Maribavir for the Treatment of Post-Transplant Refractory/Resistant Cytomegalovirus (CMV) Infection

October 7, 2021

Takeda

Antimicrobial Drugs Advisory Committee

Introduction

Michael Cronin, PharmD

Director, Global Regulatory Affairs

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Maribavir: Novel Antiviral Representing a Therapeutic Advance Over Current Therapy

Novel and differentiated MoA

Efficacious treatment of refractory with or without resistance (R/R) CMV infection

Favorable safety and tolerability profile

Post-Transplant CMV Infections Are Common and Serious Threat

- ~1/3 of overall transplant recipients will have CMV infections
- If left untreated, may progress to clinically severe, even life-threatening tissue-invasive disease
- Higher risk of complications and poor outcomes, such as graft failure and mortality
  - These complications may occur not only after symptomatic CMV disease but also after asymptomatic viremia

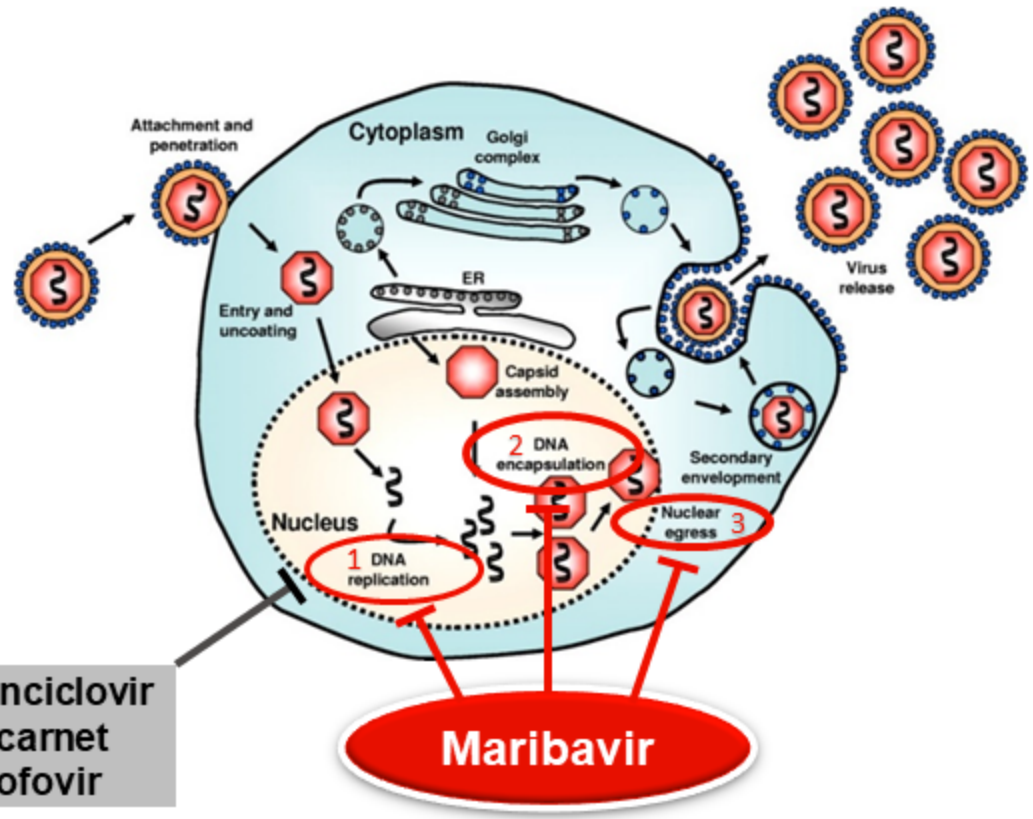
Azevedo, 2015; WHO, 2018; Avery, 2016; Razonable, 2009; Styczynski, 2018; Cho, 2019

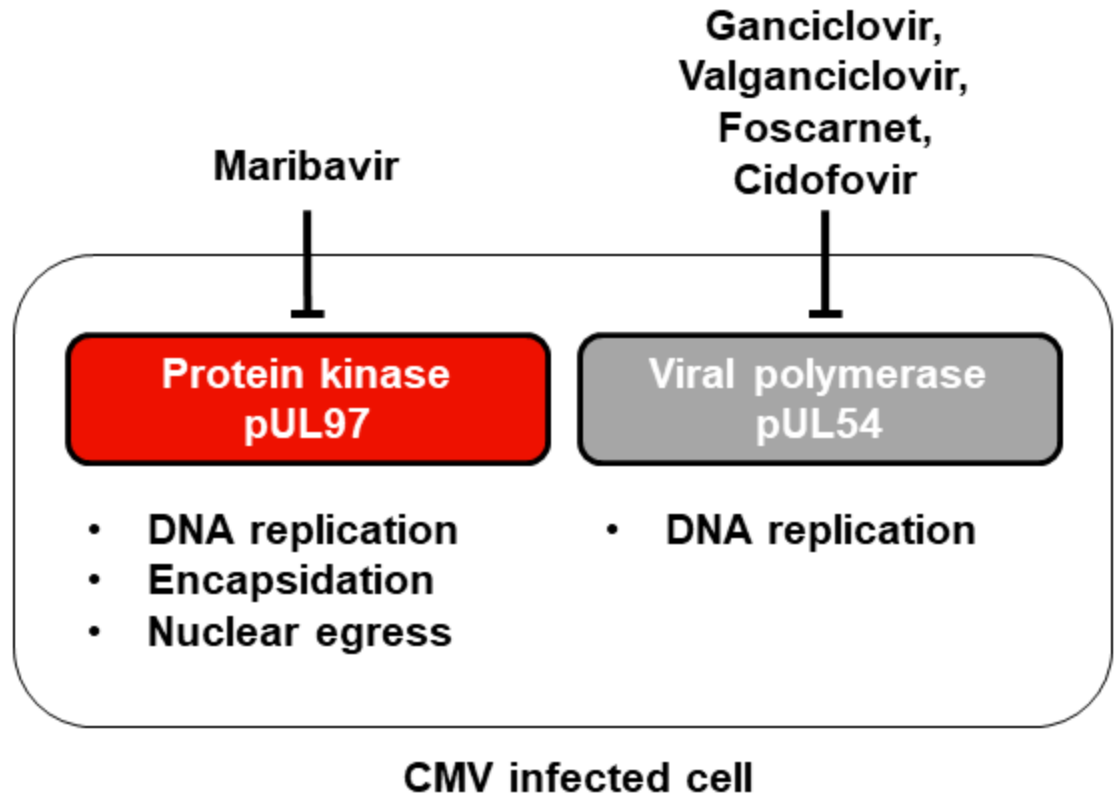
Existing CMV Antivirals Are Unapproved for Post-Transplant CMV Treatment; Limited by Toxicities

- No FDA approved treatments for post-transplant CMV
- Existing CMV antivirals (ganciclovir, valganciclovir, foscarnet, or cidofovir) are used empirically in this condition
  - Each have serious toxicities that potentially lead to failure to control CMV infection
  - Shared MoA makes them susceptible to cross-resistance
  - Ganciclovir, foscarnet, and cidofovir require IV administration
- Urgent need for efficacious and safer therapeutic option with different MoA than existing antivirals

Azevedo, 2015; WHO, 2018; Avery, 2016; Razonable, 2009; Styczynski, 2018; Cho, 2019

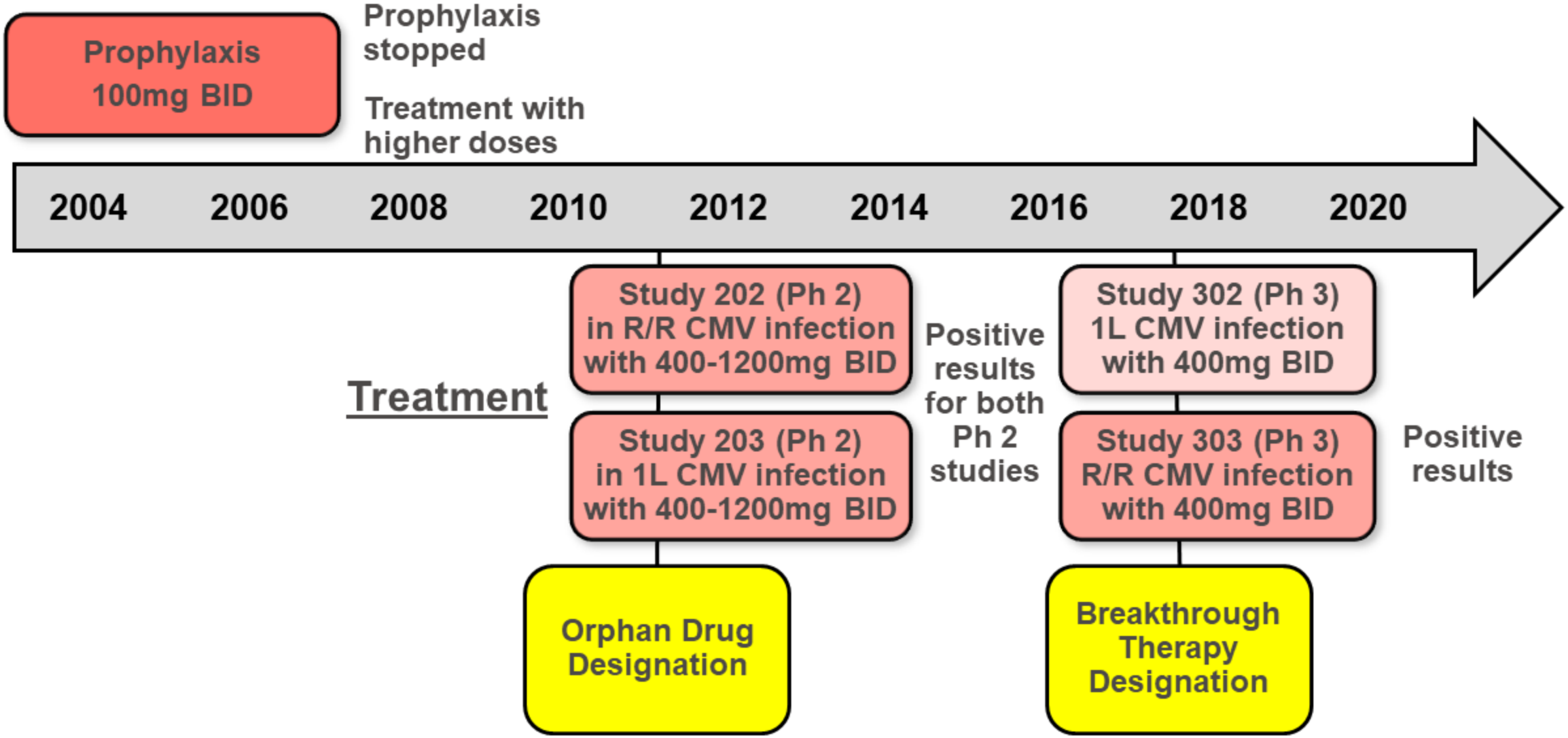
Maribavir MoA Works at 3 Points in Viral Lifecycle Unlike Existing Therapies





Novel MOA enables efficacy against drug resistant CMV

Maribavir Safety and Efficacy are Well-Characterized Across Multiple Studies with > 1,500 Subjects



Maribavir Proposed Indication and Dosing

- Proposed indication for maribavir is for the treatment of adults with post-transplant cytomegalovirus (CMV) infection and disease resistant or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet

- Recommended dosing: 400 mg BID (2 x 200 mg tablets) orally

Agenda

Unmet Need	**Camille Kotton, MD, FIDSA, FAST** Clinical Director of Transplant and Immunocompromised Host Infectious Diseases Massachusetts General Hospital
Study Design and Efficacy Results	**Martha Fournier, MD** Executive Medical Director, Clinical Sciences Takeda
Safety Results	**Adedeji Adefuye, MD, MPH, FRIPH, FRSPH** Vice President, Head of Medical Safety, Rare Diseases Takeda
Clinical Perspective	**Robin Avery, MD, FIDSA, FAST** Professor of Medicine, Division of Infectious Disease Johns Hopkins
Moderator for Q&A	**Obi Umeh, MD, MSc** Vice-President, Global Program Lead for Maribavir Rare Diseases Takeda

Overview of Post-Transplant Refractory/Resistant CMV Infection and Unmet Needs

Camille Nelson Kotton MD, FIDSA, FAST

Clinical Director, Transplant & Immunocompromised Host Infectious Diseases Group, Infectious Diseases Division, Massachusetts General Hospital

Associate Professor, Harvard Medical School

Past Chair, Infectious Disease Community of Practice, American Society of Transplantation

Hematopoietic Stem Cell and Organ Transplants Successful, Life-Saving, and Growing Fields

- 2018 – 4,992 unrelated and 4,275 related allogeneic bone marrow and cord blood transplants performed in U.S.
- 2020 – health care teams across the country performed 39,036 organ transplants from both deceased and living donors

https://unos.org/data/transplant-trends;
https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics;
https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#

Transplant Recipients at High Risk of CMV Infection: Current Management Requires Difficult Trade-Offs

- Most common infection after organ and bone marrow transplant
- More than doubles risk of transplant loss and mortality[1,2,3]

Optimal immunosuppression to manage graft function and prevent rejection

VS

Increased risk of CMV infection and disease

1. Stern, 2014; 2. Jorgenson, 2019; 3. Robin, 2017

CMV Infection Has Broad Spectrum of Disease with Goal to Prevent Progression to Symptomatic Disease

Direct Effects

Asymptomatic Viremia

CMV Viral Syndrome

- Flu-like syndrome: Fever, Malaise, Myalgia
- Leukopenia, Thrombocytopenia

Tissue-Invasive Disease

- GI diseases: Colitis, Hepatitis
- Pneumonitis
- Myocarditis
- Nephritis
- Encephalitis, Retinitis

Torres-Madriz, 2008; Kotton, 2013

Post-Transplant CMV: Initial Treatment and Risk Factors for R/R CMV

Approach to Treatment of Initial Infection

- Oral valganciclovir or IV ganciclovir +/- reduction of immunosuppression
- Goal: Treat until confirmed virologic response

Risk Factors for Developing R/R CMV

- Changing renal function requiring frequent antiviral dose adjustment with risk for suboptimal dose and/or treatment lapses
- Prolonged antiviral drug exposure
- Ongoing active viral replication or high viral loads
- More potent immunosuppressive therapy

Kotton, 2018; Griffiths and Reeves, 2021; Stern, 2014; Jorgenson, 2019; Robin, 2017

Refractory/Resistant CMV

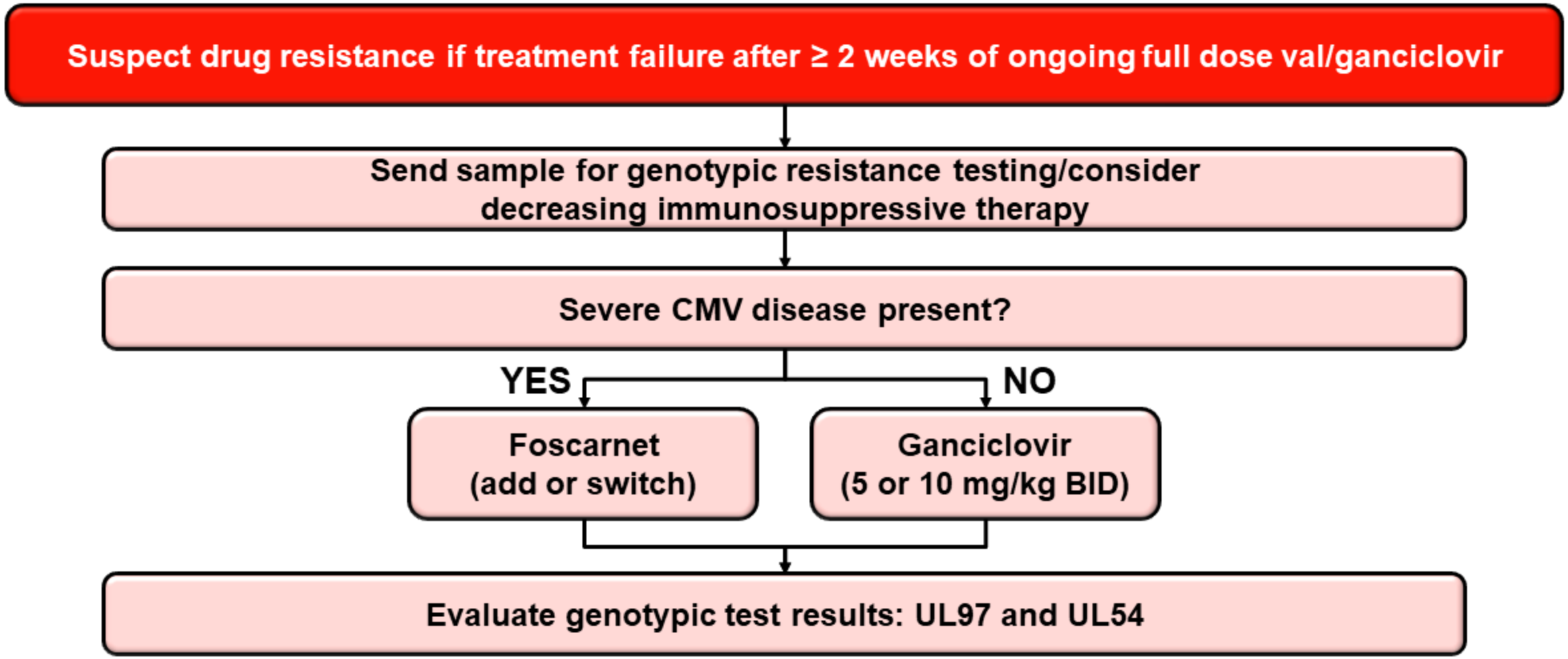
- **Refractory CMV infection**: clinical definition, with signs and symptoms of refractory disease and/or CMV viremia that fails to improve or increases after at least 2 weeks of appropriately dosed antiviral therapy
  - **A subset have defined genotypic resistance**: laboratory definition, defined as a viral genetic alteration that decreases susceptibility to 1 or more antiviral drugs

- Fortunately, person-to-person transmission of resistance has not been reported

- Most vulnerable subset of post-transplant CMV patients at highest risk for complications

Chemaly, 2018; Fisher, 2017

Management of R/R CMV: Guidelines 2018



Subsequent management based on resistance testing results

Kotton, 2018

Challenges with Management of R/R CMV Infection

Ganciclovir IV (high dose)	Foscarnet IV	Cidofovir IV
• Poorly tolerated due to neutropenia/cytopenias • May necessitate use of G-CSF	• Risk for serious renal and electrolyte toxicity • Hospitalization for IV administration	• Risk for serious renal and ocular toxicity • Hospitalization for IV administration

- Toxicities often lead to premature discontinuation, predisposition to resistance development, and subsequent virologic failure
- Decreasing immunosuppression raises risk of rejection/GvHD
- No FDA approved treatments for R/R CMV

Effective Therapies Needed for Post-Transplant Refractory CMV Infection with or without Resistance

- R/R CMV infection is associated with significant morbidity and mortality

- Current treatment options have significant limitations and toxicities

- Urgent need for therapies with better:
  - Efficacy
  - Safety and tolerability
  - Ease of administration

Efficacy

Martha Fournier, MD
Executive Medical Director, Clinical Sciences
Takeda

Efficacy for Maribavir 400 mg BID in R/R CMV from Phase 3 Pivotal Study and Supportive Phase 2 Study

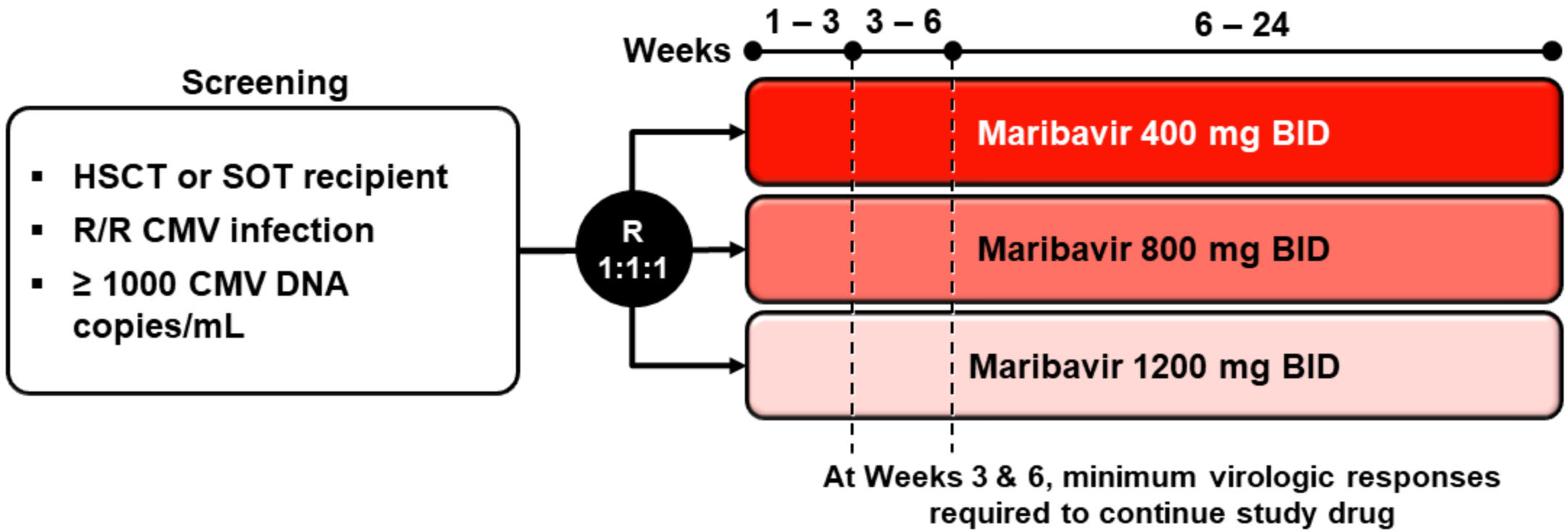
	Pivotal Phase 3 Study 303 (N = 352)	Supportive Phase 2 Study 202 (N = 120)	Phase 2 Study 203 (N = 159)
Post-transplant population	**R/R CMV**	**R/R CMV**	**Treatment naïve CMV**
Maribavir dose	**400 mg BID**	**400 mg BID 800 mg BID 1200 mg BID**	**400 mg BID 800 mg BID 1200 mg BID**
Comparator(s)	**Ganciclovir, valganciclovir, foscarnet, cidofovir**	**None**	**Valganciclovir**
Primary endpoint	**Confirmed CMV viremia clearance at Week 8**	**Confirmed CMV viremia clearance by Week 6**	**Confirmed CMV viremia clearance by Week 6**

CMV Viremia Clearance: Validated Objective Endpoint Endorsed by FDA

- CMV viremia predictive of CMV disease and mortality in transplant recipients
- CMV viremia clearance listed in FDA Guidance as validated surrogate endpoint in this indication
- Sponsor and FDA aligned on endpoints for Phase 3
  - Primary: CMV viremia clearance at a fixed timepoint
  - Key secondary: composite of CMV viremia clearance and symptom control

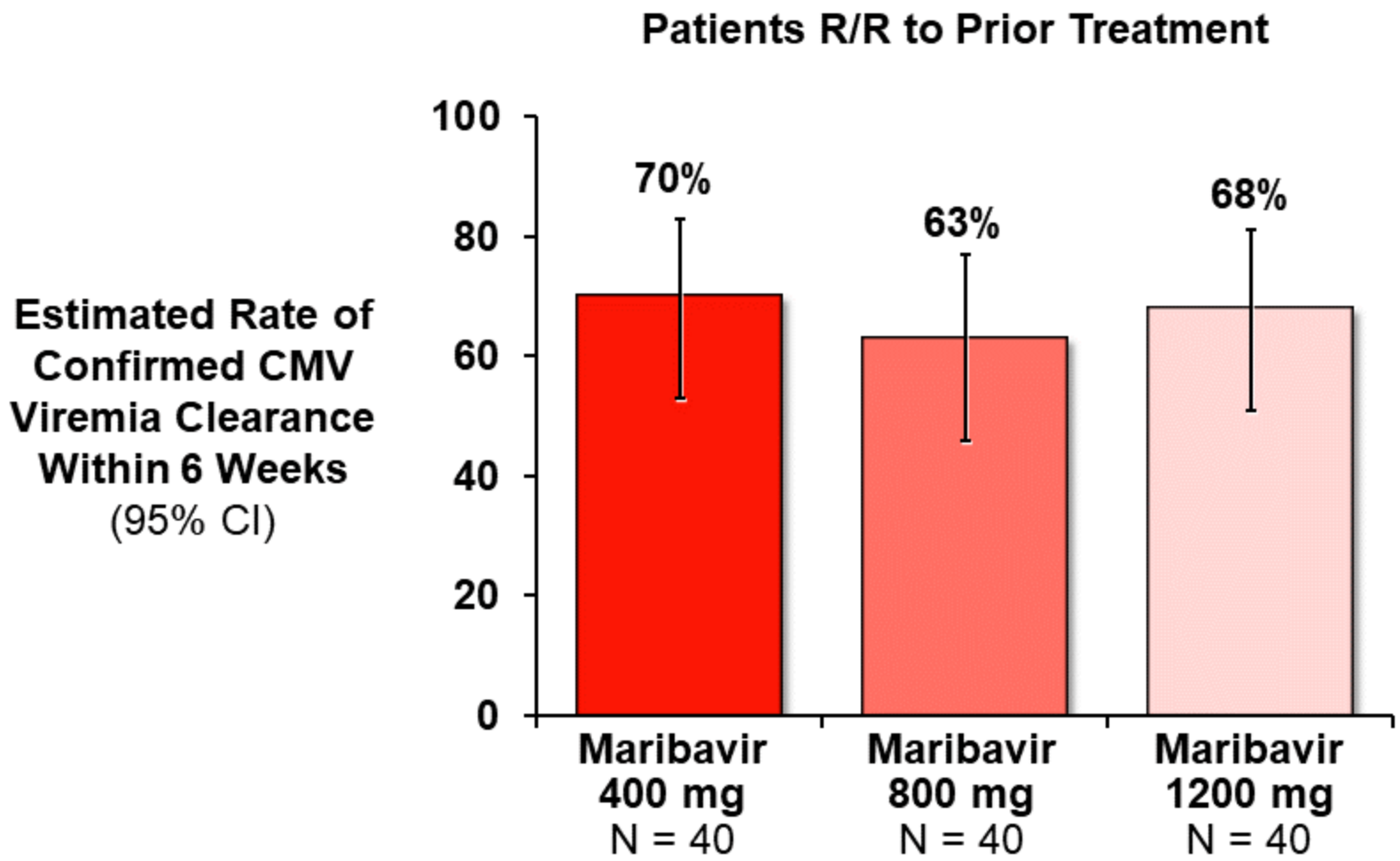
Emery, 1999; Emery, 2000; Gor, 1998; Jang, 2012; Natori, 2018.; Green, 2016; FDA Guidance, 2020

Phase 2 Study Design of Maribavir in Refractory CMV Infections with or without Resistance



- Primary endpoint: proportion of patients with confirmed undetectable plasma CMV DNA (CMV viremia clearance) within 6 weeks of treatment

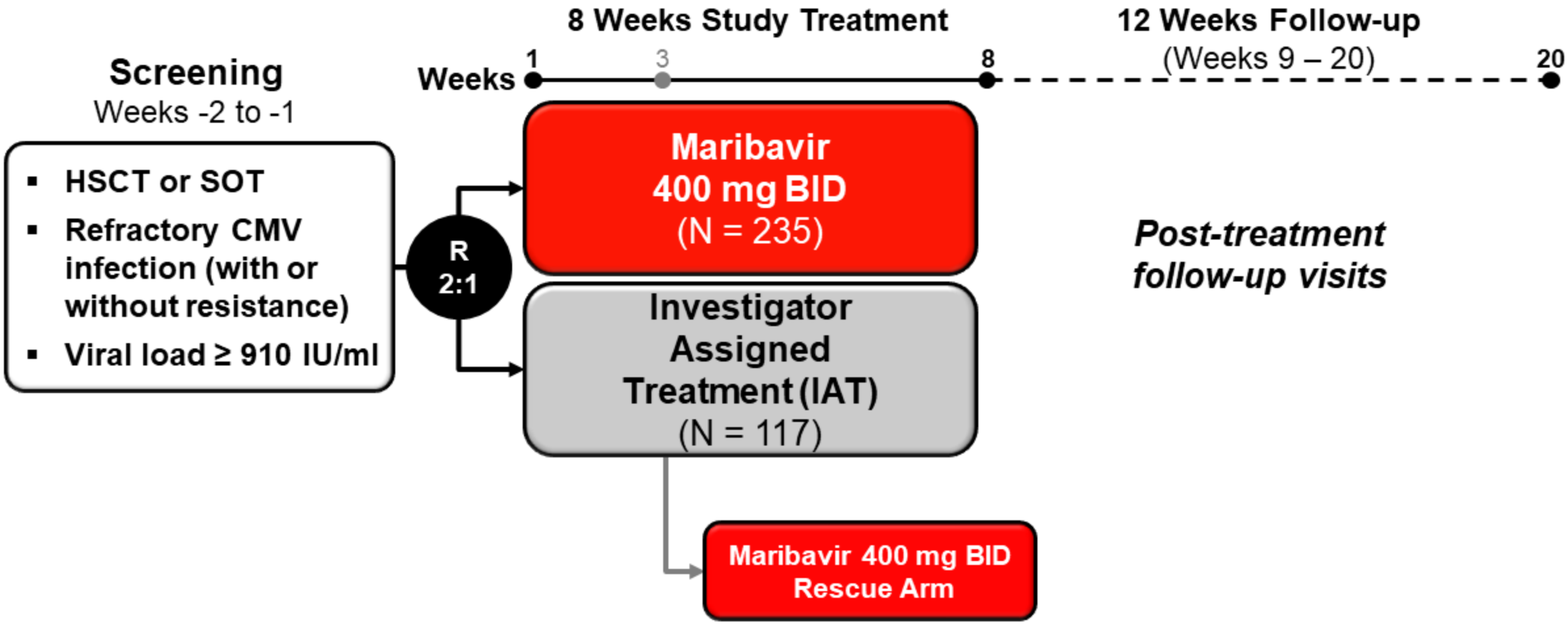
Phase 2 Efficacy Results: > 60% of Patients in All 3 Dose Arms Achieved CMV Viremia Clearance by 6 Weeks



Consistent Results Across Multiple Studies Demonstrated Maribavir 400 mg BID as Optimal Dose

- Two Phase 3 Studies using 100 mg BID for CMV prevention failed to meet primary endpoint
- Two dose-ranging (400 – 1200 mg BID) Phase 2 studies in treatment showed similar efficacy across all doses
- Safety profile of 400 mg BID was most favorable and led to its selection as Phase 3 dose

Study 303: Randomized Controlled Study in Transplant Recipients With R/R CMV



Study 303: Comparator (IAT) Arm Designed to Mimic Current Standard of Care

- Investigators could use 1 or 2 available CMV antivirals
  - Ganciclovir/valganciclovir, foscarnet, cidofovir
    - Combined therapy with cidofovir and foscarnet was prohibited
  - Enabled physicians to use same drugs in study that they would use in real world to treat their patients
- Switching between ganciclovir and valganciclovir was permitted
- Any other switch to non-study CMV antiviral besides that selected at randomization was considered a failure in primary analysis

Study 303: Inclusion / Exclusion Criteria

Key Inclusion Criteria

- ≥ 12 years of age
- Stem cell or solid organ transplant recipients
- R/R CMV infection*
- Viral load
  - ≥ 2730 IU/mL in whole blood or ≥ 910 IU/mL in plasma
- Acceptable key lab parameters:
  - ANC ≥ 1000/mm^3
  - Platelet count ≥ 25,000/mm^3
  - eGFR > 30 mL/min/1.73m^2

Key Exclusion Criteria

- Conditions besides CMV requiring use of IAT or concurrent use of experimental agents with activity against CMV
- CMV TID with CNS involvement or CMV retinitis
- Receiving leflunomide, letermovir, or artesunate
- AST or ALT > 5x ULN or total bilirubin ≥ 3x ULN unless due to CMV hepatitis
- Pregnancy, active malignancy or HIV/AIDS

***Refractory: Documented failure to achieve > 1 log10 decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with ganciclovir/oral valganciclovir, foscarnet, or cidofovir**

***Resistant: Refractory CMV infection AND documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir**

Study 303: Primary and Key Secondary Endpoints

Primary endpoint

- Confirmed clearance of plasma CMV DNA (CMV viremia clearance) at end of Week 8

Key Secondary endpoint

- CMV viremia clearance and symptom control at end of Week 8
  - Plus maintenance of treatment effect for additional 8 weeks beyond the treatment phase
    - Symptom control defined as
      - Resolution or improvement of tissue-invasive CMV disease or CMV syndrome for patients symptomatic at baseline

        OR
      - No new symptoms of tissue-invasive CMV disease or CMV syndrome for patients asymptomatic at baseline
  - Received exclusively study assigned treatment

Study 303: Additional Secondary Endpoints

- Resistance development
- Efficacy of maribavir as rescue therapy

Study 303: Baseline Demographics Similar Between Treatment Arms

	Maribavir (N = 235)	IAT (N = 117)
Age (years), mean	**54**	**52**
Male	**63%**	**56%**
Race		
White	**76%**	**74%**
Black or African American	**12%**	**15%**
Asian	**4%**	**6%**
Regions		
North America	**57%**	**61%**
Europe	**41%**	**33%**
Asia	**2%**	**6%**

Study 303: Transplant Types and Baseline Characteristics

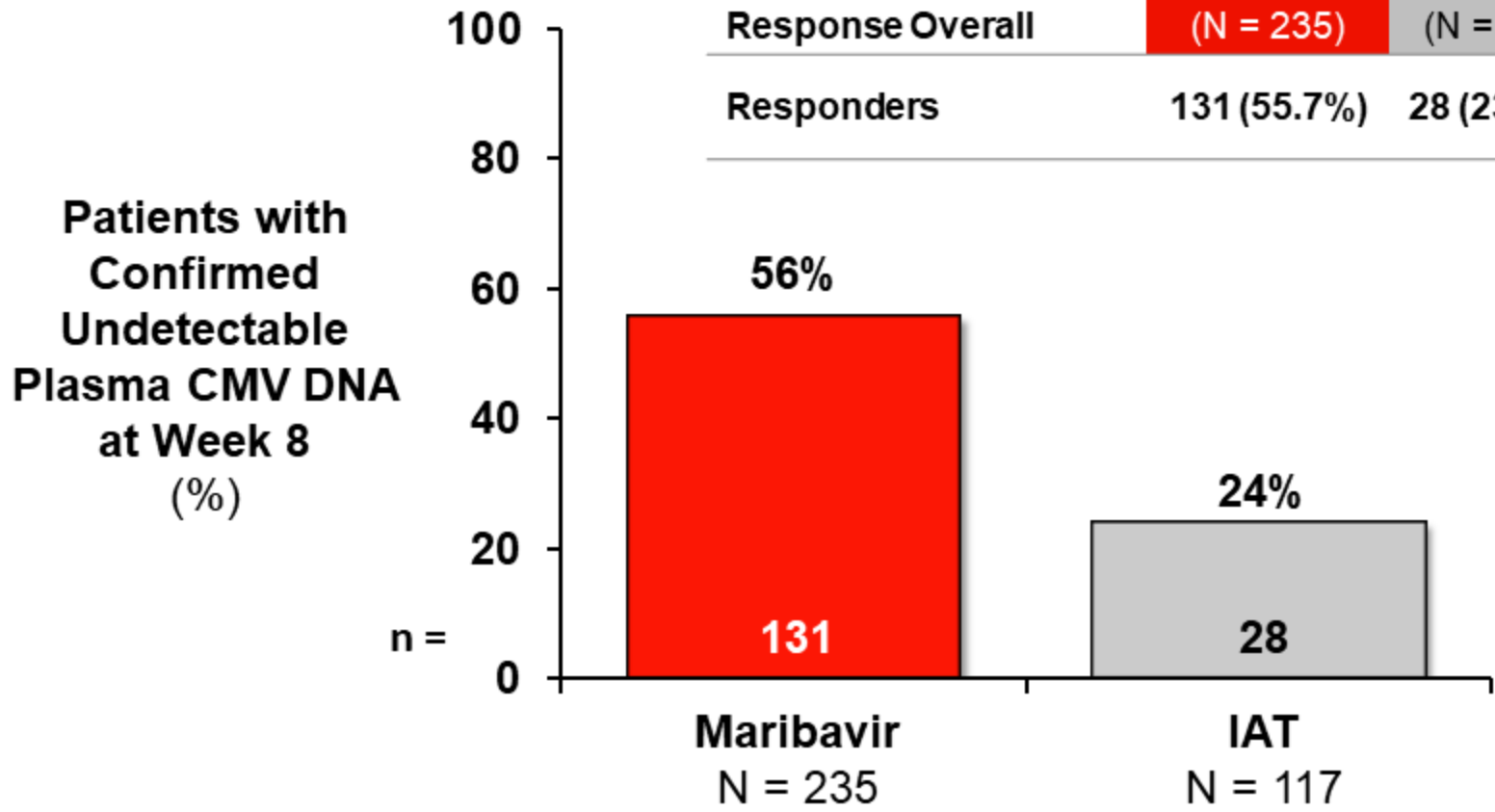
	Maribavir (N = 235)	IAT (N = 117)
Current transplant type		
Solid organ transplant	**60%**	**59%**
Kidney	**52%**	**46%**
Lung	**28%**	**32%**
Heart	**10%**	**13%**
Multiple	**4%**	**7%**
Liver	**4%**	**1%**
Pancreas	**1%**	**0**
Intestine	**< 1%**	**0**
Hematopoietic stem cell transplant	**40%**	**41%**
Baseline symptomatic CMV infection by EAC	**9%**	**7%**
Confirmed Acute GvHD	**10%**	**7%**

Study 303: Baseline Disease Characteristics Similar Between Treatment Arms

	Maribavir (N = 235)	IAT (N = 117)
Presence of CMV mutation resistant to GCV/FOS/CDV per central laboratory		
No	**41%**	**29%**
Yes	**52%**	**59%**
Unable to genotype	**8%**	**12%**
Baseline CMV DNA levels reported by central laboratory		
Low (< 9,100 IU/mL in plasma)	**65%**	**73%**
Intermediate (≥ 9,100 IU/mL and < 91,000 IU/mL in plasma)	**29%**	**21%**
High (≥ 91,000 IU/mL in plasma)	**6%**	**6%**
CMV serostatus for SOT, n (%)		
Donor positive / recipient negative (D+ / R-)	120 **(85%)**	56 **(81%)**
CMV serostatus for HSCT, n (%)		
Donor positive / recipient positive (D+ / R+)	42 **(45%)**	17 **(35%)**
Donor negative / recipient positive (D- / R+)	39 **(42%)**	26 **(54%)**

Study 303: Primary Endpoint – Maribavir Demonstrated Superior CMV Clearance vs IAT

CMV Viremia Clearance Response Overall	Maribavir (N = 235)	IAT (N = 117)	Adjusted Difference % (95% CI)	p-value
Responders	131 (55.7%)	28 (23.9%)	32.8 (22.8, 42.7)	< 0.001

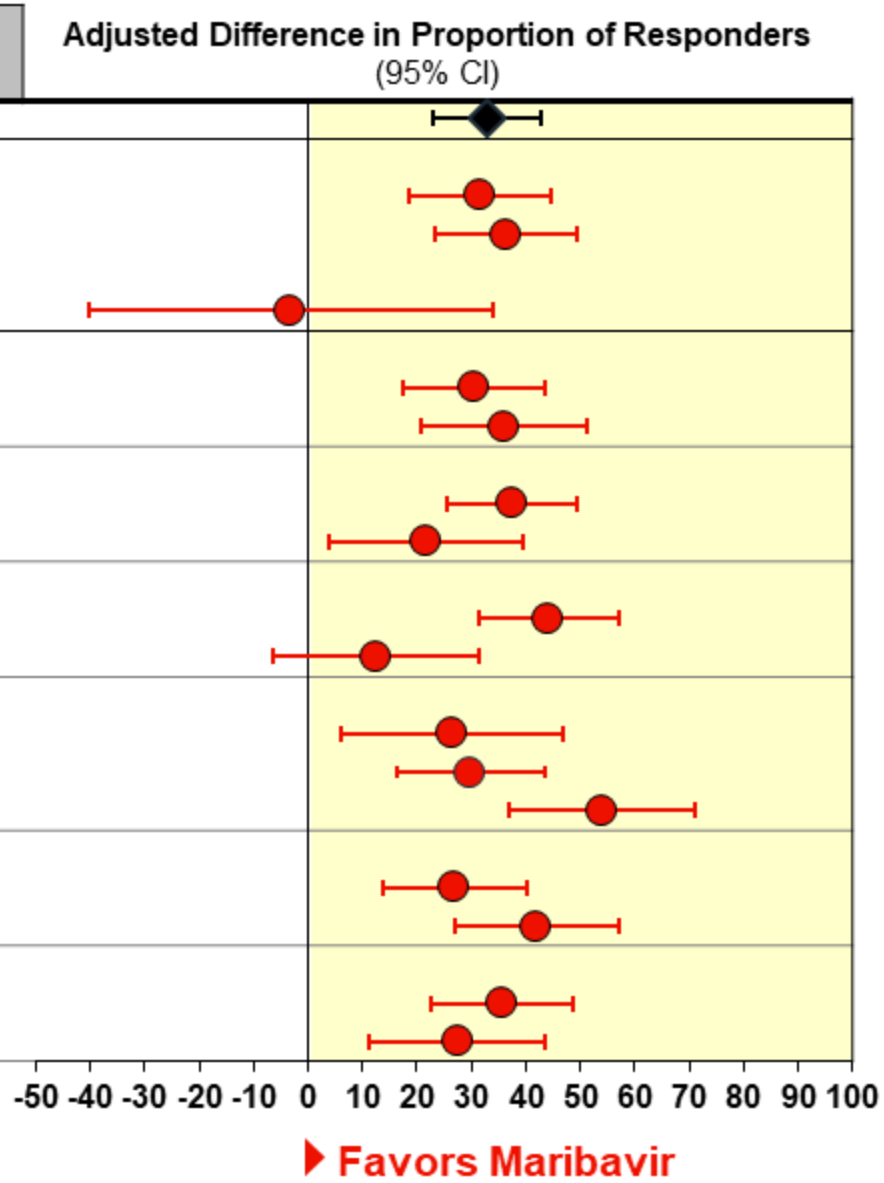


Study 303: Sensitivity Analyses Support Robustness of Primary Endpoint

Analysis	Rationale	Maribavir (N = 235)	IAT (N = 117)	p-value
CMV viremia clearance at Week 8 or at time of study discontinuation or treatment switch	Minimizes effect of either study discontinuation or treatment switch being handled as a non-response	60.0%	43.6%	0.001
CMV viremia clearance at any time during treatment phase	Measures treatment effect based on ability to achieve clearance during treatment phase; clearance in absence of other factors (i.e., tolerability)	74.0%	52.1%	< 0.001
CMV viremia clearance at Week 8 regardless of alternative CMV antiviral	Response at Week 8 regardless of use of alternative CMV antivirals for either treatment group (including rescue treatment for IAT)	59.1%	42.7%	0.002

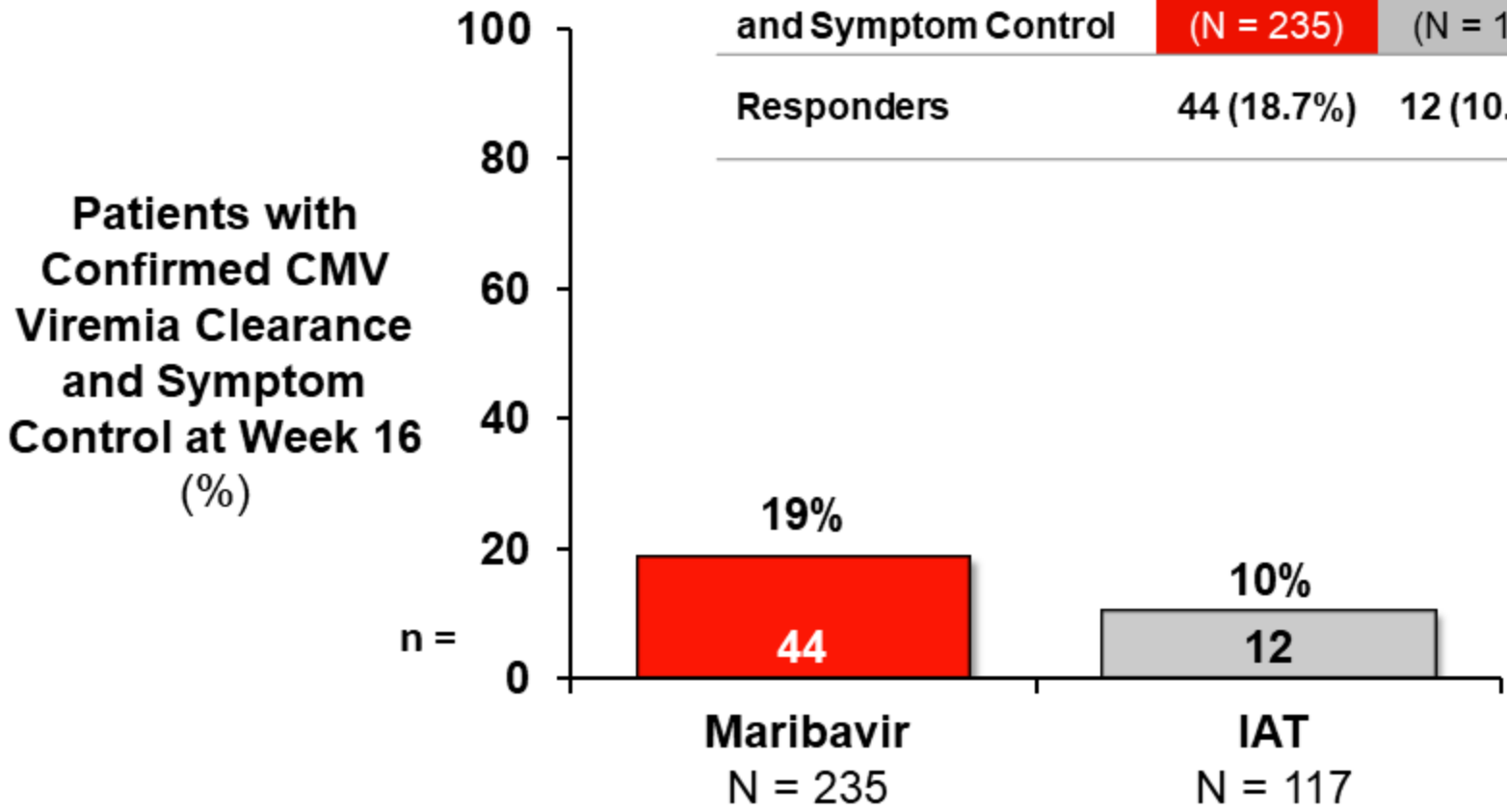
Study 303: Results Consistent Across Subgroups

	Maribavir 400 mg n/N	IAT n/N
Overall	131/235	28/117
IAT		
Ganciclovir/Valganciclovir	131/235	15/56
Foscarnet	131/235	9/47
Cidofovir	131/235	0/6
> 1 IAT	131/235	4/7
Transplant Type		
SOT	79/142	18/69
HSCT	52/93	10/48
CMV DNA Viral Load		
Low	95/153	21/85
Intermediate/High	36/82	7/32
Resistance Status		
Yes (refractory with resistance)	76/121	14/69
No (refractory without resistance)	42/96	11/34
Age Group		
18 – 44 Years	28/55	8/32
45 – 64 Years	71/126	19/69
≥ 65 Years	32/54	1/16
Enrolling Region		
North America	72/134	19/71
Europe	56/97	8/39
Sex		
Male	87/148	15/65
Female	44/87	13/52



Study 303: Key Secondary Endpoint – Superior Maintenance of CMV Viremia Clearance and Symptom Control with Maribavir at Week 16

CMV Viremia Clearance and Symptom Control	Maribavir (N = 235)	IAT (N = 117)	Adjusted Difference % (95% CI)	p-value
Responders	44 (18.7%)	12 (10.3%)	9.5 (2.0, 16.9)	0.013



Results from Other Secondary Endpoints

- Resistance development
- Efficacy of maribavir as rescue therapy

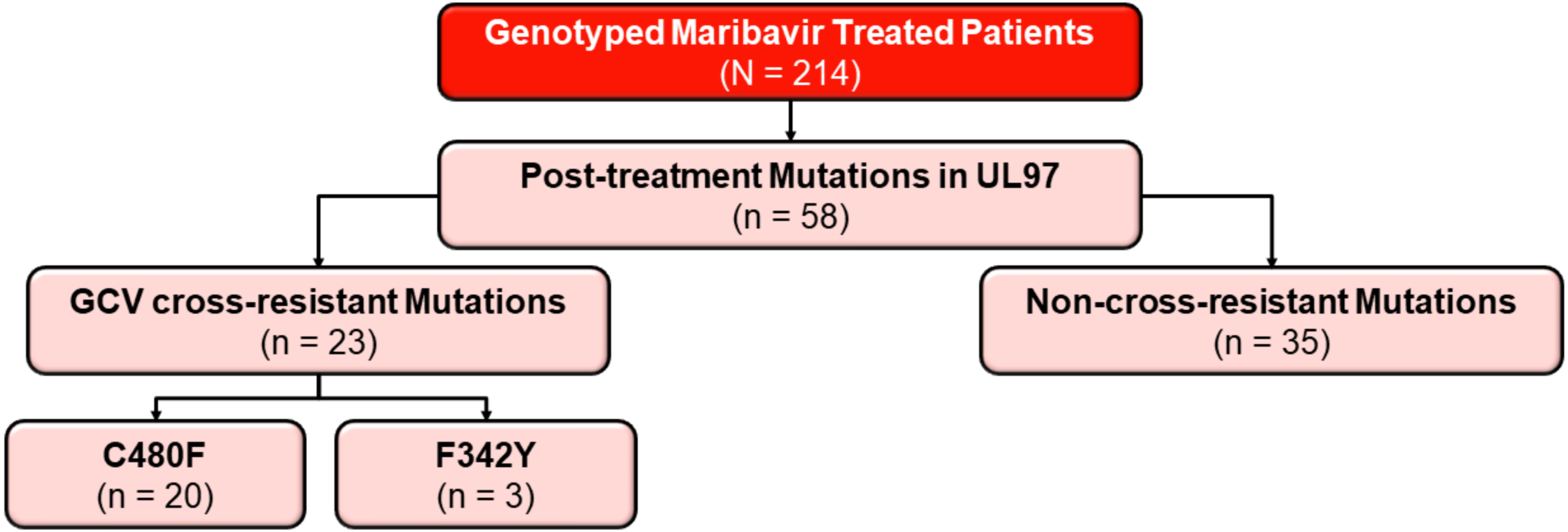
Study 303: Resistance Development

- Extensive sampling for viral resistance
  - More comprehensive and frequent compared to clinical practice
  - Samples genotyped every 4 weeks on study as well as for CMV recurrence or rebound
- Entire genes sequenced at a central specialty lab
  - UL54
  - UL97
  - UL27
- In current clinical practice, treatment is empiric and testing for resistance typically performed for increasing viral load or deterioration in clinical condition

Study 303: Baseline Resistance to Maribavir Rare

- 320/352 patients had evaluable genotype at baseline
  - ~60% had either a UL97 or UL54 mutation conferring resistance to IAT
  - Only 1% had a mutation at UL97 conferring resistance to maribavir

Study 303: Overview of Post-Baseline Resistance Development to Maribavir

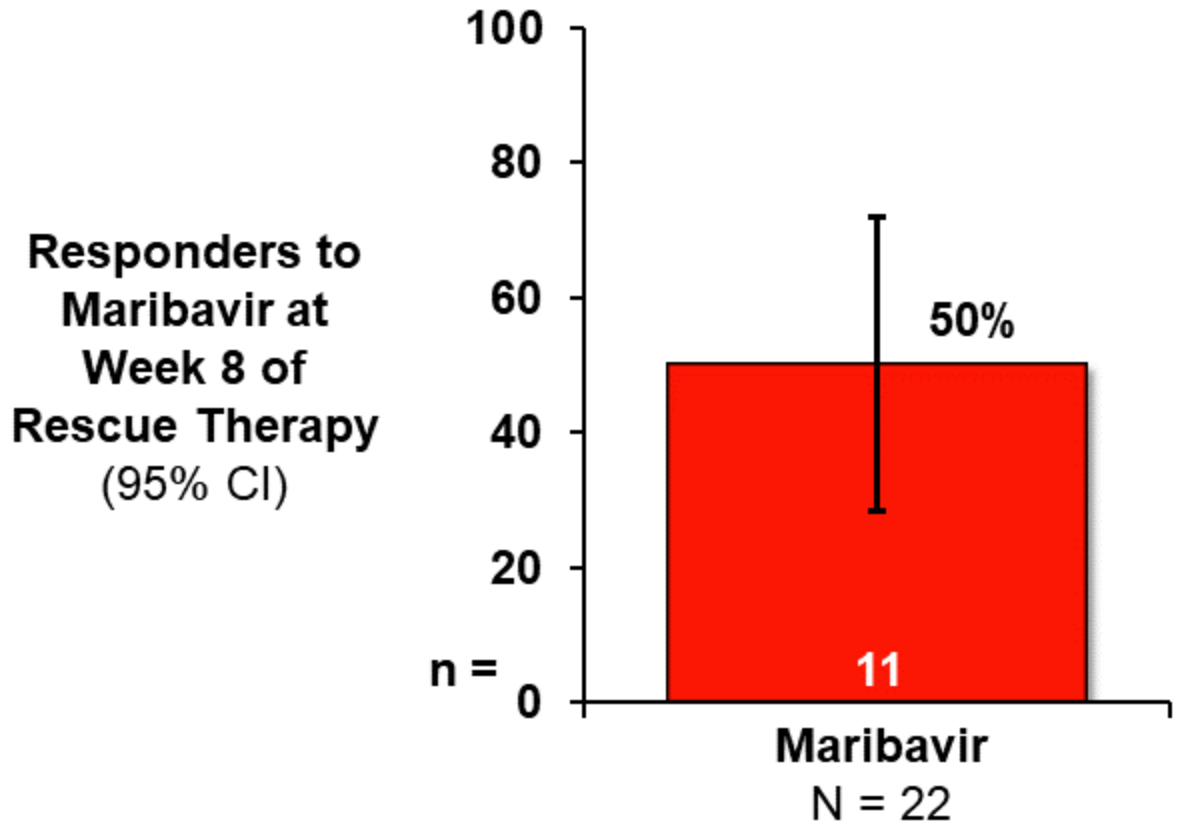


- F342Y has 4.5- and 6.0-fold increase in EC_{50} to maribavir and ganciclovir, respectively
- C480F has 224-fold and 2.3-fold increase in EC_{50} to maribavir and ganciclovir, respectively
  - Ganciclovir is a treatment option for patients who develop resistant mutation at C480F after maribavir

Maribavir Mutants Can Be Effectively Treated with Alternative CMV Antivirals

- Of 48 patients randomized to maribavir that developed maribavir mutation and subsequently treated with alternative CMV antivirals
  - 63% went on to clear viremia following treatment with alternative CMV antivirals
- Treatment options utilized on Study 303
  - Foscarnet (n = 9)
  - Letermovir (n = 2)
  - Ganciclovir/valganciclovir (n = 19)
  - > 1 agent (serial)

Study 303: Maribavir Effective in Clearing CMV Viremia at Week 8 of Rescue Therapy



Maribavir Cleared R/R CMV Infection in Transplant Recipients

- Efficacy demonstrated by pivotal Study 303
  - Study 202 supports treatment with 400 mg BID
- In pivotal Phase 3 study
  - Maribavir met primary endpoint
    - Statistical superiority over IAT in clearance of CMV viremia at Week 8
  - Maribavir met key secondary endpoint
    - Statistically significant benefit over IAT in clearance of CMV viremia and symptom control through Week 16

Clinical Safety

Adedeji Adefuye, MD, MPH, FRIPH, FRSPH

Vice President, Head of Medical Safety for Rare Diseases

Takeda

Maribavir Has a Favorable Safety Profile Compared to Currently Available CMV Antivirals

- Transplant recipients are seriously ill patients often with multiple comorbidities and receiving multiple concomitant medications
- Maribavir had a lower incidence of treatment limiting neutropenia and acute kidney injury than seen with IAT
- Rates of treatment discontinuations due to AEs were substantially lower in the maribavir arm vs IAT
- Dysgeusia in maribavir arm drove the higher overall AE rate

Maribavir's Safety Profile Well-Characterized Over Clinical Development Program

- 1,555 patients exposed to maribavir across several doses and durations, ranging from
  - 50 to 2400 mg
  - 8 to 24 weeks
- ~1/3 of patients dosed with 400 mg BID or higher
- AE rates reflect AEs, including lab abnormalities, collected at point-of-care
  - Per protocol safety labs collected every two weeks

Maribavir Well-Tolerated Allowing Longer Exposure

- Patients remained on maribavir ~50% longer

	Study 303	
Exposure to Study Drug (Days)	**Maribavir 400 mg BID** (N = 234)	**IAT*** (N = 116)
Mean	**52.5**	**36.0**
(SD)	(11.8)	(18.1)

* Ganciclovir, valganciclovir, foscarnet, cidofovir

Study 303: Maribavir Safety Profile Allows Patients to Stay Longer on Treatment

Category	Maribavir (N = 234)	IAT (N = 116)	IAT Type		
			Ganciclovir/ Valganciclovir (N = 56)	Foscarnet (N = 47)	Cidofovir (N = 6)
Any TEAE	97%	91%	91%	92%	83%
Any related TEAE	60%	49%	41%	62%	33%
Serious AE	38%	37%	38%	43%	33%
Any related serious AE	5%	14%	13%	19%	17%
Severe TEAE	32%	38%	39%	40%	33%
Any related severe TEAE	4%	21%	27%	17%	17%
TEAE leading to treatment discontinuation	13%	32%	11%	21%	17%
Any related TEAE leading to treatment discontinuation	5%	23%	5%	13%	0

AE incidence rates are unadjusted for length of exposure

Study 303: AE Overview

Preferred Term (≥ 10%)	Maribavir (N = 234)	IAT (N = 116)
AEs	97%	91%
Dysgeusia	37%	3%
Nausea	21%	22%
Diarrhea	19%	21%
Vomiting	14%	16%
Anemia	12%	12%
Fatigue	12%	9%
Pyrexia	10%	15%
CMV viremia	10%	5%
Neutropenia	9%	22%
Headache	8%	13%

AE incidence rates are unadjusted for length of exposure

Study 303: Neutropenia and Renal AEs Leading to Discontinuation Lower with Maribavir

Preferred Term	Maribavir (N = 234)	IAT Type	
		Ganciclovir/ Valganciclovir (N = 56)	Foscarnet (N = 47)
Any AE leading to discontinuation of treatment	13%	32%	36%
CMV infection	3%	0	17%
CMV viremia	2%	4%	0
Neutropenia	0	20%	0
Acute kidney injury	0	0	13%
Leukopenia	0	5%	0
Thrombocytopenia	0	7%	0
Anemia	0	4%	0
Renal failure	0	0	2%
Renal impairment	0	0	4%

AE incidence rates are unadjusted for length of exposure

Study 303: SAEs Comparable Between Groups

Preferred Term (≥ 2%)	Maribavir (N = 234)	IAT (N = 116)
Any SAE	39%	37%
CMV infection	3%	3%
Acute kidney injury	3%	3%
CMV viremia	3%	3%
Febrile neutropenia	< 1%	3%
Neutropenia	0	3%

AE incidence rates are unadjusted for length of exposure

Study 303: All-Cause Mortality

	Maribavir (N = 234)	IAT (N = 116)
Total deaths	**27 (11.5%)**	**13 (11.2%)**
Related deaths	**1 (0.4%)**	**1 (0.9%)**

Deaths are unadjusted for length of exposure

Adverse Events of Special Interest (AESIs)

- Taste Disturbances
- Immunosuppressant Drug Level Increased
- Neutropenia
- Renal Adverse Events

Taste Disturbances Well-Documented AEs of Maribavir

- Dysgeusia occurred in 46% of patients in Study 303
- Occurred early upon initiation of treatment
- Mild to moderate in severity
- Transient and mostly did not lead to premature discontinuation of treatment
  - 2 of 234 patients (< 1%) discontinued maribavir because of dysgeusia
- Did not lead to weight loss

Coadministration with Maribavir May Increase Concentration of Some Immunosuppressants

- 8% higher occurrence in maribavir group consistent with known drug-drug interaction
- Increased drug level of immunosuppressant reported as treatment-emergent SAE in 1 maribavir patient
- Proposed label will recommend therapeutic drug monitoring when maribavir is co-administered with tacrolimus, cyclosporine, everolimus, and sirolimus

Study 303: Maribavir Does Not Have the Treatment Limiting Toxicity of Neutropenia Seen with Ganciclovir/Valganciclovir

	Maribavir (N = 234)	IAT (N = 116)	IAT Type	
			Ganciclovir/ Valganciclovir (N = 56)	Foscarnet (N = 47)
Any neutropenia AE	9%	22%	34%	15%
Any febrile neutropenia AE	< 1%	4%	7%	2%
Any severe neutropenia AE	2%	10%	20%	2%
Any severe febrile neutropenia AE	< 1%	3%	5%	2%
Any neutropenia SAE**	< 1%	6%	13%	0
Neutropenia AE leading to discontinuation	0	10%	20%	0

AE incidence rates are unadjusted for length of exposure

** Includes febrile neutropenia

Study 303: Maribavir Does Not Have the Renal Treatment Limiting Toxicities Seen with Foscarnet

	Maribavir (N = 234)	IAT (N = 116)	IAT Type	
			Ganciclovir/ Valganciclovir (N = 56)	Foscarnet (N = 47)
Any renal AE	**25%**	**32%**	**18%**	**49%**
Any severe renal AE	**< 1%**	**4%**	**0**	**9%**
Any renal SAE	**7%**	**9%**	**4%**	**17%**
Renal AE leading to discontinuation	**0**	**10%**	**0**	**21%**

AE incidence rates are unadjusted for length of exposure

Maribavir Provides Safety Advantage Over Currently Used CMV Antivirals

- Avoids treatment-limiting AEs of available treatments
  - Neutropenia
  - Renal AEs
- Most common AE was taste disturbance
  - Grade 1 or 2, nonserious, rarely led to discontinuation
- Tolerable at doses up to 1200 mg BID for durations up to 24 weeks
- Tolerability allows patient to be on maribavir longer and continue to get treatment benefit

Clinical Perspective

Robin Avery, MD, FIDSA, FAST

Professor of Medicine, Division of Infectious Disease

Johns Hopkins

Post-Transplant CMV Infection and Disease Challenging for Patients and Clinicians

- Complex despite advances in prevention
  - Episode that does not resolve in 3 months
  - 2 or more recurrences
  - Tissue-invasive disease with complications
  - High viral load with multiorgan dysfunction
  - Severe intolerance to standard drugs
- Treatment decisions made before resistance testing completed
  - Testing highly specialized and results take long time
- Existing CMV antivirals problematic in terms of efficacy, toxicities, and delivery
- Major unmet need for an effective and less toxic treatment for CMV

Patient #1: Challenges with Existing Therapies for Refractory CMV

Patient	• 20-year-old female with AML • s/p HSCT (CMV D-/R+) • Admitted 5 weeks post-transplant with fever, nausea, vomiting, hypotension, tachycardia • Cultures negative except for positive CMV PCR (low viral load)

CMV Antiviral Treatment	• CMV viral load rose on ganciclovir
	  ○ Genotype negative for resistance mutations; neutropenia worsened
	• Ganciclovir changed to foscarnet with improvement in CMV viral load
	  ○ Developed acute kidney injury requiring renal replacement therapy
	• Progressed to profound neutropenia; graft loss

Outcome	• Died of multiorgan/respiratory failure and sepsis, although CMV viremia ultimately cleared

Personal Clinical Experience Aligns with Maribavir Benefits for Treatment of Post-Transplant R/R CMV

	Patient #2	Patient #3
Patient	• Lung transplant recipient • CMV pneumonitis	• Lung transplant recipient • Symptomatic CMV with high viral load
CMV Antiviral Treatment	• Resistant and refractory to ValGCV, GCV, FOS, leflunomide, CMVIg • Renal dysfunction from foscarnet • Poor performance status	• L595S GCV-R mutation • Poor tolerance of foscarnet (acute kidney injury, severe nausea, weight loss, malnutrition)
Maribavir Treatment	• Cleared CMV • Marked clinical improvement • Alive and CMV-free 5 years later	• Cleared CMV • Marked clinical improvement • Nausea resolved, gained weight • Alive and CMV suppressed for months

Avery, 2010; Papanicolaou, 2019

Conclusions: Why We Need Maribavir

- Far too many patients with R/R CMV infection have inadequate responses or harmful toxicities on currently available therapies
- Even if CMV clears, therapies may cause long-term morbidity that impairs allograft lifespan and transplant recipient QoL
- No other drug for CMV treatment combines efficacy with lack of hematologic and renal toxicity, and available orally
  - Benefit for refractory and resistant CMV using same decision process
  - Patients with CMV often express desire for drug like maribavir and frustration with side effects of available therapies
- Maribavir will be valuable addition to antiviral armamentarium and will transform landscape of CMV treatment

Moderator for Q&A

Obi Umeh, MD, MSc

Vice-President, Global Program Lead for Maribavir

Rare Diseases

Takeda

Maribavir for the Treatment of Post-Transplant Refractory/Resistant Cytomegalovirus (CMV) Infection

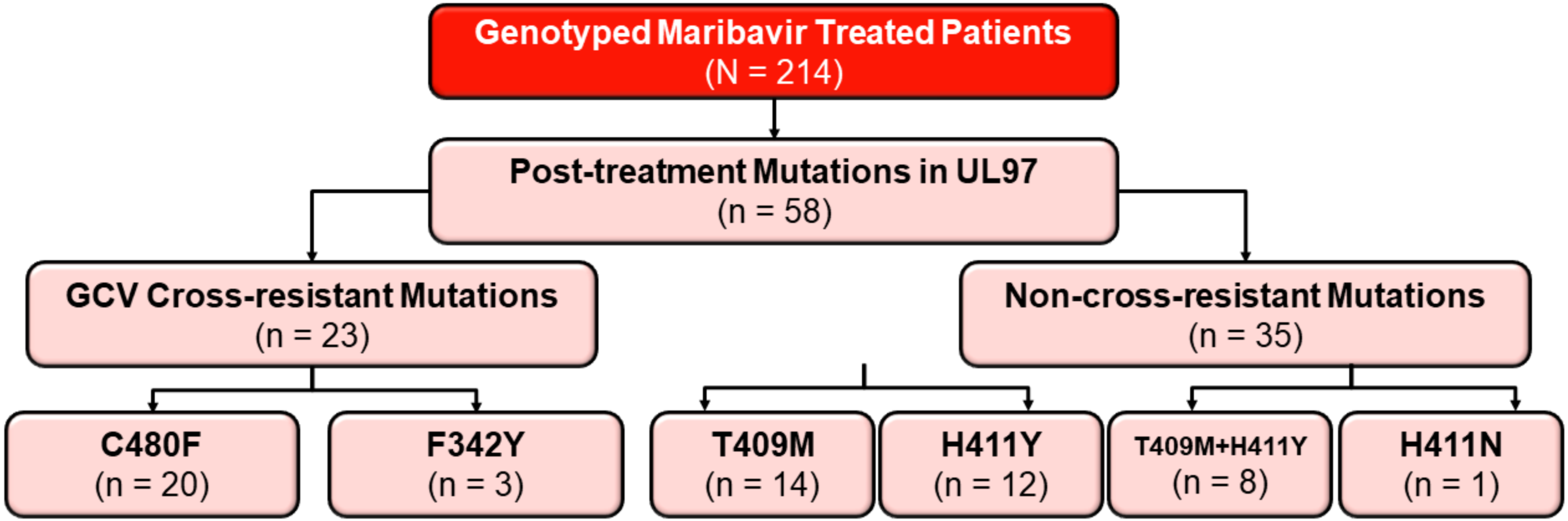
October 7, 2021

Takeda

Antimicrobial Drugs Advisory Committee

Q&A Slides Shown

Study 303: Overview of Post-Baseline Resistance Development to Maribavir



- F342Y has 4.5-fold resistance to maribavir and 6-fold resistance to ganciclovir
- C480F has 224-fold resistance to maribavir and 2.3-fold resistance to ganciclovir
  - Ganciclovir is still a treatment option for patients who develop resistant mutation at C480F after maribavir

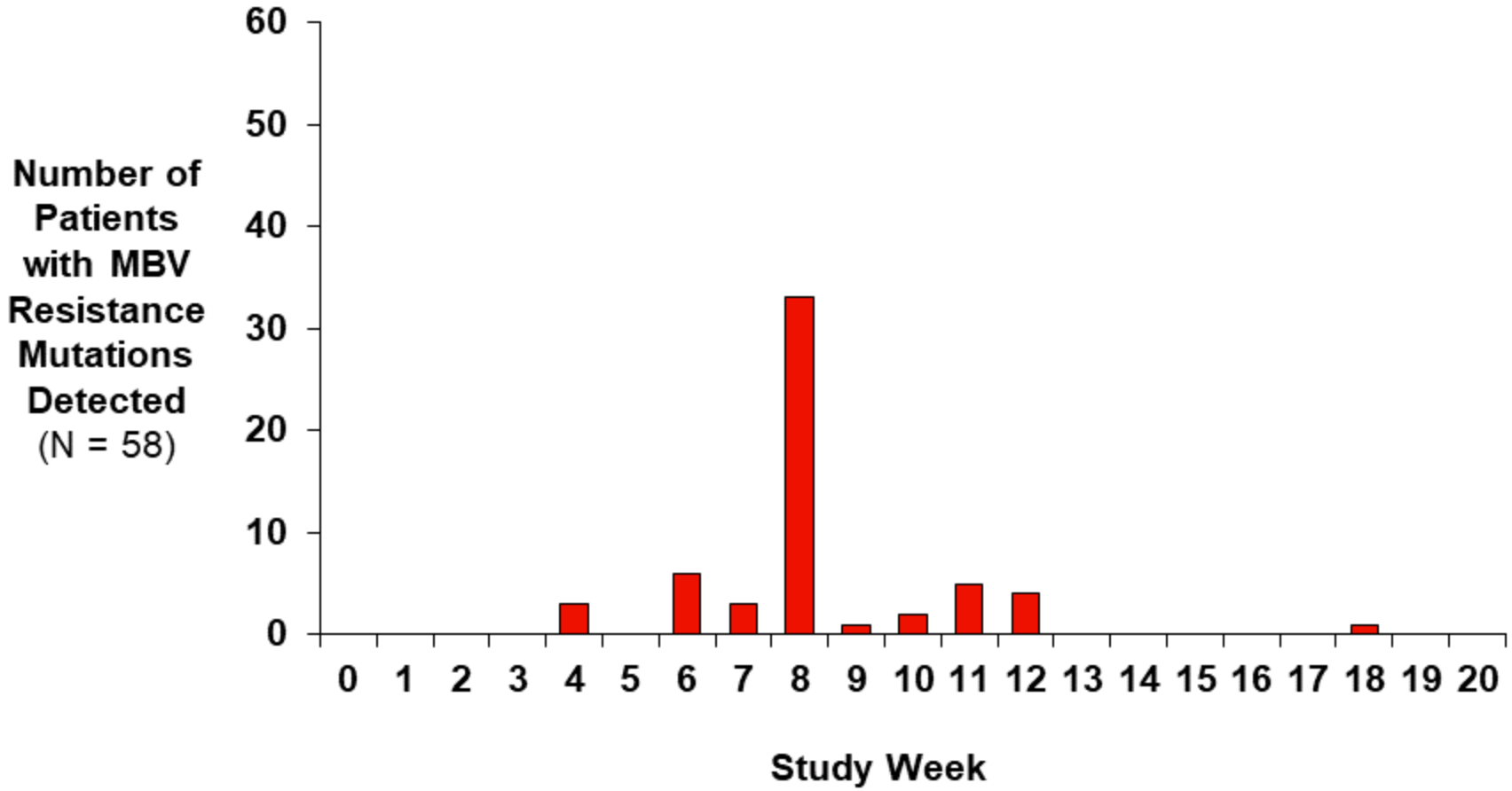
Resistance to Maribavir in Study 303

Mutation	Mutant EC_{50}/WT EC_{50}	N
C480F*	224	11
T409M	78	14
F342Y*+H411Y	56	1
H411Y	15	12
F342Y*	4.5	1
T409M+H411Y	-	8
T409M+C480F*	-	6
H411Y+C480F*	-	2
H411N	-	1
F342Y*+T409M+H411N	-	1
H411L+H411Y+C480F*	-	1

* Cross-resistant to MBV and VGCV/GCV

Timing of Maribavir Resistance Detection

- Testing done at W4, 8, 16 and 20
- Testing also done in the event of recurrence/rebound



Study 303: Sensitivity Analysis of CMV Clearance at Any Time During Treatment Phase Supports Primary Endpoint Result

	Maribavir (N = 235)	IAT (N = 117)	p-value
CMV viremia clearance at any time during treatment phase	**74.0%**	**52.1%**	**< 0.001**

- Measures treatment effect based on ability to achieve clearance during treatment phase; clearance in absence of other factors (i.e., tolerability)

Duration of IAT Aligns with Treatment Standards

- Maribavir well-tolerated allowing longer exposure

	Study 303	
Exposure to Study Drug (Days)	**Maribavir 400 mg BID** (N = 234)	**IAT*** (N = 116)
Mean	**52.5**	**36.0**
(SD)	(11.8)	(18.1)

Study 303: Sensitivity Analysis of CMV Clearance Treatment Phase Supports Primary Endpoint Result

	Maribavir (N = 235)	IAT (N = 117)	p-value
CMV viremia clearance at any time during treatment phase	**74.0%**	**52.1%**	**< 0.001**
CMV viremia clearance at Week 4 during treatment phase	**66.4%**	**48.7%**	**0.001**

Study 303: Outcomes in IAT Patients who Continued Same Agent or Switched at Randomization

- About half IAT subjects continued same anti-CMV agent as used immediately prior to randomization (50/57 val/ganciclovir)
- Primary endpoint response lower in subjects who switched to a different agent

Prior anti-CMV agent	Continued Same Agent Post-Randomization		Switched to Different Agent Post-Randomization	
	N	Primary Endpoint Response n (%)	N	Primary Endpoint Response n (%)
Total	57	14 **(24.6%)**	52	10 **(19.2%)**
V/GAN	50	14 **(28.0%)**	44	8 **(18.2%)**
FOS	7	**0**	7	1 **(14.3%)**
CDV	0	**0**	1	1 **(100%)**

Study 303: Baseline Characteristics: Resistant vs. Refractory Subgroups

	Resistant		Refractory (without Resistance)	
Baseline Characteristics	**Maribavir** (N = 121)	**IAT** (N = 69)	**Maribavir** (N = 96)	**IAT** (N = 34)
Gender: Female	**32%**	**38%**	**44%**	**62%**
Age ≥ 65	**23%**	**17%**	**23%**	**3%**
Transplant type: SOT	**85%**	**81%**	**34%**	**26.5%**
Transplant type: HSCT	**15%**	**19%**	**66%**	**73.5%**

Study 303: Summary of GVHD Occurrence at Baseline and On Treatment in Maribavir versus IAT

		Maribavir N = 235 (%)	IAT N = 117 (%)
Baseline GVHD		**29** (12.3%)	**13** (11.1%)
	Acute GVHD	**23** (9.8%)	**8** (6.8%)
	Chronic GVHD	**6** (2.5%)	**5** (4.3%)

		Maribavir N = 234 (%)	IAT N = 116 (%)	Maribavir Person-years 37.1 N = 234 (e)	IAT Person-years 13.23 N = 116 (e)
Total On Treatment GVHD		**21** (8.9%)	**5** (4.3%)	**21** (0.57)	**5** (0.38)
	New Onset GVHD	**14** (5.9%)	**4** (3.4%)	**14** (0.38)	**4** (0.30)
	Worsening GVHD	**7** (2.9%)	**1** (0.9%)	**7** (0.19)	**1** (0.08)