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A Health State Utility Model Estimating the Impact of Ivosidenib on Quality of Life in Patients with Relapsed/Refractory Acute Myeloid Leukemia

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BACKGROUND

- Acute myeloid leukemia (AML) is the most common form of leukemia in adults (Seigel 2016). Patient prognosis is poor overall, with less than 30% of patients surviving 5 years from their diagnosis (National Cancer Institute). Patients with relapsed/refractory (R/R) disease have cure rates of less than 10% (Bose 2017)
- Until recently, no new drugs had been approved for AML in the United States in over 4 decades (Bose 2017). Ivosidenib is a once-daily, oral monotherapy in clinical trials for the treatment of IDH1-mutated (mIDH1) R/R AML. The phase 1, single-arm trial showed a complete remission or complete remission with partial hematologic recovery rate of 30.4% and a favorable adverse event (AE) profile (DiNardo 2017)
- Health-related quality of life (HRQoL) is an important element when considering treatment selection, especially related to treatment toxicity. As HRQoL data was not collected in the phase 1 trial, a modeling exercise was undertaken to understand the potential utility benefit associated with ivosidenib compared to other treatments used for R/R AML

AIMS

- The objective of the study was to estimate the lifetime HRQoL impact of ivosidenib in R/R AML

METHODS

- Model Methods
  - A partitioned survival model over a lifetime (5-years, less than 1% of the population alive) time horizon with 1 week cycles, leveraging event-free survival (EFS) and overall survival (OS) curves considered the impact of clinical performance and AEs on HRQoL. Three health states were considered in the model: EFS, progressed disease (PD) and death
  - The model estimated total life years (LYs) and quality-adjusted life years (QALYs). Health state utilities are used to calculate QALYs, where 1 equals perfect health and 0 equals death. The total number of LYs is adjusted by the health state utilities to calculate QALYs (Whitehead 2010)
- Comparators
  - The model intervention of interest was ivosidenib, with data derived from a recent phase 1 clinical trial in the R/R AML population (Agios data on file)
  - Model comparators were therapies that are used to treat R/R AML, as informed by a review of treatment guidelines and discussions with practicing oncologists.
- Survival
  - Given the heterogenous data for the model comparators, two survival approaches were taken in the model:
    1. Using survival data from the phase 1 ivosidenib trial for all interventions (Agios data on file) which only considers a difference in the AE profiles of the comparators relative to ivosidenib
    2. Using published survival data from a phase 3 R/R AML clinical trial of clofarabine + cytarabine for all comparators (Faderl 2012) which considers differences in both AE profiles and survival relative to ivosidenib
- Clinical inputs
  - Duration of therapy and number of cycles
    - Interventions requiring induction and consolidation were assumed to have two cycles of treatment. Low dose cytarabine (LoDAC) and hypomethylating agents (HMAs) were administered for two and four cycles, respectively. Ivosidenib was assumed to be administered over the course of the EFS health state
  - Time to remission
    - Time to remission for ivosidenib was 12.17 weeks based on the phase 1 data (Agios data on file). For the remaining therapies, remission was assumed to be achieved upon completion of treatment
- Health State Utilities
  - Given a lack of published information on baseline HRQoL (without treatment-based adjustments) in the R/R AML population, health state utilities were derived from the published literature based on a first-line AML population (**Table 1**)
- AEs
  - AE rates were derived from the selected clinical studies for each comparator. The model only considered AEs of grade 3 or higher occurring in 5% or more of patients within each study
  - AE disutility values were derived from the literature. No disutility values were identified for tumor lysis syndrome or differentiation syndrome. Infection was used as a proxy for these conditions (**Table 2**)
  - The total disutility due to adverse events for each comparator was calculated using an additive approach. For each AE, the incidence rate was multiplied by the disutility, and these weighted disutilities were summed for each comparator in the model. The total disutility due to AEs was applied in the first model cycle

Table 1: Health State Utility Values

	Mean (SE)
Baseline AML	0.550 (0.05)
Utility of non-intensive therapy/ salvage/best supportive care	0.499 (0.05)
Remission	0.656 (0.05)
Disutility associated with induction/ consolidation	-0.155 (0.16)

Sources: Kansal 2017, Matza 2017

Table 2: AE Rates and Disutilities

	Disutility	Source for Disutility/Assumptions
Anemia	-0.090	Beusterien 2010
Arrhythmia	-0.020	ICER 2017
Bacteremia	-0.218	Stein 2017
Diarrhea	-0.176	Stein 2017
Dyspnea	-0.219	Lachaine 2015a
Electocardiogram QT Prolonged	0.000	Clinical opinion; Lachaine 2015b
Enterococcal Bacteremia	-0.218	Stein 2017
Fatigue	-0.073	Nafees 2008
Febrile Neutropenia	-0.090	Nafees 2008
Fungal Infection	-0.218	Stein 2017
Hemorrhage	-0.131	Lachaine 2015a
Hyperbillirubinemia	-0.218	Stein 2017
Hyperglycemia	-0.060	Nafees 2016
Hypertension	-0.020	ICER 2017
Hypoalbuminemia	0.000	Assumption
Hypocalcemia	0.000	Assumption
Hypokalemia	0.000	Assumption
Hyponatremia	0.000	Assumption
Hypophosphatemia	0.000	Assumption
Hypotension	-0.020	ICER 2017
Hypoxia	-0.219	Lachaine 2015a
IDH Differentiation Syndrome	-0.218	Stein 2017 - assumed same as infection
Increased Alanine Aminotransferase	0.000	Assumption
Increased Aspartate Aminotransferase	0.000	Assumption
Infection	-0.218	Stein 2017
Leukocytosis	-0.090	Nafees 2008
Leukopenia	-0.090	Nafees 2008
Liver Toxicity	-0.218	Stein 2017
Lymphopenia	-0.090	Nafees 2008
Mental Status Changes	-0.073	Nafees 2008
Mucositis or Stomatitis	-0.060	Stein 2017
Nausea	-0.048	Nafees 2008
Neutropenia	-0.090	Nafees 2008
Non-Conduction Cardiotoxicity	-0.020	ICER 2017
Pain	-0.105	Lachaine 2015a
Pneumonia	-0.218	Stein 2017
Pneumonitis or Pulmonary Infiltrates	-0.218	Stein 2017
Pyrexia	-0.110	Beusterien
Rash	-0.060	Stein 2017
Renal Failure	-0.218	Stein 2017
Sepsis	-0.218	Stein 2017
Staphylococcal Bacteremia	-0.218	Stein 2017
Thrombocytopenia	-0.090	Nafees 2008
Tumor Lysis Syndrome	-0.218	Stein 2017 - assumed same as infection
Urinary Tract Infection	-0.218	Stein 2017

- As the ivosidenib clinical trial was a single arm study in mIDH1 R/R patients and comparator publications in the same population could not be identified in the literature, several scenarios were explored to test robustness of model results:
  - **Minimum AE method:** Recognizing that the additive approach to AE disutilities potentially over-estimates the overall AE impact on HRQoL for more toxic therapies, a decrement based on the single the most impactful AE (e.g. the AE that contributes the most towards total disutility) was used for each comparator
  - **Varying health state utilities:** Given that the utility values were from the first-line setting, these values were varied by +/- 20% to understand their impact on model results
  - **Varying AE disutilities:** With disutility values being derived from a variety of sources, these values in the model were varied by +/- 20%

RESULTS

- Base Case Results (**Table 3**)
  - Assuming ivosidenib survival is identical to comparators (e.g. no relative survival benefit assumed), ivosidenib produces slightly more QALYs versus comparators, while using the survival data from Faderl, 2012 for comparators the relative QALYs gained with ivosidenib increased, driven by gains in LYs

Table 3: Base Case Results

Intervention	Using ivosidenib survival data for all treatments				Using literature-based survival for comparators			
	LYs	Ivosidenib Incremental LYs	QALYs	Ivosidenib Incremental QALYs	LYs	Ivosidenib Incremental LYs	QALYs	Ivosidenib Incremental QALYs
Ivosidenib	0.915		0.399		0.915		0.399	
LoDAC	0.915	0.000	0.369	0.030	0.834	0.081	0.341	0.058
HMAs	0.915	0.000	0.301	0.098	0.834	0.081	0.278	0.121
Daunorubicin and cytarabine fixed dose	0.915	0.000	0.030	0.369	0.834	0.081	0.023	0.376
7+3	0.915	0.000	0.257	0.142	0.834	0.081	0.239	0.160
HiDAC	0.915	0.000	0.135	0.264	0.834	0.081	0.123	0.276
Other HIC	0.915	0.000	0.316	0.083	0.834	0.081	0.295	0.104
Midostaurin+ chemotherapy	0.915	0.000	0.000	0.399	0.834	0.081	0.000	0.399

Abbreviations: LoDAC: low dose cytarabine; HMAs: hypomethylating agents; HiDAC: high dose cytarabine; HIC: high intensity chemotherapy

- Scenario Analysis
  - Minimum AE Method
    - The most impactful AEs used for each comparator were infections and hematological events. While the decrements are much smaller than in the base case with the additive approach, ivosidenib remains the most favorable intervention under both survival modeling approaches (**Table 4**)
  - Scenarios examining the impact of changing health state utilities and AE disutilities did not change model trends from the base case (**Table 4**)

Table 4: Disutility Results

Intervention	Base Case	Minimum AE method	Varying Disutilities +20%	Varying Disutilities -20%
Ivosidenib	**-0.129**	**-0.025**	**-0.155**	**-0.103**
LoDAC	-0.166	-0.041	-0.199	-0.133
HMAs	-0.225	-0.078	-0.270	-0.180
Daunorubicin and cytarabine fixed dose	-0.485	-0.090	-0.582	-0.388
7+3	-0.251	-0.046	-0.301	-0.201
HiDAC	-0.377	-0.087	-0.452	-0.301
Other HIC	-0.190	-0.044	-0.228	-0.152
Midostaurin+ chemotherapy	-0.580	-0.114	-0.697	-0.464

DISCUSSION

- This analysis showed that ivosidenib consistently produces greater QALYs versus other interventions in mIDH1 R/R AML patients
  - These results are conservative, as they do not take into account other potential benefits of ivosidenib, which can include the convenience of oral administration, the impact of stable disease, lower hospitalization rates for administration and the reduced need for transfusions
  - Given the lack of head-to-head data in the phase 1 ivosidenib trial and the limited number of published studies in the R/R AML population with both EFS and OS data, the Faderl 2012 study was used as a proxy. This data may not be representative of the population studied in the phase 1 ivosidenib trial, as it was based on patients who had received ≤2 prior regimens (Faderl 2012) and thus would be expected to demonstrate better EFS and OS than patients in the ivosidenib trial who had received a median of 2 prior regimens
- There are several additional limitations to note in this analysis:
  - Health state utilities were from the first-line AML population and AE disutilities were derived from the broader oncology literature base. However, scenario analyses varying these values produced the same trends as seen in the base case analysis
  - Patient management in R/R AML is dependent on response to treatment. This analysis simplified the pathway and assumed a conservative duration of treatment for model comparators (2 induction/ consolidation cycles, median number of cycles for other therapies)

CONCLUSIONS

- Given the potential for improved survival and its favorable AE profile versus other R/R AML therapies, ivosidenib is expected to improve HRQoL over patients' lifetimes in the mIDH1 R/R AML population
- When varying the AE disutility approach, as well as health state utility and AE disutility, the results consistently showed that ivosidenib produces greater QALYs versus other R/R AML comparators
- A key area for future research is to gather more detailed information on baseline HRQoL in the R/R AML population and use follow-up trials, other prospective studies, or historical controls to better understand patient outcomes for mIDH1 patients on new treatments, such as ivosidenib

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