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Ibrutinib in second-line relapsed/refractory mantle cell lymphoma: efficacy and safety results from the second interim analysis of the OLIMPUS study

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Key Takeaway

The second interim analysis of the OLIMPUS prospective study confirmed the effectiveness and safety of ibrutinib as a second-line treatment for MCL patients.
These findings in the real-world clinical setting are consistent with those emerged from clinical trials and strengthen the role of ibrutinib in second-line R/R MCL.

Conclusions

- The Primary Endpoint shows an elevated ORR of 73% of patients treated with ibrutinib as second line
- In a prospective evaluation, Ibrutinib appears well tolerated in this setting with only 4.7% of discontinuation due to AEs.

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Poster

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Introduction

Mantle cell lymphoma (MCL) is an aggressive, incurable disease characterized by repeated relapses. The BTK pathway is a key regulator of B-cell biology and its inhibition has been associated with favorable outcomes. Ibrutinib, the first BTK inhibitor approved, has long been considered the standard second-line treatment for R/R MCL (1, 2); however, prospective and real-world data remain limited.

Aim

- The OLIMPUS study enrolled patients affected by R/R MCL and Waldenstrom's macroglobulinemia after first-line therapy in a real-world setting.
- The objective of the study was to collect real world data from Italy and report on effectiveness and safety outcomes of patients treated with ibrutinib for R/R MCL. Specifically, the primary objective was to evaluate the overall response rate (ORR) according to Lugano criteria; secondary endpoints included duration of response (DOR), quality of response, progression-free survival (PFS) and safety.
- The present interim analysis (IA) updates and expands the population described in a previous first interim analysis, focused exclusively on the MCL cohort.

Methods

- This is a single-country, multicenter, observational, ambispective study conducted across 34 Italian centers. The study included patients with relapsed/refractory mantle cell lymphoma (R/R MCL) treated with ibrutinib in second line. The ambispective design included a retrospective cohort (patients who had started treatment within 3 months before study initiation) and a prospective cohort (patients who started treatment after study initiation).
- Overall, 106 patients with R/R MCL were enrolled. The median starting dose of ibrutinib was 560 mg. At the data cut-off (21-Nov-2025), 47 patients were still receiving treatment.
- This interim analysis reports the results on the total MCL cohort of 106 patients (IA population), whose data are extrapolated up to the last available visit at the data cut-off, with a median follow-up calculated through Kaplan-Meier analysis of 18.04 months (95%CI: 16.56-21.95).
- Additionally, the analysis included a subset of MCL patients who reached at least a 24 months follow-up at data cut-off, corresponding to the 51 MCL patients included in the first interim analysis (IA1 population). Those data were previously reported for a minimum observation time of 12 months after ibrutinib start; here the results are here updated to a median follow-up of 24.57 months (95%CI: 22.44-NR).

Results

Baseline characteristics

- In both populations, IA1 and IA, median age at enrollment was 71 years (range 35-90) with a predominance of male patients (73.6%).
- In IA patients, at diagnosis, sMIPI score was high in 33% (35/106), TP53 mutation was identified in 51% of the tested patients (16/31), and blastoid/pleomorphic histology was observed in 17% (12/71). In IA1 population, 31.4% (16/51) of patients had a high sMIPI score, with TP53 mutation identified in 58.3% (7/12) and blastoid/pleomorphic histology observed in 15.6% (5/32) of patients with the available data.
- Subjects with significant cardiovascular disease were 22/106 (20.8%) in IA patients and 17.6% in IA1 patients. The specific disease features and comorbidities at diagnosis are reported in **Table 1.**
- 58/106 patients (54.7%) were POD24, defined as R/R within 24 months from start of first line therapy.

Effectiveness: Primary and Secondary Endpoints

- Overall, out of the 92 evaluable patients (who had at least one post-baseline evaluation for the tumor response) the ORR was 73% (67/92 patients, 95% CI 62.6-81.6), with a complete response rate (CRR) of 50% (46/92) and a partial response (PR) of 23% (21/92) (**Figure 1**); results were comparable in IA1 subgroup: ORR at Month 24 was 73% (33/45, 95% CI 58.1–85.4), CRR 53% (24/45) and PR 20% (9/45). In total MCL population, 10% (9/92) had stable disease (SD), while progressive disease was recorded in 17% (16/92); for IA1 population, SD and PD were recorded both in 13% of patients (6/45).
- Progression-free survival (PFS) was evaluated up to End of Study/Last Available date (not censoring at the last available tumor assessment). At data cut-off, in the IA and IA1 cohort, PFS rate at month 24 was 57.3% (95% CI: 45.5-67.4)(**Figure 2**) and 61.5% (95% CI: 45.5-74.0) respectively; PFS rate at month 24 for POD24 patients was 46.2% (95% CI: 31.1-60.0) in IA and 48.5% (95% CI: 29.0-65.5) in IA1.
- Overall survival (OS) rate was 72.6% (95% CI: 59.8-81.9) in IA population and 80.1% (95% CI: 63.9-89.6) in IA1 subgroup.
- Median duration of response (calculated through Kaplan-Meier analysis and evaluated up to End of Study/Last Available Date) was 28.45 months (95% CI: 23.39-NR) and not reached in IA1 (Figure 3 in supplementary).

Safety and Dose Management

- Overall, during the course of the study, 24.5% of IA patients and 23.5% of IA1 patients had dose modifications, due to Treatment-Emergent Adverse Event (TEAE) and other causes; 15.1% and 8 15.7%, respectively, had dose reductions; 28.3% of IA patients and 31.4% of IA1 patients had temporary treatment interruptions.
- Prospectively (for the prospective cohort and for patients who started treatment with ibrutinib as second-line therapy within 3 months before the date of the initiation visit), in total MCL patients, 68% of patients experienced at least one TEAE, 20.8% had at least one Serious AE (SAE), 32.1% had at least one Related AE and 5.7% experienced at least one Related SAE. 37% experienced interruption of ibrutinib due to an AE, of these only 4.7% had a permanent discontinuation.
- Of all TEAE, 19.8% were of grade 3 and 7.5% of grade 4. All grades, infections were the most frequent AE (23.6%) followed by general disorders (20%) such as pyrexia (8.5%) and asthenia (4.7%); and blood disorders (20%), such as neutropenia (9.4%), anemia (7.5%). Cardiac disorders occurred in 15%, of which 6.6% of atrial fibrillation and 1.9% of cardiac failure. Only 3.8% experienced COVID-19, all of grade 1-2. G3-G5 TEAEs data are reported in Table 2 in supplementary.

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Indolent and mantle-cell non-Hodgkin lymphoma

Table 1

Characteristics at diagnosis	IA population Total (N=106) n (%)	IA1 population Total (N=51) n (%)
sMIPI		
Low	12 (11.3%)	5 (9.8%)
Intermediate	21 (19.8%)	8 (15.7%)
High	35 (33.0%)	16 (31.4%)
Unknown/Missing	38 (35.8%)	22 (43.1%)
ECOG PS		
0-1	76 (71.7%)	33 (64.7%)
2	5 (4.7%)	5 (9.8%)
≥3	0 (0%)	0 (0%)
Unknown/Missing	25 (23.6%)	13 (25.5%)
Ann Arbor stage		
Stage I-II	2 (1.9%)	0 (0%)
Stage III-IV	96 (90.6%)	48 (94.1%)
Unknown	8 (7.5%)	3 (5.9%)
Histological variant		
Classical	59 (55.7%)	27 (52.9%)
Blastoid/pleomorphic	12 (11.3%)	5 (9.8%)
Unknown	35 (33.0%)	19 (37.3%)
TP53 Mutation		
Yes	16 (15.1%)	7 (13.7%)
No	15 (14.2%)	5 (9.8%)
Not available/Missing	75 (70.8%)	39 (76.5%)
History of cardiovascular disease*		
Overall	22 (20.8%)	9 (17.6%)
Uncontrolled arrhythmias	1 (0.9%)	0 (0%)
Atrial fibrillation/ atrial flutter	10 (9.4%)	2 (3.9%)
Hypertension	9 (8.5%)	3 (5.9%)
Myocardial infarction	2 (1.9%)	1 (2.0%)
Others (valvular diseases, aneurisms, coronary heart disease, ischemic stroke, myocarditis)	9 (8.5%)	5 (9.8%)

**In IA population, 7 patients had two concomitants cardiovascular diseases, 1 had three; in IA1 population, 2 patients had two concomitant diseases*

Figure 1

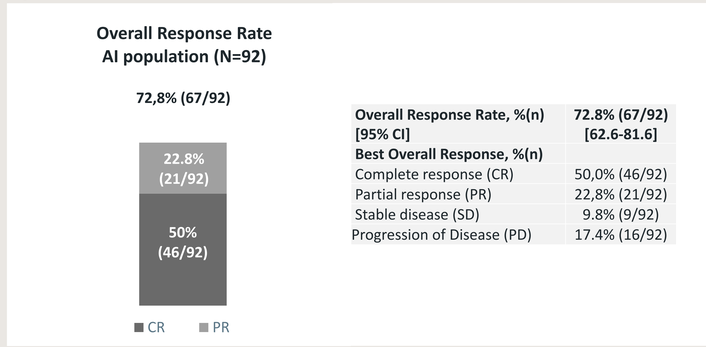

Figure 2