EE484

Multinational Real-World Data in Transplant Patients With Refractory/Resistant Cytomegalovirus Infection Enhance Cost-Effectiveness Modeling Outcomes

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Conclusions

- Incorporating real-world data (RWD) into this economic model produced results that had greater face validity and reduced uncertainty for clinicians, payers and policy makers.
- We used trial data alongside RWD to uncover a relationship between time since clearance and risk of recurrence which highlighted the importance of treatments that enable patients to achieve and maintain CMV clearance.

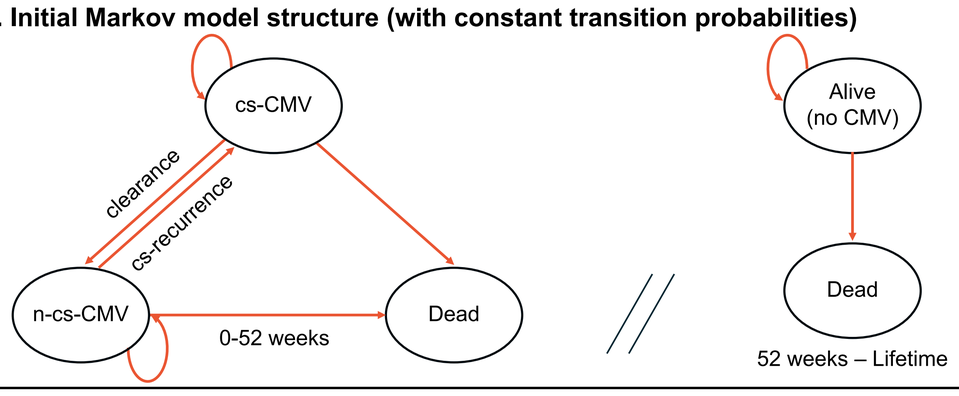
Introduction

- We investigated the cost-effectiveness of maribavir for post-transplant CMV infection in SOT and HSCT patients who were refractory (with or without resistance [R/R]) to conventional therapies.
- During model validation, clinical and economic experts expressed concern that the model results lacked face validity.
- To address this uncertainty, RWD from a multinational retrospective CMV outcomes study were used to inform enhancements to the model structure.[1,2]
- This study describes the 6-step process taken to develop a more robust and clinically plausible economic model.

1 A Markov model was conceptualized to explore the cost-effectiveness of maribavir for post-transplant R/R CMV…

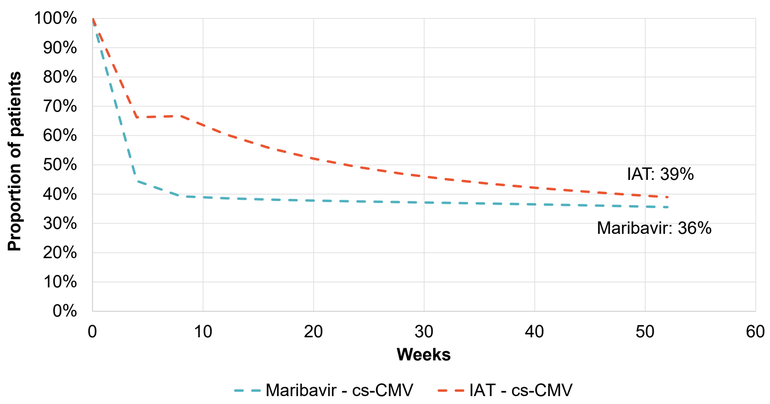
- Two consecutive Markov models were developed to capture the post-transplant journey for SOT and HSCT patients with R/R CMV (**Figure 1**).
- A 3-state CMV Markov was used for 12 months, capturing transitions between clinically significant CMV (cs-CMV), nonclinically significant CMV (n-cs-CMV), and dead health states.
- From 12 months until the lifetime horizon, patients moved to a 2-state, alive/dead model.
- In the first 12 months, transition probabilities remained constant and were estimated using data from the phase 3 SOLSTICE trial (NCT02931539).[3]
- Beyond 12 months, transitions were informed by SOT- and HSCT-specific mortality rates.[4,5]

Figure 1. Initial Markov model structure (with constant transition probabilities)



2 …results from the initial CMV Markov were validated by economic and clinical experts…

Figure 2. Patients occupying cs-CMV health state in initial model



Example of expert feedback: *"Currently in the model, at the 12-month period you have 40% of patients in the cs-CMV health state, based on what the clinicians have told us during the discussion this lacks some face validity"*

- **Figure 2** illustrates the cs-CMV health state occupancy for patients initiating treatment with IAT or maribavir from week 0 to week 52. At every time point from weeks 0 to 52, a smaller proportion of patients occupy the cs-CMV health state.
- Two clinical experts and 3 health economists raised concerns during external validation about the high percentage of patients in the cs-CMV health state at week 52 (IAT: 39%, maribavir: 36%).

3 …a logistic regression was undertaken to understand the key covariates that impact clinically significant recurrence…

- We hypothesized that the estimates for clinically significant recurrence taken from the SOLSTICE trial were driving the implausibly high proportion of patients remaining in the cs-CMV health state at week 52.
- A logistic regression analysis of recurrence between weeks 8 and 20 in the SOLSTICE trial revealed that time since clearance had a statistically significant impact on the odds of recurrence requiring treatment, with each additional day post-clearance lowering the odds by a factor of 0.95 (**Table 1**).

Table 1. Logistic regression to assess the impact of specific covariates on recurrence in the SOLSTICE trial (NCT02931539)[3]

Covariate	Adjusted OR (95% CI)	*P* value
Treatment (maribavir vs IAT)	0.32 (0.10-1.06)	0.06
Time since transplant, days	1.00 (1.00-1.00)	0.35
Transplant type (HSCT vs SOT)	1.90 (0.69-5.24)	0.22
Time since clearance, days	0.95 (0.94-0.97)	<0.001

4 …findings from the logistic regression were evaluated and confirmed using real-world evidence…

- As SOLSTICE provided data on recurrence over 12 weeks, studies with longer follow-up were needed to support the relationship between time since clearance and recurrence.
- RWD from a multinational retrospective CMV outcomes study[1,2] provided evidence that the risk of recurrence was highest immediately following a cs-CMV clearance event. Furthermore, if patients maintained clearance up to 20 weeks, the ongoing risk of recurrence remained constant (ie, time since clearance had no further impact on the risk of recurrence; **Figure 3**).
- Additionally, the RWD study demonstrated that CMV events can occur up to 82 weeks for HSCT patients and 155 weeks for SOT patients (**Figure 4**), longer than the 52 weeks assumed in the initial CMV Markov.

Figure 3. Risk of recurrence over time since clearance in CMV outcomes study[1,2]

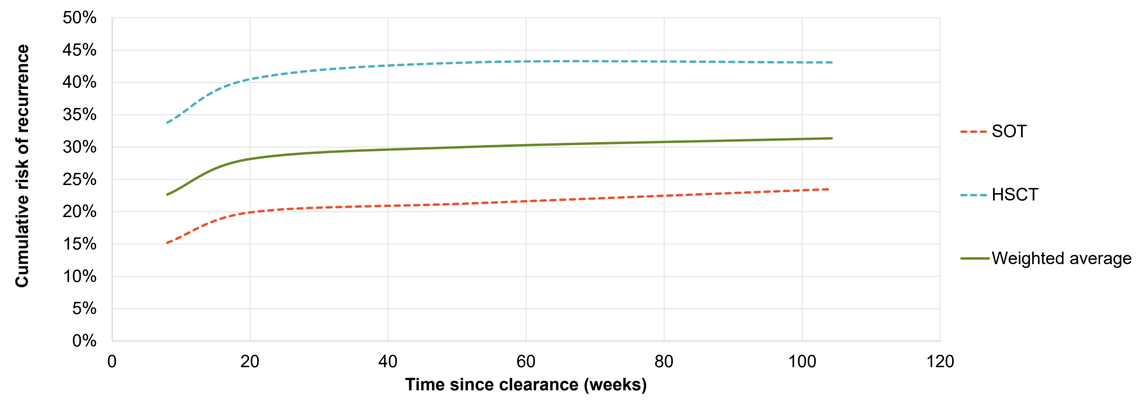
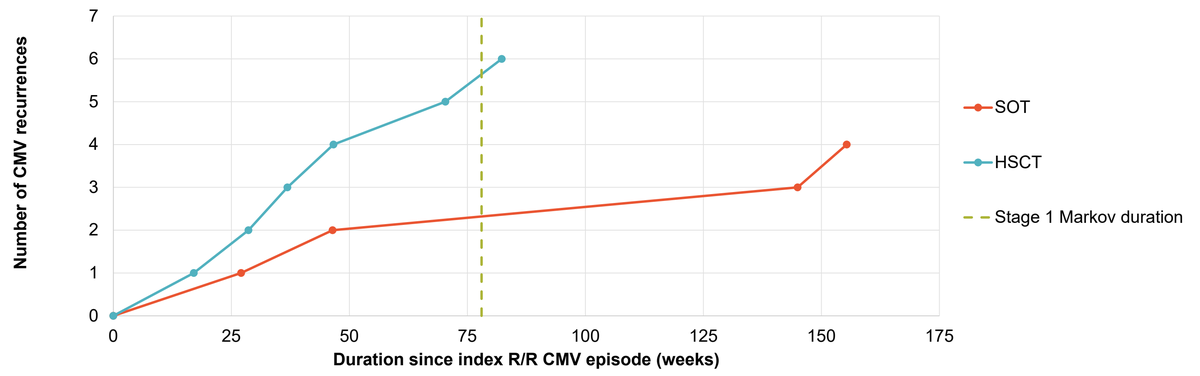


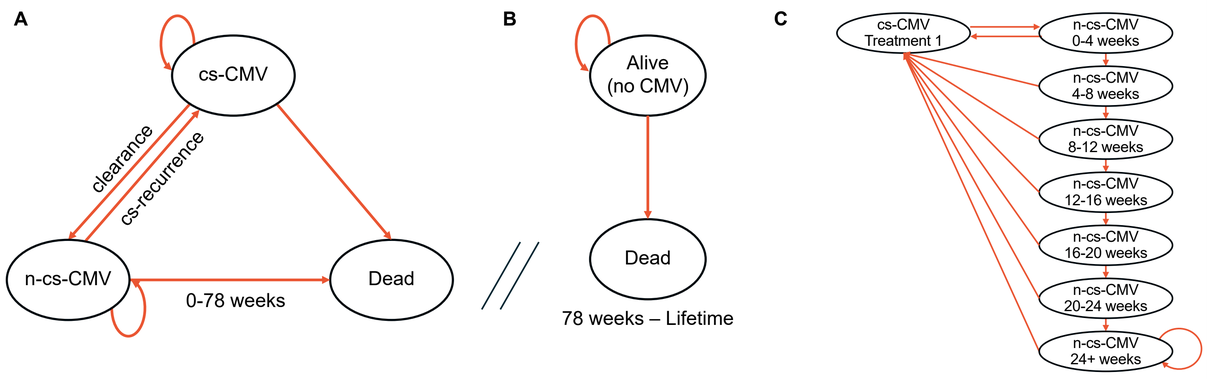
Figure 4. Estimated weeks since first R/R CMV episode in CMV outcomes study[1,2]



5 …the relationship between clearance and recurrence was incorporated into a modified CMV Markov structure…

- Implementing the findings from the logistic regression and the RWD CMV outcomes study resulted in an updated Markov model with tunnel states and time-dependent transition probabilities (**Figure 5**).
- Duration of the first Markov model was conservatively updated from 52 weeks to 78 weeks to align with the findings from the CMV outcomes study (**Figure 4**).

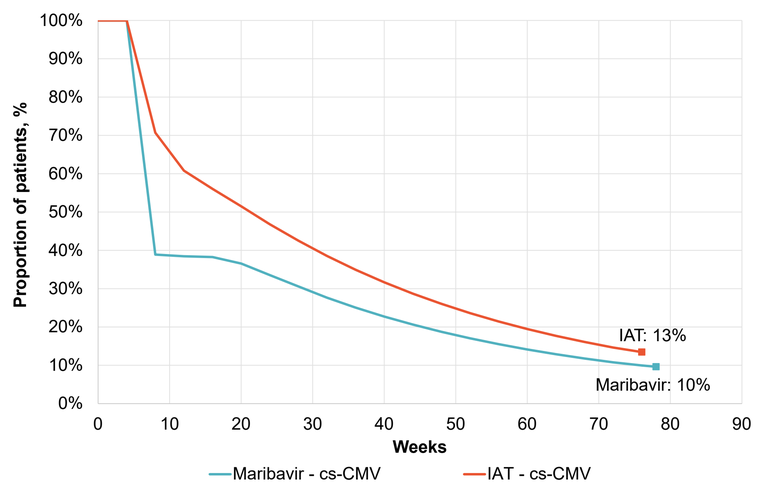
Figure 5. Final Markov model structure with time-dependent transition probabilities



6 …leveraging RWD and updating the model structure produced results with greater clinical plausibility.

- Changes to the model structure resulted in cs-CMV health-state occupancy at 78 weeks that was more consistent with expert expectations (IAT: 13%, maribavir: 10%; **Figure 6**).
- These modifications resulted in an updated ICER from £65,884 to £20,163, indicating maribavir is cost-effective at a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained.
- Using RWD enhanced face validity and clinical plausibility, and reduced uncertainty.

Figure 6. Patients occupying cs-CMV health state in final model



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ABBREVIATIONS: CMV, cytomegalovirus; cs-CMV, clinically significant cytomegalovirus; HSCT, hematopoietic stem cell transplant; IAT, investigator-assigned treatment; ICER, incremental cost-effectiveness ratio; n-cs-CMV, nonclinically significant cytomegalovirus; OR, odds ratio; QALY, quality-adjusted life-years; R/R, with or without resistance; RWD, real-world data; SOT, solid organ transplant.

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