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Trial in progress: First line Treatment of Follicular Lymphoma (FL) with Golcadomide, Rituximab +/- Nivolumab: An Umbrella Randomised Phase 2 Investigator-led Study.

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Background

Follicular lymphoma (FL) is commonly initially treated with chemotherapy plus anti-CD20 monoclonal antibody, which yields high efficacy but also significant toxicity.[1,2]

FL patients are largely aged >65 and may require treatment multiple times over their disease course thus novel regimens which enhance efficacy and minimise toxicity are **highly desirable**.

FL patient outcomes are influenced by tumour microenvironment composition and manipulation with immunotherapy.

Ikaros and Aiolos, key cell development and homeostasis transcription factors are upregulated in FL. Cereblon-modulating compounds (CELMoDs) such as golcadomide (CC-99282; Figure 1) promote degradation of these with demonstrated efficacy alone or with rituximab in FL (responses-ORR- up to 75% in heavily pre-treated FL pts).[3-5]

We reported favourable efficacy of nivolumab a PD1 inhibitor plus R in 1L treatment of FL (ORR 92% complete response CR 54%).[7-8]

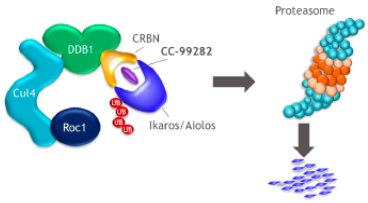

Figure 1. Golcadomide co-opts CRBN to induce proteasome mediated degradation of Ikaros and Aiolos[6]

This study ('TOP-FLOR'; NCT05788081) builds on these findings and potential immunomodulatory synergy to explore the efficacy and safety of rituximab + golcadomide, a novel CELMoD +/- nivolumab in treatment-naïve advanced stage FL pts.

Methods

This is an open label multicentre umbrella Bayesian Optimal randomised Phase II trial.

The study will randomise up to 40 eligible pts 1:1 to receive rituximab, golcadomide +/- nivolumab (20 per arm) from 5 Australian sites.

Eligibility includes:
- Patients aged ≥18 years,
- Previously-untreated, stage II-IV, grade 1-3A FL
- Performance status of 0-1
- Requiring systemic therapy.

Planned treatments:

Arm A: 8 cycles (28 days each) of golcadomide 0.4 mg po daily on days 1- 14 plus rituximab 375 mg/m2 IV day 1;
Arm B: Per Arm A plus nivolumab 480mg IV day 1

All patients in partial or complete response at end of induction receive 12-weekly rituximab maintenance (8 doses). Safety assessments will be performed prior to each cycle in accordance with CTCAE V5.0. This is illustrated in Figure 2.

Primary endpoint

CR rate in the absence of prohibitive toxicity in accordance with CTCAE V5.0 after eight cycles of rituximab, golcadomide +/- nivolumab.

Secondary endpoints

- Overall toxicity, response rate (according to modified Lugano criteria)
- Time to treatment failure
- Progression-free survival & overall survival

Exploratory endpoints

- Patient reported outcomes (PRO) as measured by EORTC-QLQ-c30 and FACT-Lym
- PET radiomics
- Tissue, blood and stool immune and genomic biomarkers

Planned Statistical Analysis

Interim assessment of 1^{O} endpoint will be conducted for 11 pts in each arm, arms will be closed for futility if fewer than 7 pts achieve the primary endpoint. Treatment arms will not be formally compared. Survival probabilities will be reported using Kaplan-Meier analysis.

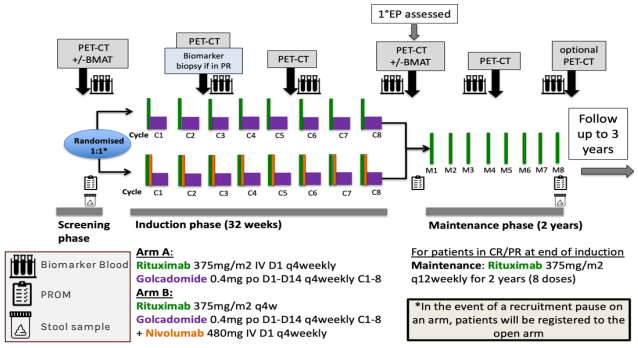

Figure 2. TOP-FLOR Study treatment and intervention schedule

Status

This trial (NCT05788081) received IRB approval on 14 July 2023 at Austin Health, Heidelberg, Australia.

Approval number: HREC/88597/Austin-2023. Trial sponsor: Olivia Newton-John Cancer Research Institute.

Five sites have been activated and are recruiting participants: Austin Health, Barwon Health, Grampians Health, Fiona Stanley Hospital and Eastern Health. First site was activated 31 Aug 2023. 23 participants have been recruited, 22 commenced treatment to date.

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