COST-EFFECTIVENESS ANALYSIS OF MIDOSTAURIN (MIDO) WITH STANDARD CHEMOTHERAPY (SOC) FOR ACUTE MYELOID LEUKEMIA (AML) IN THE UNITED KINGDOM (UK)

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SUBMITTED ABSTRACT

OBJECTIVES: MIDO is under EMA review for treatment of newly diagnosed adult patients with FLT3 mutation-positive AML who are eligible to receive stem cell transplantation (SCT). The objective of this study was to estimate the Incremental Cost Effectiveness Ratio (ICER) of utilizing MIDO+SOC followed by MIDO monotherapy, compared to SOC for newly diagnosed AML in the UK.

METHODS: A partition survival model was developed to estimate the expected outcomes and costs of treatment with MIDO+SOC vs SOC over a lifetime horizon. The model included the following health states/partitions: induction, consolidation, monotherapy, complete remission (CR), relapse, SCT treatment, SCT recovery, and post-SCT recovery. Data on CR, overall survival (OS), and frequencies of adverse events (AEs) were obtained from the MIDO Phase III clinical trial (RATIFY). OS was extrapolated beyond the trial horizon using a “cure model” approach and data from the Office for National Statistics (2013-2015). Published health state utilities were used. Routine care utilisation was based on the data used in the NICE STA for azacitidine TA399. Costs incorporated in the model included drugs and administration, AE treatment, and medical costs for hospitalisations, physician visits, and end-of-life/palliative care. Unit costs were obtained from various sources including the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care (2015).

RESULTS: Incremental life years (LYs) and quality adjusted life years (QALYs) gained by patients on MIDO+SOC vs. SOC were 1.67 and 1.47 respectively. At an incremental cost for £50,404 over a lifetime horizon, the ICER per LY was £30,263 and £34,327 per QALY. Sensitivity analysis results were also consistent with the basecase findings.

CONCLUSIONS: With a threshold of £50,000 per QALY for end-of-life treatment, MIDO is a cost-effective option for newly-diagnosed FLT3 mutation-positive AML. With limited treatments in FLT3 mutation positive AML, MIDO represents a new cost-effective option.
Midostaurin (MIDO) has been recently approved by EMA and FDA for treatment of newly diagnosed adult patients with FLT3 mutation-positive AML who are eligible to receive stem cell transplantation (SCT).

The objective of this study was to estimate the Incremental Cost Effectiveness Ratio (ICER) of utilizing MIDO+ intensive chemotherapy (Standard of Care, SOC) followed by MIDO monotherapy, compared to SOC for newly diagnosed AML in the UK.
Acute myeloid leukemia (AML) is considered a medical emergency with the lowest survival rates among leukemias.\(^1\)
If left untreated, AML is ultimately fatal from complications of bone marrow failure, typically occurring within one year of diagnosis.\(^2\)
Patients with FLT3 mutations have a worse prognosis, with higher rates of relapse and lower rates of survival.\(^3\)

### 5-year relative survival\(^3\)

<table>
<thead>
<tr>
<th>Disease</th>
<th>5-year Relative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>84.8%</td>
</tr>
<tr>
<td>ALL</td>
<td>70.1%</td>
</tr>
<tr>
<td>CML</td>
<td>63.2%</td>
</tr>
<tr>
<td>AML</td>
<td>26.0%</td>
</tr>
</tbody>
</table>

### FLT3 AML Outcomes at 5 years\(^3\)

<table>
<thead>
<tr>
<th>Mutation Level</th>
<th>% Relapse at 5 years</th>
<th>% Alive at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Mutant</td>
<td>49%</td>
<td>64%</td>
</tr>
<tr>
<td>Low level</td>
<td>42%</td>
<td>31%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>High Level</td>
<td>15%</td>
<td>82%</td>
</tr>
</tbody>
</table>
Therapy for AML consists of sequential induction systemic therapy (1-2 months) designed to obtain complete remission (CR), followed by post-remission consolidation therapy (2-4 months)\(^1\).

Receiving SCT is the ultimate goal of therapy and it usually decreases the risk of relapse\(^2\).
Background

- MIDO has been studied as add-on to intensive chemotherapy (SOC) during induction and consolidation and subsequently as a monotherapy during maintenance in the RATIFY international phase III trial of 717 patients.
- MIDO significantly reduced risk of death by 23% vs intensive chemotherapy alone, regardless of stem cell transplantation (HR=0.774, p=0.0078).
- Event-free survival, disease-free survival and remission duration were also prolonged with a median follow-up of over 5 years. 4, 5.
METHODS

- A partition survival model was developed to estimate the expected outcomes and costs of treatment with MIDO+SOC vs SOC over a lifetime horizon.

Figure 1. Model Framework
METHODS

- Data on Complete Remission, overall survival (OS), and frequencies of adverse events (AEs) were obtained from the MIDO Phase III clinical trial (RATIFY).
- OS was extrapolated beyond the trial horizon using a “cure model” approach and data from the Office for National Statistics (2013-2015), Figure 2.
- The proportion of patients in CR after trial cut-off was extrapolated based on the OS extrapolation, ensuring the CR curve was internally consistent with the OS curve.

Figure 2. Long Term Extrapolation of Overall Survival
Published health state utilities were used, Table 1.

Table 1. Health State Utilities Used in the Model

<table>
<thead>
<tr>
<th>Utility state</th>
<th>Utility values used in base case (literature)</th>
<th>Values used in scenario analysis (TTO)</th>
<th>Reference, source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction treatment*</td>
<td>0.648</td>
<td>0.162</td>
<td>6</td>
</tr>
<tr>
<td>Consolidation treatment*</td>
<td>0.710</td>
<td>0.568</td>
<td>7</td>
</tr>
<tr>
<td>Monotherapy treatment*</td>
<td>0.810</td>
<td>0.889</td>
<td>7</td>
</tr>
<tr>
<td>Complete remission</td>
<td>0.830</td>
<td>0.887</td>
<td>8</td>
</tr>
<tr>
<td>Relapse</td>
<td>0.530</td>
<td>0.505</td>
<td>9</td>
</tr>
<tr>
<td>SCT Treatment *</td>
<td>0.613</td>
<td>-0.210</td>
<td>Mapping Algorithm – 10; QLQC30 data – 11</td>
</tr>
<tr>
<td>SCT Recovery</td>
<td>0.810</td>
<td>0.748</td>
<td>Mapping Algorithm – 10; QLQC30 data – 11</td>
</tr>
<tr>
<td>Post-SCT Recovery</td>
<td>0.826</td>
<td>0.715</td>
<td>Mapping Algorithm – 10; QLQC30 data – 11</td>
</tr>
</tbody>
</table>
METHODS

- Routine care utilisation was based on the data used in the NICE STA for azacitidine NICE TA399.

- Costs incorporated in the model included:
  - drugs and administration,
  - AE treatment, and
  - medical costs for hospitalisations, physician visits, and end-of-life/palliative care.

- Unit costs were obtained from various sources including the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care (2015).
Incremental life years (LYs) and quality adjusted life years (QALYs) gained by patients on MIDO+SOC vs. SOC were 1.67 and 1.47 respectively.

At an incremental cost for MIDO+SOC £50,404 over a lifetime horizon, the ICER per LY was £30,263 and £34,327 per QALY.

Table 2. Summary of Cost-Effectiveness Results

<table>
<thead>
<tr>
<th>Time horizon</th>
<th>MIDO vs SOC</th>
<th>Δ Costs</th>
<th>Δ Benefit</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per LY</td>
<td>Lifetime</td>
<td>£50,404</td>
<td>1.67</td>
<td>£30,263</td>
</tr>
<tr>
<td>Cost per QALY</td>
<td>Lifetime</td>
<td>£50,404</td>
<td>1.47</td>
<td>Endpoint</td>
</tr>
</tbody>
</table>
RESULTS

- Probabilistic sensitivity analysis results were also consistent with the basecase findings.
- The average number of QALY gained with MIDO therapy compared to SOC was 1.45 (95% CI 0.87, 2.05). The average incremental cost was £45,899 (95% CI £7,521, £78,332), resulting in an average ICER of £31,550 (95% CI £7,015, £47,213).
- The probabilities of MIDO cost-effectiveness at thresholds of £30,000 and £50,000 were 39.2% and 97.3%, respectively.

Figure 3. Cost-Effectiveness Plane
The deterministic sensitivity analysis was relatively consistent with the base case findings, thereby validating those results.

The analysis was most sensitive to variations in stem cell therapy rate, MIDO therapy OS, differences in CR rate, and discounting rates.

Figure 3. Tornado Graph of Deterministic Sensitivity Analysis Results (ICER per QALY)
Limitations

- Where specific data were unavailable, as for the duration of SCT and recovery, estimates were obtained from interviews with clinical experts.

- Additionally, the model relied on utility values obtained from the literature and mapped to the health states: a limitation that was unavoidable, as these data were not collected during the RATIFY clinical trial.

- Lastly, patients in the SCT health state could only transition out through mortality, dictating necessarily that no relapse or subsequent therapy occurred after SCT.
With a threshold of £50,000 per QALY for end-of-life treatment, MIDO is a cost-effective option for newly-diagnosed FLT3 mutation-positive AML.

With limited treatments in FLT3 mutation-positive AML, MIDO represents a new cost-effective option.
REFERENCES