Introduction: Mantle-cell lymphoma (MCL) is a heterogeneous disease and the existence of indolent clinical forms is increasingly recognized. The aim of this study was to propose a frontline tailored treatment for indolent clinical forms with ibrutinib in combination with rituximab (IR).

Methods: This is a multicenter single-arm, open-label, phase II study with a two-stage design conducted in 14 Spanish GELTAMO sites (NCT02682641). Centralized histology, PET-CT review, minimal residual disease (MRD) studies (qPCR and NGS in peripheral blood [PB] and bone marrow [BM]) and biological studies are conducted. Previously untreated MCL patients with indolent clinical forms were eligible according to the following criteria: no symptoms attributable to MCL, ECOG 0-1, stable disease without therapy need for at least 3 months, non-blastoid variants, Ki-67 <30% and largest tumor diameter ≤3 cm. Both leukemic non-nodal and nodal forms were acceptable. Patients received ibrutinib 560 mg daily and a total of 8 doses of rituximab 375 mg/m2 (4 weekly doses during the first 28-day cycle, followed by day 1 of cycles 3, 5, 7 and 9). Ibrutinib could be discontinued after 2 years of treatment in case of sustained undetectable MRD. The primary endpoint was the rate of complete remissions (CR) achieved after 12 cycles according to the Lugano criteria.

Results: Fifty patients (Male 66%; median age 65 years) were enrolled in the study (June 2016 to December 2019, data cut-off 22 Jan 2021, median follow-up 33 months). Efficacy data of the 50 patients included four cases that were discontinued earlier due to adverse events (AE): ORR 84% and CR 80%. Regarding MRD evaluable cases (N = 45), 86% achieved undetectable MRD in PB and 64% also in BM. In CR cases, 72% had undetectable MRD in both PB and BM.

After 24 months of treatment, 19 patients were in response with undetectable MRD and discontinued ibrutinib treatment according to protocol. Four patients progressed from the disease at 12, 38, 40 and 52 months of follow-up and two of them eventually died of progression. Overall, PFS and OS estimated at 42 months were 81% (95% CI: 65-98) and 86% (95% CI: 71-100), respectively. Five patients were withdrawn from the study due to serious adverse events (one each), including skin rash, severe aplastic anemia, pancreatic adenocarcinoma, and lumbar fractures, or by decision of the patient. The most common treatment-related adverse events (AE) were diarrhea (38%), neutropenia (36%), fatigue (32%), upper respiratory infection (26%) nausea (22%), and arterial hypertension (20%). AE grades ≥ 3-4 corresponded predominantly to hematologic toxicity (22%). So far 10/50 patients have discontinued ibrutinib due to intolerance.

Conclusion: In indolent clinical forms of MCL frontline ibrutinib in combination with rituximab has a high efficacy, including undetectable MRD in the majority of cases, with a predictable toxicity profile.

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Molecular Targeted Therapies

Conflicts of interests pertinent to the abstract

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061 | THE COMBINATION OF VENETOCLAX, LENALIDOMIDE AND RITUXIMAB IN PATIENTS WITH NEWLY DIAGNOSED MANTLE CELL LYMPHOMA INDUCES HIGH RESPONSE RATES AND MRD UNDETECTABILITY

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Background: MCL is a rare lymphoma without a standard of care but several regimens have demonstrated clinical activity, the majority based on traditional chemotherapy. We hypothesized that adding venetoclax (V) to R2 would be safe and effective in MCL pts irrespective of age, morphology or stage. Here we present safety and efficacy data from the on-going phase 1b study of R2 + V in pts with newly diagnosed MCL.

Methods: This multi-center phase 1 study (NCT03523975) enrolled pts aged ≥18 yrs with untreated MCL. The primary objective was to characterize the safety and tolerability of R2 + V and determine the MTD. During induction (12 months (m)) pts received lenalidomide (L) 20 mg daily on day 1-21, Rituximab (R) was given weekly during c1 then on day 1 of every even cycle, V was escalated over 4 weeks to 400 mg beginning day 8. Each cycle is 28 days (d). The DLT period was 42 d beginning C1D8. In maintenance, R every 8 weeks for 36m, L at 10 mg or half of last dose during induction for 24 m and V for minimum 12 m. No pts have been transplanted. Pts with progression (PD) came off study. MRD was analyzed in parallel with scans during induction by clonoSEQ assay (Adaptive Biotechnologies).

Results: As of Feb. 1st, 2021, we have enrolled all 28 planned pts on study. Pt characteristics/responses are summarized in Table 1. Among the 28 pts who have received at least one dose, the

median treatment duration so far is 278d (IQR 170-560), with 24 pts still on treatment (Tx). 1 pt is off from a unrelated condition.

All pts escalated to V 400 mg w/o any DLTs noted. Treatment-emergent adverse events (TEAEs) were reported in 100% of pts, and grade 3+ TEAEs were reported in 26 (93%) patients. The most common all-grade TEAEs (≥50% of pts), regardless of relationship to study Tx, were fatigue, neutropenia and diarrhea. Grade ≥3 TEAEs reported in ≥50% pts were neutropenia (68%) and thrombocytopenia (50%). No pts have withdrawn or d/c Tx due to AEs. There was one grade 5 event, in a non-evaluable pt, related to a PE that occurred prior to DLT period.

In the 28 evaluable pts the ORR (CR/PR) was 96% (27/28 pts) with CR/CRu of 89%. Of the responding pts, two had PD, one w/ CR and one w/ PR. All pts with PD had baseline *TP53* mutation. MRD testing was successful in all pts. At time of submission 20 of 28 (71%) were MRD - at 10^{-6}.

Conclusions: Interim results show that at the MTD the combination of V 400 mg daily, L 20 mg, with R is safe with a manageable toxicity profile and a high ORR and MRD - in pts with newly diagnosed MCL. Safety data is consistent with the AE profile noted for each drug without any unexpected or unique AEs. Updated results including BH3 profiling will be presented at the meeting.

EA - previously submitted to ASCO 2021

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Keywords: Aggressive B-cell non-Hodgkin lymphoma, Combination Therapies, Ongoing Trials

Conflicts of interests pertinent to the abstract

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TABLE 1

Sex, male, % (n)	64% (18)
Age, years, median (IQR)	65 (57, 69)
Race, white, % (n)	100% (28)
Tx duration, d, median (IQR)	278 (170, 560)
Stage IV, % (n)	96% (27)
MIPI High, % (n)	64% (18)
Blast/Pleo, % (n)	21% (6)
Ki-67 ≥30%, % (n)	68% (19)
ORR	96%
CR/CRu	89%
MRD -	71%

062 | SAKK 36/13 - IBRUTINIB PLUS BORTEZOMIB AND IBRUTINIB MAINTENANCE FOR RELAPSED AND REFRACTORY MANTLE CELL LYMPHOMA: FINAL REPORT OF A PHASE I/II TRIAL OF THE EUROPEAN MCL NETWORK

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Introduction: Mantle-cell lymphoma (MCL) remains incurable with frequent relapses, limited treatment options and progressively shorter disease-free survival with every relapse. The Bruton's tyrosine kinase inhibitor ibrutinib (IBR) and the proteasome inhibitor bortezomib (BOR) have single agent activity and regulatory approval in MCL. IBR and BOR lead to a downregulation of NF-κB activity via different targets. IBR resistance involves mutations in genes of the NF-κB pathway. *In vitro*, the combination of both drugs provides synergistic cytotoxicity in BOR-sensitive and refractory MCL.

Methods: In this investigator-initiated trial, we included patients (pts.) with histologically confirmed MCL, refractory/relapsed after ≤2 lines of a non-BOR-containing chemotherapy (incl. high-dose chemotherapy), and excluded pts. with prior BOR or IBR therapy, with CNS disease, in need of anticoagulation, or active Hepatitis B, C or HIV infection. Pts. received 6 21-days cycles of IBR + BOR, followed by IBR until progression or unacceptable toxicity. The dose of the combination was established with 9 pts. in the phase I part: BOR s.c. 1.3 mg/m^2, days 1, 4, 8, 11 q3w, and IBR continuously at 560 mg/day. The primary endpoint of the phase II was the overall response rate (ORR) based on CT/MRI (*Cheson, 1999*). The null hypothesis was