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ORIGINAL RESEARCH ARTICLE

Linking the Price of Cancer Drug Treatments to Their Clinical Value

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Abstract

Background and Objective Appropriate pricing of medications is one of the ultimate goals for decision makers, but reliable data on the risk/benefit ratio are often lacking when a Marketing Authorization Application is submitted. Here we propose a method to consistently evaluate price adequacy, which we applied to six anticancer medications approved in Italy in recent years.

Methods We obtained ratios of cost per survival per day (cost/survival/day) by dividing the total costs of evaluated medications for the median survival gain in days. Each cost/survival/day corresponds to a crude score, with 0 assigned to a cost/survival/day ≥€586. The maximum price considered as adequate was €91 cost/survival/day (score 75) while a score of 100 corresponded to a cost/survival/day ≤€11, based on the thresholds set by the British National Health System (NHS) and the "willingness-to-pay" of the Italian NHS. Crude scores were then adjusted using correction factors for efficacy, safety, quality of life, and prevalence of disease.

Results None of the analyzed medications (abiraterone, afatinib, aflibercept, bevacizumab, dabrafenib, and ipilimumab) achieved a final score of 75, corresponding to adequate pricing. The final score for afatinib was the highest with 55 points. Prices of all the other drugs resulted in being inadequate, with negative final scores for bevacizumab, dabrafenib, and ipilimumab.

Conclusions This method may be considered a tool for the evaluation of appropriateness of price proposed at negotiation and could represent a reliable resource for decision-making. Furthermore, this analysis suggests that most recently approved cancer drugs in Italy do not fulfill price adequacy.

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Key Points

The definition of a medication's price should be based on the precise quantification of the value of a medicinal product. For anticancer medications, the correct definition of this value may be challenging; nevertheless its use could improve decision making for pricing and reimbursement authorities and increase pricing appropriateness. Cost-effectiveness analyses have been performed by several experts in the field for specific medications and indications, and different solutions have been proposed. A simple method was developed in 2012 by Guirgis, who evaluated cost-effectiveness of anticancer medications in the USA by attributing a percentage score that accounts for cost per survival per day, adjusted for data on efficacy, safety, and quality of life (QoL).

Here we propose a modification of the method developed by Dr. Guirgis, adapted to the Italian economic situation. An assessment of price appropriateness of six anticancer medications approved in Italy in recent years was performed, showing that pricing for most of the evaluated medications is not appropriate, as compared to their therapeutic value expressed as efficacy, safety, and QoL. This method may be considered a reliable tool for decision making, in order to implement price appropriateness during the negotiation process of a new medication application.

Potentially, this method could also be applied to evaluate price adequacy in other European Countries (adjusted for respective Gross Domestic Product per capita) and might show the inadequacy of pricing for most anticancer medications compared to their overall therapeutic value.

1 Introduction

In European Countries and the USA, oncologic care has been characterized in the last decade by a rapid and exponential growth in both the number of novel medications available and treatment expenditure per patient [1, 2].

However, despite the significant increase in treatment options, the overall patient benefits in terms of survival rates or improvement in QoL remain modest, yet account for unsustainable costs, especially for countries where the available financial resources become more limited year after year [3, 4]. Several studies in the field have documented the poor correlation between a medication's price and the objective benefit for the individual, defined as survival prolongation, degree of tumor shrinkage, or improved QoL [5, 6]. From 2005, in the USA the average price of new anticancer agents has increased from ~US$4500 to more than ~US$10,000 per patient per month of treatment [4, 7]. In 2012, the US Food and Drug Administration (FDA) granted Marketing Authorization (MA) for 12 new anticancer medications, and available data suggest that only three of them are able to significantly influence hard endpoints such as overall survival rate, while two of them increase mean survival rate by less than 2 months. Nevertheless, nine of these medications are priced at more than US$10,000 per patient per month of treatment [8].

When considering approval or denial of MA, regulators from several European countries carry out an extensive evaluation of the available data on the overall value of a given medication, but currently, the cost-effectiveness analysis does not exert a direct influence on price definition. As an example, in the UK the National Institute for Health and Care Excellence (NICE) established a threshold of £20,000–£30,000 per QALY (quality-adjusted life-year) gain to determine the cost-effective value of a medication, and this cut-off represents the preliminary step to be recommended within the National Health System (NHS) [9, 10]. However, a Cancer Drugs Fund (CDF) was created in the UK in 2010 (and will run until the end of March 2016) in order to provide additional funding to enable patient access to oncologic drugs that NICE did not consider cost-effective [11]. Nevertheless, this threshold is considered inadequate according to the methodology recently proposed by Claxton and colleagues [12].

The Italian NHS is a universalistic healthcare system that provides patients with free access to most anticancer medications approved by the European Medicines Agency (EMA), despite the constant and significant increase in drug expenditure. Antineoplastic agents and immunemodulators represent the second most relevant therapeutic category for Italian NHS drug expenditure, accounting for nearly €4 billion (€3934 million, €64.7 per capita) [13], almost entirely driven by public hospitals. With a total cost of €197.1 million, trastuzumab was the most expensive hospital medication in 2014, followed by rituximab (€152.2 million) and bevacizumab (€145.8 million).

In order to increase the appropriateness in drug prescription and use, and to face increasing financial pressure over the Italian NHS, strategies aimed at managing clinical and economic uncertainties associated with the introduction of new drugs have been developed. Such interventions are often defined as Managed Entry Agreements [14], and among them, the Performance-Based Risk-Sharing

Agreement (PBRSA) links price and reimbursement of a new technology/medication to the health outcomes, based on predefined clinical endpoints [15]. PBRSAs approved in Italy include "Cost-Sharing" (CS), "Risk-Sharing" (RS), "Payment by Result" (PbR), and "Success Fee" (SF). However, despite the high expectation, our recent analysis of the mechanisms of cost-containment strategies in Italy shows several mismanagement and procedural problems that hamper the practical application of PbR and RS [16], while data about the newly introduced reimbursement strategy SF are not yet available.

Considering the limitations of current PBRSAs, real quantification of health outcome value would significantly improve decision-making and, at the same time, would increase pricing appropriateness. Cost-effectiveness analyses have been recently proposed by several experts in the field for specific medications and indications [8, 17–19]. Seruga et al. [20] recently proposed reducing the costs of oncologic medications within defined margins of cost-effectiveness, through the introduction of a value-based pricing system, which takes into account cost per life-year gained.

Guirgis [17] developed a simple method that evaluates cost-effectiveness of anticancer drugs by attributing a percentage score that corresponds to cost per survival per day adjusted for efficacy, safety, and QoL. This author applied this method to evaluate treatments for metastatic breast cancer and non-small-cell lung cancer (NSCLC). In particular, the cost of bevacizumab was too high compared to its value in metastatic breast cancer, which would further support revoking this indication for bevacizumab, as decided in 2011 by the FDA [17].

Here we propose a modification of the Guirgis's method, and test it to assess the price appropriateness of six anticancer medications approved in Italy in recent years.

2 Methods

We determined treatment costs for six innovative anticancer agents, based on a 70-kg or 1.7-m^2 patient for the entire treatment course, calculated considering the median duration of treatment as reported in the literature [21–31]. Medications included in our analysis were: abiraterone, afatinib, aflibercept, bevacizumab, dabrafenib, and ipilimumab. Medicinal product costs were calculated using the ex-factory prices published in the Italian Official Gazette [32–38], not considering possible discounts negotiated between pricing and reimbursement authorities and pharmaceutical companies as part of a confidential agreement. Moreover, we did not consider the application of any PBRSAs because we could hardly assess the impact of such agreements on treatment costs. Ratios of cost per day of survival (cost/survival/day, as reported by Guirgis [17] were obtained by dividing the total cost of medicinal products by the median survival gain, measured in days (1 month = 30 days). Reference parameters for the assessment of survival included overall survival (OS) or progression-free survival (PFS), as reported in published pivotal trials [21–31]. We considered as clinically significant a survival gain of at least 20 % of the total life expectancy of an individual, as defined by the American Society of Clinical Oncology (ASCO) [39]. Each cost/survival/day was scored from 0 to 100, based on acceptable treatment cost thresholds set by NICE (£20,000–£30,000 per life-year gain in good health, corresponding to £1666–£2500 per month) and a correction parameter defined as "willingness-to- pay" for the Italian NHS, which is derived from the gross domestic product (GDP) per capita. Since the Italian GDP per capita corresponds to 89 % of that in Britain, as estimated by the International Monetary Fund (IMF) in 2014 [40], the Italian thresholds were defined accordingly (Table 1). Based on this estimate, anticancer medications should be paid in Italy for up to a maximum of approximately €33,000 per year of life gained in good health (per QALY), corresponding to about €2750 per month.

Starting from these parameters, the maximum price considered as adequate was equal to €91 per single survival day gained (€2750/30 days) and was assigned a score equal to 75; the 0 crude score was assigned to a cost/survival/day ≥€586; the 100 score was assigned to a cost/survival/day ≤€11 (Table 2).

Crude scores must be then adjusted according to the following correction factors (Fig. 1):

- Efficacy: 15-point reduction for lack of clinically meaningful OS data and 30-point reduction in case of OS data not being clinically meaningful.
- Safety: 15-point reduction in case of a serious adverse event (SAE) rate ≥5 % higher than controls or, depending on specific drug profiles, 0- to 10-point reduction for ≥5 % increase in rate of all grade AEs.
- Quality of life (QoL): 5- to 10-point increase in case of stabilization or improvement in QoL, respectively;

Table 1 Thresholds for the Italian National Health System (NHS) based on limits set by the British NHS and Italian willingness-to-pay

	£	€
Annual threshold UK	30,000	37,218
Annual threshold Italy (89 % UK)	26,700	33,124
Monthly threshold UK	2500	3101
Monthly threshold Italy (89 % UK)	2225	2760

Table 2 Crude score values for cost/survival/day of anticancer medications, adapted from Guirgis [17]; €91 per day gained (€2750/30 days) was considered the maximum adequate price corresponding to a 75 score; a 0 score was assigned to a cost/survival/day ≥586, a 100 score to a cost/survival/day ≤€11

Cost/survival/day (€)	Crude score
≥586	0
585–540	5
539–494	10
493–448	15
447–402	20
401–366	25
365–330	30
329–294	35
293–258	40
257–222	45
221–196	50
195–170	55
169–144	60
143–118	65
117–92	70
91–76	75
75–60	80
59–44	85
43–28	90
27–12	95
≤11	100

10-point reduction in case of deterioration; no score correction when data about QoL are not available.

- Disease prevalence: 10-point increase in case of rare disease or indication for a specific subgroup of patients with poor prognosis and lack of alternative treatment.

Depending on the final score, after adjustment for efficacy, safety, QoL, rare disease, a final decision with regard to price and reimbursement may be taken as shown hereinafter:

(a) 75–100: price is adequate and a PBRSA negotiation is not recommended;
(b) 50–74: price is inadequate and a PBRSA negotiation is recommended;
(c) 25–49: price is inadequate and should be reduced to reach a score of at least 50; if this is not applicable, a different cost-containment measure (i.e., price per volume) might be considered;
(d) 0–24: price is inadequate and should be reduced to reach a score of at least 50; if this is not applicable, the medication will not be reimbursed by NHS (class C of reimbursement).

3 Results

In this study, we analyzed price adequacy for six anticancer medications (abiraterone, afatinib, aflibercept, bevacizumab, dabrafenib, and ipilimumab) approved in Italy between 2013 and 2014, for which ex-factory prices were published in the Italian Official Gazette [32–38] and efficacy data including OS and/or PFS (Table 3) were available in literature [21–31].

Treatment costs ranged from €8820 for seven cycles of treatment with aflibercept, in patients with metastatic colorectal cancer, to €85,000 for four doses of ipilimumab, in patients with advanced (unresectable or metastatic) melanoma. Cost estimation for these medications does not include potential non-transparent discounts not reported in the Official Gazette, as well as the impact of potential PBRSA. However, we performed additional analysis taking into account additional discounts to the ex-factory price when available (data not shown for confidentiality).

Survival gain expressed in days has been derived from clinical trials carried out for new drug submission purposes, in support of MA.

For each cost/survival/day (obtained by dividing the entire treatment cost over the OS or PFS day gain), we calculated the corresponding crude score and then adjusted it for correction factors, as described in the methods section. The lowest cost/survival/day was observed for aflibercept (€133.6), leading to the highest crude score (65), whereas the highest cost/survival/day was observed for ipilimumab (€787.03), corresponding to the lowest crude score (0). Following score correction for efficacy, safety, QoL, and prevalence of the respective approved indication, none of the evaluated medications achieved a final score of 75, which we propose as appropriate pricing not requiring the negotiation of a PBRSA. However, the correction substantially increased the score for afatinib, which attained the highest final score (55, from an initial 50 crude score), corresponding to appropriate pricing that requires the application of a PBRSA (in fact, PbR was applied in this case by the Italian Medicines Agency, AIFA). Prices were not appropriate for all the other medications, with final scores negative for bevacizumab (−15, initial 30 crude score), dabrafenib (−20, initial 15 crude score) and ipilimumab (−15, initial 0 crude score). Thus, the price for all these medications should be reduced in order to achieve a score of at least 50. Aflibercept resulted in a final score of 20 because its initial crude score (65) was reduced by 30 points. This correction was carried out because aflibercet improved OS by about 10 % (13.5 vs. 12 months), a gain which does not fulfill the 20 % ASCO criteria, though statistically significant.

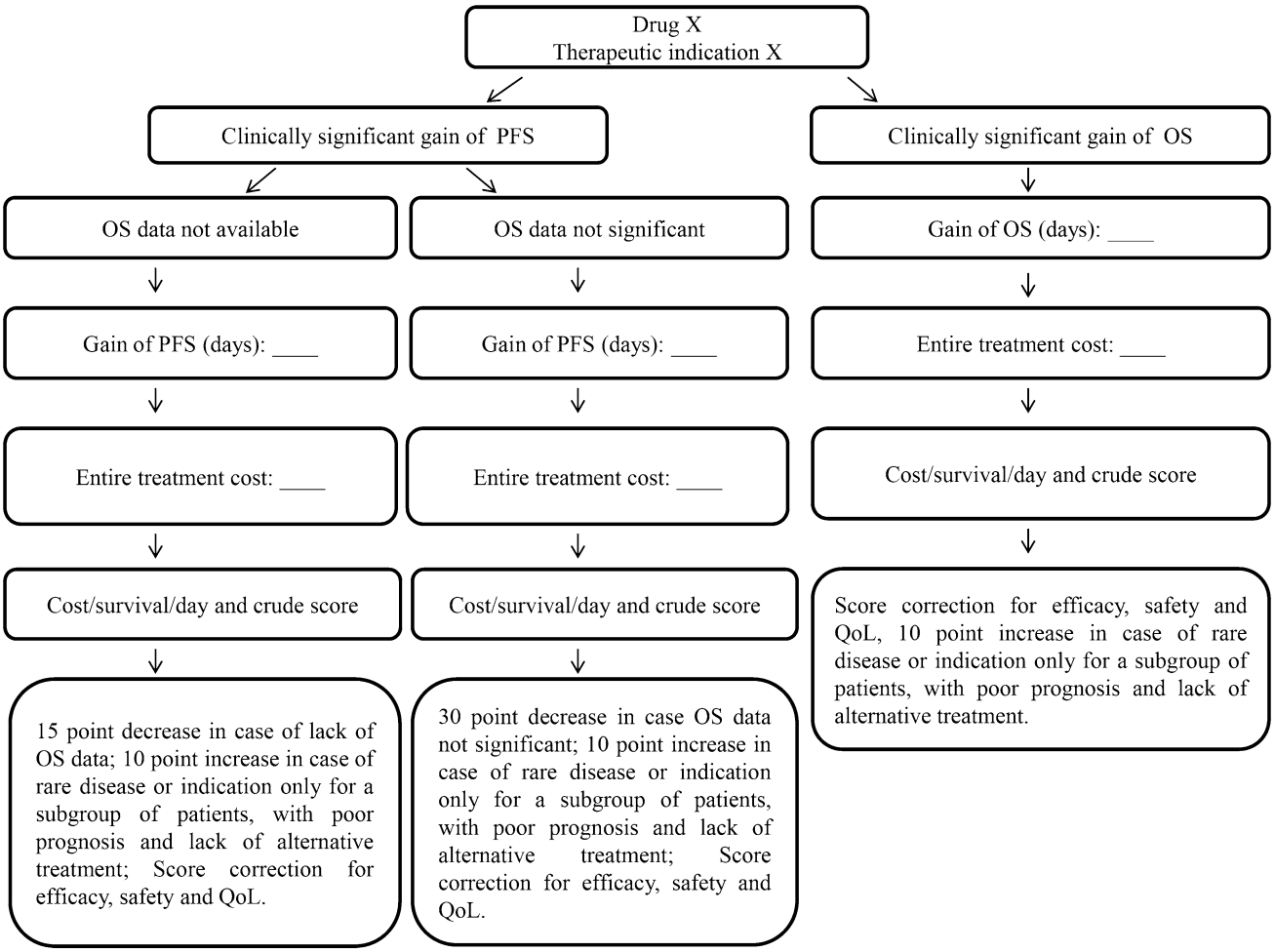

Fig. 1 Algorithm for score definition and correction. The algorithm starts with definition of cost/survival/day, corresponding to an initial crude score. Subsequently, crude score is adjusted for efficacy, safety, quality of life (QoL) and disease prevalence. Efficacy is assessed in terms of clinically significant change in overall survival (OS) and progression free survival (PFS). We consider "rare" a prevalence <1/2000, according to European Union definition

Finally, we applied our algorithm to assess the impact of distinct therapeutic indications on the final score of a given medication:

(a) abiraterone for the treatment of metastatic prostate cancer resistant to castration in adults whose disease progressed on or after a docetaxel-based chemotherapy regimen;
(b) abiraterone for treatment of metastatic prostate cancer resistant to castration in adults asymptomatic or mildly symptomatic after failure of androgen deprivation therapy, in whom chemotherapy is not yet clinically indicated.

The former indication resulted in a final score of 35, whereas the latter reached a final score of just 15, indicating that appropriate decision on pricing would benefit from an evaluation of the distinct indications for a specific medicinal product.

Even when considering additional discount to ex-factory price, none of the prices evaluated resulted in being appropriate (e.g., only a 5-point increase in the score for afatinib was detected, with a final score of 60; data not shown).

4 Discussion

In the negotiation between payers and pharmaceutical companies for new medicines' safety, efficacy, reimbursement conditions, and price appropriateness with regard to a treatment value must be defined. Price definition remains a national competence, even for drugs with centralized authorization, like oncologic medications [41, 42]. Differences exist between European countries in terms of pricing policy, leading to a difference in price setting. It is therefore clear that price is not linked to the product

Table 3 Assessment of price adequacy for six anticancer medicinal products recently approved in Italy

Drug	Therapeutic indications	Ex factory price	Entire treatment cost	OS or PFS gain (days)	Cost/survival/day	Crude Score	Score correction for efficacy, safety, QoL, and prevalence	Final score
Abiraterone	Metastatic castration resistant prostate cancer in adults whose disease has progressed on or after a docetaxel-based chemotherapy regimen	€385,000 (120 tablets; each tablet contains 250 mg)	€3,080,000 (approximately 8 months of treatment; daily dose 1000 mg)	117 (OS) abiraterone acetate + prednisone versus placebo + prednisone	€26,325	40	Data from clinical trial do not reveal an increase in grade ≥3 adverse events; however, an increase in grade 1 and 2 adverse events compared to placebo were noted (score adjustment: −5 points)	35
Abiraterone	Metastatic castration resistant prostate cancer in adults asymptomatic or mildly symptomatic after failure of androgen deprivation therapy, in whom chemotherapy is not yet clinically indicated	€385,000 (120 tablets; each tablet contains 250 mg)	€53,130 (approximately 138 months of treatment daily dose 1000 mg)	156 (OS) abiraterone acetate + prednisone versus placebo + prednisone	€34,057	30	Considering that data from clinical trial reveal an increase in grade 3 and 4 adverse events, crude score should be reduced by 15 points	15
Afatinib	EGFR-TKI-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s)	€226,520 (28 tablets; 20, 30, 40 or 50 mg)	€249,172 (approximately 11 months; daily dose 40 mg)	126 (PFS) afatinib vs. cisplatin + pemetrexed At the time of preliminary assessment, median OS was not reached in either group	€1977	50	Crude score should be reduced by 15 points for lack of evaluable OS data Incidence of grade ≥3 adverse events was similar comparing the two groups A significant improvement in QoL was reported (score adjustment: +10 points) As EGFR mutation is found in 10–15 % of adenocarcinomas in Caucasian patients, prevalence is lower than 005 % (score adjustment: +10 points)	55

Table 3 continued

Drug	Therapeutic indications	Ex factory price	Entire treatment cost	OS or PFS gain (days)	Cost/survival/day	Crude Score	Score correction for efficacy, safety, QoL, and prevalence	Final score
Aflibercept	MCRC resistant to or progressed after an oxaliplatin-containing regimen	€42,000 (4 ml of concentrate containing 100 mg of aflibercept); €84,000 (8 ml of concentrate containing 200 mg of aflibercept)	€8820 (7 cycles; 4 mg/kg of body weight administered as an intravenous infusion, followed by FOLFIRI[g] regimen)	66 (PFS) aflibercept + FOLFIRI vs. placebo + FOLFIRI OS 43 days, that results not clinically significant	€1336	65	Crude score should be reduced by 30 points for lack of a clinically meaningful improvement in terms of OS (even if OS improvement with aflibercept was statistically significant, it was 10 % greater than baseline median OS—14 months out of a total of 135 months) Incidence of grade 3 and 4 adverse events was higher in the group treated with aflibercept (score adjustment: −15 points)	20
Bevacizumab	Patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents	€32,185 (4-ml vial containing 100 mg of bevacizumab); €128,900 (16-ml vial containing 400 mg of bevacizumab)	€425,226 (12 cycles; 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of bevacizumab as single agent until disease progression; average weight of 70 kg)	120 (PFS) per bevacizumab + carboplatin + gemcitabin vs. carboplatin + gemcitabin	€35,435	30	Crude score should be adjusted with 30 points reduction for lack of a clinically meaningful improvement in terms of OS[a] Score should be adjusted removing 15 points for the presence of a greater % of serious adverse reactions compared to standard therapy	−15

Table 3 continued

Drug	Therapeutic indications	Ex factory price	Entire treatment cost	OS or PFS gain (days)	Cost/survival/day	Crude Score	Score correction for efficacy, safety, QoL, and prevalence	Final score
Dabrafenib	Unresectable or metastatic melanoma with a BRAF V600 mutation	€206,999 (28 capsules; 75 mg); €138,000 (28 capsules 50 mg); €887,139 (120 capsule, 75 mg); €591,426 (120 capsule 50 mg)	€5,322,834 (6 months, 150 mg twice daily (total daily dose of 300 mg)	114 (PFS) dabrafenib vs. dacarbazine OS data, updated as a result of a post hoc analysis, did not show a significant advantage with dabrafenib	€4669	15	Crude score should be reduced by 30 points for lack of improvement in terms of OS Incidence of grade 3 and 4 events was similar in the two treatment groups, but with dabrafenib an overall increase of adverse events was found (score adjustment: −5 points)	−20
Ipilimumab	Unresectable or metastatic melanoma in adults whose disease had progressed while they were receiving therapy for metastatic disease	€425,000 (5 mg/ml–10-ml vial, 50 mg); € 1,700,000 (5 mg/ml–40-ml vial, 200 mg)	€8,500,000 (3 mg/kg administered intravenously every 3 weeks for a total of 4 doses; average weight of 70 kg)	108 (OS) ipilimumab plus gp100 or ipilimumab alone vs. gp100 alone	€78,703	0	Clinical trial revealed an increase in grade 3 and 4 adverse events with ipilimumab (score adjustment: −15 points)	−15

Prevalence of 0.05 % = cut-off for rare disease/indication according to European Union

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCT-CTCAE)

OS overall survival, *PFS* progression-free survival, *EGFR-TKI* epidermal growth factor receptor-tyrosine kinase inhibitor, *NSCLC* non-small-cell lung cancer, *EGFR* epidermal growth factor receptor, *MCRC* metastatic colorectal cancer, *FOLFIRI* 5-fluorouracil/folinic acid/irinotecan regimen, *VEGF* vascular endothelial growth factor, *QoL* quality of life, *BRAF* B-raf proto-oncogene

value, defined as the health benefit that the product provides expressed in money [43].

Within the Policy Forum of Health Technology Assessment International, it has been observed that the definition of value is related not only to technical dimensions (such as clinical benefit, safety, cost-efficacy, etc.), but should also take into account different society and stakeholder perspectives [44]. Moreover, the lack of reliable and conclusive data on the overall risk/benefit profile or cost-effectiveness, especially in oncologic care, may represent a serious issue whenever a new drug application is submitted for MA, even when considering the technical dimensions of value.

The need for a value-based system that links a medication price to the effective benefit for patients has recently been highlighted by several groups of researchers, and many solutions have been proposed [8, 17–19, 45, 46]. Battley et al. [45] consider the cost of target therapies unsustainable because they produce modest benefits in terms of overall survival. The cost is usually accounted for by the investment in research and development [47], but, when considering the different prices of a given drug in different countries, it rather seems to reflect geopolitical and socioeconomic dynamics [5]. Lack of correlation between medication prices and their value is also highlighted by the fact that a same fixed price is applied for different approved indications. In fact, the analysis with the algorithm we propose suggests that prices would need an adjustment based on the efficacy data for a single disease, because different degrees of effectiveness relate to distinct indications [9]. Moreover, with competitive agents entering the market, prices should be reconsidered due to the availability of new treatment options [8, 9].

Recently, Mailankody and Prasad [6] reported a lack of correlation between medication prices approved by the FDA and their benefit in terms of response rate (RR), OS, or PFS. They concluded that "current pricing models are not rational but simply reflect what the market will bear" [6].

Kantarjian et al. [8] propose a value-based system for the initial price definition of a medicinal product. According to this view, the value of a novel anticancer medication should be assessed through the evaluation of several parameters that include OS or PFS extension, QoL improvement, adverse event (AE) reduction/alleviation compared with similar approved medications, and cost reduction. This system defines as extremely effective a medicinal product that prolongs survival by more than 6 months or by more than one-third of a patient's life expectancy, and sets as adequate a price in the US$50,000–US$60,000 range. Medications that demonstrate statistically significant survival benefits of 2 months or less than 15 % of a patient's life expectancy, should be considered minimally effective and would be priced below US$30,000 per year. Prices for medicinal products showing intermediate effectiveness would lie in between these two ranges. Moreover, according to the authors, these measures need to be implemented by assessing the impact of a given medication on QoL, toxicity, and other disease-related costs. Such an approach seems quite discretional in setting at approximately US$10,000 the value of a month of life gained, particularly when considering the threshold value per single month of healthy life gain, set at approximately £2500 by NICE.

In our study, we propose an algorithm based on the method published by Guirgis [17] in order to assess price adequacy of oncologic medications approved in Italy between 2013 and 2014. We chose limits of £20,000–£30,000 cost per year of life gained in good health, clearly defined by the NICE, and adapted these limits to the Italian economic situation. Considering these threshold values and the "willingness-to-pay" derived by the Italian GDP per capita (40), anticancer agents should be paid up to a maximum of approximately €33,000 per year of life gained in good health, corresponding to almost €2750 per month (89 % of the maximum value generally recognized in the UK). Our analysis shows that most of the evaluated medications do not present an appropriate price for their therapeutic value in terms of prolongation of survival, safety, or QoL. As shown in the abiraterone example, different indications result in largely variable efficacy/safety data, and price definition would benefit from a separate evaluation of the medical conditions for which the drug is approved. However, the Italian Regulatory Agency has tried to overcome this issue with the introduction of specific PBRSAs for different indications of a given drug [48].

Considering that Italian prices are the third lowest among 11 European countries (in order: Germany, Belgium, Finland, Ireland, Austria, Spain, France, UK, Italy, Portugal, and Greece), according to the most recent Osmed National Report on drug use in Italy [13], it is likely that the application of this method to evaluate price adequacy in other European countries (adjusted for respective GDP values) would show the inadequacies of most anticancer medication prices, compared to their overall therapeutic value. However, a recent study published by Vogler et al. [49] reported the highest oncologic drug prices in Switzerland, Sweden, and Germany and the lowest in Portugal, Spain, Greece, and the UK; the Italian drug prices were in the middle when considering European high income countries (Austria, Belgium, Denmark, Germany, Greece, Finland, France, Italy, Ireland, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the UK).

The method we propose, similar to Guirgis' method [17], offers the advantages of rapid evaluation of cost

versus survival and adjustment for changes in prices, survival, duration of treatment, and/or number of cycles. Limitations are represented by approximate quantification of specific scores for AEs and QoL, because the evaluation of these variables is often arbitrary and relies on the different perspectives of investigators and patients. Another limitation is the technical definition of adequate price score, that we attributed at the first quartile (score >75) and is discretionary; furthermore, our model does not capture other relevant stakeholder perspectives that may need to be taken into account to define the drug/technology "value," as recommended by the consensus reached within Health Technology Assessment international (HTAi) Policy Forum in 2013 [44]. Finally, ex-factory prices reported in the Official Gazette do not consider either the discount negotiated between the AIFA and Pharmaceutical Companies or the impact of PBRSAs. However, even when considering additional discount to ex-factory price, none of the prices evaluated showed an appropriate result. We evaluated the price at the time of launch of the product, regardless of possible price reduction over time, to help decision makers in setting appropriate pricing during the negotiation process.

5 Conclusion

In conclusion, we present a method for the evaluation of appropriateness of price proposed at negotiation that could also represent a reliable resource for decision making and for setting a price per volume discounts and/or PBRSA. This method has the advantage of providing a standardized score that allows payers to be consistent in price setting for different medicines in the oncologic area. The impact of this method on the drug approval process has yet to be established and can only be determined following implementation by regulatory agencies.

Compliance with Ethical Standards

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Conflict of interest LG, AN, VD, LL, SM, GP, AC, SS and FD declare that they have no conflicts of interest.

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