PRM122

# A COMPARISON OF MARKOV COHORT AND DISCRETE EVENT SIMULATION MODELS IN COST-EFFECTIVENESS ANALYSIS OF SORAFENIB AND EVEROLIMUS IN 3RD LINE METASTATIC RENAL-CELL CARCINOMA IN THE CZECH REPUBLIC

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## BACKGROUND

Markov cohort model (MC) and discrete-event simulation model (DES) are inherently different. Therefore, they are rarely used in economic evaluation of the same disease.

Sorafenib and everolimus are current cornerstones of 2nd line treatment for metastatic renal-cell carcinoma (mRCC) (sorafenib is used also in 1st line mRCC therapy). However, there are limited effectiveness/efficacy and cost-effectiveness studies of mRCC treatment in 3rd line.

**Figure 2. DES model structure**

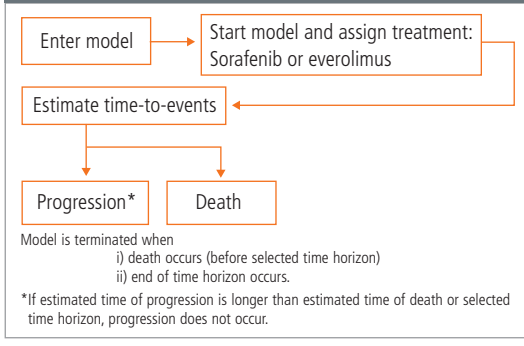
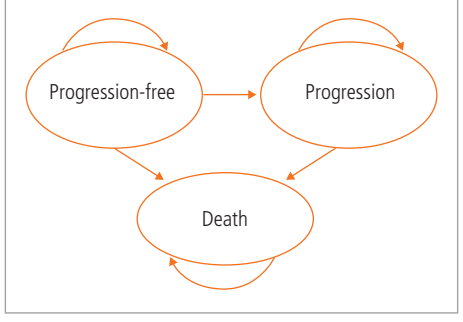



**Figure 1. Markov model structure**




## OBJECTIVES

The first objective of the study was to compare MC and DES models in simple oncologic model/setting.

The second objective was to assess the cost-effectiveness of sorafenib versus everolimus in 3rd line therapy of mRCC.

## METHODS

We developed two mirror life-time cost-utility models in TreeAge Pro 2017 using a) Markovian and b) DES approaches which projected both outcomes (quality-adjusted life-years (QALYs) and life-years-gained (LYGs)) and costs from healthcare payers' perspective. In MC model, we used weekly cycle length and three states, i.e. progression-free, progression and death. In DES model, there were two events instead of health states: progression and death. MC and DES model structures are shown in **Figure 1&2**.

There are no published randomized clinical trial (RCT) data of overall survival (OS) of everolimus solely for 3rd line therapy of mRCC. Large international observational study proved the same survival in 3rd line therapy of mRCC for sorafenib and everolimus[1] (median OS: 12.5 (95% CI: 10.6-17.1) vs. 12.4 (95% CI: 10.3-14.3) months); we therefore assumed the same OS for both therapies according to sorafenib from sorafenib's RCT of 3rd line treatment for mRCC[2]. However, given availability of other data (especially progression-free survival (PFS) or toxicity profile) of everolimus in 3rd line therapy of mRCC, we used separate PFS for both drugs from its RCTs[2,3] (patients characteristics were comparable in these two RCTs). **Figure 3** shows OS and PFS curves.

Utilities were derived from the most recent published literature (**Table 1**)[4,5]. Costs were taken from a) reimbursed lists (drug costs)[6,7] and b) previous administrative proceedings in mRCC (health state costs)[8] (**Table 2**). Costs and outcomes were discounted by 3%.

We consider Czech official willingness-to-pay threshold (WTP1) equal to €45,000 per QALY gained[9]; however, we also assume theoretical 3-times official WTP (WTP2) in cases of less costly but less efficacious intervention as suggested by some guidelines[10] and studies[11,12] (as there is obviously necessity of higher savings for QALY lost[13,14]).

In base-case DES model, 10 million simulations were performed to achieve the most stable result. Probabilistic sensitivity analysis was performed: a) in Markov model with 5,000 simulations, b) in DES model with 5,000 simulations of 10,000 individual simulations. **Table 3** summarizes the PSA setting.

**Figure 3. Overall (OS)[2] and progression-free survival (PFS)[2,3]**

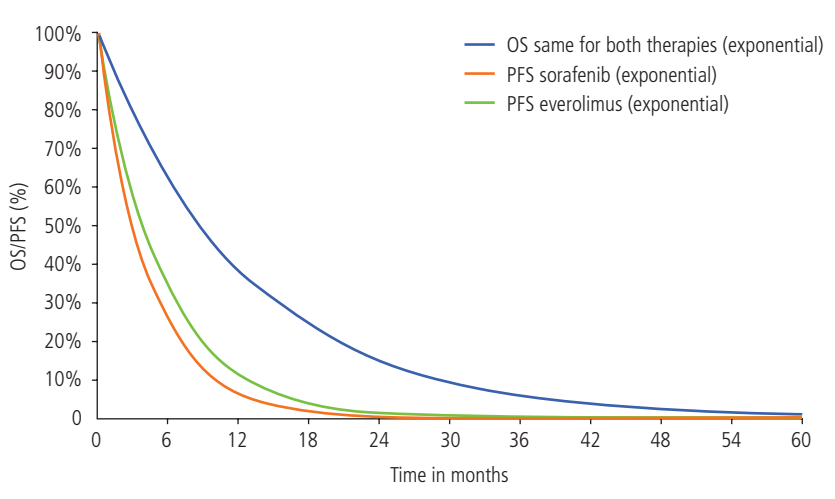



**Table 1. Utility values[4,5]**

| | Utility values |
|---|---|
| Progression-free | 0.799 |
| Progression | 0.743 |
| Death | 0.000 |

**Table 2. Costs[6,7,8]**

| | Costs (€/month) |
|---|---|
| Treatment costs | Everolimus: 3,380 |
| | Sorafenib: 3,262 |
| Health costs | Progression-free: 75 |
| | Progression: 50 |

**Table 3. PSA settings**

| Parameter | Distribution |
|---|---|
| Rates: progression and death | Normal |
| Utilities | Beta |
| Costs | Gamma |

## RESULTS

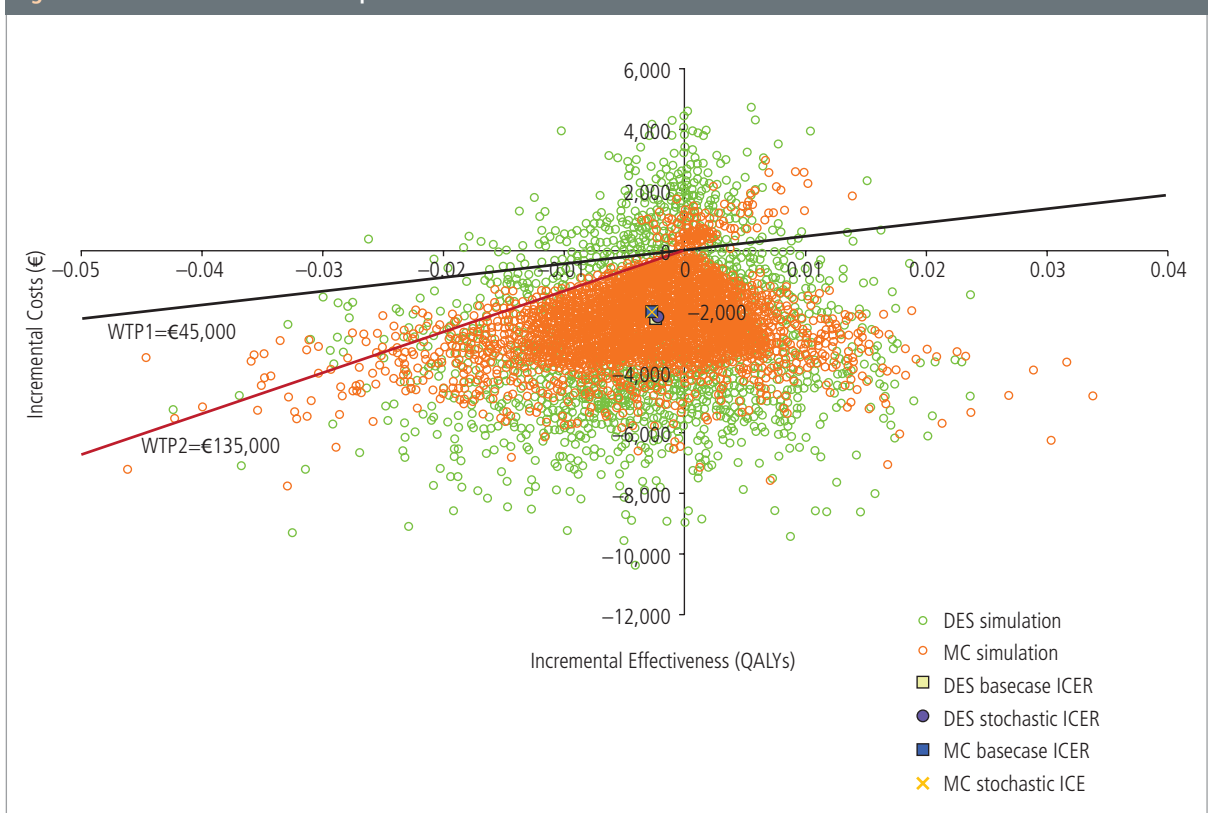
Over a life-time horizon (i.e. 10-year), sorafenib is less costly but also slightly less effective than everolimus. In MC model, sorafenib is less costly by –€2,045 (€11,558 vs. €13,603) and slightly less effective by –0.0028 QALYs (0.7815 vs. 0.7843). In DES model, sorafenib is less costly by –€2,222 (€11,319 vs. €13,541) and slightly less effective by –0.0025 QALYs (0.7818 vs. 0.7838). The ICERs, **expressed as savings per QALY lost**, are equal to €729,646 (MC) and €882,372 (DES). Sorafenib also brings highest incremental net monetary benefit (NMB) compared to everolimus equal to €1,919 (MC) and €2,109 (DES). All results are shown in **Table 4**.

The results of PSA showed that sorafenib is cost-effective with probability of 95% (MC) and 85% (DES) at the WTP1 and with probability of 93% (MC) and 82% (DES) at the WTP2, but these probabilities converge with increasing WTP threshold (**Figure 4&5**). The average probabilistic ICER is in both models very similar to the base-case ICER (**Figure 4**).

**Table 4. Base-case results of cost-effectiveness analysis (MC and DES models)**

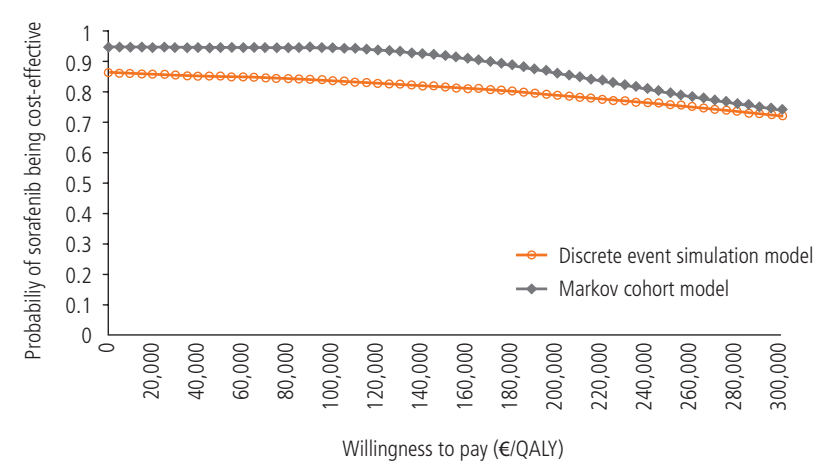
| | Sorafenib | Everolimus | Difference |
|---|---|---|---|
| | **Based on Markov cohort model** | | |
| **Total costs (€)** | **11,558** | **13,603** | **–2,045** |
| Drug costs (€) | 10,859 | 12,889 | –2,030 |
| Health costs (€) | 699 | 714 | –15 |
| – progression-free (€) | 241 | 286 | –45 |
| – progression (€) | 458 | 428 | 30 |
| **QALYs** | **0.7818** | **0.7843** | **–0.0028** |
| – progression free | 0.2139 | 0.2539 | –0.0400 |
| – progression | 0.5676 | 0.5304 | 0.0372 |
| LYGs | 1.0316 | 1.0316 | 0.0000 |
| **ICER (€/QALY)** | **729,646** (less effective and less costly, expressed as savings per QALY lost) | | |
| **Net monetary benefit (€)** | **23,609** | **21,690** | **1,919** $NMB_{sora} > NMB_{evero}$ |
| | **Based on discrete event simulation model** | | |
| **Total costs (€)** | **11,319** | **13,541** | **–2,222** |
| Drug costs (€) | 10,620 | 12,828 | –2,208 |
| Health costs (€) | 699 | 713 | –14 |
| – progression-free (€) | 244 | 285 | –41 |
| – progression (€) | 455 | 428 | 27 |
| **QALYs** | **0.7813** | **0.7838** | **–0.0025** |
| – progression free | 0.2168 | 0.2527 | –0.0359 |
| – progression | 0.5645 | 0.5311 | 0.0334 |
| LYGs | 1.0311 | 1.0311 | 0.0000 |
| **ICER (€/QALY)** | **882 372** (less effective and less costly, expressed as savings per QALY lost) | | |
| **Net monetary benefit (€)** | **23,839** | **21,731** | **2,109** $NMB_{sora} > NMB_{evero}$ |

**Figure 4. Cost-effectiveness scatter plot**




Note: MC: Markov cohort model; DES: discrete-event simulation model; WTP: willingness-to-pay threshold

**Figure 5. Cost-effectiveness acceptability curve, sorafenib-curve**




## CONCLUSIONS

**Despite their differences, MC and DES models yields almost identical results in simple 3-state/2-event oncologic model. The slight disparity might be due to computational differences, half-cycle correction, cycle length or time-to-event estimation[15]. The model also revealed that although patients treated with sorafenib progress slightly faster, their OS remains identical to everolimus.**

**Sorafenib showed that it is less costly and less efficacious than everolimus (3rd quadrant in cost-effectiveness plane). However, the differences in QALYs gained are negligible (lower by 0.3%) compared to financial savings that are brought by sorafenib (total costs lower by 15%). In 3rd quadrant, higher ICER means higher cost-effectiveness of given technology. Therefore, the ICER should be higher than WTP threshold to be declared cost-effective. We can see from the results that both WTP thresholds are well exceeded which shows a very high cost-effectiveness of sorafenib compared to everolimus in the 3rd line therapy of mRCC. In the world of fixed budgets, the savings generated by sorafenib can be used e. g. to treat more patients with mRCC.**

**To our knowledge, this is the first cost-effectiveness analysis of sorafenib in 3rd line therapy of mRCC.**

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