



Dedicated to Preventing and Treating Life-Threatening Viral Infections

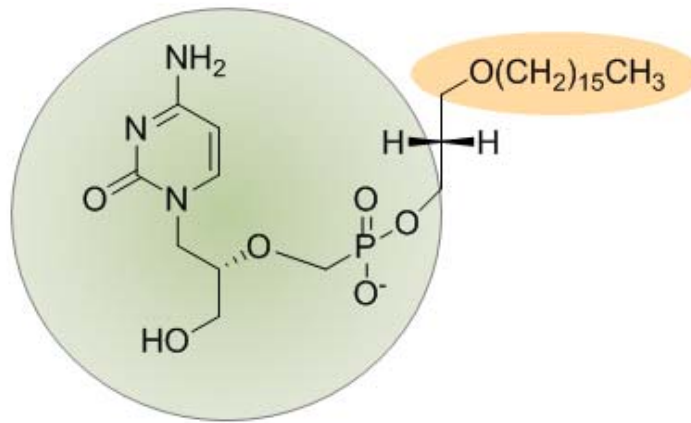
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Combination Activity and Emerging
Resistance Profile of Brincidofovir
in CMV Prevention and Treatment

Disclosures

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- Scott Foster, Dean Selleseth, Tom Brundage, Hervé Momméja-Marin, and Randall Lanier are employees of Chimerix, Inc.
- Mark Prichard is a consultant to Chimerix and receives funding for specific studies involving brincidofovir.

Brincidofovir (BCV, CMX001): Novel Antiviral

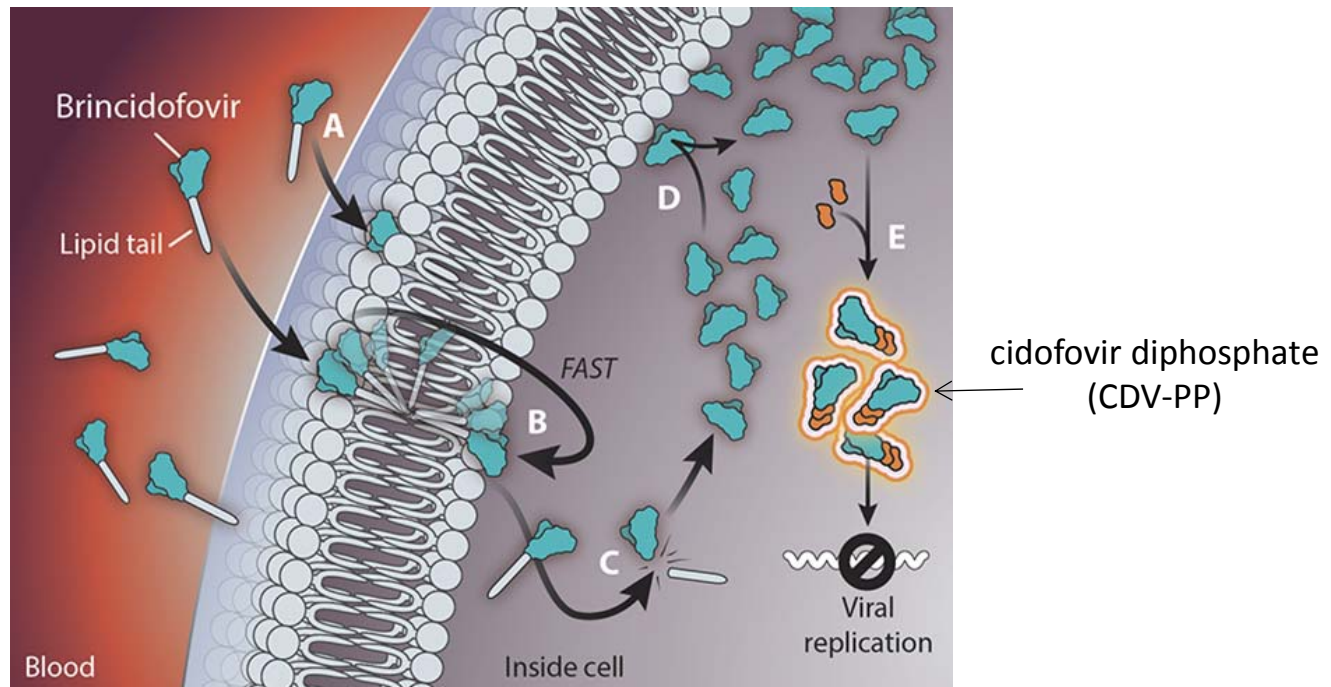


- **Broadly active against dsDNA viruses in vitro**
- **Oral delivery**
- **No evidence of kidney or bone marrow toxicity in > 1,000 subjects receiving BCV**
- **Long intracellular half-life allows twice-weekly dosing**

BCV Development Program Advancing in Three Indications

- Cytomegalovirus (CMV): Prevention in Hematopoietic Cell Transplant (HCT) Recipients
 - Enrolling Phase 3 trial SUPPRESS in adult subjects post-HSCT
- Adenovirus (AdV): Preemptive Therapy in Pediatric and Adult HCT Recipients
 - Phase 2 Preemptive therapy in adult and pediatric HSCT recipients
 - Phase 3 AdVise trial for treatment of AdV in Adults and Pediatrics
- Smallpox: Medical Countermeasure for Treatment
 - Development program based on animal efficacy and human safety

Brincidofovir Uptake and Anabolism



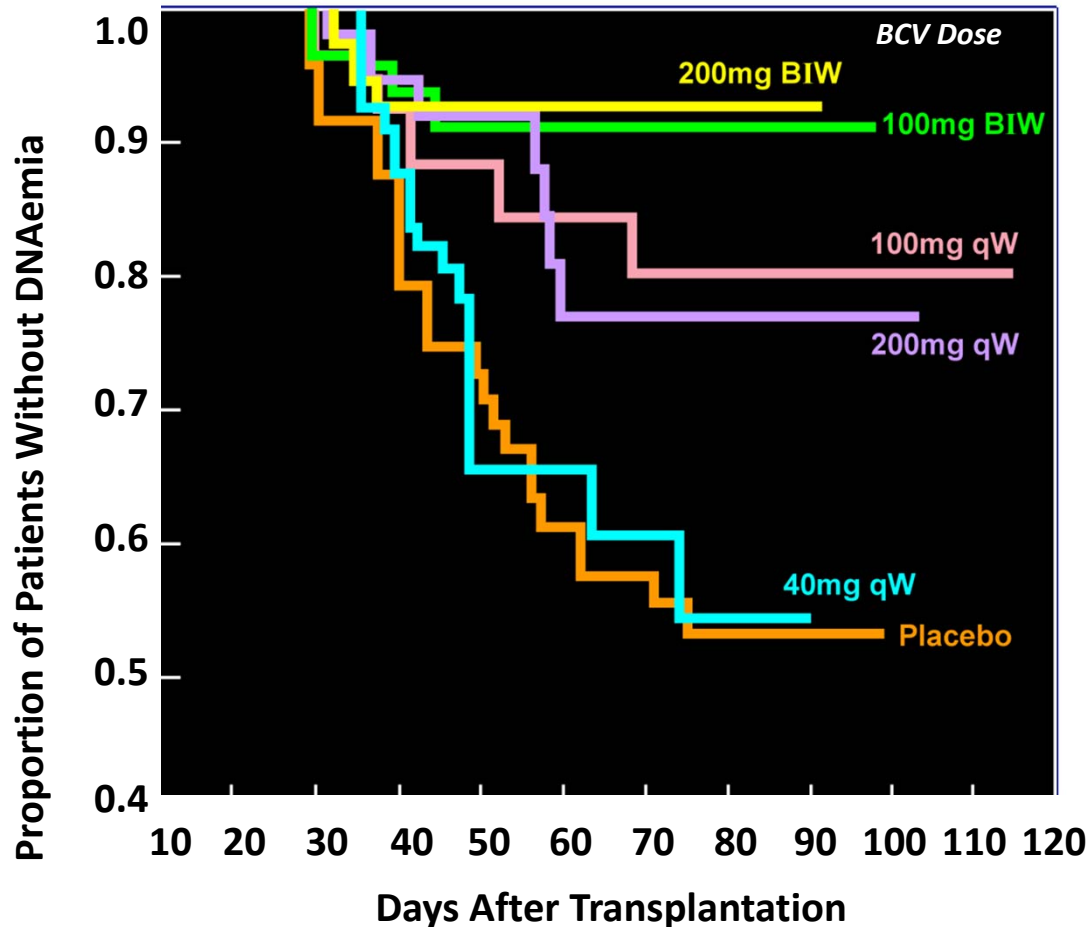
- A. The lipid tail of BCV enables insertion into the plasma membrane
- B. BCV can rapidly enter the cell through flip-flop from the outer to the inner lipid leaflet
- C. Inside the cell, the lipid tail is removed releasing cidofovir
- D. Cidofovir accumulates inside the cell since it can not pass through the plasma membrane
- E. Cidofovir is phosphorylated to the active polymerase inhibitor cidofovir diphosphate

Brincidofovir has Enhanced In Vitro Potency Compared to Cidofovir

Virus	BCV EC50 (μM)	Fold increase in activity of brincidofovir vs cidofovir*
AdV 5	0.02	65
CMV	0.001	422
Variola major	0.1	273

*EC₅₀ cidofovir/EC₅₀ Brincidofovir

Study CMX001-201: Twice-weekly BCV Dosing Prevents CMV Reactivation



- 100 mg BIW dosing better than 200 mg QW
- QW dosing retains antiviral activity but inferior to BIW
- 40 mg QW dose ineffective

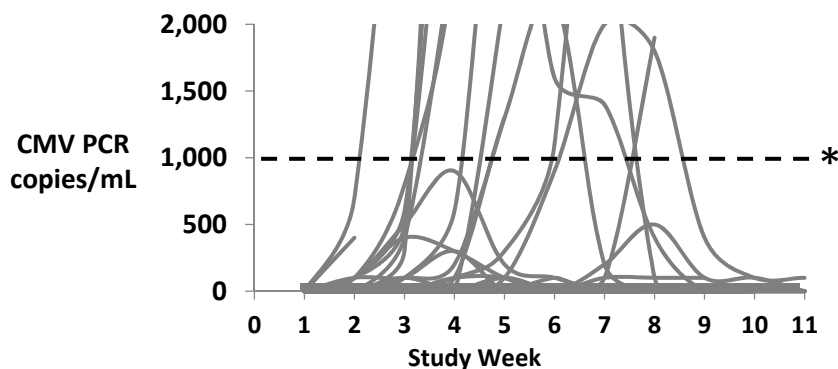
Source: Data from Study 201 presented at BMT Tandem, February 2012.

Study CMX001-201: BCV Suppressed CMV Reactivation

Placebo

- N = 47
- 15/47 \geq 1,000 c/mL

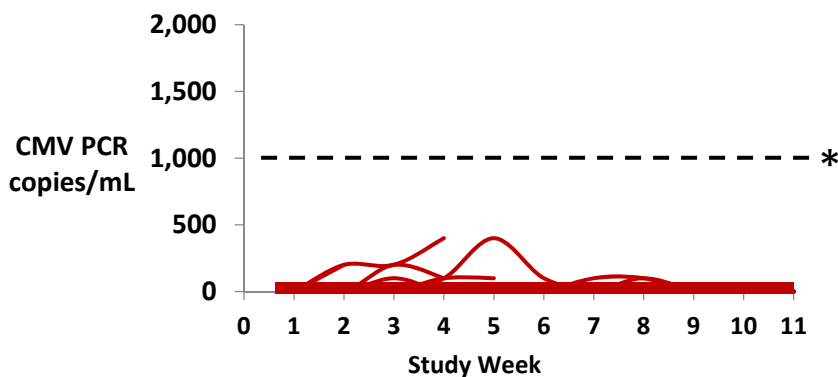
Placebo



CMX001 100 mg BIW

- N = 41
- 0/41 \geq 1,000 c/mL
- 9/41 CMV PCR+

CMX001 100 mg BIW

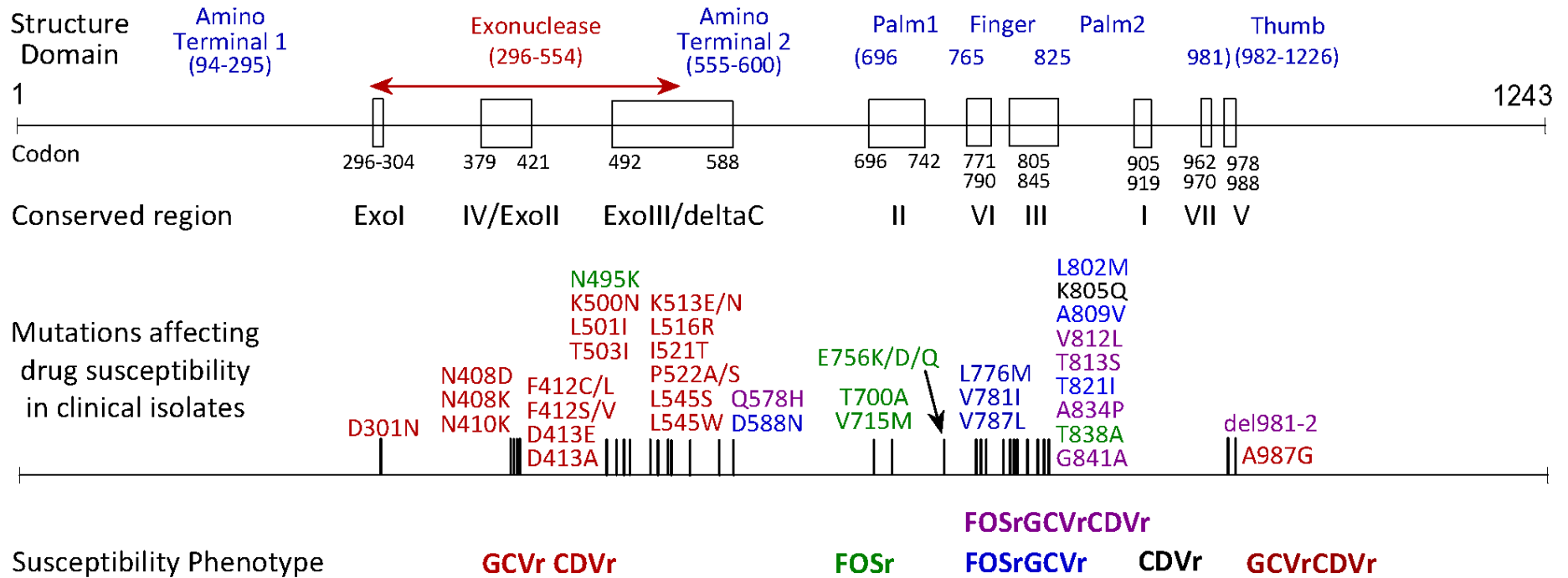


*Represents clinically relevant threshold.

Subjects CMV negative at Baseline.

Source: Data from Study 201 presented at BMT Tandem, February 2012.

BCV Resistance is Associated with Specific CMV DNA Polymerase Mutations



BCV and CDV cross resistance is expected based on shared active metabolite (CVP-PP)

Brincidofovir Primary CMV Mutation in UL54 Selected In Vitro: Impaired Replication, Retained Sensitivity to GCV and FOS

- Wild-type CMV (AD169) propagated in HFFs with BCV for 10 months to generate a BCV resistant strain (CMX001^R)

CMX001^R:

- No mutations in UL97
- One mutation in CMV polymerase UL54 → D542E
 - Recombinant >10-fold increase in EC₅₀ to CDV and BCV
 - Sensitive to GCV and FOS
 - Small plaque phenotype and slow replication

GCV = ganciclovir; FOS = foscarnet; HFF = human foreskin fibroblast

Source: James et al. AAC 2013, 57: 3321

Study CMX001-201: No Resistance-Associated Mutations (RAMs) Detected

- All subjects treated with BCV \geq 4 weeks with >500 c/mL of CMV DNA in plasma had samples submitted for genotyping (Viracor-IBT)
- UL97 Kinase: No RAMs detected
- UL54 Polymerase: R1052C detected in 3 subjects (at baseline in one case)
 - R1052C (in combination with V781I and several polymorphisms) was associated with resistance in a clinical isolate from a GCV/FOS treated patient
 - R1052C did not confer resistance to BCV, CDV, GCV or FOS in recombinant phenotyping

BCV Expanded Access Protocol: Study CMX001-350 (n=210)

- Part of BCV Expanded Access Program to treat life-threatening dsDNA viral infections in patients who had exhausted all available therapies or for whom there were no therapeutic options available

Baseline Demographics

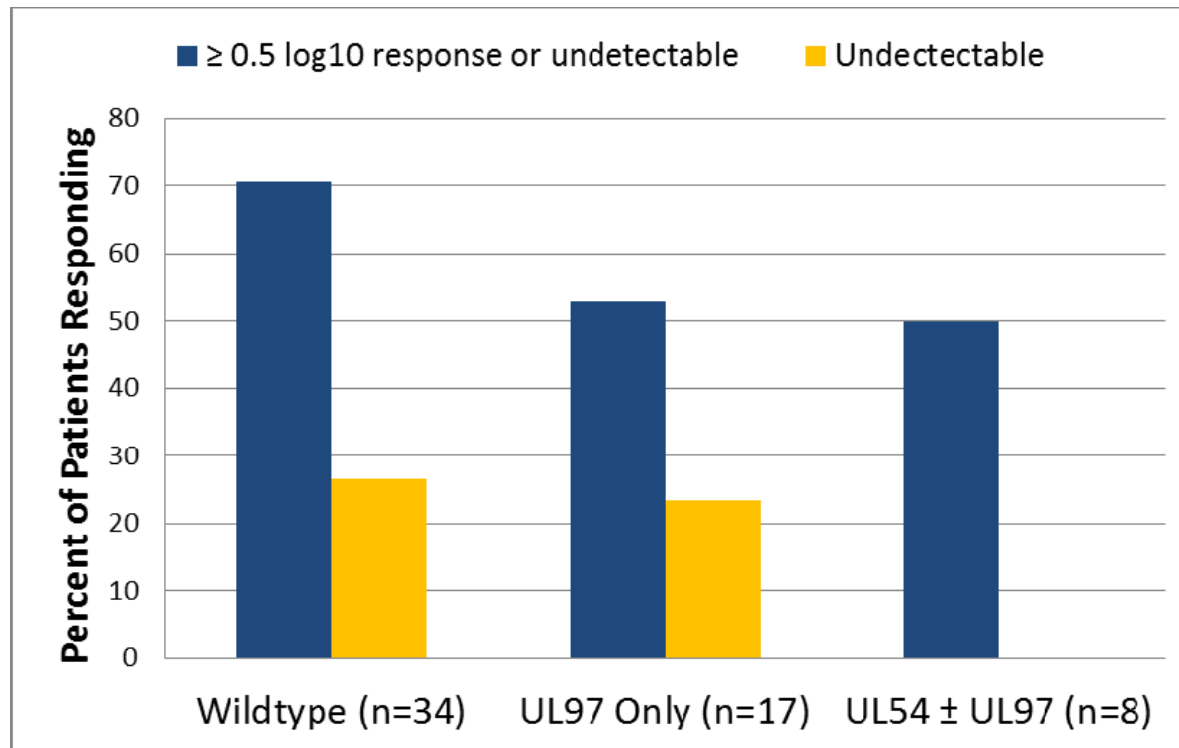
- **N = 210**
 - 68 pediatric, 142 adult
- **BCV Exposure**
 - Mean 9.5 weeks (1-43 weeks)
 - 68% > 4 weeks
 - 30% > 12 weeks
- **Immunodeficiency**
 - 153 HCT (73%)
 - 33 SOT (16%)
 - Congenital, HIV, other (11%)

dsDNA Viral Infection(s)

- **28% had two or more viral infections**
- **Primary virus:**
 - 107 – CMV
 - 61 – AdV
 - 7 – BKV
 - 35 – Other
- **CMV genotyping attempted for all subjects treated with BCV for ≥ 4 weeks and with >500 c/mL**
- **Majority of UL54 mutations observed confer GCV/CDV resistance**

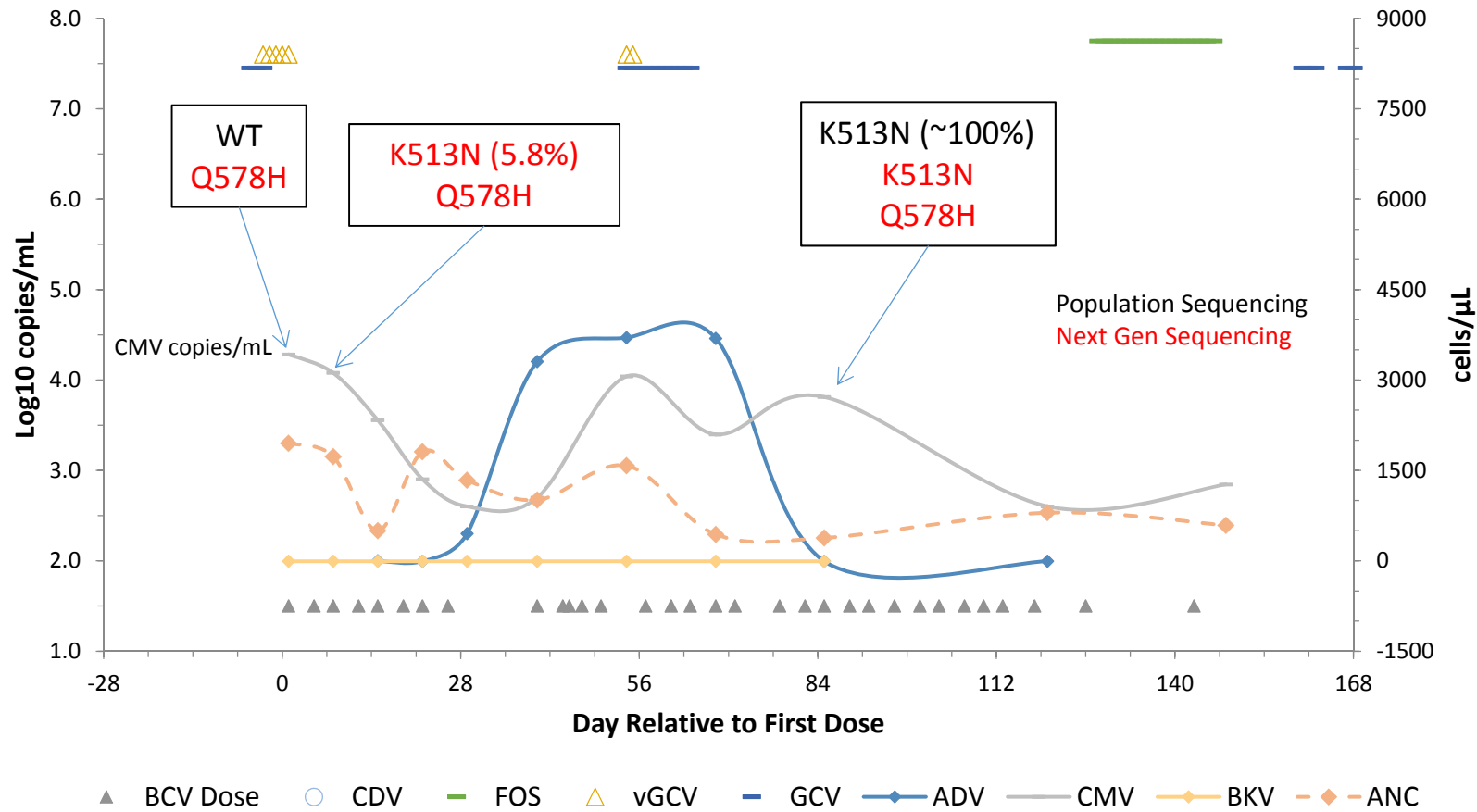
GCV = ganciclovir; FOS = foscarnet

Plasma CMV Response for Patients in Study 350 by Baseline CMV Genotype at Last Time on Therapy

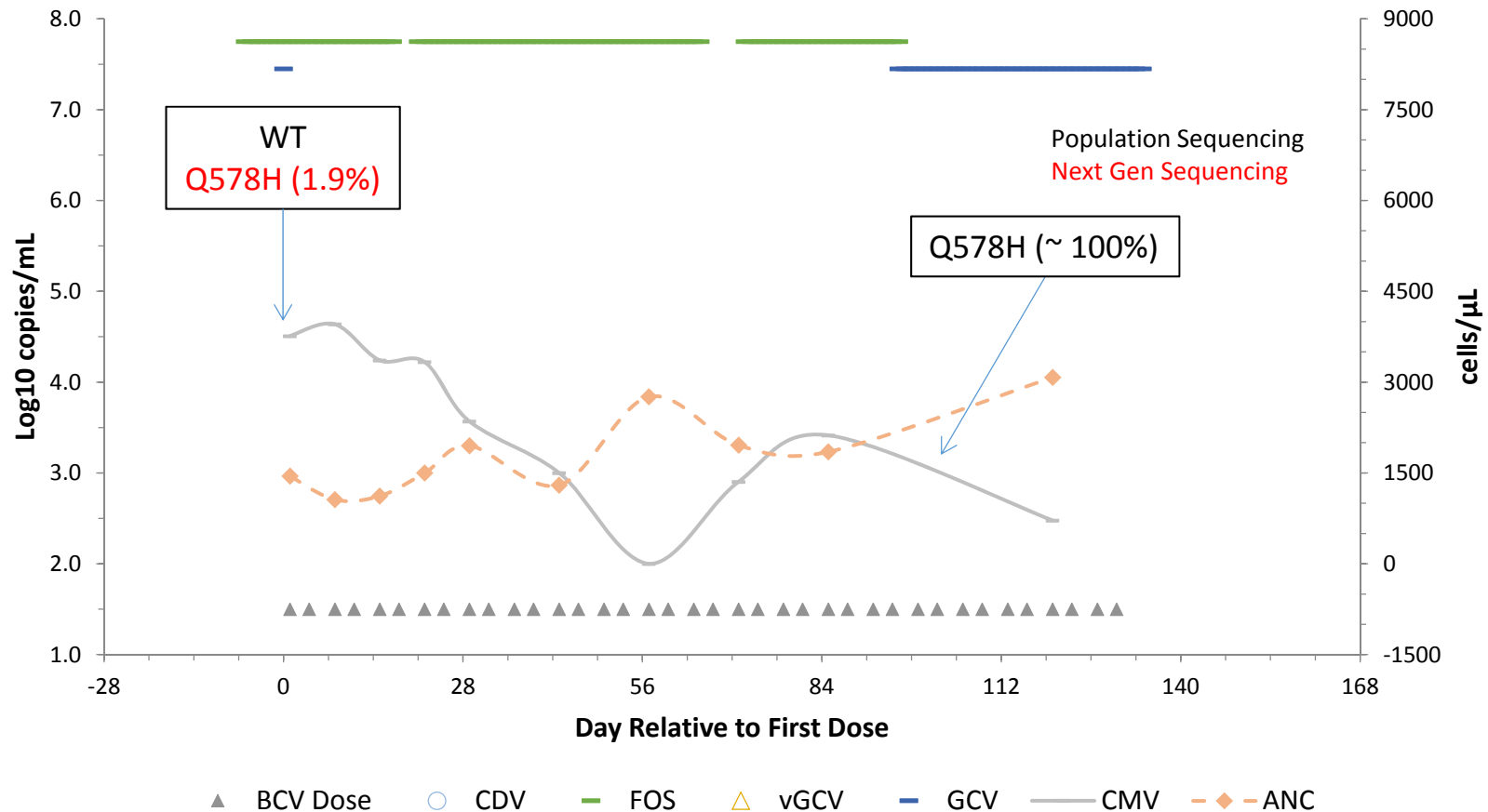


Fewer subjects with UL54 mutations at baseline reached undetected CMV levels ($p = 0.17$)

Next Generation Sequencing Revealed UL54 RAMs Early in Treatment in Some Subjects



Next Generation Sequencing Revealed UL54 RAMs Before BCV Treatment in Some Subjects



UL54 Mutations Associated with Diminished Response in CMV Therapy-Experienced (CDV, FOS, GCV) Population

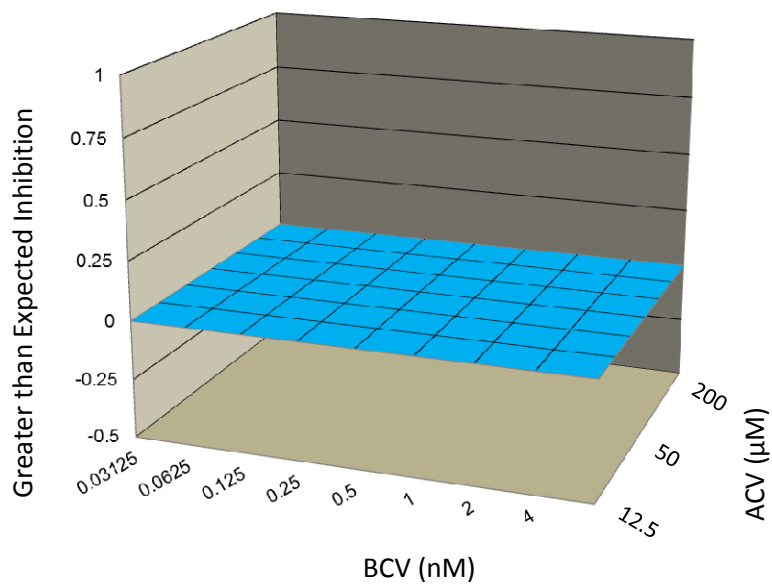
	UL54 CDV Mutation ^[1] (n=14)	No UL54 CDV Mutation (n=49)
Geometric Mean Baseline Viral Load (c/mL)	10,965	5,495
Mean log ₁₀ Change (Baseline to Last Value)	-0.43	-0.81
Proportion ≤200 c/mL at Last Value	0/14 (0%)	26/49 (53%)* ^[2]

[1] Observed at Baseline or post-Baseline (408K, 412L, 513N, K513R & P522S, 522S, 545S, 578H, 987G)

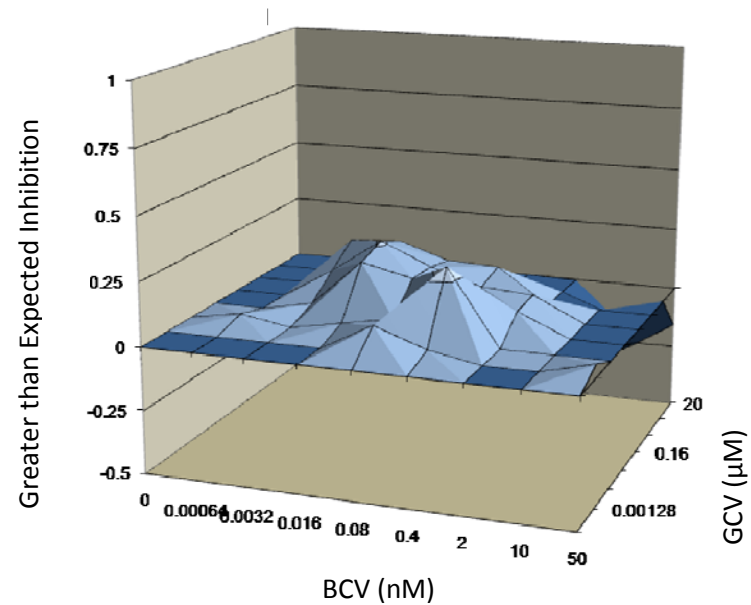
[2] p-value <0.05 using Fisher's exact test (two-sided) vs. UL54 CDV mutation group

In Vitro CMV Antiviral Synergy Studies with BCV and ACV or GCV

- *In vitro* synergy studies with BCV and ACV or GCV performed in MCR-5 and HFF cells with qPCR readout
- BCV + ACV had additive antiviral activity in vitro
- BCV + GCV had synergistic activity in vitro



BCV + ACV



BCV + GCV

Overall Summary

- UL54 mutations associated with other CMV antivirals (GCV, CDV, FOS) can cause cross resistance to BCV *in vitro*, as expected
- The rapid detection of UL54 CDV RAMs in a subset of subjects from treatment experienced subjects (Study 350) combined with the absence of CDV RAMS in naive subjects (Study 201) suggest CDV RAMS were enriched in the viral population of experienced subjects by prior anti-CMV therapy
- Next generation sequencing of selected subjects from Study 350 provided evidence for low abundance mutations at baseline in some subjects
- BCV appears to effectively preserve all other therapeutic options when used as first line therapy for HSCT patients



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