ELSEVIER

Blood 142 (2023) 4752–4755

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Initial Results from a Phase 1 Dose-Escalation Study of WVT078, a BCMA×CD3 Bispecific Antibody, in Combination with WHG626, a Gamma-Secretase (GS) Inhibitor, in Patients with Relapsed and/or Refractory Multiple Myeloma

Fredrik Schjesvold, MDPhD[1,2], Andrew Spencer, MBBS, MD FRACP, FRCPA[3], Yael C. Cohen[4,5], Enrique M Ocio, MD PhD[6], Jordi López-Pardo[7], Anna Maria Cafro, MD[8], Natalie S. Callander, MD[9], Jonathan L. Kaufman, MD[10], Meera Mohan, MD[11], Martin Wermke, MD[12], Noriko Doki, MD PhD[13], Rebecca Kan[14], Karolina Kulec[15], Gina Trabucco[14], Stan Ye[14], Romain Sechaud[16], Cornelia Quadt, MD[16], Raghav Chawla, MDPhD[16], Marc S. Raab[17]

[1] Oslo Myeloma Center, OSLO Univeristy Hospital, Oslo, Norway
[2] KG Jebsen Center for B Cell Malignancies„ University of Oslo, Oslo, Norway
[3] Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne, Australia
[4] Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[5] Department of Hematology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[6] Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain
[7] Hospital De La Santa Creu I Sant Pau, Barcelona, Spain
[8] Department of Hematology, GOM Niguarda Hospital, Milan, ITA
[9] University of Wisconsin Carbone Cancer Center, Madison, WI
[10] Winship Cancer Institute, Emory University, Atlanta, GA
[11] Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI
[12] Department of Internal Medicine I, University Hospital Dresden, Dresden, Germany
[13] Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan
[14] Novartis Institutes for Biomedical Research, Cambridge, MA
[15] Novartis Ireland Limited, Dublin, Ireland
[16] Novartis Institutes for BioMedical Research, Basel, Switzerland
[17] Heidelberg Myeloma Center, Department of Medicine V, Heidelberg University Hospital, Heidelberg, Germany

Introduction: WVT078, a potent anti-B-cell maturation antigen (BCMA)×anti-CD3 bispecific antibody (BsAb), is being investigated as a single-agent and in combination with a GS inhibitor (GSI), WHG626 (AL102), in patients (pts) with relapsed and/or refractory (r/r) multiple myeloma (MM). Single-agent WVT078 showed an acceptable safety profile in the ongoing first-in-human study with active dose range of 48-250 μg/kg (Raab, Leukemia 2023). Membrane BCMA expressed on surface of MM cells is cleaved by GS. This results in shedding of its extracellular domain (ECD) as soluble BCMA (sBCMA), which may bind to and interfere with activity of BCMA-targeting agents such as WVT078. By preventing this shedding, GSIs are postulated to increase clinical benefit of BCMA-targeting agents. WVT078 combined with WHG626 was shown to enhance anti-myeloma activity of WVT078 in vitro preclinically (Raab, Leukemia 2023), supporting rationale for this combination in r/r MM.
Methods: The combination of WVT078 and WHG626 is being investigated as part of above-mentioned phase 1 study (NCT04123418) in pts with MM who are r/r to ≥2 standard-of-care regimens, including an immunomodulatory drug, proteasome inhibitor, and anti-CD38 agent (if available). Pts who received prior BCMA chimeric antigen receptor T-cell therapy or BCMA antibody-drug conjugates therapy are included; pts with prior BCMA×CD3 BsAb treatment are excluded.
Primary objectives were to evaluate safety and tolerability and to determine recommended dose for expansion of WVT078 in combination with WHG626. Secondary objectives were to assess preliminary anti-tumor activity and characterize pharmacokinetics (PK) and immunogenicity. Key exploratory objectives included evaluation of sBCMA and characterization of immune-cell activation phenotypes. Dose escalation was guided by Bayesian Logistic Regression Model, and International Myeloma Working Group criteria were used to assess disease response. Flow cytometry was used to study pharmacodynamic (PD) effects on immunophenotype of immune cells. Immunoassay-based platform (Meso Scale Discovery) was used for assessing cytokine production and enzyme-linked immunosorbent assay for quantifying serum sBCMA levels.
Results: As of April 29, 2023, a total of 23 pts (median age, 64 years) with r/r MM were treated in dose escalation with intravenous WVT078 at 12-48 μg/kg once weekly, combined with oral WHG626 at 2-4 mg once daily, given 2 days on and 5 days

off. Eighteen pts (78.3%) discontinued treatment due to progressive disease (n=15), adverse event (AE), guardian decision and physician decision (n=1 each). Most frequent (≥20%) treatment-related AEs across all doses in the combination were cytokine release syndrome (65.2%; Grade ≥3, n=1), pyrexia (39.1%), diarrhea (34.8%), decreased appetite (26.1%), hypophosphatemia, nausea and neutropenia (21.7% each); 5 pts experienced dose-limiting toxicities (pneumonia, neutropenia, ALT/AST/lipase increase, platelet count decrease, sepsis and shoulder pain). The safety profile is consistent with WVT078 and WHG626 as single agents. A maximum tolerated dose was not reached.

The overall response rate (partial response or better; ORR) and overall complete response (CR) rate (stringent CR+CR) across all dose levels tested were 39.1% (n=9; 90% CI, 22.2, 58.3) and 13.0% (n=3; 90% CI, 3.7, 30.4), respectively; ORR at two highest dose levels combined was 57.1% (n=8/14; 90% CI, 32.5, 79.4). PK total (AUC) and maximal (Cmax) exposure to WVT078 in serum increased approximately proportionally to dose in Cycle 1. Evidence of T-cell engagement with WVT078 was demonstrated by upregulated peripheral T-cell proliferation and activation markers. WHG626 decreased serum sBCMA levels by 10% within first 24 hours of treatment prior to WVT078 dosing. WHG626 enhanced WVT078-mediated increases in serum inflammatory cytokine levels, and upregulated T-cell activation phenotype in bone marrow in a dose-dependent manner.Based on preliminary data, cytokine and clinical effects were observed at lower WVT078 doses with WVT078+WHG626 than with WVT078 alone.

Conclusions: WVT078 combined with WHG626 has an acceptable safety profile and shows preliminary evidence of clinical activity at highest doses tested. PD biomarker analysis supports postulated mechanism of action of WHG626 combined with WVT078. This is the first clinical report on combination of BCMAxCD3 BsAb and GSI in r/r MM.

Disclosures Schjesvold: *Amgen:* Other: Honoraria for lectures and educational material; *Novartis:* Other: Honoraria for lectures and educational material; *Pfizer:* Other: Honoraria for lectures and educational material; *Bristol Myers Squibb:* Consultancy, Other: Honoraria for lectures and educational material; *Targovax:* Research Funding; *Sanofi:* Consultancy, Other: Honoraria for lectures and educational material, Research Funding; *Oncopeptides:* Consultancy, Other: Honoraria for lectures and educational material, Research Funding; *Janssen-Cilag:* Consultancy, Other: Honoraria for lectures and educational material, Research Funding; *Takeda:* Consultancy, Other: Honoraria for lectures and educational material; *Celgene:* Consultancy, Other: Honoraria for lectures and educational material, Research Funding; *GlaxoSmithKline:* Consultancy, Honoraria, Research Funding; *Abbvie:* Consultancy, Other: Honoraria for lectures and educational material; *Skylite DX:* Other: Honoraria for lectures and educational material; *Daiichi Sankyo:* Other: Honoraria for lectures and educational material; *Schain:* Other: Honoraria for lectures and educational material. **Spencer:** *Roche:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Amgen:* Consultancy, Honoraria; *IDP Pharma:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Sanofi:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Antengene:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Haemalogix:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau. **Cohen:** *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Sanofi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *GSK:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Ocio:** *BMS:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Abbvie:* Consultancy; *GSK:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Speakers Bureau; *Karyopharm:* Consultancy; *Menarini:* Consultancy; *Oncopeptides:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy, Honoraria; *Regeneron:* Honoraria; *Sanofi:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria. **Kaufman:** *BMS:* Consultancy; *Sanofi:* Consultancy; *Abbvie:* Consultancy; *Incyte:* Consultancy. **Mohan:** *MJH life sciences:* Honoraria; *Institutional KL2 Award:* Other: Research Grant; *MashupMD:* Honoraria; *GlaxoSmithKline plc:* Research Funding; *Takeda Pharmaceutical Company:* Research Funding; *Ionis Pharmaceuticals:* Research Funding; *Bristol-Myers Squibb Company:* Research Funding; *Celgene Corporation:* Research Funding; *Novartis:* Research Funding; *Amgen Inc:* Research Funding; *Blood Cancer Today:* Honoraria; *Sanofi S.A:* Consultancy, Research Funding. **Wermke:** *ISA Pharmaceuticals:* Consultancy; *Bristol-Myers Squibb:* Consultancy, Other: Travel, accommodations, expenses; *Immatics:* Consultancy; *Boehringer Ingelheim:* Consultancy; *Amgen:* Consultancy, Other: Travel, accommodations, expenses; *MSD:* Consultancy; *AstraZeneca:* Consultancy, Other: Travel, accommodations, expenses; *GeMoab:* Consultancy, Other: Travel, accommodations, expenses; *Pfizer:* Consultancy, Honoraria, Other: Travel, accommodations, expenses; *Novartis:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria, Other: Travel, accommodations, expenses, Research Funding; *Lilly:* Consultancy, Honoraria; *Cellex GmbH:* Consultancy. **Doki:** *Janssen Pharmaceutical K.K.:* Honoraria; *Novartis Pharma K.K.:* Honoraria. **Kan:** *Novartis:* Current Employment. **Kulec:** *Novartis:* Current Employment. **Trabucco:** *Novartis:* Current Employment. **Ye:** *Novartis:* Current Employment. **Sechaud:** *Novartis:* Current Employment. **Quadt:** *Novartis:* Current Employment. **Chawla:** *Novartis Pharma AG:* Current Employment. **Raab:** *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *GSK:* Consultancy, Honoraria, Member-

ship on an entity's Board of Directors or advisory committees; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Heidelberg Pharma:* Research Funding; *AbbVie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Heidelberg University Hospital:* Current Employment.

Figure. Clinical activity of WVT078 in combination with WHG626

Figure 1. Summary of confirmed best overall response by dose level and across all dose levels

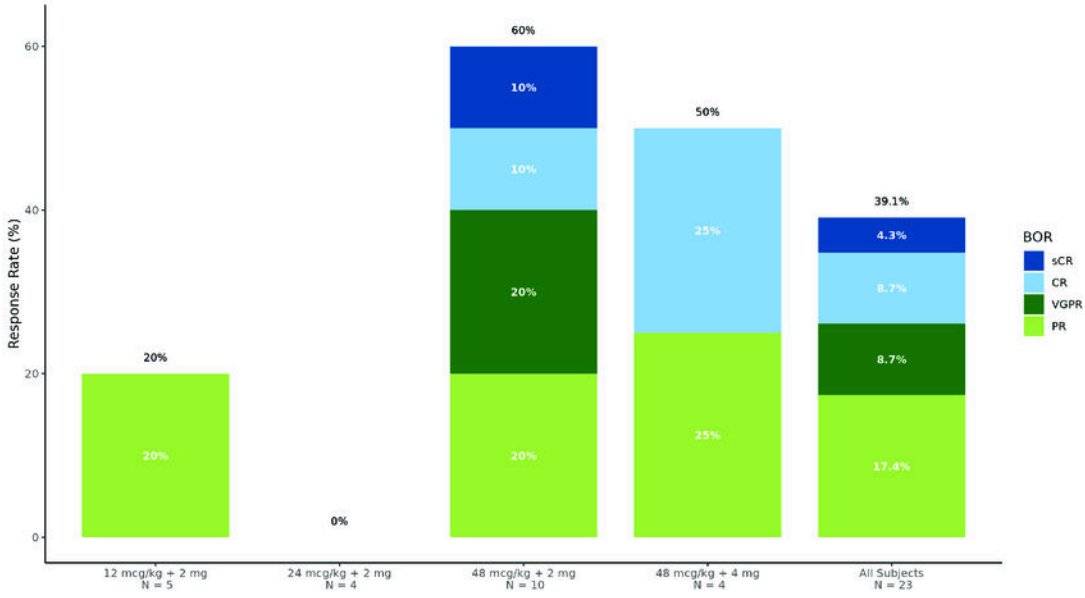
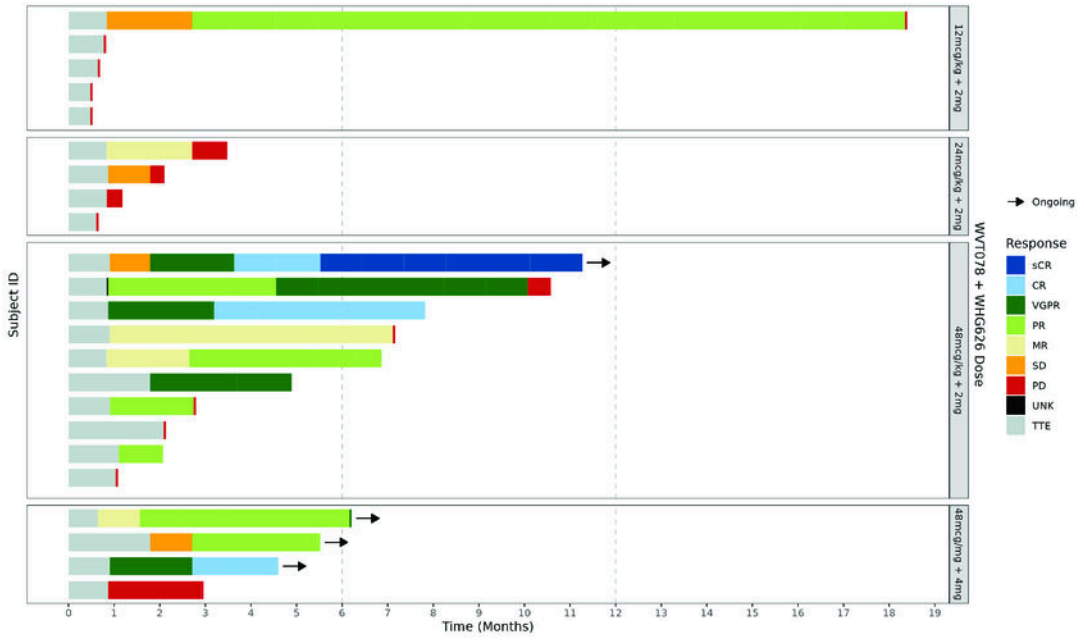


Figure 2. Swimmer plot illustrating individual patient responses over time by dose level of WVT078 in combination with WHG626



BOR, best overall response; CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; TTE, time to evaluation; UNK, unknown; VGPR, very good partial response.

Figure 1

https://doi.org/10.1182/blood-2023-177908