Twice-weekly Brincidofovir (BCV, CMX001) Shows Promising Antiviral Activity in Immunocompromised Transplant Patients with Asymptomatic Adenovirus Viremia

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Disclosures

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- Michael Grimley - None

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Adenovirus (AdV)

- AdV is a serious and often fatal viral infection in immunocompromised patients, especially in hematopoietic cell transplant (HCT) recipients
- Estimated annual incidence of AdV infections in HCT recipients ranges from 5 to 50%, and is increasing, likely secondary to increased use of T cell depleted allografts and cord blood as a donor source
- Mortality rate of up to 80%
- No antiviral drugs are currently approved for treatment of AdV infections, but due to the high mortality, cidofovir is used in spite of the high risk of renal injury or renal failure

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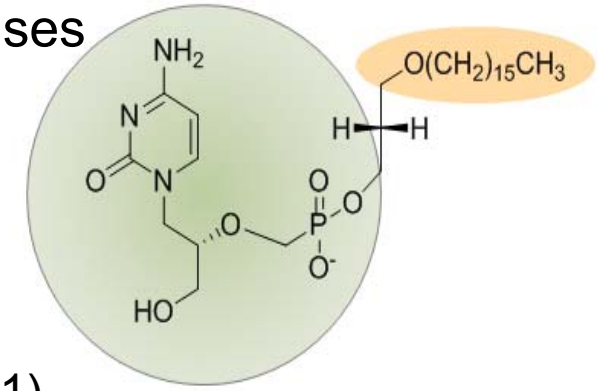
Sources: Ljungman P, Eur J Clin Microbiol Infect Disease 2004. Nihal G et al, BBMT 2012. Florescu DF et al, BBMT 2012

Brincidofovir (BCV, CMX001)

- Orally bioavailable lipid-conjugate of the nucleotide analog cidofovir (CDV)
- High intracellular concentration of the active antiviral cidofovir-diphosphate (CDV-PP) with a long $t_{1/2}$ up to 4 - 6.5 days
- Broad spectrum *in vitro* activity against dsDNA viruses
- 65-fold more potent against AdV than CDV *in vitro*
  - EC_{50} < 0.02 uM
- No evidence of nephrotoxicity
  - Not a substrate of organic anion transporter 1 (OAT-1)
  - No renal dysfunction in > 800 subjects who have received BCV to date
- Enrollment started in August 2013 in the Phase 3 SUPPRESS* trial for the prevention of CMV in HCT recipients



* CMX001-301 ClinicalTrials.gov: NCT01769170
Source: Beadle et al, AAC 2002: 46:2381-6.

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BCV Development Program Timeline

Study 202: Design based on EIND and Study 350 experience and success of preemptive therapy in CMV. Data reported September 2013 (Grimley et al, ICAAC).

Study 350: Large number of EIND requests led to initiation of Expanded Access Study 350.

Study 202: N=48
June 2011 - Feb 2013
AdV preemption

Study 350: N=210
Nov 2010 - Oct 2012

EINDs: N=230; March 2009 - March 2012
CMV, AdV, BKV, EBV, HSV, JCV, HHV, VZV, HPV

2009	2010	2011	2012	2013

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Brincidofovir Expanded Access Program

- BCV access for patients with life-threatening dsDNA viral infections and no therapeutic options
- Emergency INDs (EINDs): N>230, n=110 database, n=30 AdV
  - 100+ centers in US, Canada, France, UK, Austria, Switzerland, Spain, Israel and Chile
  - Adult and pediatric patients with CMV, AdV, BKV, EBV, HSV, JCV, HHV, VZV or HPV
  - March 2009 – March 2012 (with limited exceptions since)
- Expanded Access Study 350* (N=210 total, n=68 AdV)
  - 36 US sites, conducted from November 2010 – October 2012
  - November 2010 – July 2011: all dsDNA viruses included
  - July 2011 – October 2012: Enrollment limited to CMV, HSV or AdV
- Program currently inactive

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*CMX001-350: ClinicalTrials.gov: NCT01143181

Study 350: Overview

- Eligibility: Immediate life-threatening or serious disease or condition caused by infection with one or more dsDNA virus (Sponsor approval required)
- Subjects received BCV twice weekly (BIW) for 3 months or until virology assessments of any previously positive culture or PCR sites yield negative tests for 4 successive weeks
  - 100 mg BIW or 200 mg QW for adults (tablet)
  - 2 mg/kg BIW or 4 mg/kg QW for children (liquid)
  - treatment may have been continued for up to a total of 6 months
- Central laboratory plasma AdV viral load measurements
  - Baseline (BL): subjects may have qualified based on local results
  - During treatment (weekly, at discretion of investigator)
  - post treatment week 1 and week 4

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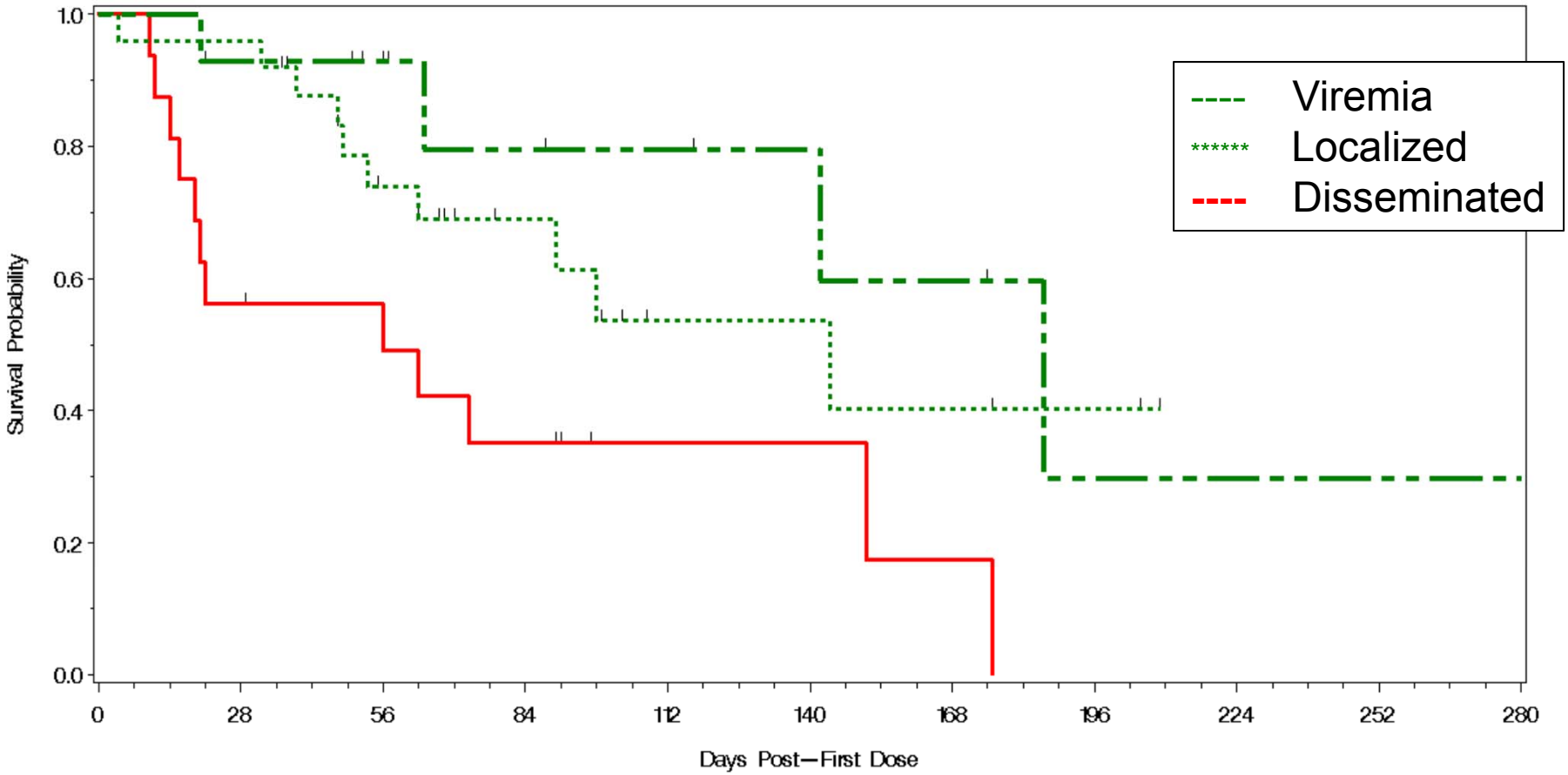
BIW = twice weekly, QW=once weekly

Study 350: All-cause mortality lower when BCV was begun for AdV viremia vs disseminated AdV



p = 0.010

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Presented at European Group for Blood and Marrow Transplantation Annual Meeting, April 2013

Study 202: Overview

- Primary objective: To evaluate the safety and efficacy of early intervention with BCV versus placebo to prevent the development of AdV disease in HCT recipients
- Randomized, double-blind, placebo-controlled study at 29 US transplant centers (June 2011-February 2013)
- Based on successful identification of early disease in CMV reactivation, targeted identification of asymptomatic AdV viremia
- Enrolled 48 pediatric and adult allogeneic HCT recipients with asymptomatic AdV viremia (serum AdV PCR ≥ 100 copies/mL)
- Subjects received BCV BIW or QW or placebo for 6-12 weeks
  - 100 mg BIW or 200 mg QW for adults (tablet)
  - 2 mg/kg BIW or 4 mg/kg QW for children (liquid)

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Study 202: Study Design

735 patients screened for AdV viremia

48 patients with AdV viremia ≥ 100 copies/mL

Stratified by ALC < 300 or ≥ 300 cells/mm^3

- BCV BIW
- BCV QW
- Placebo

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ALC = absolute lymphocyte count

Baseline Characteristics

	202 BIW n=14	350 BIW n=12	Combined n=26
Age range, years	0-55	1-68	0-68
< 12	9 (64%)	8 (67%)	17 (65%)
12-17	2 (14%)	0	2 (8%)
> 17	3 (21%)	4 (33%)	7 (27%)
Female, %	5 (36%)	6 (50%)	11 (42%)
Baseline median weight (range), kg	27 (10-98)	32 (9-109)	31 (9-109)
Baseline median ALC (range), cells/mm^3	340 (0-1650)	210 (0-2440)	305 (0-2440)
Baseline GVHD, %	4 (29%)	3 (25%)	7 (27%)
Time from transplant to first BCV dose, days			
0-<100	10 (71%)	7 (58%)	17 (65%)
100-180	3 (21%)	1 (8%)	4 (15%)
> 180	1 (7%)	4 (33%)	5 (19%)
Baseline median AdV Viremia (range), copies/mL	1250 (BLD-7.7x10^4)	4800 (100-2.2x10^7)	3700 (BLD-2.2x10^7)
Co-infected with other dsDNA virus(es)	8 (57%)	5 (42%)	13 (50%)

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GVHD = graft versus host disease, BLD = below the lower limit of detection (100 copies/mL)

Transplant Characteristics

	202 BIW n=14	350 BIW n=12	Combined n=26
Reason for transplant			
Malignancies	4 (29%)	7 (58%)	11 (42%)
Non-malignant diseases	10 (71%)	5 (42%)	15 (58%)
Conditioning / Manipulation			
Myeloablative	6 (43%)	8 (67%)	14 (54%)
Reduced intensity	7 (50%)	2 (17%)	9 (35%)
T-cell depletion	0	1 (8%)	1 (4%)
None	1 (7%)	1 (8%)	2 (8%)
Source of graft			
Bone marrow	2 (14%)	0	2 (8%)
Peripheral blood stem cells	6 (43%)	4 (33%)	10 (38%)
Cord blood	6 (43%)	4 (33%)	10 (38%)
Lung	0	1 (8%)	1 (4%)
Unknown HCT source	0	3 (25%)	3 (12%)
Type of graft			
Haploidentical	3 (21%)	0	3 (12%)
Related donor	1 (7%)	1 (8%)	2 (8%)
Unrelated donor	10 (71%)	7 (58%)	17 (65%)
Autologous	0	2 (17%)	2 (8%)
Unknown type	0	2 (17%)	2 (8%)

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Anti-viral Therapy and Follow-up

- 350 BCV BIW exposure
  - Median Days (Range): 44 (8-299)
- 350 Prior IV cidofovir within 30 days of enrollment
  - 5/12 subjects (42%)
  - Median Days (Range): 15 (1-22)
- 202 BCV BIW exposure
  - Median Days (Range): 40 (11-91)
- Subjects were followed for a median 8 weeks (range: 3 to 47 weeks) after first dose

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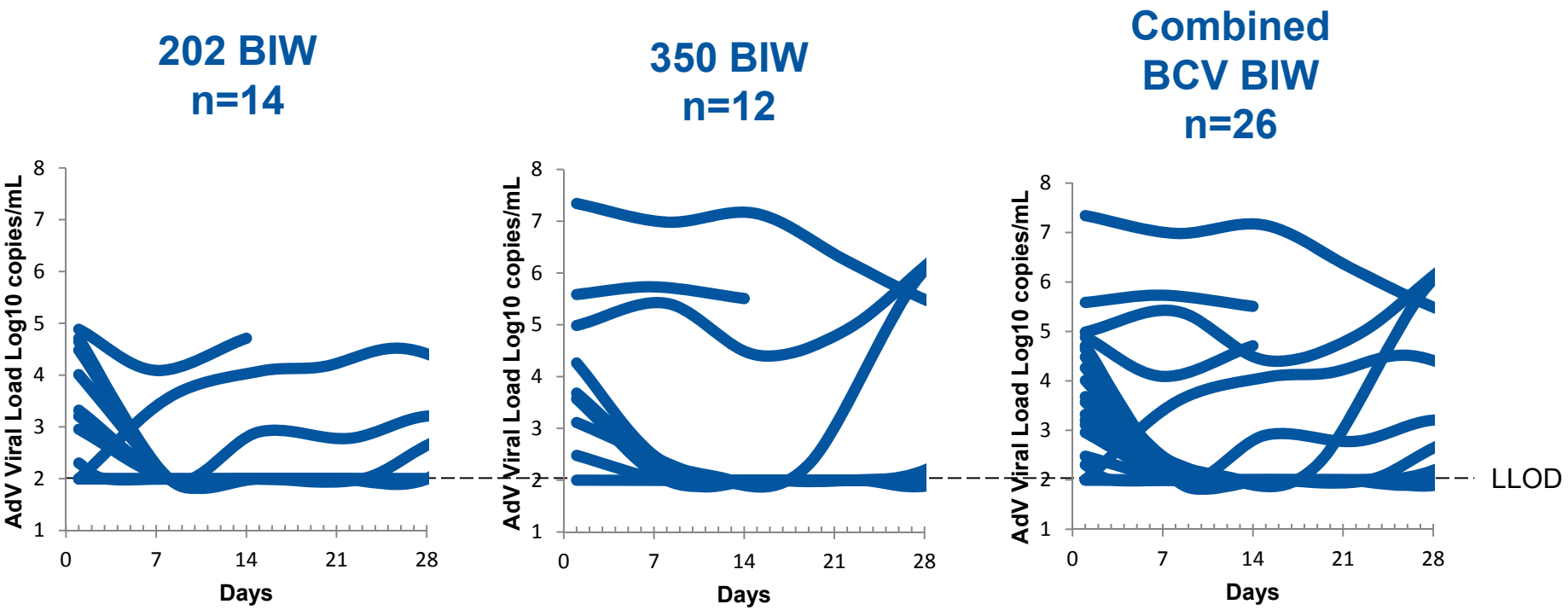
AdV Viremia – Rapid Response to BCV BIW

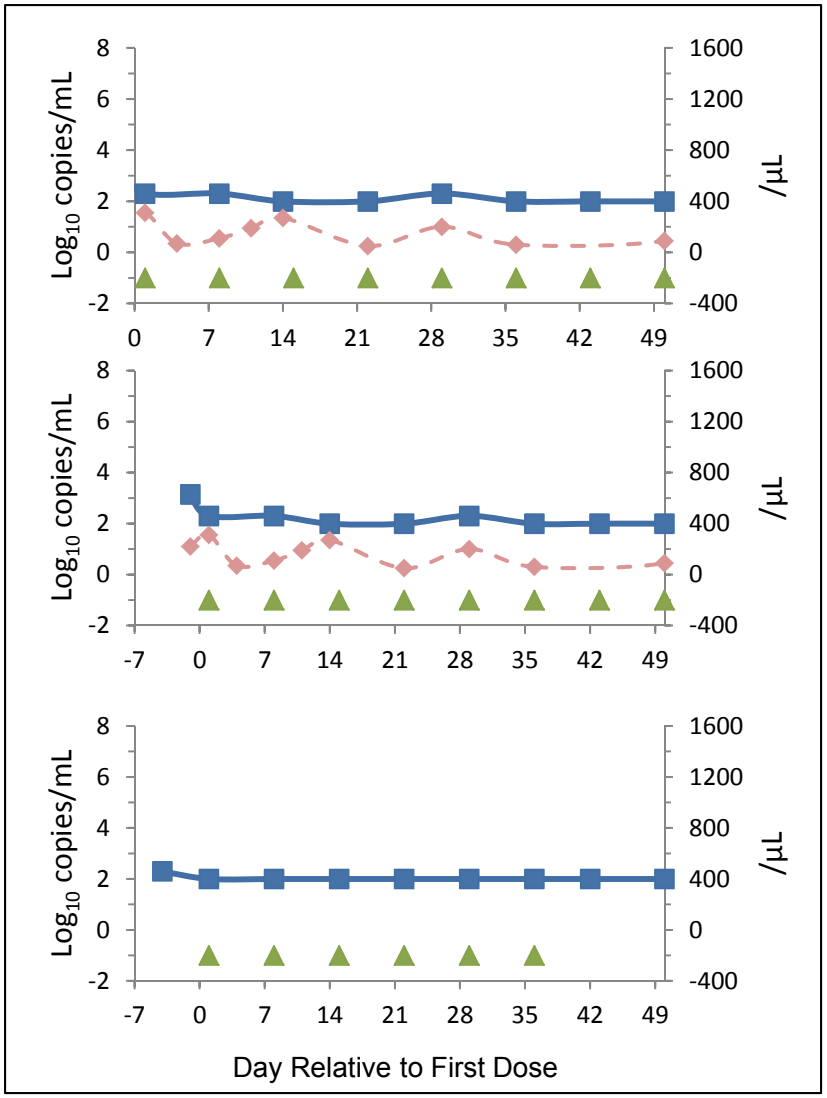


LLOD = Assay lower limit of detection (100 copies/mL)

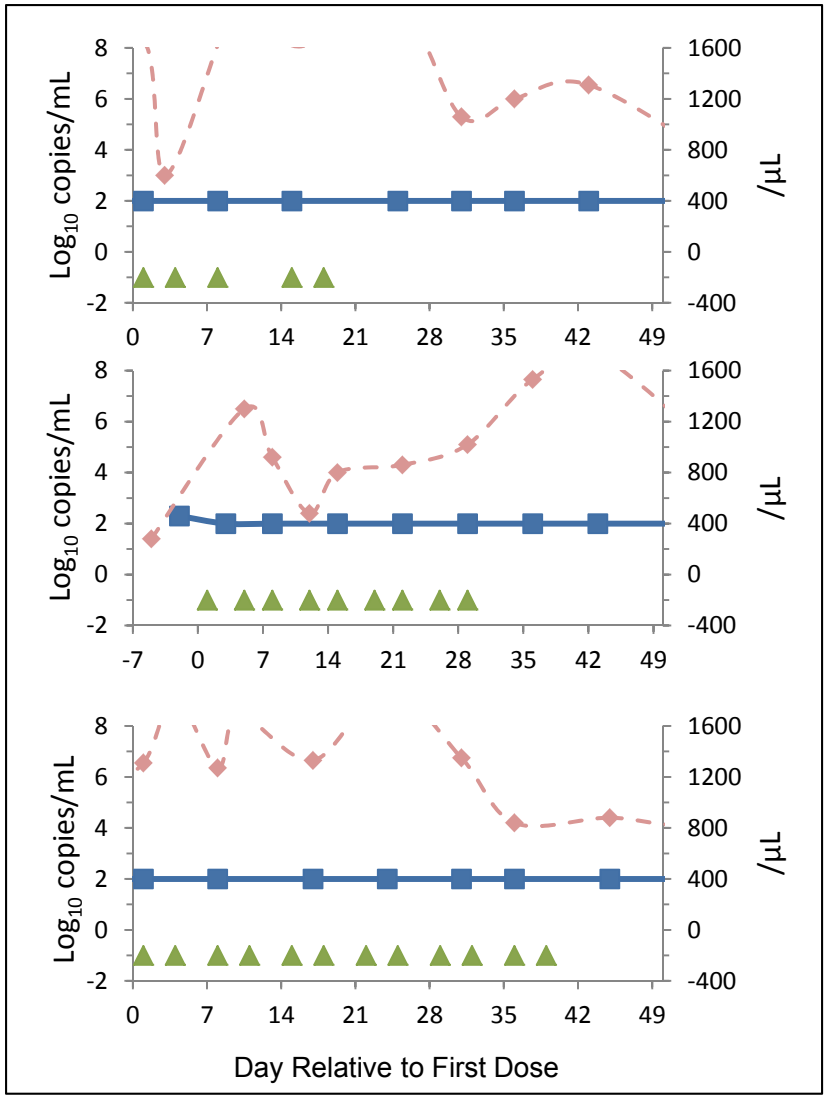
Low Level AdV Viremia Resolves Spontaneously

(100 to ≤ 1000 copies/mL at Baseline)

202 Placebo



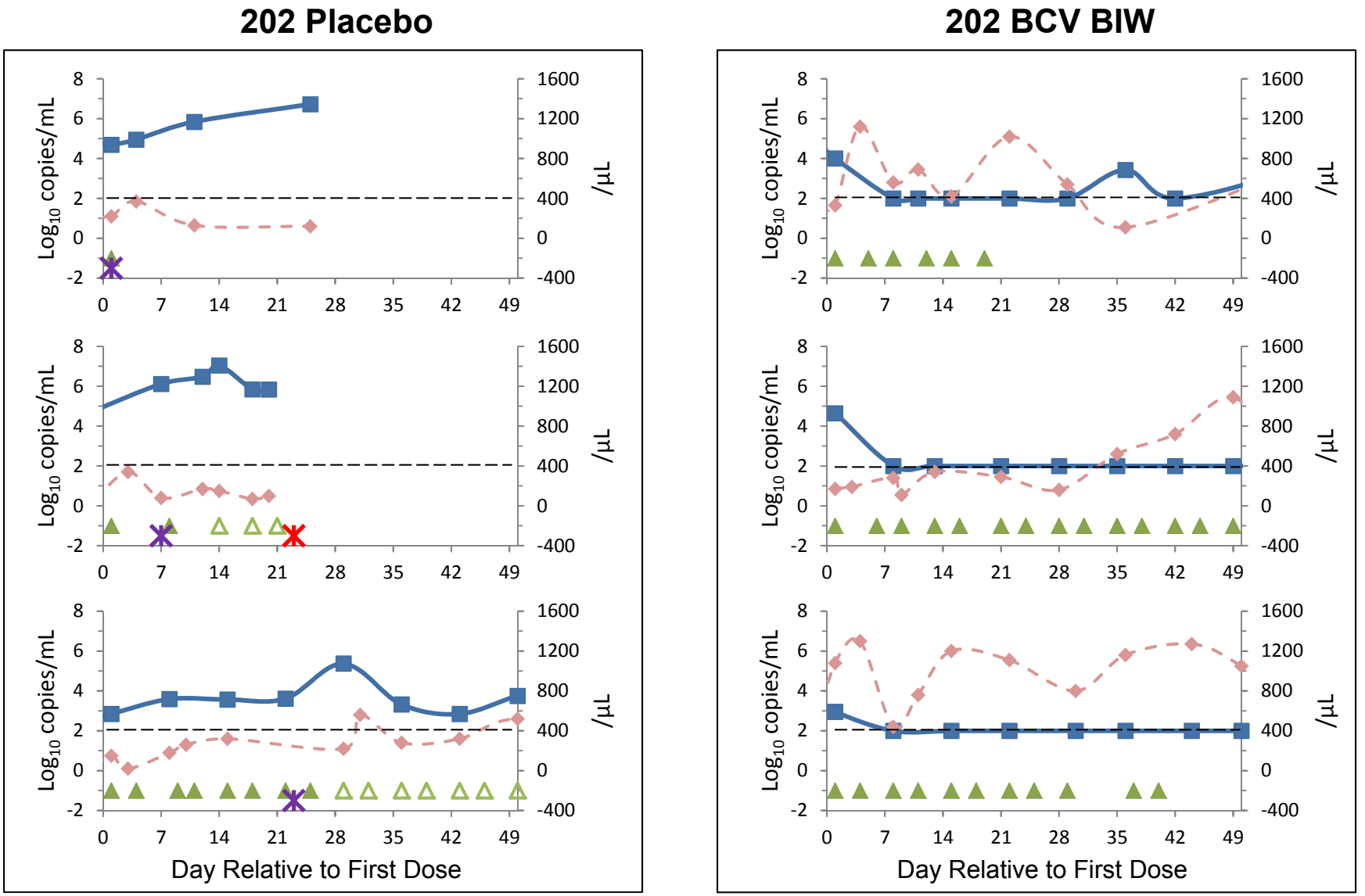
202 BCV BIW



Log10 AdV Viremia ▲ Blinded Dose Lymph (/µL)

High Level AdV Viremia Suppressed with BCV BIW

(> 1000 copies/mL at Baseline)



AdV Response

Combined BCV BIW	Baseline AdV ≤1000 c/mL n=7*	Baseline AdV >1000 c/mL n=14*
≤LLOD within first week of treatment, %	6 (86%)	8 (57%)
≤LLOD any time on treatment, %	7 (100%)	11 (79%)
Median (range) time to ≤LLOD, days	8 (7-82)	9 (8-141)
Mean (SD) decrease in viremia, log_{10} c/mL	0.3 (0.4)	1.8 (1.3)

202 Placebo	Baseline AdV ≤1000 c/mL n=10*	Baseline AdV >1000 c/mL n=8*
≤LLOD within first week of treatment, %	5 (50%)	2 (25%)
≤LLOD any time on treatment, %	9 (90%)	5 (63%)
Median (range) time to ≤LLOD, days	8 (4-78)	15 (8-50)
Mean (SD) decrease in viremia, log_{10} c/mL	0.1 (0.2)	1.1 (1.5)

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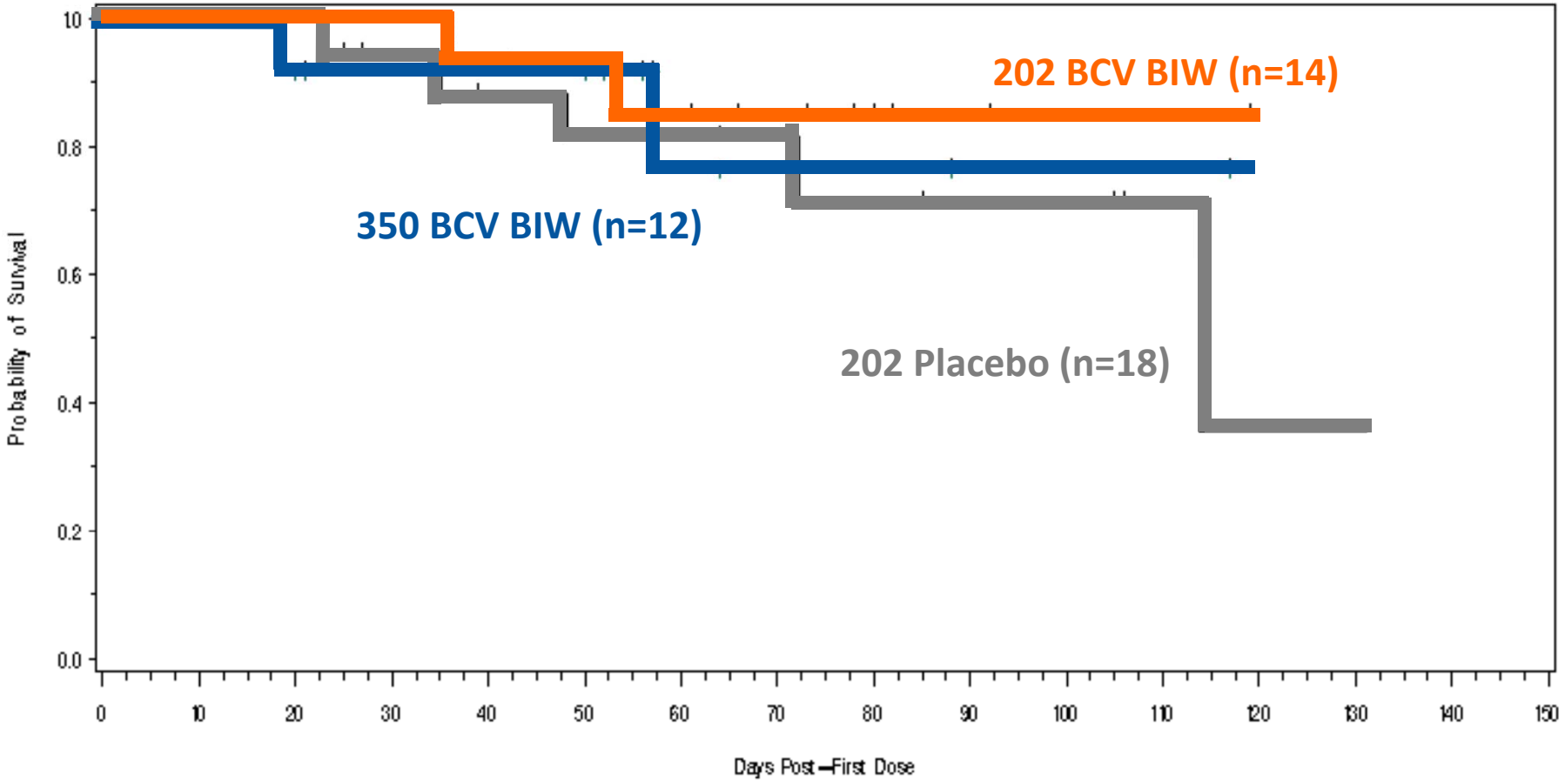
* Detectable AdV at central lab at Baseline, c/mL=copies/mL, LLOD=Assay lower limit of detection (100 copies/mL)

Non-relapse Mortality



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Non-Relapse Causes of Death

Combined BCV BIW 4/26 (15%)	Baseline AdV Viremia (copies/mL)	Minimum AdV Viremia (copies/mL)	Last AdV Viremia (copies/mL)
Intracranial hemorrhage secondary to HHV-6 meningitis and fungal meningitis	$7.7x10^4$	$5.1x10^4$	$1.7x10^6$
Coagulase-negative Staphylococcus pneumonia	Undetectable	Undetectable	Undetectable
Pseudomonas aeruginosa septic shock	Not done	Undetectable	$3.6x10^4$
Toxoplasmosis and Aspergillus infection	$3.9x10^5$	$3.2x10^5$	$3.2x10^5$

202 Placebo 5/18 (28%)	Baseline AdV Viremia (copies/mL)	Minimum AdV Viremia (copies/mL)	Last AdV Viremia (copies/mL)
Grade 4 aGvHD, HHV-6 encephalitis	$2.4x10^5$	Undetectable	Undetectable
Multiple organ failure secondary to septic shock (AdV and liver microabcesses)*	$6.1x10^4$	$6.9x10^5$	$6.9x10^5$
Aspiration pneumonia	3500	Undetectable	Undetectable
Multiple organ failure secondary to graft failure and Enterococcus sepsis*	100	Undetectable	700
Respiratory failure of unknown origin, with proven AdV enteritis*	7100	5700	$3.4x10^6$

*Received open label BCV

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Conclusions

- Brincidofovir BIW rapidly decreased AdV viremia in most patients and limited progression to non-relapse mortality in high risk transplant recipients
- Responses from the randomized trial Study 202 are similar to that of the more heterogeneous study population in the expanded access Study 350

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dsDNA = double-stranded DNA

Adenovirus and Future Trials

- Adenovirus viremia at any level may not be an appropriate singular marker for early adenovirus disease independent of clinical risk assessment or other compartments (e.g., GI, respiratory)
  - *Prospective PCR Monitoring Reveals Adenovirus Viremia is Associated with a Significant Risk of AdV Disease in T-Cell Depleted and Cord Blood Allograft Recipients*, Huang et al. (BMT Tandem 2014)
- Analyses of clinical risks and other predictors of progression may need to be included in future interventional trials of brincidofovir in patients at increased risk of adenoviral infection
- Prevention of primary or reactivated adenovirus infection is likely to be a more efficient approach to decrease mortality related to AdV infection in at-risk transplant recipients

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dsDNA = double-stranded DNA