INTRODUCTION

- CMML is a hematologic malignancy characterized by persistent monocytosis, and dysplastic and/or proliferative features, as well as the risk of transformation to acute myeloid leukemia (AML; 15% over 3–5 years). 1
- The only potential cure is allogeneic hematopoietic stem-cell transplantation (HSCT), for which many patients are not eligible due to age (median 73 to 75 years at diagnosis), comorbidities, or the absence of a match. 2
- The DNA methyltransferase inhibitors (DNMTIs) panobinostat, parenteral decitabine, and oral decitabine/cedazuril are the only agents approved by the U.S. Food & Drug Administration (FDA) for the treatment of CMML, and cedazuril is approved for non-proliferative CMML in Europe.

STUDY DESIGN

- At least 118 evaluable patients with adequate PR in Cycles 1 and 2
- Here, we present outcome data from subjects with CMML enrolled in the Phase 2 and 3 studies that led to the approval of oral decitabine/cedazuril. The present analysis reports the combined clinical experience—response, survival, safety, and pharmacodynamics—for the subset of patients with CMML in the prospective, randomized phase 2 and 3 trials of oral decitabine/cedazuril.

The phase 2 and 3 studies compared the pharmacokinetics and pharmacodynamics of oral decitabine/cedazuril with those of IV decitabine. In both studies, eligible patients were adults (≥18 years) who were candidates to receive IV decitabine (i.e., French-American-British subtypes of previously treated or untreated MDS, or CMML that scored intermediate-1 or intermediate-2, or high-risk on the International Prognostic Scoring System), with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (0 to 1 for phase 2). Only 1 prior treatment cycle with decitabine or azacitidine was permitted.

- Patients in both studies were randomized 1:1 to one of two sequences for the first two 28-day cycles: either oral decitabine/cedazuril for 5 days in cycle 1, followed by IV decitabine daily for 5 days in cycle 1 (sequence A), or the reverse order (sequence B). All patients received oral decitabine/cedazuril from cycle 3 forward. Treatment continued until disease progression, unacceptable toxicity, study withdrawal, or other reasons. Treatment could be delayed or dose reduced if judged necessary for hematologic or non-hematologic recovery, as standard with parenteral DNMTI.

RESULTS

Efficacy and Safety

- Overall response rate was 76% (CR + PR + minor CR + HI; Table 2), with 21% of patients attaining CR.
- Median times to first response (12 patients, all with MD-CMML, for whom data were available) and best response (20 patients with MD-CMML and 5 with MP-CMML) for the full cohort were 1.8 months (range 0–4) and 2.3 months (range 1–7), respectively.
- Almost two-thirds of patients (64%) who were RBC-transfusion dependent at baseline, all including those with MP-CMML, attained transfusion independence for ≥8 weeks. Nearly half of patients (46%) who were RBC-transfusion dependent at baseline, all including those with MP-CMML, attained transfusion independence for ≥8 weeks.
- Two patients (6%) were platelet-transfusion dependent at baseline; 1 attained transfusion independence for ≥8 and ≥12 weeks. Three percent (9%) were transfusion independent at all of those with MD-CMML.
- Median overall and Transformation-Free survival were 35.7 and 28.3 months, respectively (Figure 3 & 4). All patients on transformation-emergent adverse event. Most patients (94% [N=33]) had ≥1 adverse event of grade ≥3 higher severity (Table 3). The most common adverse events (overall and grade ≥3) were related to myelosuppression (neutropenia, thrombocytopenia, and anemia).