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Original Research

An Italian cost-effectiveness analysis of paclitaxel albumin (nab-paclitaxel) + gemcitabine vs gemcitabine alone for metastatic pancreatic cancer patients: the APICE study

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Abstract

Background: The APICE study evaluates the cost-effectiveness of nanoparticle albumin-bound paclitaxel (nab-paclitaxel - Nab-P) + gemcitabine (G) vs G alone in metastatic pancreatic cancer (MPC) from the Italian National Health Service (INHS) standpoint.

Research design and methods: A 4-year, 4 health states (progression-free; progressed; end of life; death) Markov model based on the MPACT trial was developed to estimate costs (Euro [€], 2017 values), and quality-adjusted life years (QALYs).

Patients were assumed to receive intravenously Nab-P 125 mg/m^2 + G 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks or G alone 1000 mg/m^2 weekly for 7 out of 8 weeks (cycle 1) and then on days 1, 8, and 15 every 4 weeks (cycle 2 and subsequent cycles) until progression.

One-way and probabilistic sensitivity analyses explored the uncertainty surrounding the baseline incremental cost-utility ratio (ICUR).

Results: Nab-P + G totals 0.154 incremental QALYs and €7082.68 incremental costs vs G alone. ICUR (€46,021.58) is lower than the informal threshold value of €87,330 adopted by the Italian Medicines Agency during 2010-2013 for reimbursing oncological drugs.

Sensitivity analyses confirmed the robustness of the baseline findings.

Conclusions: Nab-P + G in MPC patients can be considered cost-effective for the INHS.

Key-words: cost-effectiveness analysis; gemcitabine; Italy; metastatic pancreatic cancer; nab-paclitaxel

Clinical trial information:

NLM identifier: NCT00844649 available from https://clinicaltrials.gov/ct2/show/NCT00844649

1.Introduction

Pancreatic cancer is the fifth most frequent cause of cancer-related death and the fourth cause of death for middle-aged men and women [1].

In Europe pancreatic cancer affects 103,845 new patients (male: 50.04%) per year, with a prevalence of 26,615 cases (male: 51.58%) per year [2]. Incidence and prevalence of pancreatic cancer in Italy are estimated as 12,500 (male: 47.20%) and 14,695 (male: 45.00%) cases per year, respectively [2].

From 1997 onwards, gemcitabine (G) in monotherapy has become the first-line treatment for metastatic pancreatic cancer (MPC) [3]. When compared with fluorouracil G achieved a better response rate (G: 23.8%; fluorouracil: 4.8%; log-rank test p-value=0.002) and an overall survival (OS) rate beyond 12 months (G: 18.0%; fluorouracil: 2.0%; log-rank test p-value=0.0025) [3]. Both therapies were generally well tolerated [4].

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel - Nab-P; Abraxane®; Celgene Corporation, Summit, NJ, USA), a solvent-free colloidal suspension of P that incorporates nab technology, improves the efficacy of P and decreases solvent-associated adverse events (acute hypersensitivity reactions and peripheral neuropathy) [5-14].

In addition, Nab-P allows the administration of significantly higher doses of P within a shorter infusion time (30 minutes vs 180 minutes, respectively) and without premedication [15,16].

An international randomized open-label phase III study (MPACT, ClinicalTrials.gov, trial number NCT00844649) [3,17] was performed to confirm the results of a phase I-II clinical trial on previously untreated MPC patients, proving greater efficacy (median survival: 12.2 months) and manageable toxicity of Nab-P + G compared with G alone [13].

On a 1:1 basis 861 MPC patients aged≥18 years with a Karnofsky performance-status score ≥70 (100=perfect health) [18] were randomly assigned to either Nab-P (431 out of 861) + G or G alone (430 out of 861) as first-line treatments.

When compared with G alone, Nab-P + G reported a significantly higher response rate (23% vs 7%; p-value<0.001), longer median progression-free survival (PFS) (5.5 vs 3.7 months; hazard ratio [HR] for disease progression or death=0.69; p-value<0.001), and longer median OS (8.5 vs 6.7 months; HR for death=0.72; p-value<0.001).

As far as safety is concerned, the most frequent grade≥3 adverse events were neutropenia (Nab-P + G: 38%; G alone: 27%), fatigue (Nab-P + G: 17%; G alone: 7%), and neuropathy (Nab-P + G: 17%; G alone: 1%) [3]. The incidence of anaemia, thrombocytopenia and febrile neutropenia was similar in the two groups. In patients treated with Nab-P + G, grade ≥ 3 neuropathy improved to grade ≤ 1 in a median of 29 days [3].

In previous phase III trials other active regimens for MPC performed worse than Nab-P + G in improving the median OS vs G (alone or in combination with other cytotoxics) [1,3], except for the combination of erlotinib + G, which improved the median OS by about 2 weeks over G alone (6.2 vs 5.9 months; HR for death=0.82; p-value=0.038) [19].

FOLFIRINOX (a chemotherapy regimen made up of oxaliplatin, irinotecan, 5-FU, and leucovorin) proved to increase the median OS over G alone (11.1 vs 6.8 months; HR for death=0.57; p-value<0.001), but in a phase II-III trial that included fewer MPC patients with higher degrees of impairment in performance status compared with those enrolled in the MPACT study [3,17,20].

In the light of these results the European Medicines Agency and the Italian Medicines Agency approved Nab-P + G as first-line treatment for MPC [21,22].

The Abraxane Pancreatic Index Cost Effectiveness (APICE) study evaluates the cost-effectiveness [23,24] of Nab-P 125 mg/m^2+ G 1000 mg/m^2 vs G alone 1000 mg/m^2 as first-line treatment for MPC in Italy.

2. Patients and methods

2.1 Patients and treatment

As per MPACT trial [3,17], patients who had not received previous chemotherapy cycles for MPC were assumed to receive Nab-P 125 mg/m^2 + G 1000 mg/m^2 both intravenously (iv) on days 1, 8, 15, 29, 36, and 43, or G alone 1000 mg/m^2 iv weekly for 7 out of 8 weeks (cycle 1) as first-line treatments. Median relative dose intensity varied from 75% (Nab-P + G) to 85% (G alone) [3,17,20]. From cycle 2 onwards all patients were administered chemotherapy on days 1, 8, and 15 every 4 weeks, until progression.

When progressed, a proportion of patients who had previously received first-line therapy (Nab-P + G: 38%; G alone: 42%) were assumed to receive capecitabine (Nab-P + G: 4.38%; G alone: 6.56%%); 5-FU (Nab-P + G: 7.31%; G alone: 1.31%); fluorouracil + oxaliplatin (Nab-P + G: 13.15%; G alone: 17.06%); G + capecitabine (Nab-P + G: 2.92%; G alone: 3.84%); G + erlotinib (Nab-P + G: 2.92%; G alone: 3.84%); erlotinib (Nab-P + G: 1.46%; G alone: 1.31%), and FOLFIRINOX (Nab-P + G: 5.85%; G alone: 7.88%) as second-line treatment.

2.2 Markov model

Costs, life-year saved (LYS) and quality-adjusted life years (QALYs) of Nab-P + G and G alone were calculated via a Markov model [23-26] specified in Microsoft Excel® 2010.

As suggested by the senior oncologists who co-authored this paper, the Markov model stretches over a 4-year time horizon (208 weekly cycles) to take long-term MPC survivors into account and includes 4 health states (progression-free; progressed; end of life; death) (**Figure 1**).

End of life state, which was assumed to occur 4 weeks before death, was added to capture the cost associated with end of life care.

The transition probabilities estimate was based on the extrapolation of the PFS and OS reported in the MPACT trial [3,17] via Stratified Gamma and Gamma distributions, as they fit the Kaplan-Meier survival curves observed in the MPACT trial [3,17] better (i.e. showed the lowest Akaike's

and Schwarz's Bayesian information criteria) [27,28] than exponential, Weibull and Gompertz parametric distributions.

As far as toxicity is concerned, the same incidence of grade III and IV adverse events for Nab-P + G and G alone reported in the NCT00844649 trial was assumed [17] (**Table 1**). An incidence rate (IR) was calculated by dividing the number of grade III and IV adverse events for Nab-P + G and G alone by total patient-year on treatment; the IR was then converted into a cycle probability to include adverse events in the Markov model.

2.3 Effectiveness and QALYs

Four-year QALYs were calculated by multiplying LYS accrued to patients by the utility (i.e. health-related quality of life perceived by patients for each health state included in the Markov model) [23-26].

Since data on health-related quality of life of MPC patients were not collected alongside the MPACT trial [3,17], utilities for stable disease (0.80) and progression (0.75) were obtained from a research performed on a sample of US patients with advanced pancreatic cancer and MPC [29] (**Table 2**).

Utility decrements due to adverse events were also taken from literature [30-37], whereas utility for death was set at 0 [23,24].

2.4 Resource valuation

As the economic evaluation adopted the Italian National Health Service (INHS) standpoint [23,24], only INHS-funded health care resources were considered.

Data concerning INHS-funded health care resources consumed by MPC patients for premedication, chemotherapy (Nab-P; G; administration), post-medication and adverse events management (drugs; lab routines; clinical investigations; oncologist and other specialist visits; emergency room visits; inward hospitalizations and day-hospitals) were collected via an electronic questionnaire emailed to

a sample of convenience [38] in nine Italian oncology centres prominent in MPC management, which participated in the APICE study.

Time needed by hospital pharmacists, nurses and physicians for chemotherapy preparation, administration and patients assistance during ambulatory access or hospital stay was also retrieved from clinicians.

Health care resource consumption for MPC patient follow-up and end of life care was based on research assumptions.

Since the Markov model was mainly populated with data obtained from literature or based on experts' opinion, the approval of the APICE study protocol (included the abovementioned questionnaire) from the Ethics Committees of the nine oncology facilities was not required as per the existing Italian legislation [39].

All costs were expressed in Euro (€) 2017.

Costs concerning drugs, patients' assistance and follow-up, end of life care, clinical and diagnostic tests, oncologist and specialist visits, emergency room visits, General Practitioner visits (for end of life care only), transfusions and hospital stays were based on published sources (**Table 3**) [22;40-47].

As administered in a hospital setting, Nab-P + G and G alone were costed using the ex-factory price, which is about 33% lower than consumer price [22,40], and represents the maximum drug acquisition cost that the INHS pays for hospital drugs. For each cycle, the cost of Nab-P + G and G alone was calculated assuming an average body surface area of 1.70 m^2.

The remaining drugs were costed at consumer price [41].

Time spent by hospital pharmacists, nurses and physicians for preparing and administering Nab-P + G and G alone, and assisting patients, was expressed in minutes. Cost per minute (€1.797) was obtained by dividing the INHS Diagnosis-Related Group (DRG) tariff (code 410) for a day-hospital chemotherapy session (€431.18) [42] by its mean duration (240 minutes) [16].

Eventually, to avoid double-counting [24] health care resources included in the DRG tariff which were valued separately (e.g. the cost of drugs for premedication), the cost per minute was halved (€0.898).

The average cost for adverse events was determined multiplying their unit cost by the related cycle probability (obtained from IR). Whenever adverse events management required hospitalization, drugs and health care services were assumed to be included in the *per diem* full cost of hospitalization.

A 3% annual real social discount rate, calculated on a weekly basis, was applied to costs, LYS, and QALYs [23,24,48].

2.5 Cost-effectiveness and cost-utility analyses

A cost-effectiveness analysis and a cost-utility analysis were performed [23,24].

In cost-effectiveness (utility) analysis costs and LYS (QALYs) of alternative health care technologies are calculated and presented in a ratio of incremental costs (ΔC) to incremental LYS (ΔLYS for cost-effectiveness analysis) or QALYs (ΔQALYs for cost-utility analysis), termed incremental cost-effectiveness ratio (ICER) or cost-utility ratio (ICUR).

Usually, ICER (ICUR) indicates the cost of an incremental unit of effect on patients' health state (QALY) obtained with the health care technology that is more effective but also more costly than the alternative(s).

2.6 Statistical analysis

The point estimate and 95% confidence interval (95% CI) were calculated for incremental costs, incremental QALYs, ICER, adverse events IR, and adverse events IR ratio (IRR) [49-52].

Unless otherwise stated, MPC-related utilities and adverse event-related disutilities, unit costs for premedication, chemotherapy preparation and administration, post-medication, patient follow-up, end of life care and adverse events management were reported as mean (standard deviation - SD).

No SD was reported for unit cost per chemotherapy cycle with Nab-P + G and G alone, follow-up and cost for managing pulmonary embolism, as related literature [22,40,42] provided no dispersion around their point estimate.

An unstratified log-rank test for equality of PFS and OS functions was the only hypothesis test performed [53].

2.7 Sensitivity analyses

The uncertainty surrounding the baseline ICER and ICUR estimate was addressed by two different sensitivity analyses [23,24].

In the one-way sensitivity analysis, parameters were varied individually whereas the others were held at their base case values [23,24,54]. The one-way sensitivity analysis investigated the variations in ICUR due to changes in the following parameters: incremental costs; incremental QALYs; cost of a chemotherapy cycle with Nab-P + G and G alone; the most and least expensive adverse events to manage (pulmonary embolism and nausea, respectively); reductions in DRG 410 day-hospital tariff of 0% (i.e. the INHS reimburses the total cost for Nab-P + G and G alone in addition to the DRG tariff) and 80% (i.e. the DRG tariff covers lodging and meals only) [16,42,55]; utilities for stable and progressed MPC; real social discount rates (0%, 5%, 7%, 10%), that may influence ICER as health care programmes extend over years [23].

Incremental costs and incremental QALYs baseline estimates were replaced with the limits of their 95% CIs.

With the exception of real social discount rates and DRG 410 day-hospital tariff, the baseline value of the parameters considered in one-way sensitivity analysis was varied by ±10% [16,56].

Since both stratified Gamma and Gamma distributions are parameterized in accelerated time failure metric only [57], they are not suitable for HR and related 95% CI calculation. Hence, PFS and OS were not included in the one-way sensitivity analysis.

The results of one-way sensitivity analysis were reported on a Tornado chart. The axes of Tornado chart crossed at the baseline ICUR.

The relationship between time and ICER was explored by reducing the Markov model time horizon from 4 to 1 year.

Probabilistic sensitivity analysis characterizes the conjoint uncertainty affecting the baseline ICER and ICUR via a 1000-iteration Monte Carlo simulation [23,24,26,54,58].

The Markov model includes four main types of parameters: transition probabilities, hazard ratios, unit costs and utility values.

Beta distribution was fitted to transition probabilities and utility values; hazard ratios were assumed to follow a lognormal distribution, whereas unit costs were assumed to be normally distributed.

The 95% CIs for incremental costs, LYS, QALYs, and ICER were obtained by selecting the 26^{th} and the 975^{th} of the 1000 ordered iterations of the Monte Carlo simulation (percentile method) [26, 54,58,59].

Eventually, a cost-effectiveness acceptability curve and a cost-effectiveness acceptability frontier summarized the probability of Nab-P + G being cost-effective or optimal vs G alone [26,60-64]. The cost-effectiveness acceptability curve and the cost-effectiveness acceptability frontier construction were supported by an algebraic manipulation of the ICER (Net Monetary Benefit) [26,60-64].

3. Results

3.1 Markov model

Nab-P + G and G alone chemotherapy protocols end after 2.57 years (i.e. 134 cycles) and 1.88 years (i.e. 98 cycles), respectively. Questionnaires report that chemotherapy cycles are mainly administered in hospital ambulatory (Nab-P + G: 63.33%; G alone: 64.78%), followed by DH (Nab-P + G: 31.67%; G alone: 32.44%), and in-patient (Nab-P + G: 5.00%; G alone: 2.78%) settings.

The mean PFS equals 0.59 and 0.45 years (i.e. 7.1 and 5.4 months) for Nab-P + G and G alone, respectively (p-value<0.0001 by unstratified log-rank test).

The mean OS reaches 0.91 and 0.72 years (i.e. 10.9 and 8.6 months) for Nab-P + G and G alone, respectively (p-value<0.0001 by unstratified log-rank test).

As far as the most severe adverse events are concerned, chemotherapy protocols proved similar in terms of safety; only the incidence of leukopenia was higher for Nab-P + G (IRR: 1.898; 95% CI: 1.023;3.707) (**Table 4**).

Despite lacking statistical significance (IRR: 0.616; 95% CI: 0.355;1.061), Nab-P + G almost halved the incidence of abdominal pain when contrasted with G alone.

3.2 Cost-effectiveness and cost-utility analyses

After 4 years the mean total cost for Nab-P + G and G alone equals €19,002.03 and €11,919.34, respectively (incremental costs for Nab-P + G*:* €7082.68; 95% CI: €5852.09;€8670.10) (**Table 5**).

The cost-drivers are chemotherapy for Nab-P + G (33.14% of the mean total cost) and end of life care for G alone (29.35% of the mean total cost), respectively.

The overall cost for chemotherapy and related administration, pre- and post-medication, and patient assistance in first-line treatment is €7112.44 higher for Nab-P + G. This result is basically led by two factors: the higher total cost for chemotherapy cycle and the longer mean PFS for Nab-P + G.

Nab-P + G reports a higher mean cost for patient follow-up vs G alone in both first-line (+€71.14 or +18.04%) and second-line (+€16.30 or +5.49%) treatment. These findings are supported by the longer OS for Nab-P + G, which also explains the higher cost for adverse events but the lower cost for end of life care in second-line treatment.

The greatest share of costs occurs during the first year for Nab-P + G (€15,605.47 or 82.13% of the mean total cost) and G alone (€9904.27 or 83.09% of the mean total cost).

Nab-P + G produces better results than G alone on MPC patients' health state and health-related quality of life, as it saves 0.196 incremental LYS (95% CI: 0.099;0.287) and gains 0.154 incremental QALYs (95% CI: 0.088;0.220).

The ICER is €36,136,12 per incremental LYS saved (95% CI: €23,669.01;€74,569.41), whereas the ICUR shows that an incremental QALY gained with Nab-P + G costs the INHS €46,021.58 (95% CI: €33,291.60; €78,959.99).

3.3 Sensitivity analyses

The robustness of the baseline results was confirmed by sensitivity analyses.

The tornado chart shows that the widest variations on the base case ICUR are due to changes in incremental QALYs achieved by Nab-P + G (**Figure 2**). Replacing the base case estimate of incremental QALYs with the 95% CI limits confirms that Nab-P + G is more costly and more effective than G alone (ICUR=€80,725.24 or +75.41% vs baseline results; ICUR=€32,128.95 or -30.19% vs baseline results).

Differences in baseline ICUR are lower when the base case incremental costs are replaced by the 95% CI limits (ICUR=€38,025.48 or -17.37% vs baseline results; ICUR=€56,336.23 or +22.41% vs baseline results).

Mild effects on the base case ICUR follow from varying the cost of drugs for the first-line chemotherapy cycle by ±10% for Nab-P + G (ICUR=€41,929.83 or -8.89% vs baseline results; ICER=€8183.51 or +8.89% vs baseline results) or G alone (ICUR=€46,854.78 or +1.81% vs baseline results; ICUR=€45,188.39 or -1.81% vs baseline results).

As expected, varying the time horizon affects the base case findings substantively. The difference in ICUR between the first and the second year reaches 60.82% (€84,035.83 vs €52,253.62).

The probabilistic sensitivity analysis confirms that Nab-P + G is more expensive (incremental cost: €7245.27) but produces better results for patients' health state (incremental LYS: 0.196; incremental QALYs: 0.155) than G alone.

Probabilistic ICER and ICUR were consistent with those calculated in base case analysis (€39,760.30 vs €36,136,12 and €46,719.28 vs 46,021.58, respectively).

As the joint density of incremental costs and incremental QALYs lies completely on the North East sector of the cost-effectiveness plane, the limits of the 95% CI for the base case ICUR confirm that Nab-P + G is always more costly and more effective than G alone (**Figure 3**).

When compared with the recent Italian Medicines Agency unofficial threshold value for oncological drugs (€87,330; 95% CI: €37,024; €137,636) [65], the cost-effectiveness acceptability curve indicates a high probability (0.99) for Nab-P + G to be cost-effective (**Figure 4**).

Eventually, cost-effectiveness acceptability frontier shows Nab-P + G as being the optimal alternative if the INHS willingness to pay for an incremental QALY gained is at least €46,746 (**Figure 5**).

4. Discussion

The APICE study focused on a Markov model-based cost-effectiveness analysis aimed at comparing costs and QALYs of Nab-P + G and G alone as first-line treatment for MPC patients in Italy.

A significant feature of this research is that most of the health care resources for treating MPC and managing related adverse events were collected from a sample of convenience [38] of nine Italian oncology facilities on the leading edge of treating MPC.

According to the results of the APICE study, Nab-P + G produces better outcomes (i.e. longer PFS and OS) and is more cost-effective than G alone.

The baseline ICUR and the limits of its 95% CI are lower than the informal threshold value per QALY gained (€87,330) which in the recent past led the Italian Medicines Agency reimbursement decisions for oncological drugs [65]. Considering the same threshold value the probability of wrongly recommending Nab-P + G instead of G alone (i.e. 1-the probability of Nab-P + G being cost-effective, as presented on the cost-effectiveness acceptability curve) is really negligible (0.01).

The cost-effectiveness acceptability frontier suggests that INHS policy-makers should fund Nab-P + G if the willingness to pay for an incremental QALY gained is at least €46,746, which is again

lower than the threshold value informally adopted by the Italian Medicines Agency for reimbursing oncological drugs [65].

As reported elsewhere [66], although the incremental LYS and QALYs in favour of Nab + G may seem negligible when contrasted with the incremental cost, these findings should be read considering that about 50% of pancreatic cancer patients are indeed MPC patients, with an expected median OS of 4-6 months without systemic therapies [67].

Assuming that MPC affects half of 14,695 prevalent PC patients estimated for Italy [2] and that 50% of them have a Karnofsky performance-status score>70 [3] (i.e. 14,695 patients x 50% x 50%=3674 patients), a rough budget impact analysis [68] shows that over 4 years Nab-P + G would cost the INHS €26.02 million more than G alone (i.e. the incremental costs of €7082.68 incurred by Nab-P + G vs G alone multiplied by 3674 patients). This amount is fairly negligible, as it equals 0.58% of the overall gross expenditure for anticancer drugs and immune modulators funded by INHS in 2015 (€/billion 4.50) [69].

The ICUR for Nab-P + G drops below €55,000 from the second year onwards. This downtrend is due to the fact that the greatest share of costs - basically those for chemotherapy, which drive the total mean cost for Nab-P + G - accumulated over the first year. This also justifies the limited sensitivity of the base case ICUR to changes in real social discount rate, since costs (as well as LYS and QALYs) accrued during the first year are actually not discounted [23,24].

How does the APICE study compare with economic evaluations on the same topic performed in Europe?

A recent cost-effectiveness and cost-utility analysis supported by a Markov model [66] concluded that, despite higher cost (UK£5466) due to longer PFS and OS, Nab-P + G can be considered cost effective for the UK (ICER: UK£30,367; ICUR: UK£78,086, 2012 values) (€35,288 and €90,740, unadjusted for inflation) [70].

A cost-utility analysis based on a Markov model reported a slightly more favourable ICER for Spain (€41,519, 2015 values) [71].

On the basis of the results of a re-submitted Markov model-based cost-effectiveness analysis, the Scottish Medicines Consortium recommended Nab-P + G as first-line therapy for MPC [72]: the base case ICER for Nab-P + G vs G alone reached UK£52,885 at 2014 values (€61,455, unadjusted for inflation) [70].

More recently, cost-effective ICERs for Nab-P + G vs G alone, ranging from UK£41,000 to UK£46,000 at 2017 values (€44,844-€50,313, unadjusted for inflation) [70], were reported for England and Wales [73].

Some limitations may have affected the results of our cost-utility analysis.

A first limitation relates to our choice of focusing on a single comparator for Nab + G, that is G, without considering FOLFIRINOX, which also performed better than G alone in terms of OS [20], although on a sample of MPC patients who were fitter than those enrolled in the MPACT trial [3,17]. Recently, a lifetime horizon Markov model supported an indirect comparison of Nab + G vs FOLFIRINOX vs G alone as first line treatments in MPC performed for the US [74,75] using the Bucher method [76], revealed that OS for Nab + G vs FOLFIRINOX was similar (HR=1.26, 95 % CI 0.95–1.68), whereas FOLFIRINOX was superior in terms of PFS (HR=1.47, 95 % CI 1.10–1.96). There findings turned into 0.188 incremental LYS and 0.122 incremental QALYs for FOLFIRINOX vs Nab + G. However, the resulting ICER (USD358,067, 2015 values) and ICUR (USD547,480, 2015 values) (€302,090 and €461,892, unadjusted for inflation) [70] for FOLFIRINOX are probably unaffordable by any health care system.

As a second limitation, more research is needed to check whether the costs estimated on the basis of the data provided by clinicians (which are however consistent with the most recent guidelines on MPC issued by the Italian Association of Medical Oncology) [67] mirror those experienced by a random sample of Italian oncology units dealing with MPC patients.

The third limitation relates to the lack of a real-world comparative study stretching over the 4-year timespan considered in the APICE study, which obliged us to extrapolate the estimates of OS and PFS for Nab-P + G and G alone from the results of the MPACT trial [3,17].

Although this approach may make our findings too heavily reliant on statistical technicalities and research assumptions, health economic models are unavoidable whenever costs and outcomes have to be extrapolated beyond the end of a clinical trial [26,77-79]. Moreover, in the absence of long-term randomized controlled trials, rationing in the health care sector is better supported by the results provided by health economic models (even though these are only partially based on real evidence) [78], than by no guidance at all [80,81].

The fourth limitation concerns utilities, which were obtained from a sample of US patients with advanced pancreatic cancer and MPC [27]. Although QALYs for severe health states elicited from representative population samples from different countries may be similar [63], it will be empirically tested whether US utilities actually match those reported by a sample of Italian MPC patients.

Actually, utilities proved to have a considerable impact on the results of cost-effectiveness analyses on MPC [82] and may contribute, via QALYs calculation, to inequalities across health care systems as far as the reimbursement of innovative medical technologies is concerned [83].

5. Conclusion

The results of the APICE study show that, due to its higher clinical effectiveness (i.e. longer mean PFS and OS) and cost-effectiveness vs G alone, Nab-P + G is a "good value for money" health care technology for treating MPC patients in Italy.

5. Key issues

- The international randomized open-label phase III MPACT study proved greater efficacy and manageable toxicity of nanoparticle albumin-bound paclitaxel (Nab-P) + gemcitabine (G) compared with G alone in previously untreated metastatic pancreatic cancer (MPC) patients.

- The Abraxane Pancreatic Index Cost Effectiveness (APICE) study evaluates the cost-effectiveness of Nab-P 125 mg/m^2+ G 1000 mg/m^2 vs G alone 1000 mg/m^2 as first-line treatment for MPC in Italy.

- The results of the APICE study show that, due to its longer mean PFS and OS and cost-effectiveness vs G alone, Nab-P + G is a "good value for money" health care technology for treating MPC patients in Italy.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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All authors were involved in the conception and design, analysis and interpretation of the data.
CL drafted the paper, that was revised by all authors, who also approved the final version to be submitted. All authors agree to be accountable for all aspects of the work.

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●● of considerable interest

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Table 1. Comparison of grade III and IV adverse events.

Adverse event	Nab-P + G			G			Source
	Events	IR (95%CI)	Probability per cycle	Events	IR (95%CI)	Probability per cycle	
Abdominal pain	27	0.160 (0.106;0.233)	0,003	32	0.260 (0.178;0.368)	0,005	[17]
Anaemia	49	0.291 (0.215;0.385)	0,006	32	0.260 (0.178;0.368)	0,005	[17]
Asthenia	29	0.172 (0.115;0.248)	0,003	17	0.138 (0.081;0.222)	0,003	[17]
Cholangitis	10	0.059 (0.028;0.109)	0,001	6	0.049 (0.018;0.106)	0,001	[17]
Diarrhoea	26	0.155 (0.101;0.226)	0,003	6	0.049 (0.018;0.106)	0,001	[17]
Dehydration	31	0.184 (0.125;0.262)	0,004	10	0.081 (0.039;0.150)	0,002	[17]
Fatigue	77	0.458 (0.361;0.572)	0,009	37	0.301 (0.212;0.415)	0,006	[17]
Febrile neutropenia	13	0.077 (0.041;0.132)	0,001	6	0.049 (0.018;0.106)	0,001	[17]
Hyperbilirubinemia	9	0.053 (0.024;0.102)	0,001	12	0.098 (0.050;0.171)	0,002	[17]
Loss of appetite	23	0.137 (0.087;0.205)	0,003	8	0.065 (0.028;0.128)	0,001	[17]
Leukopenia	39	0.232 (0.165;0.317)	0,004	15	0.122 (0.068;0.201)	0,002	[17]
Nausea	27	0.160 (0.106;0.233)	0,003	14	0.114 (0.062;0.191)	0,002	[17]
Neutropenia	138	0.820 (0.689;0.969)	0,016	85	0.692 (0.553;0.856)	0,013	[17]
Peripheral neuropathy	32	0.190 (0.130;0.268)	0,004	0	0.000 (-)	0,000	[17]
Peripheral sensory neuropathy	34	0.202 (0.140;0.282)	0,004	1	0.008 (0.0002;0.045)	0,0002	[17]
Pneumonia	15	0.089 (0.050;0.147)	0,002	9	0.073 (0.033;0.139)	0,001	[17]
Pulmonary embolism	19	0.113 (0.068;0.176)	0,002	26	0.212 (0.138;0.310)	0,004	[17]
Thrombocytopenia	53	0.315 (0.236;0.412)	0,006	33	0.269 (0.185;0.377)	0,005	[17]
Vomiting	25	0.149 (0.096;0.219)	0,003	15	0.122 (0.068;0.201)	0,002	[17]

Abbreviations: CI, confidence interval; G, gemcitabine; IR=incidence rate; Nab-P + G, nab-paclitaxel + gemcitabine.

Table 2. Utility and disutility values.

Items	Mean (SD)	Source
MPC - Utility values		
Stable disease	0.800 (0.145)	[29]
Progressive disease	0.750 (0.156)	[29]
Grade III and IV adverse events - Disutility values		
Abdominal pain	-0.069 (0.253)	[30]
Anaemia	-0.119 (0.324)	[31]
Asthenia	-0.204 (0.403)	[31]
Cholangitis	-0.440 (0.496)	Assumed equal to the most severe adverse event[a]
Diarrhoea	-0.261 (0.439)	Adapted from [30,31]
Dehydration	0,000 (-)	Assumed no disutility
Fatigue	-0,204 (0.403)	[31]
Febrile neutropenia	-0.150 (0.357)	[32]
Hyperbilirubinemia	-0,204 (0.403)	Assumed equal to fatigue
Loss of appetite	0,000 (-)	Assumed no disutility
Leukopenia	-0.090 (0.286)	Assumed equal to neutropenia
Pneumonia	-0.440 (0.496)	[34]
Nausea	-0.048 (0.214)	[33]
Neutropenia	-0.090 (0.286)	[33]
Peripheral neuropathy	-0.113 (0.317)	[35]
Peripheral sensory neuropathy	-0.113 (0.317)	Assumed equal to peripheral neuropathy
Pulmonary embolism	-0.370 (0.483)	[36]
Thrombocytopenia	-0.108 (0.310)	[37]
Vomiting	-0.103 (0.304)	[32]

Abbreviations: MPC, metastatic pancreatic cancer; SD, standard deviation.
[a]Pneumonia.

Table 3. Unit costs (€2017).

Cost item	Nab-P + G	G	Source
Pre-progression (on treatment)	**Mean (SD)**	**Mean (SD)**	
1st line chemotherapy (drugs)[a,b]	474.85 (-)	118.19 (-)	[22,40]
1st line chemotherapy (premedication+administration+ postmedication)	376.80 (204.89)	241.37 (128.68)	Experts' opinion; [41-43]
Follow-up	120.24 (16.05)	126.59 (16.71)	Research assumptions; [41]
Pre-progression (off 1st line treatment)			
Follow-up[b]	25.82 (-)	25.82 (-)	Research assumptions; [41]
Post-progression (on treatment)			
2nd line chemotherapy (drugs)[b]	97.17 (-)	125.57 (-)	Experts' opinion; [43]
2nd line chemotherapy (premedication+administration+ postmedication)	81.02 (11.95)	91.83 (11.95)	Experts' opinion; [41-43]
Follow-up	97.17 (15.40)	125.57 (19.65)	Experts' opinion; [41]
End of life care (4 weeks to death)	882.46 (514.45)	882.46 (514.45)	Research assumptions; [44,45]
Grade III and IV adverse events			
Abdominal pain		207.37 (232.67)	Experts' opinion; [41-43,45]
Anaemia		469.21 (538.48)	Experts' opinion; [41-43,46,47]
Asthenia		125.81 (185.93)	Experts' opinion; [41-43]
Cholangitis		0.00 (-)	Included in abdominal pain
Diarrhoea		78.53 (145.38)	Experts' opinion; [41-43,46]
Dehydration		78.53 (145.38)	Assumed equal to diarrhoea
Fatigue		125.81 (185.93)	Assumed equal to asthenia
Febrile neutropenia		1027.99 (2452.08)	Experts' opinion; [41-43,46]
Hyperbilirubinemia		0.00 (-)	Assumed no resource consumption
Loss of appetite		0.00 (-)	Assumed no resource consumption
Leukopenia		205.40 (289.60)	Assumed equal to neutropenia
Pneumonia		314.16 (479.33)	Experts' opinion; [41-43,46]
Peripheral neuropathy		21.66 (43.09)	Experts' opinion; [41,43]
Peripheral sensory neuropathy		21.66 (43.09)	Assumed equal to peripheral neuropathy
Nausea		4.29 (4.48)	Experts' opinion; [41,43]
Neutropenia		205.40 (289,60)	Experts' opinion; [41-43]
Pulmonary embolism[b]		3804.09 (-)	[42]
Thrombocytopenia		145.72(265.97)	Experts' opinion; [41-43,46]
Vomiting		121.85 (205.38)	Experts' opinion; [41-43,46]

Notes: [a]Cost per mg: Nab-P + G=€2,45 + €0,07=€2,52; G=€0,07; [b]No SD was calculated, as literature provided no evidence about unit cost dispersion around the mean;
Abbreviations: G, gemcitabine; Nab-P + G, nab-paclitaxel + gemcitabine; SD, standard deviation.

Table 4. Comparison of grade III and IV adverse events.

Adverse event	IRR (95%CI)[a,b]
Abdominal pain	0.616 (0.355;1.061)
Anaemia	1.118 (0.701;1.804)
Asthenia	1.245 (0.662;2.416)
Cholangitis	1.217 (0.401;4.074)
Diarrhoea	3.164 (1.274;9.400)
Dehydration	2.263 (1.081;5.175)
Fatigue	1.519 (1.014;2.314)
Febrile neutropenia	1.582 (0.561;5.076)
Hyperbilirubinemia	0.548 (0.204;1.416)
Loss of appetite	2.099 (0.906;5.428)
Leukopenia	1.898 (1.023;3.707)
Nausea	1.408 (0.713;2.905)
Neutropenia	1.185 (0.898;1.572)
Peripheral neuropathy[c]	- (-)
Peripheral sensory neuropathy	24.824 (4.164; 1008.972)
Pneumonia	1.217 (0.499;3.153)
Pulmonary embolism	0.534 (0.279;1.002)
Thrombocytopenia	1.173 (0.745;1.870)
Vomiting	1.217 (0.617;2.483)

Notes: [a]IRR<1 favours Nab-P + G; [b]If 95%CI does not include 1, IRR is statistically significant; [c]Since the IR of peripheral neuropathy equals 0 for G, no IRR was calculated.
Abbreviations: CI, confidence interval; IRR; incidence rate ratio; Nab-P + G, nab-paclitaxel + gemcitabine.

Table 5. Mean 4-year costs and cost-effectiveness analysis (€2017).

Cost item	Nab-P + G Mean (%)	G Mean (%)	Difference[a] (%)
Pre-progression (on treatment)			
1st line chemotherapy (drugs)	6297.18 (33.14)	1282.28 (10.76)	5014.90 (70.81)
1st line chemotherapy (premedication+administration+postmedication)	4793.65 (25.23)	2696.11 (3.28)	2097.54 (29.62)
Follow-up	465.49 (2.45)	394.35 (3.31)	71.14 (1.00)
Adverse events	209.92 (1.10)	354.05 (2.97)	-144.13 (-2.03)
Pre-progression (off treatment)			
Follow-up	321.60 (1.69)	229.00 (1.92)	92.60 (1,31)
Post-progression			
2nd line chemotherapy (drugs)	1646.79 (8.67)	1773.55 (14.88)	-126.76 (-1.79)
2nd line chemotherapy (premedication+administration+postmedication)	1373.07 (7.23)	1297.06 (10.88)	76.01 (1.07)
Follow-up	313.31 (1.65)	297.01 (2.49)	16.30 (0.23)
End of life care (4 weeks to death)	3467.39 (18.25)	3498.88 (29.35)	-31.49 (-0,44)
Adverse events	113.62 (0.60)	97.06 (0.81)	16.56 (0.23)
Total	**19,002.03 (100.00)**	**11,919.34 (100.00)**	**7082.68 (100.00)**
LYS[b]	0.914	0.718	
QALYs	0.715	0.561	
Incremental costs (ΔC)	7082.68[c]		
Incremental LYS (ΔLYS)	0.196[d]		
Incremental QALYs (ΔQALYs)	0.154[e]		
ICER (ΔC/ΔLYS)	36,136,12[f]		
ICUR (ΔC/ΔQALYs)	46,021.58[g]		

Notes: [a](Cost of Nab-P + G - cost of G); [b]Progression-free LYS with Nab-P + G (G): 0.615 (0.481); [c]95% CI ΔC: €5852.09;€8670.10; [d]95%CI ΔLYS: 0.099;0.287; [e]95% CI ΔQALYs: 0.088;0.220; [f]95% CI ICER: €23,669.01;€74,569.41; [g]95% CI ICUR: €33,291.60;€78,959.99.
Abbreviations: CI, confidence interval; G, gemcitabine; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LYS, life-year saved; Nab-P + G, nab-paclitaxel + gemcitabine; QALYs, quality-adjusted life years.

Figure 1. Markov model structure.

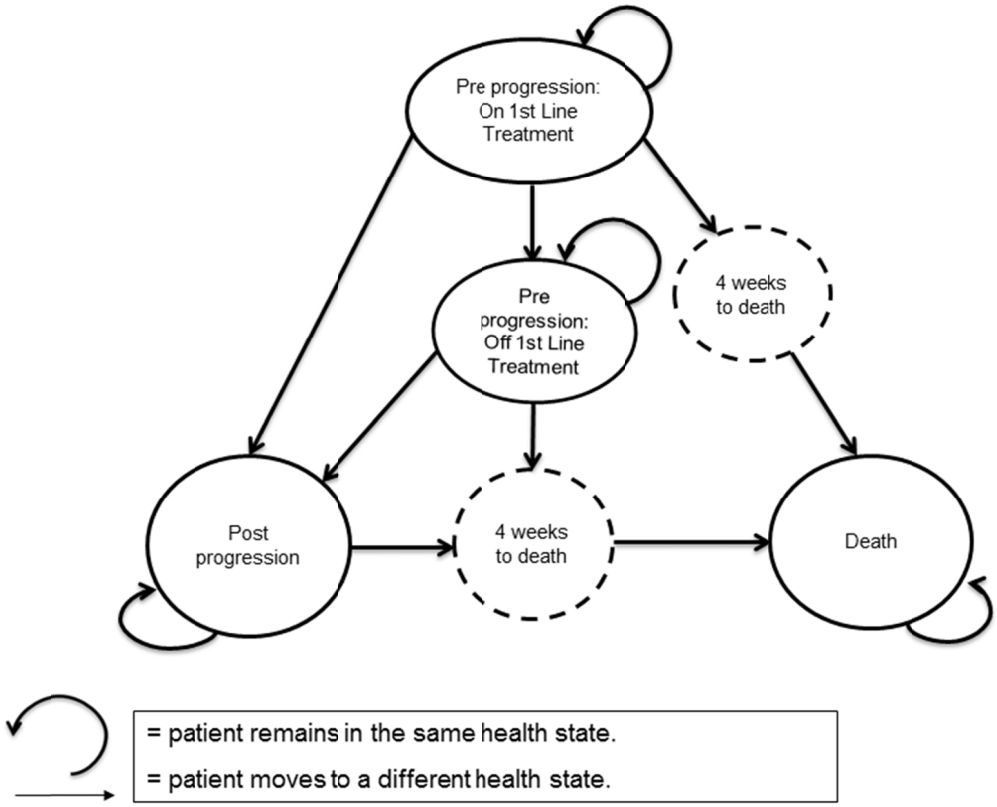
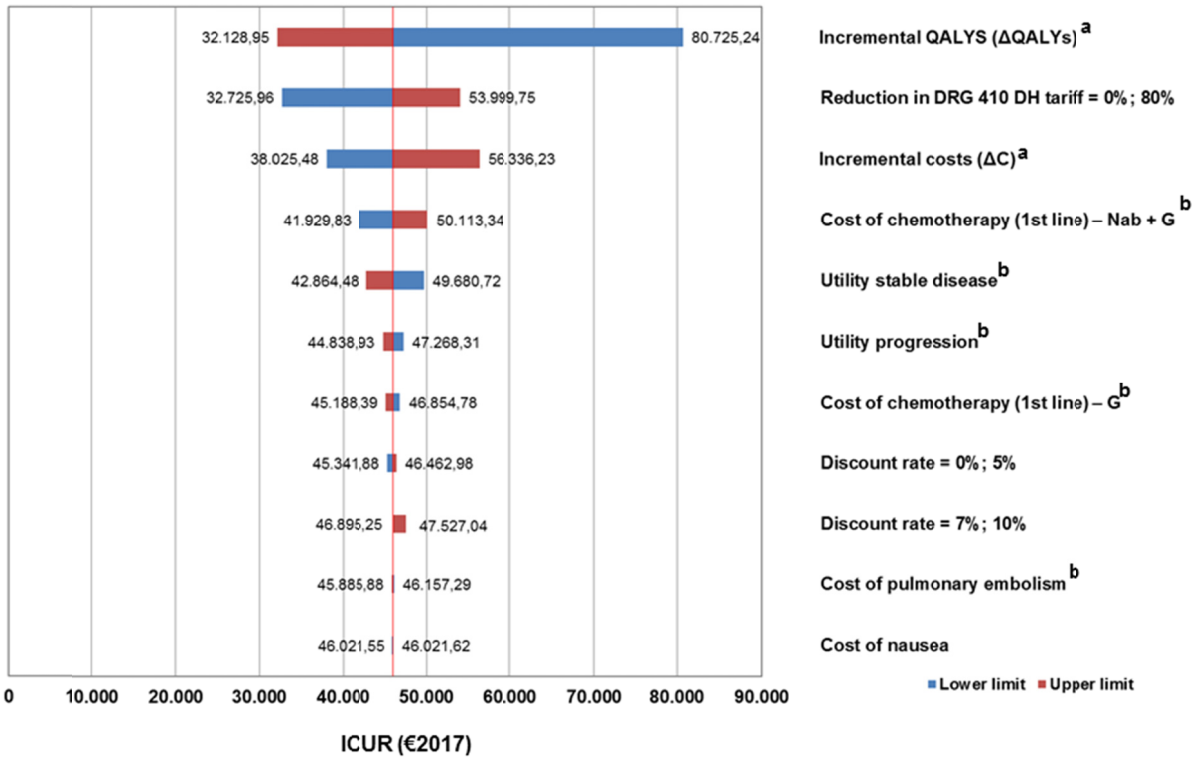
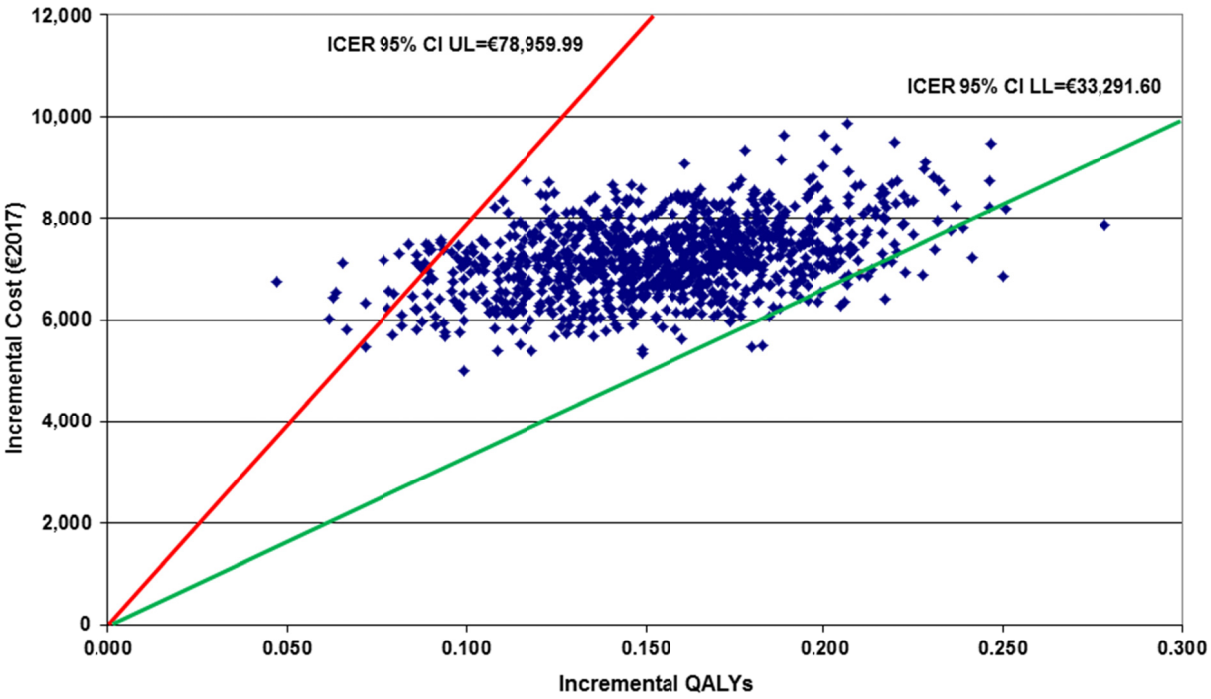


Figure 2. One-way sensitivity analysis - Tornado chart.



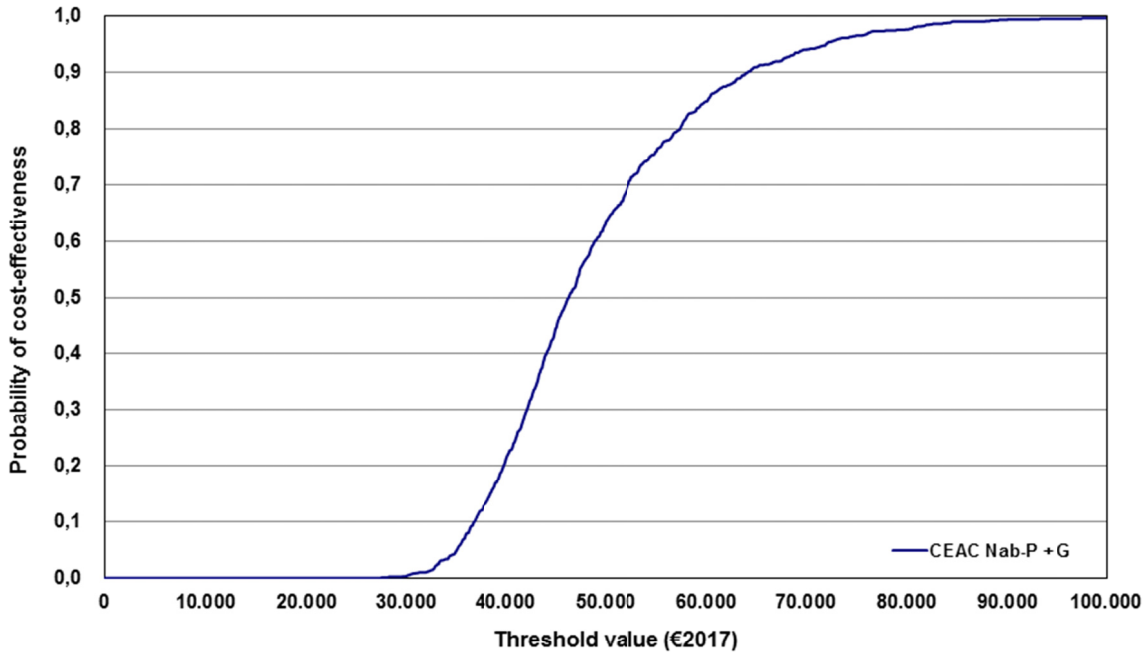
Abbreviations: CI, confidence interval; DH, day-hospital; DRG, Diagnosis-Related Group; G, gemcitabine; ICUR, incremental cost-utility ratio; Nab-P + G, nab-paclitaxel + gemcitabine; QALYs, quality-adjusted life years.
[a] Base case estimate was replaced by the limits of 95% CI; [b] base case estimate was varied by±10%.

Figure 3. Probabilistic sensitivity analysis – Cost-effectiveness plane.



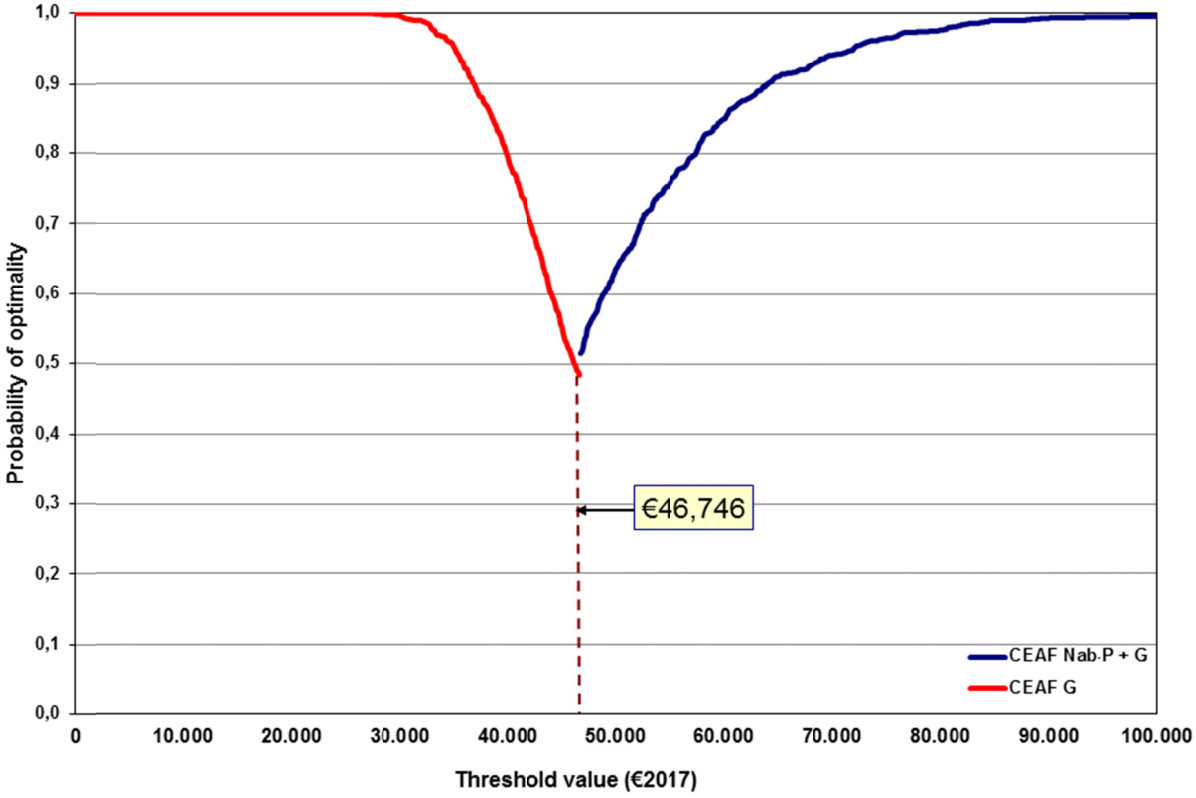
Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; LL, lower limit; QALYs, quality-adjusted life years; UL, upper limit.

Figure 4. Probabilistic sensitivity analysis – Cost-effectiveness acceptability curve.



Abbreviations: CEAC, cost-effectiveness acceptability curve; Nab-P + G, nab-paclitaxel + gemcitabine.

Figure 5. Probabilistic sensitivity analysis - Cost-effectiveness acceptability frontier.



Abbreviations: CEAF, cost-effectiveness acceptability frontier; G, gemcitabine; Nab-P + G, nab-paclitaxel + gemcitabine.
CEAF: Nab + G is the optimal alternative from a threshold value of €46,746 onwards.