Check for updates

ELSEVIER

Blood 142 (2023) 2019–2021

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Isatuximab Rescue for Inadequate Response to Lenalidomide and Dexamethasone in Transplant Ineligible Patients with Newly Diagnosed Multiple Myeloma: Primary Analysis of the Phase II Iril Study of the Australian Myeloma Research Consortium (AMaRC 18-02)

Slavisa Ninkovic, MBBS[1,2], *Costas K. Yannakou, MBBS (Hons), FRACP, FRCPA, PhD*[3], *Nicholas Murphy*[4], *Rosemary Anne Harrup*[5,6], *Craig Wallington-Gates*[7], *Magdalena Sobieraj-Teague*[7], *M Hasib Sidiqi, MBBS, FRACP, FRCPA*[8,9], *Anish Puliyayil*[10], *Wojt Janowski*[11], *John Reynolds, BSc, MSc, PhD*[12,13], *Andrew Spencer, MBBS, MD FRACP, FRCPA*[14,13], *Hang Quach, MDFRACP,FRCPA,MBBS*[15,16]

[1] Faculty of Medicine, University of Melbourne, Melbourne, Australia
[2] Haematology, St Vincent's Hospital Melbourne, Fitzroy, Australia
[3] Epworth HealthCare, Melbourne, Australia
[4] Haematology, Royal Hobart Hospital, Hobart, Australia
[5] Royal Hobart Hospital, University of Tasmania, Tasmania, Australia
[6] Royal Hobart Hospital, Tasmania, Australia
[7] Flinders Medical Centre, Bedford Park, Australia
[8] Department of Haematology, Fiona Stanley Hospital, Perth, Western Australia, Australia, Murdoch, AUS
[9] Curtin Medical School, Curtin University, Western Australia, Bentley, Australia
[10] Border Medical Oncology and Haematology, East Albury, AUS
[11] Calvary Mater Health, Newcastle, Australia
[12] Australian Centre for Blood Diseases, Monash University, Melbourne, Australia
[13] Department of Malignant Haematology & Stem Cell Transplantation, The Alfred Hospital, Melbourne, Australia
[14] Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne, Australia
[15] University of Melbourne, St. Vincent's Hospital Melbourne, Melbourne, VIC, Australia
[16] St. Vincent's Hospital Melbourne, East Melbourne, Australia

Background:
A significant proportion of transplant ineligible, treatment-naïve multiple myeloma (NDMM, TNE) patients (pts) do not proceed to second line anti-MM therapy. Given depth of response to initial therapy correlates with overall survival (OS), a deep remission should be the target for this often elderly and frail cohort of pts. Additionally, current risk-stratification models utilizing predictive biomarkers, cytogenetics, FISH, and molecular profile cannot reliably identify patients with functional high-risk MM who respond sub optimally [i.e., < partial response (PR)]to standard first line therapy. IRIL is a phase II, multicentre, response-adapted study examining treatment rescue/intensification with isatuximab (Isa), an anti-CD38 monoclonal antibody, for functional high-risk pts, defined as those not achieving pre-defined target responses to lenalidomide and dexamethasone (Rd).

Method:
TNE NDMM pts meeting IMWG criteria for treatment were eligible for enrolment. Pts commenced treatment with lenalidomide [R; 25mg D1-D21 of a 28-day cycle (c)] and dexamethasone [d; 40mg (20mg for those aged ³75 years) PO weekly]. Isa (10mg/kg IV weekly for c1, then fortnightly) was added for failure to achieve pre-defined target responses [³PR after 4c, ³VGPR after 6c, or ³CR after 9c of Rd] or progressive disease (PD) within the first 9c Rd and was continued until PD or consent withdrawal. The primary endpoint was the achievement of PR or better after an additional 6c of Isa-Rd in pts who progressed during the first 4c of Rd or did not achieve a PR after 4c of Rd (i.e., the functional high-risk subgroup). A dual-criteria, Bayesian Proof-of-Concept (PoC) design was implemented requiring an observed rate of PR (or better) after 6c Isa-Rd of ≥ 50% with a posterior probability that the true rate exceeds 37.7% of >95%. The protocol allowed the trial management committee (TMC) to halt accrual at the first demonstration of PoC. The secondary endpoints were achievement of VGPR or CR after an additional 6c Isa-Rd in pts failing to meet these milestones after 6 or 9c Rd, progression free survival (PFS), OS and safety. This is a report of a per-protocol specified interim analysis of the primary endpoint.

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/2019/2188149/blood-8622-main.pdf by guest on 18 May 2024

© 2023 by The American Society of Hematology

Results:
From June 2019 until April 2023, 68 pts [52% male, median age 78.2 years (range 65.5-91.9), R-ISS Stage I (n=11), Stage II (n=37), Stage III (n=10)] were enrolled (67 commenced treatment with Rd). At the first interim analysis, both Bayesian PoC criteria were met with the observed PR rate after up to 6 additional cycles of Isa-Rd of 73.3% with a posterior probability that the true rate exceeded 37.7%, greater than 95% (Table 1). Given PoC was demonstrated and the SARS-CoV-2 pandemic-related slower than expected accrual, the TMC terminated study recruitment. At the most recent sweep in June 2023 (Figure 1), 14/15 rescued pts have achieved a PR or better (9/15 VGPR or CR), 4 deaths have been reported (1 each of disease-related, cardiac event, trauma, cause unknown) while 8/15 pts remain on treatment. With an estimated median potential follow-up of 28 months, a preliminary estimate of PFS at 24-months is 73.3% (median PFS not reached). The safety profile for the combination Isa-Rd is similar to previously reported. 14/15 pts had any grade (Gr) adverse event (AE) reported, while 73% pts had at least 1 ³ Gr 3 AE (10 pts with Gr 3, 1 pt with Gr 4). The most common ³ Gr 3 AE were neutropenia (40%), fever (13.3%), back pain (13.3%) and mood disturbance (13.3%).

Conclusion:
A response-adapted approach to treatment of TNE NDMM pts with Isa rescue upon disease progression or failure to meet a target response to Rd is safe and effective. Isa rescue improves depth of response after 6 additional cycles of therapy in 73% of functionally high-risk patients. The study was closed to recruitment early due to demonstration of PoC of a response-adapted treatment strategy. There were no new safety signals observed from the Isa-Rd combination. Reports on secondary endpoints will be presented, 12 months following the last Isa rescued patient's 6 th cycle of IsaRd.

This study is supported by BMS/Celgene (funding), Sanofi/Genzyme (provision of Isatuximab), The Victorian Cancer Agency (funding) and the Victorian Epigenetics Group (funding).

Disclosures Harrup: *F. Hoffmann-La Roche Ltd, Beigene:* Research Funding; *F. Hoffmann-La Roche Ltd, Takeda:* Current equity holder in publicly-traded company; *FibroGen:* Research Funding. **Sidiqi:** *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Gilead:* Speakers Bureau; *BMS:* Speakers Bureau; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Antengene:* Speakers Bureau. **Reynolds:** *Abbvie:* Current equity holder in publicly-traded company, Research Funding; *HemaLogix:* Consultancy; *Novartis AG:* Current equity holder in publicly-traded company; *Novartis Australia:* Honoraria; *Alcon AG:* Current equity holder in publicly-traded company. **Spencer:** *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, 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; *Antengene:* 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; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *IDP Pharma:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Roche:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Consultancy, Honoraria. **Quach:** *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: receipt of study materials; Leadership or fiduciary role, Research Funding; *Karyopharm:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: receipt of study materials, Research Funding; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Leadership or fiduciary role; *Sanofi:* Consultancy, Other: receipt of study materials.

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/2019/2188149/blood-8622-main.pdf by guest on 18 May 2024

Table 1: Primary endpoint analysis – achievement of ≥PR following completion of an additional 6c Isa-Rd in patient failing to achieve a PR or progressing during the first 4c of Rd.

PR Rate (Simple Estimate)	11/15 (73.33%)
Median of Posterior Distribution for PR Rate	70.90%
95% Credible Interval for PR Rate	46.86%, 88.76%
Probability that the PR Rate exceeds 50.0%	0.956
Probability that the PR Rate exceeds 37.7%	0.997
1st PoC Criterion Met	Yes
2nd PoC Criterion Met	Yes

Figure 1: Disposition of patients included in the interim analysis of the primary endpoint (June 2023)

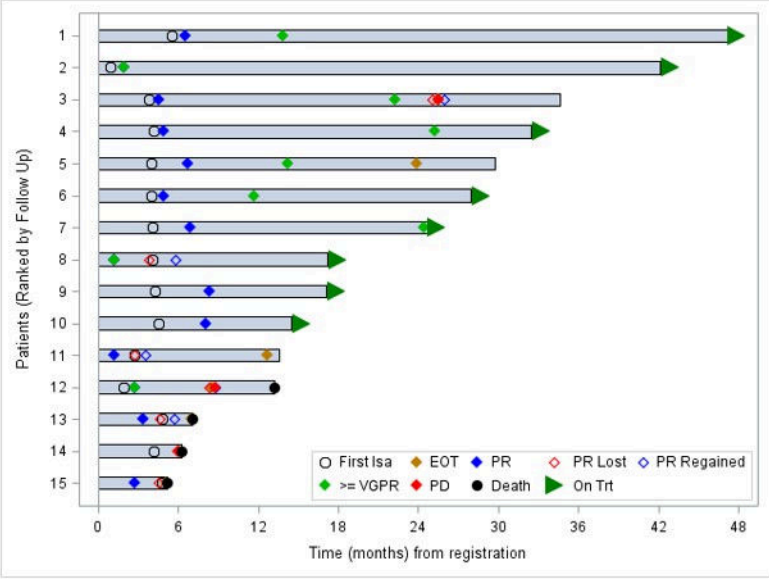

Figure 1

https://doi.org/10.1182/blood-2023-185944

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/2019/2188149/blood-8622-main.pdf by guest on 18 May 2024