Variation in the prices of oncology medicines across Europe and the implications for the future

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Abstract

Introduction/ Objectives: There are increasing concerns among health authorities regarding the sustainability of healthcare systems with growing expenditure on medicines including new high-priced oncology medicines. Medicine prices among European countries may be adversely affected by their population size and economic power to negotiate. There are also concerns that prices of patented medicines do not change once the prices of medicines used for negotiations substantially change. This needs to be investigated as part of the implications of low-cost generic oncology medicines. **Methodology**: Analysing principally reimbursed prices of patented oral oncology medicines (imatinib, erlotinib and fludarabine) between 2013 and 2017 across Europe and exploring correlations between GDP, population size, and prices. Comparing the findings with previous research regarding prices of oral generic oncology medicines. **Results**: The prices of imatinib, erlotinib and fludarabine did vary among European countries but showed limited price erosion over time in the absence of generics. There appeared to be no correlation between population size and prices. However, higher prices were seen among countries with higher GDP per capita which is a concern for lower income countries referencing these. **Discussion and Conclusion**: It is likely that the limited price erosion for patented oncology medicines will change across

Europe with increased scrutiny over their prices and value as more medicines used for pricing decisions lose their patents combined with growing pressures on the oncology drug budget. In addition, discussions will continue regarding fair pricing for new oncology medicines and other approaches given ever rising prices with research showing substantial price reductions for oral oncology medicines (up to -97.8% for imatinib) once generics become available. We are also seeing appreciable price reductions for biosimilars further increasing the likelihood of these developments.

1. Introduction

Expenditure on medicines has risen across countries in recent years, driven principally by increased prescribing volumes and increasing prices for new medicines especially those for oncology and orphan diseases (1-4). Prices of new oncology medicines have risen by ten-fold or more during the last decade (5-8), with prices per life year gained for new oncology medicines rising four-fold during the past twenty years after adjusting for inflation (6, 9). As a result, expenditure on oncology medicines now dominate pharmaceutical expenditure in high income countries, which will continue with over 500 companies actively pursuing new oncology medicines in over 600 indications (10, 11) with envisaged high price expectations (12, 13). Overall, global expenditure on oncology medicines is estimated to reach $237 billion by 2024 (14), with the cost of cancer care already accounting for up to 30% of total hospital expenditure across Europe and rising (15, 16).

This growth in expenditure on oncology medicines is putting considerable strain on European healthcare systems with their universal access unless this is addressed (4, 13, 17, 18). This is leading to calls that high prices for new oncology medicines need to be increasingly linked to a minimum improvement in clinical benefit including a minimum of three to six months additional survival versus existing regimens with even three months seen as a marginal clinical benefit (19-23). This is because European countries have funded new cancer medicines at high prices in recent years despite limited health gain and formal pricing and reimbursement processes among European them (23-26), exacerbated by the emotive nature of the disease area (12). These concerns are also leading to calls for alternative pricing and funding approaches towards new oncology medicines in Europe and wider, which include fair pricing models (25, 27-31). Fair pricing models necessarily include greater transparency in how prices are set, which is a continuing goal of the World Health Organisation (WHO) to improve access to new medicines for all patients including those for cancer (32, 33). Calls for increased transparency have also grown in recent years with greater knowledge of the low cost of goods (cost of ingredients and manufacturing) of some new cancer medicines as well as appreciable discounting by pharmaceutical companies for their biological medicines when faced with biosimilar competition (27, 34, 35). The situation is even more critical in the USA with continuing price rises for existing patented oncology medicines as well as a continuing increase in the requested price of new cancer medicines as a result of no formal pricing and reimbursement processes, leading to oncologists requesting moderation in the prices of new oncology medicines (36). However, this has failed to currently materialise reflected by estimations of US$39.5 billion for the net expenditure on 46 new oncology medicines approved in 2018 in the USA, 17 for novel drugs and 29 new indications, if all eligible patients received them (37). Potential expenditure on oncology medicines would be even greater in recent years as this figure doe not include expenditure on the other oncology medicines (37).

Once prices for medicines are established in Europe, there appears to be limited price erosion until multiple sources become available unlike the situation in the USA (38, 39). There also appears to be limited differences among European countries regarding prices for patented biological oncology medicines, with Vogler *et al* (2017) only demonstrating a 13% difference among 16 European countries for prices including bevacizumab and ipilimumab. However, they found greater differences for lower priced medicines (40). Similarly, Vokinger *et al.* (2020) observed limited differences in the monthly treatment costs for new oncology medicines among European countries; however, costs of medicines in the USA were a median of 2.31 times higher than those seen in Europe reflecting the current lack of pricing controls in the USA (39, 41). The situation in Europe may reflect extensive external referencing pricing for new medicines (25, 42), although we have seen considerable differences in the pricing of multiple sourced oncology medicines among European countries (43).

Consequently, we wanted to build on the recent findings of Vogler *et al* (2017), Vogler *et al* (2019) and Vokinger *et al.* (2020) to review the prices of oral cancer medicines over time among European countries to provide future direction to health authorities (38, 40, 41). This also involves assessing the

potential influence of Gross Domestic Product (GDP) and population sizes on the reimbursed prices of patented medicines across Europe in view of concerns that countries with smaller populations and less economic power could suffer in negotiations with resultant higher prices acknowledging though extensive external reference pricing across Europe (41, 42). These concerns were the trigger for cross country consortia to develop across Europe to enhance countries' negotiating powera for new premium priced medicines, which currently include Beneluxa, Valleta and the Nordic consortium (33, 44-46). We are aware though from our earlier findings that the prices of oral generic cancer medicines across Europe were not dependant on population sizes or the economic status of countries; however, they did fall over time with some appreciable reductions observed (43). This though may be different for patent protected oral cancer medicines. We believe the combined findings should stimulate debate about future reimbursement and pricing of existing patented oncology medicines as more oncology medicines lose their patents potentially appreciably altering their cost-effectiveness and overall value. In addition, we believe the findings can further stimulate debates regarding possible new approaches to the pricing of new oncology medicines in Europe including fair pricing models given the unsustainability of the current system. This builds on current initiatives from the WHO, European Commission and European insurers to push for greater transparency in pricing negotiations (18, 22, 28, 33).

We have chosen to concentrate on Europe for this combined research in view of their goals of equitable and universal healthcare, growing concerns with expenditure on new oncology medicines and those for orphan diseases, and multiple ongoing activities to improve the efficiency and quality of prescribing for both new and established medicines (20, 21, 25, 47-51). European countries also have formal pricing and reimbursement processes with input from health technology agencies and others, with processes the jurisdiction of each Member State, to review and refine future approaches (25, 39, 52). This contrasts with the USA with currently no formal pricing and reimbursement systems, with concerns that the system is not working leading to spending on medicines currently accounting for over 40% of global pharmaceutical spend despite the USA only having 4.5% of the world's population (39). In addition, increasing calls from US groups for the government to consider approaches and systems from among European and other countries going forward given the unsustainability of their current system (39). We have adopted a payer perspective for our research as they are key personnel involved in funding and reimbursement decisions for new oncology medicines across Europe. As a result, we used health authority databases for the combined research as they are regularly audited and reflect the prices paid by health authorities for their medicines with or without Value Added Tax (VAT) depending on the country (43, 53-55).

2. Methodology

The methodology has been extensively discussed in the first paper of Godman et al. (43). The European countries involved included: Albania, Austria, Belgium, B & H (Republic of Srpska), Bulgaria, Cyprus, Estonia, France, Germany, Greece, Italy, Kosovo, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Romania, Serbia, Slovenia, Slovakia, Spain (represented by pricing data from Catalonia with list prices similar across Spain), Sweden, and the United Kingdom (UK), which is represented by Scotland with tariff prices consistent across the UK. These countries were chosen since they not only represent a wide range of geographies, populations and GDP, but were also able to provide robust data from their administrative databases. Pricing data from health authorities is seen as reliable and robust since, as mentioned, their systems are regularly audited (43, 56). We have also used this approach in previous multiple cross-national publications when assessing utilisation and expenditure patterns for different medicines and disease areas across Europe (43, 53-55, 57-59).

This paper will principally concentrate on reimbursed prices for imatinib (L01XE01), erlotinib (L01XE03) and fludarabine (L01BB05) (60) among Western European countries since there were no generics available for these oral oncology medicines in 2015 for imatinib or 2017 for erlotinib and fludarabine, and external reference pricing is used to a lesser extent in these countries (42, 43, 53). The later availability of generics for these oral cancer medicines among Western European countries enables a longer time period to monitor any price erosion. This builds on the earlier findings of Godman et al. (43), which involved assessing reimbursed prices for generic busulfan (L01AB01), capecitabine (L01BC06), chlorambucil (L01AA02), cyclophosphamide (L01AA01), flutamide (L02BB01), imatinib (L01XE01), melphalan (L01AA03), and temozolomide (L01AX03) over time across Europe (43).

Reimbursed prices were used where possible since, as mentioned, the perspective of this paper is that of European health authorities. However, in a minority of countries procured and total prices were used, e.g. Kosovo. This is because it was impossible to break the prices down into individual components. Total prices include pharmacy remuneration and any patient co-payments. In some countries, VAT was also included in the price depending on the situation in the country. Again, it was difficult to deduct this proportion from the prices provided. Documented prices could also include any discounted prices arising from managed entry agreements (MEAs) sometimes referred to as risk sharing arrangements (51, 61). However, these were rare for individual oncology medicines in Europe before the recent rapid rises in requested prices of new oncology medicines to enhance their affordability and subsequent reimbursement (61-64). We are aware in some countries that reimbursed prices were listed but the medicines are typically dispensed in hospitals where further confidential discounts are provided, e.g. Norway and Italy, which are typically confidential.

In general, reimbursed prices were collected between 2013 and 2017 based on tablet strength. Tablet strength was chosen for comparative purposes as opposed to defined daily doses that we have used in previous cross-national research projects (53-55, 57, 58) as generally there are no defined daily doses (DDDs) for oral cancer medicines (60). The actual tablet strength chosen reflects the most used strength in a number of European countries for patients with cancer.

Initially prices were documented in the country's currency if not listed in Euros. Subsequently, where relevant, prices were converted to Euros for comparison purposes based on current exchange rates and validated by the co-authors to enhance the robustness of the findings (43, 65-72). Prices were subsequently converted to US$ based on mid-year European Central Bank exchange rates for comparison purposes with GDP per capita based principally on OECD data for 2015 and 2017 (73-75). However, prices were retained in Euros when calculating any price erosion of the patented oral oncology medicines over time. Euros were also used for comparing prices of oral generic cancer medicines as one of the principal aims of this paper was to compare prices across countries as well as any price reductions achieved (43).

The OECD was the principal source for data on GDP per capita in US$ in 2015 and 2017 (current prices and purchasing price parity) (73). This data was supplemented with additional data, e.g. Albania, Cyprus – 2018, Kosovo, Malta, Romania, and Serbia, where necessary (76-79). Data from the OECD was also principally used for population sizes in 2015 and 2017 for consistency; however, data from other sources was also used where pertinent (80-86). Country abbreviations were based on the International Organization for Standardization abbreviations (Table 1A in the Appendix) (87).

Differences in country prices were visualised as violin plots to enhance interpretation of the data. Non-parametric Spearman's rank tests were used to assess any correlation between prices of these three originator medicines and country's population size as well as their GDP per capita. The correlations were presented as Spearman's rank correlation coefficient which ranges from –1 (perfect negative correlation) to +1 (perfect positive correlation). A p-value less than 0.05 was considered statistically significant. The correlations were also visually presented using scatter plots. Calculations were performed using the software R 3.6.1 (88).

No ethical approval was needed as we were dealing with aggregated anonymised data in accordance with previous studies undertaken by the co-authors using administrative databases (43, 47, 54, 57, 89). The definition of terms used such as external reference pricing, MEAs, and value-based pricing, follow those in Vogler et al (2019) for reforms and initiatives introduced across Europe (25).

3. Results

3.1 Prices of oral generic cancer medicines across Europe

The study of Godman et al (2019) showed that there were variable approaches to the pricing of generic oral oncology medicines across Europe, similar to the situation generally for the pricing of generic medicines (43, 50, 53, 90, 91). The different approaches can be consolidated into three categories (43), and include:

- prescriptive pricing policies (price regulated market), i.e. policies with established percentage reductions for successive generics

- market forces (free market) where there is typically free pricing for generics with market forces helping to drive down prices
- mixed approach (combination) which incorporates prescriptive approaches, market forces and other mechanisms including external reference pricing among selected European countries with external reference pricing common across Europe

The differences in the adopted approaches among the various European countries resulted in appreciable differences in subsequent reimbursed prices for oral generic oncology medicines across Europe as well as appreciable differences in the price reductions seen in a number of European countries versus pre-patent loss prices (Box 1).

Box 1 – Reimbursed prices for oral generic oncology tablets across Europe in 2017 and price reductions over time (43).

A) Reimbursed prices in 2017

- Prices per 500mg capecitabine generic tablets ranged from €0.21 in Poland and €0.31 in Malta up to €2.46 in the United Kingdom (UK).
- Prices for 250mg flutamide generic tablets ranged from €0.16 in Poland and €0.23 in Greece up to €1.43 in the UK.
- Prices for temozolomide 20mg generic tablets ranged from €0.86 in Poland and €2.28 in Romania up to €17.64 in France.
- Prices of temozolomide 250mg generic tablets ranged from €9.47 in Poland and €25.87 in Sweden up to €220.52 in France.

B) Price reductions

- Reimbursed prices of generic capecitabine among European countries in 2017 were up to 93.1% below 2013 originator prices. These varied from a reduction of only 7.1% in one European country up to an ultimate price reduction of 93.1% for the multiple sourced medicine versus pre-patent loss prices.
- Reimbursed prices of generic imatinib were up to 97.8% below originator 2013 prices. These varied from a limited reduction of only 3.4% up to an appreciable reduction of 97.8% versus pre-patent loss prices.
- Reimbursed prices of generic temozolomide 20mg were up to 80.7% below 2013 originator prices. These again varied considerably depending when generic temozolomide first became available. In the case of 20mg temozolomide, these varied from no reduction up to a maximum reduction of 80.7%; the maximum reduction for 250mg was similar at 79.6%

Reimbursed prices were not indication specific, i.e. there were no differential prices once the first indication had lost its patent. In addition, the prices seen for the oral generic oncology medicines in 2017 did not appear to be affected by the population size of a country or typically by its wealth (Central and Eastern Europe versus Western European countries) compared to previous beliefs (43, 92). There were also no concerns with substitution with oral generic oncology medicines (43). This is encouraging as there have been concerns with substitution of some medicines including lithium, modified release calcium antagonists and medicines for epilepsy in view of possible issues with effectiveness and side-effects with different formulations, which limits the extent of savings ince generics become available (93).

3.2 Prices of oral originator cancer medicines across Europe

3.2.1 Imatinib

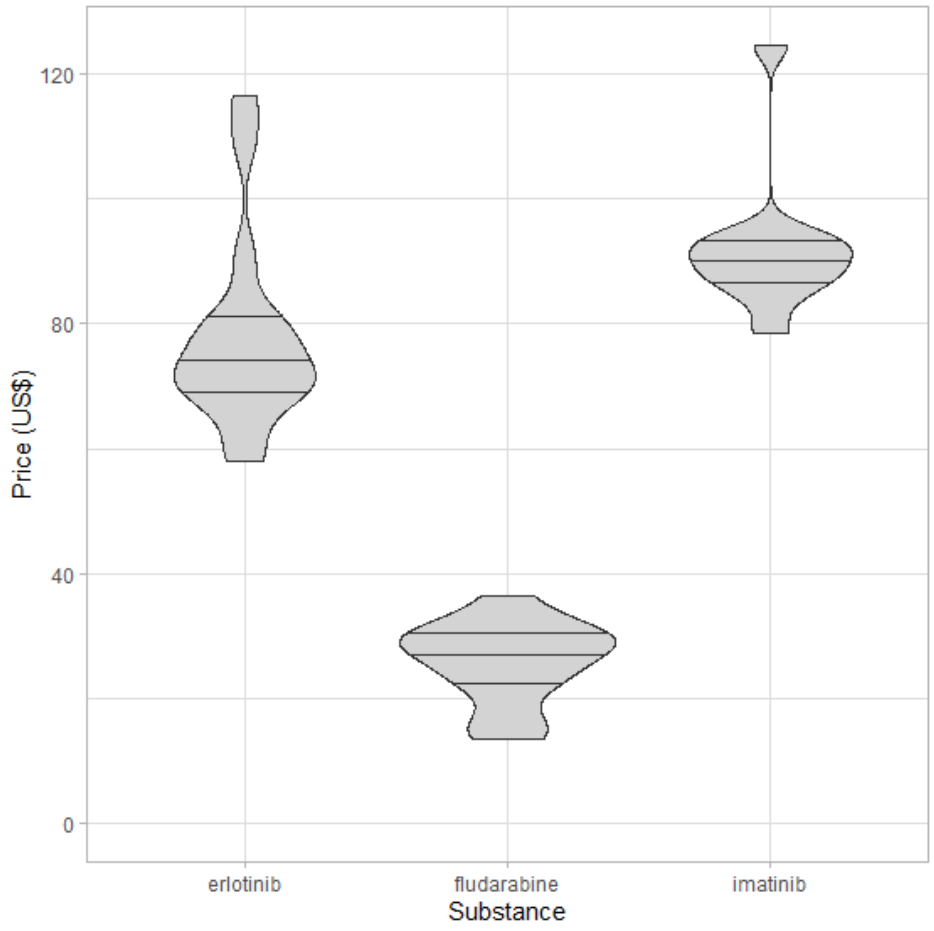
Table 1 documents the prices for originator 400mg imatinib among Western European countries in 2015 before generic availability, with Figure 1 depicting the spread of prices across the studied countries. This was because generic imatinib was already available in CEE countries before this, e.g. Albania, Estonia, Latvia, Lithuania, Romania, Serbia and Slovakia in 2013 or before, and in Poland and Slovenia in 2014 (43), and originator prices typically fall in these countries once generics become availabe (43, 50, 90).

Table 1 – Price per tablet (US$) for originator imatinib 400mg among 11 European countries in 2015 where no generic imatinib was available

Country	Price (US$)	Population (mn)	GDP per Capita (US$)	VAT Included
Cyprus	90.13	1.17	23248	Yes
Norway	88.81	5.17	60492	Yes
Austria	94.21	8.59	49954	No
Sweden	94.25	9.75	48437	No
Greece	78.60	10.86	26902	Yes
Belgium	92.17	11.24	45739	No
Netherlands	92.02	16.90	50302	No
Spain	87.65	46.45	35054	Yes
UK	86.77	64.85	42055	No
France	84.00	66.46	40841	Yes
Germany	124.68	81.20	47979	Yes
Median	90.13	11.24	45739	

All values for 2015. Conversion rate: €1 = US$ 1.1100 (mid 2015). VAT included where social security organisations are subject to VAT. Countries in order of population size. Abbreviations: mn = million; VAT = value added tax

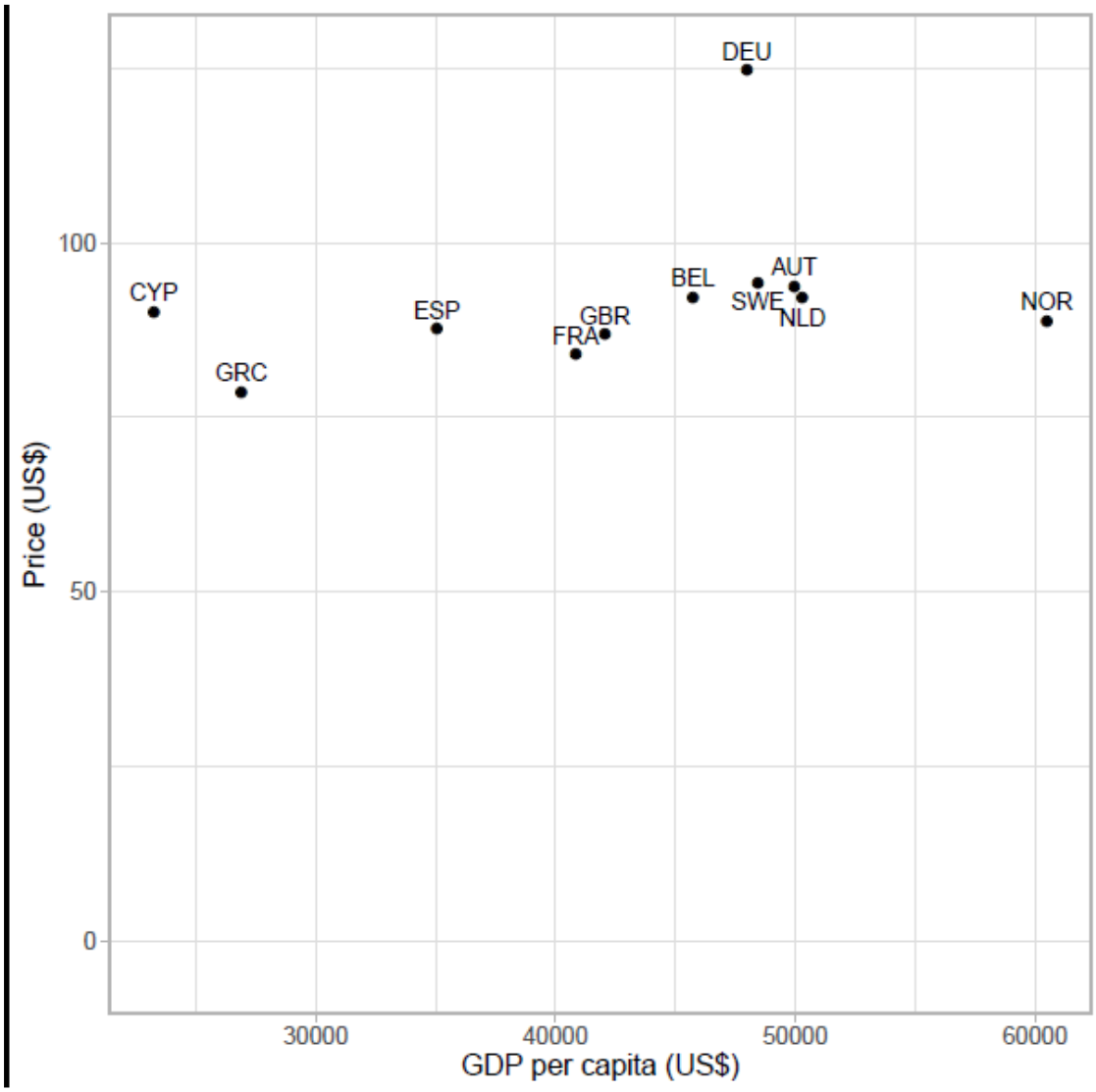
Figure 1 – Violin plots of the originator price distributions for the three substances studied, in the respective years (2015 and 2017)



Horizontal lines within the violins mark the quartiles.

Whilst the minimum price of imatinib was 12.8% below and the maximum price 4.6% above (excluding the outlier Germany at +38.3%) the median price (US$90.13), the results of the Spearman's rank test indicated no correlation (r= –0.100; p=0.776) between the price of imatinib and the countries' population size (Appendix Figure 1 A). However, there was a moderate positive correlation approaching significance (r= +0.527; p=0.100) between imatinib prices and GDP per capita (Figure 2).

Figure 2 – Scatter plot of originator imatinib prices against GDP per capita for 11 European countries where no generic imatinib existed in 2015



3.2.2 Erlotinib

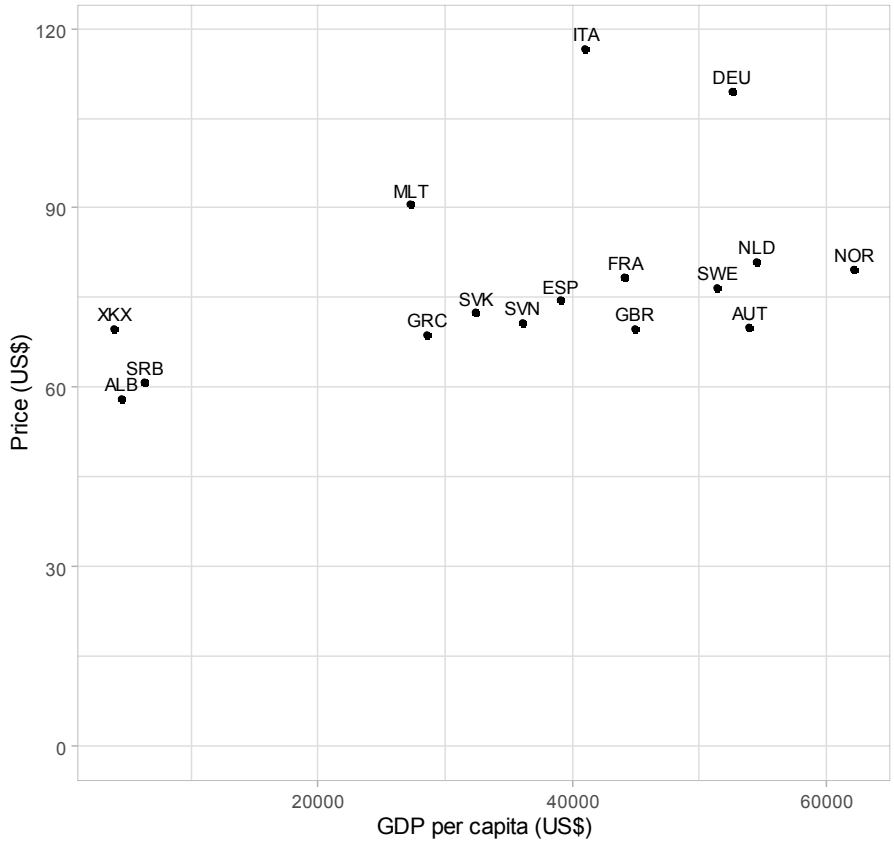
Generic erlotinib (150mg) was not available among the studied Western European countries as well as a number of CEE countries in 2017 (43). Consequently, we were able to survey prices among 16 European countries. Whilst prices varied from 20.9% below to 23.2% above (disregarding the outliers Germany and Italy at 49.0% and 58.8% respectively) the median price (73.44 US$; Table 2; Figure 1), we found no significant correlation (r=0.303; p=0.253) between the prices of erlotinib and countries' population size (Figure 2A in the Appendix). On the other hand, there was a significant moderate positive correlation (r=0.532; p=0.036) between erlotinib prices and GDP per capita (Figure 3).

Table 2 – Price per tablet (US$) for originator erlotinib 150mg among 16 European countries in 2017 where no generic erlotinib was available

Country	Price (US$)	Population (mn)	GDP per Capita (US$)	VAT Included
Malta	90.50	0.44	27241	No
Kosovo	69.73	1.83	3948	No
Slovenia	70.77	2.07	36163	No
Albania	58.08	2.87	4533	No
Norway	79.72	5.26	62182	Yes
Slovakia	72.41	5.44	32376	Yes
Serbia	60.92	7.10	6284	Yes
Austria	69.99	8.77	53895	No
Sweden	76.72	10.00	51405	No
Greece	68.83	10.77	28580	Yes
Netherlands	80.96	17.08	54504	No
Spain	74.47	46.53	39087	Yes
Italy	116.62	60.59	40981	Yes
UK	69.68	65.84	44909	No
France	78.51	66.80	44125	Yes
Germany	109.44	82.52	52574	Yes
Median	73.44	9.38	40034	

All values for 2017. Conversion rate: €1 = US$ 1.1369 (mid 2017). VAT included where social security organisations are subject to VAT. Countries in order of population size. Abbreviations: mn = million; VAT = value added tax

Figure 3 – Scatter plot of originator erlotinib prices against GDP per capita for 16 European countries where no generic erlotinib existed in 2017



There were limited differences in prices for originator erlotinib over time among the various Western European countries (Table 2). However once multiple versions become available, we would expect prices to fall rapidly as seen with generic erlotinib in the Republic of Srpska in 2017 (26.9% below 2013 originator prices), Bulgaria (34.3% below), Romania (45.7% below) and Lithuania (54.4% below 2013 originator prices) as well as with other oral cancer medicines in Europe following generic availability (43).

3.2.3 Fludarabine

Generic fludarabine was not available among Western European countries and a number of CEE countries in 2017. As a result, we were able to include prices from 16 European countries in the analysis.

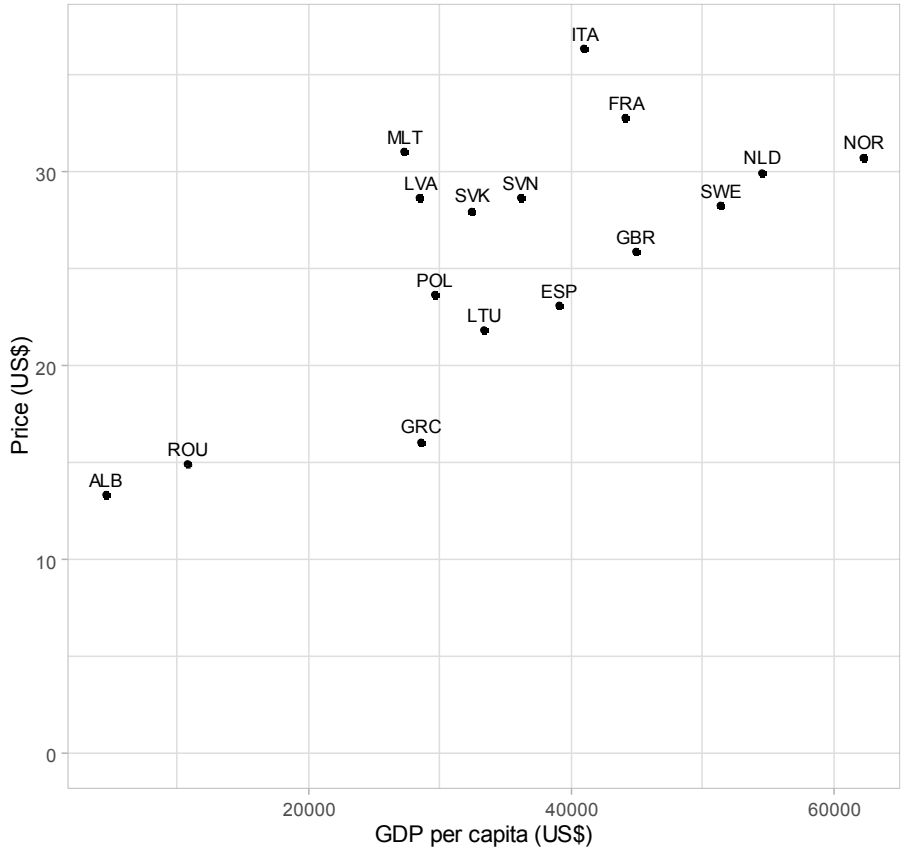
Documented prices (Table 3; Figure 1) ranged from 53% below to 29% above the median (28.09 US$). Again, we found no correlation (r=0.035; p=0.900) between the price of fludarabine and the countries' population size (Figure 3A). However, a significant moderate positive correlation (r=0.515; p=0.044) was observed between fludarabine prices and GDP per capita (Figure 4).

Table 3 – Price per tablet (US$) for originator fludarabine 10mg in 2017 among 16 European countries in 2017 where no generic fludarabine was available

Country	Price (US$)	Population (mn)	GDP per Capita (US$)	VAT Included
Malta	31.01	0.44	27241	No
Latvia	28.65	1.95	28378	Yes
Slovenia	28.62	2.07	36163	No
Lithuania	21.83	2.85	33325	Yes
Albania	13.32	2.87	4533	No
Norway	30.74	5.26	62182	Yes
Slovakia	27.96	5.44	32376	Yes
Sweden	28.23	10.00	51405	No
Greece	16.05	10.77	28580	Yes
Netherlands	29.96	17.08	54504	No
Romania	14.93	19.64	10793	Yes
Poland	23.64	37.97	29583	Yes
Spain	23.10	46.53	39087	Yes
Italy	36.34	60.59	40981	Yes
UK	25.84	65.84	44909	No
France	32.80	66.80	44125	Yes
Median	28.09	10.38	34744	

All values for 2017. Conversion rate: €1 = US$ 1.1369 (mid 2017). VAT included where social security organisations are subject to VAT. Countries in order of population size. Abbreviations: mn = million; VAT = value added tax

Figure 4 – Scatter plot of originator fludarabine prices against GDP per capita for 16 European countries where no generic fludarabine existed in 2017



Prices for both erlotinib and fludarabine were relatively stable between 2013 and 2017 among the studied Western European countries (Table 4).

Table 4 – Percentage price changes for originator erlotinib 150mg and fludarabine 10mg in 2017 vs. 2013 among Western European countries

Country	Erlotinib 150mg	Fludarabine 10mg
Malta	0.0	0.0
Norway	-12.7	-16.4
Austria	-10.7	
Sweden	-9.1	-14.0
Greece	+2.4	+2.2
Netherlands	-1.9	-0.6
Spain	0.0	-8.1
Italy	-5.0	0.0
UK	0.0	+11.3
France	-7.1	-0.5
Germany	0.0	

NB: Price changes based on initial Euro prices. Countries in order of population size.

4. Discussion

We believe this is the first study to investigate reimbursed prices over time for both patented and generic oral oncology medicines (43) across an appreciable number of European countries to provide future direction. Both studies have shown that prices of oral oncology medicines were not dependent on population sizes despite earlier concerns (43, 92), which mirrors findings from other studies (41, 94, 95). However, we are not sure why there were greater price differences than seen in the studies of Vogler et al and Vokinger et al (40, 41). This may reflect greater implementation of external reference pricing as well as greater implementation of MEAs which have grown in recent years (51, 62, 64). However, further research is needed before we can make any definitive statements. A concern though is that the prices of patented oral cancer medicines tended to be higher in countries with greater economic power (Figures 2 to 4). These countries may well be able to more aggressively negotiate confidential discounts or rebates as part of MEAs. However, patients in CEE countries that reference these countries for pricing purposes may be faced with higher co-payments, which is an issue that needs addressing. Potential ways forward include greater pricing transparency to justify higher prices in one European country over another coupled the growth in Pan-European purchasing consortia (96, 97).

Encouragingly, Godman et al (43) in their earlier study found there were no differences in the pricing approaches for oral oncology multiple sourced medicines as opposed to other disease areas. This is very different to the situation for new oncology medicines where premium prices have been granted for very limited health gain unlike other disease areas (11, 12). Encouragingly as well, prices for multiple sourced products were similar across the indications including still patented indications at the multiple source price (43). This was unlike the situation for pregabalin when generic versions were first launched where general practitioners in some countries were threatened with legal action if they prescribed generic pregabalin as opposed to the appreciably more expensive originator for a still patented indication (98). I.

Thirdly, substantial price reductions of up to 98.8% were seen following the availability of oral generic oncology medicines across Europe (Box 1) (43). These encouraging findings are important to maximise available savings from generic availability to fund increased medicine volumes, as well as new valued high-priced oncology medicines within Europe with its dual aims of universal and equitable access to all for healthcare especially as more standard medicines lose their patent. However, care must be taken that low prices for generic medicines do not lead to shortages and the removal of medicines from the market in this priority disease area (99, 100).

We also found limited price erosion for patented oral oncology medicines over time in this study (Table 4) versus the situation seen with oral generic oncology medicines in the earlier study of Godman et al (2019) where increasing competition helped lower prices (43). However, it is likely in the future there will be greater re-evaluation of the prices of existing patented oncology medicines as more oncology medicines used as benchmarks for their pricing and reimbursement negotiations lose their patents (101, 102) combined with growing pressures on oncology budgets. Such activities are also likely to grow under value based pricing considerations especially given the level of price reductions that are now being seen for oral generic oncology medicines (up to 97.8% - Box 1), biosimilars (83% reduction in expenditure on adalimumab among Danish hospitals following biosimilars) and originators with the imminent launch of biosimilars (89% price reduction in the Netherlands for Humira® just before biosimilars were launched) (35, 43, 103-105). In addition, ongoing measures among European countries to rapidly use new biosimilars for oncology and rheumatoid arthritis to conserve valuable resources without compromising care (106-110). Value-based pricing (VBP) means '*that countries set prices for new medicines and/or decide on reimbursement based on the therapeutic value which medicine offers, usually assessed through health technology assessment (HTA) or economic evaluation*' (25). Consequently under VBP, the prices of patented oncology medicines that used medicines that subsequently became available as either oral generic medicines or biosimilars as their reference for reimbursement purposes should fall following substantial changes in their 'value'. As a result, in the first instance health authorities should seek appreciably greater discounts from companies for continued reimbursement of still patented medicines as part of any existing MEA. Secondly, instigate prescribing restrictions to selected patient groups until there are actual reductions in list prices and/ or discounts (51, 104, 111). There also needs to be similar considerations for other patented oncology medicines to treat pertinent cancers and stages as the prices and value of oncology medicines targeting the same population change. In

view of these developments, it is likely that health authorities will increasingly monitor prices and value of oncology medicines and seek redress where these change.
We are aware of a number of limitations with this study discussed in the Methodology section. Despite these limitations, we believe our findings are robust and provide future direction.

5. Conclusion

There is a concern that the prices of patented oral cancer medicines tended to be higher in countries with greater economic power, which needs to be addressed going forward. However, of greater concern is that the substantial lowering of prices for generic oral oncology medicines was not universal across Europe. This may start to change as pressures on the oncology medicine budget continue to grow. Of equal concern is a current lack of the re-assessment of the price, value, and place in treatment of patented oncology medicines following the patent loss of the medicines used for pricing and reimbursement negotiations. Such pro-activity is increasingly essential given the likely growth in global expenditure for oncology medicines in the coming years fuelled by rising prevalence rates coupled with the launch of a considerable number of new high-priced oncology medicines. We will continue to monitor any developments given the number of oncology medicines losing their patents in the near future.

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Appendix

Tables

Table 1A – ISO 3166 Country Codes (Alpha-3)

Country	Country Code
Albania	ALB
Austria	AUT
Belgium	BEL
Cyprus	CYP
France	FRA
Germany	DEU
Greece	GRC
Italy	ITA
Kosovo	XKX
Latvia	LVA
Lithuania	LTU
Malta	MLT
Netherlands	NLD
Norway	NOR
Poland	POL
Romania	ROU
Serbia	SRB
Slovakia	SVK
Slovenia	SVN
Spain	ESP
Sweden	SWE
United Kingdom	GBR

Figures

Figure 1A – Scatter plot of originator imatinib prices against population size for 11 European countries where no generic imatinib existed in 2015

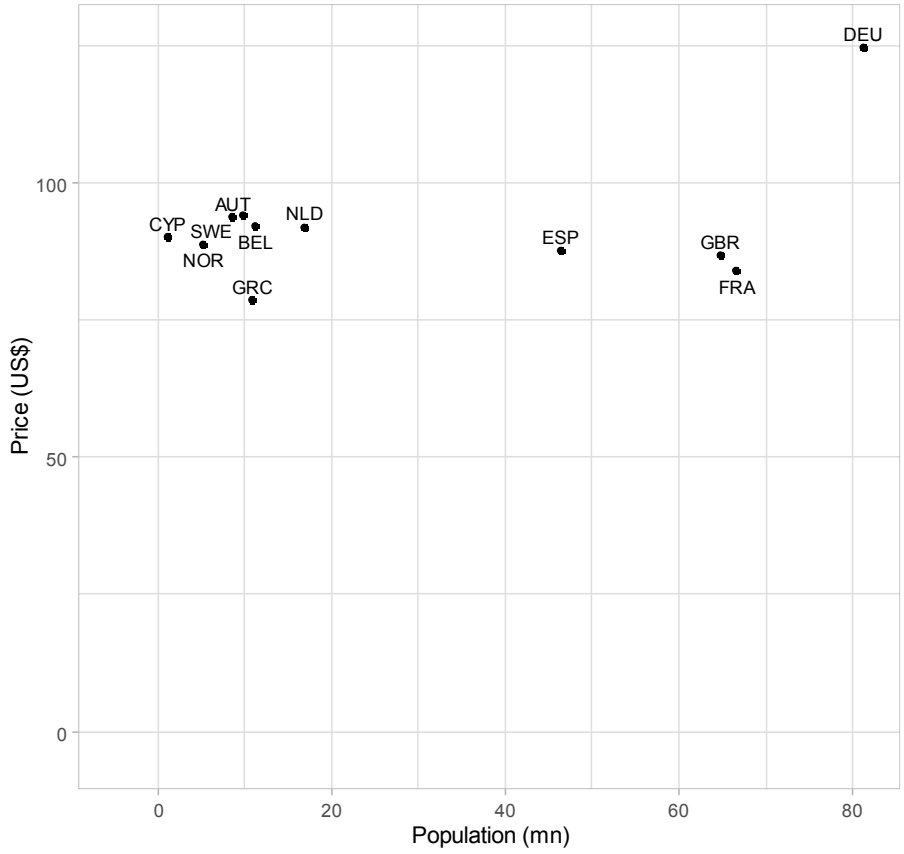

Figure 2A – Scatter plot of originator erlotinib prices against population size for 16 European countries where no generic erlotinib existed in 2017

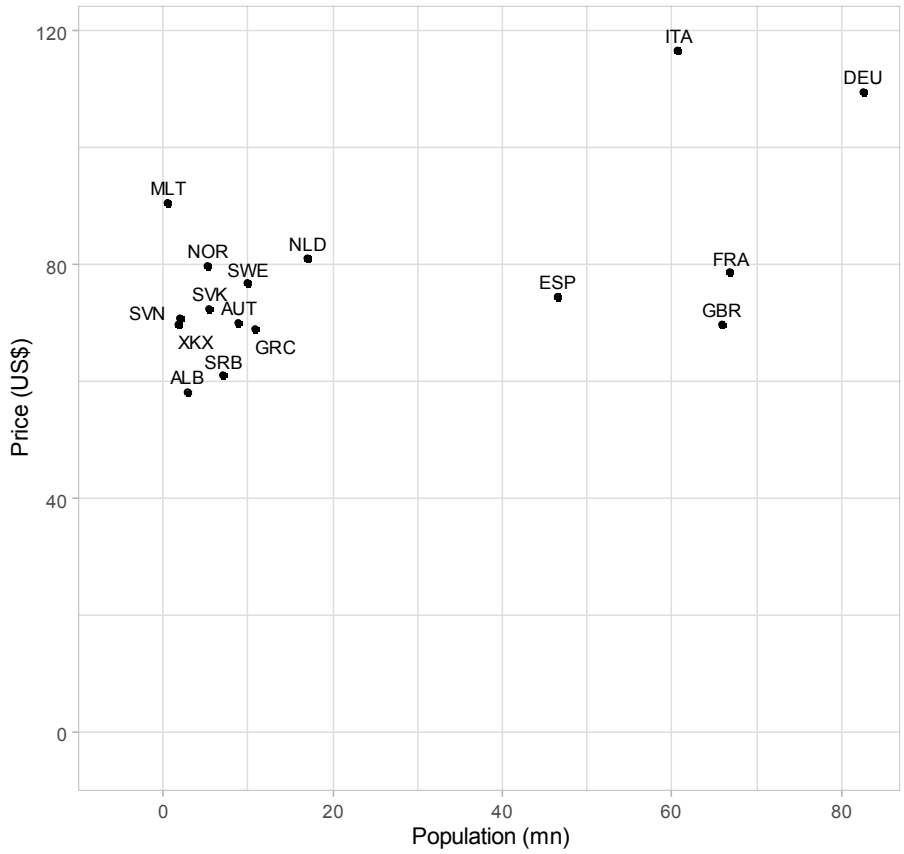

Figure 3A – Scatter plot of originator fludarabine prices against population size for 16 European countries where no generic fludarabine existed in 2017