First-in-Human Phase I Trial of a ROR1 Targeting Bispecific T Cell Engager (NVG-111) in Combination with Ibrutinib or As Monotherapy in Subjects with Relapsed Refractory Chronic Lymphocytic Leukaemia (CLL) and Mantle Cell Lymphoma (MCL)

William Townsend[1], Sarah Leong[2], David Tucker[3], Bryson Pottinger[4], Shankara Paneesha[5], Dima El-Sharkawi[6], Toby A. Eyre[7], Toby Batten[8], Mittal Shah[9], Sarah Cook[9], David Granger[9], Kieran O'Donovan[9], Amit C. Nathwani[9,10], and **Parag Jasani[11,12]**

[1]National Institute for Health Research Clinical Research Facility, University College London Hospitals NHS Foundation Trust and UCLH, London, United Kingdom; [2]NIHR Clinical Research Facility, University College London Hospitals, London, UK; [3]Royal Cornwall Hospital, Cornwall, UK; [4]Department of Haematology, Royal Cornwall Hospital, Truro, United Kingdom; [5]Birmingham Heartlands Hospital, Birmingham, UK; [6]The Royal Marsden NHS Foundation Trust, Surrey, UK; [7]Department of Haematology, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [8]Veramed, Twickenham, UK; [9]NovalGen Ltd, London, United Kingdom; [10]Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free NHS Foundation Trust, London, UK; [11]NIHR Clinical Research Facility, University College London Hospitals, London, UK; [12]Royal Free London NHS Foundation Trust, London, UK

#1810

INTRODUCTION

Receptor tyrosine kinase-like Orphan Receptor 1 (ROR1), an oncofetal protein, is highly expressed on hematological and solid tumors, with little or no expression on normal tissues[1,2].

NVG-111 is a first in class, humanized, tandem scFv ROR1xCD3 T cell engager antibody that exclusively binds to ROR1 frizzled domain (Figure 1).

NVG-111 mediates killing of ROR1+ tumors by (1) directly blocking the WNT5-ROR1 agonistic pathway and (2) facilitating synapse formation between tumor cells and T cells via a humanized CD3 binder[3].

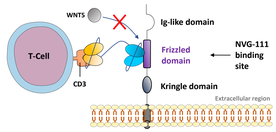


Figure 1. NVG111 One arm targets the TCR CD3 subunit, while the second binds to a tumor-associated ROR1

AIM

NVG111-101, is a multi-center, open-label, first-in-human, dose escalation Phase I/II clinical trial (ClinicalTrials.gov: NCT04763083), assessing safety and efficacy of NVG-111 in relapsed/refractory chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) subjects.

METHODS

Adaptive trial design with accelerated dose titration (ATD) in the first 3 single subject cohorts (cohort 1-3) exposed to escalated dose with each cycle of NVG-111 treatment over a range of 0.3-30µg/day. Dose escalation in subsequent multi-subject cohorts using a 3+3 design with Bayesian continual reassessment method. NVG-111 is administered as continuous intravenous infusion (cIV) in combination with ibrutinib to subjects who have achieved a stable, maximum partial response to >1 year of ibrutinib therapy (cohorts 1-4), or as monotherapy in patients who have progressed after BTKi/BCL2i treatment (cohort 4b).

Objective: (1) Assess safety and efficacy of NVG-111 either alone or in combination.
(2) Determine the Recommended Phase II Dose (RP2D).

Primary endpoints: safety (adverse events (AE), serious adverse events (SAEs), dose limiting toxicities (DLTs).

Secondary endpoints: anti-tumor activity by quantitative flow cytometry of ($CD19^+CD5^+$) CLL/MCL neoplastic cells, pharmacokinetics and biomarkers.

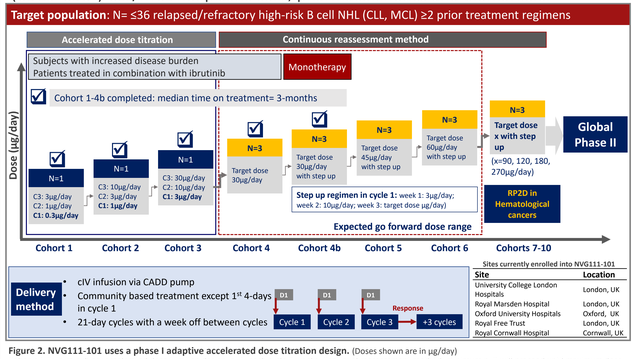


Figure 2. NVG111-101 uses a phase I adaptive accelerated dose titration design. (Doses shown are in µg/day)
Cohorts 1-3: Intra-subject accelerated dose titration design, n=1; each cycle 3 weeks. Continual reassessment method; minimum n=3 will proceed until maximum dose, with cohort 4 started at 30µg/day flat dosing and cohort 4b step up to 30µg/day. Subsequent cohorts 5-10 with step up dosing to the maximum tolerated dose or to optimal biological dose. Community based cIV treatment with 21-day cycles of NVG-111, 7-day break between cycles, but only 1st 4 days in cycle 1 requiring hospital stay.

RESULTS (clinical data cut-off date: July 31st, 2022)

NVG-111 safety profile consistent with MOA

Adverse events were limited to week 1 of cycle 1 and reversed within 1–4 days (N=9)

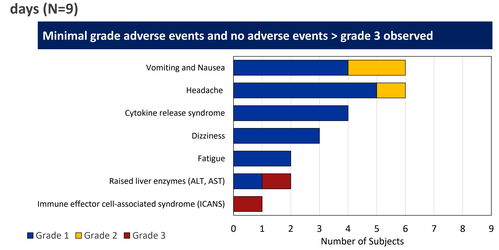


Figure 3. Summary of main treatment related adverse events in subjects (cohort 1-4b, N=9) treated with NVG-111.
ASTCT criteria are used for grading CRS and ICANs events and CTCAE v5.0 used for all other events. ASTCT = American Society for Transplantation and Cellular Therapy, CTCAE = Common Terminology Criteria for Adverse Events.

NVG-111 in combination with Ibrutinib shows clinical response in majority of patients

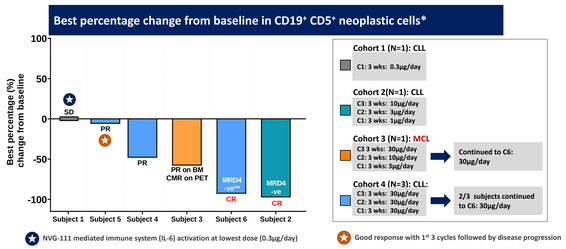


Figure 4. Summary of best percentage change from baseline in $CD19^+CD5^+$ neoplastic cells in subjects treated with NVG-111 in combination with Ibrutinib.
Neoplastic cell quantification was performed by flow cytometry and data are representative of percentage of $CD19^+$ $CD5^+$ out of total leukocytes. *** Complete response in peripheral blood, BM, bone marrow; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, CMR, Complete metabolic response; PET, positron emission .*

Evidence of activity with monotherapy

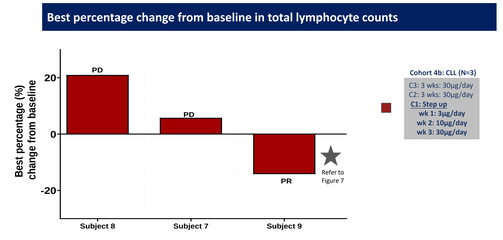
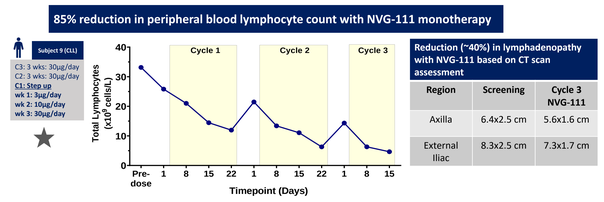


Figure 5. Summary of best percentage change of total lymphocytes from baseline in monotherapy cohort 4b.
Total lymphocyte enumerated from whole blood sample taken and quantification was performed by local diagnostic laboratory. Data shown are the best percent change in total lymphocytes from baseline. *PR, Partial response; PD, progressive disease.*

NVG-111 monotherapy induces a reduction in disease burden



Evidence of clinical response in all compartments assessed

Figure 6. Evidence of clinical response in subject 9 (CLL) treated with NVG-111 monotherapy.
Total lymphocytes enumerated from whole blood samples taken over specified time points over 3 cycles of NVG-111. Data is representative of total lymphocytes $x10^9$ cells/L. Table illustrates reduction in lymphadenopathy based on computed tomography (CT) scan assessment.

NVG-111 mediates clinically durable response

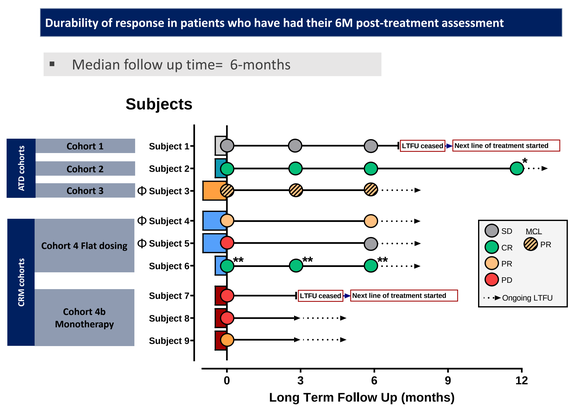
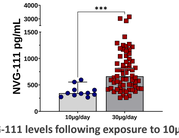


Figure 7. Summary of durability of response in subjects treated with NVG-111.
Durability of response in subjects with a minimum of 6-month post treatment assessment in cohort 1-4b and ongoing assessment in cohort 4b. *CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; *Complete response in bone marrow; ** Complete response (CR) in peripheral blood. ΦCompleted 6 cycles of NVG-111, all others have either ≤3 cycles or are currently in dosing phase of study; ## MRD analysis not validated for MCL, diagnostic is dependent on FDG-PET/CT; Dotted arrows indicate ongoing LTFU.*

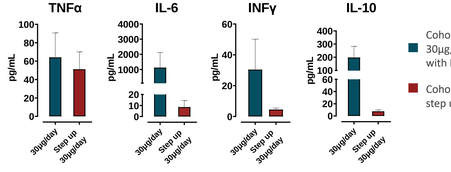
Circulating levels of NVG-111



- Greater levels of circulating NVG-111 with increased dose

Figure 8. PK analysis of NVG-111 levels following exposure to 10µg/day and 30µg/day dose.
NVG-111 determined using sensitive mesoscale discovery electrochemiluminescence assay (MSD-ECLA. Non-parametric Mann-Whitney U analysis was performed to compare the difference in serum levels of NVG-111 in subjects treated with 10 (n=3) or 30µg/day (n=6) NVG-111. Data representative of the median with 95% confidence interval of all detectable levels within respective doses; ***p<0.001.

Average peak cytokine levels following treatment with NVG-111



- Transient increase in cytokines detected with varying kinetics in cycle 1 in subjects treated with NVG-111 in combination with Ibrutinib.
- Reduced levels of all cytokines after step up to 30µg/day NVG-111

Figure 9. Average peak cytokine release following treatment with NVG-111.
Detectable levels of key cytokines; TNFα, IL-6, IFNγ and IL-10 were measured using a human high sensitivity premixed magnetic Luminex performance assay. Average peak cytokine levels in cohort 1-4 dosed at 30µg/day (dark teal bars; n=4) and step up to 30µg/day in monotherapy cohort 4b (dark red bars; n=3). Data are representative of the average peak cytokine levels ±SEM.

CONCLUSIONS

- Clear evidence of activity with NVG-111 in all subjects treated, including at low doses, as illustrated by a rise in cytokine levels.
- Evidence of clinical response in 5/6 subjects treated with NVG-111 in combination with Ibrutinib.
- NVG-111 shows activity when used as monotherapy in 1/3 subjects with bulky disease.
- CLL subjects with **low disease burden** are more likely to be rendered MRD negative.
- MCL subject achieved a CMR with deepening of response in bone marrow.
- Responses in relapsed refractory patients, appear durable for at least 6 months post completion of treatment for subjects who have a CR or PR at EoT.
- **Majority of AEs are Grade 1/2 and limited to cycles 1 and 2.**
- **All are fully reversible allowing continuation of therapy in a majority of patients**

ONGOING STUDIES

- Dose escalation of NVG-111 continues to determine recommended phase II dose as well as establishment of durability of response

REFERENCES

[1]Gohil *et al*; British Journal of Haematology, 2019
[2]Balakrishnan *et al*; Clin Cancer Res, 2017
[3]Gohil *et al*; Oncoimmunology ,2017

ACKNOWLEDGEMENTS

NCT04763083 trial is sponsored by NovalGen Ltd, UK who would like to thank the patients, clinical trials facility staff for their support with this study

CONTACT INFORMATION

Prof Amit Nathwani, CEO NovalGen Ltd, UK.
Email: a.nathwani@novalgen.co.uk