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A Review on the Prevalence and Management of Colorectal Cancer

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ABSTRACT: Cancer had become a common disease worldwide and cancer related death is also increasing in various parts of the world in spite of increased screening and diagnostic facilities available for early detection of cancer and availability of advanced care system. Changes in the diet and life style had led to alteration in the microenvironment of the cells leading to genetic changes and mutation. In this review, Colorectal cancer prevalence, risk factors for the development of colorectal cancer, pathogenesis, diagnosis and various treatment modalities available are discussed here.

KEY WORDS: Biological Agents, Cancer, Colorectal Cancer, Chemotherapy.

INTRODUCTION

Cancer is defined as abnormal division of cells. Uncontrolled cell division in the region of colon or rectum it is called as colorectal cancer (CRC). The colon, rectum and anus make up the large intestine which is the final segment of the gastrointestinal system. Large intestine absorbs water and minerals and eliminates waste. The first part of the large intestine is colon which is about 1.5 meters in length and 5 cm diameter. Colon is divided into 4 regions such as ascending colon, transverse colon, descending colon and the sigmoid colon. Colorectal cancer is caused by eating low fibre and high fatty food. Study says too much consumption of alcohol, smoking and sedentary life style can increase the risk of CRC. Presentation of Inflammatory bowel disease, a family history of colorectal cancer can also be a risk factor for the development of colon cancer. A polyp is a small growth in the lining of the colon which can develop into an adenomatous (precancerous) polyps over time. Colorectal cancers begin as small precancerous polyps which grows slowly without causing much symptoms until they become large or cancerous. Screening of these polyps at the right time can aid in the removal of them and preventing its growth into cancer. Polyps undergo various mutation in the cellular DNA and gets converted in a cancerous out growth.[1]

PREVALENCE

Colorectal cancer is the third most common type of cancer worldwide amongst men and second most common type of cancer amongst women. Almost 2 million cases were diagnosed in the year 2020. It is the second most common cause of cancer related deaths, almost 1 million deaths per year happened in the year 2020 according to WHO statistics. The burden of colorectal cancer is highest amongst Asians. More than half a million new cases and more than 280,000 deaths reported annually in China. Second highest number of deaths from colorectal cancer, almost 60,000 per year was reported by Japan.[1]

Highest incidence rates have been identified in regions of North America, Europe, Australia, New Zealand, South Korea, Japan. 45% of incidence have been identified amongst low and middle-income countries [LMICs] accounting to 52% of death in these regions. Increased incidence in the number of cases and death has been observed in regions of Eastern Europe, China and South America. Decreased incidence observed in regions of South Asia and Africa. The differences observed in these regions may be due to limitation in screening or access to early detection and health care. [2]

The incidence rates for colorectal cancer among Indian population were 4.4 per 100000 population. More than 1.4 million new cancer cases are being identified every year amongst the Indian sub-population.[3]

Five-year survival rate for stage 4 colorectal cancer at the time of diagnosis was less than a 10% which might be due to the ineffectiveness of current treatment regimens.

Worldwide, an estimated 1,931,590 colorectal cancer were newly identified during the year 2020. Incidence of CRC varies as much as six-times in different regions globally. Southern European region has the highest estimated rates (per 100,000 population, 40.6 in men and 24.5 in women), as compared to the lowest levels in south-central Asia (per 100,000 population, 6.6 in men and 4.4 in women).

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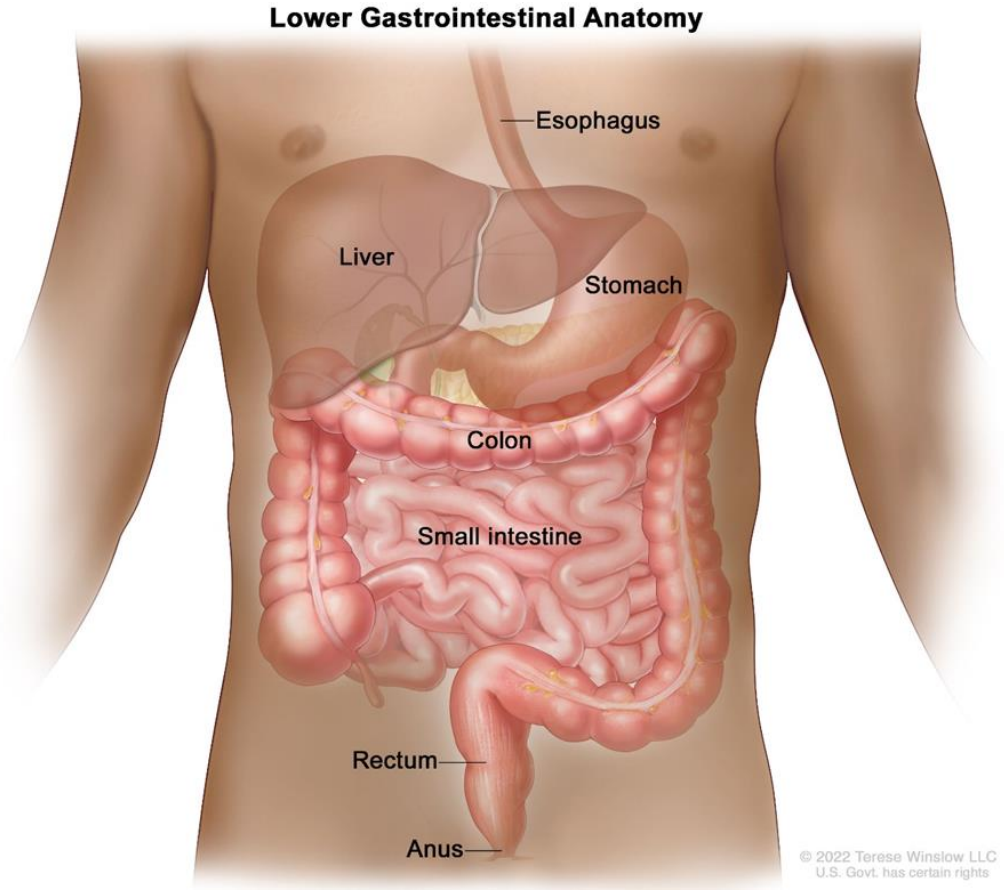
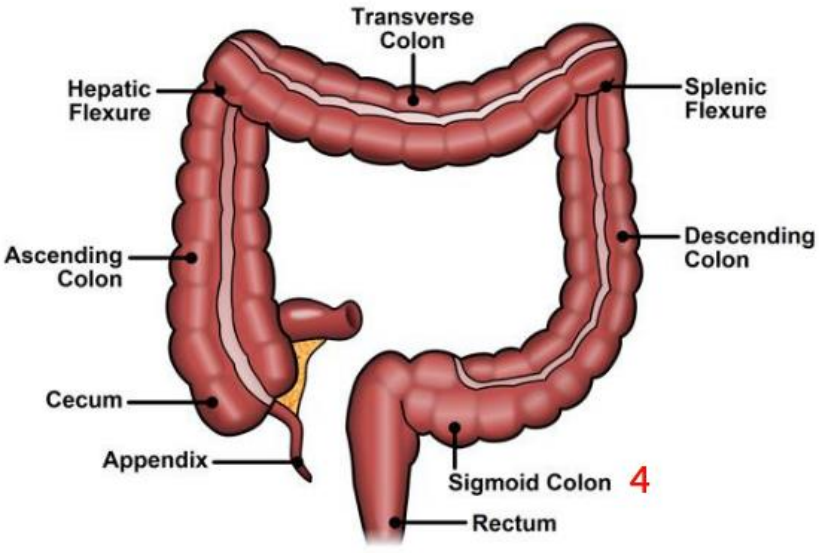
Worldwide, CRC had caused around 935,173 deaths during the year 2020, leading to 9.4% of CRC related mortality overall. As with incidence rates, mortality rates worldwide vary six-fold, with the highest estimated mortality rates at the eastern and central Europe (14.5 / 100,000), and the lowest in the regions of south-central Asia (3.2 per 100,000 population).[4]

ANATOMY





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RISK FACTORS

Some of the major risk factor for the development of colorectal cancer are: having a family history of colorectal cancer among the first-degree relative, increase in age. A personal history of colorectal adenomas, ovarian cancer. Hereditary conditions like familial adenomatous polyposis and Lynch syndrome. History of chronic ulcerative colitis or Crohn's disease. Excessive alcohol consumption, cigarette smoking, obesity, being an African-American can have a risk for the development of CRC.[5]

ETIOLOGY

AGE: Majority of CRC occurs in people above the age of 50, though it is found amongst younger adults also. The incidence had declined in older adults due to early detection and screening. But the incidence has increased in younger adults below 50 for unknown reasons.

GENETICS: Mutation of APC gene results in Familial Adenomatous Polyposis (FAP) which can develop into CRC and have a 100% risk. Hereditary non-polyposis colon cancer syndrome (HNPCC) has 40% risk of development for CRC.

RACE: Black people have a higher risk and incidence in US and also increased death rate.

GENDER: Men have higher in the incidence rate than women.

FAMILY HISTORY: About 6% have an association with inherited genetic mutation.

RARE INHERITED CONDITIONS: Lynch syndrome, Familial adenomatous Polyposis, Attenuated familial adenomatous polyposis, Gardner syndrome, Jucenile polyposis syndrome, Muir-Torre syndrome, MYH associated polyposis, Peutz-Jedhers syndrome, Turcot syndrome.

ADENOMATOUS POLYPS: Presentation of adenoma in the colon has high risk of developing into a CRC[6].

DIET: Diet rich in animal fat, red meat is linked with the development of CRC. Also diet with low fibre, low fruits and vegetable intake can also progress to CRC.

LIFE STYLE: Obesity, smoking, consumption of alcohol, excessive consumption of sweetened beverages, sedentary life style has increased the risk of development of CRC.

INFLAMMATORY DIGESTIVE TRACT: Presentation of IBD like Ulcerative colitis, Crohn's disease increases the risk of CRC.

SIGNS AND SYMPTOMS

Iron-deficiency anaemia, rectal bleeding, abdominal pain, change in bowel habits, intestinal obstruction or perforation.

PHYSICAL FINDINGS:

EARLY DISEASE: Fatigue, weight loss.

ADVANCED DISEASE: Abdominal tenderness, macroscopic rectal bleeding, palpable abdominal mass, hepatomegaly, ascites.

DIAGNOSIS: Diagnosis of CRC can be done by performing a complete blood count test, liver function tests, serum carcinoembryonic antigen.

IMAGING STUDIES: Imaging studies include chest radiography, chest computed tomography, abdominal barium study, abdominal/pelvic CT, contrast ultrasonography of the abdomen and liver, abdominal/pelvic MRI, Positron emission tomography, including fusion PET-CT scan.

OTHER PROCEDURES: Other procedures which can help in providing conclusive evidence for the presentation of CRC are Colonoscopy, Sigmoidoscopy, Biopsy of suspicious lesions, Double-contrast barium enema[7]

PATHOPHYSIOLOGY: MOLECULAR PATHWAY FOR COLORECTAL CANCER

CONVENTIONAL PATHWAY: More than 80% CRC cases are caused due to chromosomal instability pathway, which is initiated by APC mutation, followed by mutations in KRAS, PIK3CA and SMAD4, loss of heterozygosity of chromosome 18 (LOH 18q) and TP53 mutation. Colorectal cancer progression through conventional chromosomal instability pathway is associated with high levels of CIN (CIN+++), microsatellite stability (MSS) and very low levels of the CpG island methylation pathway (CIMP–).

SERRATED PATHWAY: Around 20% of CRC cases develop cancer through the serrated pathway. Serrated pathway can be divided into $CIMP^{low}$ MSS tumours (*KRAS* mutations), *BRAF*-mutant $CIMP^{high}$ MSS tumours or *BRAF* mutant $CIMP^{high}$ microsatellite instability (MSI) tumours. Serrated tumours are mostly associated with silencing of *MGMT*, *CDKN2A* or *MLH1*.

MSI PATHWAY: CRC cases are development due to dysfunctional DNA mismatch repair genes.[8]

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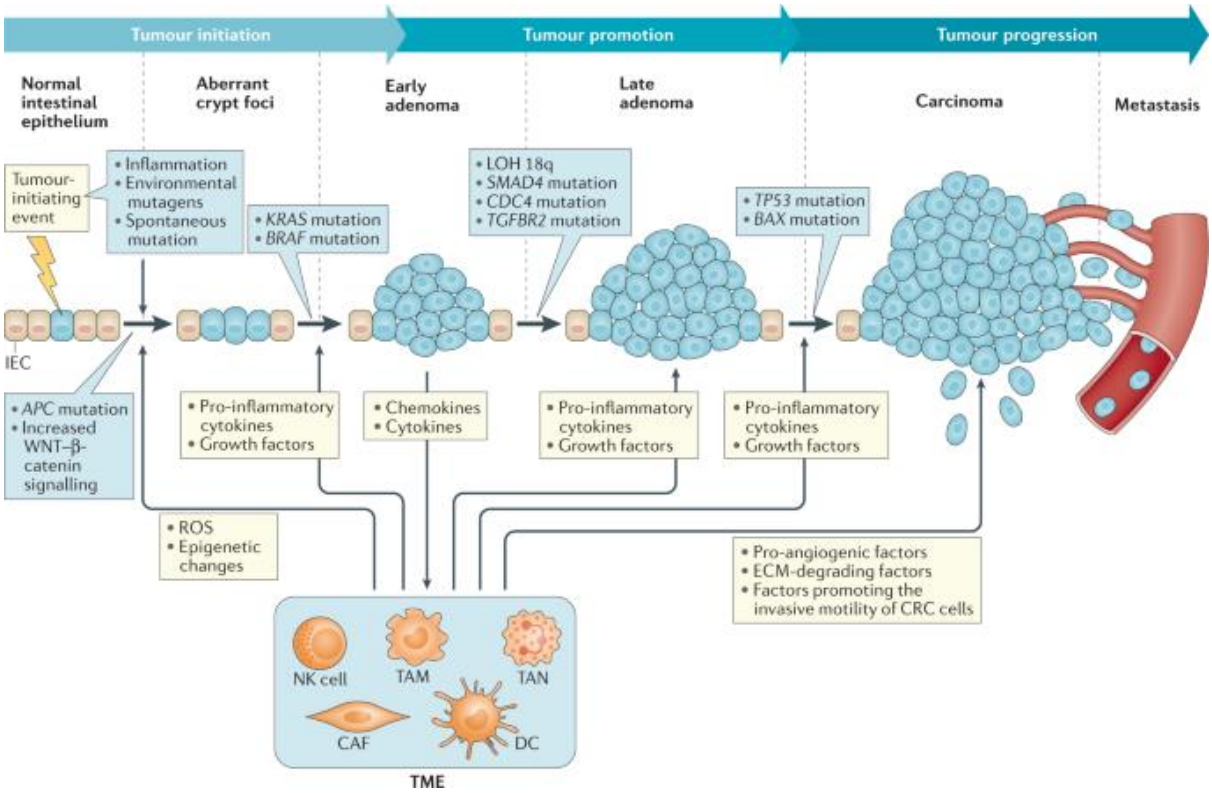
TUMOUR INITIATION AND PROMOTION



PREMALIGNANT ADENOMA: Premalignant adenoma undergoes genetic transformation and results in adenocarcinoma which can be invasive. Mutation takes place in the adenomatous polyposis gene (APC), activating oncogene c-MYC and cyclin D1 resulting in the progression towards malignancy.

KRAS MUTATION: KRAS (Kirsten rat sarcoma viral oncogene), belongs to the RAS family genes associated with tumour. KRAS binds to guanosine 5′ -triphosphate (GTP), and gets activated and is involved in the process of cell signal transduction for the regulation of cell proliferation and differentiation.

When mutations happen in the KRAS gene, the responsiveness to GAPs gets altered. Mutation results in rapid exchange for GTP, uncontrolled cell division, growth, transformation and metastasis. This also results in the development of resistance to chemotherapy and EGRF targeted therapy. KRAS mutations lead to unusual signal activation of the RAS/ RAF/MEK/ERK signalling pathway and promotes liver metastasis. KRAS mutation enhances angiogenesis by activating Vascular endothelial growth factor. KRAS mutation also affects the tumour microenvironment by increasing the glucose uptake of the tumour cells, alter glutamine metabolism and elevate autophagy. KRAS mutations causes elevated levels of glycolysis and protein expressions and metabolic alterations.[9]

DNA MISMATCH REPAIR: Deficient DNA mismatch repair results in the development of CRC. Mutations of MSH2, MLH1, and PMS2 gene results in high frequency microsatellite instability resulting in the development of hereditary nonpolyposis colon cancer syndrome.

EPIGENETICS: Abnormalities in the tumour suppressor genes or activation of oncogenes results due to abnormal DNA methylation, this can compromise the genetic balance of the cell and results in malignant transformation.

STAGING:

Stage 0 is the very early stage of cancer, this is followed by stage I, II, III, IV. Lower the number in the stage, lesser the cancer spread.

THE AMERICAN JOINT COMMITTEE ON CANCER (AJCC): TNM system of cancer staging: TNM system staging of cancer is based on the size and spread of the cancer cells.

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SIZE OF TUMOUR (T): Growth of the cancer cells in the region of the colon or rectum. This includes different layers like mucosa, muscular mucosa, submucosa, muscularis propria, subserosa and serosa.
SPREAD TO LYMPH NODES (N): The growth and spread of cancer cells to the nearby lymph nodes.
DISTANT METASTASIS (M): Cancer cells travel along the lymph nodes and reach distant organs like liver, lungs, kidney, brain and cause cancer in those organs, this is called as distant metastasis.[10]
MANAGEMENT:
Localized cancers can be completely removed by surgical procedures. Name of the surgical procedure varies based on the location of the lesion in the colon region like: right hemicolectomy (cecum, right colon), extended right hemicolectomy (proximal or middle transverse colon), left hemicolectomy (splenic flexure and left colon), sigmoid colectomy (sigmoid colon lesions), total abdominal colectomy with ileorectal anastomosis.

OTHER THERAPEUTIC OPTIONS

Cryotherapy involves application of extreme cold or freezing of the cancer tissue, causing death of the cells. Radiofrequency ablation is a technique by which high frequency radiation are passed on the affected tissue and causes destruction of the cells, hepatic arterial infusion of chemotherapeutic agents directly to liver cells for colorectal liver metastasis. Adjuvant therapy is used in selected patients who are at high risk for recurrence of tumour cells.

SYSTEMIC CHEMOTHERAPY

5-fluorouracil (5-FU) is an antimetabolite drug widely used in the treatment of colorectal cancer. 5-FU exerts its anticancer effects through inhibition of thymidylate synthase (TS) and incorporation of its metabolites into RNA and DNA.[11] Topoisomerase inhibitors are chemotherapeutic agents interfering with the topoisomerase enzymes I and II, which regulates the change in the structure of the DNA. Topoisomerase inhibitors block the ligation step of the cell cycle, which generates DNA single and double-strand breaks, leading to apoptotic cell death.[12] The platinum-containing agent oxaliplatin, and the 5-FU prodrug capecitabine are the first line drugs in the treatment of colorectal cancer.[13] The combination therapies, using FU/leucovorin and oxaliplatin and 5-FU/leucovorin and irinotecan, have become established as efficacious cytotoxic regimens for the treatment of metastatic CRC, resulting in overall survival times of approximately 2 years. [13]

BIOLOGIC AGENTS

Biological agents are substances made from living organisms used in the treatment of cancer. Biological agents like Bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor. Cetuximab, Panitumumab, monoclonal antibodies against the epidermal growth factor. Ipilimumab a CTLA-4 immune checkpoint inhibitor. Cytotoxic T lymphocyte-associated antigen (CTLA-4) is a coinhibitory transmembrane protein which binds to the B-71 and B7-2 ligands on antigen presenting cells.[15] Nivolumab is a human immunoglobulin (Ig)G4 anti-PD-1 monoclonal antibody. By binding to PD-1, an inhibitory co-receptor expressed on antigen-activated T cells, thus preventing interaction with PD-L1, resulting in the loss of inhibitory signals in T cells, and tumour recognition by cytotoxic T cells and thus restoring T-cell function.[16] Pembrolizumab is also an anti-PD-1 antibody which stimulates the body to act against the cancer cells. Ramucirumab is a monoclonal antibody against VEGFR2, it has antiangiogenic activity preventing formation of new blood vessels. It also has an inhibitory effect on the cell cycle progression.[17]

REFERENCES

1. Colorectal Cancer Facts & Figures 2020-2022. Atlanta: American Cancer Society; 2020 https://www.cancer.org/research/cancer-facts-statistics/colorectal-cancer-facts-figures.html
2. E. Gabriela Chiorean, Govind Nandakumar, Temidayo Fadelu, Sarah Temin, Ashley Efrain Alarcon-Rozas, Suyapa Bejarano, Adina-Emilia Croitoru, Surbhi Grover, Pritesh V. Lohar, Andrew Odhiambo, Se Hoon Park, Erika Ruiz Garcia, Catherine Teh, Azmina Rose, Bassem Zaki, and Mary D. Chamberlin. Treatment of Patients with Late-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline. JCO Global Oncology 2020 :6, 414-438; 2020.
3. Prachi S. Patil & Avanish Saklani & Pravir Gambhire & Shaesta Mehta & Reena Engineer & Ashwin De'Souza & Supriya Chopra & Munita Bal. Colorectal Cancer in India: An Audit from a Tertiary Center in a Low Prevalence Area. Indian J Surg Oncol. 2017 Dec;8(4):484–90. https://emedicine.medscape.com/article/277496-print

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www.ijcsrr.org

4. Colon Cancer Treatment (PDQ®)–Health Professional Version, national cancer institute. https://www.cancer.gov/types/colorectal/hp/colon-treatment-pdq#_1
5. https://www.cancer.net/cancer-types/colorectal-cancer/risk-factors-and-prevention
6. Tomislav Dragovich, N Joseph Espat. Colon cancer. Mar 08, 2022
7. https://emedicine.medscape.com/article/277496-overview
8. Schmitt, M., Greten, F.R. The inflammatory pathogenesis of colorectal cancer. Nat Rev Immunol 21, 653–667 (2021). https://doi.org/10.1038/s41577-021-00534-x
9. Mingjing Meng, Keying Zhong, Ting Jiang, Zhongqiu Liu, Hiu Yee Kwan, Tao Su. The current understanding on the impact of KRAS on colorectal cancer, Biomedicine & Pharmacotherapy. Volume 140, August 2021, 111717. https://doi.org/10.1016/j.biopha.2021.111717
10. Colorectal Cancer Early Detection, Diagnosis, and Staging. American Cancer Society cancer.org | 1.800.227.2345.
11. Longley, D., Harkin, D. & Johnston, P. 5-Fluorouracil: mechanisms of action and clinical strategies. *Nat Rev Cancer* **3**, 330–338 (2003). https://doi.org/10.1038/nrc1074
12. Shinji Kuroda, Toshiyoshi Fujiwara. Selectively replicating oncolytic adenoviruses combined with chemotherapy, radiotherapy, or molecular targeted therapy for treatment of human cancers. Gene therapy of cancer: Third edition: 2013
13. Bengt Gustavsson, Göran Carlsson, David Machover, Nicholas Petrelli, Arnaud Roth, Hans-Joachim Schmoll, Kjell-Magne Tveit, Fernando Gibson. A review of the evolution of systemic chemotherapy in the management of colorectal cancer: Clinical Colorectal Cancer, Vol. 14, No. 1, 1-10, 2015. http://dx.doi.org/10.1016/j.clcc.2014.11.002
14. Schirrmacher V. From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (Review). Int J Oncol. 2019 Feb;54(2):407-419. doi: 10.3892/ijo.2018.4661. Epub 2018 Dec 10. PMID: 30570109; PMCID: PMC6317661.
15. Lucia Festino, Vito Vanella, Martina Strudel, Paolo A. Ascierto, Chapter 7 - Molecular Mechanisms Underlying the Action of Ipilimumab Against Metastatic Melanoma, Editor(s): M.A. Hayat, Immunology, Academic Press, 2018, Pages 85-96,
16. Lim, Joline & Soo, Ross. (2016). Nivolumab in the treatment of metastatic squamous non-small cell lung cancer: A review of the evidence. Therapeutic Advances in Respiratory Disease. 10. 10.1177/1753465816661091.
17. Refolo, M.G., Lotesoriere, C., Lolli, I.R. *et al*. Molecular mechanisms of synergistic action of Ramucirumab and Paclitaxel in Gastric Cancers cell lines. *Sci Rep* 10, 7162 (2020). https://doi.org/10.1038/s41598-020-64195-x