Supplement

Cost-effectiveness analysis of oral azacitidine maintenance therapy in acute myeloid leukemia

Jan Philipp Bewersdorf, MD¹,², Kishan K. Patel¹,², Scott F. Huntington, MD, MPH, MSc¹,², and Amer M. Zeidan, MBBS, MHS¹,²#

¹: Section of Hematology, Department of Internal Medicine, Yale University School of Medicine, Yale University, New Haven, CT.
²: Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center, Yale University, New Haven, CT.

#: Corresponding author: Amer M. Zeidan, Section of Hematology, Department of Internal Medicine, Yale University, 333 Cedar Street, PO Box 208028, New Haven, CT 06520-8028; email: amer.zeidan@yale.edu
Supplemental methods:
Model construction and patient population:

The model presented here was based on the randomized, placebo-controlled, phase III QUAZAR AML-001 study. The baseline patient characteristics in the original study included patients with AML in first remission with a median age of 68 years (range 55-86), 52% were male, 91% had de novo AML, 86% had intermediate-risk cytogenetics, and 46% were positive for measurable residual disease (MRD).

We used a partitioned survival analysis similar to previous publications from our group. Patients entered the model as AML patients having achieved remission and either received oral azacitidine using dosing schedules outlined in the QUAZAR AML-001 study or no treatment (i.e. observation). Patients who experienced disease progression while receiving either oral azacitidine or observation entered a respective post-progression disease state and received salvage therapies that included intensive chemotherapy, allo-HCT, lower-intensity therapies, or best supportive care only using the distributions outlined in the QUAZAR AML-001 study. Among patients treated with lower-intensity therapies, we assumed that patients with targetable mutations in \textit{FLT3, IDH1, or IDH2} would be treated with gilteritinib, ivosidenib, or enasidenib, respectively. As the percentage of patients with these mutations was not specified in the QUAZAR AML-001 study, we assumed a prevalence of those mutations similar to AML patients included in the Cancer Genome Analysis.

Costs and utilities were modelled over a lifetime horizon. Utilities were measured in quality-adjusted life years (QALYs). Model outputs were used to calculate the incremental cost-effectiveness ratio (ICER) for oral azacitidine, which represents the
cost in 2020 US dollars (USD) of each additional QALY gained compared to observation. Using a US health care system perspective, costs and utilities were discounted by 3% annually as recommended by the second panel on cost-effectiveness in health and medicine.\(^4\) A willingness-to-pay (WTP) threshold of $150,000 per QALY gained was used to compare the ICER derived from our model to commonly used thresholds applied in cost-effectiveness analyses.\(^5\)

**Model inputs:**

RFS and OS curves were extrapolated from published QUAZAR AML-001 results.\(^2,6\) Using the original publication, we created Kaplan-Meier curves and patient-at-risk tables for RFS and OS for both study arms.\(^7\) Next, these recreated individual patient-level data were fitted to various parametric survival distributions (exponential, Gompertz, Weibull, log-logistic, log-normal, and generalized γ). The distribution with the best fit as assessed by Akaike information criterion, visual inspection, and pragmatic modelling considerations was selected for inclusion in the model. In all cases log-logistic regression distributions were chosen and parametric survival curves used in the model as well as the recreated Kaplan-Meier curves are shown in Figure 1.

Clinical parameters used in this model were derived preferentially from the original QUAZAR AML-001 study or post-hoc analyses of the trial.\(^1,8\) Costs for subsequent lines of therapy,\(^9-11\) management of complications,\(^8\) terminal\(^12\) and supportive care\(^13,14\) were derived from the literature. Due to the novelty of maintenance therapy with oral azacitidine, data on health care utilization were limited to a single publication on
hospitalizations and associated costs in the QUAZAR AML-001 trial. Costs for subsequent therapy, end-of-life care, and routine supportive care (office visits, blood transfusions) were assumed to be equal between both treatment arms. If available, costs for the Medicare population rather than commercially insured patients were used. The costs for oral medications (gilteritinib, ivosidenib, enasidenib) were derived using a methodology previously reported by the Memorial Sloan Kettering Drug Pricing Laboratory that is based on the Medicare plan finder tool. Due to the brief period between FDA approval and our study, oral azacitidine has not been included as of May, 2021 in Medicare Part B price files. We therefore estimated the cost of oral azacitidine using the published Average Wholesale Price (AWP), which was discounted in our base case analysis by 28%. We recognize AWP does not include manufacturer rebates and discounts, with prior analyses finding the actual average sales price in the US for Medicare part B medications typically 26-30% below the AWP. Further, we varied this discount between 18-38% during sensitivity analyses. All costs were adjusted for inflation using the personal consumption expenditure-health index to 2020 USD.

Utilities for early remission (months 1-6), long-term remission (>6 months), and relapsed AML were derived from the literature. As quality of life was similar between both arms in the QUAZAR AML-001 trial, we used identical utility values for oral azacitidine and observation in our analysis. 

Table 1 provides an overview of costs and clinical parameters included in this model.

Sensitivity analyses:

One-way sensitivity analyses were performed to evaluate the impact of individual parameters on the overall model. Utility values were varied with a 10% range and all
other variables were varied across a 50% range. The ranges of the various variables used in sensitivity analyses are shown in Table 1. During probabilistic sensitivity analyses, we described each parameter using a distribution and performed 10,000 Monte Carlo simulations, each time randomly sampling from the distributions of model inputs. Beta distributions were used to describe probabilities and utilities, while gamma distributions were used for costs. Results of probabilistic sensitivity analyses are shown as cost-effectiveness acceptability curves.
Supplemental Figure legends:

Supplemental Figure 1: Parametric relapse-free and overall survival curves used in the partitioned survival analysis model

Kaplan-Meier curves were re-constructed from the QUAZAR AML-001 trial and fit to parametric survival distributions. Log-logistic regression curves yielded the best fit visually and by means Akaike information criterion as well as pragmatic modelling considerations. The figure depicts both the re-constructed Kaplan-Meier survival curves (blue) and the loglogistic regression curves (red) for relapse-free survival (RFS) for oral azacitidine (panel A) and observation (placebo in QUAZAR AML-001 trial; panel B) as well as overall survival (OS) curves for oral azacitidine (panel C) and observation (panel D).
Supplemental Figure 2: Probabilistic sensitivity analysis

Supplemental Figure 2 shows a probabilistic sensitivity analysis based on 10,000 Monte Carlo simulations to assess which strategy (oral azacitidine [red] or observation [blue]) would be preferred at various willingness-to-pay thresholds. Costs and probabilities were varied by 50%, while utilities were varied by 10%. Beta distributions were used to describe probabilities and utilities, while gamma distributions were used for costs. Only one of the 10,000 iterations yielded an ICER of less than $150,000/QALY for oral azacitidine.
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