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# Clinical outcomes do not correlate with anticancer drug prices: a cross-sectional study in Italy



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**contributorship statement**

FT, NM and AA conceptualized the study; FT, AA, NM, FM, FBA, GT, and RDC designed the study; FBA, RP, IE and NM were in charge of data extraction and quality control; FM, RDC, and FT performed the data analysis; FT, RDC, FM, GT, BG and AA drafted the manuscript; all the authors contributed to the discussion and the interpretation of results, and reviewed the final version of the manuscript. All authors approved the final manuscript as submitted.

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**Abstract**:

**Objective** To investigate whether the prices of new anticancer drugs correlated with their relative benefit despite negotiation.

**Design** Retrospective cross-sectional study correlating new anticancer drugs prices with clinical outcomes

**Setting** We did a retrospective cross-sectional study including all new anticancer drugs approved by the European Medicines Agency (2010-2016) and reimbursed in Italy.

**Main Outcome(s) and Measure(s)** Information on clinical outcomes - in terms of median Overall Survival (OS), median Progression Free Survival (PFS) and Objective Response Rate (ORR) - were extracted from pivotal trials as reported in the European Public Assessment Reports available on the EMA website. Cost of a full course treatment was estimated on negotiated official and discounted prices. Regression coefficients β, their levels of significance p and the coefficients of determination $R^2$ were estimated adjusting by tumour type.

**Results** Overall, 30 new anticancer drugs (with 35 indications) were available for analysis. There was no correlation between the improvement in median OS (in weeks) and negotiated price ($R^2$= 0.067, n = 16 drugs for 17 indications). When the clinical outcomes were expressed as improvements in median PFS or ORR, 25 drugs (29 indications) were available for analysis, and again, there was no correlation with prices ($R^2$= 0.004 and 0.006, respectively).

**Conclusions and Relevance**: Our results suggest that the prices of anticancer drugs in Italy do not reflect their therapeutic benefit. Drug price negotiations, which is mandatory by law in Italy, do not



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seem to ensure that prices correlate with clinical benefits provided by cancer drugs. These results call for further efforts to establish the standard determinants of drug prices available at the time of negotiation. These findings need to be confirmed in other countries where price negotiations are in place.

**Strengths and limitations of this study**,

- This study is the first attempt to evaluate whether there were better correlations between cancer drug prices and clinical outcomes in a setting where central price negotiations are mandatory for every new medicine.
- This understanding is important for cancer policy decisions.
- In our analysis, the relationship between the clinical outcome and cost of anticancer drugs was ascertained by a simple linear regression model.
- Clinical outcome, which was the dependent variable, was expressed as absolute or percent differences in outcomes between treatment and control groups.
- The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs.

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## Background

High costs of cancer drugs and resulting financial toxicity to cancer patients are now a well-recognized problem in cancer policy throughout the world [1-8]. Various solutions are being proposed to address this problem, of which price negotiations with pharmaceutical companies is proposed as an important strategy especially in the USA [9-11]. Because the Medicare is not allowed to negotiate prices with companies, despite being mandated to cover for every U.S. Food and Drug Administration (FDA) approved drug, various experts have argued that this is the reason for high drug prices in the USA. Indeed, cancer drug prices far exceed the costs of their development and such negotiations might help to lower the prices of cancer drugs as evidenced by lower cost of cancer drugs in other developed countries compared with the USA.

However, little is known about if such negotiations would lead to better correlation between cancer drug prices and the benefits they provide. Studies have shown that drug prices do not correlate with clinical benefits for cancer drugs approved by the FDA, even though such studies have not taken central price negotiations into account [12,13]. Countries such as the United Kingdom and Italy negotiate prices and hence, the correlations might be different.

In Italy, drug price negotiation based on cost-effectiveness evaluation has been mandatory since 2001 for all medicines reimbursed by the National Health Service (NHS) [14,15]. We analysed the correlation between the prices of cancer drugs in Italy with their clinical outcomes to test the hypothesis that central price negotiations leads to better alignment of prices and benefits.



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**Methods:**

*Identification of the study sample*

All new drugs approved by the EMA via a centralized procedure between January 2010 and June 2016 for the treatment of either solid or haematologic cancers were initially identified. Generics, biosimilars, interferons and granulocyte-colony stimulating factors (G-CSFs) were excluded. Only anticancer drugs with pivotal trials based on overall survival (OS), progression-free survival (PFS) or objective response rate (ORR) and with prices that were officially negotiated in Italy by 31st December 2016 were included in the cohort for analyses.

*Data extraction*

Information on the clinical outcomes (in terms of median OS, median PFS, ORR) was extracted by two co-investigators (FBA and RP) from pivotal trials that compared new treatments with controls as reported in the European Public Assessment Reports - EPARs (summary table of the main study, Section 2.5.2) publicly available on the EMA website (www.ema.europa.eu). Survival times were expressed in weeks, and the reported OS and PFS were transformed when necessary. Information on therapeutic indication and tumour type were also retrieved.

*Drug prices*

The cost of a full course or 1-year treatment was estimated by two co-investigators (NM and IE) on the basis of the negotiated official ex-factory price (in euros) of drug packages, as published in the Official Gazette of the Italian Republic (www.gazzettaufficiale.it) and taking into account the posology as reported in the Summary of Product Characteristics (SPC). To compare prices of drugs with different schedules, in the text we refer to drug prices as the cost of a full course or a 1-year treatment. A further estimate took into account additional compulsory rebates [16] or extra-discounts



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that were agreed with pharmaceutical companies; this information is confidential to the public but is released to procurement stations within the Italian NHS (e.g., regions, hospitals, and local health units).

*Statistical analysis*

The following variables were extracted and analysed descriptively: year of approval, therapeutic indication, type of treatment and control groups, outcome data, official and confidential costs per treatment (1 year or a full course) and regulatory information (conditional/under exceptional circumstances approval, or orphan drug status).

The relationship between the clinical outcomes and cost of anticancer drugs was ascertained by a simple linear regression model. Clinical outcome, which was the dependent variable, was expressed as absolute or percent differences in outcomes between treatment and control groups. Regression coefficients β, their levels of significance p and the coefficients of determination $R^2$ were reported for each model.

We also performed several sensitivity analyses to test the robustness of the results. Specifically, we performed multiple linear regression with tumour type as the independent variable to take into account potential differences due to tumour characteristics. Moreover, we also repeated the analysis after excluding negative outcome differences (in two cases, one of the outcomes was inferior in the group receiving the new drug than in the comparison group) and actively controlled trials (considering only placebo-controlled trials). Subgroup analysis by tumour type was also attempted as exploratory analysis when a minimum number of two anticancer drugs within the same tumour type setting were observed. All statistical analyses were performed using STATA (Statacorp, version 14.0)



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*Patient and public involvement*

Patients have not been involved in the development of the research question or the design of this study. However, results of this analysis will be disseminated throughout public conferences, with statements summarizing our results, and with an open access to the published report posted in our institutional websites

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## Results

From 2010 to mid-2016, 45 new anticancer drugs for 56 different oncology indications were approved via centralized procedures by the EMA. For 40 new anticancer drugs (47 indications), the basis for the approval was a pivotal trial adopting OS, PFS or ORR as a primary outcome; the price negotiation was completed by December 2016 for only 30 new anticancer drugs 35 indications) and are included in our analysis (Table 1). Seven drugs received orphan drug status by the EMA and two (vandetanib and crizotinib) received conditional approval. Of the 35 oncology indications tested in 35 different pivotal trials which were all controlled clinical trials, the commonest indications were melanoma (7 out of 35), followed by haematological cancer (6 out of 35) and non-small cell lung cancer (4 out of 35). In 15 such trials (43%), placebo was used as the control arm. Of the 35 indications, data on OS, PFS and ORR were available for 17, 29 and 29 indications respectively. Each drug-indication pair contributed to one or more of these analyses, depending on which outcomes were reported in the EPAR.

In the treatment groups, the median improvement in the OS and PFS were 11.4 weeks (IQR 8.8-17.2; min 13.2; max 23.5) and 12.8 weeks (IQR 6.4-17; min -7.48; max 58.8), respectively; median ORR improvement in the treatment group was 21.8% (IQR 10-34.6; min -3; max 63.3). The reported ranges have negative minimum values since in two cases - nivolumab for NSCLC and regorafenib for gastrointestinal stromal tumours - the experimental treatment had a negative effect on one of the outcomes compared to the control group(in terms of PFS for nivolumab and ORR for regorafenib). The median negotiated price for a 1-year treatment was 72,392 euros (IQR 53,819-85,800; min 4,942; max 142,785), which was further discounted by 25% (on average) after applying confidential rebates. For all anticancer drugs but ipilimumab the price was calculated as 1-year treatment since the posology reported in the Summary of Product Characteristics (SPC) reported that the treatment should



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continue as long as clinical benefit is observed or until unacceptable toxicity occurs. In the case of ipilimumab the price was calculated as a course of 4 doses as reported in the SPC.

The official (ex-factory) price of new anticancer drugs and absolute clinical outcomes showed no correlation (Figure 1a-c). The relationship between the improvement in median OS (in weeks) and negotiated price was estimated for 16 drugs (17 indications), and no correlation was observed ($R^2$= 0.067). When clinical outcomes were expressed as absolute advantage in median PFS or ORR, 25 drugs (29 indications) were available for analysis, and in these cases, no correlation was observed ($R^2$= 0.004 and 0.006, respectively).

Repeating the analyses and taking into account the additional confidential rebates, which are compulsory for hospital procurement, no improvement in the benefit/price relationships was highlighted (Figure 2a-c). These findings also remained unchanged when the analyses were repeated with adjustments for tumour type (Supplementary Table 1) or when clinical outcome was expressed as a percentage of improvement instead of as an absolute difference (Supplementary Figure 1a-c). Sensitivity analyses that excluded negative improvements in outcomes over a control group (Supplementary Figure 2) and considered only data from placebo controlled trials (Supplementary Figure 3a,b) confirmed the main analysis. The exploratory subgroup analyses by tumour type did not identify specific positive correlation patterns depending on tumour setting (Supplementary Figure 4 a,b).

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## Discussion

This study is the first attempt to evaluate whether there were better correlations between cancer drug prices and clinical outcomes in a setting where central price negotiations are mandatory for every new medicine. Our study gave unexpected results to the research question, highlighting no relationships between cost of cancer drugs and benefits. Moreover, all pre-specified sensitivity and subgroup analyses confirmed the main findings. This finding will have important policy implications both for countries like USA where price negotiations are absent and for other countries like Italy where price negotiations do exist.

In our study, the correlation between drug costs and clinical outcomes was even lower than the ones previously noted in the US context [12,13], showing that negotiations did not tilt the relationship between drug prices and benefit positively. Thus, higher drug pricing remains despite the Italian legislative environment, where approval based on cost-effectiveness analysis and price negotiations have been mandatory by law since 2001 [14,15]. This finding may cast doubts on the role of the negotiation itself. However, it is important to understand that countries like Italy who do negotiate drug prices do such negotiations only for binary decisions of approval or no-approval, and do not negotiate prices in relation to the benefits. This understanding is important for cancer policy decisions.

Indeed, there is no legal policy in any country to negotiate prices differently for drugs approved on the basis of surrogate endpoints versus survival outcomes or drugs that improve survival in days versus those that improve survival in months or drugs with immature benefit risk profiles [17-21]. Although steps in the right direction, in lack of such policy, the value frameworks proposed by organizations such as ASCO, ESMO or NCCN have become little more than intellectual exercises [22-25].



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Another reason price negotiations did not achieve better price-value correlations is that because of the global market of drugs, each single country - although large – only represents a small portion of the consumer market. Thus, companies "wield the stick", setting the maximum price that the market will bear [26]. In addition, in Italy, no threshold for incremental cost-effectiveness ratio (ICER) has been determined; thus, no limit is in place to be used as a decision rule in resource allocation at the time of negotiation/reimbursement decisions. The lack of such kind of cut-off might have contributed to the negative results in our study. However, we recognize that even when a threshold for ICER is well established, such as in the UK [27], continuous exceptions have been allowed in the case of anticancer drugs. For example, an ad hoc fund established in 2010 (i.e., the Cancer Drug Fund,) was recently dismissed by the Parliament because it did not deliver meaningful value to patients or society [28].

In the EU context (where newer anticancer drugs are approved by EMA without considering the added-value or cost-effectiveness), the complexity further increases because once a marketing authorization is granted, it may become difficult to manage the reimbursement issue at a national level [29]. Moreover, it is also difficult for payers (NHS/insurance) to defend the thesis against the public opinion that an anticancer drug cannot be reimbursed because it is too expensive [29, 30]. Indeed, as our study shows, the confidential discounts following negotiations between a member state and a company do not ameliorate the correlation between treatment costs and benefits even though they reduce absolute drug prices.

Another factor that negatively influences the contractual power of negotiation is non-transparent information on drug prices across countries. Difficulties in retrieving full information on prices have been already recognized in a recent survey comparing prices of anticancer drugs in 16 EU countries,



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Australia and New Zealand [31]. Vogler et al. found that price information is scarce and not disclosed due to confidential discounts or MEAs, calling for higher transparency. The authors state that it is in the interest of policy makers to remove clauses limiting disclosure on price information because they risk overpaying when setting prices through external price referencing. This concern might be relevant in the Italian context since the negotiation procedure for reimbursement takes into account the price in other EU countries as well as the price of similar products within the same pharmacotherapeutic group [32].

We believe that two partly independent approaches could be adopted by policy makers to achieve a better balance between cancer drug prices and benefits. First, price negotiations should be more strictly based on the level of evidence as well as the magnitudes of benefit. An ICER measure (such as QALY) should represent a threshold for reimbursement, thus setting a starting point for price negotiation and adjusting the ICER threshold based on the magnitude of the relative benefit reached. If the information on the relative value is not available at the time of approval, comparisons can be performed using indirect techniques, whereas after entering the market, payers should play a major role in supporting the evidence generating process.

The second approach that could attain lower prices would require an increased transparency on the costs of drug development process, including the relative contributions from academia and public sector to the development of a drug [33-37]. For instance, research conducted to evaluate efforts of drug development processes highlighted that about half of the most transformative drugs approved by the FDA had substantial contributions to their development by academic researchers supported by government funding [33,34]; in addition, it has been estimated that the cost of late clinical development takes a limited part of the whole process [35]. It is probably the right time to appropriately acknowledge the contributions of publicly funded research during drug price negotiation with companies. Often, comparative effectiveness research is funded by public



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institutions to test different treatments in real practice on robust outcomes with longer follow up or special populations [36,37]. The findings of these studies should be linked to a continuous price re-negotiation over the life cycle of a product.

Other approaches identified as possible solutions to keep the health system sustainable address the general governance of the system, i.e., when the price is already set. In fact, a price-volume approach [38] or indication-based pricing [39,40] have been modelled, each presenting pros and cons. Moreover, given that different oncology settings appear to be oligopolistic, thus refraining from price competition, another possible solution comes from national/regional tenders among therapeutic categories when more alternatives are available [41].

The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs. Moreover, we are not aware if further (more robust) data became available at a later stage when the price was negotiated at the national level. In fact, in Italy, the Health Technology Assessment reports used for cost effective analysis at the time of reimbursement decisions are not publicly available. Regarding the price estimate, we estimated the treatment costs for 1-year treatment or for the total course in the case of ipilimumab where the treatment course lasts less than 1 year. However, the exclusion of ipilimumab would not alter the main findings. Another important limitation is that we have not considered quality of life outcomes as another metric of clinical benefit. Furthermore, a recent study has shown that quality of life outcomes are not routinely collected or published, and that the tools used to measure quality of life are varied to have a uniform metric for comparison [42]. Although we have included surrogate measures such as PFS or ORR as clinical outcomes in our analysis because they were considered as the basis for approval by the regulatory agency, these surrogate measures do not always correlate with true clinical benefits in terms of improved survival or improved quality of life [42,43].



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Moreover, additional savings were calculated "a posteriori" from the Managed Entry Agreements in place in Italy (whose information is not publicly available) and were not considered in the analyses. Another factor that might have impacted the price estimation is the rebate obtained at the regional/local level following drug tenders. However, this information was not available for the analyses and would have been not generalizable at the national level. Our study is a retrospective cross-sectional correlation study that aimed at evaluating whether central price negotiation (mandatory by law in Italy) leads to better alignment of prices and the benefits known at the time of drug approval. This means that our analysis is not aimed at comparing costs and outcomes within drug classes, as a typical cost effective study, and we never intended to assess the add values of the approved drugs in the context of all other drugs sharing the same indication. The "population"/cohort approach that we adopted has the intrinsic limitation of including drugs approved for different indications based on different clinical data packages. The consequent heterogeneity stemming from this approach was resolved adjusting the correlation analyses by tumour type or conducting several sub-analyses. Following this approach, we found results consistent with primary findings thus confirming the robustness of methods and results.

**Conclusion**

Our results suggest that price negotiations for approval decisions alone may not bring balance between prices and benefits of anticancer drugs. Other strategies, such as value based price negotiations, price negotiations strictly based on strength of evidence and price transparencies may be necessary to better achieve the drug prices and benefits balance. These results need to be confirmed in other countries where a national price negotiation exists.



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**Table 1.** Characteristics of the 30 anticancer drugs included in the analysis.

| Medicine Name | Active Substance | Clinical setting | Treatment group | Control group | PFS TRT (median in weeks) | PFS CRT (median in weeks) | OS TRT (median in weeks) | OS CRT (median in weeks) | ORR TRT (%) | ORR CRT (%) | Year First Auth. | Official negot. price (€) | Disc. price (€) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Teysuno | tegafur / gimeracil / oteracil | advanced gastric cancer in combination with cisplatin. | teysuno 25 mg/m + cisplatin 75 mg/m2 | 5-fluorouracil 1000 mg/m2 /24 + cisplatin 100 mg/m2 | | | 34.4 | 31.6 | | | 2011 | 4942 | 3479 |
| Jevtana | cabazitaxel | hormone-refractory metastatic prostate cancer . | cabazitaxel + prednisone | mitoxantrone + prednisone | 11.2 | 5.6 | 60.4 | 50.8 | 14.4 | 4.4 | 2011 | 52983 | 38254 |
| Yervoy | ipilimumab | advanced (unresectable or metastatic) melanoma | ipilimumab + placebo | peptide vaccine glycoprotein 100 (gp100) | 11.04 | 11.04 | 39.8 | 25.8 | 5.7 | 1.5 | 2011 | 71400 | 45107 |
| Votubia | everolimus | Renal angiomyolipoma associated with tuberous sclerosis complex (TSC) | everolimus | placebo | | 45.48 | | | 41.8 | 0 | 2011 | 66521 | 41424 |
| Votubia | everolimus | Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) | everolimus | placebo | | | | | 34.6 | 0 | | 53216 | 33139 |
| Halaven | eribulin | locally advanced or metastatic breast cancer | eribulin 1.23 mg/m2 (equivalent to 1.4 mg/m2 eribulin mesylate) | treatment of physician's choice | 16.14 | 9.71 | 57.57 | 45.86 | 12.2 | 4.7 | 2011 | 32300 | 28130 |
| Zytiga | abiraterone acetate | metastatic castration-resistant prostate cancer | abiraterone acetate | placebo | 22.4 | 14.4 | 68.9 | 48.7 | 29.1 | 5.5 | 2011 | 46842 | 33397 |
| Dacogen | decitabine | newly diagnosed de novo or secondary acute myeloid leukaemia (AML) | decitabine | patient's choice | 14.8 | 8.4 | 30.8 | 20 | | | 2012 | 54366 | 34346 |
| Caprelsa | vandetanib | aggressive and symptomatic medullary thyroid cancer (MTC) unresectable locally advanced or metastatic disease. | vandetanib | placebo | 122 | 77.2 | | | 45 | 13 | 2012 | 67405 | 53533 |
| Zelboraf | vemurafenib | BRAF-V600-mutation-positive unresectable or metastatic melanoma. | vemurafenib | dacarbazine | 21.28 | 6.44 | 52.8 | 39.6 | 48.4 | 5.5 | 2012 | 119929 | 108236 |
| Xalkori | crizotinib | anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). | crizotinib | pemetrexed or docetaxel | 30.8 | 12 | | | 65.3 | 19.5 | 2012 | 79538 | 57427 |



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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Xalkori | crizotinib | first-line treatment of adults with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). | crizotinib | chemotherapy | 43.6 | 28 | | | 74.4 | 45 | | 79538 | 57427 |
| Inlyta | axitinib | advanced renal-cell carcinoma (RCC) | axitinib | sorafenib | 26.8 | 18.8 | | | 19.4 | 9.4 | 2012 | 57632 | 39295 |
| Perjeta | pertuzumab | HER2-positive metastatic or locally recurrent unresectable breast cancer | pertuzumab + trastuzumab + docetaxel | placebo + trastuzumab + docetaxel | 74 | 49.6 | | | 80.2 | 69.3 | 2013 | 51643 | 46608 |
| Kadcyla | trastuzumab emtansine | HER2-positive, unresectable locally advanced or metastatic breast cancer | trastuzumab emtansine (tdm1) | lapatinib + capecitabine (lap+cap) | 38.4 | 25.6 | 123.9 | 100.4 | | | 2013 | 87215 | 75877 |
| Giotrif | afatinib | locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s); | afatinib (film-coated tablets) | pemetrexed (lyophilised powder) + cisplatin (solution for infusion) | 44.56 | 27.6 | | | 56.1 | 22.6 | 2013 | 29528 | 21853 |
| Stivarga | regorafenib | metastatic colorectal cancer (CRC) | regorafenib + best supportive care | placebo + best supportive care | 8.4 | 7.4 | 28 | 21.6 | 1 | 0.4 | 2013 | 85800 | 77434 |
| Stivarga | regorafenib | unresectable or metastatic gastrointestinal stromal tumors (GIST) | regorafenib + best supportive care | placebo + best supportive care | 21 | 4 | | | 1.5 | 4.5 | | 85800 | 77434 |
| Tafinlar | dabrafenib | unresectable or metastatic melanoma with a BRAF V600 mutation. | dabrafenib | dacarbazine | 27.6 | 10.8 | 72.8 | 62.4 | 59 | 24 | 2013 | 107935 | 87670 |
| Zaltrap | aflibercept | metastatic colorectal cancer (MCRC) | aflibercept+folfiri | placebo+folfiri | 27.6 | 18.7 | 54 | 48.4 | 19.8 | 11.1 | 2013 | 30576 | 27591 |
| Xtandi | enzalutamide | metastatic castration resistant prostate cancer | enzalutamide (mdv3100) | placebo | 33.2 | 11.6 | 74.4 | 54.4 | | | 2013 | 49184 | 31960 |
| Imnovid | pomalidomide | relapsed and refractory multiple myeloma | pom+ld-dex | hd-dex | 15.7 | 8 | | 34 | | | 2013 | 127985 | 101646 |
| Lynparza* | olaparib | platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer | olaparib | placebo | 33.6 | 19.2 | 119.2 | 111.2 | | | 2014 | 70517 | 52142 |
| Cyramza | ramucirumab | advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression | ramucirumab+ paclitaxel | placebo+paclitaxel | 17.6 | 11.6 | 38.4 | 29.6 | 27.9 | 16.1 | 2014 | 87360 | 78842 |
| Mekinist | trametinib | unresectable or metastatic melanoma with a BRAF V600 mutation. | trametinb | chemotherapy (dtic or paclitaxel) | 19.6 | 6 | 62.4 | 45.2 | 19 | 5 | 2014 | 62398 | 28157 |



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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Imbruvica | ibrutinib | chronic lymphocytic leukaemia (CLL) | ibrutinib | chlorambucil | | 75.6 | | | 82.4 | 35.3 | | 73805 | 51663 |
| Zydelig | idelalisib | chronic lymphocytic leukaemia (CLL) | idelalisib + rituximab | placebo + rituximab | | 22 | | | 74.5 | 14.5 | 2014 | 48667 | 34067 |
| Sylvant | siltuximab | multicentric Castlemans disease | siltuximab + best supportive care | placebo + best supportive care | | | | | 37.7 | 3.8 | 2014 | 66104 | 29829 |
| Keytruda | pembrolizumab | advanced(unresectable or metastatic) melanoma | ipilimumab | pembrolizumab | 22 | 11.2 | | | 33.7 | 11.9 | 2015 | 90400 | 81586 |
| Opdivo | nivolumab | advanced (unresectable or metastatic) melanoma | nivolumab 3 mg/kg | dacarbazine | 18.8 | 16.8 | | | 31.7 | 10.6 | 2015 | 81310 | 71181 |
| Opdivo | nivolumab | locally advanced or metastatic non-small cell lung cancer (NSCLC) | nivolumab 3 mg/kg | docetaxel 75 mg/m2 | 9.32 | 16.8 | 48.8 | 37.4 | 19.2 | 12.4 | | 81310 | 71181 |
| Opdivo | nivolumab | advanced renal cell carcinoma | nivolumab 3 mg/kg | everolimus100mg | 18.4 | 17.8 | 100 | 78.2 | 25.1 | 5.4 | | 81310 | in negotiation |
| Lenvima | lenvatinib mesylate | progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hrthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) | lenvatinib | placebo | 73.2 | 14.4 | | | 64.8 | 1.5 | 2015 | 68433 | 58673 |
| Cotellic | cobimetinib hemifumarate | unresectable or metastatic melanoma with a BRAF V600 mutation | cobimetinib+vemurafenib | placebo+vemurafenib | 45.2 | 24 | | | 67.8 | 44.8 | 2015 | 75374 | 54420 |
| Kyprolis | carfilzomib | multiple myeloma who have received at least one prior therapy. | carfilzomib + lenalidomide + dexamethasone | lenalidomide + dexamethasone (rd) | 105.2 | 70.4 | | | 87.1 | 67.7 | 2015 | 75900 | 44525 |

Progression Free Survival (PFS); Overall Survival (OS); Treatment Group (TRT); Control Group (CTR); Objective Response Rate (ORR); Official Negotiated Prices (Official Negot.); Discounted Prices (Disc. Prices).

*: During the evaluation at the EMA, lymparza was found to be more effective in a subgroup of patients with a specific biomarker with the following outcome results: PFS lymparza: 44,8 w; PFS control: 17,2 w; OS lymparza: 139,6 w; OS control: 127,6.



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## Figure, tables, titles and legends

**Figure 1.** Correlation between anticancer drug prices (officially negotiated) and health benefits

*Figure 1a. Official negotiated price (ex-factory) vs difference in median OS (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*

*Figure 1b. Official negotiated price (ex-factory) vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*

*Figure 1c. Official negotiated price (ex-factory) vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

**Figure 2.** Correlation between anticancer drug prices (discounted) and health benefits

*Figure 2a. Discounted price with additional compulsory rebates vs difference in median OS (16 drugs related to a single indication are included in the analysis)*

*Figure 2b. Discounted price with additional compulsory rebates vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

*Figure 2c. Discounted price with additional compulsory rebates vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication and four with two indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

**Table 1.** Characteristics of the 30 anticancer drugs included in the analysis.

Legend:

Progression Free Survival (PFS); Overall Survival (OS); Treatment Group (TRT); Control Group (CTR); Objective Response Rate (ORR); Official Negotiated Prices (Official Negot.); Discounted Prices (Disc. Prices).

*: During the evaluation at the EMA, lymparza was found to be more effective in a subgroup of patients with a specific biomarker with the following outcome results: PFS lymparza: 44,8 w; PFS control: 17,2 w; OS lymparza: 139,6 w; OS control: 127,6.

**Supplementary Table 1.** Details of the statistical analysis conducted

**Supplementary Figures 1-4.** Correlations in the sensitivity analysis conducted

*Supplementary Figure 1a. Official negotiated price (ex-factory) vs percentage improvement in median Overall Survival (OS) (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*

*Supplementary Figure 1b. Official negotiated price (ex-factory) vs percentage improvement in median Progression Free Survival (PFS) (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*



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*Supplementary Figure 1c. Official negotiated price (ex-factory) vs percentage improvement in proportion of Objective Response Rate (ORR) (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

*Figure 2. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), excluding negative outcome data (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

*Supplementary Figure 3a. Official negotiated price (ex-factory) vs median Overall Survival (OS), considering only data from placebo-controlled trials. (7drugs related to a single indication are included in the analysis)*

*Supplementary Figure 3b. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), considering only data from placebo-controlled trials. (11 drugs are included in the analysis: 10 with a single indication and one with 2 indications)*

*Supplementary Figure 4a. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication, two with two indications and one with three indication)*

*Supplementary Figure 4b. Discounted price with additional compulsory rebates vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication and three with 2 indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

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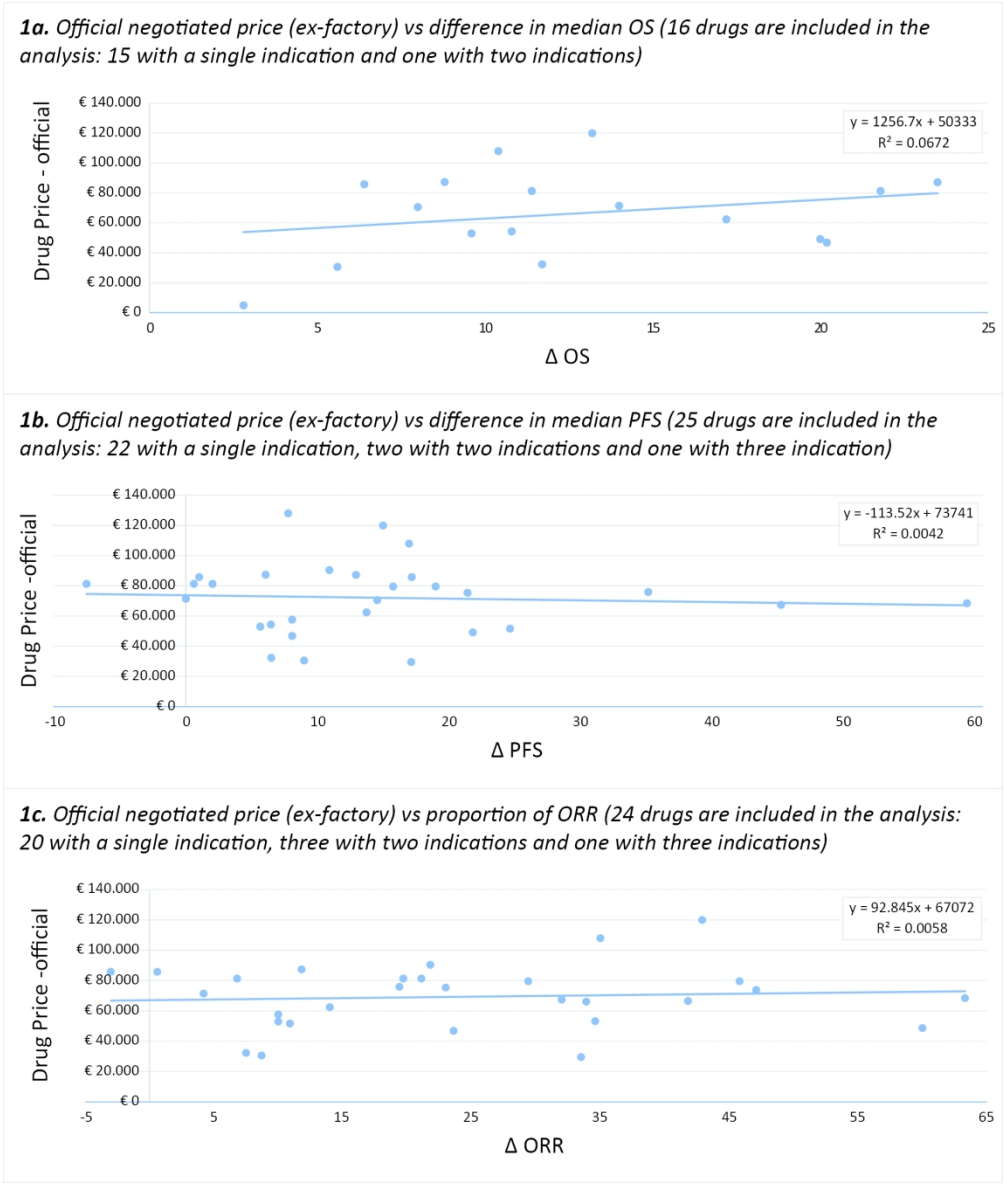


Correlation between anticancer drug prices (officially negotiated) and health benefits

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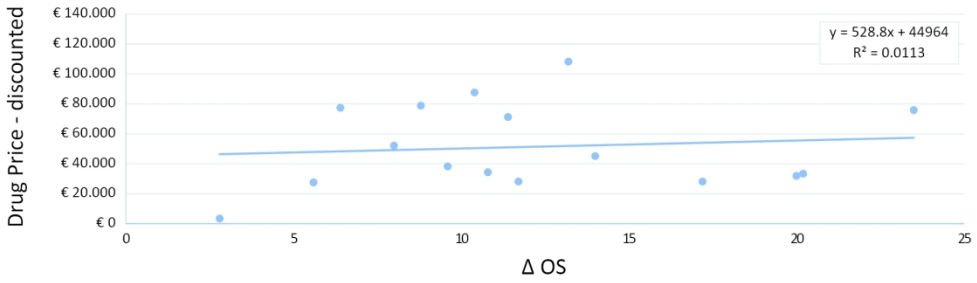
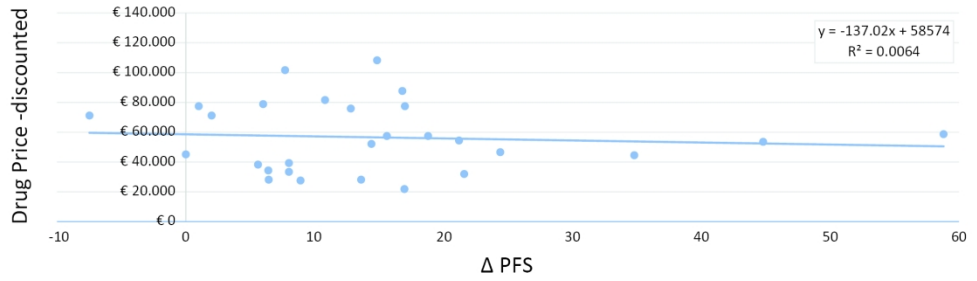
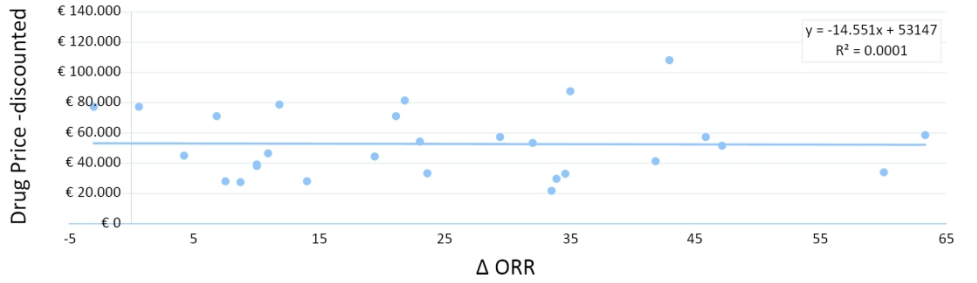
***2a.*** *Discounted price with additional compulsory rebates vs difference in median OS (16 drugs related to a single indication are included in the analysis)*




***2b.*** *Discounted price with additional compulsory rebates vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*




***2c.*** *Discounted price with additional compulsory rebates vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication and four with two indications)*

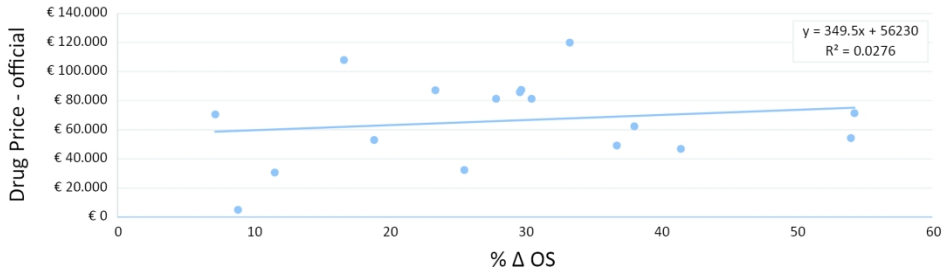



Correlation between anticancer drug prices (discounted) and health benefits

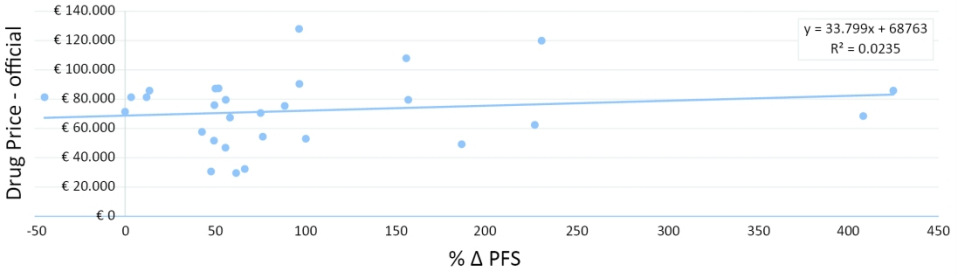
180x212mm (300 x 300 DPI)

| Dependent variable | Independent variable 1 | Independent variable 2 | Number of drugs involved in the analysis | Type of linear regression | Intercept | Coefficient of the Independent variable 1 | p value of the Independent variable 1 | Correlation coefficient: r | Coefficient of Determination: $R^2$ |
|---|---|---|---|---|---|---|---|---|---|
| Official negotiated price | Δ OS | | 17 | simple | 50332.71 | 1256.724 | 0.315 | 0.259 | 0.067 |
| Discounted price | Δ OS | | 16 | simple | 44963.88 | 528.800 | 0.695 | 0.11 | 0.0113 |
| Official negotiated price | Δ OS | tumor type | 17 | multiple | 57765.99 | 2065.264 | 0.433 | | 0.412 |
| Discounted price | Δ OS | tumor type | 16 | multiple | 55312.8 | 1391.947 | 0.614 | | 0.257 |
| Official negotiated price | % Δ OS | | 17 | simple | 56230.04 | 349.505 | 0.524 | 0.166 | 0.027 |
| Discounted price | % Δ OS | | 16 | simple | 50127.28 | 42.986 | 0.937 | 0.022 | 0.0005 |
| Official negotiated price | % Δ OS | tumor type | 17 | multiple | 72407.98 | 292.048 | 0.766 | | 0.362 |
| Discounted price | % Δ OS | tumor type | 16 | multiple | 68456.17 | 89.3936 | 0.930 | | 0.2286 |
| Official negotiated price | Δ PFS | | 29 | simple | 73741.11 | -113.515 | 0.738 | -0.065 | 0.004 |
| Discounted price | Δ PFS | | 28 | simple | 58574.12 | -137.018 | 0.687 | -0.080 | 0.006 |
| Official negotiated price | Δ PFS | tumor type | 29 | multiple | 70454.93 | -271.324 | 0.635 | | 0.338 |
| Discounted price | Δ PFS | tumor type | 28 | multiple | 56293.38 | -393.926 | 0.508 | | 0.283 |
| Official negotiated price | % Δ PFS | | 29 | simple | 68763.32 | 33.7994 | 0.427 | 0.153 | 0.024 |
| Discounted price | % Δ PFS | | 28 | simple | 52823.84 | 36.2925 | 0.392 | 0.169 | 0.028 |
| Official negotiated price | % Δ PFS | tumor type | 29 | multiple | 66564.96 | 15.935 | 0.765 | | 0.333 |
| Discounted price | % Δ PFS | tumor type | 28 | multiple | 51337.49 | 11.068 | 0.842 | | 0.266 |
| Official negotiated price | Δ ORR | | 29 | simple | 67072.16 | 92.845 | 0.696 | 0.076 | 0.006 |
| Discounted price | Δ ORR | | 28 | simple | 53147.09 | -14.550 | 0.953 | -0.010 | 0.000 |
| Official negotiated price | Δ ORR | tumor type | 29 | multiple | 62277.57 | 180.118 | 0.607 | | 0.448 |
| Discounted price | Δ ORR | tumor type | 28 | multiple | 42598.33 | 324.629 | 0.383 | | 0.450 |
| Official negotiated price | % Δ ORR | | 27 | simple | 69838.7 | 0.563 | 0.918 | 0.020 | 0.000 |
| Discounted price | % Δ ORR | | 26 | simple | 53627.54 | 0.965 | 0.864 | 0.036 | 0.001 |
| Official negotiated price | % Δ ORR | tumor type | 27 | multiple | 67262.18 | 1.719 | 0.814 | | 0.436 |
| Discounted price | % Δ ORR | tumor type | 26 | multiple | 51599.74 | 2.958 | 0.704 | | 0.405 |

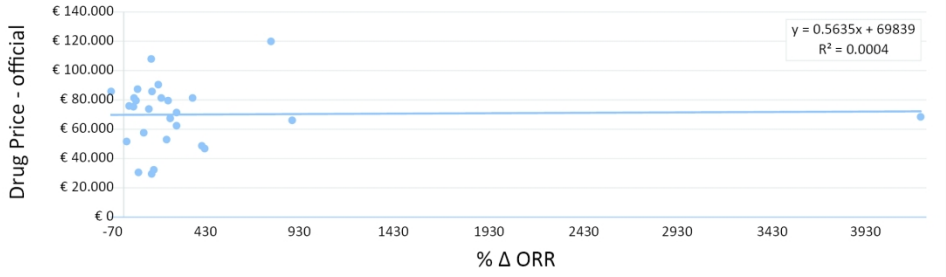
***1a.*** *Official negotiated price (ex-factory) vs percentage improvement in median Overall Survival (OS) (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*




***1b.*** *Official negotiated price (ex-factory) vs percentage improvement in median Progression Free Survival (PFS) (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*




***1c.*** *Official negotiated price (ex-factory) vs percentage improvement in proportion of Objective Response Rate (ORR) (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

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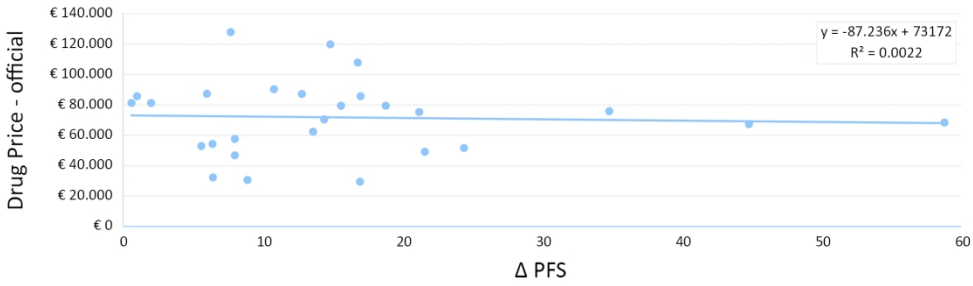
***2.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), excluding negative outcome data (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

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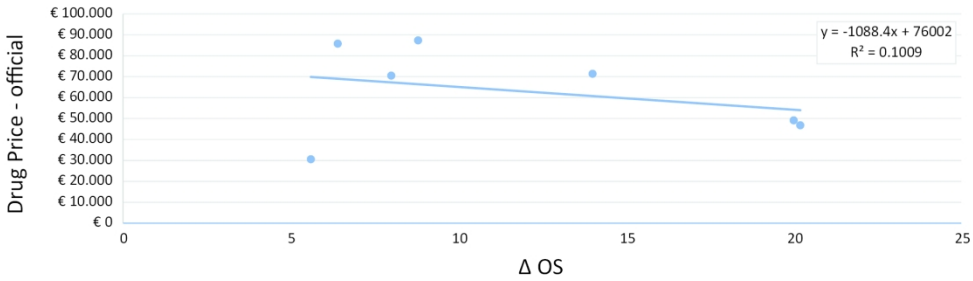
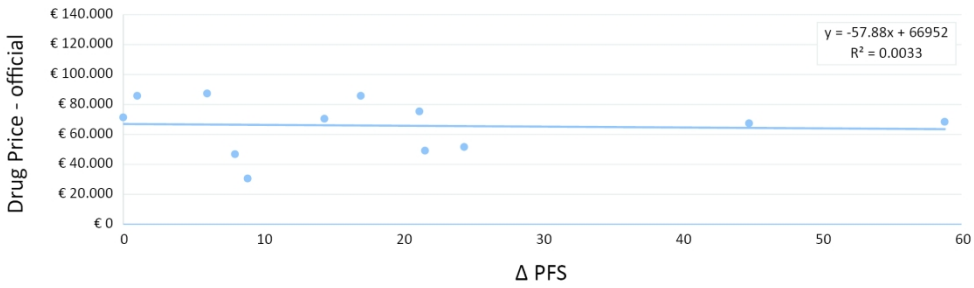
***3a.*** *Official negotiated price (ex-factory) vs median Overall Survival (OS), considering only data from placebo-controlled trials. (7drugs related to a single indication are included in the analysis)*




***3b.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), considering only data from placebo-controlled trials. (11 drugs are included in the analysis: 10 with a single indication and one with 2 indications)*

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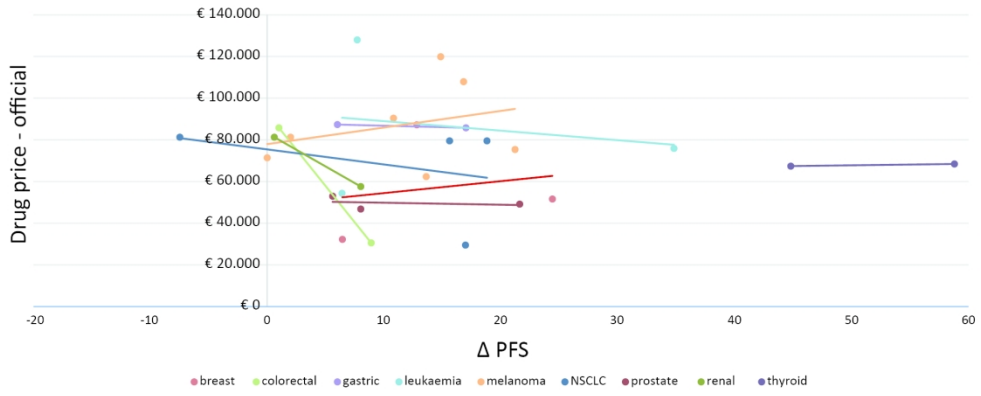
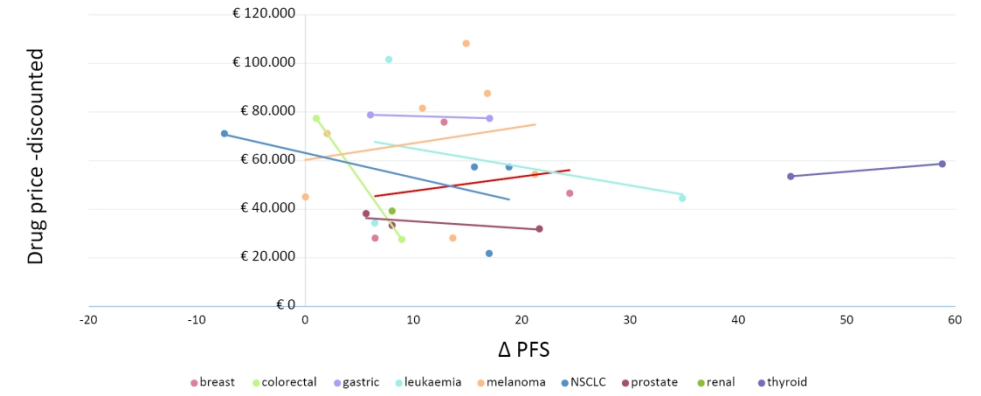
***4a.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication, two with two indications and one with three indication)*




***4b.*** *Discounted price with additional compulsory rebates vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication and three with 2 indications)*

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## STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| **Title and Abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1 (Title) P |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 2 |
| **Introduction** | | | |
| Background/Rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 4 |
| **Methods** | | | |
| Study Design | 4 | Present key elements of study design early in the paper | Page 5-6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 7 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | |
| | | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | |
| | | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 5 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed | |
| | | *Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 5 |

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| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| Data Sources/ Measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Page 5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Page 6 |
| Study Size | 10 | Explain how the study size was arrived at | Page 6 |
| Quantitative Variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | |
| Statistical Methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | Page 6 |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br><br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br><br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | Page 6 |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 8 |
| | | (b) Give reasons for non-participation at each stage | page 8 |
| | | (c) Consider use of a flow diagram | |
| Descriptive Data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | |
| | | (b) Indicate number of participants with missing data for each variable of interest | Page 8 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome Data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | Page 8-9 |

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| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| Main Results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other Analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key Results | 18 | Summarise key results with reference to study objectives | Page 10-12 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | page 13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | page 13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | page 13-14 |
| **Other Information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | cover |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.**

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# Clinical outcomes do not correlate with anticancer drug prices: a cross-sectional study in Italy



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**Title:** Clinical outcomes do not correlate with anticancer drug prices: a cross-sectional study in Italy

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**contributorship statement**

FT, NM and AA conceptualized the study; FT, AA, NM, FM, FBA, GT, and RDC designed the study; FBA, RP, IE and NM were in charge of data extraction and quality control; FM, RDC, and FT performed the data analysis; FT, RDC, FM, GT, BG, FP and AA drafted the manuscript; all the authors contributed to the discussion and the interpretation of results, and reviewed the final version of the manuscript. All authors approved the final manuscript as submitted.

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**Running head.** Anticancer drug prices and clinical outcomes in Italy

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**Abstract**:

**Objective** To investigate whether the prices of new anticancer drugs correlated with their relative benefit despite negotiation.

**Design** Retrospective cross-sectional study correlating new anticancer drugs prices with clinical outcomes.

**Setting** We did a retrospective cross-sectional study including all new anticancer drugs approved by the European Medicines Agency (2010-2016) and reimbursed in Italy.

**Main Outcome(s) and Measure(s)** Information on clinical outcomes - in terms of median Overall Survival (OS), median Progression Free Survival (PFS) and Objective Response Rate (ORR) - was extracted from pivotal trials as reported in the European Public Assessment Reports available on the EMA website. Cost of a full course treatment was estimated on negotiated official and discounted prices. Regression coefficients β, their levels of significance p and the coefficients of determination $R^2$ were estimated adjusting by tumour type.

**Results** Overall, 30 new anticancer drugs (with 35 indications) were available for analysis. There was no correlation between the improvement in median OS (in weeks) and negotiated price ($R^2$= 0.067, n = 16 drugs for 17 indications). When the clinical outcomes were expressed as improvements in median PFS or ORR, 25 drugs (29 indications) were available for analysis, and again, there was no correlation with prices ($R^2$= 0.004 and 0.006, respectively).

**Conclusions and Relevance**: Our results suggest that the prices of anticancer drugs in Italy do not reflect their therapeutic benefit. Drug price negotiations, which is mandatory by law in Italy, do not



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seem to ensure that prices correlate with clinical benefits provided by cancer drugs. These results call for further efforts to establish the standard determinants of drug prices available at the time of negotiation. These findings need to be confirmed in other countries where price negotiations are in place.

**Strengths and limitations of this study**,

- This study is the first attempt to evaluate whether there were better correlations between cancer drug prices and clinical outcomes in a setting where central price negotiations are mandatory for every new medicine.
- This understanding is important for cancer policy decisions.
- In our analysis, the relationship between the clinical outcome and cost of anticancer drugs was ascertained by a simple linear regression model.
- Clinical outcome, which was the dependent variable, was expressed as absolute or percent differences in outcomes between treatment and control groups.
- The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs.

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## Background

High costs of cancer drugs and resulting financial toxicity to cancer patients are now a well-recognized problem in cancer policy throughout the world [1-8]. Various solutions are being proposed to address this problem, of which price negotiations with pharmaceutical companies is proposed as an important strategy especially in the USA [9-11]. Because the Medicare is not allowed to negotiate prices with companies, despite being mandated to cover for every U.S. Food and Drug Administration (FDA) approved drug, various experts have argued that this is the reason for high drug prices in the USA. Indeed, cancer drug prices far exceed the costs of their development [12];such negotiations might help to lower the prices of cancer drugs as evidenced by lower cost of cancer drugs in other developed countries compared with the USA.

However, little is known about if such negotiations would lead to better correlation between cancer drug prices and the benefits they provide. Studies have shown that drug prices do not correlate with clinical benefits for cancer drugs approved by the FDA, even though such studies have not taken central price negotiations into account [13,14]. Countries such as the United Kingdom and Italy negotiate prices and hence, the correlations might be different.

In Italy, drug price negotiation based on cost-effectiveness evaluation has been mandatory since 2001 for all medicines reimbursed by the National Health Service (NHS) [15,16]. We analysed the correlation between the prices of cancer drugs in Italy with their clinical outcomes to test the hypothesis that central price negotiations leads to better alignment of prices and benefits.



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**Methods:**

*Identification of the study sample*

All new drugs approved by the EMA via a centralized procedure between January 2010 and June 2016 for the treatment of either solid or haematologic cancers were initially identified. Generics, biosimilars, interferons and granulocyte-colony stimulating factors (G-CSFs) were excluded. Only anticancer drugs with pivotal trials based on overall survival (OS), progression-free survival (PFS) or objective response rate (ORR) and with prices that were officially negotiated in Italy by 31st December 2016 were included in the cohort for analyses.

*Data extraction*

Information on the clinical outcomes (in terms of median OS, median PFS, ORR) was extracted by two co-investigators (FBA and RP) from pivotal trials that compared new treatments with controls as reported in the European Public Assessment Reports - EPARs (summary table of the main study, Section 2.5.2) publicly available on the EMA website (www.ema.europa.eu). Survival times were expressed in weeks, and the reported OS and PFS were transformed when necessary. Information on therapeutic indication and tumour type were also retrieved.

*Drug prices*

The cost of a full course or 1-year treatment was estimated by two co-investigators (NM and IE) on the basis of the negotiated official ex-factory price (in euros) of drug packages, as published in the Official Gazette of the Italian Republic (www.gazzettaufficiale.it) and taking into account the posology as reported in the Summary of Product Characteristics (SPC). To compare prices of drugs with different schedules, in the text we refer to drug prices as the cost of a full course or a 1-year treatment. A further estimate took into account additional compulsory rebates [17] or extra-discounts



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that were agreed with pharmaceutical companies; this information is confidential to the public but is released to procurement stations within the Italian NHS (e.g., regions, hospitals, and local health units).

*Statistical analysis*

The following variables were extracted and analysed descriptively: year of approval, therapeutic indication, type of treatment and control groups, outcome data, official and confidential costs per treatment (1 year or a full course) and regulatory information (conditional/under exceptional circumstances approval, or orphan drug status).

The relationship between the clinical outcomes and cost of anticancer drugs was ascertained by a simple linear regression model. Clinical outcome, which was the dependent variable, was expressed as absolute or percent differences in outcomes between treatment and control groups. Regression coefficients β, their levels of significance p and the coefficients of determination $R^2$ were reported for each model.

We also performed several sensitivity analyses to test the robustness of the results. Specifically, we performed multiple linear regression with tumour type as the independent variable to take into account potential differences due to tumour characteristics. Moreover, we also repeated the analysis after excluding negative outcome differences (in two cases, one of the outcomes was inferior in the group receiving the new drug than in the comparison group) and actively controlled trials (considering only placebo-controlled trials). Subgroup analysis by tumour type was also attempted as exploratory analysis when a minimum number of two anticancer drugs within the same tumour type setting were observed. Outlier cases were not excluded from the analyses, but their impact was evaluated and reported when relevant as a separate analysis. All statistical analyses were performed using STATA (Statacorp, version 14.0)



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*Patient and public involvement*

Patients have not been involved in the development of the research question or the design of this study. However, results of this analysis will be disseminated throughout public conferences, with statements summarizing our results, and with an open access to the published report posted in our institutional websites

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## Results

From 2010 to mid-2016, 45 new anticancer drugs for 56 different oncology indications were approved via centralized procedures by the EMA. For 40 new anticancer drugs (47 indications), the basis for the approval was a pivotal trial adopting OS, PFS or ORR as a primary outcome; the price negotiation was completed by December 2016 for only 30 new anticancer drugs (35 indications) which are included in our analysis (Table 1). Seven drugs received orphan drug status by the EMA and two (vandetanib and crizotinib) received conditional approval. Of the 35 oncology indications tested in 35 different pivotal trials which were all controlled clinical trials, the commonest indications were melanoma (7 out of 35), followed by haematological cancer (6 out of 35) and non-small cell lung cancer (4 out of 35). In 15 such trials (43%), placebo was used as the control arm. Of the 35 indications, data on OS, PFS and ORR were available for 17, 29 and 29 indications respectively. Each drug-indication pair contributed to one or more of these analyses, depending on which outcomes were reported in the EPAR.

In the treatment groups, the median improvement in the OS and PFS were 11.4 weeks (IQR 8.8-17.2; min 13.2; max 23.5) and 12.8 weeks (IQR 6.4-17; min -7.48; max 58.8), respectively; median ORR improvement in the treatment group was 21.8% (IQR 10-34.6; min -3; max 63.3). The reported ranges have negative minimum values since in two cases - nivolumab for NSCLC and regorafenib for gastrointestinal stromal tumours - the experimental treatment had a negative effect on one of the outcomes compared to the control group (in terms of PFS for nivolumab and ORR for regorafenib). The median negotiated price for a 1-year treatment was 72,392 euros (IQR 53,819-85,800; min 4,942; max 142,785), which was further discounted by 25% (on average) after applying confidential rebates. For all anticancer drugs but ipilimumab the price was calculated as 1-year treatment since the posology reported in the Summary of Product Characteristics (SPC) reported that the treatment should



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continue as long as clinical benefit is observed or until unacceptable toxicity occurs. In the case of ipilimumab the price was calculated as a course of 4 doses as reported in the SPC.

The official (ex-factory) price of new anticancer drugs and absolute clinical outcomes showed no correlation (Figure 1a-c). The relationship between the improvement in median OS (in weeks) and negotiated price was estimated for 16 drugs (17 indications), and no correlation was observed ($R^2$= 0.067). When clinical outcomes were expressed as absolute advantage in median PFS or ORR, 25 drugs (29 indications) were available for analysis, and in these cases, no correlation was observed ($R^2$= 0.004 and 0.006, respectively).

Repeating the analyses and taking into account the additional confidential rebates, which are compulsory for hospital procurement, no improvement in the benefit/price relationships was highlighted (Figure 2a-c). These findings also remained unchanged when the analyses were repeated with adjustments for tumour type (Supplementary Table 1) or when clinical outcome was expressed as a percentage of improvement instead of as an absolute difference (Supplementary Figure 1a-c). Sensitivity analyses that excluded negative improvements in outcomes over a control group (Supplementary Figure 2) and considered only data from placebo controlled trials (Supplementary Figure 3a,b) confirmed the main analysis. The exploratory subgroup analyses by tumour type did not identify specific positive correlation patterns depending on tumour setting (Supplementary Figure 4 a,b).

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## Discussion

This study is the first attempt to evaluate whether there were better correlations between cancer drug prices and clinical outcomes in a setting where central price negotiations are mandatory for every new medicine. Our study gave unexpected results to the research question, highlighting no relationships between cost of cancer drugs and benefits. Moreover, all pre-specified sensitivity and subgroup analyses confirmed the main findings. This finding will have important policy implications both for countries like USA where price negotiations are absent and for other countries like Italy where price negotiations do exist.

In our study, the correlation between drug costs and clinical outcomes was even lower than the ones previously noted in the US context [13,14], showing that negotiations did not tilt the relationship between drug prices and benefit positively. Thus, higher drug pricing remains despite the Italian legislative environment, where approval based on cost-effectiveness analysis and price negotiations have been mandatory by law since 2001 [15,16]. This finding may cast doubts on the role of the negotiation itself. However, it is important to understand that countries like Italy that negotiate drug prices do such negotiations only for binary decisions of approval or no-approval, no taking into account, during negotiation, of a clear correlation between prices and benefits. This understanding is important for cancer policy decisions.

Indeed, there is no legal policy in any country to negotiate prices differently for drugs approved on the basis of surrogate endpoints versus survival outcomes or drugs that improve survival in days versus those that improve survival in months or drugs with immature benefit risk profiles [18-22]. Although steps in the right direction, in lack of such policy, the value frameworks proposed by organizations such as ASCO, ESMO or NCCN have become little more than intellectual exercises [23-26].



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Another reason price negotiations did not achieve better price-value correlations is that because of the global market of drugs, each single country - although large – only represents a small portion of the consumer market. Thus, companies "wield the stick", setting the maximum price that the market will bear [27]. In addition, in Italy, no threshold for incremental cost-effectiveness ratio (ICER) has been determined; thus, no limit is in place to be used as a decision rule in resource allocation at the time of negotiation/reimbursement decisions. The lack of such kind of cut-off might have contributed to the negative results in our study. However, we recognize that even when a threshold for ICER is well established, such as in the UK [28], continuous exceptions have been allowed in the case of anticancer drugs. For example, an ad hoc fund established in 2010 (i.e., the Cancer Drug Fund,) was recently dismissed by the Parliament because it did not deliver meaningful value to patients or society [29].

In the EU context (where newer anticancer drugs are approved by EMA without considering the added-value or cost-effectiveness), the complexity further increases because once a marketing authorization is granted, it may become difficult to manage the reimbursement issue at a national level [30]. Moreover, it is also difficult for payers (NHS/insurance) to defend the thesis against the public opinion that an anticancer drug cannot be reimbursed because it is too expensive [30, 31]. Indeed, as our study shows, the confidential discounts following negotiations between a member state and a company do not ameliorate the correlation between treatment costs and benefits even though they reduce absolute drug prices.

Another factor that negatively influences the contractual power of negotiation is non-transparent information on drug prices across countries. Difficulties in retrieving full information on prices have been already recognized in a recent survey comparing prices of anticancer drugs in 16 EU countries,



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Australia and New Zealand [32]. Vogler et al. found that price information is scarce and not disclosed due to confidential discounts or MEAs, calling for higher transparency. The authors state that it is in the interest of policy makers to remove clauses limiting disclosure on price information because they risk overpaying when setting prices through external price referencing. This concern might be relevant in the Italian context since the negotiation procedure for reimbursement takes into account the price in other EU countries as well as the price of similar products within the same pharmacotherapeutic group [33].

We believe that two partly independent approaches could be adopted by policy makers to achieve a better balance between cancer drug prices and benefits. First, price negotiations should be more strictly based on the level of evidence as well as the magnitudes of benefit. An ICER measure (such as QALY) should represent a threshold for reimbursement, thus setting a starting point for price negotiation and adjusting the ICER threshold based on the magnitude of the relative benefit reached. If the information on the relative value is not available at the time of approval, comparisons can be performed using indirect techniques, whereas after entering the market, payers should play a major role in supporting the evidence generating process.

The second approach that could attain lower prices would require an increased transparency on the costs of drug development process, including the relative contributions from academia and public sector to the development of a drug [34-38]. For instance, research conducted to evaluate efforts of drug development processes highlighted that about half of the most transformative drugs approved by the FDA had substantial contributions to their development by academic researchers supported by government funding [34,35]; in addition, it has been estimated that the cost of late clinical development takes a limited part of the whole process [36]. It is probably the right time to appropriately acknowledge the contributions of publicly funded research during drug price negotiation with companies. Often, comparative effectiveness research is funded by public



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institutions to test different treatments in real practice on robust outcomes with longer follow up or special populations [37,38]. The findings of these studies should be linked to a continuous price re-negotiation over the life cycle of a product.

Other approaches identified as possible solutions to keep the health system sustainable address the general governance of the system, i.e., when the price is already set. In fact, a price-volume approach [39] or indication-based pricing [40,41] have been modelled, each presenting pros and cons. Moreover, given that different oncology settings appear to be oligopolistic, thus refraining from price competition, another possible solution comes from national/regional tenders among therapeutic categories when more alternatives are available [42].

The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs. Moreover, we are not aware if further (more robust) data became available at a later stage when the price was negotiated at the national level. In fact, in Italy, the Health Technology Assessment reports used for cost effective analysis at the time of reimbursement decisions are not publicly available. Regarding the price estimate, we estimated the treatment costs for 1-year treatment or for the total course in the case of ipilimumab where the treatment course lasts less than 1 year. However, the exclusion of ipilimumab would not alter the main findings. Another important limitation is that we have not considered quality of life outcomes as another metric of clinical benefit. Furthermore, a recent study has shown that quality of life outcomes are not routinely collected or published, and that the tools used to measure quality of life are varied to have a uniform metric for comparison [43]. Although we have included surrogate measures such as PFS or ORR as clinical outcomes in our analysis because they were considered as the basis for approval by the regulatory agency, these surrogate measures do not always correlate with true clinical benefits in terms of improved survival or improved quality of life [43,44].



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Moreover, additional savings were calculated "a posteriori" from the Managed Entry Agreements in place in Italy (whose information is not publicly available) and were not considered in the analyses. Another factor that might have impacted the price estimation is the rebate obtained at the regional/local level following drug tenders. However, this information was not available for the analyses and would have been not generalizable at the national level. Our study is a retrospective cross-sectional correlation study that aimed at evaluating whether central price negotiation (mandatory by law in Italy) leads to better alignment of prices and the benefits known at the time of drug approval. This means that our analysis is not aimed at comparing costs and outcomes within drug classes, as a typical cost effective study, and we never intended to assess the add values of the approved drugs in the context of all other drugs sharing the same indication. The "population"/cohort approach that we adopted has the intrinsic limitation of including drugs approved for different indications or different cancer types (with various incidence/prevalence) based on different clinical data packages. The consequent heterogeneity stemming from this approach was resolved adjusting the correlation analyses by tumour type or conducting several sub-analyses. Following this approach, we found results consistent with primary findings thus confirming the robustness of methods and results.

**Conclusion**

Our results suggest that price negotiations for approval decisions alone may not bring balance between prices and benefits of anticancer drugs. Other strategies, such as value based price negotiations, price negotiations strictly based on strength of evidence and price transparencies may be necessary to better achieve the drug prices and benefits balance. These results need to be confirmed in other countries where a national price negotiation exists.



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## Contributorship statement

FT, NM and AA conceptualized the study; FT, AA, NM, FM, FBA, GT, and RDC designed the study; FBA, RP, IE and NM were in charge of data extraction and quality control; FM, RDC, and FT performed the data analysis; FT, FM, AA, GT, BG, and RDC drafted the manuscript; All the authors contributed to the discussion and the interpretation of results, and reviewed the final version of the manuscript. All authors approved the final manuscript as submitted.

## Competing interests

The authors have no competing of interest relevant to this article to disclose and all authors works for public Universities, Public Institutions or not for profit Organizations.

## Funding

None.

## Data Availability

All data presented in the analysis have been extracted by public documents (EPARs for each drug outcomes and clinical data; regional and national administrative official documents (i.e. Gazzetta Ufficiale for prices). Data are available upon reasonable request



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**Table 1.** Characteristics of the 30 anticancer drugs included in the analysis.

| Medicine Name | Active Substance | Clinical setting | Treatment group | Control group | PFS TRT (median in weeks) | PFS CRT (median in weeks) | OS TRT (median in weeks) | OS CRT (median in weeks) | ORR TRT (%) | ORR CRT (%) | Year First Auth. | Official negot. price (€) | Disc. price (€) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Teysuno | tegafur / gimeracil / oteracil | advanced gastric cancer in combination with cisplatin. | teysuno 25 mg/m + cisplatin 75 mg/m2 | 5-fluorouracil 1000 mg/m2 /24 + cisplatin 100 mg/m2 | | | 34.4 | 31.6 | | | 2011 | 4942 | 3479 |
| Jevtana | cabazitaxel | hormone-refractory metastatic prostate cancer . | cabazitaxel + prednisone | mitoxantrone + prednisone | 11.2 | 5.6 | 60.4 | 50.8 | 14.4 | 4.4 | 2011 | 52983 | 38254 |
| Yervoy | ipilimumab | advanced (unresectable or metastatic) melanoma | ipilimumab + placebo | peptide vaccine glycoprotein 100 (gp100) | 11.04 | 11.04 | 39.8 | 25.8 | 5.7 | 1.5 | 2011 | 71400 | 45107 |
| Votubia | everolimus | Renal angiomyolipoma associated with tuberous sclerosis complex (TSC) | everolimus | placebo | | 45.48 | | | 41.8 | 0 | 2011 | 66521 | 41424 |
| Votubia | everolimus | Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) | everolimus | placebo | | | | | 34.6 | 0 | | 53216 | 33139 |
| Halaven | eribulin | locally advanced or metastatic breast cancer | eribulin 1.23 mg/m2 (equivalent to 1.4 mg/m2 eribulin mesylate) | treatment of physician's choice | 16.14 | 9.71 | 57.57 | 45.86 | 12.2 | 4.7 | 2011 | 32300 | 28130 |
| Zytiga | abiraterone acetate | metastatic castration-resistant prostate cancer | abiraterone acetate | placebo | 22.4 | 14.4 | 68.9 | 48.7 | 29.1 | 5.5 | 2011 | 46842 | 33397 |
| Dacogen | decitabine | newly diagnosed de novo or secondary acute myeloid leukaemia (AML) | decitabine | patient's choice | 14.8 | 8.4 | 30.8 | 20 | | | 2012 | 54366 | 34346 |
| Caprelsa | vandetanib | aggressive and symptomatic medullary thyroid cancer (MTC) unresectable locally advanced or metastatic disease. | vandetanib | placebo | 122 | 77.2 | | | 45 | 13 | 2012 | 67405 | 53533 |
| Zelboraf | vemurafenib | BRAF-V600-mutation-positive unresectable or metastatic melanoma. | vemurafenib | dacarbazine | 21.28 | 6.44 | 52.8 | 39.6 | 48.4 | 5.5 | 2012 | 119929 | 108236 |
| Xalkori | crizotinib | anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). | crizotinib | pemetrexed or docetaxel | 30.8 | 12 | | | 65.3 | 19.5 | 2012 | 79538 | 57427 |



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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Xalkori | crizotinib | first-line treatment of adults with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). | crizotinib | chemotherapy | 43.6 | 28 | | | 74.4 | 45 | | 79538 | 57427 |
| Inlyta | axitinib | advanced renal-cell carcinoma (RCC) | axitinib | sorafenib | 26.8 | 18.8 | | | 19.4 | 9.4 | 2012 | 57632 | 39295 |
| Perjeta | pertuzumab | HER2-positive metastatic or locally recurrent unresectable breast cancer | pertuzumab + trastuzumab + docetaxel | placebo + trastuzumab + docetaxel | 74 | 49.6 | | | 80.2 | 69.3 | 2013 | 51643 | 46608 |
| Kadcyla | trastuzumab emtansine | HER2-positive, unresectable locally advanced or metastatic breast cancer | trastuzumab emtansine (tdm1) | lapatinib + capecitabine (lap+cap) | 38.4 | 25.6 | 123.9 | 100.4 | | | 2013 | 87215 | 75877 |
| Giotrif | afatinib | locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s); | afatinib (film-coated tablets) | pemetrexed (lyophilised powder) + cisplatin (solution for infusion) | 44.56 | 27.6 | | | 56.1 | 22.6 | 2013 | 29528 | 21853 |
| Stivarga | regorafenib | metastatic colorectal cancer (CRC) | regorafenib + best supportive care | placebo + best supportive care | 8.4 | 7.4 | 28 | 21.6 | 1 | 0.4 | 2013 | 85800 | 77434 |
| Stivarga | regorafenib | unresectable or metastatic gastrointestinal stromal tumors (GIST) | regorafenib + best supportive care | placebo + best supportive care | 21 | 4 | | | 1.5 | 4.5 | | 85800 | 77434 |
| Tafinlar | dabrafenib | unresectable or metastatic melanoma with a BRAF V600 mutation. | dabrafenib | dacarbazine | 27.6 | 10.8 | 72.8 | 62.4 | 59 | 24 | 2013 | 107935 | 87670 |
| Zaltrap | aflibercept | metastatic colorectal cancer (MCRC) | aflibercept+folfiri | placebo+folfiri | 27.6 | 18.7 | 54 | 48.4 | 19.8 | 11.1 | 2013 | 30576 | 27591 |
| Xtandi | enzalutamide | metastatic castration resistant prostate cancer | enzalutamide (mdv3100) | placebo | 33.2 | 11.6 | 74.4 | 54.4 | | | 2013 | 49184 | 31960 |
| Imnovid | pomalidomide | relapsed and refractory multiple myeloma | pom+ld-dex | hd-dex | 15.7 | 8 | | 34 | | | 2013 | 127985 | 101646 |
| Lynparza* | olaparib | platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer | olaparib | placebo | 33.6 | 19.2 | 119.2 | 111.2 | | | 2014 | 70517 | 52142 |
| Cyramza | ramucirumab | advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression | ramucirumab+ paclitaxel | placebo+paclitaxel | 17.6 | 11.6 | 38.4 | 29.6 | 27.9 | 16.1 | 2014 | 87360 | 78842 |
| Mekinist | trametinib | unresectable or metastatic melanoma with a BRAF V600 mutation. | trametinb | chemotherapy (dtic or paclitaxel) | 19.6 | 6 | 62.4 | 45.2 | 19 | 5 | 2014 | 62398 | 28157 |



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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Imbruvica | ibrutinib | chronic lymphocytic leukaemia (CLL) | ibrutinib | chlorambucil | | 75.6 | | | 82.4 | 35.3 | | 73805 | 51663 |
| Zydelig | idelalisib | chronic lymphocytic leukaemia (CLL) | idelalisib + rituximab | placebo + rituximab | | 22 | | | 74.5 | 14.5 | 2014 | 48667 | 34067 |
| Sylvant | siltuximab | multicentric Castlemans disease | siltuximab + best supportive care | placebo + best supportive care | | | | | 37.7 | 3.8 | 2014 | 66104 | 29829 |
| Keytruda | pembrolizumab | advanced(unresectable or metastatic) melanoma | ipilimumab | pembrolizumab | 22 | 11.2 | | | 33.7 | 11.9 | 2015 | 90400 | 81586 |
| Opdivo | nivolumab | advanced (unresectable or metastatic) melanoma | nivolumab 3 mg/kg | dacarbazine | 18.8 | 16.8 | | | 31.7 | 10.6 | 2015 | 81310 | 71181 |
| Opdivo | nivolumab | locally advanced or metastatic non-small cell lung cancer (NSCLC) | nivolumab 3 mg/kg | docetaxel 75 mg/m2 | 9.32 | 16.8 | 48.8 | 37.4 | 19.2 | 12.4 | | 81310 | 71181 |
| Opdivo | nivolumab | advanced renal cell carcinoma | nivolumab 3 mg/kg | everolimus100mg | 18.4 | 17.8 | 100 | 78.2 | 25.1 | 5.4 | | 81310 | in negotiation |
| Lenvima | lenvatinib mesylate | progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hrthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) | lenvatinib | placebo | 73.2 | 14.4 | | | 64.8 | 1.5 | 2015 | 68433 | 58673 |
| Cotellic | cobimetinib hemifumarate | unresectable or metastatic melanoma with a BRAF V600 mutation | cobimetinib+vemurafenib | placebo+vemurafenib | 45.2 | 24 | | | 67.8 | 44.8 | 2015 | 75374 | 54420 |
| Kyprolis | carfilzomib | multiple myeloma who have received at least one prior therapy. | carfilzomib + lenalidomide + dexamethasone | lenalidomide + dexamethasone (rd) | 105.2 | 70.4 | | | 87.1 | 67.7 | 2015 | 75900 | 44525 |

Progression Free Survival (PFS); Overall Survival (OS); Treatment Group (TRT); Control Group (CTR); Objective Response Rate (ORR); Official Negotiated Prices (Official Negot.); Discounted Prices (Disc. Prices).

*: During the evaluation at the EMA, lymparza was found to be more effective in a subgroup of patients with a specific biomarker with the following outcome results: PFS lymparza: 44,8 w; PFS control: 17,2 w; OS lymparza: 139,6 w; OS control: 127,6.



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## Figure, tables, titles and legends

**Figure 1.** Correlation between anticancer drug prices (officially negotiated) and health benefits

*Figure 1a. Official negotiated price (ex-factory) vs difference in median OS (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*

*Figure 1b. Official negotiated price (ex-factory) vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*

*Figure 1c. Official negotiated price (ex-factory) vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

**Figure 2.** Correlation between anticancer drug prices (discounted) and health benefits

*Figure 2a. Discounted price with additional compulsory rebates vs difference in median OS (16 drugs related to a single indication are included in the analysis)*

*Figure 2b. Discounted price with additional compulsory rebates vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

*Figure 2c. Discounted price with additional compulsory rebates vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication and four with two indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

**Table 1.** Characteristics of the 30 anticancer drugs included in the analysis.

Legend:

Progression Free Survival (PFS); Overall Survival (OS); Treatment Group (TRT); Control Group (CTR); Objective Response Rate (ORR); Official Negotiated Prices (Official Negot.); Discounted Prices (Disc. Prices).

*: During the evaluation at the EMA, lymparza was found to be more effective in a subgroup of patients with a specific biomarker with the following outcome results: PFS lymparza: 44,8 w; PFS control: 17,2 w; OS lymparza: 139,6 w; OS control: 127,6.

**Supplementary Table 1.** Details of the statistical analysis conducted

**Supplementary Figures 1-4.** Correlations in the sensitivity analysis conducted

*Supplementary Figure 1a. Official negotiated price (ex-factory) vs percentage improvement in median Overall Survival (OS) (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*

*Supplementary Figure 1b. Official negotiated price (ex-factory) vs percentage improvement in median Progression Free Survival (PFS) (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*



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*Supplementary Figure 1c. Official negotiated price (ex-factory) vs percentage improvement in proportion of Objective Response Rate (ORR) (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

*Figure 2. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), excluding negative outcome data (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

*Supplementary Figure 3a. Official negotiated price (ex-factory) vs median Overall Survival (OS), considering only data from placebo-controlled trials. (7drugs related to a single indication are included in the analysis)*

*Supplementary Figure 3b. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), considering only data from placebo-controlled trials. (11 drugs are included in the analysis: 10 with a single indication and one with 2 indications)*

*Supplementary Figure 4a. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication, two with two indications and one with three indication)*

*Supplementary Figure 4b. Discounted price with additional compulsory rebates vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication and three with 2 indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

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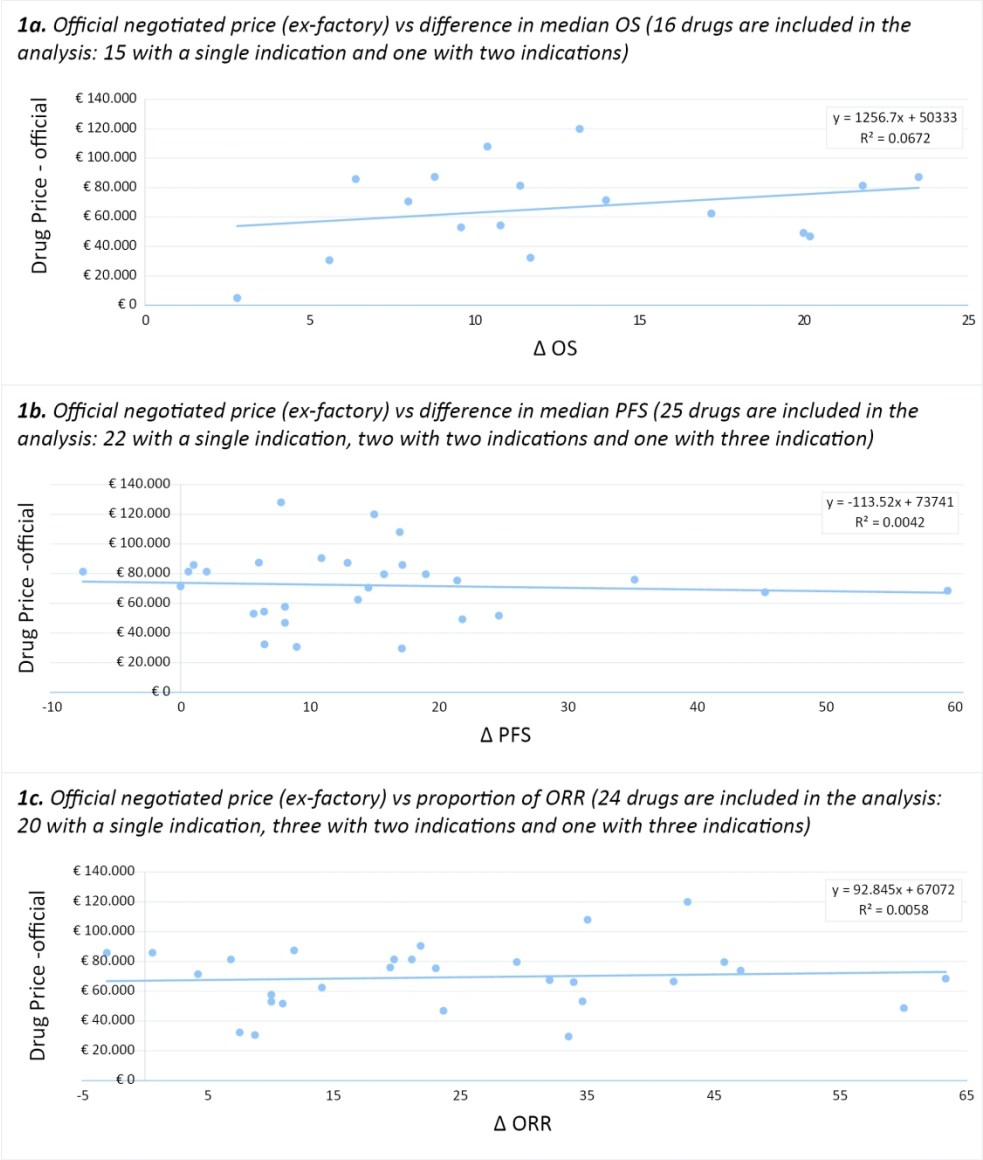


Figure 1. Correlation between anticancer drug prices (officially negotiated) and health benefits

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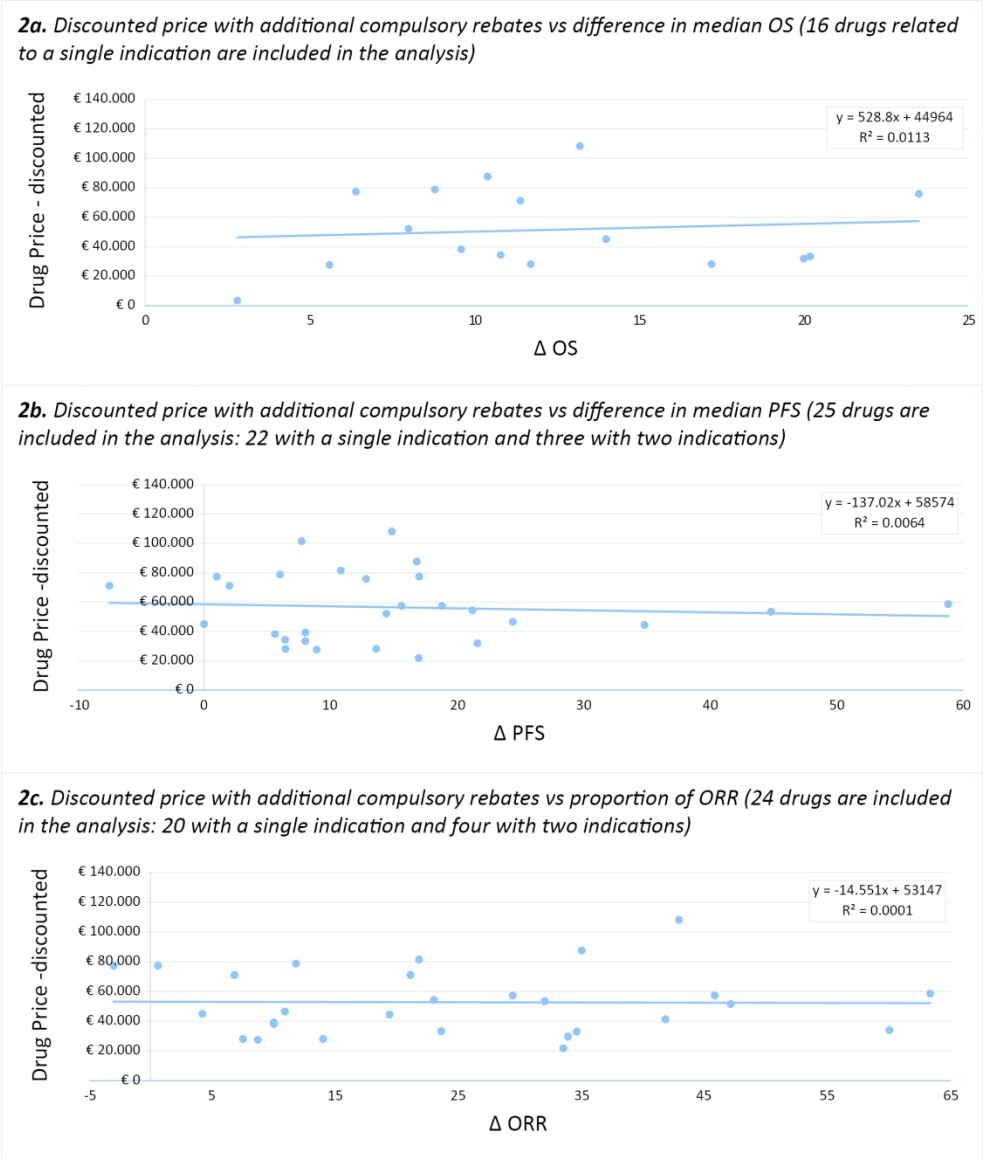



*Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)*

Figure 2. Correlation between anticancer drug prices (discounted) and health benefits

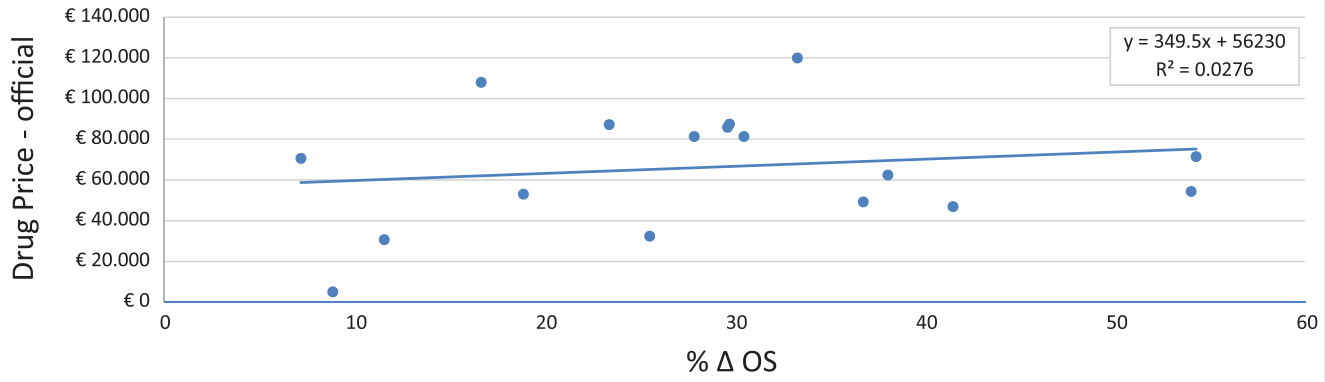
180x219mm (300 x 300 DPI)

**Supplementary Table 1.** Details of the statistical analysis conducted

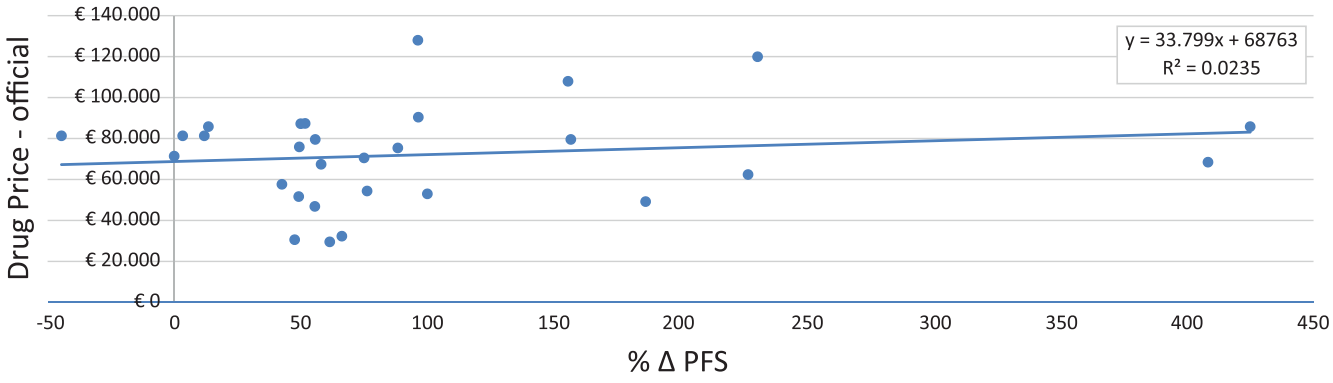
| Dependent variable | Independent variable 1 | Independent variable 2 | Number of drugs involved in the analysis | Type of linear regression | Intercept | Coefficient of the Independent variable 1 | p value of the Independent variable 1 | Correlation coefficient: r | Coefficient of Determination: $R^2$ |
|---|---|---|---|---|---|---|---|---|---|
| Official negotiated price | Δ OS | | 17 | simple | 50332.71 | 1256.724 | 0.315 | 0.259 | 0.067 |
| Discounted price | Δ OS | | 16 | simple | 44963.88 | 528.800 | 0.695 | 0.11 | 0.0113 |
| Official negotiated price | Δ OS | tumor type | 17 | multiple | 57765.99 | 2065.264 | 0.433 | | 0.412 |
| Discounted price | Δ OS | tumor type | 16 | multiple | 55312.8 | 1391.947 | 0.614 | | 0.257 |
| Official negotiated price | % Δ OS | | 17 | simple | 56230.04 | 349.505 | 0.524 | 0.166 | 0.027 |
| Discounted price | % Δ OS | | 16 | simple | 50127.28 | 42.986 | 0.937 | 0.022 | 0.0005 |
| Official negotiated price | % Δ OS | tumor type | 17 | multiple | 72407.98 | 292.048 | 0.766 | | 0.362 |
| Discounted price | % Δ OS | tumor type | 16 | multiple | 68456.17 | 89.3936 | 0.930 | | 0.2286 |
| Official negotiated price | Δ PFS | | 29 | simple | 73741.11 | -113.515 | 0.738 | -0.065 | 0.004 |
| Discounted price | Δ PFS | | 28 | simple | 58574.12 | -137.018 | 0.687 | -0.080 | 0.006 |
| Official negotiated price | Δ PFS | tumor type | 29 | multiple | 70454.93 | -271.324 | 0.635 | | 0.338 |
| Discounted price | Δ PFS | tumor type | 28 | multiple | 56293.38 | -393.926 | 0.508 | | 0.283 |
| Official negotiated price | % Δ PFS | | 29 | simple | 68763.32 | 33.7994 | 0.427 | 0.153 | 0.024 |
| Discounted price | % Δ PFS | | 28 | simple | 52823.84 | 36.2925 | 0.392 | 0.169 | 0.028 |
| Official negotiated price | % Δ PFS | tumor type | 29 | multiple | 66564.96 | 15.935 | 0.765 | | 0.333 |
| Discounted price | % Δ PFS | tumor type | 28 | multiple | 51337.49 | 11.068 | 0.842 | | 0.266 |
| Official negotiated price | Δ ORR | | 29 | simple | 67072.16 | 92.845 | 0.696 | 0.076 | 0.006 |
| Discounted price | Δ ORR | | 28 | simple | 53147.09 | -14.550 | 0.953 | -0.010 | 0.000 |
| Official negotiated price | Δ ORR | tumor type | 29 | multiple | 62277.57 | 180.118 | 0.607 | | 0.448 |
| Discounted price | Δ ORR | tumor type | 28 | multiple | 42598.33 | 324.629 | 0.383 | | 0.450 |
| Official negotiated price | % Δ ORR | | 27 | simple | 69838.7 | 0.563 | 0.918 | 0.020 | 0.000 |
| Discounted price | % Δ ORR | | 26 | simple | 53627.54 | 0.965 | 0.864 | 0.036 | 0.001 |
| Official negotiated price | % Δ ORR | tumor type | 27 | multiple | 67262.18 | 1.719 | 0.814 | | 0.436 |
| Discounted price | % Δ ORR | tumor type | 26 | multiple | 51599.74 | 2.958 | 0.704 | | 0.405 |

Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)

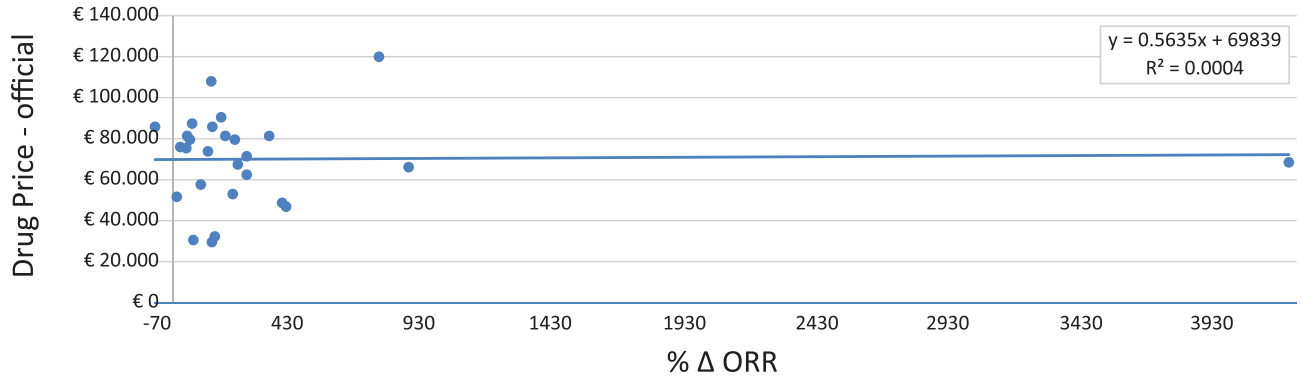
***1a.*** *Official negotiated price (ex-factory) vs percentage improvement in median Overall Survival (OS) (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*




***1b.*** *Official negotiated price (ex-factory) vs percentage improvement in median Progression Free Survival (PFS) (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*

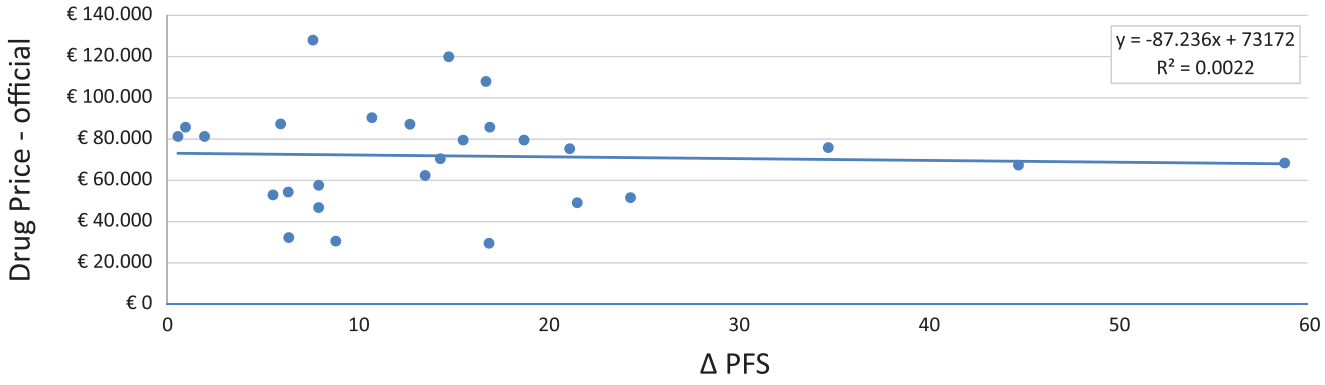



***1c.*** *Official negotiated price (ex-factory) vs percentage improvement in proportion of Objective Response Rate (ORR) (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*




*Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)*

***2.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), excluding negative outcome data (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*




*Progression Free Survival (PFS)*

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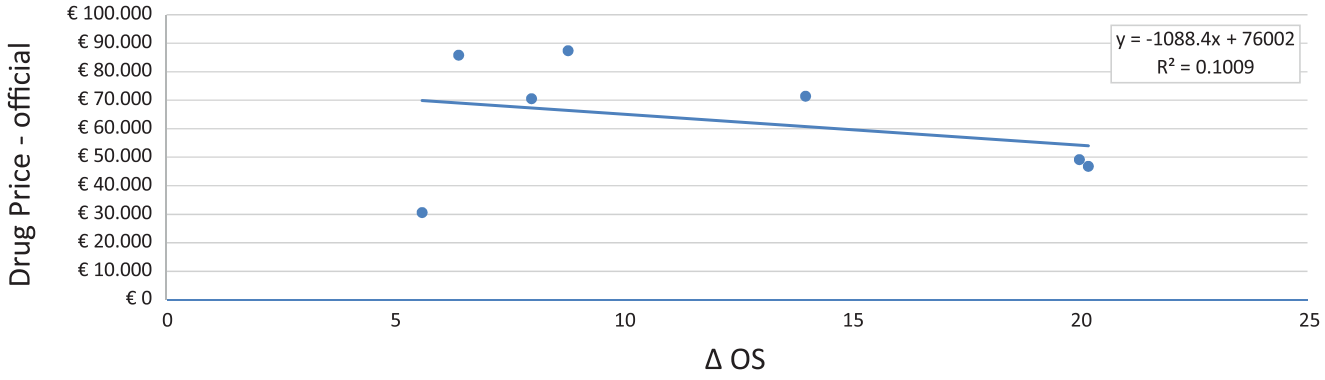
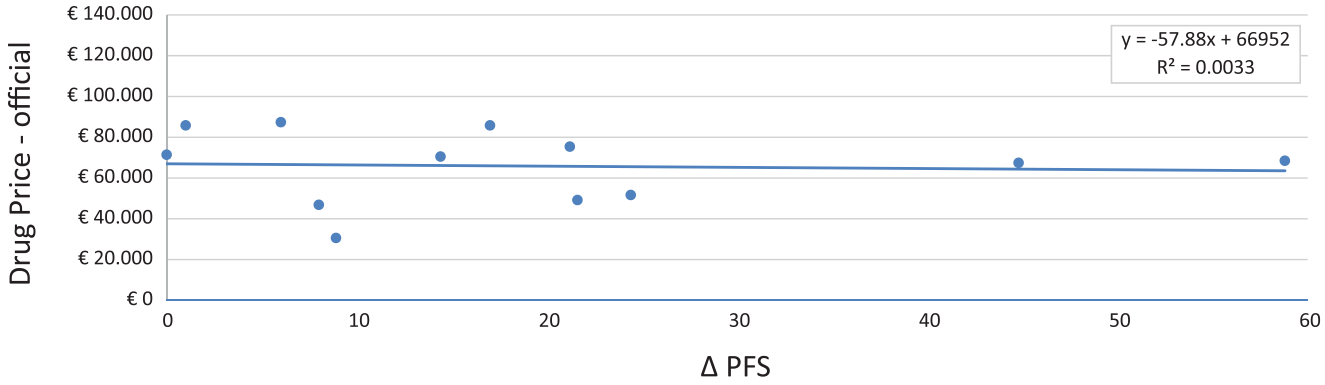
***3a.*** *Official negotiated price (ex-factory) vs median Overall Survival (OS), considering only data from placebo-controlled trials. (7drugs related to a single indication are included in the analysis)*




***3b.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), considering only data from placebo-controlled trials. (11 drugs are included in the analysis: 10 with a single indication and one with 2 indications)*




*Progression Free Survival (PFS); Overall Survival (OS)*

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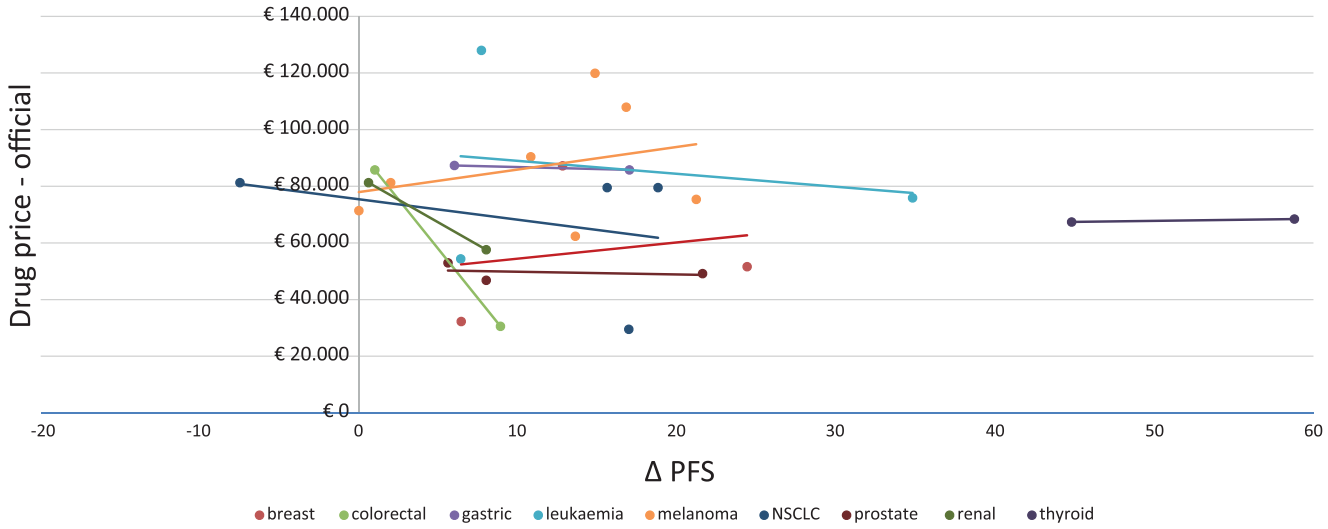
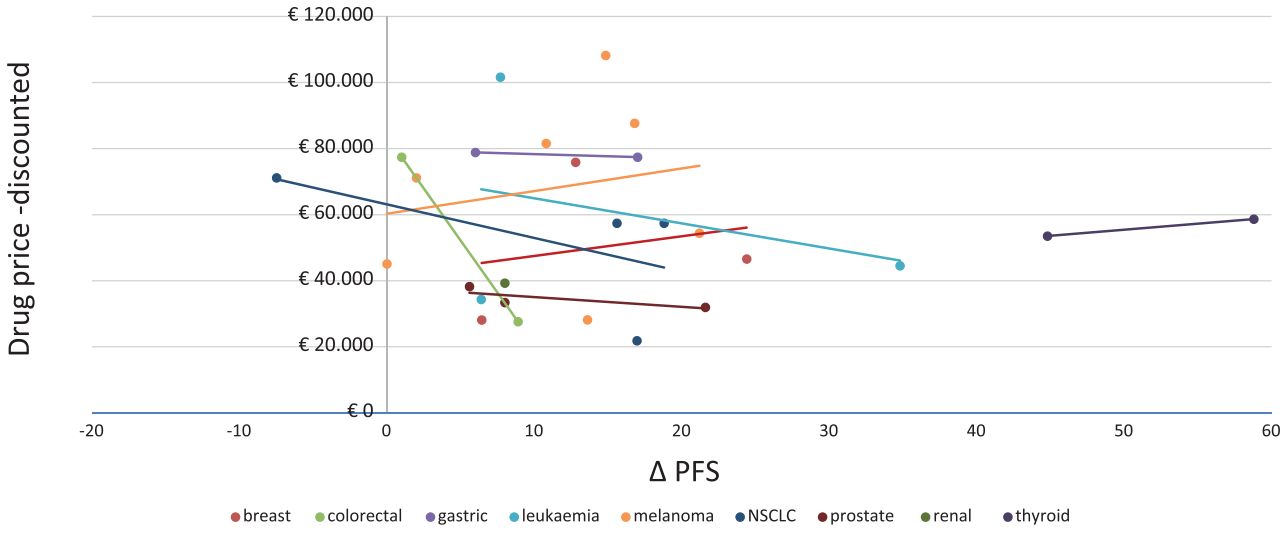
***4a.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication, two with two indications and one with three indication)*




***4b.*** *Discounted price with additional compulsory rebates vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication and three with 2 indications)*




*Progression Free Survival (PFS)*

# STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| **Title and Abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1 (Title) P |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 2 |
| **Introduction** | | | |
| Background/Rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 4 |
| **Methods** | | | |
| Study Design | 4 | Present key elements of study design early in the paper | Page 5-6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 7 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | |
| | | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | |
| | | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 5 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed | |
| | | *Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 5 |

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| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| Data Sources/ Measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Page 5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Page 6 |
| Study Size | 10 | Explain how the study size was arrived at | Page 6 |
| Quantitative Variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | |
| Statistical Methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | Page 6 |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br><br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br><br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | Page 6 |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 8 |
| | | (b) Give reasons for non-participation at each stage | page 8 |
| | | (c) Consider use of a flow diagram | |
| Descriptive Data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | |
| | | (b) Indicate number of participants with missing data for each variable of interest | Page 8 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome Data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | Page 8-9 |

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| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| Main Results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other Analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key Results | 18 | Summarise key results with reference to study objectives | Page 10-12 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | page 13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | page 13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | page 13-14 |
| **Other Information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | cover |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.**

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# Clinical outcomes do not correlate with anticancer drug prices: a cross-sectional study in Italy



| | |
|---|---|
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| | |



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**Article type:** Original article

**Title:** Clinical outcomes do not correlate with anticancer drug prices: a cross-sectional study in Italy

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**contributorship statement**

FT, NM and AA conceptualized the study; FT, AA, NM, FM, FBA, GT, and RDC designed the study; FBA, RP, IE and NM were in charge of data extraction and quality control; FM, RDC, and FT performed the data analysis; FT, RDC, FM, GT, BG, FP and AA drafted the manuscript; all the authors contributed to the discussion and the interpretation of results, and reviewed the final version of the manuscript. All authors approved the final manuscript as submitted.

The authors have no conflicts of interest relevant to this article to disclose and all authors work for public Universities, Public Institutions or non-profit organizations



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**Running head.** Anticancer drug prices and clinical outcomes in Italy

**Word Count:** 2950

**Abstract**:

**Objective** To investigate whether the prices of new anticancer drugs correlated with their relative benefit despite negotiation.

**Design** Retrospective cross-sectional study correlating new anticancer drugs prices with clinical outcomes.

**Setting** We did a retrospective cross-sectional study including all new anticancer drugs approved by the European Medicines Agency (2010-2016) and reimbursed in Italy.

**Main Outcome(s) and Measure(s)** Information on clinical outcomes - in terms of median Overall Survival (OS), median Progression Free Survival (PFS) and Objective Response Rate (ORR) - was extracted from pivotal trials as reported in the European Public Assessment Reports available on the EMA website. Cost of a full course treatment was estimated on negotiated official and discounted prices. Regression coefficients β, their levels of significance p and the coefficients of determination $R^2$ were estimated adjusting by tumour type.

**Results** Overall, 30 new anticancer drugs (with 35 indications) were available for analysis. Where data on Overall Survival were available we observed no correlation between the improvement in median OS (in weeks) and negotiated price ($R^2$= 0.067, n = 16 drugs for 17 indications). When the clinical outcomes were expressed as improvements in median PFS or ORR, 25 drugs (29 indications) were available for analysis, and again, there was no correlation with prices ($R^2$= 0.004 and 0.006, respectively).



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**Conclusions and Relevance**: Our results suggest that the prices of anticancer drugs in Italy do not reflect their therapeutic benefit. Drug price negotiations, which is mandatory by law in Italy, do not seem to ensure that prices correlate with clinical benefits provided by cancer drugs. These results call for further efforts to establish the standard determinants of drug prices available at the time of negotiation. These findings need to be confirmed in other countries where price negotiations are in place. Moreover, further investigations may verify whether outcome data obtained after drug marketing would improve the correlation between prices and therapeutic benefit.

**Strengths and limitations of this study**,

- This study is the first attempt to evaluate whether there were better correlations between cancer drug prices and clinical outcomes in a setting where central price negotiations are mandatory for every new medicine.
- This understanding is important for cancer policy decisions.
- In our analysis, the relationship between the clinical outcome and cost of anticancer drugs was ascertained by a simple linear regression model.
- Clinical outcome, which was the dependent variable, was expressed as absolute or percent differences in outcomes between treatment and control groups.
- The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs.



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## Background

High costs of cancer drugs and resulting financial toxicity to cancer patients are now a well-recognized problem in cancer policy throughout the world [1-8]. Various solutions are being proposed to address this problem, of which price negotiations with pharmaceutical companies is proposed as an important strategy especially in the USA [9-11]. Because the Medicare is not allowed to negotiate prices with companies, despite being mandated to cover for every U.S. Food and Drug Administration (FDA) approved drug, various experts have argued that this is the reason for high drug prices in the USA. Indeed, cancer drug prices far exceed the costs of their development [12];such negotiations might help to lower the prices of cancer drugs as evidenced by lower cost of cancer drugs in other developed countries compared with the USA.

However, little is known about if such negotiations would lead to better correlation between cancer drug prices and the benefits they provide. Studies have shown that drug prices do not correlate with clinical benefits for cancer drugs approved by the FDA, even though such studies have not taken central price negotiations into account [13,14]. Countries such as the United Kingdom and Italy negotiate prices and hence, the correlations might be different.

In Italy, drug price negotiation based on cost-effectiveness evaluation has been mandatory since 2001 for all medicines reimbursed by the National Health Service (NHS) [15,16]. We analysed the correlation between the prices of cancer drugs in Italy with their clinical outcomes to test the hypothesis that central price negotiations leads to better alignment of prices and benefits.



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**Methods:**

*Identification of the study sample*

All new drugs approved by the EMA via a centralized procedure between January 2010 and June 2016 for the treatment of either solid or haematologic cancers were initially identified. Generics, biosimilars, interferons and granulocyte-colony stimulating factors (G-CSFs) were excluded. Only anticancer drugs with pivotal trials based on overall survival (OS), progression-free survival (PFS) or objective response rate (ORR) and with prices that were officially negotiated in Italy by 31st December 2016 were included in the cohort for analyses.

*Data extraction*

Information on the clinical outcomes (in terms of median OS, median PFS, ORR) was extracted by two co-investigators (FBA and RP) from pivotal trials that compared new treatments with controls as reported in the European Public Assessment Reports - EPARs (summary table of the main study, Section 2.5.2) publicly available on the EMA website (www.ema.europa.eu). Survival times were expressed in weeks, and the reported OS and PFS were transformed when necessary. Information on therapeutic indication and tumour type were also retrieved.

*Drug prices*

The cost of a full course or 1-year treatment was estimated by two co-investigators (NM and IE) on the basis of the negotiated official ex-factory price (in euros) of drug packages, as published in the Official Gazette of the Italian Republic (www.gazzettaufficiale.it) and taking into account the posology as reported in the Summary of Product Characteristics (SPC). To compare prices of drugs with different schedules, in the text we refer to drug prices as the cost of a full course or a 1-year treatment. A further estimate took into account additional compulsory rebates [17] or extra-discounts



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that were agreed with pharmaceutical companies; this information is confidential to the public but is released to procurement stations within the Italian NHS (e.g., regions, hospitals, and local health units).

*Statistical analysis*

The following variables were extracted and analysed descriptively: year of approval, therapeutic indication, type of treatment and control groups, outcome data, official and confidential costs per treatment (1 year or a full course) and regulatory information (conditional/under exceptional circumstances approval, or orphan drug status).

The relationship between the clinical outcomes and cost of anticancer drugs was ascertained by a simple linear regression model. Clinical outcome, which was the dependent variable, was expressed as absolute or percent differences in outcomes between treatment and control groups. Regression coefficients β, their levels of significance p and the coefficients of determination $R^2$ were reported for each model.

We also performed several sensitivity analyses to test the robustness of the results. Specifically, we performed multiple linear regression with tumour type as the independent variable to take into account potential differences due to tumour characteristics. Moreover, we also repeated the analysis after excluding negative outcome differences (in two cases, one of the outcomes was inferior in the group receiving the new drug than in the comparison group) and actively controlled trials (considering only placebo-controlled trials). Subgroup analysis by tumour type was also attempted as exploratory analysis when a minimum number of two anticancer drugs within the same tumour type setting were observed. Outlier cases were not excluded from the analyses, but their impact was evaluated and reported when relevant as a separate analysis. All statistical analyses were performed using STATA (Statacorp, version 14.0)



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*Patient and public involvement*

Patients have not been involved in the development of the research question or the design of this study. However, results of this analysis will be disseminated throughout public conferences, with statements summarizing our results, and with an open access to the published report posted in our institutional websites

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## Results

From 2010 to mid-2016, 45 new anticancer drugs for 56 different oncology indications were approved via centralized procedures by the EMA. For 40 new anticancer drugs (47 indications), the basis for the approval was a pivotal trial adopting OS, PFS or ORR as a primary outcome; the price negotiation was completed by December 2016 for only 30 new anticancer drugs (35 indications) which are included in our analysis (Table 1). Seven drugs received orphan drug status by the EMA and two (vandetanib and crizotinib) received conditional approval. Of the 35 oncology indications tested in 35 different pivotal trials which were all controlled clinical trials, the commonest indications were melanoma (7 out of 35), followed by haematological cancer (6 out of 35) and non-small cell lung cancer (4 out of 35). In 15 such trials (43%), placebo was used as the control arm. Of the 35 indications, data on OS, PFS and ORR were available for 17, 29 and 29 indications respectively. Each drug-indication pair contributed to one or more of these analyses, depending on which outcomes were reported in the EPAR.

In the treatment groups, the median improvement in the OS and PFS were 11.4 weeks (IQR 8.8-17.2; min 13.2; max 23.5) and 12.8 weeks (IQR 6.4-17; min -7.48; max 58.8), respectively; median ORR improvement in the treatment group was 21.8% (IQR 10-34.6; min -3; max 63.3). The reported ranges have negative minimum values since in two cases - nivolumab for NSCLC and regorafenib for gastrointestinal stromal tumours - the experimental treatment had a negative effect on one of the outcomes compared to the control group (in terms of PFS for nivolumab and ORR for regorafenib). The median negotiated price for a 1-year treatment was 72,392 euros (IQR 53,819-85,800; min 4,942; max 142,785), which was further discounted by 25% (on average) after applying confidential rebates. For all anticancer drugs but ipilimumab the price was calculated as 1-year treatment since the posology reported in the Summary of Product Characteristics (SPC) reported that the treatment should



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continue as long as clinical benefit is observed or until unacceptable toxicity occurs. In the case of ipilimumab the price was calculated as a course of 4 doses as reported in the SPC.

The official (ex-factory) price of new anticancer drugs and absolute clinical outcomes showed no correlation (Figure 1a-c). The relationship between the improvement in median OS (in weeks) and negotiated price was estimated for 16 drugs (17 indications), and no correlation was observed ($R^2$= 0.067). When clinical outcomes were expressed as absolute advantage in median PFS or ORR, 25 drugs (29 indications) were available for analysis, and in these cases, no correlation was observed ($R^2$= 0.004 and 0.006, respectively).

Repeating the analyses and taking into account the additional confidential rebates, which are compulsory for hospital procurement, no improvement in the benefit/price relationships was highlighted (Figure 2a-c). These findings also remained unchanged when the analyses were repeated with adjustments for tumour type (Supplementary Table 1) or when clinical outcome was expressed as a percentage of improvement instead of as an absolute difference (Supplementary Figure 1a-c). Sensitivity analyses that excluded negative improvements in outcomes over a control group (Supplementary Figure 2) and considered only data from placebo controlled trials (Supplementary Figure 3a,b) confirmed the main analysis. The exploratory subgroup analyses by tumour type did not identify specific positive correlation patterns depending on tumour setting (Supplementary Figure 4 a,b).

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## Discussion

This study is the first attempt to evaluate whether there were better correlations between cancer drug prices and clinical outcomes in a setting where central price negotiations are mandatory for every new medicine. Our study gave unexpected results to the research question, highlighting no relationships between cost of cancer drugs and benefits. Moreover, all pre-specified sensitivity and subgroup analyses confirmed the main findings. This finding will have important policy implications both for countries like USA where price negotiations are absent and for other countries like Italy where price negotiations do exist.

In our study, the correlation between drug costs and clinical outcomes was even lower than the ones previously noted in the US context [13,14], showing that negotiations did not tilt the relationship between drug prices and benefit positively. Thus, higher drug pricing remains despite the Italian legislative environment, where approval based on cost-effectiveness analysis and price negotiations have been mandatory by law since 2001 [15,16]. This finding may cast doubts on the role of the negotiation itself. However, it is important to understand that countries like Italy that negotiate drug prices do such negotiations only for binary decisions of approval or no-approval, not taking into account, during negotiation, a clear correlation between prices and benefits. This understanding is important for cancer policy decisions.

Indeed, there is no legal policy in any country to negotiate prices differently for drugs approved on the basis of surrogate endpoints versus survival outcomes, or drugs that improve survival in days, versus those that improve survival in months or drugs with immature benefit risk profiles [18-22]. Although steps in the right direction, in lack of such policy, the value frameworks proposed by organizations such as ASCO, ESMO or NCCN have become little more than intellectual exercises [23-26].



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Another reason price negotiations did not achieve better price-value correlations is that because of the global market of drugs, each single country - although large – only represents a small portion of the consumer market. Thus, companies "wield the stick", setting the maximum price that the market will bear [27]. In addition, in Italy, no threshold for incremental cost-effectiveness ratio (ICER) has been determined; thus, no limit is in place to be used as a decision rule in resource allocation at the time of negotiation/reimbursement decisions. The lack of such kind of cut-off might have contributed to the negative results in our study. However, we recognize that even when a threshold for ICER is well established, such as in the UK [28], continuous exceptions have been allowed in the case of anticancer drugs. For example, an ad hoc fund established in 2010 (i.e., the Cancer Drug Fund) was recently dismissed by the Parliament because it did not deliver meaningful value to patients or society [29].

In the EU context (where newer anticancer drugs are approved by EMA without considering the added-value or cost-effectiveness), the complexity further increases because once a marketing authorization is granted, it may become difficult to manage the reimbursement issue at a national level [30]. Moreover, it is also difficult for payers (NHS/insurance) to defend the thesis against the public opinion that an anticancer drug cannot be reimbursed because it is too expensive [30, 31]. Indeed, as our study shows, the confidential discounts following negotiations between a member state and a company do not ameliorate the correlation between treatment costs and benefits even though they reduce absolute drug prices.

Another factor that negatively influences the contractual power of negotiation is non-transparent information on drug prices across countries. Difficulties in retrieving full information on prices have been already recognized in a recent survey comparing prices of anticancer drugs in 16 EU countries,



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Australia and New Zealand [32]. Vogler et al. found that price information is scarce and not disclosed due to confidential discounts or MEAs, calling for higher transparency. The authors state that it is in the interest of policy makers to remove clauses limiting disclosure on price information because they risk overpaying when setting prices through external price referencing. This concern might be relevant in the Italian context since the negotiation procedure for reimbursement takes into account the price in other EU countries as well as the price of similar products within the same pharmacotherapeutic group [33].

We believe that two partly independent approaches could be adopted by policy makers to achieve a better balance between cancer drug prices and benefits. First, price negotiations should be more strictly based on the level of evidence as well as the magnitudes of benefit. An ICER measure (such as QALY) should represent a threshold for reimbursement, thus setting a starting point for price negotiation and adjusting the ICER threshold based on the magnitude of the relative benefit reached. If the information on the relative value is not available at the time of approval, comparisons can be performed using indirect techniques, whereas after entering the market, payers should play a major role in supporting the evidence generating process.

The second approach that could attain lower prices would require an increased transparency on the costs of drug development process, including the relative contributions from academia and public sector to the development of a drug [34-38]. For instance, research conducted to evaluate efforts of drug development processes highlighted that about half of the most transformative drugs approved by the FDA had substantial contributions to their development by academic researchers supported by government funding [34,35]; in addition, it has been estimated that the cost of late clinical development takes a limited part of the whole process [36]. It is probably the right time to appropriately acknowledge the contributions of publicly funded research during drug price negotiation with companies. Often, comparative effectiveness research is funded by public



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institutions to test different treatments in real practice on robust outcomes with longer follow up or special populations [37,38]. The findings of these studies should be linked to a continuous price re-negotiation over the life cycle of a product.

Other approaches identified as possible solutions to keep the health system sustainable address the general governance of the system, i.e., when the price is already set. In fact, a price-volume approach [39] or indication-based pricing [40,41] have been modelled, each presenting pros and cons. Moreover, given that different oncology settings appear to be oligopolistic, thus refraining from price competition, another possible solution comes from national/regional tenders among therapeutic categories when more alternatives are available [42].

The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs. Moreover, we are not aware if further (more robust) data became available at a later stage when the price was negotiated at the national level. Thus, we cannot exclude that the correlation between drug prices and therapeutic benefit might improve taking into account data acquired after the marketing of anticancer drugs.

Another important limitation is that we have not considered quality of life outcomes as another metric of clinical benefit. Furthermore, a recent study has shown that quality of life outcomes are not routinely collected or published, and that the tools used to measure quality of life are varied to have a uniform metric for comparison [43]. Although we have included surrogate measures such as PFS or ORR as clinical outcomes in our analysis because they were considered as the basis for approval by the regulatory agency, these surrogate measures do not always correlate with true clinical benefits in terms of improved survival or improved quality of life [43,44]. Regarding the price estimate, we estimated the treatment costs for 1-year treatment or for the total course in the case of ipilimumab



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where the treatment course lasts less than 1 year. However, the exclusion of ipilimumab would not alter the main findings.

Another factor that might have impacted the price estimation is the rebate obtained at the regional/local level following drug tenders. This information was not available for the analyses and would have been not generalizable at the national level. Moreover, additional savings were expected "a posteriori" from the Managed Entry Agreements in place in Italy (whose information is not publicly available) and were not considered in the analyses.

Our study is a retrospective cross-sectional correlation study that aimed at evaluating whether central price negotiation (mandatory by law in Italy) leads to better alignment of prices and the benefits known at the time of drug approval. This means that our analysis is not aimed at comparing costs and outcomes within drug classes, as a typical cost effective study, and we never intended to assess the added values of the approved drugs in the context of all other drugs sharing the same indication. The "population"/cohort approach that we adopted has the intrinsic limitation of including drugs approved for different indications or different cancer types (with various incidence/prevalence) based on different clinical data packages. The consequent heterogeneity stemming from this approach was resolved adjusting the correlation analyses by tumour type or conducting several sub-analyses. Following this approach, we found results consistent with primary findings thus confirming the robustness of methods and results.

**Conclusion**

Our results suggest that price negotiations for approval decisions alone may not bring balance between prices and benefits of anticancer drugs. Based on the limited outcome data available at the time of reimbursement decisions (OS; PFS; ORR), prices of anticancer drugs do not reflect their therapeutic benefit. Other strategies, such as value based price negotiations, price negotiations strictly



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based on strength of evidence and price transparencies may be necessary to better achieve the drug prices and benefits balance. These results need to be confirmed in other countries where a national price negotiation exists.

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## Contributorship statement

FT, NM and AA conceptualized the study; FT, AA, NM, FM, FBA, GT, and RDC designed the study; FBA, RP, IE and NM were in charge of data extraction and quality control; FM, RDC, and FT performed the data analysis; FT, RDC, FM, GT, BG, FP and AA drafted the manuscript; all the authors contributed to the discussion and the interpretation of results, and reviewed the final version of the manuscript. All authors approved the final manuscript as submitted.

## Competing interests

The authors have no competing of interest relevant to this article to disclose and all authors works for public Universities, Public Institutions or not for profit Organizations.

## Funding

None.

## Data Availability

All data presented in the analysis have been extracted by public documents (EPARs for each drug outcomes and clinical data; regional and national administrative official documents (i.e. Gazzetta Ufficiale for prices). Data are available upon reasonable request



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**Table 1.** Characteristics of the 30 anticancer drugs included in the analysis.

| Medicine Name | Active Substance | Clinical setting | Treatment group | Control group | PFS TRT (median in weeks) | PFS CRT (median in weeks) | OS TRT (median in weeks) | OS CRT (median in weeks) | ORR TRT (%) | ORR CRT (%) | Year First Auth. | Official negot. price (€) | Disc. price (€) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Teysuno | tegafur / gimeracil / oteracil | advanced gastric cancer in combination with cisplatin. | teysuno 25 mg/m + cisplatin 75 mg/m2 | 5-fluorouracil 1000 mg/m2 /24 + cisplatin 100 mg/m2 | | | 34.4 | 31.6 | | | 2011 | 4942 | 3479 |
| Jevtana | cabazitaxel | hormone-refractory metastatic prostate cancer . | cabazitaxel + prednisone | mitoxantrone + prednisone | 11.2 | 5.6 | 60.4 | 50.8 | 14.4 | 4.4 | 2011 | 52983 | 38254 |
| Yervoy | ipilimumab | advanced (unresectable or metastatic) melanoma | ipilimumab + placebo | peptide vaccine glycoprotein 100 (gp100) | 11.04 | 11.04 | 39.8 | 25.8 | 5.7 | 1.5 | 2011 | 71400 | 45107 |
| Votubia | everolimus | Renal angiomyolipoma associated with tuberous sclerosis complex (TSC) | everolimus | placebo | | 45.48 | | | 41.8 | 0 | 2011 | 66521 | 41424 |
| Votubia | everolimus | Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) | everolimus | placebo | | | | | 34.6 | 0 | | 53216 | 33139 |
| Halaven | eribulin | locally advanced or metastatic breast cancer | eribulin 1.23 mg/m2 (equivalent to 1.4 mg/m2 eribulin mesylate) | treatment of physician's choice | 16.14 | 9.71 | 57.57 | 45.86 | 12.2 | 4.7 | 2011 | 32300 | 28130 |
| Zytiga | abiraterone acetate | metastatic castration-resistant prostate cancer | abiraterone acetate | placebo | 22.4 | 14.4 | 68.9 | 48.7 | 29.1 | 5.5 | 2011 | 46842 | 33397 |
| Dacogen | decitabine | newly diagnosed de novo or secondary acute myeloid leukaemia (AML) | decitabine | patient's choice | 14.8 | 8.4 | 30.8 | 20 | | | 2012 | 54366 | 34346 |
| Caprelsa | vandetanib | aggressive and symptomatic medullary thyroid cancer (MTC) unresectable locally advanced or metastatic disease. | vandetanib | placebo | 122 | 77.2 | | | 45 | 13 | 2012 | 67405 | 53533 |
| Zelboraf | vemurafenib | BRAF-V600-mutation-positive unresectable or metastatic melanoma. | vemurafenib | dacarbazine | 21.28 | 6.44 | 52.8 | 39.6 | 48.4 | 5.5 | 2012 | 119929 | 108236 |
| Xalkori | crizotinib | anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). | crizotinib | pemetrexed or docetaxel | 30.8 | 12 | | | 65.3 | 19.5 | 2012 | 79538 | 57427 |



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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Xalkori | crizotinib | first-line treatment of adults with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). | crizotinib | chemotherapy | 43.6 | 28 | | | 74.4 | 45 | | 79538 | 57427 |
| Inlyta | axitinib | advanced renal-cell carcinoma (RCC) | axitinib | sorafenib | 26.8 | 18.8 | | | 19.4 | 9.4 | 2012 | 57632 | 39295 |
| Perjeta | pertuzumab | HER2-positive metastatic or locally recurrent unresectable breast cancer | pertuzumab + trastuzumab + docetaxel | placebo + trastuzumab + docetaxel | 74 | 49.6 | | | 80.2 | 69.3 | 2013 | 51643 | 46608 |
| Kadcyla | trastuzumab emtansine | HER2-positive, unresectable locally advanced or metastatic breast cancer | trastuzumab emtansine (tdm1) | lapatinib + capecitabine (lap+cap) | 38.4 | 25.6 | 123.9 | 100.4 | | | 2013 | 87215 | 75877 |
| Giotrif | afatinib | locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s); | afatinib (film-coated tablets) | pemetrexed (lyophilised powder) + cisplatin (solution for infusion) | 44.56 | 27.6 | | | 56.1 | 22.6 | 2013 | 29528 | 21853 |
| Stivarga | regorafenib | metastatic colorectal cancer (CRC) | regorafenib + best supportive care | placebo + best supportive care | 8.4 | 7.4 | 28 | 21.6 | 1 | 0.4 | 2013 | 85800 | 77434 |
| Stivarga | regorafenib | unresectable or metastatic gastrointestinal stromal tumors (GIST) | regorafenib + best supportive care | placebo + best supportive care | 21 | 4 | | | 1.5 | 4.5 | | 85800 | 77434 |
| Tafinlar | dabrafenib | unresectable or metastatic melanoma with a BRAF V600 mutation. | dabrafenib | dacarbazine | 27.6 | 10.8 | 72.8 | 62.4 | 59 | 24 | 2013 | 107935 | 87670 |
| Zaltrap | aflibercept | metastatic colorectal cancer (MCRC) | aflibercept+folfiri | placebo+folfiri | 27.6 | 18.7 | 54 | 48.4 | 19.8 | 11.1 | 2013 | 30576 | 27591 |
| Xtandi | enzalutamide | metastatic castration resistant prostate cancer | enzalutamide (mdv3100) | placebo | 33.2 | 11.6 | 74.4 | 54.4 | | | 2013 | 49184 | 31960 |
| Imnovid | pomalidomide | relapsed and refractory multiple myeloma | pom+ld-dex | hd-dex | 15.7 | 8 | | 34 | | | 2013 | 127985 | 101646 |
| Lynparza* | olaparib | platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer | olaparib | placebo | 33.6 | 19.2 | 119.2 | 111.2 | | | 2014 | 70517 | 52142 |
| Cyramza | ramucirumab | advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression | ramucirumab+ paclitaxel | placebo+paclitaxel | 17.6 | 11.6 | 38.4 | 29.6 | 27.9 | 16.1 | 2014 | 87360 | 78842 |
| Mekinist | trametinib | unresectable or metastatic melanoma with a BRAF V600 mutation. | trametinb | chemotherapy (dtic or paclitaxel) | 19.6 | 6 | 62.4 | 45.2 | 19 | 5 | 2014 | 62398 | 28157 |



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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Imbruvica | ibrutinib | chronic lymphocytic leukaemia (CLL) | ibrutinib | chlorambucil | | 75.6 | | | 82.4 | 35.3 | | 73805 | 51663 |
| Zydelig | idelalisib | chronic lymphocytic leukaemia (CLL) | idelalisib + rituximab | placebo + rituximab | | 22 | | | 74.5 | 14.5 | 2014 | 48667 | 34067 |
| Sylvant | siltuximab | multicentric Castlemans disease | siltuximab + best supportive care | placebo + best supportive care | | | | | 37.7 | 3.8 | 2014 | 66104 | 29829 |
| Keytruda | pembrolizumab | advanced(unresectable or metastatic) melanoma | ipilimumab | pembrolizumab | 22 | 11.2 | | | 33.7 | 11.9 | 2015 | 90400 | 81586 |
| Opdivo | nivolumab | advanced (unresectable or metastatic) melanoma | nivolumab 3 mg/kg | dacarbazine | 18.8 | 16.8 | | | 31.7 | 10.6 | 2015 | 81310 | 71181 |
| Opdivo | nivolumab | locally advanced or metastatic non-small cell lung cancer (NSCLC) | nivolumab 3 mg/kg | docetaxel 75 mg/m2 | 9.32 | 16.8 | 48.8 | 37.4 | 19.2 | 12.4 | | 81310 | 71181 |
| Opdivo | nivolumab | advanced renal cell carcinoma | nivolumab 3 mg/kg | everolimus100mg | 18.4 | 17.8 | 100 | 78.2 | 25.1 | 5.4 | | 81310 | in negotiation |
| Lenvima | lenvatinib mesylate | progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hrthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) | lenvatinib | placebo | 73.2 | 14.4 | | | 64.8 | 1.5 | 2015 | 68433 | 58673 |
| Cotellic | cobimetinib hemifumarate | unresectable or metastatic melanoma with a BRAF V600 mutation | cobimetinib+vemurafenib | placebo+vemurafenib | 45.2 | 24 | | | 67.8 | 44.8 | 2015 | 75374 | 54420 |
| Kyprolis | carfilzomib | multiple myeloma who have received at least one prior therapy. | carfilzomib + lenalidomide + dexamethasone | lenalidomide + dexamethasone (rd) | 105.2 | 70.4 | | | 87.1 | 67.7 | 2015 | 75900 | 44525 |

Progression Free Survival (PFS); Overall Survival (OS); Treatment Group (TRT); Control Group (CTR); Objective Response Rate (ORR); Official Negotiated Prices (Official Negot.); Discounted Prices (Disc. Prices).

*: During the evaluation at the EMA, lymparza was found to be more effective in a subgroup of patients with a specific biomarker with the following outcome results: PFS lymparza: 44,8 w; PFS control: 17,2 w; OS lymparza: 139,6 w; OS control: 127,6.



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## Figure, tables, titles and legends

**Figure 1.** Correlation between anticancer drug prices (officially negotiated) and health benefits

*Figure 1a. Official negotiated price (ex-factory) vs difference in median OS (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*

*Figure 1b. Official negotiated price (ex-factory) vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*

*Figure 1c. Official negotiated price (ex-factory) vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

**Figure 2.** Correlation between anticancer drug prices (discounted) and health benefits

*Figure 2a. Discounted price with additional compulsory rebates vs difference in median OS (16 drugs related to a single indication are included in the analysis)*

*Figure 2b. Discounted price with additional compulsory rebates vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

*Figure 2c. Discounted price with additional compulsory rebates vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication and four with two indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

**Table 1.** Characteristics of the 30 anticancer drugs included in the analysis.

Legend:

Progression Free Survival (PFS); Overall Survival (OS); Treatment Group (TRT); Control Group (CTR); Objective Response Rate (ORR); Official Negotiated Prices (Official Negot.); Discounted Prices (Disc. Prices).

*: During the evaluation at the EMA, lymparza was found to be more effective in a subgroup of patients with a specific biomarker with the following outcome results: PFS lymparza: 44,8 w; PFS control: 17,2 w; OS lymparza: 139,6 w; OS control: 127,6.

**Supplementary Table 1.** Details of the statistical analysis conducted

**Supplementary Figures 1-4.** Correlations in the sensitivity analysis conducted

*Supplementary Figure 1a. Official negotiated price (ex-factory) vs percentage improvement in median Overall Survival (OS) (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*

*Supplementary Figure 1b. Official negotiated price (ex-factory) vs percentage improvement in median Progression Free Survival (PFS) (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*



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*Supplementary Figure 1c. Official negotiated price (ex-factory) vs percentage improvement in proportion of Objective Response Rate (ORR) (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

*Figure 2. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), excluding negative outcome data (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

*Supplementary Figure 3a. Official negotiated price (ex-factory) vs median Overall Survival (OS), considering only data from placebo-controlled trials. (7drugs related to a single indication are included in the analysis)*

*Supplementary Figure 3b. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), considering only data from placebo-controlled trials. (11 drugs are included in the analysis: 10 with a single indication and one with 2 indications)*

*Supplementary Figure 4a. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication, two with two indications and one with three indication)*

*Supplementary Figure 4b. Discounted price with additional compulsory rebates vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication and three with 2 indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

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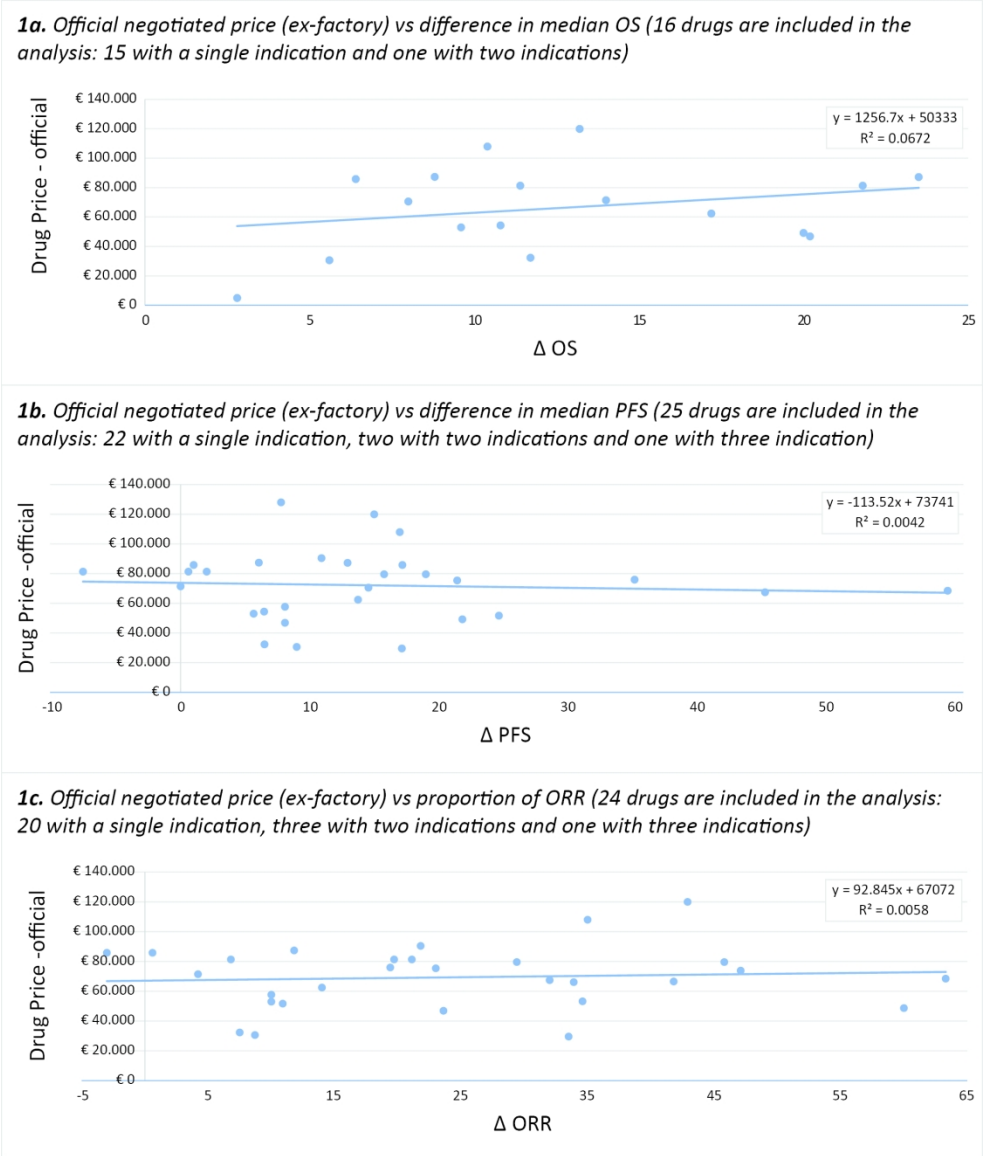


Figure 1. Correlation between anticancer drug prices (officially negotiated) and health benefits

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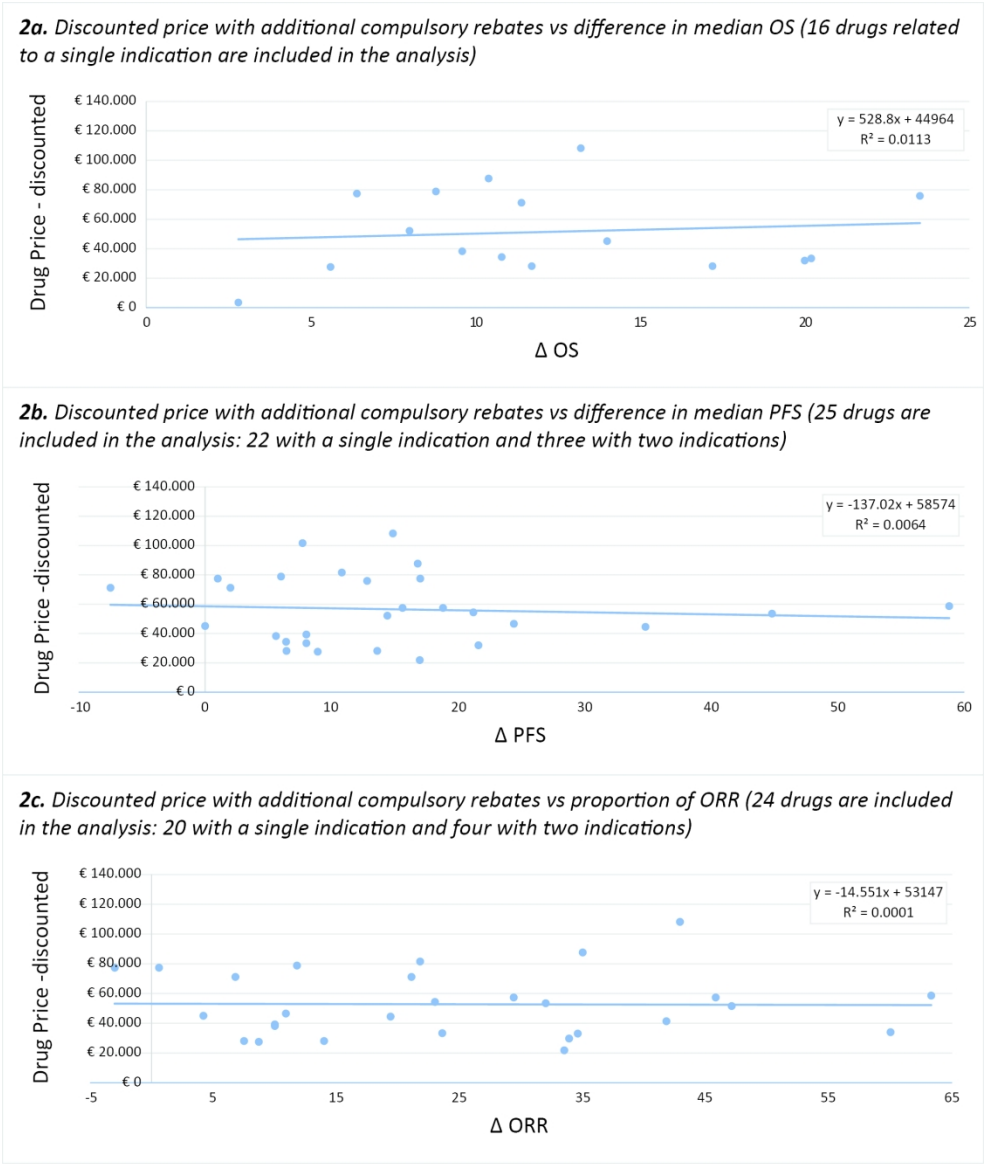



*Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)*

Figure 2. Correlation between anticancer drug prices (discounted) and health benefits

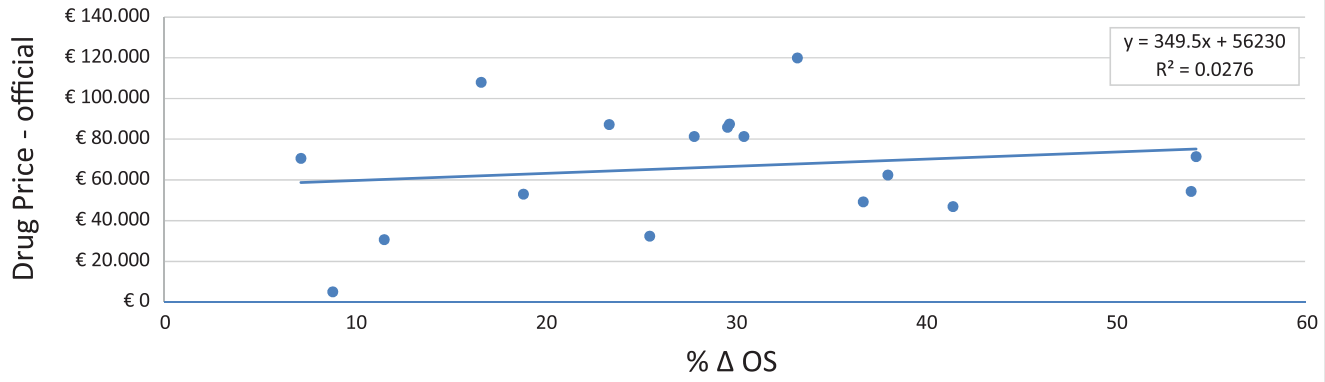
180x219mm (300 x 300 DPI)

**Supplementary Table 1.** Details of the statistical analysis conducted

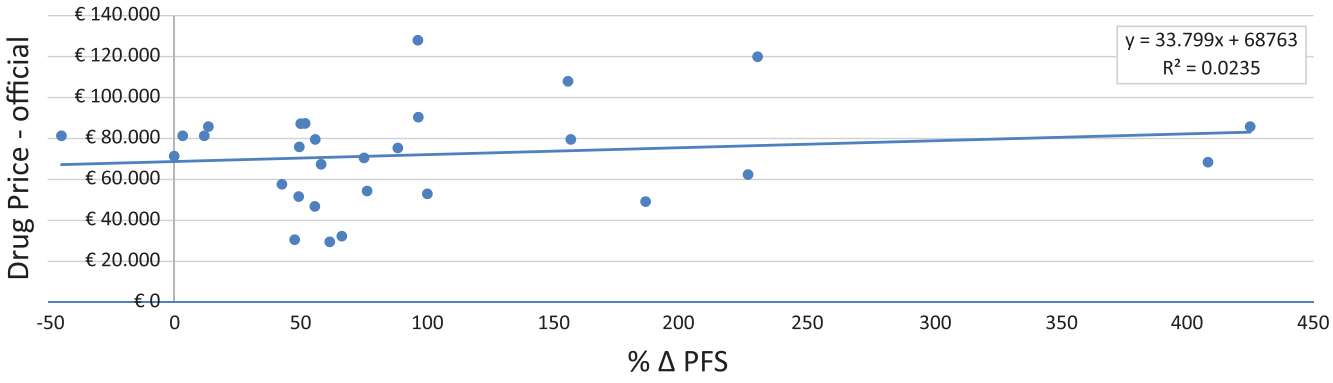
| Dependent variable | Independent variable 1 | Independent variable 2 | Number of drugs involved in the analysis | Type of linear regression | Intercept | Coefficient of the Independent variable 1 | p value of the Independent variable 1 | Correlation coefficient: r | Coefficient of Determination: $R^2$ |
|---|---|---|---|---|---|---|---|---|---|
| Official negotiated price | Δ OS | | 17 | simple | 50332.71 | 1256.724 | 0.315 | 0.259 | 0.067 |
| Discounted price | Δ OS | | 16 | simple | 44963.88 | 528.800 | 0.695 | 0.11 | 0.0113 |
| Official negotiated price | Δ OS | tumor type | 17 | multiple | 57765.99 | 2065.264 | 0.433 | | 0.412 |
| Discounted price | Δ OS | tumor type | 16 | multiple | 55312.8 | 1391.947 | 0.614 | | 0.257 |
| Official negotiated price | % Δ OS | | 17 | simple | 56230.04 | 349.505 | 0.524 | 0.166 | 0.027 |
| Discounted price | % Δ OS | | 16 | simple | 50127.28 | 42.986 | 0.937 | 0.022 | 0.0005 |
| Official negotiated price | % Δ OS | tumor type | 17 | multiple | 72407.98 | 292.048 | 0.766 | | 0.362 |
| Discounted price | % Δ OS | tumor type | 16 | multiple | 68456.17 | 89.3936 | 0.930 | | 0.2286 |
| Official negotiated price | Δ PFS | | 29 | simple | 73741.11 | -113.515 | 0.738 | -0.065 | 0.004 |
| Discounted price | Δ PFS | | 28 | simple | 58574.12 | -137.018 | 0.687 | -0.080 | 0.006 |
| Official negotiated price | Δ PFS | tumor type | 29 | multiple | 70454.93 | -271.324 | 0.635 | | 0.338 |
| Discounted price | Δ PFS | tumor type | 28 | multiple | 56293.38 | -393.926 | 0.508 | | 0.283 |
| Official negotiated price | % Δ PFS | | 29 | simple | 68763.32 | 33.7994 | 0.427 | 0.153 | 0.024 |
| Discounted price | % Δ PFS | | 28 | simple | 52823.84 | 36.2925 | 0.392 | 0.169 | 0.028 |
| Official negotiated price | % Δ PFS | tumor type | 29 | multiple | 66564.96 | 15.935 | 0.765 | | 0.333 |
| Discounted price | % Δ PFS | tumor type | 28 | multiple | 51337.49 | 11.068 | 0.842 | | 0.266 |
| Official negotiated price | Δ ORR | | 29 | simple | 67072.16 | 92.845 | 0.696 | 0.076 | 0.006 |
| Discounted price | Δ ORR | | 28 | simple | 53147.09 | -14.550 | 0.953 | -0.010 | 0.000 |
| Official negotiated price | Δ ORR | tumor type | 29 | multiple | 62277.57 | 180.118 | 0.607 | | 0.448 |
| Discounted price | Δ ORR | tumor type | 28 | multiple | 42598.33 | 324.629 | 0.383 | | 0.450 |
| Official negotiated price | % Δ ORR | | 27 | simple | 69838.7 | 0.563 | 0.918 | 0.020 | 0.000 |
| Discounted price | % Δ ORR | | 26 | simple | 53627.54 | 0.965 | 0.864 | 0.036 | 0.001 |
| Official negotiated price | % Δ ORR | tumor type | 27 | multiple | 67262.18 | 1.719 | 0.814 | | 0.436 |
| Discounted price | % Δ ORR | tumor type | 26 | multiple | 51599.74 | 2.958 | 0.704 | | 0.405 |

Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)

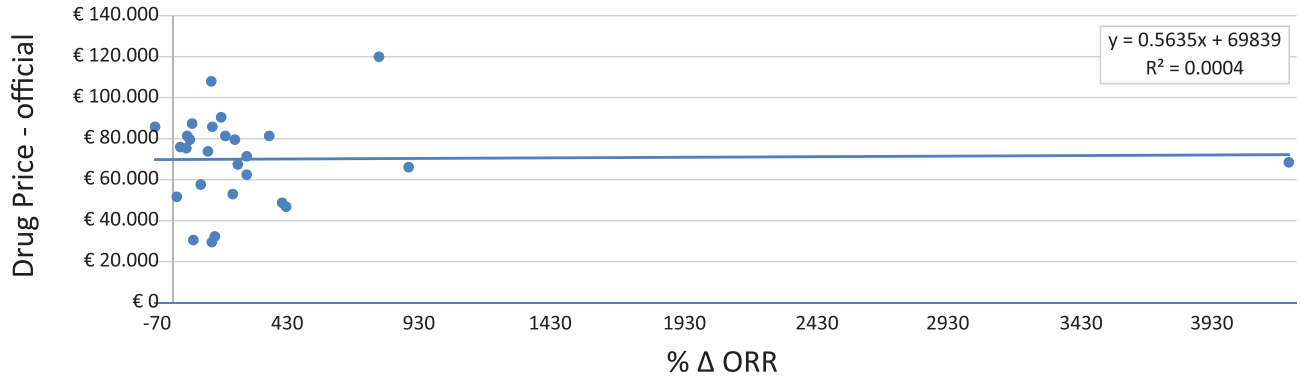
***1a.*** *Official negotiated price (ex-factory) vs percentage improvement in median Overall Survival (OS) (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*




***1b.*** *Official negotiated price (ex-factory) vs percentage improvement in median Progression Free Survival (PFS) (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*

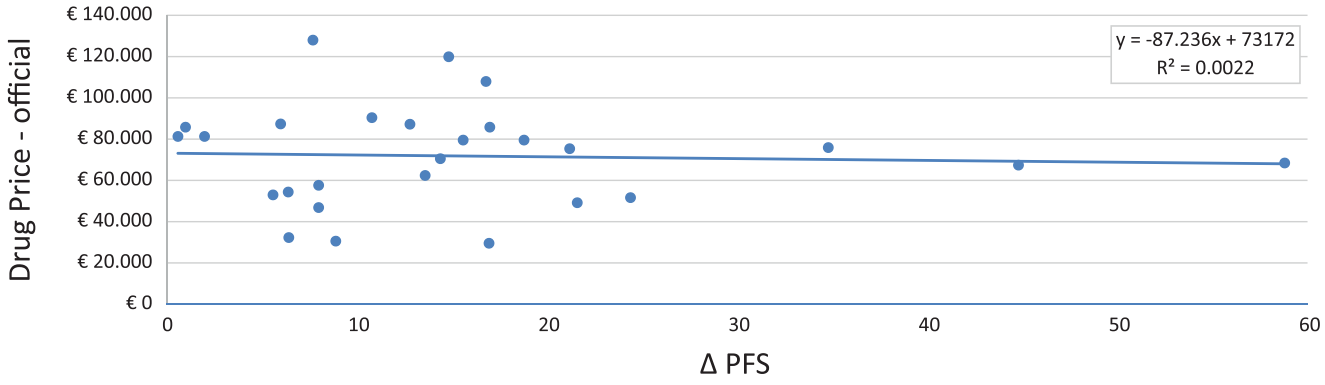



***1c.*** *Official negotiated price (ex-factory) vs percentage improvement in proportion of Objective Response Rate (ORR) (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*




*Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)*

***2.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), excluding negative outcome data (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*




*Progression Free Survival (PFS)*

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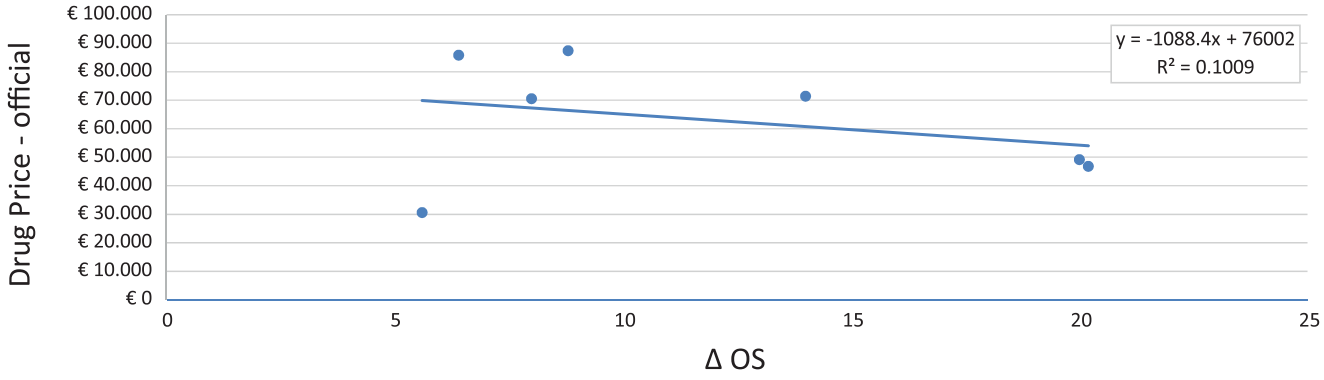
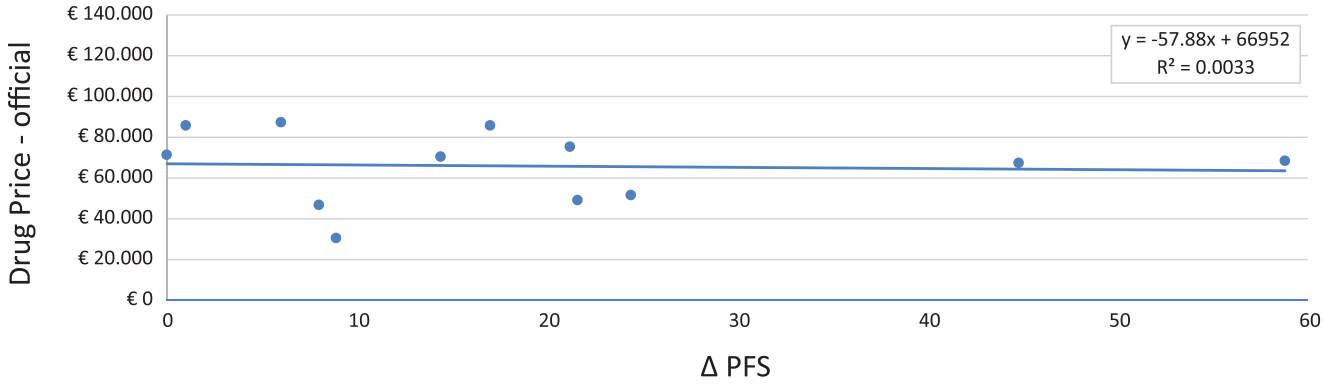
***3a.*** *Official negotiated price (ex-factory) vs median Overall Survival (OS), considering only data from placebo-controlled trials. (7drugs related to a single indication are included in the analysis)*




***3b.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), considering only data from placebo-controlled trials. (11 drugs are included in the analysis: 10 with a single indication and one with 2 indications)*




*Progression Free Survival (PFS); Overall Survival (OS)*

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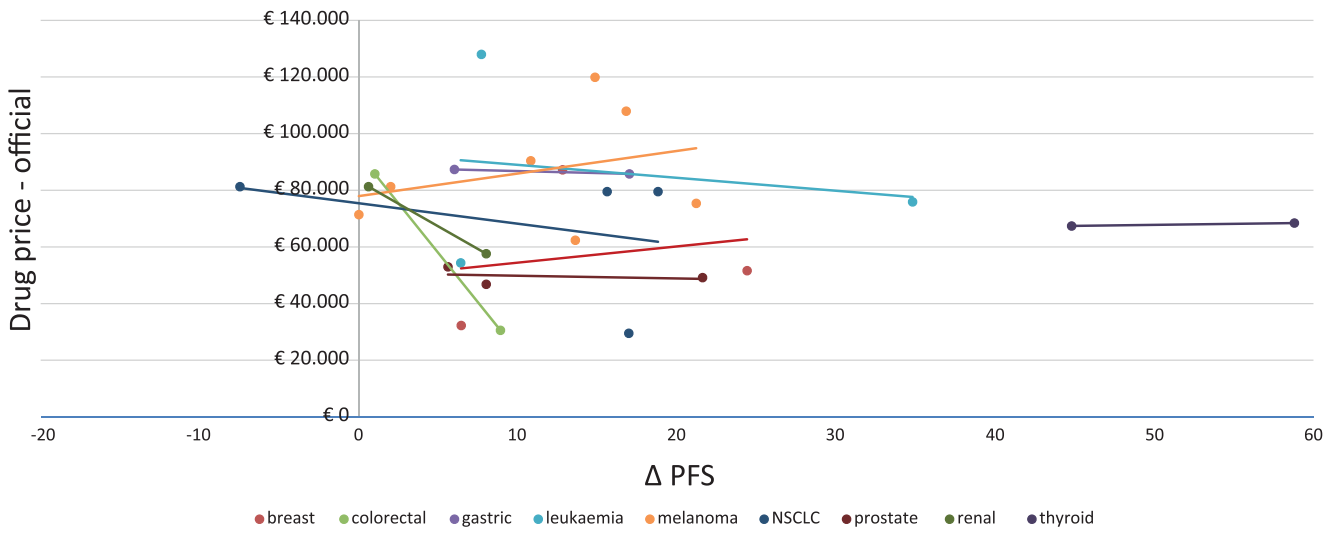
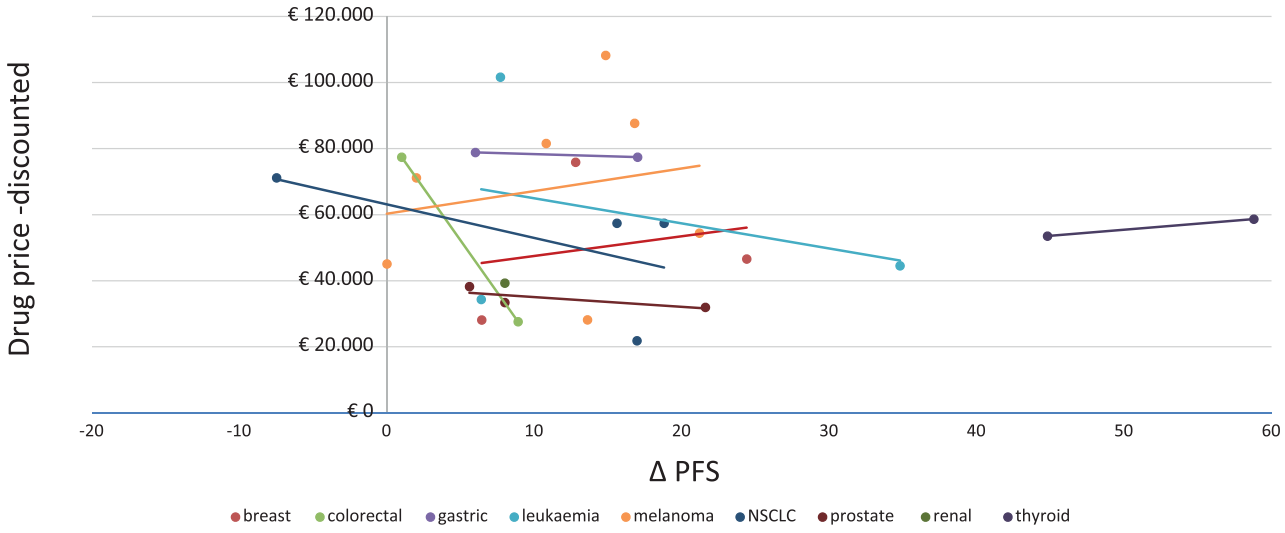
***4a.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication, two with two indications and one with three indication)*




***4b.*** *Discounted price with additional compulsory rebates vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication and three with 2 indications)*




*Progression Free Survival (PFS)*

BMJ Open

# Anticancer drug prices and clinical outcomes: a cross-sectional study in Italy

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**contributorship statement**

FT, NM and AA conceptualized the study; FT, AA, NM, FM, FBA, GT, and RDC designed the study; FBA, RP, IE and NM were in charge of data extraction and quality control; FM, RDC, and FT performed the data analysis; FT, RDC, FM, GT, BG, FP and AA drafted the manuscript; all the authors contributed to the discussion and the interpretation of results, and reviewed the final version of the manuscript. All authors approved the final manuscript as submitted.

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**Running head.** Anticancer drug prices and clinical outcomes in Italy

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**Abstract**:

**Objective** To investigate whether the prices of new anticancer drugs correlated with their relative benefit despite negotiation.

**Design** Retrospective cross-sectional study correlating new anticancer drugs prices with clinical outcomes.

**Setting** We did a retrospective cross-sectional study including all new anticancer drugs approved by the European Medicines Agency (2010-2016) and reimbursed in Italy.

**Main Outcome(s) and Measure(s)** Information on clinical outcomes - in terms of median Overall Survival (OS), median Progression Free Survival (PFS) and Objective Response Rate (ORR) - was extracted from pivotal trials as reported in the European Public Assessment Reports available on the EMA website. Cost of a full course treatment was estimated on negotiated official and discounted prices. Regression coefficients β, their levels of significance p and the coefficients of determination $R^2$ were estimated adjusting by tumour type.

**Results** Overall, 30 new anticancer drugs (with 35 indications) were available for analysis. Where data on Overall Survival were available we observed no correlation between the improvement in median OS (in weeks) and negotiated price ($R^2$= 0.067, n = 16 drugs for 17 indications). When the clinical outcomes were expressed as improvements in median PFS or ORR, 25 drugs (29 indications) were available for analysis, and again, there was no correlation with prices ($R^2$= 0.004 and 0.006, respectively).



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**Conclusions and Relevance**: Our results suggest that the prices of anticancer drugs in Italy do not reflect their therapeutic benefit. Drug price negotiations, which is mandatory by law in Italy, do not seem to ensure that prices correlate with clinical benefits provided by cancer drugs. These results call for further efforts to establish the standard determinants of drug prices available at the time of negotiation. These findings need to be confirmed in other countries where price negotiations are in place. Moreover, further investigations may verify whether outcome data obtained after drug marketing would improve the correlation between prices and therapeutic benefit.

**Strengths and limitations of this study**,

- This study is the first attempt to evaluate whether there were better correlations between cancer drug prices and clinical outcomes in a setting where central price negotiations are mandatory for every new medicine.
- This understanding is important for cancer policy decisions.
- In our analysis, the relationship between the clinical outcome and cost of anticancer drugs was ascertained by a simple linear regression model.
- Clinical outcome, which was the dependent variable, was expressed as absolute or percent differences in outcomes between treatment and control groups.
- The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs.

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## Background

High costs of cancer drugs and resulting financial toxicity to cancer patients are now a well-recognized problem in cancer policy throughout the world [1-8]. Various solutions are being proposed to address this problem, of which price negotiations with pharmaceutical companies is proposed as an important strategy especially in the USA [9-11]. Because the Medicare is not allowed to negotiate prices with companies, despite being mandated to cover for every U.S. Food and Drug Administration (FDA) approved drug, various experts have argued that this is the reason for high drug prices in the USA. Indeed, cancer drug prices far exceed the costs of their development [12];such negotiations might help to lower the prices of cancer drugs as evidenced by lower cost of cancer drugs in other developed countries compared with the USA.

However, little is known about if such negotiations would lead to better correlation between cancer drug prices and the benefits they provide. Studies have shown that drug prices do not correlate with clinical benefits for cancer drugs approved by the FDA, even though such studies have not taken central price negotiations into account [13,14]. Countries such as the United Kingdom and Italy negotiate prices and hence, the correlations might be different.

In Italy, drug price negotiation based on cost-effectiveness evaluation has been mandatory since 2001 for all medicines reimbursed by the National Health Service (NHS) [15,16]. We analysed the correlation between the prices of cancer drugs in Italy with their clinical outcomes to test the hypothesis that central price negotiations leads to better alignment of prices and benefits.



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**Methods:**

*Identification of the study sample*

All new drugs approved by the EMA via a centralized procedure between January 2010 and June 2016 for the treatment of either solid or haematologic cancers were initially identified. Generics, biosimilars, interferons and granulocyte-colony stimulating factors (G-CSFs) were excluded. Only anticancer drugs with pivotal trials based on overall survival (OS), progression-free survival (PFS) or objective response rate (ORR) and with prices that were officially negotiated in Italy by 31st December 2016 were included in the cohort for analyses.

*Data extraction*

Information on the clinical outcomes (in terms of median OS, median PFS, ORR) was extracted by two co-investigators (FBA and RP) from pivotal trials that compared new treatments with controls as reported in the European Public Assessment Reports - EPARs (summary table of the main study, Section 2.5.2) publicly available on the EMA website (www.ema.europa.eu). Survival times were expressed in weeks, and the reported OS and PFS were transformed when necessary. Information on therapeutic indication and tumour type were also retrieved.

*Drug prices*

The cost of a full course or 1-year treatment was estimated by two co-investigators (NM and IE) on the basis of the negotiated official ex-factory price (in euros) of drug packages, as published in the Official Gazette of the Italian Republic (www.gazzettaufficiale.it) and taking into account the posology as reported in the Summary of Product Characteristics (SPC). To compare prices of drugs with different schedules, in the text we refer to drug prices as the cost of a full course or a 1-year treatment. A further estimate took into account additional compulsory rebates [17] or extra-discounts



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that were agreed with pharmaceutical companies; this information is confidential to the public but is released to procurement stations within the Italian NHS (e.g., regions, hospitals, and local health units).

*Statistical analysis*

The following variables were extracted and analysed descriptively: year of approval, therapeutic indication, type of treatment and control groups, outcome data, official and confidential costs per treatment (1 year or a full course) and regulatory information (conditional/under exceptional circumstances approval, or orphan drug status).

The relationship between the clinical outcomes and cost of anticancer drugs was ascertained by a simple linear regression model. Clinical outcome, which was the dependent variable, was expressed as absolute or percent differences in outcomes between treatment and control groups. Regression coefficients β, their levels of significance p and the coefficients of determination $R^2$ were reported for each model.

We also performed several sensitivity analyses to test the robustness of the results. Specifically, we performed multiple linear regression with tumour type as the independent variable to take into account potential differences due to tumour characteristics. Moreover, we also repeated the analysis after excluding negative outcome differences (in two cases, one of the outcomes was inferior in the group receiving the new drug than in the comparison group) and actively controlled trials (considering only placebo-controlled trials). Subgroup analysis by tumour type was also attempted as exploratory analysis when a minimum number of two anticancer drugs within the same tumour type setting were observed. Outlier cases were not excluded from the analyses, but their impact was evaluated and reported when relevant as a separate analysis. All statistical analyses were performed using STATA (Statacorp, version 14.0)



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*Patient and public involvement*

Patients have not been involved in the development of the research question or the design of this study. However, results of this analysis will be disseminated throughout public conferences, with statements summarizing our results, and with an open access to the published report posted in our institutional websites

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## Results

From 2010 to mid-2016, 45 new anticancer drugs for 56 different oncology indications were approved via centralized procedures by the EMA. For 40 new anticancer drugs (47 indications), the basis for the approval was a pivotal trial adopting OS, PFS or ORR as a primary outcome; the price negotiation was completed by December 2016 for only 30 new anticancer drugs (35 indications) which are included in our analysis (Table 1). Seven drugs received orphan drug status by the EMA and two (vandetanib and crizotinib) received conditional approval. Of the 35 oncology indications tested in 35 different pivotal trials which were all controlled clinical trials, the commonest indications were melanoma (7 out of 35), followed by haematological cancer (6 out of 35) and non-small cell lung cancer (4 out of 35). In 15 such trials (43%), placebo was used as the control arm. Of the 35 indications, data on OS, PFS and ORR were available for 17, 29 and 29 indications respectively. Each drug-indication pair contributed to one or more of these analyses, depending on which outcomes were reported in the EPAR.

In the treatment groups, the median improvement in the OS and PFS were 11.4 weeks (IQR 8.8-17.2; min 13.2; max 23.5) and 12.8 weeks (IQR 6.4-17; min -7.48; max 58.8), respectively; median ORR improvement in the treatment group was 21.8% (IQR 10-34.6; min -3; max 63.3). The reported ranges have negative minimum values since in two cases - nivolumab for NSCLC and regorafenib for gastrointestinal stromal tumours - the experimental treatment had a negative effect on one of the outcomes compared to the control group (in terms of PFS for nivolumab and ORR for regorafenib). The median negotiated price for a 1-year treatment was 72,392 euros (IQR 53,819-85,800; min 4,942; max 142,785), which was further discounted by 25% (on average) after applying confidential rebates. For all anticancer drugs but ipilimumab the price was calculated as 1-year treatment since the posology reported in the Summary of Product Characteristics (SPC) reported that the treatment should



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continue as long as clinical benefit is observed or until unacceptable toxicity occurs. In the case of ipilimumab the price was calculated as a course of 4 doses as reported in the SPC.

The official (ex-factory) price of new anticancer drugs and absolute clinical outcomes showed no correlation (Figure 1a-c). The relationship between the improvement in median OS (in weeks) and negotiated price was estimated for 16 drugs (17 indications), and no correlation was observed ($R^2$= 0.067). When clinical outcomes were expressed as absolute advantage in median PFS or ORR, 25 drugs (29 indications) were available for analysis, and in these cases, no correlation was observed ($R^2$= 0.004 and 0.006, respectively).

Repeating the analyses and taking into account the additional confidential rebates, which are compulsory for hospital procurement, no improvement in the benefit/price relationships was highlighted (Figure 2a-c). These findings also remained unchanged when the analyses were repeated with adjustments for tumour type (Supplementary Table 1) or when clinical outcome was expressed as a percentage of improvement instead of as an absolute difference (Supplementary Figure 1a-c). Sensitivity analyses that excluded negative improvements in outcomes over a control group (Supplementary Figure 2) and considered only data from placebo controlled trials (Supplementary Figure 3a,b) confirmed the main analysis. The exploratory subgroup analyses by tumour type did not identify specific positive correlation patterns depending on tumour setting (Supplementary Figure 4 a,b).

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## Discussion

This study is the first attempt to evaluate whether there were better correlations between cancer drug prices and clinical outcomes in a setting where central price negotiations are mandatory for every new medicine. Our study gave unexpected results to the research question, highlighting no relationships between cost of cancer drugs and benefits. Moreover, all pre-specified sensitivity and subgroup analyses confirmed the main findings. This finding will have important policy implications both for countries like USA where price negotiations are absent and for other countries like Italy where price negotiations do exist.

In our study, the correlation between drug costs and clinical outcomes was even lower than the ones previously noted in the US context [13,14], showing that negotiations did not tilt the relationship between drug prices and benefit positively. Thus, higher drug pricing remains despite the Italian legislative environment, where approval based on cost-effectiveness analysis and price negotiations have been mandatory by law since 2001 [15,16]. This finding may cast doubts on the role of the negotiation itself. However, it is important to understand that countries like Italy that negotiate drug prices do such negotiations only for binary decisions of approval or no-approval, not taking into account, during negotiation, a clear correlation between prices and benefits. This understanding is important for cancer policy decisions.

Indeed, there is no legal policy in any country to negotiate prices differently for drugs approved on the basis of surrogate endpoints versus survival outcomes, or drugs that improve survival in days, versus those that improve survival in months or drugs with immature benefit risk profiles [18-22]. Although steps in the right direction, in lack of such policy, the value frameworks proposed by organizations such as ASCO, ESMO or NCCN have become little more than intellectual exercises [23-26].



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Another reason price negotiations did not achieve better price-value correlations is that because of the global market of drugs, each single country - although large – only represents a small portion of the consumer market. Thus, companies "wield the stick", setting the maximum price that the market will bear [27]. In addition, in Italy, no threshold for incremental cost-effectiveness ratio (ICER) has been determined; thus, no limit is in place to be used as a decision rule in resource allocation at the time of negotiation/reimbursement decisions. The lack of such kind of cut-off might have contributed to the negative results in our study. However, we recognize that even when a threshold for ICER is well established, such as in the UK [28], continuous exceptions have been allowed in the case of anticancer drugs. For example, an ad hoc fund established in 2010 (i.e., the Cancer Drug Fund) was recently dismissed by the Parliament because it did not deliver meaningful value to patients or society [29].

In the EU context (where newer anticancer drugs are approved by EMA without considering the added-value or cost-effectiveness), the complexity further increases because once a marketing authorization is granted, it may become difficult to manage the reimbursement issue at a national level [30]. Moreover, it is also difficult for payers (NHS/insurance) to defend the thesis against the public opinion that an anticancer drug cannot be reimbursed because it is too expensive [30, 31]. Indeed, as our study shows, the confidential discounts following negotiations between a member state and a company do not ameliorate the correlation between treatment costs and benefits even though they reduce absolute drug prices.

Another factor that negatively influences the contractual power of negotiation is non-transparent information on drug prices across countries. Difficulties in retrieving full information on prices have been already recognized in a recent survey comparing prices of anticancer drugs in 16 EU countries,



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Australia and New Zealand [32]. Vogler et al. found that price information is scarce and not disclosed due to confidential discounts or MEAs, calling for higher transparency. The authors state that it is in the interest of policy makers to remove clauses limiting disclosure on price information because they risk overpaying when setting prices through external price referencing. This concern might be relevant in the Italian context since the negotiation procedure for reimbursement takes into account the price in other EU countries as well as the price of similar products within the same pharmacotherapeutic group [33].

We believe that two partly independent approaches could be adopted by policy makers to achieve a better balance between cancer drug prices and benefits. First, price negotiations should be more strictly based on the level of evidence as well as the magnitudes of benefit. An ICER measure (such as QALY) should represent a threshold for reimbursement, thus setting a starting point for price negotiation and adjusting the ICER threshold based on the magnitude of the relative benefit reached. If the information on the relative value is not available at the time of approval, comparisons can be performed using indirect techniques, whereas after entering the market, payers should play a major role in supporting the evidence generating process.

The second approach that could attain lower prices would require an increased transparency on the costs of drug development process, including the relative contributions from academia and public sector to the development of a drug [34-38]. For instance, research conducted to evaluate efforts of drug development processes highlighted that about half of the most transformative drugs approved by the FDA had substantial contributions to their development by academic researchers supported by government funding [34,35]; in addition, it has been estimated that the cost of late clinical development takes a limited part of the whole process [36]. It is probably the right time to appropriately acknowledge the contributions of publicly funded research during drug price negotiation with companies. Often, comparative effectiveness research is funded by public



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institutions to test different treatments in real practice on robust outcomes with longer follow up or special populations [37,38]. The findings of these studies should be linked to a continuous price re-negotiation over the life cycle of a product.

Other approaches identified as possible solutions to keep the health system sustainable address the general governance of the system, i.e., when the price is already set. In fact, a price-volume approach [39] or indication-based pricing [40,41] have been modelled, each presenting pros and cons. Moreover, given that different oncology settings appear to be oligopolistic, thus refraining from price competition, another possible solution comes from national/regional tenders among therapeutic categories when more alternatives are available [42].

The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs. Moreover, we are not aware if further (more robust) data became available at a later stage when the price was negotiated at the national level. Thus, we cannot exclude that the correlation between drug prices and therapeutic benefit might improve taking into account data acquired after the marketing of anticancer drugs.

Another important limitation is that we have not considered quality of life outcomes as another metric of clinical benefit. Furthermore, a recent study has shown that quality of life outcomes are not routinely collected or published, and that the tools used to measure quality of life are varied to have a uniform metric for comparison [43]. Although we have included surrogate measures such as PFS or ORR as clinical outcomes in our analysis because they were considered as the basis for approval by the regulatory agency, these surrogate measures do not always correlate with true clinical benefits in terms of improved survival or improved quality of life [43,44]. Regarding the price estimate, we estimated the treatment costs for 1-year treatment or for the total course in the case of ipilimumab



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where the treatment course lasts less than 1 year. However, the exclusion of ipilimumab would not alter the main findings.

Another factor that might have impacted the price estimation is the rebate obtained at the regional/local level following drug tenders. This information was not available for the analyses and would have been not generalizable at the national level. Moreover, additional savings were expected "a posteriori" from the Managed Entry Agreements in place in Italy (whose information is not publicly available) and were not considered in the analyses.

Our study is a retrospective cross-sectional correlation study that aimed at evaluating whether central price negotiation (mandatory by law in Italy) leads to better alignment of prices and the benefits known at the time of drug approval. This means that our analysis is not aimed at comparing costs and outcomes within drug classes, as a typical cost effective study, and we never intended to assess the added values of the approved drugs in the context of all other drugs sharing the same indication. The "population"/cohort approach that we adopted has the intrinsic limitation of including drugs approved for different indications or different cancer types (with various incidence/prevalence) based on different clinical data packages. The consequent heterogeneity stemming from this approach was resolved adjusting the correlation analyses by tumour type or conducting several sub-analyses. Following this approach, we found results consistent with primary findings thus confirming the robustness of methods and results.

**Conclusion**

Our results suggest that price negotiations for approval decisions alone may not bring balance between prices and benefits of anticancer drugs. Based on the limited outcome data available at the time of reimbursement decisions (OS; PFS; ORR), prices of anticancer drugs do not reflect their therapeutic benefit. Other strategies, such as value based price negotiations, price negotiations strictly



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based on strength of evidence and price transparencies may be necessary to better achieve the drug prices and benefits balance. These results need to be confirmed in other countries where a national price negotiation exists.

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## Contributorship statement

FT, NM and AA conceptualized the study; FT, AA, NM, FM, FBA, GT, and RDC designed the study; FBA, RP, IE and NM were in charge of data extraction and quality control; FM, RDC, and FT performed the data analysis; FT, RDC, FM, GT, BG, FP and AA drafted the manuscript; all the authors contributed to the discussion and the interpretation of results, and reviewed the final version of the manuscript. All authors approved the final manuscript as submitted.

## Competing interests

The authors have no competing of interest relevant to this article to disclose and all authors works for public Universities, Public Institutions or not for profit Organizations.

## Funding

None.

## Data Availability

All data presented in the analysis have been extracted by public documents (EPARs for each drug outcomes and clinical data; regional and national administrative official documents (i.e. Gazzetta Ufficiale for prices). Data are available upon reasonable request



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**Table 1.** Characteristics of the 30 anticancer drugs included in the analysis.

| Medicine Name | Active Substance | Clinical setting | Treatment group | Control group | PFS TRT (median in weeks) | PFS CRT (median in weeks) | OS TRT (median in weeks) | OS CRT (median in weeks) | ORR TRT (%) | ORR CRT (%) | Year First Auth. | Official negot. price (€) | Disc. price (€) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Teysuno | tegafur / gimeracil / oteracil | advanced gastric cancer in combination with cisplatin. | teysuno 25 mg/m + cisplatin 75 mg/m2 | 5-fluorouracil 1000 mg/m2 /24 + cisplatin 100 mg/m2 | | | 34.4 | 31.6 | | | 2011 | 4942 | 3479 |
| Jevtana | cabazitaxel | hormone-refractory metastatic prostate cancer . | cabazitaxel + prednisone | mitoxantrone + prednisone | 11.2 | 5.6 | 60.4 | 50.8 | 14.4 | 4.4 | 2011 | 52983 | 38254 |
| Yervoy | ipilimumab | advanced (unresectable or metastatic) melanoma | ipilimumab + placebo | peptide vaccine glycoprotein 100 (gp100) | 11.04 | 11.04 | 39.8 | 25.8 | 5.7 | 1.5 | 2011 | 71400 | 45107 |
| Votubia | everolimus | Renal angiomyolipoma associated with tuberous sclerosis complex (TSC) | everolimus | placebo | | 45.48 | | | 41.8 | 0 | 2011 | 66521 | 41424 |
| Votubia | everolimus | Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) | everolimus | placebo | | | | | 34.6 | 0 | | 53216 | 33139 |
| Halaven | eribulin | locally advanced or metastatic breast cancer | eribulin 1.23 mg/m2 (equivalent to 1.4 mg/m2 eribulin mesylate) | treatment of physician's choice | 16.14 | 9.71 | 57.57 | 45.86 | 12.2 | 4.7 | 2011 | 32300 | 28130 |
| Zytiga | abiraterone acetate | metastatic castration-resistant prostate cancer | abiraterone acetate | placebo | 22.4 | 14.4 | 68.9 | 48.7 | 29.1 | 5.5 | 2011 | 46842 | 33397 |
| Dacogen | decitabine | newly diagnosed de novo or secondary acute myeloid leukaemia (AML) | decitabine | patient's choice | 14.8 | 8.4 | 30.8 | 20 | | | 2012 | 54366 | 34346 |
| Caprelsa | vandetanib | aggressive and symptomatic medullary thyroid cancer (MTC) unresectable locally advanced or metastatic disease. | vandetanib | placebo | 122 | 77.2 | | | 45 | 13 | 2012 | 67405 | 53533 |
| Zelboraf | vemurafenib | BRAF-V600-mutation-positive unresectable or metastatic melanoma. | vemurafenib | dacarbazine | 21.28 | 6.44 | 52.8 | 39.6 | 48.4 | 5.5 | 2012 | 119929 | 108236 |
| Xalkori | crizotinib | anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). | crizotinib | pemetrexed or docetaxel | 30.8 | 12 | | | 65.3 | 19.5 | 2012 | 79538 | 57427 |



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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Xalkori | crizotinib | first-line treatment of adults with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). | crizotinib | chemotherapy | 43.6 | 28 | | | 74.4 | 45 | | 79538 | 57427 |
| Inlyta | axitinib | advanced renal-cell carcinoma (RCC) | axitinib | sorafenib | 26.8 | 18.8 | | | 19.4 | 9.4 | 2012 | 57632 | 39295 |
| Perjeta | pertuzumab | HER2-positive metastatic or locally recurrent unresectable breast cancer | pertuzumab + trastuzumab + docetaxel | placebo + trastuzumab + docetaxel | 74 | 49.6 | | | 80.2 | 69.3 | 2013 | 51643 | 46608 |
| Kadcyla | trastuzumab emtansine | HER2-positive, unresectable locally advanced or metastatic breast cancer | trastuzumab emtansine (tdm1) | lapatinib + capecitabine (lap+cap) | 38.4 | 25.6 | 123.9 | 100.4 | | | 2013 | 87215 | 75877 |
| Giotrif | afatinib | locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s); | afatinib (film-coated tablets) | pemetrexed (lyophilised powder) + cisplatin (solution for infusion) | 44.56 | 27.6 | | | 56.1 | 22.6 | 2013 | 29528 | 21853 |
| Stivarga | regorafenib | metastatic colorectal cancer (CRC) | regorafenib + best supportive care | placebo + best supportive care | 8.4 | 7.4 | 28 | 21.6 | 1 | 0.4 | 2013 | 85800 | 77434 |
| Stivarga | regorafenib | unresectable or metastatic gastrointestinal stromal tumors (GIST) | regorafenib + best supportive care | placebo + best supportive care | 21 | 4 | | | 1.5 | 4.5 | | 85800 | 77434 |
| Tafinlar | dabrafenib | unresectable or metastatic melanoma with a BRAF V600 mutation. | dabrafenib | dacarbazine | 27.6 | 10.8 | 72.8 | 62.4 | 59 | 24 | 2013 | 107935 | 87670 |
| Zaltrap | aflibercept | metastatic colorectal cancer (MCRC) | aflibercept+folfiri | placebo+folfiri | 27.6 | 18.7 | 54 | 48.4 | 19.8 | 11.1 | 2013 | 30576 | 27591 |
| Xtandi | enzalutamide | metastatic castration resistant prostate cancer | enzalutamide (mdv3100) | placebo | 33.2 | 11.6 | 74.4 | 54.4 | | | 2013 | 49184 | 31960 |
| Imnovid | pomalidomide | relapsed and refractory multiple myeloma | pom+ld-dex | hd-dex | 15.7 | 8 | | 34 | | | 2013 | 127985 | 101646 |
| Lynparza* | olaparib | platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer | olaparib | placebo | 33.6 | 19.2 | 119.2 | 111.2 | | | 2014 | 70517 | 52142 |
| Cyramza | ramucirumab | advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression | ramucirumab+ paclitaxel | placebo+paclitaxel | 17.6 | 11.6 | 38.4 | 29.6 | 27.9 | 16.1 | 2014 | 87360 | 78842 |
| Mekinist | trametinib | unresectable or metastatic melanoma with a BRAF V600 mutation. | trametinb | chemotherapy (dtic or paclitaxel) | 19.6 | 6 | 62.4 | 45.2 | 19 | 5 | 2014 | 62398 | 28157 |



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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Imbruvica | ibrutinib | chronic lymphocytic leukaemia (CLL) | ibrutinib | chlorambucil | | 75.6 | | | 82.4 | 35.3 | | 73805 | 51663 |
| Zydelig | idelalisib | chronic lymphocytic leukaemia (CLL) | idelalisib + rituximab | placebo + rituximab | | 22 | | | 74.5 | 14.5 | 2014 | 48667 | 34067 |
| Sylvant | siltuximab | multicentric Castlemans disease | siltuximab + best supportive care | placebo + best supportive care | | | | | 37.7 | 3.8 | 2014 | 66104 | 29829 |
| Keytruda | pembrolizumab | advanced(unresectable or metastatic) melanoma | ipilimumab | pembrolizumab | 22 | 11.2 | | | 33.7 | 11.9 | 2015 | 90400 | 81586 |
| Opdivo | nivolumab | advanced (unresectable or metastatic) melanoma | nivolumab 3 mg/kg | dacarbazine | 18.8 | 16.8 | | | 31.7 | 10.6 | 2015 | 81310 | 71181 |
| Opdivo | nivolumab | locally advanced or metastatic non-small cell lung cancer (NSCLC) | nivolumab 3 mg/kg | docetaxel 75 mg/m2 | 9.32 | 16.8 | 48.8 | 37.4 | 19.2 | 12.4 | | 81310 | 71181 |
| Opdivo | nivolumab | advanced renal cell carcinoma | nivolumab 3 mg/kg | everolimus100mg | 18.4 | 17.8 | 100 | 78.2 | 25.1 | 5.4 | | 81310 | in negotiation |
| Lenvima | lenvatinib mesylate | progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hrthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) | lenvatinib | placebo | 73.2 | 14.4 | | | 64.8 | 1.5 | 2015 | 68433 | 58673 |
| Cotellic | cobimetinib hemifumarate | unresectable or metastatic melanoma with a BRAF V600 mutation | cobimetinib+vemurafenib | placebo+vemurafenib | 45.2 | 24 | | | 67.8 | 44.8 | 2015 | 75374 | 54420 |
| Kyprolis | carfilzomib | multiple myeloma who have received at least one prior therapy. | carfilzomib + lenalidomide + dexamethasone | lenalidomide + dexamethasone (rd) | 105.2 | 70.4 | | | 87.1 | 67.7 | 2015 | 75900 | 44525 |

Progression Free Survival (PFS); Overall Survival (OS); Treatment Group (TRT); Control Group (CTR); Objective Response Rate (ORR); Official Negotiated Prices (Official Negot.); Discounted Prices (Disc. Prices).

*: During the evaluation at the EMA, lymparza was found to be more effective in a subgroup of patients with a specific biomarker with the following outcome results: PFS lymparza: 44,8 w; PFS control: 17,2 w; OS lymparza: 139,6 w; OS control: 127,6.



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## Figure, tables, titles and legends

**Figure 1.** Correlation between anticancer drug prices (officially negotiated) and health benefits

*Figure 1a. Official negotiated price (ex-factory) vs difference in median OS (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*

*Figure 1b. Official negotiated price (ex-factory) vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*

*Figure 1c. Official negotiated price (ex-factory) vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

**Figure 2.** Correlation between anticancer drug prices (discounted) and health benefits

*Figure 2a. Discounted price with additional compulsory rebates vs difference in median OS (16 drugs related to a single indication are included in the analysis)*

*Figure 2b. Discounted price with additional compulsory rebates vs difference in median PFS (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

*Figure 2c. Discounted price with additional compulsory rebates vs proportion of ORR (24 drugs are included in the analysis: 20 with a single indication and four with two indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

**Table 1.** Characteristics of the 30 anticancer drugs included in the analysis.

Legend:

Progression Free Survival (PFS); Overall Survival (OS); Treatment Group (TRT); Control Group (CTR); Objective Response Rate (ORR); Official Negotiated Prices (Official Negot.); Discounted Prices (Disc. Prices).

*: During the evaluation at the EMA, lymparza was found to be more effective in a subgroup of patients with a specific biomarker with the following outcome results: PFS lymparza: 44,8 w; PFS control: 17,2 w; OS lymparza: 139,6 w; OS control: 127,6.

**Supplementary Table 1.** Details of the statistical analysis conducted

**Supplementary Figures 1-4.** Correlations in the sensitivity analysis conducted

*Supplementary Figure 1a. Official negotiated price (ex-factory) vs percentage improvement in median Overall Survival (OS) (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*

*Supplementary Figure 1b. Official negotiated price (ex-factory) vs percentage improvement in median Progression Free Survival (PFS) (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*



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*Supplementary Figure 1c. Official negotiated price (ex-factory) vs percentage improvement in proportion of Objective Response Rate (ORR) (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*

*Figure 2. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), excluding negative outcome data (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*

*Supplementary Figure 3a. Official negotiated price (ex-factory) vs median Overall Survival (OS), considering only data from placebo-controlled trials. (7drugs related to a single indication are included in the analysis)*

*Supplementary Figure 3b. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), considering only data from placebo-controlled trials. (11 drugs are included in the analysis: 10 with a single indication and one with 2 indications)*

*Supplementary Figure 4a. Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication, two with two indications and one with three indication)*

*Supplementary Figure 4b. Discounted price with additional compulsory rebates vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication and three with 2 indications)*

Legend: Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR);

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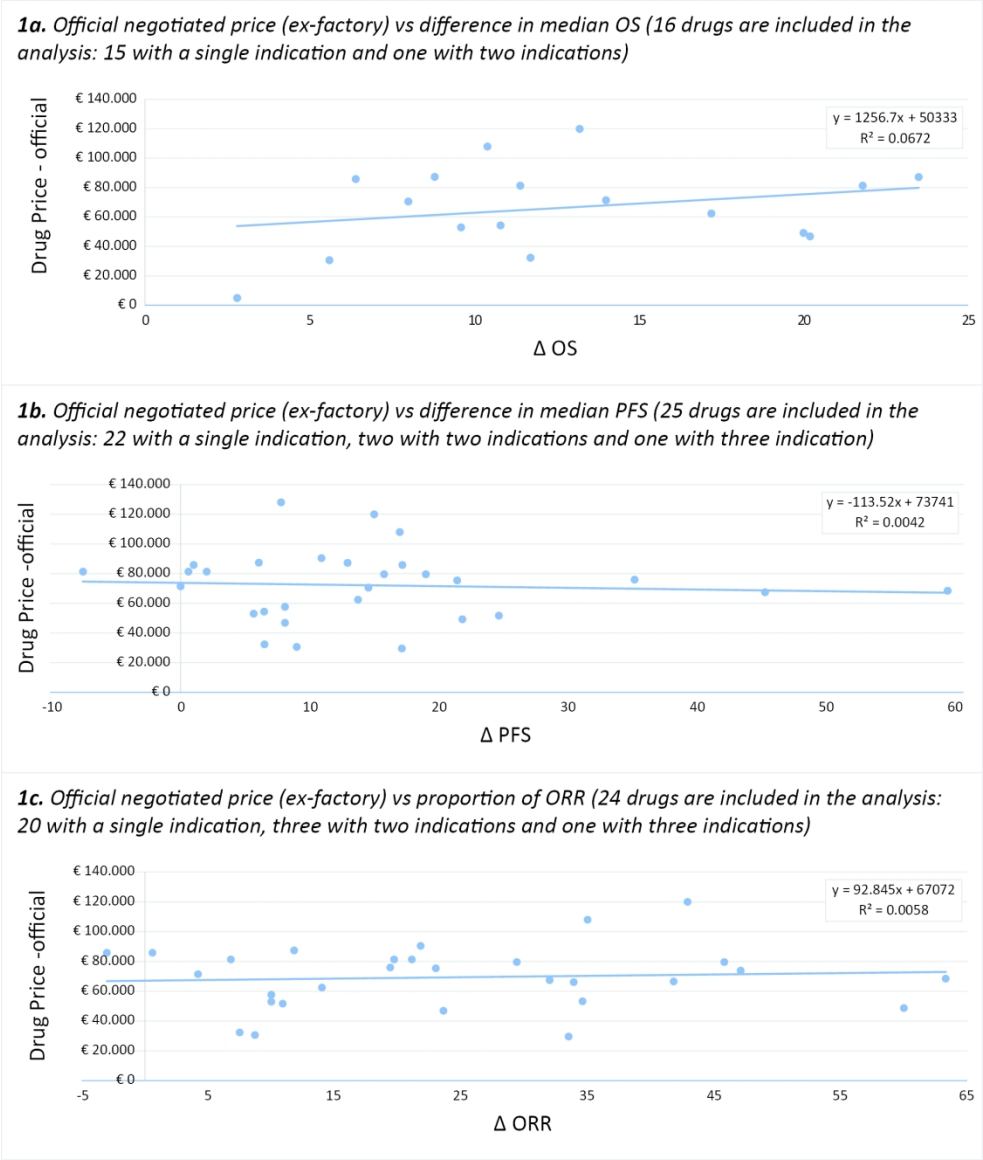


Figure 1. Correlation between anticancer drug prices (officially negotiated) and health benefits

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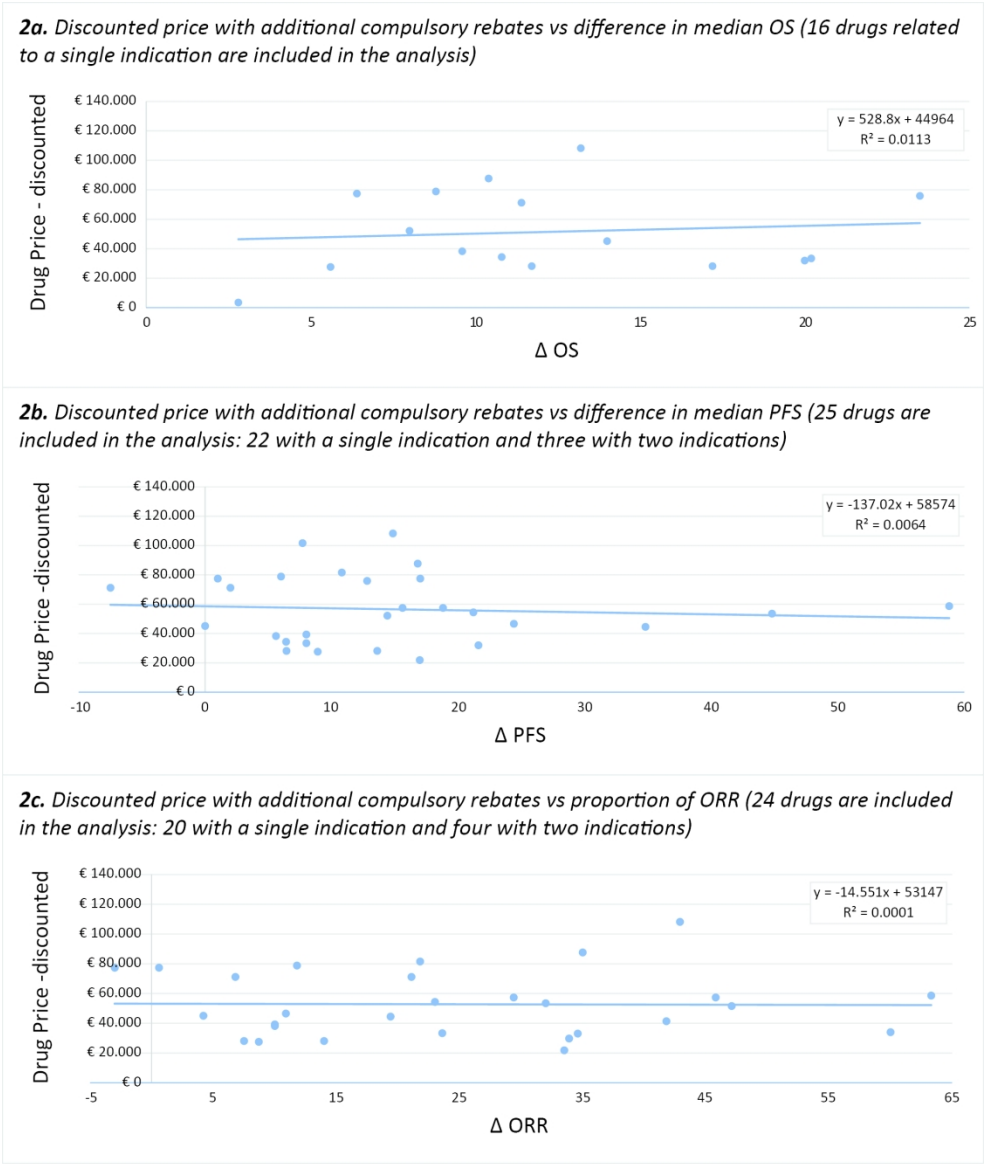



*Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)*

Figure 2. Correlation between anticancer drug prices (discounted) and health benefits

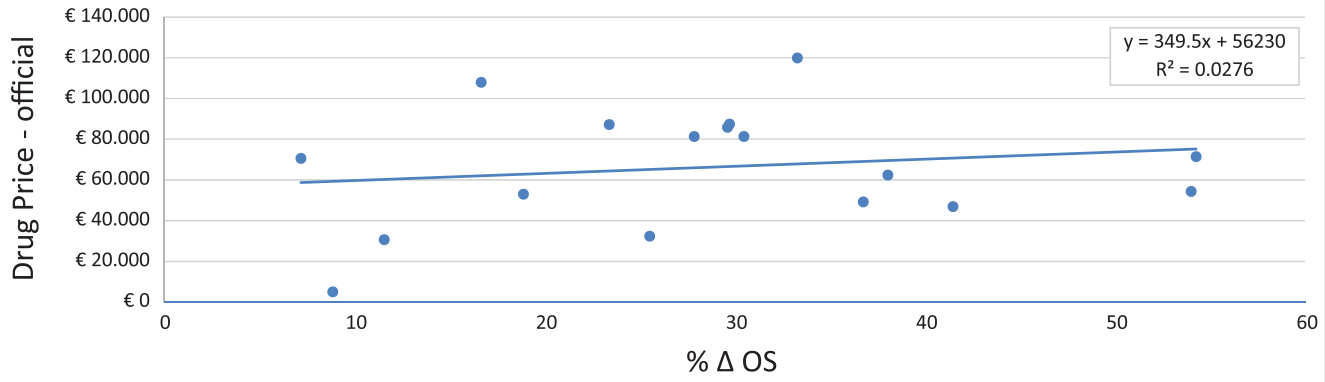
180x219mm (300 x 300 DPI)

**Supplementary Table 1.** Details of the statistical analysis conducted

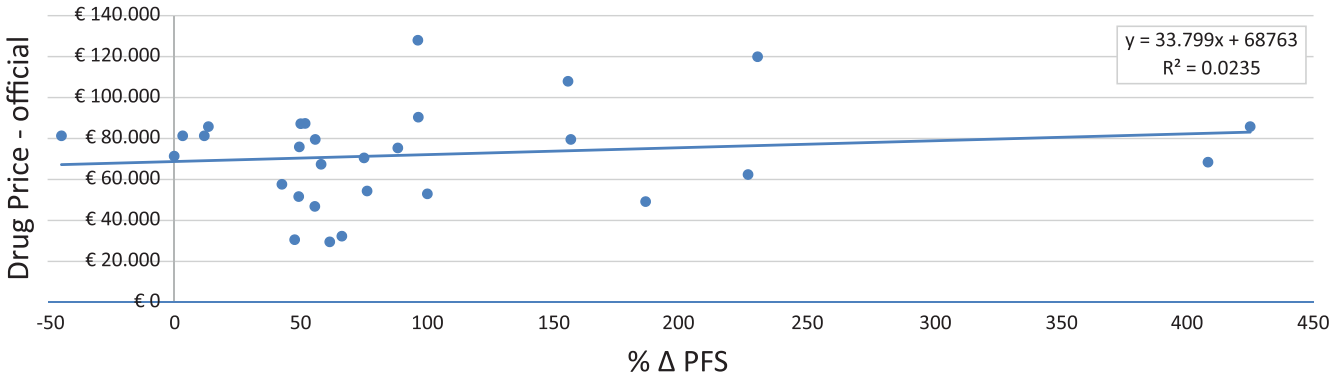
| Dependent variable | Independent variable 1 | Independent variable 2 | Number of drugs involved in the analysis | Type of linear regression | Intercept | Coefficient of the Independent variable 1 | p value of the Independent variable 1 | Correlation coefficient: r | Coefficient of Determination: $R^2$ |
|---|---|---|---|---|---|---|---|---|---|
| Official negotiated price | Δ OS | | 17 | simple | 50332.71 | 1256.724 | 0.315 | 0.259 | 0.067 |
| Discounted price | Δ OS | | 16 | simple | 44963.88 | 528.800 | 0.695 | 0.11 | 0.0113 |
| Official negotiated price | Δ OS | tumor type | 17 | multiple | 57765.99 | 2065.264 | 0.433 | | 0.412 |
| Discounted price | Δ OS | tumor type | 16 | multiple | 55312.8 | 1391.947 | 0.614 | | 0.257 |
| Official negotiated price | % Δ OS | | 17 | simple | 56230.04 | 349.505 | 0.524 | 0.166 | 0.027 |
| Discounted price | % Δ OS | | 16 | simple | 50127.28 | 42.986 | 0.937 | 0.022 | 0.0005 |
| Official negotiated price | % Δ OS | tumor type | 17 | multiple | 72407.98 | 292.048 | 0.766 | | 0.362 |
| Discounted price | % Δ OS | tumor type | 16 | multiple | 68456.17 | 89.3936 | 0.930 | | 0.2286 |
| Official negotiated price | Δ PFS | | 29 | simple | 73741.11 | -113.515 | 0.738 | -0.065 | 0.004 |
| Discounted price | Δ PFS | | 28 | simple | 58574.12 | -137.018 | 0.687 | -0.080 | 0.006 |
| Official negotiated price | Δ PFS | tumor type | 29 | multiple | 70454.93 | -271.324 | 0.635 | | 0.338 |
| Discounted price | Δ PFS | tumor type | 28 | multiple | 56293.38 | -393.926 | 0.508 | | 0.283 |
| Official negotiated price | % Δ PFS | | 29 | simple | 68763.32 | 33.7994 | 0.427 | 0.153 | 0.024 |
| Discounted price | % Δ PFS | | 28 | simple | 52823.84 | 36.2925 | 0.392 | 0.169 | 0.028 |
| Official negotiated price | % Δ PFS | tumor type | 29 | multiple | 66564.96 | 15.935 | 0.765 | | 0.333 |
| Discounted price | % Δ PFS | tumor type | 28 | multiple | 51337.49 | 11.068 | 0.842 | | 0.266 |
| Official negotiated price | Δ ORR | | 29 | simple | 67072.16 | 92.845 | 0.696 | 0.076 | 0.006 |
| Discounted price | Δ ORR | | 28 | simple | 53147.09 | -14.550 | 0.953 | -0.010 | 0.000 |
| Official negotiated price | Δ ORR | tumor type | 29 | multiple | 62277.57 | 180.118 | 0.607 | | 0.448 |
| Discounted price | Δ ORR | tumor type | 28 | multiple | 42598.33 | 324.629 | 0.383 | | 0.450 |
| Official negotiated price | % Δ ORR | | 27 | simple | 69838.7 | 0.563 | 0.918 | 0.020 | 0.000 |
| Discounted price | % Δ ORR | | 26 | simple | 53627.54 | 0.965 | 0.864 | 0.036 | 0.001 |
| Official negotiated price | % Δ ORR | tumor type | 27 | multiple | 67262.18 | 1.719 | 0.814 | | 0.436 |
| Discounted price | % Δ ORR | tumor type | 26 | multiple | 51599.74 | 2.958 | 0.704 | | 0.405 |

Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)

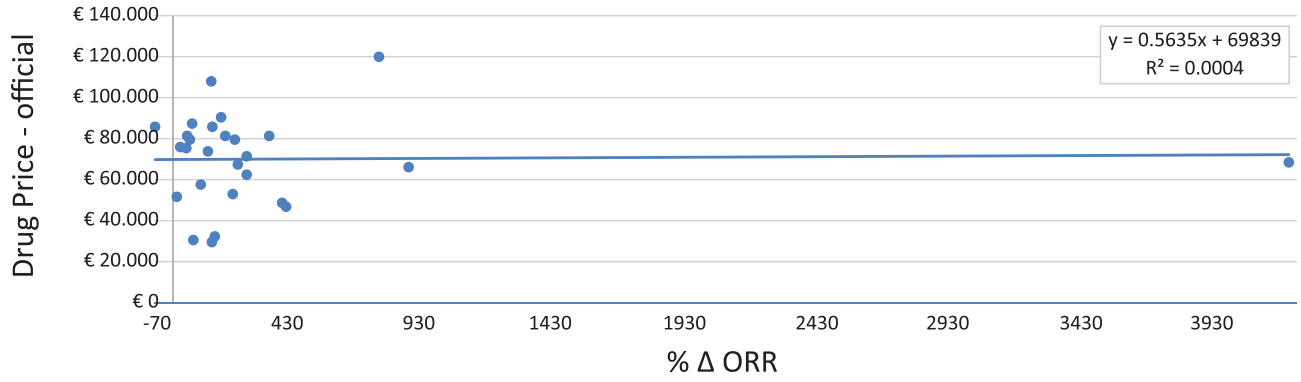
***1a.*** *Official negotiated price (ex-factory) vs percentage improvement in median Overall Survival (OS) (16 drugs are included in the analysis: 15 with a single indication and one with two indications)*




***1b.*** *Official negotiated price (ex-factory) vs percentage improvement in median Progression Free Survival (PFS) (25 drugs are included in the analysis: 22 with a single indication, two with two indications and one with three indication)*

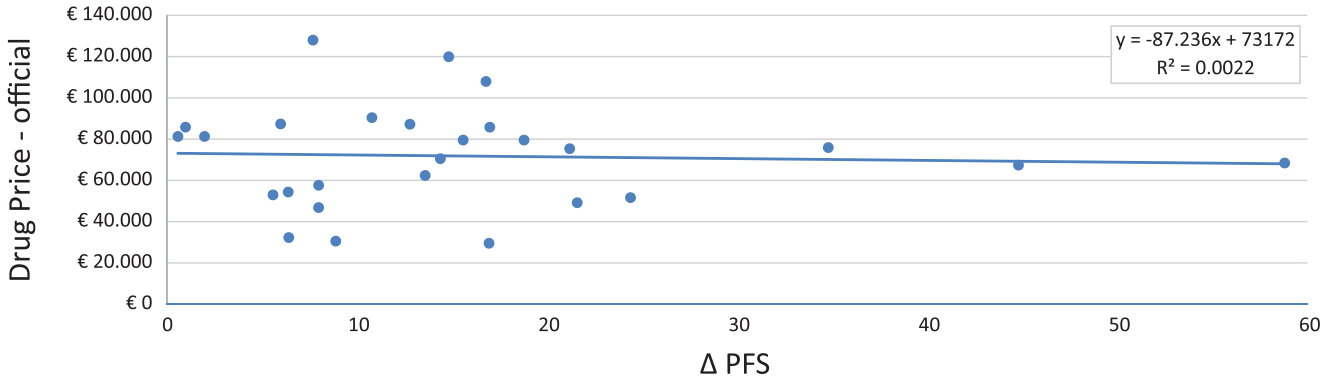



***1c.*** *Official negotiated price (ex-factory) vs percentage improvement in proportion of Objective Response Rate (ORR) (24 drugs are included in the analysis: 20 with a single indication, three with two indications and one with three indications)*




*Progression Free Survival (PFS); Overall Survival (OS); Objective Response Rate (ORR)*

***2.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), excluding negative outcome data (25 drugs are included in the analysis: 22 with a single indication and three with two indications)*




*Progression Free Survival (PFS)*

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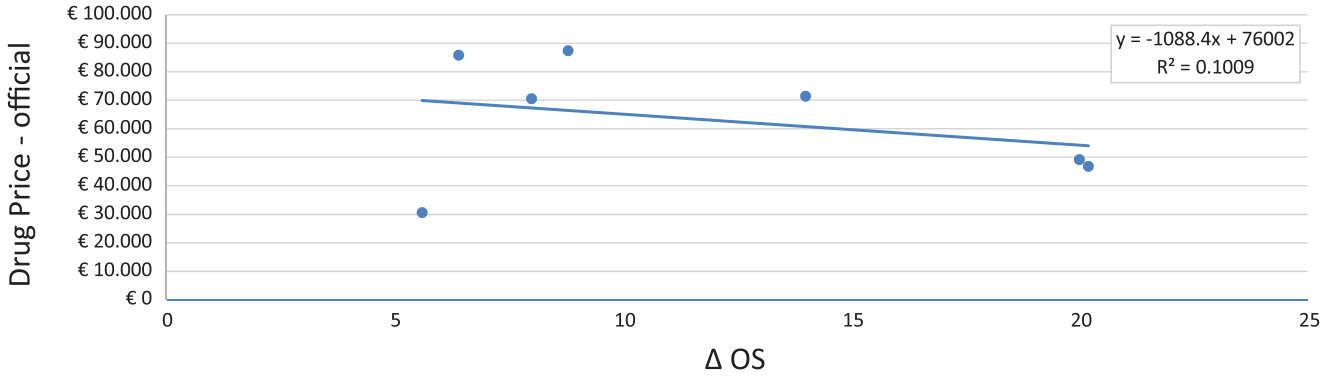
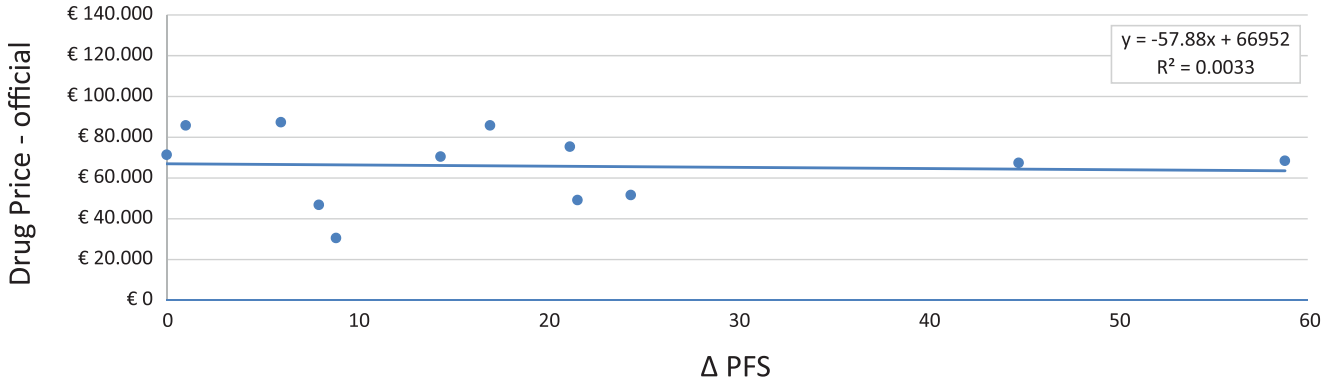
***3a.*** *Official negotiated price (ex-factory) vs median Overall Survival (OS), considering only data from placebo-controlled trials. (7drugs related to a single indication are included in the analysis)*




***3b.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), considering only data from placebo-controlled trials. (11 drugs are included in the analysis: 10 with a single indication and one with 2 indications)*




*Progression Free Survival (PFS); Overall Survival (OS)*

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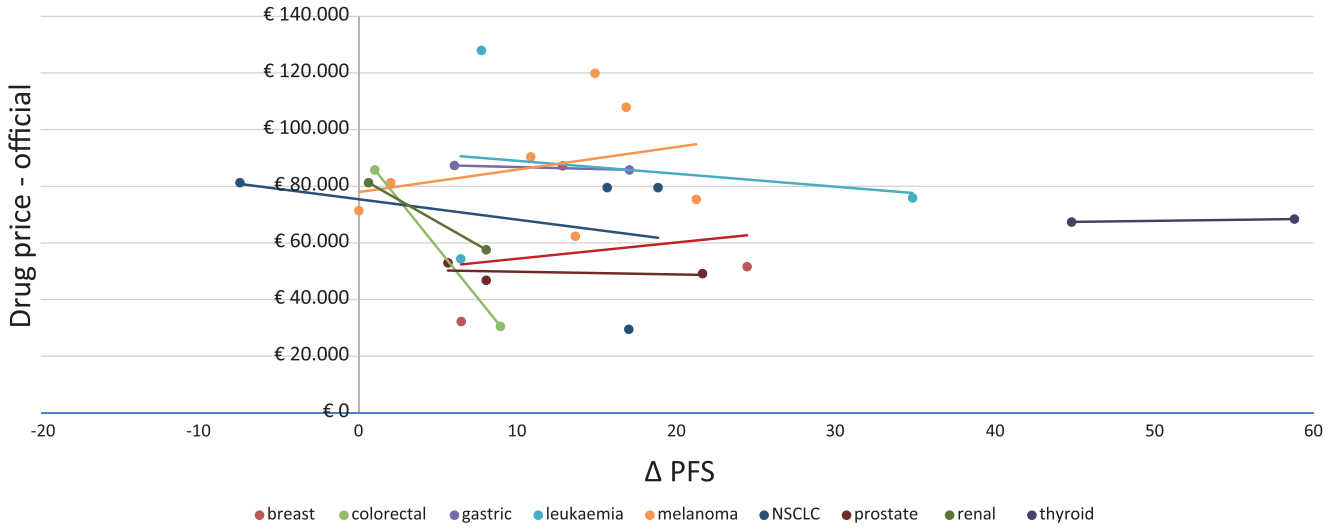
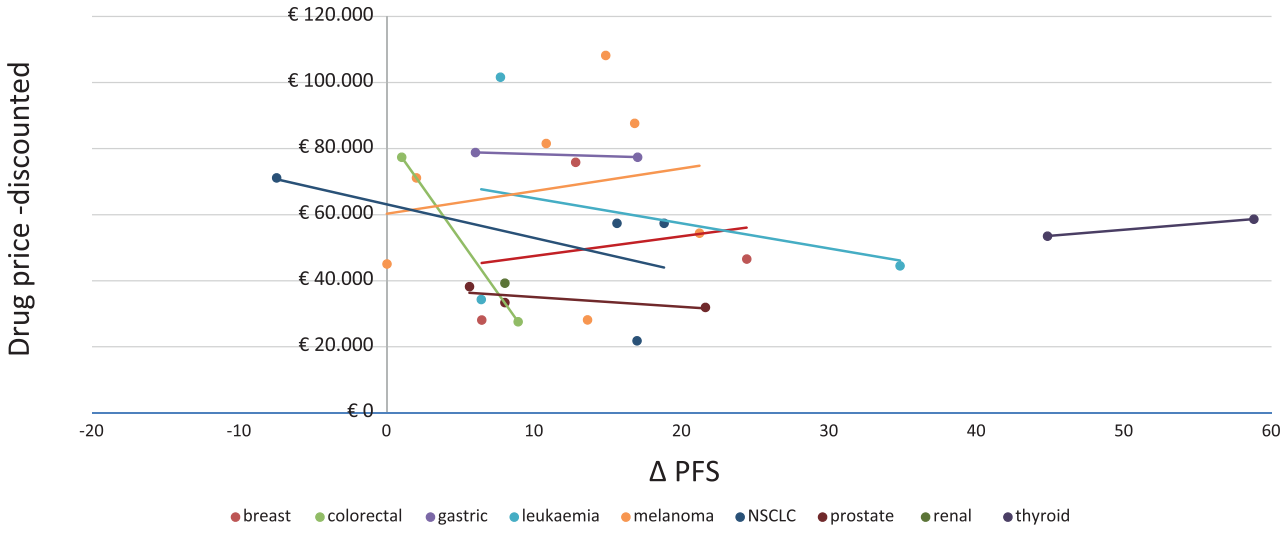
***4a.*** *Official negotiated price (ex-factory) vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication, two with two indications and one with three indication)*




***4b.*** *Discounted price with additional compulsory rebates vs median Progression Free Survival (PFS), stratified by type of cancer (at least 2 indications for each cancer type). (24 drugs are included in the analysis: 21 with a single indication and three with 2 indications)*




*Progression Free Survival (PFS)*

## STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| **Title and Abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1 (Title) P |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 2 |
| **Introduction** | | | |
| Background/Rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 4 |
| **Methods** | | | |
| Study Design | 4 | Present key elements of study design early in the paper | Page 5-6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 7 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | |
| | | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | |
| | | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 5 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed | |
| | | *Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 5 |

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| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| Data Sources/ Measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Page 5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Page 6 |
| Study Size | 10 | Explain how the study size was arrived at | Page 6 |
| Quantitative Variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | |
| Statistical Methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | Page 6 |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br><br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br><br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | Page 6 |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 8 |
| | | (b) Give reasons for non-participation at each stage | page 8 |
| | | (c) Consider use of a flow diagram | |
| Descriptive Data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | |
| | | (b) Indicate number of participants with missing data for each variable of interest | Page 8 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome Data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | Page 8-9 |

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| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| Main Results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other Analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key Results | 18 | Summarise key results with reference to study objectives | Page 10-12 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | page 13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | page 13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | page 13-14 |
| **Other Information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | cover |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.**

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