Planned Interim Analysis of a Phase 2 Study Evaluating the Combination of Pracinostat, a Histone Deacetylase Inhibitor, and Azacitidine in Patients with High-/Very-High-Risk Myelodysplastic Syndrome

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BACKGROUND
Higher risk myelodysplastic syndrome (MDS) is a serious disease associated with an increased risk of leukaemia or death. Anti-cytokine therapies, high-dose chemotherapy followed by allogeneic stem cell transplantation are recommended for some patients with high-risk disease. MDS is a highly heterogeneous disease with patients presenting with varying degrees of disease activity. Standard treatments are used for patients with lower-risk disease, whereas therapies that target histone deacetylase (HDAC) or DNA methyltransferase enzymes are used for patients with higher-risk disease. For patients with high-risk disease, aggressive therapies, such as azacitidine (AZA), decitabine (DA), or the HDAC inhibitor vorinostat, are used to improve outcomes.

Major surgery within 28 days prior to first study treatment

In 18 subjects evaluable for response assessment at the end of Cycle 2

Marrow bone marrow biopsy and aspirate within 28 days prior to Day 1 Eastern Cooperative Oncology Group (ECOG) performance score of 0-2

In the prior Phase 2 study, pracinostat was administered at 60 mg/day on 3 alternate days in 28-day cycles with step-down dose to 45 mg in case of poor tolerability in combination with AZA at 100 mg/m² per day with a step-down dose to 45 mg/m² at the end of Cycle 2. To determine the effective dose, a step-down dose to 45 mg/m² was administered as an initial dose.

RESULTS
The CR rate of 29% is encouraging; further follow-up is needed to determine the long-term efficacy of pracinostat and AZA in patients with high-risk MDS.

Baseline Characteristics

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Safety

For the pre-planned interim analysis, a pre-defined discontinuation rate due to adverse events (AEs) of ≤10% in the first 4 cycles (i.e., “early discontinuations”) and an overall response rate of ≥3 rates are required. To expand to Cycle 1b, where approximately 20 additional patients will be treated for a total of 60 patients evaluable for response assessment. A sample size of 60 patients was considered sufficient to detect a substantial effect on overall response rate compared to historical controls treated with AZA alone.

Decision to expand to Stage 1b was based on review of safety data by an Independent Data Monitoring Committee (IDMC) in consultation with the study sponsor.

The primary efficacy endpoint is overall response rate (ORR) defined as complete remission (CR), partial remission (PR) and unconfirmed partial remission (CRu). Response duration is performed after 2.5 years of therapy, and then every 6 months or as clinically indicated.

Efficacy is being evaluated by investigator assessments based on hematological and physical examination data, bone marrow biopsy, and bone marrow aspirate and biopsy, as well as transaminases and uric acid. Discontinuation due to adverse events is considered at the NCI/CTCAE (v4.03).

- In 18 subjects evaluable for response assessment at the end of Cycle 2, the subset of patients who received at least 3 cycles had an overall response rate of 29%.
- For 12 of the 29 evaluable patients, the median time to diagnosis was 1 month and they were generally split between high- and very-high-risk MDS.
- For the remaining 33 (60%) patients, the median duration on therapy was 4.7 months (range, 0.5-32.5 months).
- 14 patients (25%) had received >6 cycles of therapy.

Table 2. Reason for Discontinuation (N = 22)

Reason |
--- |
No. of Patients (%) |
Discontinuation due to adverse events |
18 (82) |
Discontinuation due to decrease in performance status (PS) |
7 (32) |
Discontinuation due to disease progression |
6 (27) |
Discontinuation due to patient choice |
2 (9) |
Deaths |
1 (5) |

Table 3. Baseline Characteristics and Disease Activity

Characteristic | Pracinostat + AZA (n = 60) | AZA alone (n = 55)
--- | --- | ---
Sex | | |
Female | 35 (58%) | 40 (73%)
| | | |
Age (years) | | |
Mean (range) | 68 (47-89) | 67 (43-91)
| | | |
**No. (%)** | | |
< 50 years | 13 (22%) | 15 (27%)
≧ 50 years | 47 (78%) | 40 (73%)
MDS Subtype (WHO) | | |
MDS with multilineage dysplasia | 22 (40%) | 19 (35%)
| | | |
MDS with excess blasts-1 | 10 (18%) | 11 (20%)
| | | |
MDS with excess blasts-2 | 2 (4%) | 2 (4%)
| | | |
MDS with isolated del(5q) | 5 (9%) | 4 (7%)
| | | |
MDS with isolated del(17p) | 1 (2%) | 0 (0%)
| | | |
MDS-IPSS-R (in MDS only) | | |
N = 57 | | |
Grade 2 | 23 (40%) | 21 (38%)
| | | |
Grade 3 | 22 (40%) | 19 (35%)
| | | |
Grade 4 | 4 (7%) | 4 (7%)
| | | |
Cytogenetic Risk Groups | | |
Good | 2 (3%) | 2 (3%)
| | | |
Intermediate | 20 (34%) | 15 (27%)
| | | |
Intermediate-2 | 12 (21%) | 12 (22%)
| | | |
Intermediate-3 | 1 (2%) | 0 (0%)
| | | |
Bad | 21 (37%) | 25 (45%)
| | | |
Very Bad | 1 (2%) | 1 (2%)
| | | |
Median Time from Diagnosis (months) | | |
To start study drug | 0 (0-17.9) | 0 (0-17.9)

Patient Disposition

- As of October 25, 2018, 22 patients (40%) had discontinued study drug due to adverse events.
- Five patients (9%) discontinued due to adverse events, of which 2 (4%) were considered early discontinuations (within the first 3 cycles).
- For the remaining 33 (60%) patients, the median duration on therapy was 4.7 months (range, 0.5-32.5 months).
- 14 patients (25%) had received >6 cycles of therapy.

Table 4. Key Adverse Events in Current Study Compared to Prior Study

Adverse Event | Grade ≥3 | All Grades | Grade ≥3 | All Grades |
--- | --- | --- | --- | ---
Non-Hematologic | | | | |
Constitution | 7 | 8 | 4 | 5 |
Fever | 4 | 5 | 2 | 3 |
Fatigue | 3 | 4 | 2 | 3 |
Anemia | 2 | 3 | 1 | 2 |
Hematologic | | | | |
Anemia | 33 | 40 | 33 | 40 |
Neutropenia | 20 | 23 | 15 | 18 |
Thrombocytopenia | 26 | 27 | 26 | 27 |
Deaths | 2 | 2 | 4 | 4 |

Table 5. Best Disease Response

Endpoints | | | |
--- | --- | --- | ---
Complete response (CR) | 0% | 0% | 0% |
Complete response with incomplete blood count recovery (CRi) | 0% | 0% | 0% |
Very good partial response (VGPR) | 0% | 0% | 0% |
Good partial response (GPR) | 0% | 0% | 0% |
No change (NC) | 100% | 100% | 100% |
Worst Response | 0% | 0% | 0% |

CONCLUSIONS
This study evaluating the efficacy and safety of pracinostat + AZA showed that the median duration of therapy for the group of 45 patients was lower than the dose 60 mg evaluated in the prior study. The incidences of adverse events that led to early discontinuations in the prior study were lower for non-hematologic/grade 4 non-hematologic events, and at least as good for hematology-related events in the current study; it is noteworthy that patients in this study were higher risk MDS than the prior study.

Adverse event discontinuation rate due to adverse events in the first 18 months was higher than the rate reported in the prior study and that reported in patients with AZA alone. As such, the patients in this study receive a better and further follow-up is needed to ascertain the safety and efficacy of pracinostat + AZA.

The incidences of key adverse events that led to early discontinuations were lower in the current study than for the most of the current study, which also showed lower

REFERENCES

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