



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

**623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL****Phase II Trial of Ibrutinib in Previously Untreated High-Risk Smoldering Mantle Cell Lymphoma**

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**Background:** Mantle cell lymphoma (MCL) patients usually require immediate therapy, however about 20% of newly diagnosed MCL patients can be initially observed. A subgroup of patients who are suitable for initial observation but exhibit high-risk features are of particular concern as they have a propensity to progress. We consider these patients as high-risk smoldering MCL (defined below). Generally, these patients are observed without systemic therapy for 18-24 months. We investigated the impact of single-agent ibrutinib on time to progression for these patients who would otherwise be observed.

**Methods:** This is a single center, single arm, investigator-initiated phase 2 clinical trial (NCT03282396). High-risk smoldering MCL included one or more of the following criteria: non-blastoid/pleomorphic variant, Ki-67 of 15-30%, white blood cell count of  $15-30 \times 10^9/L$ , lymph nodes  $\leq 5$  cm, TP53 mutated or wild type, del17p, MYC positive, complex karyotype, presence of KMT2D, BIRC3, or  $\geq 1$  other somatic mutations, and were asymptomatic without any clinical indication to start systemic therapy. Major exclusion criteria included significant disease-related symptoms, blastoid/pleomorphic variants, Ki-67  $>30\%$ , bulky tumors  $>5$  cm. Patients received ibrutinib 560 mg P.O. daily in 28-day cycles and continued until progression, transformation, drug intolerance, or up to 5 years. The primary endpoint was progression-free survival (PFS). Secondary endpoints were safety, response rate, and duration of response (DOR). Response was measured using the Lugano criteria. It is expected that the current trial will achieve a median PFS time of about 18 months, which would be an improvement over PFS reported on high-risk patients under a watch and wait approach. The median follow-up time was 23.4 months.

**Results:** Twenty patients were enrolled (Table 1). The median age was 60.5 years (range 38-79). Most were male ( $n=15/20$ ). At baseline, 13 patients (65%) had bone marrow involvement and 15 patients (75%) had gastrointestinal tract involvement. Seven patients (35%) had TP53 alterations. One patient was not evaluable for response due cessation of therapy after less than 1 cycle due to new onset atrial fibrillation. Among 19 evaluable patients, the best overall response rate was 94.7% ( $n=18/19$ ). Of those who had a positive PET at baseline and were evaluable for PET response, 92.9% ( $n=13/14$ ) achieved a PET complete response (CR). Of those with bone marrow involvement at baseline, 30.7% ( $n=4/13$ ) achieved CR by flow cytometry. Of those with baseline gastrointestinal tract involvement, 33.3% ( $n=5/15$ ) achieved histologically confirmed CR. The median number

of cycles received was 16 (range 0-32). The median PFS and DOR were not reached. Seven patients discontinued therapy: atrial fibrillation (n=3), progressive disease (n=1), infection (n=1), lung cancer (n=1). The most frequent grade 3 toxicities were diarrhea (n=2, 10%), atrial fibrillation (n=1, 5%), infection (n=1, 5%), mucositis (n=1, 5%), and syncope (n=1, 5%). No grade 4 toxicities occurred. No deaths on study occurred.

Conclusions: Ibrutinib demonstrated significant efficacy with manageable toxicities in previously untreated patients with high-risk smoldering MCL.

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**OffLabel Disclosure:** Ibrutinib in previously untreated smoldering mantle cell lymphoma

**Table 1. Patient Characteristics and Outcomes**

	All Patients (n=20)
<b>Median Age (years, range)</b>	60.5 (38-79)
<b>Gender (male)</b>	15
<b>Disease Characteristics at Baseline</b>	
PET Positive	70% (n=14/20)
Bone Marrow Involvement	65% (n=13/20)
Gastrointestinal Tract Involvement	75% (n=15/20)
<b>High-Risk Features</b>	
Ki-67 15-30%	55% (n=11/20)
TP53 Alteration	35% (n=7/20)
Multiple Somatic Mutations	35% (n=7/20)
Complex Karyotype	15% (n=3/20)
MYC Positive	10% (n=2/20)
WBC count 15-30 x 10 <sup>9</sup> /L	25% (n=5/20)
LN diameter 3-5 cm	15% (n=3/20)
<b>Best Response</b>	
ORR	94.7% (n=18/19)
PET CR	92.9% (n=13/14)
Bone Marrow CR	30.7% (n=4/13)
Gastrointestinal Tract CR	33.3% (n=5/15)
PR	52.6% (n=10/19)
SD	5.3% (n=1/19)
<b>Median Follow-up (months, 95% CI)</b>	23.4 (19.2-27.5)
<b>Median PFS</b>	Not Reached
<b>Median DOR</b>	Not Reached

Legend: WBC=white blood cell; LN=lymph node; ORR=overall response rate; PET=positron emission tomography; CR=complete response; CR\*=complete response with histologically confirmed clearance of bone marrow and gastrointestinal tract; PR=partial response; SD=stable disease; CI=confidence interval; PFS=progression-free survival; DOR=duration of response

**Figure 1**

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