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Black Disparities in Targeted Therapy Clinical Trials – A Call for Future Reset

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Simply Summarie: *Targeted therapies target specific genes or molecules involved in cancer growth and survival more so than normal cells, consequently their side effects are fewer than conventional chemotherapy. Blacks are underrepresented in clinical trials involving cancer therapeutics including targeted therapies. This makes generalization of the data from these trials to the black population questionable because of possible differences in host and tumor biology depending on the race. This in turn might lead to disparities in treatment outcomes. Our study aims to highlight disparities in trial inclusion based on the data available from some of the pivotal and interesting targeted therapy trials including the ones that led to FDA approvals. We also review existing literature on how cancer treatment and treatment responses might differ based on the patient's race. In the end, we provide suggestions to enable better recruitment in clinical trials moving forward.*

Abstract: *Studies show marked disparities in the relative risk of cancer death between Black Americans and White Americans even after adjusting for the stage at diagnosis and age. This may be explained by disparities in different aspects of cancer care including providing equal screening opportunities, availability of proper treatment options and inclusivity in clinical trials. To our knowledge, our study is the first descriptive study on Black disparities in targeted therapy clinical trials. We collected data on Black inclusivity from pivotal clinical trials as well as trials of special interest involving targeted therapies in some of the commonly encountered cancers. Our results show that most targeted therapy trials included in our review were multinational including some participating countries with very few or no Blacks and therefore had very poor Black representation with an average of around 1-3%. Also, some trials lacked transparent data on the racial demographics raising concerns on the generalizability of data when extrapolated to treat the Black population. We have reviewed existing literature on differences in cancer biology and host biology depending on the race and end with suggestions to improve Black inclusivity in clinical trials.*

Keywords: *Blacks; Disparities; Targeted therapy; Clinical trials*

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I. INTRODUCTION

Blacks or African Americans (AAs) constitute about 13.4% of the population in the United States (U.S.) (2019 U.S. census bureau)[1]. National data reveal improved Black-White racial disparity in cancer death rates since 1990. The cancer death rate disparities between Black males and White males have decreased from 47% to 19% and from 19% to 13% between females from 1999-2017. Despite improved disparities in death rates between AAs and Whites, there is still a significant gap in the relative risk for death between the two racial groups regardless of age and cancer stage at the diagnosis (33% higher relative risk of death after a cancer diagnosis in Blacks compared to Whites)[2]. There are two hypotheses that contribute to these racial disparities in cancer outcomes. The first is racial differences in providing suitable treatment and the other is from differences in treatment responses[3]. Our study is a descriptive study on racial disparities in trial participation involving targeted therapies as non-chemotherapy options are becoming more and more the standard of care. To our knowledge, this is the first effort to study racial disparities in the participation of the most recent practice-changing trials.

Targeted therapies have revolutionized the treatment of many cancers like lung cancer, breast cancer, colon cancer, multiple myeloma and chronic myeloid leukemia (CML) by their ability to deliver the drug with high specificity and by being less toxic compared to conventional chemotherapy[4]. For example, advanced stage (stage III or IV) non-small cell lung cancer (NSCLC) patients previously had very limited treatment option as the tumor is relatively insensitive to chemotherapy. In an era of targeted therapy, patients with NSCLC harboring epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) gene rearrangements have significantly improved outcomes as compared to chemotherapy as these can be targeted with EGFR-tyrosine kinase inhibitors or ALK-tyrosine kinase inhibitors (ALK-TKIs) respectively[5]. The dawn of targeted therapy along with Next Generation Gene sequencing has shifted medicine from "one size fits all" to more personalized treatment paradigms that could potentially curtail health care costs in the future. Considering that targeted agents are important milestones in the future of cancer therapy, the current concern is on the need for improved efforts on fairness in the inclusion of minorities like AAs in trials involving targeted therapy.

II. MATERIALS AND METHODS

We used the latest clinical guidelines for the widely used targeted therapies in different types of cancers like breast cancer, prostate cancer, colon cancer, lung cancer, liver cancer, renal cell cancer, melanomas and leukemias. We included small molecule inhibitors, monoclonal antibodies, and antibody-drug conjugates. We searched PubMed, Google Scholar and Medscape using mesh terms incorporating the selected therapy and the selected cancer type, example “(Sorafenib [MeSH Terms]) AND (renal cell cancer [MeSH Terms]”. We identified pivotal clinical trials that lead to drug approval or clinical trials of special interest for each type of cancer mentioned above. We excluded trials that included smaller numbers of patients and trials other than in English language. If there was no data available on Black inclusivity in the manuscript or under the results column of a trial (at clinical trials.gov), it was recorded as "No data available”. Twelve out of the 84 studies included were non-randomized phase 1 or phase 2 trials. Most studies were multinational with very few studies (7 out of 84) based mainly in the USA.

III. RESULTS

Investigational agent(s)	Study name	Ref.	Study year	Total population of study	Percentage of Blacks	Type of the study	Single or combined	Indication
Trastuzumab vs observation	HERA	[6]	2001	3387	Black-0.6%	Phase 3	Single	HER2-positive early stage breast cancer
Doxorubicin, Cyclophosphamide and Paclitaxel with or without Trastuzumab	NSABP B-31	[7]	2000	2102	No data available	Phase 3	Combined	HER2-positive, node positive breast cancer
Doxorubicin, Cyclophosphamide and Paclitaxel with or without Trastuzumab	NCCTG N9831	[7]	2000	1944	No data available	Phase 3	Combined	HER2-positive, node positive or high-risk node negative breast cancer
Trastuzumab Emtansine	KAMILLA	[8]	2012	2002	Black- 1%	Phase 3	Single	HER2-positive advanced breast cancer
Trastuzumab Emtansine vs Lapatinib plus Capecitabine	EMILIA	[9]	2009	991	Black- 5 %	Phase 3	Single	HER2-positive advanced breast cancer
Trastuzumab Emtansine vs treatment of physician's choice	TH3RESA	[10]	2011	602	No data available	Phase 3	Single	HER2-positive advanced breast cancer
Lapatinib vs Trastuzumab vs Lapatinib plus Trastuzumab	Neo-ALTTO	[11]	2008	455	Black-1.7%	Phase 3		HER2-positive early breast cancer
Doxorubicin and Cyclophosphamide followed by Paclitaxel plus Trastuzumab or Lapatinib or both	NSABP protocol B-41	[12]	2007	529	Black-8%	Phase 3	Combined	HER2-positive operable breast cancer
Lapatinib plus Capecitabine vs Capecitabine		[13]	2004	408	No data available	Phase 3	Combined	HER2-positive advanced breast cancer
Fluorouracil, Epirubicin, and Cyclophosphamide followed by Paclitaxel plus Trastuzumab or Lapatinib or both	CHER-LOB	[14]	2006	121	No data available	Phase 2	Combined	HER2-positive operable breast cancer
Trastuzumab and Pertuzumab without and with metronomic Cyclophosphamide	EORTC 7511-10114	[15]	2013	80	No data available	Phase 2	Combined	Her 2 positive advanced breast cancer
Trastuzumab and Docetaxel plus Placebo vs	CLEOPATRA	[16]	2008	808	Black- 3.7%	Phase 3	Combined	HER2-positive advanced breast cancer

Trastuzumab and Docetaxel plus Pertuzumab								
Exemestane with and without Everolimus	BOLERO-2	[17]	2009	724	Black-2.3%	Phase 3	Combined	ER positive, HER2 negative advanced breast cancer
Olaparib vs standard single-agent chemotherapy (Capecitabine, Eribulin or Vinorelbine)	OlympiAD	[18]	2014	302	Black-1.7%	Phase 3	Single	Germline BRCA mutation positive and HER2 negative metastatic breast cancer
Erlotinib vs Placebo	SATURN	[19]	2006	889	No data available	Phase 3	Single	Advanced NSCLC
Erlotinib vs standard Docetaxel or Pemetrexed regimens	TITAN	[20]	2006	424	No data available	Phase 3	Single	Advanced NSCLC
Erlotinib vs standard chemotherapy (i.e Cisplatin plus Docetaxel or Gemcitabine or Carboplatin plus Docetaxel or Gemcitabine)	EURTAC	[21]	2007	173	No data available	Phase 3	Single	EGFR mutation positive NSCLC
Erlotinib vs Placebo		[22]	2001	731	Black-4%	Phase 3	Single	NSCLC after first line or second line chemotherapy
Alectinib	NP28761	[23]	2013	87	No data available	Phase 2	Single	Stage IIIB-IV, ALK-positive NSCLC
Alectinib	NP28673	[24]	2013	138	No data available	Phase 2	Single	ALK-positive NSCLC including those with CNS metastasis
Alectinib vs Crizotinib	ALEX	[25]	2014	303	Black-1.3%	Phase 3	Single	ALK-positive NSCLC
Ceritinib vs Pemetrexed or Docetaxel	ASCEND-1	[26]	2011	304	Black-1.3%	Phase 3	Single	ALK-rearranged advanced NSCLC
Crizotinib	PROFILE1001	[27]	2006	149	No data available	Phase 1	Single	Locally advanced or metastatic ROS1 rearrangement positive NSCLC
Crizotinib vs Pemetrexed or Docetaxel		[28]	2009	347	No data available	Phase 3	Single	Locally advanced or metastatic ALK positive NSCLC
Afatinib vs Cisplatin-Pemetrexed	LUX-Lung 3	[29, 30]	2009	345	No data available	Phase 3	Single	EGFR mutation-positive lung adenocarcinoma
Afatinib vs Cisplatin-Gemcitabine	LUX-Lung 6	[29, 31]	2010	364	No Blacks	Phase 3	Single	EGFR mutation-positive lung adenocarcinoma
Afatinib vs Gefitinib	LUX-Lung-7	[32]	2011	319	Black-0.3%	Phase 2	Single	EGFR mutation positive lung adenocarcinoma
Gefitinib vs	IPASS	[33]	2006	1217	No data	Phase 3	Single	Stage IIIB or IV non–small-

Carboplatin plus Paclitaxel					available			cell lung cancer
Osimertinib	AURA	[34]	2013	603	Black-0.8%	Phase 1/2	Single	EGFR T790M mutation positive advanced NSCLC
Osimertinib	AURA2	[35]	2014	210	Black-1.4%	Phase 2	Single	EGFR T790M mutation positive advanced NSCLC
Osimertinib vs platinum Premetrexed	AURA 3	[36]	2014	419	Black-1.1%	Phase 3	Single	EGFR T790M mutation positive advanced NSCLC
Osimertinib vs Gefitinib or Erlotinib	FLAURA gobal cohort	[37]	2014	556	Black-0.7%	Phase 3	Single	EGFR T790M mutation positive advanced NSCLC
Paclitaxel and Carboplatin alone or Paclitaxel and Carboplatin plus Bevacizumab		[38]	2002	850	Black-5.2%	Phase 3	Combined	Recurrent or advanced newly diagnosed NSCLC
Traztuzumab plus chemotherapy (Fluorouracil, Cisplatin or Capecitabine) or chemotherapy alone	ToGA	[39]	2005	584	Black-0.5%	Phase 3	Combined	HER2-positive gastric or gastro-oesophageal junction cancer
Cabozantinib vs Placebo	CELESTIAL	[40]	2013	707	Black-2.7%	Phase 3	Single	Advanced hepatocellular cancer, Child–Pugh class A
Lenvatinib vs Sorafenib	REFLECT	[41]	2013	954	Black-1.4%	Phase 3	Single	Unresectable hepatocellular carcinoma
Olaparib vs Placebo	POLO	[42]	2014	154	Black-3.2%	Phase 3	Single	Metastatic pancreatic adenocarcinoma BRCA1 or BRCA2 germline mutations
Regorafenib vs Placebo	CORRECT	[43]	2010	760	Black-1.8%%	Phase 3	Single	Metastatic Fbevaal cancer
FOLFOX4 + Panitumumab vs FOLFOX4	PRIME	[44]	2006	1183	Black-1.9%	Phase 3	Combined	Metastatic colorectal cancer
Cetuximab Plus FOLFIRI vs FOLFIRI	CRYSTAL	[45]	2004	1221	No data available	Phase 3	Combined	EGFR positive metastatic colorectal cancer
Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin vs Irinotecan, Fluorouracil, and Leucovorin plus Placebo		[46]	2000	813	Black-11.5%	Phase 3	Combined	Metastatic colorectal Cancer
Fluorouracil and Leucovorin (FU/LV) Plus Bevacizumab vs FU/LV plus Placebo		[47]	2000	209	Black-8.5%	Phase 2	Combined	Metastatic colorectal Cancer
Cabozantinib vs Sunitinib	CABOSUN	[48]	2013	157	Black-3.2%	Phase 2	Single	Locally advanced or metastatic renal cell Carcinoma.
Pazopanib	VEG107769	[49]	2006	435	Black-0.22%	Phase 3	Single	Locally advanced or

								metastatic renal cell carcinoma.
Pazopanib vs Sunitinib	COMPARZ	[50, 51]	2008	1110	Black-1.3%	Phase 3	Single	Locally advanced or metastatic renal Cell Carcinoma.
Pazopanib vs Sunitinib	PISCES	[52]	2010	168	Black-0.5%	Phase 3	Single	Locally advanced or metastatic renal cell carcinoma.
Everolimus vs Placebo	RECORD-1	[53]	2006	416	Black- No data	Phase 3	Single	Metastatic clear cell renal-cell carcinoma
Sunitib vs Interferon alpha		[54]	2004	750	Black-1.87%	Phase 3	Single	Metastatic clear cell renal-cell carcinoma
Sorafenib vs Placebo	TARGET	[55]	2003	903	No data available	Phase 3	Single	Metastatic clear-cell renal-cell carcinoma
Temsirolimus vs Interferon alpha vs Temsirolimus plus Interferon alpha	ARCC	[56]	2003	626	Black-4%	Phase 3		Metastatic renal-cell carcinoma
Axitinib vs Sorafenib		[57]	2009	288	Black-0.3%	Phase 3	Single	Metastatic renal-cell carcinoma, clear cell type
Axitinib vs Sorafenib	AXIS	[58]	2008	723	Black-0.7%	Phase 3	Single	Metastatic renal-cell carcinoma, clear cell type
Cabozantinib vs Everolimus	METEOR	[59]	2013	658	Black-1.4%	Phase 3	Single	Metastatic renal cell Carcinoma.
Cabozantinib vs Prednisone	COMET-1	[60]	2012	1028	Black-1.9%	Phase 3	Single	Metastatic castration-resistant prostate cancer
Olaparib vs Enzalutamide or Abiraterone	PROfound	[61]	2017	387	Black-2%	Phase 3	Single	Metastatic castration-resistant prostate cancer
Blinatumomab vs Standard of Care (SOC) Chemotherapy	TOWER	[62]	2014	405	Black-1.9%	Phase 3	Single	Relapsed or refractory acute lymphoblastic leukemia
Inotuzumab ozogamicin vs standard intensive chemotherapy	INOVATE	[63]	2012	218	Black-1.3%	Phase 3	Single	Relapsed or refractory acute lymphoblastic leukemia
Ibrutinib	PCYC-1104-CA	[64]	2011	111	No data available	Phase 2	Single	Relapsed or refractory mantle-cell lymphoma
Ibrutinib vs Ofatumumab	RESONATE	[65]	2012	391	No data available	Phase 3	Single	Relapsed or refractory CLL or SLL
Bendamustine and Rituximab with vs without Ibrutinib	HELIOS	[66]	2012	578	Black-2.4%	Phase 3	Combined	Relapsed or refractory CLL or SLL
Venetoclax–Rituximab vs Bendamustine–Rituximab	MURANO	[67]	2014	389	Black-0.5%	Phase 3	Combined	Relapsed or refractory chronic lymphocytic leukemia.
Venetoclax	Study M13-982	[68]	2013	107	No data available	Phase 2	Single	CLL patients with 17p deletion
Venetocla-Azacitidine vs Venetoclax-Decitabine	Study M14-358	[69]	2014	145	Black-2.25%	Phase 1/2	Combined	Elderly patients with acute myeloid leukemia
Venetoclax plus low dose	Study M14-387	[70]	2014	82	Black-1.6%	Phase 1/2	Combined	Acute myeloid leukemia

Cytarabine								
Daunorubicin plus Cytarabine with and without Gemtuzumab Ozogamicin	ALFA-0701	[71]	2007	280	N/A	Phase3	Combined	Untreated acute myeloid leukemia
Ivosidenib	AG120-C-001	[72, 73]	2014	201	Black-5.9%	Phase 1	Single	Acute myeloid leukemia with an IDH1 mutation
Enasidenib	AG221-C-001	[74, 75]	2013	343	Black-5.5%	Phase1/2	Single	Advanced hematologic malignancies with an IDH2 mutation
Daunorubicin, Cytarabine with and without Midostaurin		[76]	2008	717	Black-2.4%	Phase 3	Combined	Newly diagnosed acute myeloid leukemia with FLT3 mutation
Gilteritinib vs salvage chemotherapy	ADMIRAL	[77]	2015	371	Black-5.7%	Phase 3	Single	Relapsed or refractory acute myeloid leukemia with FLT3 mutation
Imatinib vs Interferon-α with Cytarabine	IRIS	[78]	2000	1106	Black-5%	Phase 3	Single	Newly diagnosed Philadelphia chromosome positive chronic phase-chronic myelogenous leukemia
Dasatinib vs Imatinib	DASISION	[79]	2007	519	Black-0.5%	Phase 3	Single	Newly diagnosed Philadelphia chromosome positive chronic phase-chronic myelogenous leukemia
Dasatinib vs Imatinib	START R CA 180-017	[80]	2005	150	Black-2%	Phase 2	Single	Philadelphia- positive chronic myeloid Leukemia-C, resistant to low dose imatinib
Dasatinib	START C CA 180-013	[81]	2005	387	Black-3.8%	Phase 2	Single	Chronic phase chronic myeloid leukemia patients resistant or intolerant to imatinib
Nilotinib vs Imatinib	ENESTnd	[82]	2007	846	Black-3.5%	Phase 3	Single	Newly diagnosed Philadelphia chromosome positive chronic phase-chronic myelogenous leukemia
Bosutinib vs Imatinib	BEFORE	[83]	2014	487	Black-4.1%	Phase 3	Single	Newly diagnosed Philadelphia chromosome positive chronic phase-chronic myelogenous leukemia
Bortezomib, Melphalan, and Prednisone with vs without Daratumumab	ALCYONE	[84]	2014	706	Black-0.8%	Phase 3	Combined	Newly diagnosed Multiple Myeloma ineligible for stem-cell transplantation
Lenalidomide and Dexamethasone with vs without Daratumumab	POLLUX	[85]	2014	569	Black-2.8%	Phase 3	Combined	Relapsed or refractory Multiple Myeloma

Bortezomib and Dexamethasone with vs without Daratumumab	CASTOR	[86]	2014	498	Black-3.6%	Phase 3	Combined	Relapsed or refractory Multiple Myeloma
Dabrafenib Plus Trametinib vs Vemurafenib	COMBI-v	[87]	2012	704	Black-0.1%	Phase 3	Combined	Unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma
Dabrafenib vs Dabrafenib plus Trametinib	COMBI-d	[88]	2012	422	Black-0.2%	Phase 3		Unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma
Dabrafenib vs Dacarbazine	BREAK-3	[89]	2010	251	No blacks	Phase 3	Single	BRAF mutation positive advanced or metastatic melanoma
Vemurafenib vs Dacarbazine	BRIM-3	[90]	2010	675	No blacks	Phase 3	Single	BRAF mutation positive advanced or metastatic melanoma

Table 1. Targeted therapy clinical trials and Black inclusion rate

A. Breast Cancer

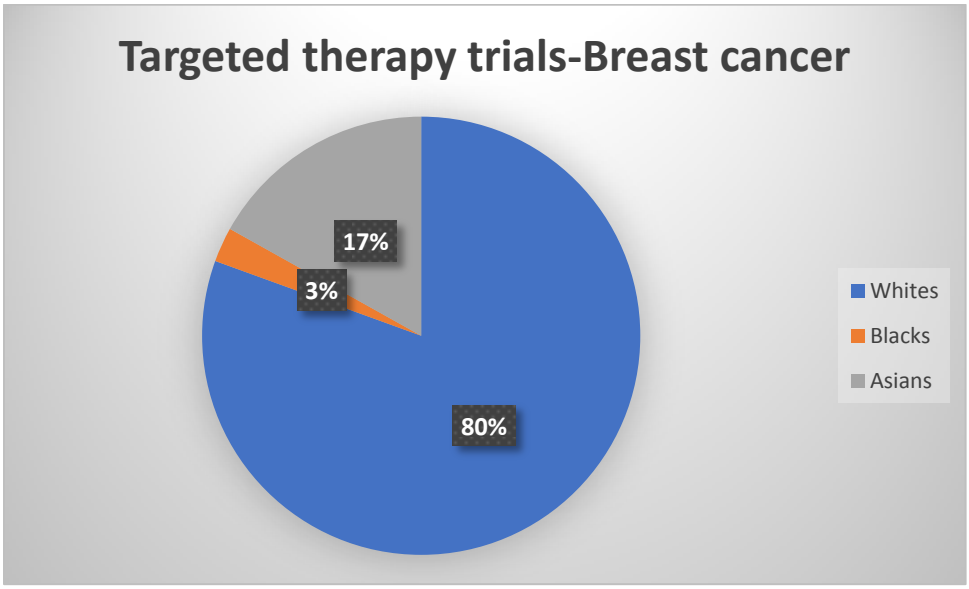

Figure 1. Black inclusion in breast cancer trials

On an average, breast cancer trials included in our review included about 3% blacks (Figure 1). Even the HERA trial that studied Trastuzumab in a significantly larger number of women (3387 patients) with HER-2 positive primary breast cancer after locoregional therapy and neoadjuvant or adjuvant chemotherapy included only 0.6% Black women compared to 83.15% White women. The trials involving HER-2 targeted therapy (Trastuzumab, Trastuzumab Emtansine, Pertuzumab and Lapatinib) in our review had about 0.5% to 8% of Black patients (Table 1). Also, the OlympiAD trial which studied Olaparib compared to standard chemotherapy in germline BRCA mutated metastatic breast cancer patients had only 1.7% Black patients included[18].

The incidence of breast cancer is less in AA women compared to white women (126.7 per 100,000 females compared to 130.8 cases per 100,000 females from 2012-2016) but they are more likely to be diagnosed with advanced disease (43% vs 34% in white women) and have higher death rates compared to white women (28.7% vs 20.3%, 2013-2017)[91, 92]. Along with socioeconomic components like poverty and lack of insurance, beliefs among Black women that they are at lower risk for breast cancer regardless of their family history, lower preferences for surgical treatment and lower referrals for mammography by their primary physician contribute to racial disparities in breast cancer[93-95]. In addition, black women have low vitamin D levels, as dense melanin in their skin limits vitamin D absorption from the sun. And, low vitamin D levels have been associated with the poorly prognostic triple negative breast tumors[96]. Also, Black women have more coexisting comorbidities like hypertension, obesity, diabetes mellitus, cardiovascular and pulmonary disease limiting treatment options[97].

B. Colorectal Cancer

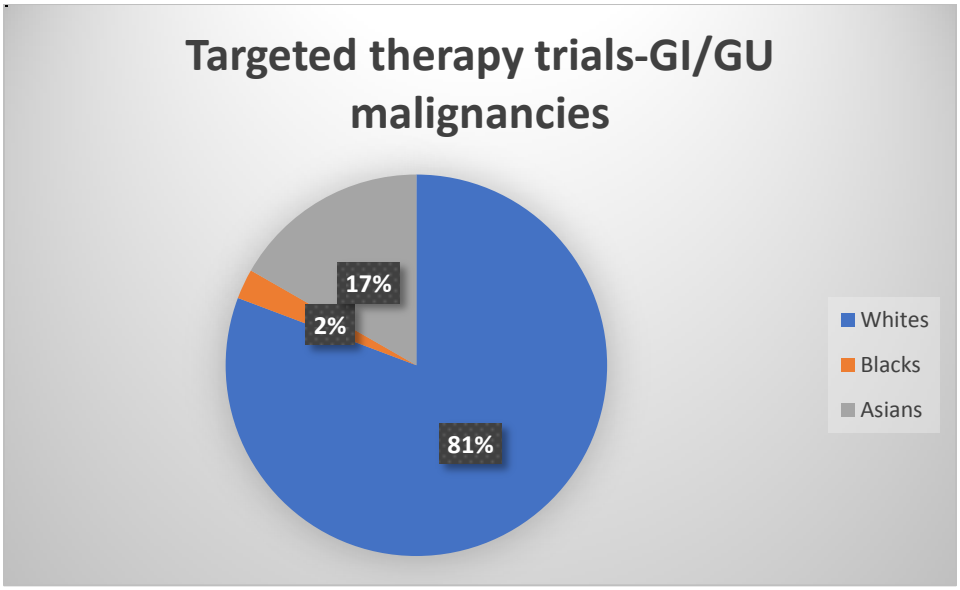

Figure 2. Black inclusion in Gastrointestinal (GI)/Genitourinary (GU) cancer trials

Overall Gastrointestinal cancer trials including hepatocellular cancers and genitourinary cancer trials including prostate cancer had about 2% Black inclusivity (Figure 2). For Colorectal cancer (CRC), our data shows that the percentage of Black inclusivity was < 2% in the CORRECT trial (Regorafenib) as well as the PRIME (Panitumumab) trial and no data was available on the CRYSTAL trial (Cetuximab). Surprisingly trials involving Bevacizumab had better representation of blacks at 8-11% compared to other targeted therapy colon cancer trials included in our review (Table 1).

CRC is another cancer where the incidence and mortality rates per 100,000 are considerably higher in Blacks compared to Whites [45.7 versus (vs) 38.6 and 19 vs 13.8 respectively][98]. Differences like lower likelihood of participation in screening among Blacks with a positive family history of CRC, inaccurate knowledge of family history and inadequate follow-up of abnormal screening on colonoscopy leads to diagnosis at a more advanced stage[99]. AAs are also more likely to be diagnosed at a younger age and with more proximal tumors. In one study 10.6% of CRC in AAs were diagnosed before 45 years compared to 5.5% in Whites[100]. Biology of CRC is also different with more proximal tumors, more frequent KRAS mutations and less frequent microsatellite instability among Blacks with colorectal cancers[101, 102].

C. Hepatocellular Cancer

The CELESTIAL trial, a pivotal phase III trial that lead to FDA approval of Cabozantinib in advanced previously treated hepatocellular carcinoma patients included only 2.7% Blacks[7]. The REFLECT (Lenvatinib), SHARP and AP (Sorafenib) trials in advanced unresectable hepatocellular cancer patients included only about 1.5% Blacks on an average[103] (Table 1).

According to cancer statistics 2020, AAs with primary hepatocellular carcinoma have higher incidences and mortality rates compared to Whites (17.9 vs 10.5 per 100,000 and 8.6 vs 5.8 per 100,000 respectively). These rates include hepatocellular carcinoma and cancers of intrahepatic bile ducts combined[98]. The lower survival rates are because of more advanced tumor stages at diagnosis and lower rates of curative treatment including surgery, and liver transplantation[104-106]. With targeted therapies like sorafenib, Lenvatinib, Cabozantinib, regorafenib and Bevacizumab playing a major role in the treatment paradigm of unresectable hepatocellular cancer, Blacks need better representation in these trials.

D. Renal Cancer

Based on our review data the METEOR trial that studied Cabozantinib (a small molecule inhibitor of c-Met and VEGFR2 tyrosine kinases) in advanced renal cell carcinoma patients previously treated with one or more VEGFR tyrosine-kinase inhibitors included only 1.4% of Black patients, whereas, around 80% were Whites. Similarly, in the AXIS trial where Axitinib was compared with sorafenib in clear cell renal cell carcinoma (ccRCC) patients only about 0.7% were Blacks. Blacks were underrepresented in the COMPARZ and PISCES trials comparing pazopanib with sunitinib in treatment naive patients with ccRCC with 1.3% and 0.5% of Blacks in each trial respectively. The TARGET (sorafenib) and RECORD-1 (Everolimus) trials were either minimally inclusive or had no data on Black inclusion despite being phase 3 FDA approval trials (Table 1).

The rates of kidney and renal pelvic cancers in Black men is 25.4 per 100,000 compared to 22.5 per 100,000 in White men. Similarly, the rates are higher among Black women at 13.1 per 100,000 compared to 11.4 per 100,000 among White women[98]. Seventy percent of these cancers are clear cell cancers. Other less common types include papillary and chromophobe tumors[107]. While the clear cell subtype is more common among AAs compared to White Americans, AAs have a greater risk of renal cell cancer (RCC) in general than White Americans but have lower nephrectomy rates[108]. In addition, a study examining tumor data sets from 419 White and 19 AA patients with clear cell renal cell carcinoma found that AA patients have less frequent VHL mutations and correspondingly lower hypoxia-inducible factor (HIF) and VEGF pathway activation suggesting less responsiveness to VEGF targeted therapy[109]. Thus, the tumor biology is different among different racial groups supporting the need for better Black inclusivity in clinical trials involving RCC.

E. Prostate Cancer

The COMET-1 phase 3 trial that studied Cabozantinib in comparison to Prednisone in 1028 patients with metastatic castration-resistant prostate cancer and the PROfound trial (a FDA approval trial) which studied the BRCA inhibitor Olaparib in patients with metastatic castration resistant prostate cancer (mCRPC) had only about 2% Black's enrolled in each (Table 1).

These low numbers are despite prostate cancer being 1.75 times more common in Black men (179.2 vs 101.7 per 100,000) compared to White men[98]. Prostate cancer presents at a younger age and at more advanced stages in Black men[110]. A large study of 1801 AA men who met NCCN criteria for very low risk cancer and thereby would be candidates for active surveillance but elected to undergo radical prostatectomy showed larger tumor burden, disease upgrading, positive surgical margins and adverse pathology at prostatectomy. This in turn on multivariable analysis resulted in AA race alone being an independent predictor of adverse oncologic outcomes in the same study[111]. AA men also present with higher prostate specific antigen (PSA) levels, probably because of higher tumor volumes overall in these men[112]. Conversely, anterior tumors of the prostate gland which are poorly PSA producing, more aggressive and less likely to be picked up on a digital rectal exam are more prevalent in AA explaining at least partially why AAs progress on active surveillance compared to European American men (EAM)[113, 114]. All these high-risk features translate to significantly higher mortality rates (38.7 vs 18 per 100,000) in AAs with prostate cancer compared to White men[98]. Genetically AAs have a higher frequency of BMP2 (20p12) and CXCR4 (2q22) gene upregulation, both of which are associated with metastasis[115]. A study of BRCA1 and BRCA2 genes via sequencing of archived DNA specimens from prostate

cancer patients undergoing radical prostatectomy (n=1139) showed more frequent pathogenic and variants of uncertain significance (VUS) BRCA1/2 gene mutations in AA men compared to White men (7.3% vs 2.2%). This translated to a trend towards increased metastasis in these patients[116]. Considering these facts, the American cancer society recommends initiating prostate cancer screening discussions at 45 years of age in AA men compared to 50 years of age in men with average risk[117].

F. Lung Cancer

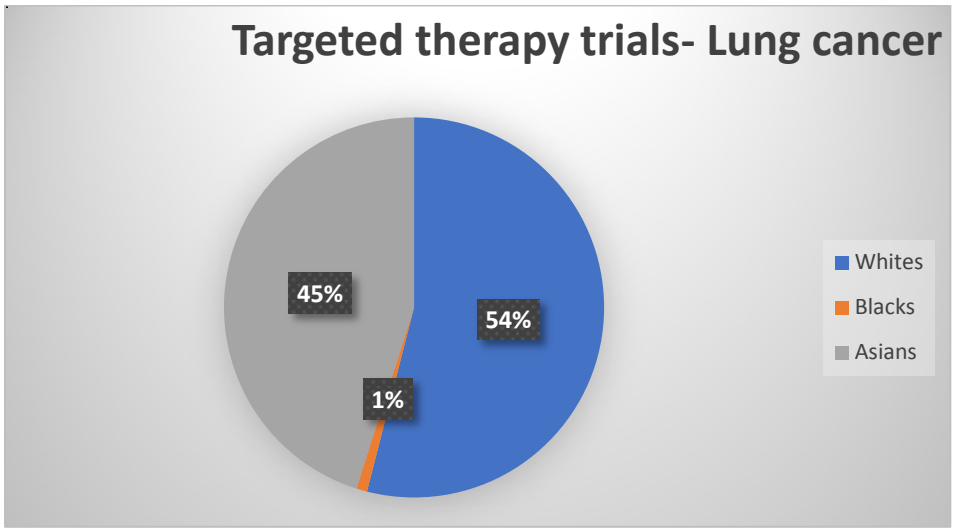

Figure 3. Black inclusion in lung cancer trials

There was a paucity on Black inclusivity data in the EURTAC trial which is phase 3 trials that lead to FDA approval of erlotinib in EGFR mutation positive NSCLC with no prior chemotherapy for metastatic disease. Similarly the ALK inhibitor trials IPASS (Gefinitib), LUX-Lung 3 and 6 (Afatinib), PROFILE 1001 (Crizotinib), NP28761 and NP28763 (Alectinib), SATURN and TITAN (erlotinib) had Asians and Whites as the majority of their patients with no transparent data on the percentage of Blacks included in these trials. Other ALK inhibitor trials like ALEX (Alectinib) and ASCEND (Ceritinib) included about 1.3% of Blacks each and the LUX-Lung 7 trial (Afatinib) included about only 0.3% Blacks. The lung cancer trials involving the anti-EGFR agent Osimertinib (AURA, AURA2, AURA3 and FLAURA global cohort) had about 0.7-1.4% Black inclusivity. Compared to above trials and like trials involving Bevacizumab in colorectal cancer, Bevacizumab studies in lung cancer had better representation of Blacks at about 5% (Table 1). Overall inclusion rates of Blacks in lung cancer trials were poor at around 1% (Figure 3).

These low inclusion rates are regardless of the following facts. The incidence and mortality rates for lung cancer is more in Black males and White females compared to White males and Black females respectively[98]. Studies have shown that Blacks are susceptible to lung cancer from lighter smoking, and later onset of smoking compared to Whites[118, 119]. Also, racial disparities in lung cancer incidence persists even in never smokers[120]. Total nicotine equivalent which is used in studies as a more complete measure of nicotine uptake has been found to be more in Blacks compared to Whites even after adjusting for the cigarettes per day and CYP2A6 activity, the enzyme that metabolizes nicotine[121, 122]. Genetically Blacks were less likely than Whites to carry driver mutations in genes like EGFR, KRAS, NRAS, HER2, ALK, BRAF, PIK3CA and MEK1 which in turn influences decision making in lung cancer treatment using targeted therapies[123-125].

G. Melanoma

The melanoma trials, COMBI-v, COMBI-d and the BREAK trials that studied the BRAF targeted therapy Dabrafenib and the BRIM trial that studied Vemurafenib (another BRAF targeted therapy) in BRAF mutation positive advanced melanoma had very poor Black inclusivity ranging from 0.2%-0% (Table 1). Interestingly this translates to numbers close to zero on an average in melanoma trials. This can at least be partially explained by the lower incidence rates of melanoma in Blacks compared to Whites (33.0 per 100,000 and 20.2 per 100,000 in White men and women respectively vs 1.2 per 100,000 and 1.0 per 100,000 among AA men and women respectively)[126, 127]. Despite lower incidences, melanoma survival rates lag for the Black population and, the histologic types of melanoma associated with poorer prognosis are more common in this population. For example, acral lentiginous melanoma (ALM) is associated with poor survival rates, and a greater proportion of melanomas diagnosed among Blacks are ALM than are melanomas diagnosed among Whites[128].

H. Multiple Myeloma And Leukemias

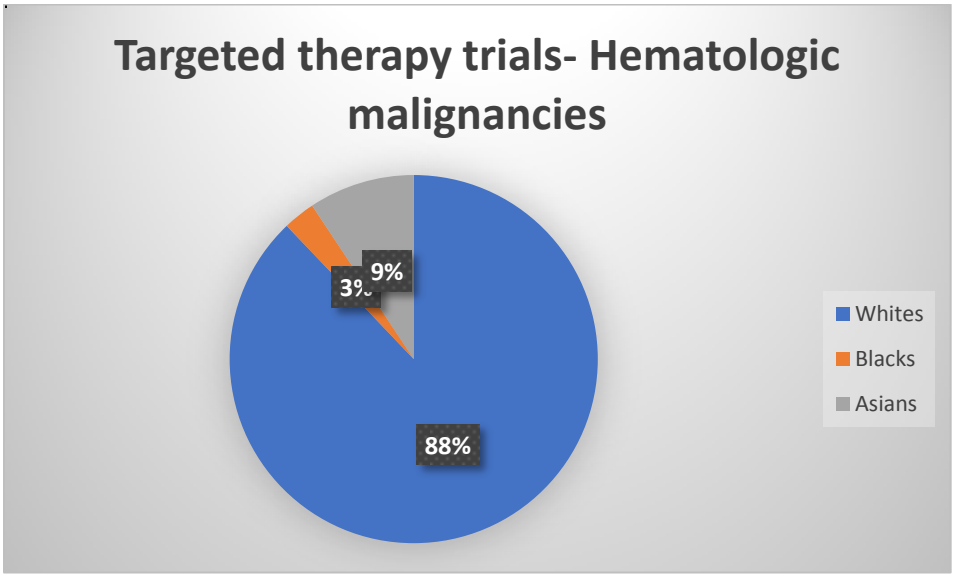

Figure 4. Black inclusion in hematologic cancer trials

The percentage of Blacks in trials involving multiple myeloma (MM) and other hematologic malignancies included in our review is about 2% (Figure 4). The FDA approval trials for Daratumumab in patients with relapsed or refractory MM, POLLUX trial (Daratumumab with Lenalidomide and Dexamethasone) and CASTOR trial (Daratumumab with Bortezomib and Dexamethasone) had about 2.8% and 3.6% Blacks in the trial respectively. Similarly, the ALCYONE trial which fetched FDA approval for Daratumumab combination with Bortezomib, Melphalan, and Prednisone in newly diagnosed MM patients was inclusive of only about 0.8% Blacks (Table 1). The MURANO trial for Venetoclax with rituximab in elapsed or refractory CML, the IRIS trial for Imatinib and the DASISION trial for Dasatinib in newly diagnosed chronic phase-CML patients included about 0.5%, 5% and 0.5% Blacks respectively. All three trials lead to FDA approvals of these drugs despite low Black representation. The AML trials, AG120-C-001 (Ivosidenib; IDH1 inhibitor), AG221-C-001 (Enasidenib; IDH2inhibitor) and the ADMIRAL trial (Gilteritinib; FLT3 inhibitor) each had >5% Blacks represention (Table 1).

These low inclusion numbers are a source of concern as Black Americans are twice at risk of MM and are diagnosed at younger ages compared with Whites[129, 130]. Blacks with family history of MM were more at odds of developing the disease compared to Whites (OR: 20.9, 95% CI: 2.59 to 168 vs OR: 2.04, 95% CI: 0.83 to 5.04) in one study[131]. A study of 718 MM patients from Multiple Myeloma Research Foundation (CoMMpass study) genetic and clinical data showed higher frequency of certain

mutations among Black patients. Namely, BCL7A, BRWD3, and AUTS2 gene mutations that are involved in translocations causing B cell malignancies were more frequent among the Blacks representing disparities in biology depending on race[132].

IV. DISCUSSION

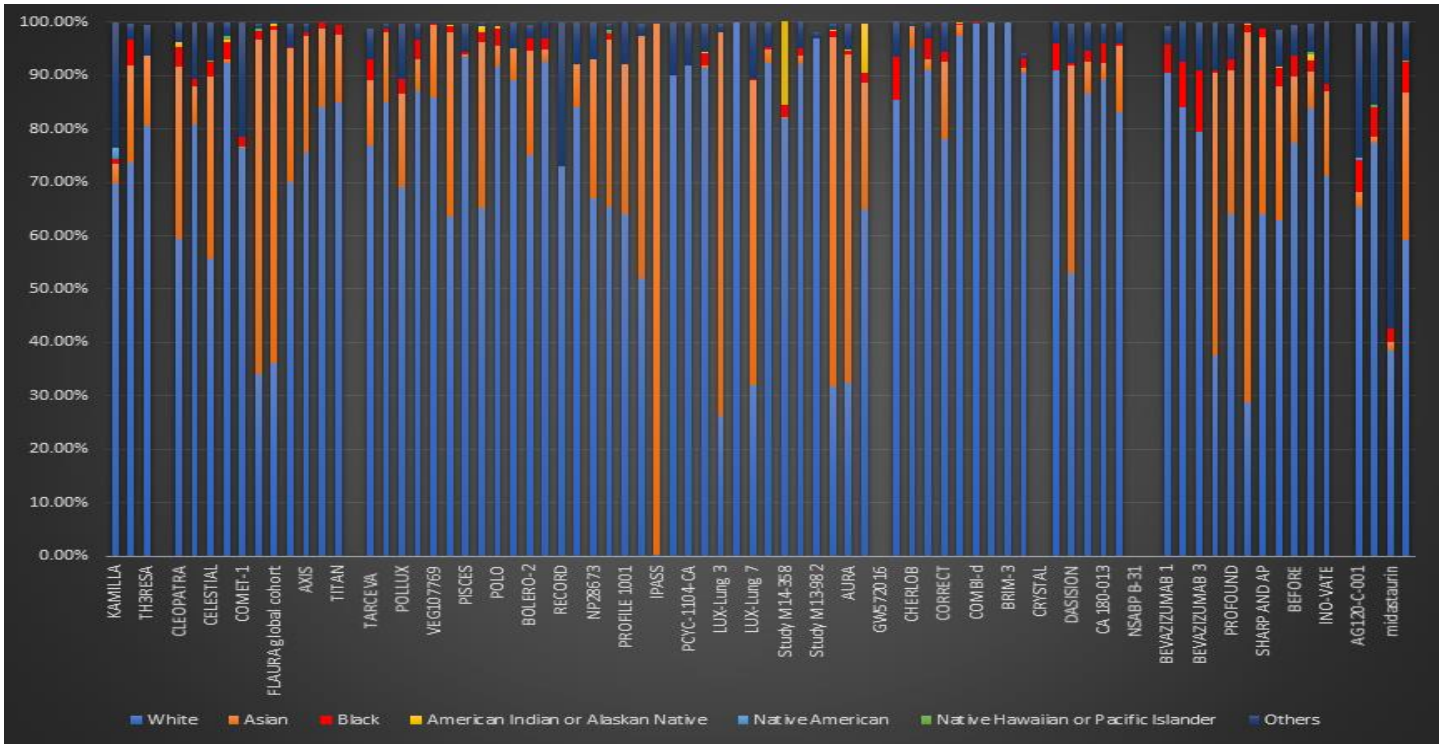

Figure 5. Racial disparities in trial participating

Our results show that most targeted therapy trials including ones that led to FDA approvals had poor representation of Black population (Figure 5). Most trials included in our review were multinational with very few or no Blacks in some participating countries. Given the percentage of Whites collectively included in these multinational trials (about 60-70% on an average) and with whites constituting about 70% of the US population[1], it may be reasonable to extrapolate these results to the White population living in the USA. But, Black inclusion rates on an average was only about 1-3% in the trials included in our review (Figure 2-4). Also, The LUX-Lung 6 (Afatinib) in stage IIIB or IV EGFR mutation-positive lung adenocarcinoma patients had 100% Asians and no other racial groups including blacks, because of the study location (China, Korea and Thailand). Similarly, BREAK-3 (Dabrafenib) and BRIM-3 (Vemurafenib) trials in malignant melanoma had about 100% Whites, and no other racial groups. Also, there was a paucity of data on racial demographics in may trials like NSABP B-31 and NCCTG N9831 (Trastuzumab), EORTC 7511-10114 (Trastuzumab and Pertuzumab), EURTAC (Erlotinib), CRYSTAL (Cetuximab) and ALFA-0701 (Gemtuzumab Ozogamicin). The above findings raise concerns on the validity of these results when used to treat the Black population living in the USA.

We are aware that several factors influence cancer treatment including clinical trial participation. A study of psychosocial aspects of BRCA screening among African American (AA) women showed that AA women may underuse available services. Reasons included lack of knowledge on cancer incidence and the role of genetics, concerns about confidentiality and fears of being "used" in research [133]. This along with lack of commercial development in minority low-income neighborhoods results in geographic clustering of health care delivery systems in high income neighborhoods, which in turn makes minority communities less likely to

receive newer therapies including therapies in clinical trials [134-136]. In addition, the number of available physicians and other providers may be affected by lower quality of community amenities in the low-income minority communities[137]. Also, race in the U.S. correlates with socioeconomic status (SES) and SES in turn correlates with adequate insurance coverage[138, 139]. Lack of a good insurance coverage might result in denial to cover expenses associated with a clinical trial although clinical trial insurance by the trial investigator or sponsor might cover these costs. This might be a significant barrier to clinical trial enrollment. A recent study demonstrates physician and researcher prejudices that racial minorities like AA's patients are less promising trial candidates, which may result in withholding of trial opportunities [140].

Even if all the above factors are accounted for, differences in genetic alterations, tumor microenvironment and organellar disparities combined with genetic polymorphisms affecting drug sensitivities would add to racial disparities in cancer outcomes. Mutations in p53 tumor suppressor genes have been associated with poor prognosis in many cancers. Studies have demonstrated higher p53 mutations than previously known in AA breast cancer patients compared to European American (EA) breast cancer patients (odds ratio, 4.00; 95% confidence interval, 1.77-9.01 in one study and 19.4% vs 13.1%; $P < 0.05$ in another study) and the difference remained statistically different even after adjusting for age [141, 142]. In addition, studies using breast cancer tissues from AAs and EAs or Caucasians have demonstrated differences in tumor microenvironment[143]. These differences may in turn contribute to differences in tumor progression, aggressiveness, metastasis and treatment outcomes[144].

Also, single nucleotide polymorphisms (SNPs) result in differential distribution of allelic variants across races (Africans vs Caucasians). Depending on the allelic variant for the enzyme, patients may have normal, increased, decreased or absent CYP enzyme function which in turn influences treatment responses[145]. For example, CYP3A enzyme family is responsible for the metabolism of the vinca alkaloids used in the treatment of ALL. Greater than 70% of AAs carry at least one CYP3A5*1 allele (with most enzyme activity) and thereby express active CYP3A5 enzyme, whereas Caucasians express other alleles (CYP3A5*3, CYP3A5*6, and CYP3A5*7) with almost no enzyme activity. This translated to increased vincristine neurotoxicity risk in Caucasian children with ALL compared to AA children in one study[146].

Thus, given the differences in biology it is reasonable to doubt the generalizability of the efficacy and safety data from these trials with the very small numbers of Black patients enrolled in these clinical trials. The confidence for generalizability becomes even more limited by the fact that the Black patients enrolled in these trials may not be representative of the broader Black population with multiple comorbidities, as such patients would be excluded from most trials.

V. THE FUTURE RESET: CLOSING RACIAL DISPARITIES IN CLINICAL TRIALS

We think that knowledge gaps such as those described above can only be fixed through better trial inclusion rates. A few potential ways to reset the future would be, 1) Increasing diversity among cancer care providers, as this would enable better navigation through cultural, societal, and historical factors that influence trial recruitment. 2) Making the healthcare workforce aware that subconscious bias and prejudices not only do exist but also interfere with their ability to serve socially dissimilar patients. 3) Allocation of research resources and incentives from trial sponsors to recruit racial minorities like AAs. 4) Identifying and engaging community stakeholders. 5) Improving communication skills among care providers to enable meaningful conversations with the patient and becoming their trusted partners. 6) Recruiting more Black patients from countries with a considerable Black population to compensate for countries with fewer or no Blacks. 7) Making sure to maintain distributive justice during healthcare policy making. Our review being a retrospective study has the inherent risk of selection bias. The aim of this review was to provide an overview of data on Black inclusivity in targeted therapy clinical trials and to underscore the prevalence of racial disparities among such trials. This review may not be comprehensive of all forms of targeted therapies like cancer vaccines, gene therapy etc. In addition, though other racial groups like Hispanics and Native Americans continue to be underrepresented, discussing all such disparities would be beyond the scope of this review.

VI. CONCLUSION

With tumor related differences, biologic differences, differences in social, economic and lifestyle factors as well as with targeted therapies becoming important milestone in the future, Blacks need better representation in clinical trials moving forward.

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