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Drug costs and benefits of medical treatments in high-unmet need solid tumours in the Nordic countries



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ABSTRACT

Introduction: Regional and hospital decision-makers increasingly require analyses assessing the cost-benefit profile of new cancer drugs. This analysis evaluates the cost-benefit profile of nano albumin-bound paclitaxel (nab-paclitaxel) in pancreatic cancer, versus other drugs indicated in high-unmet need solid tumour indications in Nordic countries (Sweden, Denmark, Finland, Norway and Sweden).

Methods: For a selected number of cancer drugs, approved for metastatic cancer or non-curable treatment intention patients by the European Medicine Agency (EMA) after 2000, and indicated in high-unmet need solid tumours (defined as OS in first line for trial comparator ≤ 12 months), a regression analysis was conducted. Overall treatment costs of cancer drugs, divided by OS and PFS months, were related to the clinical improvement offered versus trial comparator.

Results: Eleven of 42 drugs (26.2%) with at least one indication in solid tumours met inclusion criteria. On average, a good ($R^2 = 0.5359$) fit between costs per OS month and OS relative benefit versus trial comparator was observed. Nab-paclitaxel offered an OS improvement of +27% versus trial comparator (average improvement: +31%), at a cost per OS month of €1,684 (average cost: €2,247). Correlation between costs per PFS month and relative PFS benefit versus trial comparator was still observed, but the goodness of fit was lower ($R^2 = 0.1853$) than for the OS analysis.

Conclusion: Treatment costs of new cancer therapies should reflect their clinical value, consistently among different indications with comparable characteristics. Nab-paclitaxel, recently approved in pancreatic cancer, showed a similar cost per OS or PFS month ratio compared to other drugs for high-unmet need solid tumours.

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1. Introduction

In the last two decades many cancer treatments have been developed to offer prolonged survival to patients with metastatic cancer. These new treatments have significantly improved survival of certain cancers [1]. However, there are still certain types of high unmet need advanced and/or metastatic tumors, associated with poor prognosis and a median survival less than a year, for which therapies have added only modest numerical increase in survival. Lung, pancreatic, liver, and gastric cancer, certain forms of aggres-

sive breast cancer and melanoma, are only some examples of such high unmet need conditions [2–5]. On parallel, the costs of cancer treatments are increasing rapidly [6,7]. From a policy-making perspective, this means that increasing economic efforts are required to fund the use of more effective and/or less toxic therapies [8]. In a context where the economic resources are limited, there is a need of respecting budget constraints and consequently decisions on budget allocation become extremely difficult to take [9,10].

Policy makers, budget holders, and physicians as well, have the responsibility of deciding how to allocate the assigned budget, taking into account the clinical situation of the patients, and the economic sustainability of the system. To find a balance for these two contrasting drivers, decision makers in all the healthcare sys-

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tem levels must be provided with the necessary information both from a clinical and an economical perspective.

In particular, there is a relevant need to define objective methodologies comparing the cost-effectiveness of drugs in oncology. The typical questions for health economists are: “At certain price conditions, is drug X cost-effective vs. drug Y, for a given cancer?” and “Is this cost-effectiveness of drug X acceptable?” A number of robust methodologies exist to address these question, ranging from cost-effectiveness analysis to cost-utility analysis, using progression free survival, overall survival, quality adjusted survival (with QALYs, quality adjusted life years) as main outcomes [11–13]. Common problems with these analyses are that they are cumbersome and need extensive data of quality of life, further line treatments, and end of life costs for the analysis. At the time of decision these data are often missing and QALYs are impossible to analyze [14]. However, policy makers and budget holders, have other difficult questions to answer, that are beyond the one-to-one comparison in a single disease: “cost of drug X in cancer A is aligned to cost of drug Y in cancer B, in a way that the cost of both drugs reflect their own value”? This question is crucial for those public or private institutions ensuring that investments must be consistent across conditions, in order to avoid access inequalities.

A simple and easy-to-use method should be developed to facilitate the decision makers in determining how to allocate the budget for such serious diseases. For this purpose, the present study aims to suggest a method to compare innovative therapies for high unmet-need solid tumours, considering their drug costs in relation with their clinical benefits.

This article represents an attempt to define a method to address this issue. More specifically, this method was used to compare the economic value of nano-albumin bound paclitaxel (nab-paclitaxel, recently approved by the European Medicines Agency in pancreatic cancer) [15,16], versus other therapies approved in high-unmet-need solid tumours. The analysis correlates the cost of treatment of a group of drugs approved for high-unmet need cancer types, with the additional overall survival (OS) and progression free survival (PFS) benefits provided by the drugs.

2. Methods

This analysis aims to evaluate the cost profile of nano-albumin bound paclitaxel (nab-paclitaxel) in pancreatic cancer versus other therapies in high-unmet need solid tumour indications. The analysis was performed for four Nordic countries (Norway, Sweden, Denmark and Finland) using the health care funder’s perspective. In this analysis treatment costs of drugs were related to their clinical benefit, expressed as absolute efficacy (cost per month of PFS and OS) and relative efficacy versus trial comparator (% PFS and OS months gained).

2.1. Drug selection

Data regarding the drugs’ clinical efficacy (comparator, treatment duration, PFS, OS), posology, co-administration of other cancer therapies (i.e. chemotherapy) and duration of treatment was retrieved from the European Medicine Agency (EMA) website [17], using European Public Assessment Reports (EPARs). Where clinical data was not available, a supplementary published literature search was performed to fill the gap [see Table 1 for references].

The drug searches were performed on March 1st, 2015. For this analysis, we included drugs which: (i) had received the EMA approval after 2000; (ii) had been authorized in at least one metastatic cancer indication; (iii) were indicated in a high unmet need condition (hereby defined as a condition for which the drug

comparator in the registration trial achieved a maximum OS of 12 months).

2.2. Posology and duration of treatment

In order to calculate cost of cancer treatments, standard posology, as reported in EPARs (and relative clinical trials), was used. Calculation of posology was determined assuming to treat a hypothetical patient of 65 Kg, with body surface area (BSA) of 1.73 m². Duration of treatment was retrieved from EPARs, and if not available in the EPARs, from relative published literature [see Table 1 for references].

For those treatment cases in which the amount of active substance exceeded the required posology, the amount of exceeding drug was assumed wasted. For example, if a certain treatment in a hypothetical patient required 2.8 vials, costs were calculated considering 3 vials, assuming that the remaining amount of drug (0.2 vials) could not be used to treat another patient. Duration of treatment was assumed to be equal to that observed in the clinical trial settings.

2.3. Costs

The total cost of each treatment was calculated using pharmacy purchasing price for Denmark [18], Norway [19] and Sweden [20], and wholesaler prices for Finland [21] (which are comparable to pharmacy prices in the other countries). For Finland, wholesaler prices were calculated multiplying the public prices reported in the official source [21] by a coefficient used to convert public prices into wholesaler prices [extrapolated from [22]].

Prices were converted from local currencies to Euros (using average exchange rates over the period January–March 2015, 3 months: 1 Danish Crown: €0.1340; 1 Norwegian Crown: €0.1139; 1 Swedish Crown: €0.1090 [23]). For those therapies having multiple packaging and/or doses, same amount of therapy could be associated to different treatment costs. In this case, the lowest cost achievable was used for the analysis.

Costs of drugs given in association with the study drug (e.g. gemcitabine, co-administered to nab-paclitaxel, or cisplatin, co-administered to S-1) were included in the analysis. Finally, the total cost per patient was obtained for each treatment and for all the Nordic countries in analysis.

2.4. Tumor incidence data

Epidemiology data regarding incident tumor cases (in 2012, latest update) was retrieved for each analyzed Nordic country to estimate the size of the populations that could be treated, and to estimate the related economic impact [24]. The number of diagnosed cases (which took into account whether the therapy was indicated in a specific subgroup of patients, e.g. human epidermal growth factor receptor 2 [HER2] positive gastric cancer for trastuzumab and BRAF mutated in melanoma for vemurafenib) was then transformed in crude incidence rates (expressed number of cases per 100,000 inhabitants), using population data of the Nordic countries [25]. Crude incidence rates were finally used in correlation graphs (x–y scatterplots), where the size of the dots associated to a drug/condition was proportional to tumor incidence. The summary of tumor crude incidence rates is shown in Table 2.

2.5. Analyses

With this analysis, we aimed to examine whether the incremental benefit provided by a drug, versus its trial comparator, predicted the monthly cost per OS/PFS month achieved. Costs per OS and PFS month (or TTP month if PFS was not available) were calculated

Table 1
Drugs' data collected from European Public Assessment Reports.

Therapy	Indication (year of EMA approval)	Posology of study drug	Duration of treatment	Approved drug used in combination	Posology of the approved drug used in combination	Comparator	OS (months)	OS compar. (months)	OS relative benefit (%)	PFS (months)	PFS compar. (months)	PFS relative benefit (%)
Bevacizumab	Lung (2007)	7.5 or 15 mg/kg every 3 weeks + carboplatin/paclitaxel	7.0 cycles (4.9 months) [39]	Carboplatin/paclitaxel	Paclitaxel: 200 mg/m2 Carboplatin: AUC = 6.0 Both drugs given once of every 3-week cycle for up to 6 cycles	Platinum-based chemotherapy and carboplatin	12.3	10.3	19.4%	6.4	4.8	33.3%
Cetuximab	Head and neck (2004)	LD: 400 mg/m2 MD: 250 mg/m2, every week	18 weekly cycles (4.2 months) [40]	Cisplatin or carboplatin + 5-fluorouracil	Cisplatin: 100 mg/m2 5-fluorouracil: 1,000 mg/m2 [41], co-administered to cetuximab	Cisplatin or carboplatin plus 5-fluorouracil	10.1	7.4	36.5%	5.6	3.3	69.7%
Erlotinib	Pancreas (2006)	100 mg once daily or 150 mg once daily	3.6 months (daily treatment) [42,43]	Gemcitabine	Gemcitabine: 1,000 mg/m2, Cycle 1—Days 1, 8, 15, 22, 29, 36 and 43 of an 8 week cycle; Cycle 2 and subsequent cycles—Days 1, 8 and 15 of a 4 week cycle	Gemcitabine alone	6.4	6.0	6.7%	3.8	3.6	5.6%
Ipilimumab	Melanoma (2011)	3 mg/kg every 4 weeks	4.0 cycles (fixed amount of cycles; 2.8 months) [44]	–	–	–	10.1	6.4	57.8%	2.9	2.8	3.6%
Nab-Paclitaxel	Pancreas (2014)	125 mg/m2 on Days 1, 8, and 15 of each 28-day cycle	4.2 cycles (3.9 months) [15,16]	Gemcitabine	Gemcitabine: 1,000 mg/m2, co-administered to nab-paclitaxel	Gemcitabine alone	8.5	6.7	26.9%	5.5	3.7	48.6%
Pemetrexed	Mesothelioma (2004)	500 mg/m2, every 3 weeks	6.0 cycles (4.2 months) [45]	Cisplatin	Cisplatin: 75 mg/m2, after completion of pemetrexed infusion	Cisplatin alone	12.1	9.3	30.1%	5.7	3.9	46.2%
Ramucirumab (combination)	Stomach (2014)	8 mg/kg, on days 1 and 15 of each 28 day cycle	4.6 cycles (4.4 months) [35]	Paclitaxel	Paclitaxel: 80 mg/m2, on days 1, 8 and 15 of a 28 day cycle	Paclitaxel alone	9.6	7.4	29.7%	4.4	2.9	51.7%
Ramucirumab (monotherapy)	Stomach (2014)	8 mg/kg, every 2 weeks	4.8 cycles (2.1 months) [35]	–	–	–	5.2	3.8	36.8%	2.1	1.3	61.5%
S-1	Stomach (2011)	25 mg/m2, twice daily for 21 days, every 4 weeks	4.0 cycles (3.7 months) [46]	Cisplatin	Cisplatin: 75 mg/m2, on Days 1 through 5 repeated every 4 weeks	Cisplatin	8.6	7.9	8.9%	4.8	5.5	-12.7%
Temsirolimus	Kidney (2007)	25 mg once weekly	17.0 cycles (4.0 months) [47]	–	–	–	10.9	7.3	49.3%	3.8	1.9	100.0%
Trastuzumab	Stomach (2009)	LD: 8 mg/kg ; MD: 6 mg/kg every 3 weeks	8.0 cycles (5.6 months) [48]	Chemotherapy (capecitabine or 5-fluorouracil and cisplatin)	Capecitabine: 1,000 mg/m2, twice daily for 14 days every 3 weeks for 6 cycles. 5-fluorouracil: 800 mg/m2/day given every 3 weeks for 6 cycles	Capecitabine or 5-fluorouracil and cisplatin	13.8	11.1	24.3%	6.7	5.5	21.8%
Vemurafenib	Melanoma (2012)	960 mg twice daily	3.1 months (daily treatment) [34,49,50]	–	–	Dacarbazine	13.6	9.7	40.2%	6.9	1.6	318.9%

Note: AUC = area under the curve. LD = loading dose. MD: maintenance dose. The analysis only includes treatments approved for newly diagnosed (first-line) patients, with the exception of ramucirumab, which is indicated after disease progression with chemotherapy [35]. Nevertheless, ramucirumab clinical data from second-line randomized trials were included as this therapy is indicated in a high-unmet need condition (gastric cancer) with a <12 months OS expectation for treatment-naïve patients (cfr S-1 and trastuzumab).

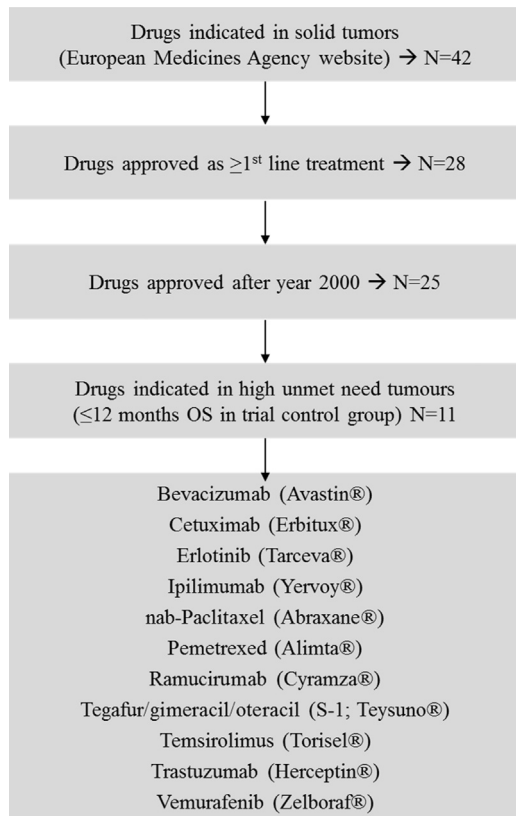


Fig. 1. Algorithm of drug search.

dividing the overall cost of treatment (drug costs over the entire period) by the number of months of OS and PFS achieved with the treatment, respectively.

Second, a linear regression analysis was performed (overall and by country) in order to evaluate dependency of cost per OS/PFS month on incremental benefit achieved. The incremental benefit was expressed as the relative improvement in OS/PFS achieved with the treatment, compared to its trial alternative. Robust regression was evaluated to test goodness of fit. For those cases with poor R^2 (<0.5), determined by observations with high leverages and residuals, a robust regression was attempted to re-calculate R^2 . Robust weighted regression excluded observations with >0.25 Cook distance and weighted the remaining observations according to their residual distances from the means.

Since treatment costs could be affected by patients' characteristics, a simple sensitivity analysis, based on variations of $\pm 10\%$ body surface area (BSA) and $\pm 10\%$ weight, compared to the base case assumption (BSA = 1.73 m²; weight: 65 Kg), was performed to test analysis conclusions. Additional sensitivity analyses were conducted to evaluate results under the assumption of absence of drug wastage.

Analyses were performed for each country, and then aggregated calculating mathematical averages

3. Results

From EMA database, 42 drugs with at least one indication in solid tumours within 20 years were detected. Eleven of these (26.2%), met the selection criteria and were included in the analysis (Fig. 1): bevacizumab in non-small cell lung cancer (NSCLC), cetuximab in head and neck cancer (HNC), erlotinib in pancreatic cancer (PancC); ipilimumab in melanoma, nab-paclitaxel in PancC, pemetrexed in mesothelioma, ramucirumab in gastric cancer (or

gastro-oesophageal junction) cancer, used as both in monotherapy and in combination; S-1 (tegafur/gimeracil/oteracil) in gastric cancer (GC); temsirolimus in renal cell carcinoma (RCC), trastuzumab in HER2 positive GC and vemurafenib in BRAF V600 mutation-positive melanoma (BRAF melanoma).

Table 1 reports the information extracted from EPARs [15,26–35] and from published clinical trials [see Table 1 for references], which was used to calculate treatment costs and related outcomes. Except for three therapies (temsirolimus, ipilimumab and vemurafenib), the remaining agents are administered in combination with chemotherapy and compared versus chemotherapy alone (i.e. tested as add-on therapy trials). Only ipilimumab is administered up to the maximum number of cycles ($N=4$), while the remaining therapies are discontinued at time of intolerance or disease progression. Median PFS and OS in the comparator arm (proxy of disease prognosis with standard, alternative options) were 3.5 and 7.4 months, respectively, confirming the high level of unmet clinical needs for these conditions

Table 3 reports the overall drug costs of the chosen therapies (including costs of drugs given in association, if any) in the Nordic countries. Small variability of average costs by country was observed (range: €21,844–€22,799), but it was not statistically significant (test F for variance: 0.9243). On the other side, internal cost variability was high (average of the four countries: €1,761–€66,243) with S-1 and erlotinib being the less expensive treatments, and ipilimumab and vemurafenib the most expensive ones. Economic impact of chemotherapies given in association to the study drugs was not negligible, especially for erlotinib, and nab-paclitaxel, which are co-administered with gemcitabine.

Tables 4 and 5 show results of the cost per OS and PFS months gained respectively. Considering the average of the four Nordic countries, the drug associated with the lowest cost per OS was S-1 (€205 per OS month gained), while the one with the highest was ipilimumab, (€6,642 per OS month gained). The same trends were observed for all countries and for PFS, too. Average costs of nab-paclitaxel were €1,684 per month of OS gained and €2,602 per month of PFS gained. Figs. 2 and 3 show results of the regression analyses between cost per OS and PFS, respectively, and relative clinical benefits achieved versus trial comparator (Figs. 4 and 5 show results of correlation between costs and absolute benefit vs. trial comparator). Drugs positioned below the regression line had a cost-benefit profile more advantageous than the average. Analysis shows that drugs with higher relative benefit had generally higher costs per OS or PFS gained. A good prediction was found for OS ($R^2 = 0.5359$). For PFS analysis, linear regression was associated to poor fit ($R^2 < 0.01$). This was driven by two observations: ipilimumab (high residual) whose cost per PFS month was higher than the mean monthly costs, considered its relatively low PFS advantage, and vemurafenib (high leverage), whose PFS effect was higher than the mean, considered its cost. When robust regression was performed to minimize the effects of these unexpected observations, R^2 improved (0.1853), but remained much lower than for OS analysis. In both analyses, nab-paclitaxel was found not above regression lines, indicating that its cost was, at least, aligned to the clinical value offered

Analysis of individual countries led to similar results for costs per OS and PFS month as shown in Figs. 6 and 7. Overall, results indicated that the overall cost of treatment for a drug reflected much better the OS endpoint achievement, rather than the PFS achievement.

Finally, one-way sensitivity analysis conducted on BSA and weight demonstrated some variability of results depending on patient's characteristics (Table 6). For drugs administered at fixed doses (temsirolimus, ipilimumab, vemurafenib) costs remained equal. Among drugs administered according to BSA or weight, treatment costs (and consequentially costs per OS and PFS) changed,

Table 2
Tumor crude incidence rates/100,000 standard population [calculated from: [24,25]].

Indication	Crude incidence rate (new cases/100,000 subjects)				
	Denmark	Norway	Sweden	Finland	Note
Pancreas	18.3	21.3	14.7	10.2	–
Mesothelioma ^a	1.3	1.6	1.2 ^b	>1.0 ^b	Estimated incidence of mesothelioma was not available from Globocan [24]. In alternative, the publication of Bianchi et al. was used [51].
Lung	69.6	39.3	48.5	34.9	–
Head & neck	29.0	18.0	17.8	17.0	–
Stomach	3.0	3.2	2.6	2.3	Incidence of gastric cancer was multiplied by 27%, the estimated frequency of HER2+ cases [52].
Kidney	13.4	16.1	15.8	11.6	–
Melanoma	28.6 (14.3)	22.4 (11.2)	30.2 (15.1)	30.7 (15.3)	Incidence rates in parenthesis are referred to BRAF mutation, which represents about 50% of melanomas [53].

^a Statistics on mesothelioma not available from Globocan.

^b Pleural mesothelioma only.

Table 3
Overall treatment costs, by therapy and country.

Therapy	Denmark		Norway		Sweden		Finland		Average of the 4 Nordics	
	Total drug costs (€)	Cost of study drug (% vs. total drug costs) ^a	Total drug costs (€)	Cost of study drug (% vs. total drug costs) ^a	Total drug costs (€)	Cost of study drug (% vs. total drug costs) ^a	Total drug costs (€)	Cost of study drug (% vs. total drug costs) ^a	Total drug costs (€)	Cost of study drug (% vs. total drug costs) ^a
Bevacizumab	17,928	90%	24,685	59%	18,969	91%	17,963	96%	19,886	82%
Cetuximab	23,509	96%	18,813	95%	22,916	96%	20,239	97%	21,369	96%
Erlotinib	6,808	93%	10,116	55%	7,427	85%	7,201	91%	7,888	78%
Ipilimumab	65,521	100%	62,406	100%	68,884	100%	68,882	100%	66,423	100%
Nab-paclitaxel	12,562	97%	14,625	73%	15,124	94%	14,943	96%	14,313	90%
Pemetrexed	16,285	99%	11,983	97%	17,171	98%	17,625	99%	15,766	98%
Ramucirumab (combination)	38,865	95%	43,458	81%	37,474	98%	36,718	99%	39,129	93%
Ramucirumab (monotherapy)	17,551	100%	16,854	100%	17,513	100%	17,362	100%	17,320	100%
S-1	1,840	93%	1,685	78%	1,900	84%	1,620	87%	1,761	86%
Temsirolimus	14,380	100%	13,618	100%	16,022	100%	15,757	100%	14,944	100%
Trastuzumab	19,485	95%	18,006	92%	21,708	98%	21,345	96%	20,136	95%
Vemurafenib	28,107	100%	25,984	100%	28,478	100%	22,477	100%	26,262	100%

^a Since certain therapies are given in combination, they will account for a certain proportion of overall therapy costs. Drugs given as monotherapy account for the entire therapy costs (100%).

Table 4
Costs per month of overall survival, by therapy and country.

Therapy	Indication	Absolute benefit (months)	Relative benefit (%)	Cost per month of OS (€/month)				
				Denmark	Norway	Sweden	Finland	Average of 4 Nordics
Bevacizumab	Lung	2.0	19%	1,458	2,007	1,542	1,460	1,617
Cetuximab	Head & neck	2.7	36%	2,328	1,863	2,269	2,004	2,116
Cyramza (alone)	Stomach	1.4	37%	3,375	3,241	3,368	3,339	3,331
Cyramza (in association)	Stomach	2.2	30%	4,048	4,527	3,904	3,825	4,076
Erlotinib	Pancreas	0.4	7%	1,064	1,581	1,160	1,125	1,232
Ipilimumab	Mesothel.	4.0	67%	6,552	6,241	6,888	6,888	6,642
Nab-paclitaxel	Stomach	1.8	27%	1,478	1,721	1,779	1,758	1,684
Pemetrexed	Stomach	2.8	30%	1,346	990	1,419	1,457	1,303
S-1	Stomach	0.7	9%	214	196	221	188	205
Temsirolimus	Kidney	3.6	49%	1,319	1,249	1,470	1,446	1,371
Trastuzumab	Stomach (HER2+)	2.7	24%	1,412	1,305	1,573	1,547	1,459
Vemurafenib	Melanoma (BRAF)	3.90	40%	2,067	1,911	2,094	1,653	1,931
Average of products	–	2.2	31%	2,222	2,236	2,307	2,224	2,247

especially for cetuximab, nab-paclitaxel, pemetrexed and ramucirumab. For these cases, modification of BSA or weight did determine the usage of more/less vials, compared to the base case. For nab-paclitaxel, a 10% increase of the BSA (from 1.73 m² to 1.90 m²) practically did not modify cost per OS and PFS (variation: +0.36%, while a 10% decrease of the BSA) (from 1.73 m² to 1.56 m²) determined a variation of –30.7% for the same outcome. Consistent variation of results were also observed under the assumption of no

wastage. As expected, cost per month of OS and PFS decreased for all drugs administered intravenously. Specifically for nab-paclitaxel, the cost reduction from base case analysis was about 26%.

4. Discussion

With the present analysis we aimed to address two main topics. First, we wanted to apply a simple quali-quantitative method to

Table 5
Costs per month of progression free survival (€/month), by product and country.

Therapy	Indication	Absolute benefit (months)	Relative benefit (%)	Cost per month of PFS (€/month)				
				Denmark	Norway	Sweden	Finland	Average of 4 Nordics
Bevacizumab	Lung	1.6	33%	2,801	3,857	2,964	2,807	3,107
Cetuximab	Head & neck	2.3	70%	4,198	3,359	4,092	3,614	3,816
Erlotinib	Pancreas	0.2	6%	1,815	2,698	1,980	1,920	2,103
Ipilimumab	Melanoma	0.1	4%	22,909	21,820	24,085	24,084	23,225
Nab-paclitaxel	Pancreas	1.8	49%	2,284	2,659	2,750	2,717	2,602
Pemetrexed	Mesothel.	1.8	46%	2,857	2,102	2,102	3,092	2,538
Ramucirumab (combination)	Stomach	1.5	52%	8,833	9,877	8,517	8,345	8,893
Ramucirumab (monotherapy)	Stomach	0.8	62%	8,358	8,026	8,339	8,268	8,248
S-1	Stomach	-0.7	-13%	383	351	396	338	367
Temsirolimus	Kidney	1.9	100%	3,784	3,584	4,216	4,147	3,933
Trastuzumab	Stomach (HER2+)	1.2	22%	2,908	2,688	3,240	3,186	3,005
Vemurafenib	Melanoma (BRAF)	5.2	319%	4,091	3,782	4,145	3,272	3,823
Average of products	-	1.5	62%	5,435	5,400	5,569	5,482	5,472

Note: N/A = not available.

Table 6
Results of sensitivity analysis.

Therapy	Cost per month of OS (€/month)					
	Base case	+10% BSA	-10% BSA	+10% weight	-10% weight	No wastage
Bevacizumab	1,617	1,636	1,597	1,801	1,525	1,550
Cetuximab	2,116	2,137	1,736	2,116	2,116	1,837
Erlotinib	1,232	1,242	1,212	1,232	1,232	1,019
Ipilimumab	6,642	6,642	6,642	8,303	6,642	6,476
Nab-paclitaxel	1,684	1,690	1,167	1,684	1,684	1,244
Pemetrexed	1,303	1,346	1,147	1,303	1,303	1,164
Ramucirumab (combination)	4,076	4,137	4,076	4,076	3,440	3,531
Ramucirumab (monotherapy)	3,331	3,331	3,331	3,331	2,771	2,882
S-1	205	225	185	205	205	193
Temsirolimus	1,371	1,371	1,371	1,371	1,371	1,143
Trastuzumab	1,459	1,466	1,454	1,459	1,459	996
Vemurafenib	1,931	1,931	1,931	1,931	1,931	1,931

Therapy	Cost per month of PFS (€/month)					
	Base case	+10% BSA	-10% BSA	+10% weight	-10% weight	No wastage
Bevacizumab	3,107	3,144	3,069	3,461	2,930	2,979
Cetuximab	3,816	3,855	3,132	3,816	3,816	3,313
Erlotinib	2,103	2,120	2,068	2,103	2,103	1,738
Ipilimumab	23,225	23,225	23,225	29,033	23,225	22,644
Nab-paclitaxel	2,602	2,612	1,803	2,602	2,602	1,922
Pemetrexed	2,538	2,631	2,239	2,538	2,538	2,471
Ramucirumab (combination)	8,893	9,026	8,893	8,893	7,506	7,703
Ramucirumab (monotherapy)	8,248	8,248	8,248	8,248	6,861	7,136
S-1	367	404	331	367	367	346
Temsirolimus	3,933	3,933	3,933	3,933	3,933	3,277
Trastuzumab	3,005	3,021	2,995	3,005	3,005	2,052
Vemurafenib	3,823	3,823	3,823	3,823	3,823	3,823

test whether the cost of a drug reflected its real clinical value, comparing pharmaceutical treatments approved for different oncology uses. Then we wanted to test the method, analyzing the practical case of the comparison between nab-paclitaxel versus other pharmacological treatments that could represent a good benchmark.

Regarding the first topic, the analysis showed a good consistency between the sustained cost per OS month for a drug, and the relative OS increase offered by the drug vs. its trial comparator. According to this analysis, the higher is the clinical benefit, the higher is the cost per OS month, reflecting that budget holders in Nordic countries recognized consistently the value of the drugs. In this analysis, there were not large deviations from the expected trend. Unlike the OS analysis, the PFS analysis did not produce similar results, and the correlation between cost per PFS month and PFS relative benefit was mainly reduced by three drugs: ipilimumab, vemurafenib, ramucirumab. Ipilimumab was not associated to PFS advantage vs. trial comparator (2.86 months for ipilimumab; 2.76 placebo months for placebo; [44]); vemurafenib was associated to

a relevant, statistically significant PFS advantage (6.9 months for vemurafenib, vs. 1.6 months for placebo). Ramucirumab was not associated to a ≥ 0.25 Cook distance, however its cost per PFS month was higher than expected (average of all observations), if correlated to the relative PFS gain. These observations decreased the overall goodness of regression; moreover, regardless of these drugs, the relation between costs and PFS advantage was less clear than the OS relation, especially in certain countries (Norway and Sweden).

Several considerations can be made to explain this trend for the PFS analysis. In the ipilimumab trial, for example, OS was the clinically important and primary endpoint [44]. Likely, PFS could be an un-appropriate indicator for this drug. As a matter of fact, European Public Assessment Report does not report PFS data and clearly indicates that, if tolerated, the 4-cycles treatment should be continued and completed regardless of clinical response and early progression of the disease [29], suggesting that the drug could have a kind of “delayed” effect, making PFS endpoint not extremely relevant. As a matter of fact, ipilimumab was the drug associated with the

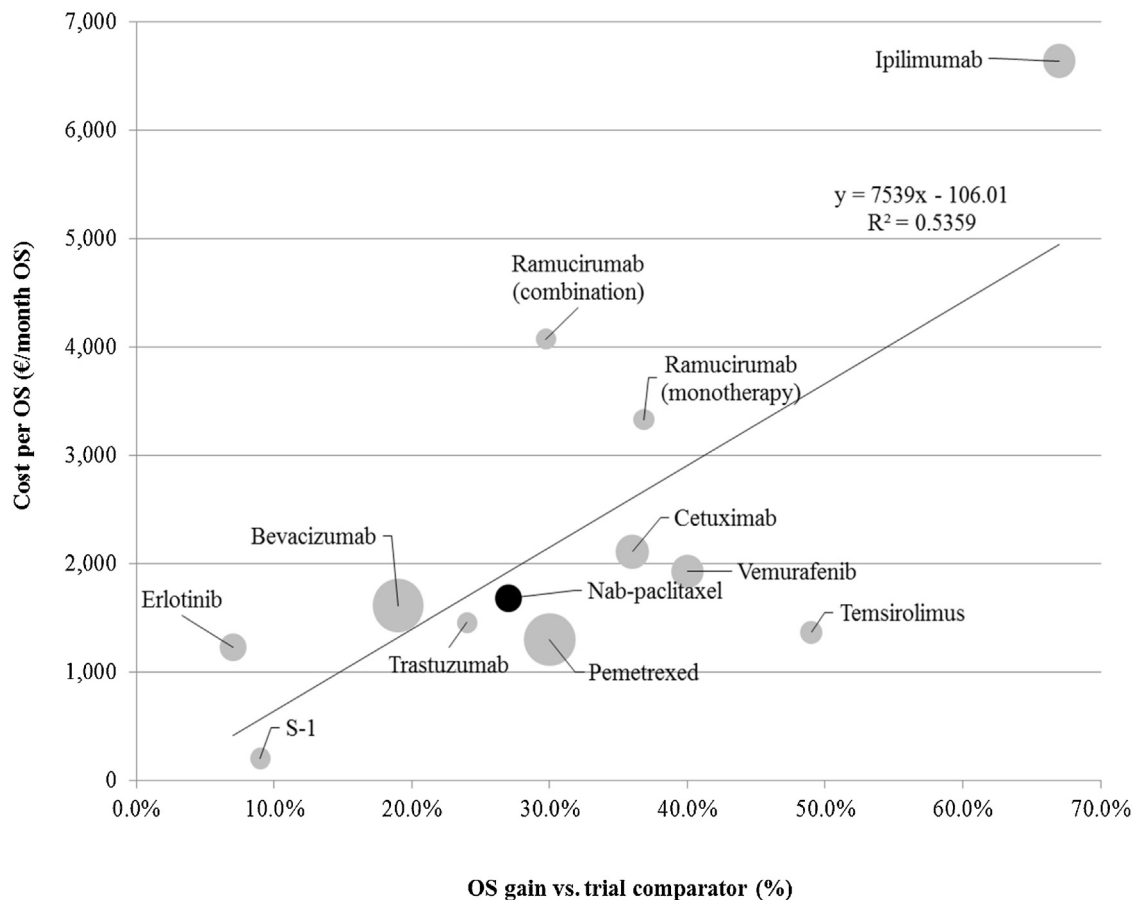


Fig. 2. Costs per month of OS (€/month) vs. OS benefit: average data of the four Nordic countries. Size of bubbles is proportional to incidence rates [Table 2]. ● = 10–20 cases per 100,000 persons/year. †Cost per OS month was found statistically dependent on OS gain vs. trial comparator.

highest OS advantage. Vemurafenib showed clear advantages in both PFS and OS, but it should be mentioned that the drug works only in a subgroup of patients (BRAF mutation patients). Similarly, trastuzumab, the other drug approved for use in a subpopulation (HER2+ gastric cancer) had a favorable ratio between costs and clinical benefit.

Focusing on nab-paclitaxel analysis, the drug cost per month of OS and PFS shows an overall favorable profile.

In our view, the quali-quantitative approach adopted in this analysis, with certain refinements, can be transformed into a good tool for decision makers to evaluate consistency of decisions across different oncology areas. Of course, the method cannot be considered a pure quantitative tool to anchor pricing and reimbursement decisions, but it can definitely help to avoid inconsistencies in budget allocation.

The major issue for such approach is to define the conditions/criteria to detect comparators for a certain therapies, particularly when deciding on how to allocate healthcare funds. In our analysis, we detected benchmarks for nab-paclitaxel using a set of criteria (i.e. solid tumors, drugs predominantly used in naïve patients, approved after year 2000, indicated in conditions associated to poor prognosis). We considered such selection criteria objective and appropriate to reduce the potential heterogeneity of comparisons. However, it could be argued that certain inclusion criteria were not used at all (e.g. include/exclude therapies indicated in specific patients' subgroups; include/exclude therapies based on the epidemiological impact of the associated condition). In our view, a good compromise on the number of selection criteria should be made, in order to ensure that comparison would remain

valid and informative, and to keep a good number of therapies for comparison

Our focus on objective criteria, such as median times-to-event, may introduce an oversimplification of important considerations in the selection of the most appropriate therapy: long-term survival benefits in small patient groups are not included in the analysis of medians of a patient population and underestimated in this approach when compared to real-life clinical practice. An evaluation of more comprehensive, and complex, health-economic analysis and studies is required to fully evaluate the benefit of these therapies across all sub-groups of patients. Additional considerations to opportunity costs and sensitivity analysis to address uncertainty in calculations, for example, are not included in this analysis but are standard to a thorough health-economic analysis.

In the present analysis, we used incidence data to estimate the potential patient population eligible for each treatment. Of course this approach is not extremely accurate to determine the budget impact associated to a certain therapy, as incidence and treatment duration are only two of the several factors determining the amount of drug use. A substantial number of patients with metastatic disease will not receive any chemotherapy at all due to usually old age or poor performance status [36–38]. On the other side, the more accurate approach, which would consist in determining the number of treated patients using national drug consumptions, would be equally difficult to implement. In fact, this analysis would require availability of national data, drug use during comparable periods of time (the use of a drug generally increases over time, and changes according to the availability of therapeutic alternatives). Finally, for certain therapies indicated for multiple conditions (e.g.

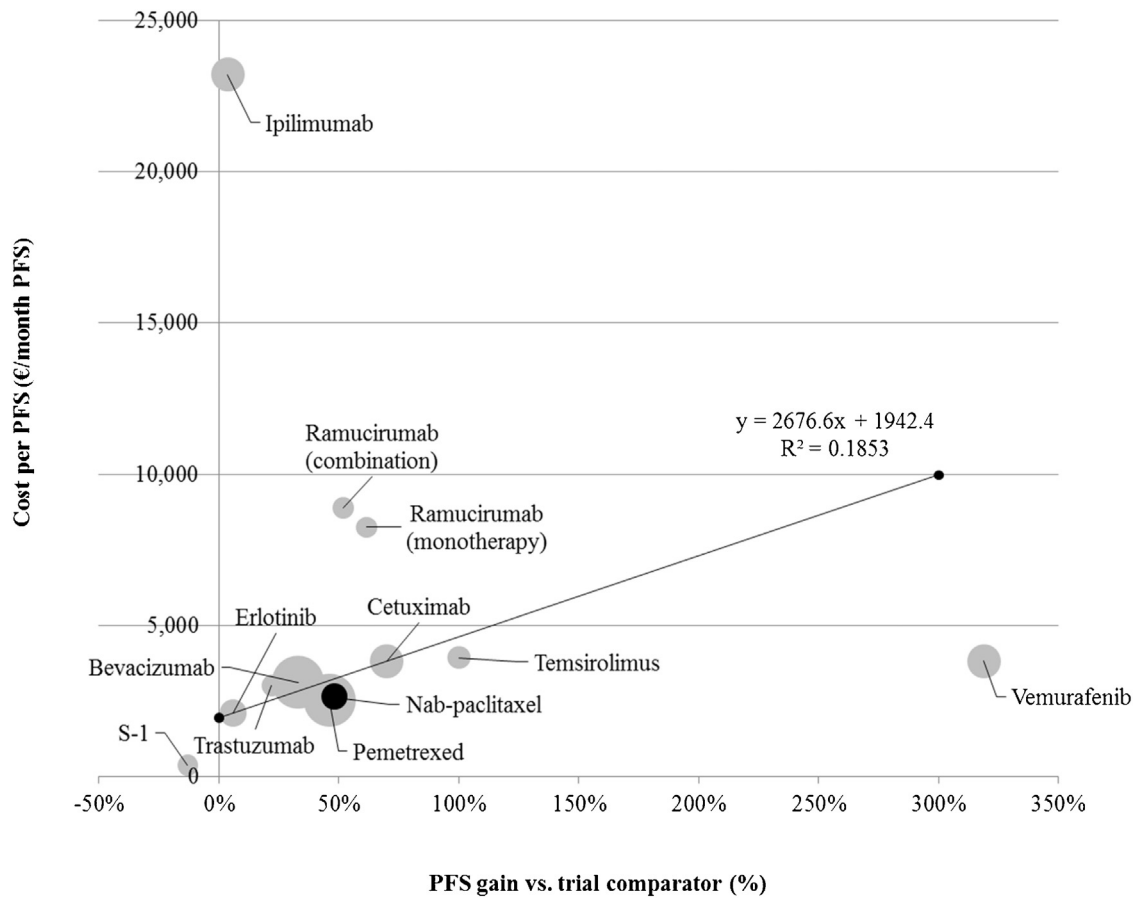


Fig. 3. Costs per month of PFS (€/month) vs. PFS benefit, average data of the four Nordic countries*. Size of bubbles is proportional to incidence rates [Table 2]. ● = 10–20 cases per 100,000 persons/year. *Calculated through robust regression. †Cost per PFS month was found statistically dependent on PFS gain vs. trial comparator.

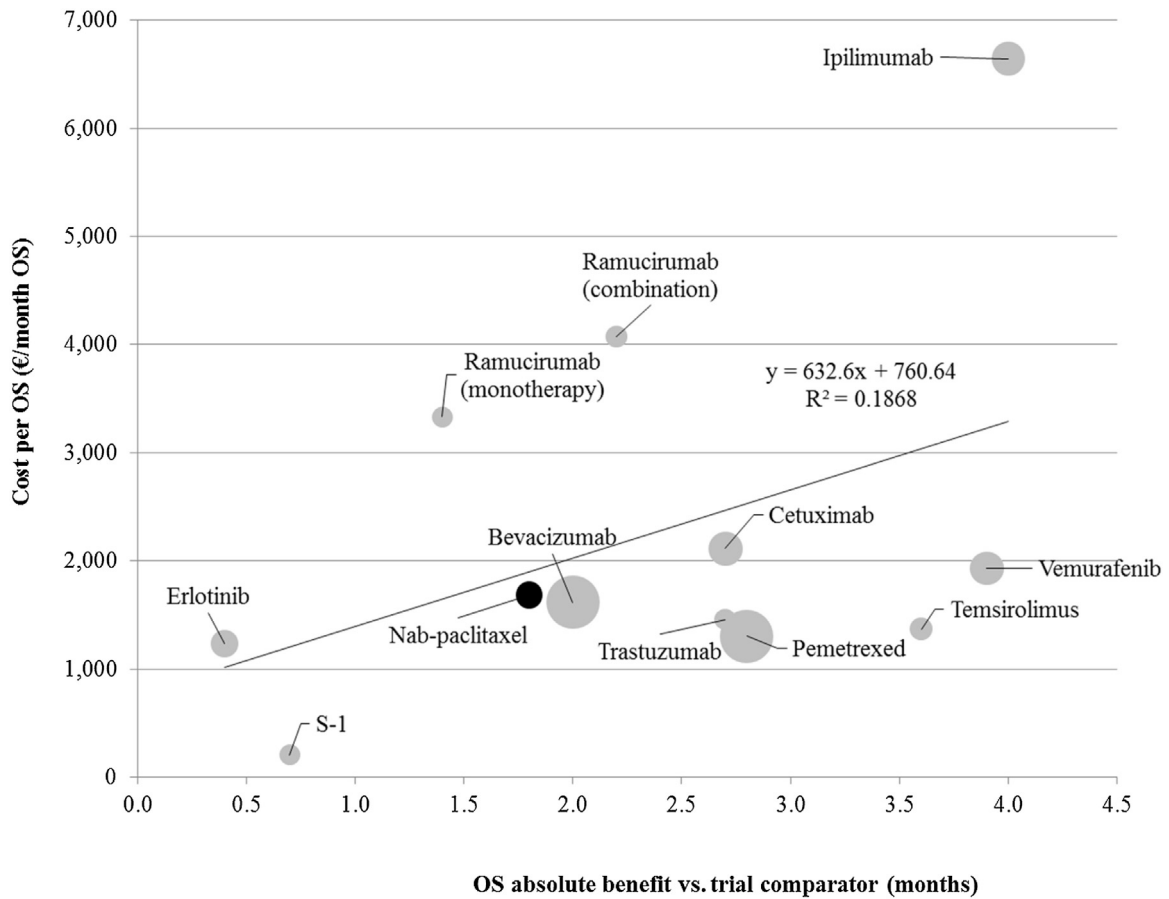
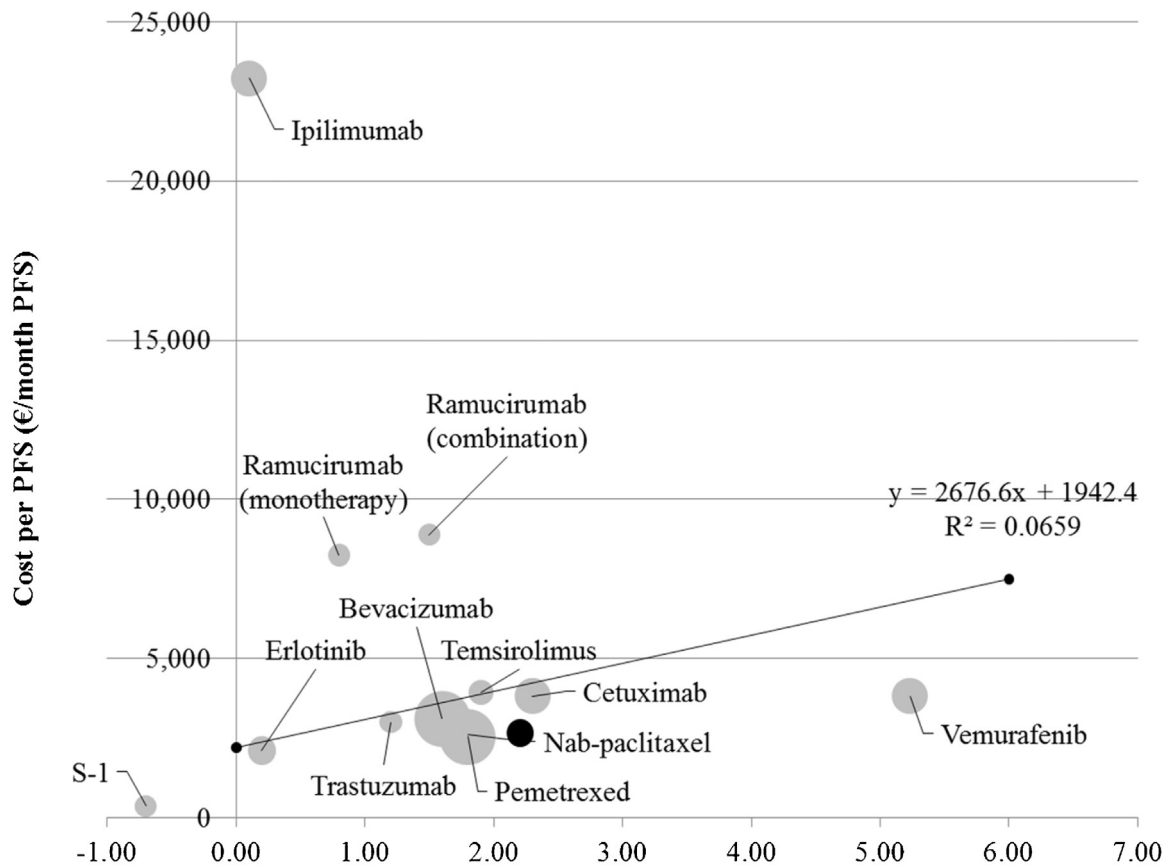


Fig. 4. Costs per month of OS (€/month) vs. OS absolute benefit vs. trial comparator.



PFS absolute benefit vs. trial comparator (months)

Fig. 5. Costs per month of PFS (€/month) vs. PFS absolute benefit vs. trial comparator.

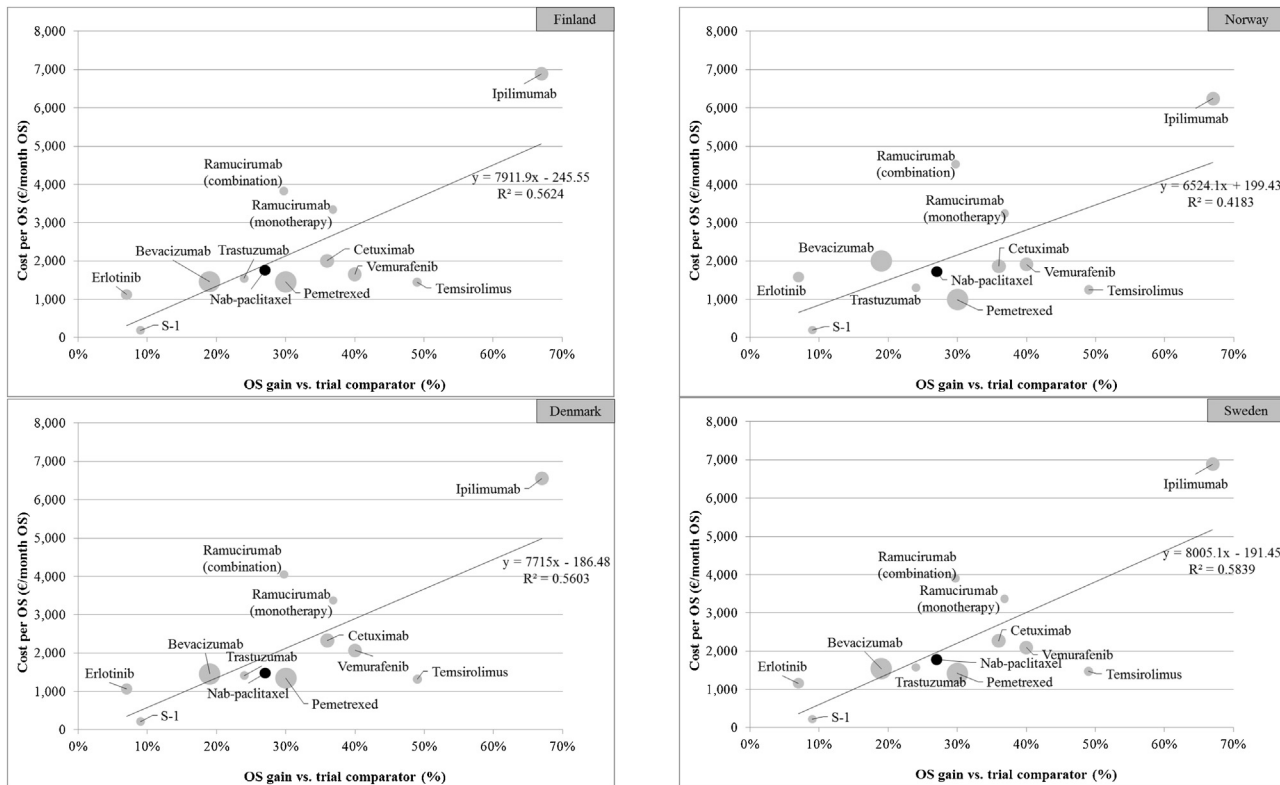


Fig. 6. Costs per month of OS (€/month) vs. OS benefit, by product and country.

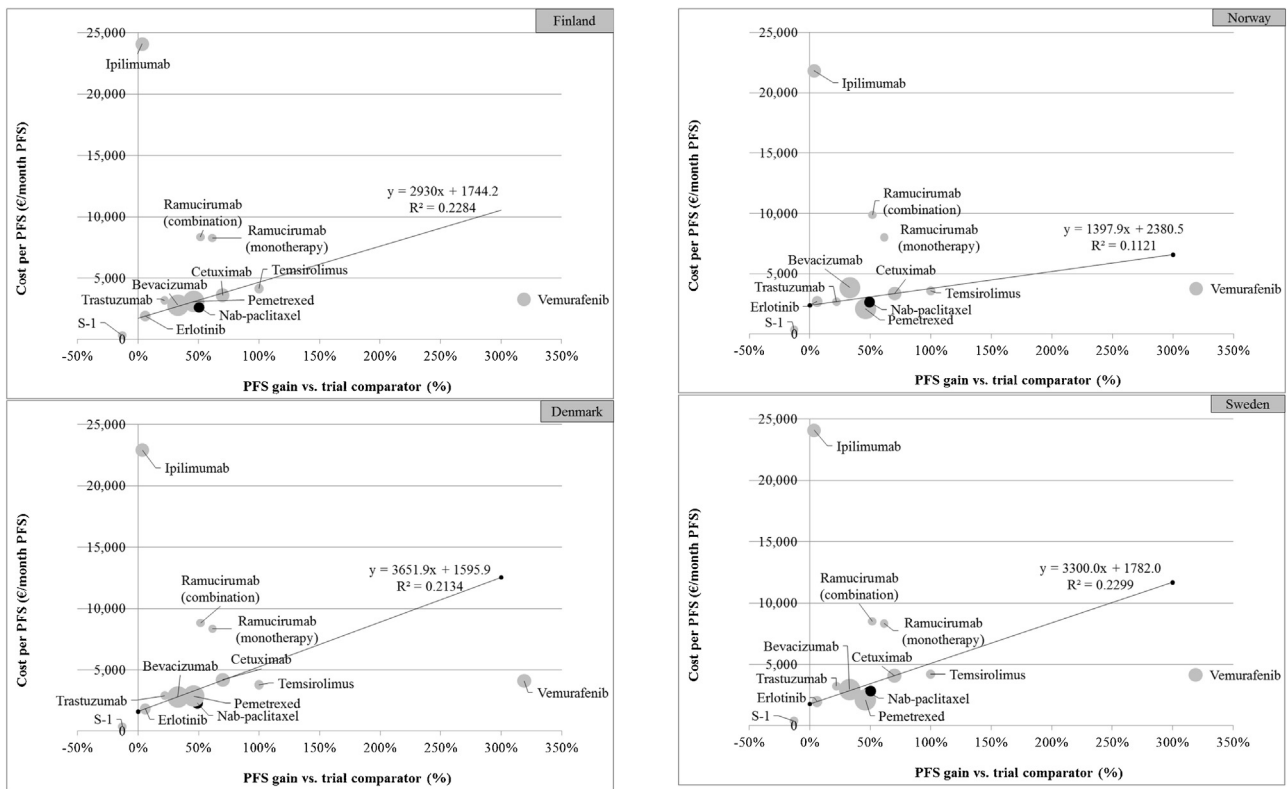


Fig. 7. Costs per month of PFS (€/month) vs. PFS benefit, by product and country*. Size of bubbles is proportional to incidence rates [Table 2]. ● = 10–20 cases per 100,000 persons/year. #Cost per PFS month was found statistically dependent on PFS gain vs. trial comparator.

trastuzumab, bevacizumab) it would be necessary to stratify use by indication, which is almost impossible with current available data.

Other refinements could increase the validity of this type of analysis. First, cost of treatment could be adjusted by dose intensity. As a matter of fact, in certain clinical trials, therapeutic dosage could have been decreased/increased to take into account risk-benefit factors. In the nab-paclitaxel pivotal trial, for example, dose intensity was 81% [16]. This correction was not applied in our analysis, as similar information was not available for all investigated therapies, but this aspect could be taken into account for further research using this approach. Second, prices used in these analyses should include all those forms of discounts/rebates (price-volume, cost sharing, payment by results agreements, etc.) that could affect costs of treatment. Finally, a systematic approach collecting all published evidence on a certain drug/indication, integrating or pooling clinical data with meta-analytic approaches, would make the analyses even more accurate, although this could affect its easiness-to-use.

Summarizing, we believe that decision making in healthcare, and specifically in oncology, is a very complicated process that cannot be converted into a “perfect” algorithm. Many factors related to the individuality of a disease and to the clinical needs of patients that cannot be simply measured or calculated with formulas. However, analytical tools, such as the one we proposed, could simply offer an additional hint to take decisions or to make sure that the decision respects certain rules

Conflict of interest

G. Furneri has received a compensation from Celgene Nordics. F. Rodrigues is a Celgene’s employee. P. Österlund, H. Sorbye, P. Pfeiffer and A. Johnsson received no fee for this publication.

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The funding sources had no involvement in study design; in the collection, analysis and interpretation of data and in the writing of the article

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