Budget impact analysis of ivosidenib in combination with azacitidine for the treatment of previously untreated mIDH1 positive acute myeloid leukaemia (AML) patients, ineligible for intensive induction chemotherapy in Greece

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ISPOR Europe 2024 | Barcelona, Spain| 17 - 20 November 2024 EE282

Introduction

- Acute Myeloid Leukemia (AML) is a malignancy of hematopoietic stem cells, characterised by impaired cell differentiation, leading to the buildup of immature blood cells in the bone marrow and decreased production of healthy blood cells, diagnosed through bone marrow aspirates and peripheral blood examination [1, 2].
- AML can occur at any age but is most common in older adults, particularly those aged 85-89 [3], with a higher prevalence in males (57%) than females (43%) [4].
- AML treatment typically involves intensive chemotherapy (IC) with anthracyclines and high-dose cytarabine, followed by consolidation or stem-cell transplantation. For patients ineligible for IC, non-intensive therapies such as hypomethylating agents or venetoclax combined with azacitidine (AZA) are used [5-9].
- Ivosidenib (IVO), a targeted isocitrate dehydrogenase 1 mutated (mIDH1) inhibitor, is approved by European Medicines Agency (EMA), in combination with AZA for AML patients with mIDH1 mutations who are ineligible to receive standard induction chemotherapy [10].
- In the AGILE phase 3 clinical trial, the primary overall survival (OS) results were sustained with long-term follow-up, showing a median OS of 29.3 months for patients receiving IVO+AZA versus 7.9 months for those receiving placebo (PBO+ AZA) [11].

Objective

To estimate the budgetary impact from the introduction of IVO+AZA in previously untreated patients with mIDH1+ AML, ineligible for intensive induction chemotherapy in Greece.

Methodology

- An international BIM model was locally adapted to assess the budget impact of introducing IVO into the treatment mix for previously untreated AML patients with mIDH1, who are ineligible for IC (**Table 1**), from the perspective of the Greek National Public Payer (EOPYY).
- The model compares two scenarios: the "baseline scenario" (current market shares of available treatments) and the "projected scenario" (market share changes after IVO's introduction) over a five-year period (2025–2029).
- No discount rate was applied due to the short-term nature of the analysis.
- Treatment-specific annual mortality rates were included in the analysis, highlighting the low mortality rate associated with IVO (**Table 2**).
- Local market share estimates with and without IVO were based on Servier Hellas market forecast estimates (**Table 3**).
- All costs were considered from EOPYY perspective and were extrapolated to 2024 values (€) (**Table 4**).
- The treatment acquisition costs were calculated based on their ex-factory prices as they were published in the latest drug price bulletin issued by the Greek ministry of health [12], after applying all legal discounts.

Results

- The introduction of IVO will increase the number of AML patients under treatment, with projections showing a rise from 14 to 37 patients between the first and fifth years of analysis.
- The overall costs associated with the use of IVO are expected to increase by €198,381 in the first year and €1,380,295 in the fifth year due to its progressive market utilization for AML patients with mIDH1 who are ineligible for IC (**Table 5 and Figure 1**).
- Sensitivity analyses showed no major differences compared to the base case results. Under all sensitivity scenarios, the reimbursement of IVO in the AML market in Greece resulted in a limited budget impact for the payer, considering its promising clinical benefits for patients with mIDH1 who are ineligible to receive IC.

Conclusion

The inclusion of IVO for AML treatment was predicted to result in an annual average budget impact of €804,074, over a five-year time frame. This increase is rather limited, especially considering the low annual mortalities associated with IVO, which in turn lead to an increase in the total number of patients under treatment.

Table 1: Eligible patient population inputs

	% of patients	Number of patients	Source
Incident AML patients	0.005%	427	Internal data
mIDH1 positive patients	8.00%	34	Bullinger 2017 [13]
% of AML patients ineligible to receive IC	40.00%	14	Internal data; NICE TA 765 [14]

Figure 1: Incremental budget impact analysis results

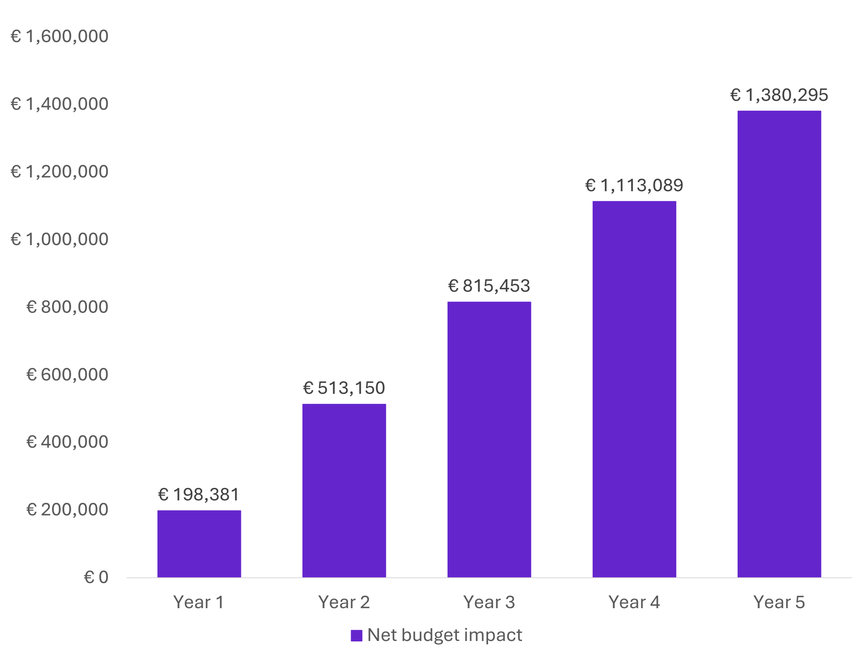

Table 2: Treatment specific annual mortalities

	Annual mortalities	Source
Ivosidenib + azacitidine	22.30%	Calculated based on the KM from AGILE June 30, 2022 data cut
Azacitidine	42.40%	Calculated based on the KM from AGILE June 30, 2022 data cut
Venetoclax + azacitidine	34.80%	Calculated based on the pseudo KM from VIALE-A ASH 2022
Decitabine	66.05%	Calculated based on the median OS reported in Cashen 2010 [15]

Table 3: Five- year market shares with and without Ivosidenib

Market share in baseline scenario					
	Year 1	Year 2	Year 3	Year 4	Year 5
Ivosidenib + Azacitidine	0%	0%	0%	0%	0%
Azacitidine	39%	33%	30%	30%	30%
Venetoclax + Azacitidine	59%	66%	70%	70%	70%
Decitabine	2%	1%	0%	0%	0%
Market share in projected scenario					
	Year 1	Year 2	Year 3	Year 4	Year 5
Ivosidenib + Azacitidine	10%	20%	30%	40%	50%
Azacitidine	29%	16%	8%	4%	4%
Venetoclax + Azacitidine	59%	63%	62%	56%	46%
Decitabine	2%	1%	0%	0%	0%

Table 4: Dosing scheme and costs used in the analysis

Drug acquisition and route of administration						
Treatment	Unit Strength (mg)	Pack size	IV	SC	Oral	Sources
Ivosidenib + Azacitidine						
Ivosidenib	250	60	0%	0%	100%	
Azacitidine	100	1	0%	100%	0%	
Azacitidine (monotherapy)	100	1	0%	100%	0%	AGILE SCR [16]; DiNardo 2020 [17]; Local clinical experts.
Venetoclax + Azacitidine						
Venetoclax	100	112	0%	0%	100%	
Azacitidine	100	1	0%	100%	0%	
Decitabine	50	1	50%	50%	0%	
Concomitant Medication and Subsequent Treatments Costs						
Medication	**Unit strength (mg or ml)**	**Pack size**	**Package cost (€)**			**Source**
Ondansetron	4	15	11.91			Latest available reimbursement List of medicines issued by the Greek Ministry of Health
Meropenem	1000	10	85.98			
Piperacillin sodium; tazobactam sodium	2g; 250mg	1	2.44			
Levofloxacin	250	10	3.34			
Potassium chloride	1700	100	4.93			
Metoclopramide	10	20	1.76			
Furosemide	40	12	1.22			
Allopurinol	100	30	1.28			
Hydroxycarbamide	500	100	26.03			
Adverse Events						
Adverse Event	**Cost per episode (inflated to 2024)**	**Source**				
Anaemia	€ 92	Loupas, M.A., et al., 2022 [18]				
Bacteraemia	€ 498	Government gazzette (FEK B' 7262/21-12-2023); DRG R65B				
Decreased appetite	€ 55	Loupas, M.A., et al., 2022 [18]				
Diarrhoea	€ 78	Loupas, M.A., et al., 2022 [18]				
Dyspnoea	€ 24	Data on file				
Electrocardiogram QT prolonged	€ 946	Data on file				
Fatigue	€ 49	Loupas, M.A., et al., 2022 [18]				
Hypokalaemia	€ 18	Loupas, M.A., et al., 2022 [18]				
Hyponatraemia	€ 289	Gourzoulidis, G., et al., 2018 [19]				
Hypotension	€ 56	Gourzoulidis G.,et al., 2020 [20]				
Other infections (excl. pneumonia)	€ 148	Data on file				
Leukopenia	€ 138	Loupas, M.A., et al., 2022 [18]				
Neutropenia	€ 117	Data on file				
Neutrophil count decreased	€ 189	Data on file				
Platelet count decreased	€ 174	Gourzoulidis, G., et al. 2022 [21]				
Pneumonia	€ 1,053	Data on file				
Syncope	€ 1,326	Government gazzette (FEK B' 7262/21-12-2023); DRGs F70A & F70B				
Sepsis	€ 2,490	Loupas, M.A., et al., 2022 [18]				
Thrombocytopenia	€ 113	Data on file				
Differentiation syndrome	€ 1,150	Government gazzette (FEK B' 7262/21-12-2023); DRG R63H				

Table 5: Base-case budget impact analysis results

	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost without ivosidenib in the market (Baseline scenario)	€738,026	€893,244	€975,913	€1,011,102	€1,032,633
Total cost with ivosidenib in the market (Projected scenario)	€936,407	€1,406,394	€1,791,365	€2,124,191	€2,412,927
Annual incremental cost of introduction of ivosidenib	€198,381	€513,150	€815,453	€1,113,089	€1,380,295

AML: Acute Myeloid Leukemia; AZA: azacitidine; EMA: European Medicines Agency; FDA: Food and Drug Administration; IC: intensive chemotherapy; IVO: Ivosidenib; mIDH1: targeted isocitrate dehydrogenase 1 mutated.

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