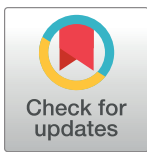


## REVIEW

## Advancing oncology drug therapies for sub-Saharan Africa

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## Abstract

Cancer incidence is rising across sub-Saharan Africa (SSA), and is often characterized by late-stage presentation, early age of onset and poor survival. While a number of oncology drugs are now improving the length and quality of life for cancer patients in high-income countries, significant disparities in access to a range of oncology therapeutics exist for SSA. A number of challenges to drug access such as drug costs, lack of infrastructure and trained personnel must be urgently addressed to advance oncology therapies for SSA. We present a review of selected oncology drug therapies that are likely to benefit cancer patients with a focus on common malignancies in SSA. We collate available data from seminal clinical trials in high-income countries to highlight the potential for these therapeutics to improve cancer outcomes. In addition, we discuss the need to ensure access to drugs within the WHO Model List of Essential Medicines and highlight therapeutics that require consideration. Available and active oncology clinical trials in the region is tabulated, demonstrating the significant gaps in access to oncology drug trials across much of the region. We issue an urgent call to action to address drug access due to the predicted rise in cancer burden in the region in coming years.

## Introduction

Cancer incidence is rising across sub-Saharan Africa (SSA), and is often characterized by late-stage presentation, early age onset, aggressive disease and poor survival [1]. The distinct cancer epidemiology in SSA is driven by a high burden of infectious disease-related cancers, combined with rising lifestyle-related cancers due to factors such as increased tobacco use and excess body weight [2]. In addition, changes to female reproductive patterns and an ageing population are contributing to cancer risks [1]. Highly prevalent infectious diseases in SSA are causally associated with malignancies including cervical cancer and Kaposi sarcoma [3]. Cancers for which preventative measures are routinely offered in high income countries (HIC), such as breast, prostate and cervical cancer are advanced at presentation in SSA, because of a lack of organized screening and early detection programs [4]. In addition, evidence suggests that differences

between tumour molecular subtypes prevalent in SSA impacts mortality in the absence of effective therapeutics [5]. This changing profile of risks and rising burden of cancer requires urgent and comprehensive approaches to expand access to oncology therapeutics in SSA.

Our understanding of the epidemiology of cancer in SSA is limited by a dearth in reliable cancer registries [6, 7], however, it is predicted that in SSA the cancer burden will double by 2050 [3]. Available data from cancer registries demonstrates increasing breast cancer incidence in 9 countries across the four SSA regions [3]. Registry data from Kampala, Uganda and Harare, Zimbabwe found a 4.5% and 4.9% average annual increase in breast cancer incidence, respectively. In addition, trends in 8 SSA countries over a 10-25-year period, found increasing incidence of cervical cancer, especially in Eastern Africa [8]. The cumulative risks and ASIR of prostate cancer have increased over time in the region [9]. For example, in Kampala, Uganda, an average annual percentage increase of 5.2% was found between 1991–2010 for prostate cancer [10]. Although few studies have discussed temporal trends in Kaposi Sarcoma (KS) in SSA, it is apparent that HIV-attributable KS is the highest in the region compared to other world regions [11]. Furthermore, the incidence of early-onset cancers is also rising globally. Risk factors implicated include multigenerational changes in diet, lifestyle, obesity, environment and the microbiome, and their interactions with genomic and/or genetic susceptibilities [12].

The rapid evolution of precision oncology therapies is increasingly transforming the length and quality of life for cancer patients in HICs. In SSA, however, in many settings, basic levels of cancer care, treatment and palliation are limited. Such inequities in treatment access contribute to the generally poor survival outcomes across most malignancies. In 2020, Africa's contribution to global cancer mortality (7.2%) was greater than its contribution to global cancer incidence (5.7%), indicating higher case fatality rates compared with other regions [1]. Multiple barriers affect the ability of many cancer patients in SSA to access treatment and realize the benefits of advances in oncology drug therapies. These range from lack of infrastructure for molecular testing for driver mutations and biomarker expression, managing the unique set of adverse effects of newer drugs, such as immunotherapies, and shortages in healthcare workers adept in specialized cancer care. The cost of many new Food and Drug Administration (FDA) approved oncology drugs remains prohibitive, and there are extremely limited opportunities for access to these agents even in controlled clinical trials in the region. For patients, evidence suggests a lack of education and poor awareness of cancer signs and symptoms results in late-stage presentation. In Rwanda, lower education levels were significantly associated with lengthy delays to cancer diagnosis [13] and symptoms were attributed to benign co-morbid disease [13–15]. Seeking care from a traditional healer contributes to further delays and there is evidence that stigma and a lack of social support form additional barriers [16, 17]. Furthermore, geographic inequities in access to cancer facilities across SSA impacts cancer outcomes [18].

Despite these challenges, concerted efforts must be made to ensure inequities in access to cancer therapies are urgently addressed in SSA. Here, we review certain oncology drugs that are likely to have high-impact and durable benefit if expanded in SSA. We focus on cancers in SSA that have a high prevalence and high burden of disease including Kaposi sarcoma, prostate cancer, breast cancer, cervical cancer, and non-small cell lung cancer. In the context of advanced disease at presentation for most of these cancers in SSA, priorities are suggested to advance access to therapies in the region, with a focus on first-line treatments which have the greatest potential for therapeutic impact.

## Kaposi sarcoma

SSA carries a disproportionate burden of Kaposi sarcoma (KS) due to the endemic nature of the human herpes virus-8 and the human immunodeficiency virus (HIV) and acquired

immunodeficiency syndrome (AIDS) epidemic. The incidence of KS in SSA has increased 20-fold since the onset of the HIV epidemic in the early 1980s [19]. KS is relatively rare globally, however, there were approximately 34,000 new cases and 15,000 deaths in 2020, largely in Southern and Eastern Africa. There are regional variations in SSA with highest age-standardised incidence rates (ASIR) found in Southern Africa approximating 9/100,000, compared with 6/100,000 in Eastern Africa, and 0.9/100,000 in Western Africa.<sup>1</sup> Available data from the Africa Cancer Registry Network found a rapid increase in KS prior to antiretroviral therapy (ART), however, an overall average decline after ART between 2000 and 2010 and 2011–2016 [20]. While ART has reduced the incidence of AIDS associated KS, there remains ongoing significant morbidity and mortality from KS in the region [21].

Management for AIDS associated KS is driven by tumor location, extent of disease, CD4 + T cell count and overall clinical condition. Since most cases of KS that require intensive treatment are associated with HIV, it is imperative for all patients living with HIV to receive ART. Cutaneous lesions can be treated with ART, topical alitretinoin or imiquimod cream, radiation therapy, intralesional vinblastine chemotherapy, or local excision. However, in SSA, patients often present later in the disease course with advanced cutaneous, oral, visceral, or nodal disease. In HICs, chemotherapy with liposomal daunorubicin is recommended for advanced disease given its favorable toxicity profile.

Paclitaxel, however, has similar efficacy with 78% 2-year survival compared to 79% for liposomal daunorubicin (Table 1) [22]. A study of AIDS-associated Kaposi sarcoma in SSA and South America demonstrated the superiority of paclitaxel compared to etoposide, and bleomycin with vincristine. These findings were significant in that paclitaxel survival benefits may be comparable to liposomal daunorubicin, yet it is much more affordable and readily available in SSA [23]. As the first large clinical trial comparing chemotherapy for KS in SSA in over a decade, this study underscores the paucity of clinical trials for KS in SSA compared to the significant burden of disease in the region (Table 2). There is comparatively less interest in studying novel therapies for KS, however, one recently published trial of 17 patients in France demonstrated preliminary efficacy of pembrolizumab [24].

## Prostate cancer

Prostate cancer is the leading cause of cancer death among men in 48 countries, including many in SSA [19]. There is, however, substantial regional variation in the incidence of prostate cancer across SSA, with the highest ASIR in the region found in Southern Africa approximating 66/100,000 in 2020, compared with Western and Eastern Africa where ASIR approximates 30/100,000 [1]. Mortality rates are high in SSA, with age-standardized mortality rates (ASMR) in 2020 approximating 22/100,000, 20/100,000 and 16/100,000 in Southern, Western and Eastern Africa respectively. While data are very limited, a median overall survival of only 11 months was reported for metastatic castrate resistant prostate cancer (mCRPC) in a series from Nigeria [25]. Treatment with surgical castration is widespread in SSA, with limited use of luteinizing hormone releasing hormone (LHRH) analogues, oral anti-androgens (bicalutamide and flutamide), or docetaxel [26, 27]. For metastatic prostate cancer, androgen deprivation therapy can provide symptom relief and improve survival. The disease invariably becomes resistant to hormone therapy however, leading to development of mCRPC.

Newer generation oral hormone therapy may have an expanded role in SSA, in both the castrate-sensitive and castrate-resistant settings. Abiraterone is a well-tolerated drug which blocks synthesis of androgens and is given in combination with low dose prednisone. Based on data showing significant survival benefit, abiraterone with prednisone was initially approved by the US FDA in 2011 for patients with mCRPC who had received prior chemotherapy and

Table 1. Selected review of high impact clinical trials\* related to recommended current standard of care for common malignancies.

Tumor Type	Drug	Overall Survival (OS)	Progression-free Survival (PFS)	Dates of patient enrollment	Study Population	n	Trial (Reference)
Kaposi Sarcoma	Paclitaxel vs. pegylated liposomal doxorubicin	At 2 years, OS 79% vs. 78%	17.5 vs 12.2 mo	1998–2002	HIV associated KS	73	Cianfrocca et al. Cancer. 2010
	Paclitaxel vs. intravenous bleomycin + vincristine vs. oral etoposide		At 48 weeks, 64% vs. 50% vs. 20%	2013–2018	Advanced AIDS associated KS	334	Krown, et al. Lancet 2020
Prostate	Abiraterone + Prednisone vs. Placebo	53.3 months vs. 36.5 months with placebo; HR 0.66		2013–2014	Newly diagnosed metastatic castrate sensitive	1199	LATITUDE
	Docetaxel + ADT vs. ADT. alone	58 versus 47 months With ADT alone; HR 0.72	33 vs. 14.8 mo; HR 0.47	2006–2012	Newly diagnosed metastatic castrate sensitive	790	CHAARTED
	Abiraterone + Prednisone vs. ADT alone	83% versus 76% with ADT alone at 3 years; HR 0.63		2011–2014	Newly diagnosed metastatic castrate sensitive	1917	STAMPEDE
	Enzalutamide + ADT vs. ADT alone	80% vs 72% at 3 years	Clinical Progression—EFS at 3 years, 68% and 41%, HR 0.40; PSA progression—EFS at 3 yrs —67% vs. 37; HR -0.39	2014–2017	Newly diagnosed metastatic castrate sensitive	1125	ENZAMET
	Apalutamide + ADT vs. ADT alone (prior docetaxel allowed but not concurrent)	82% vs 74% at 2 years, favoring apa HR 0.67	rPFS at 24 months 68% vs 48% favoring apa HR 0.48	2015–2017	Newly diagnosed metastatic castrate sensitive	1052	TITAN
Breast	Pertuzumab + Trastuzumab/ Docetaxel vs. Trastuzumab/Docetaxel alone	41.8% vs. 54.4%; HR 0.6	18.7 vs. 12.4 mo; HR 0.68	2008–2010	HER2+ metastatic, unresectable, or locally recurrent breast cancer	808	CLEOPATRA
	Trastuzumab for 1 year, Trastuzumab for 2 years, or observation only	Survival rates at 12 years were 79% in the 1-year group, 80% in the 2-year group, and 73% in the observation group	Rates of 10-year disease-free survival were 69% in both trastuzumab groups and 63% in the observation group.	2001–2005	HER2-positive breast cancer after standard adjuvant chemotherapy	5081	HERA
	Trastuzumab deruxtecan vs. Trastuzumab emtansine	At 12 months, the percentage of patients who were alive without disease progression, as assessed by blinded independent central review, was 75.8% (95% CI, 69.8 to 80.7) with trastuzumab deruxtecan as compared with 34.1% (95% CI, 27.7 to 40.5) with trastuzumab emtansine	Median PFS was not reached (95% CI, 18.5 to could not be estimated) in the trastuzumab deruxtecan group and was 6.8 months (95% CI, 5.6 to 8.2) in the trastuzumab emtansine group.	2018–2020	HER2-positive metastatic breast cancer after progression on taxane and trastuzumab (second line)	524	DESTINY-Breast03
	Anastrozole/Letrozole + Abemacicib vs. placebo	46.7 vs. 37.3 mo, HR 0.757	6.4 vs 9.3 mo., HR, 0.553	2014–2015	HR+/HER2-negative advanced breast cancer	669	MONARCH-2
	Fulvestrant + Ribociclib vs. placebo	57.8% vs. 45.9% at 42 mo, HR 0.72	33.6 vs. 19.2 mo, HR 0.55	2015–2016	HR+/HER2-negative advanced breast cancer	726	MONALEESA-3
	Fulvestrant + Palbociclib vs. placebo	39.7 mo. vs. 29.7 mo., HR 0.72	9.5 vs. 4.6 mo, HR 0.46	2013–2014	HR+/HER2-negative advanced breast cancer	521	PALOMA-3
	Atezolizumab plus nab-Paclitaxel vs. placebo plus nab-Paclitaxel	21.3 mo vs. 17.6 mo; HR 0.84	7.2 mo vs. 5.5 mo; HR 0.8	2015–2017	Untreated locally advanced or metastatic TNBC	902	IMpassion130

(Continued)

Table 1. (Continued)

Tumor Type	Drug	Overall Survival (OS)	Progression-free Survival (PFS)	Dates of patient enrollment	Study Population	n	Trial (Reference)
Cervical	Cisplatin + Paclitaxel vs. Cisplatin + Topotecan	15 vs. 12.5 mo, HR 1.2	7.6 v. 5.7 mo, HR 1.39	2009–2012	Metastatic or recurrent	452	GOG-240
	Chemotherapy (Paclitaxel + Cisplatin or Carboplatin +/- Bevacizumab) + Pembrolizumab vs. Placebo	53% vs. 42% at 24 mo, HR 0.64	10.4 vs. 8.2 mo, HR 0.62)	2018–2020	PD-L1 positive metastatic or unresectable, not previously treated in the recurrent or metastatic setting	548	KEYNOTE-826
Lung	Pembrolizumab + chemotherapy	61.7% vs. 52.2% at 12 mo; HR 0.55	34.1% vs. 17.3% at 12 mo; HR <1	2016–2017	metastatic non-squamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous treatment for metastatic disease	616	KEYNOTE-189
	Osimertinib vs. comparator TKIs	38.6 mo vs. 31.8 mo; HR 0.8	18.9 mo vs. 10.2 mo; HR 0.46	2014–2016	previously untreated advanced NSCLC with an EGFR mutation (exon 19 deletion or L858R allele)	556	FLAURA

\*Most studies have been performed in HICs

Legend: OS—overall survival; PFS—progression free survival; HR—hazard ratio; ADT—androgen deprivation therapy; KS—Kaposi Sarcoma; NSCLC—non small cell lung cancer; mo—months

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then expanded to chemotherapy-naïve patients. Due to significant benefits in the castrate-sensitive group, indications were expanded in 2018 for patients with newly diagnosed castrate-sensitive metastatic prostate cancer. Overall, the therapy was well tolerated with notable side effects being hypertension and hypokalemia [28]. Updated data from the STAMPEDE study demonstrated a median survival of 6.6 years with addition of abiraterone with prednisone to standard androgen deprivation therapy (ADT), compared with 3.8 years with ADT alone [29]. Survival benefits have also been demonstrated with addition of either enzalutamide or apalutamide to ADT in patients with newly diagnosed mCRPC (Table 1). The addition of chemotherapy with docetaxel also has a demonstrated survival benefit [30]. The emerging evidence clearly demonstrates that intensifying therapy for men with metastatic prostate cancer earlier in disease course, even in the castrate-sensitive setting, has clear survival advantage.

PARP inhibitors, such as olaparib, have a role in patients with mCRPC with certain molecular profiles, particularly BRCA 2 [31]. Molecular profiling capabilities are, however, required, and the extent of BRCA 2 mutations in SSA populations remains poorly characterized at present. Therapeutic options including chemotherapy, immunotherapy and radiopharmaceuticals also clearly have an established role for management of mCRPC, however rapidly expanding availability of newer generation oral hormone therapy is likely to have important impacts. This is reflected by the inclusion of abiraterone with prednisone in the World Health Organization (WHO) Model List of Essential Medicines (MLEM) (Table 2). Though enzalutamide and apalutamide also have proven benefit in the castrate-sensitive metastatic prostate cancer setting, abiraterone may be preferred for several reasons. As the first of the newer generation hormone therapies to become available, abiraterone will likely have multiple generic options available first, with hopes of reduced pricing in the future. Cost savings could also be achieved by alternative dosing with food [32].

Table 2. Overview of oncology drugs in the WHO model list of essential medicines for common malignancies in sub-Saharan Africa.

	WHO MLEM oncology therapies	Biosimilars/ generic availability	Patent expiry date	WHO recommended essential diagnostic tests	Number of active pharmacologic intervention trials by cancer in SSA (as of 10/31/21)
Kaposi Sarcoma	Bleomycin Doxorubicin Paclitaxel Vincristine Vinblastine (topical)	Generics available for all		N/A	3 (3 in Uganda, 1 each in South Africa, Malawi, Kenya)
Prostate	Abiraterone Bicalutamide Docetaxel Leuprorelin Prednisolone	Generics available for all	Abiraterone—2027	Prostate specific antigen (PSA)	6 (6 in South Africa)
Breast	Anastrozole Carboplatin Cyclophosphamide Docetaxel Doxorubicine Fluorouracil Leuprorelin Methotrexate Paclitaxel Tamoxifen Trastuzumab*	Generics available for all *Trastuzumab biosimilar available		Estrogen and progesterone receptors via IHC; ERBB2/HER2 expression via IHC	15
Cervical	Carboplatin Cisplatin paclitaxel	Generics available for all		Pap smear	2 (1 in South Africa, 1 in Ghana)
Lung	Carboplatin Cisplatin Erlotinib Etoposide Gemcitabine Paclitaxel Vinorelbine	Generics available for all	Erlotinib -2020 (expired)	N/A	14 (14 in South Africa)

Legend: N/A- not applicable; IHC- immunohistochemistry

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## Breast cancer

The incidence rates of breast cancer in SSA are low compared to HICs, however, these rates are rapidly rising [6]. In Southern Africa ASIR approximated 50/100,000 in 2020 with mortality rates among the world's highest due to late-stage presentation and lack of screening programs [1]. In addition, evidence suggests a higher percentage of hormone receptor negative or triple negative disease in the region, both of which are associated with a poorer prognosis [33].

Treatment for breast cancer greatly differs based on hormonal status and human epidermal growth factor (HER2) expression status. Accurate profiling, however, is dependent on methods used for tissue collection, fixation, and immunohistochemical staining, which are not standardized in SSA. Hormonal therapy, including drugs such as tamoxifen and aromatase inhibitors (anastrozole, letrozole, or exemestane), is indicated for hormone-receptor positive tumors. While access to aromatase inhibitors remains limited, tamoxifen is inexpensive and even free of charge in some countries, making it the most readily available drug for breast cancer in SSA [33–35]. Consequentially, patients whose hormone receptor status is unknown may empirically receive tamoxifen. While routine testing for hormone receptor status prior to treatment initiation is uncommon, in a recent meta-analysis of five East African countries, 55% of women with breast cancer were estrogen receptor (ER) positive compared to 72% in the

United States [36]. However, only those who are hormone receptor positive are expected to benefit from treatment with tamoxifen, hence patients are often exposed to the potential harms of tamoxifen with no therapeutic advantage [37, 38].

The predominant chemotherapy regimens for patients with HER2 negative disease are anthracycline based regimens such as doxorubicin and cyclophosphamide followed or preceded by a taxane (paclitaxel or docetaxel), or anthracycline free regimens such as docetaxel and cyclophosphamide. The WHO MLEM includes agents such as carboplatin, cyclophosphamide, doxorubicin, and paclitaxel, but availability and access to these drugs appears limited. For example, in a population-based registry study of 834 patients in 11 countries in SSA, only 33.6% received chemotherapy, of which 52% received an anthracycline based regimen and 32% received an anthracycline with a taxane [39].

The advent of HER2 targeted drugs have transformed the management and prognosis of HER2 positive breast cancer in HICs. The HERA trial established the role of trastuzumab after adjuvant chemotherapy in HER2 positive breast cancer patients by demonstrating significantly improved disease-free survival (DFS) and overall survival (OS) [40, 41]. Unfortunately, trastuzumab has historically been cost-prohibitive [42]. While some studies estimate that 50% of facilities in SSA have trastuzumab available, less than 5% of patients were able to afford it [33]. The advent of biosimilars since 2019, however, are now facilitating price reductions to \$600–800 dollars per vial in SSA countries (Table 2) [43].

There is a high incidence of triple negative breast cancer (TNBC) in SSA, and this breast cancer pathologic subtype is negatively associated with survival [44, 45]. Two immunotherapy drugs, atezolizumab and pembrolizumab, are approved for use in the US in combination with chemotherapy for patients with metastatic TNBC whose tumors have high expression of PD-L1, based on the results of the IMpassion130 and KEYNOTE-355 trials [46, 47]. Unfortunately, predictive biomarker testing that is required to identify patients with PD-L1 positive tumors is not widely available in SSA. In addition, immunotherapy is associated with rare but serious adverse events that require routine monitoring and specialized management. Therefore, there is a need to develop further training and infrastructure to support the use of these effective drugs.

Other targeted drugs are integral parts of the treatment landscape for metastatic breast cancer, such as targeting PI3Kinase, mammalian target of rapamycin, and cyclin dependent kinases (CDKs). Of these drugs, the CDK 4/6 inhibitors have shown the greatest benefit and the fewest side effects. The addition of CDK4/6 inhibitors to hormonal therapy with aromatase inhibitors or fulvestrant showed a significant and clinically meaningful survival benefit in first- and second-line metastatic settings (see Table 1) [48–50]. Given the limited toxicity profile of CDK4/6 inhibitors compared to chemotherapy and their oral administration, they have the potential to improve care more widely in SSA (see Table 2). The challenge for implementation is the elevated cost of CDK4/6 inhibitors, as well as the limited availability of tumor profiling.

## Cervical cancer

In SSA, cervical cancer (CC) is the leading cause of female cancer related death and the second most common cancer among women [4, 8]. Globally, the highest incidence and mortality rates are in SSA with ASIR of 40/100,000 in Eastern Africa and 37/100,000 in Southern Africa in 2020 [1]. This higher incidence in SSA parallels HIV-infection rates—as an AIDS-defining illness HIV-positive women have a 6-fold higher risk of CC due to higher infection and persistence rates of cervical oncogenic Human Papilloma Virus (HPV) genotypes. Primary prevention through adolescent HPV vaccination programs have been launched in SSA, however, will take several decades to impact CC incidence [51]. In addition, expanding coverage of

accessible, affordable, and high-performance cervical screening programs has been challenging due to financial, logistic, and sociocultural barriers [52]. Due to the preventable nature of CC, the WHO has launched a strategy for the global elimination of cervical cancer focusing on rapid scale-up of vaccination, screening and treatment of pre-cancers and CC.

The standard of care for management of patients with locally advanced CC disease is chemoradiation. The preferred chemotherapy in conjunction with radiation is cisplatin [53]. A study which included twenty-nine centers from twelve SSA countries found that appropriate chemotherapeutic agents were available in 86% of centers. However, one-third of centers reported having to delay treatments or substitute with alternate chemotherapeutic agents due to inconsistent supply. In addition, almost half of the centers utilized neoadjuvant chemotherapy due to delays in availability of surgery and radiotherapy [54].

Radiotherapy is integral to the management of advanced CC but there is limited access in SSA due to the need for trained personnel for equipment maintenance and optimal implementation [55]. In addition, maintenance and repair of linear accelerators and lack of access to a stable and reliable power supply may result in downtime of equipment, ultimately leading to treatment delays for patients [56]. In an observational study of 632 patients from eight SSA countries, only 13% of patients with known stage I–III CC received primary external beam radiation therapy and brachytherapy [57].

In addition to concurrent chemoradiotherapy for localized disease, chemoimmunotherapy (with pembrolizumab in combination with a platinum doublet) was FDA approved in October 2021 for persistent, recurrent, or metastatic cervical cancer patients whose tumors are PD-L1 positive [58]. Given many women progress while waiting for radiotherapy, improving access to testing for PD-L1 status and the capacity of providers with expertise in managing immunotherapy, should be considered to expand the feasibility of this option in SSA.

## Lung cancer

The burden of lung cancer in SSA is expected to increase in parallel to the tobacco epidemic, with greater affordability and marketing of tobacco products in the region [4]. In SSA, lung cancer rates are highest in Southern Africa with ASIR of 27/100,000 in 2020 compared with Eastern Africa with ASIR of 4/100,000 [1]. In HICs, molecular targeted therapies for lung cancer have achieved substantial survival benefits. Current standards for management of lung cancer involve first identifying histologic subtype via immunohistochemistry (IHC) to differentiate between small cell (SCLC), non-small cell (NSCLC), or squamous cell lung cancer (SLC). In most HICs, testing NSCLC for mutations in EGFR, BRAF, KRAS, and ALK and ROS1 gene rearrangements via liquid biopsy, next-generation sequencing (NGS), and/or fluorescent in-situ hybridization is common [59, 60]. At a minimum, mutations in EGFR, ALK status, and PDL1 status via IHC should be known before starting first-line systemic therapy because regimens for patients with these mutations can differ drastically [59].

Traditionally, recommended treatment for patients with metastatic NSCLC has been chemotherapy with a platinum-based combination regimen. However, median survival for patients receiving chemotherapy alone approximates to 10 months, with 1-year survival of only 30–40%, and 5-year overall survival of approximately 6% [61–66]. Survival rates are higher for stage IV NSCLC patients who are eligible for either targeted therapy or immunotherapy regimens, which increased overall survival from 10 to 24 months in those receiving EGFR- tyrosine kinase inhibitor (TKI) therapy versus those who did not [67–72]. Afatinib, erlotinib and gefitinib are therefore included in the WHO MLEM. However, patients often develop mutations which result in resistance to these agents. Osimertinib, which inhibits both EGFR sensitizing mutations and T790M, a common resistance mutation in EGFR mutated



NSCLC, was approved in 2020 in the United States, however, is not listed in the WHO MLEM at present. Osimertinib, has achieved median overall survival exceeding 45 months, far greater than other TKIs. [73]. The notable impact of osimertinib for NSCLC suggests that it should be the TKI of choice and considered in the WHO MLEM.

In the population of stage IV NSCLC patients without a driver mutation, immunotherapy with pembrolizumab is recommended either as a single agent in patients with high PDL1 expression, or in combination with chemotherapy in those with low PDL1 expression. In patients with PDL1 expression in at least 50% of tumor cells, overall survival is doubled in patients who receive pembrolizumab monotherapy compared with those who receive chemotherapy (30 vs 14.2 months) [74]. Long-term data from trials have shown 5-year survival for patients upwards of 23% for those who received first-line pembrolizumab monotherapy [66, 68]. Overall survival was also improved by chemotherapy regimens combined with pembrolizumab regardless of PD-L1 expression levels [75].

The number of agents that are approved and under investigation for NSCLC are increasing worldwide, however, access remains extremely limited in most settings in SSA (Table 2) [76]. One review of lung cancer management in South Africa noted that for private sector patients with EGFR mutations, only erlotinib is available for first line use, osimertinib is available in the second line setting and crizotinib is the only drug available for ALK positive patients [76].

For management of NSCLC to be optimal in SSA, identifying mutations in EGFR and PDL1 expression are essential to direct care. In addition, EGFR inhibitors, particularly osimertinib, and immunotherapy, particularly pembrolizumab, are two targeted therapies that have the potential to improve outcomes of NSCLC patients in SSA if given as first-line.

### Tissue agnostic therapeutics for multiple solid tumors

Both hereditary and sporadic cancers arising at several anatomical sites including colon, rectum, endometrium, ovary and gastric adenocarcinoma may have mismatch repair deficiency (dMMR) or microsatellite instability-high (MSI-H), which have treatment implications [77]. In an analysis of MSI-H in 39 tumor types across 11,139 samples, MSI-H was found in 31% of endometrial cancers, 19% of stomach and 19.7% of colon adenocarcinomas [78]. While far more research is needed, available data suggests even higher rates of MSI-H were found in solid tumors from SSA. For example, in a sample of 90 colorectal cancer biospecimens in Ghana and 83 specimens in Nigeria, MSI-H was found in 41% and 43% of samples respectively [79, 80]. Another study of 83 cases from KwaZulu Natal in South Africa, found MSI-H in 31.3% of colorectal cancer patients below age 35 years, and 12% in cases over 50 years [81].

The US FDA granted accelerated approval of pembrolizumab in May 2017 for patients with advanced previously treated solid tumors found to be MSI-H which has heralded the potential for histology-agnostic management regardless of site of origin for solid tumors [82]. Pembrolizumab approval was based on safety and efficacy results in 149 patients with MSI-H solid tumors that had progressed after standard treatment, who were enrolled in one of five multi-center, single-arm clinical trials (KEYNOTE-016, -164, -012, -028, and -158) [83]. The overall response rate was 39.6%, and importantly, responses lasted six months or more for 78% percent of responders, with 7.4% achieving complete responses [84].

Therapeutics that are tissue -agnostic raise the prospect of enabling the use of a select range of drugs across a wide range of solid tumors, with potential advantages in terms of costs, training and infrastructure needs in resource limited settings in SSA, especially if research suggests higher rates of MSI-H among SSA populations. A small number of trials of pembrolizumab which are histology-agnostic are, therefore, being conducted in South Africa evaluating gastro-intestinal and gynecological cancers.

## Discussion

In SSA, the choice of public sector pharmaceuticals is often guided by the WHO MLEM, which are selected based on three broad criteria including disease prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative cost-effectiveness. In addition, resource stratified guidelines are published by the National Comprehensive Cancer Network, however, evidence regarding the translation of guidelines into real-world practice is lacking. A survey of oncologists across low-, middle-, and high-income nations demonstrated concordance with the WHO MLEM but found significant barriers to the availability of therapies included in the WHO MLEM [85]. While even basic levels of palliative care or consistent supply of cytotoxic agents are still not widely available in many SSA settings, the inclusion of immunotherapies in the 2019 WHO MLEM signals an increasing recognition of the potential advantages of precision therapeutics in LMICs. While the 2019 MLEM only listed immunotherapy for metastatic melanoma due to high prices and concerns regarding effective administration in settings without appropriate infrastructure, one could argue that if capacity is built for treatment of melanoma, wider indications to NSCLC and other solid tumors will be feasible, widening the population for which quality of life and survival benefits may be realized.

The availability of molecular profiling of cancers is of paramount importance, particularly for certain cancers such as lung cancer for which targeted therapies have had a major impact on prognosis.

The presence of BRCA1/2 mutations in breast and prostate cancer, as well as BRAF mutations in melanoma, are other examples where molecular profiling can impact cancer therapeutics. Unfortunately, data on genomic profiles of cancer in patients in SSA is extremely limited [86]. Of worldwide cancer publications addressing genomics, only 0.016% evaluated people from SSA. Authorship by researchers based in SSA was limited even in manuscripts evaluating African populations, which was noted as a barrier to advancing the knowledge base in this field [87]. Rotimi et al performed a comprehensive literature review evaluating the published literature on cancer genomics in African populations between 1990–2019. Overall, there was a paucity of data, with the majority of SSA populations remaining largely unstudied. While breast cancer was studied most extensively, studies were predominantly limited to populations in North Africa which may not be representative of SSA. BRCA1 and BRCA2 mutations were noted in high frequency in Nigerian women, and some studies included South African and Senegalese populations. Data regarding genomic alterations in populations of prostate cancer patients in SSA was minimal, including data on frequency of BRCA1, BRCA2 or other homologous recombination repair genes [88]. For lung cancer, most notably EGFR, ALK and PD-L1 expression has had a significant impact on management, however, there is very limited data available of molecular profiles of lung cancer patients in SSA. Available data on EGFR expression in African populations is limited to North African populations [89].

We recognize that costs and cost-effectiveness concerns are important factors in realistically increasing availability of a broad range of oncology drug therapies in SSA. The moral need, however, to advance therapeutics and reduce the significantly high case-fatality rates from cancer in SSA remains an urgent global imperative. As such, the need for high levels of investment in cancer care has been acknowledged by all member states of the World Health Assembly in 2017, with the scale up national cancer prevention and control aligned to achieving the 2030 Agenda for Sustainable Development. To this end, several global organizations are challenging cost pressures such as the WHO medicines patent program, pooled procurement approaches, voluntary licensing and there are moves by the World Economic Forum to create enabling governance, regulatory and ethical environments to broaden the reach of precision therapies and diagnostics world-wide [90]. There is a need to harness the global drive to develop newer

therapeutics that can transform cancer care, and global interest in including more diverse patient populations in clinical trials. Historically, a number of barriers including laboratory infrastructure, trained personnel and slow regulatory approval processes have delayed successful implementation of oncology clinical trials in SSA [91]. Future efforts, however, must expand clinical trial capacity to ensure inclusion of SSA populations in new and pre-clinical studies to improve access to the pipeline of new therapeutics, while forging avenues to expand access to existing approved therapeutics in SSA. Furthermore, in coming years, it is likely that generics and biosimilars will rapidly introduce new oncology drug pricing competition bringing the promise of advanced therapies to the emerging economies of SSA.

## Supporting information

**S1 File. Inclusivity in global research questionnaire.**  
(DOCX)

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