Background: Mantle cell lymphoma (MCL) is not yet curable and new agents are needed for relapsed and refractory disease. An oral immunomodulatory agent such as lenalidomide could be effective with minimal toxicities especially when combined with the anti-CD20 antibody rituximab.

Purpose: To determine the maximum tolerated dose (MTD) in phase I; and to evaluate lenalidomide could be effective with minimal toxicities especially when combined with rituximab needed for relapsed and refractory disease. An oral immunomodulatory agent such as lenalidomide plus rituximab in phase II for patients with relapsed/refractory MCL.

Patients and Methods: Patients received oral lenalidomide (range 10–25 mg) on days 1–21 of every 28-day cycle, and intravenous rituximab weekly for 4 doses during cycle 1. Treatment continued until disease progression or severe toxicity.

Results: A total of fifty-two (52) patients were enrolled, including 14 in phase I and 46 in phase II (8 from phase 1). Median number of prior therapies for all 52 patients was two (range 1–4). The MTD was oral lenalidomide 20 mg daily, 21 days on and 7 days off plus intravenous rituximab 375 mg/m2 for 4 doses. The median duration of treatment was 5 cycles (range 1–29). Two DLTs were grade 3 hypercalcemia and grade 4 non-neutropenic fever. The combination was very well tolerated; the primary grade 3 hematological toxicity was thrombocytopenia (19.2 months (95% CI, 17.0 months – not reached)). The median progression-free survival was 15.6 months (95% CI, 8.3–20.8 months). Median duration of remission was 25.1 months (95% CI, 19.8 months – not reached).

Conclusion: Oral lenalidomide plus rituximab is well tolerated and highly effective in patients with relapsed/refractory MCL.

109 ORAL LENALIDOMIDE PLUS 4 DOSES OF RITUXIMAB INDUCED PROLONGED REMISIONS IN RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA: A COMPLETED PHASE I/II CLINICAL TRIAL

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Background: Lenalidomide is an oral immunomodulatory agent and a potent inducer of apoptosis. However, lenalidomide dose escalation studies have been limited, with only 15, 20, and 25 mg given in phase I studies. Higher doses are needed to determine the maximum tolerated dose (MTD). In this phase I/II study, we aimed to determine the MTD of lenalidomide in newly diagnosed mantle cell lymphoma (MCL) patients with prior chemotherapy failures.

Methods: Patients with newly diagnosed MCL, age ≤ 75, WHO performance status ≤ 2, and a minimum of two prior chemotherapy regimens were eligible. Patients were randomized to receive escalating doses of lenalidomide (20-45 mg) daily for 21 days, and rituximab 375 mg/m² weekly for 4 doses. The MTD was defined as the highest dose that induced ≤ 1 DLT per 28-day cycle.

Results: Forty-two patients were enrolled, and 32 were evaluable for toxicity and response. The recommended phase II dose was 35 mg/day. At the MTD, 19/28 patients achieved MCR, and 11/28 achieved MPR. Median PFS was 18.9 months (95% CI, 14.5-33.0 months), and median OS was 33.0 months (95% CI, 14.5-43.0 months). Grade 3 and 4 toxicities included neutropenia in 23% and 14% of patients, thrombocytopenia in 10% and 7%, and anemia in 6% and 4%

Conclusion: Oral lenalidomide plus rituximab is well tolerated and highly effective in patients with relapsed/refractory MCL.
Methods: OFAR2 consisted of oxaliplatin 30mg/m² D1-4; fludarabine 30mg/m²; Ara-C 0.5g/m²; rituximab 375mg/m² D3; and pegfilgrastim 6mg D6. Fludarabine and Ara-C were given on D2-3 (level 1) D2-4 (level 2) or D2-5 (level 3) every 4 wks.

Results: Overall, 102 patients (CLL 67, RS 35) were treated [Phase 1 ("3+3" design) n=12; Phase II, n=90]. Dose-limiting toxicities were G4 diarrhea and G4 sepsis (2/3 patients, level 3). Level 2 was the maximum tolerated dose (MTD). Of 102 patients, 62% were >60 yrs, 73% had Rai 3-4 stage, 72% b2-microglobulin ‡4 g/dL, 83% unmutated IGVH, 76% ZAP70+, 37% 17p del and 13% had 11q del. The median follow-up was 19 months. Results in patients treated at the MTD are shown in Table.

In patients with 17p del and 11q del, the response rates were 33% and 60%, respectively (median survival, 13 and 5.8 months).

The most common toxicity was hematologic (neutropenia 76% of patients; anemia 50%; thrombocytopenia 84%).

Conclusion: OFAR2 had antileukemic activity in poor-risk RS and CLL. OFAR2 was superior to OFAR1 in aggressive CLL. OFAR1 was superior to OFAR2 in RS. All patients who underwent SCT as postremission therapy remained alive, confirming our prior observation that patients with RS or relapsed/refractory CLL who respond to treatment should undergo SCT as postremission therapy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RS, N = 31</th>
<th>Refractory CLL, N = 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2</td>
<td>6.5 3</td>
</tr>
<tr>
<td>nPR</td>
<td>0</td>
<td>0 9</td>
</tr>
<tr>
<td>PR</td>
<td>9</td>
<td>29 21</td>
</tr>
<tr>
<td>Overall response</td>
<td>Median (95% CI), 1-yr</td>
<td>Median (95% CI), 1-yr</td>
</tr>
<tr>
<td>Overall survival</td>
<td>6.6 (4.6, 40+)</td>
<td>29% 22 (14.4, 40+)</td>
</tr>
<tr>
<td>FFS</td>
<td>3.0 (1.6, 4.8)</td>
<td>11% 4.5 (3.4, 5.9)</td>
</tr>
</tbody>
</table>

Sponsored in part by an ASCO Career Development Award to Dr Tsimberidou and Sanofi research funding.

113 SHORT COURSE FLUDARABINE, MITOXANTRONE, RITUXIMAB FOLLOWED BY 90Y-IBRITUMOMAB TIUXETAN IN UNTREATED INTERMEDIATE/HIGH-RISK FOLLICULAR LYMPHOMA: A PHASE II TRIAL

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Background: An innovative approach combining induction chemotherapy and subsequent consolidation with 90Yttrium-ibrutinumab-tiuxetan (90Y-IT) has been upgraded by shortening the chemotherapy duration and by insertion of rituximab, in untreated follicular non-Hodgkin’s lymphoma (NHL).

Patients and Methods: A prospective, single-arm, open-label, multicenter, non-randomised phase II trial to evaluate efficacy and safety of a short fludarabine, mitoxantrone and rituximab (FMR) induction followed by radioimmunotherapy, in untreated, intermediate/high-risk, follicular NHL patients. Fifty-five patients were treated using a sequential treatment schedule consisting of 4 induction cycles of FMR chemo-immunotherapy, and a subsequent consolidating single administration of 90Y-IT, 8-12 weeks later. Patients were eligible for radioimmunotherapy if at least in partial response (PR) after induction, with normal platelet and granulocyte counts and a bone marrow infiltration ≤25%. Primary study endpoints were response rate and hematological toxicities; secondary endpoints were overall survival (OS) and progression-free survival (PFS).

Results: All patients received 4 induction cycles of FMR, with an overall response rate of 96.4% (38 complete responses, CR, and 15 PR). Fifty-one patients (38 in CR and 13 in PR) received 90Y-IT. By the end of the treatment, 49/55 patients achieved a CR. With a median follow-up of 21.3 months (95%CI 18.7-23.7), the estimated 3-year PFS was 80.6% (95%CI 73.7-92.8) and the 3-year OS 100.0%. Twenty-one patients showed grade ≥3 hematological toxicities.

Conclusions: This study has established the feasibility, tolerability, and efficacy of a regimen composed by a short FMR induction with a 90Y-IT consolidation in untreated intermediate/high-risk follicular NHL patients.