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POSTER ABSTRACTS

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Obinutuzumab, Lenalidomide and Venetoclax in Patients with Treatment-Naïve Advanced-Stage Follicular Lymphoma: First Results of the Investigator-Initiated Phase Ib/II, Multicenter Leverage Study

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Background
Follicular lymphoma (FL) is the most common indolent lymphoma. The most widely used initial treatment is chemo-immunotherapy, however conventional cytotoxic agents may result in acute and late toxicities which can be problematic. There is a need for active novel treatment approaches with more favorable safety profiles.

Methods
We designed a phase Ib/II study of obinutuzumab, lenalidomide and venetoclax in patients with treatment-naïve follicular lymphoma. Key inclusion criteria included non-contiguous or bulky stage II-IV disease, meeting GELF criteria for treatment, adequate organ function and performance status. Treatment was divided into 2 phases, induction (6 x 28-day cycles) and maintenance (12 x 56-day cycles). During induction, patients received fixed doses of obinutuzumab (1000mg D1, 8, 15 cycle 1; D1 of C2-6) and lenalidomide 20mg days 1-21 from C2-6. Venetoclax was given from C1-6 and the dose was escalated, according to a 3+3 design with 4 dose levels (DL) tested: DL 1: 400mg daily D1-10, DL 2: 800mg D1-10, DL 3: 400mg D1-28 and DL 4: 800mg D1-28. After 6 cycles, patients who attained complete response (CR) received obinutuzumab maintenance (1000mg every 8 weeks for 2 years). Patients who attained partial response received a further 6 cycles of lenalidomide (10mg D1-28) and venetoclax (at the same dose given in induction) in addition to the obinutuzumab maintenance. Patients who experienced SD discontinued study in favour of alternate therapy.
The primary endpoint of phase Ib was recommended phase II dose (RP2D). The primary endpoint of phase II was intention to treat CR rate by investigator assessment at end of induction by Lugano 2014. Key secondary endpoints included safety, objective response rate (ORR), progression free survival (PFS), overall survival and quality of life. This interim analysis focuses on the RP2D, safety and preliminary efficacy data.

Results
As of 13 Mar 2023, 36 patients have been enrolled of whom 26 completed end of induction phase and are included in this interim analysis. Eighteen patients were treated in dose escalation (3, 6, 3 and 6 at dose levels 1-4, respectively) and 18 in expansion phase. The baseline characteristics are summarized in **Table 1.** The median relative dose intensity was >90% for all 3 agents. One dose limiting toxicity (DLT) occurred (grade 3 ALT elevation possibly related to venetoclax on C1D1, which resolved within 48 hours) and no maximum tolerated dose was reached. Dose level 4 (venetoclax 800mg daily D1-28) was the RP2D. The only grade≥3 AEs to occur in more than two patients were neutropenia (65%), without febrile neutropenia. The most common any grade AEs were nausea (50%), diarrhea (46%), maculopapular rash (31%), thrombocytopenia (27%), fatigue (23%) and constipation (23%). One patient developed biochemical TLS. 7 patients prematurely discontinued study treatment due to progressive disease (PD) in 2, and 1 case of each DLT, COVID-19, grade≥3 cytopenias lasting >28 days, upper respiratory infection and development of a second malignancy requiring systemic therapy. At the end of induction, the

CR and ORR were 81% and 92%, respectively. The 2 PD events were both found at the end of induction restaging, and biopsy revealed histologic transformation to diffuse large B-cell lymphoma. Updated data (including PFS) will be presented at the meeting.

Conclusion

The combination of obinutuzumab, lenalidomide and venetoclax is a highly active and safe combination in patients with treatment-naïve high tumor burden FL. No unexpected safety signals were identified. Enrolment to phase II is ongoing at 4 Australian sites. This trial is registered at clinicaltrials.gov (NCT03980171)

Disclosures Cheah: *Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Astrazenecca:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Lilly:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *TG therapeutics:* 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, Speakers Bureau; *Menarini:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Dizal:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Genmab:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *BMS:* Consultancy, Honoraria, Research Funding. **Lewis:** *Janssen:* Honoraria; *Loxo/Lilly:* Other: Travel, Accommodations, Expenses and Trial Steering Committee; *Merck/MSD:* Other: Advisory Board participant; *Roche:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria. **Bennett:** *Abbvie:* Other: Travel support. **Wight:** *Abbvie:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Otsuka:* Consultancy, Honoraria; *MDI:* Consultancy, Honoraria; *Beigene:* Consultancy, Honoraria; *MSD:* Consultancy, Honoraria. **Seymour:** *AbbVie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *AstraZeneca:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche Ltd:* Research Funding; *Beigene:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Hoffmann-La Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *TG Therapeutics:* Consultancy; *Genor Bio:* Membership on an entity's Board of Directors or advisory committees; *Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees.

OffLabel Disclosure: follicular lymphoma is an off label indication for venetoclax

Table 1 baseline characteristics

	Total (n=26)
Sex Male Female	 18 (69%) 8 (31%)
Median age (range), years	53.5 (34 – 78)
LDH Elevated Normal missing	 3 (12%) 20 (77%) 3 (20%)
Stage IIX III IV	 2 (8%) 4 (15%) 20 (77%)
ECOG Performance status 0 1	 23 (88%) 1 (12%)
B symptoms	4 (15%)
PRIMA-PI Low (0) Intermediate (1) High (2)	 8 (31%) 13 (50%) 5 (19%)

Figure 1

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