

An Italian cost-effectiveness analysis of paclitaxel albumin (nab-paclitaxel) versus conventional paclitaxel for metastatic breast cancer patients: the COSTANza study

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Purpose: Paclitaxel albumin (nab-paclitaxel) is a nanoparticle albumin-bound paclitaxel formulation aimed at increasing therapeutic index in metastatic breast cancer. When compared to conventional paclitaxel, nab-paclitaxel has a reported longer time to progression, higher response, lower incidence of neutropenia, no need for premedication, shorter time of administration, and in pretreated metastatic breast cancer patients, extended overall survival. This study investigates the cost-effectiveness of nab-paclitaxel versus conventional paclitaxel for pretreated metastatic breast cancer patients in Italy.

Materials and methods: A Markov model with progression-free, progressed, and dead states was developed to estimate costs, outcomes, and quality adjusted life years over 5 years from the Italian National Health Service viewpoint. Patients were assumed to receive nab-paclitaxel 260 mg/m² three times weekly or conventional paclitaxel 175 mg/m² three times weekly. Data on health care resource consumption was collected from a convenience sample of five Italian centers. Resources were valued at Euro (€) 2011. Published utility weights were applied to health states to estimate the impact of response, disease progression, and adverse events on quality adjusted life years. Three sensitivity analyses tested the robustness of the base case incremental cost-effectiveness ratio (ICER).

Results and conclusion: Compared to conventional paclitaxel, nab-paclitaxel gains an extra 0.165 quality adjusted life years (0.265 life years saved) and incurs additional costs of €2506 per patient treated. This translates to an ICER of €15,189 (95% confidence interval: €11,891–€28,415). One-way sensitivity analysis underscores that ICER for nab-paclitaxel remains stable despite varying taxanes cost. Threshold analysis shows that ICER for nab-paclitaxel exceeds €40,000 only if cost per mg of conventional paclitaxel is set to zero. Probabilistic sensitivity analysis highlights that nab-paclitaxel has a 0.99 probability to be cost-effective for a threshold value of €40,000 and is the optimal alternative from a threshold value of €16,316 onwards. Based on these findings, nab-paclitaxel can be considered highly cost-effective when compared to the acceptability range for ICER proposed by the Italian Health Economics Association (€25,000–€40,000).

Keywords: metastatic breast cancer, nab-paclitaxel, conventional paclitaxel, cost-effectiveness analysis, Italy

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Introduction

According to the most recent epidemiological data, incidence and prevalence of breast cancer in Italy are reported to be 78.4 and 686.2 cases per 100,000 inhabitants per year.^{1,2} Taxanes (paclitaxel and docetaxel) play major roles for treating metastatic

breast cancer (MBC).^{3,4} Paclitaxel albumin (nab-paclitaxel; Abraxane[®]; Celgene Corporation, Summit, NJ, USA) is the first of a new class of anticancer agents that incorporates nanoparticle albumin bound (nab) technology. Nab technology has been developed to obtain solvent free formulations of hydrophobic cytotoxic drugs.⁵

Research has also suggested that the albumin component improves the localization of cytotoxics to the tumor site.⁵⁻⁷ However, the formulation of taxanes requires the inclusion of solvent and surfactant excipients that have been associated with dose limiting adverse events (AEs), such as acute hypersensitivity reactions and peripheral neuropathy.⁸⁻¹⁰

Nab-paclitaxel was developed with the aim of increasing therapeutic index in MBC and has been recognized as an important treatment option for this disease.^{3,4} An international, randomized, open-label, Phase III study was performed at 70 sites (28 Russia/Ukraine sites, 350 patients; 22 United States/Canada sites, 37 patients; and 20 United Kingdom sites, 67 patients) to confirm preclinical studies demonstrating superior efficacy and reduced toxicity of nab-paclitaxel compared with conventional paclitaxel.¹¹ Patients were randomly assigned to 3-week cycles of either nab-paclitaxel 260 mg/m² intravenously (IV) without premedication (132 out of 229 overall patients received nab-paclitaxel as second line or greater therapy) or conventional paclitaxel 175 mg/m² IV with premedication (136 out of 225 overall patients received conventional paclitaxel as second-line or greater therapy). Most women in second-line or greater therapy had previously received anthracycline therapy (77%), and none had prior exposure to taxanes for MBC.

Nab-paclitaxel demonstrated significantly higher response rates compared to conventional paclitaxel for all patients (33% versus 19%, respectively; $P = 0.001$) and for those who were pretreated as well (27% versus 13%, respectively; $P = 0.006$). Nab-paclitaxel reported significantly longer time to progression (TTP) versus conventional paclitaxel for all patients (23.0 versus 16.9 weeks, respectively; hazard ratio [HR] = 0.75; $P = 0.006$) and for those who received the study drug as a second-line or greater therapy (20.9 versus 16.1 weeks, respectively; HR = 0.73; $P = 0.020$). In pretreated patients who received nab-paclitaxel instead of conventional paclitaxel, the difference in overall survival (OS) was statistically significant (56.4 versus 46.7 weeks, respectively; HR = 0.73; $P = 0.024$). At the time of the analyses (October 2004), the median censoring time for overall patient survival was 103 weeks for the nab-paclitaxel group and 101 weeks for the conventional paclitaxel group.

The incidence of grade 4 neutropenia was significantly lower for nab-paclitaxel versus conventional paclitaxel (9% versus 22%, respectively; $P = 0.001$) despite a 49% higher paclitaxel dose. Also, despite the absence of premedication and shorter time of administration, no hypersensitivity reactions occurred with nab-paclitaxel.

In 2008, on the basis of improved response and extended OS in the pretreated subgroup of patients,¹¹ nab-paclitaxel received a marketing authorization from the European Medicines Agency for the treatment of MBC in adult patients who have failed first-line treatment and for whom standard, anthracycline-containing therapy is not indicated.^{12,13}

The aim of the COST-effectiveness Analysis of Nab-paclitaxel (COSTANza, a feminine name in Italian) study was to perform a model-based cost-effectiveness analysis of IV nab-paclitaxel 260 mg/m²,^{14,15} three times weekly (the approved schedule for second-line MBC treatment),¹⁶ versus conventional IV paclitaxel 175 mg/m² three times weekly monotherapy regimens in MBC patients as a second-line treatment whenever standard, anthracycline-containing therapy is not indicated.¹³

Materials and methods

Patients and treatment

Baseline characteristics of patients included in the economic evaluation were assumed to match those of patients included in the abovementioned randomized controlled trial (RCT) aimed at comparing nab-paclitaxel versus conventional paclitaxel in patients with MBC.¹¹ Patients were assumed to have a body surface area of 1.70 m².

State-transition model

A spreadsheet supported, 5-year (87 cycles), three-state (progression free, progressed, and death) Markov model^{14,17} was developed in Microsoft Excel[®] 2003 (version 11, Microsoft Corporation, Redmond, WA, USA) to compare cost and quality adjusted life years (QALYs) of nab-paclitaxel versus conventional paclitaxel.

A 5-year period lifetime horizon for MBC patients was chosen as it was considered appropriate by foreign institutional advisory bodies who issued recommendations for the use of nab-paclitaxel for the same indication.^{18,19} Transition probabilities among Markov model states were estimated via the Weibull distribution. The Weibull distribution was used to generalize progression-free survival (PFS) and OS, in order to extrapolate survival in the model beyond the follow-up of the abovementioned RCT that compared nab-paclitaxel versus conventional paclitaxel.¹¹ From the same

RCT the incidence of grade 3 and 4 AEs for nab-paclitaxel and conventional paclitaxel was obtained (Table 1). The model assumes all AEs occurred during the first cycle of chemotherapy only.

Effectiveness, utility, and QALYs

Effectiveness outcomes for nab-paclitaxel and conventional paclitaxel included response in nonprogressed patients, TTP, and OS.¹¹

Utility is indicative of patients' preferences over different health states. Utility is bounded between zero (ie, death or health state considered worse than death) and one (ie, perfect health) regardless the disease under evaluation.^{14,15} Utilities representing health-related quality of life for each state included in the Markov model (stable disease: 0.65; responder: 0.81; progression: 0.45; death: 0) were drawn from a pooled analysis of MBC utility weights.²⁰ Utility decrements due to the occurrence of AEs such as febrile neutropenia or infection (−0.21), or nonspecific toxicity in responders (−0.14) and patients with stable disease (−0.11) were also considered.²⁰

QALYs calculation consisted in multiplying patients' years of life saved for the utility related to each health state. QALYs were then aggregated across the 5-year time horizon assumed in the Markov model.

Resource consumption and associated costs

As cost-effectiveness analysis was performed following the Italian National Health Service (INHS) viewpoint, only health care resources provided by INHS were identified, quantified, and costed. Health care resources included drugs, personnel time, outpatient services, and hospitalization

related to chemotherapy as well as AEs management. Part of health care resource consumption was collected from a convenience sample of five Italian oncological centers at the forefront in MBC treatment between June and July 2011.²¹

An ad hoc, spreadsheet-supported questionnaire aimed at collecting health care resource consumption for premedication, chemotherapy, administration, postmedication, and AEs management (drugs; clinical investigations, oncologist and specialist visits provided in an outpatient setting; inpatient admissions and day hospitals [DH]), as well as nurses' and physicians' time for chemotherapy preparation, administration, and patients' surveillance in outpatient, DH, and inpatient settings, was sent to the five participating oncological centers to be filled out by a senior oncologist. After all questionnaires were returned and completed (end of summer 2011), one follow-up phone call, which aimed at obtaining some clarifications on the answers given, took place with all five senior oncologists. If necessary, the answers were modified on the basis of the discussion with the clinicians.

Health care resource consumption was obtained from published sources for end of life care,²² and estimated on the grounds of few research hypotheses for supportive care and patients' assessment. All costs were expressed in Euro (€), year 2011 values.

Costs for drugs, patients' surveillance, assessment and support, best supportive care following progression, end of life care, clinical and diagnostic tests, oncologist and specialist visits, transfusions, and hospitalizations were obtained from published sources (Table 2).^{22–29} Since they are administered in health care facilities, nab-paclitaxel and generic conventional paclitaxel were valued at ex factory price, which is around 33% off consumer price, whereas other drugs were valued at consumer price. The costs of drugs and health care services administered during hospitalization were considered included in the daily full cost of the hospital stay.

Physicians' and nurses' time for preparing and administering taxanes, as well as for patients' surveillance, were determined on a per minute basis considering the average duration of a DH chemotherapy session for MBC patients in Italy (240 minutes).²⁷ Each minute was then valued by dividing the INHS Diagnosis Related Group (DRG) tariff (code 410) for chemotherapy performed in DH setting (€427.76) by 240 minutes (€1.78).²⁹ In order to avoid double counting (ie, costing the same resource twice),¹⁵ the cost of nab-paclitaxel and conventional paclitaxel, which was already calculated separately, and the cost per minute was eventually halved

Table 1 Comparison of grade 3 and 4 adverse events: relative frequencies

| Adverse event | Nab-paclitaxel | Conventional paclitaxel |
|-----------------------------|----------------|-------------------------|
| Neutropenia | 30.57% | 46.22% |
| Febrile neutropenia | 1.75% | 0.89% |
| Infection | 4.80% | 3.11% |
| Anemia | 0.87% | 0.44% |
| Diarrhea | 0.44% | 1.33% |
| Nausea | 3.49% | 0.44% |
| Nervous system | 11.35% | 2.67% |
| Pain (included arathralgia) | 14.85% | 6.22% |
| Asthenia | 8.30% | 3.11% |
| Myalgia | 7.42% | 1.78% |
| Vomiting | 3.93% | 1.33% |
| Stomatitis | 1.75% | 0.44% |

Table 2 Unit costs (€2011)

| Cost item (mean ± SD) | Nab-paclitaxel | Conventional paclitaxel | Source |
|---|--------------------------|-------------------------|-------------|
| Chemotherapy cycle | | | |
| Taxanes ^a | 1063.70 (–) ^b | 814.77 (–) | 23,24 |
| Premedication | 0.45 (±0.90) | 9.22 (±5.29) | 25,26 |
| Preparation, administration and patient surveillance – physicians' and nurses' time | 62.38 (±15.86) | 150.96 (±68.55) | 27,29 |
| Administration – drugs others than taxanes ^c | 16.79 (±22.38) | 10.50 (±7.66) | 25,26 |
| Postmedication | 5.19 (±10.38) | 10.75 (±12.48) | 25,26 |
| Assessment and support – patients receiving chemotherapy | | 203.85 (–) | 22,28 |
| Assessment and support – patients off treatment | | 150.81 (–) | 22,28 |
| Best supportive care following progression | | 344.77 (–) | 22,28 |
| End of life care | | 1193.00 (–) | 22,28 |
| Grade 3 and 4 adverse events | | | |
| Anemia | | 3061.86 (±1655.70) | 25,26,28,29 |
| Asthenia | | 133.26 (±230.27) | 25,26,28,29 |
| Diarrhea | | 196.08 (±354.48) | 25,26,28,29 |
| Febrile neutropenia | | 2387.75 (±1975.89) | 25,26,28,29 |
| Infection | | 463.45 (±282.21) | 25,26,28,29 |
| Myalgia | | 30.51 (±42.15) | 25,26,28,29 |
| Nausea | | 52.17 (±52.26) | 25,26,28,29 |
| Nervous system | | 79.78 (±66.03) | 25,26,28,29 |
| Neutropenia | | 1245.89 (±620.46) | 25,26,28,29 |
| Pain (included arthralgia) | | 36.38 (±50.76) | 25,26,28,29 |
| Stomatitis | | 585.00 (±772.98) | 25,26,28,29 |
| Vomiting | | 212.27 (±369.34) | 25,26,28,29 |

Notes: ^aCost per mg: nab-paclitaxel = €2.45; conventional paclitaxel = €2.80; ^bwhen cost estimate was based upon research hypotheses, no SD was calculated; ^cantiemetics.

Abbreviation: SD, standard deviation.

(€0.89). This procedure was probably quite conservative, as drugs for chemotherapy can well absorb up to 80% of DRG 410 DH tariff in Italy.³⁰

The mean cost for each AE was calculated by weighting its unit cost for the relative frequency in nab-paclitaxel and conventional paclitaxel patients (Tables 1 and 2).¹¹

As recommended by reference literature and Italian guidelines on the economic evaluation of health care programs, costs and QALYs were discounted on a 3-week basis using a 3% annual real social rate.^{14,15,31}

Cost-effectiveness analysis

Cost-effectiveness analysis is aimed at calculating the ratio of the difference in terms of both costs (incremental cost or ΔC) and QALYs (incremental QALYs or $\Delta QALYs$) between alternative health care programs (ie, nab-paclitaxel versus conventional paclitaxel).^{14,15}

The ratio of incremental cost to incremental QALYs (ie, $[\text{Cost}_A - \text{Cost}_B]/[\text{QALYs}_A - \text{QALYs}_B]$) is named the incremental cost-effectiveness ratio (ICER; ie, $\Delta C/\Delta QALYs$).^{14,15} In general, ICER means the cost of obtaining an incremental

effectiveness unit (eg, an incremental QALY) by adopting the health care program that is more costly and more effective than the comparator(s).

Statistical analysis

Relative AE frequencies are reported (Table 1). Point estimate and the 95% confidence interval (95% CI) were determined for hazard ratios (HR), odds ratios (OR), relative risk (RR), and risk differences (RD). Statistical significance was reached whenever the 95% CI did not contain the null value (ie, 1 for HR, OR, and RR; 0 for RD).³²

Unless otherwise stated, resource volume and unit costs for premedication, chemotherapy preparation, and administration, as well as patients' surveillance, postmedication, and AEs management, were calculated on the grounds of the information provided by the five oncological centers participating at this research project, and were reported as the mean (\pm standard deviation).

Utility weights and unit 5-year costs for chemotherapy cycle with taxanes, patients' assessment and support, best supportive care following progression, and end of life care

were reported as point estimates only, as no assumption about their dispersion around the mean was made in the base case analysis. No hypothesis test was performed.

Sensitivity analyses

Sensitivity analysis allows for uncertainty in the economic evaluation of health care programs.¹⁵ Three different sensitivity analyses tested the robustness of the base case results.

A one-way sensitivity analysis, in which variables are changed one at a time while keeping the other ones at their baseline levels,^{14,15,33} was carried out on: RR for response to therapy; HR for TTP and OS; cost of both taxanes; AEs with the highest and the lowest mean unit cost for their management (anemia and myalgia, respectively); reduction in DRG 410 DH tariff of 0% (ie, assuming that the whole cost of taxanes is funded by INHS outside the DRG tariff) and 80% (ie, the highest expected share of DRG 410 DH tariff consumed by drugs for chemotherapy);³⁰ utility values for: stable disease, stable responders and disease progression; real social discount rate (0%, 5%, 7%, 10%), that usually plays a relevant role as health care programs stretch over time.¹⁴

As far as the RR for response to therapy, HR for TTP, and OS are concerned, the base case estimate was replaced with the lower and the upper limit of the 95% CI.

For the remaining variables included in the one-way sensitivity analysis other than real social discount rate and DRG 410 DH tariff, a $\pm 10\%$ variation of the base case value was applied, consistently with the approach followed in a previous economic evaluation on lung cancer carried out in Italy.³⁴ The impact of the duration of the Markov model on ICER was also considered.

In a threshold analysis, the base case cost per mg of conventional paclitaxel was reduced until nab-paclitaxel was no more cost-effective. A probabilistic sensitivity analysis took into account the uncertainty surrounding the base case ICER estimate via a 1000-iteration Monte Carlo simulation.^{14,15,33,35,36}

The percentile method was used to calculate the 95% CI for the ICER by picking the 26th and the 975th iterations of the Monte Carlo simulation.^{35–39} In addition, the cost-effectiveness of nab-paclitaxel versus conventional paclitaxel was further explored via a cost-effectiveness acceptability curve (CEAC) and a cost-effectiveness acceptability frontier (CEAF).

On the grounds of available evidence,⁴⁰ CEAC reports the probability for nab-paclitaxel to be cost-effective over a range of different threshold values per QALY gained,^{15,41,42}

whereas CEAF,^{36,41} constructed by exploiting an algebraic manipulation of the ICER named net monetary benefit,^{36,41–44} highlights from which threshold value onwards nab-paclitaxel is the optimal alternative versus conventional paclitaxel.

Results

State-transition model

For both taxanes chemotherapy ends after the first year (ie, 18 cycles). The analysis of questionnaires highlights that chemotherapy cycles are usually administered in DH (80%), followed by ambulatory (14%), and inpatient (6%) settings.

The proportion of responders is significantly higher for nab-paclitaxel (0.40) when compared to conventional paclitaxel (0.23; RR: 1.75; 95% CI: 1.30–3.87). Median PFS is 0.52 and 0.40 years (ie, 6.2 months and 4.8 months) for nab-paclitaxel and conventional paclitaxel, respectively. TTP is significantly longer for nab-paclitaxel (HR: 0.72; 95% CI: 0.55–0.94). Median OS is significantly longer for nab-paclitaxel (1.27 years versus 1.04 years; HR: 0.73; 95% CI: 0.56–0.96).

For the sake of brevity, only AEs that differ significantly between nab-paclitaxel and conventional paclitaxel are reported (Table 3). Nab-paclitaxel outperforms conventional paclitaxel in reducing the incidence of neutropenia (OR: 1.95; 95% CI: 1.33–2.87), whereas conventional paclitaxel performs better than nab-paclitaxel in limiting nausea (OR: 0.12; 95% CI: 0.02–0.99), nervous system impairments (OR: 0.21; 95% CI: 0.09–0.53), pain (including arthralgia; OR: 0.38; 95% CI: 0.20–0.73), asthenia (OR: 0.35; 95% CI: 0.15–0.86), and myalgia (OR: 0.23; 95% CI: 0.07–0.68).

Table 3 Comparison of grade 3 and 4 adverse events: odds ratios and risk differences

| Adverse event | Parameter | Point estimate ^a | 95% CI ^b |
|----------------------------|-----------|-----------------------------|---------------------|
| Neutropenia | OR | 1.95 | 1.33–2.87 |
| Febrile neutropenia | OR | 0.50 | 0.09–2.78 |
| Infection | OR | 0.64 | 0.24–1.67 |
| Anemia | OR | 0.51 | 0.05–5.63 |
| Diarrhea | OR | 3.08 | 0.32–29.85 |
| Nausea | OR | 0.12 | 0.02–0.99 |
| Nervous system | OR | 0.21 | 0.09–0.53 |
| Pain (included arthralgia) | OR | 0.38 | 0.20–0.73 |
| Asthenia | OR | 0.35 | 0.15–0.86 |
| Myalgia | OR | 0.23 | 0.07–0.68 |
| Vomiting | RD | 0.03 | –0.003–0.06 |
| Stomatitis | RD | 0.01 | –0.01–0.03 |

Notes: ^aOR > 1 or RD < 0 favor nab-paclitaxel; ^bif 95% CI does not include 1 (0), OR (RD) is statistically significant.

Abbreviations: CI, confidence interval; OR, odds ratio; RD, risk difference.

Table 4 Mean 5-year costs and cost-effectiveness analysis (€2011)

| Cost item | Nab-paclitaxel | Conventional paclitaxel (%) | Difference ^a |
|--|---------------------|-----------------------------|-------------------------|
| Chemotherapy | 5935 (40.75) | 4170 (34.58) | 1765 (70.42) |
| Chemotherapy administration, premedication, and postmedication | 473 (3.25) | 929 (7.70) | -455 (-18.17) |
| Assessment and support: patients receiving chemotherapy | 1137 (7.81) | 1043 (8.65) | 94 (3.75) |
| Assessment and support: patients off treatment | 766 (5.26) | 485 (4.02) | 281 (11.23) |
| Best supportive care following progression | 4921 (33.79) | 4139 (34.33) | 782 (31.20) |
| End of life care | 1153 (7.92) | 1168 (9.68) | -14 (-0.58) |
| Adverse events | 178 (1.22) | 124 (1.03) | 54 (2.14) |
| Total | 14,564 (100.00) | 12,058 (100.00) | 2506 (100.00) |
| QALYs ^{b,c} | 0.805 | 0.640 | |
| Incremental cost (ΔC) | 2506 | - | - |
| Incremental QALYs ($\Delta QALYs$) | 0.165 | - | - |
| ICER ($\Delta C/\Delta QALYs$) | 15,189 ^d | | |

Notes: ^aCost of nab-paclitaxel – cost of conventional paclitaxel; ^bprogression-free life years saved with nab-paclitaxel (conventional paclitaxel): 0.615 (0.481); ^clife years saved with nab-paclitaxel (conventional paclitaxel): 1.439 (1.173); ^d95% CI ICER: €11,891–€28,415.

Abbreviations: QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; CI, confidence interval.

Resource consumption associated costs and cost-effectiveness analysis

Mean 5-year cost for nab-paclitaxel and conventional paclitaxel reaches €14,564 and €12,058, respectively (Table 4). For both nab-paclitaxel and conventional paclitaxel, the cost driver is chemotherapy (40.75% and 34.58% of the mean 5-year cost, respectively), whereas AE management accounts for the least relevant share of costs (1.22% and 1.03% of the mean 5-year cost, respectively).

The sum of cost for premedication, chemotherapy administration, patients' surveillance, and postmedication is 49% lower for nab-paclitaxel (€473; range: €287–€924 versus €929; range: €319–€1564, respectively). This finding is mainly driven by the shorter mean time for chemotherapy administration and patients' surveillance that favors nab-paclitaxel (70.00 ± 17.80 minutes versus 169.40 ± 76.92 minutes).

Focusing on the mean infusion time only, the difference in favor of nab-paclitaxel (27.50 ± 5.00 minutes versus 105.00 ± 70.36 minutes) is even more noteworthy. In addition, four out of five oncologists reported no need for premedication for nab-paclitaxel, whereas premedication was deemed necessary for all patients on conventional paclitaxel.

Costs for the assessment and support of patients receiving and off chemotherapy were higher for nab-paclitaxel. This finding is highly related to the longer TTP associated with nab-paclitaxel treatment. Nab-paclitaxel reports higher cost for best supportive care following progression, but lower cost for end of life care. Those two findings are related to the longer OS for nab-paclitaxel patients even after they have progressed.

As expected, most of the costs are accrued during the first year of the Markov model for both nab-paclitaxel (€10,393, or 71% of the mean 5-year cost) and conventional paclitaxel (€9125, or 76% of the mean 5-year cost).

When compared to conventional paclitaxel, the mean 5-year cost is €2506 higher for nab-paclitaxel (Table 4). Nab-paclitaxel is also more effective than conventional paclitaxel. During the 5-year period, nab-paclitaxel gains an extra 0.134 progression-free life years (0.615 versus 0.481) and saves 0.265 life years more than conventional paclitaxel (1.439 versus 1.173). When expected survival is weighted for utility, this results in 0.165 incremental QALYs for nab-paclitaxel (0.805 versus 0.640).

ICER indicates that each QALY gained with nab-paclitaxel would cost the INHS €15,189 (95% CI: €11,891–€28,415).

Sensitivity analyses

Sensitivity analyses confirm the robustness of the base case findings.

One-way sensitivity analysis underscores that ICER is sensitive to variations in the cost of nab-paclitaxel and conventional paclitaxel (Table 5). Conversely, replacing the base case estimate of the main clinical results with the 95% CI limits as well as reductions in the DRG 410 DH tariff have a negligible effect on ICER amount. Interestingly, the ICER remains stable and never exceeds €18,787, regardless of the hypotheses tested through one-way sensitivity analysis.

As expected, the Markov model time horizon plays a relevant role in determining the ICER amount. The difference between a 1- and 2-year span of time is quite remarkable,

Table 5 One-way sensitivity analysis (cost in €2011)

| | LL 95% CI | ICER | UL 95% CI |
|---|---------------------------------|--------|---------------------------------|
| Base-case analysis | | 15,189 | |
| Sensitivity analysis | | | |
| RR for response – nab-paclitaxel versus conventional paclitaxel | 15,766 | | 14,356 |
| HR for TTP – nab-paclitaxel versus conventional paclitaxel | 14,737 | | 15,791 |
| HR for OS – nab-paclitaxel versus conventional paclitaxel | 14,833 | | 15,719 |
| | -10% base case parameter | | +10% base case parameter |
| Cost of chemotherapy – conventional paclitaxel | 17,717 | | 12,661 |
| Cost of chemotherapy – nab-paclitaxel | 11,591 | | 18,787 |
| Cost of anemia | 15,181 | | 15,197 |
| Cost of myalgia | 15,188 | | 15,190 |
| Utility stable disease | 15,184 | | 15,194 |
| Utility progression | 15,751 | | 14,666 |
| Utility stable responder | 16,268 | | 14,244 |
| Reduction in DRG 410 DH tariff = 0% | | 12,615 | |
| Reduction in DRG 410 DH tariff = 80% | | 16,733 | |
| Discount rate = 0% | | 15,119 | |
| Discount rate = 5% | | 15,236 | |
| Discount rate = 7% | | 15,283 | |
| Discount rate = 10% | | 15,534 | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LL, lower limit; CI, confidence interval; UL, upper limit; RR, relative risk; HR, hazard ratio; TTP, time to progression; OS, overall survival; DRG, diagnosis related group; DH, day hospital.

as the ICER in the first year is 53% higher than in the second year (€23,445 versus €15,369). Interestingly, as discussed later on, differences in ICER values flatten out as time horizon increases, and they substantially overlap from year 3 (€15,085) to 5 (€15,189).

Threshold analysis shows that ICER for nab-paclitaxel becomes higher than €40,000 only assuming that conventional paclitaxel is freely delivered to INHS facilities (Figure 1).

When contrasted against the lower and the upper limits (€25,000 and €40,000, respectively) of the acceptability range for ICER proposed by the Italian Health Economics Association (AIES),³¹ CEAC highlights that the probability for nab-paclitaxel to be cost-effective is 0.96 and 0.99 (Figure 2, Panel A).

In cost-effectiveness terms, the probability of making the wrong decision by recommending nab-paclitaxel instead of

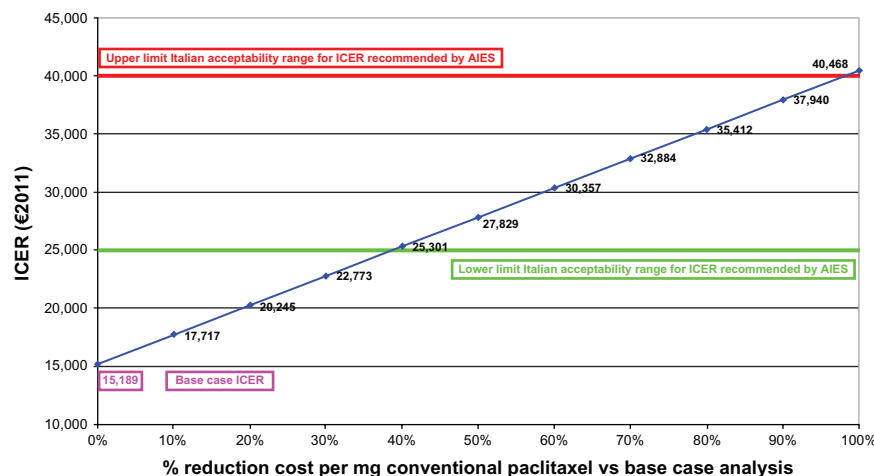


Figure 1 Threshold analysis for nab-paclitaxel.

Abbreviations: ICER, incremental cost-effectiveness ratio; AIES, Italian Health Economics Association.

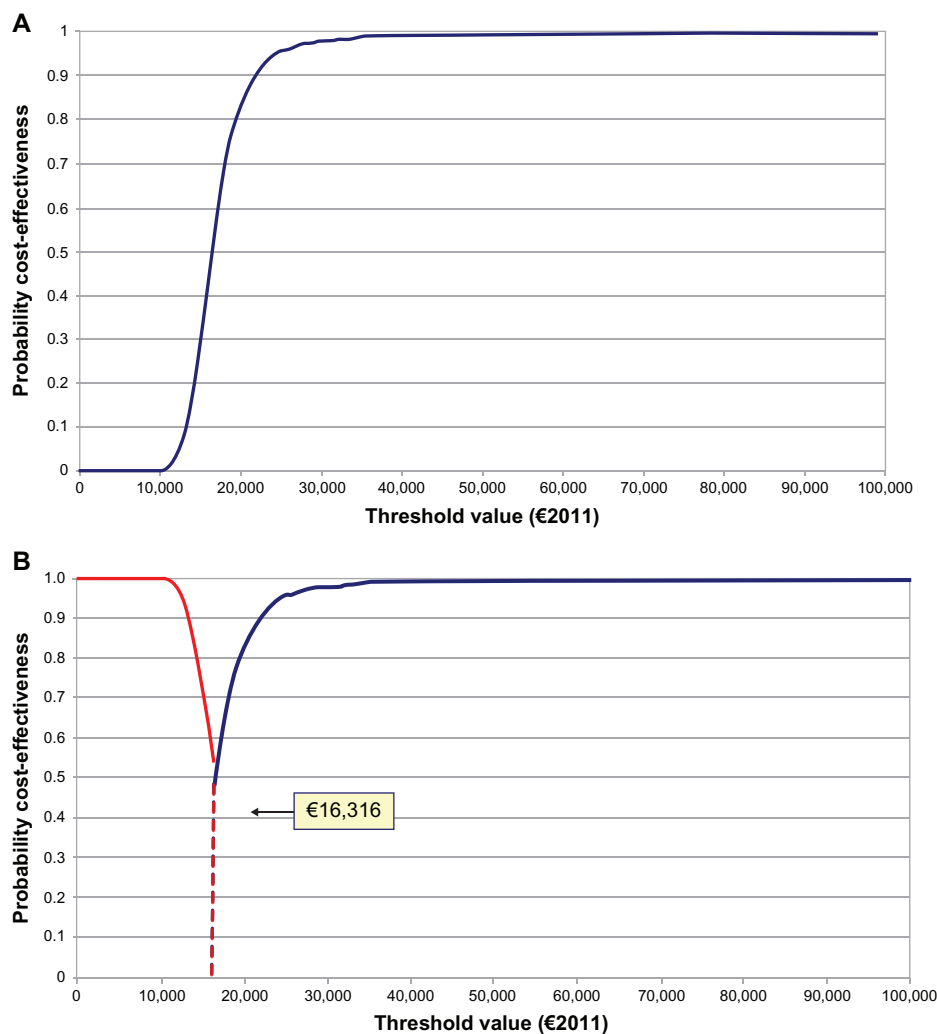


Figure 2 Probabilistic sensitivity analysis. **(A)** Cost-effectiveness acceptability curve for nab-paclitaxel. **(B)** Cost-effectiveness acceptability frontier. **Note:** Nab-paclitaxel is the optimal alternative from a threshold value of €16,316 onwards.

conventional paclitaxel is given by the complement of the probability of being cost-effective. In our study, it is worth noting that the probability of wrongly recommending nab-paclitaxel steeply decreases from 0.04 to 0.01, moving along the bounds of the acceptability range for ICER proposed by AIES. Finally, CEAF reports nab-paclitaxel to be the optimal alternative from a threshold value of €16,316 onwards (Figure 2, Panel B).

Discussion and conclusion

We performed a Markov model supported cost-effectiveness analysis to compare costs and QALYs of nab-paclitaxel and conventional paclitaxel in MBC patients. As far as the cost side is concerned, the most relevant share of health care resources allocated to MBC treatment and related AE management were identified and quantified empirically from a convenience sample of five Italian reference centers for MBC treatment.

This economic evaluation has four main limitations. Firstly, due to the absence of patient level empirical comparative study covering a time span consistent with the assumed survival horizon for MBC patients, the Markov model extrapolated estimates for 5-year OS and PFS, as well as costs for both nab-paclitaxel and conventional paclitaxel from the results of a pivotal comparative trial.¹¹ Despite the fact that this approach may cause our results to appear conditional on statistical technicalities and research hypotheses, modeling is commonly utilized in economic evaluation of health care programs when it comes to project costs and outcomes beyond the end of clinical trials.^{36,45} Besides, whenever long-term RCT results are lacking, it sounds wiser to support rationing in the health care sector with the available, although only partially empirical, evidence provided by models rather than relying on no guidance at all.^{46,47}

The second limitation rests on the fact that utilities come from one UK source. However, utilities are usually more robust than cost data when applied to different national settings.¹⁵ Moreover, utility values played a quite negligible role in leading the results of the economic evaluation, as shown by one-way sensitivity analysis. Nevertheless, it would be interesting to elicit utility values from a sample of Italian MBC patients for a future cost-effectiveness analysis.

The third limitation concerns the assumption that AEs affect costs and QALYs for the first cycle of chemotherapy only. However, since no variation in the incidence of AEs during the following chemotherapy cycles is reported in the pivotal trial,¹¹ and given that chemotherapy cycles end during the first year of the Markov model, this assumption does not impact on the ICER, since cost and outcomes occurring during the first year considered in an economic evaluation of health care programs are not discounted.

The last limitation relates to the fact that part of health care resource consumption was obtained from a convenience sample of five Italian oncological centers at the forefront in MBC treatment, which obviously differs from a random sample of health care facilities caring for MBC patients in Italy.²¹

Our results show that both the base case ICER and the related extremes of Monte Carlo 95% CI fall below the bounds of the acceptability range per QALY gained (€25,000–€40,000), which was recently proposed by an AIES working group.³¹

Nab-paclitaxel is obviously cost-effective when ICER is contrasted against the most widely quoted threshold values for Europe (€50,000) and the USA (US\$50,000).^{48,49} Moreover, for a threshold value higher than €28,415 (ie, the upper extreme of the 95% CI for the base case ICER), INHS policymakers can be 95% confident that nab-paclitaxel is cost-effective when compared to conventional paclitaxel.⁴⁴

It seems important to highlight that these findings are supported by better outcomes associated with nab-paclitaxel, both in terms of higher response, longer TTP, and longer OS, and in terms of a shorter time of administration. This last result favorably impacts on the costs of nab-paclitaxel.

A higher ICER of UK £25,209 at 2009 values (€28,817, unadjusted for inflation)⁵⁰ for nab-paclitaxel was determined for the UK with a similar Markov model.¹³ However, quantitative comparisons between economic evaluations performed in different countries, even with roughly the same model of health care system (like Italy and the UK), should be handled very carefully, due, at minimum, to possible differences in unit costs for health care resource.⁴⁴

According to CEAF, INHS decision makers should endorse nab-paclitaxel from a threshold value of €16,316 onwards. It is noteworthy that this threshold value is well below the lower limit of the AIES acceptability range.³¹ In addition, it is interesting for INHS decision makers that ICER dramatically decreases below €20,000 from year 2 onward. The time-dependent downward trend of the ICER seems to be fully explained by the fact that most of the costs, especially those related to chemotherapy that actually led to the 5-year mean cost for both nab-paclitaxel and conventional paclitaxel, had accrued during the first year of the Markov model. This also explains why base case ICER is not that sensitive to changes in discount rate, since costs (and QALYs) that occur during the first year are, in fact, left undiscounted.^{14,15}

In conclusion, the findings of our research show that nab-paclitaxel is both more clinically effective (higher response, longer TTP, and longer OS), and cost-effective (affordable ICER for the INHS) than conventional paclitaxel in Italy.

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