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Jacobs Journal of Internal Medicine

Review Article

New Cancer Therapies for the 21st Century: A Two Decade Review of Approved Drugs and Drugs in Development in the United States

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Received: 08-20-2015

Accepted: 09-08-2015

Published: 10-14-2015

Abstract

The approval of cancer drugs by the United States Food and Drug Administration have increased progressively over the past two decades with a trend towards the adoption of targeted drugs which are more precise in their mechanisms of action. Advances in genetic profiling, immunohistochemical analysis of tumors, biomarker development, and a renewed appreciation of the tumor microenvironment have produced a new generation of targeted chemical and biological therapies. These innovations are the fruits of basic research in molecular and cellular biology, biochemistry, and immunology.

Purpose: To elucidate the paradigm shift in cancer drug development that has impacted the lives of patients in terms of quality of life, tumor responses, over-all survival, and potential cures.

Methods: This review is based on an examination of published literature using the National Center for Biotechnology Information (NCBI), the USFDA/National Institutes of Health (NIH) websites, USFDA approved product literature, Center Watch, industry-sponsored websites, and clinicaltrials.gov websites. Cancer drugs are classified and described based on their proposed mechanisms of action.

Results: The last two decades witnessed a paradigm shift in cancer drug development toward molecular targeted therapies and targeted drug delivery. Molecular targets include tyrosine kinase receptors, serinethreonine kinase signaling pathways, and growth factors. An increasing number of antibody-based therapies have emerged. Improvements in drug delivery include the use of albumin-bound nanoparticles for targeting the enhanced permeability and retention effects seen in tumors. Recent developments in the fields of cancer immunotherapy and gene therapy are exceedingly encouraging.

Conclusions: A review of USFDA-approved drugs and cancer drugs in clinical development, based on their mechanisms of action, is presented. The progressive shift in cancer drug development towards targeted therapies and cancer immunotherapy raises hope for improved outcomes for many types of cancer in the future.

Keywords: Kinase Inhibitors; Monoclonal Antibodies; Cancer Immunotherapy; Targeted Drug Delivery; Cancer gene therapy; Sarcoma

List of Abbreviations

USFDA	United States Food and Drug Administration
NCBI	National Center for Biotechnology Information
NIH	National Institutes of Health
EPR	Enhanced permeability retention
EGFR	Epidermal growth factor receptor
VEGFR	Vascular endothelial growth factor receptor
ER	Estrogen receptor
PR	Progesterone receptor
PDGFR	Platelet-derived growth factor receptor
ALK	Anaplastic lymphoma kinase
NSCLC	Non-small cell lung cancer
FISH	Fluorescence in situ hybridization
CML	Chronic myeloid leukemia
GIST	Gastrointestinal stromal tumor
CRC	Colorectal cancer
mTOR	Mammalian target of rapamycin
MPS1	Monospindle 1
CDK	Cyclin dependent kinase
RECIST	Response evaluation criteria in solid tumors
PFS	Progression-free survival
HR	Hazard ratio
RCC	Renal cell carcinoma
TSC	Tuberous sclerosis complex
EC	Endothelial cells
HPV	Human papilloma virus
GLA	Glucopyranosyl lipid A
TLR4	T lymphocyte receptor 4
GM-CSF	Granulocyte macrophage stimulating factor
HSV	Herpes simplex virus
CTLA4	Cytotoxic lymphocyte antigen 4
PD1	Programmed death receptor 1
MDM2	Human homologue of mouse double minute 2
CSF1	Colony stimulating factor 1
CSF1R	Colony stimulating factor 1 receptor
Br-IP	Bromo-isophosphoramide mustard
STS	Soft tissue sarcoma
SPA	Special protocol assessment
HDAC	Histone deacetylase
CTCL	Cutaneous T cell lymphoma
PTCL	Peripheral T-cell lymphoma
DC	Dendritic cells
CTL	Cytotoxic lymphocytes
TME	Tumor microenvironment

Introduction

Cancer is the second most common cause of death in the US, claiming 590,000 Americans per year, more than 1,500 people each day. The number of new cancer patients diagnosed in 2015 was over 1.6 million in the U.S. alone, not including patients with noninvasive cancers and/or skin cancers (American Cancer Society Cancer Facts, 2015). The Agency for Healthcare Research and Quality estimated the overall annual costs of cancer care at more than $227 billion (in 2012): including $89 billion for direct medical costs in the U.S. Much of the overall healthcare costs of treating cancer are derived from management of the deleterious side effects of radiation and conventional chemotherapy. Nonetheless, the chemotherapy market is currently the fastest growing segment of the pharmaceutical industry. There is a trend in the chemotherapy industry towards the creation of new targeted drugs which are much more precise in their mechanisms of action. It is estimated that these targeted drugs will continue to take the place of conventional chemotherapy drugs in the future. This review describes the recent advances in cancer drug development in the United States in the past two decades.

Methods

This review is based on an examination of published literature using pubmed central at the National Center for Biotechnology Information (NCBI), the United States Food and Drug Administration (USFDA) website, FDA package inserts, Center Watch, industry-sponsored websites and clinicaltrials.gov. A list of all USFDA-approved cancer drugs may be found at the FDA website. Current drugs in clinical development may be found at www.clinicaltrials.gov. A roster for gene therapy vector and vaccine protocols may be found at the Office of Biotechnology Activities website.

To gain an understanding of the basis of pharmaceutical drug development, these drugs are classified and described based on their proposed mechanisms of action. The mechanism of action is generally thought to represent the action of the active drug moiety itself. However, the mechanisms/logistics of drug delivery and biodistribution are crucial in balancing the tumoricidal effects of a drug with its systemic toxicity. Hence, we have included a section on targeted drug delivery as a mechanism of enhancing drug efficacy while reducing systemic adverse reactions.

Results

Table 1 lists the major and sub- classifications of drugs according to mechanism of action. Table 2 lists examples of FDA-approved cancer drugs, and Table 3 lists cancer drugs that are currently in clinical trials.

Table 1. Classification of Drugs According to Mechanism of Action.

Major Class	Subclass	Molecular Targets
Protein kinase inhibitors	Tyrosine kinase inhibitors, receptor and non-receptor	EGFR, PDGFR, VEGFR, ER, PR, HER2
	Serine threonine kinase inhibitors	m-TOR, MPS1, BRAF
Multiple site inhibitors	Rececptor kinase and specific site inhibitors	RAF/MEK/ERK, bcr/abl, CDK4/ CDK6, Hsp90, MDM2, CSF-1
Immunological therapies	Monoclonal antibodies	EGFR, VEGR, VEGF, HER2 , RANKL, TRC105
	Interferon alpha-2b to enhance immune response	Cancer cells, viruses
	Cancer vaccine	HPV
	G305 cancer vaccine	NYESO-1
	Reximmune-C and Reximmune-C2 cancer vaccine	GM-CSF
	Immune checkpoint inhibitors	CTLA4, PD-1, PD-L1
Alkylating agents	Trabectidin, evofosfamide	
Biological/ Cell and Gene Therapies	Sipuleucel-T (Dendritic cells) fused with common prostatic antigen	Prostatic acid phosphatase + GM-CSF
	Rexin-G, anti-cyclin G1 retrovector	Cyclin G1
	LV305 lentivector	NYESO-1

I. Protein kinase inhibitors

There are two types of protein kinases: tyrosine kinases and serine-threonine kinases. Tyrosine kinases are generally found spanning the cell membrane (the receptor kinase) but may also reside in the cytoplasm of the cell (the non-receptor kinase). Serine-threonine kinases involved in signal transduction and cell cycle control are found in the cell nucleus, as well as the cytoplasm. Mutations in these protein kinases can result

in unregulated cell growth which leads to the generation of cancerous cells, thus making them strategic targets for the development of new selective inhibitors for cancer therapy.

Table 2. Examples of USFDA Approved Drugs According to Mechanism of Action.

Generic Name of Drug (Trade Name)	Mechanism of Action	Cancer Indication
Axitinib (Inlyta)	VEGFR 1,2,and 3 inhibitor	Renal cell CA
Belinostat (Beleodaq)	Histone deacetylase inhibitor	Peripheral T-cell lymphoma
Bevacizumab (Avastin)	Monoclonal antibody against VEGF	Colon CA, non-small cell lung CA, breast CA, glioblastoma
Cetuximab (Erbitux)	Monoclonal antibody against EGFR	EGFR+ colorectal CA
Dabrafenib (Tafinlar)	BRAF inhibitor	BRAF V600E+ V600K+ Melanoma
Denosumab (Xgeva)	Monoclonal antibody against RANKL	Giant cell tumor of bone, solid tumors with skeletal metastasis
Erlotinib (Tarceva)	EGFR inhibitor	Non-small cell lung CA, pancreas CA
Everolimus (Afinitor)	mTOR inhibitor	Renal cell CA, giant cell astrocytoma
Gefitinib (Iressa)	EGFR inhibitor	Non-small cell lung CA
HPV vaccine (Gardasil)	Immune therapy against HPV	Cervical, vulvar, anal CA
Imatinib (Gleevec)	Bcr-Abl inhibitor	Philadelphia chromosome + CML, GIST
rInterferon alfa-2b (Intron A)	Immune cytokine therapy	Melanoma, hairy cell leukemia, follicular lymphoma
Ipilimumab Yervoy)	Immune checkpoint inhibitor	Melanoma
Lapatinib (Tykerb)	EGFR and EGFR2 inhibitor	Her2+ breast CA
Nab-paclitaxel (Abraxane	Albumin-bound paclitaxel nanoparticles	Pancreas CA, non-small cell lung CA
Nilotinib (Tasigna)	Fusion protein bcr/abl inhibitor	Philadelphia chromosome + CML
Nivolumab (Opdivo)	Immune checkpoint inhibitor	Melanoma
Palbociclib (Ibrance)	CDk4/Cdk6 inhibitor	ER+, HER2- Breast CA
Pazopanib (Votrient)	Multiple receptor kinase, VEGFR inhibitor	Renal cell CA
Pembrolizumab (Keytruda)	Immune checkpoint inhibitor	Melanoma
Pertuzumab (Perjeta)	Monoclonal antibody against HER2	HER2+ breast CA
Regorafenib (Stivarga)	Multiple pathway inhibitor	Colorectal CA
Sipuleucel-T (Provenge)	Dendritic cells expressing prostatic acid phosphatase (PAP) antigen	Hormone refractory prostate CA
Sorafenib (Nexavar)	RAF/MEK/ERK, VEGFR/PDGFR inhibitor	Renal cell CA; HCC
Sunitinib (Sutent)	PDGFR and VEGF inhibitor	GIST, renal cell CA, pancreatic neuroendocrine tumors
Temsirolimus (Torisel)	mTOR inhibitor	Renal cell CA
Trastuzumab (Herceptin)	Monoclonal antibody against HER2	HER2+ breast CA, gastric cancer
Vemurafenib (Zelboraf)	BRAF inhibitor	BRAF V600E+ Melanoma
Vorinostat (Zolinza)	Histone deacetylase inhibitor	Cutaneous T-cell lymphoma

Abbreviations: CML, chronic myeloid leukemia; HCC, hepatocellular carcinoma; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor ; HPV, human papillomavirus.

Table 3. Examples of Drugs in Development According to Mechanism of Action.

Generic Name of Drug (Trade Name)	Mechanism of Action	Cancer Indication
Aldoxorubicin	Albumin targeted small molecule	Sarcoma, ovarian CA
BAY1217389	MPS1 inhibitor	Lung CA, breast CA
Evofosfamide (TH302)	Prodrug alkylating agent	Soft tissue sarcoma, pancreas CA
FPA008	CSF1R inhibitor	Pigmented villonodular synovitis
G305	Immune therapy with NYESO-1 antigen	NYESO-1+ melanoma, sarcoma, ovarian CA, breast CA, bladder CA, lung CA
Ganetespib	Hsp90 inhibitor	Lung CA
LV305	Lentivector expressing NYESO-1	NYESO-1+ melanoma, sarcoma, ovarian CA, breast CA, bladder CA, lung CA
Reximmune-C	Immune therapy bearing GM-CSF	All solid tumors
Reximmune-C2	Immune therapy bearing GM-CSF	Hepatocellular CA, liver metastasis
Rexin-G	Retrovector bearing anti-cyclin G1	All solid tumors
RG7112	MDM2 inhibitor	Multiple myeloma, sarcoma, breast CA , glioblastoma multiforma
Ridaforolimus[73]	mTOR inhibitor	Sarcoma
Trabectidin[74-75]*	Alkylating agent	Soft tissue sarcoma
TRC105	mAb against endoglin or CD105	
Zalypsis (PM 00104)	Marine-derived synthetic alkaloid	Solid tumors, multiple myeloma

*Abbreviations: mTOR, mammalian target of rapamycin; GM-CSF, granulocyte-macrophage colony stimulating factor; MDM2, human homologue of mouse double minute 2; * approved in Europe, human papillomavirus.*

IA. Tyrosine kinase inhibitors

IA1. Receptor kinase inhibitors

Receptor tyrosine kinase is a class of transmembrane receptors with tyrosine kinase activity, containing an intracellular segment and an extracellular component. Upon receptor-ligand binding, the intracellular segment transfers a phosphate group from ATP to a protein within a cell, resulting in phosphorylation of the protein which activates a signal transduction cascade that ultimately regulates cell function, including cell division. The extracellular component receives specific signals from outside of the cell by binding directly to them. Signaling molecules are usually growth factors or hormones. Under normal conditions, the cascades of protein phosphorylation are tightly regulated by protein phosphatases located inside the cell. In the case of a cancer cell, a mutated, overexpressed, or dysregulated tyrosine kinase could lead to persistent tyrosine kinase/signaling activity, resulting in unregulated cell growth and uncontrolled cellular proliferation [1].

Various receptors are found on the cell surface, including receptors for growth factors such as epidermal growth factor (EGFR), vascular endothelial growth factor (VEGFR), and platelet- derived growth factor (PDGFR), or receptors for estrogen (ER) or progesterone (PR). These receptor tyrosine kinases are over-expressed in many different types of cancer. This characteristic enables the development of specific or targeted kinase inhibitors depending on the specific receptor that is over-expressed in the cancer cells .Tyrosine kinase inhibitors block the activity of the cognate protein kinases by binding directly to them, thus, disrupting the signal transduction pathway. Examples of receptor tyrosine kinase inhibitors include gefitinib (Iressa) and erlotinib (Tarceva) which bind to the epidermal growth factor receptor (EGFR), lapatinib which bind to both EGFR and EGFR type 2, and sunitinib (Sutent) which bind and inhibit both platelet derived growth factor receptor (PDGFR) and the vascular endothelial growth factor receptor (VEGFR) itself [1]. Pazopanib (Votrient) is a multiple tyrosine receptor kinase inhibitor including VEGFR [2,3]. Axitinib (Inlyta) is a receptor kinase inhibitor of VEGFR1, 2 and 3[4].

Anaplastic lymphoma kinase (ALK), is a tyrosine kinase receptor, also known as CD246 (cluster of differentiation 246). Rearrangements or mutations of ALK causes dysregulation of the signaling pathways in cell growth and differentiation. Uncontrolled cell proliferation then results that promotes the generation of cancerous cells [5,6]. Crizotinib (Xalkori) is a tyrosine receptor kinase inhibitor that is used in the treatment of patients with locally advanced or metastatic non-small cell lung

cancer (NSCLC) whose tumors are positive for the anaplastic lymphoma kinase (ALK) marker, detected by an FDA approved fluorescence in situ hybridization (FISH) assay. Crizotinib gained conditional approval based on response rate. There is no report available relating to overall survival advantage with crizotinib (Product Information). Ceritinib (Xykadia) is a tyrosine receptor kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have failed crizotinib therapy. Ceritinib gained accelerated approval based on tumor response rate and duration of response[7].

IA2. Non-receptor/cytoplasmic tyrosine kinase inhibitors

Non-receptor tyrosine kinases are a subgroup of protein family tyrosine kinases that can transport the phosphate group from ATP to a tyrosine residue of a protein, a process known as phosphorylation. Dysregulation of this enzymatic function can give rise to cancer cells.

Inhibitors of non-receptor kinases include imatinib, pazopanib, sorafenib and regorafenib.

Imatinib (Gleevec) binds the catalytic cleft of the tyrosine kinase BCR-ABL which is constitutively expressed in chronic myelogenous leukemia (CML) [8], thus disrupting its activity. Imatinib is also effective in gastrointestinal stromal tumors (GIST) by inhibiting c-kit, a tyrosine kinase that is constantly "turned on" in GIST [9,10].

Pazopanib (Votrient) and sorafenib (Nexavar) targets a complex pathway, including RAF/MEK/ERK pathway in tumor cells causing apoptosis, and tyrosine kinase VEGFR/PDGFR in tumor vasculature inducing anti-angiogenesis. Pazopanib and sorafenib are approved for renal cell carcinoma [11]. Nilotinib (Tasinga) inhibits the abnormal fusion protein bcr-abl and is often given to imatinib-resistant patients [12].

Regorafenib (Stivarga) is an inhibitor of both receptor and cytoplasmic tyrosine kinases involved in numerous complex signaling pathways. Regorafenib is indicated for the treatment of patients with chemotherapy-resistant metastatic colorectal cancer (CRC) and imatinib-resistant GIST [12].

IB. Serine-Threonine Kinase Inhibitors

Serine-threonine kinase inhibitors include inhibitors of cyclin dependent kinase 4 and 6 (CDK4 and 6), inhibitors of the mammalian target of Rapamycin (mTOR) and monopolar spindle 1 (MPS1) inhibitors.

IB1. Cyclin dependent kinase 4 and 6 (CDK4 and 6) Inhibitor

CDK4 and CDK6 are serine threonine kinases that promote progression from G1 to S2 phase of the cell cycle. Palbociclib (Ibrance) is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6, inhibits cell proliferation in ER-positive breast cancer cells by arresting progression from G1 to S phase of the cell cycle[13,14]. Palbociclib is indicated in ER-positive, HER2 negative breast cancer based on the success of a randomized, multicenter, open-label trial in postmenopausal women with ER-positive, HER2-negative, advanced (locally advanced or metastatic) breast cancer who had not received previous systemic treatment for advanced disease. The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.0 (RECIST). Median investigator-assessed PFS was 20.2 months in the palbociclib plus letrozole arm and 10.2 months in the letrozole alone arm. Overall response rate in patients with measurable disease (investigator assessment) was higher in the palbociclib plus letrozole compared to the letrozole alone arm (55.4% versus 39.4%) [15]. The USFDA granted palbociclib breakthrough therapy designation in April, 2013 based on preliminary evidence of clinical activity in this patient population. This accelerated approval is based on demonstration of an improvement in PFS. Continued approval for this indication is be contingent upon verification and description of clinical benefit in an on-going confirmatory trial.

IB2. mTOR Inhibitors

The Mammalian Target Of Rapamycin (mTOR) is a phylogenetically conserved serine-threonine kinase that performs many cellular functions. It is activated by various mitogens, growth factors and other nutrients, resulting in cell growth, cell proliferation and angiogenesis, among other functions [16]. Mutations of these kinases result in uncontrolled kinase activity, cell growth and unregulated cellular proliferation, resulting in the formation of cancerous cells [17]. Therefore, mTOR is a strategic target for the development of inhibitors. The most conventional mTOR inhibitors are known as rapalogs (rapamycin and its analogs), which are effective in certain types of tumors[18]. Examples of mTOR inhibitors include temsirolimus [17], everolimus [16], and ridaforolimus, formerly deforolimus [19].

Temsirolimus (Torisel) is indicated for renal cell carcinoma and non-Hodgkin's lymphoma [20].

Everolimus (Afinitor) is indicated for the treatment of advanced hormone receptor-positive, HER2- negative breast cancer, neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib, renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery, tuberous sclerosis complex (TSC) with unresectable subependymal giant cell astrocytoma [21]. Ridaforolimus is currently being investigated in a Phase 3 clinical trial for soft tissue and bone sarcoma [22].

IB3. Monopolar spindle 1 (MPS1) inhibitors

Monopolar spindle 1 (MPS1) is a serine threonine kinase that is overexpressed in certain types of cancer including lung and breast cancer. MPS1 inhibitors are mitosis-promoting drugs that, when used in combination with mitosis inhibitors such as vinca alkaloids, taxanes, result in chromosomal aggregation errors and ultimately cell death. MPS1 inhibition in combination with microtubule-interfering agents is expected to improve the therapeutic efficacy of mitosis inhibitors and to overcome the problem of paclitaxel resistance. A phase 1 study of a MPS1 inhibitor, BAY1217389, in combination with intravenous paclitaxel is on-going [22].

IB4. BRAF Inhibitors

BRAF is a serine threonine kinase that act via the RAS/MAPK pathway which regulates growth and cell division, differentiation, migration and apoptosis. The BRAF gene is an oncogene and mutations in BRAF is commonly found in melanoma and other types of cancer. The most common BRAF mutation in melanoma is V600E [23]. Therefore, the BRAF V600E mutation is a target for inhibitor therapy. An example of a BRAF inhibitor is Vemurafenib (Zelboraf), which was recently shown to improve survival in patients with melanoma and BRAF V600E mutations [23].

II. Inhibitors of specific sites

Inhibitors of specific sites include inhibitors of heat shock protein 90 (Hsp90) inhibitors, the human homologue of mouse double minute 2 (MDM2), colony stimulating factor 1 (CSF1), histone deacetylase (HDAC) and p53 tumor suppressor protein.

IIA. Heat shock protein 90 (Hsp90_ inhibitor)

Hsp90, a 90 kDa molecule, plays a key role in the conformational maturation, stability and function of certain proteins within the cell, many of which are involved in signal transduction, cell cycle regulation and apoptosis, including kinases, transcription factors and hormone receptors [24]. It is upregulated in a variety of tumor cells. Ganetespib is a synthetic small-molecule inhibitor of Hsp90 as well as multiple kinases such as c-Kit, EGFR and Bcr-Abl. Ganetespib is currently being evaluated in a broad range of cancer clinical trials, including the global Phase 2b/3 GALAXY trial in non-small cell lung cancer. In these trials, ganetespib has shown anti-tumor activity in chemotherapy-resistant patients with lung cancer, breast cancer, and other tumor types with less severe liver and ocular toxicity than those observed with other Hsp90 inhibitors [24].

IIB. Human homologue of Mouse Double Minute 2 (MDM2) Inhibitors

MDM2 is a human ubiquitous protein that blocks the transcriptional activation of p53, a tumor suppressor [25,26]. MDM2 inhibits p53 by promoting p53 degradation, blocking p53 activation, and exporting p53 from nucleus to cytoplasm. Because of the critical inhibitory role of MDM2 on p53, inhibitors that block the interaction of MDM2 and p53 would be a potential anti-cancer drug. The MDM2-p53 interaction has been mapped to the first ~120 amino acid residues at the N-terminus of MDM2 and to the N-terminus of the transactivation domain of p53 [27,28]. MDM2 is amplified in certain tumor types. An MDM2 antagonist, RG7112, a small molecule that bind MDM2 and neutralize its interaction with p53 has been developed and is being evaluated in a phase 1 clinical trial using RG7112 as a treatment for multiple myeloma, liposarcoma, estrogen receptor positive breast cancer and gliobastoma multiforme [22].

IIC. Colony Stimulating Factor -1 (CSF-1) Inhibitors

A novel protein, known as interleukin 34 (IL-34), is a key regulator of monocyte and macrophage activity whose receptor has been identified as CSF1R. Both interleukin 34 (IL34) and CSF1 bind to and activate monocytes and macrophages and are found in inflamed joints of rheumatoid arthritis patients. FPA008 blocks the binding of both CSF1 and IL-34 to CSF1R, thereby inhibiting the activity and survival of these cells. A phase 1 study using a CSF-1 inhibitor (FPA008) for pigmented villonodular synovitis is currently being tested at the Sarcoma Oncology Center, Santa Monica, CA [22]. Another CSF1R inhibitor, PLX3397, currently being tested in a clinical trial for PVNS appears to have profound activity [29].

IID. Histone deacetylase inhibitors

Vorinostat (Zolinza) is a histone deacetylase (HDAC) inhibitor indicated for the treatment of cutaneous manifestations in patients with cutaneous T cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies [30]. Belinostat (Beleodaq) is a histone deacetylase inhibitor indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is approved under accelerated approval based on tumor response rate and duration of response [31].

IIE. Inhibitor of p53 tumor suppressor protein

Zalypsis (PM0014) is a new marine-derived synthetic alkaloid that has significant *in vitro* and *in vivo* activity against both solid and hematologic malignancies via p53-dependent and p53-independent mechanisms, and is currently being evaluated in early phase clinical trials for solid tumors and multiple myeloma [32].

III. Immunological Approaches to Cancer Therapy

The immunological approaches to cancer therapy include the use of monoclonal antibodies against specific cell surface receptors, recombinant interferon alpha-2b, cancer vaccines such as the human papillomavirus (HPV) vaccine and G305, the NYESO-1 vaccine, Reximmune-C and immune checkpoint

inhibitors.

Monoclonal antibodies are designed to bind to receptors that are over-expressed in cancer cells, thus blocking the signal transduction pathways needed for cancer cell proliferation. Recombinant interferon alpha-2b, and the HPV and NYESO-1 vaccines enhance the immune response against HPV and cancer cells bearing NYESO-1 antigen respectively. Reximmune-C is designed to recruit immune cells to the tumor microenvironment for in situ autoimmunization, and immune checkpoint inhibitors enhance T-cell responses against cancer cells by blockade of immunosuppressive molecules found on T cells.

IIIA. Monoclonal Antibodies

The use of monoclonal antibodies for cancer therapy has gained increasing popularity with the medical community, and at least 16 monoclonal antibodies have been approved by the USFDA for hematologic malignancies and solid tumors [33]. Human monoclonal antibodies are generated using transgenic mice or phage display libraries by transporting human IgG genes into the murine genome and then, immunizing the transgenic mouse against a selected antigen. This leads to the production of fully humanized monoclonal antibodies, which largely eliminates the problems of biocompatibility [34,35].

The mechanisms of action include direct binding with the cognate receptor (receptor blockade), delivery of a cytotoxic or radioactive drug [36], complement- or antibody- dependent cytotoxicity, and precise effects on cells in the tumor microenvironment [37-40]. Examples of humanized monoclonal antibodies include bevacizumab, trastuzumab, pertuzumab, and denosumab [37-40].

Bevacizumab (Avastin) is a monoclonal antibody directed against the vascular endothelial growth factor (VEGF) itself, which is secreted locally by certain tumors to generate their blood supply. It is indicated for the treatment of colon cancer, breast cancer and other types of solid tumors.

Cetuximab (Tarceva) is a monoclonal antibody that binds the epidermal growth factor receptor (EGFR) tyrosine kinase to inhibit its activity. EGFR is over-expressed in certain cancer types and is indicated for the treatment of pancreatic cancer and colon cancer.

Trastuzumab (Herceptin) and pertuzumab (Perjeta) are monoclonal antibodies against the HER2 receptor which is overexpressed in carcinoma of breast. It is indicated for treatment of breast cancer.

Denosumab (Xgeva) is a monoclonal antibody that binds to RANK –Ligand (RANK-L), a cytokine member of the tumor necrosis family, that activates RANK, a tyrosine kinase receptor found in osteoblasts. Binding of RANK-L with RANK activates the signaling pathway that favors osteoclastogenesis and bone resorption. Denosumab has a high affinity and specificity for RANK-L and can thus bind and thereby neutralize the activity of RANK-L [40].

TRC105 is a monoclonal antibody that binds endoglin, or CD105, a cell membrane glycoprotein that is overexpressed on proliferating endothelial cells (EC). The monoclonal antibody TRC105 is in clinical development in phase 1 and 2 clinical trials [41].

IIIB. Interferon alfa-2b, recombinant (Intron A)

Recombinant interferon alfa-2b was approved in 1995 for the treatment of malignant melanoma as adjuvant therapy in surgically resected, disease-free patients who were at high risk for systemic recurrence. These included patients with lesions of Breslow thickness greater than 4 mm, or patients with lesions of any Breslow thickness with primary or recurrent nodal involvement. USFDA approval was based on a successful pivotal Phase III study using Intron A versus observation in 280 patients. Intron A-treated patients had a significant increase in relapse- free and overall survival ($p < 0.01$) compared to observation patients [42].

IIIC. Human papilloma virus (HPV) vaccine

Gardasil is a human papillomavirus (HPV) vaccine that helps protect against 4 types of HPV. In girls and young women ages 9 to 26, Gardasil helps protect against 2 types of HPV that cause 70% of cervical cancer cases, 70% of vaginal cancer cases, and up to 50% of vulvar cancer cases. In males and females ages 9 to 26, Gardasil helps protect against about 80% of anal cancer cases and 90% of genital warts cases [43].

IIID. G305

G305 is a recombinant full-length NY-ESO-1 protein mixed with glucopyranosyl lipid A (GLA, a TLR4 agonist). In a phase 1 clinical trial, patients with advanced or metastatic melanoma, sarcoma, ovarian, breast, bladder, or NSCLC expressing NY-ESO-1 by immune-histochemical (IHC) analysis were dosed with 250 mcg of G305 and increasing doses of GLA given intramuscularly every 3 weeks for 3 doses. The results showed that G305 was immunogenic with 6 of 12 patients achieving stabilization [44].

IIIE. Reximmune-C and Reximmune-C2

Reximmune-C is a pathotropic (disease-seeking) retroviral-based nanoparticle displaying a tumor-targeting motif on its envelope and a cytokine gene, GM- CSF, as its genetic payload. In a phase 1 clinical trial using an optimal dose of Rexin-G (see Biological/Cell and Gene Therapies section) and escalating doses of Reximmune-C (The Genevieve Protocol) [45], there were no treatment-related adverse events, nor was circulating GM-CSF protein elevated in post- treatment serum sam-

ples. Histopathologic examination of biopsied tumors demonstrated vector localization and paracrine secretion of GM-CSF in tumors, with varying degrees of apoptosis, necrosis, reparative fibrosis, and tumor infiltrating lymphocytes (expressing CD4, CD8, or CD20), indicating an immunologic response. In 16 treated patients, median progression-free survival was greater than 6 months, and the median over-all survival was greater than 15 months.

One year survival rate was 86% in patients who received the highest dose of Reximmune-C. These findings suggested that the strategic combination of Rexin-G plus Reximmune-C is safe and well-tolerated, and may help control tumor growth and prolong survival, thus advancing the protocol and the molecular biotechnologies of personalized cancer vaccination as a promising approach [45]. A derivative of Reximmune-C (Reximmune-C2) is currently being evaluated in a clinical trial in Manila, Philippines. The clinical trial title is "A Phase 1 Dose Escalation Trial to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Reximmune-C2 (HSV- Thymidine Kinase-m2 and hGM-CSF) in Refractory Patients with Primary Hepatocellular Carcinoma or Tumors Metastatic to the Liver" (http://psmo.org.ph/clinical-trials/).

IIIF. Immune Checkpoint Inhibitors

Immune check point inhibitors have become a mainstay of therapy for melanoma and are currently being developed for various solid tumors including renal cell carcinoma, non-small cell lung cancer, ovarian cancer, head and neck cancer and lymphoma. The underlying principle is to thwart the defenses (checkpoints) that tumors utilize to cripple the immune system. Examples of FDA-approved immune checkpoint inhibitors include monoclonal antibodies ipilimumab, nivolumab, and pembrolizumab [46,47].

Ipilimumab (Yervoy) is a fully humanized monoclonal antibody that blocks the human cytotoxic T-lymphocyte antigen (CTLA-4) which tumors use to overturn the immune system. CTL4 is one of several co-inhibitory molecules that help in controlling the T-cell response to stimuli/cancer cells. Cancer cells bind to the CTL-4 antigen to avoid their destruction by cytotoxic T cells. In a pivotal phase III study, ipilimumab in combination with a glycoprotein 100 (gp100) peptide vaccine improved overall survival in Stage III or IV unresectable melanoma. These results, together with two other supportive studies, formed the basis of FDA approval for unresectable or metastatic melanoma [48,49].

Nivolumab (Opdivo) is a human antibody that blocks the programmed death receptor-1 (PD-1).

It is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

This indication is approved under accelerated approval by the USFDA [49].

Pembrolizumab (Keytruda) is a human programmed death receptor-1 (PD-L1)-blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval based on tumor response rate and durability of response [50].

IV. Alkylating agents

Alkylating agents are antineoplastic agents that attach an alkyl group to the guanine base of DNA, usually, at the number 7 nitrogen atom of the purine ring. Advances in technology has given rise to new alkylating agents with less toxic side effects. These include trabectidin and evofosfamide.

IVA. Trabectedin (Yondelis)

Trabectedin is a new alkylating agent that is currently approved in Europe, and is currently being evaluated in a pivotal Phase 3 study using trabectedin versus dacarbazine for liposarcoma and leiomyosarcoma previously treated with an anthracycline and ifosfamide. Unlike other alkylating agents, trabectedin binds specifically to the minor groove of DNA at the guanine position N2 instead of N7 [51,52].

IVB. Evofosfamide (formerly TH302)

Evofosfamide (formerly TH-302) is designed to be administered as a prodrug that is activated only under hypoxic conditions commonly found in the tumor microenvironment. Within regions of tumor hypoxia, evofosfamide releases bromo-isophosphoramide mustard (Br-IPM), a potent DNA alkylating agent [53]. Br-IPM kills tumor cells by forming DNA crosslinks, rendering cells unable to replicate their DNA and divide as well as by interfering with the transcription of DNA to make essential proteins. Once activated in hypoxic tissues, Br-IPM can also diffuse into surrounding oxygenated regions of the tumor and kill cells there via a "bystander effect" [53]. Because of its preferential activation in the targeted hypoxic regions of solid tumors, evofosfamide may be less likely to produce broad systemic toxicity seen with untargeted cytotoxic chemotherapies.

Evofosfamide is currently under evaluation in two Phase 3 trials: one in combination with doxorubicin versus doxorubicin alone in patients with locally advanced unresectable or metastatic soft tissue sarcoma (STS), and the other in combination with gemcitabine versus gemcitabine and placebo in patients with locally advanced unresectable or metastatic pancreatic cancer (the MAESTRO trial). Both Phase 3 trials are being con-

ducted under Special Protocol Assessment (SPA) agreements with the FDA [22].

V. Biological/Cell and Gene Therapies

Stem cell therapy has come of age, but gene therapy is currently still in development. Several hematopoietic stem cell therapies have been approved by the FDA for transplantation purposes. The only cell-based therapy directed for cancer is Sipuleucel-T. Gene therapy vectors in development include a retroviral-based vector, Rexin-G, and a lentiviral-based vector, LV305.

VA. Cell-based therapy

Sipuleucel-T cells are autologous mononuclear cells attached to a fusion protein consisting of a prostatic acid phosphatase enzyme (a common prostate cancer antigen) linked to granulocyte- macrophage colony-stimulating factor (GM-CSF). This immunotherapy strategy aims to induce a host immune response against the tumor antigen. A pivotal phase III clinical study showed that sipuleucel-T significantly improved median overall survival in men with metastatic castration- resistant prostate cancer compared with placebo, albeit no difference in progression-free survival was noted [54].

VB. Retroviral vector expressing a dominant negative cyclin G1 construct (Rexin-G)

Rexin-G is a pathotropic (disease-seeking) retrovector-based nanoparticle exhibiting a tumor targeting motif on its membrane glycoprotein, gp70, and bearing a cytocidal genetic payload, a dominant negative cyclin G1 gene [55-59]. The targeting motif is derived from the propeptide domain, D2, of coagulation factor von Willebrand factor. When injected intravenously, the targeted nanoparticle seek out and accumulates in primary and metastatic tumors where collagenous proteins are exposed in the tumor microenvironment. This brings the drug within the vicinity of cancer cells, enhancing its effective concentration in tumors wherein it then delivers its genetic payload via its native viral binding, fusion and entry mechanisms. The encoded dominant negative cyclin G1 gene is then expressed in tumor cells, which blocks the G1 phase of the cell cycle resulting in apoptosis and cell death.

Two dose-escalating phase I trials using Rexin-G in gemcitabine-failed pancreatic cancer were conducted. The first trial tested 3 dose levels of Rexin-G. A total of 12 patients were enrolled.

No serious adverse event was noted at Dose III. The best tumor response was stable disease in one patient. The second trial tested higher doses of Rexin-G, wherein Dose Level I was 1 x 10^{11} cfu per day, three times a week for 4 weeks, and Dose Level 2 was 2 x 10^{11} cfu per day, three times a week for 4 weeks. Treatment cycles were repeated if there was no toxicity. A total of 13 patients were enrolled, 6 in dose level I and 7 in dose level II. There was no dose limiting toxicity (DLT) observed. On intent-to-treat analysis, the tumor control rate was 50% (3/6) and 85.7% (6/7 with one partial response) of patients at dose level 0-I and II, respectively. The median overall survival was 2.6 months at Dose 0-1, and 9.3 months at Dose II [57]. Subsequently, the study was extended to a total of 20 patients wherein no DLT was observed, and the intent-to-treat analysis of over-all survival was 9.3 months at Dose III (3 x 10^{11} cfu). One patient achieved a complete remission after 9 months of Rexin-G treatment [58]. In 2009, the USFDA granted RexinG fast-track designation as second-line treatment for pancreatic cancer. This designation was based on a phase II/III pivotal two-arm randomized study which would validate the survival benefit of Rexin-G as single agent therapy *versus* physician's choice in gemcitabine-refractory pancreatic cancer.

VC. Lentiviral vector expressing NYESO-1 antigen (LV305)

LV305 is a replication-incompetent, integration-deficient, hybrid lentiviral-based vector that targets dendritic cells (DC) to induce expression of NY-ESO-1, a testicular carcinoma antigen, which is highly expressed in certain tumor types. The purpose is to generate and expand the cytotoxic lymphocytes (CTLs) against tumors expressing NY-ESO-1 for induction of anti-tumor immunity. LV305 is currently being tested in U.S. based clinical trials including the Sarcoma Oncology Center. Adults with previously treated, advanced or metastatic melanoma, sarcoma, breast, lung or ovarian cancers expressing the NY-ESO-1 protein by IHC are eligible. Initial results presented at the 2015 ASCO annual meeting showed no DLT or SAE in 12 patients. At the highest dose given (1010 vg), 4 of 6 patients showed disease stabilization with one patient achieving a 13.8% tumor regression, while 2 patients had progressive disease. Evidence of strong T cell responses were also noted. Data from the mid and high dose are pending. The plan is to include immune checkpoint inhibitor therapy in a future clinical study in order to augment the immune response [60].

Targeting the tumor microenvironment (TME) for enhanced drug delivery, a promising approach.

Among the various approaches to specifically target drug-loaded carrier systems to pathological sites within the body, there is passive targeting, based on the longevity of the pharmaceutical carrier in the blood and its accumulation in sites with compromised vasculature, and there is active targeting, based on attachment of specific ligands to pathologic features of the tumor microenvironment.

1. Passive Targeted Drug Delivery

Nab-paclitaxel and aldoxorubicin falls in the category of passive targeted drug delivery, which is based on the enhanced permeability and retention (EPR) effects that result from the

abnormal vascularity of the tumor microenvironment.

1a. Nab-paclitaxel (Abraxane)

Nab-paclitaxel is albumin-bound paclitaxel. In preclinical studies, albumin-bound paclitaxel particles showed antitumor activity as a single agent and synergistic activity in combination with gemcitabine in murine models of pancreatic cancer. In particular, nab-paclitaxel improved the intratumoral concentration of gemcitabine [61-62].

In a pivotal Phase 3 study involving 861 patients with metastatic pancreatic adenocarcinoma, nab- paclitaxel plus gemcitabine significantly improved overall survival by 1.8 months, with a survival rate of 35% at one year compared to 22% with gemcitabine alone. The results of this pivotal study formed the basis of FDA approval of nab-paclitaxel for pancreatic cancer [63]. While the development and market approval of the paclitaxel albumin nanoparticle, Abraxane, represents a landmark for albumin-based drug delivery and nanomedicine, more recent clinical studies performed in a directly comparative manner have had a sobering effect: The results of a recent NCI-sponsored Phase III breast cancer trial comparing paclitaxel with albumin-based nabpaclitaxel (Abraxane) determined that i.v. paclitaxel (Taxol) performed just as good or better than Abraxane, with significantly less toxicity [64]. Interestingly, previous preclinical studies utilized tumor-homing peptides and fluorescent conjugates to demonstrate that peptide-targeted Abraxane is more effective than untargeted Abraxane in tumor targeting and treatment [65].

At the very least, it can be stated that drugs such as Taxol and Abraxane—which are administered at necessarily high (equi-toxic) doses—could be further improved by active targeting [65], which would enable lower (not higher) doses of taxanes to become more clinically effective.

1b. Aldoxorubicin (Formerly INNO-206)

Aldoxorubicin is a prodrug of doxorubicin that binds covalently to circulating serum albumin via an acid sensitive linker that is conjugated to the drug. Albumin-bound aldoxorubicin accumulates preferentially and passively in tumors, thus decreasing biodistribution to normal organs, particularly the heart, bone marrow and gastrointestinal tract. The hypoxic acidic tumor microenvironment then favors cleavage of the acid sensitive linker generating free doxorubicin directly at the tumor site. In clinical trials, the use of aldoxorubicin appears to be associated with less systemic toxicity and greater efficacy, plausibly due to rapid drug accumulation in tumors.

There were no observed cardiac toxicities and no drug-related patient deaths [66-69].

A pivotal global Phase 3 clinical trial is on-going, using aldoxorubicin versus investigator's choice as second line treatment of metastatic, locally advanced or unresectable soft tissue sarcoma. Investigator's choice is limited to doxorubicin, ifosfamide, dacarbazine or pazopanib, or gemcitabine plus docetaxel. The primary endpoint of the study is progression-free survival (PFS), and secondary endpoints include overall survival, response rates and safety [22].

2. Active Targeted Drug Delivery

The first, and so far only, actively-targeted gene delivery systems for cancer were developed and tested in clinical trials circa 2000-2010. These products, Rexin-G and Reximmune-C, are genetically modified, humanized retroviral vectors displaying a tumor targeting motif on their membrane envelope glycoproteins, gp70. The tumor targeting moiety was derived from the D2 domain of coagulation von Willebrand factor. When injected intravenously, these pathotropic (disease seeking) nanoparticles actively seek-out and accumulate in primary and metastatic tumors by binding to collagenous proteins that are exposed due to tumor invasion, extracellular remodeling and neoangiogenesis. The effective intratumoral concentration of these pathology-targeted vectors are thus enhanced in the vicinity of target cancer cells, enabling binding, fusion and entry of the nanoparticles for targeted gene delivery with commensurate improvements in safety and efficacy [70-72].

Rexin-G and Reximmune-C are targeted nanoparticle-based gene delivery systems that were tested in five U.S. based clinical trials for pancreatic cancer, sarcoma, osteosarcoma and breast cancer [55-58] and 3 clinical trials for all solid malignancies conducted in Manila, Philippines [45,71-72].

Rexin-G bears a dominant-negative mutant construct of human cyclin G1 [71] while Reximmune-C carries a cytokine, granulocyte-macrophage colony-stimulating factor [72]. Two U.S.-based studies showed that the use of Rexin-G as monotherapy for advanced metastatic disease was associated with improved over-all survival in chemotherapy-resistant sarcoma (40% one-year survival) [55-56] and gemcitabine-failed pancreatic cancer (9.3 months median overall survival) [57-58], providing the basis for three USFDA Orphan Drug approvals for osteosarcoma, soft tissue sarcoma, and pancreatic cancer. A phase 3 clinical trial of Rexin-G as second-line therapy for advanced pancreatic cancer gained fast track designation by the USFDA in 2009. This targeted vector could have been the first gene therapy product to gain approval by the USFDA, and it had already gained accelerated approval in the Philippines. Finally, a combination regimen using sequential intravenous administration of Rexin-G and Reximmune-C (The Genevieve Protocol) was conducted in the Philippines for chemotherapy resistant solid malignancies [45]. This dual targeted approach aimed at both tumor eradication and in situ cancer vaccination. Rexin-G was given first, to kill the cancer cells and expose tumor antigens, followed by Reximmune-C administration to

recruit the host immune cells to the tumor site, thus inducing an in situ autoimmunization. This first-in-human targeted gene therapy regimen showed a one-year survival duration of 86% in a Phase 1 study [45]. A Phase 1 study using Reximmune-C2, a derivative of Reximmune-C, is ongoing in the Philippines.

Discussion

Previously approved chemotherapy agents depended on plasma concentration and saturation kinetics of the drug to obtain efficacy with a narrow margin of safety. Often, there is a race to eradicate the cancer before inducing lethal side effects. In this review article, we presented the major advances in oncology drug development, mainly in the United States. A paradigm shift toward a targeted approach has become apparent. Drug targets include the tyrosine kinase and serine-threonine kinase signaling pathways. An increasing number of synthetic small molecules targeting receptor tyrosine kinases have gained USFDA approval. These include inhibitors of EGFR (e.g. erlotinib, gefitinib and lapatinib), VEGFR(e.g. sorafenib, pazopanib and axitinib) [2-4], both VEGFR and PDGFR (e.g. sunitinib), and inhibitors of mutated ALK receptors (e.g. crizotinib and ceritinib) [5-7]. Additionally, drugs that target the non-cellular tyrosine kinase signaling pathways are currently in the market. These drugs include inhibitors of BCR-ABL and its fusion protein, bcr /abl (e.g. imatinib and nilotinib respectively) [8,9,12], RAF/MEK/ERK (e.g. sorafenib) [11], CDK4 and CDK6 (e.g. palbociclib) [14] and multiple tyrosine kinase pathway inhibitors (e.g. regorafenib). Next, certain inhibitors of the serine-threonine kinase signaling pathways including mTOR inhibitors (e.g. sirolimus, temsirolimus, everolimus) [17-21], and BRAF inhibitors[23] (e.g. vemurafenib, dabrafenib), have been approved, and a number of biosimilars are currently in clinical trials.

Of special interest is the rapidly developing field of cancer immunotherapy and targeted drug delivery with the USFDA approval of at least 16 monoclonal antibodies [37-39], a number of cancer vaccines [43], and targeted nanoparticle delivery systems [63]. Monoclonal antibodies targeting VEGF (e.g. bevacizumab), HER2 receptors (e.g. trastuzumab and pertuzumab) as well as the EGFR (e.g. cetuzimab) have gained FDA approval. Monoclonal antibodies that target immune checkpoints such as CTL4 (e.g. ipilimumab), PD-1 (e.g. nivolumab and pembrolizumab) are becoming increasingly popular and are already in the market [47-50]. Cell-based immune therapy, exemplified by sipuleucel-T for advanced prostate cancer, is the first of its kind to gain USFDA approval [54].

To date, there are no gene therapy products approved in the United States. However, two targeted gene vectors are worthy of mention. Rexin-G and Reximmune-C are targeted retrovectors, bearing a cytocidal dominant negative cyclin G1 construct and a cytokine GM-CSF gene respectively. The survival rates seen with Rexin-G when used as salvage therapy are comparable with cancer drugs used as first-line therapy with no serious adverse events [56,58]. Additionally, the combination of Rexin-G and Reximmune-C resulted in a notable 86% one year survival in chemotherapy-resistant cancer patients with minimal toxicity [45]. The combined use of immune checkpoint inhibitors with gene therapy vectors raises interesting possibilities.

Conclusion

In the past two decades, cancer drug development has focused largely on targeting receptors and their complex signaling pathways to abort the cell division cycle and induce apoptosis in cancer cells. More recently, research efforts have shifted toward activating the immune system and/or targeting the tumor microenvironment (TME) for novel therapeutic strategies [47-50]. Indeed, interactions between cancer cells and normal cells populating the TME—tumor infiltrating lymphocytes, tumor-associated vasculature, and stromal cells—regulate cancer progression and metastasis, while the presence of CD8+ CTLs in the TME is predictive of a favorable prognosis in terms of response to treatment and duration of survival. A major advancement in cancer immunology is the concept of blocking the immune tolerance which allows cancer cells to avoid immune surveillance. Consistent with this concept, enhancement of the T cell responses by blockade of immune suppressive checkpoints (CTLA, PD-1) is associated with prolonged survival in some patients with melanoma and NSCLC. However, the use of these checkpoint inhibitors is associated with immune-mediated toxicity (autoimmune disease) which is a formidable sequela that requires chronic immune suppression,[47-50] which could then lead to second malignancies.

Targeted approaches to enhancing antitumor immunity could conceivably utilize the unique properties of the TME itself (i.e., TME-targeting) to therapeutic advantage: (i) to compartmentalize the bioactivity of the immune checkpoint inhibitors and/or (ii) to focus the biodistribution of targeted gene therapy vectors bearing immunomodulatory cytokine genes to the TME. The addition of these TME-targeting strategies to existing protocols could potentially isolate the T cell responses within the tumors and reduce the immune-mediated systemic reactions associated with the cancer immunotherapy. Evidence to support this TME-targeting strategy is the prolonged duration of survival (86% one year survival) with minimal to no toxicity reported with the use a tumor-targeted retrovector bearing a GM-CSF gene [45]. Looking forward into the future, the advent of immune checkpoint inhibitors of the T cell regulatory pathways raises hope for the induction of long term antitumor immunity [47]. The development of TME-targeted anti-cancer and immuno-oncologic drugs may improve both safety and efficacy, induce durable remissions in a larger number of patients with a greater number of tumor types, and potentially contribute to a cure for cancer.

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