



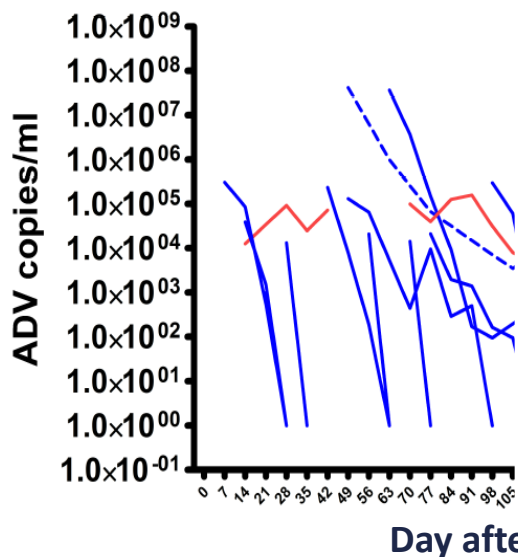
The adenovirus challenge: an update

Prof. Thomas Lion, MD, PhD, MSc
CCRI/ LabDia Labordiagnostik GmbH
Thomas.Lion@CCRI.at

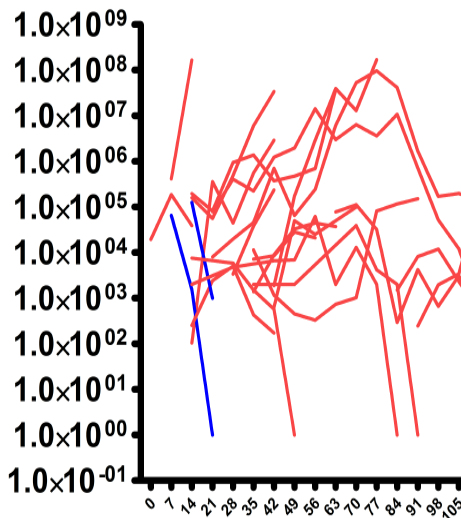
Brincidofovir vs Cidofovir in pediatric HCST recipients

Hiwarkar P et al. Blood 2017, 129(14):2033-2037

Oral Brincidofovir



i.v. Cidofovir



80% of pediatric HCT patients cleared plasma with BCV (median 4 wks)

35% cleared with i.v. CDV (median 9 wks)

Unlike CDV, BCV cleared viremia independently of immune reconstitution

Preemptive therapy safety profile:

BCV: 1/18 discontinued therapy for GI AEs

CDV: 9/23 patients showed renal toxicity

Basis for approval (licencing) of antiviral drugs

Evidence for (superior) efficacy and safety



Only clinical outcome data currently accepted by FDA and EMA

Problems in the presence of pre-existing evidence for efficacy/superiority of a novel drug



- ➡ Difficult to perform placebo- or comparator drug-controlled clinical studies (particularly in the pediatric setting with severely affected pts)
- ➡ Inability to use only clinical endpoints (survival data) for clinical studies acceptable as evidence for (superior) efficacy

Basis for approval of antiviral drugs

Possible solution → acceptability of virological endpoints as adequate evidence



Exploitation of available data
to provide supporting evidence for adequacy of virological endpoints



Retrospective analysis of data from multi-center study on allo-SCT in pediatric ALL
[Forum* 1 study: ~1800 patients at >120 centers in 32 countries]

→ Estimated occurrence of invasive HAdV infections: 5-10% → ~100 patients

* Forum: For omitting radiation under majority age

Possible endpoints for retrospective HAdV study

Primary composite endpoint (PCE) for clinical outcome:

HAdV viremia-free survival at day 180

Correlation of PCE with



- Adenoviremia
- Kinetics + maximum HAdV load in PB
- Kinetics + maximum HAdV load in stool

Secondary endpoints

(comparison d100 vs d180)

- Immunosuppression-free survival
- GvHD-free survival (acute and chronic GvHD)
- Co-infection-free survival (bacterial, fungal, and viral other than HAdV)
- Organ toxicity + CTC (Clinical Trial Complications)
- Secondary partial/complete graft failure
- Cell therapy (DLI, stem cell boost, virus-specific T-cells)
- Antiviral therapy*

Current status

- Identification of pediatric transplant centers as potential participants
- Study proposal in preparation
- Remaining tasks: statistical design and CRA recruitment

Preliminary Results of Phase 2a Clinical Trial to Evaluate Safety, Tolerability and Antiviral Activity of Intravenous Brincidofovir in Immunocompromised Patients with Adenovirus Infection

Michael Grimley¹, Gabriela M. Maron², Carlos A. Gomez³, Vinod K. Prasad⁴, Jasmeen Dara⁵, Thomas Lion⁶, Genovefa A. Papanicolaou⁷, Koji Fukushima⁸, Robert F. Wynn⁹, Michael J. Boeckh¹⁰

¹Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; ²St. Jude Children's Research Hospital, Memphis, TN, USA; ³University of Nebraska Medical Center, Omaha, NE, USA; ⁴Duke Children's Hospital and Health Center, Durham, NC, USA; ⁵University of California, San Francisco, San Francisco, CA, USA; ⁶St. Anna Children's Cancer Research Institute, Vienna, Austria; ⁷Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁸SymBio Pharmaceuticals Limited, Tokyo, Japan; ⁹Royal Manchester Children's Hospital, Manchester, GBR; ¹⁰Fred Hutchinson Cancer Center, Seattle, WA, USA

The study was funded by SymBio Pharmaceuticals Limited, Tokyo, Japan

Study Objective and Patient Population

Study objective: To assess the safety, tolerability, and antiviral activity of IV BCV using multiple ascending doses in sequential cohorts (*ClinicalTrials.gov NCT04706923*)

Inclusion Criteria

- Age ≥ 2 months
- AdV viremia determined within 7 days before initiation of IV BCV
 - Plasma AdV $>10,000$ copies/mL or 2 samples with second result higher than the first and both $>1,000$ copies/mL)
- Either (a) have disseminated AdV disease or (b) have an underlying immunocompromised state, and have asymptomatic AdV infection or localized AdV disease

Exclusion Criteria

- Patients who weigh ≥ 120 kg
- NIH/NCI CTCAE Grade 2 or higher diarrhea (i.e., increase of ≥ 4 stools per day over usual pre-transplant stool output) within 7 days prior to Day 1
- NIH Stage 4 acute GVHD of the skin (i.e., generalized erythroderma with bullous formation) within 7 days prior to Day 1
- NIH Stage 2 or higher acute GVHD of the liver (i.e., bilirubin >3 mg/dL [SI: >51 $\mu\text{mol/L}$]) within 7 days prior to Day 1
- NIH Stage 2 or higher acute GVHD of the gut (i.e., diarrhea >556 mL/m²/day for pediatric subjects [or >1000 mL/day for young adults as applicable, at centers in the United States only], or severe abdominal pain with or without ileus) within 7 days prior to Day 1

Study Design

14-week open-label, multiple ascending dose confirmation, multicenter trial

COHORT 1: IV BCV 0.2 mg/kg BIW 4 weeks^{*,#} (n=6)

COHORT 2: IV BCV 0.3 mg/kg BIW 4 weeks^{*,#} (n=6)

COHORT 3: IV BCV 0.4 mg/kg BIW 4 weeks^{*,#} (n=6)

COHORT 4: IV BCV 0.4 mg/kg QW 4 weeks^{*,#} (n=6)

Follow-up
(30 days
post last
BCV
dose)

Primary Endpoints

Treatment-related
adverse events

Secondary Endpoints

- Change in AdV viremia[†] from baseline up to 4 weeks
- Time-averaged change for AdV viremia[†] from baseline up to 4 weeks
- Peak AdV viral load after onset of AdV viremia[†] up to 4 weeks

^{*}If 2 consecutive confirmatory AdV viral load samples are not below the limit of detection (25 copies/mL), total treatment period may be extended up to 14 weeks.

[#]Dose for Cohort 1, Cohort 2, or Cohorts 3 and 4 was 0.2 mg/kg, 0.3 mg/kg, or 0.4 mg/kg for patients weighing <50 kg and 10 mg, 15 mg, or 20 mg, respectively, for patients weighing ≥50 kg.

[†]Dose escalation was done if recommended by Sponsor and Data Safety Monitoring Board in accordance with dose-escalation criteria.

^{*}AdV viral load was measured using standardized quantitative PCR (lower limit of detection: 25 copies/mL; lower limit of quantification: 190 copies/mL; and upper limit of quantification: 10¹⁰ copies/mL)⁹
AdV, adenovirus; BCV, brincidofovir; BIW, twice weekly; IV, intravenous; PCR, polymerase chain reaction; QW, once weekly.

Primary Endpoint: Safety and Tolerability

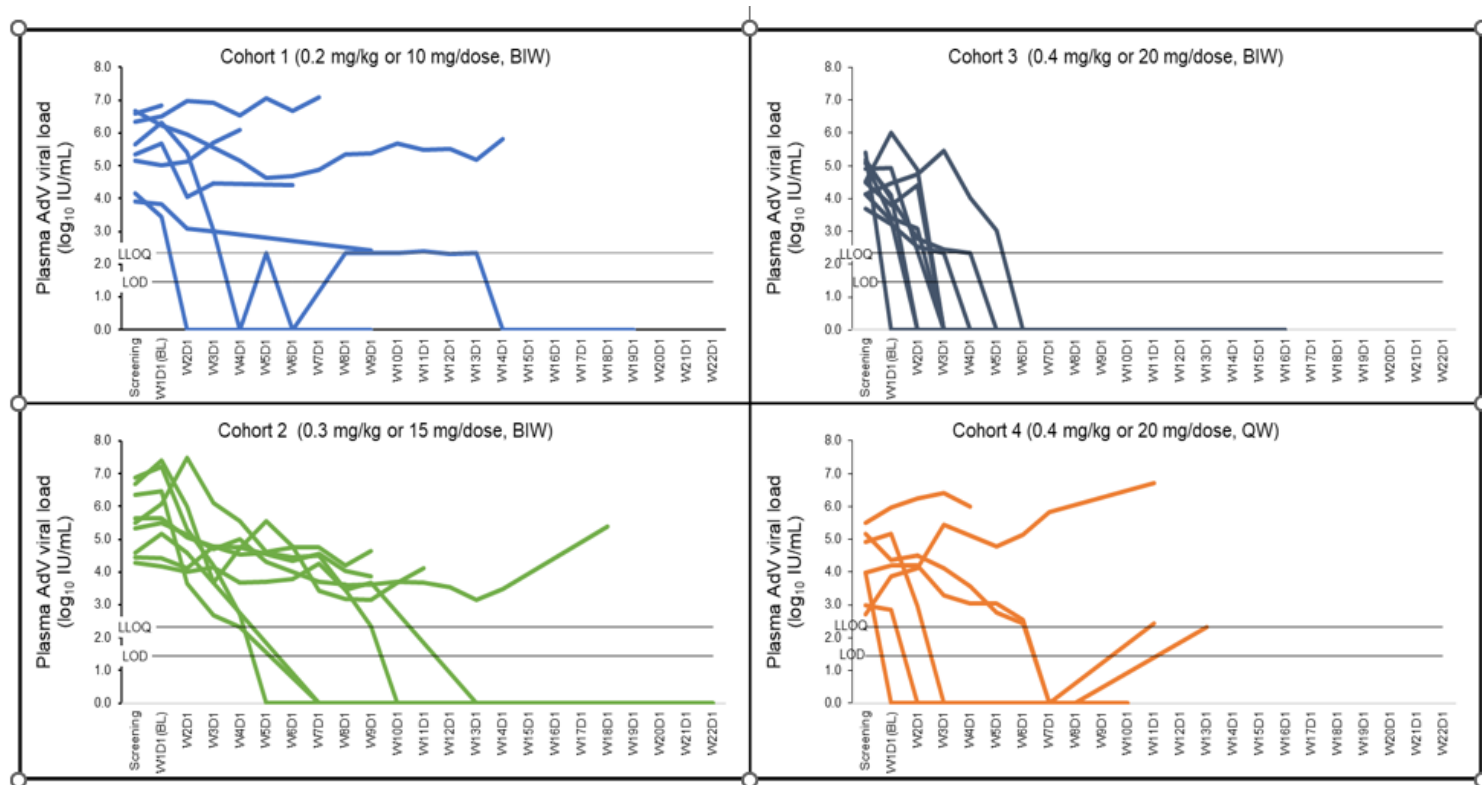
- Of the 27 patients enrolled, treatment-related AEs were observed in only 7 patients
- No serious treatment-related AEs observed including GI and hepatic toxicities
- All treatment-related AEs were reversible and resolved after the completion of the treatment
- AEs reported were not dose dependent

	Cohort 1* (IV BCV 0.2 mg/kg) n=8	Cohort 2 (IV BCV 0.3 mg/kg) n=9	Cohort 3* (IV BCV 0.4 mg/kg) n=10
Treatment-related AEs, n (%)	2 (25)	3 (33)	2 (20)
Diarrhea	1	1	-
Elevated ALT	1*	-	1*
Elevated LDH	1*	-	-
Elevated AST	1*	-	1*
Nausea	-	1	1
Arrhythmia	-	-	1*
Transaminitis	-	1	-

*Multiple AEs may have occurred in a single patient.

AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; BCV, brincidofovir; GI, gastrointestinal; IV, intravenous; LDH, lactate dehydrogenase.

Efficacy: Antiviral Activity of IV BCV was Dose-Dependent

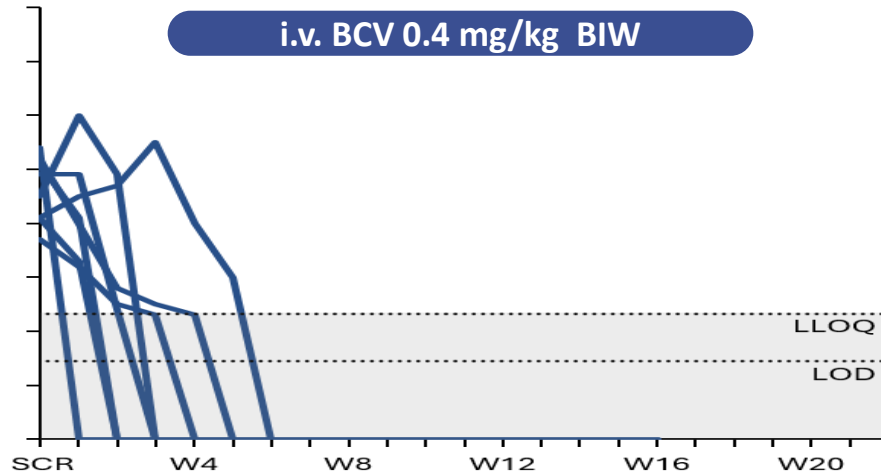


Zero viral load indicates that the test result was below the lower LOD.

AdV, adenovirus; BCV, brincidofovir; IV, intravenous; LLOQ, lower limit of quantification; LOD, limit of detection; SCR, screening.

Interim Results of a Phase 2a Clinical Trial (ATHENA Study)

High Efficacy of i.v. BCV in Immunocompromised Patients ➡ Dose-Dependent



Basis for a phase 3 clinical trial

Poster number : P 103
Session Title: Clinical Trials
Date: Thursday October 17, 2024
Time: 12:15 PM - 1:30 PM

AdV viremia Clearance and Clinical Response in Patients with Disseminated or Organ Disease after Treatment with i.v. BCV

	Cohort 1 n=8	Cohort 2 n=9	Cohort 3 n=10	Cohort 4 n=7
Patients with AdV disease, n	8	8	9	6
Viremia clearance by W5D1, n (%)	1 (12.5)	1 (12.5)	8 (88.9)	3 (50.0)
Viremia clearance by end of study, n (%)	2 (25.0)	5 (62.5)	9 (100.0)	4 (66.7)
Resolved/improved disease, n (%)	2 (100.0)	4 (80.0)	9 (100.0)	4 (100.0)
Resolved disease, n	2	3	6	4
Improved disease, n	0	1	3	0
No viremia clearance by end of study, n (%)	6 (75.0)	3 (37.5)	0 (0.0)	2 (33.3)
Resolved/improved disease, n (%)	2 (33.3)	0	0	0
Resolved disease, n	1	0*	0	0*
Improved disease, n	1	0	0	0

One patient with no data at end of study (patient died).

AdV, adenovirus; BCV, brincidofovir; D, day, IV, intravenous; W, week

Summary

i.v. BCV 0.4 mg/kg BIW displayed the greatest efficacy



- rapid clearance of AdV viremia in all patients
- well tolerated (no serious GI/hepatic toxicity)
- sustained virological response
- efficacy across different adenovirus species
- viral clearance correlated with clinical responses
(resolved disease (n=6), improved disease (n=3))
- in patients with rapid clearance of the virus from PB
delayed response kinetics of intestinal adenovirus load

Thank you!

