



## The 65th ASH Annual Meeting Abstracts

## ORAL ABSTRACTS

**623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL****A Window Study of Acalabrutinib & Rituximab, Followed By Chemotherapy & Autograft (ASCT) in Fit Patients with Treatment Naïve Mantle Cell Lymphoma (MCL): First Report of the Investigator-Initiated Australasian Leukaemia & Lymphoma Group NHL33 'Wamm' Trial**

Eliza A Hawkes, MD<sup>1</sup>, Sze Ting Lee, MBBS, FRACP, FAANMS, PhD<sup>2</sup>, Leonid Churilov, PhD<sup>3</sup>, Tasman Armytage, MBBS<sup>4</sup>, Georgina Hodges, FRACP, MBBS, FRCPA<sup>5</sup>, Chan Yoon Cheah, MBBS<sup>6</sup>, Joel Wight<sup>7</sup>, Nicole Wong Doo, MBBS, MDFRACP, FRCPA<sup>8</sup>, Matthew Ku, MBBS, PhD<sup>9</sup>, Stephen S. Opat, MBBS, FRACP, FRCPA<sup>10</sup>, Tara Cochrane, MBBS, FRCPA, FRACP<sup>11</sup>, Greg Hapgood, MD, PhD<sup>12</sup>, Hui-Peng Lee, MD<sup>13</sup>, Rishu Agarwal<sup>14</sup>, Wendi Lin<sup>15</sup>, Minu Koshy<sup>16</sup>, Mannu Walia, PhD<sup>17</sup>, Liudmyla Olenko<sup>18</sup>, Paul Sung-Hao Yeh, MBBS, PhD<sup>19</sup>, Bianca Devitt, MBBS, FRACP, PhD<sup>20</sup>, Allison A Barraclough, BSc, FRACP, FRCPA, MBBS<sup>21</sup>

<sup>1</sup> Dept of Haematology & Medical Oncology and Olivia Newton John Cancer Research Institute, Austin Health, Melbourne, Australia

<sup>2</sup> Dept Molecular Imaging and Therapeutics, Austin Health, Heidelberg, Australia

<sup>3</sup> University of Melbourne, Parkville, AUS

<sup>4</sup> Gosford Hospital, Gosford, Australia

<sup>5</sup> Clinical Haematology, Barwon Health, Geelong, Australia

<sup>6</sup> The University of Western Australia, Perth, Australia

<sup>7</sup> Dept Haematology, Townsville Hospital, Townsville, AUS

<sup>8</sup> Department of Haematology, Concord Hospital, University of Sydney, New South Wales, Australia, Concord, AUS

<sup>9</sup> St Vincent's Hospital, Melbourne, AUS

<sup>10</sup> School of Clinical Sciences, Monash University, Melbourne, Australia

<sup>11</sup> Department of Haematology, Gold Coast University Hospital, Southport, Australia

<sup>12</sup> Princess Alexandra Hospital, Brisbane, AUS

<sup>13</sup> Flinders Hospital, Adelaide, Australia

<sup>14</sup> Pathology, Austin Health, MOUNT WAVERLEY, AUS

<sup>15</sup> Dept Pathology, Austin Health, Heidelberg, AUS

<sup>16</sup> Dept Pathology, Austin Health, Heidelberg, Australia

<sup>17</sup> Australasian Leukaemia and Lymphoma Group, Melbourne, Australia

<sup>18</sup> University of Melbourne, Parkville, Australia

<sup>19</sup> Monash Health/Monash University, Clayton, AUS

<sup>20</sup> Medical Oncology, Eastern Health Clinical School, Box Hill, Australia

<sup>21</sup> Haematology Department Fiona Stanley Hospital Murdoch, wa, Australia

**Introduction**

Bruton's tyrosine kinase inhibitors (BTKi) have improved 1<sup>st</sup> line therapy efficacy in elderly (Wang NEJM 2022) and young, fit, MCL-the latter with intermittent dosing during RCHOP in an alternating RCHOP/cytarabine-based regimen (Dreyling Blood 2022). However direct combination of BTKi & intensive chemo is toxic in DLBCL studies. (Kuruvilla Haematol Oncol 2017). The highly selective BTKi, acalabrutinib (A), has proven efficacy and tolerability in relapsed MCL (Wang Lancet 2018). RDHAOx chemotherapy (rituximab, dexamethasone, cytarabine, oxaliplatin) prior to ASCT provides a complete response (CR) rate of 77% and favourable toxicity compared to many induction regimens (Le Gouill Blood 2017). Furthermore, Obinutuzumab-DHAP yields undetectable minimum residual disease (MRD) in 85% of young MCL patients. (Le Gouill Haematol Oncol 2019). Here we report the primary endpoint from the Australasian Leukaemia & Lymphoma Group phase 2 'WAMM' trial exploring a 'sandwich' model of an acalabrutinib-rituximab (AR) 'window' before RDHAOx +/- ASCT, followed by fixed-duration AR-maintenance to improve therapy response and minimise additional toxicity.

**Methods**

NHL33'WAMM' (ACTRN12619000990123) is a multicentre single-arm phase 2 trial. Key eligibility included: age 18-70 years, untreated histologically-proven stage II-IV MCL, ECOG <2; no contraindications to ASCT or BTKi. Pts received 2 cycles of AR (AR window); 'A' dose; 100mg BD PO, 'R' dose; 375mg/m<sup>2</sup> IV (day 1) every 4 weeks, followed by RDHAOx x4 cycles. Those with an objective response (CR or partial response-PR) underwent BEAM ASCT (carmustine, etoposide, cytarabine, melphalan) then AR maintenance (A; 1yr continuous & R; 3-monthly x 8 cycles). Those who did not undergo BEAM ASCT were able to remain on study and proceed to maintenance AR in the event of ongoing response. Co-primary endpoints (EP) were safety; defined by lack of prohibitive toxicity causing treatment cessation AND PET-determined complete response (CR) rate after AR+RDHAOx. Secondary EP include overall response rates (ORR), toxicity, overall survival (OS) & progression-free survival (PFS), MRD negativity rates and quality of life. Only Grade 3+ toxicity related to acalabrutinib was collected during the ASCT period. Baseline whole exome sequencing was performed to identify mutations, MRD analysis was done by LymphoTrack® Dx and MRD Assay platform (Invivoscribe, Inc) using Illumina® MiSeq. This study was the first Australian blood cancer trial to use telehealth and a 'hub-and-spoke' transplant model.

### Results

44 pts were enrolled from Sept 2020 to Apr 2022 (43 evaluable for the primary endpoint). Baseline characteristics were typical of a young MCL cohort: median age 59 years (Interquartile range 54-64), 77% were male, ECOG was 0-1 in 98%, 84% had stage IV, lactate dehydrogenase was elevated in 35%, Ki-67 >30% in 66% and blastoid/pleomorphic histology 9%. TP53 by NGS will be reported at presentation.

CR rate post AR+RDHAOx induction was 88%; (95%CI 72-95) with ORR 95% and no prohibitive toxicity. AR window ORR was 93% (CR 57%). MRD negativity was achieved in 18% (7/38) post AR window, and 94% (34/36) post RDHAOx. 43 patients remained evaluable for response after R-DHAOX and pre-maintenance with 35 (80%) who underwent ASCT and 38 (86%) who commenced AR maintenance; 7 remain on maintenance. Response in specific subgroups will be reported at the meeting. At data lock, 35 pts (81%) experienced ≥1 G3+ adverse events during induction or maintenance phases, most common were neutropenia (58% of pts), febrile neutropenia (27%), thrombocytopenia (25%), diarrhea (14%). No G5 treatment-related events have occurred to date. There have been 22 SAEs, most common were COVID (3), febrile neutropenia (2) and fever (2). 5 deaths have been reported: 4 in pts with progressive disease and 1 COVID pneumonitis during AR maintenance. After a median follow up of 22 months (range 17-28m), the 2-year OS was 89%.

Analysis of survival, quality of life and biomarkers will be reported with more mature follow up.

### Conclusion

AR delivered in a sandwich approach is active and safe. An AR window yields a high ORR and compared to historical studies, improves post-chemo induction CR rates and MRD negativity. A telehealth model allowed rapid recruitment in a rare cancer.

**Disclosures Hawkes:** Gilead: Membership on an entity's Board of Directors or advisory committees; Astra Zeneca: Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses, Research Funding, Speakers Bureau; Janssen: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Novartis: Membership on an entity's Board of Directors or advisory committees, Other; Regeneron: Speakers Bureau; Antengene: Membership on an entity's Board of Directors or advisory committees; Specialised Therapeutics: Honoraria, Membership on an entity's Board of Directors or advisory committees; Beigene: Other; Merck Sharpe & Dohme: Membership on an entity's Board of Directors or advisory committees; Roche: Membership on an entity's Board of Directors or advisory committees, Research Funding; Merck KgA: Research Funding; Bristol-Myers Squibb: Membership on an entity's Board of Directors or advisory committees, Research Funding. **Cheah:** F. Hoffmann-La Roche Ltd, Janssen, Gilead, AstraZeneca, Lilly, TG therapeutics, Beigene, Novartis, Menarini, Daizai, Abbvie, Genmab. **BMS:** Consultancy; F. Hoffmann-La Roche Ltd, Janssen, Gilead, AstraZeneca, Lilly, TG therapeutics, Beigene, Novartis, Menarini, Daizai, Abbvie, Genmab. **BMS:** Honoraria; BMS, F. Hoffmann-La Roche Ltd, Abbvie; **MSD, Lilly:** Research Funding. **Wight:** Otsuka: Consultancy, Honoraria; Merck Sharpe Dohme: Consultancy, Honoraria; Janssen: Consultancy, Honoraria, Other: travel expenses; Abbvie: Consultancy, Honoraria; **MDI:** Consultancy, Honoraria; **Beigene:** Consultancy, Honoraria. **Ku:** Roche: Consultancy, Membership on an entity's Board of Directors or advisory committees. **Opat:** Gilead: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; **Beigene:** Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; **Astra Zeneca:** Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; **Pharmacyclics:** Honoraria, Research Funding; **Merck Sharpe & Dohme:** Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; **Novartis:** Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; **Abbvie:** Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; **CSL Behring:** Membership on an entity's Board of Directors or advisory committees; **Antengene:** Membership on an entity's Board of Directors or advisory committees; **Janssen Cilag:** Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; **Roche:** Honoraria, Research Funding; **Takeda:** Membership on an entity's Board of Directors or advisory committees. **Cochrane:** Janssen-Cilag: Speakers Bureau; **Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:** Research Funding; **Beigene:** Research Funding. **Lee:** Takeda: Honoraria; **Beigene:** Honoraria; **Gilead:** Other: Travel expenses. **Yeh:** Astellas: Speakers Bureau. **Barracough:** Roche: Honoraria; **Gilead:** Consultancy, Honoraria.

**OffLabel Disclosure:** Acalabrutinib for mantle cell lymphoma

**Table 1: Response to induction AR + RDHA0x according to PET/CT and MRD status**

	AR window N=44 n(%)	Post AR plus RDHA0x N=43 n(%)	Pre maintenance N= 43 n(%)
<b>ORR (by PET)</b>	40 (93%)	41 (95%)	40 (93%)
<b>Complete response</b>	25 (57%)	38 (88%)	40 (93%)
<b>Partial response</b>	15 (34%)	3 (7%)	0
<b>Stable disease</b>	2 (5%)	0	0
<b>Progressive disease</b>	2 (5%)	2 (5%)	3 (7%)
<b>Not evaluable</b>	0	1 (withdrew consent)	1 (withdrew consent)
<b>MRD testing</b>	N=38	N=36	
<b>MRD detected</b>	31 (82%)	2 (6%)	
<b>MRD not detected</b>	7 (18%)	34 (94%)	
<b>No suitable clonal marker identified for MRD monitoring</b>	4	4 (XX%)	
<b>MRD sample not available (off trial or missed)</b>	2	4	

Figure 1

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