

Economic Evaluation of Sorafenib versus Best Supportive Care in Advanced Renal Cell Carcinoma: An Updated Cost-Effectiveness Analysis

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ABSTRACT

Background: An earlier economic evaluation based on the Phase III TARGET study showed that sorafenib was cost-effective compared to best supportive care (BSC) in advanced renal cell carcinoma (RCC) (ASCO 2006).

Recently, the latest overall survival data from the Phase III TARGET study were presented (ASCO 2007).

The objective of this study was to update the earlier economic model with the latest clinical data to evaluate the cost-effectiveness of sorafenib + BSC versus BSC alone in advanced RCC from a United States payer perspective.

Methods: A Markov model was developed to project lifetime survival and costs associated with sorafenib+BSC and BSC alone.

The model tracked patients with advanced RCC through three states – progression-free survival (PFS), progression, and death. Transition probabilities varied for each 3-month period and were obtained from the TARGET data.

Treatment effectiveness was measured in life-years (LY) gained. Resource utilization included pharmacy/drug, administration, physician visits, monitoring, and adverse events. Costs and survival benefits were discounted annually at 3%. Univariate and probabilistic sensitivity analyses were conducted.

Results: The lifetime per patient costs were \$92,222 and \$36,634 for sorafenib+BSC and BSC alone, respectively. The incremental survival benefit with sorafenib+BSC versus BSC alone was 0.88 life years.

The incremental cost-effectiveness ratio (ICER) of sorafenib+BSC versus BSC alone was \$63,219 per LYG.

Results were sensitive to variation in sorafenib and BSC survival after progression as well as to sorafenib cost. There was a 95% probability that sorafenib would be cost-effective vs. BSC alone, using a threshold of \$95,000 or less.

Conclusions: Updating the model with the most recent clinical trial data resulted in an incremental cost-effectiveness ratio within the established threshold that society is willing to pay for cancer care (i.e., \$50,000–\$100,000 per LY).

Thus, consistent with earlier findings, sorafenib+BSC appears to be cost-effective in the management of advanced RCC.

INTRODUCTION

- Cancers of the kidney comprise 2–3% of all malignant adult tumors.
- Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for approximately 85% of the cases.
- Management of advanced RCC remains a considerable challenge. At the time of this study, treatment options were limited to resection of the metastases, palliative nephrectomy, and immunotherapy with interferon- α or interleukin-2. However, as few patients were eligible for these treatments, best supportive care (BSC) was the mainstay of treatment at the time the clinical study was started and run.
- Approved by the FDA in December 2005 for advanced RCC, sorafenib is an oral multi-kinase inhibitor that targets several serine/threonine and receptor tyrosine kinases believed to be required for angiogenesis.
- The Treatment Approaches in Renal cancer Global Evaluation Trial (TARGET), a Phase III study, demonstrated that sorafenib plus BSC significantly prolonged progression-free survival (PFS) compared with placebo + BSC alone in patients with advanced RCC. Furthermore, overall survival was longer for sorafenib than with BSC (hazard ratio: 0.71).
- Recently the latest overall survival data from the TARGET study were presented at ASCO 2007. The results of this study showed a trend in increased OS for sorafenib compared with placebo (hazard ratio: 0.88). However the final OS results were confounded due to crossover of BSC patients to sorafenib. A pre-planned secondary analysis censoring placebo data demonstrated significant survival advantage for sorafenib (hazard ratio: 0.78)

OBJECTIVE

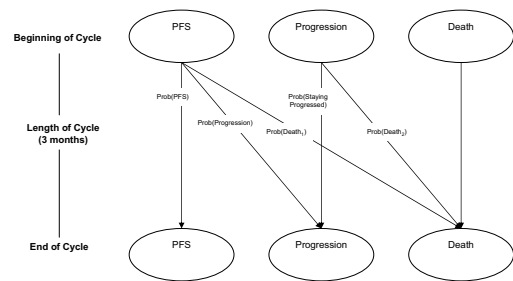
- The original model used TARGET data from May 2005.
- The objective of this updated analysis was to re-examine model results with more recent TARGET data (i.e., available from the September 2006 dataset).
- The study was conducted from a US managed care perspective.

STUDY DESIGN

General Framework and Model Structure

- Using probabilities from the latest TARGET data, a Markov model was developed to project lifetime clinical effectiveness of sorafenib + BSC or BSC alone.
- The Markov model tracked patients with advanced RCC over their lifetime through three mutually exclusive health states: PFS, progression, and death (Figure 1)

Figure 1. Markov model of the natural history of patients with advanced renal cell carcinoma



- For example, patients who are progression free in the current cycle will, in the next cycle:
 - Remain progression free [PFS] with the probability [Prob(PFS)]
 - Transition to the disease progression state [Progression] with the probability [Prob(Progression)]
 - Transition to death [Death] with the probability [Prob(Death1)]
- Patients who experience disease progression in the current cycle will, in the next cycle:
 - Remain in the progression state [Progression] with the probability [Prob(Staying progressed)]
 - Transition to death [Death] with the probability [Prob(Death2)]
- The Markov process stops when there are >99% of patients in the Death state

CLINICAL INPUTS

The clinical transition probabilities were based on the results of TARGET.

- Prob(PFS) and Prob(Progression) were obtained from the Kaplan–Meier curves, whereas Prob(Staying progressed) was based on the survival data among progressed patients.
- Prob(Death1) = 1 – [Prob(PFS) + Prob(Progression)]
- Prob(Death2) = 1 – Prob(Staying progressed).
- Patients in the BSC arm were permitted to crossover to receive sorafenib beginning in May 2005 upon an FDA decision based on a review of interim data. To avoid underestimating the true effect of sorafenib, only the sorafenib arm was updated with the new overall survival data.
- Sorafenib
 - The September 2006 overall survival (OS) data of sorafenib were used to obtain the probability of death after progression.
- Best Supportive Care
 - No changes were made to the existing base case model. For the BSC group, data from the May 2005 analysis were still used (up to 12 months).
- A parametric method was used to estimate the probability of death after progression from the overall survival (OS) data for sorafenib
 - The September 2006 survival data were used for the OS probabilities of sorafenib at the end of each cycle.
 - The OS probabilities for the sorafenib cohort were projected from the survival function built from patient-level data. A log-normal distribution was fitted to the OS data. This survival function was assumed to best predict future OS probabilities.

For the BSC cohort

- As data beyond 12 months were not available, the probabilities of PFS and Progression after 12 months were assumed to change at a constant quarterly rate extrapolated from the probabilities of the last two available time points.
- Similarly, survival data among progressed patients beyond 9 months were extrapolated based on the last two available time points. The constant incremental death rate after 9 months was assumed to be the average of incremental death rates at 6 months and 9 months
- Compared to the original model, only the probability of death after progression for sorafenib was changed. All other probability variables remain the same because only OS data were available beyond 2005.
- The probability of death after progression was based on overall survival, as well as PFS and TTP.

Adverse Events (AEs)

- The incidence of AEs was obtained from TARGET. Characterization of AE management was consistent with clinical trial data and the literature, supplemented with input from two practicing oncologists. For the purposes of the model comparison, AEs of any grade were utilized except for anemia, neutropenia, and diarrhea, of which only grades 3 and 4 were used
- AEs were subdivided into two categories: short-term and long-term events. Short-term events (e.g., pancreatitis) were assumed to incur a one-time cost, applied to the first 3-month cycle, whereas long-term events (e.g., hypertension) were assumed to result in repeated costs incurred over the course of the treatment period

Table 1. Probabilities of Death after Progression for Sorafenib - the first 3 years

| Time (Months) | Cumulative Probability of PFS | Cumulative Probability of Progression | Probability of death after progression | Overall Survival |
|---------------|-------------------------------|---------------------------------------|--|------------------|
| 3 | 0.70800 | 0.27400 | | 0.956 |
| 6 | 0.44700 | 0.54100 | 0.425 | 0.850 |
| 9 | 0.26700 | 0.70300 | 0.220 | 0.739 |
| 12 | 0.15400 | 0.82500 | 0.203 | 0.640 |
| 15 | 0.08882 | 0.89689 | 0.169 | 0.556 |
| 18 | 0.05123 | 0.93924 | 0.150 | 0.485 |
| 21 | 0.02955 | 0.96420 | 0.137 | 0.425 |
| 24 | 0.01704 | 0.97891 | 0.126 | 0.375 |
| 27 | 0.00983 | 0.98757 | 0.120 | 0.332 |
| 30 | 0.00567 | 0.99268 | 0.114 | 0.295 |
| 33 | 0.00327 | 0.99568 | 0.107 | 0.264 |
| 36 | 0.00189 | 0.99746 | 0.103 | 0.237 |

ECONOMIC INPUTS

Resource Use and Costs

- Sources for resource utilization inputs were the published literature and clinical experts.
- Unit costs for procedures came from published literature or CMS reimbursement rates

UPDATED ANALYSES

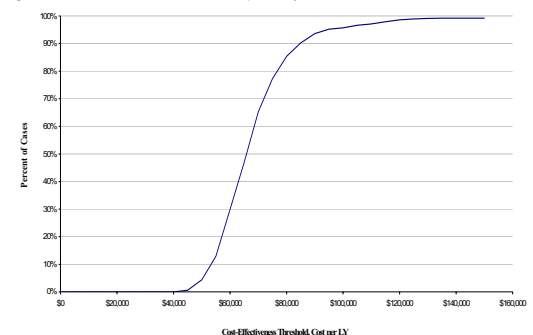
Cost-Effectiveness Analysis

- Incremental cost-effectiveness analyses were conducted
- The total cost of treatment was estimated for each treatment
- Survival was calculated in each cycle based on the number of patients in each health state. Life-years gained in each cycle were combined to determine the total life-years gained
- The incremental cost-effectiveness ratio (ICER) was calculated as the ratio of the difference in total costs to the difference in total life years between the comparators
- Given the limited data availability and reliability of extrapolated data after Year 1, the analyses were conducted at two different time horizons: 1-year and lifetime horizon. Costs and health benefits were discounted at 3% per annum
- Targeted Scenario Analysis
 - To examine the impact of the OS estimation on results, targeted scenario analyses were conducted
 - ◆ To generate a conservative and an optimistic estimate of the ICERs, the lower bound and upper bound, respectively, of the 95% CI of OS probabilities at all time points were used
- Probabilistic Sensitivity Analysis
 - A probabilistic sensitivity analysis was conducted for the main analysis to construct an acceptability curve and estimate the 95% CI of the resulting ICER. Monte Carlo simulations were used (1,000 iterations/trials).
- Median survival time projected in the Markov process was approximately 18 months for sorafenib patients and 14 months for BSC patients.
- Lifetime per patient costs were \$92,222 and \$36,634 for sorafenib+BSC and BSC alone, respectively.
- The incremental survival benefit with sorafenib+BSC versus BSC alone was 0.88 life years.
- The incremental cost-effectiveness ratio (ICER) of sorafenib+BSC versus BSC alone was \$63,219 per LYG.
- Results were sensitive to variation in sorafenib and BSC survival after progression as well as to sorafenib drug cost. There was a 95% probability that sorafenib would be cost-effective vs. BSC alone, using a threshold of \$95,000 or less.

Table 2. Sorafenib+BSC vs. BSC over a Lifetime Horizon

| | Total Costs | LY | Marginal Cost | Marginal Effect: LY Gained | ICER per LY Gained |
|--|-------------|-------|---------------|----------------------------|--------------------|
| Original Model Results (from the original model using May 2005 data) | | | | | |
| BSC only | \$36,634 | 1.250 | -- | -- | -- |
| Sorafenib+ | \$103,502 | 2.520 | \$66,868 | 1.2691 | \$52,688 |
| Updated Analysis Results (updating the sorafenib probability of death after progression based on Sep 2006 OS data) | | | | | |
| BSC only | \$36,634 | 1.250 | -- | -- | -- |
| Sorafenib+ | \$92,222 | 2.130 | \$55,588 | 0.8793 | \$63,219 |
| Scenario Analysis (using lower bound of sorafenib OS data) | | | | | |
| BSC only | \$36,634 | 1.250 | -- | -- | -- |
| Sorafenib+ | \$84,723 | 1.871 | \$48,089 | 0.6201 | \$77,547 |
| Scenario Analysis (using upper bound of sorafenib OS data) | | | | | |
| BSC only | \$36,634 | 1.250 | -- | -- | -- |
| Sorafenib+ | \$100,029 | 2.400 | \$63,395 | 1.1491 | \$55,169 |

Figure 2. Cost-effectiveness acceptability curve for sorafenib vs. BSC



DISCUSSION

- Findings from the supplementary analysis may reflect the benefit of sorafenib observed from the trial more accurately
 - The most recent 3-year clinical trial data have shown an approximately 3.5-month difference in survival between sorafenib and BSC (based on 3-year sorafenib and 17-month BSC data)
 - This analysis estimated a 4-month survival difference between sorafenib and BSC at the end of 3 years
- The main analysis showed that the life years gained for BSC and sorafenib were 1.25 vs. 2.13, respectively, with an ICER of \$63,219 per LYG when the sorafenib incremental death rate after progression were derived from the September 2006 OS data.
- The sensitivity analyses showing that 95% of ICER results of 1,000 simulation runs were less than \$95,000 per LYG attests to the robustness of the model.
- Limitations
 - These findings need to be interpreted with caution due to the limited data availability and different methods used for data extrapolation.
 - ◆ For example, for the sorafenib group, different data sources were used for PFS, TTP, and death after progression.
 - The inclusion of comparator therapies was not possible due to the lack of published data at the time of this analysis on key efficacy variables, such as PFS and progression

CONCLUSIONS

- The incremental cost per life-years gained achieved by sorafenib + BSC falls within the range deemed acceptable by clinical oncologists (\$50,000 - \$100,000 per LY gained).
- The results from these analyses using the most updated OS data from TARGET study (Sep 2006) are consistent with an earlier economic model showing sorafenib is cost-effective compared to BSC in advanced RCC