Ovarian Cancer Treatment mapping

August 2021

WORLD
OVARIAN
CANCER
COALITION

Contents

Introduction & approach

- The World Ovarian Cancer Coalition is undertaking a piece of work exploring access to medicines for ovarian cancer around the world, in low, middle and high-income countries.
- Phased approach with 13 countries in scope: Australia, Bangladesh, Canada, India, Italy, Mexico, Nigeria, South Africa, Sudan, UK, Uruguay, USA and Zambia.
- Compile comprehensive list of ovarian cancer treatments available globally, using agreed sources e.g., NCCN.
- Create an 'Essential List of Ovarian Cancer Treatments' which includes at least one of each 'type' of drug available i.e., 1) chemotherapies for epithelial (first-line and recurrent); 2) chemotherapies for non-epithelial ovarian cancers (first line and recurrent); 3) VEGF-A inhibitors; 4) PARP inhibitors and 5) hormone therapies.
- Treatments for newly diagnosed and recurrent ovarian cancer, covering epithelial and non-epithelial types and only drugs that have been approved in countries have been selected.
- A survey of ovarian cancer product manufacturers about their product only has been undertaken. Companies approached: AstraZeneca (AZ), Roche, Clovis and GlaxoSmithKline (GSK).
- A survey for a small group of clinicians seeking validation on the approach in creating 'essential list of ovarian cancer treatments' and asking about availability and reimbursement of the list above.

Project motivation and limitations

Why this work is being undertaken:

- to allow WOCC members to reflect on access to medicines in their own countries, how women's health may be being impacted and if there is anything they need to be doing to work on barriers to access.
- To raise the profile of ovarian cancer in the global conversation about access to medicines, and contribute to the debate on access to new targeted therapies in lower income countries

- The work contained in this report is intended only as a snap shot of the current situation, it does not extend it's conclusions outside scope of the time frame in which it was carried out (March 2021-September 2021).

Project timeline

Ongoing

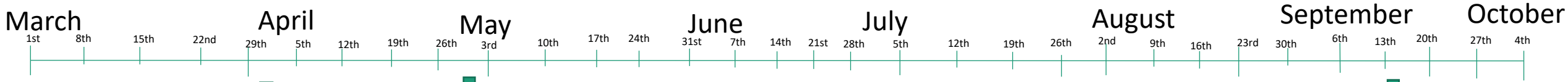
Desk research and analysis

Pharma survey fieldwork

Engagement with pharma

Clinician survey fieldwork

World Ovarian Cancer Coalition calls



Deliverables

Ovarian Cancer medicines list

Clinician survey

Interim slide deck

Interim slide deck V2

Final slide deck

Meetings with AZ, GSK, Clovis and Roche individually

Meeting with select clinicians to discuss results and next steps
Action point: Agree attendees

Survey status

Clinician country	Responded
India	X
Bangladesh	X
South Africa	X
Zambia	X
Canada	X
Italy	X
UK	X
Uruguay	X
Australia	X
Mexico	X
Nigeria	X
Sudan	X
USA	X
Zimbabwe	X

Industry	Responded
GSK (niraparib)	X
AZ (olaparib)	X
Clovis (rucaparib)	
Roche (bevacizumab)	X

Background information for clinicians

The World Ovarian Cancer Coalition is undertaking a piece of work exploring access to medicines for ovarian cancer around the world, in low, middle and high-income countries. We are in the early stages of developing a pilot for this work and would appreciate your input on what we should focus on.

We are approaching a limited number of clinicians in varied settings. Based on our knowledge and desk research to date, we believe we should focus on a selected range of treatments, and see whether they are available in a wide range of countries - what we call an essential list of ovarian cancer medicines, which includes:

- treatments for newly diagnosed and recurrent ovarian cancer, covering epithelial and non-epithelial types

- drugs that have been approved in a number of geographical locations, but not novel drugs awaiting assessment

- the list includes at least one of each 'type' of drug available i.e., 1) chemotherapies for epithelial (first-line and recurrent); 2) chemotherapies for non-epithelial ovarian cancers (first-line and recurrent); 3) VEGF-A inhibitors; 4) PARP inhibitors and 5) hormone therapies.

Questions to clinicians

We value your views on their inclusion, any omissions and availability and reimbursement for each, and on any other issues you may feel are important.

1. Please place an 'X' by any drug if you feel it should be EXCLUDED from the Essential list of ovarian cancer drugs. Please give your reasoning. If you feel none should be excluded, leave blank.

2. Are there drugs in the following categories we have missed in our 'Essential List' above and if so, why should we include them?

3. Please state if the following drugs are available in your country (routinely, occasionally), and who pays for them (state, insurance, patient, compassionate access scheme), by placing an 'X' in the relevant field.

4. Do you agree with our approach of ensuring there is at least one of the drug types available in a location (e.g., at least one PLATINUM therapy, one TAXANE, one HORMONE treatment, one PARP and VEGF-A inhibitor) rather than trying to find out access to absolutely every drug in every location?

Proposed changes to ‘Essential list’ from clinician survey (Q1)

	Comments by country	Votes for exclusion
Chemotherapy agents		
A Platinum therapy e.g. Carboplatin (1st/ 2nd line)	UK: Remove references to 2nd line - you can give platinum 5th line if patients are still likely to respond.	0
A taxane therapy e.g. Paclitaxel (1st/ 2nd line)	UK: I would separate taxane given in conjunction with platinum and taxane given as single agent in platinum resistant disease.	0
Topotecan (2nd line)	UK: Almost no-one gives topotecan and certainly not second line. **Bangladesh**: Level of activity is low in recurrent disease. So not essential. From my clinical experience, I did get enough benefit.	2
VEGF-A inhibitor		
Bevacizumab	**Bangladesh**: Cost-effectiveness. Zambia: The cost versus benefit ratio to classify it as essential for LMICs cannot be justified. It is not yet on the WHO essential medicines list that undergoes a rigorous process through the working group.	2
PARP inhibitors		
Olaparib	Zambia: The cost versus benefit ratio to classify it as essential for LMICs cannot be justified. It is not yet on the WHO essential medicines list that undergoes a rigorous process through the working group. India: Due to serious cost implications and questionable survival advantage Olaparib, Rucaparib and Niraparib all 3 cannot be termed as 'essential' drug in ALL settings of the world. Based on patients need one of these 3 can be an optional medication for patients in developing countries. However, discussion about these drug is 'essential'. UK: Only need one parp inhibitor - can really use any one of these 3. Olaparib used longest, and perhaps most familiarity and easiest. **Summary: Questionable cost vs benefit ratio in LMICs. Suggest choosing 1 PARP not all 3. UK suggests Olaparib.**	1
Rucaparib		2
Niraparib		2
Hormone treatment		
Anastrozole	Canada: Similar or same activity as letrozole. Nigeria: not commonly indicated.	2
Letrozole	Nigeria: not commonly indicated.	1
Tamoxifen	Nigeria: not commonly indicated.	1

Essential drugs agreed by 13 clinicians surveyed (Q1)	**Chemotherapy for epithelial ovarian cancer**: platinum therapy e.g. cisplatin, gemcitabine (2nd line) and pegylated liposomal doxorubicin (2nd line).
	Chemotherapy for non-epithelial ovarian cancer: bleomycin, etoposide and cisplatin.
	Hormone treatment: letrozole and tamoxifen.

Suggested additions to 'Essential List' (Q2)

Zambia:

Chemotherapy for non-epithelial ovarian cancer (EOC): Ifosfamide and vinblastine for 2nd line.
Reason: They are on the WHO essential medicines list for ovarian cancer.

Australia:

Chemotherapy for EOC: Oral cyclophosphamide for 2nd/subsequent lines - a good palliative option for patients who are seeking an oral agent.

Nigeria:

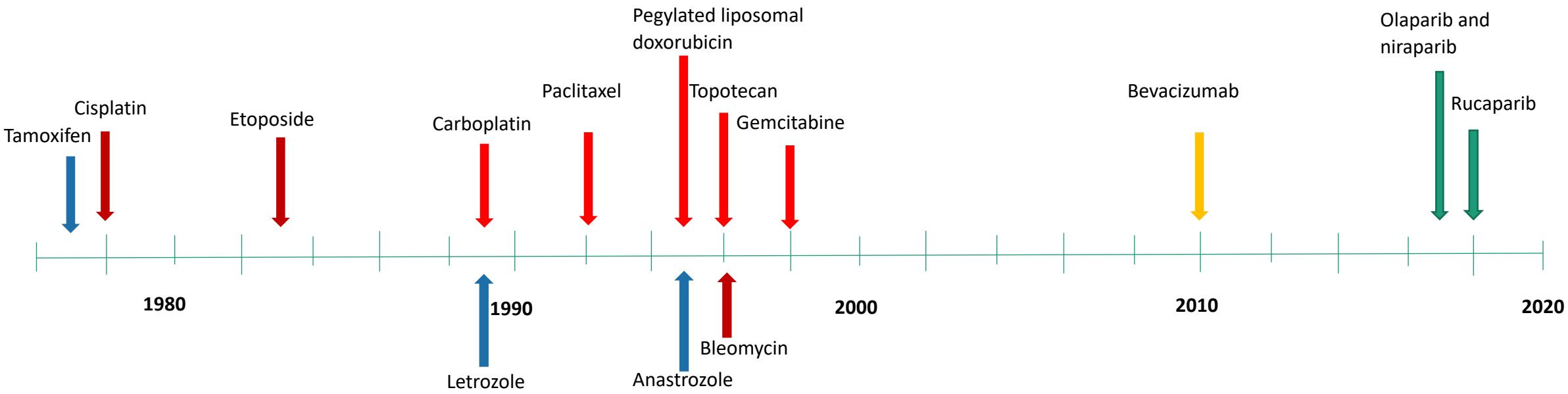
Chemotherapy for EOC: Cisplatin, cyclophosphomide as part of CAP REGIMEN (cyclophosphomide, adriamycin and cisplatin) may be used for indigent patients who cannot afford recommended first line therapy.

Availability of 'Essential' drugs (Q3)

	Drugs	Routinely available	Occasionally available	Not available	Notes
EOC chemotherapy	A platinum therapy e.g. Carboplatin (1st/ 2nd line), a taxane therapy e.g. Paclitaxel (1st/ 2nd line) Gemcitabine (2nd line)	South Africa, India, Canada, Uruguay, Bangladesh, Italy, UK, Australia, USA, Nigeria, Mexico, Sudan	Zambia		Zambia: (gemcitabine) hopefully available soon.
	Topotecan (2nd line)	India, Canada, Bangladesh, Italy, UK, Australia, USA, Nigeria,	South Africa, Mexico, Sudan?	Zambia, Uruguay?	Sudan stated patients pay but no availability data. Assumed occasionally available
	Pegylated liposomal doxorubicin (2nd line)	India, Canada, Bangladesh, Italy, UK, Australia, USA, Nigeria	Zambia, Mexico, Sudan?	Uruguay?	South Africa: only available in private sector. Sudan stated patients pay but no availability data. Assumed occasionally available
Non EOC chemotherapy	Bleomycin, Etoposide, Cisplatin	South Africa, India, Canada, Uruguay, Bangladesh, Italy, UK, Australia, USA, Nigeria, Mexico, Sudan	Zambia		
VEGF-A inhibitor	Bevacizumab	India, Canada, Bangladesh, Italy, Uruguay, Australia, USA, Nigeria	UK, Mexico, Sudan	Zambia	South Africa: available only in private sector. Canada: available for some evidence-based indications.
PARP inhibitors	Olaparib	Canada, Bangladesh, Italy, Uruguay, UK, Australia, USA	India, Nigeria, Mexico	Zambia Sudan	South Africa: available only in private sector.
	Rucaparib	Italy, UK, USA	Nigeria	Bangladesh, Uruguay? Australia, Mexico, Zambia, Canada, India, South Africa? Sudan	Bangladesh: available soon.
	Niraparib	Canada, Italy, UK, Australia, USA	Nigeria	Uruguay? Mexico, Zambia, Bangladesh, India, South Africa? Sudan	
Hormone treatments	Letrozole	India, Canada, Uruguay, Bangladesh, Italy, UK, Australia, USA, Nigeria Sudan	Zambia, Mexico	South Africa?	
	Anastrozole, Tamoxifen	South Africa, India, Canada, Uruguay, Bangladesh, Italy, UK, Australia, USA, Nigeria, Sudan	Zambia, Mexico		

EOC, epithelial ovarian cancer; PARP, poly ADP ribose polymerase; VEGF-A, vascular endothelial growth factor A

Timeline of when each agent was first approved by the FDA



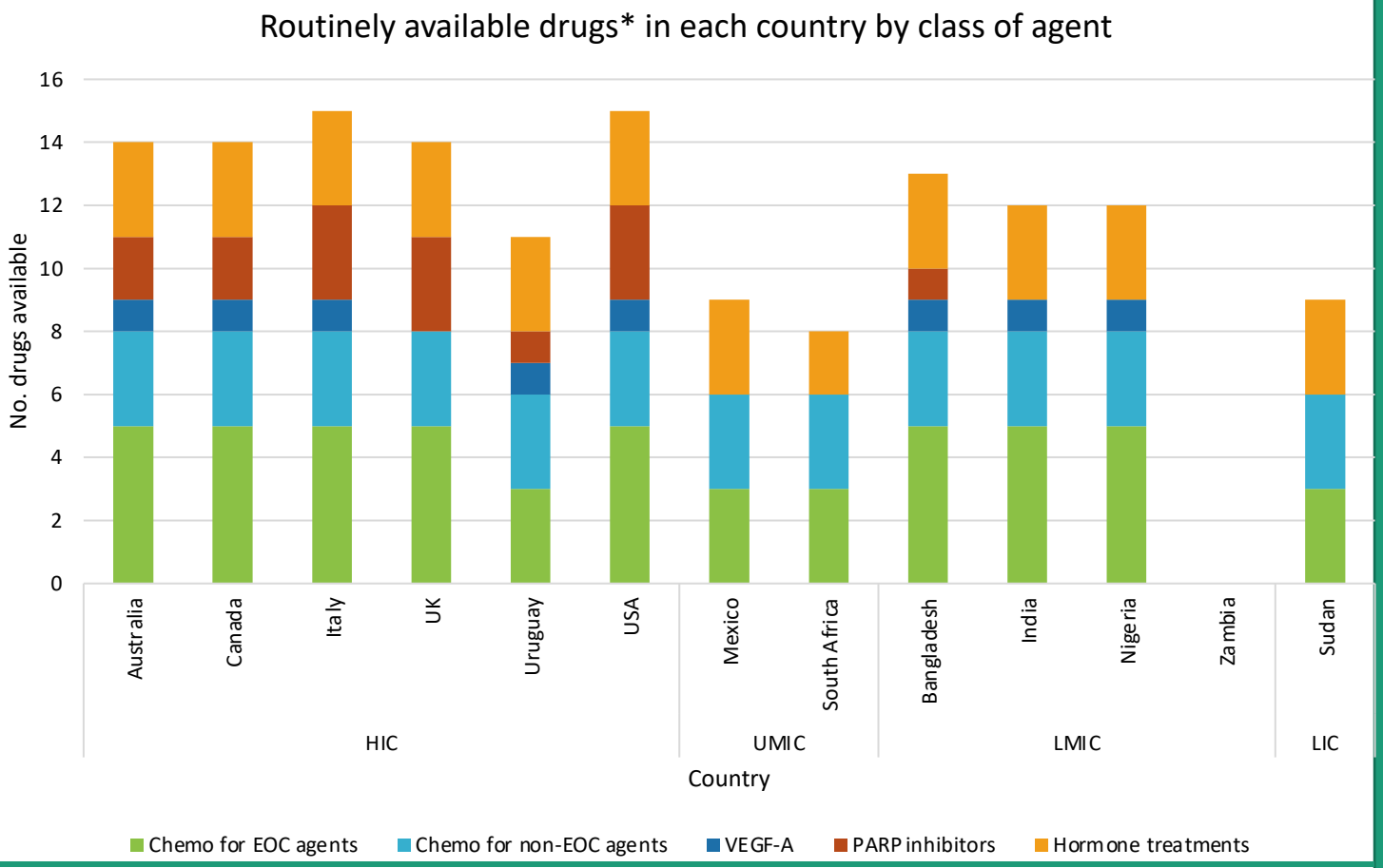
The timeline shows when each agent was approved for the treatment of ovarian cancer by the U.S. FDA as a guideline for how long each agent has been available for clinical use.

Chemotherapy for epithelial ovarian cancer is shown in light red and chemotherapy for non-epithelial ovarian cancer in shown in dark red.

Hormone treatments are shown in blue.

The more recent targeted agents are shown in yellow (VEGF-A inhibitor) and PARP inhibitors in green.

Availability of ‘essential’ drugs by country



EOC, epithelial ovarian cancer; HIC, high income countries; LMIC, lower middle income countries; PARP, poly adenosine diphosphate-ribose polymerase; UMIC, upper middle income countries; VEGF, vascular endothelial growth factor.

*15 drugs in total

The graph shows the availability of the 5 different groups of ‘essential’ ovarian cancer drugs represented by the different colours.

Each bar represents one of the 13 countries surveyed so far.
Below the country name the income bracket (HIC, UMIC LMIC and LIC) into which each country falls is shown.

Points from this graph

1. HICs tend to have more drug classes routinely available to clinicians. For example Australia has drugs from each of the 5 categories.
2. In each individual group of agents, HICs tend to have more options. For example they may have tamoxifen, anastrozole and letrozole routinely available of the hormone treatments.
3. UMICs and Sudan appear to have the lowest routine access to the essential medicines compared with HICs and all LMICs except Zambia.

Analysis of routinely available drugs (continued)

4. UMICs, LMICs and the LIC tend to have fewer drug classes routinely available and within the classes, fewer agents routinely available. Zambia is an extreme example of this as none of the essential ovarian drugs are routinely available.

5. There is a trend towards greater availability in class and overall number of drugs in HICs compared with UMICs, LMICs and the LIC.

6. Mexico, South Africa, Uruguay, Zambia and Sudan are the only countries in which all chemotherapy agents for EOC are not routinely available out of those assessed.

7. The only countries that do not have PARP inhibitors routinely available are Mexico, Nigeria, South Africa, Zambia India and Sudan.

Routine and occasional availability of ‘essential’ drugs*

This graph includes any agents indicated to be available occasionally in addition to routinely available drugs.

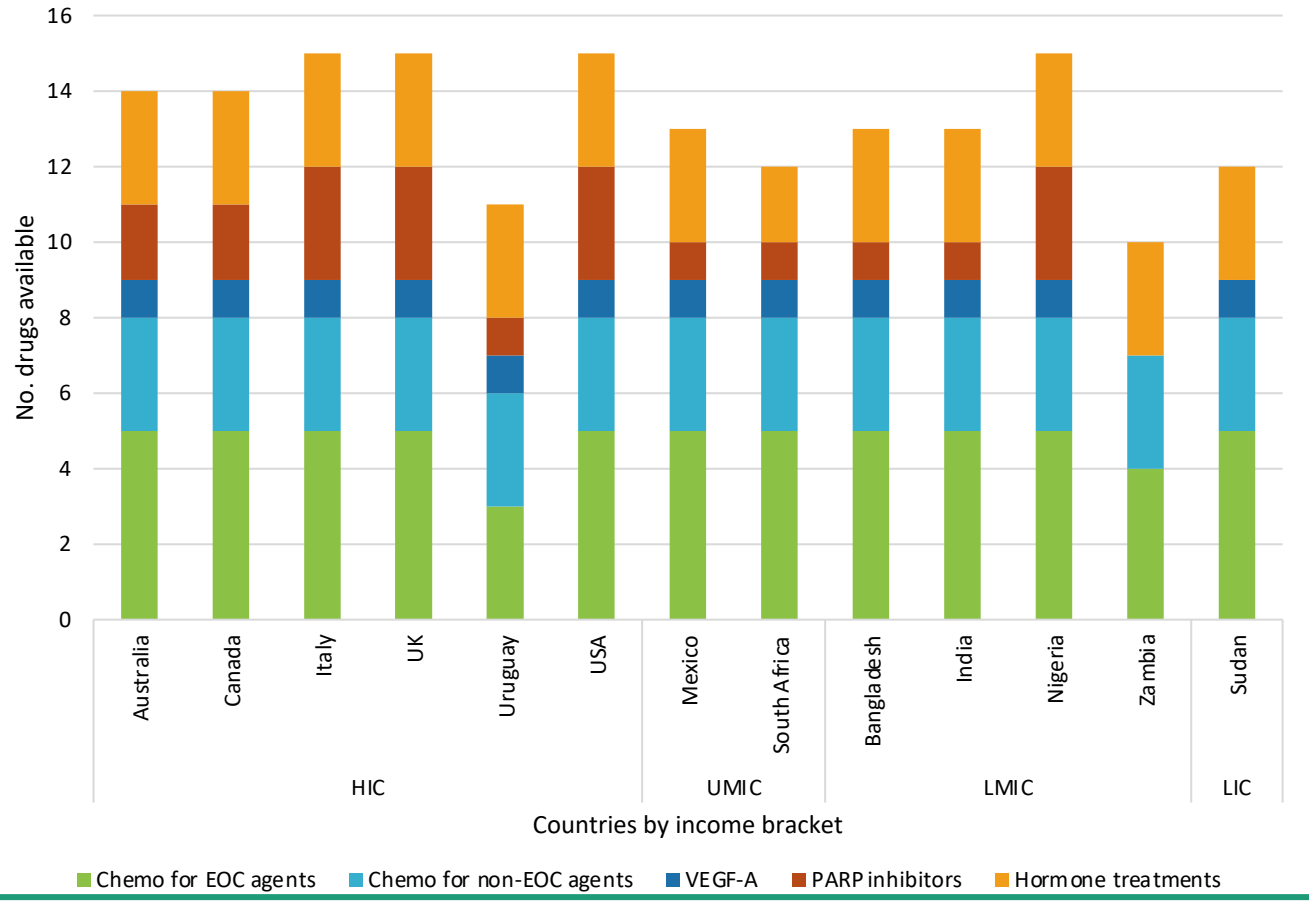
Points to note

1. Zambia has access to the older chemotherapy and hormone treatments occasionally but targeted agents remain unavailable.

2. While Uruguay has access to agents from each treatment group, fewer agents in each are available in comparison to other HICs.

3. Nigeria has access to all 15 agents which is unusual outside of the HIC group.

4. While there are a few outliers, there is a tendency for HICs to have access to more of the essential agents than UMICs, LMICs and the LIC.



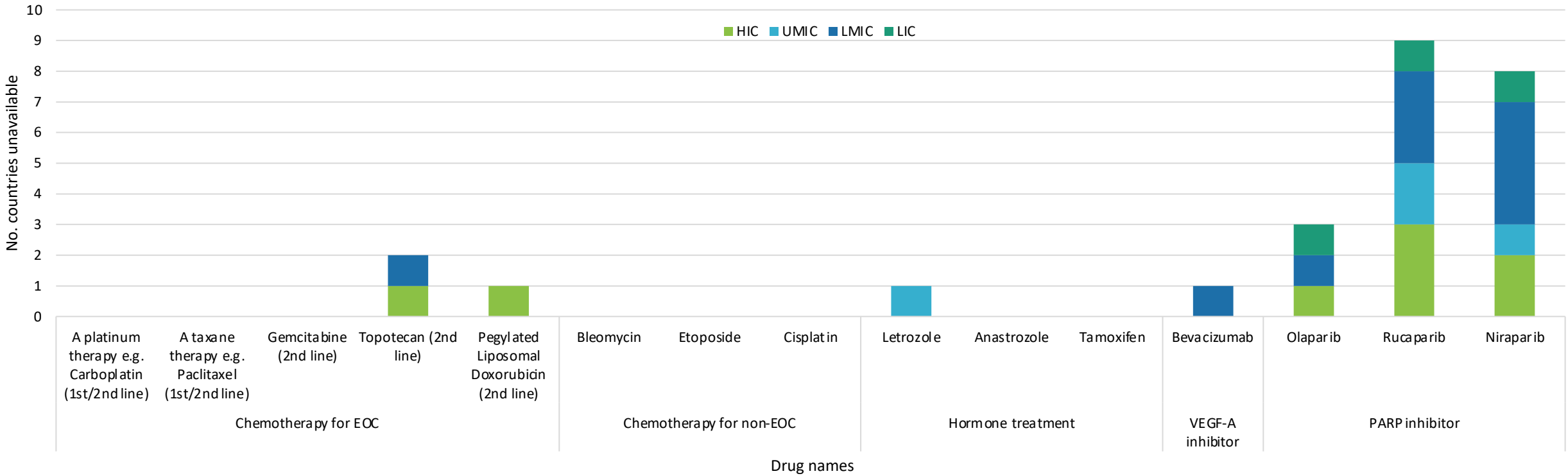
*Occasional availability for South Africa includes drugs only available in private sector.
EOC, epithelial ovarian cancer; HIC, high income countries; LMIC, lower middle income countries; PARP, poly adenosine diphosphate-ribose polymerase; UMIC, upper middle income countries; VEGF, vascular endothelial growth factor.

Lack of availability according to drug type

The graph below examines which specific drugs are unavailable as represented by each individual bar, while the height of the bar shows the number of countries in which the drugs are unavailable. The colours on the bars show how the total number of countries can be split up in terms of income bracket.

Points to note

1. The PARP inhibitors are the most frequently unavailable class of agents in the countries surveyed and out of this group rucaparib is the most commonly problematic agent whereas olaparib is more commonly available.
2. Chemotherapy agents for non-EOC are available in all countries. However, topotecan and pegylated liposomal doxorubicin appear to be unavailable in 1 HIC and 1 LMIC and 1 HIC, respectively. Letrozole is also unavailable in South Africa.



EOC, epithelial ovarian cancer; HIC, high income countries; LMIC, lower middle income countries; PARP, poly adenosine diphosphate-ribose polymerase; UMIC, upper middle income countries; VEGF, vascular endothelial growth factor.

Who pays for 'Essential' drugs? (Q3)

	Drugs	State pay	Patients pay	Insurance pay	Pharma pay	Notes
EOC chemotherapy	A Platinum therapy e.g. Carboplatin (1st/2nd line), A Taxane therapy e.g. Paclitaxel (1st/2nd line) Gemcitabine (2nd line)	**Zambia, India, Canada, Uruguay, Italy, UK, South Africa, Australia, Mexico, Sudan**	**Bangladesh, India, Zimbabwe, Nigeria**	**India, Zambia, USA**		**Zambia**: Only 3% of population has private insurance. **Canada** (gemcitabine only): province pays for one 2nd line.
	Topotecan (2nd line)	**India, Canada, Italy, UK, South Africa, Australia, Mexico**	**Bangladesh, India, Zimbabwe, Nigeria, Sudan**	**India, USA**		**Canada**: province pays for one 2nd line.
	Pegylated Liposomal Doxorubicin (2nd line)	**Zambia, India, Canada, Italy, UK, Australia, Mexico**	**Bangladesh, India, Uruguay, Zimbabwe, South Africa, Nigeria, Sudan**	**India, Zambia, South Africa, USA**		**Canada**: province pays for one 2nd line.
Non EOC chemotherapy	Bleomycin, Etoposide, Cisplatin	**Zambia, India, Canada, Uruguay, Italy, UK, Australia, Mexico, Sudan**	**Bangladesh, India, Zimbabwe, Nigeria**	**India, Zambia, USA**		
VEGF-A inhibitor	Bevacizumab	**India, Uruguay, Italy, UK, Australia, Mexico**	**Bangladesh, India, Zimbabwe, South Africa, Nigeria, Mexico, Sudan**	**South Africa, USA**		**Uruguay**: In some circumstances the state pays. **Italy**: State does not pay for Pt-resistant relapse.
PARP inhibitor	Olaparib	**Italy, Canada, Uruguay, Australia, Mexico**	**Bangladesh, India, Zimbabwe, South Africa, Nigeria, Sudan**	**South Africa, USA**	**Mexico**	
	Rucaparib	**Italy, Australia**	**Zimbabwe, Nigeria, Sudan**	**USA**		
	Niraparib	**Italy, Canada**	**Zimbabwe, Nigeria, Sudan**	**Canada, USA**	**Australia**	
Hormone treatment	Letrozole, Anastrozole, Tamoxifen	**Zambia, India, Uruguay, Italy, , South Africa? Australia, Mexico, Sudan**	**Bangladesh, India, Zimbabwe, Canada, Nigeria, Mexico**	**Zambia, Canada, USA**		

EOC, epithelial ovarian cancer; PARP, poly ADP ribose polymerase; Pt, platinum; VEGF-A, vascular endothelial growth factor A

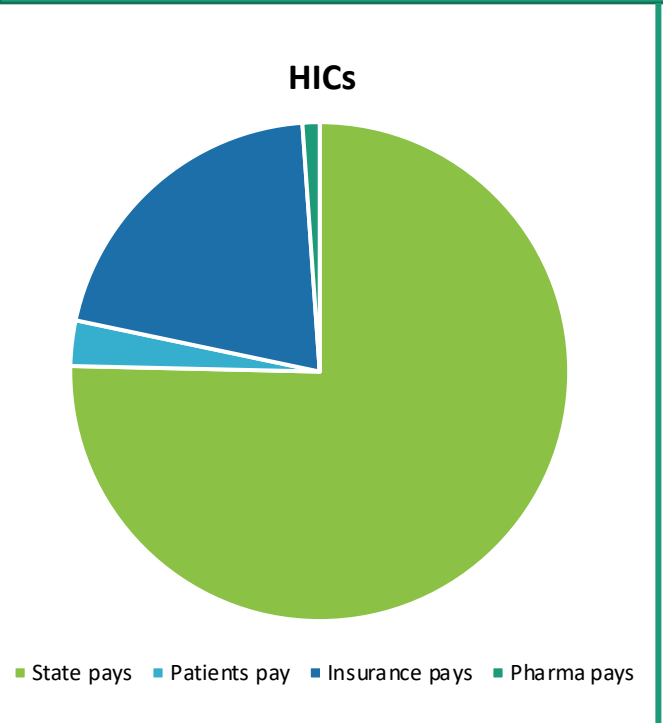
Payer split by country income bracket

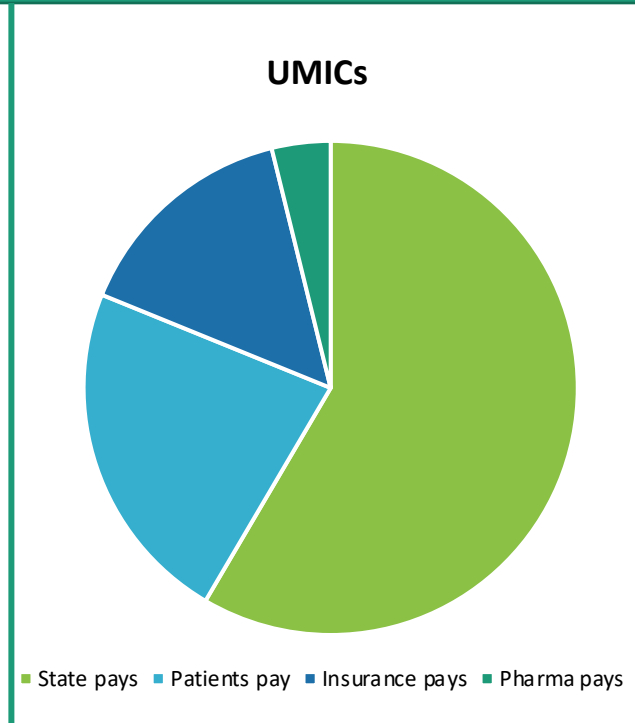
Points to note

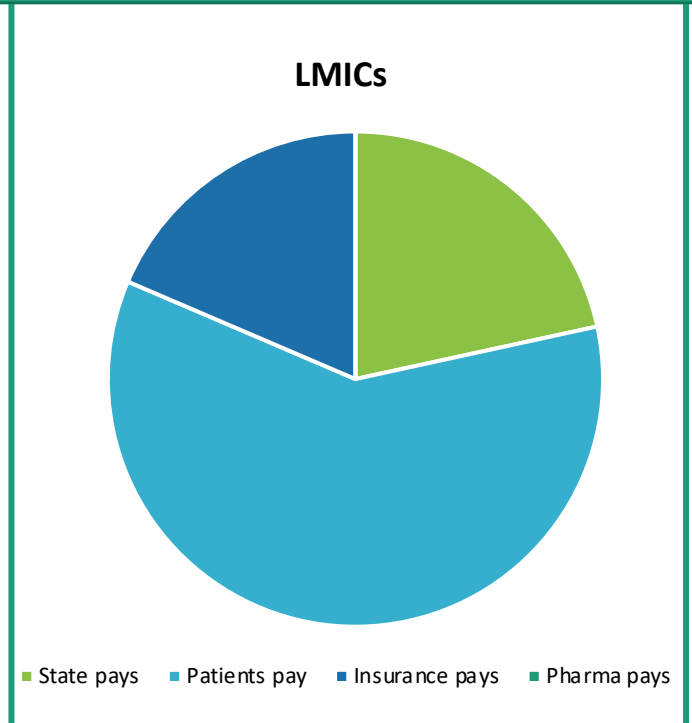
In HICs the state appears to pay for ~75% of drugs on the essential medicine list, a greater percentage compared with UMICs or LMICs. In HICs and UMICs the state pays for more medicine than in LMICs.

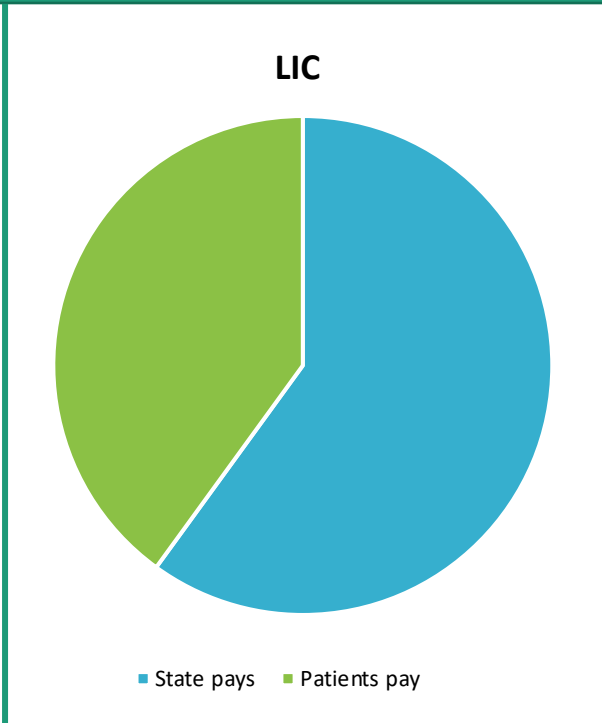
In LMICs and the LIC patients appear to pay for >50% of the agents on the essential medicine list, more than either the state or insurance.

Pharmaceutical companies are not involved in paying for essential medicines in the LMICs and the LIC surveyed.

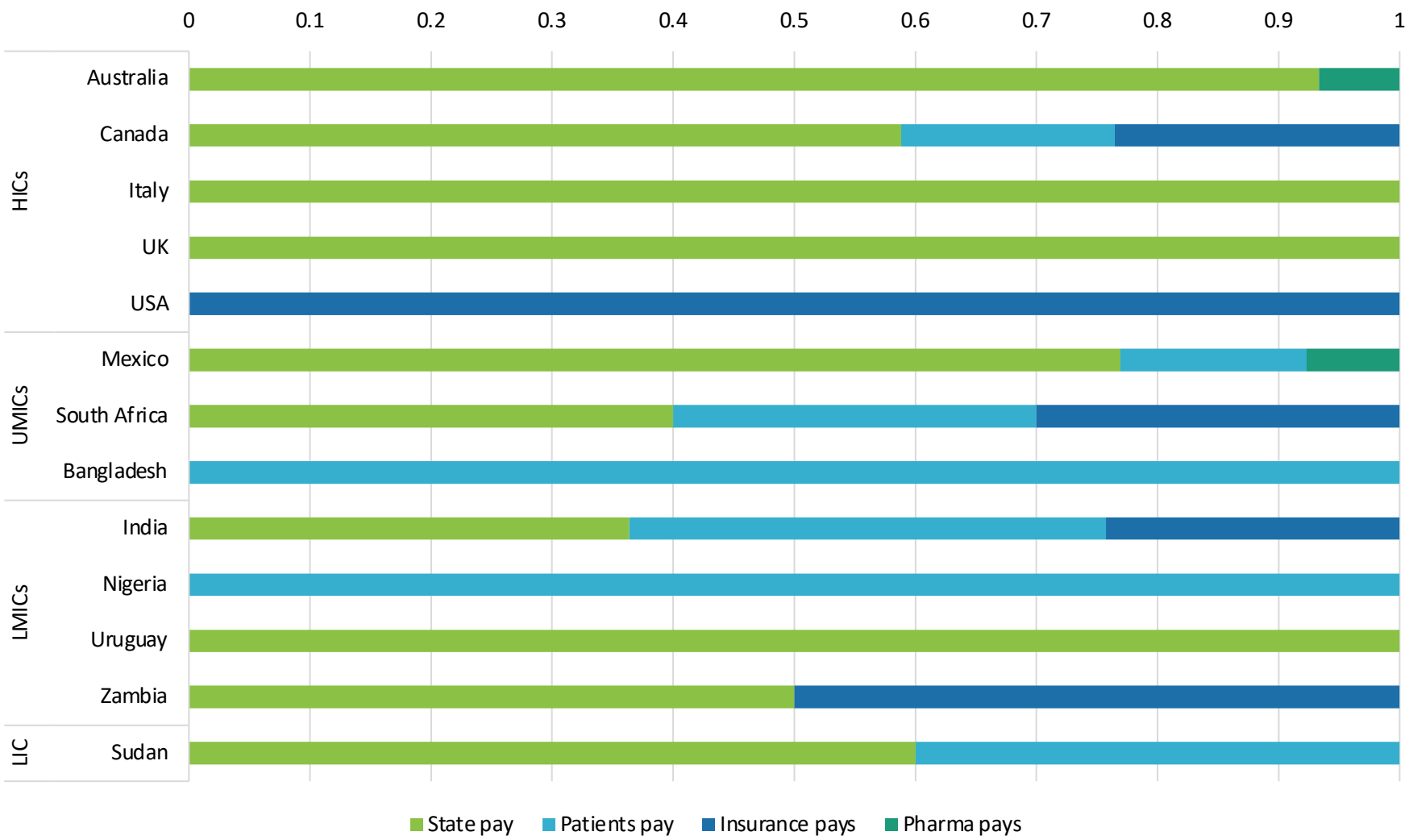








Sources of healthcare expenditure by country

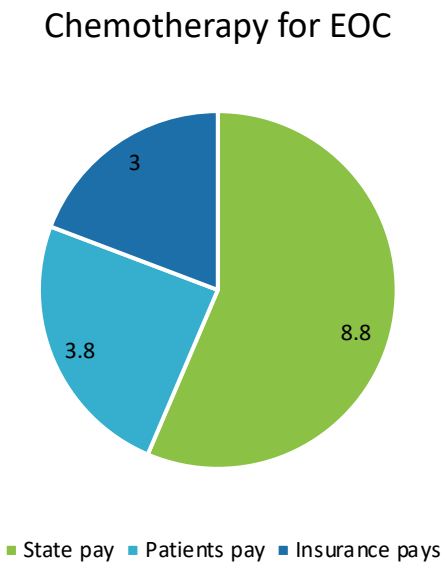


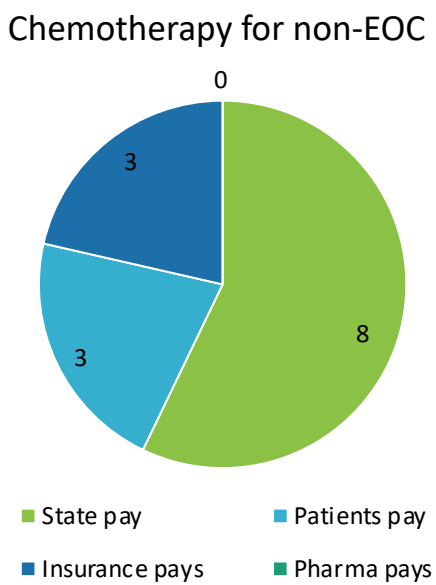
The graph shows for the total number of drugs available per country what proportion are covered by each payer group.

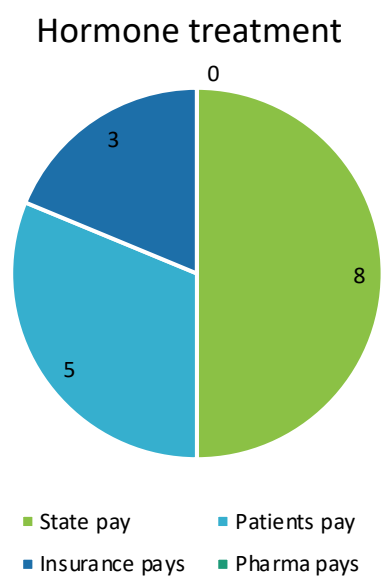
Points to note:

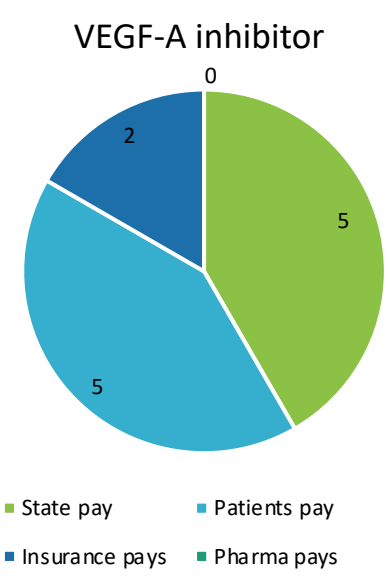
- For the HICs most drugs are covered by the state with the exception of the US which is covered by insurance.
- Patients have greater OOP in the LMICs and LIC compared with HICs and UMICs.
- Only in Australia and Mexico does pharma pay for any agents.

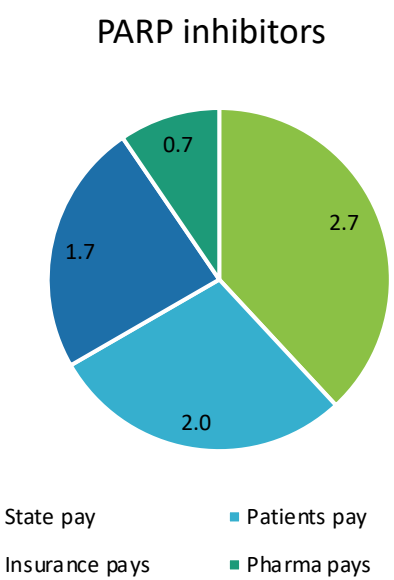
Payer division for different drug classes











This slide shows the proportion of drugs that are paid for by the state, insurance, pharmaceutical companies and patients across the 5 different drug classes.

Points to note

- To generate these pie charts the average number of countries that used each payer class was calculated across the drugs in the class. For instance, for the hormone treatments there are 3 agents within the class. The number of countries in which anastrozole was paid for by the state was added to the results for tamoxifen and letrozole and divided by 3 to get the mean value.

- For the chemotherapy agents the most common method payer was the state. Hormone and VEGF-A treatments were fairly similar although patients paid for a slightly greater proportion. The targeted agents showed a reduced proportion was paid by the state.

- Pharmaceutical companies only paid for PARP inhibitors.

Agree with approach of 1 drug type available in a location? (Q4)

Clinician comments		
Agree	**Disagree**	**No comments**
• **Bangladesh**: no comment • **Canada**: no comment • **Zambia**: no comment • **USA**: Yes, agree • **Nigeria**: Yes • **Sudan**: I agree • **South Africa**: I agree that minimum requirement is platinum and a taxane for chemotherapy. What would second line be if resistant to these? Also agree that at least one hormonal treatment is important whether it be tamoxifen, anastrozole etc. Targeted agents will depend on the patients financial means in certain countries, especially in Africa. Even in our private sector, this may not be affordable. • **Australia**: Yes, although value of a VEGF inhibitor is probably over-stated and likely to be of most value to patients with recurrent platinum resistant disease who have lots of recurrent ascites, rather than the initial front-line maintenance setting.	• **Italy**: Not completely, for instance we may need both carboplatin and cisplatin in case of hypersensitivity reaction. Also tamoxifen is different from letrozole and anastrozole, not interchangeable. Also the indication for PARP inhibitors are not the same, so we may need all of them.	• **India** • **UK** • **Uruguay**

Questions to pharmaceutical companies

AstraZeneca, Roche, Clovis and GSK

- For which indication(s) is X licensed ?
- In which countries is X licensed and for which indication(s)?
- In which countries is X reimbursed and for which indication(s)?
- Is there an Access Program that allows pre-approval in place for X and where?
- Is there an Access Program that allows Compassionate Use by the manufacturer/by physician and where?
- What further barriers to access exist for X?

Industry response: GSK (niraparib)

Current list of approved countries broken up by line of therapy with approvals via partners noted:

1L maintenance	2L maintenance	3L+ treatment
Argentina	Argentina	Japan (Takeda)
Brazil	Australia	South Korea (Takeda)
Canada	Brazil	Taiwan (Takeda)
China (Zai Lab)	Canada	USA
EU	China (Zai Lab)	
Israel (Medison)	EU	
Japan (Takeda)	Hong Kong (Zai Lab)	
South Korea (Takeda)	Israel (Medison)	
Switzerland	Japan (Takeda)	
Taiwan (Takeda)	Macau (Zai Lab)	
USA	South Korea (Takeda)	
	Switzerland	
	Taiwan (Takeda)	
	USA	

Current list of countries where we have Zejula (niraparib) reimbursement

1L: USA, UK

2L: USA, Israel, Austria, Czech Republic, Denmark, Finland, France, Germany, Italy, Ireland, Latvia, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland, Slovenia, UK, South Korea, Macao, Hong Kong, China

Key points:

- All are HICs except China and Brazil which are UMICs
- Although approved in many HICs, it is only reimbursed as a 1L maintenance therapy in the US and UK, the latter through the CDF - so within HICs, there are differences in terms of access

Roche (bevacizumab)

Bevacizumab licensing for the treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer

Country		UK and Italy	US	Canada	Australia	Uruguay	Mexico	South Africa	Bangladesh	India	Nigeria	Zambia	Sudan
Lines of therapy													
1st line		Y			Y	Y	Y	Y	Y	Y	Y		
≤2 lines of previous therapy		Y	Y	Y	Y	Y	Y	Y					
Timing													
1st recurrence		Y		Y	Y	Y							
Any recurrence			Y	Y	Y	Y	Y	Y		Y	Y		
Agents													
Combination	Carboplatin and gemcitabine	Y	Y	Y	Y	Y	Y	Y					
	Carboplatin and paclitaxel	Y	Y		Y	Y	Y	Y	Y	Y	Y		
	Paclitaxel, topotecan or pegylated liposomal doxorubicin	Y	Y	Y	Y	Y	Y	Y		Y			
Disease status													
Platinum	Sensitive	Y	Y	Y	Y	Y	Y	Y			Y		
	Resistant	Y	Y	Y	Y	Y	Y	Y		Y			
Advanced		Y	Y		Y	Y			Y	Y	Y		
Bevacizumab/ VEGF inhibitor/ VEGFR-targeted agent naïve		Y		Y	Y	Y							

Bevacizumab reimbursement (research results)

Reimbursed	Indication	Not reimbursed	Notes
UK	Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer.[1]	Australia	Only reimburse Mvasi, a biosimilar as of June 2021.[8]
Italy	The drug has received classification H status for the treatment of bevacizumab in combination with carboplatin and paclitaxel, indicated for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.[2]	Uruguay	Does not include coverage of bevacizumab in recurrent endothelial or epithelial ovarian cancer (2017). In Uruguay, there is no reimbursement in the private sector.[9]
US	Medicare: • Avastin, in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection. • Avastin, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens. • Avastin, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[3]	India	India currently does not have a mechanism for reimbursement of drugs, biologics and medical devices. Out-of-pocket expenditure by patients is the primary means of financing of drugs, biologicals and medical devices.[10]
		Nigeria	As regards pricing and reimbursement of drugs, biologicals and medical devices, there is currently no fixed mechanism in place for drug price control or reimbursement in Nigeria.[11]
Canada	In combination with paclitaxel and carboplatin for the front-line treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer patients with high risk of relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients.[4]	South Africa	Until more affordable biosimilars are available in South Africa, it will be difficult to advocate for the inclusion of bevacizumab on the national EML for cancer conditions.[12]
Mexico	In combination with carboplatin and paclitaxel is indicated for the treatment of first line of cancer advanced (stages III B, III C and IV) epithelial ovarian, tubal fallopian or primary peritoneal. Avastin in combination with carboplatin and gemcitabine is indicated for the treatment of epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer relapsing and platinum sensitive[5-7]	Sudan	Avastin doesn't appear on WHO EML for coverage in Sudan.[13] (Patients pay indicated in survey).
		Bangladesh	The Bangladesh essential medicine list 2008 does not include Avastin.[14-16]

Bevacizumab is not available in Zambia

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AZ: Lynparza (olaparib) reimbursement

	Country	PSR-OC	1L OC BRCAm	1L OC HRD
HICs	**Australia**	Reimbursed in BRCAm	Reimbursed	Reimbursement process ongoing
	Canada	Reimbursed in BRCAm	Reimbursed	NA: Refer to regulatory information
	Italy	Reimbursed in BRCAm	Reimbursed	Available through Cnn program – reimbursement process ongoing
	UK (England)	Funded through CDF - BRCAm	Funded through CDF	Funded through CDF
	Uruguay	Not currently reimbursed, OOP only	Not currently reimbursed, OOP only	Refer to regulatory information
	USA	Reimbursed	Reimbursed	Reimbursed
UMICs	**Mexico**	PVT coverage + partial PUB + PAP	PVT coverage + partial PUB + PAP	PVT coverage + partial PUB + PAP
	South Africa	Not currently reimbursed, OOP only	Not currently reimbursed, OOP only	NA: Refer to regulatory information
LMICs	**Bangladesh**	NA: Refer to regulatory information	NA: Refer to regulatory information	NA: Refer to regulatory information
	India	Patient access program in place / OOP only	Patient access program in place / OOP only	Patient access program in place / OOP only
	Nigeria	NA: Refer to regulatory information	NA: Refer to regulatory information	NA: Refer to regulatory information
	Zambia	NA: Refer to regulatory information	NA: Refer to regulatory information	NA: Refer to regulatory information
LICs	**Sudan**	NA: Refer to regulatory information	NA: Refer to regulatory information	NA: Refer to regulatory information

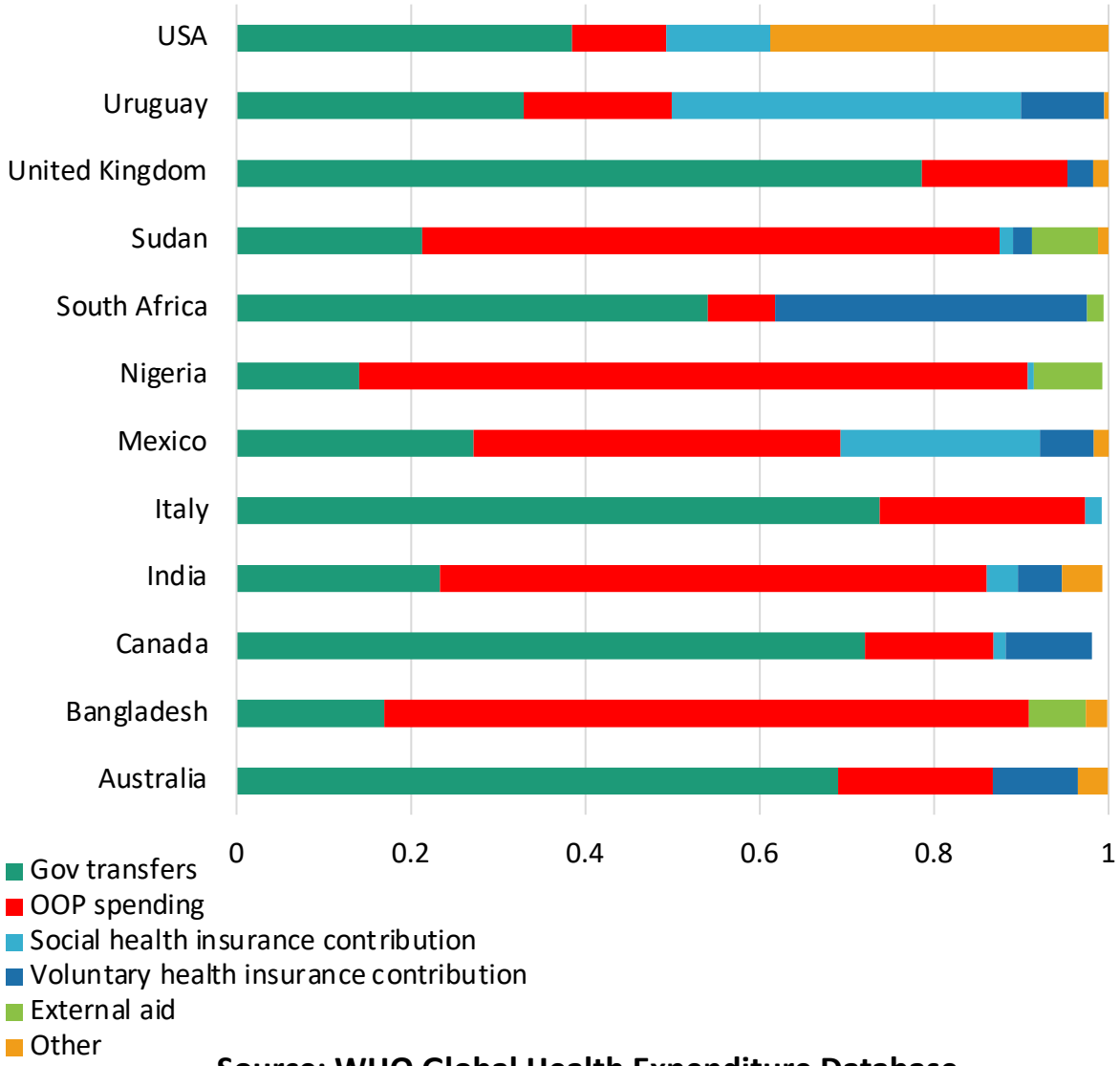
CDF, Cancer Drugs Fund in UK (Eng); Cnn, class C non-negotiated; HICs, high income countries; LMICs lower middle income countries; LICs, low income countries; OC, ovarian cancer; PAP, patient access program; PSR, platinum sensitive relapse; PVT, private; PUB, public funding; OOP, out of pocket; TBC, to be confirmed; UMICs, upper middle income countries.

AZ olaparib indications

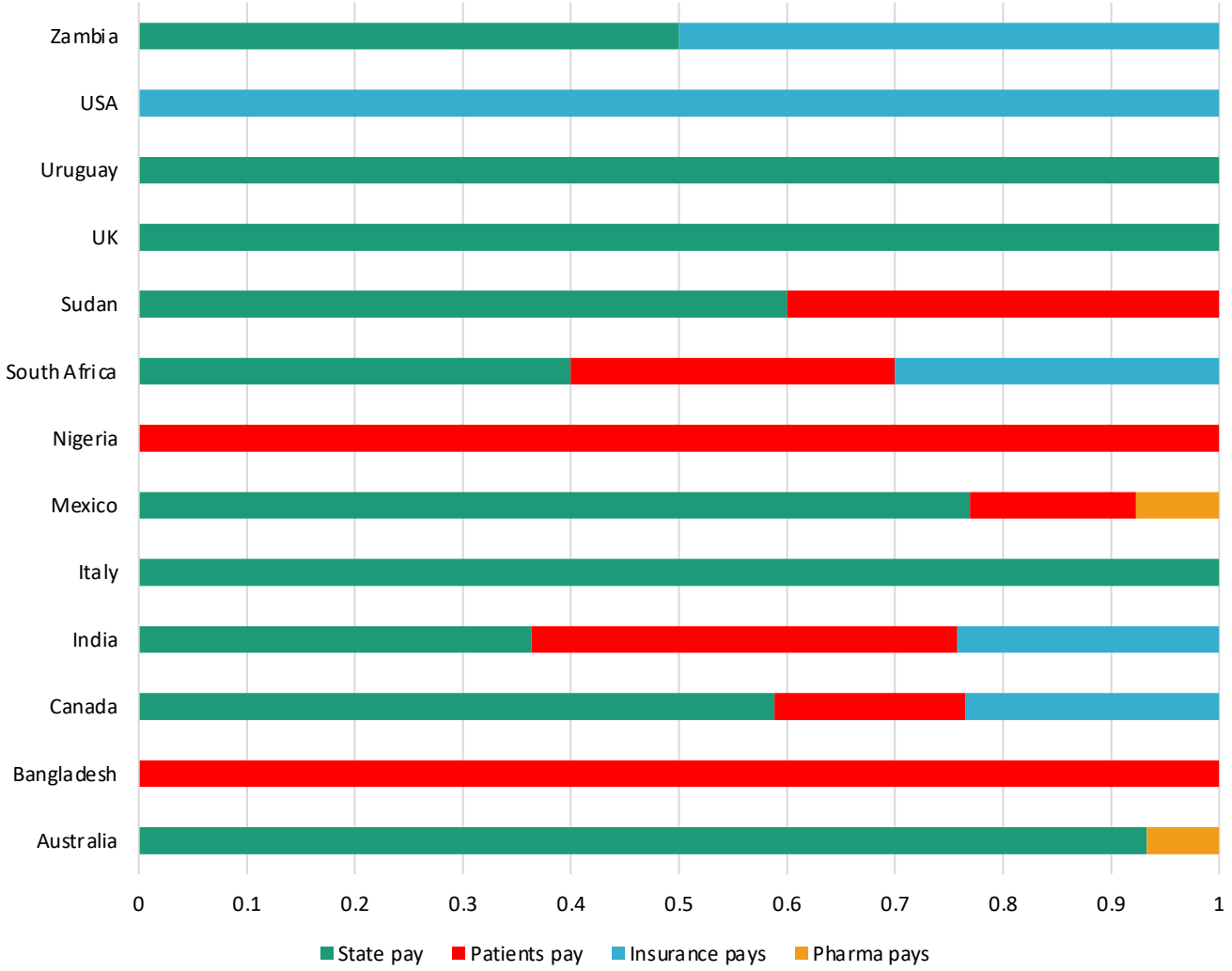
Country	Indication approved		
	PSR-OC	1L OC BRCAm	1L OC HRD
Indication	LYNPARZA® is prescribed as **monotherapy** for the maintenance treatment of adult patients with high-grade relapsed epithelial ovarian, fallopian tube or primary peritoneal cancer who have a response (complete response or partial response) to platinum based chemotherapy.	LYNPARZA® is prescribed as **monotherapy** for the maintenance treatment of adult patients with advanced BRCA-mutated (germline or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy.	LYNPARZA® **in combination with bevacizumab** is indicated for maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: - a deleterious or suspected deleterious BRCA mutation (germline or somatic), and/or - genomic instability
Australia	Y. Prior treatment must have included at least 2 courses of platinum-based regimens.	Y	Y
Canada	Y	Y	NR
Italy	Y	Y. Specifies advanced means (FIGO stages III and IV) and BRCA 1/2 mutations	Y. Specifies advanced means (FIGO stages III and IV) and BRCA 1/2 mutations
UK	Y	Y. Specifies advanced means (FIGO stages III and IV) and BRCA 1/2 mutations	Y. Specifies advanced means (FIGO stages III and IV) and BRCA 1/2 mutations
Uruguay	TBC	TBC	TBC
USA	Y and advanced gBRCA-mutated ovarian cancer after 3 or more lines of chemotherapy- LYNPARZA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines	Y, specifies a deleterious or suspected deleterious germline or somatic BRCA-mutation	Y
Mexico	Y	Y	Y. Specifies BRCA 1/2 mutations
South Africa	Y	Y	NR
Bangladesh	NA	NA	NA
India	Y	TBC	Y
Nigeria	NA	NA	NA
Zambia	NA	NA	NA
Sudan	NA	NA	NA

HRD, homologous recombination deficiency; platinum sensitive relapse; NA, not approved; NR, not registered; OC, ovarian cancer

Sources of health expenditure: WHO research compared with results from HCPs



Source: WHO Global Health Expenditure Database



Healthcare expenditure by country (HCP)

Sources of healthcare expenditure

- Comparing the results from the WHO with our limited sample of only 15 therapeutic agents and only 4 categories of payers, nonetheless similar trends emerge.
- For Australia, the UK, Italy and Canada government funding is the largest source of funding for medicines.
- For Mexico and South Africa there was more of an even split between different payment groups in the WHO data. Our results were fairly similar though Mexico appeared to still gain most funding through government support.
- In Bangladesh, India and Nigeria OOP expenditure was the main payer class in our research, which agrees with the data from the WHO.

Summary of clinician findings

The World Ovarian Cancer Coalition is undertaking a piece of work exploring access to medicines for ovarian cancer around the world, in low, middle and high-income countries. To do this a survey was sent to clinicians in 15 countries with differing levels of income (according to the World Bank definition), to validate the approach of creating an 'essential list of ovarian cancer treatments' and asking about availability and reimbursement of the list. We would like to convene a small group of experts to assess the findings (listed below), and discuss implications and potential reasons behind the results, as well as seeking views on our call for an essential medicines list for ovarian cancer.

Results of the clinician survey

Routinely available drugs in each country by class of agent:

1. High Income Countries (HICs) tend to have more drug classes routinely available to clinicians. For example Australia has drugs from each of the 5 categories.

2. In each class of agents, HICs tend to have more options e.g., they may have all 3 hormone treatments routinely available.

3. Upper-middle income countries (UMICs) and Sudan appear to have the lowest routine access to the essential medicines compared with HICs and all lower-middle income countries (LMICs), with the exception of Zambia. UMICs and Sudan appear to have the lowest routine access to the essential medicines compared with HICs and all LMICs except Zambia.

4. UMICs, LMICs and the low income country (LIC) tend to have fewer drug classes routinely available and within the classes, fewer agents routinely available. Zambia is an extreme example of this as none of the essential ovarian drugs are routinely available.

5. There is a trend towards greater availability in class and overall number of drugs in HICs compared with UMICs, LMICs and the LIC.

6. Mexico, South Africa, Uruguay, Zambia and Sudan are the only countries in which all chemotherapy agents for EOC are not routinely available out of those assessed.

7. The only countries that do not have PARP inhibitors routinely available are Mexico, Nigeria, South Africa, Zambia India and Sudan.

Routine and occasional availability of 'essential' drugs

1. Zambia has access to the older chemotherapy and hormone treatments occasionally, but targeted agents remain unavailable.
2. While Uruguay has access to agents from each treatment group, fewer agents in each are available in comparison to other HICs.
3. Nigeria has access to all 15 agents, which is unusual outside of the HIC group.
4. While there are a few outliers, there is a tendency for HICs to have access to more of the 'essential' agents than UMICs, LMICs and the LIC.

Summary – clinician findings (cont.)

Which drugs/classes tend to be unavailable?

1. The PARP inhibitors are the most frequently unavailable class of agents in the countries surveyed and out of this group rucaparib is the most commonly problematic agent whereas olaparib is more commonly available.
2. Chemotherapy agents for non-EOC are available in all countries. However, topotecan and pegylated liposomal doxorubicin appear to be unavailable in 1 HIC and 1 LMIC and 1 HIC, respectively. Letrozole is also unavailable in South Africa.

Sources of healthcare expenditure

1. For the HICs most drugs are covered by the state with the exception of the US which is covered by insurance.
2. Patients have greater OOP in the LMICs and the LIC compared with HICs and UMICs.
3. Only in Australia and Mexico does pharma pay for any agents.

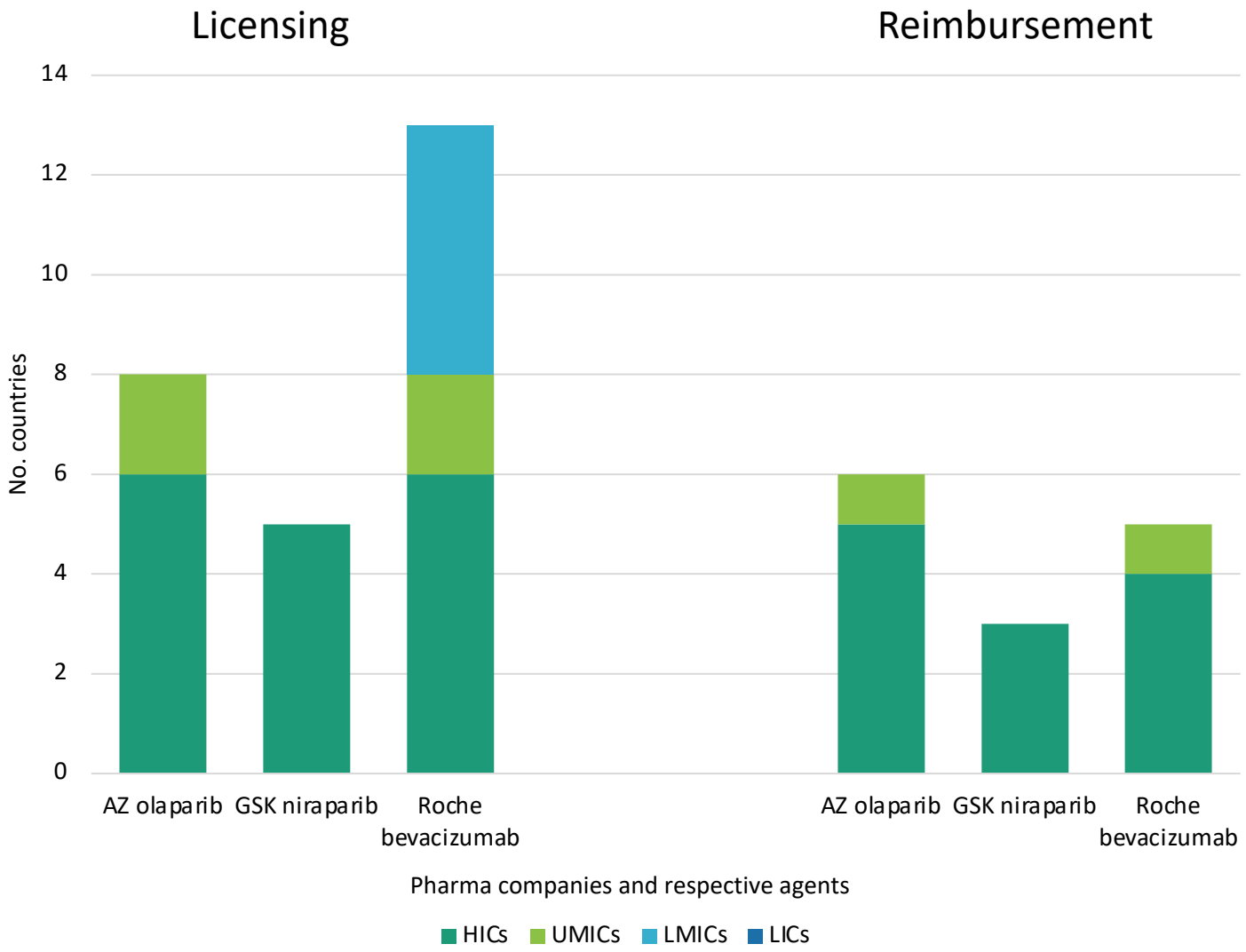
Who pays for the drugs?

1. In HICs the state appears to pay for ~75% of drugs on the 'essential' medicine list, a greater percentage compared with UMICs or LMICs. In HICs and UMICs the state pays for more medicine than in LMICs.
2. In LMICs and the LIC patients appear to pay for >50% of the agents on the 'essential' medicine list, more than either the state or insurance.
3. Pharmaceutical companies are not involved in paying for 'essential' medicines in the LMICs and the LIC surveyed.
4. For the chemotherapy agents the most common method payer was the state. Hormone and VEGF-A treatments were fairly similar although patients paid for a slightly greater proportion. The targeted agents showed a reduced proportion was paid by the state.
5. Pharmaceutical companies only paid for PARP inhibitors.

Discussion points from clinician survey results

- Are the conclusions of our report in agreement with your own experience?
  - If yes, can you expand upon any points raised?
  - If not, please clarify what aspects are different.
- How valuable is an EML for OC with at least one treatment from each drug class?
- What's the minimum requirement in terms of total number of drugs? (at present we have 15 drugs). Are all agents needed within a class, for example are all PARPs required or just one? What is the value of using a VEGF-A inhibitor? Is this list adequate for managing patients across the whole spectrum of disease from newly diagnosed to relapsed/ refractory patients?
- What are the challenges of introducing this list? Can LICs get access to targeted therapies and are they cost-effective in these regions? What other barriers to access can be foreseen? Are there ways to overcome these barriers?
- Do we need to add more countries to the list? In particular, would having more LICs give a clearer picture (currently only Sudan has been surveyed in this category)?
- Have we missed anything?

Summary of pharmaceutical company survey results



The graph on the left indicates the results from the 3 pharmaceutical companies so far. These have been plotted assuming a drug is either licensed or unlicensed (ignoring the number of licenses).

From the pharma results we can see that for the newer agent olaparib licensing and reimbursement occurred in HICs and UMICs.

Niraparib was only licensed and reimbursed in HICs

For bevacizumab there are also LMICs in which the agent is licensed but the drug is only reimbursed in HICs and UMICs.

UICC report

Key findings from UICC report (2019) on access to cancer treatments

- Inadequate public financing for universal access to essential medicines and leads to significant out-of-pocket (OOP) spending.
- Registration of products can take years (up to 5!) and limited negotiating power leads to inability to get the best prices and sustained supply.
- Medecin Sans Frontieres – lack of transparency on pricing of cancer medicines esp., on R&D and IP has led to market monopolies esp., for novel therapies. Need a socially responsible contract between public and private sectors as a first step to equitable access.
- Funds never enough to cover all therapies so trade off needed and based on value of novel therapies.
- Different systems have differing approaches to establishing 'value' e.g., economic value = C/E + BI considered; comparative effectiveness v commonly used active comparators; multi criteria assessment – economic factors, clinical value considered.
- Negotiation between Govt and Industry core part of P&R and could be overcome by e.g., managed entry agreements, negotiated access.
- Weak healthcare (HC) systems: fragmented and lack of investment in prevention and awareness campaigns, screening for early diagnosis, retention of HC workforce.
- ESMO – more resources needed generally, lack of health insurance schemes leading to OOP.

UICC report

Key findings from UICC report (2019) on access to cancer treatments cont.

- Inadequate/ inefficient procurement and supply says WHO due to outdated/ absent treatment guidelines on prescribing practices.
- Most treatments on WHO EML are off patent (generics and biosimilars) but often unavailable in LMICs.
- WHO: pooled procurement by UNDP and UNICEF could improve procurement.
- ESMO made available tools to improve treatment e.g., Guidelines for HCPs and Patients and development of a scale to assess magnitude of clinical benefit of novel therapies.
- ESMO – barriers to access divided in 2: access to innovative and access to inexpensive medicines. Countries should have their own national EML based on WHO's and systems in place to protect these medicines from shortages
- IFPMA – create regulatory reliance to increase speed of regulatory approval of established and newer medicines.
- Solutions: Nat Cancer Strategy: early diagnosis, screening, access to novel treatments. Invest in data systems (cancer registries). Alternative pricing mechanisms (WHO report on Cancer medicines pricing). More transparency around IP esp., of novel therapies. Improve HC and supply chain and others thought pricing policies – which is more important?
- Solutions: Universal HC needs to be high on agenda – investment in cancer control and health infrastructure to support this. Explaining health insurance – channelling taxes effectively and encouraging employers to make contributions to health issuance to lessen burden on OOP on patients. Clear and reliable data needed.

WHO report

WHO report on pricing of cancer medicines (2019)

- In general the countries with lower income had lower availability of cancer medicines or availability of cancer medicines only with higher OOP costs [non-European countries looking at WHO EML and breast, prostate, renal cell, melanoma, lung cancers].
- Availability of cancer medicines should be in considered within context of:
- Different countries and HC system contexts e.g., some cancers may not be necessary or useful e.g., no genetic profiling or skills of HC workers to safely prescribe and administer and some medicines may only confer marginal benefits and do more harm than good.
- 2017 Punjab study (Pakistan) showed higher availability of higher priced originators then lower priced generics and higher availability in private sector than public.
- Local production and transfer of technology needed e.g., storage facilities and reliable distribution network.

Key findings

- Women in HICs and UMICs have greater access to agents on the EML. In the countries surveyed more of the therapeutic agents on the list were routinely available and these countries were more likely to have government programs in place to allow for reimbursement of OC medication.
- This was backed up by the results from pharmaceutical countries which showed that EML medicines were more likely to be licensed and reimbursed in HICs and UMICs.
- In particular, newer agents such as PARP inhibitors were the least likely to be available in low income countries.
- Patients in the LMICs and the LIC surveyed depend on OOP expenditure for drug access, which effectively means the majority of women cannot afford to be treated for OC even if EML treatments are available in these countries.
- Ensuring availability is not enough in LMICs and the LIC. Therapeutic agents must be made affordable to women in these countries, which is a difficult and complicated task.

WOCC statement

The WOCC is shocked at the huge variation in access to ovarian cancer treatments as result of the research we have carried out looking at differences between high and low income countries.

WOCC approached a number of clinicians in 13 countries globally covering high, low-middle and low income countries and asked about their experience of access to treatments and who pays for them. Alongside this, we asked four manufacturers of the newer VEGF-A and PARPi treatments.

Clinicians told us that of the five different 'classes' of ovarian cancer drugs – chemotherapies for EOC, chemotherapies for non-EOC, hormone treatments, PARPi, VEGF-A - that high income countries tend to have more of these classes routinely available to clinicians and within each class there are more options. Upper middle and lower middle tend to have fewer drug classes routinely available with Zambia having none of the 'essential' ovarian cancer drugs routinely available.

The PARP inhibitors are the most frequently unavailable class of agents in the countries surveyed with 10 out of the 13 countries surveyed saying at least one was not available and only 3 saying all 3 were available.

Most shocking is that patients in LMIC appear to pay for more than half of the drugs on the essential medicines list, more than the state or insurance.

In high income countries, the state appears to pay for about three quarters of the drugs on the 'essential list', a greater percentage than in UMICs or LMICs.

Discussion points

- Are the conclusions of our report in agreement with your own experience?
  - If yes, can you expand upon any points raised?
  - If not, please clarify what aspects are different.
- Do any areas require further investigation?
- If there is inequality in access to agents on the EML, what do you think are the reasons for this? Please include both country-specific issues and more global points.
- Can any of these issues be solved? If so how?
- What are the actions at a global level as a result of this?

What are the actions for WOCC members?

- Please reflect on our findings and afterwards we would appreciate you feedback.
- We will in turn provide a template/ toolkit to enable members to carryout a similar data finding exercise in their own country.

Appendix 1– useful articles

- https://www.biospectrumindia.com/news/43/18764/bdr-pharma-launches-ovarian-and-prostate-cancer-tablets-in-india.html
- https://ca.gsk.com/en-ca/media/press-releases/2021/gsk-s-zejula-is-recommended-for-reimbursement-by-cadth-and-inesss-for-advanced-ovarian-cancer-following-response-to-first-line-platinum-based-chemotherapy/
- Garcia, A., & Singh, H. (2013). Bevacizumab and ovarian cancer. *Therapeutic advances in medical oncology*, *5*(2), 133–141. https://doi.org/10.1177/1758834012467661.
- https://www.who.int/publications/m/item/technical-report-on-pricing-of-cancer-medicines-and-its-impacts - WHO report on Pricing of Cancer Medicines and its impacts (2019)

Appendix 2: AZ research

Access programs

- Within the high-income countries chosen for Wave 1, two types of patient access program can be identified:
    - early access regulatory tools such as the Cnn program in Italy, which allows early access to drugs after regulatory approval
    - “bridging” programs where patients who would normally have to pay for a drug are able to access it free-of-charge as a bridge until reimbursement is provided. One such “bridging” program was recently closed in Australia in newly diagnosed BRCAm OC (SOLO1), due to the Commonwealth Government’s decision to reimburse this indication.
- In addition to the above access programs, patient support programs are also available in the United States to mitigate any costs shared by insurers with patients in order to support broader, more equitable access.
- In low and middle income countries, where reimbursement systems are less well developed and the predominant funding mechanism for patients paying for drugs is self-funding / out-of-pocket, then patient assistance programs are typically used to support access.
- Out of the Wave 1 countries, AZ provides patient assistance programs in Mexico, South Africa and India. These patient access programs typically contribute towards the affordability for patients through the provision of free-of-charge goods, as well as other services and are typically managed through third party organisations. In Mexico for example, where there is a variety of different funding mechanisms for pharmaceuticals, including private insurance, public funding but also OOP/ self-pay, AZ supports patients paying OOP for Lynparza through the provision of a patient assistance program which provides means-tested free-of-change goods in addition to those paid for by individual patients. This program takes into account the large differences in wealth within Mexico but also looks to provide differential support dependent on the episode of care costs across Lynparza’s different indications.

AZ research: early access and compassionate use programs

- Early access programs (pre-approval) are supported broadly by the pharmaceutical industry.
- AstraZeneca up until recently provided an early access program for Lynparza for patients with newly diagnosed BRCAm ovarian cancer (SOLO1). This program entered 201 patients from France under an ATU and a total of 382 patients were entered from the rest of the global program (583 patients in total). This program is now closing as regulatory approvals and reimbursement are increasingly being established in the countries within which it operated.
- **AstraZeneca currently does not support a compassionate use program for Lynparza**, however *ad hoc* requests from clinicians / patients are received sporadically. These request are managed at a country level on a case-by-case basis and in line with local regulations and legislation.

AZ research: additional barriers to access

- Access to medicine is a complex and multi-factorial issue. In some countries access to surgery and even access to basic chemotherapy poses a significant barrier to use of new technologies. At a more fundamental level, in some countries e.g. India, transportation from rural areas to hospitals can also create a further barrier to equitable access to healthcare.
- While differences in the level of access to healthcare and pharmaceuticals exist across countries, it should be recognised that there are also high levels of inequalities within countries. An example of a country with significant internal disparities in terms of access to medicines is South Africa (South Africa has the highest GNI index in the world at 63% according to Worldbank estimates). Interestingly, pricing systems exist in South Africa that make it challenging for drugs to be provided at a lower cost to certain parts of the population than to others. This has the potential to further impede access for the less wealthy populations, but in turn this need for legislation changes to support broader affordability needs to be balanced against a risk of system exploitation.
- However, even in high-income countries where adequate reimbursement is available, barriers still exist to access for some patients. Examples of such barriers include delays to reimbursement after regulatory approval, as well as in the case of Lynparza, delays in the introduction of diagnostic capabilities in a country and complex funding pathways for diagnostic reimbursement.