



# CHIMERIX

H. C. WAINWRIGHT HEALTHCARE CONFERENCE

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**APRIL 9, 2018**

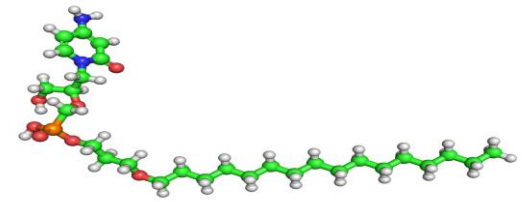
# Forward-Looking Statements

*These slides and the accompanying oral presentation contain forward-looking statements and information within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks, uncertainties and other factors, including the possibility that there may not be a viable continued development path for brincidofovir, that any clinical trials we may conduct will not demonstrate adequate efficacy and safety of brincidofovir, that the FDA and other regulatory authorities may not approve brincidofovir or brincidofovir-based regimens, and that marketing approvals, if granted, may have significant limitations on their use. As a result, brincidofovir may never be successfully commercialized. In addition, Chimerix may be unable to file for regulatory approval for brincidofovir with other regulatory authorities. Similar risks and uncertainties apply to our development of CMX521. These risks, uncertainties and other factors could cause actual results to differ materially from those referred to in the forward-looking statements. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in Chimerix's Annual Report on Form 10-K for the year ended December 31, 2017 and other documents subsequently filed with or furnished to the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Chimerix, and Chimerix assumes no obligation to update any such forward-looking statements.*

# CMRX: Developing Solutions for Immunocompromised Patients

- Experienced and committed management team with successful track records developing significant antiviral drugs and first-in-indication commercial launches
- Brincidofovir: first broad-spectrum antiviral in development
  - Oral BCV in late-stage development for treatment of smallpox and adenovirus
  - New IV BCV formulation for prevention of serious viral infections in transplant recipients and treatment of viral diseases in the growing immunocompromised patient population
- Proprietary lipid-conjugate technology has led to two clinical-stage compounds
  - Brincidofovir (CMX001, BCV) and CMX157, licensed to ContraVir
- CMX521: newest investigational compound for norovirus
- Chimerix remains well-capitalized to achieve our planned milestones with \$228M at the end of 2017
- Patent protection into 2034 for brincidofovir, and 2036 for CMX521

# Brincidofovir (BCV, CMX001)



- Broad-spectrum antiviral with high *in vitro* potency against all herpes viruses, adenovirus subtypes, other DNA viruses that cause human disease
- Oral and IV formulations in development
  - Both formulations deliver BCV to blood and cells known to carry DNA viruses.
  - Cleavage of lipid side-chain occurs in the cell, delivering the active antiviral directly to the site of viral replication.
  - Not associated with kidney toxicity or hematologic toxicity<sup>1,2</sup>
- Potential indications:
  - Treatment of serious AdV infection and disease
  - Treatment of smallpox
  - Prevention of serious viral infections in stem cell transplant recipients (HCT)
  - Treatment of BK virus in kidney and HCT transplant recipients

***BCV is the only broad spectrum antiviral with demonstrated potency against a variety of DNA viruses, a high barrier to resistance, no kidney or hematologic toxicity, and patent protection until 2034***



# Brincidofovir: Potent Broad Spectrum Antiviral

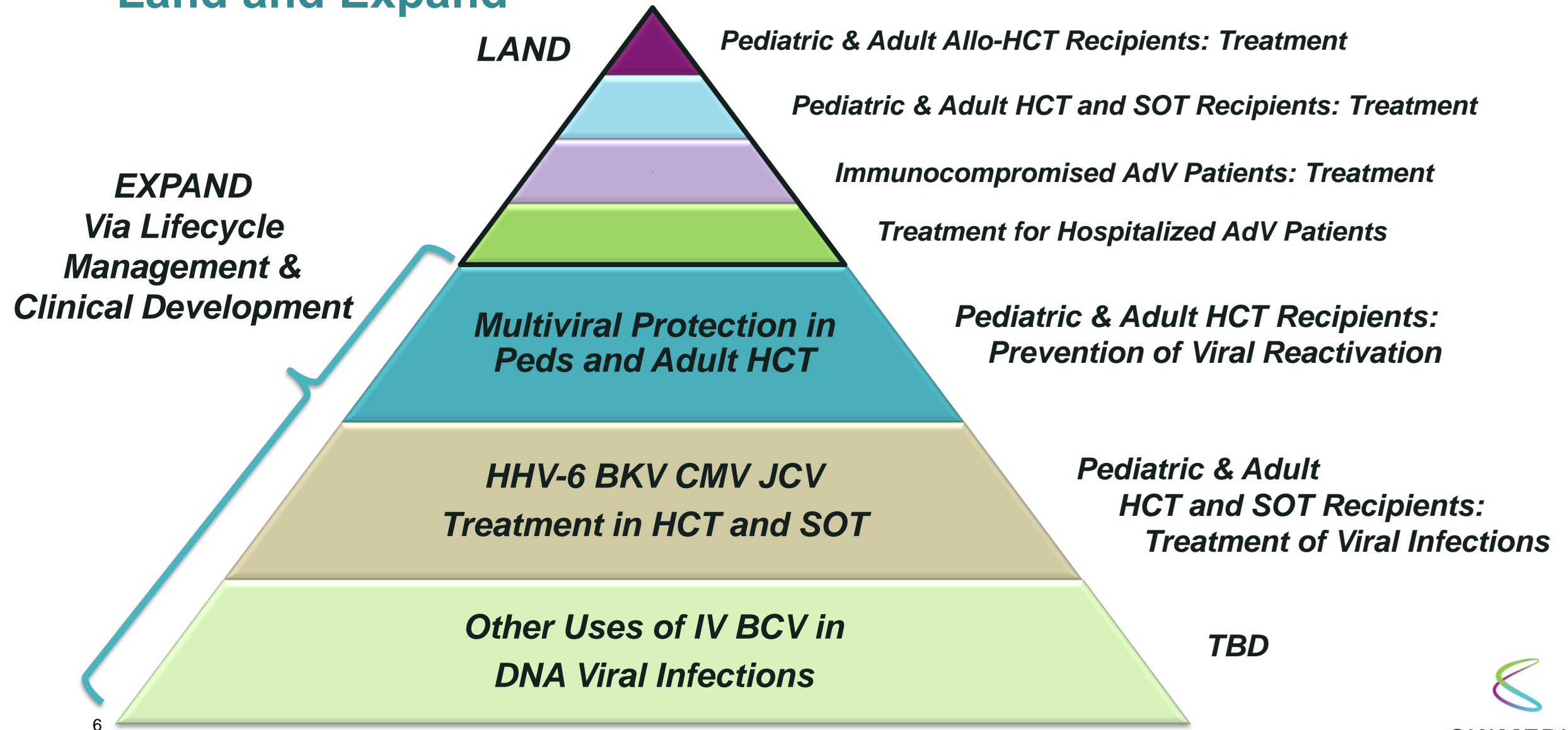
Viral Family	Virus	BCV	Cidofovir	Maribavir	Letermovir	Ganciclovir*	Foscarnet	Acyclovir
Herpes	Cytomegalovirus	0.001	0.4	0.31	0.005	3.8	50-800	>200
	Epstein-Barr Virus	0.03	65.6	0.63	>10	0.9	<500	6.2
	Human Herpesvirus 6	0.003	2.7	Inactive	>10	5.8	16	10
	Human Herpesvirus 8	0.02	2.6	Inactive	—	8.9	177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

Potency expressed as EC<sub>50</sub> = concentration in µM required to reduce viral replication by 50% *in vitro*; “—” indicates no data.

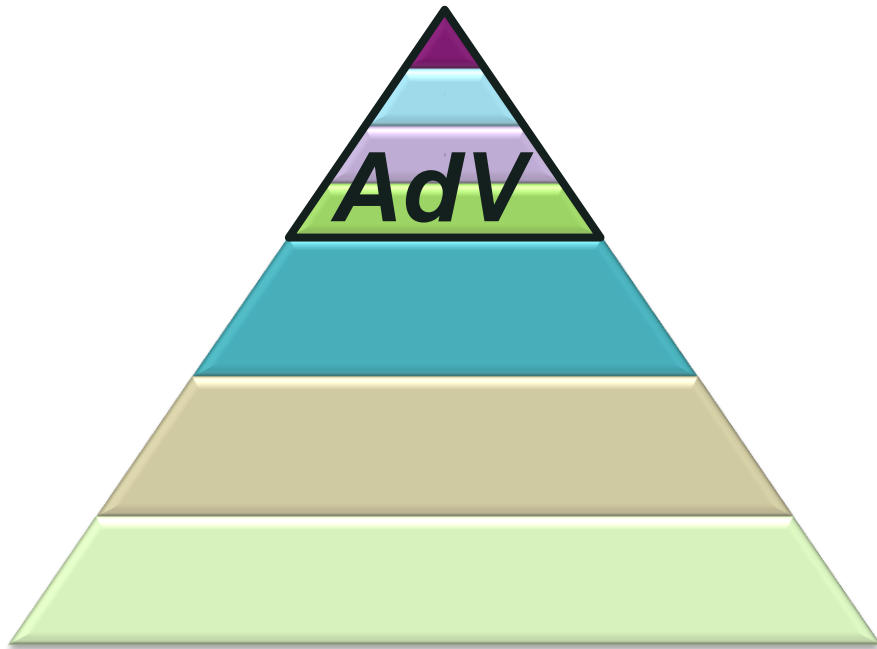
\*Valganciclovir is rapidly converted to ganciclovir *in vivo*; ganciclovir is the relevant compound for cell activity studies.

Source: Data are compiled from multiple sources and include multiple materials and methodologies.

# Building Full Potential Value for Oral and IV Brincidofovir: “Land and Expand”



# “Land”: First Indication Oral Brincidofovir for Adenovirus



## Populations for initial indication:

- Pediatric allo-HCT recipients
- Adult allo-HCT recipients

## Populations with available dosing information:

- Hospitalized adults
- Immunocompromised patients

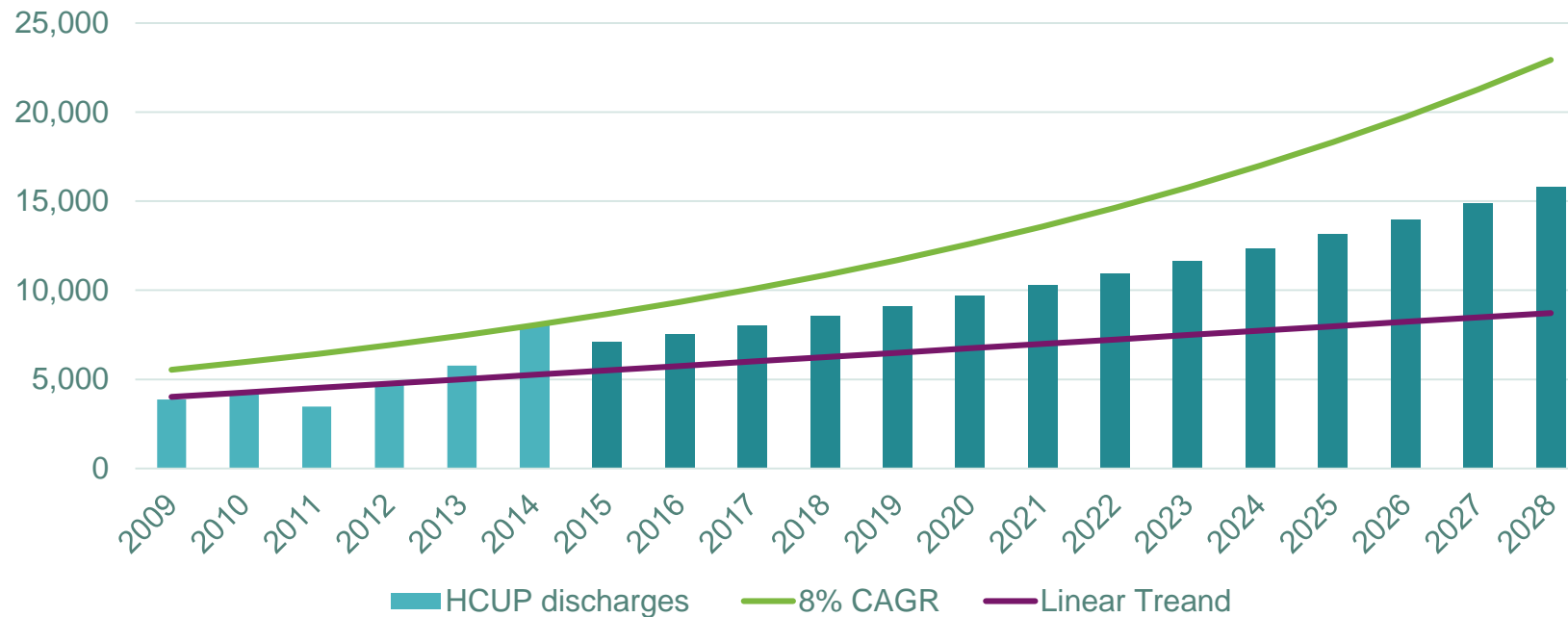
## ■ Focus for 2018: “***Stick the Landing***”

- Recruiting the global AdAPT trial in pediatric transplant recipients
- Provide additional data for adult transplant and other non-transplant populations known to have serious adenovirus infections
- Support probability of success in EU and US with publications on adenovirus
- Orphan Drug designation informs price point

# ~8000 AdV Hospitalizations Annually in the US Beyond Transplant

## U.S. AdV-Related Hospital Discharges: 2009-2014 Actual, Trended From 2015

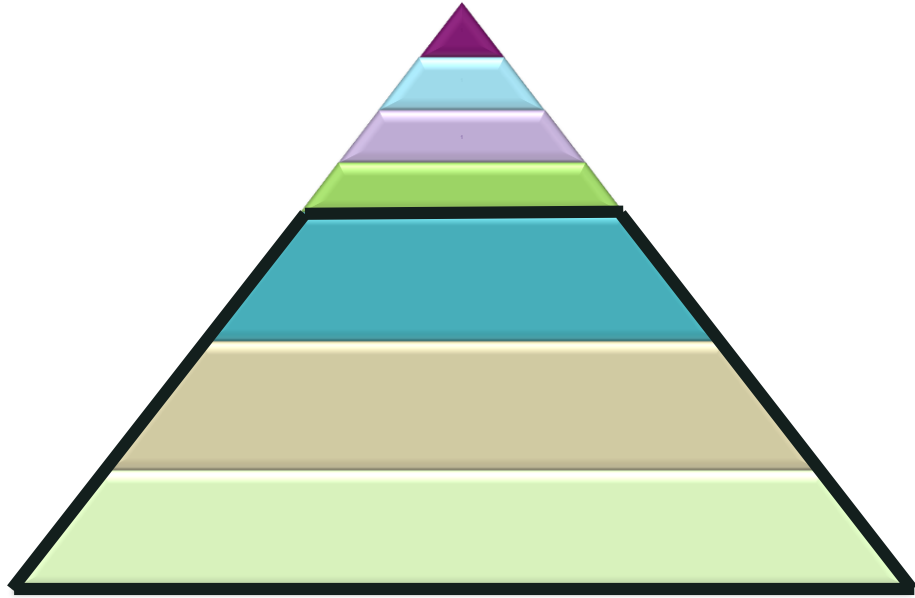
HCUP Discharges – All-listed Diagnosis Codes Adenovirus (079.0, 008.62, 480.0)



- In addition to stem cell and organ transplant recipients, other at-risk populations include newborns with severe combined immunodeficiency (SCID), individuals on chemotherapy or biologics for autoimmune diseases, and reported outbreaks with adenovirus in communities



## IV Brincidofovir: Multi-Viral Prevention



### Populations for first indication:

- Pediatric HCT recipients – focus on AdV
- Adult HCT recipients – multiviral prevention, particularly in high risk transplants
- Populations for subsequent indications or with available dosing information:
  - Kidney transplant recipients
  - BKV, CMV

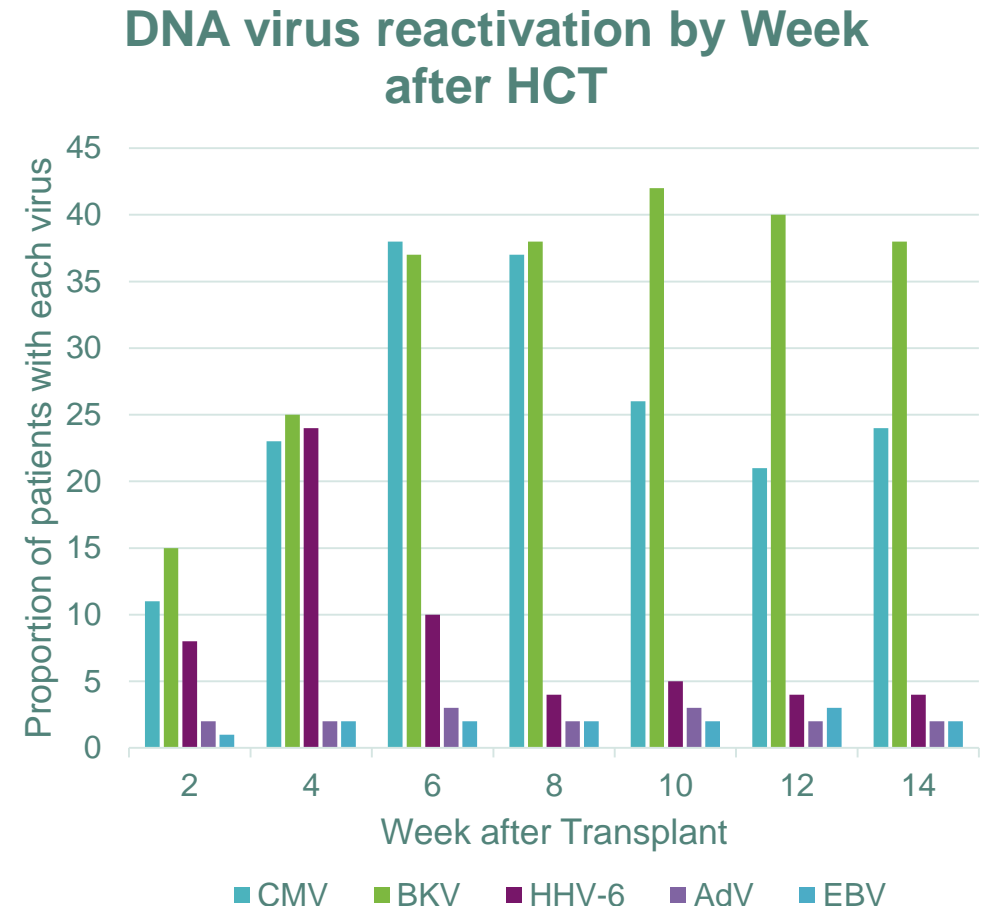
- Prevention of viral disease recognized as significant unmet need in both pediatric and adult HCT recipients
  - 90% of all HCT recipients had at least one DNA virus reactivate in the first post-transplant year
- Potential for utility in:
  - Recurrent Respiratory Papillomatosis (HPV), Glioblastoma (CMV), HPV-positive head and neck cancers

# Stem Cell Transplant (HCT) Recipients are at High Risk of Viral Disease and Mortality

- Allogeneic stem cell transplant (HCT) recipients face 20% mortality in the first year after transplant
- DNA viruses commonly reactivate in these patients as early as the first week after transplant

## Risks for higher mortality:

- Reactivation of more than one virus<sup>1</sup>
- Increased viral burden: quantity and duration of CMV, AdV, EBV, HHV6, BKV in plasma<sup>2</sup>







400+ HCT Recipients at Fred Hutchison Cancer Research Center

<sup>1</sup> Hill JA et al. Blood. 2017 Apr 20;129(16):2316-2325

<sup>2</sup> Hill JA et al. Clin Infect Dis. 2018 Jan 18;66(3):368-375

# BCV Market Potential: Growing Transplant and Immunocompromised Patient Populations

				
TRANSPLANTS PER YEAR	U.S.	European Union (28)	ROW	TOTAL
<b>HCT</b>				
Allogeneic	8,700	16,400	8,500	33,400
Autologous	15,000	21,700	12,000	47,700
<b>HCT TOTALS</b>	<b>23,700</b>	<b>38,100</b>	<b>20,500</b>	<b>81,100</b>
<b>SOT</b>				
Kidney	19,860	20,000	40,700	79,300
Liver	7,800	7,400	10,500	25,000
Other SOT	5,940	4,500	1,400	13,800
<b>SOT TOTALS</b>	<b>33,600</b>	<b>31,900</b>	<b>52,600</b>	<b>118,100</b>
<b>TOTAL TRANSPLANT</b>	<b>57,300</b>	<b>70,000</b>	<b>73,100</b>	<b>199,200</b>

US HCT: 2015 figures from CIBMTR. Auto-HCT are increased by 20% to account for under-reporting to CIBMTR. US SOT: 2016 figures from Organ Procurement and Transplantation Network (OPTN). EU HCT: JR Passweg, et al., HSCT in Europe 2014, [nature.com/bmt](http://nature.com/bmt), 2016. ROW HCT: 2013 figures from EBMT Activity Office (Bone Marrow Transplantation 2015 (50);476-482). TOTAL HCT: US + EU + ROW. EU & TOTAL SOT: Newsletter Transplant – International Figures On Donation And Transplantation 2014; EDQM, volume 20, 2015. ROW SOT: Total - EU - US

# Why Are We Excited About 2018?

- AdAPT trial of short-course **oral BCV for adenovirus** enrolling and data expected in 2019; if positive, data should support first regulatory approval
- Lack of GI side-effects with multiple doses of **IV BCV** supports progression to Phase 2 patient studies in 2018, leading to potential studies in prevention and treatment of multiple viruses including AdV, CMV, and BKV in 2019
- Regulatory submissions for marketing approval of **oral BCV for smallpox** are planned for 2019
- **CMX521**, the first direct-acting antiviral specific for norovirus, is now in clinical stage development
- We have patent protection through 2034 and sufficient capital to progress oral BCV to value-generating data and/or procurement contracts

# Data-Rich 2018 and 2019 Ahead of Regulatory Decisions

Compound	Indication	1H 2018	2H 2018	2019
Oral BCV	Adenovirus	❖ Enrolling AdAPT ❖ AdVance Data	❖ Enrolling AdAPT ❖ Enrolling Adult AdV Study	❖ <b>AdAPT Data</b>
	Smallpox	❖ Pivotal mouse study	❖ Pivotal mouse study ❖ Pivotal rabbit study	❖ MAA submission ❖ NDA submission
IV BCV	Adenovirus and CMV	❖ Initiate Phase 2 in adult HCT	❖ Phase 2 in adult HCT	❖ Initiate MVP pivotal trial
CMX521	Treatment of Chronic Norovirus	❖ Ph 1 single dose study	❖ Ph 1 multiple dose study	❖ Norovirus: Challenge / Proof-of-Concept trial
	Prevention of Norovirus Outbreaks			

# AdAPT Underway – Data Expected in 2019

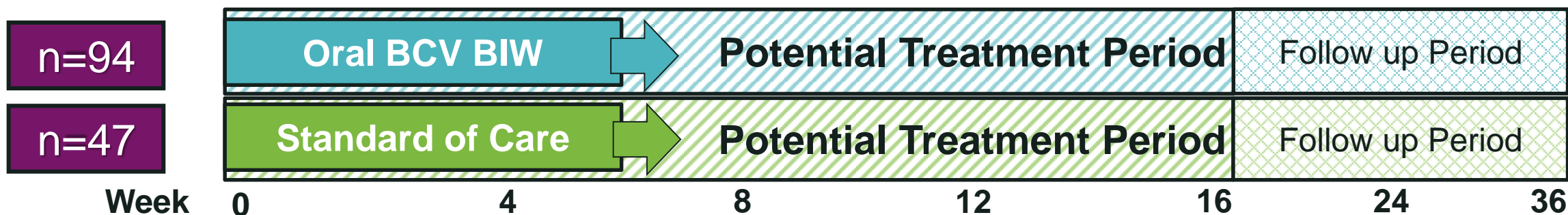


- Study being conducted in US, UK and EU
- Short-course oral treatment for acute life-threatening adenovirus infections
  - Potent antiviral with high barrier to resistance
  - Rapid reduction of AdV viral load in blood and other compartments
  - Short-course treatment minimizes risk of side effects

All timelines are estimated

# AdAPT: Adenovirus after Allogeneic Pediatric Transplantation

- **Open label, comparative study** of **oral BCV** vs. standard of care (SoC) in AdV viremia
  - Pediatric T-cell depleted allo-HCT recipients during first 100 days of HCT
- **Short-course therapy**: “Treat-to-clear” paradigm
  - BCV or SoC administered until AdV is cleared from plasma
- **Primary endpoint**: AdV average viral burden over 16 weeks = **AdV AAUC**
- **Study size**: N=141 to be randomized 2:1 to oral BCV or local standard of care

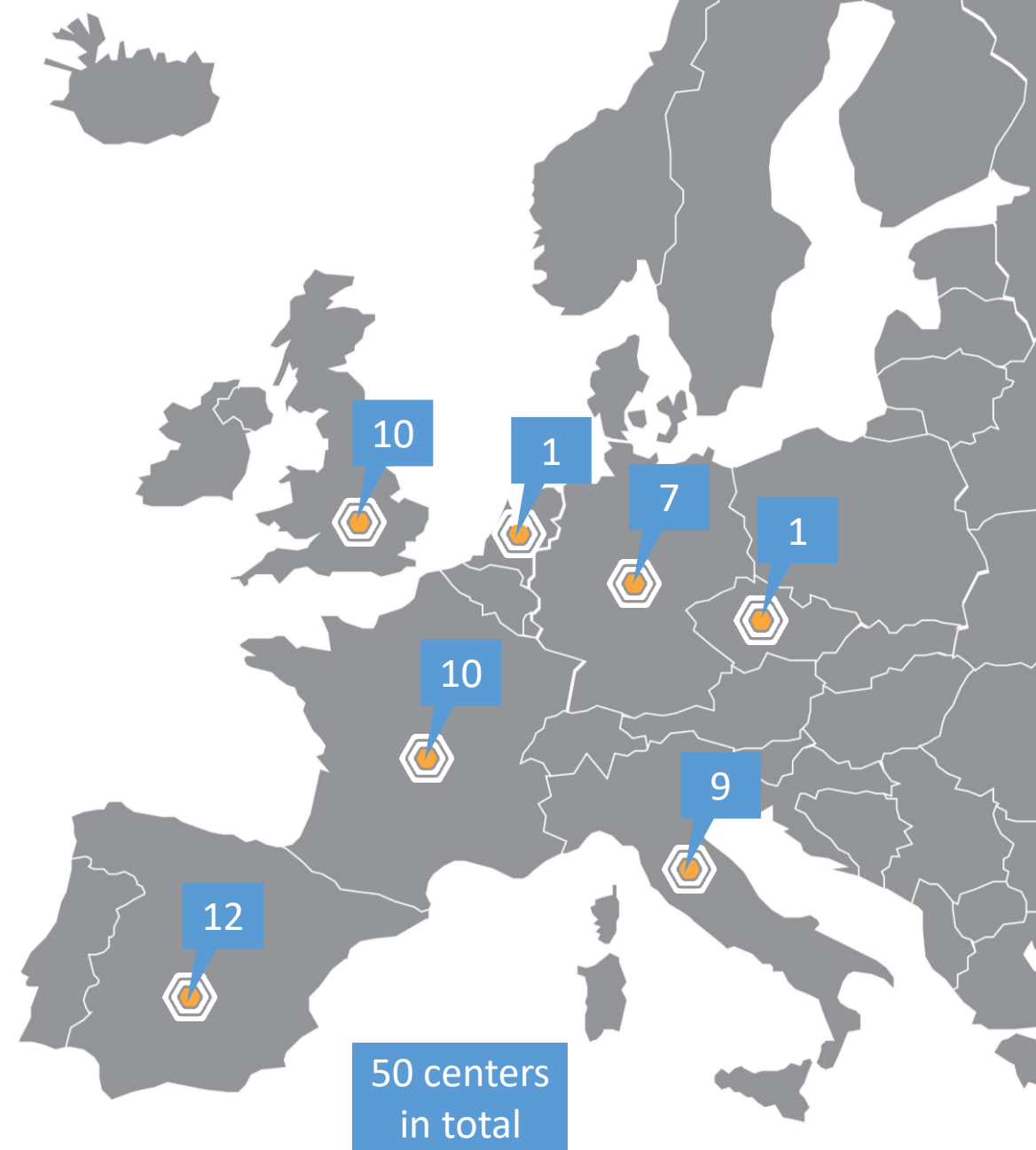


# Planned Epidemiologic Studies To Support Correlation of AdV Viral Burden with Mortality

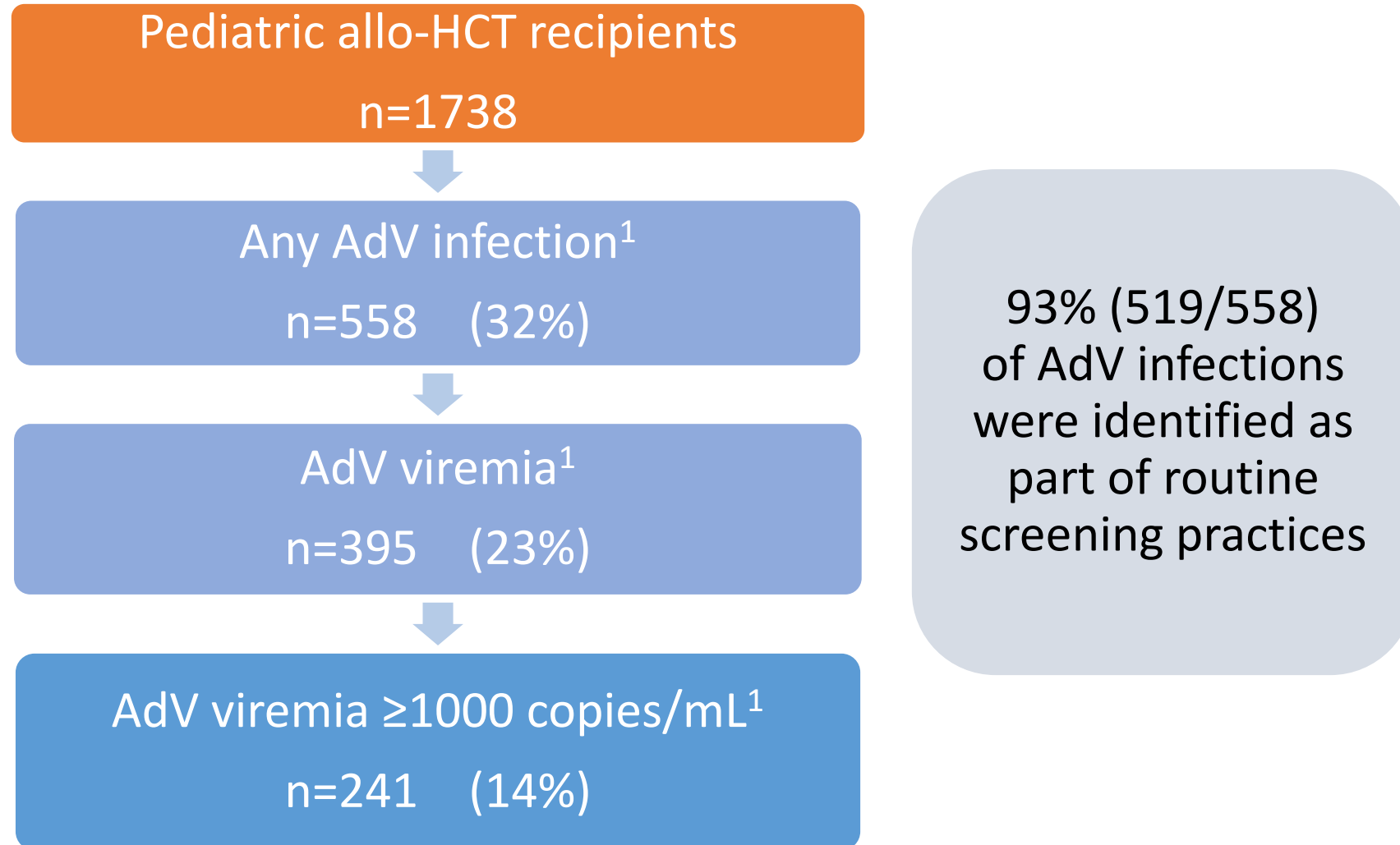
- Multiple independent analyses from transplant centers across Europe and the US are crucial to demonstrate that AdV viral burden and specifically, AdV AAUC matters
  - Boeckh (FHCRC), Papanicolaou (MSKCC), Lion (St Anna), Wynn (Manchester) are publishing and presenting analyses of correlation between AdV viral burden (Adv AAUC) and mortality
- **AdVance: correlation of AdV viral burden with hazard for mortality to be presented at EBMT, subsequent publications**
- Meta-analysis of publications (AdVance plus others) showing relationship of AdV viral load, AdV disease and mortality

# The AdVance Study

- AdVance is a retrospective, multicenter, multinational study of the incidence, management and clinical outcomes of AdV infection in allo-HCT recipients
  - Data from transplants January 2013 to September 2015
  - Quantitative and qualitative data were extracted for: incidence of AdV infection, AdV viremia, and clinically relevant AdV viremia ( $\geq 1000$  copies/mL) within 6 months of transplant
    - Results were stratified by age (pediatric [ $<18$  years] vs adult)



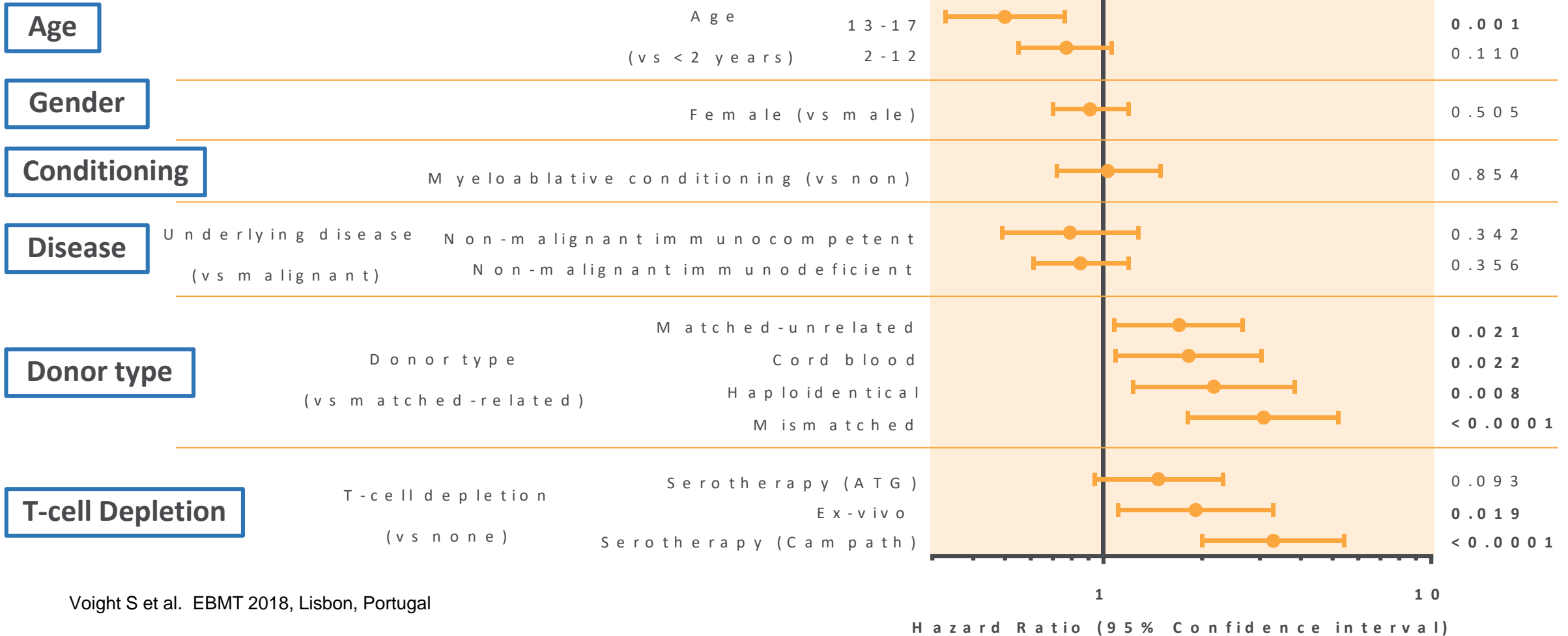
# AdV Occurs in 1 in 3 Pediatric HCT Recipients



<sup>1</sup>Within 6 months of transplant  
Voight S et al. EBMT 2018, Lisbon, Portugal

# Age, donor type, and use of T-cell depletion were prognostic factors for AdV viremia ≥1000 copies/mL in pediatric patients

## Pediatric allo-HCT recipients



Voight S et al. EBMT 2018, Lisbon, Portugal

# Use of Intravenous Cidofovir is Common



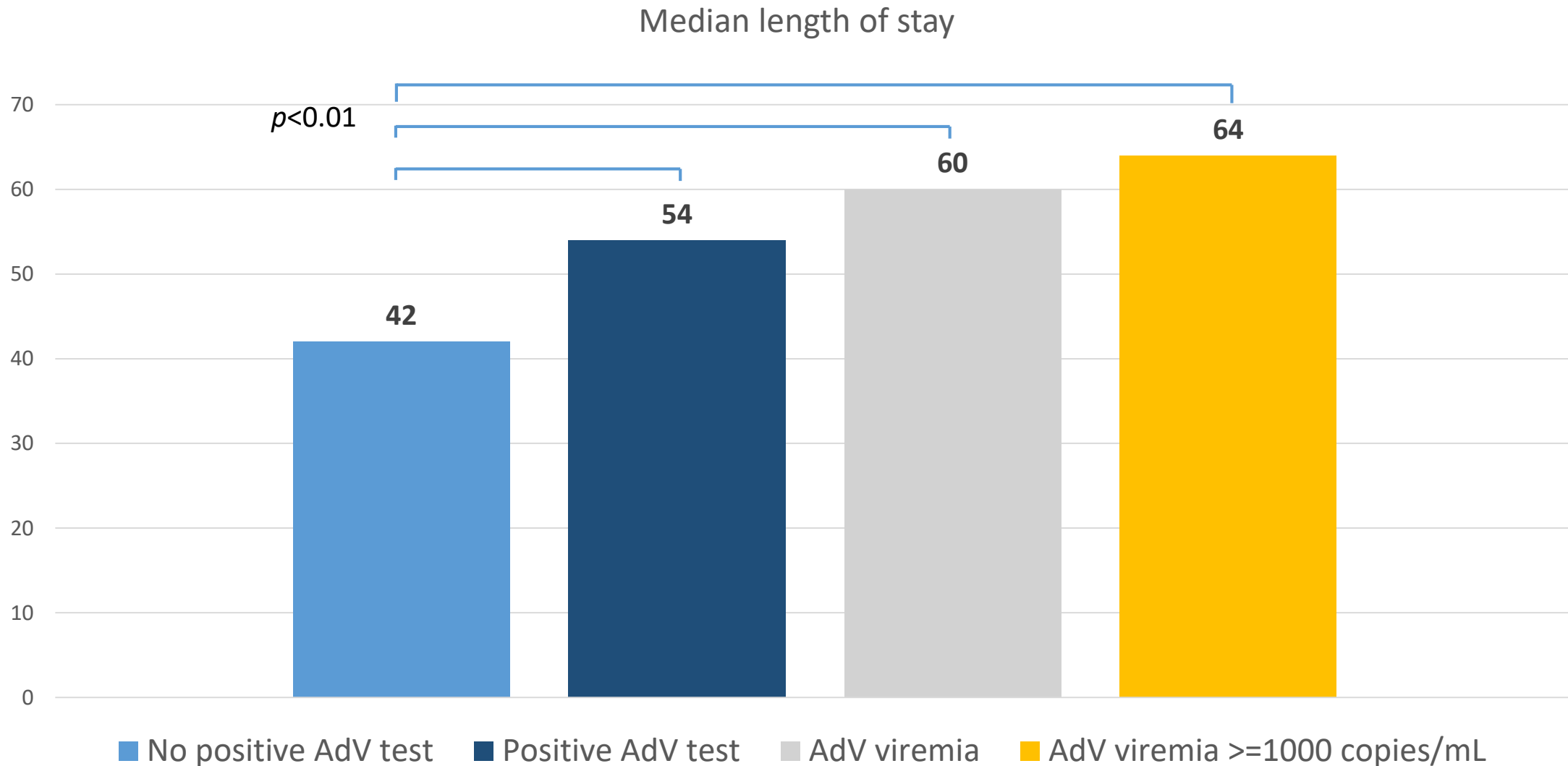
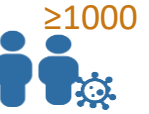
- Consistent with the ECIL-4 guidelines, off-label cidofovir was the preferred first-line treatment for AdV infection, with the majority of physicians using 5 mg/kg per week<sup>1</sup>

	Physicians who treat pediatric patients n=29	Physicians who treat adult patients n=14
<b>Use of a standard regimen</b>	97%	86%
<b>Comprising:</b>		
<b>Starting dose</b>		
1 mg/kg 3 times a week	28%	7%
5 mg/kg per week	69%	79%
<b>Maintenance dose</b>		
1 mg/kg 3 times a week	34%	14%
5 mg/kg per week	62%	72%

- Cidofovir is considered first-line in spite of toxicity concerns and lack of efficacy data
- Brincidofovir appeared to be the second choice of treatment
- Cell-based therapy and ribavirin were less frequently used

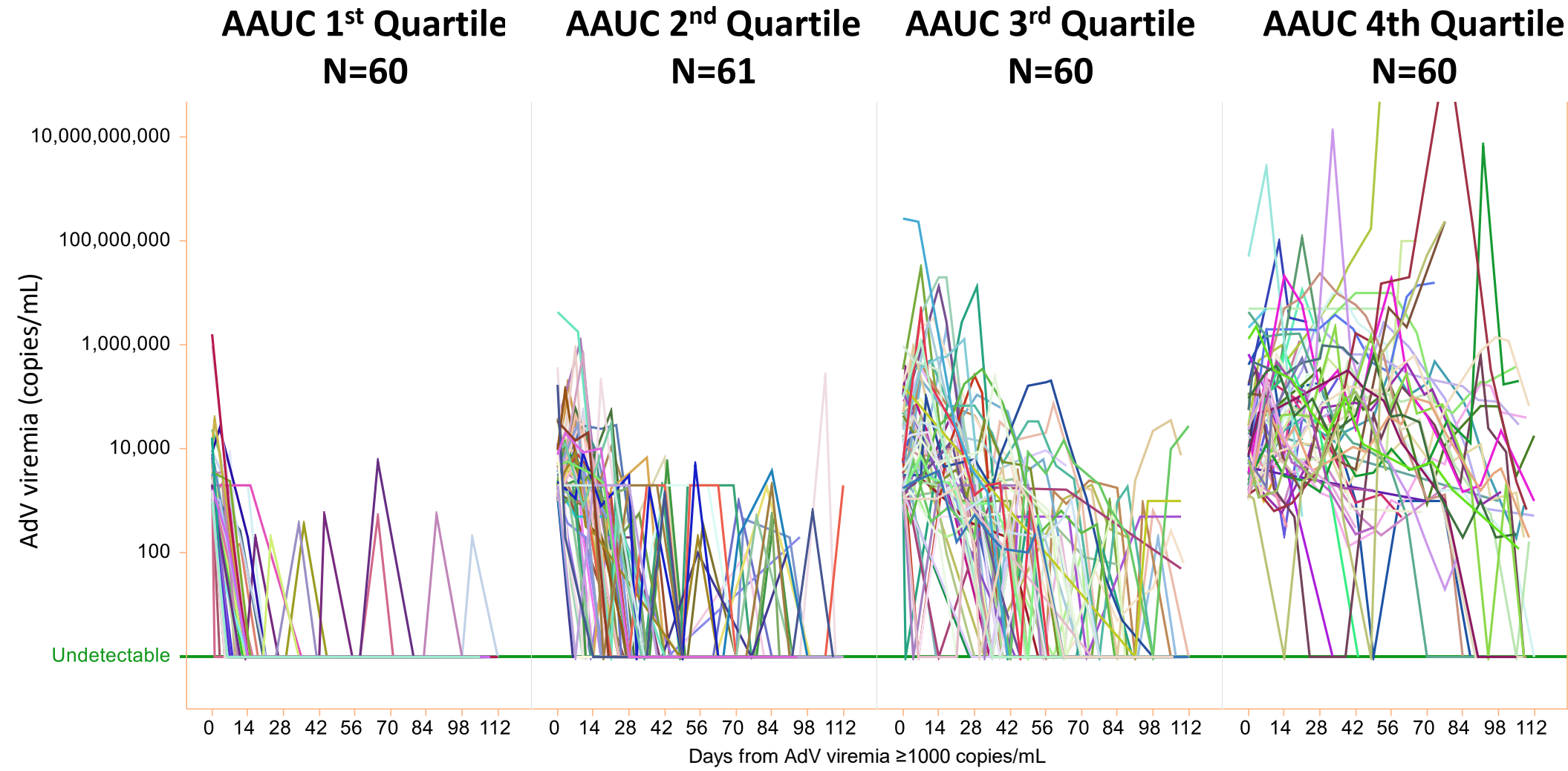
1. Matthes-Martin, S. et al. *Transpl Infect Dis* 2012;14:555–563  
Voight S et al. EBMT 2018, Lisbon, Portugal

# AdV Viremia Leads to ~3 Weeks of Additional Hospitalization



Pérez-Martínez A et al. EBMT 2018, Lisbon, Portugal

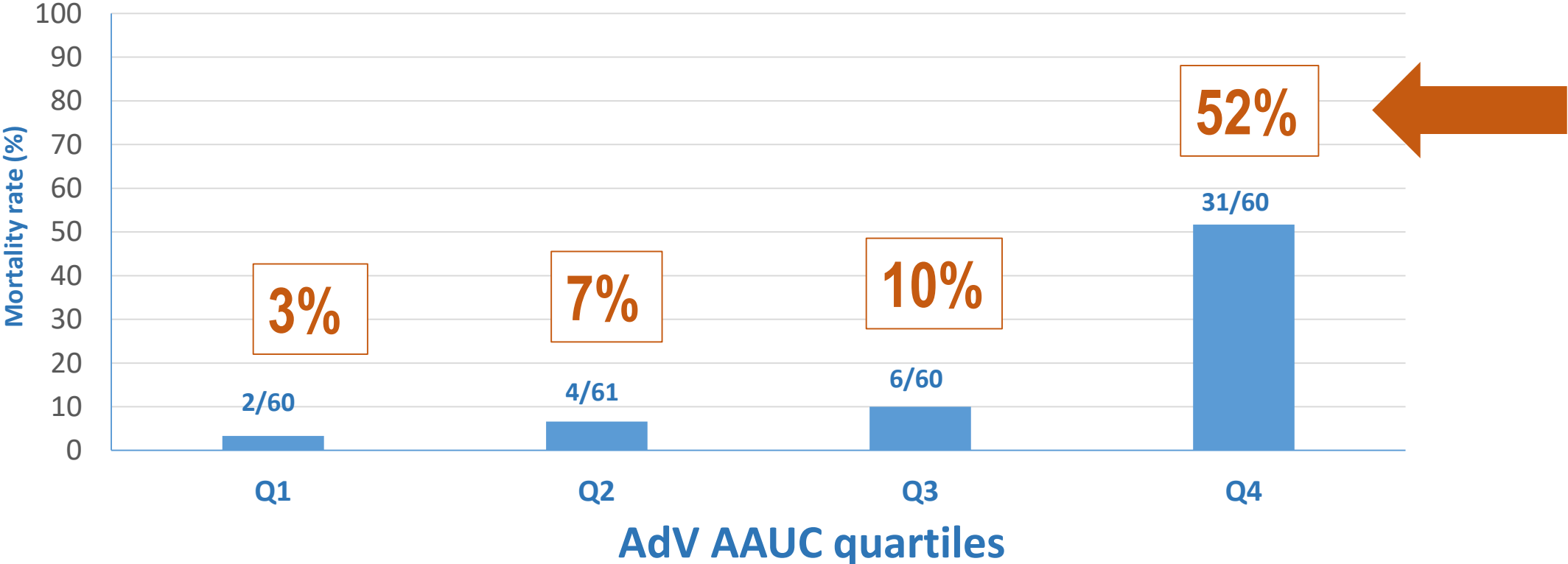
# AdV Peak and Persistence Over Time are Higher in Upper AAUC Quartiles



M. Zecca et al EBMT 2018, Lisbon, Portugal

# Higher AdV AAUC Was Associated with Higher Mortality

All cause mortality 6 months after first AdV viremia  $\geq 1000$  copies/mL

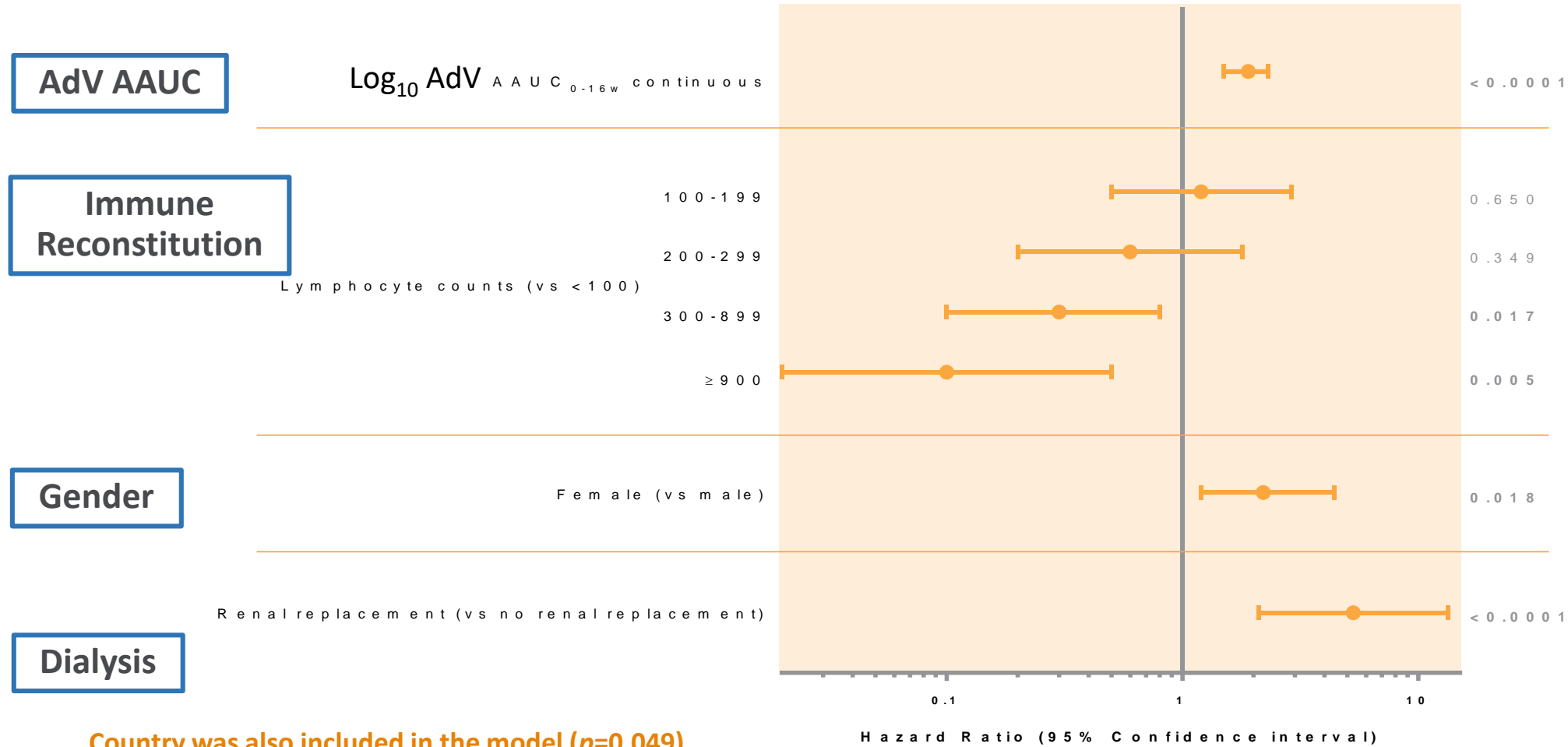


\*comparable findings in non-relapse mortality

M. Zecca et al EBMT 2018, Lisbon, Portugal

# AdV Viral Burden Associated with Mortality Independent of Immune Reconstitution

⚙ Pediatric allo-HCT recipients with AdV viremia  $\geq 1000$  copies/mL *p-value*



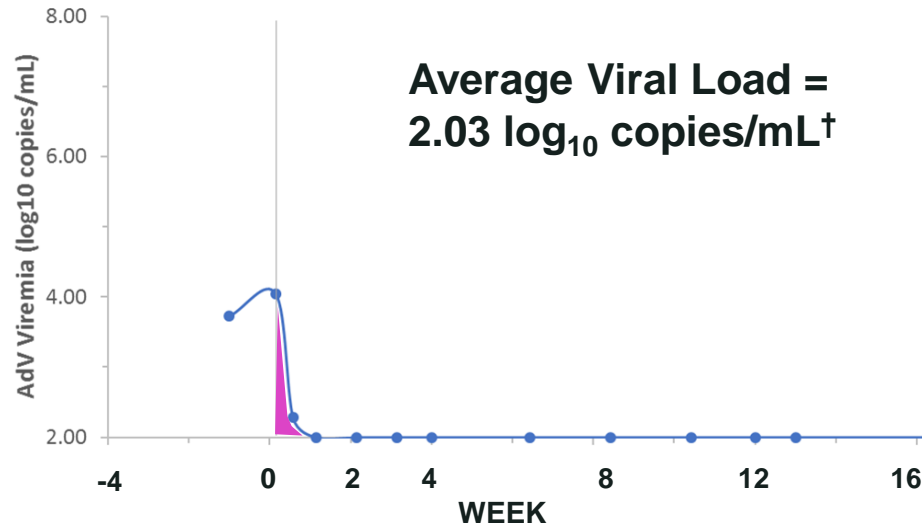
Country was also included in the model ( $p=0.049$ )

M. Zecca et al. EBMT 2018, Lisbon, Portugal

# Rapid Antiviral Effect of Oral Brincidofovir vs Local SOC\* is Best Reflected in AdV Average Area Under the Curve (AAUC)

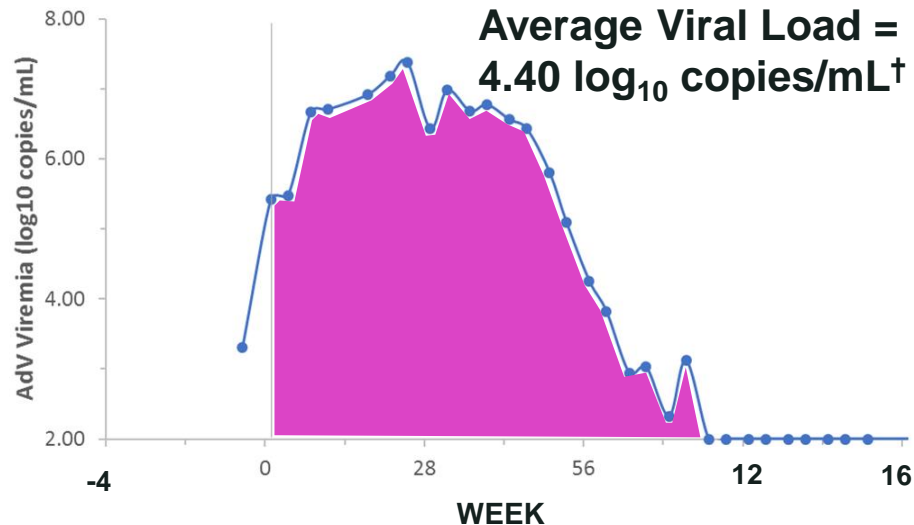
## Oral BCV from Advise

3 yr old pt  
41 days post-TCD  
HCT



## Local Standard of Care (SoC) from Advance

2 yr old pt  
19 days post-HCT



- AdV viremia after transplant is predictive of rapid progression to AdV disease and death
- Oral BCV has demonstrated rapid clearance of AdV viremia
- BCV does not require immune reconstitution to provide AdV viral load reductions
- AdAPT has 90% power to detect  $>0.6 \log_{10}$  copies/mL difference in AdV AAUC

\*Local standard-of-care may include reduction of immunosuppressants or off-label IV cidofovir

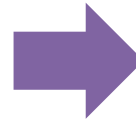
† Lower limit of detection: 2 log copied/mL



## IV BCV: Fulfilling the Potential of Brincidofovir

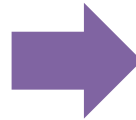
Early development work shows great promise for the IV formulation

IV BCV delivers uniform exposure to key organs



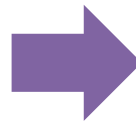
Does not over-expose gut which should allow for long-term tolerability

IV BCV delivers more drug to difficult-to-reach compartments, especially the brain



Supports evaluation of IV BCV for viral brain infections, such as HHV6 encephalitis or JC virus

IV BCV profile may allow for both treatment and prevention of DNA viral infection

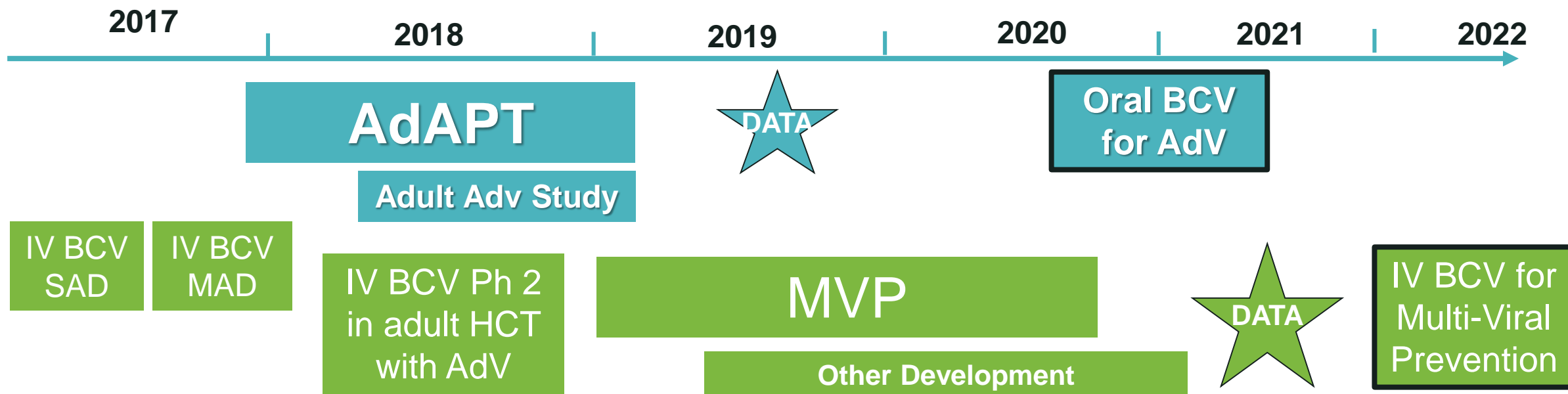


Potential for once-weekly dosing and improved tolerability could allow for broader use in multiple viruses

## IV BCV Multiple Dose Study Demonstrates Improved GI Tolerability

- MAD dosing complete: 10 mg twice weekly, 20 mg once weekly for 2-4 weeks
  - No diarrhea at 10 mg IV twice weekly
    - IV BCV 10 mg provided plasma drug levels equivalent to oral BCV 100 mg which demonstrated antiviral activity in prior studies
  - No dose limiting clinical adverse events
- Phase 2 IV BCV patient studies starting in 1H 2018
  - Demonstrate PK and tolerability of multiple doses in adult HCT recipients
  - Evaluate relationship between dose and change from baseline in AdV in blood and stool
  - Data expected 2H 2018

# Anticipated Brincidofovir Milestones and Regulatory Decisions



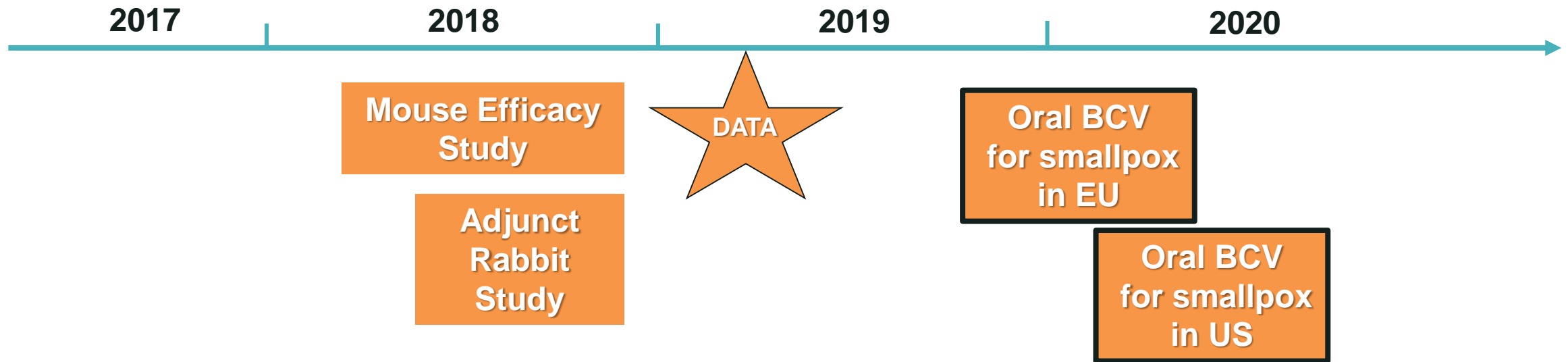
- Phase 2 IV BCV data to support dose-selection for MVP pivotal trial
- IV BCV offers the promise of longer term dosing with improved tolerability
- Open-label Phase 2 IV BCV studies in adult patients to read out throughout 2018

All timelines are estimated

# Brincidofovir: Oral Antiviral With Demonstrated Activity Against Smallpox

- Oral BCV has demonstrated survival benefit in two animal models of fatal orthopoxvirus infections:
  1. Rabbitpox virus model replicates human smallpox pathophysiology: 100% survival demonstrated in animals that received immediate treatment with brincidofovir. Results from this study to be submitted to FDA as “weight of the evidence” with NDA.
  2. Mouse pox / ectromelia replicates the respiratory infection route of human smallpox infection
- European regulators have indicated that data from completed studies are sufficient for MAA submission; preparations are underway
- FDA alignment on rabbit and mice as two animal efficacy models; NDA planned for 2019 after completion of pivotal studies

# Brincidofovir for Smallpox: Completing Studies and Proceeding Toward Filing of Marketing Application



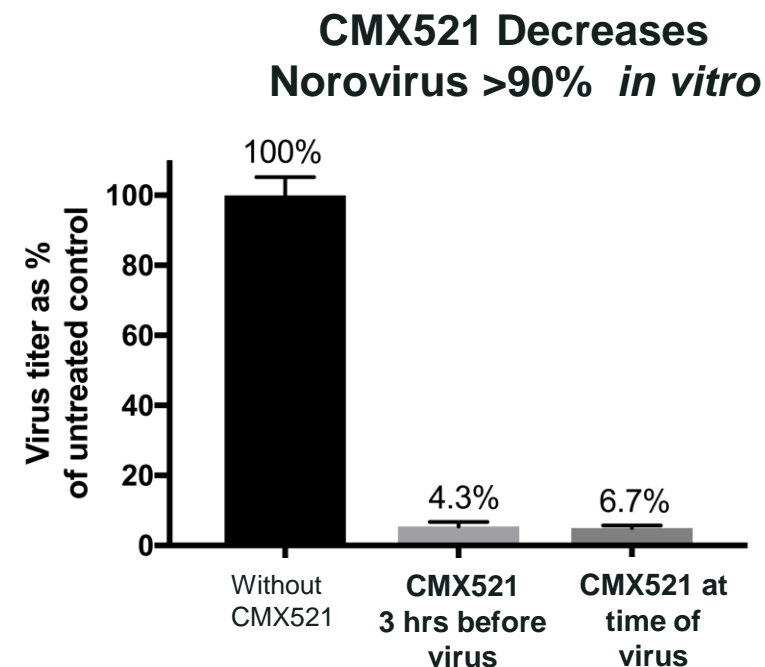
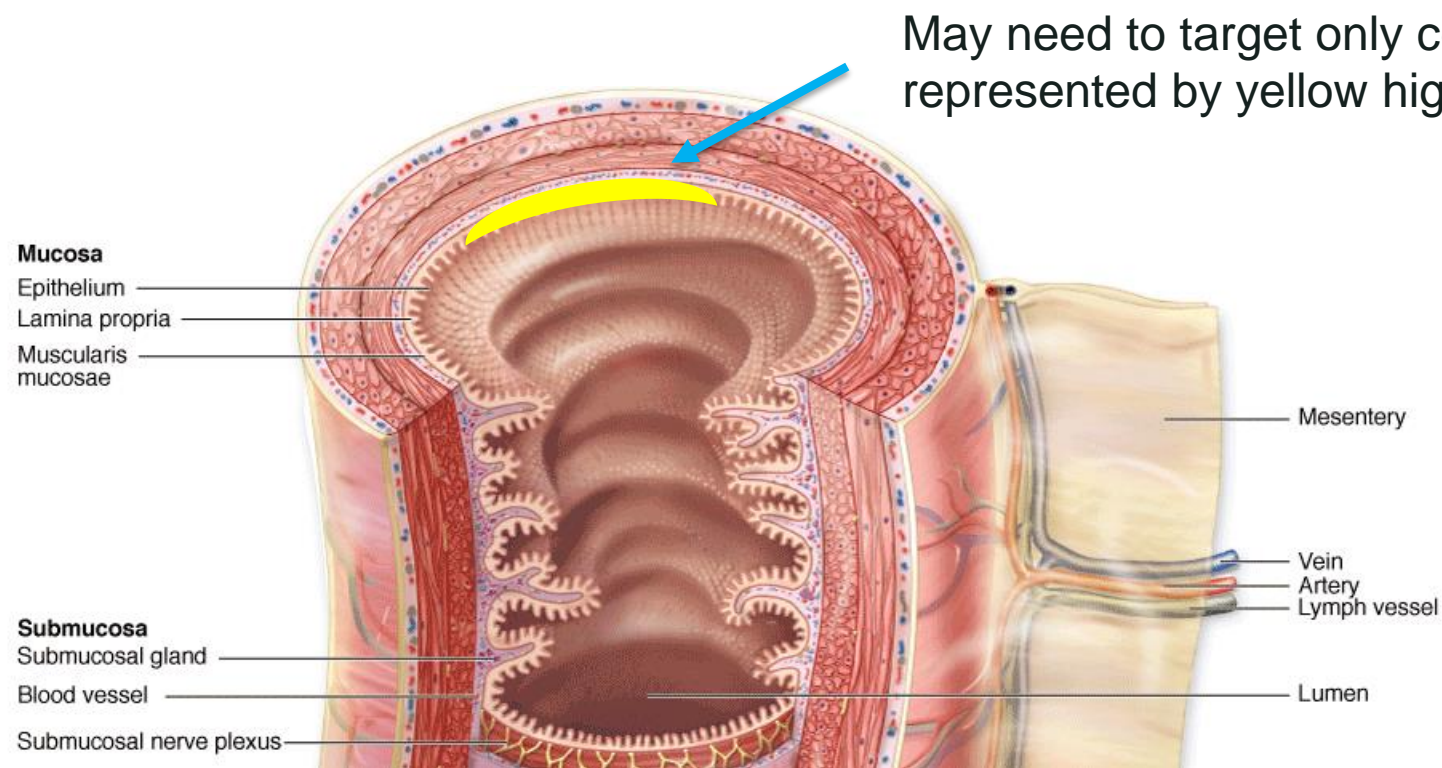
- MAA filing for smallpox is anticipated in 2019 in EU
- Plan to initiate pivotal mouse and rabbit efficacy studies in 2018
- Data from pivotal efficacy studies could support filing for smallpox in 2019 in US

All timelines are estimated

# CMX521: The First Specific Antiviral for Norovirus

- A nucleoside from the Chimerix Chemical Library, CMX521:
  - targets the polymerase, an enzyme essential for viral replication
  - targets a portion of the virus that remains consistent across diverse strains
  - has demonstrated *in vitro* antiviral activity against all norovirus genotypes tested
- First subject was dosed in December 2017, data anticipated in 2018
  - Intestinal biopsies will determine intracellular drug levels for the target cells
  - Drug levels in intestinal cells that achieve effective *in vitro* concentrations could de-risk program
- ~700 million cases of norovirus each year
- Tremendous economic toll: >\$60 billion/yr

# Treatment Target is the Gut Epithelium



## Norovirus replicates in epithelium of the gut

- *In vitro*, efficacious levels of active antiviral reached at 2-4 hours after drug exposure
- Active antiviral half-life is 24 hours: suggests once-daily dosing

# Two Distinct Norovirus Opportunities

## ■ Treatment of Chronic Norovirus





- Increasingly recognized in immunocompromised patients:
  - Stem cell transplant recipients
  - Solid organ transplant recipients
  - Other immunocompromised patients including those on biologics
- Asymptomatic shedders who increase public health risks
  - Food handlers, healthcare workers

## ■ Prevention of Norovirus Outbreaks

- At-risk individuals who have been exposed to a *confirmed* case of norovirus
- Individuals who may be at risk due to a local outbreak without confirmed exposure
- Individuals who elect to or need to be protected from a potential outbreak



# CMRX: Four Active Clinical Programs in 2018

Program	Indication	Pre-clinical	Phase 1	Phase 2	Phase 3	Status	Anticipated Approval
Short-course Oral BCV	AdV Treatment					AdAPT enrolling	2021
	Smallpox					Animal Rule models progressing	2020
IV BCV	Multi-viral Prevention					Ph 2 in patients 2018	2022
CMX521	Norovirus					SAD/MAD in 2018	2023

- Chimerix remains well-capitalized with \$228M at the end of 2017
- Patent protection into 2034 for brincidofovir, and 2036 for CMX521