Minireview

Cancer drug development: The missing links

Ajaikumar B Kunnumakkara[1], Devivasha Bordoloi[1], Bethsebie Lalduhsaki Sailo[1], Nand Kishor Roy[1], Krishan Kumar Thakur[1], Kishore Banik[1], Mehdi Shakibaei[2], Subash C Gupta[3] and Bharat B Aggarwal[4]

[1]Cancer Biology Laboratory, DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB), Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Guwahati 781039, India; [2]Faculty of Medicine, Institute of Anatomy, Ludwig Maximilian University of Munich, Munich D-80336, Germany; [3]Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India; [4]Inflammation Research Center, San Diego, CA 92109, USA
Corresponding author: Ajaikumar B Kunnumakkara. Email: kunnumakkara@iitg.ac.in

Impact statement

The success rate for cancer drugs which enter into phase 1 clinical trials is utterly less. Why the vast majority of drugs fail is not understood but suggests that pre-clinical studies are not adequate for human diseases. In 1975, as per the Tufts Center for the Study of Drug Development, pharmaceutical industries expended 100 million dollars for research and development of the average FDA approved drug. By 2005, this figure had more than quadrupled, to $1.3 billion. In order to recover their high and risky investment cost, pharmaceutical companies charge more for their products. However, there exists no correlation between drug development cost and actual sale of the drug. This high drug development cost could be due to the reason that all patients might not respond to the drug. Hence, a given drug has to be tested in large number of patients to show drug benefits and obtain significant results.

Abstract

Although better science and technology has been linked with better health care, however, reality is much different. Although America and most of Europe are equipped with most advanced science and technology, paradoxically cancer incidence is highest in the world. This indicates that science and technology alone is not sufficient in treating diseases like cancer. It is also now well recognized that more than 95% of the drugs/compounds that kill either cancer cells in culture or regress the tumors in animals, fail in phase I clinical trials in humans, indicating that most pre-clinical models of cancer are inadequate. In addition, most of the anticancer drugs that are approved by the regulatory agencies such as FDA either has no effect on the overall survival of the cancer patient or may provide an increase in few months in overall survival. This is despite the fact that most targeted therapies that are currently available are highly expensive; thus suggesting the lack of affordability. This review is meant to focus on some of these problems in detail and then provide potential solutions since most cancers are caused by multiple genes, and thus multi-targeted therapies are needed such as natural products which are inexpensive, safe and have been used for thousands of years for both prevention and treatment of cancer.

Keywords: Cancer, drugs, patient survival, pre-clinical, clinical, cost

***Experimental Biology and Medicine* 2019; 244: 663–689. DOI: 10.1177/1535370219839163**

Introduction

Cancer is a group of more than 200 neoplastic diseases, caused by diverse deregulated cell signaling cascades.[1] It represents the leading causes of morbidity as well as mortality across the globe and over the coming two decades, its incidence is predicted to increase by approximately 70%.[2,3] Among all the cancers, lung cancer is reported to be most commonly diagnosed one followed by female breast cancer, prostate cancer, and colorectal cancer. Notably, lung cancer also represents the most common cause of death due to cancer followed by colorectal cancer, stomach cancer, and liver cancer.[4] Further, lung cancer is the most common cancer and the leading cause of cancer death among males, whereas breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among females.[4,5] Consumption of tobacco and alcohol, obesity, insufficient physical activity, exposure to ultraviolet radiation, and various dietary factors which include insufficient fruit, non-starchy vegetables, and fiber; red/processed meat are predicted to be strongly associated with the risk of diverse cancer types.[6–8] Cancer occurs as a result of the dysregulation of as many as 500 different genes which may

happen over a very long duration of time (20–30 years) till the symptoms become apparent.[1] Large-scale sequencing of human cancer genome has revealed 1007 somatic mutations in 274 megabases of DNA which corresponds to the coding exons of 518 protein kinase genes in 210 different human cancers comprising of 169 primary tumors, two early cultures, and 39 immortal cancer cell lines. The majority of the somatic mutations are predicted to be ''passengers'' with no role in the development of cancer, whereas "driver" mutations were well evinced to play role in oncogenesis.[9] These mutations can be of different classes such as missense mutations, silent mutations, nonsense mutations, frame-shift mutations, insertions/deletions, and non-coding mutations. Among these, single nucleotide mutations are most common in kidney clear-cell carcinoma, hepatocellular carcinoma, acute myeloid leukemia, colorectal carcinoma, glioblastoma multiform, and endometrial carcinoma excluding the serous-like subtype. On the other hand, majority of lung and head and neck squamous cell carcinomas and all serous ovarian and breast carcinomas display copy-number variations.[10] Notably, not only the variants in protein-coding regions of the genome but also the somatic and germline variants occurring in non-coding parts play important role in promoting tumorogenesis by affecting gene expression through diverse mechanisms.[11] An integrative analysis of a total of 930 tumor whole genomes and matched transcriptomes identified a network of 193 non-coding loci in which mutations were found to disrupt the expression of target gene.[12] Clustered regularly interspaced short palindromic repeats (CRISPR) barcoding also offers a well-suited method to functionally annotate specific mutations and study the sub-clonal mutations' dynamics in heterogeneous tumor populations.[13] A recent meta-analysis performed at the Broad Institute which includes 2957 whole exomes and 126 whole genomes from 27 cancer types clearly depicted the mutational heterogeneity in diverse cancer types.[14] Further, Roerink *et al*. carried out a study to examine the nature as well as extent of intratumor diversification by characterizing organoids obtained from various single cells from three colorectal cancers and adjacent normal intestinal crypts. They found that colorectal cancer cells exhibited mutational diversification with more somatic mutations compared to normal colorectal cells.[15]

Cancer progresses in a stepwise fashion where the initiated cells, nodules, polyps or the development of papillomas progress further leading to more malignant condition. As mentioned, altered gene expression and their aberrant function are the key features of cancer. The alteration of proto-oncogenes into oncogenes may give rise to malignancy. Further, mutations can also convert proto-oncogenes into carcinogenic oncogenes.[16,17] For instance, mutations in *ras* gene is observed in diverse tumors with varied incidence rate. Mutations in 12, 13, or 61 codon of one of the three *ras* genes namely, K-ras H-*ras*, and N-*ras* convert them into active oncogenes. Importantly, the highest incidences have been reported in adenocarcinomas of the pancreas (90%), whereas 50% in the colon and thyroid tumors and 30% in case of lung tumors and myeloid leukemia.[18] Further, activation of nuclear factor kappa B (NF-κB) has also been linked with multiple processes in cancer cells such as proliferation, invasion, metastasis, angiogenesis, chemoresistance, and radioresistance.[17,19,20] Another important signal which is reported to get overactivated in diverse range of tumors is phosphatidylinositol 3,5 trisphosphate production by phosphatidylinositol 3-kinase (PI3K), which in turn elicits a cascade of cellular responses including growth, proliferation, survival, and motility of cells ultimately leading to tumor progression.[21] Further, dysregulation of the Keap1-Nrf2 pathway which is actively involved in the regulation of cytoprotective responses to oxidative and electrophilic stress was also reported in cancer cells.[22] Again, Wnt signaling is another key cascade involved in the regulation of development and stemness, was found to play predominant role in different cancer types.[23] In addition, different oxygen-derived species like hydrogen peroxide, superoxide radical, hydroxyl radical, and singlet oxygen are implicated to have active role in carcinogenesis.[16] Furthermore, germline polymorphisms or mutations in DNA damage response (DDR) genes may also lead to the development of cancer.[24]

Problems with pre-clinical models for human cancer

The paradigm of translational oncology has shifted remarkably over the past decade, characterized by the launching of highly sophisticated molecular tools into the clinic.[25] However, there exists a missing connection between preclinical data and clinical findings. Although, a significantly huge amount of money is spent in the pre-clinical settings for target validation and drug optimization, most of the therapies fail in the clinical trials till date. This can be due to the reason that the models used in the pre-clinical setting are not the adequate ones to effectively mimic human responses.[26]

Cell lines

Almost three-fourth of the total publications in cancer research are based on the application of 112 different cell lines.[9] There are multiple reasons behind the usage of cancer cell lines as pre-clinical model of cancer such as they are cost-effective, immortalized, mostly homogeneous, easily perpetuated, and genetically alterable. Further, they possessed several intrinsic characteristics of cancer and have many genetic profiles and genomic modifications similar to that of primary human cancers.[27,28] Further, cell lines confidently recapitulate the oncogenic alterations such as integrating somatic mutations, DNA methylation, copy number alterations, and gene expression identified in tumors. Moreover, it exerts usefulness in correlating the drug sensitivity/resistance with the alterations indicating the significance of tissue lineage in regulating drug response.[29] Owing to these, they possess manifold intrinsic advantages for cancer research and development of novel cancer therapies. Notably, although highly convenient, these models are associated with several limitations as well.[9,27] For example, existence of genomic instability which may result in differences between the original

tumor and the respective cell line, culture conditions that can alter the morphology, gene expression pattern, genomic profile, cellular pathways and culture environment from that of the original tumor, loss of natural tumor heterogeneity, etc.[27] Further, the generic transformations that occur upon culturing of the cancer cells are not restored when regrown *in vivo*. Besides, cancer cells in the *in vitro* condition grow in absence of stroma which include lymphatic vessels and blood, associated fibroblasts and immune cells, and lack a complex extracellular matrix. Therefore, *in vitro* data often exhibits fundamental mismatch with those obtained from clinical findings and hence this can be regarded as one prime reason behind the failure of novel drug development.[28] In a study conducted by Pathak *et al*. suggested that in order to evaluate the efficacy of a novel compound against cancer, the use of only murine cells is not sufficient but a variety of cancer cells, including those of human origin should be used. They observed that anvirzel, an extract of oleander (*Nerium oleander*), and oleandrin, the compound derived from it, effectively killed human cancer cells, but were unable to do the same in murine cancer cells. From these results, it is evident that anvirzel and oleandrin function in a species-specific manner and hence evaluating their effect only in murine cells will not help in getting proper idea of their effectiveness against human cancers.[30]

Animal models

Not only with *in vitro*, there are several problems associated with the *in vivo* models of cancer as well. For *in vivo* studies, different small-animal models of human cancer have been generated such as inbred strains that develop cancer spontaneously, rodents wherein cancer is induced through postnatal exposure to chemical mutagens or intrauterine, and mice in which tumors are induced with the help of bacterial or viral infection.[31] Mice and humans are believed to possess various notable similarities naturally as they are known to have diverged from each other.[32] Hence various mouse models are extensively used in cancer research as they provide prime resource for cancer chemoprevention studies as well for developing novel cancer therapeutics through recapitulation of human disease in mice and also enabling the researchers to study both normal and aberrant gene interactions in different tumor types.[33] The most commonly used animal model is athymic nude mice model because they have inhibited immune system due to which they are unable to reject human tumors. Besides, transgenic, gene knock out, xenograft, orthotopic, zebrafish, and several other animal models are used for carrying out different experiments.[9] These models are extensively used to study the processes of carcinogenesis, role of specific gene target in cancer together with cancer drug development and thus they offer a strong basis for evaluating the various aspects of translational and clinical oncology.[9,28]

The foremost shortcomings of the use of these animal models are their inability to recapitulate the link between the tumor and its microenvironment completely and the requisite of an immunocompromised host.[31] Basically, these animal models do not have the ability to reflect all the features of human cancer impeccably. This can be attributed to the presence of non-malignant cells and extracellular matrix within the microenvironment for the maintenance of tumor. Notably, the interactions between malignant and non-malignant cells decide the tumor fate and which in turn determines novel therapeutic regimen. However, replacement of these individual components with animal counterparts in the tumor site may change the tumor microenvironment remarkably. Further, inhibited immune system of animals in order to avoid rejection of human implants results in compromised normal function of the immune cells in the tumor microenvironment.[28] The risks of over dependence on mice has been highlighted in a recent 'experiment of nature' wherein the mice deficient in RIPK1, a protein kinase that regulates cell death, immediately died right after birth due to the essential role of RIPK1. However, this deleterious effect of RIPK1 was not observed in case of patients with inactivated RIPK1 gene as the loss of RIP1 solely induced immunodeficiency in the human.[34]

In addition, cell line xenograft models possess multiple limitations despite their diverse range of applications such as genomic divergence upon extensive passages like differed gene expression, chromosome rearrangements, karyotype alterations, and disrupted growth rates.[28] Recently, patient-derived xenograft (PDX) mice models have gained notable attention in cancer research. However, the engraftment rate of different cancer tissues into mouse is highly variable and therefore some human tumor subtypes are not represented in these PDX mouse collections.[35] Notably, latest advances in the *in vitro* 3D culture techniques such as organoids have offered new opportunities to develop more physiological and novel human cancer models for translation of basic cancer research into novel treatment approaches for patients with cancer.[36] Further, human organ chips which recreate organ-level physical microenvironments, tissue–tissue interfaces, and vascular perfusion also helps in studying tissue development and pathophysiology. It serves as an important tool for studying how molecular, cellular, physical, and chemical cues work alone as well as together, to impact human tissue development and disease.[37]

Failure of most anticancer drugs in phase I trials in human

Despite the advances in understanding of cancer biology and deriving different novel therapeutic targets, the translation of these understanding into therapies is poor due to higher failure rate (90%). The high failure rate could be due to non-consideration of factors such as clinical translation, drug delivery, drug pharmacokinetics, pre-clinical models, and tumor physiology, which are critical factors.[38]

Phase I trials in human are carried out to evaluate the safety and determine the maximum tolerated dose (MTD) of the drug of interest. While carrying out the same, the investigators of the trial must attribute the adverse effects as related or unrelated to drug studied. In general, the side effects related to drug studied are only taken into consideration which defines the MTD.[39] These adverse events are

known as dose-limiting toxicities (DLTs) which change according to the cancer types and the studied drug and should be pre-defined clearly before starting the study. Notably, the toxicities generated should not be life-threatening or irreversible to be regarded as DLTs; they simply have to be severe enough to terminate the treatment with that dose of the drug.[40]

Challenges associated with phase I trials

Phase I oncology trials are associated with several inherent challenges. Patients who did not respond to the all existing standard therapies are generally enrolled in this phase of trial. Therefore, there exist very limited treatment options for them with utterly short-life expectancy.[41] Over the last two decades, a good deal of studies have entered from pre-clinical to the phase I trial in human. However, the response rate obtained was around 4–10% only with a median overall survival (OS) of six months.[42] For instance, Smith *et al*. conducted two phase I clinical trials on the combination of idelalisib, rituximab, and lenalidomide in follicular lymphoma and mantle cell lymphoma. The doublets lenalidomide–rituximab and idelalisib–rituximab were combined safely and found effective in several clinical lymphoma settings. But several adverse effects such as fevers, hypotension, and rash, hepatotoxicity and pulmonary infiltrates were observed. Therefore, both the trials were dismissed.[43] Another phase I trial was conducted to access the safety and tolerability of idelalisib, lenalidomide, and rituximab in case of relapsed and refractory lymphoma. The trial enrolled a total of 11 patients of whom three had mantle cell lymphoma and eight had follicular lymphoma. In this trial, four patients were found to experience dose-limiting toxicities after 9–20 days of initiation of treatment, coinciding with rituximab infusions. Therefore, both studies were amended to eliminate rituximab, however two patients developed grade 3 rashes and for one patient grade 3 aspartate aminotransferase elevation was reported. As this trial was unsuccessful in meeting the primary endpoint of safety and tolerability, it was terminated. Collectively, this phase I trial led to the interpretation that the combination of idelalisib, lenalidomide, and rituximab is highly toxic and these trials serve as warning notes as new combinations are designed.[44] Further, the results of a phase I clinical trial of BEZ235 in advanced renal cell carcinoma (RCC) patients was reported by Carlo *et al.* in the year 2016. BEZ235 is a dual pan-class phosphoinositide 3-kinases (PI3K) and mammalian target of rapamycin (mTOR) inhibitor which is presently undergoing phase I/II clinical trials in solid tumors and hematologic malignancies. In this study, Carlo *et al.* reported increased administration of BEZ235 resulted in increased incidence of grade 3–4 side effects in 50% of the patients without objective responses in the evaluable patients. As pan-PI3K inhibitor attempts to stop the effect of total PI3K in tumor, it fails to exploit dependency to a particular isoform which in turn could avoid redundant effects through inhibition of other isoforms which have no role to play.[45,46] Therefore, a new clinical trial is undergoing to assess the effectiveness of isoform specific PI3Ka inhibitor namely BYL719, together with everolimus in advanced RCC and pancreatic neuroendocrine tumor (PNET) patients.[45] Therefore, besides, effectiveness, emerging toxicities, and tolerability issues should be cautiously evaluated while assessing the biological agents either alone or in combination and should strictly be performed in clinical setting.

Attrition and phase I trials

Importantly, attrition is the foremost concern in anticancer drug development as up to 95% of drugs checked in phase I trials are not achieving the marketing authorization causing the process of drug development an extremely inefficient and costly affair.[47] In the United States, drug costs are also the focus of political discourse.[48] It is imperative that this problem is addressed throughout the entire drug development process in order to improve efficiency which will consequently benefit the patients with more profitable drugs. Mainly three approaches must be followed to decrease the cancer drug attrition rates; first better pre-clinical models must be included for the study, secondly clinical trials must incorporate the predictive and pharmacodynamic biomarkers and there should be more collaboration between the industry, academia, and regulators to guarantee that the interests of all the stakeholders are met.[47]

Efficacy of anticancer drugs approved and patient survival

Cancer is an utterly complex cluster of diseases with complicated processes of clinical development for oncotherapies. Before a new drug or biologic finally gets approved by the Food and Drug Administration (FDA), it passes through ample *in vitro* and *in vivo* research, and clinical trials spanning several years. Due to the complexity of cancer, clinical research for these anticancer drugs takes around 1.5 years on average longer than drugs for other diseases.[49] Long time taken for developing novel cancer therapeutics can partly be attributed to the slow progress in clinical development.[50] In the last two decades, the number of therapeutic regimens developed against cancer has doubled annually which can be attributed to the marked improvements achieved in cancer research through human genome sequencing, identification of vital signaling pathways, growth factors, and their receptors resulting in approximately 1884 phase I, 3436 phase II, and 1025 phase III cancer clinical trials[49] (Table 1). But surprisingly, the success rate for cancer drugs from phase III clinical trials to final approval remains as low as 3.4% only.[52] A recent study reported that drugs and agents against cancer which are sponsored by small and medium-size companies possess remarkably less chance of getting approved. Not only that, the extent of benefit obtained in a clinical trial is found to be often less compared to the one predicted at the time of trial design as evinced by an analysis of 235 recently published data of phase III randomized clinical trials (RCTs), where 62% of the trials failed to obtain statistically significant results.[53] As a matter of fact, the median progress in survival of patients with solid tumors treated with 71 drugs was found to be 2.1 months only.[54]

Table 1. Efficacy of drugs against cancer approved by FDA in the last 10 years.

Drug	Cancer	Trial	Efficacy
Drugs approved in 2018			
Abemaciclib (VERZENIO) vs. PBO	Breast cancer	MONARCH 3	28.2 vs. 14.8 mo[a]
Abiraterone acetate (Zytiga) + prednisone	CSPC	LATITUDE	Median OS was not estimable
Afatinib (Gilotrif)	NSCLC	LUX-Lung 2, LUX-Lung 3, LUX-Lung 6	66%[b]
Apalutamide (Erleada) vs. PBO	Prostate cancer	SPARTAN	40.5 vs. 16.2 mo[d]
Brentuximab vedotin (Adcetris) + Chemotherapy vs. chemotherapy	cHL	ECHELON-1	Median PFS was not reached
Bevacizumab (Avastin) + CP vs. CP	Ovarian cancer	GOG-0218	12.8 vs. 12.0 mo[a]; 43.8 vs. 40.6 mo[c]
Cemiplimab-rwlc (LIBTAYO)	CSCC	R2810-ONC-1423, R2810-ONC-1540	47%[b] (metastatic); 49%[b] (locally advanced
Dabrafenib (TAFINLAR) + trametinib (MEKINIST) vs. PBO	Melanoma	COMBI-AD	Improved RFS in treatment
Dabrafenib + trametinib	Thyroid cancer	BRF117019	61%[b]
Dacomitinib vs. gefitinib	NSCLC	ARCHER	14.7 vs. 9.2 mo[a]
Durvalumab (Imfinzi) vs. PBO	NSCLC	PACIFIC	16.8 vs. 5.6 mo[a]
Duvelisib (COPIKTRA) vs. ofatumumab	CLL, SLL	NCT02004522	16.4 vs. 9.1 mo[a]; 78% vs. 39%[b]
Encorafenib (BRAFTOVI) + binimetinib (MEKTOVI) vs. vemurafenib	Melanoma	COLUMBUS	14.9 vs. 7.3 mo[a]; 63% vs. 40%[b]
Enzalutamide (XTANDI) vs. PBO	CRPC	PROSPER	36.6 vs. 14.7 mo[d]
Iobenguane I 131 (AZEDRA)	PPGL	Study IB12B	–
Ipilimumab (YERVOY) + Nivolumab	CRC	CheckMate-142	46%[b]
Ivosidenib (Tibsovo)	AML	AG120-C-001	32.8%[g]
Lenvatinib (Lenvima) vs. sorafenib	HCC	REFLECT	7.3 vs. 3.6 mo[a]; 13.6 vs. 12.3 mo[c]
Linatumomab (Blincyto)	ALL	BLAST	35.2 mo[f] (CR1); 12.3 mo[f] (CR2)
Lutetium Lu 177 dotatate (LUTATHERA)	GEP-NETs	NETTER-1	16%[b]
Nilotinib (TASIGNA)	Ph+ CML-CP	CAMN107A2120	MMR 64.0%
Nivolumab (Opdivo) + ipilimumab (Yervoy) vs. sunitinib	RCC	CheckMate-214	41.6% vs. 26.5%[b]
Nivolumab (Opdivo)	SCLC	CheckMate-032	12%[b]
Olaparib (Lynparza) vs. chemotherapy	Breast cancer	OlympiAD	7.0 vs. 4.2 mo[a]
Osimertinib (Tagrisso) vs. SOC	NSCLC	FLAURA	18.9 vs. 10.2 mo[a]; 77% vs. 69%[b]
Pembrolizumab (Keytruda)	PMBCL	KEYNOTE–170	45%[b]
Pembrolizumab (Keytruda)	Cervical cancer	KEYNOTE-158	14.3%[b]
Pembrolizumab (KEYTRUDA) + PemC vs. PemC	NSCLC	KEYNOTE-189	8.8 vs. 4.9 mo[a]; 48% vs.19%[b]
Ribociclib (Kisqali) vs. PBO	Breast cancer	MONALEESA-7	27.5 vs. 13.8 mo[a]
Rucaparib (Rubraca) vs. PBO	Peritoneal cancer	ARIEL3	10.8 vs. 5.4 mo[a]
Tisagenlecleucel (KYMRIAH)	B-cell lymphoma	JULIET	50%[b]; 32%[g]
Venetoclax (VENCLEXTA) + RTX vs. bendamustine + RTX	CLL/SLL	MURANO	92% vs. 72%[b]
Drugs approved in 2017			
Abemaciclib (VERZENIO)	Breast cancer	MONARCH 1	19.7%[b]
Acalabrutinib (Calquence)	MCL	LY-004	81%[b]; 40%[g]
Alectinib (ALECENSA) vs. crizotinib	NSCLC	ALEX	25.7 vs. 10.4 mo[a]; 79% vs. 72%[b]
Avelumab (BAVENCIO)	Urothelial cancer	–	16.1%[b]
Avelumab (BAVENCIO)	MCC	JAVELIN Merkel 200	33%[b]
Axicabtagene ciloleucel (YESCARTA)	B-cell lymphoma	–	72%[b]; 51%[g]
Blinatumomab (BLINCYTO) vs. SOC chemotherapy	ALL	TOWER	7.7 vs. 4.0 mo[c]
Bosutinib (BOSULIF) vs. imatinib	PH + CML	BFORE	MMR 47.2% vs. 36.9%
Brentuximab vedotin (ADCETRIS)	pcALCL vs. MTX/bexarotene	ALCANZA	17 vs. 4 mo[a]; 16% vs. 2%[g]
Brigatinib (ALUNBRIG) 90 mg/day vs. 180 mg/day	NSCLC	ALTA	48% vs. 53%[b]
Cabozantinib (Cabometyx) vs. sunitinib	RCC	CABOSUN	8.6 vs. 5.3 mo[a]
Ceritinib (ZYKADIA) vs. Pt-pemetrexed	NSCLC	ASCEND-4	16.6 vs. 8.1 mo[a]; 73%[b]
Copanlisib (ALIQOPA)	FL	Phase II	58.7%[b]
Dabrafenib (TAFINLAR) + trametinib (MEKINIST)	NSCLC	BRF113928	63%[b]
Dasatinib (SPRYCEL)	PH + CML	Phase I & II	–
Enasidenib (IDHIFA)	AML	AG221-C-001	23%[g]
Gemtuzumab ozogamicin (Mylotarg) vs. BSC	AML	AML-19	4.9 vs. 3.6 mo[c]

(continued)

Table 1. Continued.

Drug	Cancer	Trial	Efficacy
Lenalidomide (Revlimid) vs. PBO	MM	CALGB 100104, IFM 2005-02	111 vs. 106 mo[c] (CALGB); 84 vs. 88 mo[c] (IFM)
L-encap-DAU + ARA-C (VYXEOS) vs. DAU + ARA-C	AML	CLTR0310-301	9.6 vs. 5.9 mo[c]
Midostaurin (RYDAPT) vs. PBO	AML	–	Significant increase in OS
Neratinib (NERLYNX) vs. PBO	Breast cancer	ExteNET	IDFS- 94.2% vs. 91.9%
Niraparib (ZEJULA) vs. PBO	Peritoneal cancer	NOVA	21 vs. 5.5 mo[a] (BRCA mutation); 9.3 vs. 3.9 mo[a] (no BRCA mutation)
Nivolumab (OPDIVO)	HCC	CheckMate-040	14.3%[b]
Nivolumab (OPDIVO)	CRC	CheckMate-142	32%[b]
Nivolumab (OPDIVO)	Urothelial cancer	–	19.6%[b]
Nivolumab (OPDIVO) vs. ipilimumab	Melanoma	CheckMate-238	Recurrences/deaths- 34% vs. 45.5%
Obinutuzumab (GAZYVA) vs. RTX	FL	GALLIUM	91% vs. 88%[b]
Olaparib (Lynparza) vs. PBO	Ovarian cancer	SOLO-21	9.1 vs. 5.5 mo[a]
Osimertinib (TAGRISSO) vs. chemotherapy	NSCLC	AURA3	10.1 vs. 4.4 mo[a]; 65% vs. 29%[b]
Ozogamicin (BESPONSA)	ALL	INO-VATE ALL	35.8%[g]
Palbociclib (IBRANCE) + letrozole vs. PBO	Breast cancer	PALOMA-2	24.8 vs. 14.5 mo[a]
Pembrolizumab (KEYTRUDA)	Gastric cancer	KEYNOTE 059	13.3%[b]
Pembrolizumab (KEYTRUDA)	cHL	–	69%[b]
Pembrolizumab (KEYTRUDA) vs. Pt-chemotherapy	Urothelial cancer	KEYNOTE-045	21% vs. 11%[b]; 10.3 vs. 7.4 mo[c]
Pembrolizumab (KEYTRUDA) + PemC vs. PemC	NSCLC	KEYNOTE-021	13.0 vs. 9 mo[a]; 55% vs. 29%[b]
Pertuzumab (PERJETA) + trastuzumab vs. PBO	Breast cancer	APHINITY	IDFS-8.2% vs. 10.6%
Ribociclib (KISQALI) + LET vs. PBO+ LET	Breast cancer	MONALEESA-2	52.7% vs. 37.1%[b]
Drugs approved in 2016			
Abozantinib (CABOMETYX) vs. EVR	RCC	–	7.4 vs. 3.8 mo[a]; 21.4 vs. 16.5 mo[c]
Atezolizumab (Tecentriq)	Urothelial cancer	–	14.8%[b]
Atezolizumab (TECENTRIQ) vs. Dox	NSCLC	OAK, POPLAR	13.8 vs. 9.6 mo[c] (OAK); 12.6 vs. 9.7 mo[c] (POPLAR)
Daratumumab (DARZALEX) + lenalido- mide +DXM vs. lenalidomide + DXM	MM	POLLUX	Median PFS was not reached
Eenetoclax (VENCLEXTA)	CLL	–	80%[b]
Eribulin (HALAVEN®) + dacarbazine	Liposarcoma	–	13.5 vs. 11.3 mo[c]
Lenvatinib +EVR vs. EVR	RCC	–	14.6 vs. 5.5 mo[a]
Nivolumab (Opdivo)	cHL	–	65%[b]; 8.7 mo[e]
Nivolumab (OPDIVO) vs. ICC	SCCHN	CheckMate-141	7.5 vs. 5.1 mo[c]
Obinutuzumab (Gazyva)+ bendamustine vs. bendamustine	FL	–	Median PFS was not reached
Palbociclib (IBRANCE) + fulvestrant vs. PBO + fulvestrant	Breast cancer	–	9.5 vs. 4.6 mo[a]
Pembrolizumab (KEYTRUDA	HNSCC	–	16%[b]; 2.4–27.7 mo[e]
Pembrolizumab (KEYTRUDA) vs. Pt - chemotherapy	NSCLC	–	10.3 vs. 6.0 mo[a]
Rizotinib (Xalkori)	NSCLC	–	66%[b]; 18 mo[e]
Rucaparib (RUBRACA)	Ovarian cancer	–	54%[b]; 9.2 mo[e]
Drugs approved in 2015			
Alectinib (ALECENSA)	NSCLC	–	61%[b]; 9.1 mo[e]
Brentuximab vedotin (ADCETRIS) vs. PBO	cHL	PBO controlled	42.9 vs. 24.1 mo[a]
Carfilzomib (Kyprolis) + lenalidomide + DXM vs. lenalidomide + DXM	MM	PX-171-009 ASPIRE	26.3 vs. 17.6 mo[a]
Cobimetinib (COTELLIC) + vemurafenib vs. vemurafenib	Melanoma	Controlled	2.3 vs. 7.2 mo[a]; 70% vs. 50%[b]
Dabrafenib + trametinib vs. dabrafenib + PBO	Melanoma	–	9.3 vs. 8.8 mo[a]; 66% vs. 51%[b]; 25.1 vs. 18.7 mo[c]
Daratumumab (DARZALEX)	MM	Open label	29%[b]
Gefitinib (IRESSA) vs. CBP/PTX	NSCLC	Open-label	10.9 vs. 7.4 mo[a]; 67% vs. 41%[b]; 9.6 vs. 5.5mo[e]
Ipilimumab (Yervoy) vs. PBO	Melanoma	Controlled	26 vs. 17 mo[f]
Irinotecan liposome (ONIVYDE) + 5FU/LV vs. 5FU/LV	Pancreatic cancer	Open-label	3.1 vs. 1.5 mo[a]; 6.1 vs. 4.2 mo[c]
Ixazomib (NINLARO) + lenalidomide + DXM vs. PBO + lenalidomide + DXM	MM	–	20.6 vs. 14.7 mo[a]
Lenvatinib (Lenvima) vs. PBO	Thyroid cancer	E7080-G00-303	18.3 vs. 3.6 mo[a]; 65% vs. 2%[b]
	MM	–	

(continued)

Table 1. Continued.

Drug	Cancer	Trial	Efficacy
Lotuzumab (EMPLICITI) + enalidomide + DXM vs. lenalidomide +DXM			19.4 vs. 14 mo[a]; 78.5% vs. 65.5%[b]
Necitumumab (PORTRAZZA) + GC vs. GC	NSCLC	–	5.7 vs. 5.5 mo[a]; 31% vs. 29%[b]
Nivolumab (Opdivo) vs. Dox	NSCLC	Open-label	19% vs. 12%[b]; 12.2 vs. 9.4 mo[c]
Nivolumab (Opdivo) vs. EVR	RCC	–	21.5% vs. 3.9%[b]; 25.0 vs. 19.6 mo[c]
Nivolumab (Opdivo) + ipilimumab vs. ipilimumab	Melanoma	Active-controlled	8.9 vs. 4.7 mo[a]; 60% vs. 11%[b]
Osimertinib (TAGRISSO)	NSCLC	Open label	57%[b] (study 1); 61%[b] (study 2)
Palbociclib (IBRANCE) + LET vs. LET	Breast cancer	Open-label	20.2 vs. 10.2 mo[a]; 55.4% vs. 39.4%[b]
Panobinostat (FARYDAK) + bortezomib + DXM vs. PBO + bortezomib + DXM	MM	PBO-controlled	10.6 vs. 5.8 mo[a]; 8.5% vs. 41.4%[b]
Pembrolizumab (KEYTRUDA)	NSCLC	Open-label	41.0%[b]
Pembrolizumab (Keytruda) Q2W vs. Q3W vs. ipilimumab	Melanoma	–	34% vs. 33% vs. 12%[b]
Ramucirumab (CYRAMZA) + FOLFIRI vs. PBO + FOLFIR	CRC	–	5.7 vs. 4.5 mo[a]; 13.3 vs. 11.7 mo[c]
Sonidegib (Odomzo)	BCC	–	58%[b]
Trabectedin (Yondelis) vs. DTIC	Liposarcoma	Open–label	4.2 vs. 1.5 mo[a]; 7% vs. 6%[b]; 13.7 vs. 13.1 mo[c]
Trifluridine/tipiracil (LONSURF) vs. PBO	CRC	PBO-controlled	7.1 vs. 5.3 mo[c]
Drugs approved in 2014			
Amucirumab (Cyramza) + BSC vs. PBO + BSC	GEJ	I4T-IE-JVBD	5.2 vs. 3.8 mo[c]
Belinostat (BELEODAQ)	PTCL	–	25.8%[b]; 8.4 mo[e]
Bevacizumab (Avastin) + PTX vs. PTX	Ovarian/fallopian tube/peritoneal cancer	AURELIA	6.8 vs. 3.4 mo[a]; 16.6 vs. 13.3 mo[c]
Bevacizumab + chemotherapy vs. chemotherapy	Cervical cancer	–	16.8 vs. 12.9 mo[c]
Blinatumomab (BLINCYTO)	R/R ALL	MT103-211	6.7 mo[e]
ceritinib (ZYKADIA)	NSCLC	Open-label	44%[b]; 7.1 mo[e]
Ibrutinib (IMBRUVICA)	MCL	–	58.3%[b]
Idelalisib (Zydelig) + RTX vs. PBO + RTX	CLL	PBO-controlled	Median PFS was not reached
Lanreotide (somatuline depot) vs. PBO	GEP-NETs	Trial 2-55-52030-726	Median PFS was not reached
Laparib (Lynparza)	Ovarian cancer	–	34%[b]; 7.9 mo[e]
Nivolumab (OPDIVO) vs. ICC	Melanoma	Open-label	32%[b]
Ofatumumab (Arzerra) + CBC vs. CBC	CLL	Open-label	22.4 vs. 13.1 mo[a]
Pembrolizumab (KEYTRUDA)	Melanoma	Trial P001	24%[b]
Ramucirumab (Cyramza) + PTX vs. PBO + PTX	GEJ	I4T-IE-JVBE	9.6 vs. 7.4 mo[c]
Ramucirumab (Cyramza) + Dox vs. PBO+ Dox	NSCLC	I4T-MC-JVBA	10.5 vs. 9.1 mo[c]
Trametinib (Mekinist) + dabrafenib vs. dabrafenib	Melanoma	Open-label	76% vs. 54%[b]; 10.5 vs. 5.6 mo[e]
Drugs approved in 2013			
Ado-tras emtansine (KADCYLA) vs. LAP + CAP	Breast cancer	Open-label	9.6 vs. 6.4 mo[a]; 30.9 vs. 25.1 mo[c]
Afatinib (Gilotrif) vs. chemotherapy	NSCLC	Open-label	11.1 vs. 6.9 mo[a]; 50.4% vs. 19.1%[b]
Bevacizumab (Avastin) + chemotherapy vs. chemotherapy	CRC	Open-label	5.7 vs. 4.0 mo[a]; 11.2 vs. 9.8 mo[c]
Crizotinib (Xalkori) vs. chemotherapy	NSCLC	Open-label	7.7 vs. 3.0 mo[a]; 7.4 vs. 5.6 mo[e]
Dabrafenib (TAFINLAR) vs. dacarbazine	Melanoma	Open-label	5.1 vs. 2.7 mo[a]; 52% vs. 17%[b]
Ibrutinib (IMBRUVICA)	MCL	–	66%[b]; 17.5 mo[e]
Obinutuzumab (GAZYVA) + CBC vs. CBC	CLL	Open-label	23.0 vs. 11.1 mo[a]
Lenalidomide (REVLIMID)	MCL	–	26%[b]; 16.6 mo[e]
Pertuzumab (PERJETA) + Tras + Dox vs. Tras + Dox	Breast cancer	–	pCR rate 39.3% vs. 21.5%
Pomalidomide (POMALYST) + DXM vs. pomalidomide	MM	CC-4047-MM-002	29% vs. 7%[b]
PTX (albumin-bound) + GEM vs. GEM	Pancreatic cancer	Open-label	5.5 vs. 3.7 mo[a]; 23% vs. 7%[b]
Ra 223 dichloride (Xofigo) vs. PBO	Prostate cancer	Open-label	14.0 vs. 11.2 mo[c]
Sorafenib (NEXAVAR) vs. PBO	Thyroid cancer	PBO-controlled	10.8 vs. 5.8 mo[a]; 2% vs. 1%[b]
Trametinib (MEKINIST) vs. chemotherapy	Melanoma	Open-label	4.8 vs. 1.5 mo[a]; 22% vs. 8%[b]
Drugs approved in 2012			
Axitinib (Inlyta) vs. sorafenib	RCC	Open-label	6.7 vs. 4.7 mo[a]
Cabozantinib (COMETRIQ) vs. PBO	Thyroid cancer	PBO controlled	11.2 vs. 4.0 mo[a]
Carfilzomib injection (Kyprolis)	MM	–	22.9%[b]

(continued)

Table 1. Continued.

Drug	Cancer	Trial	Efficacy
Cetuximab (Erbitux) + FOLFIRI vs. FOLFIRI	CRC	CRYSTAL	8.9 vs. 8.1 mo[a]; 19.6 vs. 18.5 mo[c]
Enzalutamide (XTANDI) vs. PBO	Prostate cancer	PBO controlled	18.4 vs. 13.6 mo[c]
Everolimus (Afinitor) + exemestane vs. Exemestane + PBO	Breast cancer	–	7.8 vs. 3.2 mo[a]; 12.6% vs. 1.7%[b]
Pazopanib (VOTRIENT) vs. PBO	STS	PBO controlled	4.6 vs. 1.6 mo[a;] 12.6 vs. 10.7 mo[c]
Pertuzumab injection (PERJETA) + Tras + Dox vs. PBO + Tras + Dox	Breast cancer	PBO controlled	18.5 vs. 12.4 mo[a]
PTX (albumin-bound; ABRAXANE) vs. PTX	NSCLC	Protocol CA031	33% vs. 25%[b]; 6.9 vs. 6.0 mo[e]
Regorafenib (Stivarga) vs. PBO	CRC	Study 14387	2.0 vs. 1.7 mo[a]
RTX infusion	NHL	RATE trail	–
VinCRIStine sulfate LIPOSOME injection (Marqibo)	ALL	HBS407	4.6%[g]
Vismodegib (ERIVEDGE)	BCC	–	30.3%[b]; 7.6 mo[e]
Ziv-aflibercept injection (Zaltrap) + FOLFIRI vs. FOLFIRI + PBO	CRC	Phase III	6.9 vs. 4.7 mo[a]; 13.5 vs. 12.06 mo[c]
Drugs approved in 2011			
Abiraterone acetate (Zytiga) +prednisone	Prostate cancer	RPC	14.8 vs. 10.9 mo[c]
AEC (Erwinaze)	ALL	EMTP	–
Brentuximab Vedotin	ALCL	–	86%[b]
Cetuximab (Erbitux) + 5-FU	SCCHN	Clinical	19.1 vs. 18.2 mo[c]
Crizotinib (XALKORI)	NSCLC	–	50%[b]
Denosumab (Prolia) vs. PBO	Prostate/Breast cancer	DBPC	Significant effect 24 vs. 12 mo
Everolimus (Afinitor) vs. PBO	Pancreatic cancer	RC	11.0 vs. 4.6 mo[a]
Ipilimumab injection (YERVOY) tumor vaccine	Melanoma	DBPC	10 vs. 6 mo[c]
Rituximab (Rituxan)	B-cell NHL	Phase III	46%[a]
Sunitinib (Suten) vs. PBO	Pancreatic cancer	RC	10.2 vs. 5.4 mo[a]
Vemurafenib (ZELBORAF) vs. dacarbazine prednisone vs. PBO	Melanoma	Random	OS 6.2 vs. 4.5 mo
Vandetanib vs. PBO	Thyroid cancer	DBPC	No significant OS
Drugs approved in 2010			
Cabazitaxel (Jevtana) vs. mitoxantrone	Prostate cancer	Random	Median survivals 15.1 vs. 12.7 mo
Dasatinib (Sprycel) vs. imatinib	CML	RC	MMR 52.1% vs. 33.8%
Erlotinib (Tarceva)	NSCLC	DBPC	hazard ratios 0.69[a,] 0.77[c]
Eribulin mesylate (Halaven)	Breast cancer	EMBRACE	10.6 mo[c]
Nilotinib (Tasigna) vs. imatinib	CML	RC	MMR 44% vs. 22%
Rituximab (Rituxan) vs. FC	CLL	ML17102	39.8 vs. 31.5 mo[a]
Rituximab (Rituxan) vs. FC	CLL	BO17072	39.8 vs. 31.5 mo[a]
Tykerb (lapatinib) vs. PBO + letrozole	Breast cancer	RPC	35.4 vs. 13.0 weeks[a]

5FU: fluorouracil; AEC: asparaginase *Erwinia chrysanthemi*; ALL: acute lymphoblastic leukemia; ALCL: anaplastic large cell lymphoma; AML: acute myeloid leukemia; ARA-C: cytarabine; BCC: basal cell carcinoma; BSC: best supportive care; CAP: capecitabine; CBP: carboplatin; CBC: chlorambucil; CCyR: complete cytogenic response; cHL: classical Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; cp: carboplatin + paclitaxel; CR: complete remission; CRPC: castration-resistant prostate cancer; CSCC: cutaneous squamous cell carcinoma; CSPC: castration-sensitive prostate cancer; DAU: daunorubicin; DBPC:double-blind, placebo-controlled; DoR: duration of response; DXM: dexamethasone; Dox:docetaxel; DTIC: dacarbazine; EVR: everolimus; FC: fludarabine and cyclophosphamide; FL: follicular lymphoma; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; GC: gemcitabine and cisplatin; GEP-NETs: gastroenteropancreatic neuroendocrine tumors; GEJ: gastric or gastroesophagal junction; ICC: investigator's choice of chemotherapy; IDFS: invasive disease-free survival; LAP: lapatinib; L-encap: liposome encapsulated; LET: letrozole; LV: leucovorin; MCC: Merkel cell carcinoma; MCL: mantle cell lymphoma; mCRC: metastatic colorectal cancer; MFS: metastasis-free survival; MMR: MajoR molecular response; mo: months; MRD: minimal residual disease; MTX: methotrexate; MM: multiple myeloma; NHL: Non-Hodgkin's lymphoma; NSCLC: non-small cell lung cancer; ORR: overall response rate; ORR4: objective response rate lasting 4 months; OS: overall survival; PBO: placebo; pcALCL: primary cutaneous anaplastic large cell lymphoma; PemC: premetrexed and carboplatin; PFS: progression-free survival; PH + CML: Philadelphia chromosome positive chronic myelogenous leukemia; Ph + CML-CP: Philadelphia chromosome positive chronic myeloid leukemia in chronic phase; PHEO: pheochromocytoma; PMBCL: primary mediastinal large B-cell lymphoma; pCR: pathological complete response; PFS: progression-free survival; Pt: platinum; PPGL: pheochromocytoma/paraganglioma; PTCL: peripheral T-cell lymphoma; PTX: paclitaxel; Q2W: 10 mg/kg intravenously every 2 weeks; Q3W: 10 mg/kg every 3 weeks; Ra: radium; RC: randomized controlled; RCC: renal cell carcinoma; RPC: randomized, placebo-controlled; R/R ALL: relapsed or refractory B-cell precursor acute lymphoblastic leukemia; RFS: relapse-free survival; RTX: rituximab; SCCHN: squamous cell carcinoma of the head and neck; SCLC: small cell lung cancer; SLL: small lymphocytic lymphoma; SOC: standard-of-care; STS: soft tissue sarcoma; Tras: trastuzumab.

aMedian PFS.
bORR.
cMedian OS.
dMFS.
eMedian DoR.
fRFS.
gCR rate.
This information has been gathered from: https://www.fda.gov.[51]

There are a few examples of transformative cancer medicines with huge benefits to the patients.[55] For instance, in 2001, imatinib was approved for second-line therapy against chronic myeloid leukemia (CML) on the basis of hematologic and cytogenic response rates in trial participants. Six years after initial approval, the Insulin Resistance Intervention After Stroke study reported imatinib-treated CML patients had 0% disease progression rate with an estimated OS rate of 88%.[49] However, in most of the cases, the available cancer drugs exert survival benefits only to a marginal extent. In an evaluation of 71 drugs approved for treating solid tumors between 2002 and 2012, the median improvement in OS in pivotal trials was found to be only 2.1 months. Further, out of 47 consecutive approvals for cancer drugs, only 9% showed a relative improvement in survival of 25% or an absolute increase of 2.5 months.[56] Another report also showed that out of the 62 new active anticancer molecules approved by the FDA and EMA during 2003–2013, 53 were assessed by the Australian, English, or French, or health technology assessment agencies through May 2015. Among these 53 drugs, 23 increased OS by three months or more, six of them improved the OS by less than three months, and eight caused increased OS by an unknown magnitude whereas the remaining16 failed to increase OS over best alternative treatments. Although 22 of 53 new medicines were found to cause an increase in quality of life (QoL), 24 reduced patient safety.[55] A systemic review and analysis was conducted by Jawed *et al*. to ascertain what percentage of the life expectancy gain in locally advanced and metastatic colorectal cancer (mCRC) in the past 20 years is as a result of novel therapies versus improvements in supportive care or secular trends and to thereby inform approaches for treatment development. The OS of patients with mCRC showed gradual improvement over the last two decades, with gains from chemotherapy, lead-time bias, and improved locoregional strategies and supportive care. First-line therapies showed modest but consistent gains; however, gains due to second-line therapies have been unsatisfactory.[57]

Noteworthy to mention, the biological rebellion has offered us diverse targets against cancer; consequently, a plethora of relatively specific drugs are in the process of development whereas some of them are already in use after attaining approval. Although some patients are benefiting from those drugs, but the results of large randomized trials are often very discouraging.[58] For instance, almost two decades back, Mendelsohn and Baselga developed the first agents which target epidermal growth factor receptor (EGFR) pathway and showed quite encouraging outcomes in the *in vitro* setting. However, it exerted utterly low response rates in phase II trials in lung cancer whereas no significant response was observed in case of renal, colon, ovarian, and breast cancer. Similarly, gefitinib which showed 9–19% response rate initially was approved for non-small cell lung cancer (NSCLC). However, in subsequent randomized trial, the survival advantage was not achieved and hence the FDA limited the scope of its approval.[59] Further, combination of BRAF and MEK inhibitors, which was expected to be highly effective and mitigate drug response in the patients with melanoma showed complete response in only 13% of the patients with a median progression-free survival (PFS) of 11.4 months in all patients exemplifying the need of better therapies.[60] A phase III trial, ICON7 was conducted in 1528 women with ovarian cancer to access the efficacy of bevacizumab with standard chemotherapy. It was found that bevacizumab in combination with platinum-based chemotherapy failed to increase the OS but an OS benefit was observed in poor-prognosis patients, thus indicating the importance of optimal usage of bevacizumab for the management of ovarian cancer.[61] In addition, arsenic has been used for treating chronic myelogenous leukemia (CML) in the 19th century in western medicine. Notably, arsenic trioxide (As_2O_3) has been found to induce complete remissions in acute promyelocytic leukemia (APL) patients. At the same time, As_2O_3 has been a well-known carcinogen and its administration was found to exert adverse effects on patients leading to its discontinued use against CML. Although, it is usually well-tolerated by APL patients, side effects are encountered in a majority of patients receiving As_2O_3. Thus it is evident that As_2O_3 is toxic to cells other than APL cells clearly suggesting it to have other effects or targets.[62]

Accelerated approval of drugs

Accelerated approval is an expedited regulatory pathway that permits a drug to get approval from the FDA on the basis of an endpoint which is regarded "reasonably likely to predict a clinical benefit". Drugs obtained accelerated approval must be further assessed in post-marketing studies to confirm the desired clinical benefit and may be promoted to "regular" approval if clinical benefit is confirmed or may be withdrawn from the market otherwise.[63] Immune checkpoint inhibitors like nivolumab or pembrolizumab target the programmed death receptor 1/programmed death ligand 1 (PD-1/PDL-1) and PDL-2 interaction.[64] The evaluation of the efficacy of PD-1 blockade in cancer patients having advanced mismatch repair-deficient (dMMR) cancers in 12 different tumor types showed sensitivity to immune checkpoint blockade, irrespective of the tissue of origin.[65] The FDA granted accelerated approval to pembrolizumab (Keytruda, Merck & Co) for the treatment of patients having unresectable or metastatic, microsatellite instable-high (MSI-H) or dMMR solid tumors that have progressed prior therapy and have no suitable treatment options. Till date, this is the first drug approved for use on the basis of a molecular biomarker, not traditional histopathologic diagnosis.[66] The approval was based on data obtained from 149 MSI-H or dMMR cancer patients registered across five uncontrolled, multi-cohort, multicenter, single-arm clinical trials. A maximum of 24 months of treatment was administered and overall response rate (ORR) obtained was 39.6% whereas responses lasted six months or more for 78% of those who responded to pembrolizumab. The common adverse effects to pembrolizumab include constipation, cough, decreased appetite, diarrhea, dyspnea, fatigue, musculoskeletal pain, nausea, pyrexia, and rash. Pembrolizumab exerted immune-mediated side effects, including pneumonitis, colitis, hepatitis, endocrinopathies, and

nephritis.[51,66,67] Another drug which achieved FDA's accelerated approval is ponatinib, a BCR-ABL tyrosine kinase inhibitor (TKI), the sixth drug approved for the management of CML or Philadelphia chromosome–positive acute lymphoblastic leukemia and indicated for patients showing refractory or intolerance to prior TKI therapy (Iclusig, Ariad Pharmaceuticals). On 31 October 2013, the FDA suspended marketing and sales of ponatinib. Just seven weeks later, the FDA partially reversed that decision, permitting use of the drug under a narrower indication. The primary advantage or benefit of this drug is its distinctive ability to target a gatekeeper mutation in BCR-ABL, the T315I transition, which confers resistance against all other approved TKI drugs; however, during withdrawal of ponatinib, the FDA indicated that the adversity of the drug, i.e. a substantial rise in arterial and venous thrombosis, outweighed the benefits.[68]

Use of surrogate endpoints

The efficacy of drugs approved via traditional and accelerated approval processes has been accepted by FDA through the use of surrogate endpoints. However, the method of surrogate endpoints brings the uncertainty regarding the risks and benefits of a drug as clinical value is not checked directly. Thereby it can introduce useless or even harmful therapies if the prediction of the benefit to the cancer patients could not be made or even if the drug has the inferior effect than expected benefit with larger than expected adverse effects.[69] Kim and Prasad investigated the surrogate–survival correlation in 55 FDA surrogate-based approved cancer drugs. It was found that 14 out of 25 accelerated approvals and 11 out of 30 traditional approvals lacked formal analyses of the strength of the surrogate–survival correlation, thus implying the need to reconsider this method of drug approval.[70] Most trial-level meta-analyses showed poor correlation between surrogate end points and the OS.[71] It has been reported that 18 out of the 36 cancer drugs approved by the FDA based on surrogate endpoints between 2008 and 2012 did not show OS benefit.[72] An analysis of 65 eligible trials by Prasad *et al.* showed that more than half (52%) of reported correlations were of low strength, 25% showed medium strength, and only 23% were highly associated with survival. Hence, supportive evidence of the use of surrogate end points as means of approval of new cancer drugs and determining treatment options for cancer patients is limited.[71] Therefore, one of the prime reasons for inflated cost of cancer therapy is that new drugs which have no significant clinical benefit get approved by the FDA and are available in the market at prices similar to the most expensive ones.[72] Further, Kemp and Prasad demonstrated that the trend of using surrogates in oncology is common and increasing. Although, the association of surrogates used and clinically meaningful outcomes is either unknown or weak. Therefore, there should be restricted use of surrogate outcomes in situations where it has shown robust ability to predict meaningful benefits, in cases which are difficult to handle with limited treatment options.[73] Another study suggested that if the drug approval is based on the surrogate end point like the response rate or PFS, the subsequent studies must be performed and the drug's effect on OS must be clarified.[74] The findings of Wilkerson and Fojo suggested that the PFS cannot be taken as a surrogate for OS. It is however, the measure of benefit during therapy and cannot predict the tumor growth after termination of the treatment. Therefore, PFS should not replace OS in regulatory approval consideration.[75]

Randomized clinical trials

Randomized clinical trials (RCTs) are the main assessment carried out for novel therapeutics where study drugs have been traditionally tested in the sickest patients and later developed in a more wider population.[76] It is observed that in most of the clinical settings, there is statistically significant under-representation of the elderly patients; aged $\geq$70 years.[77] Therefore, although the benefit of most cancer drugs are seen in carefully selected, young, healthy populations, evidence exist that the real-world use of novel anticancer drugs may fail to retain the same benefits observed in clinical trials. For example, sorafenib tosylate, an oral TKI, is the only FDA-approved therapy for advanced or metastatic hepatocellular cancer. The pivotal, placebo-controlled trial leading to FDA approval enrolled patients with a median age of 65 years. In this population, sorafenib extended median survival by 2.8 months resulting in its approval. However, in reality, they fail to validate the results of the pivotal sorafenib trial. Second, they show that in actuality, the outcomes are far poorer than that of the trial.[56] Therefore, strategies may be required to evaluate cancer therapies for the elderly patients in clinical trials and develop cancer care among the elderly people.[56] However, to the few sections of biomedical authors, medical practices have been analogized with the parachute as they believe that all the medical practices carry large magnitude of benefit and performing RCTs are unnecessary. However, the ground reality is at far and the most parachute analogies in medicine can be treated as inappropriate, incorrect, or misused.[78]

Genome driven treatment approaches

Notably in the present days, patients eligible for genome-driven treatment has increased, which could help a minority of patients with advanced cancer. The estimated number of patients qualified for genome-targeted therapy was 28,729 out of 564,830 patients with metastatic cancer in 2006. By 2018, this number had improved to 50,811 (8.33%) from a total of 609,640. In case of genome-informed therapy, the eligible number of patients was 59,301 (10.50%) out of 564,830 in 2006.[79] On 6 March 2018, the US FDA granted the first marketing authorization to a personal genomics and biotechnology company namely 23andMe, in order to access three BRCA1 or BRCA2 mutations to identify women with higher risk of breast cancer. This authorization was based on the accuracy and reproducibility of the test for three BRCA mutations that are most prevalent in people of Ashkenazi Jewish descent, but which also occur in the general population. Consumers simply need to mail a swab of saliva to

23andMe and get the results in a time span of 6–8 weeks at $199.3.[80] However, sometimes in these online gene tests, direct-to-consumer results and third-party analyses may be wrong. For instance, Dr Joshua Clayton of 29-year-old age sent a sample of his saliva to 23andMe in order to learn about his ancestry. His report was a quite ordinary one with no new disclosures. But when he sent the profile created by 23andMe to a separate company called Promethease for an extensive in-depth analysis for genetic mutation, he was detected with a mutation linked to Lynch syndrome, a serious genetic disorder which leads to potentially deadly cancers at an early age. However, after subsequent genetic test at another company with expertise in medical diagnostics, he finally got to know that he did not have the mutation as the result was wrong. Therefore, the third-party analysis of raw DNA is not as rigorous as that done in a certified laboratory and hence their results cannot be considered as conclusive at all.[81] Further, in the present days, people suffering from advanced cancer have been offered the hope of precision cancer medicine (PCM).[82] PCM is a concept in which targeted therapies are adapted to match the complexity of the cancer genome.[83] It employs genetic testing of the patients to find the most suitable drugs targeting specific mutation in the tumor, hoping for facilitating better outcome of the patients. However, precision treatments neither improve the patients' survival nor induce better outcome in controlled studies. Thus, precision strategy requires further verification before using it for primary care.[84] In addition, this method of treatment faces the criticism of overhyping as the pace of development of the genome-guided drug is very slow and patients who are likely to be benefitted from these drugs are very less in number.[82]

Blood-based approaches

One of the recently developed method based on the blood test namely tumor mutational burden (TMB) might prove to be beneficial in cancer treatment. It would be of more help where collecting tissues from the cancer patients is difficult and moreover, it is less invasive. The need of the hour is to develop those tests which can help in the prediction of immunotherapy especially the checkpoint inhibitors which can enable the immune cells to attack the tumors. The recently approved drug targeting has transformed cancer care and TMB test can certainly improve the treatment. Due to the high importance, FDA has designated the blood TMB test a "breakthrough device".[85] In 2016, the US FDA approved the use of Epi proColon, the first blood-based screening test for colon cancer that relies on the detection of the methylated septin 9 gene (SEPT9). This screening method addresses the limitation of conventional methods of screening such as stool-based tests and may potentially increase the number of individuals who undergo colon cancer screening. However, a clinical trial showed that SEPT9 test considerably enhanced sensitivity but significantly reduced specificity compared to fecal immunohistochemistry testing. Hence, whether this blood-based assay will reduce colorectal cancer mortality remains questionable.[86]

Analysis of cytostatic and cytotoxic agent

Ever since the traditional cancer chemotherapy and novel target-based agents were developed, the significance of cytostasis in therapies against cancer has always been controversial. Cytostatic drugs stop cancer cell proliferation without killing them. Notably, agents which are presently considered as cytotoxic have been observed to cause cytostasis or clinically stable disease for many years and were considered as ineffective. Therefore, the method of analysis of value of a putative cytostatic agent in a randomized phase III study should be different from that of a cytotoxic agent.[87]

Drug development duration and dosing options

Aforementioned, it takes almost 6–12 years to develop an anticancer drug starting from discovery to final approval. To illustrate the significance of rapid drug approval, Stewart *et al*. calculated life-years possibly saved if selected agents were approved faster using 27 trials showing survival benefits. They found that if the time required to take a drug from discovery to approval is lessened to five years, the median life-years saved per example would have been 523,890 globally. This clearly implies that a considerable amount of life-years could be saved plausibly through increased efficiency of novel drug development for advanced neoplasms.[88] Further, in the development of different oral agents against cancer, dosing options are random and limited by pills' size. Prasad *et al*. reported that this limited dosing options frequently resulted in large dose adjustments in response to toxicity which might lead to reduced real-world clinical effectiveness of oral anticancer agents resulting in differed outcomes than those achieved in registration trials.[89] The immigration policy that halts the entry of best from coming to train as well as work in the United States and discourages the American trainees and faculty from traveling to other countries is a regressive step which will ultimately harm the patients and America's place as a global leader in healthcare and innovation.[90]

Non-inferiority trials

Intensified interest in comparative effectiveness research has made one-on-one assessments between drugs against cancer quite common. One strategy is non-inferiority trials, which often rely on points other than efficacy, like safety, QoL, convenience, and cost to update treatment decisions. As no specific guidelines exist in this regard, therefore these comparisons can emphasize randomly on specified endpoints or draw conclusions regardless of limited participation and treatment time surveyed and thus risks abusing of patient-reported outcomes.[91] Further, the phrase "unmet medical need" requires a clearer definition and standardization as it is generally used to describe cancers that are rare, with little or no curative potential and poor survival outcome. However, it is also used to refer commonly diagnosed cancers, indolent, having several treatment options with better survival rate. Lu *et al*. identified 237 cancer indications which are regarded by the authors as "unmet

medical need". Out of these 237 indications, the term was mostly used for breast cancer indications (30/237 citations) followed by lung (24/237), hepatocellular (18/237), and prostate cancer (13/237).[92]

Clarified ethical conduct and geriatric oncology in low- and middle-income countries

In addition, conducting RCTs for cancer medicine in low- and middle-income countries have raised questions such as, what could be the suitable control arms and what the obligation of trials sponsors towards the host communities. It is noteworthy that a placebo-controlled trial can be ethical if the tested treatment has a feasibility of being employed in the host community. Many of these trials would not have been possible in developed countries like US as majority of clinicians would have objected in subjecting their patients where they have 50% chance of being randomly assigned to interventions considered inferior by previous studies. Thus, it is imperative to clarify the ethical conduct of clinical trials in the developing countries.[93] Additionally, the recent days have witnessed a faster pace of population aging in middle-income countries as compared to the high-income countries. Mexico which belongs to middle-income countries having the second largest economy in Latin America is also undergoing rapid population aging and the number of new cancer cases in the overall population is expected to increase up to 75% by 2030 and nearly 60% in the elderly population (aged $\geq$65). The elderly population of Mexico suffers extreme poverty with low education attainment and devoid of any health insurance schemes. As a result of these problems, the elderly people in Mexico are more prone to the effects of the rising cancer burden and encounters difficulty in measuring high-quality cancer care. Therefore, it is recommended that geriatric oncology should be Mexico's urgent public policy.[94]

Emphasis on the consideration of proven therapies

Further, reports suggest that cancer drugs or combinations that have not completed the phase I, II, or III stages of drug development have been used to treat cancer patients who have exhausted recommended treatment options. Mailankody and Prasad believed that unsafe drugs or combinations should not be applied regardless of theoretical efficacy or cost.[95] The systematic evaluation of cancer drugs approved by the EMA between 2009 and 2013 showed that the most drugs came to the market without any evidence of benefit on the QoL or survival of cancer patients. In addition, if survival gains over existing treatment options or placebo were observed, they were found to be minimal.[96] The study by Lammers *et al.* indicated that the substantial percentage (36.0%) of approved cancer drug have not presented efficacy data within 30 days of approval. Moreover, it was observed that the efficacy data are difficult to find from other sources. Adding to this problem, the current policies adopted by newer, costly drugs, and broadening market share may dampen the sponsors from applying for the formal approval, depending on the robust studies, for the off-label uses of drugs.[97] In order to reduce the delay and improve the access of cancer drugs including those which were earlier considered but not approved by National Institute for Health and Care Excellence, the NHS Cancer Drugs Fund was established in 2010. However, the evaluation of its impact on the society has suggested that it has not served meaningful value to the cancer patients.[98] The process of overturning an accepted practice such as diagnostic test, medication, or procedure is known as the medical reversal. It can be due to the inferior effect to a pre-existing, less intensive, or less invasive one. It can be the result of the inferior effect than no intervention. The need of the hour is to prove the efficacy of the interventions rather than just assuming that all the new therapy certainly leads to a better outcome. The emphasis should be on the consideration of only proven therapies along with the preparedness for the setbacks.[99]

Hazard ratio

In comparison to Kaplan–Meier plot, which emphasizes the number of patients persisting to do well at the completion of the time of interest, the hazard rate and hazard ratio focus on the opposite that is the patients who have not done well and would face a hazardous event. The hazard ratios data give the clearer picture of the treatment success and should be included in all the reports of clinical trials.[100]

Thus it is evident that clinical trials are one of the main aspects for determining the safety and efficacy of drugs. However, it is observed that they are quite expensive, time-consuming, and require ample resources. Nevertheless, it is worth to invest in high-quality clinical trial data to get the proper and strong evidence to ultimately benefit the cancer patients.[101]

Cost of anticancer drugs approved by the FDA

The economic burden imposed by cancer is escalating due to the rise in the cost of cancer drugs at an unprecedented rate[102] (Table 2). In US, cetuximab treatment for 18 weeks against NSCLC costs around $80,000 in average, which translates into $800,000 to extend the life of one patient by a year. Similarly, bevacizumab costs $90,000 to treat an average patient whereas erlotinib and sorafenib cost approximately $16,000–$34,000 for one patient.[132] Notably, in the past decade, funding by the government of US and others for cancer research has stagnated, whereas the demand for investment has grown remarkably due to the ever increasing incidence of cancer across the globe.[102] A study by Moore *et al*. suggested that the high cost of the trials was associated with proving the efficacy of new agents as non-inferior to the already available drugs. Moreover, trials are expensive due to the involvement of the larger patient populations so as to attain statistical power to provide evidence for smaller therapeutic regimen.[227] The average launch price of anticancer drugs, adjusted for inflation and health benefits, was found to increase by 10% annually from 1995 to 2013.[228] As per the report by the IMS Institute for Healthcare Informatics, cancer drugs' global market has reached $100 billion in annual sales.[229] It was reported that from 138 pivotal

Table 2. Cost of FDA approved drugs for cancer.

Drug name	Target	Cancer	Treatment cost	References
Abemaciclib	CDK-4,-6	Breast cancer	$10,948/month	[103,104]
Abiraterone acetate	CYP17A1	Prostate cancer	$5000/month	[105]
Adcetris	CD30	Lymphoma	$100,000	[106]
Ado-Trastuzumab Emtansine	HER-2	Breast cancer	$5325.25 (160 mg vial)	[107]
Afatinib	ErbB	NSCLC	EUR12,364/10 years	[108]
Aldesleukin	IL2RA, IL2RB, IL2RG	RCC	$6000–8000/course	[103,109]
Alectinib	ALK	NSCLC	£87,000(average)/32 months	[110]
Apalutamide	AR	Prostate cancer	$10,000	[111]
Arsenic trioxide	TR	APL	$15,582/28 days	[103,112]
Asparaginase	Asparagine	ALL	$42.00 (10,000 IU vial)	[103,113]
Atezolizumab	PDL-1	Bladder cancer	$12,500/month	[114]
Avelumab	PDL-1	mMCC	$9275.00/28 days	[115]
Axicabtagene ciloleucel	CD-19	BCL	$373,000	[116]
Axitinib	VEGFR	RCC	£27,000/6.4 months	[117]
Azacitidine	DNMT1	Leukemia	$6000/28 days	[103,118]
Bendamustine	Mitotic checkpoints	CLL, B-cell NHL	$8640/1 TC	[119]
Bevacizumab	VEGF	Colon cancer	£1848.80/month	[120]
Bexarotene	RXR	CTCL	$214.67 (1 capsule)	[103,121]
Blinatumomab	CD19,CD3D	ALL	$55,594.20/28 days	[103,122]
Bortezomib	Proteasome	MM	$121,007/year	[123]
Bosutinib	Abl, Src kinases	CML	£44,799/year	[124]
Busulfan	DNA	Leukemia	€1.18/mg (oral)	[103,125]
Brigatinib	ALK	NSCLC	$17,100/month	[126]
Cabazitaxel	Microtubule	Prostate cancer	£3696/1 TC	[127]
Cabozantinib	MET, VEGFR2, RET	RCC	£4800/1 TC	[128,129]
Carfilzomib	Proteasome	MM	$10,000/28 cycles	[130]
Ceritinib	ALK	NSCLC	$111,468/6 months	[131]
Cetuximab	EGFR	NSCLC	$80,000/18 weeks	[132]
Chlorambucil	–	CLL	$22,417	[133]
Cobimetinib	MAP2K1	Melanoma	€79,433	[103, 134]
Crizotinib	ALK	NSCLC	€6457/month	[135]
Cyclophosphamide	NR1I2	Breast cancer	$1751/visit	[103,136]
Cytarabine	DNA polymerase beta	Leukemia	$12.08/2 g	[103,137]
Dabrafenib	B-raf, ERK, MAPK	Melanoma	£1400/year	[103,138, 139]
Dacarbazine	B-raf	Melanoma	$3600/month	[140]
Dactinomycin	DNA topoisomerase 2	GTN	$308.01/5 days	[103,141]
Daratumumab	ADP-ribosyl cyclase 1	Multiple myeloma	R$596,335/year	[103,142]
Dasatinib	Src	CML	£30,477.00/year	[143]
Decitabine	DNA methyltransferase	AML	$170,506/year	[103,144]
Degarelix	GnRH	Prostate cancer	$4411/year	[103,145]
Denileukin diftitox	IL-2α, IL-2 β	CTCL	$1648/300 mcg vial	[103,146]
Dinutuximab	Ganglioside GD2	Neuroblastoma	£127,800/course	[103,147]
Docetaxel	Microtubule	Breast, prostate cancer	US$16,235/9.5 TC	[103,148]
Doxorubicin HCL	–	Ovarian cancer	9614.72 euros	[149]
Enasidenib	IDH2	AML	$24,872/month	[150]
Enzalutamide	Androgen receptor	Prostate cancer	$60,000/8 months	[103,151]
Eribulin	Bcl-2, Tubulin beta-1 chain	Breast cancer	Rs. 4.8 lakh	[103,152]
Eribulin mesylate	–	Breast cancer	€18,694/month	[153]
Erlotinib	EGFR	NSCLC	£6800/125 days	[154]
Etoposide phosphate	DNA topoisomerase	SCLC	$26,026.70/6 cycles	[103,155]
Etoposide	DNA topoisomerase 2-α; -β	SCLC	$26,764.48/6 cycles	[103,155]
Everolimus	mTOR	RCC	$186/day	[103,156]
Exemestane	CYP19A1	Breast cancer	$180/month	[103,157]
Filgrastim	G-CSFR	Breast cancer	€7915/year	[103,158]
Fluorouracil injection with leucovorin	TS	–	$933/8 months	[103,159]
Fluorouracil-Topical	TS	Skin cancer	$2444/year	[103,160]
FOLFIRI	–	Colorectal cancer	$36,922/10-day cycle	[103,161]
FOLFIRINOX	–	Pancreatic cancer	$13,404	[103,162]
Fulvestrant	Estrogen receptor alpha	Breast cancer	£1084/month	[103,163]
Gefitinib	EGFR	Lung cancer	$1029.94/month	[103,164]
Gemcitabine	TS, RNR	Pancreatic cancer	$1363/month	[165]

(continued)

Table 2. Continued.

Drug name	Target	Cancer	Treatment cost	References
Glucarpidase	Methotrexate	Cancers	$27,000/1000 unit vial	103,166
Granisetron	5-HOTR	–	MYR 73.5	103,167
Hycamtin	DNA topoisomerase 1	Ovarian cancer	$7832.07	103,168
Hydroxyurea	RDR-LS	CML	15,566 pound sterlings	103,169
Ibritumomab Tiuxetan	CD20	NHL	£8535/15 years	103,170
Ibrutinib	Bruton's tyrosine kinase	CLL	$18,506/month	171
Idelalisib	P110δ	CLL, FL, SLL	$14,449/20 months	103,170
Imatinib mesylate	BCR-ABL, RET	CML	110,103 pound sterlings	103,172
Imatinib	BCR-ABL, RET, ABL1	CML	$60,390/year	103,173
Imiquimod	TLR-7,8	Skin cancer	€526 (mean cost)/year	103,174
Inotuzumab Ozogamicin	CD22	ALL	$57,623.40/21 days	103, 175
Ipilimumab	CTLA4	Melanoma	$30,000/injection	103,176
Ixabepilone	Microtubule	Breast cancer	$4609.81(75 mg dose)	177
Lanreotide acetate	SSTR-2,-5	NET	$84,856/year	103,178
Lapatinib	ErbB1, ErbB2	Breast cancer	£20,969/year	179
Lenalidomide	TNF-α, IL-6	MM	$63,385/year	180,181
Lenvatinib	–	Thyroid cancer	$15,000/month	182
Leuprolide acetate	GnRHR	Prostate cancer	$1532/kit	103,183
Lomustine	Stathmin-4, DNA	Brain tumor	$648.88/100 mg	103,184
Lutetium Lu 177- Dotatate	SSTR-1,-2,-3,-4,-5	GEP-NETs	$47,500/dose	103,185
Melphalan	DNA	Myeloma	$27,000	103,186
Midostaurin	PDGF-Rβ & Rα, VEGF, FLT3	AML	$14,990/28 days	103,187
Mitomycin C	–	Bladder cancer	£220.74/instillation	103,188
Necitumumab	EGFR	NSCLC	$1745/month	103,189
Nelarabine	POLA1	ALL	$4000.00/day	103,190
Nilotinib	ABL1, c–Kit	CML	$10,360/month	103,191
Niraparib	PARP	Ovarian cancer	$20,032/month	192
Obinutuzumab	CD20	CLL	$41,300/month	103,193
Ofatumumab	CD20	CLL	£63,542/year	103,194
Olaparib	PARP	Ovarian cancer	$13,440/month	195
Osimertinib	EGFR	Lung cancer	$17,028.90/month	164
Paclitaxel	Microtubule, BCl-2	Breast cancer	$865/cycle	103,196
Palbociclib	CDK 4 and 6	Breast cancer	$9850/4 weeks	197
Panitumumab	EGFR	CRC	$100,000/year	103,198
Pazopanib	VEGFR, PDGFR	RCC	£2745.96 (average)/6 weeks	199
Pembrolizumab	PD-1	Cervical cancer	$51.79/mg	103,200
Pemetrexed	TS, purH, DHFR, GART	NSCLC	$24,000	103,201
Pertuzumab	ERBB2	Breast cancer	$187,000/course	103,202
Pomalidomide	Cereblon	MM	$13.700/4 weeks TC	103,203
Ponatinib	BCR-ABL	CML	$199,000/year	103,204
Radium 223 Dichloride	DNA	Prostate cancer	$69,000/course (6 injections)	103,205
Regorafenib	VEGFR1-3, c-KIT, TIE-2, RET, PDGFR-β, FGFR-1, RAF-1, B-raf, p38 MAPK	Colorectal cancer	10,080 yuan/week	206,207
Ribociclib	CDK-4,-6	Breast cancer	$10,950(for 600 mg)/28 days	103,208
Rituximab	C1QB, C1QC	CLL	$13,702/dose	103,209
Rucaparib	PARP, CYP2D6	Ovarian cancer	$13,740/30 days	103,210
Sipuleucel-T	PAP	Prostate cancer	$22,683/month	103,211
Sonidegib	Smoothened homolog	BCC	$146,876/year	103,212
Sorafenib	B-raf; VEGF	RCC	$6064/month	103,213
Sunitinib	VEGFR, PDGFR	RCC	£3139/6 weeks TC	214
Tamoxifen citrate	ER-α,-β, PKC	Breast cancer	$167/month	103,213
Temozolomide	–	Brain cancer	$2195/month	103,213
Temsirolimus	mTOR	RCC	$5000/month	215
Thalidomide	Cereblon, TNF, NF-kB	MM	$3555.74	103,216
Thioguanine	–	Leukemia	$122/month	103,213
Tisagenlecleucel	CD19	Leukemia	$475,000/infusion	103,217
Trabectedin	–	Sarcomas	$10,408.52/28 days	103,218
Trastuzumab	ERBB2, EGFR	Breast cancer	$70,000/year	103,219
Trifluridine	Thymidine phosphorylase	Colorectal cancer	$10,947.70/TC	220
Vandetanib	VEGF-A, EGFR, PTK6, RET, Ang1R	Thyroid cancer	$5460.00/28 days	103,221
Vemurafenib	B-raf	Melanoma	$13,000/month	103,140
Venetoclax	Bcl-2	CML	$1760.88/28 days	103,222
Vincristine sulfate	Tubulin	ALL	$46,800.00/28 days	223

(continued)

Table 2. Continued.

Drug name	Target	Cancer	Treatment cost	References
Vismodegib	Smoothened homolog	BCC	$75,000/10 months	103,224
Ziv-Aflibercept	VEGF	CRC	$1600/4 mL	103,225
Zoledronic acid	FPP, GGPS1, hydroxylapatite	MM	$140/dose	103,226

5-HOTR: 5-hydroxytryptamine receptor 3A; ALL: acute lymphoblastic lymphoma; AML: acute myelogenous leukemia; Ang1R: angiopoietin-1 receptor; APL: acute promyelocytic leukemia; BCC: basal cell carcinoma; BCL: B-cell lymphoma; C1QC: complement C1q subcomponent subunit C; C1QB: complement C1q subcomponent subunit B; CDK: cyclin-dependent kinase; CLL: chronic lymphocytic leukemia; CTCL: cutaneous T-cell lymphoma; CTLA4: cytotoxic T-lymphocyte protein 4; CYP19A1: cytochrome P450 19A1; CYP2D6: cytochrome P450 2D6; DHFR: dihydrofolate reductase; DNMT1: DNA (cytosine-5)-methyltransferase 1; EGFR: epidermal growth factor receptor; FL: follicular lymphoma; FPP: farnesyl pyrophosphate; GART: trifunctional purine biosynthetic protein adenosine-3; G-CSFR: granulocyte colony-stimulating factor receptor; GEP-NETs: gastroenteropancreatic neuroendocrine tumors; GGPS1: geranylgeranyl pyrophosphate synthase; GnRH: gonadotropin-releasing hormone receptor; GnRHR: gonadotropin-releasing hormone receptor; GTN: gestational trophoblastic neoplasia; IDH2: isocitrate dehydrogenase-2; IL2RA: interleukin-2 receptor subunit alpha; IL2RB: interleukin-2 receptor subunit beta; IL2RG: cytokine receptor common subunit gamma; MAP2K1: mitogen-activated protein kinase kinase 1; mMCC: metastatic Merkel cell carcinoma; MM: multiple myeloma; NET: neuroendocrine tumor; NHL: Non-Hodgkin's lymphoma; NR1I2: nuclear receptor subfamily 1 group I member 2; P110δ: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; PARP: poly(ADP-ribose) polymerase; PD-1: programmed cell death protein 1; PDGF-R: platelet-derived growth factor receptors; PD-L1: programmed cell death 1 ligand 1; PKC: protein kinase C; POLA1: DNA polymerase alpha catalytic subunit; PTK6: protein-tyrosine kinase 6; PurH: bifunctional purine biosynthesis protein PURH; RCC: renal cell carcinoma; RDR-LS: ribonucleoside-diphosphate reductase large subunit; RNR: ribonucleotide reductase; RXR: retinoic acid receptor; SLL: small lymphocytic lymphoma; SSTR: somatostatin receptor; TC: treatment cycle; TLR: toll-like receptor; TNFRSF8: tumor necrosis factor receptor superfamily member 8; TR: thioredoxin reductase; TS: thymidylate synthase; VEGF: vascular endothelial growth factor.

clinical trials conducted during the year 2015–2016, 59 novel therapeutic agents were approved by the FDA, at the expense worth approximately $19.0 million.[227] Remarkably, the anticancer drugs are much more expensive than the drugs from other divisions of health care which raises concern to the patients, physicians, policy researchers, and also the society.[230,231] In addition, novel radiotherapy technology which includes proton therapy also comes with a massively high price tag.[232] Recently, an analysis of US Securities and Exchange Commission filings for drug companies with no drugs on the US market which obtained FDA approval for cancer drug from 1 January 2006 to 31 December 2015 was carried out including 10 companies and drugs. They found that the median time taken by these companies to develop a drug was 7.3 years. The study also reported that five drugs received accelerated approval from the FDA, five received regular approval and the median cost of drug development was $648.0 million.[233] Further, a report by Mailankody and Prasad has indicated that the price of cancer drugs is not based on novelty as the median wholesale price of 30 next-in-class drugs approved over a period of five years and 21 novel drugs were found to be almost same.[230] Recently, there has been a drastic hike in the price of older drugs. For instance, Turing Pharmaceuticals increased the price of one tablet by 5000% (from $13.50 to $750). Again, the price of EpiPen was increased to more than $600 which earlier costed $100. The rise in the price of older drugs is highly objectionable considering the fact that the expenses for research and development was occurred quite before and almost definitely been recouped.[234] Additionally, it is also noteworthy that there exists a very little difference in prices of drugs approved on the basis of response rate with those approved depending on the time-to-event end points.[230] These clearly imply that the current pricing models of cancer drugs are highly non-rational. Further, the fact that the prices of drugs against cancer vary around the world and that no uniformity exists in the variation.[235] The survey on the official prices of 31 cancer drugs in 18 different countries as published by Vogler and colleagues has shown sizable differences in price for the same drug in these countries. Thus, the price of cancer is not only limited to human suffering, but it increases the burden on the national GDPs as well due to premature mortality and morbidity.[236] This strongly demands the need for greater transparency.[235] Further, aiming to lower the costs and improve the value, the Centers for Medicare & Medicaid Services has proposed several measures such as improving incentive for better clinical care, discounting or eliminating patient cost sharing, feedback on physician's prescription, and pricing of drugs based on its effectiveness.[237] Although the cost-effectiveness analyses showed the tremendous cost of some cancer drugs as reasonable, majority of novel hematologic malignancy drugs failed to meet the value for the price. Further, empirical evidence revealed that most cancer drugs do not reach the conventional cost effectiveness thresholds, thus implying the crucial requirement to reconsider the current pricing of cancer drugs.[238] The examination of the work for the contribution of National Institutes of Health (NIH) funding to published research linked with 210 new molecular entities (NMEs) approved by the FDA during 2010–2016 suggested that the NIH contributes to new drug approvals through research is greater than earlier expected. Moreover, it was found that the NIH research budget was more concentrated on the basic research for translating the new products. Any decrease in the funding can result in the slow pace of the research which could cause the delay in the outcome in terms of the emergence of new drugs in the near future.[239] The examination of the presence of financial ties to drug makers among academics with research productivity showed a positive correlation. However, further analysis must be extended to validate these findings and if proven some policies must be framed to provide alternative incentives to physicians who could not make industry payments.[240] The analysis of the differences in the guidelines for the approval of anticancer drugs by the National Comprehensive Cancer Network (NCNN) and FDA indicated that the NCCN recommendations are weak. It was observed that the NCCN defends the coverage of expensive, toxic cancer drugs

based on weak indication.[241] Further, the study on evaluating the benefits of the US FDA's pediatric exclusivity program extension (2007–2012) by Sinha *et al.* has suggested that it provided significant information about the safety and efficacy of drugs used for pediatric population. Although, it was observed that the cost to consumers was high and the clinical trial was costlier.[242]

Potential solutions to the problem for prevention and treatment of cancer

Development of new drugs till the final approval by FDA is extremely expensive which costs around two billion dollars. Although the chief reason behind this excessive high cost remains unknown, high failure rates of trials related to novel drug discovery at the pre-clinical and clinical settings contribute enormously to it. Although many mono-targeted therapies have been developed for diverse cancers, such strategies have had little effect in the prevention or treatment of different malignancies.[243] Targeted therapy which involves different strategies such as monoclonal antibodies, prodrug, small molecule inhibitors, and nanoparticulate antibody conjugates has gained enormous attention in the recent days due to their specificity towards cancer cells without causing toxicity to off-target cells. However, newest findings suggest that tumor heterogeneity with reference to molecular targets leads to failure of these targeted therapies in many cases.[244] Some potential solutions for the prevention and treatment of cancer are illustrated below.

Natural therapies

Since ages, compounds derived from Mother Nature, especially plants have been the primary source of medicine and health not only due to their safety, affordability, effectiveness but also due to their ability to modulate multiple cell signaling pathways. Further, increasing lines of evidence clearly imply that more than 70% of the current drugs are of natural origin.[245–247] Notably, a vast majority of world's population relies on plants for their primary healthcare.[245] Reports suggest that people of Southeast Asian countries possess lower risk of developing colon, gastrointestinal, prostate, breast, and some other cancers due to their dietary habits as dietary constituents are considered to offer protection against diverse cancers.[248] Dietary phytochemicals contain various active components with potent chemopreventive properties such as curcumin, genistein, resveratrol, diallyl sulfide, *S*-allyl cysteine, allicin, lycopene, capsaicin, diosgenin, [6]-gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins, eugenol, isoeugenol, isothiocyanates, indole-3-carbinol, isoflavones, phytosterols, folic acid, β-carotene, and flavonoids. These components are extremely safe, possess multi-targeting ability, cost-effective, bioavailable, and also serve as better ligands for biologically active proteins.[249,250] A recent paper reported that insectivorous plants which are rich in secondary metabolites provide benefits against cancer. For instance, metabolites like napthoquinones, phenolic acids, and flavonoids are present in the plants such as *Drosera indica*, *Dionaea muscipula*, Darlingtonia, and Sarracenia, which contribute enormously to their potent anticancer property.[251]

For the period of 2005 to 2007, a total of 13 different drugs based on natural products were approved and five of them represented the first members of new classes of drugs: exenatide, ziconotide, ixabepilone, retapamulin, and trabectedin. Further, the structures of these natural products possess high chemical diversity, biochemical specificity, and various other molecular features, making them highly promising as lead structures for drug design.[252,253] Despite these advantages and the past achievements, research into natural products in drug discovery screening in the pharmaceutical companies have decreased remarkably in the last decade. This might be due to the apparent difficulties associated with natural products which include technical obstructions in screening them in high-throughput assays against different molecular targets.[254] For instance, one such highly promising medicinal plant is *Azadirachta indica*, commonly known as neem, belonging to Mahogany family. Various parts of this plant have been used for the treatment of diverse human ailments since olden times and also showed anticancer effect in the preclinical findings. Despite the identification of more than 300 components from neem, the effect of only very few were assessed in details.[245] Deciphering the effect and mechanism of action of all the compounds present in such precious medicinal plants hold immense prospect in the development of novel therapeutic strategies against diverse cancer types. Notably, recent advances in genomics and structural biology provide a clearer picture of the diversity of proteins targeted by molecules of natural origin thereby developing an interest in natural products for drug discovery.[249,252,253,255] Overthrowing the technical disadvantages associated with natural product research definitely provides better opportunities to unravel the biological features of previously inaccessible natural product sources. Further, chemical diversity of natural products is perfectly suitable to provide the core scaffolds for novel drugs and therefore further developments in using newer natural products and chemical libraries based on them possess enormous prospect in drug discovery crusades.[253] Additionally, a method of drug discovery involving the generation of natural products' based molecular diversity in combination with synthetic procedures undoubtedly displays the most well-suited solution to discover and develop effective drugs.[256]

Multi-targeted agents

Till date, different drugs have been developed against various targets such as tyrosine kinases, diverse membrane proteins, and enzymes for the treatment of varied cancer types and they also obtained FDA approval (Figures 1–4). Interestingly, one leading paradigm in drug discovery is to develop regimens with high selectivity to act on individual drug targets.[257,258] With this mono-targeted approach, many novel entities have been designed and further got approval as drugs.[257] However, these drugs had hardly exerted efficacy against cancer as it is a complex disease characterized by diverse molecular and genetic variations. Due to this enormous biological diversity, targeting a single

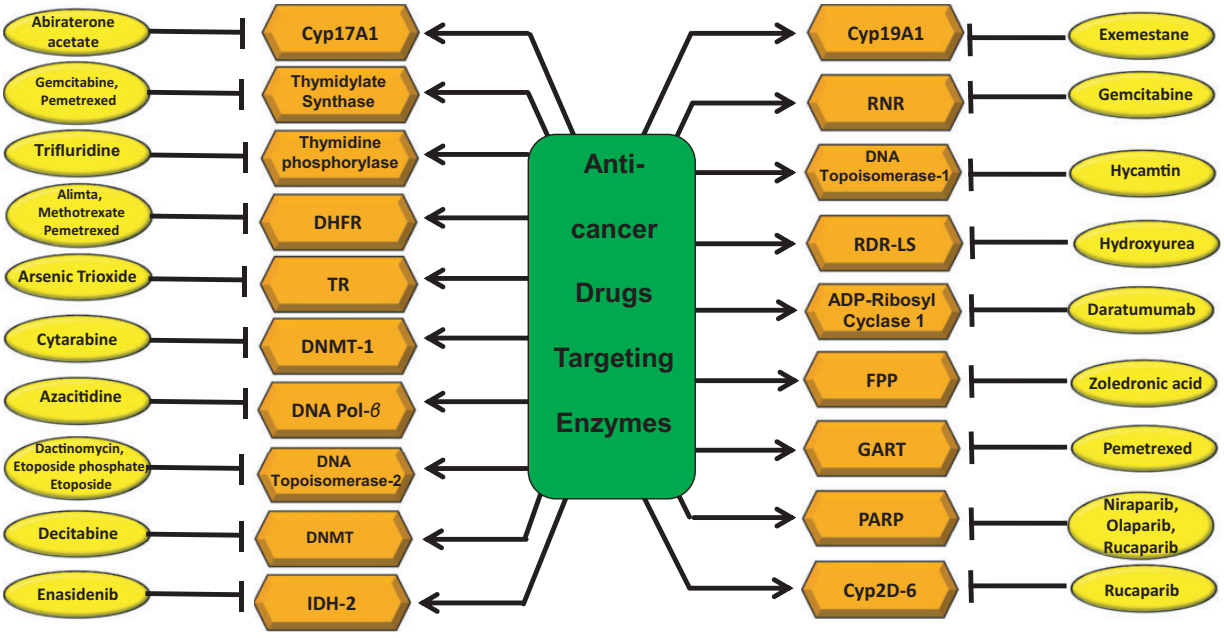

Figure 1. Different drugs approved by the FDA which target enzymes. (A color version of this figure is available in the online journal.)

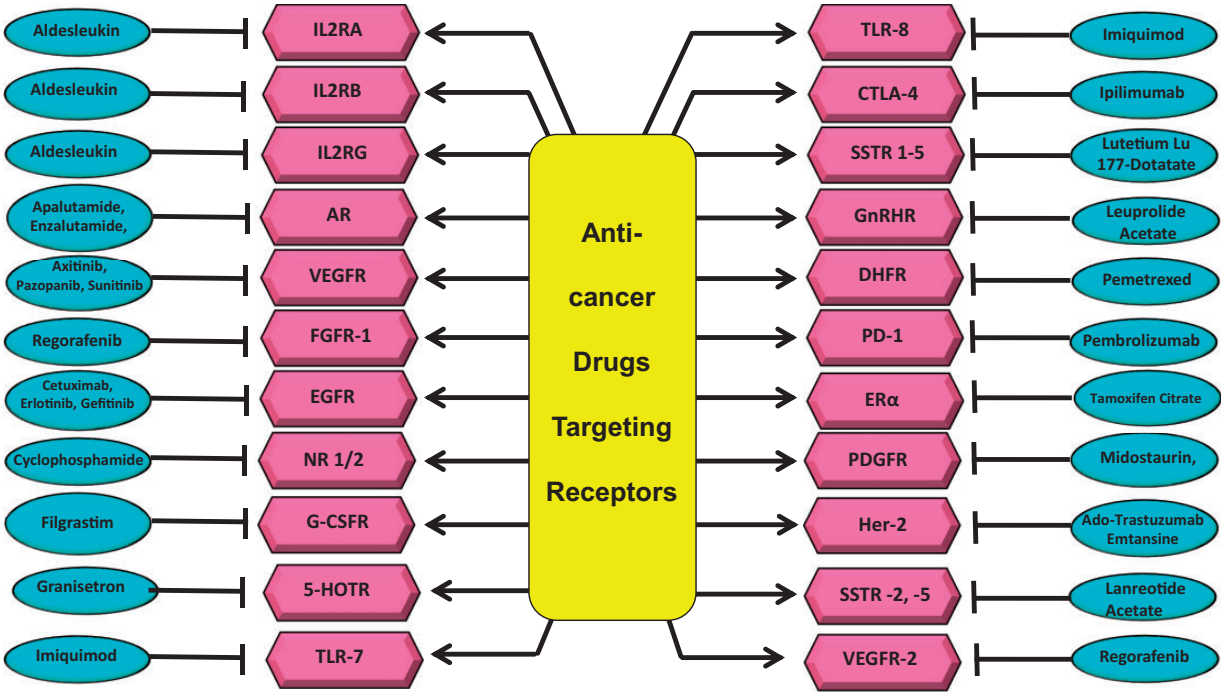

Figure 2. Different drugs approved by the FDA which target receptors. (A color version of this figure is available in the online journal.)

target is not sufficient to combat cancer. Instead, multi-targeting approach holds prospect in this regard.[259,260] Multi-targeted therapeutics can be accomplished either through combination of single targeted drugs or via administration of a multi-targeted agent. The combinatorial treatment approach using agents with distinctive molecular mechanisms is considered to be highly promising for better efficacy as use of multiple agents is frequently limited by drug–drug interactions and dose-limiting toxicities. In addition, the use of a single agent is generally much more cost-effective than two separate agents.[257,261] Some other important yet added advantages of using a single multi-targeted agent include the avoidance of different bio-availabilities as well as pharmacokinetics and metabolism of each component within the combination regimen. Further, the simplified dosing regimen would greatly aid in enhancing the therapeutic efficacy and exert minimal side effects.[257] These findings clearly indicate that the use of more unspecific agents with ability to modulate different targets simultaneously offer high prospect.[259] Increasing

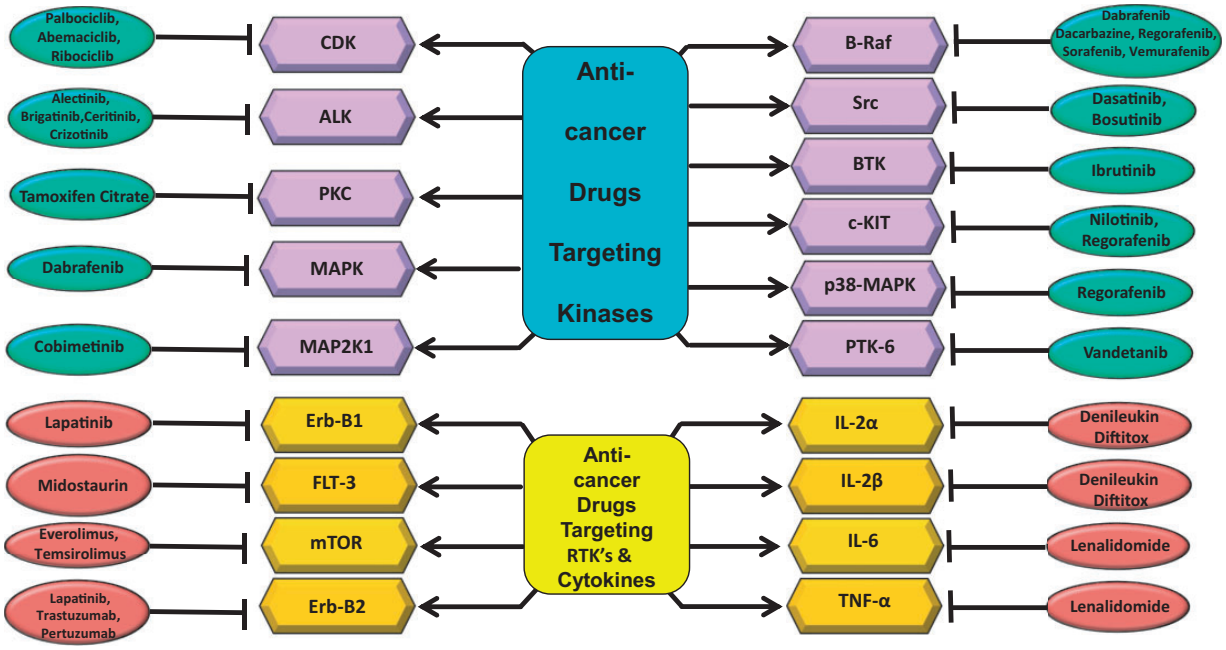

Figure 3. Different drugs approved by the FDA which target kinases, RTKs and cytokines. (A color version of this figure is available in the online journal.)

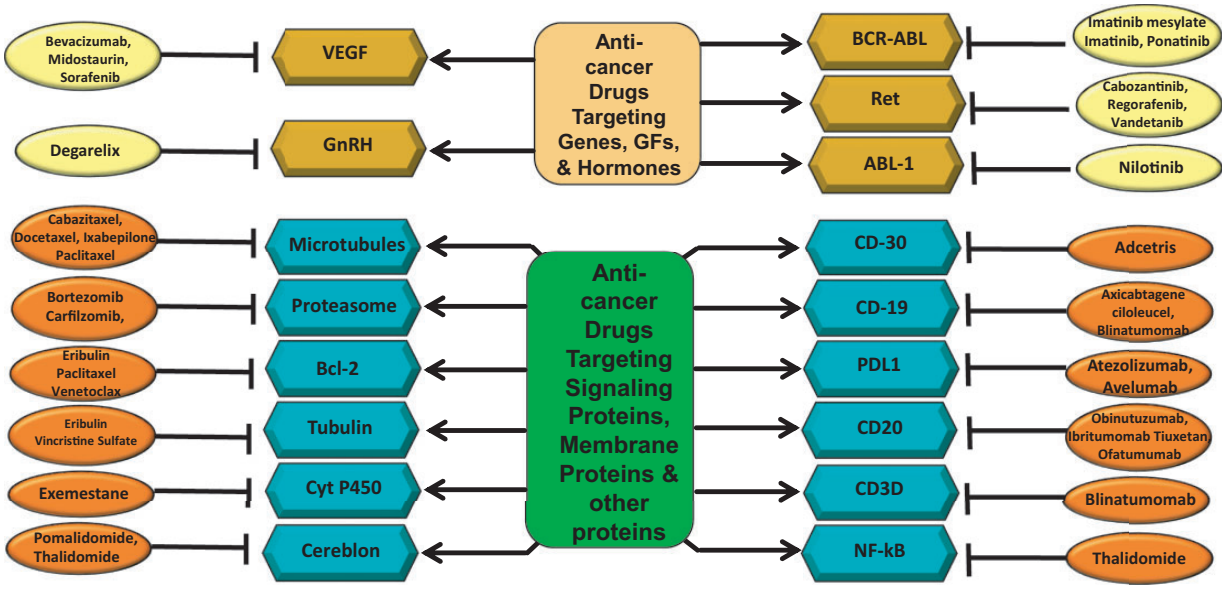

Figure 4. Different drugs approved by the FDA which target other signaling molecules. (A color version of this figure is available in the online journal.)

lines of evidence suggest that "natural products" such as isoflavones, indole-3-carbinol, and curcumin inhibited the growth and induced apoptosis of cancer cells effectively by targeting multiple signaling pathways *in vitro* without causing much toxicity to the normal cells. Therefore, these non-toxic "natural products" could be of immense use in combination with conventional chemotherapeutic agents as well for treating diverse human malignancies effectively without exerting much toxicity.[261–263] For example, curcumin, a component of a spice native to India, was found to exhibit potent antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities. It modulates diverse transcription factors, inflammatory cytokines, enzymes, kinases, and various other proteins and can regulate the growth of tumor cells effectively through modulation of multiple cell signaling cascades. Further, it was also reported that curcumin can interact with almost all the targets regulated by FDA-approved anticancer drugs.[264–266] Again, silymarin, another multi-targeting agent also showed anti-inflammatory as well as anti-metastatic activity and modulated the expressions of cell cycle regulators and proteins involved in apoptosis.[267] Recent studies identified niclosamide as an effective anti-cancer agent with ability to inhibit Wnt/β-catenin, mTORC1, STAT3, NF-κB, and Notch signaling pathways. Further, it was also reported to target mitochondria in

cancer cells to induce cell cycle arrest, growth inhibition, and apoptosis.[268] In addition, tocotrienols, analogs of vitamin E also have gained considerable attention due to their effectiveness and their ability to inflect various targets which are strongly involved in cancer cell proliferation, survival, invasion, angiogenesis, and metastasis. Further, tocotrienols can chemosensitize cancer cells to celecoxib, doxorubicin, erlotinib, gefitinib, gemcitabine, paclitaxel, statin, etc. effectively.[269,270]

Thus it is well affirmed that targeting different biochemical and molecular signaling pathways provides the most well suited and effective strategy to deal with carcinogenesis and overcome resistance to mono-targeted agents. Therefore, exploration of more of these multi-targeted agents, especially those of natural origin and their thorough investigation in pre-clinical and clinical setting would definitely pave way towards successful prevention and treatment of diverse neoplasms.

Cost

Cost of novel anticancer drugs are extremely high which affects the patients and payers globally.[271] For the last 25 years, well-meaning bureaucratic functionaries have introduced numerous new guidelines without consulting any clinical investigators or field testing which resulted in delayed development of new treatments, subdued innovation together with driven up drug costs remarkably.[272] The use of costly therapies with minimal benefits for their approved and unproven indications contributes hugely to the growing cost of cancer care, also known as "financial toxicity" which results in poor health-related and non-health-related issues to the patients.[273,274] Moreover, the survival benefits of certain newer anticancer drugs may be just a few months more than that of the already existing treatment but at a reasonably higher cost.[271] Considering the complication of this matter, evidently, no single solution will suffice. Adopting approaches like macroeconomic basis of cancer costs' re-engineering, education of policy makers, and a transparent regulatory system might offer some potent solutions to this problem.[275] A fair drug price is of vital importance which not only reflects its true benefit but also the societal and personal costs. Further, deciding the price of cancer drugs solely by pharmaceutical companies could make our health care system as well as Medicare completely penniless and is absolutely unfair not only to the cancer patients, but also to the whole society.[276] Another plausible approach is the introduction of generic and biosimilar drugs. Generic drugs are same as brand-name drugs which are used in similar treatment programs for the approved indication and also at comparable dosing levels. On the other hand, biosimilar drugs possess high similarity with the FDA-approved biological agent, with no clinically meaningful differences with regard to safety, efficacy, or purity. Filgrastim-sndz which was developed in 2015 is the first FDA-approved biosimilar drug as an alternative to filgrastim to treat neutropenia in cancer patients. Compared to filgrastim, the cost of biosimilar filgrastim-sndz is around 15% lower in the USA and 30% lower in Europe.[231] Thus they offer a relatively inexpensive treatment choice and may provide relief to the increasing costs of cancer drugs. However, design of strategies to obtain enhanced uptake of biosimilar drugs is highly critical. Another plausible solution is the development and use of biomarkers of drug response to enable reduced use of costly drugs which are improbable to benefit the patients on the basis of disease characteristics. For example, screening for PD-1 and/or PDL-1 provides targeted treatment and reduces the use of expensive PD-1/PDL-1 inhibitors in patients who would not benefit. However, impact of biomarker screening may depend on the approval status of a drug in relation to the discovery of the biomarker.[277] Aforementioned, FDA approved pembrolizumab based on molecular biomarker for patients bearing MSI-H or dMMR solid tumors which have progressed on prior therapy. Approval of such drugs has interweaved the translation of basic science to clinical settings, restricting treatment on the basis of genetic subgroups and the flexibility of the FDA to approve drugs on the basis of early as well as favorable data.[66] In addition, the application of dose individualization concept depending on body surface area may cause reduced expenditure of anticancer drugs. A study was conducted to determine if the rational application of dose individualization leads to reduction in anticancer drugs' costs where 18 different anticancer drugs were given 939 times. They found that if dosage was sternly based on body surface area, drug costs would have been 509,664 Euro. Rounding off to total ampoules with a dose margin of maximum 10% would have caused 8.6% lessening of cost.[278]

Safety

The cancer drugs approved by FDA are mostly associated with adverse side effects. Therefore strategies to overcome these toxicities are of vital importance. For instance, doxorubicin (adriamycin) exerts notable anticancer effect, particularly in solid tumors. Further, it was reported to exhibit a higher therapeutic index compared to some other anticancer drugs like daunorubicin, with minor change in its structure. However, cardiotoxicity generated due to its use presents a major limitation. Nevertheless, it can be prevented by liposomal encapsulation as liposomal-encapsulated doxorubicin is reported to exert less cardio toxicity and it was also approved by FDA for treating ovarian cancer and multiple myeloma. Various reports suggest that treatment related toxicities can be prevented through different pharmacologic substances such as α-tocopherol, ascorbate, vitamin E, and *N*-acetylcystein. Vitamin E and ascorbate are antioxidants which were found to inhibit the formation of free radicals. Qishenyiqi pills were also reported to cause improved cardiac activity through inhibiting the apoptosis of myocardial cells. Again, *N*-acetyl cysteine is shown to increase non-protein sulfhydryl contents of heart, thereby preventing drug induced cardiomyopathy.[279] Therefore encapsulation with these substances may provide protection against cardiotoxicity induced by anticancer drugs. In addition, cytoprotective agents reduce the toxicity related to anticancer treatment and also help to increase the dose as well as dose intensity of radio and chemotherapy. One such organic thiophosphate is

amifostine, which provides selective protection to the normal tissues as well different organs without exerting much toxicity. Clinical studies depicted that amifostine provided protection against nephrotoxicity, neurotoxicity, myelotoxicity, mucositis, and esophagitis in patients treated with radio and chemotherapy. Amifostine is well tolerated in 740 or 910 mg/m^2 doses and interestingly, studies in both pre-clinical and clinical settings did not report to hinder the antitumor efficacy due to its use.[280]

Prevention and treatment

It is well evinced that only 5–10% of all cancer cases is attributed to genetic defects, whereas environment toxins, unhealthy lifestyle, and diet account for the remaining 90–95% cases. Of all cancer-related deaths, almost 25–30% are due to use of tobacco, 30–35% are associated with unhealthy diet, approximately 15–20% are due to infections, and the remaining are caused by other factors such as exposure to radiation, stress, physical inactivity, and environmental pollutants.[281] As mentioned, maintaining a healthy diet plays an inevitable role in cancer prevention. Low use of fibers, consumption of red meat and an imbalance of omega-3, -6 fats may enhance the risk of cancer. On the other hand, high intake of fruits and vegetables may considerably lower the risk of cancer. Moreover, use of digestive enzymes and probiotics as oral supplements is another anticancer dietary measure.[282] The chemoprotective effect of fruits and vegetables also holds true for different cancer types including cancers of the colon, esophagus, endometrium, oral cavity, lung, pharynx, pancreas, and stomach.[283,284] Therefore, by embracing a healthy diet which include smoking cessation, increased intake of fruits and vegetables, moderate use of alcohol, caloric restriction, minimal meat consumption, use of whole grains, and maintaining a healthy lifestyle regime including regular exercise, less direct exposure to sunlight, use of vaccinations, and regular check-ups, this deadly disease can be prevented.[285]

In addition, personalized cancer medicine offers a huge benefit in the treatment of cancer. It can be done through a national facilitated access program and registry for off-label use of targeted anticancer drugs. With the help of such program, patients can be benefited by receiving the targeted agent matched to their tumor profile.[286] Again, centrosome clustering mechanisms are also attractive theranostic targets against cancer.[285] When cancer is diagnosed, besides medical consultation, cancer patients seek advice and counsel from close family and friends. Hence, medical advice in the care of a friend, loved one, or close associate by an oncologist can be of immense help.[287] Further, the Ayurveda, Siddha, and Unani (ASU) education system require a reform at every level to produce expert, resourceful and informed graduates who can certainly contribute to the betterment of the society.[288]

Conclusion

Cancer is an extremely complex disease caused by the deregulation of multiple genes, proteins, and pathways. Advancements in molecular biology and high throughput screening technologies led to the development of different target specific drugs for the treatment of cancer. But unfortunately, none of them is effective and devoid of toxicities and hence fails to combat cancer despite the fact they are extremely expensive. As a matter of fact, in almost all the cases, taking a single drug against cancer from discovery to testing to market costs around $1 billion. This review summarizes the advantages as well as limitations associated with various aspects of cancer diagnosis as well as treatment. While cell lines and animal models possess ample advantages for cancer research and development of novel cancer therapies, reports indicate that these pre-clinical models are highly incomplete and data obtained from them shows a fundamental mismatch with those obtained from clinical findings. This presents a major obstacle in the development of effective anticancer drugs. It is well evinced that inflection of numerous transduction cascades presents a convincing tactic to the actuality of carcinogenesis and the growing issue of emerging chemoresistance. Therefore, a multidisciplinary drug discovery approach which includes the generation of novel molecular multiplicity from natural sources, together with synthetic procedures might offer key solution to the discovery and development of safe, effective and affordable drugs against diverse neoplasms.

Author Contributions: BBA and ABK contributed to the study design and writing. DB, BLS, and NKR performed bibliographic search, writing, and artwork. KKT and KB contributed to figures, tables, and reference editing. SCG and MS contributed to proofread and writing.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Department of Biotechnology awarded to Ajaikumar B Kunnumakkara by Department of Biotechnology (DBT), Government of India. The author Bethsebie Lalduhsaki Sailo acknowledges the DST INSPIRE and Kishore Banik acknowledges the UGC New Delhi for providing them the fellowship.

REFERENCES

1. Hasima N, Aggarwal BB. Cancer-linked targets modulated by curcumin. *Int J Biochem Mol Biol* 2012;**3**:328–51
2. Bordoloi D, Sailo BL, Manteghi N, Padmavathi G, Kunnumakkara AB. *Introduction and basic concepts of cancer. Cancer cell chemoresistance and chemosensitization*. Hackensack, NJ: World Scientific, 2018, pp.1–14.
3. Bordoloi D, Banik K, Shabnam B, Padmavathi G, Monisha J, Arfuso F, Dharmarajan A, Mao X, Lim LHK, Wang L, Fan L, Hui KM, Kumar AP, Sethi G, Kunnumakkara AB. TIPE family of proteins and its implications in different chronic diseases. *Int J Mol Sci* 2018;**19**:E2974
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and

mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424
5. Thakur KK, Bordoloi D, Kunnumakkara AB. Alarming burden of triple-negative breast cancer in India. *Clin Breast Cancer* 2018;**18**:e393–9
6. Whiteman DC, Wilson LF. The fractions of cancer attributable to modifiable factors: a global review. *Cancer Epidemiol* 2016;**44**:203–21
7. Harsha C, Banik K, Bordoloi D, Kunnumakkara AB. Antiulcer properties of fruits and vegetables: a mechanism based perspective. *Food Chem Toxicol* 2017;**108**:104–19
8. Khwairakpam AD, Bordoloi D, Thakur KK, Monisha J, Arfuso F, Sethi G, Mishra S, Kumar AP, Kunnumakkara AB. Possible use of *Punica granatum* (pomegranate) in cancer therapy. *Pharmacol Res* 2018;**133**:53–64
9. Aggarwal BB, Danda D, Gupta S, Gehlot P. Models for prevention and treatment of cancer: problems vs promises. *Biochem Pharmacol* 2009;**78**:1083–94
10. Yi S, Lin S, Li Y, Zhao W, Mills GB, Sahni N. Functional variomics and network perturbation: connecting genotype to phenotype in cancer. *Nat Rev Genet* 2017;**18**:395–410
11. Khurana E, Fu Y, Chakravarty D, Demichelis F, Rubin MA, Gerstein M. Role of non-coding sequence variants in cancer. *Nat Rev Genet* 2016;**17**:93–108
12. Zhang W, Bojorquez-Gomez A, Velez DO, Xu G, Sanchez KS, Shen JP, Chen K, Licon K, Melton C, Olson KM, Yu MK, Huang JK, Carter H, Farley EK, Snyder M, Fraley SI, Kreisberg JF, Ideker T. A global transcriptional network connecting noncoding mutations to changes in tumor gene expression. *Nat Genet* 2018;**50**:613–20
13. Drost J, Clevers H. Who is in the driver's seat: tracing cancer genes using CRISPR-barcoding. *Mol Cell* 2016;**63**:352–4
14. Watson IR, Takahashi K, Futreal PA, Chin L. Emerging patterns of somatic mutations in cancer. *Nat Rev Genet* 2013;**14**:703–18
15. Roerink SF, Sasaki N, Lee-Six H, Young MD, Alexandrov LB, Behjati S, Mitchell TJ, Grossmann S, Lightfoot H, Egan DA, Pronk A, Smakman N, van Gorp J, Anderson E, Gamble SJ, Alder C, van de Wetering M, Campbell PJ, Stratton MR, Clevers H. Intra-tumour diversification in colorectal cancer at the single-cell level. *Nature* 2018;**556**:457–62
16. Waris G, Ahsan H. Reactive oxygen species: role in the development of cancer and various chronic conditions. *J Carcinog* 2006;**5**:14
17. Aggarwal BB, Sung B. NF-κB in cancer: a matter of life and death. *Cancer Discov* 2011;**1**:469–71
18. Bos JL. ras oncogenes in human cancer: a review. *Cancer Res* 1989;**49**:4682–9
19. Monisha J, Roy NK, Bordoloi D, Kumar A, Golla R, Kotoky J, Padmavathi G, Kunnumakkara AB. Nuclear factor kappa B: a potential target to persecute head and neck cancer. *Curr Drug Targets* 2017;**18**:232–53
20. Padmavathi G, Roy NK, Bordoloi D, Arfuso F, Mishra S, Sethi G, Bishayee A, Kunnumakkara AB. Butein in health and disease: a comprehensive review. *Phytomedicine* 2017;**25**:118–27
21. Vivanco I, Sawyers CL. The phosphatidylinositol 3-kinase AKT pathway in human cancer. *Nat Rev Cancer* 2002;**2**:489–501
22. Kansanen E, Kuosmanen SM, Leinonen H, Levonen AL. The Keap1-Nrf2 pathway: mechanisms of activation and dysregulation in cancer. *Redox Biol* 2013;**1**:45–9
23. Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. *Oncogene* 2017;**36**:1461–73
24. Curtin NJ. DNA repair dysregulation from cancer driver to therapeutic target. *Nat Rev Cancer* 2012;**12**:801–17
25. Doroshow JH, Kummar S. Translational research in oncology-10 years of progress and future prospects. *Nat Rev Clin Oncol* 2014;**11**:649–62
26. Wilding JL, Bodmer WF. Cancer cell lines for drug discovery and development. *Cancer Res* 2014;**74**:2377–84
27. Daniela F, Filomena A, Raquel C. The importance of cancer cell lines as in vitro models in cancer methylome analysis and anticancer drugs testing. *Oncogenomics Cancer Proteomics* 2013;139–66
28. Gardaneh M. Human cancer modeling: recapitulating tumor heterogeneity towards personalized medicine. *Multidiscip Cancer Invest* 2017;**1**:1–12
29. Iorio F, Knijnenburg TA, Vis DJ, Bignell GR, Menden MP, Schubert M, Aben N, Gonçalves E, Barthorpe S, Lightfoot H, Cokelaer T, Greninger P, van Dyk E, Chang H, de Silva H, Heyn H, Deng X, Egan RK, Liu Q, Mironenko T, Mitropoulos X, Richardson L, Wang J, Zhang T, Moran S, Sayols S, Soleimani M, Tamborero D, Lopez-Bigas N, Ross-Macdonald P, Esteller M, Gray NS, Haber DA, Stratton MR, Benes CH, Wessels LFA, Saez-Rodriguez J, McDermott U, Garnett MJ. A landscape of pharmacogenomic interactions in cancer. *Cell* 2016;**166**:740–54
30. Pathak S, Multani AS, Narayan S, Kumar V, Newman RA. Anvirzel, an extract of *Nerium oleander*, induces cell death in human but not murine cancer cells. *Anticancer Drugs* 2000;**11**:455–63
31. Gutmann DH, Hunter-Schaedle K, Shannon KM. Harnessing preclinical mouse models to inform human clinical cancer trials. *J Clin Invest* 2006;**116**:847–52
32. Day CP, Merlino G, Van Dyke T. Preclinical mouse cancer models: a maze of opportunities and challenges. *Cell* 2015;**163**:39–53
33. Zhang W, Moore L, Ji P. Mouse models for cancer research. *Chin J Cancer* 2011;**30**:149–52
34. Hurtley S. Humans as model of human disease. *Res Sci J* 2018;**361**:763–4
35. Jackson SJ, Thomas GJ. Human tissue models in cancer research: looking beyond the mouse. *Dis Model Mech* 2017;**10**:939–42
36. Drost J, Clevers H. Organoids in cancer research. *Nat Rev Cancer* 2018;**18**:407–18
37. Ingber DE. Developmentally inspired human 'organs on chips'. *Development* 2018;**145**:dev156125
38. Adams DJ. The Valley of Death in anticancer drug development: a reassessment. *Trends Pharmacol Sci* 2012;**33**:173–80
39. Eaton A, Iasonos A, Gounder MM, Pamer EG, Drilon A, Vulih D, Smith GL, Ivy SP, Spriggs DR, Hyman DM. Toxicity attribution in phase I trials: evaluating the effect of dose on the frequency of related and unrelated toxicities. *Clin Cancer Res* 2016;**22**:553–9
40. Braun TM. The current design of oncology phase I clinical trials: progressing from algorithms to statistical models. *Chin Clin Oncol* 2014;**3**:2
41. Mark V, Hendrik-Tobias A. Challenges of patient selection for phase I oncology trials. *Drug Discov Dev IntechOpen* 2015;65–82
42. Molife LR, Alam S, Olmos D, Puglisi M, Shah K, Fehrmann R, Trani L, Tjokrowidjaja A, de Bono JS, Banerji U, Kaye SB. Defining the risk of toxicity in phase I oncology trials of novel molecularly targeted agents: a single centre experience. *Ann Oncol* 2012;**23**:1968–73
43. Smith SM, Pitcher BN, Jung SH, Bartlett NL, Wagner-Johnston N, Park SI, Richards KL, Cashen AF, Jaslowski A, Smith SE, Cheson BD, Hsi E, Leonard JP. Safety and tolerability of idelalisib, lenalidomide, and rituximab in relapsed and refractory lymphoma: the Alliance for Clinical Trials in Oncology A051201 and A051202 phase 1 trials. *Lancet Haematol* 2017;**4**:e176–82
44. Sonali MS, Brandelyn NP, Sin-Ho J, Nancy LB, Nina WJ, Steven IP, Kristy LR, Amanda FC, Anthony J, Scott ES, Bruce DC, Eric H, John PL. Safety and tolerability of idelalisib, lenalidomide, and rituximab in relapsed and refractory lymphoma: the Alliance for Clinical Trials in Oncology A051201 and A051202 phase 1 trials. *Lancet Haematol* 2017;**4**:Pe176–82
45. Pongas G, Fojo T. BEZ235: when promising science meets clinical reality. *Oncologist* 2016;**21**:1033–4
46. Roy NK, Bordoloi D, Monisha J, Padmavathi G, Kotoky J, Golla R, Kunnumakkara AB. Specific targeting of Akt kinase isoforms: taking the precise path for prevention and treatment of cancer. *Curr Drug Targets* 2017;**18**:421–35
47. Moreno L, Pearson AD. How can attrition rates be reduced in cancer drug discovery? *Expert Opin Drug Discov* 2013;**8**:363–8
48. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates?. *Nat Rev Drug Discov* 2004;**3**:711–5
49. Goss TF, Picard EH, Tarab A. *Recognizing value in oncology innovation*. Boston, MA: Boston Healthcare, 2012
50. Stein WD, Figg WD, Dahut W, Stein AD, Hoshen MB, Price D, Bates SE, Fojo T. Tumor growth rates derived from data for patients in a clinical trial correlate strongly with patient survival: a novel strategy for evaluation of clinical trial data. *Oncologist* 2008;**13**:1046–54

51. US Food and Drug Administration, https://www.fda.gov (accessed 31 August 2018)
52. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics* 2019;**20**:273–86
53. Amiri-Kordestani L, Fojo T. Why do phase III clinical trials in oncology fail so often. *J Natl Cancer Inst* 2012;**104**:568–9
54. Prasad V. Do cancer drugs improve survival or quality of life? *BMJ* 2017;**359**:j4528
55. Salas-Vega S, Iliopoulos O, Mossialos E. Assessment of overall survival, quality of life, and safety benefits associated with new cancer medicines. *JAMA Oncol* 2017;**3**:382–90
56. Mailankody S, Prasad V. Overall survival in cancer drug trials as a new surrogate end point for overall survival in the real world. *JAMA Oncol* 2017;**3**:889–90
57. Jawed I, Wilkerson J, Prasad V, Duffy AG, Fojo T. Colorectal cancer survival gains and novel treatment regimens: a systematic review and analysis. *JAMA Oncol* 2015;**1**:787–95
58. Fojo T, Parkinson DR. Biologically targeted cancer therapy and marginal benefits: are we making too much of too little or are we achieving too little by giving too much?. *Clin Cancer Res* 2010;**16**:5972–80
59. Bates SE, Fojo T. Epidermal growth factor receptor inhibitors: a moving target?. *Clin Cancer Res* 2005;**11**:7203–5
60. Massey PR, Prasad V, Figg WD, Fojo T. Multiplying therapies and reducing toxicity in metastatic melanoma. *Cancer Biol Ther* 2015;**16**:1014–8
61. Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Park-Simon TW, Rustin G, Joly F, Mirza MR, Plante M, Quinn M, Poveda A, Jayson GC, Stark D, Swart AM, Farrelly L, Kaplan R, Parmar MK, Perren TJ. ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015;**16**:928–36
62. Fojo T, Bates S. Arsenic trioxide (As(2)O(3)): still a mystery. *Cell Cycle* 2002;**1**:183–6
63. Wilson WH, Schenkein DP, Jernigan CL, Woodcock J, Schilsky RL. Reevaluating the accelerated approval process for oncology drugs. *Clin Cancer Res* 2013;**19**:2804–9
64. Fuereder T. Immunotherapy for head and neck squamous cell carcinoma. *Memo* 2016;**9**:66–9
65. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;**357**:409–13
66. Prasad V, Kaestner V, Mailankody S. Cancer drugs approved based on biomarkers and not tumor type-FDA approval of pembrolizumab for mismatch repair-deficient solid cancers. *JAMA Oncol* 2018;**4**:157–8
67. Prasad V, Kaestner V, Mailankody S. Clarification of the FDA accelerated agnostic approval of pembrolizumab and the opportunities arising from the required confirmatory studies-reply. *JAMA Oncol* 2018;**4**:1300–1
68. Prasad V, Mailankody S. The accelerated approval of oncologic drugs: lessons from ponatinib. *JAMA* 2014;**311**:353
69. New Drug Approval, United States Government Accountability Office. *FDA needs to enhance its oversight of drugs approved on the basis of surrogate endpoints*, https://www.gao.gov/new.items/d09866.pdf (2009, accessed 3 September 2018)
70. Kim C, Prasad V. Strength of validation for surrogate end points used in the US Food and Drug Administration's approval of oncology drugs. *Mayo Clin Proc* 2016;**91**:713–25
71. Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses. *JAMA Intern Med* 2015;**175**:1389–98
72. Rupp T, Zuckerman D. Quality of life, overall survival, and costs of cancer drugs approved based on surrogate endpoints. *JAMA Intern Med* 2017;**177**:276–7
73. Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions. And are they currently overused? *BMC Med* 2017;**15**:134
74. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US Food and Drug Administration approvals. *JAMA Intern Med* 2015;**175**:1992–4
75. Wilkerson J, Fojo T. Progression-free survival is simply a measure of a drug's effect while administered and is not a surrogate for overall survival. *Cancer J* 2009;**15**:379–85
76. Vaduganathan M. Modern drug development which patients should come first?. *JAMA* 2014;**312**:2619–20
77. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004;**22**:4626–31
78. Hayes MJ, Kaestner V, Mailankody S, Prasad V. Most medical practices are not parachutes: a citation analysis of practices felt by biomedical authors to be analogous to parachutes. *CMAJ Open* 2018;**6**:E31–8
79. Marquart J, Chen EY, Prasad V. Estimation of the percentage of US patients with cancer who benefit from genome-driven oncology. *JAMA Oncol* 2018;**4**:1093–8
80. Gill J, Obley AJ, Prasad V. Direct-to-consumer genetic testing: the implications of the US FDA's first marketing authorization for BRCA mutation testing. *JAMA* 2018;**319**:2377–8
81. The online gene test finds a dangerous mutation. It may well be wrong, https://www.nytimes.com/2018/07/02/health/gene-testing-disease-nyt.html (2018, accessed 31 October 2018)
82. Kaiser J. Is genome-guided cancer treatment hyped?. *Science* 2018;**360**:365
83. Moscow JA, Fojo T, Schilsky RL. The evidence framework for precision cancer medicine. *Nat Rev Clin Oncol* 2018;**15**:183–92
84. Prasad V. Perspective: the precision-oncology illusion. *Nature* 2016;**537**:S63
85. Garber K. Blood test may predict cancer immunotherapy benefit. *Science* 2018;**360**:1387
86. Parikh RB, Prasad V. Blood-based screening for colon cancer: a disruptive innovation or simply a disruption?. *JAMA* 2016;**315**:2519–20
87. Rixe O, Fojo T. Is cell death a critical end point for anticancer therapies or is cytostasis sufficient?. *Clin Cancer Res* 2007;**13**:7280–7
88. Stewart DJ, Stewart AA, Wheatley-Price P, Batist G, Kantarjian HM, Schiller J, Clemons M, Bradford JP, Gillespie L, Kurzrock R. The importance of greater speed in drug development for advanced malignancies. *Cancer Med* 2018;**7**:1824–36
89. Prasad V, Massey PR, Fojo T. Oral anticancer drugs: how limited dosing options and dose reductions may affect outcomes in comparative trials and efficacy in patients. *J Clin Oncol* 2014;**32**:1620–9
90. Armstrong K, Anderson ME, Carethers JM, Loscalzo J, Parmacek MS, Wachter RM, Zeidel ML. International exchange and American medicine. *N Engl J Med* 2017;**376**:e40
91. Burotto M, Prasad V, Fojo T. Non-inferiority trials: why oncologists must remain wary. *Lancet Oncol* 2015;**16**:364–6
92. Lu E, Shatzel J, Shin F, Prasad V. What constitutes an "unmet medical need" in oncology? An empirical evaluation of author usage in the biomedical literature. *Semin Oncol* 2017;**44**:8–12
93. Prasad V, Kumar H, Mailankody S. Ethics of clinical trials in low-resource settings: lessons from recent trials in cancer medicine. *J Glob Oncol* 2015;**2**:1–3
94. Aggarwal A, Unger-Saldaña K, Lewison G, Sullivan R. The challenge of cancer in middle-income countries with an ageing population: Mexico as a case study. *ecancermedicalscience* 2015;**9**:536
95. Mailankody S, Prasad V. Thinking systematically about the off-label use of cancer drugs and combinations for patients who have exhausted proven therapies. *Oncologist* 2016;**21**:1031–2
96. Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency:

retrospective cohort study of drug approvals 2009–13. *BMJ* 2017;**359**:j4530
97. Lammers A, Wang R, Cetnar J, Prasad V. Time from US Food and Drug Administration approval to publication of data for cancer drugs: a comparison of first and subsequent approvals. *Blood Cancer J* 2017;**7**:637
98. Aggarwal A, Fojo T, Chamberlain C, Davis C, Sullivan R. Do patient access schemes for high-cost cancer drugs deliver value to society?-lessons from the NHS Cancer Drugs Fund. *Ann Oncol* 2017;**28**:1738–50
99. Cifu AS, Prasad VK. Medical debates and medical reversal. *J Gen Intern Med* 2015;**30**:1729–30
100. Blagoev KB, Wilkerson J, Fojo T. Hazard ratios in cancer clinical trials – a primer. *Nat Rev Clin Oncol* 2012;**9**:178–83
101. Ross JS. Clinical trials – we get what we pay for. *JAMA Intern Med* 2018;178:1457
102. Fojo T, Giannakakou P. Decade in review – funding in cancer research: National Cancer Institute awards – a work in progress. *Nat Rev Clin Oncol* 2014;**11**:634–6
103. Drugbank, https://www.drugbank.ca/drugs (2016, accessed 2 November 2018)
104. STAT. FDA approves Lilly pill for common advanced breast cancer. https://www.statnews.com/2017/09/29/fda-verzenio-breast-cancer/ (2017, accessed 2 November 2018)
105. Prostate.net. What is the cost of zytiga? https://prostate.net/articles/cost-of-zytiga (2013, accessed 2 November 2018)
106. *Medical News Today*. Adcetris may cost $4,500 per vial, or over $100,000 for a course of lymphoma treatment, https://www.medicalnewstoday.com/articles/233141.php (2011, accessed 2 November 2018)
107. *Pharmacy Times*. Ado-trastuzumab Emtansine (Kadcyla), https://www.pharmacytimes.com/publications/health-system-edition/2013/july2013/ado-trastuzumab-emtansine-kadcyla (2013, accessed 2 November 2018).
108. Pignata M, Chouaid C, Le Lay K, Luciani L, McConnachie C, Gordon J, Roze S. Evaluating the cost-effectiveness of afatinib after platinum-based therapy for the treatment of squamous non-small-cell lung cancer in France. *CEOR* 2017;**9**:655–68
109. Pink Sheet. Chiron/cetus' proleukin (IL-2) therapy will cost $6,000-$8,000 per course, https://pink.pharmaintelligence.informa.com/PS020819/CHIRONCETUS-PROLEUKIN-IL2-THERAPY-WILL-COST-60008000-PER-COURSE (1992, accessed 2 November 2018)
110. National Institute for Health and Care Excellence. Technology appraisal guidance-alectinib for untreated ALK-positive advanced non-small-cell lung cancer, https://www.nice.org.uk/guidance/ta536/documents/final-appraisal-determination-document%20https://prescriptionhope.com/alecensa-alectinib (2018, accessed 16 October 2018)
111. Drug Topics. Apalutimide for prostate cancer: what to know, http://www.drugtopics.com/new-products/apalutimide-prostate-cancer-what-know (2018, accessed 2 November 2018)
112. pan-Canadian Oncology Drug Review. *pan-Canadian oncology drug review nal economic guidance report*. Arsenic trioxide (trisenox) for acute promyelocytic leukemia, https://www.cadth.ca/sites/default/files/pcodr/pcodr-trisenox-apl-fn-egr.pdf (2014, accessed 2 November 2018)
113. International Medical Products Price Guide, Management Sciences for Health. Asparaginase, http://mshpriceguide.org/en/single-drug-information/?DMFId=69&searchYear=2014 (2016, accessed 2 November 2018)
114. Lash A. Xconomy, in immuno-oncology's latest win, FDA OK's Genentech Drug, https://xconomy.com/san-francisco/2016/05/18/in-immuno-oncologys-latest-win-fda-oks-genentech-drug/ (2016, accessed 2 November 2018).
115. Pan-Canadian Oncology Drug Review. pCODR Expert Review Committee (pERC) final recommendation, https://www.cadth.ca/sites/default/files/pcodr/pcodr_avelumab_bavencio_mcc_fn_rec.pdf (2018, accessed 2 November 2018)
116. Healio, Immuno-oncology. UK panel rejects CAR T-cell therapy due to cost, https://www.healio.com/hematology-oncology/lymphoma/news/online/%7Bd32cc851-3898-4caf-81e9-0e8cc841e2f2%7D/uk-panel-rejects-car-t-cell-therapy-due-to-cost (2018, accessed 2 November 2018)
117. UKMi, London Cancer New Drugs Group. Axitinib as an option for second line advanced renal cell carcinoma with progression after tyrosine kinase inhibitor, https://www.medicinesresources.nhs.uk/upload/documents/Evidence/Drug%20Specific%20Reviews/Axitinib%20as%20an%20option%20for%20second%20line%20advanced%20renal.pdf (2013, accessed 2 November 2018)
118. Ontario Public Drug Programs, Ministry of Health and Long-Term Care. Azacitidine, http://www.health.gov.on.ca/en/pro/programs/drugs/ced/pdf/vdaza.pdf (2011, accessed 2 November 2018)
119. Leong H, Bonk ME. Bendamustine (treanda) for chronic lymphocytic leukemia: a brief overview. *P T* 2009;**34**:73–6
120. News-Medical, Life Science. Avastin (bevacizumab) price, https://www.news-medical.net/health/Avastin-(Bevacizumab)-Price.aspx (2018, accessed 2 November 2018)
121. Geskin L, Malone DC. An exploratory cost-effectiveness analysis of systemic treatments for cutaneous T-cell lymphoma. *J Dermatolog Treat* 2018;**29**:522–30
122. *CADTH, pan-Canadian oncology drug review nal economic guidance report*. Blinatumomab (Blincyto) for pediatric acute lymphoblastic leukemia, https://www.cadth.ca/sites/default/files/pcodr/pcodr_blinatumomab_blincyto_all_pediatric_fn_egr.pdf (2017, accessed 2 November 2018)
123. Durie B, Binder G, Pashos C, Khan Z, Hussein M, Borrello I. Total cost comparison in relapsed/refractory multiple myeloma. *J Med Econ* 2013;**16**:614–22
124. National Institute for Health and Care Excellence. *Final appraisal determination – bosutinib for previously treated chronic myeloid leukaemia*, https://www.nice.org.uk/guidance/ta299/documents/chronic-myeloid-leukaemia-bosutinib-final-appraisal-determination-document2 (2013, accessed 16 October 2018)
125. Berger K, Schopohl D, Rieger C, Ostermann H. Economic and clinical aspects of intravenous versus oral busulfan in adult patients for conditioning prior to HSCT. *Support Care Cancer* 2015;**23**:3447–54
126. Elliott W, Chan J. Relias Media, the trusted source for healthcare information and continuing education. Pharmacology update, Brigatinib Tablets (Alunbrig), https://www.reliasmedia.com/articles/140851-brigatinib-tablets-alunbrig (2017, accessed 16 October 2018)
127. National Institute for Health and Clinical Excellence. *Final appraisal determination-Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen*, https://www.nice.org.uk/guidance/ta255/documents/prostate-cancer-cabazitaxel-final-appraisal-determination-document2 (2012, accessed 16 October 2018)
128. Meng J, Lister J, Vataire AL, Casciano R, Dinet J. Cost-effectiveness comparison of cabozantinib with everolimus, axitinib, and nivolumab in the treatment of advanced renal cell carcinoma following the failure of prior therapy in England. *CEOR* 2018;**10**:243–50
129. Grullich C. Cabozantinib: a MET, RET, and VEGFR2 tyrosine kinase inhibitor. *Recent Results Cancer Res* 2014;**201**:207–14
130. *Managed Markets Network Journals*, Clinical Care Targeted Communications Group. LLC. How much will Amgen's carfilzomib for multiple myeloma cost, https://www.ajmc.com/newsroom/how-much-will-amgens-carfilzomib-combination-treatment-for-multiple-myeloma-cost (2018, accessed 16 October 2018)
131. Dalal AA, Guerin A, Mutebi A, Culver KW. Treatment patterns, clinical and economic outcomes of patients with anaplastic lymphoma kinase-positive non-small cell lung cancer receiving ceritinib: a retrospective observational claims analysis. *J Drug Assess* 2018;**7**:21–7
132. Fojo T, Grady C. How much is life worth: cetuximab, non-small cell lung cancer, and the $440 billion question. *J Natl Cancer Inst* 2009;**101**:1044–8
133. Reyes C, Gazauskas G, Becker U, Moreno S, Veenstra DL. Cost-effectiveness analysis of obinutuzumab versus ofatumumab for previously untreated chronic lymphocytic leukemia (CLL). *Blood* 2014;**124**:1324
134. National Centre for Pharmacoeconomics. Cost-*e*ffectiveness of *c*obimetinib (Cotellic®) for the *t*reatment of *u*nresectable or *a*dvanced *m*etastatic *m*elanoma with a BRAF *V600: mutation, only in combination with*

vemurafenib, http://www.ncpe.ie/wp-content/uploads/2016/04/Web-summary-cobimetinib.pdf (2017, accessed 2 November 2018)
135. National Centre for Pharmacoeconomics. *Cost effectiveness of crizotinib (Xalkori®) for the treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)*, http://www.ncpe.ie/wp-content/uploads/2013/02/Summary-Crizotinib-20130826-with-additional-info-2.pdf (2013, accessed 2 November 2018)
136. Kruse GB, Amonkar MM, Smith G, Skonieczny DC, Stavrakas S. Analysis of costs associated with administration of intravenous single-drug therapies in metastatic breast cancer in a U.S. population. *JMCP* 2008;**14**:844–57
137. Kuznar W. American Health & Drug Benefits, decitabine more cost-effective than conventional induction in older patients with AML, http://www.ahdbonline.com/issues/2014/february-2014-vol-7-no-1-special-issue-ash-2013-payers-perspectives-in-oncology/1648-decitabine-more-cost-effective-than-conventional-induction-in-older-patients-with-aml (2013, accessed 2 November 2018)
138. Novartis, Novartis oncology universal co-pay assistance program, https://www.hcp.novartis.com/products/tafinlar-mekinist/advanced-melanoma/access/ (2018, accessed 2 November 2018)
139. Summary of product characteristics. Tafinlar, https://www.ema.europa.eu/documents/product-information/tafinlar-epar-product-information_en.pdf (2018, accessed 2 November 2018)
140. Curl P, Vujic I, van 't Veer LJ, Ortiz-Urda S, Kahn JG. Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma. *PLoS One* 2014;**9**:e107255
141. Lertkhachonsuk AA, Hanvoravongchai P. Comparison of cost-effectiveness between actinomycin D versus methotrexate-folinic acid in the treatment of low-risk gestational trophoblastic neoplasia. *J Reprod Med* 2016;**61**:230–4
142. Del Rey C, Asano E. Accumulated treatment cost of new therapies in multiple myeloma: comparing the combination of daratumumab, bortezomib and dexamethasone with carfilzomib and dexamethasone for who have received at least one prior therapy in Brazil. *Value Health* 2017;**20**:A876
143. Cost effectiveness of crizotinib (Xalkori) for the treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). National Centre for Pharmacoeconomics, http://www.ncpe.ie/wp-content/uploads/2013/02/Summary-Crizotinib-20130826-with-additional-info-2.pdf (2013, accessed 16 October 2018)
144. Wiles S, Kabalan M, Sharma R, Shatzel J, Pang J, Yi D, Alatovic I, Saif S, Narasimha D, LaPenna J, Troitino A, Attwood K, Yin Y, Wetzler M. Decitabine is more cost effective than standard conventional induction therapy in elderly acute myeloid leukemia patients. *Blood* 2013;**122**:2699
145. National Institute for Health and Care Excellence. *Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia. Technology appraisal guidance [TA425]*, https://www.nice.org.uk/guidance/ta425/chapter/2-The-technologies (2016, accessed 16 October 2018)
146. Geskin L, Malone DC. An exploratory cost-effectiveness analysis of systemic treatments for cutaneous T-cell lymphoma. *J Dermatolog Treat* 2018;**29**:522–30
147. National Institute for Health and Care Excellence. *Appraisal consultation document. Dinutuximab for treating high-risk neuroblastoma*, https://www.nice.org.uk/guidance/gid-tag507/documents/appraisal-consultation-document (2015, accessed 2 November 2018)
148. ClaimSecure, Drug Review. Firmagon – new hormone therapy for the treatment of advanced prostate cancer, https://www.claimsecure.com/content/pdfs/en-CA/DrugReviews/DrugReview_Vol9_Issue5_en.pdf (2010, accessed 16 October 2018)
149. Ojeda B, de Sande LM, Casado A, Merino P, Casado MA. Cost-minimisation analysis of pegylated liposomal doxorubicin hydrochloride versus topotecan in the treatment of patients with recurrent epithelial ovarian cancer in Spain. *Br J Cancer* 2003;**89**:1002–7
150. OptumRx, Clinical Services Department. Idhifa (enasidenib) – new orphan drug approval, https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-approvals/drugapprovals_idhifa_2017-0801.pdf (2017, accessed 16 October 2018)
151. Prostate.net. What is the cost of xtandi? https://prostate.net/articles/cost-of-xtandi (2013, accessed 2 November 2018)
152. Shetty N, Gupta S. Eribulin drug review. *South Asian J Cancer* 2014;**3**:57–9
153. Hurtaud A, Donnadieu A, Escalup L, Cottu PH, Baffert S. Costs associated with eribulin treatment for patients with metastatic breast cancer in a comprehensive cancer center in France. *Breast* 2016;**30**:73–9
154. National Institute for Health and Clinical Excellence. *Final appraisal determination – erlotinib for the treatment of non-small-cell lung cancer*, https://www.nice.org.uk/guidance/ta162/documents/lung-cancer-nonsmallcell-erlotinib-final-appraisal-determination2 (2008, accessed 16 October 2018)
155. Doyle JJ, Dezii CM, Sadana A. A pharmacoeconomic evaluation of cisplatin in combination with either etoposide or etoposide phosphate in small cell lung cancer. *Semin Oncol* 1996;**23**:51–60
156. Ontario Public Drug Programs, Ministry of Health and Long-Term Care. Everolimus, http://www.health.gov.on.ca/en/pro/programs/drugs/ced/pdf/afinitor.pdf (2011, accessed 16 October 2018)
157. Ontario Public Drug Programs, Ministry of Health and Long-Term Care. Exemestane (for early breast cancer), http://www.health.gov.on.ca/en/pro/programs/drugs/ced/pdf/exemestane.pdf (2008, accessed 2 November 2018)
158. Tilleul P, Jacot W, Emery C, Lafuma A, Gourmelen J. Management and cost analysis of cancer patients treated with G-CSF: a cohort study based on the French national healthcare insurance database. *J Med Econ* 2017;**20**:1261–7
159. Suh DC, Powers CA, Barone JA, Shin H, Kwon J, Goodin S. Full costs of dispensing and administering fluorouracil chemotherapy for outpatients: a microcosting study. *Res Social Adm Pharm* 2010;**6**:246–56
160. Yoon J, Phibbs CS, Chow A, Weinstock MA, Veterans affairs keratinocyte carcinoma chemoprevention Trial Group. Impact of topical fluorouracil cream on costs of treating keratinocyte carcinoma (nonmelanoma skin cancer) and actinic keratosis. *J Am Acad Dermatol* 2018;**79**:501–7.e2
161. Kuznar W. Value based cancer care, cost-effectiveness comparison: FOLFIRI versus FOLFOX, http://www.valuebasedcancer.com/issue-archive/2011/february-2011-vol-2-no-1/vbcc-448/ (2011, accessed 2 November 2018)
162. Attard CL, Brown S, Alloul K, Moore MJ. Cost-effectiveness of folfirinox for first-line treatment of metastatic pancreatic cancer. *Curr Oncol* 2014;**21**:e41–51
163. National Institute for Health and Clinical Excellence. *Final appraisal determination. Fulvestrant for the treatment of locally advanced or metastatic breast cancer*, https://www.nice.org.uk/guidance/ta239/documents/breast-cancer-metastatic-fulvestrant-final-appraisal-determination-document2 (2011, accessed 2 November 2018)
164. In The Journals Plus. *HemOncToday*. Osimertinib not cost-effective for EGFR-mutated lung cancer, https://www.healio.com/hematology-oncology/lung-cancer/news/in-the-journals/%7B0c4e2499-4e39-408d-baf6-43618fe00a0c%7D/osimertinib-not-cost-effective-for-egfr–mutated-lung-cancer (2018, accessed 16 October 2018)
165. Goldstein DA, Krishna K, Flowers CR, El-Rayes BF, Bekaii-Saab T, Noonan AM. Cost description of chemotherapy regimens for the treatment of metastatic pancreas cancer. *Med Oncol* 2016;**33**:48
166. Scott JR, Zhou Y, Cheng C, Ward DA, Swanson HD, Molinelli AR, Stewart CF, Navid F, Jeha S, Relling MV, Crews KR. Comparable efficacy with varying dosages of glucarpidase in pediatric oncology patients. *Pediatr Blood Cancer* 2015;**62**:1518–22
167. Keat CH, Ghani NA. Cost-effectiveness analysis of granisetron-based versus standard antiemetic regimens in low-emetogenic chemotherapy: a hospital-based perspective from Malaysia. *Asian Pac J Cancer Prev* 2013;**14**:7701–6
168. Prasad M, Ben-Porat L, Hoppe B, Aghajanian C, Sabbatini P, Chi DS, Hensley ML. Costs of treatment and outcomes associated with second-line therapy and greater for relapsed ovarian cancer. *Gynecol Oncol* 2004;**93**:223–8

169. Warren E, Ward S, Gordois A, Scuffham P. Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase. *Clin Ther* 2004;**26**:1924–33
170. Shanafelt TD, Borah BJ, Finnes HD, Chaffee KG, Ding W, Leis JF, Chanan-Khan AA, Parikh SA, Slager SL, Kay NE, Call TG. Impact of ibrutinib and idelalisib on the pharmaceutical cost of treating chronic lymphocytic leukemia at the individual and societal levels. *J Oncol Pract* 2015;**11**:252–8
171. Sorensen SV, Peng S, Dorman E, Cote S, Tambour M, Pan F, Sengupta N. The cost-effectiveness of ibrutinib in treatment of relapsed or refractory chronic lymphocytic leukemia. *Health Econ Outcome Res* 2016;**2**:2
172. Scottish Medicines Consortium. Ibritumomab tiuxetan (Zevalin®). Schering Health Care Ltd, https://www.scottishmedicines.org.uk/files/ibritumomab_tiuxetan__Zevalin__Resubmission_FINAL_June_2007_for_website.pdf (2007, accessed 2 November 2018)
173. Kuznar W. American Health & Drug Benefits, once off patent, imatinib will be the most cost-effective treatment for newly diagnosed CML, http://www.ahdbonline.com/issues/2015/february-2015-vol-8-special-issue-payers-perspectives-in-oncology/1905-once-off-patent-imatinib-will-be-the-most-cost-effective-treatment-for-newly-diagnosed-cml (2015, accessed 16 October 2018)
174. Arits AH, Spoorenberg E, Mosterd K, Nelemans P, Kelleners-Smeets NW, Essers BA. Cost-effectiveness of topical imiquimod and fluorouracil vs. photodynamic therapy for treatment of superficial basal-cell carcinoma. *Br J Dermatol* 2014;**171**:1501–7
175. pan-Canadian Oncology Drug Review. *Initial economic guidance report*. Inotuzumab ozogamicin (besponsa) for acute lymphoblastic leukemia, https://cadth.ca/sites/default/files/pcodr/pcodr_inotuzumab_besponsa_ALL_in_egr.pdf (2018, accessed 2 November 2018)
176. Fellner C. Ipilimumab (yervoy) prolongs survival in advanced melanoma: serious side effects and a hefty price tag may limit its use. *P T* 2012;**37**:503–30
177. Egerton N. Ixabepilone (ixempra), a therapeutic option for locally advanced or metastatic breast cancer. *P T* 2008;**33**:523–31
178. Ayyagari R, Neary M, Li S, Rokito A, Yang H, Xie J, Benson AB 3rd. Comparing the cost of treatment with octreotide long-acting release versus lanreotide in patients with metastatic gastrointestinal neuroendocrine tumors. *Am Health Drug Benets* 2017;**10**:408–15
179. National Institute for Health and Care Excellence. *Final appraisal determination – Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer*, https://www.nice.org.uk/guidance/gid-tag387/documents/breast-cancer-advanced-or-metastatic-lapatinib-final-appraisal-determination6 (2009, accessed 16 October 2018)
180. Goss TF, Szende A, Schaefer C, Totten PJ, Knight R, Jädersten M, Hellström-Lindberg E, List AF. Cost effectiveness of lenalidomide in the treatment of transfusion-dependent myelodysplastic syndromes in the United States. *Cancer Control* 2006;**13**:17–25
181. Kotla V, Goel S, Nischal S, Heuck C, Vivek K, Das B, Verma A. Mechanism of action of lenalidomide in hematological malignancies. *J Hematol Oncol* 2009;**2**:36
182. Takeuchi S, Shiga T, Hirata K, Taguchi J, Magota K, Ariga S, Gouda T, Ohhara Y, Homma R, Shimizu Y, Kinoshita I, Tsuji Y, Homma A, Iijima H, Tamaki N, Dosaka-Akita H. Early prediction of lenvatinib treatment efficacy by using (18)F-FDG PET/CT in patients with unresectable or advanced thyroid carcinoma that is refractory to radioiodine treatment: a protocol for a non-randomized single-arm multicenter observational study. *BMJ Open* 2018;**8**:e021001
183. Drugs.com. Lupron depot prices, coupons and patient assistance programs, https://www.drugs.com/price-guide/lupron-depot (2018, accessed 2 November 2018)
184. Marsh T. GoodRx, why was there a 500% price increase on cancer treatment lomustine?, https://www.goodrx.com/blog/why-was-there-a-500-increase-on-cancer-treatment-lomustine/ (2017, accessed 2 November 2018)
185. *Reuters*. FDA clears radioactive drug for cancer that killed Steve Jobs, https://in.reuters.com/article/advanced-accelerator-fda/fda-clears-radioactive-drug-for-cancer-that-killed-steve-jobs-idINKBN1FF2RA (2018, accessed 2 November 2018)
186. Gulbrandsen N, Wisloff F, Nord E, Lenhoff S, Hjorth M, Westin J; Nordic Myeloma Study Group. Cost-utility analysis of high-dose melphalan with autologous blood stem cell support vs. melphalan plus prednisone in patients younger than 60 years with multiple myeloma. *Eur J Haematol* 2001;**66**:328–36
187. *Reuters*. U.S. FDA approves Novartis' leukemia treatment, https://www.reuters.com/article/us-novartis-fda-idUSKBN17U246 (2017, accessed 2 November 2018)
188. *Bladder cancer: diagnosis and management*. London: National Institute for Health and Care Excellence, 2015. https://www.ncbi.nlm.nih.gov/books/NBK356297/ (2015, accessed 2 November 2018)
189. Helwick C. Will necitumumab be cost-effective?. *Am Health Drug Benets* 2015;**8**:11
190. Prior authorization approval criteria, Arranon (nelarabine). file:///C:/Users/Kirshan/Downloads/Arranon_nelarabine.pdf.pdf (2006, accessed 2 November 2018)
191. Forbes. Could a cancer drug reverse Parkinson's disease?, https://www.forbes.com/sites/emilymullin/2015/10/21/could-a-cancer-drug-reverse-parkinsons-disease/#1c524ed7f6b5 (2015, accessed 16 October 2018)
192. Wolford JE, Bai J, Minion LE, Keller R, Eskander RN, Chan JK, Monk BJ, Tewari KS. Cost-effectiveness of maintenance therapy in advanced ovarian cancer: paclitaxel, bevacizumab, niraparib, rucaparib, olaparib, and pembrolizumab. *J Clin Oncol* 2018;**36**:5508
193. Pappas AL. Pharmacy times, Obinutuzumab (Gazyva), https://www.pharmacytimes.com/publications/health-system-edition/2014/may2014/obinutuzumab-gazyva (2014, accessed 2 November 2018)
194. Hatswell AJ, Thompson GJ, Maroudas PA, Sofrygin O, Delea TE. Estimating outcomes and cost effectiveness using a single-arm clinical trial: ofatumumab for double-refractory chronic lymphocytic leukemia. *Cost Eff Resour Alloc* 2017;**15**:8
195. Bath C. The ASCO post, PARP inhibitors have 'clear benefit' for patients with ovarian cancer and BRCA mutations, but when and at what cost, http://www.ascopost.com/issues/may-25-2015/parp-inhibitors-have-clear-benefit-for-patients-with-ovarian-cancer-and-brca-mutations-but-when-and-at-what-cost/ (2015, accessed 16 October 2018)
196. Vu T, Ellard S, Speers CH, Taylor SC, de Lemos ML, Hu F, Kuik K, Olivotto IA. Survival outcome and cost-effectiveness with docetaxel and paclitaxel in patients with metastatic breast cancer: a population-based evaluation. *Ann Oncol* 2008;**19**:461–4
197. Mamiya H, Tahara RK, Tolaney SM, Choudhry NK, Najafzadeh M. Cost-effectiveness of palbociclib in hormone receptor-positive advanced breast cancer. *Ann Oncol* 2017;**28**:1825–1831
198. Peck P. Medpage today, FDA approves vectibix (panitumumab) for advanced colorectal cancer, https://www.medpagetoday.com/gastroenterology/coloncancer/4199 (2006, accessed 16 October 2018)
199. Amdahl J, Diaz J, Sharma A, Park J, Chandiwana D, Delea TE. Cost-effectiveness of pazopanib versus sunitinib for metastatic renal cell carcinoma in the United Kingdom. *PLoS One* 2017;**12**:e0175920
200. Andrews A. Treating with checkpoint inhibitors – figure $1 million per patient. *Am Health Drug Benets* 2015;**8**:9
201. Ontario Public Drug Programs. Ministry of Health and Long-Term Care. Pemetrexed (for non-small cell lung cancer), http://www.health.gov.on.ca/en/pro/programs/drugs/ced/pdf/pemetrexed1.pdf (2008, accessed 16 October 2018)
202. Chernew ME, Newcomer LN, Swain SM. Treatment and cost implications of pertuzumab. *Am J Manag Care* 2012;**18**:SP151–3
203. Zander T, Aebi S, Pabst T, Renner C, Driessen C. Spotlight on pomalidomide: could less be more?. *Leukemia* 2017;**31**:1987–9
204. OncLive. Ponatinib (CML) Pricing gets a blast from congress, https://www.onclive.com/web-exclusives/ponatinib-cml-pricing-gets-a-blast-from-congress (2016, accessed 16 October 2018)
205. Prostate.net. What is the cost of xofigo? https://prostate.net/articles/cost-of-xofigo (2016, accessed 2 November 2018)

206. Zhu S, Liu J, Sun W, Tao L, Xiao D. Cost-effectiveness analysis of regorafenib for third-line metastatic colorectal cancer compared to cetuximab plus irinotecan in China. *J Health Med Econ* 2018;**4**:5
207. Strumberg D, Schultheis B. Regorafenib for cancer. *Expert Opin Investig Drugs* 2012;**21**:879–89
208. Suri G, Mistry R, Young KC, Hettle R, May JR, Brixner D, Oderda G, Biskupiak J, Tang D, Bhattacharyya D, Bhattacharyya S. Cost effectiveness of ribociclib plus letrozole versus palbociclib plus letrozole for the treatment of post-menopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer from a US private third-party payer perspective. *Value Health* 2017;**20**:A436
209. Consumersunion. Is the cost reasonable? one dose of cancer drug rituxan, https://consumersunion.org/outrageous-health-costs/cancer-drug-markup/ (2018, accessed 2 November 2018)
210. Benzinga Clovis' Rubraca Vs. TESARO's Niraparib, https://www.benzinga.com/analyst-ratings/analyst-color/16/12/8825438/clovis-rubraca-vs-tesaros-niraparib (2016, accessed 16 October 2018)
211. Anassi E, Ndefo UA. Sipuleucel-T (provenge) injection: the first immunotherapy agent (vaccine) for hormone-refractory prostate cancer. *P T* 2011;**36**:197–202
212. Kish T, Corry L. Sonidegib (Odomzo) for the systemic treatment of adults with recurrent, locally advanced basal cell skin cancer. *P T* 2016;**41**:322–5
213. Cancer drug costs for a month of treatment at initial Food and Drug Administration Approval, https://www.mskcc.org/sites/default/files/node/25097/documents/chemo-prices-table-bach-center-health-policy-and-outcomes-6-13-14.pdf (accessed 2 November 2018)
214. National Institute for Health and Care Excellence. *Sunitinib for the rst-line treatment of advanced and/or metastatic renal cell carcinoma, Technology appraisal guidance [TA169]*, https://www.nice.org.uk/guidance/ta169/chapter/3-the-technology (2009, accessed 16 October 2018)
215. Ontario Public Drug Programs, Ministry of Health and Long-Term Care. Temsirolimus, http://www.health.gov.on.ca/en/pro/programs/drugs/ced/pdf/torisel.pdf (2011, accessed 16 October 2018)
216. Garrison LP Jr, Wang ST, Huang H, Ba-Mancini A, Shi H, Chen K, Korves C, Dhawan R, Cakana A, van de Velde H, Corzo D, Duh MS. The cost-effectiveness of initial treatment of multiple myeloma in the U.S. with bortezomib plus melphalan and prednisone versus thalidomide plus melphalan and prednisone or lenalidomide plus melphalan and prednisone with continuous lenalidomide maintenance treatment. *Oncologist* 2013;**18**:27–36
217. Lin JK, Lerman BJ, Barnes JI, Boursiquot BC, Tan YJ, Robinson AQL, Davis KL, Owens DK, Goldhaber-Fiebert JD. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. *J Clin Oncol* 2018;36:3192-3202
218. Pan-Canadian Oncology Drug Review. pCODR Expert Review Committee (pERC) final recommendation, https://www.cadth.ca/sites/default/files/pcodr/pcodr_trabectedin_yondelis_lile_scarcoma_in_rec.pdf (2016, accessed 2 November 2018)
219. Nordqvist C. Medical News Today. One year on herceptin for breast cancer ideal, https://www.medicalnewstoday.com/articles/250912.php (2012, accessed 2 November 2018)
220. The Medical Letter. The medical letter on drugs and therapeutics. In: Brief: trifluridine/tipiracil (lonsurf) for metastatic colorectal cancer, https://secure.medicalletter.org/w1496f (2016, accessed 16 October 2018)
221. Pan-Canadian Oncology Drug Review. pCODR Expert Review Committee (pERC) Final Recommendation, https://www.cadth.ca/sites/default/files/pcodr/pcodr_vandetanib_caprelsa_mtc_fn_rec.pdf (2017, accessed 16 October 2018)
222. Pan-Canadian Oncology Drug Review. *Initial economic guidance report*. Venetoclax (Venclexta) for chronic lymphocytic leukemia, https://www.cadth.ca/sites/default/files/pcodr/pcodr_venetoclax_venclexta_cll_in_egr.pdf (2017, accessed 2 November 2018)
223. Rocky Mountain, uniform pharmacy prior authorization request form. Marqibo (vincristine sulfate liposome injection), https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=20&cad=rja&uact=8&ved=2ahUKEwiL27T5hYneAhVQX30KHYh4BdE4ChAWMAl6BAgCEAI&url=https%3A%2F%2Fwww.rmhp.org%2F%2Fmedia%2FRMHPdotOrg%2FFiles%2FPDF%2FLearning-Center%2FPrior-Auth-Services%2FPA-Forms-Medicaid%2FMarqibo-vincristine-sulfate-liposome-injection.ashx%3Fla%3Den&usg=AOvVaw1GgpHIsyC3PM_IzWWbKznN (2018, accessed 2 November 2018)
224. Fellner C. Vismodegib (erivedge) for advanced Basal cell carcinoma. *P T* 2012;**37**:670–82
225. Joondeph BC. Retina today, will a new low-cost option join the anti-VEGF fold?, http://retinatoday.com/2016/04/will-a-new-low-cost-option-join-the-anti-vegf-fold (2018, accessed 2 November 2018)
226. Healio. Zoledronic acid more cost-effective than denosumab for bone metastases, https://www.healio.com/hematology-oncology/breast-cancer/news/in-the-journals/%7B9758e0f5-093a-4d95-bd8b-d742f9dee199%7D/zoledronic-acid-more-cost-effective-than-denosumab-for-bone-metastases (2017, accessed 2 November 2018)
227. Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated costs of pivotal trials for novel therapeutic agents approved by the US Food and Drug Administration, 2015–2016. *JAMA Intern Med* 2018;178:1451-1457
228. Howard DH, Bach PB, Berndt ER, Conti RM. Pricing in the market for anticancer drugs. *J Econ Perspect* 2015;**29**:139–62
229. Herper M. The cancer drug market just hit $100 billion and could jump 50% in four years. *Forbes*, https://www.forbes.com/sites/matthewherper/2015/05/05/cancer-drug-sales-approach-100-billion-and-could-increase-50-by-2018/ (2015, accessed 3 September 2018)
230. Mailankody S, Prasad V. Five years of cancer drug approvals: innovation, efficacy, and costs. *JAMA Oncol* 2015;**1**:539–40
231. Prasad V, De Jesus K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncol* 2017;**14**:381–90
232. Prasad V, Fojo T, Brada M. Precision oncology: origins, optimism, and potential. *Lancet Oncol* 2016;**17**:e81–6
233. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern Med* 2017;**177**:1569–75
234. Prasad V, Wang R, Afifi SH, Mailankody S. The rising price of cancer drugs – a new old problem? *JAMA Oncol* 2017;3:277-278
235. Fojo T, Lo AW. Price, value, and the cost of cancer drugs. *Lancet Oncol* 2016;**17**:3–5
236. Sullivan R, Aggarwal A. Health policy: putting a price on cancer. *Nat Rev Clin Oncol* 2016;**13**:137–8
237. Mailankody S, Prasad V. Implications of proposed medicare reforms to counteract high cancer drug prices. *JAMA* 2016;**316**:271–2
238. Prasad V, Mailankody S. How should we assess the value of innovative drugs in oncology? Lessons from cost-effectiveness analyses. *Blood* 2015;**126**:1860–1
239. Galkina Cleary E, Beierlein JM, Khanuja NS, McNamee LM, Ledley FD. Contribution of NIH funding to new drug approvals 2010–2016. *Proc Natl Acad Sci U S A* 2018;**115**:2329–34
240. Kaestner V, Edmiston JB, Prasad V. The relation between publication rate and financial conflict of interest among physician authors of high-impact oncology publications: an observational study. *CMAJ Open* 2018;**6**:E57
241. Wagner J, Marquart J, Ruby J, Lammers A, Mailankody S, Kaestner V, Prasad V. Frequency and level of evidence used in recommendations by the National Comprehensive Cancer Network guidelines beyond approvals of the US Food and Drug Administration: retrospective observational study. *BMJ* 2018;**360**:k668
242. Sinha MS, Najafzadeh M, Rajasingh EK, Love J, Kesselheim AS. Labeling changes and costs for clinical trials performed under the US Food and Drug Administration pediatric exclusivity extension 2007 to 2012. *JAMA Intern Med* 2018;**178**:1458–66
243. Prasad S, Gupta SC, Aggarwal BB. Serendipity in cancer drug discovery: rational or coincidence. *Trends Pharmacol Sci* 2016;**37**:435–50
244. Padma VV. An overview of targeted cancer therapy. *Biomedicine* 2015;**5**:19

245. Gupta SC, Prasad S, Tyagi AK, Kunnumakkara AB, Aggarwal BB. Neem (*Azadirachta indica*): an Indian traditional panacea with modern molecular basis. *Phytomedicine* 2017;**34**:14–20
246. Roy NK, Deka A, Bordoloi D, Mishra S, Kumar AP, Sethi G, Kunnumakkara AB. The potential role of boswellic acids in cancer prevention and treatment. *Cancer Lett* 2016;**377**:74–86
247. Banik K, Harsha C, Bordoloi D, Lalduhsaki Sailo B, Sethi G, Leong HC, Arfuso F, Mishra S, Wang L, Kumar AP, Kunnumakkara AB. Therapeutic potential of gambogic acid, a caged xanthone, to target cancer. *Cancer Lett* 2018;**416**:75–86
248. Aggarwal BB, Sethi G, Baladandayuthapani V, Krishnan S, Shishodia S. Targeting cell signaling pathways for drug discovery: an old lock needs a new key. *J Cell Biochem* 2007;**102**:580–92
249. Deorukhkar A, Krishnan S, Sethi G, Aggarwal BB. Back to basics: how natural products can provide the basis for new therapeutics. *Expert Opin Investig Drugs* 2007;**16**:1753–73
250. Gullett NP, Ruhul Amin AR, Bayraktar S, Pezzuto JM, Shin DM, Khuri FR, Aggarwal BB, Surh YJ, Kucuk O. Cancer prevention with natural compounds. *Semin Oncol* 2010;**37**:258–81
251. Rahaman ST, Sai PR. A short review on carnivorous plants and recent developments in the field of cancer research. *iJP* 2018;**5**:205–12
252. Siddiqui AA, Iram F, Siddiqui S, Sahu K. Role of natural products in drug discovery process. *Int J Drug Develop Res* 2014;**6**:172–204
253. Harvey AL. Natural products in drug discovery. *Drug Discov Today* 2008;**13**:894–901
254. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. *Nat Rev Drug Discov* 2015;**14**:111–29
255. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. *Nat Rev Drug Discov* 2005;**4**:206–20
256. Vuorelaa P, Leinonenb M, Saikkuc P, Tammelaa P, Rauhad JP, Wennberge T, Vuorela H. Natural products in the process of finding new drug candidates. *Curr Med Chem* 2004;**11**:1375–89
257. Fu RG, Sun Y, Sheng WB, Liao DF. Designing multi-targeted agents: an emerging anticancer drug discovery paradigm. *Eur J Med Chem* 2017;**136**:195–211
258. Fojo T. Commentary: novel therapies for cancer: why dirty might be better. *Oncologist* 2008;**13**:277–83
259. Jimeno A, Hidalgo M. Multitargeted therapy: can promiscuity be praised in an era of political correctness. *Crit Rev Oncol Hematol* 2006;**59**:150–8
260. Kunnumakkara AB, Banik K, Bordoloi D, Harsha C, Sailo BL, Padmavathi G, Roy NK, Gupta SC, Aggarwal BB. Googling the Guggul (Commiphora and Boswellia) for prevention of chronic diseases. *Front Pharmacol* 2018;**9**:686
261. Sarkar FH, Li Y. Harnessing the fruits of nature for the development of multi-targeted cancer therapeutics. *Cancer Treat Rev* 2009;**35**:597–607
262. Zheng W, Zhao Y, Luo Q, Zhang Y, Wu K, Wang F. Multi-targeted anticancer agents. *Curr Top Med Chem* 2017;**17**:3084–98
263. Padmavathi G, Rathnakaram SR, Monisha J, Bordoloi D, Roy NK, Kunnumakkara AB. Potential of butein, a tetrahydroxychalcone to obliterate cancer. *Phytomedicine* 2015;**22**:1163–71
264. Kunnumakkara AB, Bordoloi D, Harsha C, Banik K, Gupta SC, Aggarwal BB. Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. *Clin Sci* 2017;**131**:1781–99
265. Bordoloi D, Roy NK, Monisha J, Padmavathi G, Kunnumakkara AB. Multi-targeted agents in cancer cell chemosensitization: what we learnt from curcumin thus far. *Recent Pat Anticancer Drug Discov* 2016;**11**:67–97
266. Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S, Aggarwal BB. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol* 2017;**174**:1325–48
267. Ramasamy K, Agarwal R. Multitargeted therapy of cancer by silymarin. *Cancer Lett* 2008;**269**:352–62
268. Li Y, Li PK, Roberts MJ, Arend RC, Samant RS, Buchsbaum DJ. Multitargeted therapy of cancer by niclosamide: a new application for an old drug. *Cancer Lett* 2014;**349**:8–14
269. Sailo BL, Banik K, Padmavathi G, Javadi M, Bordoloi D, Kunnumakkara AB. Tocotrienols: the promising analogues of vitamin E for cancer therapeutics. *Pharmacol Res* 2018;**130**:259–72
270. Kunnumakkara AB, Sung B, Ravindran J, Diagaradjane P, Deorukhkar A, Dey S, Koca C, Yadav VR, Tong Z, Gelovani JG, Guha S, Krishnan S, Aggarwal BB. {Gamma}-tocotrienol inhibits pancreatic tumors and sensitizes them to gemcitabine treatment by modulating the inflammatory microenvironment. *Cancer Res* 2010;**70**:8695–705
271. Jackson K, Nahata MC. Rising cost of anticancer medications in the United States. *Ann Pharmacother* 2017;**51**:706–10
272. Steensma DP, Kantarjian HM. Impact of cancer research bureaucracy on innovation, costs, and patient care. *J Clin Oncol* 2014;**32**:376–8
273. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics – the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. *JAMA Otolaryngol Head Neck Surg* 2014;**140**:1225–36
274. Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: understanding and stepping-up action on the financial toxicity of cancer treatment. *CA Cancer J Clin* 2018;**68**:153–65
275. Sullivan R, Peppercorn J, Sikora K, Zalcberg J, Meropol NJ, Amir E, Khayat D, Boyle P, Autier P, Tannock IF, Fojo T, Siderov J, Williamson S, Camporesi S, McVie JG, Purushotham AD, Naredi P, Eggermont A, Brennan MF, Steinberg ML, De Ridder M, McCloskey SA, Verellen D, Roberts T, Storme G, Hicks RJ, Ell PJ, Hirsch BR, Carbone DP, Schulman KA, Catchpole P, Taylor D, Geissler J, Brinker NG, Meltzer D, Kerr D, Aapro M. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;**12**:933–80
276. Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: Justum Pretium – the just price. *J Clin Oncol* 2013;**31**:3600–4
277. Lopes G, Vulto A, Wilking N, van Harten W, Meier K, Simoens S. Potential solutions for sustaining the costs of cancer drugs. *Eur Oncol Haematol* 2017;**13**:102–7
278. Mertens S, de Jongh FE. [Lower costs for anticancer drugs by safety margin around calculated dose and by fine-tuning on ampoule strength]. *Ned Tijdschr Geneeskd* 2009;**153**:B162
279. Zafar MZ. Pharmacological study and overcome the cardiotoxicity associated with anticancer drug doxorubicin. *QualPrim Care* 2017;**25**:368–71
280. Griggs JJ. Reducing the toxicity of anticancer therapy: new strategies. *Leuk Res* 1998;**22**:S27–33
281. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res* 2008;**25**:2097–116
282. Divisi D, Di Tommaso S, Salvemini S. Diet and cancer. *Acta Biomed* 2006;**77**:118–23
283. Monisha J, Padmavathi G, Roy NK, Deka A, Bordoloi D, Anip A, Kunnumakkara AB. NF-κB blockers gifted by Mother Nature: prospectives in cancer cell chemosensitization. *Curr Pharm Des* 2016;**22**:4173–200
284. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. *J Am Diet Assoc* 1996;**96**:1027–39
285. Schilsky RL. Implementing personalized cancer care. *Nat Rev Clin Oncol* 2014;**11**:432–8
286. Ogden A, Rida PC, Aneja R. Let's huddle to prevent a muddle: centrosome declustering as an attractive anticancer strategy. *Cell Death Differ* 2012;**19**:1255–67
287. Beer TM, Prasad V. Taking care of our friends and neighbors: DeVita's the death of cancer and the challenge of letting go. *JAMA Oncol* 2017;**3**:16–7
288. Patwardhan K. Governance of higher education in Indian systems of medicine: issues, concerns, and challenges. Perspectives on governance of higher education, Bharati Vidyapeeth Deemed University Pune, India, 2010, pp.127–39