ORIGINAL ARTICLE
ARTIGO ORIGINAL

Economic evaluation of the SP142 versus 22C3 PD-L1 assays in the treatment of atezolizumab plus *nab*-paclitaxel for patients with advanced triple negative breast cancer in the Brazilian private healthcare system

Avaliação econômica dos testes de PD-L1 SP142 versus *22C3 no tratamento com atezolizumabe mais nab-paclitaxel em pacientes com câncer de mama triplo-negativo avançado no sistema de saúde suplementar no Brasil*

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Keywords:
SP142, TNBC, economic evaluation

ABSTRACT

Objective: The aim of the study was to demonstrate the economic impact of two PD-L1 immunohistochemistry (IHC) assays, SP142 versus 22C3, in the treatment with atezolizumab plus *nab*-paclitaxel in patients with advanced triple negative breast cancer (aTNBC) in the Brazilian private healthcare system (BPHS). **Methods:** The study performed two analyses: one per patient and other of the potential population projected for the BPHS (budget impact analysis). Data of progression-free survival and overall survival were extracted from a post hoc analysis of the IMpassion130 trial to develop a partitioned-survival model to simulate the economic impact of the treatment with atezolizumab plus *nab*-paclitaxel guided by the SP142 and 22C3 assays on patients with aTNBC. The analyses included only direct costs that were based on CBHPM (*Classificação Brasileira Hierarquizada de Procedimentos Médicos*) and CMED (Câmara de Regulação do Mercado de Medicamentos) PF18% tables. A univariate sensitivity analysis was performed with the parameters varying ± 20%. **Results:** The study has demonstrated that the SP142 assay has the potential to save –BRL 179,730 with the treatment of atezolizumab plus *nab*-paclitaxel per patient with aTNBC in five years. **Conclusion:** The SP142 assay can optimize the use of atezolizumab plus *nab*-paclitaxel avoiding its prescription in patients who will not have a significant clinical improvement.

Palavras-chave:
SP142, CMTN, avaliação econômica

RESUMO

Objetivo: O objetivo do estudo foi demonstrar o impacto econômico de dois testes de imuno-histoquímica, SP142 versus 22C3, no tratamento com atezolizumabe + *nab*-paclitaxel em pacientes com câncer de mama triplo-negativo avançado (CMTNa) no sistema de saúde suplementar (SSS) no Brasil. **Métodos:** O estudo realizou duas análises: uma por paciente e outra na população potencial projetada para o SSS (análise de impacto no orçamento). Dados de sobrevida livre de progressão e de sobrevida global foram extraídos da análise *post hoc* do estudo IMpassion130 para o desenvolvimento de um modelo de sobrevida particionado que simulasse o impacto econômico do tratamento com atezolizumabe + *nab*-paclitaxel direcionado pelos testes SP142 e 22C3 em pacientes com CMTNa. A análise considerou somente os custos diretos baseados nas tabelas CBHPM (Classificação Brasileira Hierarquizada de Procedimentos Médicos) e CMED (Câmara de Regulação do Mercado de Medicamentos) PF18%. Uma análise de sensibilidade univariada foi realizada variando os parâmetros em ± 20%. **Resultados:** O estudo demonstrou que o teste SP142 apresenta um

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potencial de economia de -179.730 reais (BRL) no tratamento de atezolizumabe + *nab*-paclitaxel por paciente com CMTNa em cinco anos. **Conclusão:** O uso do teste SP142 possibilita otimizar o uso de atezolizumabe + *nab*-paclitaxel evitando a sua prescrição em pacientes que não irão se beneficiar de forma significativa.

Introduction

Breast cancer is the most prevalent cancer among women globally. Regardless of the country's socioeconomic status, the incidence of this type of cancer occupies the first positions among female malignancies. In 2018 there were 2.1 million new cases worldwide, which is equivalent to 11.6% of all estimated cancers (Bray *et al.*, 2018; Ferlay *et al.*, 2019).

In Brazil, according to the National Cancer Institute (INCA) 66,280 new cases of breast cancer are estimated in 2020. Without considering non-melanoma skin tumors, female breast cancer is the first most frequent cancer in all Brazilian regions (Instituto Nacional de Câncer José Alencar Gomes da Silva, 2019).

Breast cancer has several molecular subtypes defined based on gene expression patterns (Perou *et al.*, 2000). The characterization of this heterogeneity defines how the patients will be treated. The main breast cancer subtypes are defined by three tumor markers: estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2–neu (HER2) (Howlader *et al.*, 2014). These subtypes determine the possibility of treatment such as hormones and anti-HER2 therapies (Prado-Vazquez *et al.*, 2019).

Triple negative breast cancer (TNBC) comprises a heterogeneous subgroup defined by a lack of ER and PR expression and a lack of HER2 overexpression (Pal *et al.*, 2011; Prado-Vazquez *et al.*, 2019). TNBC accounts for around 15% of all breast cancers (Pal *et al.*, 2011) and it has an aggressive clinical course and a poor prognosis. Unlike other subtypes that overexpress hormone receptors or HER2, TNBC is not responsive to hormone therapy or HER2-directed agents such as trastuzumab (Haffty *et al.*, 2006; Bauer *et al.*, 2007; Dent *et al.*, 2007; Morris *et al.*, 2007; Rakha *et al.*, 2007). These factors highlight the need for new alternatives of treatment for those patients (Pal *et al.*, 2011).

Atezolizumab is a monoclonal antibody that acts as an immunotherapy, binding to programmed cell death ligand 1 (PD-L1) and enhancing T-cell activity against tumor cells (Krishnamurthy & Jimeno, 2017). Its efficacy and safety have been shown in a phase III study, IMpassion130, which assessed the anticancer activity of atezolizumab plus *nab*-paclitaxel compared with placebo plus *nab*-paclitaxel in patients with untreated advanced TNBC (aTNBC) (Schmid *et al.*, 2018).

The results of the study have demonstrated superiority of the atezolizumab plus *nab*-paclitaxel therapy with a significant improvement in overall survival (OS) compared to placebo plus *nab*-paclitaxel (25.0 versus 15.5 months; hazard ratio = 0.62; 95% CI 0.45 to 0.86), as well as in progression-free survival (PFS) (7.5 versus 5.0 months; hazard ratio = 0.62; 95% CI 0.49 to 0.78; P < 0.001) in PD-L1 positive patients (Schmid *et al.*, 2018).

In a post hoc analysis of IMpassion130, the 22C3 and SP263 PD-L1 IHC assays were evaluated for analytical agreement with SP142 and their association with clinical activity of atezolizumab plus *nab*-paclitaxel. This analysis showed that the SP142 assay can identify aTNBC patients most likely to benefit from the treatment with atezolizumab plus *nab*-paclitaxel (Rugo *et al.*, 2019).

The study aimed to estimate the economic impact of the SP142 and 22C3 assays in the first line treatment with atezolizumab plus *nab*-paclitaxel of patients with aTNBC in the private healthcare system in Brazil.

The study compared only two PD-L1 IHC assays SP142 versus 22C3, because patients with SP142 negative and 22C3 positive results did not demonstrate significant clinical benefit with atezolizumab plus *nab*-paclitaxel compared to *nab*-paclitaxel in PFS (hazard ratio = 0.81; 95% CI, 0.61 to 1.09) and OS (hazard ratio = 0.92; 95% CI, 0.64 to 1.31) (Rugo *et al.*, 2019).

Methods

Eligible patient

The study considered the patients diagnosed with aTNBC who lack ER and PR expression and also lack HER2 overexpression. Patients with aTNBC were considered eligible to atezolizumab plus *nab*-paclitaxel if they were positive for PD-L1 expression.

Intervention

The PD-L1 assays evaluated in this study were: SP142 (tumor-infiltrating immune cells 1%) and 22C3 (combined positive score 1). Both assays were compared due to the post hoc analysis of IMpassion130 evaluated the association of their results with clinical activity of atezolizumab plus *nab*-paclitaxel (Rugo *et al.*, 2019). The study compared only SP142 assay with 22C3 assay because patients with SP142 negative and 22C3 positive did not demonstrate a significant clinical benefit for PFS and OS (Rugo *et al.*, 2019).

Time horizon

The horizon recommended by the National Guidelines for the elaboration of budget impact analysis is five years (Ministério da Saúde [Brasil]. Secretaria de Ciência-Tecnologia e Insumos e Tecnologia, 2014).

Perspective

The perspective of the study was the Brazilian Private Healthcare system. In Brazil, patients with health insurance have access to outpatient cancer therapies, therefore they have access to atezolizumab and *nab*-paclitaxel. It is estimated a

coverage rate of 24.2% of the Brazilian population with health plan (Agência Nacional de Saúde Suplementar, 2020).

Model

The study was developed based on a decision model and a partitioned-survival model. Both models were used in this study in order to simulate the diagnostic result of PD-L1 assays (decision model) and to follow the patient under treatment (partitioned-survival model).

Decision model

The decision model was selected to simulate the eligibility of the patient for the combined treatment of atezolizumab plus *nab*-paclitaxel guided by the SP142 and 22C3 assays (Figure 1).

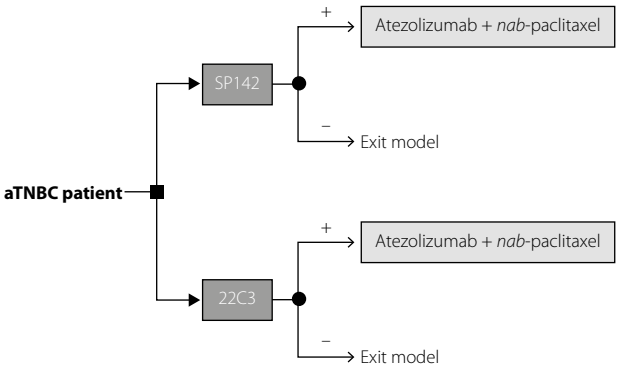


Figure 1. Decision model.

Only the patient positive for the SP142 or 22C3 assay was considered eligible for the treatment with atezolizumab plus *nab*-paclitaxel.

Partitioned-survival model

As the prescribing information for atezolizumab recommends the treatment until the disease progression, a partitioned-survival model was performed to follow the patients under treatment guided by the SP142 and 22C3 assays. The partitioned-survival model was used in order to simulate a dynamic scenario, in which new patients with positive results for PD-L1 expression are treated, while other patients stop treatment because they progress or die. The model assumed monthly cycles with a time horizon of 5 years. All patients started in the progression-free (PF) and could either transit to progression, transit to death, or remain PF.

Accuracy data

The accuracy data from the SP142 and 22C3 assays were extracted from a post hoc analysis of the IMpassion130 study (Rugo *et al.*, 2019). Prevalences of PD-L1 expression by SP142 (tumor infiltrating immune cells ≥ 1%) and 22C3 (positive combined score ≥ 1) were 46% and 81%, respectively (Rugo *et al.*, 2019). These results were used in the decision model for PD-L1 positive results in which 46% of the patients were positive with SP142 and 81% were positive with 22C3.

Clinical data

Clinical data were extracted from the PFS and OS curves of the post hoc analysis of IMpassion130 (Rugo *et al.*, 2019). The curves were projected for 5 years, through an exponential distribution for PFS and a log-logistic distribution for OS that presented the best fit of the data for both assays (Table 1).

Table 1. Parametric distribution

	PFS	OS
SP142	Exponential	Log-logistic
22C3	Exponential	Log-logistic

Use of resources and costs

Only the direct medical costs (diagnostic procedure, drug acquisition, management of adverse events) were considered. Indirect costs, which is the cost of lost productivity as a result of the morbidity, were not included.

Diagnostic procedure

The costs of PD-L1 IHC assays, SP142 and 22C3, were the only costs considered as a diagnostic procedure. The CBHPM table does not have a specific code for PD-L1. For the analysis the cost of both procedures was considered to be BRL 1,331.14, according to the CBHPM code 4.06.01.17-0 (Diagnostic procedure in an immunohistochemistry panel [two to five reactions]). This code was used because it is on the list of mandatory reimbursement procedures in the private healthcare system (Agência Nacional de Saúde Suplementar [ANS], 2018; Associação Médica Brasileira [AMB], 2018). It is important to highlight that most health insurances use their own tables with outdated value. However, the CBHPM table was used because it is considered the national reference for reimbursement of medical procedures.

Drug treatment

The unit costs of medicines were obtained from the price list of the Medicines Market Regulation Chamber (CMED) of March 2020, considering the factory price (PF 18%) (Câmara de Regulação do Mercado de Medicamentos (CMED), 2020). The posology of atezolizumab plus *nab*-paclitaxel therapy was based on the prescribing information for atezolizumab (Produtos Roche Químicos e Farmacêuticos S.A., 2020) (Table 2).

Unit cost of adverse events

In the study, only adverse events (AEs) of grade 3 or 4 of the combined therapy of atezolizumab plus *nab*-paclitaxel whose incidence rate was higher than 2% were considered. The frequencies of occurrence of each event were obtained from the pivotal study IMpassion130 (Schmid *et al.*, 2018). The micro-costing of adverse events was obtained through the standard use of resources as defined by expert opinion. The micro-costing considered the unit cost of medical procedures and drugs to manage the adverse events based

Table 2. Unit cost and dosages

Drug	Dosage	Reference	Price (PF 18%)
Atezolizumab	840 mg on days 1 and 15 for each cycle (28 days)	(Produtos Roche Químicos e Farmacêuticos S.A., 2020)	BRL 17,796.29
Nab-paclitaxel	100 mg per square meter on days 1,8 and 15 for each cycle (28 days)	(Produtos Roche Químicos e Farmacêuticos S.A., 2020)	BRL 1,035.94

on the price list of CMED and the CBHPM table (Associação Médica Brasileira [AMB], 2018; Câmara de Regulação do Mercado de Medicamentos [CMED], 2020) (Table 3).

Table 3. Adverse events unit cost

Events	Cost per event (BRL)
Anemia	5,432.30
Fatigue	439.38
Peripheral neuropathy	541.58
Peripheral sensory neuropathy	541.58
Neutropenia	5,118.10

Discount

An annual discount rate of 5% was applied for outcomes and costs in accordance with the recommendations of the Methodological Guidelines for Economic Assessment Studies in Health Technologies, published by the Ministry of Health in Brazil (Ministério da Saúde [Brasil]. Secretaria de Ciência-Tecnologia e Insumos e Tecnologia., 2014).

Sensitivity analysis

For economic studies that support decision making, it is essential to quantify the uncertainties involved in their results and to identify the variables that most affect these uncertainties. In this study, a univariate sensitivity analysis was performed with parameters varying by ± 20%.

Budget impact analysis

The study performed two analyses: per patient (budget impact analysis per patient-individual simulation model) and on the potential population projected for the BPHS (budget impact analysis of the eligible patient population – population simulation model).

1. Budget impact analysis per patient

The analysis per patient assumed the follow-up of a patient tested by each of the diagnostic PD-L1 assay, SP142 and 22C3.

2. Budget impact analysis of eligible patient population

In order to estimate the maximum impact on BPHS, a budget impact analysis of total eligible patient population was developed. The population analysis considers a dynamic scenario, in which new patients are tested for PD-L1 expression and treated, if positive, with the combined therapy of atezolizumab plus *nab*-paclitaxel, while other patients are no longer treated either by progression or death.

2.1 Market share

In Brazil, the laboratories have the autonomy to choose the PD-L1 assay and therefore they can use an assay that is not approved as a companion diagnosis by the FDA.

In order to estimate the maximum budget impact of SP142 compared to 22C3 on the BPHS, two scenarios were considered: (1) patients tested only with SP142 and (2) patients tested only with 22C3 in order to estimate the maximum impact of the assays on the BPHS (Table 4).

2.2 Population eligible in the Brazilian Private Healthcare System (BPHS)

The patient flow for obtaining the population eligible for the SP142 and 22C3 assays considered the incidence of breast cancer in Brazil (approximately 66,280 new cases in 2020) (Instituto Nacional de Câncer José Alencar Gomes da Silva, 2019). A rate of 15% was applied to these patients with TNBC (Pal *et al*., 2011) as well as the percentage of 21.6% in stages III and IV diagnosed with TNBC (calculated based on the study Howlader *et al*., 2014). Due to the lack of data for stage IIIb, the percentage of patients in stage III was used to calculate patients in advanced stage. As the perspective of the study is the BPHS, a health insurance coverage rate of 24.2% (April/2020) was applied to the final population (Agência Nacional de Saúde Suplementar, 2020) (Figure 2). The coverage rate of 24.2% is related to the population in Brazil who has a health plan.

The population of interest was projected for 5 years based on the population projection by the Brazilian Institute

Table 4. Market share

Scenario 1	2020	2021	2022	2023	2024
SP142	0%	0%	0%	0%	0%
22C3	100%	100%	100%	100%	100%
Scenario 2	**2020**	**2021**	**2022**	**2023**	**2024**
SP142	100%	100%	100%	100%	100%
22C3	0%	0%	0%	0%	0%

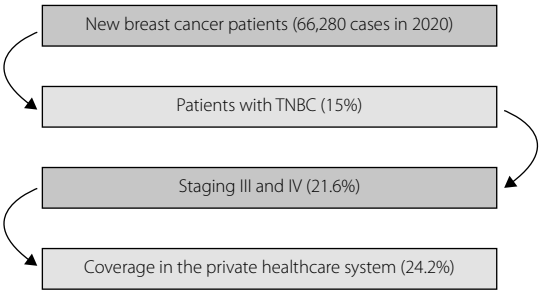
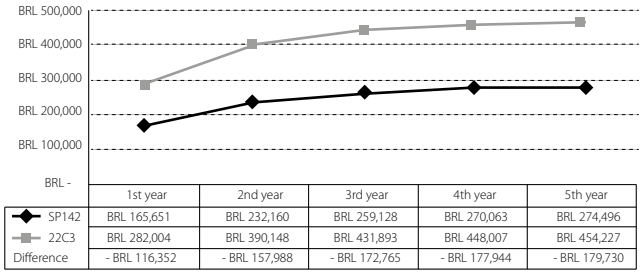


Figure 2. Patient flow.



	1st year	2nd year	3rd year	4th year	5th year
SP142	BRL 165,651	BRL 232,160	BRL 259,128	BRL 270,063	BRL 274,496
22C3	BRL 282,004	BRL 390,148	BRL 431,893	BRL 448,007	BRL 454,227
Difference	- BRL 116,352	- BRL 157,988	- BRL 172,765	- BRL 177,944	- BRL 179,730

Figure 3. Cost of treatment over the years per patient.

of Geography and Statistics (IBGE) (Instituto Brasileiro de Geografia e Estatística [IBGE], 2018).

Results

The results of the economic assessment per patient comparing the 5-year economic impact of the SP142 versus 22C3 assays are shown in Table 5.

The evaluation of PD-L1 expression by the SP142 assay can generate savings of –BRL 179,730.42 with the combined treatment of atezolizumab plus *nab*-paclitaxel in five years compared to the 22C3 assay. This saving represents a reduction of 39.6% in costs per patient and it is determined, predominantly, by identifying the patient most likely to benefit from the combined therapy of atezolizumab plus *nab*-paclitaxel and avoiding its prescription in patients who will not benefit from it.

Figure 3 shows the expenditures on combined therapy guided by both assays over five years.

Univariate sensitivity analysis

The results of the sensitivity analysis are represented in the tornado diagram shown in Figure 4.

The univariate sensitivity analysis results showed that even though the model parameters were varied, the evaluation of treatment eligibility by the SP142 assay remains an economical alternative compared to the 22C3 assay.

Budget impact analysis

For the budget impact analysis, the results obtained by the patient flow are shown in Table 6.

The results of the analysis showed that the SP142 assay has a maximum potential to save approximately 1.2 billion BRL over five years with the treatment of atezolizumab plus *nab*-paclitaxel (Figure 5).

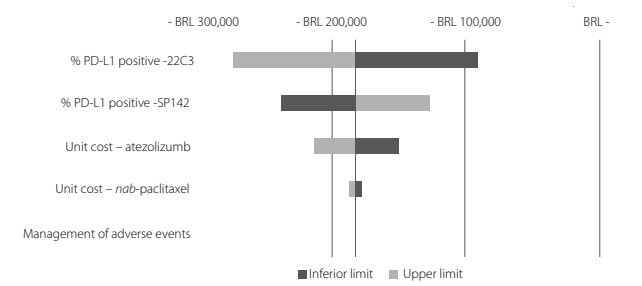


Figure 4. Tornado diagram.

Table 6. Population eligible for the assays

	2020	2021	2022	2023	2024
Patients eligible for the assays	520	524	527	531	534

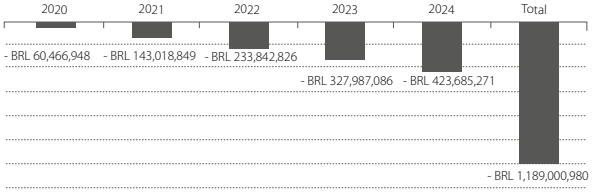


Figure 5. Budget impact analysis.

It is important to note that this analysis simulated a scenario in which all patients with aTNBC are tested for PD-L1 expression and if they were positive, they would be treated with atezolizumab plus *nab*-paclitaxel.

Table 5. Cost comparison results (per patient over 5 years)

	SP142	22C3	Difference
Procedures	BRL 1,331.14	BRL 1,331.14	BRL -
Cost of treatment	BRL 272,870.30	BRL 452,381.33	-BRL 179,511.03
Adverse events	BRL 294.94	BRL 514.33	-BRL 219.39
Total cost	BRL 274,496.38	BRL 454,226.80	-BRL 179,730.42

Discussion

Optimizing the use of health resources and controlling spending have been a challenge for healthcare systems. The adoption of high-quality diagnostic tests that can identify patients most likely to benefit from high-cost treatment and thus avoid waste with those who do not, can be a control mechanism.

Economic evaluations are useful studies to compare different technologies for the same pathology. Few studies have evaluated the economic impact of diagnostic tests on the optimization of high-cost therapies.

The present study aimed to show the importance of evaluating the expression of PD-L1 in patients with advanced TNBC by the SP142 assay, the only assay approved as a companion diagnostic test by the Food and Drug Administration (FDA) for the treatment of atezolizumab plus *nab*-paclitaxel in patients with aTNBC (U.S. Food and Drug Administration, 2020).

The post hoc analysis of the IMpassion130 study showed that patients identified by the SP142 assay are more likely to benefit from atezolizumab plus *nab*-paclitaxel (Rugo *et al.*, 2019). In addition to providing a greater clinical benefit, the present study demonstrated that the SP142 assay has the potential to bring savings to the system by optimizing the use of immunotherapy and avoiding its use in those patients who will not benefit from it.

Conclusion

The lack of knowledge of companion diagnostic tests by pathologists, oncologists and payers can have economic impact on the healthcare system. The present study demonstrated the importance of using a specific assay, SP142, to guide the treatment of atezolizumab plus *nab*-paclitaxel in patients with advanced TNBC.

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