OPEN ACCESS

The role of clinical trials in the sustainability of the Italian national health service cancer drug expenditure

Lorenzo Gasperoni ,[1] Alessandro Cafaro,[1] Eleonora Ferretti,[2] Valentina Di Iorio,[1] Oriana Nanni,[3] Carla Masini [1]

[1]Oncological Pharmacy Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Emilia Romagna, Italy
[2]Hospital Pharmacy, Azienda USL Modena, Modena, Emilia-Romagna, Italy
[3]Unit of Biostatistics and Clinical Trials, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Emilia Romagna, Italy

Correspondence to
Dr Lorenzo Gasperoni, Oncological Pharmacy Unit, IRST, Meldola 47014, Emilia-Romagna, Italy; lorenzo.gasperoni@irst.emr.it

Received 7 March 2022
Accepted 19 April 2022
Published Online First 16 May 2022

EAHP Statement 1: Introductory Statements and Governance.

To cite: Gasperoni L, Cafaro A, Ferretti E, *et al*. *Eur J Hosp Pharm* 2023;**30**:96–100.

ABSTRACT

Objective Clinical trials offer new and potentially more effective therapeutic options for cancer patients and a potential cost-saving opportunity, especially considering that trial drugs are provided free-of-charge. The aim of this study was to analyse drug-related cost savings in clinical trials in a cancer institute over a 3 year period. The cost savings relate to the pharmaceutical expenditure of our centre, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori".

Methods We conducted a retrospective analysis of patients taking part in interventional clinical cancer trials approved by a local independent Ethics Committee between 1 January 2018 and 31 December 2020. The standard of care (SOC) was identified as the standard treatment that would have been offered to a patient if he/she had not been enrolled in the study. The sum of SOC costs of all patients represents the potential cost avoidance during the study period. Results were stratified by year, trial promoter, trial phase and tumour type. The same approach was used to perform a secondary analysis of compassionate use programmes.

Result In the 3 year analysis, 1,257 patients were treated with experimental therapies in 244 clinical trials, of which 157 were profit and 87 academic. Results showed an overall cost savings of €13,266,518, more than 50% of which (€7,035,009) was related to phase III studies. Profit clinical trials generated €9,069,764 (68.4%) of the drug cost savings compared with €4,196,754 (31.6%) of academic studies. The stratification for tumour type was €3,552,592 (26.8%) genitourinary cancer, €3,268,074 (24.6%) melanoma, €2,574,127 (19.4%) haematological malignancies, €2,330,791 (17.6%) lung cancer, €728,149 (5.5%) gastrointestinal cancer, €557,608 (4.2%) rare tumours and €255,178 (1.9%) breast cancer. The secondary analysis on compassionate use included 122 patients involved in 28 different access programmes and revealed cost savings of €1,649,550.

Conclusion The results of our analysis point to the benefits of participating in and planning clinical trials for the public healthcare sector.

SUMMARY BOX

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although data from the literature show potential savings from the use of experimental cancer treatments, the continuous increase in the cost of commercialised innovative cancer drugs makes it essential to constantly monitor the situation. D'Ambrosio *et al* reported annual savings of around €6 million using a data-projection method.

WHAT THIS STUDY ADDS

⇒ Our analysis covered a 3 year period that took into account the change in drug prices during that time.

⇒ The results of our analysis highlight the benefits of drug cost savings gained by investing in clinical progress via clinical trials. The results highlight a notable contribution also from academic clinical studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite a general increase in cost savings over the 3 year period thanks to investment in clinical trials, the savings were not proportional to the annual pharmaceutical expenditure. Our analysis highlights the importance of investing in clinical trials for the National Health Service to offset the increase in expenditure for cancer drugs and to sustain affordable healthcare services.

BACKGROUND

The most recent health data from the WHO tracks the high incidence of cancer in 2020. In Europe, more than 4 million new cases were reported, of which over 400 000 were in Italy.[1] Drug costs are the main component of healthcare expenditure and have increased over the last few decades. Such costs must always be considered in relation to the positive impact of available drug treatments for cancer patients.[2 3] On the basis of data from Rapporto OsMed (National Report on the use of Medicines in Italy) for 2019, antineoplastic drugs represented the first therapeutic category with the highest public health expenditure equal to €6,038 million and 26% of the total expenditure of the Italian National Health Service.[4] The urgent need for innovative drugs impacts pharmaceutical company investments and leads to increased drug prices.[5 6] Strategies have been introduced to limit increasing costs. These strategies include using generics and biosimilars or managed entry agreements (MEA). MEAs are a well established instrument designed to balance rapid access to innovative drugs while containing health expenditure by binding drug use to value- or outcomes-based

negotiation agreements to maximise the cost-benefit ratio.[7] The use of MEAs has increased over time in response to high prices for new drugs, especially those for cancer.[8 9] In Italy, at regional level, working groups have been established to develop recommendations and guidelines to use drugs appropriately. Specifically, the multidisciplinary GReFO group (Regional Group for Cancer Drugs) based in the Emilia Romagna region, uses a transparent, reproducible and flexible evaluation process based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. This enables GReFO to produce useful guidelines to promote appropriate drug prescription and to favour the governance of pharmaceutical expenditure by local healthcare authorities. Despite the use of such strategies, there was an increase in antineoplastic drug spending in 2018 compared with 2017 (+9.7%) and in 2019 compared with 2018 (+7.1%).[4 10]

A recent analysis conducted in an Italian cancer institute reported monthly savings of > €500,000 in pharmaceutical expenditure from the enrolment of patients in clinical trials.[11] Sponsored clinical trials, in addition to providing new and potentially better therapeutic alternatives for cancer patients, are a potential opportunity for cost savings given that trial drugs are provided free-of-charge. In academic clinical trials, if the marketing authorisation holder supports studies by supplying the drugs used, their costs do not impact the National Health Service. For example, a retrospective 2 year cost attribution analysis was conducted in a single UK centre investigating specific costs associated with cancer clinical trial protocols (drugs, nursing staff, imaging, laboratory tests and visits). The findings showed that participating in either commercial or non-commercial trials led to cost savings, the most important deriving from the provision of free drugs by the sponsor.[12] Data from the literature suggest that clinical trials with investigational antineoplastic drugs result in substantial cost savings, thus constituting a potentially exceptional framework for clinical progress and an important resource for healthcare governance.[13–16]

On confirmation that a pharmaceutical company can supply study drugs free-of-charge, cost savings can be further calculated on the basis of the compassionate use of the drugs. On 7 September 2017, the Italian Ministry of Health issued a new decree on the compassionate use of a medicinal product. This established that access to the drug requires the approval of an Ethics Committee and confirmation from the pharmaceutical company of its ability to supply study drugs free-of-charge.[17] Compassionate use refers to the use of a drug that has proven effective in clinical trials, outside of the trial itself. It is generally reserved for patients with serious or rare life-threatening diseases for whom there are no further valid therapeutic alternatives, for those who cannot be included in a clinical trial or, for the purpose of therapeutic continuity, for patients already treated with clinical benefit within the context of a concluded clinical trial (at least phase II). Thus, although compassionate use does not always represent the only therapeutic alternative, it may be the best therapeutic option while waiting for new drug registration or new indications for available treatments.

Taking into account that the quantification of savings is important to further encourage research and innovation through planning that takes into account economic benefits, we conducted a study to determine drug-related cost savings in clinical trials and to assess compassionate use in an Italian cancer institute over a 3 year period. The cost savings relate to the pharmaceutical expenditure of the institute during this time.

METHOD

Our institute (IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori") is a cancer institute in which pharmaceutical resource expenditure represents about 30% of the total budget. In 2018, expenditure for cancer drugs was €25,020,283 (3,902 treated patients), €26,052,780 in 2019 (4,532 treated patients) and €28,061,263 in 2020 (4,202 treated patients). We conducted a retrospective analysis on patients enrolled in interventional oncological and oncohaematological clinical trials approved by the local independent Ethics Committee between 1 January 2018 and 31 December 2020 and carried out at our centre. We considered both commercially sponsored profit trials and academic trials in different phases of clinical research (phase I, II, III and IV) and in neoadjuvant, adjuvant or metastatic settings.

For all protocols included in the analysis (at least one cycle of therapy administered during the 3 year period for at least one patient), the standard of care (SOC) was identified as the standard treatment that would have been offered to the patient if he/she had not been enrolled in the study on the basis of Italian Medicines Agency (AIFA) reimbursement criteria, Italian Association of Medical Oncology (AIOM) guidelines and GReFO recommendations (in the event their indications were more stringent). Given that AIOM guidelines are updated annually, the SOC may have changed during the 3 year period analysed. For example, the combination of chemotherapy and immunotherapy with nab-paclitaxel and atezolizumab to treat patients with locally advanced unresectable or metastatic triple-negative breast cancer with a of PDL one tumour proportion score ≥1 was authorised by AIFA in July 2020[18] and represents the SOC from the date of authorisation.[19] Our analysis considered the SOC at the date on which the patient was enrolled in the study. For some patients, there was no standard antineoplastic treatment available and the SOC was defined as the best supportive care (BSC).

For each patient, the SOC cost was estimated by considering the administration of a number of treatment cycles sufficient to cover the 3 year period of observation. For patients enrolled before 1 January 2018 but undergoing experimental therapy during the study period, we only counted a sufficient number of treatment cycles to cover the duration of the analysis. For those recruited during the 3 year period but whose experimental therapy continued beyond the end of the analysis, we only considered the number of treatment cycles administered up to the end of the analysis period. If the SOC included a specific number of treatment cycles as an upper limit of duration and the patient was enrolled for a longer period, we counted the maximum number of cycles of the SOC. A standard weight of 65 kg and body surface area of 1.7 m2 was considered for dose calculation. We considered the most recent drug price charged by the pharmaceutical company over the course of the treatment year, including local negotiated discounts and value added tax. Patient SOC costs were calculated by multiplying the SOC number of administration cycles by the dose in milligrams by the price per milligram. When the defined SOC was BSC, no savings were considered. Ancillary therapies and premedications were not considered when calculating cost savings. Although academic studies do not normally lead to drug cost savings, we defined the SOC for academic studies but only valued it as savings in the event that the marketing authorisation holder supported the study by providing the drugs free-of-charge. The sum of SOC costs of all patients represented the potential cost avoidance of the standard of care over the 3 year analysis period.

Table 1 Characteristics of experimental therapies

	Profit	Academic	Total
Experimental therapies	514	743	1257
Trial phase	**Profit**	**Academic**	**% of experimental therapies**
I	13	4	1.4
I/II	46	1	3.7
II	61	560	49.4
II/III	13	5	1.4
III	377	159	42.6
IV	4	14	1.4
Cancer type	**Profit**	**Academic**	**% of experimental therapies**
Breast cancer	34	104	11.0
Gastrointestinal cancer	65	64	10.3
Genitourinary cancer	203	141	27.4
Haematological malignancy	51	57	8.6
Lung cancer	84	39	9.8
Melanoma	45	24	5.5
Rare tumours	32	314	27.5

Results were stratified by year, promoter (profit or academic), phase (I, II, III, IV) and tumour type (breast, gastrointestinal, genitourinary, lung, haematological malignancies, melanoma and rare tumours).

The same approach was used to perform a secondary analysis of therapeutic use programmes including compassionate use, treatment on a named-patient basis, early access and expanded access. Cost savings were valued only when the therapeutic use did not represent the only therapeutic option, that is, the SOC was not BSC. All data are presented in descriptively. Absolute and relative frequencies for categorical data, mean for quantitative data are provided.

RESULTS

From 1 January 2018 to 31 December 2020, 1,257 patients were treated with experimental therapies in 244 clinical trials, of which 157 were profit and 87 academic. The characteristics of experimental therapies are reported in table 1.

Among the latter, 709 (56.4%) did not generate cost savings either because the defined SOC was BSC or the investigational drug was not provided by the sponsor. Specifically, profit experimental therapies did not generate cost savings in 21.6% of patients (111 out of 514) compared with 80.5% (598 out of 743 patients) of academic experimental treatments.

The results of our analysis showed an overall cost savings of €13,266,518 during the 3 year period, over 50% of which came from phase III studies (figure 1).

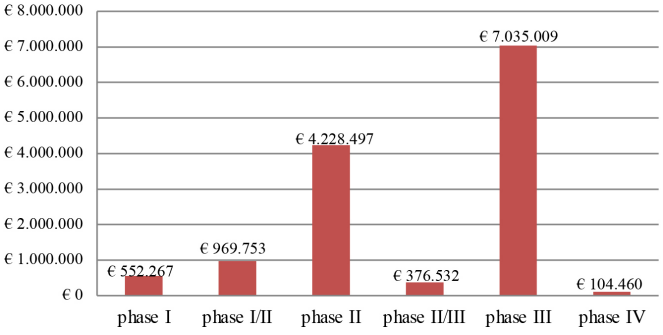

Figure 1 Cost savings per study phase. €, euro.

Table 2 Average per patient cost savings per tumour type per year

Cancer type	2018	2019	2020
Breast cancer	€ 1,079.22	€ 786.81	€ 813.21
Gastrointestinal cancer	€ 3,804.51	€ 4,210.52	€ 5,264.15
Genitourinary cancer	€ 7,559.88	€ 6,081.25	€ 6,978.79
Haematological malignancy	€ 11,892.60	€ 14,140.74	€ 17,711.11
Lung cancer	€ 17,316.97	€ 12,214.32	€ 10,293.72
Melanoma	€ 33,826.69	€ 31,544.32	€ 22,464.52
Rare tumours	€ 2,798.75	€ 888.06	€ 812.17

€, euro.

Profit clinical trials generated 68.4% of drug cost savings (€9,069,764), compared with 31.6% of academic studies (€4,196,754). Cost savings amounted to €4,423,539 in 2018 (70.7% profit, 29.3% academic), €4,353,599 in 2019 (66.9% profit, 33.1% academic) and €4,489,379 in 2020 (67.6% profit, 32.4% academic). The stratification of cost savings among tumour types was as follows: 26.8% genitourinary cancer, 24.6% melanoma, 19.4% haematological malignancies, 17.6% lung cancer, 5.5% gastrointestinal cancer, 4.2% rare tumours and 1.9% breast cancer.

On average, cost savings generated by experimental treatment of a single patient during the analysed period (3 years) were €10,554, recording a higher average cost for patients enrolled in sponsored profit trials than in academic trials, respectively €17,645 and €5,648. Taking into account the analysis year by year, average per patient cost savings were €8,116.59 in 2018, €6,449.78 in 2019 and €6,802.09 in 2020.

Table 2 explains the average per patient cost savings per tumour type per year.

The secondary analysis on compassionate use included 122 patients involved in 28 different access programmes. Among these, 35 (28.7%) did not generate cost savings either because the defined SOC was BSC (n=17) or because the drug for compassionate use was associated with another drug not supplied free-of-charge that was definable as SOC (n=18). The results of the analysis revealed total cost savings of €1,649,550. This accounted for €300,409 in 2018, €649,875 in 2019 and €699,266 in 2020. The stratification of cost savings among tumour types was as follows: 54.2% lung cancer (five access programmes, 35 patients), 25.5% genitourinary cancer (four programmes, 21 patients), 9.8% melanoma (five programmes, 33 patients), 4.1% haematologogical malignancies (seven programmes, 13 patients), 6.2% rare tumours (four programmes, 4 patients), 0.2% gastrointestinal cancer (three programmes, 16 patients) and 0% breast cancer (no patients). On average, cost savings generated by compassionate use for a single patient during the analysed period were €13,520.

The sum of cost savings for clinical trials and compassionate use programmes was €4,723,948 in 2018, equivalent to 18.9% of the expenditure for cancer drugs in our institute. In 2019, the sum was €5,003,474 (19.2% of cancer drug expenditure) and in 2020, €5,188,645 (18.5% of cancer drug expenditure).

DISCUSSION

The results from our study confirm that investing in clinical research represents an important opportunity. Clinical trials guarantee additional therapeutic options and early access to innovative therapies for eligible patients, without further burdening the healthcare system. Our study focused solely on cancer drug resources, without considering the cost of ancillary therapies, medical devices or human resources. Grants from sponsors were

also excluded from the analysis. Clinical trials and compassionate use resulted in savings of almost 20% in cancer drug expenditure at our institute, contributing substantially to the sustainability of our National Health Service. Although cost savings increased in 2020 (+3.7% compared with 2019), they nonetheless represented the lowest savings in the 3 year period of analysis in terms of cancer drug expenditure, i.e. 18.5% (-0.7% compared with 2019). Cancer drug spending is constantly increasing, mainly due to the introduction of reimbursement for high cost innovative drugs or new indications. In a recent analysis conducted in another Italian cancer institute, D'Ambrosio *et al* reported annual savings of around €6 million (almost entirely from sponsored clinical trials) using a data-projection method based on a 4 week analysis.[11] The solidity of our results lies in the fact that our analysis covered a 3 year period that took into account the changes in drug prices during that time. The impact of changes in drug prices stands out in melanoma and lung cancer data in table 2, in which, over the course of 3 years, the average cost savings per patient fell considerably due to a decrease in the costs of immunotherapy treatments, mainly defined as SOC. A strength of our study is its inclusion of patients with any tumour type (not only solid tumours) taking part in a clinical trial regardless of phase or type (profit or academic). The annual savings in clinical trials of around €4.4 million, with a notable contribution from academic clinical studies (31.6%), is the result of a direct analysis and represents, as in the D'Ambrosio *et al* projection,[11] about 20% of savings on the annual expenditure for oncological drugs.

Stratification allows comparison of results between tumour types within our study. For example, drug savings generated by genitourinary and melanoma clinical trials are similar in terms of the total sum over the 3 years. However, genitourinary savings are the result of 344 patients treated with experimental therapies and average cost savings per patient which are much lower than melanoma. Only 69 patients were treated with experimental melanoma therapies, but melanoma recorded the highest average per patient cost savings.

Medicines authorised by the European Medicines Agency (EMA) are marketed in individual member states after varying periods of time. This timing can severely penalise patients. It is therefore essential to ensure these therapies are more readily available.[20] The results of our secondary analysis underline the growth of therapeutic use programmes such as compassionate use programmes, treatment on a named-patient basis, early access programmes and expanded access programmes. In many cases, compassionate use represents an early access tool to bridge the gap between approval and reimbursement timelines. Jommi *et al* in 2021 estimated that avoided drug costs reported in compassionate use studies measuring only drug costs ranged from €1,746 to €49,301 per patient.[21] Our analysis confirms that the guarantee of the free supply of drugs by the pharmaceutical company for compassionate use represents an important economic opportunity.

Not all investigational therapies provide clinical benefits over SOC or BSC. Our study focused on drug cost savings of interest to the health service payer. A limitation of our study is that not all drugs, even if they are provided free-of-charge, add benefit to individual patients. The drugs themselves may not be effective and may result in serious adverse events for some patients. The price of cancer drugs has increased exponiently but some of these increases cannot be justified by the clinical benefits observed. We do not suggest patients be enrolled in trials for economic reasons, but these results suggest that economic investment in clinical trials, including academic ones, are an opportunity to offer more treatment options to patients in a sustainable way.

CONCLUSIONS

In the last 20 years in oncology, investing human and economic resources in clinical trials has resulted in clinical progress and achievement at the pharmacological level. Pharmaceutical companies have borne the economic cost of investing in drug trials, especially profit clinical trials. This has inevitably affected the price of approved drugs. Although the high standards required in conducting a clinical trial undoubtedly condition the centres involved, the possibility of the timely availability of a greater number of therapeutic options and the potential economic advantage in terms of grants and drug resources turn clinical trials into concrete opportunities. The results of our analysis indicate the importance of encouraging growth in clinical trial planning in the public healthcare sector.

Correction notice This article has been corrected since it was published Online First. Affiliations and Acknowledgements section has been updated.

Acknowledgements The authors thank Gráinne Tierney and Cristiano Verna for editorial assistance. This work was partly supported, thanks to the contribution of Ricerca Corrente, by the Italian Ministry of Health within the research line 'Appropriateness, outcomes, drug value and organizational models for the continuity of diagnostic-therapeutic pathways in oncology'.

Contributors All authors made substantial contributions to the concept and design of the manuscript. LG, AC, EF and VDI made substantial contributions to acquisition, analysis and interpretation of data. LG drafted the manuscript. ON and CM made critical revisions for important intellectual content and supervised the manuscript. All authors read and approved the final manuscript. LG is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Lorenzo Gasperoni http://orcid.org/0000-0001-6427-0809
Carla Masini http://orcid.org/0000-0002-8744-0708

REFERENCES

1 International Association of Cancer Registries. The global cancer Observatory. Available: https://gco.iarc.fr/today/home [Accessed 1 mar 2021].
2 Camps Herrero C, Caballero Díaz C, Blasco Cordellat A. [Pharmacoeconomics and cost of cancer drugs]. *Farm Hosp* 2010;34 Suppl 1:12–15.
3 Parker-Lue S, Santoro M, Koski G. The ethics and economics of pharmaceutical pricing. *Annu Rev Pharmacol Toxicol* 2015;55:191–206.
4 The Medicines Utilisation Monitoring Centre. National report on medicines use in Italy, 2019. Available: https://www.aifa.gov.it/en/-/l-uso-dei-farmaci-in-italia-rapporto-osmed-2019 [Accessed 1 Mar 2021].
5 Gronde Tvander, Uyl-de Groot CA, Pieters T. Addressing the challenge of high-priced prescription drugs in the era of precision medicine: a systematic review of drug life cycles, therapeutic drug markets and regulatory frameworks. *PLoS One* 2017;12:e0182613.
6 Masters GA, Krilov L, Bailey HH, *et al*. Clinical cancer advances 2015: annual report on progress against cancer from the American Society of clinical oncology. *J Clin Oncol* 2015;33:786–809.
7 Ferrario A, Arāja D, Bochenek T, *et al*. The implementation of managed entry agreements in central and eastern Europe: findings and implications. *Pharmacoeconomics* 2017;35:1271–85.
8 Howard DH, Bach PB, Berndt ER, *et al*. Pricing in the market for anticancer drugs. *J Econ Perspect* 2015;29:139–62.
9 Gonçalves FR, Santos S, Silva C, *et al*. Risk-Sharing agreements, present and future. *Ecancermedicalscience* 2018;12:823.

10 The Medicines Utilisation Monitoring Centre. National report on medicines use in Italy, 2018. Available: https://www.aifa.gov.it/en/-/rapporto-osmed-20-1 [Accessed 1 Mar 2021].
11 D'Ambrosio F, De Feo G, Botti G, *et al*. Clinical trials and drug cost savings for Italian health service. *BMC Health Serv Res* 2020;20:1089.
12 Liniker E, Harrison M, Weaver JMJ, *et al*. Treatment costs associated with interventional cancer clinical trials conducted at a single UK institution over 2 years (2009-2010). *Br J Cancer* 2013;109:2051–7.
13 Calvin-Lamas M, Portela-Pereira P, Rabuñal-Alvarez MT, *et al*. Drug cost avoidance in prostate cancer clinical trials. *Actas Urol Esp* 2015;39:553–7.
14 Mañes-Sevilla M, Romero-Jiménez R, Herranz-Alonso A, *et al*. Drug cost avoidance in clinical trials of breast cancer. *J Oncol Pharm Pract* 2019;25:1099–104.
15 Bredin C, Eliasziw M, Syme R. Drug cost avoidance resulting from cancer clinical trials. *Contemp Clin Trials* 2010;31:524–9.
16 Tang PA, Hay AE, O'Callaghan CJ, *et al*. Estimation of drug cost avoidance and pathology cost avoidance through participation in NCIC clinical Trials Group phase III clinical trials in Canada. *Curr Oncol* 2016;23:7–13.
17 Discipline of the therapeutic use of medicinal products subjected to clinical trials. *Official Gazette of the Italian Republic general series n. 256 of 2*, 2017.
18 Determination n. *DG 757/2020 of 14 July 2020. Official Gazette of the Italian Republic general series n. 188 of 28*, 2020.
19 Italian Association for Medical Oncology (AIOM). Breast neoplasms guidelines, 2020. Available: https://www.aiom.it/linee-guida-aiom-2020-neoplasie-della-mammella/ [Accessed 1 Mar 2021].
20 Italian Association of Medical Oncology (AIOM). Early access in Italy. rules that define early access to anti-cancer drugs. scientific documents, 2019. Available: https://www.aiom.it/early-access-in-italia-2/ [Accessed 1 Mar 2021].
21 Jommi C, Pantellini F, Stagi L, *et al*. The economic impact of compassionate use of medicines. *BMC Health Serv Res* 2021;21:1303.