells is low, suggesting a potential strategy for circumventing tumor resistance mechanisms [Stromnes et al. 2010]. NX-1607 is an oral, small molecule inhibitor of CBL-B that has been shown to enhance antigen recall, reduce T cell exhaustion and increase cytokine production upon T cell receptor stimulation, overcoming suppressive signals from the TME [Gosling et al. 2019; Rountree et al. 2021; Gallotta et al. 2022]. Moreover, preclinical studies in mouse lymphoma models have demonstrated that NX-1607 can induce robust, T cell-dependent tumor regression. By bolstering the effectiveness of inherent T- and NK-mediated anti-tumor responses and enhancing antigen recall, NX-1607 offers potential as a supportive and rejuvenating agent for CAR-T or NK cell therapies in patients with hematologic malignancies who have developed resistance.

Methods: NX-1607-101 is a first-in-human, multicenter, open-label, Phase 1a/1b dose-escalation/expansion trial evaluating safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and preliminary anti-tumor activity of NX-1607, an oral investigational new drug, in several advanced malignancies, including DLBCL (see Figure). Key eligibility criteria: adults with selected measurable metastatic/unresectable malignancies for which standard therapy with proven clinical benefit does not exist or is no longer effective or appropriate. Eligible tumor types - see Figure. Prior treatment with checkpoint inhibitors and CAR-T therapy is allowed with protocol-defined washout. In the ongoing Phase 1a portion (3+3 dose escalation), patients receive NX-1607 monotherapy at doses ranging from 5 up to 100 mg each day of a 21-day cycle. The primary objective of Phase 1a is to evaluate safety/tolerability and establish the maximum tolerated dose and recommended Phase 1b dose (RP1bD). In the Phase 1b portion (dose expansion), patients with select advanced malignancies, including DLBCL are being enrolled and

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receive NX-1607 monotherapy at the RP1bD determined during Phase 1a. The primary objective of Phase 1b is to evaluate the anti-tumor activity of NX-1607 at the RP1bD in expansion cohorts. Tumor response will be assessed based on RECIST v1.1, modified RECIST, or Revised Response Criteria for Malignant Lymphoma for DLBCL. All patients are evaluable for safety based on standard safety criteria. Up to 304 patients will be enrolled at approximately 20 sites in the UK and US and treated until disease progression or unacceptable toxicity. Dose escalation is ongoing. Clinical trial information: NCT05107674. Study contact: nx1607101@nurixtx.com

Disclosures Collins: Beigene: Consultancy, Honoraria, Research Funding, Speakers Bureau; Astra Zeneca: Consultancy, Honoraria, Research Funding; Pfizer: Research Funding; Amgen: Research Funding; BMS: Research Funding; Daiichi Sankyo: Consultancy, Honoraria; Takeda: Consultancy, Honoraria, Speakers Bureau; Gilead: Consultancy, Honoraria, Speakers Bureau; Roche: Consultancy, Honoraria, Speakers Bureau. Townsend: F. Hoffmann La Roche Ltd: Research Funding; F. Hoffmann La Roche Ltd, Gilead, Takeda: Other: Travel grants; ADC Therapeutics: Consultancy, Membership on an entity's Board of Directors or advisory committees; Kite Gilead: Consultancy; Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees; F. Hoffmann La Roche Ltd, Takeda, Gilead, BMS: Honoraria; F. Hoffmann-La Roche Ltd, BMS, Gilead, Takeda, ADC Therapeutics: Consultancy. Abdulgawad: Kite (a Gilead pharmaceuticals company): Honoraria. Nam**buri:** Janssen: Honoraria; Genentech: Honoraria; BMS: Honoraria. **Krebs:** Bayer: Consultancy; Guardant Health: Consultancy; Janssen: Consultancy, Honoraria, Other: Travel Expenses, Speakers Bureau; OM Pharma: Consultancy; Roche: Consultancy, Honoraria, Other: Travel Expenses, Research Funding, Speakers Bureau; Seattle Genetics: Consultancy; Novartis: Research Funding; AstraZeneca: Speakers Bureau; Immutep: Other: Travel expenses. Evans: Astra Zeneca, Ascelia, Eisai, Genentech, MSD, Roche, Seagen, Medivir, Bicycle Therapeutics: Consultancy; Astra Zeneca, Basilea, Bayer, Celgene, MiNa Therapeutics, Roche, Sierra, Lilly, Eisai, Glaxo Smith Kline, Novartis, Bicycle Therapeutics, Johnson & Johnson, CytomX, Adaptimmune Bristol-Myers Squibb, MSD, Medivir, Versatem, Nucana, Immnuocore, Berg, Beig: Research Funding; Astra Zeneca, Ascelia, Bayer, Bristol Myers Squibb, Eisai, Genentech, Nucana, MSD, Roche, Seagen, Medivir, Bicycle Therapeutics, Ewopharma: Honoraria; Astra Zeneca, Ascelia, Bayer, Bristol Myers Squibb, Eisai, Genentech, Nucana, MSD, Roche, Medivir, Ewopharma: Speakers Bureau; MSD, Nucana: Other: Support to attend international conferences. Blagden: Oxford Drug Design, Simbec-Orion, Ellipses, Theolytics, Pathios, Terra VC: Consultancy; RNA Guardian: Current equity holder in private company; Cancer Research UK: Honoraria; 2009: WO1999062548A9; 2015 WO2016075455A1: Patents & Royalties. Plummer: Pierre Faber, Bayer, Novartis, BMS, Cybrexa, Ellipses, CV6 Therapeutics, Immunocore, Genmab, Astex Therapeutics, Medivir, Sanofi Aventis: Honoraria, Other: Advisory board attendance; Alligator Biosciences, GSK, Onxeo and SOTIO Biotech AG, AstraZeneca: Honoraria, Other: IDMC member; AstraZeneca, Novartis, Bayer, MSD, BMS: Honoraria, Other: Delivery of educational talks and chairing educational meetings; MSD, BMS: Other: Travel support for congress attendance. Sharp: ICR: Current Employment; Astellas Pharma and Merck Sharp & Dohme.: Honoraria; Sanofi, Roche-Genentech and Nurix.: Other: Travel Expenses; DE Shaw Research and CHARM Therapeutics.: Consultancy. Cole: Nurix Therapeutics, Inc.: Current Employment, Current equity holder in publicly-traded company. Rogers: Nurix Therapeutics, Inc.: Current Employment, Current equity holder in publicly-traded company. Chan: Nurix Therapeutics, Inc.: Current Employment, Current equity holder in publicly-traded company. Whelan: Nurix Therapeutics, Inc.: Current Employment, Current equity holder in publicly-traded company. El-Sharkawi: Abbvie, ASTEX, AstraZeneca, BeiGene, Janssen, Kyowa Kiirin: Consultancy; Abbvie, AstraZeneca, BeiGene; Gilead, Janssen, Lily, Novartis, F. Hoffman-La Roche, Takeda: Honoraria; Royal Marsden NHS Foundation trust: Current Employment; Abbvie: Speakers Bureau.

OffLabel Disclosure: NX-1607 is an oral, small molecule inhibitor of CBL-B that has been shown to enhance antigen recall, reduce T cell exhaustion and increase cytokine production upon T cell receptor stimulation, overcoming suppressive signals from the tumor microenvironment.

https://doi.org/10.1182/blood-2023-172875

Figure. NX-1607-101 study design



Figure 1