Original Article

Recent advances in Monoclonal antibodies based formulation used in the management of CRC

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Abstract

One of the most frequent malignancies in the world is colorectal cancer (CRC), killing millions of people each year. Many therapeutic antibodies have been developed as key sources of blockbuster medications for colorectal cancer therapy as a result of recent developments in recombinant DNA technology. In last 20 years, mab-based cancer treatments have been the most successful therapeutic method for both solid tumors and hematologic malignancies. Moreover, we examine the present state of monoclonal antibodies in clinical development and FDA approval for colorectal cancer therapy. These antibodies are used in drug targeting delivery and recognition of cancer cells specifically. Among all the monoclonal antibodies used for colorectal cancer bevacizumab, cetuximab, and panitumumab are used prominently as compared to others like ramucirumab, onartuzumab, nivolumab, and ipilimumab. In this article, we studied a different type of formulation used in colorectal cancer based on monoclonal antibodies. Mainly used formulations are nanoparticles, nanotubes, immunoliposomes, micelles, alginate beds, hydrogels, nano micelles, nanocages, and liposomes. Among all these formulations, nanoparticles conjugated with antibodies show the targeted release, best penetration efficacy, compatibility, stability, and enhance the activity of a drug.

Keywords: monoclonal antibody, cetuximab, panitumumab, colorectal cancer, bevacizumab.

INTRODUCTION

Colorectal cancer cases increases rapidly over the past few years, according to a survey in 2012, It is the 2nd most frequent cancer in women (0.61 million cases per year) and the 3rd most frequent cancer in men (0.74 million cases per year) in the world, as well as one of the leading causes of cancer deaths (Boelens et al., 2016). In 2020, these are increases to about 1.93 million cases per year and 0.94 million caused deaths (Xi & Xu, 2021). In 2040, these cases were around 3.1 million and the death rate also increased. These cases are mainly increasing with age and their incidence is much in men as compared to women.

Cancer is a disease derived from the abnormal growth of cells if this growth is occur in the colon and rectum, it is called CRC (colorectal cancer). These colons are divided into ascending, descending, sigmoid and transverse colons (Cancer & Test, 2022). This cancer is mainly arising from the epithelial cells of the colon and rectum in the GIT(gastrointestinal tract) (Boelens et al., 2016),(Tsumoto et al., 2019),(Maleki et al., 2013).

The main symptoms of colorectal cancer are cramping pain, dark and black stool, decreased appetite, change in bowel habits, discomfort in the lower abdomen, blood in the stool, and bleeding from the rectum (Koo et al., 2019).

Causes of colorectal cancer/ risk factors (Haggar & Boushey, 2009)

- High-fat diet which contains meat or red meat
- History of Adenomatous Polyps
- Heavy alcohol use

- Tobacco intake
- Family history
- Smoking
- Physical Activity and Obesity
- Nutritional Practices
- History of polyps or cancer
- Age
- Genetic syndromes
- History of Inflammatory Bowel Disease(IBD)

Treatment for cancer

There are many treatments for cancer that mainly depend on cancer types such as breast, colon, skin, and many other cancers. Many patients used single therapy, and many patients are treated by combination therapy such as radiation therapy and surgery, chemotherapy and surgery, etc. In all treatments of cancer, a monoclonal antibody is best because as compared to others their side effects are less, easily targeted and patient compliance. The various types of cancer treatments (Kaur et al., 2020),(Saini et al., 2020).

- Stem cell transplant
- Hormone therapy
- Surgery
- Radiation therapy
- Chemotherapy
- Immunotherapy
- Monoclonal antibody

Stem cell transplant

In this treatment, a cancer patient's blood-forming stem cells are restored after being damaged by severe doses of radiation or chemotherapy. The stem cells are generated in a variety of blood cells that are required for good health. The most common blood cells are:

Red blood cells (RBCs): transport oxygen throughout the body.

WBC (White Blood Cells): White blood cells are part of the immune system and assist the body fight infection.

Platelets: aid in the coagulation of blood (Wicha et al., 2006),(Seo et al., 2007),(Mimeault et al., 2007).

Hormone therapy

This therapy uses hormones to block and reduce the progression of malignancies like prostate and breast cancer (Shook, 2011).

Surgery

To stop or limit the growth of the disease and eliminate cancer from the body, the surgeon may remove lymph nodes.

Radiation therapy

In this treatment of cancer, High doses of radiation are used in this therapy to treat cancer by shrinking tumors and killing cancer cells (Luqmani, 2005),(Formenti & Demaria, 2013),(Boeckman et al., 2005).

Chemotherapy

Chemicals are used in this therapy to treat cancer by killing cancer cells and shrinking tumors, but they have severe side effects (Paul & Sa, 2021),(Zhang et al., 2010).

Immunotherapy

Medication or other treatments are used to boost the immune system in this therapy. Treatment with adoptive cells and checkpoint inhibitors is an example (Sambi et al., 2019).

In all treatments of cancer, we used monoclonal antibodies treatment for cancer in this article due to their targeted drug delivery, site-specific action, enhanced safety, lower toxicity, and many other effects also.

Monoclonal antibody

Monoclonal antibodies were first produced by Kohler and Milstein in 1975 for both laboratory and clinical immunology (Academic et al., 1998). Monoclonal antibody-based cancer treatment is now the most effective treatment option for both hematologic and solid tumour cancers. Due to this, these are used in huge amounts for cancer treatment and their success rate is increasing day by day (Scott et al., 2012). Antibodies or antibody receptors are y-shaped proteins produced by the immune system in millions. Each antibody is searching for a specific antigen on the surface of a foreign cell. When an antibody recognizes a sick cell, it binds to the antigen and aids the immune system in killing it.

The major side effect of monoclonal antibodies is redness, trouble breathing, needle site skin reactions, sinus congestion, heart palpitations, and risk of infection, soreness, pain, swelling, and chills.

Monoclonal antibodies are mainly used due to

- Targeted drug delivery
- Site-specific
- Reduces deaths and hospitalization
- Treat and prevent many infections caused by viruses or bacteria
- Enhanced safety and lower toxicity
- Compared to chemotherapy reduce side effects
- Improved patient survival

Global market of Monoclonal Antibody

MAB market rates are predicted to rise from $45.50 billion in 2020 to $49.90 billion in 2021, representing a 9.4% compound annual growth rate (CAGR). At a compound annual growth rate of 9%, market rates are estimated to reach $69.89 billion in 2025. The market rates are expected to reach $69.89 billion in 2025 at a compound annual growth rate of 9%. Major companies that play an important role in the market of MABs are Eli Lilly Company, Bristol Myers Company, GlaxoSmithKline, Johnson & Johnson, F. Hoffmann-La Roche Ltd, Novartis AG, and Amgen, Merck & Co., Genmab AS, and Spectrum Pharmaceuticals (Squibb & Lilly, 2022).

Classification of monoclonal antibodies based on source

These antibodies are mainly prepared from human and mouse protein. These are divided into four categories based on their formation these are shown in figure 1 (Tabll et al., 2015),(Susan, 2008),(Jin et al., 2021).

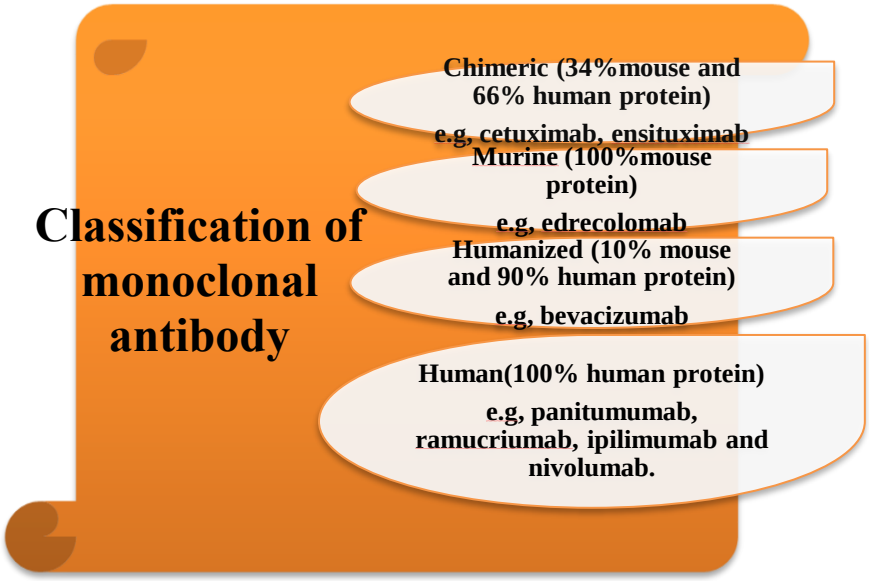

Figure 1: - Classification of monoclonal antibody

Current status of monoclonal antibody for colorectal cancer treatment:-

In this, we discuss in detail of monoclonal antibodies which are used in colorectal cancer which are shown in table 1.

Table 1:-US FDA approved monoclonal antibodies in the treatment of colorectal cancer (Firer & Gellerman, 2012)

Monoclonal antibody	Company	Receptor/ Target	Antibody Type	Uses	Year FDA approved	References
Bevacizumab	Genentech	VEGF-A	Humanized IgG1	Brain, kidney, colon, rectum, lung, and breast cancer	2004	(Yoshizaki et al., 2010), (Moorkens et al., 2020)

Cetuximab	Imclone systems	EGFR	Chimeric IgG1	Advanced bowel, colorectal, Head and neck cancer	2004	(Graham et al., 2004)
Panitumumab	Abgenix Inc.	EGFR	Human IgG2	Colon and rectum cancer	2006	(Keating et al., n.d.)
Ramucirumab	Imclone systems	VEGFR 2	Human IgG1	Stomach, colorectal, and non-small cell lung cancer	2014	(Verdaguer et al., 2016)
Onartuzumab	Genentech	C-MET	Humanized IgG1	Neoplasm, lung, gastric, colorectal, and glioblastoma cancer	Undergoing clinical trials	(Bendell et al., 2017)
Ipilimumab	BMS	CTLA4	Human IgG1	Skin, kidney, liver, lung and colorectal cancer	2011	(Mansh, 2011)
Nivolumab	Ono Phar. & Medarex	PD-1	Humanized IgG4	Urothelial, Hodgkin lymphoma, colorectal and esophageal cancer	2021	(Guo et al., 2017)

EGFR, Epidermal growth factor receptor; CTLA4, Cytotoxic T lymphocyte-associated antigen; C-MET, Mesenchymal-epithelial transition factor; PD-1, programmed cell death protein; VEGF-A, Vascular endothelial growth factor

1. Cetuximab

Cetuximab (Erbitux®), was first developed by Merck and Imclone systems. It's an EGFR receptor-binding monoclonal antibody. It's made up of a mixture of human and mouse proteins. It consists of two chains; heavy and kappa light chains (Gurdal et al., 2019),(Chung et al., 2008),(X. X. Li et al., 2015).

Cetuximab was first assumed to be a blocker that exclusively bound to domain III of the EGFR ECD and blocked connections between every known EGFR ligand and the receptor. Furthermore, its EGFR binding promotes receptor internalization while simultaneously decreasing the amount of EGFR protein expressed on the cell surface, as a result, Transcription and downstream signalling pathways dependent on EGFR are inhibited. As a result, cetuximab is thought to be more likely to stimulate ADCC than panitumumab, which contains IgG2. As a result, cetuximab inhibits tumour invasiveness, angiogenesis, and metastatic spread.

The main side effect of cetuximab is Eye pain, acne-like rash, chest pain, fainting, slow heartbeats, increased thirst and urination, redness, shortness of breath, and increased sensitivity to light.

Mechanism of action:

Their mechanism of action is mainly dependent on the EGFR receptor; cetuximab is bind with this receptor and inhibits cancer cells which are shown in figure 2

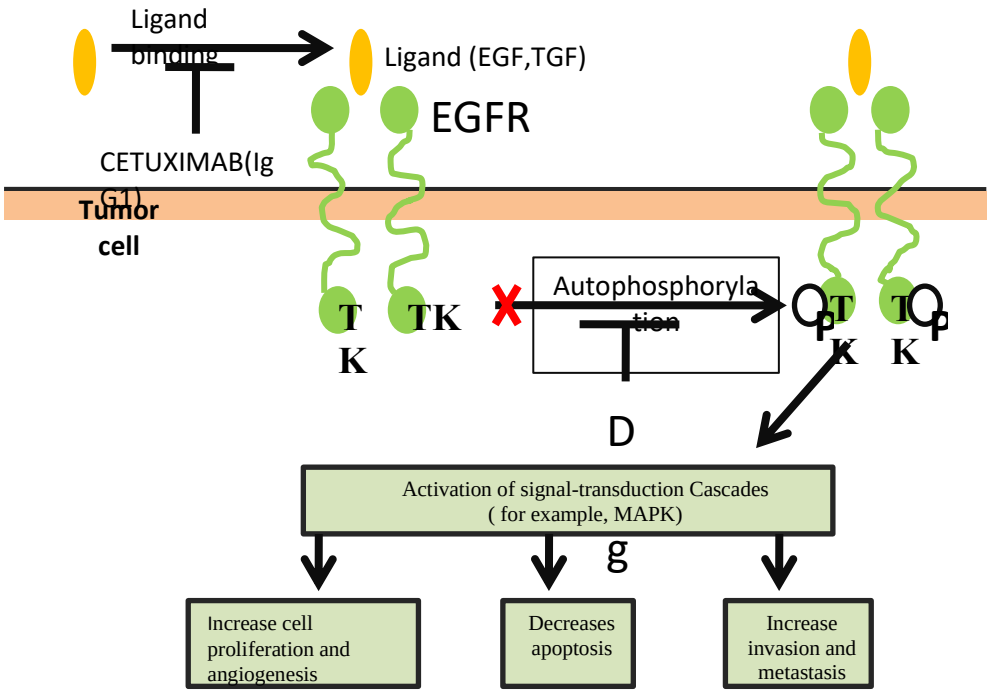

Figure 2:- Mechanism of action of Cetuximab

Abbreviation: -TGF, Transforming growth factor; MAPK, mitogen-activated protein kinases; TK, Tyrosine kinase; P, Phosphorylation; Epidermal growth factor;

Recent investigational studies on cetuximab formulation for colorectal cancer

There are many formulations for the treatment of CRC, but monoclonal antibodies-based formulations are more effective and easily targeted cancer cells. Significant research has been done globally on monoclonal antibodies as carriers for colorectal cancer. In vivo MRI imaging study conducted by Chang K. et.al. Revealed that antibody-drug conjugated nanoparticles have varied kinetics in tumours, offering useful insights into nanoparticle bio-application. In conclusion, MFSN Ctx allows for in vivo non-invasive imaging and quantification of EGFR expression, which could lead to a therapeutically applicable technique for noninvasive diagnosis and monitoring of therapy response in humans EGFR-expressing malignancies. In all formulations of cetuximab, nano formulations are good as compared to other formulations such as liposomes, micelles, microsphere, micro balloons, and alginate beds. A nano formulation of cetuximab shows better affinity, specificity, penetration efficacy, and compatibility.

Table 2:- Different formulations of cetuximab(Graham et al., 2004)

Monoclonal antibody	**Formulation**	**Bioactive**	**Target**	**Dose of monoclonal antibody**	**Finding**	**Apoptosis analysis**	**References**
	Magnet – fluorescent silica NPs(MFSN)	----------	EGFR	2 mg/ml	. good intravenous injection effect .detection of EGFR cancer using in-vivo	----------	(Cho et al., 2010)

Cetuximab					approaching		
	Immunoliposomes -	Celecoxib	EGFR overexpressing cells and cycloxygenase-2 (COX-2)	---------	**.** improve intracellular efficacy **.** shows sustained release of drug	Celecoxib activates proapoptotic protein NAG-1, which might activate apoptosis.	(Limasale et al., 2015)
	Carbon nanotubes	7-ethyl-10-Hydroxycamptothecin	EGFR and over expressed cancer cell	---------	**.** good biocompatibility **.**efficient cellular uptake **.**appropriate drug linking manner **.**use in biomedical field	Induced significant apoptosis, Control(8.29%) C225(10.13%) SWNT23/ pyCPT(37.830	(P. C. Lee et al., 2013)
	0-carboxymethyl Chitosan nanoparticles	Paclitaxel	EGFR	2mg/ml	**.**good gastro-resistant activity **.**easy deliver in high ph	Paclitaxel act on G1 and S stage and induced apoptosis	(Maya et al., 2013)
	Liposomes	Oxaliplatin	EGFR	---------	**.** better selectivity **.**enhanced cancer cell death **.** better delivery	cell proliferation signals triggering apoptosis	(Zalba et al., 2015)
	Micelles	IR-780 iodide	EGFR	50 microleter	**.**improve cancer treatment **.** improved efficacy	Increased apoptosis in an HCT-116 cancer cell and weak response in SW-620	(Khiavi et al., 2019)
	Chitosan-pectinate nanoparticles	Curcumin	EGFR	1mg/ml	**.**active targeting **.**good potential for tumour targeting	Curcumin act on G2/M stage and induced apoptosis	(Sabra et al., 2019)

	Poly (lactic-co-glycolic acid) Nanoparticles	Temozolomide	EGFR Over expressing	--------	. enhanced chemotherapeutic effect . higher cellular uptake .higher up regulation	Apoptosis induced 82.7% in U-87 cells	(Duwa et al., 2020)

2. Bevacizumab

Bevacizumab (AvastinR) was first developed by Genentech. It is an IgG1 monoclonal antibody that is humanized and targets sections of 5–6 of VEGF165, often known as VEGF-A, and suppresses angiogenesis by blocking the interaction between VEGFR2 and VEGF-A. As a result, bevacizumab blocks angiogenic signalling induced by VEGF-A and VEGFR2 interaction(Yoshizaki et al., 2010). It is an antiangiogenic drug used to treat certain types of cancers such as kidney, colon, rectum, lung, or breast cancer. The development of new blood vessels is known as angiogenesis. Endothelial cell differentiation, migration, growth, and development of normal tissues and cells are all part of this process(Krämer & Lipp, 2007).

Major side effects of bevacizumab are hypertension, wound healing complications, gastrointestinal perforation, asymptomatic proteinuria, and thromboembolic events.

Mechanism of action:

Their mechanism is mainly dependent on the VEGF receptor. Bevacizumab binds with that receptor and inhibit all process and enhance cell death which is shown in figure 3.

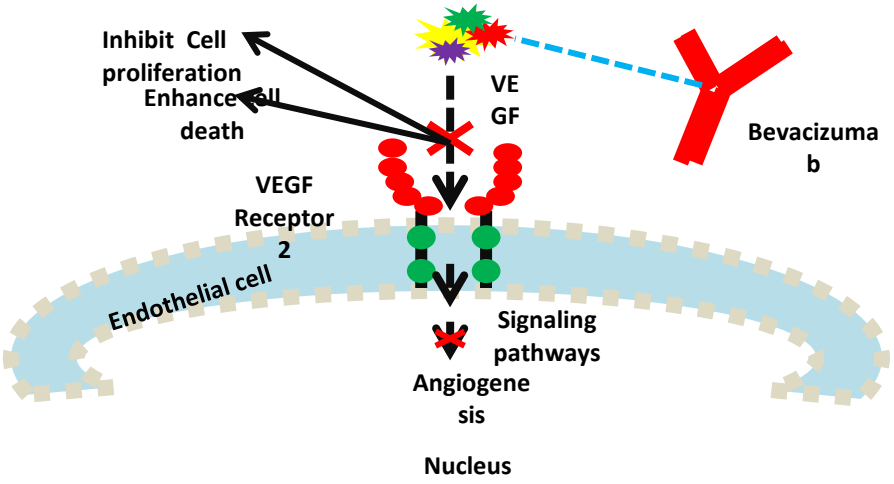

Figure 3:- Mechanism of action of bevacizumab

VEGF, vascular endothelial growth factor;

Recent investigational studies on bevacizumab formulation for colorectal cancer

Hedrick J. Et. al, prepared a formulation of injectable biodegradable hydrogels with the help of vitamin D-functionalized polycarbonates. Due to shear strain during the injection procedure, the hydrogel injection was created with the help of polymer and exhibited reversible mechanical properties. It's utilized as a drug reservoir to distribute bevacizumab for metastatic cancer treatment over time and reduce injection frequency, making treatment more convenient and improving patient compliance. In all formulations of bevacizumab, nano formulations are good because as compared to the micro formulation and others they show better stability, penetration, and efficacy.

Table 3:- Different formulations of Bevacizumab

Monoclonal Antibody	Formulation	Bioactive	Targets	Polymer Used	Dose of monoclonal antibody	Findings	References
Bevacizumab	Injectable Biodegradable Hydrogels	Vitamin D-Functionalized Polycarbonates	VEGF	PEG	--------	. drug reservoir for sustained delivery . enhanced patient compliance .improve treatment convenience	(A. L. Z. Lee et al., 2015)
	siRNA nanoparticles	Sulfo-LC-SPDP	VEGF	Thiolated - glycol Chitosan	---------	. better potential . improve therapeutic efficacy .overcome resistance	(Goo et al., 2017)
	Nanomicelles	D-alpha-tocopheryl polyethylene glycol succinate (TPGS)	VEGF	Polyethylene glycol 1000	2,5 mg/ml	.better stability .good therapeutic efficacy . used as a theranostic agent	(Tesan et al., 2016)
	Mesoporous silica nanoparticles (MSNs)	miR-328	VEGF	Polyethylene glycol	0.5 ml	. increased binding ability .exhibit multifunctional bio conjugates	(Y. Li et al., 2018)
	PLGA nanoparticles	Bevacizumab	VEGF	Poly(lactic-co-glycolic acid) & PLGA 5004A	25mg/ml	. controlled release .increase half-life, shelf-life . increase structural stability of encapsulated mabs	(Sousa et al., 2017)

3. Panitumumab

Panitumumab was approved as a monotherapy for treating patients with mCRC and wild-type KRAS tumours by the European Union (EU) in December 2007 and the United States Food and Drug Administration (FDA) in September 2006(Han van Krieken et al., 2017). It's a monoclonal antibody made entirely of human IgG2 that primarily interacts with the EGFR receptor. As compared to cetuximab, by their rates of infusion-related reactions between the two agents (Mehta et al., 2020),(Cartenì et al., 2007),(Trojan et al., 2015).

Panitumumab was licensed by the US Food and Drug Administration in 2006 for the treatment of patients with EGFR-expressing metastatic colorectal cancer, who had progressed on an irinotecan, oxaliplatin, or fluoropyrimidine-containing regimens. It was later approved for the treatment of EGFR-positive and wild-type KRAS patients with resistant metastatic CRCs. It is currently the only monoclonal antibody that uses KRAS as a predictive biomarker and first and second-line treatment of metastatic colorectal cancer in conjugation.

Major side effects of panitumumab are the growth of eyelashes, constipation, vomiting, nausea, diarrhoea, abdominal pain, and tiredness.

Mechanism of action:

Their mechanism is mainly depending on the EGFR receptor. Panitumumab is bind with this receptor and inhibits cancer cells which are shown in figure 4

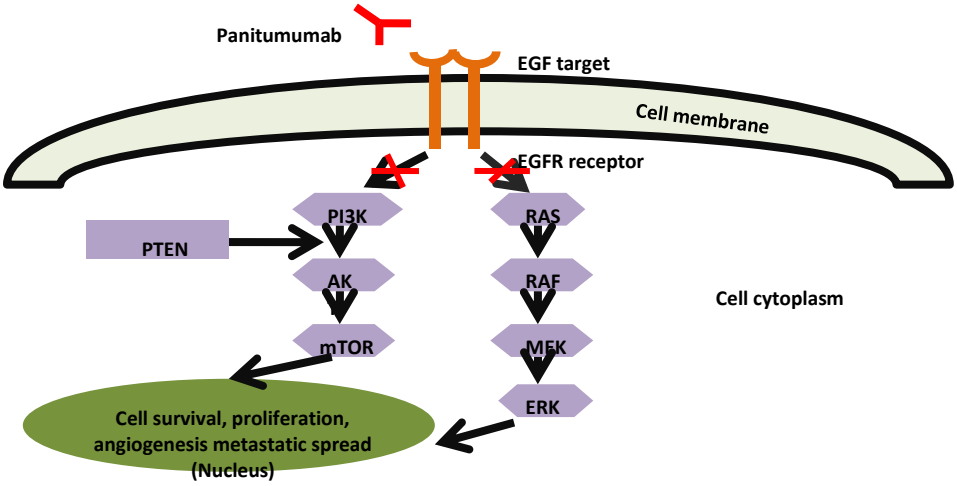

Figure 4:- mechanism of action of panitumumab(Mehta et al., 2020),(Tay et al., 2015),(Zenonos, 2013),(Dubois & Cohen, 2009)

PTEN, phosphate and tensin homolog; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; RAS, rat sarcoma viral oncogene homolog; RAF, v-Raf murine sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase; EsK, extracellular signal-regulated kinase; P13K, phosphoinositide-3-kinase.

Table 4:- Different formulations of panitumumab

Monoclonal antibody	Formulation	Bioactive	Target	Polymer used	Dose of monoclonal antibody	Findings	References
Panitumumab	pH-Sensitive Apoferritin Nanocages	Oxaliplatin	EGFR	Polyethylene glycol	17 µM	.high EGFR expression . facilitated Time-dependent drug	(Lin et al., 2018)
	Nanoparticles	Temozolomide	EGFR Over expressing Glioblastoma Cells	poly(lactic-co-glycolic acid)	50, 100, 200, 500, 1000 µg/mL	.improve therapeutic efficacy . efficient delivery	(Banstola et al., 2020)
	^{89}Zr-DFO-panitumumab	Zirconium	HER1-expressing carcinomas	----------	5 mg	. high radiochemical purity .specific activity	(Wei et al., 2014)
	IRDye800 conjugate	----------	EGFR-expressing cancers	----------	2.5 ml	. high yield and purity . high sensitivity and specificity	(Article, 2014)

4. Ramucirumab

Ramucirumab was first developed by Imclone and Dyax. It interacts with the VEGF receptor and is a completely human monoclonal IgG1 antibody. It is mainly used in stomach, colorectal, and non-small cell lung cancer (Verdaguer et al., 2016).

Ramucirumab was produced as a therapeutic antibody for the treatment of tumors using a Dyax's phage antibody library. Ramucirumab was approved by the FDA in 2014 as a single-agent treatment for advanced gastro-esophageal or gastric cancer using platinum and fluoropyrimidine-based chemotherapy. The major side effects of ramucirumab are hypertension, headache, nosebleed, intestinal obstruction, hyponatremia, and arterial blood clots.

Mechanism of action:

Ramucirumab acts on the VEGF receptor and inhibits their growth and causes cell death. Vascular endothelial growth factor-A is a proangiogenic factor that promotes permeability and blood vessel dilation and helps in new blood-vessels formation. VEGF-A acts mainly on two receptors which are VEGFR-1 and VEGFR-2.

VEGFR-1 stimulates and transmits weak signals and shows angiogenesis and vasculogenesis.

VEGFR-2 shows proangiogenic actions of VEGF-A & strong signal transmission.

Sometimes VEGFR-3 also occurs, which mediates growth, development process, and lymphatic penetration that help in metastasis and show lymphangiogenesis (Singh & Parmar, 2015),(Verdaguer et al., 2016).

5. Onartuzumab

Onartuzumab (MetMAb) is a humanized monoclonal antibody that binds to the semaphorin domain of c-MET; it was developed by Genentech and is a human IgG1 with a monovalent arm (South San Francisco, CA, USA). After dimerization or oligomerization by HGF binding, downstream signals are transduced by c-MET. HGF/c-MET signaling has also been linked to the progression of numerous malignancies, making it a promising target for drug development (Merchant et al., 2013),(Xiang et al., 2013),(Spigel et al., 2013).

Mechanism of action:

It binds to the c-MET receptor's domain, preventing HGF (hepatocyte growth factor) from connecting to the receptor and activating it, resulting in cell death.

6. Ipilimumab

Fully humanised monoclonal antibody ipilimumab (Yervoy®), developed by Medarex (Princeton, NJ, USA), binds to the CTLA-4 ECD, inhibits CTLA-4 from interacting with B7-1 or B7-2, and ultimately maintains T-cell cytotoxicity to target cancer cells. (Mansh, 2011),(D'Angelo et al., 2017).

The major side effects of ipilimumab are dizziness, fever, rash, headache, fatigue, nausea, vomiting, and pruritus.

Mechanism of action:

In normal T-cell functioning, MHC and CD80/CD86 of APC are bound with TCR and CD28 of T-cell and activate this. In a cancer cell, ipilimumab binds to CTLA-4 and blocks its interaction with CD80/CD86, and inhibits cancer cells (Sondak et al., 2011).

7. Nivolumab

Nivolumab (Opdivo®), a completely human monoclonal antibody created by Medarex (Princeton, NJ, USA), binds to the IgV domain of PD-1. The antibody is composed of an IgG4-constant region with an S228P mutation in the hinge region and a variable sequence grafted into the human kappa region. Nivolumab binds to the N-terminal loop of PD-1 specifically, as opposed to an epitope for pembrolizumab. Immune checkpoint inhibitor nivolumab boosts T cells' cytotoxicity so that they can more efficiently eradicate malignant tumours.(Sundar et al., 2015),(Guo et al., 2017).

Nivolumab was first approved by the US FDA in 2014 for the treatment of metastatic melanoma patients, and subsequently in 2015 for lung cancer patients. Currently, nivolumab immunotherapy is frequently utilized to treat mCRC (Deeks, 2014),(Golshani & Zhang, 2020).

The major side effects of nivolumab are increased lipase level, increased ALT level, maculopapular rash, decreased appetite, fatigue, nausea, and increased amylase level.

Mechanism of action:

A human immunoglobulin G4 (IgG4) monoclonal antibody called nivolumab binds to the PD-1 receptor on T cells and prevents it from interacting with the PD-L2 and PD-L1 receptors, inhibiting cancer cell growth and proliferation (Zugazagoitia et al., 2016),(Golshani & Zhang, 2020).

CONCLUSION:

Colorectal cancer and its treatments, such as symptoms, signs, treatment, and formulation of cetuximab, bevacizumab, and panitumumab, were detailed in this review study. Colorectal cancer treatments include surgery, monoclonal antibody, chemotherapy, immunotherapy, hormone therapy, stem cell therapy, and radiation therapy. Many medications, such as oxaliplatin and irinotecan, are utilized in chemotherapy, and in targeted therapies like monoclonal antibodies including cetuximab, bevacizumab, panitumumab, ipilimumab, ramucirumab, nivolumab, and onartuzumab. Radiation therapies that destroy cancer cells employ a variety of radiation to treat cancer. Immunotherapy strengthens the immune system's ability to fight cancer cells with various medications.

FUTURE PERSPECTIVES:

In the future all therapies of cancer monoclonal antibodies-based treatment are best because they show affinity and specificity for a target antigen, help in the production of selective stereo-specific monoclonal antibodies, reduce cost in targeting delivery, and enhanced drug action, applicable for new types of catalytic and bispecific antibodies.

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CONFLICTS OF INTEREST:

There are no potential conflicts of interest among the authors.

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