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MONOCLONAL ANTIBODY: A MOLECULAR TARGETED THERAPIES FOR CANCER TREATMENT

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ABSTRACT

The systemic use of cytotoxic agents to disrupt mitosis in rapidly dividing cancer cells, with foreseeable dose-limiting haematological toxicities. Targeted therapies affect specific cellular molecular mechanisms promoting cancer cell survival and proliferation, enabling treatment tailored to specific tumour characteristics. The key pathways include the hormonal axis, growth factor receptor-mediated tyrosine kinases and cellular immune system. Monoclonal antibodies can target extracellular ligands or cell surface growth factor receptors. Tyrosine kinase inhibitors prevent signal transduction from the intracellular portion of the receptors. Monoclonal antibodies represent a major advance in treatment of acute lymphoblastic leukemia (ALL). Targeted delivery of these agents based on leukemic cell-surface receptor recognition, improves efficacy and minimizes off-target toxicity. The antigens CD19, CD20, CD22 and CD52, are the most common antigens to which monoclonal antibodies in B-cell ALL have been directed. This review will focus on mechanisms of action and clinical applications to monoclonal antibody therapy in the context of cancer.

KEYWORDS: Cancer, immunotherapy, Monoclonal antibodies, targeted therapy, tyrosine kinase inhibitors.

INTRODUCTION

Cancer can be defined as a disease in which a group of abnormal cells grow uncontrollably by disregarding the normal rules of cell division. Normal cells are constantly subject to signals that dictate whether the cell should divide, differentiate into another cell or die.[1]

Cancer cells develop a degree of autonomy from these signals, resulting in uncontrolled growth and proliferation. If this proliferation is allowed to continue and spread, it can be fatal. In fact, almost 90% of cancer-related deaths are due to tumour spreading a process called metastasis.[2] The concept of utilizing immunotherapy for the treatment of cancer has been enticing to researchers and clinicians for over a century. Cancer immunotherapy encompasses knowledge gained from a wide range of disciplines and has the potential to procure the 'magic bullet' for the treatment of cancer. The advent of hybridoma technology in 1975 and the development of chimeric, humanized, and human antibodies have increased the availability and utility of immunotherapy for the treatment of cancer [3] Currently, eleven antibodies are approved for use in oncology, nine of those occurring in the past decade.[4] By targeting tumors through specific or associated antigens, it is possible to selectively eliminate tumor cells and maintain an acceptable toxicity profile. Therapeutic antibodies that target immune cells are also being developed with the goal of breaking local tolerance and stimulating the patient's anti-tumor immune response. As with other treatment modalities, immunotherapy is far from perfect and requires additional study to optimize clinical response and overcome therapeutic resistance.

STRUCTURE

Antibodies, or immunoglobulins (Igs), exist in five separate forms denoted from differences in their constant region, which gives them unique properties and functions. They are IgA, IgD, IgE, IgG, and IgM, with IgG being the isotype most commonly used in cancer immunotherapy. Antibodies have two antigen binding fragments (Fabs) and one constant fragment (Fc). The Fab confers antigen specificity via complementarity determining regions (CDRs) while the Fc domain connects IgG antibodies to immune effector mechanisms by engaging Fc_ receptors (Fc_Rs) on natural killer (NK) cells, neutrophils, monocytes, dendritic cells (DCs) and eosinophils.[5] The Fc region also binds neonatal Fc receptors (FcRns), which is thought to protect circulating antibodies from degradation.[6]

Table 1: Classification of Therapeutic Antibodies Based on Their Function.

Action	Antibody Target
Tumor cell killing	CD2, CD3[a], CD4, CD25[a], CD30[a], CD52[a], CCR4[a], KIR3DL2
T-cell activation	PD-1[a], PD-L1[a], CTLA-4[a], CD137, OX40
Tumor microenvironment	CD25[a], PD-1[a], PD-L1[a], CD137, OX40, STAT3
Immune priming	CD40, CD137

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen; KIR3DL2, killer cell immunoglobulin-like receptor 3DL2; PD-1, programmed death-1. In clinical practice.

Immune Checkpoint Targets (Immunotherapy)

- Tumours evade recognition and destruction by the immune system (immunosurveillance) through several immune inhibition mechanisms.
- The monoclonal antibodies ipilimumab (against CTLA-4) and nivolumab (against PD-1) block two distinct pathways of T cell inhibition. This up-regulates the immune response and allows the recognition and destruction of tumour cells.
- Ipilimumab and nivolumab have demonstrable efficacy in both malignant melanoma and lung cancer.[7]

Monoclonal Antibodies

Monoclonal antibodies utilize the specificity of the fragment antigen-binding region of the antibody to target specific therapeutic epitopes. Modern antibodies are either chimeric mouse ehuman or fully human, with the latter felt to be less immunogenic.[8] They target either extracellular ligands (the compounds that activate the receptor), for example bevacizumab on vascular endothelial growth factor (VEGF), or the cell surface receptors themselves, for instance cetuximab on EGFR. Bevacizumab and cetuximab have demonstrated efficacy in colorectal cancers.[8] Similarly to chemotherapy, they are usually delivered by intravenous infusion.

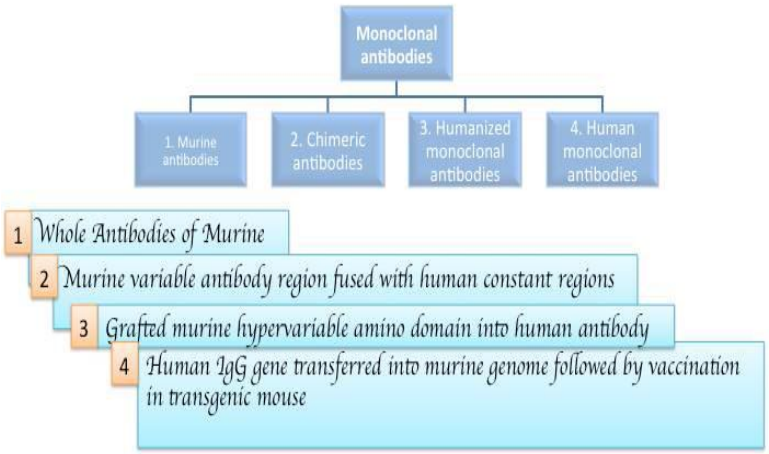

Figure 1: Types of therapeutic Monoclonal antibodies and their production methods.

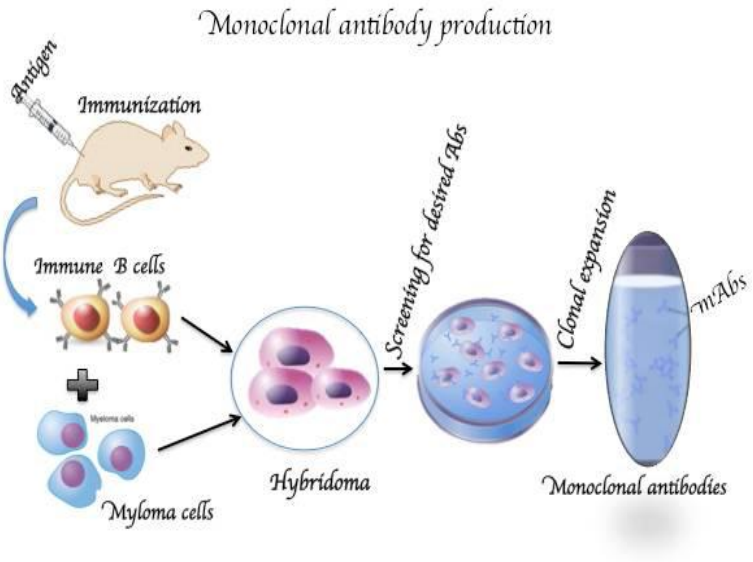

Figure 2: Steps involved in the production of Monoclonal antibodies (MAbs).

Antibody Drug Conjugates

Antibody drug conjugates combine a monoclonal antibody with a cytotoxic to deliver the cytotoxic directly to the targeted cells. The antibody targets and binds to a specific extracellular receptor, leading to internalization of the complex, thus delivering the cytotoxic payload only to those cells expressing the targeted receptor. TDM-1 is a conjugate of trastuzumab and the cytotoxic emtansine and has been shown to improve survival in patients with metastatic human epidermal growth factor 2 receptor (HER2) positive breast cancer.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are monoclonal antibodies that target key regulatory points in the cellular immune system such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1 (PD-1). As with growth factor-targeting antibodies, they target either the receptor (e.g. the anti-CTLA-4 monoclonal antibody ipilimumab or the anti-PD-1 antibody nivolumab) or the ligand (e.g. programmed cell death ligand 1 (PD-L1)). They facilitate immune recognition and destruction of cancer cells, and have proven efficacy in malignant melanoma and NSCLC.[9]

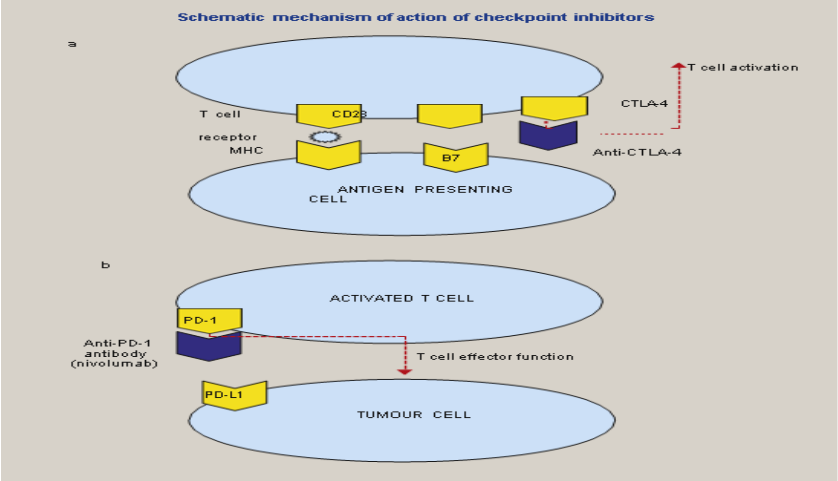

Figure 3(a): During antigen presentation and T cell activation, the expression of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) causes an immune-inhibitory response. The anti-CTLA-4 antibody blocks this pathway, enhancing anti-tumour T-Cell activation and proliferation. (b) The interaction of the programmed death-1 (PD-1) on the surface of activated T cells with the ligand (PD-L1) on the surface of tumour cells causes an immune inhibitory response. Anti-PD-1 antibodies such as nivolumab block this interaction, enhancing anti- tumour T cell survival and effector function. MHC, major histocom- patibility complex.

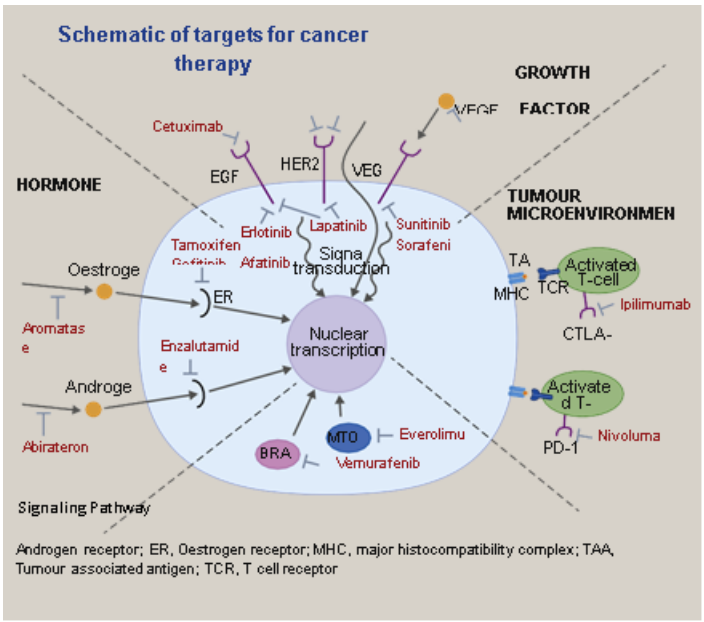

Figure 4: Hormone therapies target ligand synthesis or intracellular hormone receptors. Growth factor targets include; ligands e.g. Bevacizumab, growth factor receptors e.g. Traztuzumab, and tyrosine kinases e.g. Erlotinib. Specific enzyme inhibitors target cell signalling pathways e.g. Vemurafenib and BRAF. Immune checkpoint inhibitors target tumour micro-environment by enhancing T-cell mediated immune response via MHC.

MOLECULAR TARGETED THERAPY IN ANTICANCER

Researchers have developed anticancer drugs with a higher precision of molecular targeting. The cellular targets are genetically altered in cancer cells and are essential to tumor development and survival. Oncoprotein or oncogenes targets, which are mainly involved in various signaling pathways, are primarily products of gene fusions, obtained or functional mutations or over expressed oncogenes.

Molecular Targeted Therapy For Human Epidermal Receptor 2 (HER2) Positive Breast Cancer

Apart from lung cancer, death rate of breast cancer among women in the world is higher than that of other cancers. Human epidermal receptor 2 (HER2) positive breast cancer (HER2+ BC) belongs to a subtype of breast cancer with HER2 gene amplification and HER2 protein overexpression, and accounts for about 25% of all breast cancers.[10] HER2-containing heterodimers are capable of activating both of the key signaling pathways: the cell proliferative RAS/Raf/MAPK pathway and the cell survival PI3K/Akt pathway.[11] HER2 is an ideal target for developing therapeutic strategies for the treatment of HER2+ BC. Breast cancers are divided into four subtypes: luminal A (Estrogen Receptor (ER)+, Progestogen Receptor (PR)+, HER2 and Ki67 (which is a proliferation marker) <14%), luminal B (ER+, PR+, HER2 and Ki67 _14% or ER+, PR+, HER2+), HER2 positive breast cancer (HER2+, ER and PR) and basal-like (ER, PR and HER2).[12] Due to these complex subtypes, it is a challenge to diagnose and cure different molecular subtypes of breast cancers. For the treatment of HER2+ BC, HER2 targeted therapeutic methods are divided into monoclonal antibodies, small molecule tyrosine kinase inhibitors (TKIs), antibody–drug conjugates (ADC) and other anti-HER2 agents. Trastuzumab (Herceptin, Genetech) and pertuzumab (Perjeta, Genetech) are the first FDA approved monoclonal antibody agents that are specific for tyrosine kinase. Lapatinib (Tykerb, GlaxoSmithKline) is the second FDA approved HER2 targeted agent, which is a small molecule TKIs. Neratinib (HKI-272, Puma Biotechnology) and Afatinib (BIBW-2992, Boehringer Ingelheim) are another two dual TKIs. Trastuzumab–emtansine (T-DM1, Genetech) is an antibody drug conjugate combining an anti-microtubule cytotoxic chemical agent with trastuzumab.

Molecular Targeted Therapy For Vascular Endothelial Growth Factor Receptor (VEGFR) In Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths accounting for approximately 80% of primary liver cancer cases and usually develops as a consequence of underlying liver disease. The majority of HCC is diagnosed at an advanced stage of disease and is not a candidate for surgical interventions. VEGF is the primary stimulus for tumor angiogenesis and an endogenous cytokine that induces capillary endothelial cell proliferation. VEGF binds to vascular endothelial growth factor receptor (VEGFR) and promotes cell proliferation and angiogenesis by activating the MAPK pathway (also known as Ras/Raf/MEK/ERK pathway). FGF2 is a potent angiogenic factor in HCC and can augment VEGF-mediated HCC angiogenesis. It may evade resistance to VEGFR modulating agents.[13] Sorafenib (Nexavar; Whippany, NJ), the only approved agent, is the inhibitor of platelet-derived growth factor receptor (PDGFR) and VEGFR.[14] It was showed to be the first effective antiangiogenic therapy for advanced RCC and HCC. Sorafenib induces tumor cell proliferation and tumor angiogenesis by inhibiting the Raf/MEK/ extracellular signal-regulated kinase pathway. It also inhibits intracellular Raf kinase (Raf-1) to target the MAPK signal transduction pathway. Dovitinib is a potent inhibitor of VEGFRs, FGFRs, and PDGFRb, which are related to antitumor activity such as antiproliferative and antiangiogenic effects. Preliminary efficacy for dovitinib has been also reported in patients with metastatic melanoma, metastatic RCC, breast cancer, and acute myeloid leukemia. Cheng AL *et al.* demonstrated antitumor activity of dovitinib was superior to that of sorafenib and antiangiogenic effects that correlated with FGFR, PDGFRb, and VEGFR2 signaling pathway activation.

Molecular Targeted Therapy For VEGF and mTOR Pathway in Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the seventh most common cancer in men and the ninth most common in women and accounts for 2–3% of all malignant diseases in adults. In the treatment of patients with RCC, partial nephrectomy for small tumors and radical nephrectomy for large tumors were the gold-standard treatments. The standard of care for RCC has evolved rapidly with the approval of six targeted therapies by the US FDA and European Medicines Agency since 2006. One of most important treatments is aimed to block the activity of vascular endothelial growth factor (VEGF), which is also a major tumor growth factor for RCC. The TKIs (sorafenib, sunitinib, and pazopanib) and anti-VEGF antibody bevacizumab are commonly used drugs that have a direct effect on the VEGF

pathway. mTOR inhibitors (Temsirolimus and everolimus) are also used in clinic.[15] Regulation of the activation of the mammalian target of rapamycin (mTOR) pathway was mediated through a series of complex signaling interactions that linked growth factor receptor signaling (e.g. activation of the Akt/protein kinase-B pathway and phosphoinositide-3 kinase activation). Temsirolimus showed anti-tumor activity in a phase II trial in patients with treatmentrefractory metastatic RCC that seemed pronounced in a retrospective analysis of a poor-risk subset of patients. VEGF and mTOR pathways have been established to be the relevant therapeutic targets based on the underlying molecular biology of RCC.[16] Sunitinib-treated patients had a longer median overall survival for interferon-treated patients. Of note, several patients who were randomly assigned to interferon received sunitinib or other active targeted treatment, or both, on disease progression, probably under powering this trial to detect a difference in overall survival. The very high median numbers noted for overall survival in this trial in comparison with historical controls support that targeted treatment has extended the lives of patients with metastatic RCC. Sunitinib has emerged as a front-line standard of care in metastatic RCC.[17]

Oncogenic Mutant Epidermal Growth Factor Receptor (EGFR)

Oncogenic mutations in epidermal growth factor receptor (EGFR) are frequently found in non-small cell lung cancer (NSCLC) patients, justifying the clinical testing of the first generation anti-EGFR tyrosine kinase inhibitors (TKIs) named gefitinib and erlotinib. However, despite showing an initial response, up to 70% of EGFR mutant NSCLC patients develop resistance. Better EGFR inhibitors that are irreversible and more selective have been developed[18], but even with these new treatments disease progression always occurred that was associated with drug resistance and increased genomic instability. In addition to the *EGFR* T790M mutation (found in 50% of treated patients), several resistance mechanisms have been identified, including acquired RTK *MET* gene amplification (20%) and *PIK3CA* mutations (5%).[19] These resistance mechanisms share the same underlying concept: they enable the cancer cell to maintain its intracellular growth signaling pathways, including the PI3K/Akt pathway, in the presence of the EGFR TKI. In this context, combination therapies are currently being tested. In lung cancers, PIK3CA mutations are not oncogenic drivers and are frequently identified concurrently with KRAS or EGFR mutations.[20] The relevance of oncogenic mutation of PIK3CA as a predictive marker of response to TKIs was investigated. Although a clinical retrospective study demonstrated that concurrent PIK3CA mutation in NSCLC patients with EGFR-mutant (or KRAS-mutant) is a poor prognosis factor, the clinical outcome of TKI therapy

targeting EGFR was not affected by the presence of PIK3CA mutations[21], in contrast to in vitro results.[22,23] In a Phase I study combining the pan-PI3K inhibitor XL147 (pilaralisib) with the EGFR-TKI erlotinib in solid tumors, safety profiles were manageable, while clinical results were disappointing.[24] In this study, however, only one patient harbored an EGFR mutation, and only three of 29 patients had PIK3CA amplification or mutation, and thus a lack of dependence on the PI3K pathway could have biased the result. Given the limited size of the patient cohorts studied, further studies will be necessary to identify better markers of sensitivity to the combination of anti-EGFR TKIs and PI3K inhibitors.

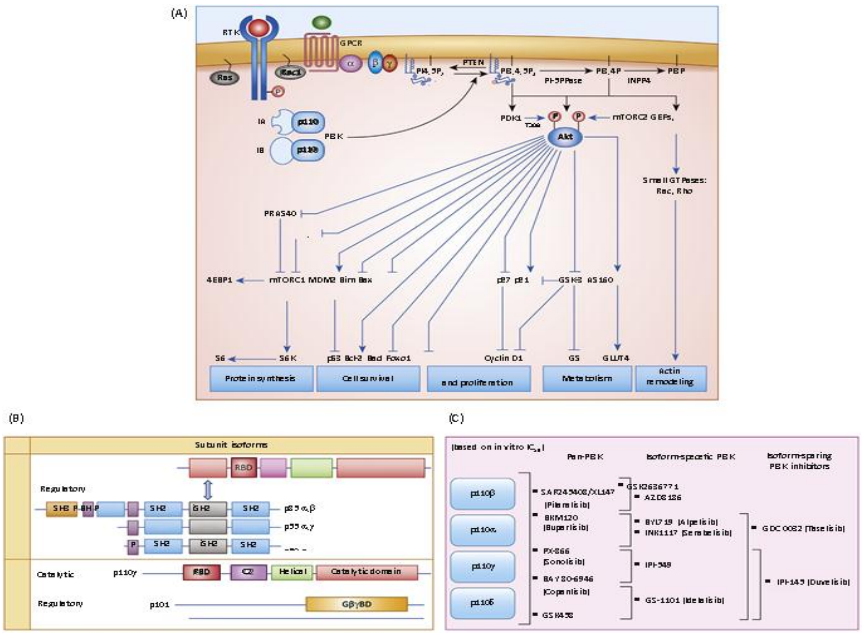

Figure 5: The PI3K Pathway in Cancer. (A) Phosphatidylinositol-3-kinase (PI3K) upstream activators, downstream effectors, and associated functions. Class I PI3Ks are activated by recruitment to the plasma membrane through phosphorylated tyrosines in receptor tyrosine kinases (RTKs), direct binding to small GTPases such as Ras and Rac1, or to free dimeric Gbg upon G protein-coupled receptor (GPCR) activation. [25,26] When PI3Ks are activated by upstream signals, PI3,4,5P_3 (PIP_3) is generated from PI4,5P_2 (PIP_2), and this recruits and activates several effectors at the plasma membrane, including the serine/threonine kinase Akt, leading to its subsequent activation (pAkt). Akt controls cell properties partly through the indirect phosphorylation of multiple protein targets including mTOR and ribosomal protein S6 (pS6). The tumor-suppressor PTEN converts PIP_3 back to PIP_2. (B) Subunit isoforms of class I PI3K. There are four well-described heterodimeric class I PI3K isoforms (a, b, d, and g). PI3Ka and PI3Kb are ubiquitously expressed, whereas PI3Kd and PI3Kg are preferentially expressed in

leucocytes or the vascular system. They are composed of a regulatory subunit (p85 or p101/87) and a catalytic subunit (p110a, b, d, and g encoded by PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively). (C) Preclinical names of pan-PI3K inhibitors and isoform-specific PI3K inhibitors used in the clinic and their generic names. Oral pan-PI3K inhibitors aim to target the catalytic subunits of all isoforms of class I PI3K at close to the inhibitory concentration (IC_{50}); so-called isoform-selective PI3K inhibitors usually present a significantly lower IC_{50} for one of the four isoforms (by at least a factor of 100), with selectivity generally being demonstrated in cell culture.

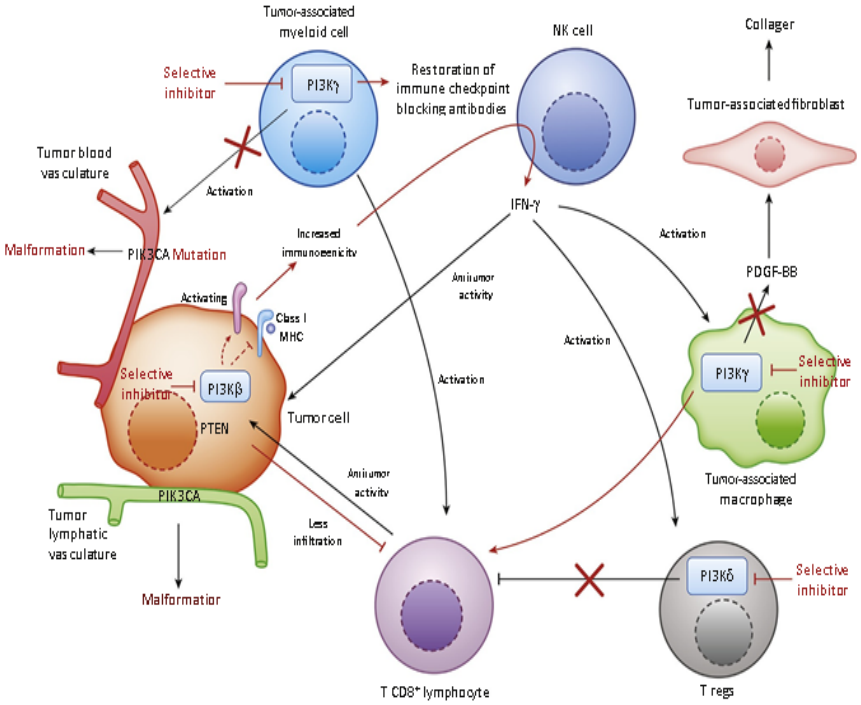

Figure 6: Targets of PI3K Inhibitors in the Tumor Stroma: Certainties and Speculation. In hematologic malignancies, PI3K*b* inhibition is associated with upregulation of activating ligands and downregulation of MHC class I in tumor cells, leading to a strong natural killer (NK) interferon-*g* response which increases tumor cell susceptibility to NK-mediated lysis.[27] *PTEN* inactivation in melanoma results in PI3K hyperactivity and decreases cytotoxic $CD8^+$ T cell infiltration, reducing antitumor immunity.[28] PI3K*d* inhibition in regulatory T cells (T regs) disrupts their suppressive function and enables $CD8^+$ T cells to successfully attack tumors.[29] Similarly, PI3K*g* blockade in oncogenic Kras-driven pancreatic tumors reprograms tumor-associated macrophages (TAMs) to stimulate $CD8^+$ T cell-mediated tumor suppression, and inhibits the PDGF-BB secretion in TAMs, resulting in reduced collagen secretion by tumor-associated fibroblasts (TAFs) that is potentially responsible for reduced fibrosis in tumors.[30] Pharmacologic or genetic

inactivation of PI3K*g* in tumor-associated myeloid cells is responsible for inhibition of angiogenesis[31], restores sensitivity to immune checkpoint blocking antibodies, and promotes $CD8^+$ T cell-mediated tumor suppression.[32] Mutations in *PIK3CA* are responsible for malformations of tumor blood and lymphatic vasculatures, suggesting potential effects of PI3K*a* selective inhibitors on these compartments.[33–36] The action of PI3K-targeting drugs could be potentially extended to all cellular compartments in the tumor involved in the regulation of its progression, dissemination, and metabolism, including TAFs, adipocytes, and mesenchymal stem cells.

Table 2: Phase-I Clinical Trials Targeting PI3K.[37-42]

References	Number of patients	Toxicity		Pharmacodynamic biomarkers	Predictive biomarkers
		Grade 3/4	All grades		
Shapiro *et al.* [37] XL 147	69	13% -Rash -Diarrhea	63.80% -Skin toxicity (26%) -Nausea/diarrhea (20%) -Decreased appetite (11.6%) -Hyperglycemia (7.2%)	Tumor and skin biopsies: -Partial reduction of PI3K pathway in all tumors (9/9 by IHC) was more potent than in the skin; and partial reduction of the MEK pathway -Modest action on tumor cell proliferation, no effect on tumor cell apoptosis	Tumor tissue -*PIK3CA* mutation: no correlation -*PTEN* alteration by IHC: no correlation
Rodon *et al* [38] BKM120	83	39.80% -Rash (7.2%) -Hyperglycemia (8.4%) -Diarrhea (3.6%), -Asthenia (3.6%)	92.80% -Nausea and diarrhea (32.5%) -Decreased appetite (32.5%) -Hyperglycemia (31.3%) -Rash (28.9%)	Tumor and skin biopsies: -pAKT, pS6, and p4EBP1: partial reduction (IHC) FDG-PET: dose-dependent decrease in FDG-tracer uptake at day 28 of cycle 1. No correlation with clinical response	Tumor tissue -*PIK3CA* mutation: no correlation -Loss of PTEN expression by IHC: no correlation -*KRAS* mutation: no correlation
Hong *et al.*[39] PX-866	84	12–15% -Asthenia -	76.20% -Diarrhea (48.8%)	Platelets (n = 10 patients) -Decreased	Tumor tissue -*PIK3CA*

		Vomiting/diarrhea -Elevated AST	-Nausea (38.1%) vomiting (25%) -Asthenia (16.7%)	pAKT/total AKT ratio No correlation with adverse events or clinical response	mutation: no correlation -*KRAS* mutation: no correlation
Sarker *et al.* [40] GDC-0941	60	15% -Rash -Diarrhea	76.70% -Nausea (28%) and vomiting (15%) -Diarrhea (19%) -Rash (14%)	Platelet-rich plasma (Luminex): -pAKT: dose- and concentration-dependent decrease Tumor biopsy: -Decrease of pS6 and pAkt (IHC) FDG PET: decrease of FDG-tracer uptake. No correlation with clinical response	ctDNA -*PIK3CA* mutation in ctDNA Tumor tissue -*PIK3CA* amplification (FISH) and PTEN status IHC: no correlation
Munster *et al.* [41] GSK 458	170	NA -Diarrhea (8%) -Hyperglycemia (6%) -Skin rash (5%)	100% -Asthenia (45%) -Diarrhea (45%) and nausea (42%) -Decreased appetite (30%) Vomiting (26%)	Tumor biopsy: -pAKT, pERK, p70s6K (IHC). No correlation with dose or *PIK3CA* mutation status FDG-PET: decreased FDG-tracer uptake. No correlation with clinical response Glucose and insulin	Tumor tissue -*PIK3CA* mutation: no correlation
Blagden *et al.* [42] CH5132799	38	NA -Diarrhea (10%) -Hyperglycemia (13%) -Elevated transaminases	NA -Diarrhea (34%) -Nausea (32%) -Stomatitis (29%) -Fatigue (29%) -Rash (24%)	Platelet-rich plasma (Luminex): -pAkt: dose-dependent decrease Tumor biopsy: pAkt decreased >50% in two of three patients FDG-PET: Decreased FDG tracer uptake	Tumor tissue -*PIK3CA*, *KRAS*, *BRAF* mutations

Therapeutic applications of Monoclonal antibodies (MAbs)

Recent advances in genetic engineering have made possible efforts to improve the therapeutic application of mAbs by identifying new targets with improved efficacy for use in clinical practice.[43] Their use in immunoprophylaxis or immunotherapeutics have been extensively applied to infectious diseases, as carriers for toxic substances delivery to tumors or as tools

for identifying, locating and target neoplasms.[44] They have also been used in the treatment of several types of cancers, immune diseases, arthritis and metabolic diseases. Their therapeutic applications include cancer therapy, human and animal disease therapy, preparation of vaccines, suppression of immune response and purification of hormones.[45]

CONCLUSION

Monoclonal antibody therapy has revolutionized the treatment of cancer and will continue to be an important treatment modality for cancer in the decades to come. Clinical success of antibody therapy is dependent on understanding the effects of antibody therapy on tumor biology and the anti-cancer immune response. monoclonal antibodies, the strongest growth therapeutics in the pharmaceutical industry and marketing, increasingly enter to different stages of clinical trials as alone entities or in combination with other therapies (e.g., traditional cytotoxic chemotherapy, radiation therapy, other antibodies, vaccines and biologic agents). This review has summarized the strides made over the past 25 years for developing new, selective, therapeutic strategies based on the evolution of various antibody forms and an identification of new cellular targets. Molecular biology has been at the basis of developing this new generation of antigen-binding molecules. As new target molecules and receptors on tumor cells are identified in the future, the experiences gained with the use of current immunoconjugates will enable a more rapid translation to clinical evaluation and use when next-generation antibodies and immunoconjugates are developed.

REFERENCES

1. Hanahan, D and Weinberg, RA Hallmarks of cancer. Cell, 2000; 100: 57–70.
2. Alison, MA (2001) Cancer. www.els.net (introductory article).
3. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science, 2011; 331: 1565–70.
4. Reichert JM. Antibody-based therapeutics to watch in 2011. MAbs, 2011; 3: 76–99.
5. Weiner LM, Surana R, Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. Nat Rev Immunol, 2010; 10: 317–27.
6. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol, 2007; 7: 715–25.
7. Tobias J, Hochhauser D, eds. Cancer and its management. Chichester West Sussex, England: Wiley-Blackwell, 2010; 77e106. Chapter 6, Systemic treatment for cancer.
8. Weiner G. Building better monoclonal antibody-based therapeu- tics. Nat Rev Cancer,

2015; 15: 361e70.

9. Shin DS, Ribas A. The evolution of checkpoint blockade as a cancer therapy: what's here, what's next? Curr Opin Immunol, 2015; 33: 23e35.
10. Wahler J, Suh N. Targeting HER2 positive breast cancer with chemopreventive agents. Curr Pharmacol Rep., 2015; 1: 324–335.
11. Ménard S, Pupa SM, Campiglio M, Tagliabue E. Biologic and therapeutic role of HER2 in cancer. Oncogene., 2003; 22: 6570–6578.
12. Orphanos G, Kountourakis P. Targeting the HER2 receptor in metastatic breast cancer. Hematol Oncol Stem Cell Ther., 2012; 5: 127–137.
13. Antoniou EA, Koutsounas I, Damaskos C, Koutsounas S. Remission of psoriasis in a patient with hepatocellular carcinoma treated with sorafenib. In Vivo., 2016; 30: 677–680.
14. Cheng AL, Thongprasert S, Lim HY, et al. Randomized, open-label phase 2 study comparing frontline dovitinib versus sorafenib in patients with advanced hepatocellular carcinoma. Hepatology., 2016; 64: 774–784.
15. Négrier S, Gravis G, Pérol D, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol., 2011; 12: 673–680.
16. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet., 2009; 373: 1119–1132.
17. Afriansyah A, Hamid AR, Mochtar CA, Umbas R. Targeted therapy for metastatic renal cell carcinoma. Acta Med Indones. 2016; 48: 335–347.
18. Juchum, M. et al. Fighting cancer drug resistance: oppor- tunities and challenges for mutation-specific EGFR inhibitors. Drug Resist. Updat. 2015; 20: 12–28.
19. Sequist, L.V. et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci. Transl. Med. 2011; 3: 75ra26.
20. Chaft, J.E. et al. Coexistence of PIK3CA and other oncogene mutations in lung adenocarcinoma-rationale for comprehensive mutation profiling. Mol. Cancer Ther., 2012; 11: 485–491.
21. Eng, J. et al. Impact of concurrent PIK3CA mutations on response to EGFR tyrosine kinase inhibition in EGFR-mutant lung cancers and on prognosis in oncogene-driven lung adeno- carcinomas. J. Thorac. Oncol., 2015; 10: 1713–1719.
22. Engelman, J.A. et al. Allelic dilution obscures detection of a biologically significant resistance mutation in EGFR-amplified lung cancer. J. Clin. Invest., 2006; 116: 2695–2706.

23. Ihle, N.T. et al. The phosphatidylinositol-3-kinase inhibitor PX-866 overcomes resistance to the epidermal growth factor receptor inhibitor gefitinib in A-549 human non-small cell lung cancer xenografts. Mol. Cancer Ther., 2005; 4: 1349–1357.
24. Soria, J.-C. et al. Phase I dose-escalation study of pilaralisib (SAR245408, XL147), a pan-class I PI3K inhibitor, in combination with erlotinib in patients with solid tumors. Oncologist, 2015; 20: 245–246.
25. Baer, R. et al. Pancreatic cell plasticity and cancer initia- tion induced by oncogenic Kras is completely dependent on wild-type PI 3-kinase p110a. Genes Dev. 2014; 28: 2621–2635.
26. Guillermet-Guibert, J. The p110beta isoform of phos- phoinositide 3-kinase signals downstream of G protein-coupled receptors and is functionally redundant with p110gamma. Proc. Natl. Acad. Sci. U. S. A. 2008; 105: 8292–8297.
27. Bommarito, D. et al. Enhancement of tumor cell suscep- tibility to natural killer cell activity through inhibition of the PI3K signaling pathway. Cancer Immunol. Immunother., 2016; 65: 355–366.
28. Peng, W. et al. Loss of PTEN promotes resistance to T cell-mediated immunotherapy. Cancer Discov. 2016; 6: 202–216.
29. Ali, K. et al. Inactivation of PI(3)K p110d breaks regulatory T-cell-mediated immune tolerance to cancer. Nature, 2014; 510: 407–411.
30. Kaneda, M.M. et al. Macrophage PI3Kg drives pancreatic ductal adenocarcinoma progression. Cancer Discov. 2016; 6: 870–885.
31. Schmid, M.C. et al. Receptor tyrosine kinases and TLR/IL1Rs unexpectedly activate myeloid cell PI3kg, a single convergent point promoting tumor inflammation and progres- sion. Cancer Cell, 2011; 19: 715–727.
32. De Henau, O. et al. Overcoming resistance to checkpoint blockade therapy by targeting PI3Kg in myeloid cells. Nature 2016; 539: 443–447.
33. Castillo, S.D. et al. Somatic activating mutations in Pik3ca cause sporadic venous malformations in mice and humans. Sci. Transl. Med., 2016; 8: 332ra43.
34. Limaye, N. et al. Somatic activating PIK3CA mutations cause venous malformation. Am. J. Hum. Genet., 2015; 97: 914–921.
35. Boscolo, E. et al. AKT hyper-phosphorylation associated with PI3K mutations in lymphatic endothelial cells from a patient with lymphatic malformation. Angiogenesis, 2015; 18: 151–162.
36. Castel, P. et al. Somatic PIK3CA mutations as a driver of sporadic venous malformations.

Sci. Transl. Med. 2016; 8: 332ra42.

37. Shapiro, G.I. et al. Phase I safety, pharmacokinetic, and pharmacodynamic study of SAR245408 (XL147), an oral pan- class I PI3K inhibitor, in patients with advanced solid tumors. Clin. Cancer Res., 2014; 20: 233–245
38. Rodon, J. et al. (2014) Phase I dose-escalation and -expansion study of buparlisib (BKM120), an oral pan-class I PI3K inhibitor, in patients with advanced solid tumors. Invest. New Drugs, 2014; 32: 670–681.
39. Hong, D.S. et al. A multicenter phase I trial of PX-866, an oral irreversible phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors. Clin. Cancer Res., 2012; 18: 4173–4182.
40. Sarker, D. et al. First-in-human phase I study of pictilisib (GDC-0941), a potent pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, in patients with advanced solid tumors. Clin. Cancer Res., 2015; 21: 77–86.
41. Munster, P. et al. First-in-human Phase I study of GSK2126458, an oral pan-class I phosphatidylinositol-3-kinase inhibitor, in patients with advanced solid tumor malignancies. Clin. Cancer Res., 2016; 22: 1932–1939.
42. Blagden, S. et al. First-in-human study of CH5132799, an oral class I PI3K inhibitor, studying toxicity, pharmacokinetics, and pharmacodynamics, in patients with metastatic cancer. Am. Assoc. Cancer Res., 2014; 20: 5908–5917.
43. Xiong W, Huang W, Jiao Y, Ma J, Yu M, Ma M, Wu H, Tan D. Production, purification and characterization of mouse monoclonal antibodies against human mitochondrial transcription termination factor 2 (MTERF2). Protein Expr Purif, 2012; 82(1): 11–19.
44. Mumaw MM, de la Fuente M, Arachiche A, Wahl JK, Nieman MT. Development and characterization of monoclonal antibodies against Protease Activated Receptor 4 (PAR4). Thromb Res, 2015; 135(6): 1165– 1171.
45. Liu JKH, The history of monoclonal antibody development – Progress, remaining challenges and future innovations. Ann Med Surg, 2014; 3(4): 113–116.