

The Economic Burden of Managing Grade ≥3 AEs Following Treatment of Inoperable/Metastatic HR-Positive/HER2-Negative Breast Cancer in Italy, Spain, and the United States

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Introduction

- Breast cancer is the most commonly diagnosed cancer worldwide, accounting for significant global morbidity and mortality;¹ in 2020, there were 2.3 million people diagnosed with breast cancer (11.7% of cancer diagnoses) and 685,000 deaths (6.9% of cancer deaths) globally.¹
- Hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) is the most common subtype, accounting for ~70% of breast cancer diagnoses,² and has a 5-year survival rate of 30% in the metastatic setting.²
- In patients with pretreated, inoperable or metastatic HR+/HER2- breast cancer, the onward treatment options, including chemotherapy and antibody-drug conjugates (ADCs), are limited and have varied toxicity profiles.^{3,4}
- The economic burden of managing severe toxicities in this patient population remains unclear.

Methods

Inclusion of AE incidence

- Treatment-related adverse event (TRAE) data were extracted from Phase 3 trial reports evaluating Dato-DXd (TROPION-Breast01), SG (TROPICS-02), and the respective ICC arms (ICC arms in both trials comprised of capecitabine, eribulin, vinorelbine, or gemcitabine).^{3,6}
- Inclusion of AEs was based on the all-grade TRAE incidence reporting cut-offs or thresholds, defined as the minimum proportion of patients that experienced an AE in at least one trial arm. The highest cut-off (≥10%; TROPICS-02) was then used to determine inclusion of AEs, for which the incidence rate of Grade ≥3 AEs was included in the cost calculator.
- For TROPION-Breast01, adverse events of special interest (AESIs) were also incorporated, irrespective of the all-grade incidence, including interstitial lung disease (ILD) or pneumonitis; infusion-related reaction;[†] oral mucositis/stomatitis; mucosal inflammation; and ocular

Table 1. The list of diagnosis codes

Adverse events	CCSR (US)	DRG (Italy)	DRG (Spain)
Abdominal pain	SYM006	183	251-1
Alopecia	INJ030	284	385-1
Anaemia	NEO074	574	663-1
Asthenia	SYM007	247	351-1
Constipation	DIG025	183	249-1
Decreased appetite	SYM016	297	421-1
Diarrhoea	SYM006	179	249-1
Fatigue	SYM007	247	351-1
Increased ALT or AST	SYM017	206	283-1
Infusion-related reaction [†]	INJ037	453	813-1
ILD or pneumonitis	RSP016	90, 93	142-1
Leukopenia	BLD007	574	663-1
Lymphopenia	BLD007	399	663-1
Mucosal inflammation*	DIG003	189	254-1
Nausea	SYM004	189	249-1
Neuropathy	INJ030	35	058-1
Neutropenia	BLD007	574	663-1
Ocular surface events	EYE005	44	82-1
Oral mucositis/stomatitis	NEO074 / DIG003	189	115-1
PPE	SKN002	284	385-1
Thrombocytopenia	BLD006	574	661-1
Vomiting	SYM004	189	249-1

*Other than oral mucositis/stomatitis

[†]IRR was later removed as AESI for the Dato-DXd clinical program.

Objectives

The research objectives were to:

- Develop a cost calculator to estimate the total healthcare costs of managing Grade ≥3 adverse events (AEs) following treatment for inoperable/metastatic HR+/HER2- BC with ADCs (datopotamab deruxtecan [Dato-DXd] and sacituzumab govitecan [SG]) and investigator's choice of chemotherapy (ICC).
- Estimate the costs for Italy, Spain, and the United States (US).
- Identify key cost drivers of the total costs of managing Grade ≥3 AEs.

Limitations

- The base case analysis considered inpatient costs only, in line with previous research;⁵ this is likely to overestimate total costs for all treatments given that specific AEs, despite severity, may be managed in the outpatient setting.

surface events. AESIs were not reported for the full trial population in the TROPICS-02 publication⁹ and hence were not included in the cost calculator.

Inpatient unit costs of AE management

- Given the severity of AEs, in the base case it was assumed that all patients are treated in the inpatient setting. For each AE, the International Classification of Diseases, Tenth Revision (ICD-10) code was assigned based on the description of the AE.^{7,8}
- For the US, ICD-10 codes were mapped to the Clinical Classifications Software Refined (CCSR) code using a widely available mapping algorithm (Table 1).⁹ The unit costs for 2021 were sourced from the Healthcare Cost and Utilization Project (HCUPnet) and inflated to 2024.^{10,11}
- For Italy and Spain, the diagnosis-related group (DRG) codes were identified using the description of the ICD-10 codes and online resources (Table 1).^{8,12} Unit costs were sourced from health ministry public databases and inflated to 2024.¹³⁻¹⁶

Results

AE incidence

- For Dato-DXd and ICC, oral mucositis/stomatitis and neutropenia were the most common Grade ≥3 AEs occurring in 7 and 31% of patients, respectively. Neutropenia was the most common Grade ≥3 AE for SG and ICC, affecting 51 and 38% of patients, respectively.

Base case analysis: Inpatient costs

- Across both trials and all treatments, total per-patient costs of managing Grade ≥3 AEs were highest in the US, followed by Italy and Spain (Figure 1).
- Dato-DXd was associated with substantially lower absolute per-patient costs versus ICC, based on AE rates from TROPION-Breast01 across all three countries: US, \$2,736 vs \$9,588; Italy, €603 vs €2,373; Spain, €445 vs €1,316.
- Conversely, SG was associated with higher absolute costs versus ICC, based on AE data from TROPICS-02: US, \$16,167 vs \$12,667; Italy, €4,108 vs €3,196; Spain, €2,259 vs €1,770.
- This represents a per-patient reduction in Grade ≥3 AE management costs for Dato-DXd over ICC of 71% (\$6,852), 75% (€1,769), and 66% (€871) for the US, Italy, and Spain, respectively.
- For SG versus ICC, Grade ≥3 AE costs were 28% (\$3,500), 29% (€911), and 28% (€489) higher in the US, Italy, and Spain, respectively.

- A scenario analysis was conducted to assess the impact of this assumption on the conclusions, which remained valid across countries. Future work is needed to address considerable variability and uncertainty in the costs associated with AE management in the outpatient setting.
- Some heterogeneity in baseline demographic and disease characteristics across the trials may impact the relative incidence rates of AEs. Therefore, the results are reported versus the respective ICC arms in the studies.
- The results report the average per-patient cost of managing Grade ≥3 AEs. However, AE management may differ between individuals and must consider co-existing conditions.

The application of CCSR and DRG codes to AEs was validated with key external experts (KEEs).

Outpatient model inputs

- A scenario analysis considered management of AEs across both the inpatient and outpatient settings. The proportion of patients with Grade ≥3 AEs managed in the outpatient setting and the associated unit costs were identified via a targeted literature review and KEE interviews.

Cost calculations

- The average per-patient cost of Grade ≥3 AE management was calculated by multiplying the AE incidence by the inpatient unit cost (base case) or a weighted average of inpatient and outpatient unit costs (scenario analysis).

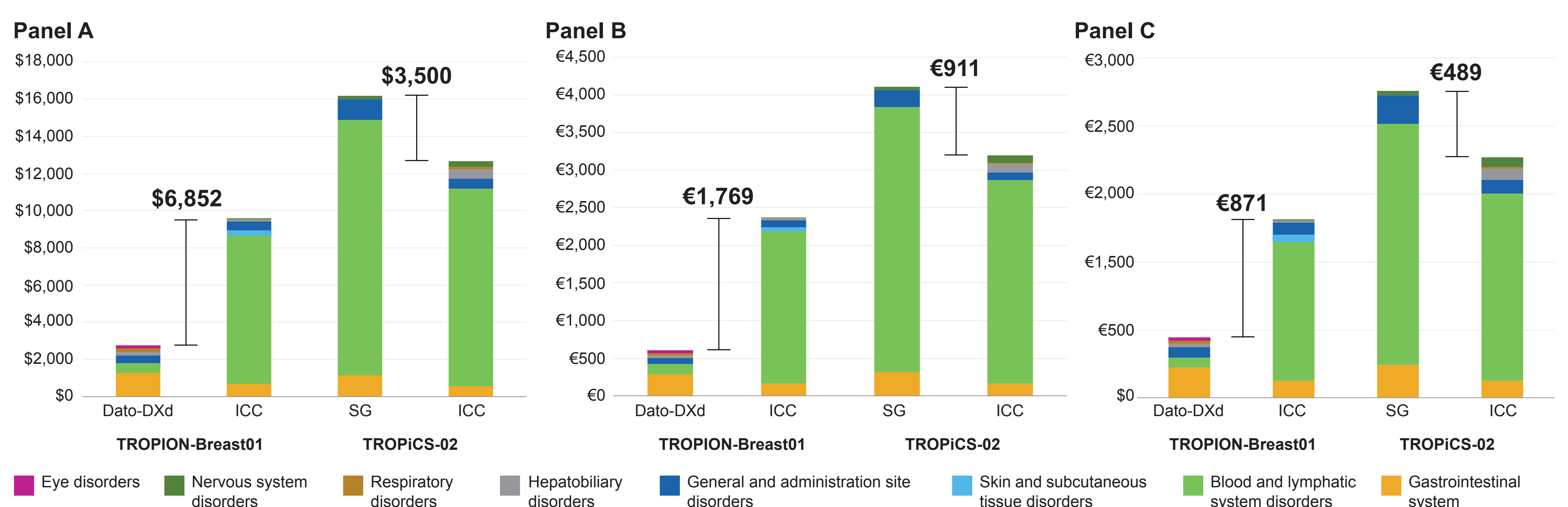
- Management of neutropenia (blood/lymphatic system disorders; Figure 1) is a substantial cost driver, particularly for treatment with SG (in TROPICS-02) and ICC (in both TROPICS-02 and TROPION-Breast01), as these treatments are associated with higher rates of neutropenia than Dato-DXd. When neutropenia was excluded from the analysis, AE costs associated with ICC and SG were substantially reduced, as anticipated. However:

- In TROPION-Breast01, Dato-DXd remained AE cost saving across all three countries (incremental savings for Dato-DXd versus ICC: US, 26%; Italy, 33%; Spain, 22%).
- In TROPICS-02, absolute costs for SG and ICC were both reduced, with SG remaining more costly across all three countries (incremental costs for SG versus ICC: US, 19%; Italy, 22%; Spain, 21%).

Scenario analysis: Inpatient/outpatient costs

- Including a mix of inpatient and outpatient care for AE treatment resulted in a reduction in the overall Grade ≥3 AEs management costs across all treatments and countries analysed.
- In this scenario, Dato-DXd was still associated with reductions in per-patient AE costs versus ICC: US, 40%; Italy, 40%; Spain, 22%.
- For SG, Grade ≥3 AE costs were 18%, 17%, and 13% higher versus ICC in the US, Italy, and Spain, respectively.

Figure 1. Base case results for the US (Panel A), Italy (Panel B), and Spain (Panel C)



Conclusion

On the basis of trial-reported Grade ≥3 AE incidence rates, it was estimated that, pending approval, Dato-DXd would be associated with lower costs of AE management compared with ICC in Italy, Spain, and the US; in contrast, SG was estimated to lead to higher costs of AE management compared with the respective ICC. These conclusions remained in a number of scenarios accounting for key drivers and AE management settings.

Disclosures

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Abbreviations

AE, adverse event; AESI, adverse event of special interest; ADC, antibody-drug conjugate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCSR, Clinical Classifications Software Refined; Dato-DXd, datopotamab deruxtecan; DRG, diagnosis-related group; HCUPnet, Healthcare Cost and Utilization Project; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; ICC, investigator's choice of chemotherapy; ICD-10, International Classification of Diseases, Tenth Revision; ILD, interstitial lung disease; KEE, key external expert; PPE, palmar-plantar erythrodysesthesia; SG, sacituzumab govitecan; TRAE, treatment-related adverse event; US, United States.