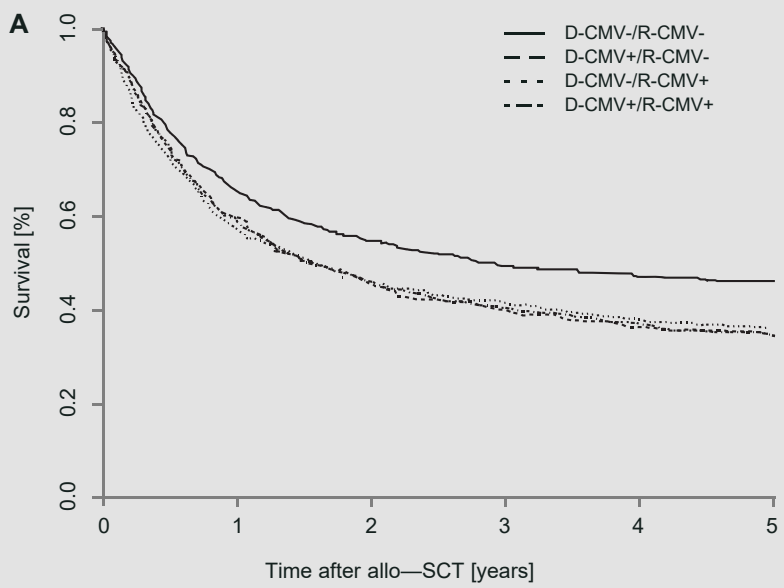
SUPPRESS DATA REVIEW
CMV FORUM, JUNE 2016

M. Michelle Berrey, MD, MPH

CMV Seropositive Patients Have Lower Survival, Even with Preemptive Therapy

- CMV seropositive patients (and/or seronegative recipients of HCT from seropositive donor) have lower overall survival vs. CMV D-/R- [reviewed in (1)]
  - Mechanism: non-relapse related (predominantly infectious) mortality
  - More pronounced after T-cell depleted or MM/URD HCT
- In recent EBMT analysis, CMV seropositivity of either donor or recipient reduced 2 year survival in ALL patients (46% vs 55% in CMV -/-)[2]

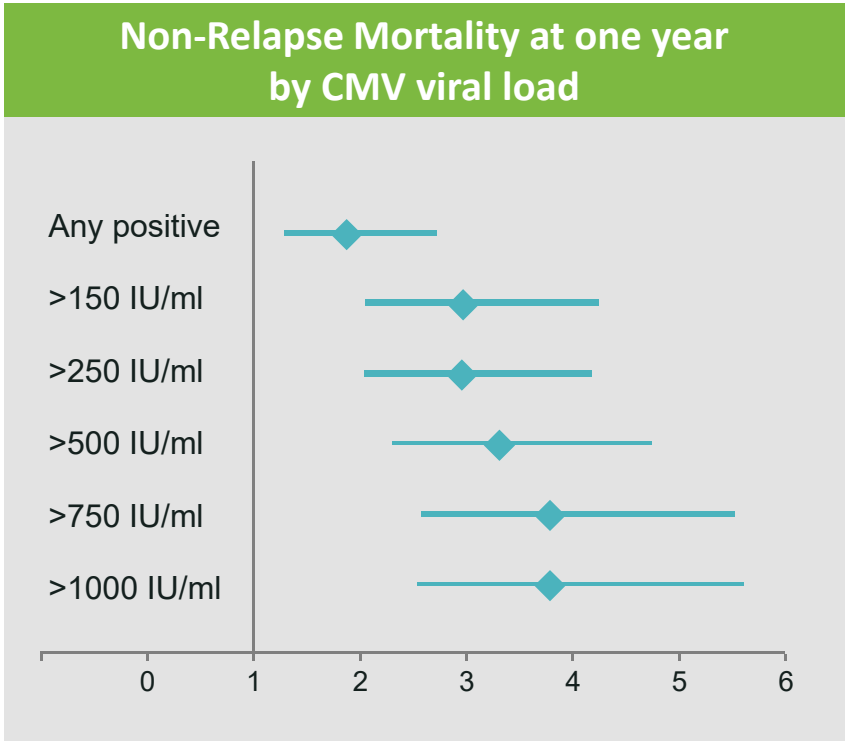
Survival by CMV serostatus [2]



[1] Boeckh and Nichols, Blood 2004;103:2003-2008
[2] Schmidt-Hieber et al, Blood 2013;122(19):3359-3364

Reactivation of CMV Increases Mortality Rate in HCT Recipients

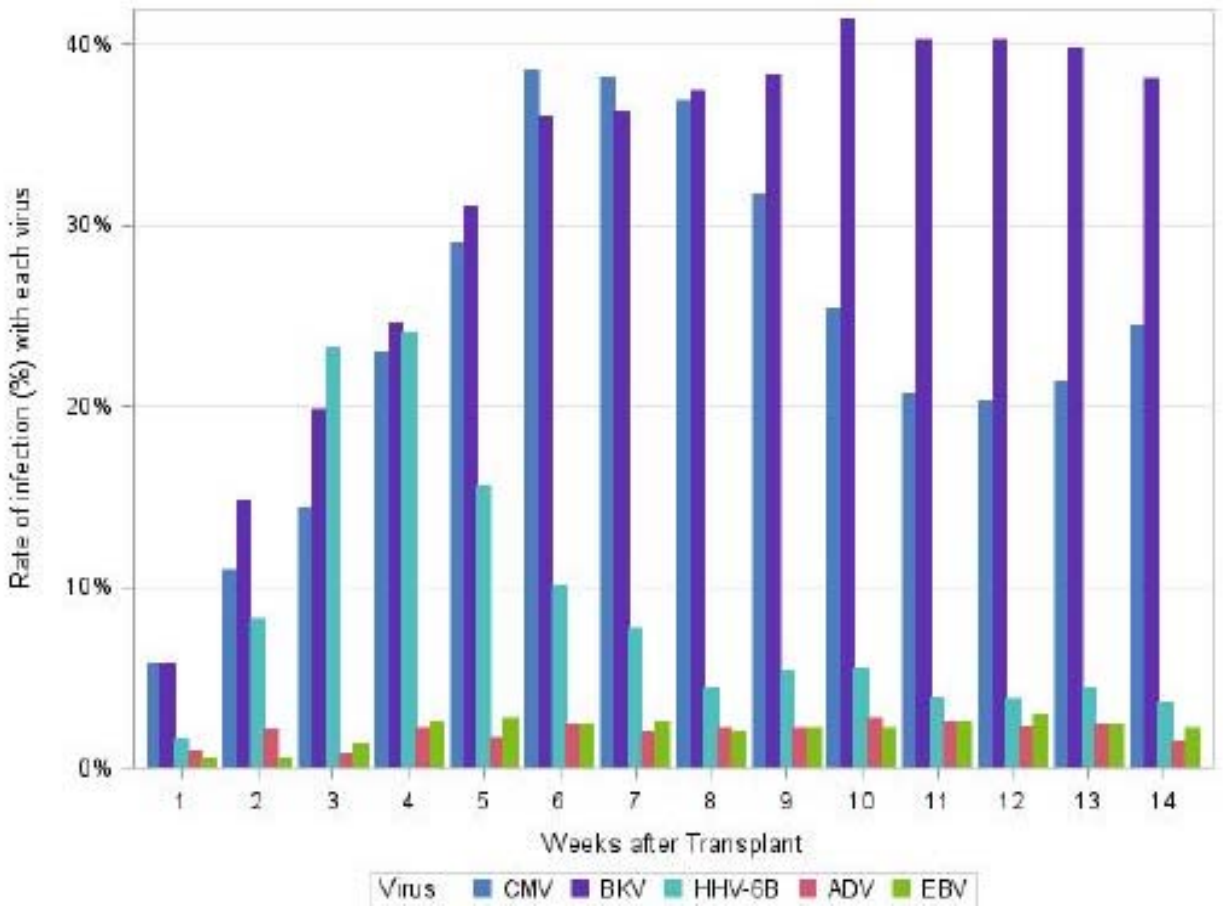
- Non-relapse mortality in FHCRC cohort was 18% at one year (167/926)
- Any positive plasma CMV DNA was associated with two-fold hazard for mortality, with higher HR observed in those with higher CMV viral loads
  - Implication #1: CMV preemptive therapy does not fully address mortality disadvantage
  - Implication #2: if preventing CMV viremia improves outcomes, it should be considered valid surrogate



FHCRC, 2007-2013
Green ML et al. ICAAC 2014, Washington DC.

DNA Viral Infections Are Frequent, Persistent and Associated with Mortality after Allogeneic HCT

- Weekly plasma samples through 100 days post-HCT were tested at the FHCRC for 404 HCT recipients
- Multiple DNA virus detection was associated with increased mortality, even after controlling for acute GVHD
- Improved prevention strategies are needed



Hill J et al. Tandem BMT 2016, Honolulu, HI.

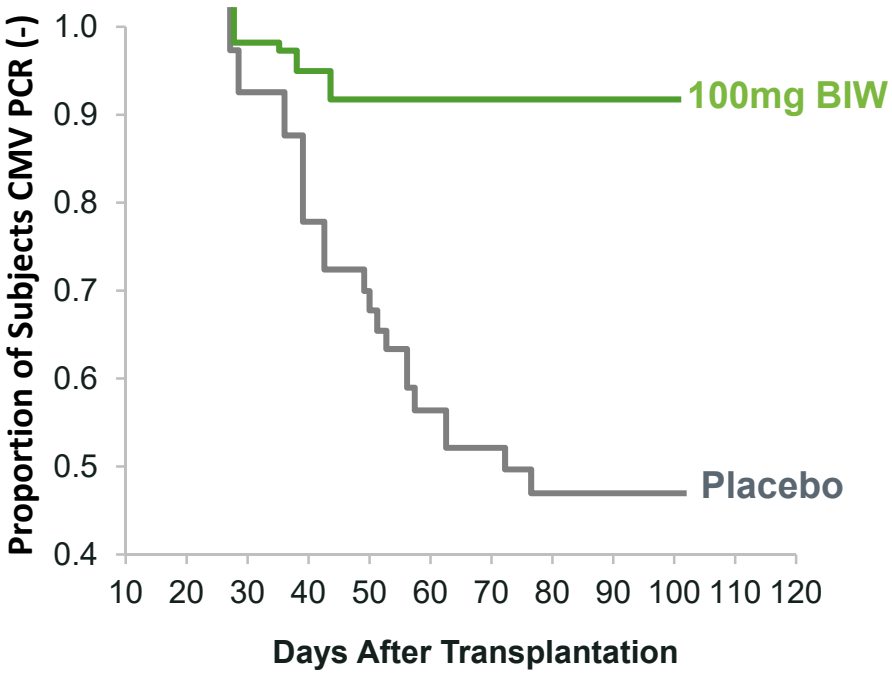
Brincidofovir (BCV): A broad spectrum antiviral

Viral Family	Virus	Brincidofovir	Cidofovir	Ganciclovir*	Foscarnet	Acyclovir	Maribavir	Letermovir
Herpes	Cytomegalovirus (CMV, HHV-5)	0.001	0.4	3.8	50-800	>200	0.31	0.005
	Epstein-Barr Virus (EBV, HHV-4)	0.03	65.6	0.9	<500	6.2	0.63	>10
	Human Herpesvirus 6 (HHV-6A)	0.003	2.7	5.8	16	10	Inactive	>10
	Human Herpesvirus 8 (HHV-8)	0.02	2.6	8.9	177	>100	Inactive	—
	Herpes Simplex Virus 1 (HSV-1)	0.01	3.0	0.7	92-95	3.8	Inactive	>10
	Herpes Simplex Virus 2 (HSV-2)	0.02	6.5	2.5	91-96	4.4	Inactive	>10
	Varicella Zoster Virus (VZV, HHV-3)	0.0004	0.5	1.3	39.8	3.6	Inactive	>10
Adenovirus	Adenovirus (AdV-B7)	0.02	1.3	4.5-33	Inactive	>100	—	>10
Polyoma	BK Virus (BKV)	0.13	115	>200	Inactive	>200	—	—
	JC Virus (JCV)	0.045	>0.1	—	Inactive	—	—	—
Papilloma	Human Papillomavirus 11 (HPV-11)	17	716	Inactive	—	Inactive	—	—
Pox	Variola	0.1	27	—	—	—	—	—
	Vaccinia	0.8	46	>392	Inactive	>144	—	—

Successful CMV Prevention in Dose-Ranging Phase 2 Study

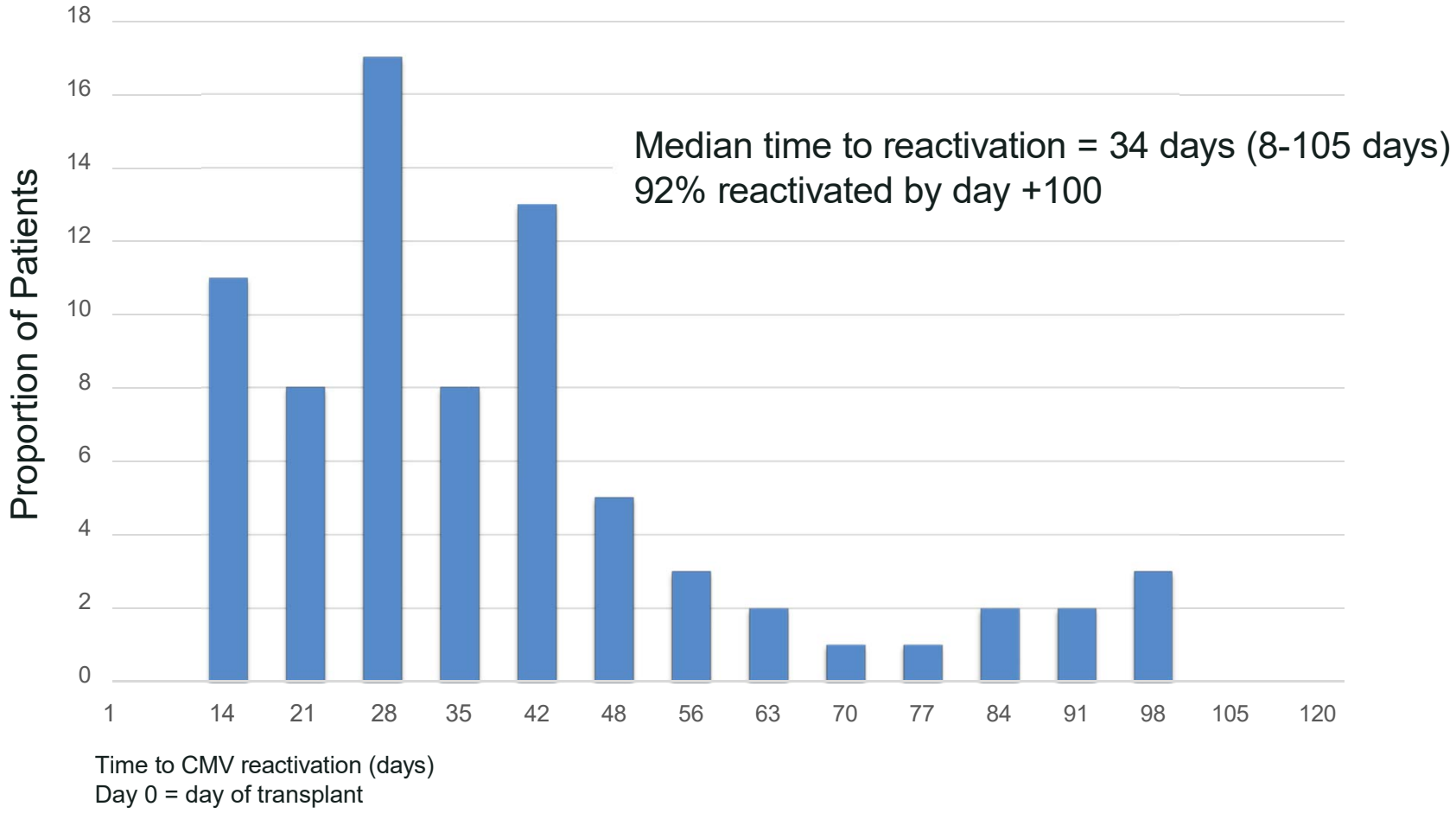
- High risk allogeneic HCT recipients (CMV R+)
- BCV 100 mg BIW selected on basis of CMV suppression, safety, and tolerability
- No nephrotoxicity – improved eGFR compared to pbo
- Hematologic safety – which allowed earlier dosing in SUPPRESS to prevent viral reactivation in first weeks after transplant
- No resistance detected

Brincidofovir Prevented CMV Reactivation in HCT Recipients in Study 201



Marty et al, NEJM, January 2013
Beadle et al AAC 2002;46:2381-6.

Earlier Dosing After Transplant Pursued to Prevent Early CMV Reactivation



Jain et al; NIH BMT Tandem March, 2014

SUPPRESS

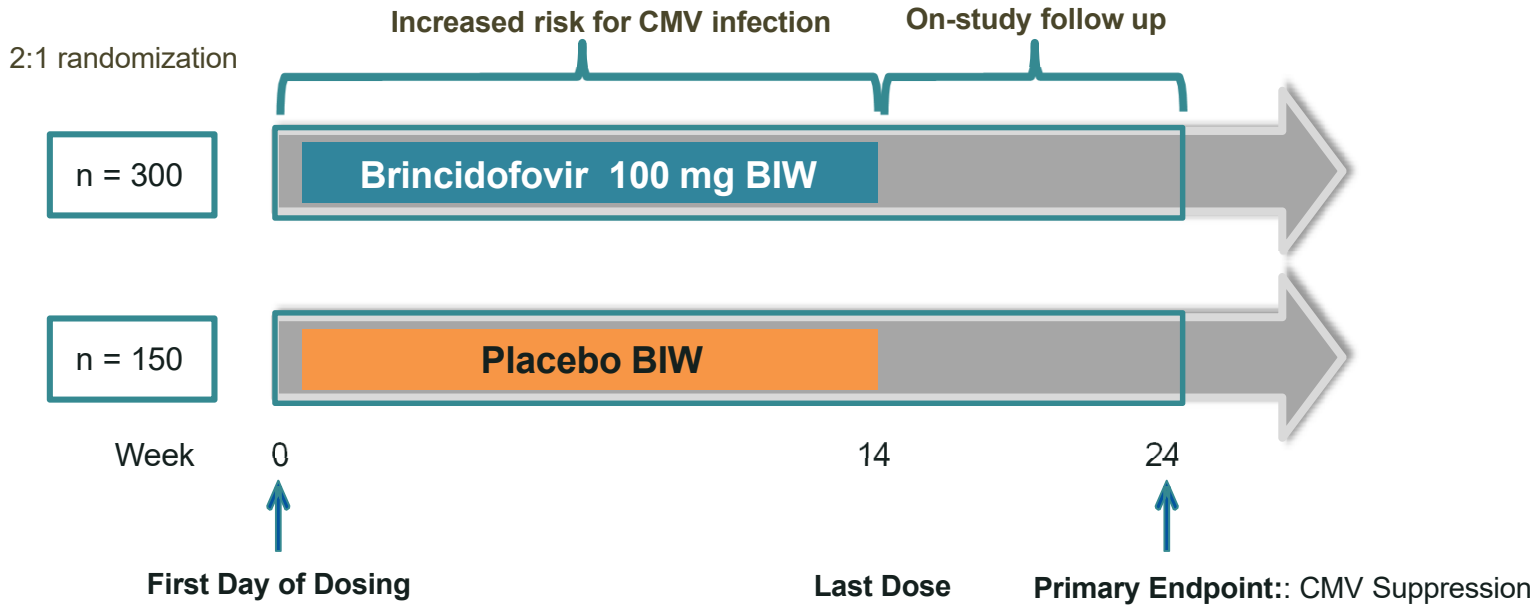
BRINCIDOFOVIR FOR PREVENTION OF CYTOMEGALOVIRUS (CMV) AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN CMV-SEROPOSITIVE PATIENTS:

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP PHASE 3 TRIAL

Francisco M. Marty, Drew J. Winston, Roy F. Chemaly, Michael J. Boeckh, Kathlene M. Mullane, Tsiporah B. Shore, Genovefa A. Papanicolaou, Marion E. Morrison, Thomas M. Brundage, and Herve Mommeja-Marin

Phase 3 SUPPRESS Trial

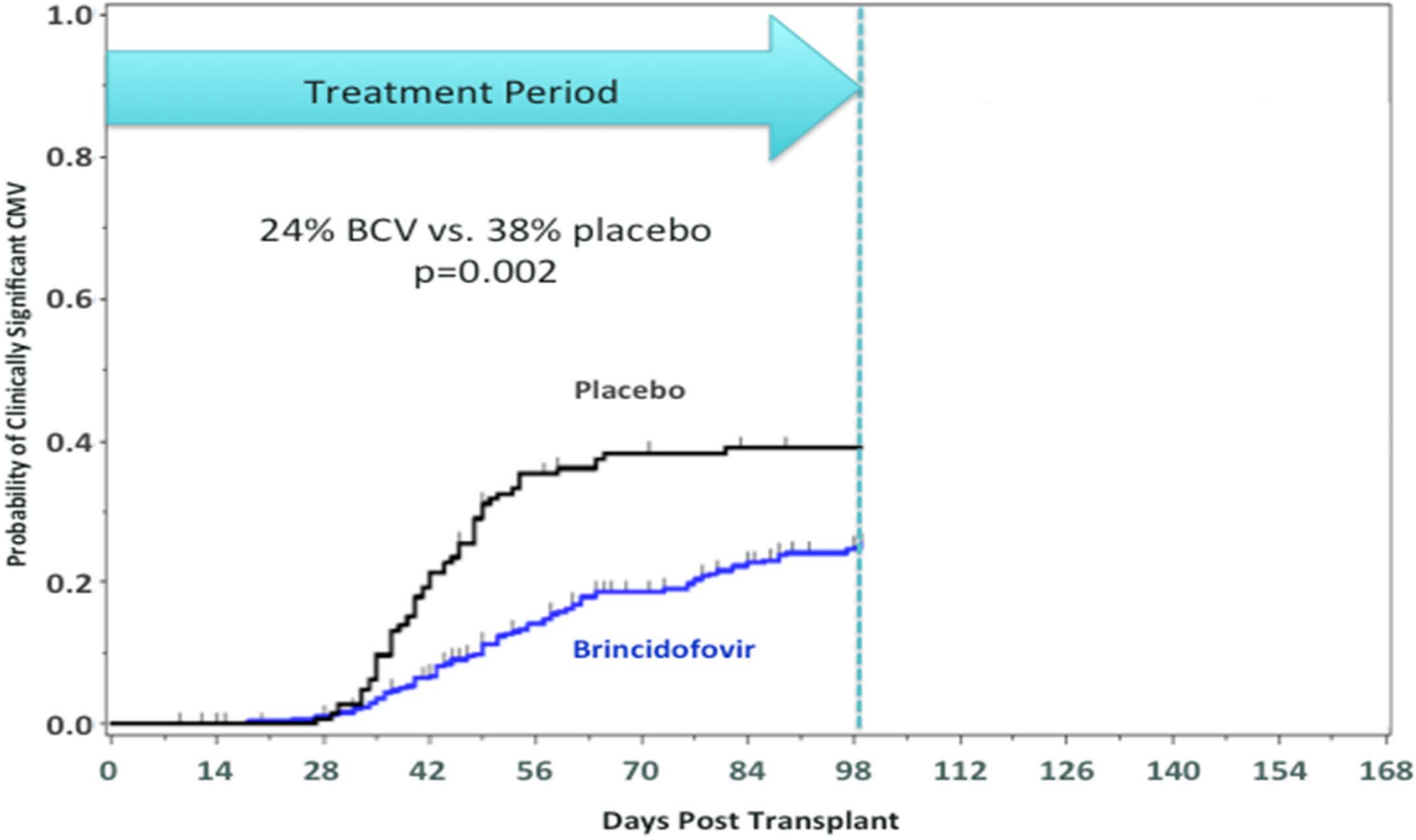
- **Population:** High-risk allogeneic HCT recipients, evidence of prior CMV infection (CMV R+)
- **Primary endpoint:** Prevention of CMV infection through Week 24
- **Design:** Superiority vs. current standard of care (placebo and monitoring)
- **Power:** >85% power to detect 50% reduction in CMV events vs. placebo
- **Dosing:** Began when patient can swallow tablet; twice-weekly through Week 14



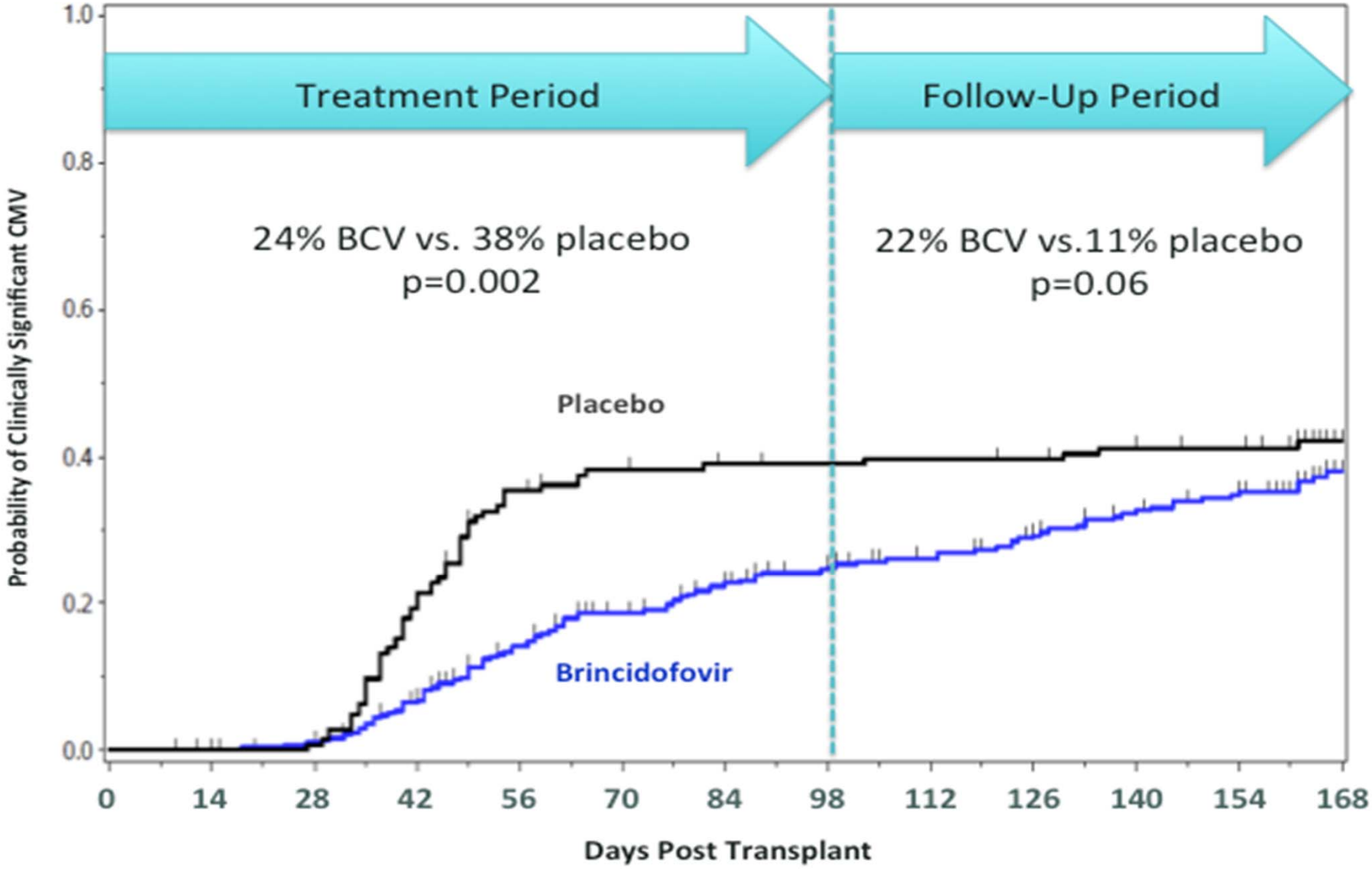
SUPPRESS Phase 3 Results

- During the on-treatment period through Week 14 after HCT:
  - Statistically lower proportion of subjects in the brincidofovir arm had CMV reactivation, consistent with the positive antiviral effect of the compound seen in Phase 2
  - CMV reactivation in the placebo arm occurred predominantly in the 1st 60 days after HCT
- During the 10 weeks off-treatment from Week 14 to Week 24:
  - An increase in CMV infections was observed in subjects randomized to BCV
- At Week 24, a numerical but non-statistically significant increase in mortality was noted in subjects randomized to BCV
- CMV infections and mortality in the brincidofovir arm were strongly correlated with high-dose corticosteroids and other immunosuppressive agents which were given in response to diagnoses of GI graft-versus-host-disease (GVHD)

SUPPRESS: Fewer Subjects Reactivated CMV During On-drug Period



SUPPRESS: More Infections Occurred on BCV Arm During Off-drug Period



GVHD Events on BCV were Predominantly Gut, not Skin, Suggesting Diagnosis was Driven by Diarrhea

N (%)	Brincidofovir (n=303)			Placebo (n=149)		
GVHD Stage	Skin	Liver	Gut	Skin	Liver	Gut
Stage 1	49 (16.2)	3 (1.0)	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)	0	3 (2.0)	3 (2.0)

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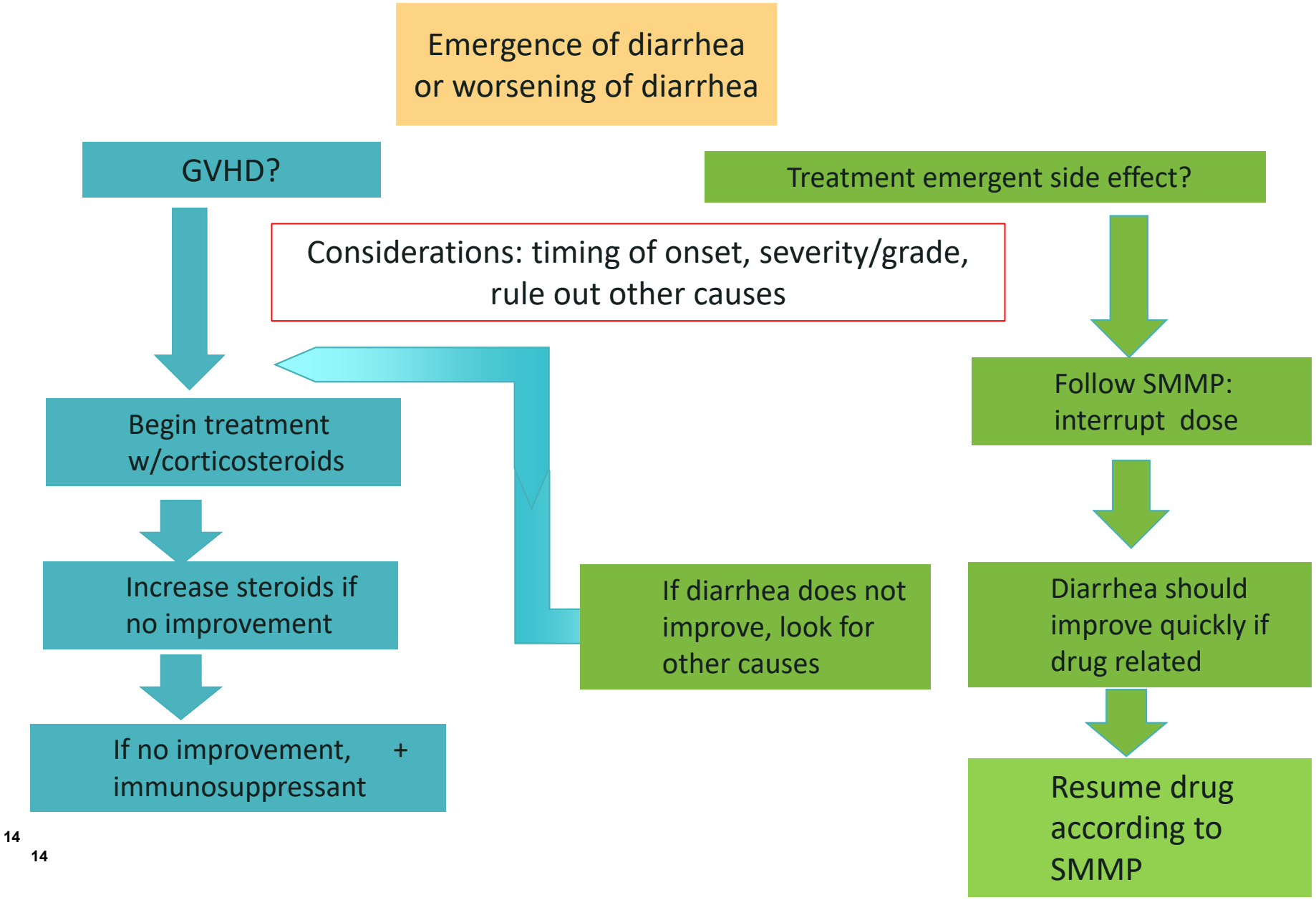
How Was Diarrhea Managed in SUPPRESS?



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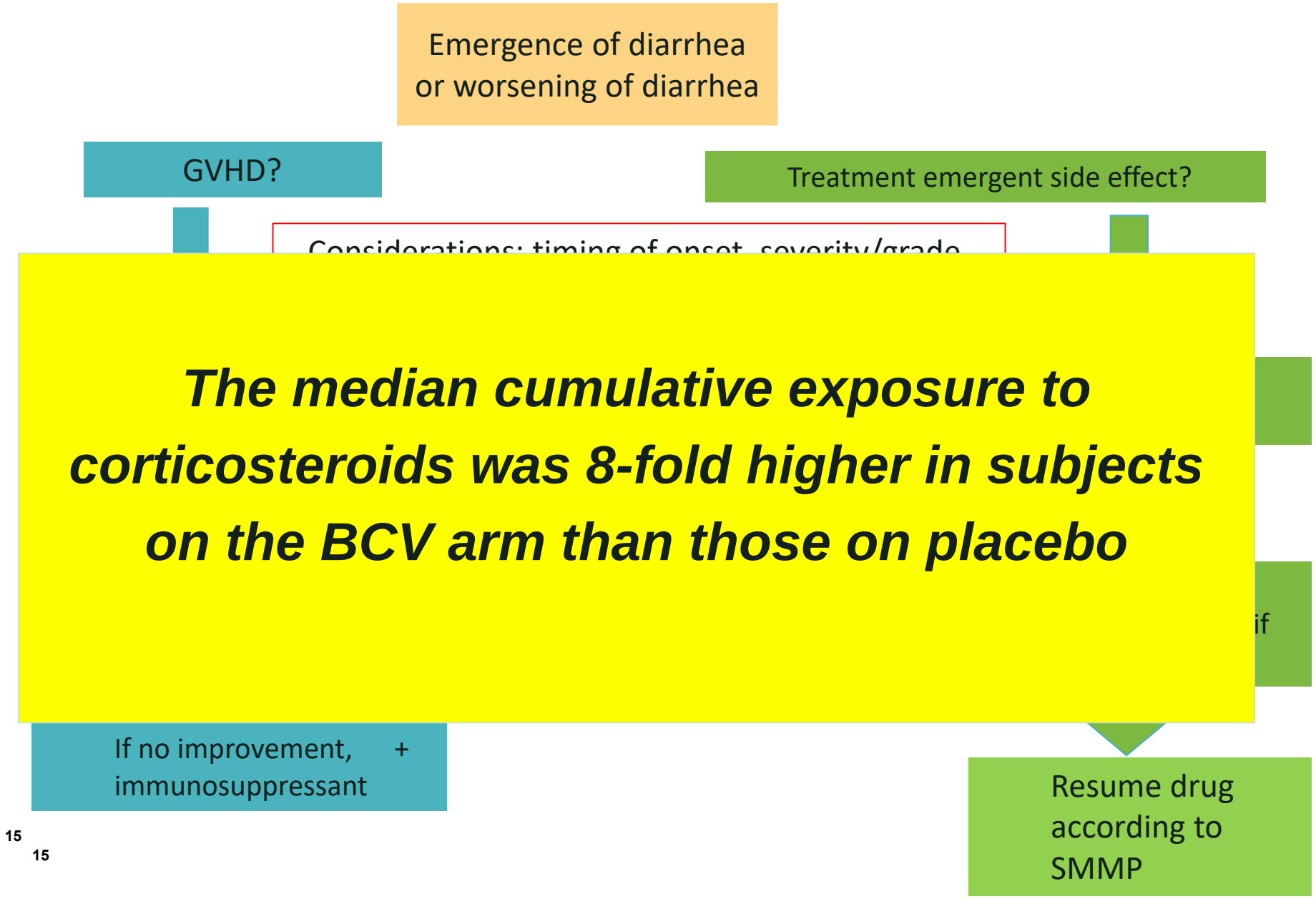

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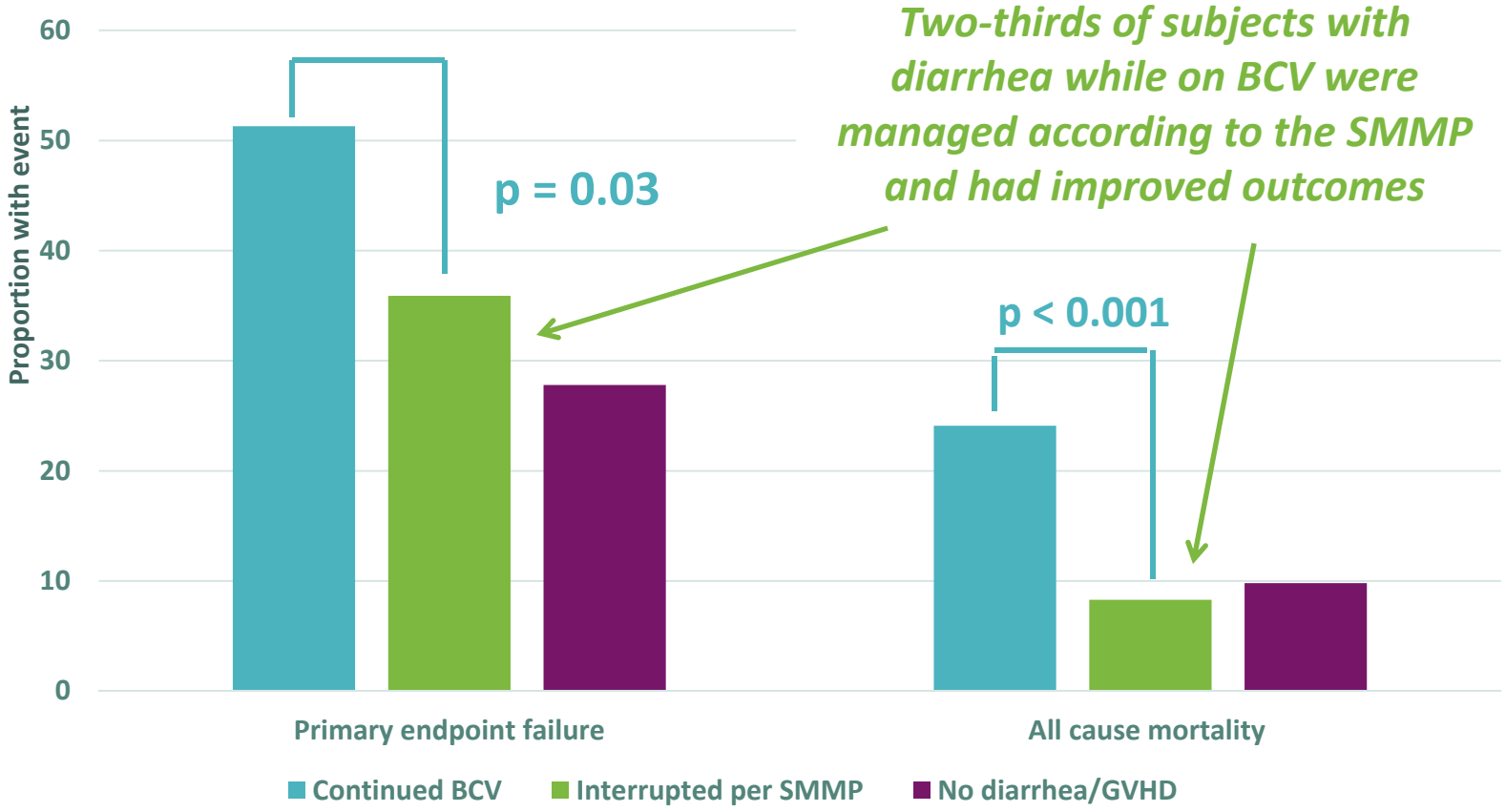
SUPPRESS: Divergence from Ph 2 was Driven by Presumptive Diagnosis of GVHD, Treatment with Steroids

- GI adverse events known to occur with brincidofovir may mimic the presentation of gut GVHD:
  - A colon biopsy from a kidney transplant recipient with diarrhea on BCV had crypt apoptotic bodies consistent with GVHD
  - Responded to interruption of study drug

- Increased rate of presumptive gut GVHD in BCV cohort, but:
  - Many patients were diagnosed based on clinical presentation
  - Comparable rates and severity skin GVHD
- Diarrhea persisted in those patients who continued BCV dosing
  - Lead to increased steroid use and some second-line immune suppressing agents (monoclonal Ab, biologics, etc.) in patients considered to have “steroid refractory GVHD”

Among Subjects on BCV With Diarrhea, Interruption of Study Drug Lead to CMV Prevention and Lower Mortality



Brincidofovir Intravenous Formulation

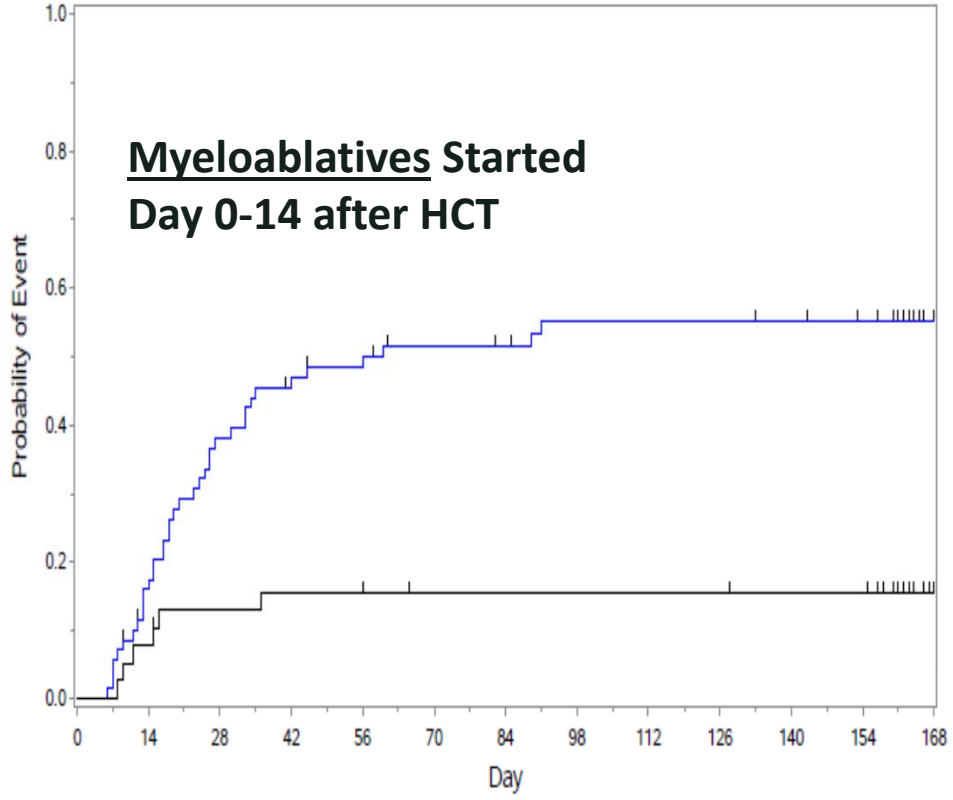
- Bypassing the gut appears to avoid local irritation and decrease incidence of diarrhea
- Preliminary data from 28 day preclinical study shows that IV BCV has a significantly lower risk of GI effects
  - Maintained body weight during dosing
  - No evidence of injury in preliminary review of the GI tract
- Maintains established benefits: broad spectrum, no myelotoxicity, no nephrotoxicity
- FTIH study anticipated 3Q 2016, bridge to drug levels in plasma from ongoing programs & incorporate into next CMV prevention study in HCT

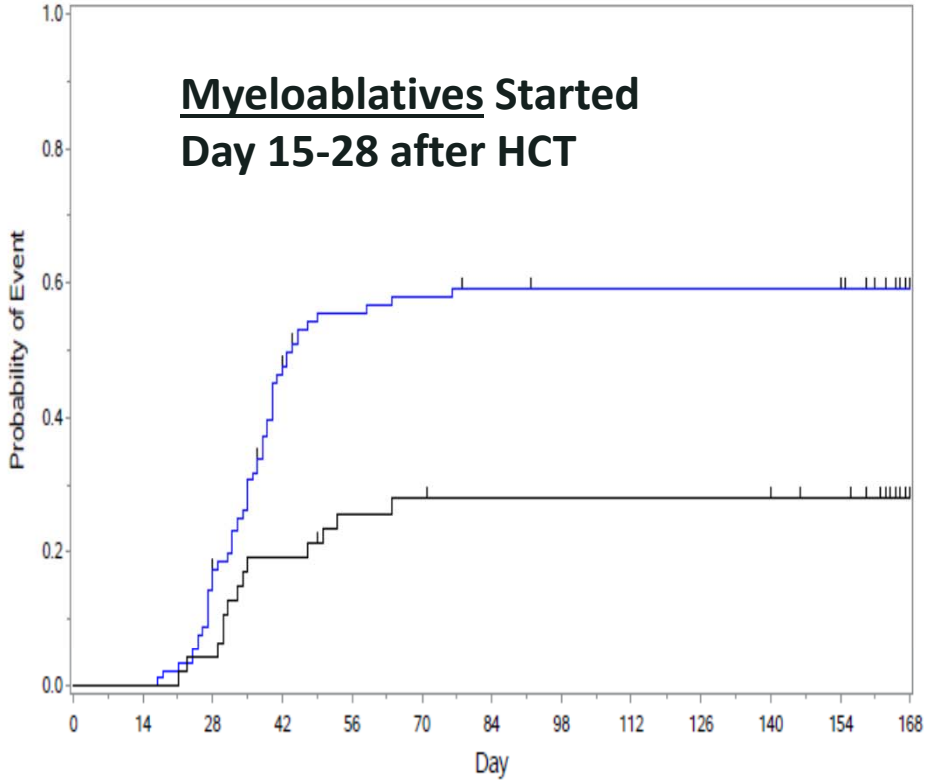
IV Brinci Clinical Program

- Phase I (FTIH Protocol): Dosing planned 3Q 2016
  - Part 1 Single Dose Escalation, Part 2 Absolute Bioavailability
- Phase II (Multi-Dose in Patients): Start early 2017
  - Envisage 28 day, dose ranging, PK, safety, and efficacy studies in kidney transplant recipients with BKV viremia
  - Goals: confirm GI safety, identify IV dose that approximates oral 100mg BIW exposure, establish exposure-response for BK
- Phase III (Pediatric and/or Adult Patient Trials): Start late 2017/2018
  - Registrational trial in adult HCT patients for the prevention of CMV and other dsDNA viruses
  - Study in pediatric and/or adult HCT patients infected with AdV may be pursued
  - Treatment of BKV viremia or nephropathy after kidney transplant

THANK YOU

Early Initiation Did Not Result in More AEs Leading to Treatment Interruption or D/C





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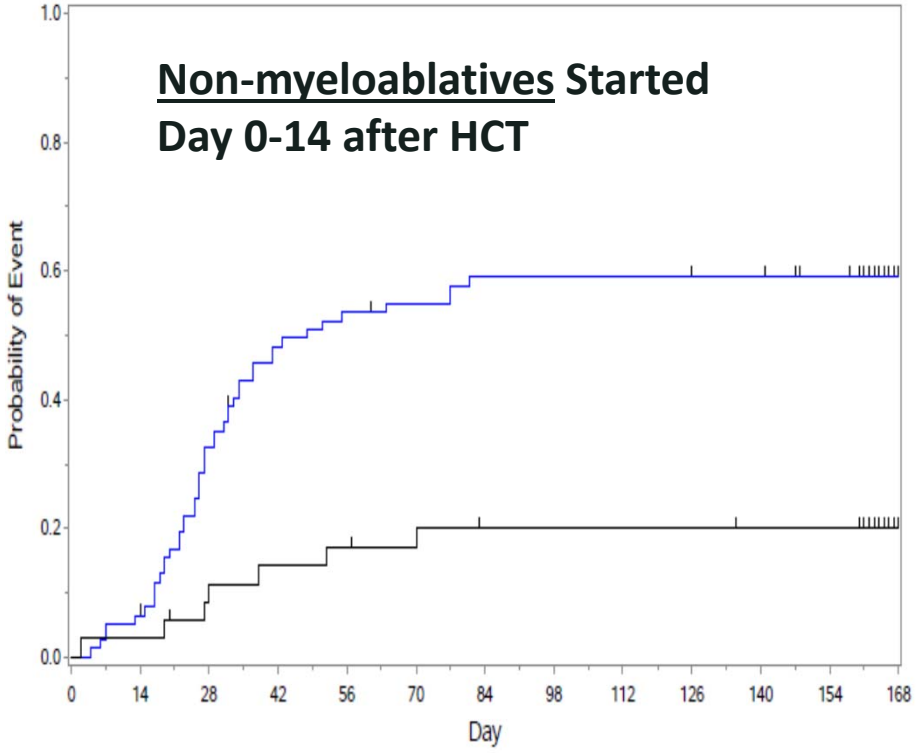
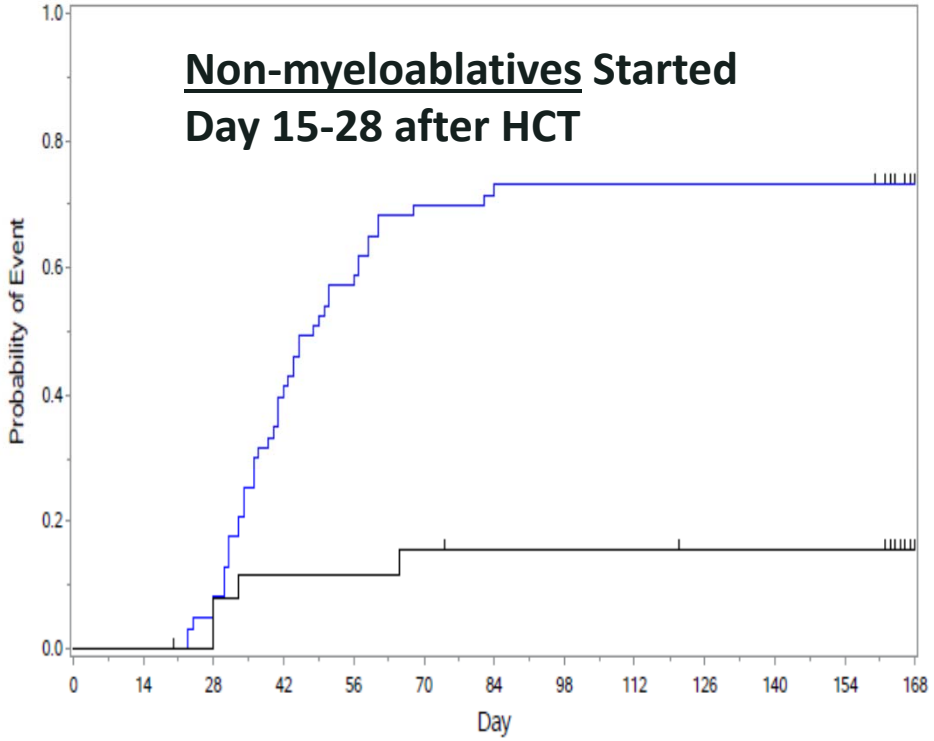
Early Initiation Did Not Result in More AEs Leading to Treatment Interruption or D/C





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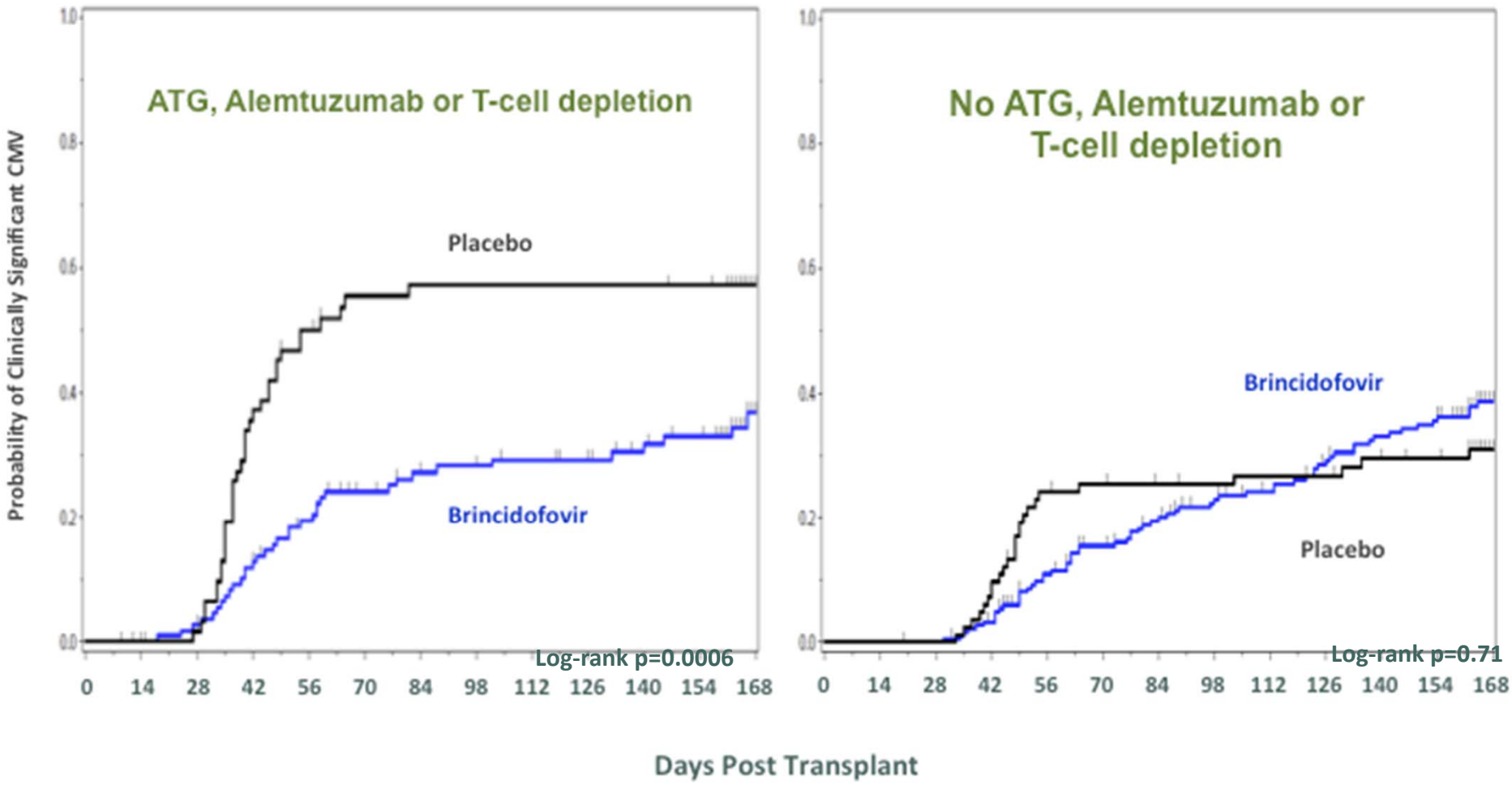
T-cell Depleted Patients (in vivo or ex vivo) Had Fewer CMV Events on BCV



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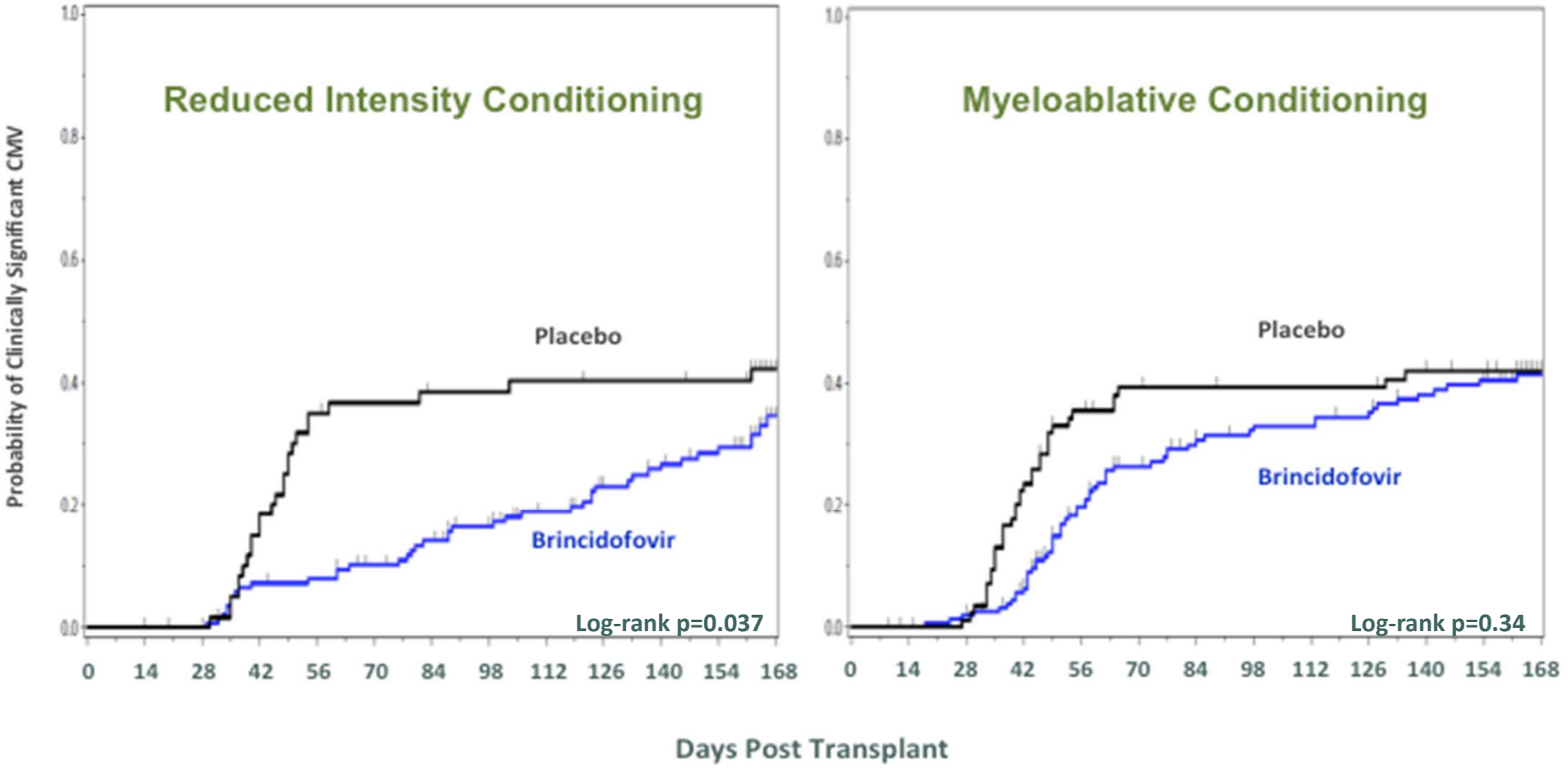
Non-myeloablative HCT Recipients Had Fewer CMV Events on BCV



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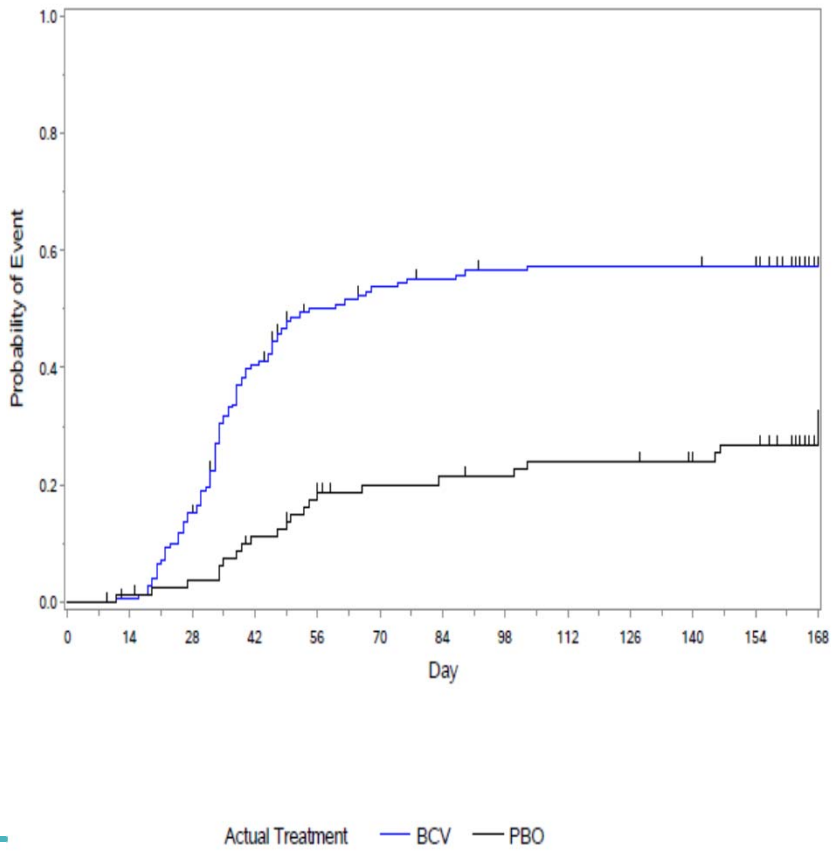
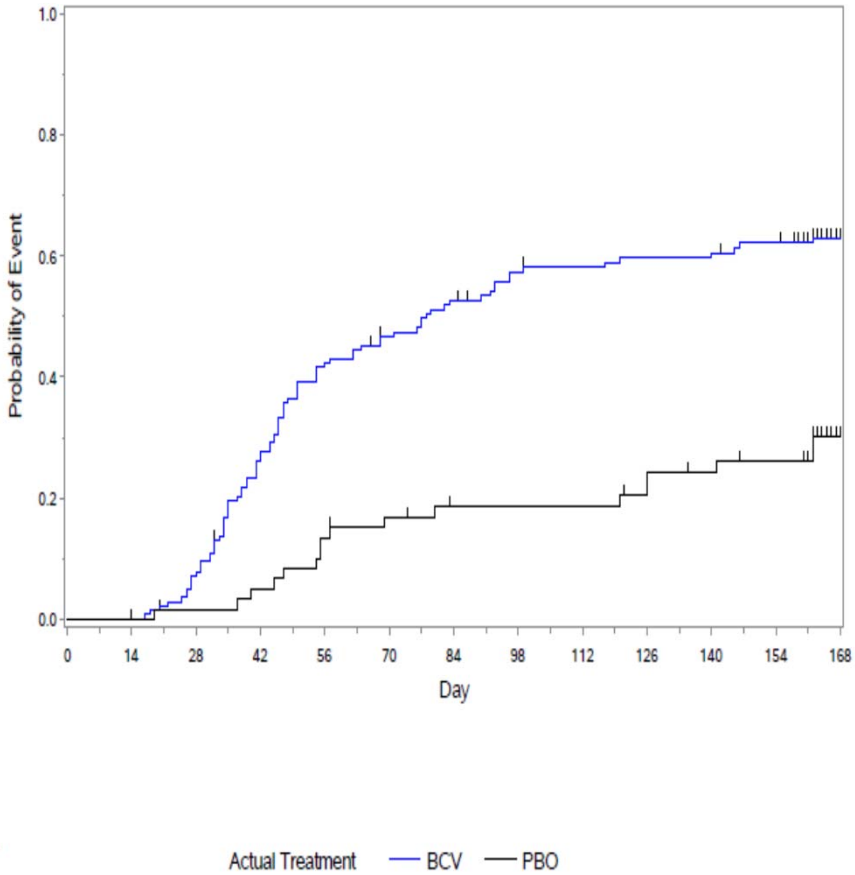
Grade 2+ aGVHD:
Similar in myelo and non-myeloablative

Myeloablative Conditioning



Non-myeloablative Conditioning



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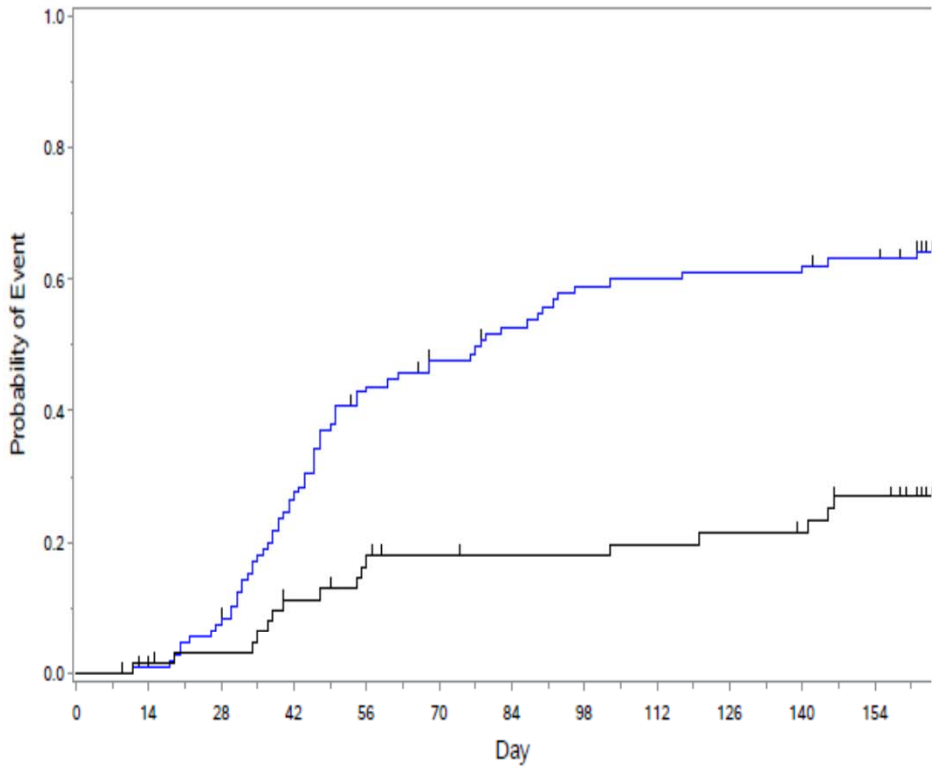
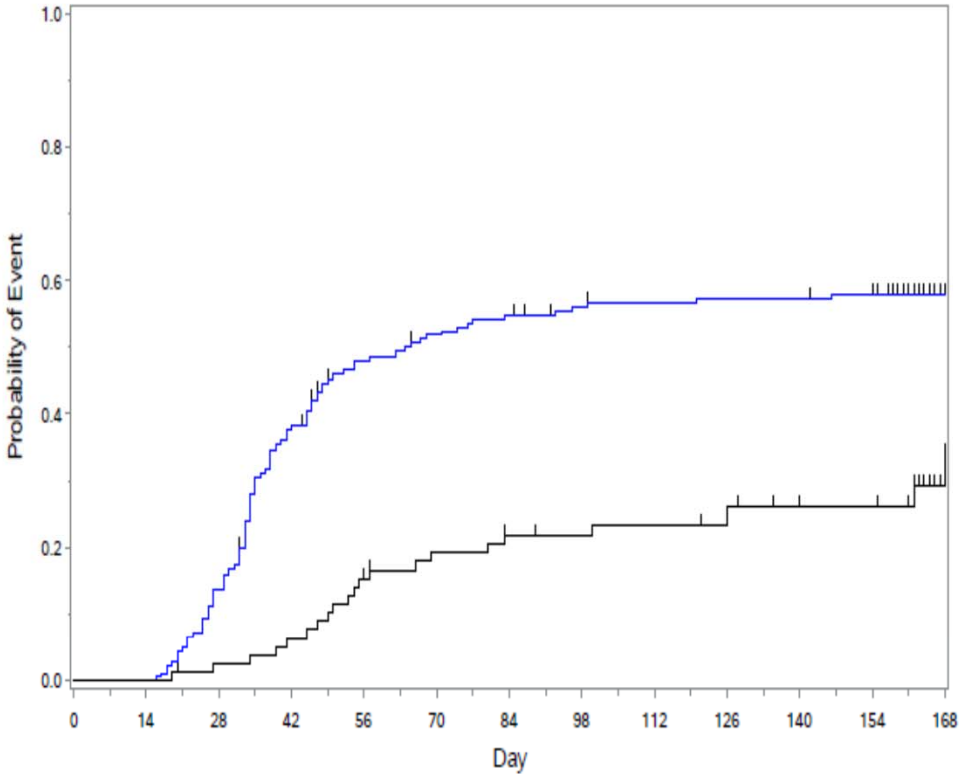
Grade 2+ aGVHD: Similar in TCD and non-TCD

T-cell Depleted HCT Recipients



Recipients of Non-TCD Transplants



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