The Economic Impact of Compassionate Use of Medicines

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Abstract

BACKGROUND: Compassionate use programs (CUP) for medicines respond to the ethical imperative of providing earlier access to medicines to patients not recruited in trials. While the economic impact of clinical trials has been already investigated, no evidence on the net economic benefit of CUP exists. This research aims to fill the information gap by estimating the economic consequences of 11 CUP in Italy conducted between May 2015 and December 2020 from the perspective of health care payers. Eight programs concern cancer treatments, two refer to drugs for spinal muscular atrophy, and one is indicated for multiple sclerosis.

METHODS: The net economic benefit includes the avoided costs from the Standard of Care (SoC) the patients would have received if they had not joined the CUP, and costs not covered by the pharmaceutical industry but instead sustained by payers, such as those associated to adverse events (only severe sides effects resulting in hospitalisation and attributed to CUP medicines), and costs for combination therapies and diagnostic procedures not used with the SoC. The SoC costing relied on publicly available data. Information on adverse events and diagnostic procedures was retrieved from the CUP and monetized using the relevant fee for episode or service. One CUP was excluded since a SoC was not identified.

RESULTS: 2,712 patients were treated in the 11 CUP, where SoC was identified. The SoC mean cost per patient ranges from €11,415 to €20,299. The total cost of the SoC ranged between €31.0 and €55.1 million. The mean cost per patient covered by hospitals hosting CUP was equal to €1,646, with a total cost of €4.5 million. The net economic benefit ranged from €26.5 million to €50.6 million (€17.8 million - €42.0 million for cancer treatments).

CONCLUSIONS: Despite research limitations, this paper illustrates for the first time the net economic impact of CUP in oncology patients from a payer perspective. It is important to integrate these estimates with the prospective effects of CUP implementation, i.e., the economic value of the comparative benefit profile of medicines used in CUP versus the SoC, including effects from a societal perspective.

Background

Access to unauthorized treatments can be achieved through participation in clinical trials (CT) or through early access programs. The latter includes different mechanisms, and different terminologies often to the same effect, such as individual named-patient, managed access, compassionate use, early, pre-approval, or expanded access programs [1].

CUP (Compassionate Use Programs) allow for the unauthorized use of a medicine outside a CT, where the cost of treatment is borne by the industry. While the primary objective of a CT is to generate evidence on the safety and efficacy of a treatment against an unmet need, that of a CUP is addressing an unmet medical need for ethical reasons [1]. According to the Regulation (EC) No 726/2004 of the European Parliament, a CUP allows “a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product” to have access to a product that is subject of an application for marketing authorisation or of a CT [2, 3].

Until recently, patients in Italy with a specific disease with no treatment option were provided access through their physician, to innovative drugs authorised for use abroad, unauthorised drugs under CT, as well as drugs different from the ones authorised for the intended therapeutic indication (off-label) [4]. In 2017, a new decree from the Ministry of Health came into effect [5] reflecting the above EU regulations, while also authorising, as per previously, the use in CUP of off-label licensed products and labelled products not yet licensed in Italy. By way of this decree, the definition encompasses patients that can access unauthorized medicines, on a named basis as well as in a group program through their physician, who suffer from severe and rare diseases or life-threatening conditions, who have no other valid therapeutic alternatives, and who cannot be recruited in a CT or who had previously participated in a CT and demonstrated positive health outcomes, and can in this way be guaranteed continuity of care outside the CT. Authorization for conducting a CUP is based on evidence from ongoing Phase III CT, Phase II for life threatening or severe diseases, and Phase I for drugs for rare diseases or rare cancers, provided that Phase I results demonstrate efficacy and safety of the medicinal product at a given dosage and schedule of administration.

CUP bring value both to patients and to the pharmaceutical companies. For patients, this is manifested in the health benefit they may provide to participants, who access a treatment earlier in the evolution of their pathology, and thus avoid health deterioration due to long waiting times until official market authorization. On the other hand, through CUP pharmaceutical companies can already respond rapidly and efficiently to the demand for an unmet need prior to authorization, thus streamlining the transition and launch of the product to market with real-world evidence [4]. The latter can play an important role in regulatory decisions and can be incorporated in the registration and pricing of a product [6]. CUP can thus bring value also to society and to third party payers in economic terms, who may benefit from avoiding part of the cost for treating a severely ill patient with the existing SoC, whose relative effectiveness is often questionable, by instead shifting the difference to the industry, which will cover for most of the investigative treatment’s costs under the CUP.

Our aim was to investigate the economic impact of CUP. Before conducting the study, a non-exhaustive desk review was performed on Pubmed and Google Scholar to identify relevant research presenting evidence on the costs avoided and costs sustained by third payers for the treatment of patients enrolled in CUP. Keywords used in the search included: "cost avoidance" or "economic impact" or "cost saving" or "economic value" and “compassionate use” or “early access”. No specific papers were found on CUP. We extended the analysis to "clinical trial(s)". A total of 21 studies were identified, with most evidence published for Spain and the USA (4 papers each), followed by Canada and Italy (3 papers each), while singular publications present data also for Australia, Turkey, Germany, UK, France, Austria, and Taiwan. Of these studies, one pertained to the measurement of costs of specific side-effects during clinical trials, and one comprised of a grey literature report on the total impact and savings incurred by clinical trials in the US. These two studies are excluded from the following description of available evidence but are included as references in Table 1.

Table 1
Evidence on the economic impact of Clinical Trials

Ref. ID	Country	Therapeutic Area	# of trials	Phase	# of patients	Year(s)	Cost items included (medicines, diagnostics, side effects, trial management, others)	Methods (clinical trial data / clinical trial protocol / mixed)	Main findings (total cost avoided / mean cost avoided per patient recruited)
[10]	Australia	Haematology	36	I, II, III	245	2006–2017	Medicines	Clinical trial data	€ 4278116.09 total cost avoided
[8]	Austria	Multiple	1029	I, II, III, IV	23331	2012–2017	Medicines, diagnostics, side effects, others	Clinical trial protocol	€ 100.53mi saved annually
[11]	Canada	Cancer	21	III	4674	1999–2011	Medicines, diagnostics	Clinical trial protocol	The total Drug Cost Avoidance (DCA) was estimated at € 20308422 of which targeted therapy constituted 43% (five trials). The combined Pathology Cost Avoidance (PCA) and DCA was € 23356118 for a cost avoidance per patient of € 5447.83.
[12]	Canada	Cancer	37	I/II, II, III	250	2001–2006	Medicines	Clinical trial protocol	Drug specific cost avoidance per patient: € 7.99 - € 169885.51
									Potential drug specific cost avoidance per patient: € 9.62 - € 195000.48.
									Actual drug cost avoidances according to tumour group were calculated showing a median range of € 936.74 - € 16157.14 per patient between tumour groups. The median range for potential drug cost avoidance was substantially higher from € 6712.93 - € 31727.89 per patient.
[13]	Canada	Breast cancer	8	III	97	2006–2009	Medicines, diagnostics, trial management, others	Clinical trial data	Mean total cost difference between CT and SOC patients of € 4601 (95% confidence interval: € 94 - € 9109 p = 0.046)
[14]	France	Oncology - Haematology	27	III	177	2011–2016	Medicines	Mixed	Total cost savings were € 5218mi
									Mean cost saving per patient was € 19182.7 ± € 29865.7
[15]	Germany	Oncology	88	Un-specified	Un-specified	2002–2005	Medicines	Mixed	€ 5.1mi potential drug cost savings
									€ 1.5mi actual drug cost savings
[16]	Italy	Lung cancer	12	Un-specified	44	2010	Medicines, diagnostics	Clinical trial contract	€ 243154 drug cost savings
[17]	Italy	Oncology	34	I, II, III	126	2017	Medicines	Clinical trial protocol	Average hospital saving of € 5487 per patient treated in pharma sponsored studies and € 206 for investigator-led studies
									€ 517658 in a month for drugs that otherwise would have been loaded on the Italian National Health Service
[7]	Italy	Oncology - Haematology	29	II, III	189	2011–2016	Medicines	Mixed	Total avoided costs of € 330000
									Potential total avoided costs at national level would range from 320 to 360 million €/year
[18]	Spain	Lung cancer	12	I, II, III	69	2016	Medicines	Clinical trial data	The overall avoided cost was € 474428. 65. The average cost per clinical trial was € 39535.72 and per patient was € 6875.77
[19]	Spain	Prostate cancer	5	III	136	1996–2013	Medicines	Clinical trial data	€ 696002 total cost avoidance
									€ 139200 average cost avoidance per clinical trial

**Grey literature report on cumulative economic impact of industry trials in the USA in one year. §Side-effects costs*

Ref. ID	Country	Therapeutic Area	# of trials	Phase	# of patients	Year(s)	Cost items included (medicines, diagnostics, side effects, trial management, others)	Methods (clinical trial data / clinical trial protocol / mixed)	Main findings (total cost avoided / mean cost avoided per patient recruited)
									€ 5118 average cost avoidance per patient
[20]	Spain	Breast cancer	37	I, II, III	89	2014–2016	Medicines	Clinical trial protocol	80% of cost savings were derived from phase III trials
									€ 957246 total cost avoidance
									€ 10756 average cost avoidance per patient
[21]	Spain	Oncology	38	Un-specified	261	2017–2018	Medicines	Clinical trial (unspecified)	Avoided cost: € 3482662 / year; and what supposes € 13343/patient
[22]	Taiwan	Multiple	194	I, II, III, IV	2883	2008	Medicines	Clinical trial data	Average cost avoidance of € 39456/trial-year or € 26531/participant-year
[9]	Turkey	Multiple	174	I, II, III, IV	1437	2006–2010	Medicines	Clinical trial data	€ 212478657 government saving
[23]	UK	Oncology	53	II, III	357	2009–2010	Medicines, diagnostics, trial management, others	Clinical trial protocol	€ 436763 (2009) and € 344833 (2010) overall treatment cost savings
[24]*	USA	Multiple	6199	0, I, II, III, IV	1100000	2013	Medicines, diagnostics, trial management, others	Clinical trial data	Estimates of Overall Economic Impact of Industry-Sponsored Clinical Trial Activities at U.S. Trial Sites 2013:
									Direct – Research activities at clinical trial sites around the country € 7392 bn
									Indirect and Induced – Vendors and suppliers to trial sites; Consumer purchases by researchers and workers engaged in or supporting the clinical trial process € 11394 bn
									Total € 18787 bn
[25] §	USA	Lung cancer	4	III	31	2017	Medicines, diagnostics, trial management, side effects, others	Clinical trial data	The mean cost to treat an event of grade 3 nausea was € 12135 and the mean cost to treat an event of grade 3–4 thrombocytopenia was € 3678 when including hospitalization costs.
									The mean costs to treat an event of grade 3–4 thrombocytopenia combined excluding and including hospitalization costs were € 544885 (SD = € 1283.15) and € 3678 (SD = € 8418.80) respectively
[26]	USA	Oncology and AIDS	255	Un-specified	756	1996-97	Medicines	Clinical trial data	€ 2.7 mil cost avoidance in drug costs
[27]	USA	Multiple	107	Un-specified	Un-specified	2000–2002	Medicines	Mixed	Mean drug cost avoidance €2417117 per year

**Grey literature report on cumulative economic impact of industry trials in the USA in one year. §Side-effects costs*

In the remaining 19 publications, the number of clinical trials included ranged from 4 – 1,029 with recruitment of 44 – 23,331 patients. The majority (74%) of the publications report cost-savings on the cost of medicines, while the rest also include costs for diagnostics, clinical trial management, side effects, and other cost items. Costs were converted from the reported currencies to Euros using the average exchange rate of the year of the most recent data presented in each paper. Sources of information included clinical trial data (7 studies out of 19) and protocols (6 trials out of 19), four studies employed mixed methods (data and protocols), one extracted data from clinical trial contracts, while for one study the source of data was not available. The average cost savings on all cost items reported in the available evidence range from €47.43 to €49,301 per patient and from €575 to €968,000 per clinical trial. Avoided drug costs reported in studies measuring only medicine costs ranged from €1,746 to €49,301 per patient and from €10,588 to €193,259 per clinical trial. The total reported avoided costs ranged from €4,601 for 97 patients to €212.5 million for 14,370 patients. Finally, three studies [7, 8, 9] were able to provide projected annual cost avoidance estimates on a national scale which average to €217.7 million per year. As evidenced in Table 1, studies were included that reported total costs for multiple pathologies and multiple clinical trial phases. This is one of the reasons for the large range of cost avoidance found in the literature,

combined also with other factors such as the duration patients remain on a trial, which may vary across therapeutic areas, the number of days in each cycle a drug is administrated, the number of clinic visits, and the price of the drugs.

Since no evidence was found on the economic impact of CUP, our research aimed at filling the literature gap on the net economic impact of CUP from the perspective of the health care payer. Our research questions were: what would payers have paid for treating patients if they were not included into a CUP (averted costs thanks to CUP)? What are the incremental costs incurred by health care payers due to the CUP (incremental costs due to CUP)?

Methods

The research was carried out for patients enrolled in CUP launched by Roche in Italy from 2016 to 2020 (2,745 patients). These programs concerned 8 medicines / indications for cancer (1,641 patients, 59.8% of all patients), one for primary progressive multiple sclerosis (1,045, 38.1% of patients), and two for spinal muscular atrophy (59, 2.1% of all patients) (Table 2).

Table 2
Compassionate Use Programs considered in the analysis

# of CUP	Molecule	Indication	Indication (short)	# of patients
MO29499	Alectinib	Adult patients with Anaplastic Lymphoma Kinase (ALK)-positive advanced Non-Small Cell Lung Cancer (NSCLC)	Non-Small Cell Lung Cancer 1	21
MO40066	Alectinib	Adul patients with ALK-positive advanced NSCLC, previously treated with crizotinib	Non-Small Cell Lung Cancer 2	226
ML39740	Atezolizumab	Adult patients with locally advanced or metastatic Urothelial Carcinoma (UC) after prior platinum-containing chemotherapy, or considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%	Urothelial Carcinoma	222
AL41528	Atezolizumab	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy (patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before)	Non-Small Cell Lung Cancer	125
AL41712	Atezolizumab	Adult patients with unresectable locally advanced or metastatic Triple-Negative Breast Cancer (TNBC), whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease	Triple-Negative Breast Cancer	41
M029476	Cobimetinib	Adult patients with unresectable or metastatic Melanoma with a BRAF V600 mutation,	Melanoma	228
MA30130	Ocrelizumab	Adult patients with Primary Progressive Multiple Sclerosis (PPMS) (in terms of disease duration and level of disability) and with imaging features characteristic of inflammatory activity	Primary Progressive Multiple Sclerosis	1,045
AG40852	Entrectinib	Adult and paediatric patients 12 years of age and older with solid tumours expressing a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior NTRK inhibitor or who have no satisfactory treatment options	Solid tumours (NTRK)	1
		Adult patients with ROS1-positive advanced NSCLC, not previously treated with ROS1 inhibitors	Non-Small Cell Lung Cancer	5
AG40661	Polatuzumab Vedotin	Adult patints with relapsed/refractory Diffuse Large B-Cell Lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.It is indicated in combination with the treatment of adult patients with	Diffuse Large B-Cell Lymphoma	151
AG41381	Risdiplam	Patients from 2 months old with 5q spinal muscular atrophy (SMA) Type 1, Type 2 or Type 3, or those who have up to 4 copies of SMN2 gene (Type 1)	Spinal Muscular Atrophy Type 1	28
AG42025	Risdiplam	Patients from 2 months old with 5q Spinal Muscular Atrophy (SMA) Type 1, Type 2 or Type 3, or those who have up to 4 copies of SMN2 gene (Type 2)	Spinal Muscular Atrophy Type 2	31
AL41711	Trastuzumab emtansine	Adult patients with HER2-positive, unresectable locally advanced or metastatic Breast Cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: (i) received prior therapy for locally advanced or metastatic disease, or (ii) developed disease recurrence during or within six months of completing adjuvant therapy.	Breast Cancer	621
Total # of patients				2,745

The CUP database includes anonymised information on patients (gender and age), compassionate use treatment (CUT), medicines used in combination (duration, dose), side effects classified according to MedDRA® [28], their severity, and whether, according to the company providing the CUT and/or by the hosting health care centre, they were associated to the CUT (Table 3).

Table 3
Input data for the economic impact evaluation of CUP

# of CUP	Molecule	Indication (short)	Standard of Care	Combination medicines		Diagnostic test	Hospitilisations for side effects*
MO29499	Alectinib	Non-Small Cell Lung Cancer 1	Ceritinib (1) Crizotinib (2)	-		Partially used with the SoC	-
MO40066	Alectinib	Non-Small Cell Lung Cancer 2	Docetaxel (1) Pemetrexed low dosage (2) Pemetrexed high dosage (3) Ceritinib (4)	-		Used with the SoC	-
ML39740	Atezolizumab	Urothelial Carcinoma	Docetaxel (1) Nivolumab (2) Pembrolizumab (3)	-		Used with the SoC	7 (3.2%)
AL41528	Atezolizumab	Non-Small Cell Lung Cancer	Pemetrexed low dosage (1) Pemetrexed high dosage (2) Bevacizumab + carboplatino + paclitaxel (3)	-		Used with the SoC	1 (0.8%)
AL41712	Atezolizumab	Triple-Negative Breast Cancer	Nab-paclitaxel	Nab-paclitaxel	Covered by the sponsor	Covered by the sponsor	2 (4.9%)
M029476	Cobimetinib	Melanoma	Nivolumab (1) Vemurafenib (2) Dabrafenib + trabetinib (3)	Vemurafenib	Not covered by the sponsor	Used with the SoC	14 (6.1%)
MA30130	Ocrelizumab	Primary Progressive Multiple Sclerosis	Rituximab	-		Not covered by the sponsor	13 (1.2%)
AG40852	Entrectinib	Solid tumours (NTRK)	No	-		Not covered by the sponsor	-
		Non-Small Cell Lung Cancer	Crizotinib	-		Used with the SoC	-
AG40661	Polatuzumab Vedotin	Diffuse Large B-Cell Lymphoma	Bendamustine + rituximab (1) Lenalidomide (648 List) (2)	Bendamustine + rituximab	Covered by the sponsor	-	20 (13.2%)
AG41381	Risdiplam	Spinal Muscular Atrophy Type 1	Nusinersen	-		-	-
AG42025	Risdiplam	Spinal Muscular Atrophy Type 2	No	-		-	-
AL41711	Trastuzumab emtansine	Breast Cancer	Trastuzumab + Capecitabina (1) Lapatinib + Capecitabina (2)	-		Not covered by the sponsor	-
Total			2713 patients with SoC				57 (2.1%)

** # of patients / % of patients recruited*

Averted costs are represented by the SoC costs that would have been covered by health care providers if patients were not included in the CUP.

Costs generated by the CUP include:

- costs of medicines given in combination with CUT and not covered by the company providing CUT for CUP;
- costs of diagnostic procedures not covered by the company (procedure beyond the normal clinical practice) and that would have not been used with the SoC;
- costs of side effects generated by the CUT.

In principle, the economic impact evaluation should include the net economic effect of the CUT due to its impact on disease progression, compared to the SoC. However, the CUP dataset did not include data on the effectiveness of the CUT. Furthermore, were this data were available, they should have been, in most cases, extrapolated in the longer-term to capture the impact on averted costs. This extrapolation, beyond being out of scope, would have implied a case-control simulation, where for the 'control' arm (SoC or no treatment) data were not available.

Averted costs of the SoC were estimated in three steps.

First, we identified programs where the SoC did not exist when the patient started the CUT: this was the case of risdiplam for Type 2 Spinal Muscular Atrophy – SMA (31 patients) and entrectinib for solid tumours expressing a neurotrophic tyrosine receptor kinase – NTRK - gene fusion (1 patient).

Second, the SoC for all other CUT was identified on the grounds of pivotal studies for CUT (where SoC was used as an active comparator), European/National Guidelines, or Regional Documents, and was validated by clinicians.

Finally, the mean SoC cost per patient was estimated, i.e., unit price per dose * mean number of doses. In Italy, as in many other countries, public prices do not necessarily coincide with actual prices paid by hospitals, due to hidden discounts negotiated at central and regional levels and/or the effects of financial or outcome-based managed entry agreements (MEA) [29]. In 2017, discounts and MEA accounted for 25% and 12% of public price, respectively, for all medicines procured by hospitals [30]. As this information is not publicly available for each single medicine, we relied on actual prices published in regional documents, where those were available. Where they were not, we calculated the cost as the public price, due for all non-innovative medicines, i.e., net of the compulsory discounts (5 + 5%), per mg * unit dose retrieved from SmPC (Summary of Product Characteristics) in mg * median/mean treatment duration derived from SmPC or pivotal trials or other documents.

The cost of combination therapy not covered by the company providing the CUT was calculated for each patient as the price, i.e., net of compulsory discounts (5 + 5%), * unit dose from the CUP dataset * treatment duration from the CUP dataset.

In Italy, diagnostic procedures and inpatient care are reimbursed through fee-for-service and fee-for-episode schemes, respectively [31]. The fee-for-service for ambulatory care was monetized using the most updated regional fees [32, 33], because the national ones have not been updated since 1996 [34]. Hospitalisation fees were retrieved from the national database and are up to date as of 2012. Hospitalisations are classified according to the DRG – Diagnostic-Related Group – system (ICD-9-CM 2007 version and Medicare DRG classification 24th version) [35]. Labels used with MedDRA® do not correspond to a DRG classification, thus the e-DRGs platform [36] was used to associate the MedDRA® denomination with the relevant DRG (and fee).

Results

Input data are illustrated in Table 3: identified SoC; combination therapies - whether they are covered by the company providing the CUT or health care payers; diagnostic tests - whether they are covered by the company providing the CUT or used also with the SoC or covered by health care payers; hospitalisations due to side effects of the CUT or the relevant combination therapy. Side effects of CUT or combination therapies resulted in hospitalisation for 2.1% of patients.

Table 4 highlights the averted mean cost per patient due to avoided treatment with the SoC, and the mean cost increment for hospitals due to the CUP program. The former ranges from €3,002 (rituximab for Primary Progressive Multiple Sclerosis) to €200,000 (nusinersen for Type-1 SMA). Diagnostic tests are mostly either covered by the company or would have been used also with the SoC. The three exceptions are represented by:

Table 4
Mean averted and incremental cost per patient due to each CUP

# of CUP	Molecule	Indication	Mean cost per patient of SoC				Sources	Mean cost per patient of combination drugs	Mean cost per patients of diagnostic test	Mean cost per (recruited) patient of side effects	Mean cost per (hospitalised) patient of side effects
			SoC1	SoC2	SoC3	SoC4					
MO29499	Alectinib	Non-Small Cell Lung Cancer 1	20350 €	44,860 €	-	-	SoC1 [61]; SoC2 [61–62]	-	106 €	-	-
ML40066	Alectinib	Non-Small Cell Lung Cancer 2	2984 €	9,700 €	11,080 €	14,500 €	SoC1 [59–60] SoC2 and SoC3 [46] SoC4 [59]	-	-	-	-
ML39740	Atezolizumab	Urothelial Carcinoma	3674 €	12902 €	32223 €	-	SoC1 [54–55] SoC2 [56–57] SoC3 [57–58]	-	-	60 €	1922 €
AL41528	Atezolizumab	Non-Small Cell Lung Cancer	9395 €	10732 €	33229 €	-	SoC1 and SoC2 [46] SoC3 [43–45]	-	-	11 €	1404 €
AL41712	Atezolizumab	Triple-Negative Breast Cancer	7104 €	-	-	-	SoC1 [48–49]	-	-	90 €	1848 €
M029476	Cobimetinib	Melanoma	33824 €	39991 €	41274 €	-	SoC1 [51] SoC2 [50–51] SoC3 [51]	16086 €	-	125 €	2029 €
MA30130	Ocrelizumab	Primary Progressive Multiple Sclerosis	3002 €	-	-	-	SoC1 [52–53]	-	20 €	27 €	2139 €
AG40852	Entrectinib	Non-Small Cell Lung Cancer	79019 €	-	-	-	SoC1 [61]	-	-	-	-
AG40661	Polatuzumab Vedotin	Diffuse Large B-Cell Lymphoma	55583 €	56658 €	-	-	SoC1 [36–41] SoC2 [3842]	-	-	151 €	2488 €
AG41381	Risdiplam	Spinal Muscular Atrophy Type 1	200000 €	-	-	-	SoC1 [63]	-	-	-	-
AL41711	Trastuzumab emtansine	Breast Cancer	3780 €	19576 €	-	-	SoC1 and SoC2 [47]	-	253 €	-	-
Total										45 €	2184 €

- IHC (Immuno-Histo-Chemistry) and follow-up bilirubin and albumin protein (alectinib for adult patients with Anaplastic Lymphoma Kinase (ALK)-positive advanced Non-Small Cell Lung Cancer - NSCLC);

- Hepatitis B testing to identify patients at risk of reactivation with ocrelizumab;
- Fluorescent In-Situ Hybridization (FISH) for trastuzumab emtansine.

The mean cost per hospitalised patient due to adverse events amounts to €2,184, ranging from €1,404 to €2,488 (Table 4). As 57 patients presented severe side effects resulting in hospitalisation, the mean cost per patient equals to €45.
The mean averted cost per patient due to avoided use of the SoC ranged from €11,415 to €20,299 and from €13,555 to €28,235 for all programs and cancer CUP, respectively. The mean incremental cost of all CUP (combination therapies, diagnostic tests, and hospitalisations due to side effects) amounted to €1,646, and to €2,694 for cancer CUPs. Total savings for payers ranged from €26.5 million (€17.8 for cancer CUP) to €50.6 million (€41.9 million for cancer CUPs) (Table 5). Mean savings per patient ranged from €10,861 to €25,559.

Table 5
Mean and total averted, incremental cost and net costs of CUP

All programs (2713 patients)			
		Min	**Max**
Averted cost			
Mean cost per patient of SoC	a	11,415 €	20,299 €
Total costs of SoC	b	30,967,593 €	55,072,260 €
Incremental cost*			
Mean cost per patient of CUP	c	1,646 €	
Total cost of CUP	d	4,466,187 €	
Net cost			
Net cost per patient	e = c-a	-9,768 €	-18,653 €
Total net costs	f = d-b	-26,501,406 €	-50,606,073 €
Onco programs (1640 patients)			
		Min	**Max**
Averted cost			
Mean cost per patient of SoC	g	13,555 €	28,253 €
Total costs of SoC	h	22,230,423 €	46,335,090 €
Incremental cost*			
Mean cost per patient of CUP	i	2,694 €	
Total cost of CUP	j	4,418,000 €	
Net cost			
Net cost per patient	k = i-g	-10,861 €	-25,559 €
Total net costs	l = j-h	-17,812,424 €	-41,917,091 €

Appendix 1 lists the averted costs, incremental costs, and net costs for each CUP. Net costs are mostly driven by the mean averted cost of the SoC, and the number of patients recruited in the CUP.

Discussion

This paper has investigated, for the first time in the literature, the economic consequences of 11 CUP for medicines from the perspective of health care payers in Italy. Avoided costs of treating patients with the SoC, if existing and reimbursed, incremental costs of diagnostics, combination therapies, and side effects of CUT were included. Savings generated by the CUP ranged from €26.5 million (€10.9k per patient) to €50.5 million (€25.6k per patient), depending on the SoC used as an alternative to the CUT.

These findings cannot be fully compared with the economic impact of a CT. If Italian studies on CT are considered, including only medicines [7, 17] and diagnostic procedures [17], the mean savings per patient treated are higher in our findings. This is mainly caused by the higher cost of the hypothetical SoC used in clinical practice.

It is important that policy makers and health care managers appropriately and carefully consider this evidence.

First, the findings represent costs avoided from the perspective of health care payers and not of the society as a whole.

Secondly, incremental costs, despite quite negligible, are costs generated by CUP, whereas avoided costs are contingent upon the actual use of alternative treatments.

Thirdly, costs of medicines are variable and coincide with expenditure. Costs of diagnostic testing and inpatient care have been estimated using the respective fee-for-service/episode. Fees represent a cost/expenditure for payers, whereas, from the perspective of providers, they represent revenue and do not necessarily correspond to cost.

Finally, net savings from compassionate use should not justify delays in decision-making on P&R upon approval of the medicine, on the grounds of shifting the burden from the payer to the industry. In principle, any early access program, like compassionate use, should terminate when the drug is approved. However, delays in P&R decisions [65] have resulted in pharmaceutical companies prolonging CUP, to avoid interruptions in the continuity of care. Further, companies should not expect to secure reimbursement and/or a higher price for their medicines on the grounds of the latter's subjection into a CUP. On the one hand, not all medicines used in CUP were approved for reimbursement in Italy. On the other hand, prices should reflect value [66] and not whether the relevant medicine has been granted an early access.

Our study has some limitations.

The first and most important one is that we have not estimated the future impact on costs of CUT compared to the SoC. CUP are not accompanied by systematic collection of data on effectiveness and resource consumption (apart from diagnostic testing and hospitalisations due to adverse events). An estimation of future net costs of the CUT would have required to adapt, through micro-simulation, published cost-effectiveness analyses on patients treated in CUP. Such a "dynamic" study was out of scope as our objective was to estimate the costs incurred throughout the duration of CUPs but not after. In addition, should we have adapted existing evidence from cost-effectiveness studies comparing the CUT to the SoC, we would be able to rely only on one study conducted in Italy [67].

Secondly, our analysis adopted the perspective of health care payers. To this end, the impact of CUP on other third payers (e.g., social insurance schemes for absence from work) and patients and their relatives (e.g., remunerated / informal care provided) was not considered. Indeed, for some diseases, like multiple sclerosis, costs beyond health care may play an important role.

Thirdly, since the comparative impact on disease progression and future cost avoidance were not included, we did not carry out an economic impact analysis where no alternative to the CUT was available. The scientific understanding of key molecular pathways and the development of new molecular entities in most of the diseases targeted by the examined CUP present opportunities to fill unmet needs, even in areas with already existing alternatives.

The absence of a long-term follow-up of patients recruited in CUP did not allow for the evaluation of the CUP effects on therapeutic sequencing. It may happen that the SoC is used after the CUT, or vice versa when patients are not recruited in the CUP (i.e., they are first treated with the SoC and after with the CUT, once it has been approved for reimbursement).

Furthermore, our analysis did not include an estimate of the cost of adverse events for the SoC, that should have been retrieved from the literature (unless it is used as a comparator in trials for the CUT). We are not able to conclude on whether this averted cost would have compensated the incremental cost of treating side effects of CUT that have not produced a hospitalisation, as this was not considered in the present analysis. We were also not always able to include the effect of discounts and MEA in the calculation of the cost of the SoC. Finally, the costs of nusinersen for Type-1 Spinal Muscular Atrophy refer to data from the first year of treatment, since real world data on treatment duration beyond the first year were not available.

Incremental costs for diagnostic procedures were estimated on the grounds of the presumed clinical practice with the SoC and assuming maximum impact for the health care payers. For example, we decided to include (i) IHC (Immuno-Histo-Chemistry) to detect Anaplastic Lymphoma Kinase (ALK)-positive, despite its use with crizotinib as an alternative to alectinib for adult patients with advanced NSCLC and (ii) FISH for trastuzumab emtansine, despite its with trastuzumab as a neo-adjuvant therapy. If the cost of these two diagnostic procedures were eliminated, the incremental cost would decrease from €4.5 million to €4.3 million with a net economic benefit ranging from €26.7 million (instead of €26.5) to €50.8 million (instead of €50.6 million).

Finally, while different SoC were identified, we did not have any information on their use in clinical practice. This information could have allowed for the calculation of a weighted mean cost per patient receiving the respective SoC. Thus, we are only able to provide a minimum and maximum average averted cost per patient, where the actual mean cost depends on the present market share of each single SoC.

Nevertheless, despite these limitations, this paper constitutes the first evidence on the economic advantages of the compassionate use of medicines.

Conclusion

CUP have been introduced to guarantee earlier access to medicines for patients not recruited in trials, responding to the ethical imperative of facing unmet needs. In this paper, we have also demonstrated that CUP have important advantages from an economic viewpoint. Beyond their economic impact, they can serve as an important source of data, enhancing information availability during the approval and pricing and reimbursement (P&R) processes. This, however, would imply more systematic data collection, including on clinical outcomes and on the impact from the perspective of patients, as well as on health resources. Such 'piggy-back' data collection would also inform a more comprehensive economic evaluation of these programs.

In conclusion, CUP for medicines represent an opportunity to accelerate patient access to medicines for rare and severe diseases, in cases where patients have not been recruited or are not eligible for recruitment in clinical trials. For clinicians who have not been involved in clinical trials, they represent an opportunity to

familiarise with medicines likely to become available in clinical practice. For health payers they present also cost saving opportunities for health payers and these savings could be larger if the societal perspective is considered.

Abbreviations

- ALK Anaplastic Lymphoma Kinase
- CUP Compassionate Use Program(s)
- CT Clinical Trial(s)
- CUT Compassionate Use Treatment(s)
- DCA Drug Cost Avoidance
- FISH Fluorescent In Situ Hybridization
- DLBCL Diffuse Large B-Cell Lymphoma
- DRG Diagnosis-Related Group
- IHC Immuno-Histo-Chemistry
- MEA Managed Entry Agreements
- MedDRA Medical Dictionary for Regulatory Activities
- NSCLC Non-Small Cell Lung Cancer
- NTRK Neurotrophic Tyrosine Receptor Kinase
- PCA Pathology Cost Avoidance
- P&R Price & Reimbursement
- PPMS Primary Progressive Multiple Sclerosis
- SMA Spinal Muscular Atrophy
- SoC Standard of Care
- TNBC Triple-Negative Breast Cancer
- UC Urothelial Carcinoma

Declarations

Ethics approval

This study does not require ethics approval and consent to participate.

Consent for publication

Consent for publication is not needed.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

- CJ received research grants from Abbvie, Alnylam, Amgen, Astrazeneca, Bayer, BMS, Boehringer I, Celgene, EuroQoL Foundation, FSK, Gilead, Janssen C, MSD, Novartis, Roche, Pfizer, Sandoz, Sanofi, Takeda, Teva for his research activity and acted as a speaker and or consultant for Amgen, Astrazeneca, BMS, Celgene, CSL Behring, Dephaforum, Gilead, Incyte, MA Provider, MSD, Roche, Sanofi, Takeda, Wellmera (now Alira Health).
- FP and LS are employed by Roche Italy.
- MC received research grants from Amgen, Novartis and Roche for her research activity.
- MV declares no competing interests.

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Authors' contributions

- CJ co-designed the work, contributed to the analysis and data interpretation, and drafted the paper (with the exception of the 'Background Section').
- FP and LS worked on data extraction, contributed to interpretation of data and revised the paper.
- MC co-designed the work, contributed to the analysis and data interpretation and revised the paper.
- MV drafted the 'Background section' of the paper, contributed to data interpretation and revised the paper.

- All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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