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A REVIEW ON TRANSLATIONAL PERSPECTIVE AND EFFICACY OF DIFFERENT ENGINEERED THERAPEUTIC ANTIBODIES

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ABSTRACT: From bench to bedside, clinical research had always played as a convenient tool in the field of cancer biology to inquire about the effectiveness of different anticancer drugs on different human-derived cancer cell lines. According to the American Cancer Society, nearly 4000 new cases and 1600 deaths predicted in 2019 in the United States. Besides, to these alarming statistics, rising cost and health-related complications associated with treatments had made the research of cell lines on the anticancer drug more relevant. This article providing a comprehensive review of cancer, advanced development of the anticancer drugs, and a brief inference on progression-free survival rate (PFS) of the following anticancer and engineered monoclonal antibody drugs are discussed.

INTRODUCTION: In the epoch of being healthy cancer has been diagnosed in one out of 10 men and women. Nuclei of normal cells containing DNA made up of nucleotides gets damaged causing mutation. The mutations caused due to exposure of harmful UV radiations; decrease in exercises; increase in specific types of diets that cause quandaries in the cell cycle. According to numerous data collected from different programs; centers and registries exhibited that in spite of early detection and quality of treatment still, cancer remains a terminal health peril amongst people around the globe. Possible studies report about the incidence rate of cancer that is 20% more in men than in women.

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Surveys conducted in the United States of America exhibited that breast, prostate; lung & bronchus are the most common types of cancer found in males and females. As cancer is not homogeneous it makes the treatment complicated because there may be three, four, five, or six different slight variations in the cancer cells as known cancer is the constellation of over two hundred diseases having similar characteristics but are different from each other in their mechanism. Common treatments directed to patients are surgery or radiation or chemotherapy. The regular treatment is known as chemotherapy, where various anticancer drugs alone or synergism of drugs are administered by IV.

The objective of this review is to assemble different cancer cell lines from the American Type Culture Collection (ATCC) and MI Bioresearch with their histotype and morphology with effect on different anticancer drugs along with engineered monoclonal antibodies (mAbs) simultaneously including a comparative investigation on progression-free survival (PFS) to decline the rate of cancer in near future.

Role of Cancer Cell Lines: When cells were cultured in-vitro, it propagated into primary culture followed by sub-culture to produce cell lines and distinguished into two kinds of cultures:

(1) Monolayer (anchorage-dependent) culture: cells cultured from an organ or tissue such as epithelial cells and fibroblasts. (2) The suspension (anchorage-independent) culture: cells cultured from hematopoietic cells such as leukemia cells; multiple melanoma cells. Cancer cell lines procured from patients who underwent aggressive cancers. Advancement in cancer pathobiology shows the availability of different innovative models to review various kinds of diseases [1]. Study of cancer relies on the use of primary tumors [2]; paraffin-embedded samples[2]; cancer cell lines [2]; xenografts [1, 3-4]; tumor primary cell cultures and/or genetically engineered mice [5]. Cell lines emerge as an expedient alternative to overcome different concerns; easily manipulate and can be molecularly characterized in the development of unique anticancer drugs.

Additionally, it also helps to discern the action mechanism of already used chemotherapeutic drugs. According to various experiments conducted at the laboratories and literature surveys exhibited, to examine the therapeutic efficacy of different FDA approved anticancer drugs on cell lines of *Homo sapiens* (human), *Mus musculus* (Mouse), *Caviaporcellus* (Guinea pig), *Sarcophilus harrisii* (Tasmanian devil) (*Sarcophilus laniarius*), *Chlorocebus aethiops* (Green monkey) were used [4].

TABLE 1: DIFFERENT TYPES OF HISTOTYPES AND MORPHOLOGY OF CELL LINES DERIVED FROM HUMANS *(HOMO SAPIENS)* FOR TREATING DIFFERENT CANCERS [4, 6-7]

Histotype	Cell Lines	Morphology	Disease	Species
Adrenal	NCI-H295R	Epithelial	Carcinoma [6]	*Homo sapiens*
Bladder	5637	Epithelial	Grade II carcinoma	*Homo sapiens*
	HT-1376		Grade III carcinoma	
	J82		Transitional cell carcinoma[6]	
	SW 780			
	T24			
	T24-Luc-Neo			
	T24P			
Bone	MG-63	Fibroblast	Osteosarcoma	*Homo sapiens*
	Saos-2	Epithelial	Multipotential sarcoma[4]	
	SJSA-1	Fibroblast[6]		
Brain	BT142	Neurosphere	Oligoastrocytoma Grade III	*Homo sapiens*
	D54-Luc	Not specified	Glioblastoma	
	DBTRG (tumor)	Fibroblast	Grade IV, glioma	
	DBTRG-05MG	Not specified	glioblastoma	
	Gli36-DsRed-R-	Epithelial	Malignant glioblastoma	
	Luc (rescued)	Fibroblast	Astrocytoma, glioma	
	LN-18	Not specified	Astrocytoma	
	LN-229	Fibroblast	Likely glioblastoma	
	LN-827(pMMP-	Epithelial	Glioblastoma	
	LucNeo)	Pleomorphic	Cancer [6]	
	M059K	Astrocytoid[6]		
	SF-295			
	SF-539			
	SF-767			
	SNB-19			
	U-87 MG			
	U-87 MG-luc			
	U251			
	U251-Luc-mCh-			
	Puro: Human			
	Glioblastoma[8]			
Cervical	Ca Ski	Epithelial	Epidermoid carcinoma	*Homo sapiens*
	HeLa		Adenocarcinoma	
	KB		Papilloma, carcinoma[6]	
Colon	C2BBe1	Epithelial	Colorectal adenocarcinoma	*Homo sapiens*
	Caco-2	Epithelial-like	Dukes' type D	
	Colo-205-Luc #2		Dukes' type C[6]	

	Colo-205 DLD-1			
Epidermoid	A431	Epithelial	Epidermoid carcinoma[6]	*Homo sapiens*
Epithelial	HEKn (Human Epithelial Keratinocytes)	Cobblestone appearance	skin cancer	*Homo sapiens*
Erythroleukemia	HEL HEL 92.1.7 HEL 92.1.7-Luc-Neo HEL-Luc-Neo TF-1a TF-1a-Luc-Neo	Lymphoblast	Erythroleukemia[6]	*Homo sapiens*
Esophageal	OE33	Epithelial like	Barrett adenocarcinoma[4]	*Homo sapiens*
Ewig's Sarcoma-Bone	A4573	Not specified	Ewing sarcoma[4]	*Homo sapiens*
Fibroblast	Hs 895.T TE 353.Sk TE 354.T	Fibroblast	Melanoma	*Homo sapiens*
Fibrosarcoma	HT-1080	Epithelial	Fibrosarcoma	*Homo sapiens*
Gastric	GIST-T1 NCI-N87 NUGC-4 SNU-5	Submucosal Epithelial Spherical with free-floating cells Epithelial	Gastrointestinal stromal tumor Signet ring cell gastric adenocarcinoma Gastric carcinoma	*Homo sapiens*
Head and Neck (squamous cell carcinoma)	CAL 27 FaDu	Epithelial	squamous cell carcinoma[6]	*Homo sapiens*
Leukemia (Acute Promyelocytic)	HL-60	myeloblastic	acute promyelocytic leukemia	*Homo sapiens*
Leukemia (AML)	EOL-1 Kasumi-1 Kasumi-3 MOLM-13 MV-4-11 NOMO-1 THP-1	Lymphoblast Myeloblast most cells are round growing in suspension lymphoblast single round cells monocyte	Cancer acute myeloblastic leukemia Adult acute myeloid leukemia biphenotypic B myelomonocytic leukemia hematopoietic neoplasm acute monocytic leukemia[6]	*Homo sapiens*
Leukemia (B-ALL)	NALM6 Reh RS4;11	Lymphocyte-like lymphoblast	acute lymphoblastic leukemia (ALL) acute lymphocytic leukemia (non-T; non-B)[6]	*Homo sapiens*
Leukemia (CML)	K-562 K-562-Luc2	lymphoblast	chronic myelogenous leukemia (CML) BCR-ABL1 positive[6]	*Homo sapiens*
Leukemia (Plasma Cell)	ARH-77	Lymphoblast	plasma cell leukemia[6]	*Homo sapiens*
Leukemia (T-ALL)	CCRF-CEM DND-41-Luc-mCh-Puro MOLT-4 Jurkat Jurkat-Clone E6-1 MOLT-4	Lymphoblast	Acute lymphoblastic leukemia Acute T-cell leukemia[6]	*Homo sapiens*
Liposarcoma	SW 872	Fibroblast	Liposarcoma	*Homo sapiens*
Liver	Hep 3B2.1-7 Hep G2	Epithelial	Hepatocellular carcinoma	*Homo sapiens*
Lung (Adenosquamous)	NCI-H596	Epithelial	Adenosquamous carcinoma[6]	*Homo sapiens*
Lung (Anaplastic Carcinoma)	Calu-6	Epithelial	Anaplastic carcinoma[6]	*Homo sapiens*
Lung(Bronchioalveolar)	NCI-H322M	Epithelial	squamous cell carcinoma mesotheliom[6]	*Homo sapiens*
Lung (NSCLC)	A549 Calu-1	Epithelial like Epithelial	Carcinoma Grade III,	

	Calu-3	Epithelial	Epidermoidcarcinoma	
	HCC827	Epithelial-like	Adenocarcinoma	
	HCC4006	Epithelial	Non-small cell lung cancer	
	NCI-H125		Stage 3B, bronchoalveolar carcinoma	
	NCI-H1299			
	NCI-H23		Mucoepidermoid pulmonary carcinoma	
	NCI-H1975			
	NCI-H1703		Papillary adenocarcinoma	*Homo sapiens*
	NCI-H1299-p53-V138		Large cell lung cancer	
			Stage 2 adenocarcinoma	
	NCI-H1650		Adenocarcinoma[6]	
	NCI-H2110			
	NCI-H292			
	NCI-H3122			
	NCI-H441			
	NCI-H460			
	NCI-H522			
	PC-9			
Lung (SCLC)	DMS 114	Epithelial	Carcinoma,	*Homo sapiens*
	NCI-H446	Floating aggregates	small cell lung cancer	
	NCI-H69	Epithelial	carcinoma, small cell lung cancer[6]	
	NCI-H82			
	SHP-77			
Lung (Squamous)	EBC-1	Metastatic site:skin(epithelial)	Squamous cell lung carcinoma[6]	*Homo sapiens*
	SK-MES-1	Epithelial		
Lymphoma (B-Cell)	DB	Lymphoblast	Large cell lymphoma[6]	*Homo sapiens*
Lymphoma (B-NHL)	Farage	Lymphoblast	Non-Hodgkin's B cell lymphoma	*Homo sapiens*
	GRANTA-519	Lymphoblast-like	Mantle cell lymphoma	
	SU-DHL-6		Large cell lymphoma; diffuse mixed histiocytic and lymphocytic lymphoma; follicular B cell lymphoma[6]	
Lymphoma (Burkitt's)	Daudi	Lymphoblast	Burkitt's lymphoma	*Homo sapiens*
	NAMALWA			
	Raji		Burkitt's lymphoma (American)[6]	
	Ramos			
Lymphoma (Cutaneous T Cell - Sezary Syndrome)	HuT 78	Lymphoblast	Sezary Syndrome and Mycosis fungoides[6]	*Homo sapiens*
Lymphoma (Diffuse Mixed)	HT	Lymphoblast	diffuse mixed lymphoma[6]	*Homo sapiens*
	SU-DHL-6			
Lymphoma (DLBCL)	OCI-Ly1 LN	Bone marrow	Diffuse large B-cell lymphoma	*Homo sapiens*
	OCI-Ly19-Luc-Neo	Lymphoblast-like	Large Cell Lymphoma	
		Bone marrow	B-cell non-Hodgkin lymphoma	
	OCI-Ly3-Luc-mCh-Puro	Lymphoblast	Large cell lymphoma	
			Diffuse large B-cell lymphoma	
	SU-DHL-10		diffuse large cell lymphoma; non-Hodgkin's B cell lymphoma	
	SU-DHL-10-LN-High			
	SU-DHL-16		Diffuse large B-cell lymphoma[6]	
	SU-DHL-4-Luc-mCh-Puro			
	SU-DHL-8			
	TMD8			
	Toledo-Luc-Neo			
	WSU-DLCL2			
Lymphoma (Malignant NHL)	NK-92MI	Lymphoblast	malignant non-Hodgkin's lymphoma[6]	*Homo sapiens*
Lymphoma (T-NHL)	KARPAS 299	Peripheral blood	Anaplastic large cell lymphoma[6]	*Homo sapiens*

Mammary/Breast	BT-20 BT-474 HCC1395 HCC70 Hs 578Bst Hs 578T MCF-7 MCF10A MDA-MB-231 MDA-MB-361 MDA-MB-453 MDA-MB-468 SK-BR-3 MX-1 T47D UISO-BCA1 ZR-75-1	Epithelial Fibroblast Epithelial Epithelial Epithelial Epithelial Epithelial Epithelial Epithelial Epithelial Epithelial	Invasive ductal carcinoma TNM stage I, grade 3, primary ductal carcinoma TNM stage IIIA, grade 3, primary ductal carcinoma Normal Invasive ductal carcinoma Fibrocystic disease Breast adenocarcinoma Metastatic carcinoma Adenocarcinoma Breast carcinoma Invasive ductal carcinoma Breast carcinoma Invasive ductal carcinoma[6]	*Homo sapiens* *Homo sapiens*
Melanoma	A2058 A375 COLO-829 G-361 LOX IMVI M14 MDA-MB-435S OCM-1 SK-MEL-28 SK-MEL-5 UACC-62 WM-115 WM-266-4	Epithelial Fibroblast Epithelial Axillary lymph node Subcutaneous Spindle-shaped Subcutaneous Polygonal Stellate Epithelial	Amelanotic melanoma Cutaneous melanoma Malignant melanoma Amelanotic melanoma Amelanotic melanoma Amelanotic melanoma Cutaneous melanoma Malignant melanoma Melanoma[6]	*Homo sapiens*
Myeloma	JJN-3-Luc MM.1S (pMMP-Luc-Neo) NCI-H929 NCI-H929-Luc-mCh-Puro OPM-2 RPMI 8226 U266B1	Mononuclear Lymphoblast round to polygonal cells Lymphoblast	immunoglobulin A lambda myeloma plasmacytoma; myeloma[6]	*Homo sapiens*
Neuroblastoma	SK-N-AS SK-N-FI SK-N-SH	Epithelial	Neuroblastoma[6]	*Homo sapiens*
Neuroendocrine Skin	MKL-1	Loosely packed floating aggregates with irregular outline and no central necrosis	Metastasis[4]	*Homo sapiens*
Normal Fibroblast	Hs 895.Sk	Fibroblast	Normal	*Homo sapiens*
Ovarian	A2780-Luc A2780 IGROV-1 IGROV1-Luc-Mch-Puro NIH:OVCAR-3 OV-90 OVCAR-3 OVCAR-4 OVCAR-5 OVCAR-8-Luc-mCh-Puro OVCAR-8 SK-OV-3 SKOV-3-luc-D3[11]	Epithelial	Cancer Ovarian endometrioid adenocarcinoma Adenocarcinoma grade 3, stage IIIC, malignant papillary High grade ovarian serous adenocarcinoma Adenocarcinoma[6]	*Homo sapiens*
Pancreatic	Bx-PC-3 BxPC-3-Luc2	Epithelial Polygonal	Adenocarcinoma Carcinoma	*Homo sapiens*

	Capan-1 Capan-2 KP4 MI PaCa-2-Luc MiaPaCa-2 PANC-1 PANC-1-Luc-mCh-Puro SU-86.86	Epithelial	Epithelioidcarcinoma Ductal carcinoma	
Placental Choriocarcinoma	BeWo	Epithelial	Choriocarcinoma	*Homo sapiens*
Prostate	22Rv1 CWR-22-R DU 145-Luc DU-145 LnCap LnCap FGC PC-3-Luc PC-3 PC-3M-Luc-C6 VCaP[10]	Epithelial	Carcinoma Grade IV adenocarcinoma Cancer	*Homo sapiens*
Renal	769-P 786-O 786-O-Luc-Neo (rescued) A-498 ACHN Caki-1 HEK 293 TK-10	Epithelial	Renal cell adenocarcinoma Carcinoma Renal cell adenocarcinoma Clear cell carcinoma Neurological disease Cancer, carcinoma [4,6]	*Homo sapiens*
Vulva	SK-LMS-1	Fibroblast	Leiomyosarcoma	*Homo sapiens*

Antibody engineering, where various antibody domains are combined to generate customized antibodies showing specialized binding properties and desirable effector functions [9]. This hybridoma technology was developed by Köhler and Milstein and now to improve the therapeutic efficacy to treat cancer, antibodies are engineered to make mutant proteins of higher affinity or small molecular variants or changed functional properties of the original antibody. Lately, this technology has led to the approval by the United States Food and Drug Administration (FDA) of 21 antibodies for cancer immunotherapy [10]. Therefore, different FDA approved anticancer drugs with their mode of action (MoA), pharmacology and cell lines worked on are shown:

Muromonab-cluster of differentiation 3 (CD3) (Orthoclone OKT3®) was the very first approved monoclonal antibody by the United States Food and Drug Administration (FDA) [11].

Using the hybridoma technology IgG2a antibody developed that blocked CD3-mediated activation of T cells and was instrumental in the prevention of organ rejection after transplantation.

Later, it was witnessed that patients with Orthoclone OKT3® developed a significant percentage of anti-drug antibodies known as a "human anti-mouse antibody" (HAMA) response leading to the inactivation and removal of the murine antibody and prevents the use of multiple administrations of the antibody required for cancer therapy.

An antibody made by combining genetic material from a nonhuman source (mouse) with genetic material from a human being to increase efficacy and decreasing immunogenicity is called chimerization and used in treatments.

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Approved oncology therapeutic antibodies are human IgG1, IgG2, and IgG4.

Rituximab was the first chimeric therapeutic antibody to treat cancer.

Newly engineered antibodies are:

Cyramza (Ramucirumab): A recombinant human IgG1 monoclonal antibody to treat hepatocellular carcinoma (HCC) [12-14].

Herceptin Hylecta: (Combination of trastuzumab with hyaluronidase enzyme) is a humanized antibody to treat HER2-overexpressing breast cancer [16].

Polivy (Polatuzumabvedotin-piiq): Supposed to be a chimeric therapeutic antibody as it is indicated for use in combination with bendamustine plus Rituxan (rituximab) (BR) to treat large B-cell lymphoma [18, 48-49].

Tecentriq (Atezolizumab): Humanized mono-clonal antibody specified to treat extensive-stage small cell lung cancer and triple-negative breast cancer [50, 61].

Gazyva (Obinutuzumab): It is a humanized antibody used to treat previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) [51].

Panitumumab (Vectibix®): It is the first fully humanized IgG2 approved drug [52].

Trastuzumab: It is the humanized IgG1 therapeutic antibodies to treat cancer, such as metastatic breast cancer [53].

Avelumab (Bavencio): It is an FDA approved humanized IgG1 monoclonal antibody directed to PD-L1 that blocks the binding between PD-1 and PD-L1 without affecting PD-1/ PD-L2 interactions to treat Merkel cell carcinoma and urothelial carcinoma. The mode of action demonstrates the potential to utilize both adaptive and innate immune mechanisms to destroy cancer cells [45].

Pharmacology: It is treating metastatic Merkel cell carcinoma (MCC) of adults and pediatric patients around 12 years or above, urothelial carcinoma [11].

Mode of Action: Being a PD-L1 blocking antibody where it binds through the FG loops 7 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. In this manner, the interaction releases the inhibitory effects of PD-L1 on the immune response resulting in the restoration of immune responses, including anti-tumor immune responses. The mode of action demonstrates the potential to utilize both adaptive and innate immune mechanisms to destroy cancer cells [22, 33].

Cell Lines Effect: Worked against a panel of triple-negative breast cancer (TNBC) cells.

Panobinostat: A histone deacetylase (HDAC) inhibitor is an FDA approved new agent for multiple myeloma. According to literature surveys, it demonstrates that panobinostat is applied when bortezomib shows no response, still, it's not clear how these drugs work. HDAC inhibitors target epigenetics that is they change the pattern of genes the cell expresses and not the genes themselves. The function of the HDAC inhibitor is it blocks the removal of acetyl groups from histone proteins and reactivates silenced genes. In phase III PANORAMA trial included a total of 768 patients who had relapsed or had refractory MM. Before this trial, all the patients had already received one to three treatments. Trial's result showed that the combination of panobinostat and bortezomib offered the opportunity to extend the duration of PFS and overcome the potential bortezomib resistance [11, 27].

Pharmacology: Evidence shows and indicates that HDAC inhibitors work differently in Multiple Myeloma (MM).

Mode of Action: Deacetylase (DAC) inhibitor is responsible for regulating the acetylation of proteins in the body along with different functions in various vital processes, including replication and repair of DNA; remodeling of chromatin; transcription; progression of the cell cycle; protein degradation and cytoskeletal reorganization. Mode of action of panobinostat is inhibition of class I; class II and class IV proteins also DAC proteins are overexpressed in Multiple Myelomas (MM) [11].

Cell Lines Worked Against: From literature, the study has shown that panobinostat showed cytotoxic activity worked against cell lines such as KMS-12PE, KMS-18, LP-1, NCI H929, KMS-11, RPMI8226, OPM-2, and U266.

Ixazomib (NINLARO): It is the first oral proteasome inhibitor with lenalidomide for the treatment of MM, who has at least received one

prior therapy. It is a boronate proteasome inhibitor also an N-capped dipeptidyl leucine boronic acid. The mechanism of action is reversible. It binds and inhibits the beta 5 chymotrypsin-like proteolytic site of the 20S proteasome with a half-maximal IC_{50} [26].

Pharmacology: It induces apoptosis in multiple myeloma cells, treating Hepatocellular carcinoma (HCC) [25].

Mode of Action: This second-generation proteasome inhibitor (PI) is an N-capped dipeptidyl leucine boronic acid. It reversibly inhibits the CT-L proteolytic (β5) site of the 20S proteasome. When its concentration increases, likewise seem to inhibit the proteolytic β1 and β2 subunits and induce accumulation of ubiquitinated proteins [11, 24].

Cell Lines Worked Against: HepG2, Hep3B, SNU-475, the cytotoxic effect on IMR-32, NGP, NB-19, SH-SY5Y, SK-N-AS, and the chemoresistant LA-N-6 cell line.

Bortezomib: Bortezomib (originally PS-341 and marketed as Velcade by Millennium Pharmaceuticals) is the first therapeutic proteasome inhibitor that was tested in humans that degrades pro-apoptotic proteins such as p53. The role of bortezomib is to interrupt this process and resulting in the destruction of cancerous cells [11].

Pharmacology: This agent is used for the treatment of multiple myeloma [11].

Mode of Action: It is a proteasome inhibitor type drug. It removes excess protein and breaks down into its constituent parts so that the cell can reuse it. Proteasome inhibitors work in such a manner that it blocks the function of proteasome followed by the accumulation of protein in the cell, which becomes toxic to the cell and causes it to die. This is particularly important in myeloma cells as they make lots of proteins and so really rely on proteasome to function properly. Therapies targeting the proteasome can specifically kill myeloma cells rather than all of the cells in the body. Bortezomib being a reversible inhibitor in mammalian cells degrades ubiquitinated proteins. The active site of the proteasome has chymotrypsin-like, trypsin-like, and postglutamyl peptide hydrolysis activity. In addition, bortezomib appears to increase the sensitivity of cancer cells to traditional anticancer agents (*e.g.,* gemcitabine, cisplatin, paclitaxel, irinotecan, and radiation) [11].

Cell Lines Effect: From literature, it has been studied that bortezomib has effects on human breast cancer cell lines such as ANBL-6 BR, HCC 1937, MCF 7, MDA-MB-231, MDA-MB-468, SK-BR-3, BT-474 [28].

Palbociclib: For the treatment of postmenopausal in women with estrogen receptor (ER)-positive; human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer an endocrine-based therapy for metastatic disease used which is an oral, selective, small-molecule inhibitor of CDK4 and CDK6 [11, 29, 35].

Pharmacology: It is a combination drug with antiestrogens, letrozole for the treatment of breast cancer cell lines [11, 19].

Mode of Action: Palbociclib is a kinase inhibitor drug where CDK4 and CDK6 along with their regulatory partner cyclin D1, play a key role in regulating the G1- to S-phase cell-cycle transition where regulation of the retinoblastoma (Rb) protein is phosphorylated [11].

Cell Lines Effect: liver cancer cell lines, *in-vitro*, in *ex-vivo* HCC samples, in a genetically engineered mouse model of liver cancer and in human HCC xenografts *in-vivo*.

Pembrolizumab: Pembrolizumab commonly known as Keytruda, is a protein-based humanized monoclonal antibody used for treating Melanoma, Non-Small Cell Lung Cancer and Head and Neck Cancer by blocking the interaction between PD-1 and its ligands PD-L1 and PD-L2 [8, 11, 44].

Pharmacology: It is a protein-based humanized monoclonal antibody drug used for treating patients with metastatic melanoma [44].

Mode of Action: Pembrolizumab acts as a checkpoint inhibitor where T lymphocyte plays a key role. Being an antibody-drug that targets the T-cell receptor of programmed cell death protein (PD-1) present on the cell surface, inhibits the binding of ligands (PD-L1 and PD-L2) of PD-1 ensued by inducing an antitumor immune response.

Upregulation of PD-1 ligands is a mechanism for tumors to circumvent antitumor immune response [8, 34, 44].

Cell Lines Effect: From the literature, it has been investigated that it shows effects on PD-1 cell line (host cell line-HEK293), M109 [6, 41].

Rituxam (Rituximab): It is a recombinant DNA derived humanized monoclonal antibody. It recognizes CD20, a receptor found exclusively on the surface of both normal and malignant B lymphocytes [11].

Pharmacology: Rituximab is used for treatment of CD20-positive non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis. The antibody leads to selective killing of β-cells [23, 30].

Mode of Action: Rituximab or Rituxan is recombinant DNA derive humanized monoclonal antibody used as therapy for treating a broad variety of β-cells malignancies. It recognizes a receptor named CD20 found on the surface of both normal cells and malignant cells. The function of the drug is to bind with the receptor CD20 and destroy the target cell. From various in vitro studies conducted suggest that Rituxan depletes circulating B-cells and reduces the size of B cell lymphomas in different ways. Various studies assert that this humanized monoclonal antibody drug kills B-cells through Complement Dependent Cytotoxicity (CDC) or Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) [46].

Cell Lines Effect: From the literature, it has been investigated that it shows effects on NK-92; NK-92MI [6, 37].

Lenalidomide: Revlimid or Lenalidomide is an immunomodulatory synergistic drug [11].

Pharmacology: Lenalidomide is an anticancer drug having immunomodulatory and antiangio-genic properties that modify the immune system function and prevents the proliferation of blood vessels to treat patients with multiple myeloma (MM), transfusion-dependent anemia in myelo-dysplastic syndromes and mantle cell lymphoma [11].

Mode of Action: Revlimid performs dual action of antitumor and an immunomodulatory effect. The tumoricidal effects of this anti-cancer drug induce cell cycle arrest, facilitates apoptosis of tumor cells, reduces angiogenesis, stromal cell support, and severance to the production factors that promotes myeloma cell survival and proliferation. Revlimid inhibits the cell cycle of myeloma cells by increasing the expression of tumor suppressor genes such as CDK inhibitors and the family of early growth response genes.

The up-regulation of these genes in the presence of Revlimid arrests the cell cycle and prevents the division of myeloma cells. It activates the effector proteins of apoptosis called caspases and facilitates the release of pro-apoptotic signals such as cytochrome C inside the cell that increases the sensitivity of tumor cell factors stimulating apoptosis that increases tumor cell death. *In-vitro* drug synergism study of Dexamethasone with Revlimid has shown enhanced tumor cell apoptosis; inhibition of angiogenesis to the tumor cells by reducing vascular endothelial growth factor and IL-6 levels. Revlimid inhibits the adhesion of myeloma cells to bone marrow stromal cells. The proposed immunomodulatory effect of Revlimid increases the activation and proliferation of various immune cells by facilitating interaction between antigen-presenting cells (APC) and T-cells. It also increases the expression of cytokines that control the proliferation, differentiation, and survival of various immune cells that release cytokines which further stimulates immune cell proliferation that activates T-cells and NK cells activity leading to increased activity against myeloma cells causing them to undergo apoptosis [11].

Cell Lines Effect: Studies from the literature shows that Revlimid has been examined on these human MM-cell lines such as MM.1S, INA-6, RPMI-8226, MM.1R, KMS12PE, and U266 individually or in combination with other drugs [6].

Letrozole: It is an oral non –steroidal aromatase inhibitor introduced for the adjuvant treatment of hormonally-responsive breast cancer [11].

Pharmacology: Aromatase inhibitors inhibit the action of the aromatase, an enzyme which converts androgens into estrogens by a process called aromatization to treat breast cancer [11].

Mode of Action: Aging declines the production of ovarian estrogen. Therefore, to convert adrenal

androgens to estrone and estradiol after post-menopause aromatase enzyme plays a significant role. Aromatase catalyzes the rate-limiting step in estrogen biosynthesis.

Letrozole is an enzyme inhibitor drug that inhibits the conversion of androgens to estrogens by competitive inhibition. Binding to the heme of the cytochrome P450 subunit of the aromatase enzyme results in the reduction of estrogen biosynthesis in all tissues. Women treated with letrozole significantly lowers serum estrone, estradiol, and estrone sulfate [11, 20, 31].

Cell Lines Effect: From literature, the study has shown that letrozole-treated cell lines are MCF-7, AC1, T47D [47].

Progression-Free Survival Analysis of Different Treatments:

TABLE 2: PROGRESSION FREE SURVIVAL STUDY AND STATUS OF TREATMENTS

S. no.	Treatment Used	Progression-Free Survival (PFS) [approx]	Status of treatment
1	Bortezomib	30.8 months	FDA approved and active clinical trials ongoing [38-39,46]
	Lenalidomide	14.8 months	
2	Palbociclib and Letrozole	24.8 months	FDA approved and active clinical trials ongoing [38-39,46]
	Letrozole only	16.8 months	
	Placebo and Letrozole	14.5 months	
3	PPC*	10.1 months (after 24 months)	FDA approved and active Clinical trials ongoing[18]
	PC*	4.9 months (after 24 months)	
	Chemotherapy	8.9 months (after 14.5 months)	
4	Rituximab with bendamustine	24 months	FDA approved and active clinical trials ongoing [2,38-39]
	R-CHOP* in phase II trial	9 months	
	Rituximab and GM-CSF*	16.5 months	
	Rituximab monotherapy	23.5 months	
	R-CHOP	10.3 months	
	CHOP*	10.3 months	
5	Placebo (First-line therapy) Age- <70	7.3 months	FDA approved and active clinical trials ongoing[38,39]
	Lenalidomide (First-line therapy)	52.5 months	
	Placebo (Second-line therapy) Age <70	32.7 months (after 71 months)	
	Lenalidomide (Second-line therapy)	52.5 months (after 71 months)	
6	PAN-BTZ-Dex*	12.3 months (Prior IMid) 10.6 months (Bortezomib plus Prior IMid) 12.5 months (Bortezomib and an IMid)	FDA approved and active (PANAROMA 1 trial)[37,39]
	Pbo-BTZ-Dex*	7.4 months (Prior IMid) 5.8 months (Bortezomib plus Prior IMid) 4.7 months (Bortezomib and an IMid)	
7	IRd*	20.6 months	FDA approved and active but not approved as maintenance therapy following autologous stem cell transplant (ASCT) [23-24,39]
	Rd*	14.7 months	
8	Avelumab	Under analysis	FDA approved and active (phase III JAVELIN)[39]
9	Venetoclax plus Obinutuzumab	67 % more after 29 months of median follow up	FDA approved and active [65]
10	Panitumumab plus FOLFOX4*	23.9 months	FDA approved and completed (phase III PRIME) [66-68]
11	Trastuzumab plus Paclitaxel or Docetaxel	Improved by 1.5 months	FDA approved (Phase 3)[69]
12	Polivy (polatuzumabvedotin-piiq) with bendamustine plus Rituxan®	Improved (no cancer detected)	FDA approved (phase Ib/II randomised study)

*PPC (Pembrolizumab, pemetrexed and carboplatin chemotherapy); *PC (Pemetrexed and Carboplatin), chemotherapy and Pembrolizumab; *R-CHOP (Rituximab Cyclophosphamide Hydroxydaunomycin Oncovin ® Prednisolone); *CHOP; GM-CSF (Granulocyte macrophage colony-stimulating factor); *Panobinostat plus bortezomib & dexamethasome (PAN-BTZ-Dex); *Placebo plus bortezomib & dexamethasone (Pbo-BTZ-Dex); *Ixazomib & Lenalidomide – dexamethasone (IRd); *Lenalidomide- dexamethasone (Rd); *Folinic acid, fluorouracil and oxaliplatin (FOLFOX)

DISCUSSION AND CONCLUSION: This review article concentrated on different cancer cell lines worked on with newly FDA approved anticancer drugs as therapy; antibody engineering, their efficacy as treatment followed by the status of the treatment.

Lately, an emerging technology antibody engineering holding the copious scope in the treatment of cancer providing new types of antibodies from the bench to the bedside by decreasing immunogenicity, transforming half-life, enhancing efficacy, and increasing tumor-targeting. The first segment of the paper has an accumulation of different cancer cell lines with their histotype, morphology in a tabular manner from various databases, cell line banks, followed by newly FDA approved engineered mAbs showing their effect on different anticancer drugs with their mode of action and pharmacology. Later in tabularly form, the progression-free survival (PFS) rate and the status of treatment of the anticancer drugs alone or combined with others.

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