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Cost-effectiveness of Immune Checkpoint Inhibitors and Chemotherapy in Triple-negative Breast Cancer: a Scoping Review

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ABSTRACT

Triple-negative breast cancer (TNBC) is an aggressive malignancy associated with poor clinical outcomes and substantial economic burden. Standard chemotherapy treatment offers limited survival benefits, whereas immune checkpoint inhibitors (ICIs) have broadened therapeutic options. This review evaluates the cost-effectiveness of ICIs compared to conventional chemotherapy in TNBC and aims to identify which ICI provides the most favorable economic value. Using the PICO framework, which focuses on TNBC patients receiving chemotherapy as intervention and ICIs as comparators. The primary outcomes include incremental cost-effectiveness ratio (ICER), quality-adjusted life years (QALYs), and/or life years gained (LYG). The articles were selected based on the PRISMA strategy. A comprehensive selection of articles published from January 2020 to December 2024 was analyzed from PubMed, Google Scholar, Cochrane, and Scopus. TNBC commonly shows high tumor T-cell infiltration and Programmed Death Ligand-1 (PD-L1) expression, making ICIs such as atezolizumab and pembrolizumab viable treatment options. Atezolizumab improved progression-free survival (PFS) but was not found to be cost-effective in Singapore or the U.S. Pembrolizumab, however, significantly improved event-free survival (EFS) and demonstrated cost-effective across multiple countries, including Egypt, the United States of America (USA), and Switzerland. Sacituzumab govitecan, despite survival benefits in metastatic TNBC, showed high ICERs and poor cost-effectiveness. Pembrolizumab combined with chemotherapy appears to be more cost-effective than atezolizumab for PD-L1-positive TNBC patients. Meanwhile, sacituzumab govitecan has not been demonstrated to be cost-effective.

ABSTRAK

Triple-negative breast cancer (TNBC) merupakan subtipe yang sangat agresif dan dikaitkan dengan luaran klinis yang buruk serta menyebabkan beban ekonomi yang substansial. Perawatan kemoterapi standar menawarkan manfaat kelangsungan hidup yang terbatas, sedangkan. *immune checkpoint inhibitors* (ICIs) telah memperluas pilihan terapi. Tinjauan ini bertujuan untuk mengevaluasi efektivitas biaya dari penggunaan ICIs dibandingkan dengan kemoterapi konvensional pada pasien TNBC, serta bertujuan mengidentifikasi jenis ICIs yang paling *cost-effective.* Tinjauan ini menggunakan kerangka PICO, yang berfokus pada pasien TNBC yang menerima kemoterapi standar sebagai intervensi dan ICIs sebagai pembanding. Luaran utama yang diamati meliputi *incremental cost-effectiveness ratio* (ICER), *quality-adjusted life years* (QALYs), dan/atau *life years gained* (LYG). Artikel yang digunakan pada tinjauan ini dipilih dengan mengikuti pedoman PRISMA> Pilihan artikel antara Januari 2020 hingga Desember 2024 dianalisis dari data PubMed, Google Scholar, Cochrane, dan Scopus. TNBC umumnya memiliki infiltrasi sel T tumor yang tinggi serta ekspresi PD-L, sehingga menjadikan ICIs, seperti atezolizumab dan pembrolizumab sebagai alternatif terapi yang rasional. Atezolizumab meningkatkan *progression-free survival* (PFS), namun tidak dinilai *cost-effective*, bahkan pada pasien dengan ekspresi PD-L1 positif. Sebaliknya, pembrolizumab menunjukkan peningkayan *event-free survival* (EFS) yang signifikan dan dinilai *cost-effective* di berbagai negara, termasuk mesir, Amerika, dan Swiss. Sacituzumab govitecan, meskipun memberikan manfaat kelangsungan hidup pada TNBC metastatik, menunjukkan nilai ICER yang tinggi dan efektivitas biaya yang buruk. Pembrolizumab yang dikombinasikan dengan kemoterapi dinilai lebih hemat biaya dibandingkan dengan atezolizumab untuk pasien TNBC positif PD-L1. Sementara itu, sacituzumab govitecan belum terbukti *cost-effective*.

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INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer globally among women. Breast cancer deaths are ranked fifth worldwide.[1] The number of breast cancer cases increases from year to year. In 2018, there were 2.1 million cases, and increase in 2020 with 2.23 million cases.[1,2] Triple-negative breast cancer (TNBC) is a type of breast cancer that lacks the expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptors.[2,3] It usually occurs in young, black women and accounts for around 15-20% of all breast cancers.[2]

TNBC is an aggressive disease that affects not only the health of patients but also imposes a significant economic burden on the broader community and healthcare centers. Additionally, TNBC patients have a much higher risk of recurrence and visceral metastasis, leading to worse clinical outcomes. The incidence of TNBC is more common among young people, resulting in a greater economic burden, with average direct medical costs ranging from $20,000 to over $100,000 per year for stages I-III and from $100,000 to $300,000 per year in stage IV TNBC. Furthermore, TNBC places a considerable economic burden from the perspective of the US Medicare, with the cumulative cost of treatment involving three or more chemotherapy regimens estimated at $143,150. The estimated cost of treatment with three or more chemotherapy regimens is $143,150.[4] In Indonesia, the Ministry of Health initiated the breast cancer control strategy in 2007 by the Ministry of Health, and the program includes general examinations in every primary health care facility for women between 30 and 50 years old. The screening also highly informs the patients to undergo the mammography examination, which is all covered by national health insurance. Yet, the challenge remains to overcome the disparities in the wide range of Indonesia's coverage (the accessibility). The trastuzumab-only study in Indonesia for breast cancer chemotherapy evaluated and showed cost-effectiveness with a value of US$6,428 per quality-adjusted life year (QALY) for ICER analysis.[5] A study led by Yuliana *et al*,[6] conducted in Hassanuddin University, Makassar, Indonesia, stated that the combination of chemotherapies of Paclitaxel, Epirubicin, and Cyclophosphamide is shown cost-effective with an average cost-effectiveness ratio (ACER) method, with a value of IDR 80,819, and ICER analysis with a value of IDR83,651.

Definitive surgical resection is the mainstay approach for the treatment of early-stage breast cancer. Treatment options for TNBC were previously limited. The National Comprehensive Cancer Network (NCCN) recommends anthracyclines or taxanes as preferred first-line chemotherapy options for patients who have not previously received these agents in the neoadjuvant or adjuvant setting, with specific dosing regimens outlined in the guidelines. Neoadjuvant chemotherapy has been the standard of care for high-risk early-stage TNBC (eTNBC). For metastatic TNBC (mTNBC), the standard chemotherapy includes taxanes, gemcitabine, and platinum-based agents. However, chemotherapy shows limited efficacy, with a median survival of 13.3 months, and these patients continue to face a high risk of recurrence and death. It is pointing to the urgent, unmet need for novel therapies that can augment the effectiveness of chemotherapy. The development of immunotherapies targeting immune checkpoint components such as PD-1 or its ligand (PD-L1) that suppress the T cell-mediated antitumor response has expanded the treatment options for TNBC. Their efficacy is also enhanced when they are used in combination with standard chemotherapy drugs.[4,7]

Phase III clinical trials showing efficacy by taking advantage of tumor DNA repair deficiencies linked to

BRCA1/2 mutations support treatment with poly (ADP-ribose) polymerase (PARP) inhibitors or platinum-based agents like cisplatin or carboplatin for people with BRCA mutations. In cases of disease progression following first-line therapy, the NCCN advises the sequential administration of alternative single-agent chemotherapies, maintained continuously as tolerated. For patients who are no longer responsive to or unable to tolerate chemotherapy, sacituzumab govitecan—a Trop-2-directed antibody-drug conjugate that delivers SN-38, the active metabolite of irinotecan—has been approved for use in this setting.[8]

There are currently few studies assessing the cost-effectiveness of immune checkpoint inhibitors (ICIs), given they are still relatively new in the treatment of triple-negative breast cancer (TNBC). Therefore, this scoping review aims to map existing evidence, identify gaps in the literature, and compare the cost-effectiveness of ICIs with current chemotherapeutic options for TNBC. This review specifically seeks to determine which ICI provides the most favorable economic value.

METHODS

Searching Strategy

The inclusion criteria for the research were based on the original article and presented by the PICO criteria (population, intervention, comparator, and outcome). The population studied consists of patients with TNBC who received chemotherapy as the intervention. Immune checkpoint inhibitors were used as comparators to standard chemotherapy for TNBC, with outcomes measured in terms of ICER, expressed as QALY and/or life years gained (LYG).

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Review (PRISMA-ScR) 2018 guidelines. Article searches were conducted using electronic databases such as PubMed, Google Scholar, Cochrane, and Scopus. The article search strategy used several keywords based on the PICO criteria, arranged using Boolean operators: “triple negative breast cancer” “chemotherapy” “immune checkpoint inhibitors” “cost-effectiveness” and “treatment”. The inclusion criteria used in this systematic review were (1) articles published between 2020 and 2024; (2) original research articles, (3) articles that are written in English. The selection process was conducted in two phases. First, titles and abstracts were screened independently by two reviewers (the authors S and H) based on the predefined inclusion criteria. Articles that met the eligibility criteria were then subjected to full-text screening for final inclusion by author V. In addition, author V evaluated the included studies using the CHEERS checklist to assess their quality. Author A and I served as independent reviewers who reviewed the entire scoping process to ensure the reliability of the methodology and findings.

Data analysis

The obtained articles were then subjected to an analytical approach with the following information: (1) type of cancer; (2) choice of therapy; (3) measured outcomes; (4) choice of model; (5) cycle length; (6) time horizon; (7) discount rate; (8) research perspective; (9) type of sensitivity analysis; (10) funding source. To conclude from the results of each study included in this review, ICER per QALY and/or LYG and cost-effectiveness threshold were used. Each study that met the inclusion and exclusion criteria was evaluated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria.

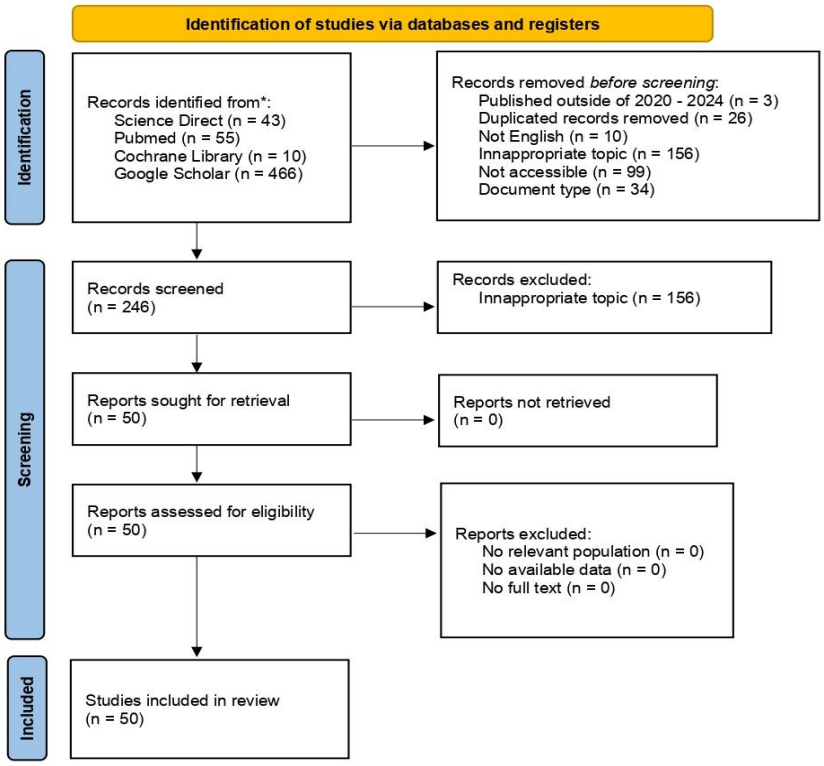

FIGURE 1. PRISMA flow diagram for the selection of eligible studies in this review

RESULTS

A total of 12 economic evaluation studies were included in this review covering various countries and perspectives. The studies evaluated the cost-effectiveness of ICIs or chemotherapy in TNBC using different clinical trial data, comparators, time horizons, and health system perspectives.

Atezolizumab plus nab-paclitaxel versus nab-paclitaxel alone was the subject of two investigations conducted in Singapore and the USA using data from the Impassion130 experiment. The Singapore study applied a 5-year time horizon while the US study used a 10-year time horizon, both applying a 3% discount rate.[9,10]

Five studies evaluated KEYNOTE-522 data, analyzing the cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus neoadjuvant chemotherapy alone. These studies were conducted in Switzerland, the US, Hong Kong, and Egypt, using perspectives ranging from third-party payers to a societal perspective. Time horizons varied from 32 years to lifetime and discount rates were mostly 3%, except for Egypt, which used 3.5%.[7,11-13]

Three studies investigated sacituzumab govitecan based on the ASCENT trial. Two studies were conducted in the US, both applying a 10-year time horizon and 3% discount rate from a payer perspective. Three studies from China evaluated sacituzumab govitecan with 10-year or 5-year time horizons and two of them applying 5% discount rates.[2,14-17]

All studies included in this review were assessed using the CHEERS 2022 checklist developed by ISPOR to ensure that they contained the essential components of pharmacoeconomic reporting. Most studies met almost all the checklist items, indicating comprehensive and transparent reporting of their economic evaluations (TABLE 2).

TABLE 1. Characteristic of literature studies

Country, author, year	Population	Year of data collection	Intervention and comparator	Perspective	Time horizon	Discount rate (%)
Singapore, Phua *et al.*,[9]	IMpassion130	2018	Atezolizumab + nab-paclitaxel **vs** nab-paclitaxel	Singaporean healthcare	5 years	3
US, Wu and Ma,[10]	IMpassion130	2018	Atezolizumab + nab-paclitaxel **vs** nab-paclitaxel	US payer	10 years	3
Swiss, Favre-Bulle *et al.*,[11]	KEYNOTE-522	2022	Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab **vs** neoadjuvant chemotherapy + placebo followed by adjuvant placebo	Swiss third-party payer	Lifetime (51 years)	3
US, Huang *et al.*,[7]	KEYNOTE-522	2022	Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab **vs** neoadjuvant chemotherapy + placebo followed by adjuvant placebo	US third-party payer	Lifetime (51 years)	3
Hongkong, Kwong *et al.*,[12]	KEYNOTE-522	2022	Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab **vs** neoadjuvant chemotherapy + placebo followed by adjuvant placebo	Hongkong third-party payer	32 years	3
Egypt, Pöllinger *et al.*,[13]	KEYNOTE-522	2022	Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab **vs** neoadjuvant chemotherapy + placebo followed by adjuvant placebo	Egyptian societal	Lifetime	3,5
US, Huang *et al.*,[4]	KEYNOTE-355	2021	Pembrolizumab/ chemotherapy **vs** chemotherapy	US third-party payer	20 years	3
US, Lang *et al.*,[14]	ASCENT trial	2021	Sacituzumab govitecan **vs** chemotherapy	US payer	10 years	3
US, Xie *et al.*,[15]	ASCENT trial	2021	Sacituzumab govitecan **vs** chemotherapy	US payer	10 years	3
China, Wu *et al.*,[16]	ASCENT trial	2022	Sacituzumab govitecan **vs** single-agent treatment of physician's choice (TPC)	Chinese health-care	10 years	5
China, Wang *et al.*,[17]	ASCENT trial	2022	Sacituzumab govitecan **vs** chemotherapy	Chinese health-care	10 years	5
China, Chen *et al.*,[2]	ASCENT trial	2020	Sacituzumab govitecan **vs** single-agent chemotherapy	Chinese and US healthcare	5 years	5 (China); 3 (US)

TABLE 2. CHEERS 2022 checklist

Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Phua *et al.*,[9]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1
Wu *et al*,[10]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1
Favre-Bulle *et al.*,[11]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Huang *et al.*,[7]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Kwong *et al.*,[12]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Pöllinger *et al*,[13]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Huang *et al.*,[7]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1
Lang *et al.*,[14]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Xie *et al.*,[15]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Wu *et al.*,[16]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Wang *et al.*,[17]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Chen *et al.*,[2]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

The studies included in this review utilized diverse modelling approaches and employed different types of sensitivity analysis to test the robustness of their outcomes. The TABLE 3 summarizes key findings from these studies, highlighting the approaches, LYG, total costs, ICERs, and conclusions regarding cost-effectiveness.

Two studies examined the combination of atezolizumab and nab-paclitaxel in advanced TNBC.. In Singapore, Phua *et al.* reported that although this combination provided a modest gain in life years compared to nab-paclitaxel alone (2.308 vs 1.672 Lys) and the ICER was S$ 324,550/QALY, making nab-paclitaxel monotherapy more cost-effective.[9] In contrast, a study by Wu and Ma found that adding atezolizumab to nab-paclitaxel was considered cost-effective only among PD-L1-positive subgroups.[18]

Several trials evaluated pembrolizumab's cost-effectiveness for high-risk early-stage TNBC. In Switzerland, Favre-Bulle *et al.*[11] demonstrated a substantial life-year gain in the pembrolizumab group (18.47 Lys) with an ICER of 14,114 CHF/QALY, supporting the cost-effectiveness of pembrolizumab. Similarly, in the US, Huang *et al.*,[7] reported an ICER of $27,285/QALY, favoring pembrolizumab combined with chemotherapy over chemotherapy alone in terms of cost-effectiveness. Consistent findings were reported in Hong Kong and Egypt, which suggested pembrolizumab is a cost-effective option.[12,13]

Sacituzumab govitecan was evaluated in multiple contexts. In the US, studies by Lang *et al.*,[14] and Xie *et al.*,[15] found high ICERs of $778,772/QALY and $1,252,295/QALY, respectively, indicating that standard chemotherapy remains more cost-effective. In China, Wu *et al.* reported a lower ICER of $44,792/QALM, suggesting Sacituzumab govitecan could be economically viable in certain conditions,[16] whereas Wang *et al.*,[2] and Chen *et al.*,[17] found the ICERs of Sacituzumab govitecan are significantly higher.

TABLE 3. Analysis of literature studies

Country, author, year	Disease	Model	Sensitivity analysis	Outcome/QALY	Cost	ICER	Cost effective
Singapore, Phua *et al.*,[9]	Advanced TNBC	Three-state partitioned-survival	One-way, PSA	QALYs Atezolizumab + Nab-paclitaxel 2.308 LYs Nab-paclitaxel 1.672 LYs	Atezolizumab + Nab-paclitaxel S$ 173,623 Nab-paclitaxel S$ 56,563	Atezolizumab + Nab-paclitaxel vs Nab-paclitaxel S$ 324,550/QALY	Nab-paclitaxel
US, Wu *et al*,[10]	Advanced TNBC	Markov	One-way, PSA	QALYs Atezolizumab + Nab-paclitaxel 2.034 LYs Nab-paclitaxel 1.847 LYs	Atezolizumab + Nab-paclitaxel $193,159 Nab-paclitaxel $113,368	Atezolizumab + Nab-paclitaxel vs Nab-paclitaxel $281,448/QALY	Atezolizumab + Nab-paclitaxel in PD-L1-positive advanced TNBC
Swiss, Favre-Bulle *et al.*,[11]	High-risk, Early-stage TNBC	Markov	One-way, PSA	QALYs Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab 18.47 LYs Neoadjuvant chemotherapy followed by adjuvant placebo 14.67 LYs	Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab 128,692 CHF Neoadjuvant chemotherapy followed by adjuvant placebo 85,254 CHF	Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab vs neoadjuvant chemotherapy followed by adjuvant placebo 14,114 CHF/QALY	Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab
US, Huang *et al.*,[7]	High-risk, Early-stage TNBC	Markov	One-way, DSA, PSA	QALYs Pembrolizumab in combination with chemotherapy as neoadjuvant treatment and continued as a single-agent adjuvant treatment after surgery 17.75 LYs Chemotherapy 14.39 LYs	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment and continued as a single-agent adjuvant treatment after surgery $235,918 Chemotherapy $156,872	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment and continued as a single-agent adjuvant treatment after surgery vs chemotherapy $27,285/QALY	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment and continued as a single-agent adjuvant treatment after surgery
Hong Kong, Kwong *et al.*,[12]	High-risk, Early-stage TNBC	Markov	One-way, PSA	QALYs Pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by adjuvant pembrolizumab 16.33 LYs Neoadjuvant chemotherapy 13.28 LYs	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by adjuvant pembrolizumab 967,743 HKD Neoadjuvant chemotherapy 636,550 HKD	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by adjuvant pembrolizumab vs neoadjuvant chemotherapy 135,200 HKD/QALY	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by adjuvant pembrolizumab
Egypt, Pöllinger *et al.*,[13]	High-risk, Early-stage TNBC	Markov	One-way, DSA, PSA	QALYs Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab 16.47 LYs Neoadjuvant chemotherapy + placebo followed by adjuvant placebo 13.55 LYs	Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab $186,849 Neoadjuvant chemotherapy + placebo followed by adjuvant placebo $84,412	Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab vs neoadjuvant chemotherapy + placebo followed by adjuvant placebo $45,476/QALY	Pembrolizumab + chemotherapy/ pembrolizumab
USA, Huang *et al.*,[4]	Untreated metastatic TNBC with PD-L1 combined positive score ≥10	Partitioned-survival	One-way, DSA, PSA	QALYs Pembrolizumab/ chemotherapy 2.99 LYs Chemotherapy 2.16 LYs	Pembrolizumab/ chemotherapy $284,122 Chemotherapy $156,416	Pembrolizumab/ chemotherapy vs chemotherapy $182,732/QALY	Pembrolizumab/ chemotherapy
USA, Lang *et al.*,[14]	Metastatic TNBC	Partitioned-survival	One-way, PSA	QALYs Sacituzumab govitecan 1.205 LYs (classic mode/full population) Chemotherapy 0.868 LYs (classic mode/full population)	Sacituzumab govitecan $281,093.5 Chemotherapy $76,793.6	Sacituzumab govitecan vs chemotherapy $778,771.9/QALY	Chemotherapy

Country, author, year	Disease	Model	Sensitivity analysis	Outcome/QALY	Cost	ICER	Cost effective
USA, Xie *et al.*,[15]	Relapsed Metastatic TNBC	Decision-analytic	One-way, PSA	QALYs Sacituzumab govitecan 1.1373 LYs (full population) Chemotherapy 0.8198 LYs (full population)	Sacituzumab govitecan $395,470 Chemotherapy $102,433	Sacituzumab govitecan vs chemotherapy $1,252,295/QALY	Chemotherapy
China, Wu *et al.*,[16]	Metastatic TNBC	Partitioned-survival	One-way, PSA	QALMs Sacituzumab govitecan 12.29 months Single-agent TPC 7.12 months	Sacituzumab govitecan $237,821 TPC $6442	Sacituzumab govitecan vs TPC $44,792/QALM	TPC
China, Wang *et al.*,[17]	Metastatic TNBC	Partitioned-survival	One-way, PSA	QALYs Sacituzumab govitecan 1.06 LYs (full population) Chemotherapy 0.75 LYs (full population)	Sacituzumab govitecan $99,779.52 Chemotherapy $18,000.92	Sacituzumab govitecan vs chemotherapy $323,603.84/QALY	Chemotherapy
China, Chen *et al.*,[2]	Metastatic TNBC	Partitioned-survival	One-way, PSA	QALYs Sacituzumab govitecan 1.28 LYs (Chinese) Single-agent chemotherapy 0.87 LYs (Chinese)	Sacituzumab govitecan 2,501,955 yen (Chinese) Single-agent chemotherapy 244,112 yen (Chinese)	Sacituzumab govitecan vs single-agent chemotherapy 6,375,856 yen/QALY (Chinese)	Single-agent chemotherapy
				Sacituzumab govitecan 1.28 LYs (US) Single-agent chemotherapy 0.87 LYs (US)	Sacituzumab govitecan $304,393 (US) Single-agent chemotherapy $129,000 (US)	Sacituzumab govitecan vs single-agent chemotherapy $501,123/QALY	Single-agent chemotherapy

Abbreviations: DSA: deterministic sensitivity analysis; ICER: incremental cost effectiveness ratio; LY: life year PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; TNBC: triple-negative breast cancer; TPC: treatment of physician's choice

DISCUSSION

Patients with TNBC have shown a higher incidence of possessing a robust tumor T-cell infiltrate than those with other breast cancer subtypes. Immune checkpoint proteins, such as programmed death ligand-1 (PD-L1) have also been found to be significantly upregulated in TNBC.[9]

Programmed cell death protein 1 (PD-1) contributes to immune suppression and promote self-tolerance by regulating T-cell activity, inducing apoptosis of antigen-specific T-cells and inhibiting apoptosis of regulatory T-cells. Programmed cell death ligand 1 (PD-L1), a transmembrane protein, acts as a co-inhibitory factor in immune response. When it binds to PD-1, it suppresses the proliferation of PD-1-positive cells, inhibits cytokine secretion, and induces apoptosis. PD-L1 also plays an important role in various malignancies, where it can attenuate the host immune response to tumor cells.[19]

Atezolizumab, a PD-L1 inhibitor, has been shown to a significant improvement in PFS by 20% compared with nab-paclitaxel monotherapy in the intention-to-treat population (median PFS 7.2 vs 5.5 months) and by 38% in the pre-defined subgroup of patients with PD-L1 expression on 1% of tumor-infiltrating immune cells (median PFS 7.5 vs 5.0 months). These data were obtained from IMpassion130, which was one of the first phase 3 trials of the immune checkpoint inhibitors conducted in patients with previously untreated, metastatic, or locally advanced TNBC. It was a multicentre, double-blind,

randomized controlled trial conducted in 41 countries.[9]

Pembrolizumab is a high-affinity humanized monoclonal PD-1antibody that inhibits the interaction between PD-1 receptor, PD-L1, and programmed death ligand 2 (PD-L2).[7,12] The phase 3 KEYNOTE-522 trial was conducted to evaluate the efficacy and safety of pembrolizumab plus chemotherapy followed by pembrolizumab compared with chemotherapy alone. Pembrolizumab treatment was associated with significantly better 36-month EFS compared with placebo (84.5% vs 76.8%).[13] In the KEYNOTE-522 trial, patients were randomly assigned to receive either pembrolizumab+chemotherapy or chemotherapy alone. In the neoadjuvant phase of the pembrolizumab+chemotherapy arm, pembrolizumab (200 mg administered once every 3 weeks (Q3W) on day 1 of cycles 1-8) in combination with chemotherapy (4 cycles of paclitaxel plus carboplatin followed by 4 cycles of doxorubicin or epirubicin plus cyclophosphamide) was administered to the patients. After completing neoadjuvant treatment, patients underwent definitive surgery within 3-6 weeks. In the adjuvant phase, radiation therapy as indicated or pembrolizumab as a single agent was administered Q3W for 9 cycles. Chemotherapy is considered a base case comparator to pembrolizumab+chemotherapy as a management strategy for high-risk eTNBC in the neoadjuvant phase.[12]

Sacituzumab govitecan is a new antineoplastic agent containing the irinotecan active metabolite (SN-38). Sacituzumab govitecan is an antibody drug conjugate (ADC) that has the powerful killing effect of tumor-targeting property by targeting trophoblast cell surface antigen 2 (Trop-2). It was fully approved according to the results of the phase 3 ASCENT trial, which revealed the significant survival benefit of Sacituzumab govitecan compared with chemotherapy (median PFS 5.6 months vs 1.7 months, hazard ratio of 0.41, $p<0.001$).[17]

Cost effectiveness analysis of the novel therapeutic agents

The ICER was calculated as the incremental cost per additional QALY gained between the intervention group and the standard treatment group. When the ICER was lower than the specified willingness-to-pay (WTP) threshold, the intervention was considered to be cost-effective.

Atezolizumab

The addition of atezolizumab to the nab-paclitaxel regimen does not represent good value for money in the treatment of advanced PD-L1-positive TNBC. This study was conducted from the perspective of the Singapore healthcare system, considering direct healthcare costs such as medication, intravenous drug administration, doctor consultations, blood tests, scans, and palliative care, while excluding drug-related adverse event costs. The addition of atezolizumab to nab-paclitaxel was associated with an ICER of S$324,550 per QALY gained.[9]

The economic evaluation using the Markov model was conducted in the US to assess the addition of atezolizumab for advanced TNBC. When PD-L1 status was unknown, adding atezolizumab to nab-paclitaxel resulted in an ICER of $281,448 per QALY gained. When atezolizumab plus nab-paclitaxel was administered for the subpopulation with PD-L1-positive after PD-L1 expression was tested, the ICER was $183,508/QALY gained and $196,073/QALY when PD-L1 status was confirmed. A study demonstrated that atezolizumab plus nab-paclitaxel, at a WTP threshold of $200,000/QALY, is likely to be a cost-effective option for patients with advanced TNBC testing PD-L1-positive in a US payer setting.[10]

One-way sensitivity analyses were

performed to explore the impact of uncertain model parameters on the ICER. ICER was most sensitive to the time horizon of the model and the cost of atezolizumab. Extending the time horizon to 10 years lowered the ICER to S$266,198 per QALY gained. The ICER was also sensitive to cost variations of atezolizumab. When the cost was varied by 20% the ICER ranged widely from S$273,058 to $376,041 per QALY gained. Unlike other countries, there is no explicit fixed cost-effectiveness threshold in Singapore. However, the combination of atezolizumab and nab-paclitaxel had less than 1% likelihood of being cost-effective between a threshold range of S$0 and S$188,333.[9]

Pembrolizumab

Pembrolizumab was approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of high-risk eTNBC in combination with chemotherapy as neoadjuvant therapy followed by single-agent adjuvant therapy after surgery in July 2021 and May 2022, respectively.[12] The phase 3 KEYNOTE-522 trial was conducted to evaluate the efficacy and safety of neoadjuvant and adjuvant pembrolizumab compared with chemotherapy alone. Pembrolizumab treatment was associated with significantly better 36-month EFS compared with placebo (84.5% vs 76.8%).[13]

Based on an Egyptian cost-effectiveness study, the incremental cost per QALY gained with pembrolizumab+chemotherapy/ pembrolizumab compared with chemotherapy alone for patient with high-risk eTNBC was EGP218,285 ($45,476) which is lower than the Egyptian WTP threshold of EGP398,439 ($83,008).[13] Those align with cost-effectiveness studies in other countries. In the US, a study which also employed a Markov model stated that pembrolizumab+chemotherapy/ pembrolizumab was associated with an ICER of $27,285 (2021 USD) per QALY gained which is below commonly cited US WTP threshold recommended by the Institute of Clinical and Economic Review ($50,000 to $150,000 per QALY).[7]

The calculated ICER for pembrolizumab plus chemotherapy versus chemotherapy alone was CHF14,114 (2022 values) per QALY gained, based on data from a comparable study carried out in Switzerland.[11] In Hong Kong, the addition of pembrolizumab for high-risk patients with eTNBC, which is anticipated over a 32-year time horizon, results in an ICER of HKD 135,200 (2022 values) per QALY gained compared to chemotherapy alone.[12]

The economic value of adding pembrolizumab to chemotherapy, compared to chemotherapy alone or atezolizumab plus nab-paclitaxel, in patients with mTNBC, has also been evaluated using data from the KEYNOTE-355 and IMpassion 130 trials. The ICER of pembrolizumab addition was $182,732 (2021 values) per QALY gained compared with chemotherapy alone. Meanwhile, compared with atezolizumab plus nab-paclitaxel, additional pembrolizumab was associated with an incremental cost per QALY gain of $44,157.[4]

Pembrolizumab in combination with chemotherapy as neoadjuvant treatment and continued as a single-agent adjuvant treatment improves patients' life expectancy and QALYs compared with chemotherapy alone, according to third-party payers. This regimen is projected to be a cost-effective treatment option for patients with high-risk eTNBC and mTNBC.

Incremental gains in QALYs of pembrolizumab interventions were associated with an increase in total costs for the treatment of eTNBC. In the US, pembrolizumab + chemotherapy/ pembrolizumab had a 99% probability of

being cost-effective versus chemotherapy based on probabilistic sensitivity analysis (PSA) demonstration.[7] In Switzerland and Hong Kong, the ICER was most sensitive to parameters determining EFS extrapolations for both therapy arms, and the results were moderately sensitive to variations in the cost of pembrolizumab, the exponential rate of transition from distant metastasis (DM) to death, and total metastatic disease cost.[11,12] While in Egypt, the average ICER across 1,000 iterations was EGP225,232 ($46,923) per QALY gained, which is lower than the Egyptian cost-effectiveness threshold of EGP398,439 ($83,008).[13]

The clinical effectiveness of pembrolizumab demonstrated better PFS and overall survival (OS) on both stage of early and late of TNBC. Pembrolizumab plus chemotherapy study in phase-3 of KEYNOTE-355 (NCT02819518) study, demonstrated significant results and improvement in TNBC patients among Hong Kong, Japan, Korea, Malaysia, and Taiwan. The patients received 200mg pembrolizumab for 3 weeks. Clinical shown that pembrolizumab has a higher combined positive score (CPS) towards the PDL-1 expression in the study.[20] Another randomized clinical study in Japanese patients who received the combination of 200 mg of pembrolizumab and chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine) showed improvement in OS and PFS.[21]

Sacituzumab govitecan

Sacituzumab govitecan received accelerated approval by the Food and Drug Administration (FDA) for the treatment of adult patients with mTNBC who have received at least 2 prior therapies for metastatic disease in April 2020. Unlike immune checkpoint inhibitors, sacituzumab govitecan acts independently of PD-L1 expression or immune activity. Sacituzumab govitecan is an antibody-drug conjugate targeting trophoblast cell-surface antigen 2 (Trop-2) expressing cells and selectively delivering SN-38, an active metabolite of irinotecan.[22]

Trop-2 is expressed on the vast majority of epithelial carcinomas, including breast, colon, prostate, pancreatic, urothelial, and lung cancers. In breast cancer, Trop-2 is associated with lymph node metastasis and poorer survival. SN-38 is membrane-permeable, enabling both targeted cell apoptosis and a bystander effect on neighboring tumor cells regardless of Trop-2 expression. This feature supports its efficacy across various epithelial solid tumor expressing Trop-2. Sacituzumab govitecan is generally well-tolerated with manageable gastrointestinal and hematologic toxicities comparable in frequency to other commonly used chemotherapies.[22-24]

The ASCENT trial demonstrated that sacituzumab govitecan significantly improved median PFS to 5.6 months compared to 1.7 months with standard chemotherapy in patients with TNBC. However, the treatment was associated with high ICERs, estimated at $778,771.9 (2021 values) per QALY gained in the US and $323,603.84 (2022 values) per QALY gained in China full population group. The cost-effectiveness acceptability curves (CEACs) were developed to estimate the probability that each treatment would be considered cost-effective across a range of WTP thresholds. The CEACs indicated that the probability of sacituzumab govitecan being cost-effective was close to 0% at a WTP threshold of $150,000/QALY in the US and at three times GDP per capita per QALY in China ($38,201.19/QALY).[14,17]

One-way sensitivity analysis showed that the cost of sacituzumab govitecan, weight, and utility of PFS were the main driving factors that have a significant impact on ICER. However, all varying parameters did not lead to the ICER to be below the threshold. Those various studies conclude that sacituzumab govitecan appeared not cost-effective for patients with metastatic TNBC.

Comparison of atezolizumab, pembrolizumab, and sacituzumab govitecan in tnbc treatment

Atezolizumab has demonstrated clinical benefit by improving PFS in advanced PD-L1-positive TNBC; however, its OS benefit remains inconsistent. Following the FDA's withdrawal of its indications for TNBC in 2021, the clinical use of atezolizumab has become significantly limited, although it continues to be used in some countries. Moreover, atezolizumab is generally not considered cost-effective compared to chemotherapy.[9,25,26] In comparison with other immune checkpoint inhibitors, an indirect evaluation found that pembrolizumab combined with nab-paclitaxel is more cost-effective than the same combination with atezolizumab.[4]

Pembrolizumab, on the other hand, has shown both clinical and economic advantages in TNBC treatment. A retrospective randomized study in early-stage TNBC reported that pembrolizumab combined with neoadjuvant chemotherapy (NACT) improved EFS, OS, and pathological complete response (pCR) compared to dose-dense adjuvant chemotherapy (ddAC).[27] Cost-effectiveness analyses have consistently shown that pembrolizumab is more cost-effective than both atezolizumab and sacituzumab govitecan, with ICERs closer to or below the willingness-to-pay thresholds. Pembrolizumab is used as a first-line treatment for metastatic TNBC in the US with an ICER of $182,732 per QALY.[4,7,12] As an adjuvant therapy, it also demonstrated cost-effectiveness for high-risk early-stage TNBC, with an ICER of $27,785 per QALY in the US and similar results in Hong Kong.[7,12]

Sacituzumab govitecan, unlike ICIs, offers benefit in refractory YNBC due to its unique mechanism targeting Trop-2, enabling selective delivery of a cytotoxic payload (SN-38) directly to tumor cells. This bystander effect allows the drug to impact even This bystander effect enables the drug to impact directly to tumor cells. Despite these promising clinical benefits, several studies have concluded that Sacituzumab govitecan appears not to be cost-effective compared to chemotherapy in patients with mTNBC. Price reduction is essential to make it a preferred treatment option. Additionally, a "reduced dose" strategy has been proposed in clinical settings to help manage treatment costs. Nevertheless, there is a lack of evidence and clinical trials to support the effectiveness of this dose-reduction strategy in mTNBC patients.[14]

CONCLUSION

Pembrolizumab combined with chemotherapy appears to be more cost-effective than atezolizumab for PD-L1-positive TNBC patients. Its cost-effectiveness has been supported across multiple countries, including the USA, Switzerland, Egypt, Hong Kong, and Singapore. Meanwhile, sacituzumab govitecan has not been demonstrated to be cost-effective based on evidence from studies conducted across multiple countries.

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