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2016 BMT Tandem Meetings

Brincidofovir for Prevention of Cytomegalovirus after Allogeneic Hematopoietic Cell Transplantation in CMV-Seropositive Patients

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trial

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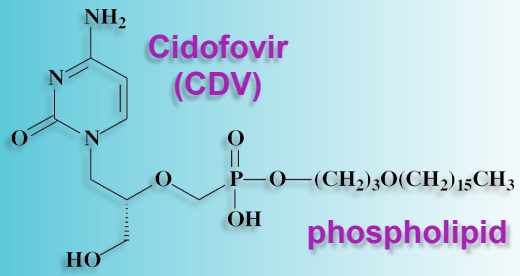
Honolulu • 20 February 2016

Cytomegalovirus in Allogeneic HCT Recipients

- CMV is the most common clinically significant viral infection in allogeneic HCT
- Preemptive therapy reduces the incidence of CMV disease, but CMV seropositivity and early CMV reactivation remain associated with higher mortality in HCT
- Antiviral prophylaxis may be a way to further address the impact of CMV in Allogeneic HCT

Teira et al Blood 2016;Online 16Feb
Ljungman et al CID 2014;59:473-81
Marty et al Blood 2007;110:490-500

Brincidofovir



CMX001

BCV

- Viral DNA polymerase inhibitor that achieves high intracellular antiviral concentrations, active against double-stranded DNA viruses *in vitro*
- Orally bioavailable without evidence of myelotoxicity or nephrotoxicity
- Phase 2 dose escalation trial: BCV 100 mg twice weekly beginning after engraftment through day +90 significantly prevented CMV events vs. placebo
  - 10% vs. 37% (p=0.001); completion rate, 60% vs. 54%
  - Diarrhea was the dose limiting toxicity at 200 mg BIW
  - Diarrhea, other GI symptoms and acute GVHD were more frequent in BCV-treated patients at doses >100mg/week
  - Acute GVHD diagnoses and treatment were driven by diarrhea

Beadle et al AAC 2002;46:2381-6
Marty et al NEJM 2013;369:1227-36

Study Objective

compare the efficacy of brincidofovir to placebo for prevention of CMV

Primary Efficacy Endpoint

- Incidence of **clinically significant CMV infection** through week 24 post-HCT
  - Onset of CMV disease, or
  - Initiation of anti-CMV Preemptive Therapy, based on *central laboratory confirmation* of CMV viremia and *CMV disease risk*
  - Missing data for Week 24 for any reason were considered failures (events) for the primary analysis (death, withdrawal of consent, loss to follow up, other)

Ljungman et al CID 2002;34:1094-97

Study Objective

compare the safety and tolerability of brincidofovir to placebo

Safety Endpoints

- TEAEs, especially ≥ Grade 3 TEAEs
- Diarrhea and other gastrointestinal events
- Acute GVHD, in particular GI GVHD, adjudicated by a blinded GVHD Adjudication Committee
- Hepatobiliary laboratory events
- TEAEs leading to dose interruption, dose reduction, or drug discontinuation

AE: adverse event • **TEAE**: treatment-emergent AE • **GAC**: GVHD adjudication committee

Key Entry Criteria

- ≥ 18 years of age
- Allogeneic HCT recipient
- CMV seropositive (CMV R+)
- No CMV viremia at screening (≤5 days from start)
- No acute liver injury (ALT>5xULN, TBili>2xULN)
- No GI stage ≥2 acute GVHD
- Able to ingest and absorb oral medications
- Able to begin study drug before day +28
  - *Patients were allowed to start study drug pre- or post-engraftment*

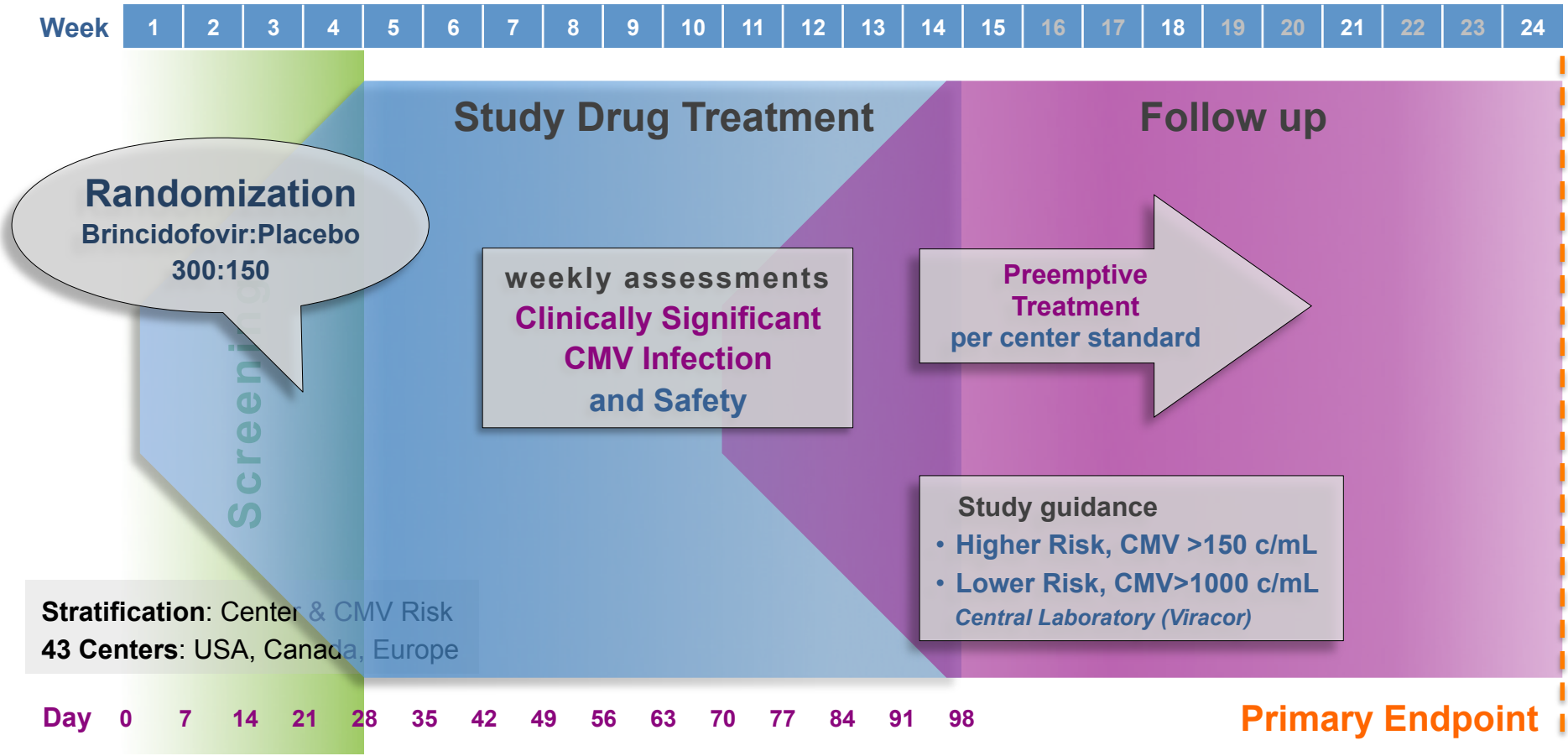
Key Design Concepts

Risk for Clinically Significant CMV Infection

- **Higher Risk**
  - T-cell depletion
  - ATG or alemtuzumab use
  - Cord blood or haploidentical HCT
  - HCT from unrelated or mismatched donors
  - ≥1 mg/kg of prednisone or equivalent for treatment of acute GVHD or other conditions
- **Lower Risk**
  - HCT from matched related donors without higher risk covariates

Green et al BBMT 2012;18:1687-99
Boeckh & Ljungman Blood 2009;113:5711-9

Study Schema



Safety Monitoring and Management Plan Summary

Diarrhea	Definition	Guidance to Investigator
Grade 1	< 4 BM/day <500 cc/24h	Assess for potential infectious and non-infectious causes, **continue** study drug
Grade 2	4-6 BM/day 500-1000 cc/24h	**Consider holding** study drug if >3 days of diarrhea or other grade 2 GI AEs
Grade 3	≥7 BM/day >1000 cc/24h	**Interrupt dosing** • If high-risk of GVHD or other GVHD organ involvement, steroids. If improvement or resolution with steroids, can resume • If low-risk of GVHD, hold on steroids for 3 days, await GI improvement

- Interruption of up to 4 doses (18 days)
- If diarrhea or ALT elevation recurs after resuming drug, then **modify** dose to 200mg/week or **reduce** dose to 100mg/week

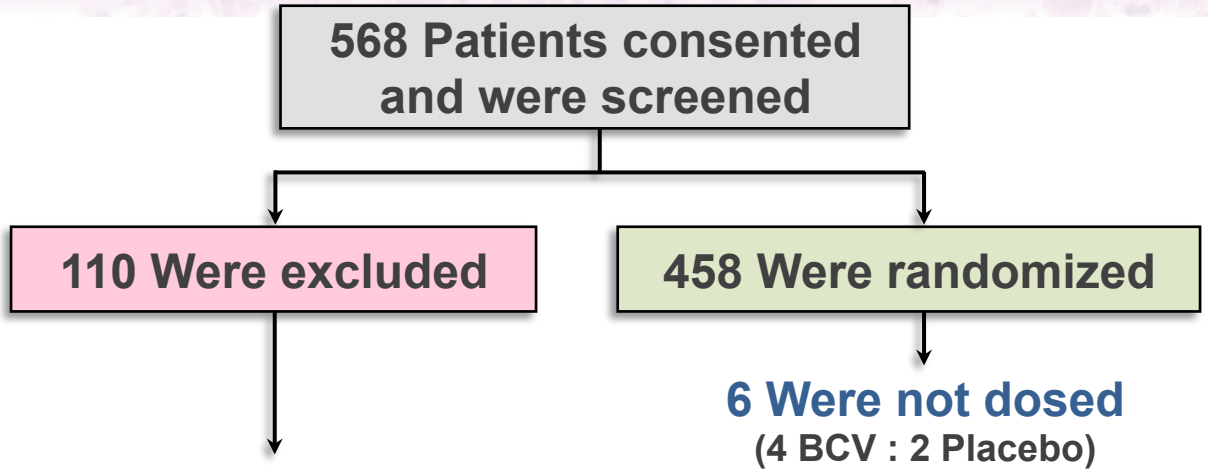
Marty et al NEJM 2013;369:1227-36

Participant Flow

Screening

Recruitment from
August 2013 – June 2015

Study Unblinded
December 2015



Most common reasons

79	(72%)	CMV viremia detected prior to randomization
8	(7%)	Withdrew consent
4	(4%)	Unable to start treatment ≤ day +28
3	(3%)	Unable to take or absorb oral medications
2	(2%)	Exclusionary values for ALT, AST or bilirubin
14	(13%)	Other reasons

Characteristics ITT population — Stratification

CMV Infection Risk N (%)	Brincidofovir 303	Placebo 149
As Randomized		
Higher risk	213 (70.3)	105 (70.5)
Lower risk	90 (29.7)	44 (29.5)
Actual		
Higher risk	223 (73.6)	109 (73.2)
Lower risk	80 (26.4)	40 (26.8)

Characteristics Intent-to-treat Population

	Brincidofovir	Placebo
N (%)	303	149
Median age, y (min, max)	56 (18, 77)	54 (20, 75)
Male sex	163 (53.8)	98 (65.8)
White race	255 (84.2)	123 (82.6)
Hispanic or Latino	27 (8.9)	13 (8.7)
Median weight, kg (min, max)	78.7 (42.2, 122.0)	75.3 (44.0, 138.3)
Donor CMV serostatus		
Seropositive (D+)	154 (50.8)	84 (56.4)
Seronegative (D–)	143 (47.2)	60 (40.3)
Not documented	6 (2.0)	5 (3.4)

Characteristics Intent-to-treat Population

	Brincidofovir	Placebo
N (%)	303	149
Conditioning regimen		
Myeloablative	162 (53.5)	86 (57.7)
Reduced Intensity	134 (44.2)	61 (40.9)
Source of stem cells		
Peripheral blood	241 (79.5)	113 (75.8)
Bone marrow	41 (13.5)	24 (16.1)
Cord blood	19 (6.3)	11 (7.4)
Donor Matching & Relatedness		
Matched Unrelated	148 (48.8)	62 (41.6)
Matched Related	97 (32.0)	52 (34.9)
Mismatched	23 (7.6)	15 (10.1)
Haploidentical	14 (4.6)	8 (5.4)
T-cell depletion	36 (11.9)	20 (13.4)
ATG use	85 (28.1)	47 (31.5)
Alemtuzumab use	26 (8.6)	12 (8.1)

Subject Disposition

Reasons for discontinuing study treatment through week 14 (day +100)

	Brincidofovir	Placebo
N (%)	303	149
CMV treatment	47 (15.5)	51 (34.2)
Adverse event	77 (25.4)	11 (7.4)
Withdrawal by subject	28 (9.2)	9 (6.0)
Investigator decision	9 (3.0)	4 (2.7)
Death on study drug	12 (4.0)	1 (0.7)
Other	14 (4.6)	4 (2.7)
Completed Treatment	116 (38.3)	69 (46.3)

Subject Disposition

Reasons for discontinuing study participation prematurely through Week 24

	Brincidofovir	Placebo
N (%)	303	149
Discontinued Prematurely	71 (23.4)	27 (18.1)
• Death	46 (15.2)	15 (10.1)
• Withdrew consent	23 (7.6)	11 (7.4)
• Loss to follow-up	1 (0.3)	0
• Other	1 (0.3)	1 (0.7)
Completed Study	232 (76.6)	122 (81.9)

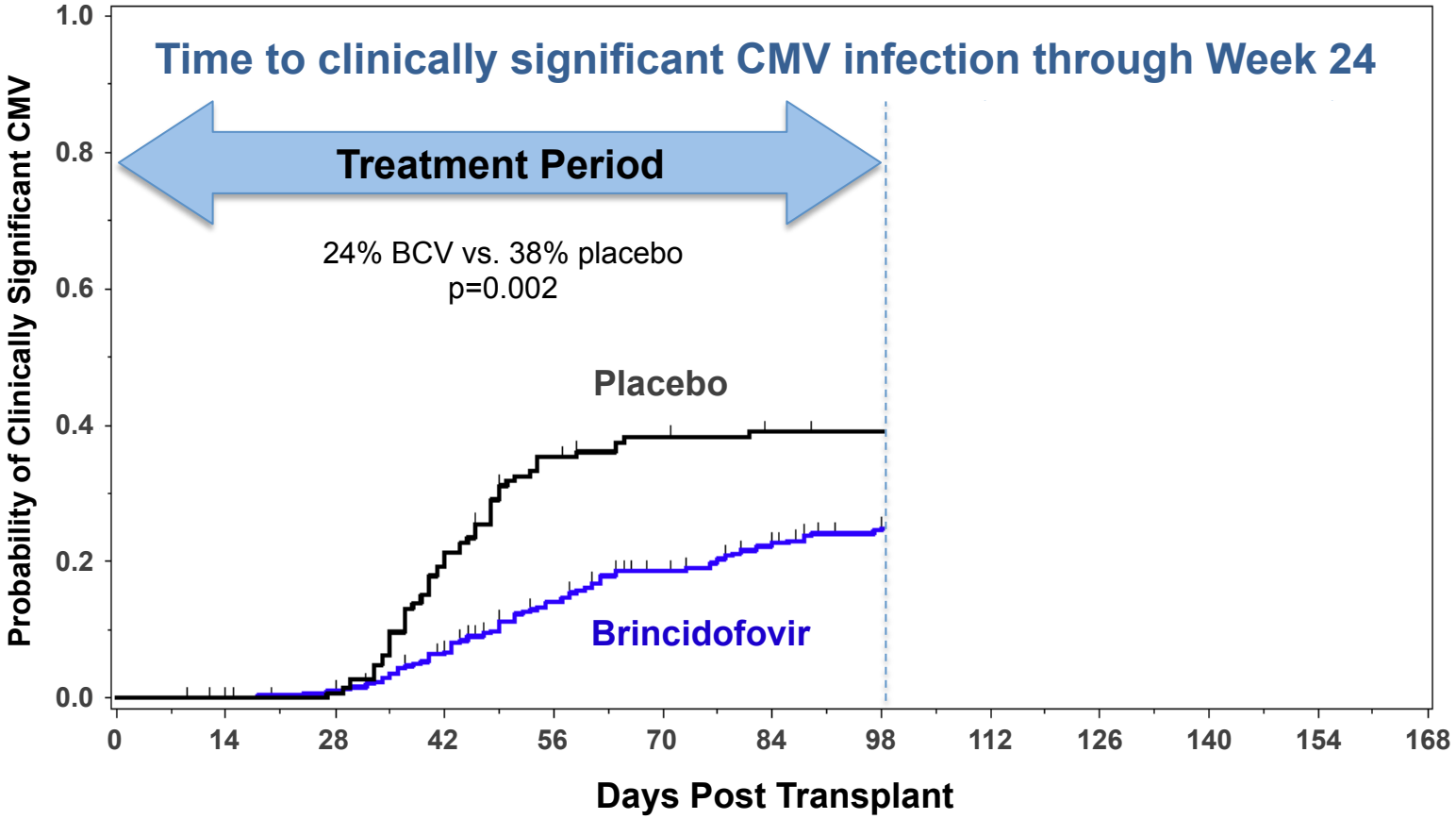
Primary Endpoint

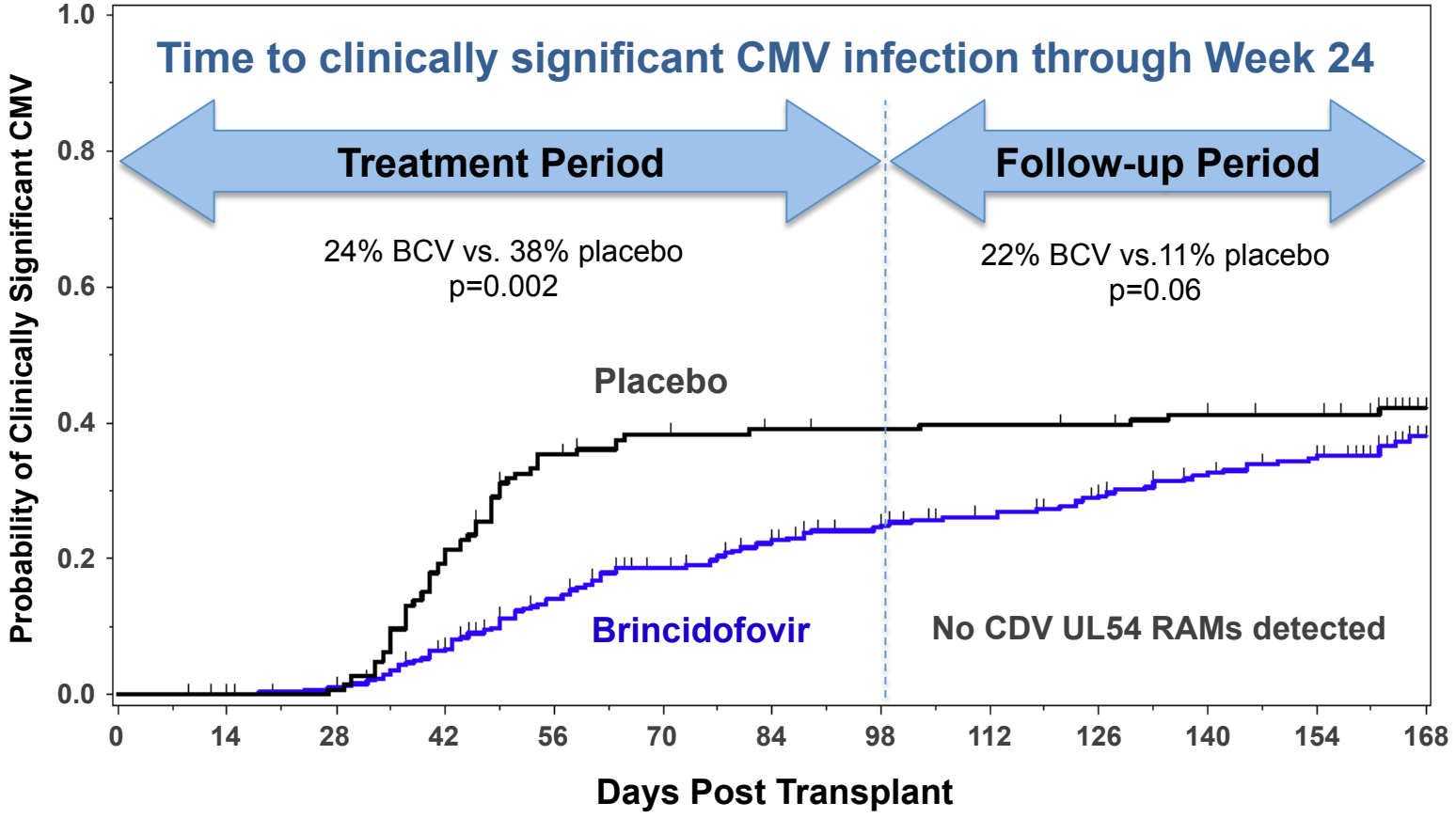
Clinically significant CMV infection Through Week 24

	Brincidofovir	Placebo
N (%)	303	149
Clinically significant CMV infection, week 24*	155 (51.2)	78 (52.3)
CMV end-organ disease	13 (4.3)	5 (3.4)
Preemptive Rx for CMV	88 (29.0)	56 (37.6)
Death without CMV	33 (10.9)	6 (4.0)
Missing outcome	21 (6.9)	11 (7.4)

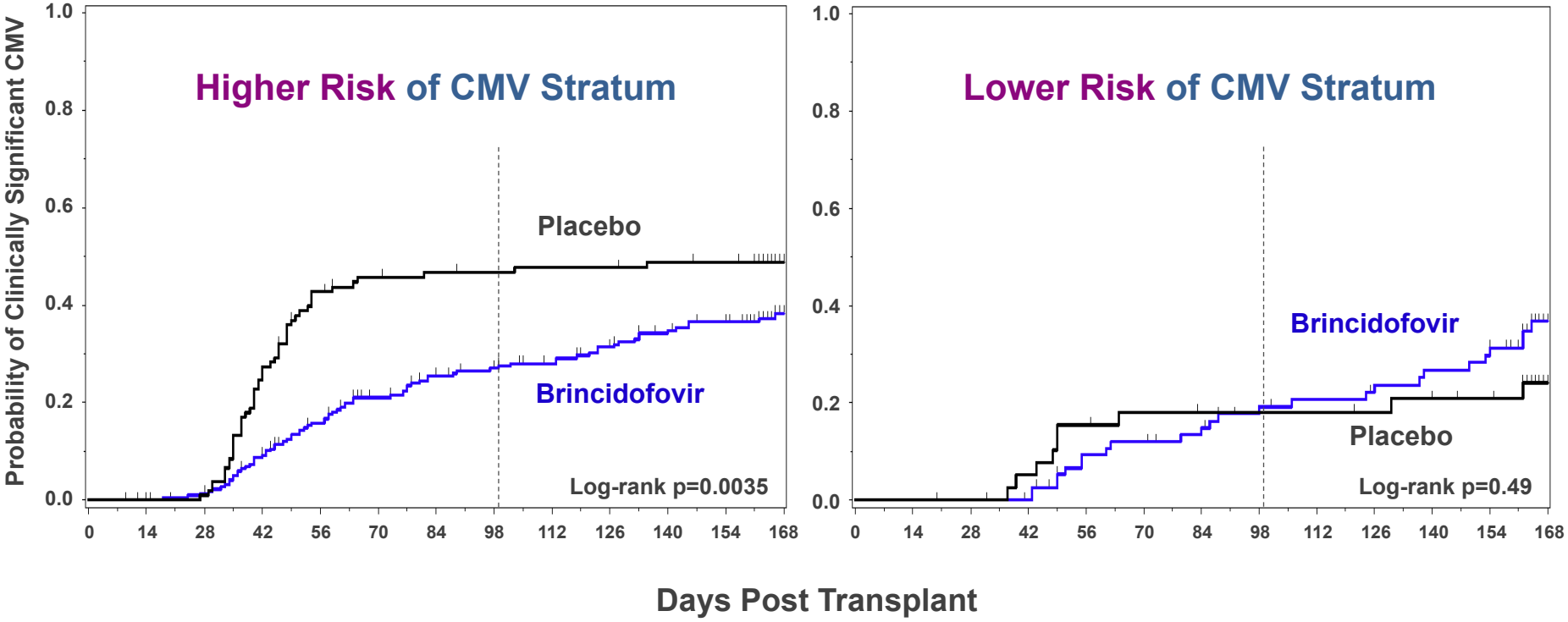
* For patients with >1 event, primary endpoint assigned by hierarchy listed here

CMH Odds Ratio 0.95 (95% CI, 0.64–1.41)

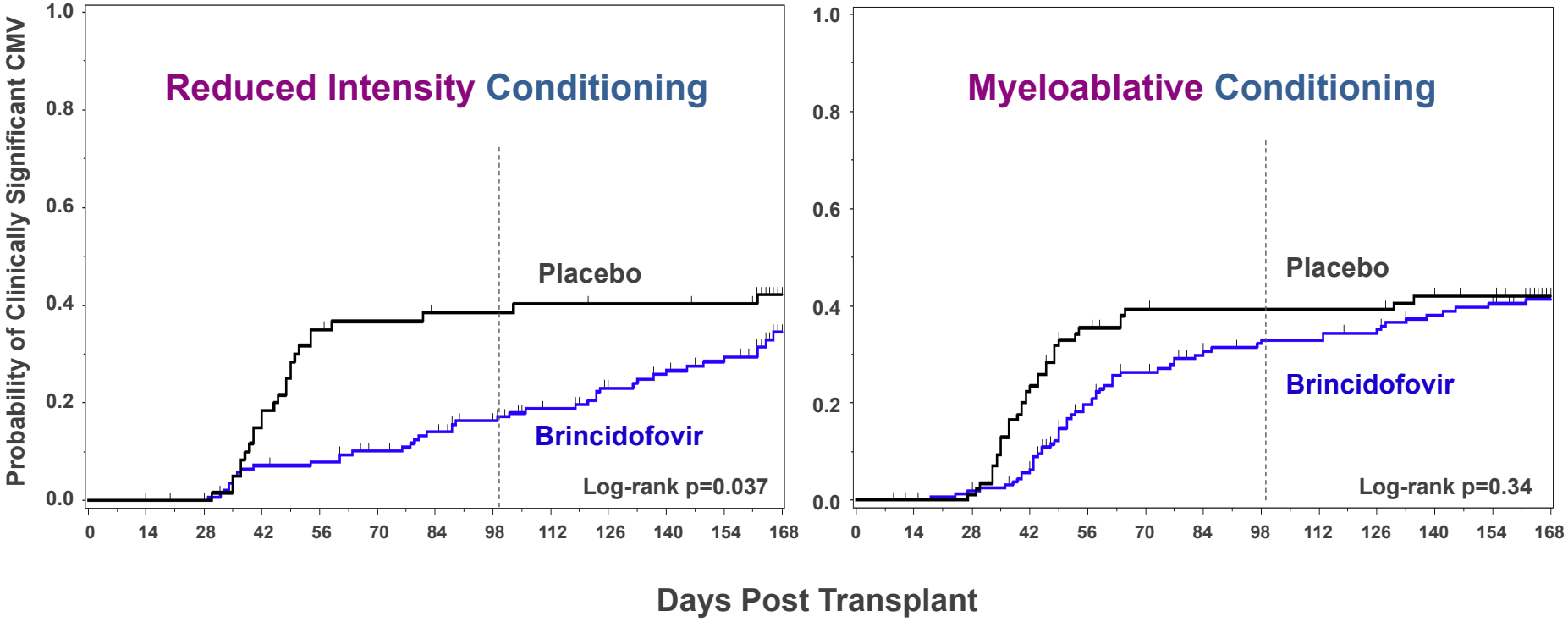

Time to clinically significant CMV infection through Week 24
Treatment Period
24% BCV vs. 38% placebo
p=0.002
Placebo
Brincidofovir
Probability of Clinically Significant CMV
1.0
0.8
0.6
0.4
0.2
0.0
0
14
28
42
56
70
84
98
112
126
140
154
168
Days Post Transplant


Time to clinically significant CMV infection through Week 24
Treatment Period
Follow-up Period
24% BCV vs. 38% placebo
p=0.002
22% BCV vs.11% placebo
p=0.06
Placebo
Brincidofovir
No CDV UL54 RAMs detected
Probability of Clinically Significant CMV
1.0
0.8
0.6
0.4
0.2
0.0
0
14
28
42
56
70
84
98
112
126
140
154
168
Days Post Transplant

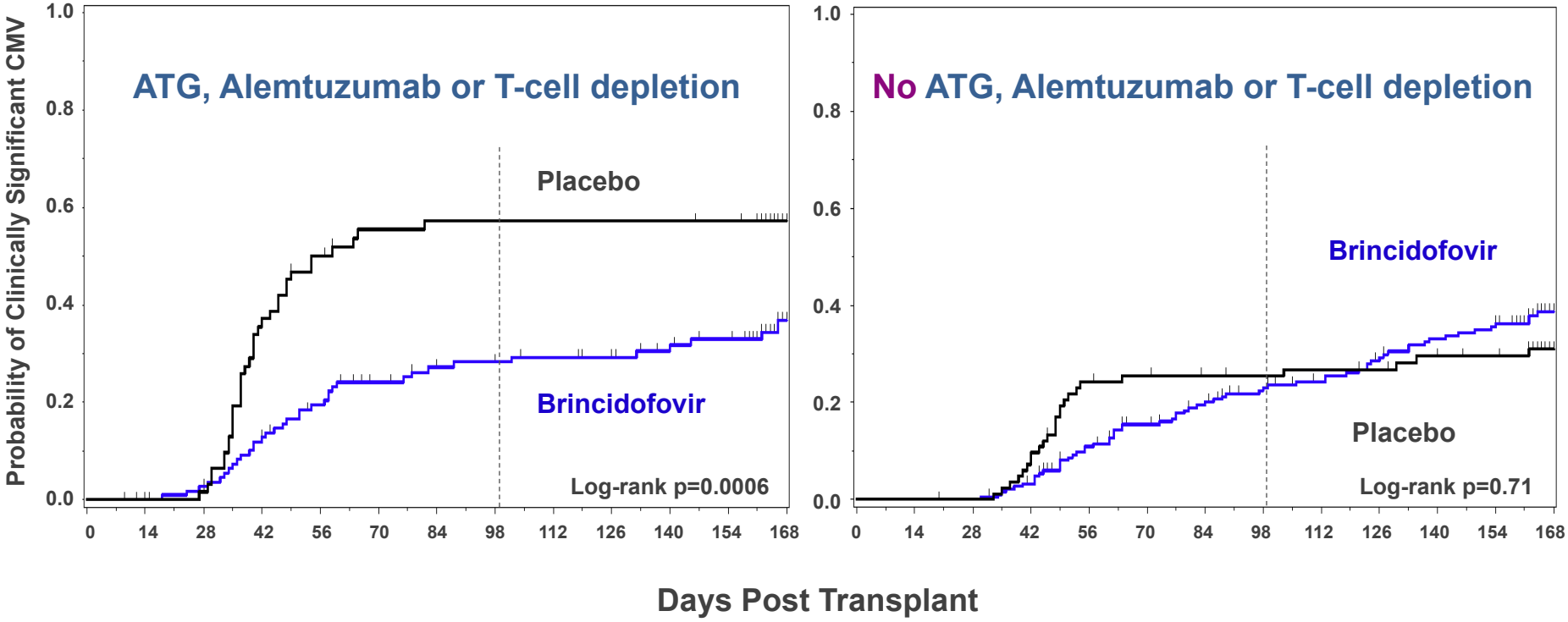
Patients at higher risk for CMV reactivation had better results on BCV



Reduced intensity HCT recipients had better results on BCV



Ex vivo or in vivo T-cell depletion patients had better results on BCV



Safety Analysis

Overall Summary of Adverse Events

	Brincidofovir	Placebo
N (%)	303	149
TEAE, any grade	302 (99.7)	146 (98.0)
CTCAE grade ≥3	203 (67.0)	56 (37.6)
Serious TEAE	173 (57.1)	56 (37.6)
TEAE leading to drug discontinuation	79 (26.1)	11 (7.4)
TEAE leading to drug interruption or change	136 (44.9)	22 (14.8)

AE: adverse events • **TEAE**: treatment-emergent AE • **CTCAE**: Common Terminology Criteria for AE

Safety Analysis

Most Relevant Common Adverse Events, all grades

N (%)	Brincidofovir (n=303)	Placebo (n=149)
Diarrhea	184 (60.7)	54 (36.2)
Acute GVHD	173 (57.1)	48 (32.2)
Abdominal pain	104 (34.3)	26 (17.4)
Nausea	93 (30.7)	29 (19.5)
Vomiting	74 (24.4)	25 (16.8)
Peripheral edema	52 (17.2)	18 (12.1)
Hyperglycemia	48 (15.8)	11 (7.4)
Hypokalemia	47 (15.5)	10 (6.7)
Hypomagnesemia	38 (12.5)	12 (8.1)
ALT elevation	34 (11.2)	9 (6.0)

Safety Analysis

Acute GVHD adjudicated events by blinded GAC

N (%)	Brincidofovir (n=303)	Placebo (n=149)
Likely GVHD	141 (46.5)	33 (22.1)
Presumptive GVHD	60 (19.8)	36 (24.2)
Unlikely GVHD	12 (4.0)	6 (4.0)
Grade I GVHD	25 (8.3)	25 (16.8)
Grade II GVHD	89 (29.4)	33 (22.1)
Grade III GVHD	78 (25.7)	8 (5.4)
Grade IV GVHD	12 (4.0)	5 (3.4)

Blinded GAC was unable to distinguish acute GVHD vs. BCV-induced diarrhea

Safety Analysis

Acute GVHD adjudicated events by blinded GAC

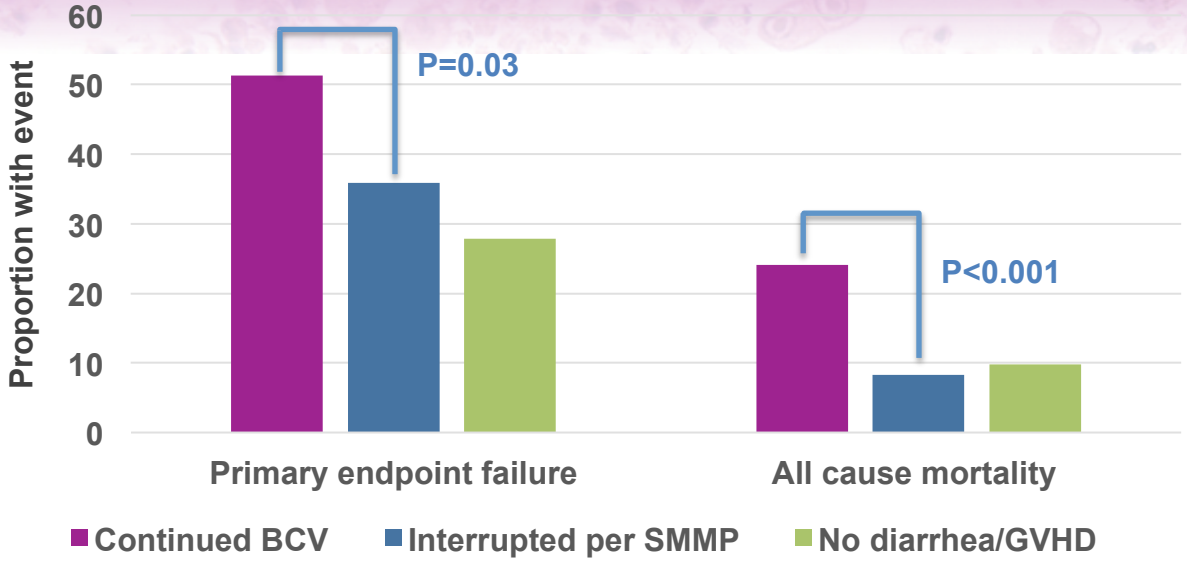
N (%)	Brincidofovir (n=303)			Placebo (n=149)		
Acute GVHD Organ Stage	Skin	Liver	Gut	Skin	Liver	Gut
Stage 1	49 (16.2)	9 (3.0)	88 (29.0)	24 (16.1)	1 (0.7)	28 (18.8)
Stage 2	42 (13.9)	14 (4.6)	40 (13.2)	18 (12.1)	0	7 (4.7)
Stage 3	22 (7.3)	7 (2.3)	33 (10.9)	8 (5.4)	3 (2.0)	2 (1.3)
Stage 4	0	6 (2.0)	13 (4.3)	3 (2.0)	3 (2.0)	3 (2.0)

- **Eight-fold higher use of corticosteroids in the brincidofovir arm**
  Median cumulative prednisone-equivalent of 26 mg/kg vs. 3 mg/kg through week 14

Gastrointestinal Toxicity: BCV effect or Acute GVHD?

- **Did diarrhea lead to empirical GVHD treatment?**
  - Patients were often treated for acute GVHD, with or without holding BCV
  - Holding BCV per SMMP improved outcomes
- **Was GI GVHD misdiagnosed?**
  - Gut biopsy showed apoptosis attributed to acute GVHD, but may in fact have been BCV-related apoptosis (e.g., mycophenolate)
- **Did BCV induce GVHD?**
  - BCV could induce host mucosal injury and generate an alloimmune response
  - However, steroids and continuing BCV was generally not effective

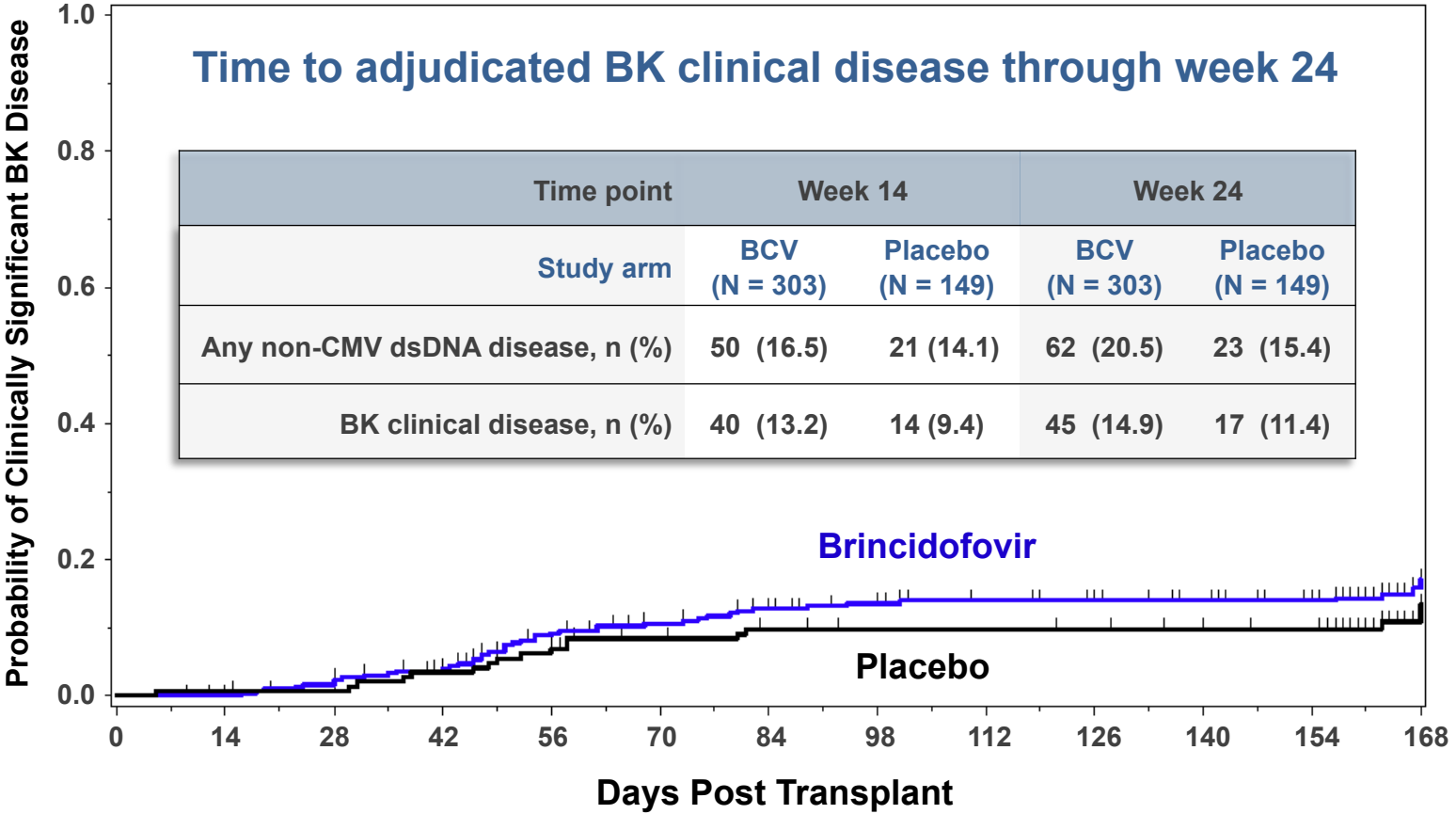
Interruption per SMMP Associated with Better Outcomes among Brincidofovir Patients



- 258 BCV-treated patients had diarrhea grade ≥1 or GI GVHD events by week 8 post-transplant
  - 36% were treated for GVHD and BCV dosing continued
  - 64% followed SMMP, interruption until symptoms improved
- Both failure on the primary endpoint and mortality were improved when SMMP followed

Time to adjudicated BK clinical disease through week 24

Time point	Week 14		Week 24	
Study arm	BCV (N = 303)	Placebo (N = 149)	BCV (N = 303)	Placebo (N = 149)
Any non-CMV dsDNA disease, n (%)	50 (16.5)	21 (14.1)	62 (20.5)	23 (15.4)
BK clinical disease, n (%)	40 (13.2)	14 (9.4)	45 (14.9)	17 (11.4)



Preliminary Efficacy Conclusions

- This trial did not meet its Week 24 endpoint to prevent CMV events after brincidofovir prophylaxis up to Week 14 post transplant
- Brincidofovir prevented CMV events during treatment, especially in patients at higher risk of CMV reactivation (recipients of ATG or alemtuzumab, T-cell depletion)
- No CMV cidofovir-associated antiviral resistance seen
- Preliminary analyses show no benefit against clinical BK events at 100mg twice weekly

Preliminary Safety Conclusions

- **BCV 100 mg twice weekly demonstrated GI adverse events and was associated with increased diagnosis and treatment for acute GVHD**
  - **BCV administration closer to Day 0, intended to prevent earlier CMV events, led to increased GI events, most notably in patients who received myeloablative conditioning**
  - **Treatment for GVHD was associated with increased morbidity, mortality and post-prophylaxis CMV events**
  - **Closely following the protocol's SMMP attenuated the impact of these adverse events**
- **No myelotoxicity or nephrotoxicity were observed on BCV**

Path Forward for Brincidofovir

- **Refine strategies to improve outcomes in HCT recipients**
  - Timing of initiation (particularly in myeloablatives)
  - Alternative routes of administration (IV)
  - Enhance education regarding safety management
- **Optimize risk – benefit**
  - Patients at higher risk for viral reactivation
  - Patients with adenovirus disease
  - Secondary CMV prophylaxis


Thank you!
Photo by Eric Esterle • 500px