Maribavir Versus Investigator-Assigned Therapy for Refractory Cytomegalovirus Infection (With/Without Resistance) in Hematopoietic Cell Transplant Recipients: Subgroup Safety Analysis of a Phase 3 Study

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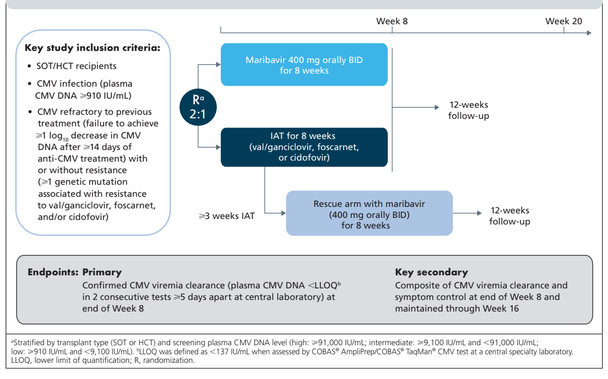
INTRODUCTION

- Use of conventional anti-cytomegalovirus (anti-CMV) therapies in hematopoietic cell transplant (HCT) recipients may be limited by the associated safety events: myelotoxicity, nephrotoxicity, and electrolyte abnormalities.[1,2]
- Maribavir is a potent and orally bioavailable antiviral with multimodal anti-CMV activity.[3,4]
- In the Phase 3 SOLSTICE study (NCT02931539), maribavir was superior to investigator-assigned therapy (IAT; val/ganciclovir, foscarnet, or cidofovir) for the primary endpoint of CMV viremia clearance at Week 8 (55.7% vs 23.9%, respectively) in HCT/solid organ transplant (SOT) recipients with refractory CMV infection (with or without resistance).[5]
  - A consistent benefit of maribavir versus IAT for the primary endpoint was seen for HCT recipients (55.9% vs 20.8%, respectively) in a subgroup analysis.[5]
- The objective of the analyses reported here was to provide additional baseline characteristics and safety data for the HCT subgroup of the SOLSTICE trial.

METHODS

- The Phase 3 SOLSTICE study was a randomized, open-label, multicenter, active controlled study of maribavir compared with IAT in HCT and SOT recipients with refractory cytomegalovirus infection (with/without resistance) aged ⩾12 years.
- Patients were randomized 2:1 to maribavir 400 mg twice daily (BID) or IAT for an 8-week treatment period with 12 weeks follow-up (**Figure 1**).
- Pre-specified analyses for HCT recipients included evaluation of graft outcomes (graft-versus-host disease [GvHD], graft loss) in the randomized set (patients randomized to receive treatment), and any treatment-emergent adverse events (TEAEs) and treatment-related TEAEs in the safety set (all patients who received a dose of study drug).

Figure 1. SOLSTICE study design



[a]Stratified by transplant type (SOT or HCT) and screening plasma CMV DNA level (high: ⩾91,000 IU/mL; intermediate: ⩾9,100 IU/mL and <91,000 IU/mL; low: ⩾910 IU/mL and <9,100 IU/mL). [b]LLOQ was defined as <137 IU/mL when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV test at a central specialty laboratory.
LLOQ, lower limit of quantification; R, randomization.

RESULTS

Patient population and baseline characteristics

- Overall, 352 patients were randomized; of these, 141 had HCT (randomized set: maribavir, n=93; IAT, n=48). One patient in each group did not receive a dose of study drug (safety set: maribavir, n=92; IAT, n=47 [20 val/ganciclovir, 18 foscarnet, 5 cidofovir, 4 >1 IAT]).
- Baseline characteristics are presented in **Table 1**.
- A greater proportion of patients in the maribavir group than in the IAT group had acute GvHD at baseline.

Table 1. Baseline characteristics of HCT recipients

Characteristics	Maribavir (n=93)	IAT (n=48)
Age, years		
Median	58.0	53.0
Range	19–77	19–72
Male sex	48 (51.6)	20 (41.7)
Race		
White	66 (71.0)	35 (72.9)
Black or African American	5 (5.4)	3 (6.3)
Asian	8 (8.6)	7 (14.6)
Other	12 (12.9)	3 (6.3)
Missing	2 (2.2)	0
CMV serostatus		
D+/R+	42 (45.2)	17 (35.4)
D−/R+	39 (41.9)	26 (54.2)
D+/R−	6 (6.5)	3 (6.3)
D−/R−	5 (5.4)	1 (2.1)
Missing	1 (1.1)	1 (2.1)
Type of transplant		
Autologous	1 (1.1)	0
Allogeneic	92 (98.9)	48 (100.0)
Type of preparative conditioning regimen[a]		
Myeloablative	47 (51.1)	16 (33.3)
Non-myeloablative	17 (18.5)	12 (25.0)
Reduced intensity conditioning regimen	28 (30.4)	17 (35.4)
Not applicable	0	1 (2.1)
Missing	0	2 (4.2)
History of transplant(s) prior to current transplant		
No	79 (84.9)	40 (83.3)
Yes	14 (15.1)	8 (16.7)
Acute GvHD	23 (24.7)	8 (16.7)
Chronic GvHD	6 (6.5)	5 (10.4)
Corticosteroids for systemic use[b]	35 (38.0)	21 (44.7)
Immunosuppressants[b]	76 (82.6)	38 (80.9)
Presence of CMV mutation resistant to ganciclovir/foscarnet/cidofovir per central laboratory results		
No	63 (67.7)	25 (52.1)
Yes	18 (19.4)	13 (27.1)
Unable to genotype	12 (12.9)	10 (20.8)

Data are n (%) unless specified otherwise. Baseline is defined as the last value on or prior to the first dose date of study-assigned treatment, or date of randomization for patients who did not receive study-assigned treatment. IAT treatment group included val/ganciclovir, foscarnet, and cidofovir.
[a]Percentages calculated using the subgroup total as the denominator. [b]Assessed for the safety set, therefore denominators are n=92 and n=47 for the maribavir and IAT arms, respectively.
D, donor; R, recipient.

Table 2. Summary of TEAEs and treatment-related TEAEs[a]

Patients, n (%)	Maribavir (n=92)	IAT (n=47)
Any TEAE	91 (98.9)	45 (95.7)
Any treatment-related TEAE	46 (50.0)	25 (53.2)
Any serious TEAE	43 (46.7)	21 (44.7)
Any treatment-related serious TEAE	3 (3.3)	5 (10.6)
Any TEAE leading to treatment discontinuation	20 (21.7)	20 (42.6)
Any treatment-related TEAE leading to treatment discontinuation	6 (6.5)	11 (23.4)
Any serious TEAE leading to death	10 (10.9)	5 (10.6)
Any treatment-related serious TEAE leading to death	0	1 (2.1)

[a]The on-treatment observation phase started at the time of study treatment initiation through 7 days after the last dose of study treatment (21 days for cidofovir), or until maribavir rescue treatment or non-study CMV treatment initiation, whichever was earlier. TEAEs were defined as any adverse event occurring during the on-treatment observation phase. IAT treatment group included val/ganciclovir, foscarnet, and cidofovir.

Table 3. TEAEs reported by >10% of HCT recipients in either the maribavir or IAT treatment arm

Preferred term, patients, n (%)	Maribavir (n=92)	IAT (n=47)	By IAT type[a] Val/ganciclovir (n=20)	By IAT type[a] Foscarnet (n=18)
Nausea	26 (28.3)	15 (31.9)	5 (25.0)	8 (44.4)
Dysgeusia	25 (27.2)	3 (6.4)	1 (5.0)	0
Diarrhea	21 (22.8)	10 (21.3)	5 (25.0)	3 (16.7)
Vomiting	20 (21.7)	14 (29.8)	5 (25.0)	5 (27.8)
Pyrexia	18 (19.6)	9 (19.1)	2 (10.0)	5 (27.8)
Neutropenia	16 (17.4)	13 (27.7)	9 (45.0)	4 (22.2)
Anemia	15 (16.3)	7 (14.9)	4 (20.0)	3 (16.7)
Decreased appetite	12 (13.0)	7 (14.9)	3 (15.0)	3 (16.7)
Fatigue	12 (13.0)	2 (4.3)	2 (10.0)	0
Abdominal pain	11 (12.0)	1 (2.1)	0	1 (5.6)
Edema peripheral	9 (9.8)	5 (10.6)	2 (10.0)	2 (11.1)
Headache	8 (8.7)	9 (19.1)	5 (25.0)	3 (16.7)
Dyspnea	7 (7.6)	5 (10.6)	3 (15.0)	2 (11.1)
Thrombocytopenia	6 (6.5)	6 (12.8)	5 (25.0)	1 (5.6)
Hypokalemia	6 (6.5)	7 (14.9)	0	6 (33.3)
Hypertension	5 (5.4)	5 (10.6)	1 (5.0)	3 (16.7)

[a]Data for cidofovir and >1 IAT were excluded due to low patient numbers (n=5 and n=4, respectively). The on-treatment observation phase started at the time of study treatment initiation through 7 days after the last dose of study treatment (21 days for cidofovir), or until maribavir rescue treatment or non-study CMV treatment initiation, whichever was earlier. TEAEs were defined as any adverse event occurring during the on-treatment observation phase. IAT treatment group included val/ganciclovir, foscarnet, and cidofovir.

Graft outcomes

- Before rescue or alternative anti-CMV therapy, 25/93 (26.9%) patients treated with maribavir and 10/48 (20.8%) patients treated with IAT experienced new GvHD.
- One patient on maribavir had graft loss after Day 124 of the study.
- The median time to new GvHD after first dose of study-assigned treatment was longer in patients treated with IAT (47 [2–123] days) than with maribavir (33 [4–98] days); however, the range was wide for both treatment groups.

Overall safety profile for HCT recipients

- TEAEs occurred in 98.9% of patients receiving study-assigned maribavir and 95.7% of patients receiving IAT (**Table 2**).
- Overall, 50% of patients on maribavir and 53.2% of patients on IAT experienced treatment-related TEAEs.
- A total of 21.7% of patients who received maribavir experienced TEAEs that led to treatment discontinuation compared with 42.6% of patients who received IAT.
- The most common TEAEs were nausea, diarrhea, vomiting, and dysgeusia (**Table 3**).
- More patients experienced dysgeusia with maribavir than with IAT (**Tables 3** and **4**).
- The frequency of hypokalemia TEAE was lower for patients treated with maribavir than with foscarnet (**Table 3**).
- A smaller proportion of patients treated with maribavir than with val/ganciclovir experienced neutropenia (**Tables 3** and **4**).

Table 4. Treatment-related TEAEs reported by >10% of HCT recipients in either the maribavir or IAT arm

Preferred term, patients, n (%)	Maribavir (n=92)	IAT (n=47)	By IAT type[a] Val/ganciclovir (n=20)	By IAT type[a] Foscarnet (n=18)
Dysgeusia	23 (25.0)	1 (2.1)	1 (5.0)	0
Nausea	11 (12.0)	7 (14.9)	1 (5.0)	4 (22.2)
Vomiting	10 (10.9)	3 (6.4)	0	2 (11.1)
Neutropenia	4 (4.3)	6 (12.8)	6 (30.0)	0
Thrombocytopenia	0	5 (10.6)	4 (20.0)	1 (5.6)

[a]Data on cidofovir and >1 IAT were excluded due to low patient numbers (n=5 and n=4, respectively). The on-treatment observation phase started at the time of study treatment initiation through 7 days after the last dose of study treatment (21 days for cidofovir), or until maribavir rescue treatment or non-study CMV treatment initiation, whichever was earlier. TEAEs were defined as any adverse event occurring during the on-treatment observation phase. IAT treatment group included val/ganciclovir, foscarnet, and cidofovir.

CONCLUSIONS

- A small proportion of patients experienced adverse graft outcomes (GvHD and graft loss) in both treatment groups.
- A lower proportion of HCT recipients discontinued treatment with maribavir than with IAT.
- A higher proportion of HCT recipients treated with maribavir experienced dysgeusia than patients treated with IAT.
- Lower rates of neutropenia and hypokalemia were observed with maribavir than with val/ganciclovir and foscarnet, respectively.

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This poster is intended for healthcare providers.