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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Time Limited Exposure to a ROR1 Targeting Bispecific T Cell Engager (NVG-111) Leads to Durable Responses in Subjects with Relapsed Refractory Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL)

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Background: Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an oncofetal protein that is absent or expressed at low levels in normal adult tissues but overexpressed in a range of malignancies including CLL and MCL. NVG-111 is a humanized first in class, tandem scFv, ROR1xCD3 bispecific T cell engager. NVG-111 mediates potent killing of ROR1 $^{+}$ tumors by engaging a unique epitope on the Frizzled domain of ROR1 and redirecting T cell activity via the CD3 binder engineered for attenuated cytokine release.

Methods: In this phase 1, first-in-human, dose-escalation study (ClinicalTrials.gov identifier: NCT04763083), NVG-111 was evaluated in relapsed/refractory CLL and MCL subjects with an ECOG PS of 0-2 who received ≥2 prior lines of treatment including a Bruton tyrosine kinase inhibitor (BTKi). Bayesian continual reassessment method with overdose control was implemented to guide escalation over a dose range of 0.3-45ug/day. Each subject received at least one dose of NVG-111, administered as a continuous intravenous infusion (cIV) over 21 days followed by 7 days off drug (=1 cycle). NVG-111 was administered in combination (N=8) with ibrutinib to subjects who had achieved a partial response to >1 year of ibrutinib therapy, or as monotherapy in subjects that progressed after covalent BTKi/B-cell lymphoma 2 inhibitor (BCL2i) (N=4). Primary objective was safety, with the secondary objectives being efficacy (overall response rates [ORR], minimal residual disease (MRD) measured by ERIC-compliant flow cytometry and duration of response [DoR]). Serum cytokine levels were determined using a human high sensitivity cytokine premixed magnetic Luminex assay and T cell function was longitudinally evaluated using cytometry by time of flight (CyTOF) analysis.

Results: Between May 2021 and July 2023 12 subjects (10 males and 2 females, median age 60 years) completed a maximum of 6 cycles of treatment with NVG-111 (median=3 cycles [range 1-6 cycles]). Pharmacokinetic and pharmacodynamic data demonstrated systemic NVG-111 exposure and exposure-dependent NVG-111 targeting of ROR1 on circulating tumor cells. Adverse events (AEs) related to NVG-111 occurred in 10 subjects (83%), with the most common being nausea (58%), headaches (67%), and fatigue (33%), majority of which were grade 1 or 2. Grade 1(71%) or 2(29%) cytokine release syndrome (CRS) occurred in 58% of subjects during week 1 of cycle 1 except in one subject who had a second grade 1 CRS in cycle 2. Grade 3 dose limiting toxicities (DLTs) occurred in three subjects (25%) consisting of transient elevation of liver enzymes (ALT and AST) in one subject dosed at 3ug/day, immune effector cell-associated neurotoxicity syndrome-like symptoms (ICANS) in one subject dosed at 30ug/day and headache in one subject dosed at 45ug/day. All AEs were fully reversible with no late emergent grade 3 or greater toxicities. Evidence of T cell activation was observed in all 12 subjects with peak cytokine levels at the 30µg/day

dose levels (mean±SEM): TNFα, 43±17pg/ml; IL6, 566±541pg/ml; IFNɣ, 18±12pg/ml; and IL10, 103±56pg/ml. Furthermore, T cell profiling showed an increase in cytotoxic $CD8^+$ T cell activation marker expression during each NVG-111 treatment cycle without evidence of T cell exhaustion. Efficacy was evaluable in 11 subjects with objective clinical responses observed in 55% (6/11), including two subjects with clear evidence of single agent activity. Amongst these, three CLL subjects were rendered MRD negative in peripheral blood and one MCL subject achieved complete metabolic response by the Lugano criteria. Two subjects had stable disease but in one of these subjects there was a >50% reduction in peripheral blood lymphocytosis and a 40% reduction in lymphadenopathy. Despite time limited exposure to NVG-111, the restricted mean survival time for DoR is currently 13.6 months (SEM 3.07), the median is not yet calculable with response ongoing in four subjects. The median progression-free survival currently is 18.7 months (95% CI 2.6 - not calculable).

Conclusion: These data provide clinical proof of concept for selective targeting of ROR1 with a TCE leading to objective evidence of antitumor activity with encouraging response durability even in CLL patients known to have defective T cell function. The safety profile was consistent with the mechanism of action. Further evaluation of this promising molecule is ongoing.

Disclosures Townsend: *F. Hoffmann La Roche Ltd, Takeda, Gilead, BMS:* Honoraria; *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Kite Gilead:* Consultancy; *ADC Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann La Roche Ltd, Gilead, Takeda:* Other: Travel grants; *F. Hoffmann La Roche Ltd:* Research Funding; *F. Hoffmann-La Roche Ltd, BMS, Gilead, Takeda, ADC Therapeutics:* Consultancy. **Shah:** *NovalGen Ltd:* Current Employment, Current holder of *stock options* in a privately-held company. **Batten:** *Veramed:* Current Employment. **Tucker:** *Abbvie:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Immunovant:* Consultancy; *Amgen:* Honoraria; *Roche:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Takeda:* Honoraria. **Paneesha:** *Astra Zeneca:* Honoraria; *Gilead:* Honoraria; *Abbvie:* Honoraria; *Janssen:* Honoraria. **El-Sharkawi:** *Abbvie:* Speakers Bureau; *Abbvie, AstraZeneca, BeiGene; Gilead, Janssen, Lily, Novartis, F. Hoffman-La Roche, Takeda:* Honoraria; *Abbvie, ASTEX, AstraZeneca, BeiGene, Janssen, Kyowa Kiirin:* Consultancy; *Royal Marsden NHS Foundation trust:* Current Employment. **Eyre:** *Beigene:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *AbbVie:* Consultancy, Honoraria, Speakers Bureau; *Incyte:* Consultancy; *Loxo@Lilly:* Consultancy, Honoraria, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Speakers Bureau; *Autolus:* Consultancy; *Roche:* Consultancy, Honoraria, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *KITE Gilead:* Consultancy, Honoraria, Speakers Bureau. **Zheng:** *Astellas:* Honoraria. **Granger:** *NovalGen Ltd:* Current Employment, Current holder of *stock options* in a privately-held company; *Crescendo Biologics:* Current holder of *stock options* in a privately-held company; *Haleon:* Current equity holder in publicly-traded company; *GSK:* Current equity holder in publicly-traded company, Patents & Royalties. **O'Donovan:** *NovalGen Ltd:* Current Employment, Current holder of *stock options* in a privately-held company. **Nathwani:** *Genethon:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties, Research Funding; *MRC:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties, Research Funding; *LifeArc:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties, Research Funding; *BioMarin:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties, Research Funding; *Freeline:* Consultancy, Current equity holder in private company, Patents & Royalties; *NovalGen Ltd:* Current Employment, Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties, Research Funding. **Jasani:** *Abbvie:* Honoraria; *Astra Zeneca:* Honoraria.

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