

Prevention of CMV Disease in Allogeneic Stem Cell Transplant Recipients

Ganciclovir

- Prophylaxis - Ganciclovir initiated in all patients at engraftment and continued until day 100 post-transplantation
- Preemptive therapy - Ganciclovir initiated only in patients who become positive for CMV antigen or CMV DNA in blood after transplantation
- Limitation - frequent neutropenia

Foscarnet and Cidofovir

- Second-line agents
- Renal toxicity

MARIBAVIR

- **Chemical class-Benzimidazole**
- **Mechanism - Inhibits UL97 viral protein kinase**
 - **Inhibit viral encapsidation**
 - **Inhibit nuclear egress of viral particles**
- **In vitro, more potent than ganciclovir against CMV, including CMV strains resistant to ganciclovir**
- **Oral bioavailable (>50%)**
- **Phase I study in HIV - patients**
 - **Decreased CMV titers in semen**
 - **Taste disturbance, skin rash**
 - **No myelosuppression**

OBJECTIVE

Evaluate the safety, tolerability, and anti-CMV activity of oral maribavir in CMV-seropositive allogeneic stem cell transplants

STUDY DESIGN

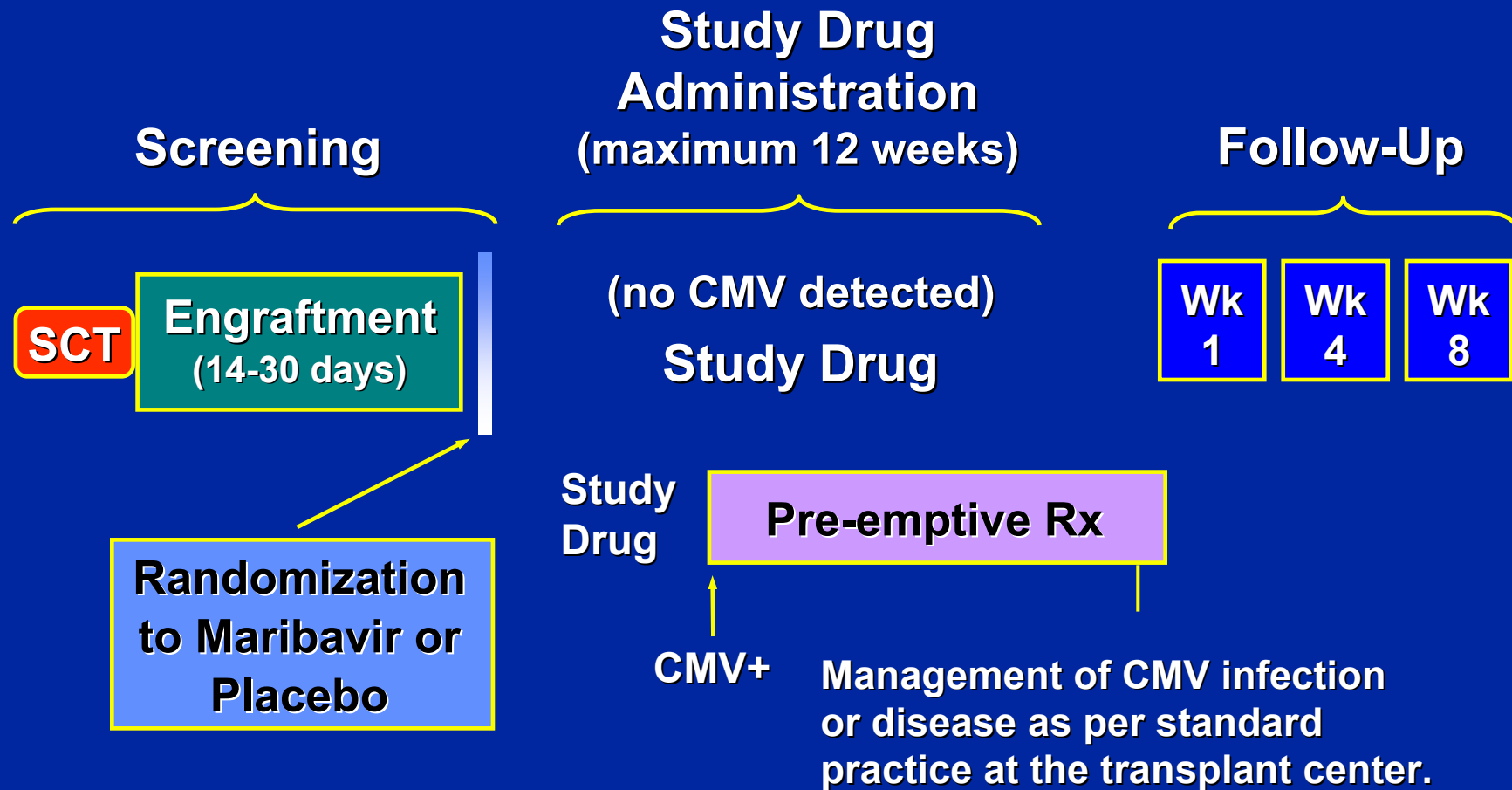
- Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study
- Adult (≥ 18 years) CMV-seropositive recipient of first allogeneic SCT
- Have transplant engraftment (ANC $\geq 500/\text{mm}^3$)
- No detectable CMV infection post-transplant (negative CMV pp65 antigenemia assay and negative plasma CMV DNA PCR assay)
- No prior post-transplant anti-CMV treatment (ganciclovir, foscarnet, high-dose acyclovir, CMVIG)

STUDY DESIGN

- After transplant engraftment, patients randomized to receive oral placebo or oral maribavir at doses of:
 - 100 mg BID; 400 mg QD; 400 mg BID
- Duration of study drug: up to 12 weeks
- CMV surveillance weekly
 - CMV pp65 antigenemia, and
 - Plasma CMV DNA PCR
- If CMV infection or disease detected, study drug stopped and preemptive therapy with ganciclovir or other antiviral could be initiated

CMV Prophylaxis in SCT

Study Design



Patient Characteristics

| | M A R I B A V I R | | | |
|---------------------------------|-------------------|-----------------------|----------------------|-----------------------|
| | Placebo N=28 | 100 mg BID N=28 | 400 mg QD N=28 | 400 mg BID N=27 |
| Median age (range), yrs. | 43 (22-61) | 46 (19-59) | 48 (22-64) | 51 (19-62) |
| Sex, male/female | 15/13 | 17/11 | 18/10 | 10/17 |
| Underlying disease | | | | |
| Acute leukemia | 14 (50%) | 16 (57%) | 16 (57%) | 16 (59%) |
| Lymphoma | 3 (11%) | 1 (4%) | 5 (18%) | 3 (11%) |
| Myelodysplastic syndrome | 4 (14%) | 2 (7%) | 2 (7%) | 2 (7%) |
| Chronic leukemia | 5 (18%) | 5 (18%) | 3 (11%) | 3 (11%) |
| Other | 2 (7%) | 4 (14%) | 2 (7%) | 3 (11%) |
| Donor Type | | | | |
| Related | 15 (54%) | 16 (57%) | 14 (50%) | 14 (52%) |
| Unrelated | 13 (46%) | 12 (43%) | 14 (50%) | 13 (48%) |

Patient Characteristics

| | M A R I B A V I R | | | |
|-----------------------------|-------------------|-----------------------|----------------------|-----------------------|
| | Placebo N=28 | 100 mg BID N=28 | 400 mg QD N=28 | 400 mg BID N=27 |
| Stem-cell source | | | | |
| PBSC | 23 (82%) | 21 (75%) | 24 (86%) | 21 (78%) |
| Bone marrow | 2 (7%) | 6 (21%) | 2 (7%) | 3 (11%) |
| Core blood | 3 (11%) | 1 (4%) | 2 (7%) | 3 (11%) |
| Conditioning regimen | | | | |
| Myeloablative | 20 (71%) | 22 (79%) | 17 (61%) | 19 (70%) |
| Non-myeloablative | 8 (29%) | 6 (21%) | 11 (39%) | 8 (30%) |
| Donor CMV serostatus | | | | |
| Positive | 11 (39%) | 16 (57%) | 17 (61%) | 14 (52%) |
| Negative | 17 (61%) | 12 (43%) | 11 (39%) | 13 (48%) |

CMV Infection or Disease within 100 Days after Transplant

| | M A R I B A V I R | | | |
|---|-------------------|---------------|--------------|---------------|
| | Placebo | 100 mg BID | 400 mg QD | 400 mg BID |
| <u>Evaluable patients, N</u> | <u>N=28</u> | <u>N=27</u> | <u>N=27</u> | <u>N=26</u> |
| CMV infection or disease based on: | | | | |
| CMV pp65 antigenemia | 11 (39%) | 4 (15%)* | 5 (19%) | 4 (15%) |
| Plasma CMV DNA PCR | 13 (46%) | 2 (7%)* | 3 (11%)* | 5 (19%)* |
| Use of anti-CMV therapy | 16 (57%) | 4 (15%)* | 8 (30%) | 4 (15%)* |
| CMV disease | 3 (11%) | 0 | 0 | 0 |

* p≤0.05, Cochran-Mantel-Haenszel test

CMV Disease within 100 Days after Transplant

| | M A R I B A V I R | | | |
|------------------------------|-------------------|---------------------------|---------------|---------------|
| | Placebo | 100 mg BID | 400 mg QD | 400 mg BID |
| Evaluable patients, N | N=28 | N=27 | N=27 | N=26 |
| CMV disease | 3 (11%)* | 0 | 0 | 0 |
| | | p=0.09[†] | p=0.08 | p=0.09 |

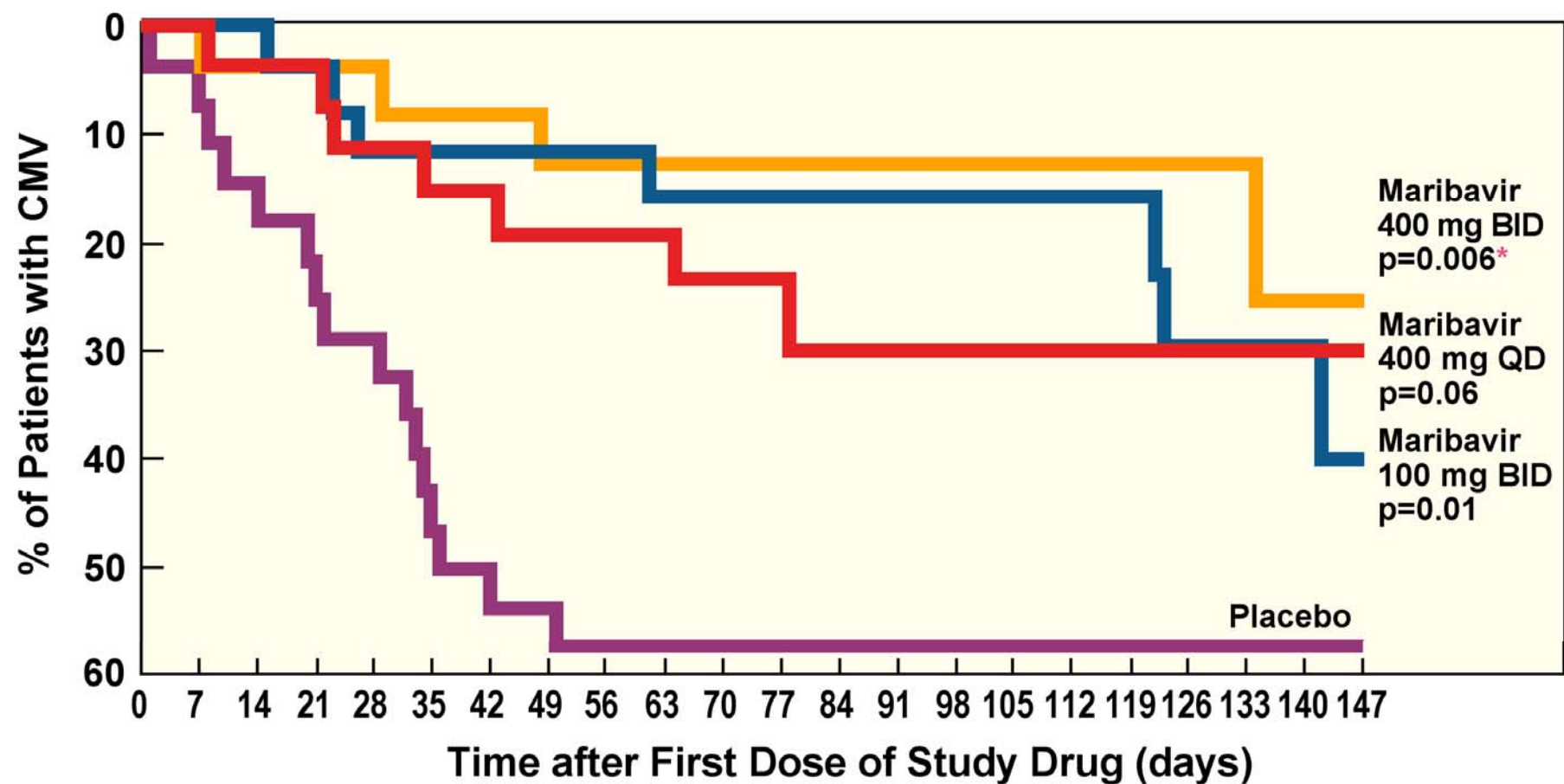
* CMV enteritis (D 42)

CMV enteritis (D 80)

CMV pneumonia (D 45)

[†] Cochran-Mantel Haenszel test

Time to Onset of CMV Infection or Disease



*Cox proportional hazard regression model

Adverse Events Related to Study Drug

MARIBAVIR

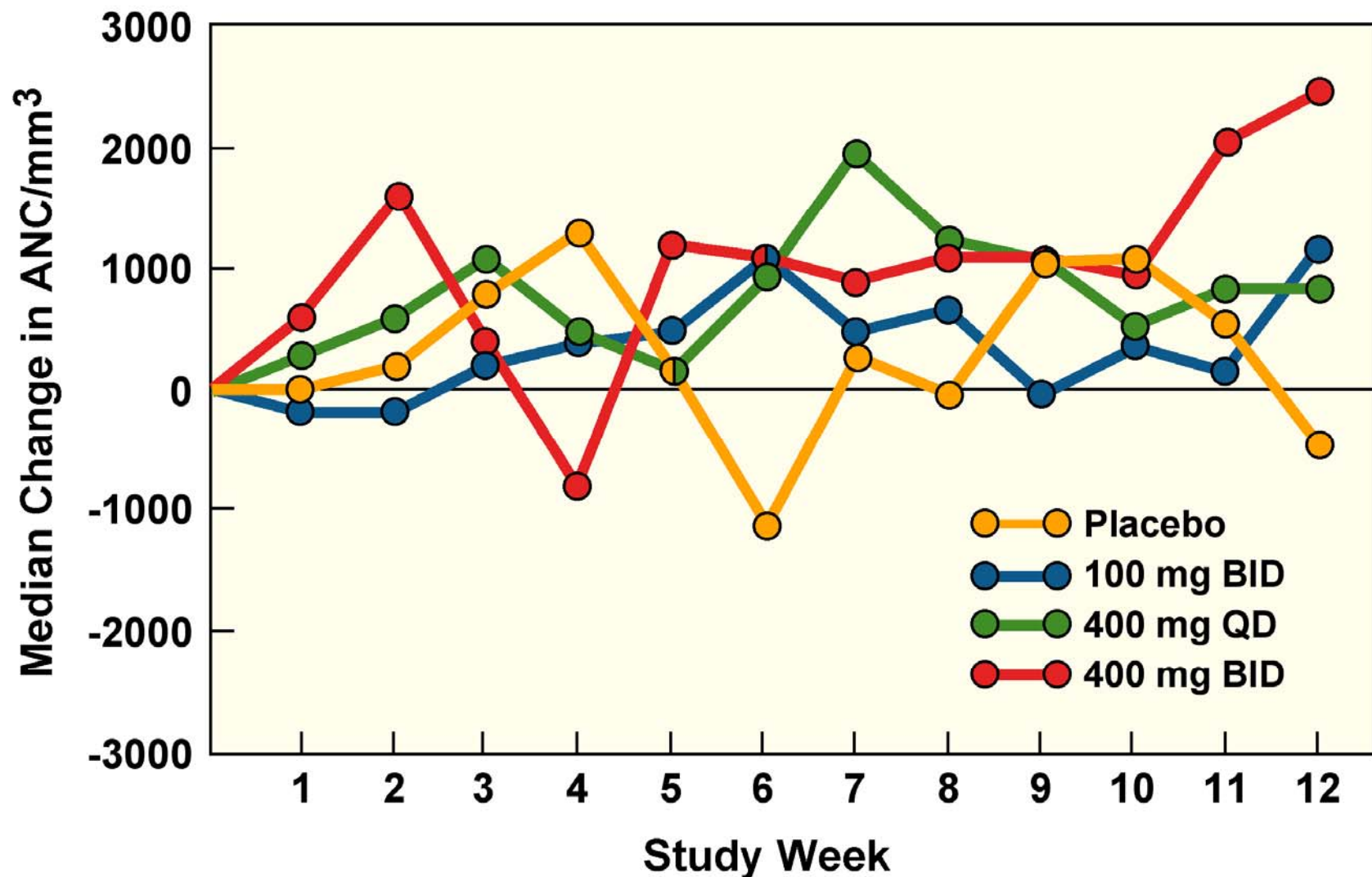
| | Placebo N=28 | 100 mg BID N=28 | 400 mg QD N=28 | 400 mg BID N=26 |
|--|-----------------|-----------------------|----------------------|-----------------------|
| N of patients with ≥ 1 adverse event | 5 (18%) | 10 (36%) | 8 (29%) | 14 (54%) |
| Adverse Events (AE) | | | | |
| Taste disturbance | 0 | 6 (21%) | 5 (18%) | 8 (31%) |
| Nausea | 0 | 2 (7%) | 4 (14%) | 4 (15%) |
| Vomiting | 1 (4%) | 3 (11%) | 3 (11%) | 1 (4%) |
| Diarrhea | 0 | 1 (4%) | 1 (4%) | 0 |
| Rash | 1 (4%) | 2 (7%) | 1 (4%) | 0 |
| Myelosuppression | 1 (4%) | 1 (4%) | 0 | 0 |
| Others | 2 | 7 | 4 | 5 |
| N of patients discontinuing study drug due to AE | 3 (11%) | 4 (14%) | 3 (11%) | 9 (35%) |

Incidence of Neutropenia While Receiving Study Drug

MARIBAVIR

| | Placebo N=28 | 100 mg BID N=28 | 400 mg QD N=28 | 400 mg BID N=26 |
|---|-----------------|-----------------------|----------------------|-----------------------|
| Patients with any occurrence of ANC: | | | | |
| < 1000/mm ³ | 4 (14%) | 6 (21%) | 5 (18%) | 4 (15%) |
| < 750/mm ³ | 4 (14%) | 4 (14%) | 3 (11%) | 3 (12%) |
| < 500/mm ³ | 2 (7%) | 3 (11%) | 2 (7%) | 1 (4%) |

Median Change in ANC from Baseline During Treatment with Study Drug



Graft - Versus - Host Disease (GVHD) During Study Period

| | M A R I B A V I R | | | |
|---|-------------------|---------------|--------------|---------------|
| | Placebo | 100 mg BID | 400 mg QD | 400 mg BID |
| | N=28 | N=28 | N=28 | N=26 |
| N of patients with ≥ grade 2 acute GVHD | 13 (46%) | 4 (14%) | 8 (29%) | 6 (23%) |

Mortality During Study Period

| | M A R I B A V I R | | | |
|-------------------------------|-------------------|-----------------------|----------------------|-----------------------|
| | Placebo N=28 | 100 mg BID N=28 | 400 mg QD N=28 | 400 mg BID N=26 |
| N of deaths | 6 (21%) | 4 (14%) | 3 (11%) | 3 (12%) |
| Causes of death | | | | |
| Relapse of leukemia | 3 | 1 | 2 | 1 |
| GVHD | 2 | 1 | 0 | 1 |
| Bacterial/fungal infection | 1 | 0 | 1 | 0 |
| TTP | 0 | 1 | 0 | 1 |
| Chemotherapy toxicity | 0 | 1 | 0 | 0 |

CONCLUSIONS

- **Maribavir prophylaxis reduces incidence of CMV infection compared to placebo in allogeneic SCT**
- **All maribavir doses tested (100 mg BID, 400 mg QD, 400 mg BID) had similar efficacy in prevention of CMV infection**
- **There were no cases of CMV disease in any maribavir patient, but 3 cases in placebo group**

CONCLUSIONS

- **Maribavir has a favorable safety profile in SCT and does not cause myelosuppression**
- **Taste disturbance, nausea, and diarrhea are the most common adverse events associated with maribavir and may be dose-related
(400 mg BID >100 mg BID or 400 mg QD)**
- **Further controlled studies of maribavir prophylaxis in allogeneic SCT are indicated to establish efficacy for prevention of CMV disease**