Cost-Effectiveness of Pembrolizumab in Combination With Chemotherapy for the Treatment of Patients With Locally Advanced or Metastatic *HER2*-Negative Gastric or Gastroesophageal Cancer in Mexico

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Introduction

- The incidence of gastric cancer varies worldwide and, despite advancements in diagnosis and treatment, the overall prognosis for advanced gastric cancer remains poor, with a 5-year survival rate of <30%, largely due to late-stage diagnosis[1,2]
- According to GLOBOCAN, there were over 968,000 new cases of gastric cancer in 2022, resulting in approximately 660,000 deaths. This positions gastric cancer as the fifth leading cause of death worldwide[3]
- In Mexico, approximately 9,516 people were diagnosed with gastric cancer in 2022, categorizing the country as having an intermediate incidence of gastric cancer, with rates ranging from 10 to 20 cases per 100,000 inhabitants. There were 7,226 reported deaths due to gastric cancer, making it the sixth leading cause of cancer deaths in Mexico among individuals >20 years old[4]
- Regarding gastroesophageal junction (GEJ) neoplasms, the majority are adenocarcinomas (90%), while the remainder is classified as squamous cell carcinomas or unspecified carcinomas. This information is supported by the Global Burden of Disease report[4]
- Gastric cancer imposes a large economic burden on health systems globally, with its average annual costs surpassing high-incidence cancers such as lung and colorectal cancers.[5] In Mexico in 2015, the annual cost of gastric cancer was estimated to be $4.7 billion[6]
- KEYNOTE-859 assessed pembrolizumab with chemotherapy vs placebo with chemotherapy for first-line treatment of *HER2*-negative, locally advanced unresectable, or metastatic gastric or GEJ adenocarcinoma. Results indicated significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) for those receiving pembrolizumab[7]

Objective

This study evaluated the cost-effectiveness of pembrolizumab in combination with chemotherapy for the treatment of patients with locally advanced unresectable or metastatic *HER2*-negative gastric or GEJ adenocarcinoma in Mexico from the public payer´s perspective

Methods

- A 3–health state partitioned survival model was used to project health outcomes for patients over a lifetime time horizon using data from the KEYNOTE-859 trial. The health states were progression-free (PF), progressed disease (PD), or death
- The perspective was that of the Mexican public payer. Costs and outcomes were calculated over a time horizon of 5 years for the base case analysis. The costs in Mexican pesos included drug acquisition, drug administration, adverse event (AE),t, subsequent treatment, disease management, progression cost, and end of life. For the scenario analysis, costs and outcomes were calculated over a time horizon equivalent to 10 years, 20 years, and lifetime, ie, 30 years; results reflected the discount of 5%
- Indirect treatment comparison through network meta-analysis (NMA) was used to evaluate the relative effects of various interventions. NMA synthesizes data from multiple randomized controlled trials, even when treatments are not directly compared within each trial. It integrates both direct and indirect evidence to provide comprehensive estimates of treatment effects, assuming there are no systematic differences in study or patient characteristics
- The NMA results included estimates of each intervention's effects relative to the reference treatment (pembrolizumab + fluoropyrimidine-platinum doublet FP/LT), summarized by medians and 95% confidence intervals derived from the posterior distributions. Time-to-event outcomes, including OS and PFS, were analyzed using both constant and time-varying hazard ratios
- An incremental cost-effectiveness ratio (ICER) was calculated using the incremental life-years (LYs) for the outcomes and costs of treatment and management with pembrolizumab + chemotherapy vs nivolumab + doublet chemotherapy in patients with locally advanced unresectable or metastatic *HER2*-negative gastric or GEJ adenocarcinoma. Additionally, the net monetary benefit (NMB), which measures the net benefit measured in cost compared with an accepted threshold was calculated. The model was parametrized using data from the KEYNOTE-859 trial for the pembrolizumab + chemotherapy (intervention arm). Utility inputs were derived from the EuroQoL 5-dimension 5-level (EQ-5D-5L) data collected in KEYNOTE-859 using a Mexican values set[8]

Table 1. Overview of model inputs and data sources

Model input	Data sources
Eligible patient characteristics	KEYNOTE-859 trial
Dosage, treatment duration, AE rates, subsequent treatments and durations	KEYNOTE-859 trial and pivotal clinical trials to inform comparator data
OS/PFS	Network Metanalysis
Disease management costs and associated frequencies	Costos Unitarios IMSS 2024, Tabulador de cuotas de recuperación, INCAN 2024, Gómez-Ulloa et al. (2020)
Progression cost	Costos Unitarios por Nivel de Atención Médica, IMSS 2024
Drug acquisition and administration cost	Costos Unitarios por Nivel de Atención Médica, IMSS 2024
AE treatment costs	Grupos Relacionados con el Diagnóstico Hospitalario, IMSS 2017
Utility data	KEYNOTE-859 trial data using Mexican algorithm

Results

Base case analysis

In the ITT population, the cost effectiveness (CE) results are presented in **Table 2**. Pembrolizumab + chemotherapy dominated nivolumab + doublet chemotherapy, which implies that the intervention is cost saving compared to nivolumab + doublet chemotherapy. Pembrolizumab + chemotherapy was estimated to provide an incremental LY gain of 0.029 LY per patient and a cost reduction of $104,656 compared to nivolumab + doublet chemotherapy (ICER -3,568,160). Most of the additional cost of nivolumab + doublet chemotherapy compared to pembrolizumab + chemotherapy was due to additional drug administration, disease management, progression, subsequent treatment and terminal care costs.

Table 2. Cost-effectiveness deterministic results

Comparator	Total costs (MXN$)	Total LYs	Incremental costs (MXN$)	Incremental LYs	ICER (MXN$/LY)	NMB
NIVO + CHEMO	$2,951,854	1.72	-	-	-	-
PEM + CHEMO	$2,847,198	1.75	-$104,656	0.029	Dominant	$125,973

CE, cost-effectiveness; CHEMO, chemotherapy; NIVO, nivolumab; PEM, pembrolizumab.

- The probabilistic results were in line with the deterministic results. CE probabilistic results are presented in **Table 3**

Table 3. Cost-effectiveness probabilistic results

Comparator	Total costs (MXN$)	Total LYs	Incremental costs (MXN$)	Incremental LYs	ICER (MXN$/LY)	NMB
NIVO + CHEMO	$2,953,317	1.71	-	-	-	-
PEM + CHEMO	$2,838,441	1.75	-$114,876	0.033	Dominant	$125,973

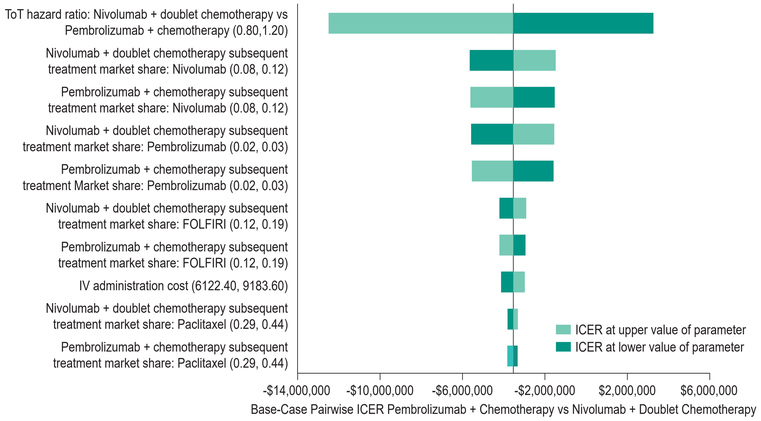
Scenario analysis results for the ITT population

Within the scenario analysis, costs and outcomes were calculated over a lifetime horizon (30 years) and pembrolizumab + chemotherapy were dominant: -$1,627,579. At a WTP threshold of MXN$726,768 per LY gained, the NMB of Pembrolizumab + chemotherapy was $125,973 compared with nivolumab + doublet chemotherapy.

Sensitivity analyses

The Deterministic sensitivity analisys (DSA) showed that when varying model inputs by either their reported 95% CI, ±20%, or using standard error, the model is most sensitive to changes in time on treatment (ToT) hazard ratio (assumed to be the same as the PFS hazard ratio), followed by proportions of patients receiving subsequent treatments and intravenous administration costs. As the ToT hazard ratio has such a large impact on the ICER, the lower value of the parameter (0.80) leads to an ICER of -$12,459,174 (**Figure 1**)

Figure 1. Tornado diagram



Conclusions

Over a five-year horizon, pembrolizumab + chemotherapy resulted in a total cost saving of -$104,656 compared to nivolumab with doublet chemotherapy for patients with locally advanced or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma within Mexico's healthcare system. This analysis demonstrated that pembrolizumab combined with chemotherapy was the dominant strategy.

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