IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

"Novel Treatment of Dostarlimab on Colorectal Cancer"

[1]Samruddhi Manoj Jagdale, [2]Vikas D. Kunde

Pravara Rural Education Society's College of Pharmacy (for women), Chincholi, Nashik, India

Abstract:-

Dostarlimab (JEMPERLI), a PD-1 monoclonal antibody, is used to treat adult patients with advanced or recurrent endometrial cancer who have progressed while receiving treatment with a platinum-containing regimen or after receiving prior therapy. This application was swiftly approved based on the rate of tumour response and the length of the response, both of which were determined using an FDA-approved test. The continuation of approval for this indication is dependent on additional confirmatory trials proving and proving therapeutic benefit. The clinical trial NCT04165772 showed a rectal cancer remission rate of 100% in June 2022. This clinical trial demonstrated that it is possible to match a tumor's genetics with its treatment. Patients are still being enrolled in this research trial, A few decades ago, the incidence of colorectal cancer was low. Nonetheless, it has emerged as a common malignancy and now represents 10% of cancer-related deaths in western nations. The "surge" in colorectal cancer cases in developed nations is thought to be caused by an ageing population, poor modern eating practises, and an increase in risk factors like smoking, inactivity, and obesity. Laparoscopic surgery for primary disease, more aggressive resection of metastatic disease (such as liver and pulmonary metastases), radiotherapy for rectal cancer, and neoadjuvant and palliative chemotherapies are some of the new treatments for primary and metastatic colorectal cancer that have emerged, giving patients more options. On cure rates and long-term survival, these new therapy alternatives haven't made much of a difference.

Keywords: - Dostarlimab, Jemperli, Monoclonal Antibody, Colorectal cancer.

1.Introduction:

The general living standard around the globe has increased, and there is greater access to quality healthcare, which has greatly aided in disease diagnosis and treatment. The average life expectancy in the majority of the world's regions has been impacted by these policies. Yet, despite the fact that these medical advancements have reduced communicable disease mortality rates globally, cancer-related mortality has climbed by roughly 40% over the previous 40 years. 13 million individuals are predicted to pass away from cancer in 2030, with a further 60% increase anticipated in the following 15 years.[1] Modes: The main causes of cancer-related mortality have also changed, attributable to alterations in disease incidence, introduction of screening programmes and therapeutic improvements. Colorectal cancer was rather rare in 1950, but has become a predominant cancer in Western countries, now accounting for approximately 10% of cancer-related mortality. Reasons explaining this increased incidence include population ageing and the preponderance of poor dietary habits, smoking, low physical activity and obesity in western countries. The change in incidence is not only apparent in the rates of sporadic disease, but also in some familial cancer syndromes. Indeed, given that rates of Helicobacter pylori infection (a causative factor of gastric cancer) have fallen dramatically, colorectal cancer is now the predominant presentation of Lynch syndrome (a hereditary non-polyposis type of colorectal cancer), whereas carriers of this syndrome used to be predominantly affected by gastric cancer The key contributors to cancer-related mortality have also altered as a result of changes in disease incidence, the implementation of screening programmes, and advancements in therapeutics. Until 1950, colorectal cancer was relatively uncommon, but today it is a common malignancy in Western nations, accounting for 10% of cancer-related deaths. The ageing of the population as well as the prevalence of unhealthy eating habits, smoking, inactivity, and obesity in western nations all

contribute to this rising occurrence. Not only are rates of sporadic disease indicative of the shift in incidence, but also some familial cancer syndromes. In fact, colorectal cancer is now the most common manifestation of Lynch syndrome due to the substantial decline in incidence of Helicobacter pylori infection, a cause of gastric cancer (a hereditary non-polyposis type of colorectal cancer). [2,3]

2.About colorectal cancer: -

Cancer is a condition in which the body's cells proliferate unchecked. Colorectal cancer is a type of cancer that develops in the colon or rectum. It is also known as colon cancer informally.

Although colorectal cancer is one of the main causes of cancer death in the US, it doesn't have to be. Screening for colorectal cancer saves lives. Precancerous polyps, which are abnormal growths in the colon or rectum that can be removed before they develop into cancer, can be found by screening. Moreover, screening aids in the early detection of colorectal cancer, when therapy is most effective. Nine out of ten persons with colorectal cancer who receive prompt diagnosis and treatment are still alive five years later.[4]

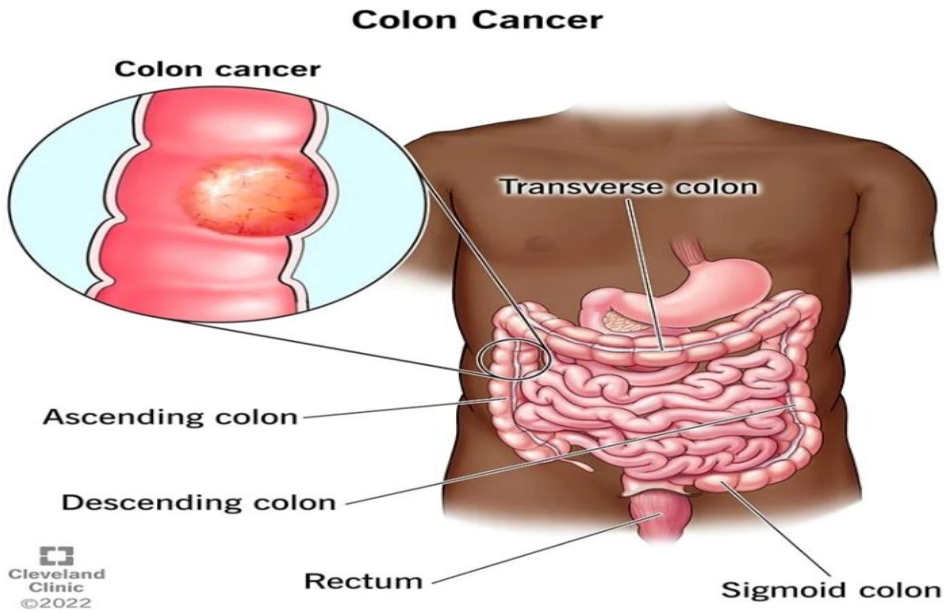

Fig.1 Anatomy of colon cancer
(Source: https://my.clevelandclinic.org/health/diseases/14501-colorectal-colon-cancer)

3.Risk factors of colorectal cancer: -

Many lifestyle-related factors have been linked to colorectal cancer. In fact, more than half of all colorectal cancers are linked to risk factors that can be changed. Colorectal cancer arises when the DNA in cells in the colon or rectum develop mutations that may make them unable to control growth and division. These mutant cells frequently perish or are attacked by the immune system. However, a tumour in the colon or rectum can develop when certain altered cells get past the immune system and continue to grow unchecked.

Although the actual origin of colorectal cancer is unknown, many risk factors have a high correlation with an elevated risk of the disease:

- Usage of diet tobacco
- Smoking
- Heavy drinking

Also, those who have a family history of colorectal cancer or certain hereditary cancer syndromes are at an increased risk of getting the disease.[5]

4.Symptoms of colorectal cancer

Early warning signs of colorectal cancer in the early stages may include abrupt weight loss and/or stools that are narrow and ribbon-like. Other early indications of colorectal cancer include the following:

- Rectal haemorrhage that may be dark crimson or brilliant red in colour
- Little stools
- Tenesmus, which is the sensation of needing to urinate but having nothing come out
- Anemia brought on by a lack of iron
- Persistent stomach ache

- Unaccounted-for weight loss

Even though other, less dangerous illnesses including haemorrhoids, ulcers, and Crohn's disease can also produce these symptoms, they should be discussed with a doctor. Even if it only occurs sometimes, blood in the stool should never be disregarded. All of these symptoms are nonspecific. In other words, they could also be caused by other diseases such as irritable bowel syndrome (IBS), inflammation of the lining of stomach (gastritis), a peptic ulcer, a food intolerance or an inflammatory bowel disease. the Bowel cancer is only rarely the cause, especially in people under the age of 40.[6][7] Colorectal (bowel) cancer doesn't cause any symptoms at first and often goes undetected until it has reached a later stage. Certain symptoms may be signs of colorectal cancer, but they are usually caused by another, non-cancerous condition.

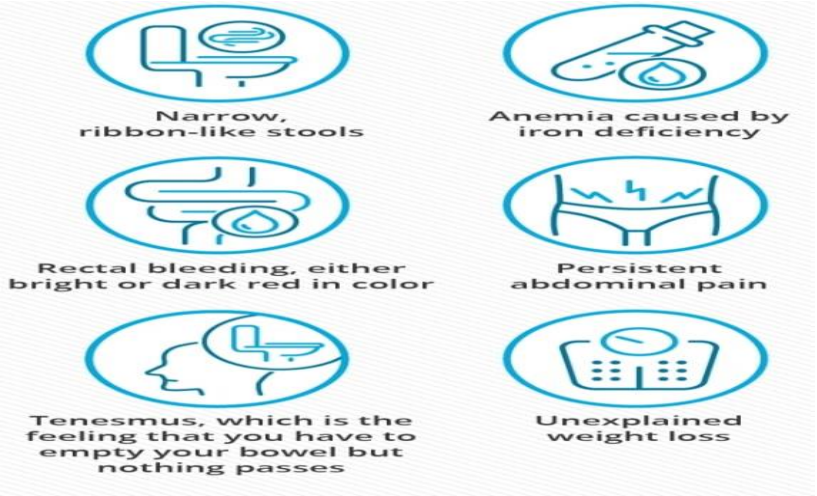

Fig.2 Symptoms of CRC
(Source: https://www.cancercenter.com/cancer-types/colorectal-cancer/symptoms)

The second most lethal cancer for both sexes combined is colorectal cancer (CRC), which is also the third most frequent diagnosis. Strong environmental and genetic risk factors for CRC both exist. Except for younger persons (under 50 years old), the incidence of new cases and mortality has been consistently dropping over the past few years, presumably due to an increase in cancer screening and improved treatment options. Familial Adenomatous Polyposis and Lynch syndrome are two hereditary disorders that account for about 5% of all CRC. An accumulation of genetic changes, either somatic (acquired) or germline (inherited), over the course of roughly 10 to 15 years is necessary for the transformation of the normal colonic epithelium into a precancerous lesion and finally an invasive carcinoma.[8]

Cellular proliferation that is out of control is cancer. The phrase "colorectal cancer" or "colon cancer" is used to describe this uncontrolled cellular development when it occurs in the colon or rectum area.[9] The epidemiology of colorectal cancer may change drastically depending on geographical locations. It is the second and third most prevalent type of cancer in females and males respectively. Incidence and mortality rates of this type of cancer is significantly lower in females than males.[10]

5.Stages of colorectal cancer

After a colorectal cancer diagnosis, doctors determine the stage of the disease before deciding how best to treat it. Most cancer types, including colorectal cancer, are grouped into stages ranging from 0 to 4. Stages are based on the cancer's size, location and spread within the body. To establish the stage of colorectal cancer, the care team typically considers all of the information gathered during tests, exams or procedures leading up to a diagnosis. In some cases, additional tests may be recommended.

Test used in staging of colorectal cancer. Some of the diagnostic tests that play a role in staging colorectal cancer include:

1. Biopsy
2. Magnetic resonance imaging (MRI)
3. Computed tomography (CT) scan
4. Ultrasound exam Chest X-ray
5. Lymph node biopsy Surgery
6. Complete blood count
7. Carcinoembryonic antigen (CEA) test.

Stages of colorectal cancer:-

A. Stage 0 colorectal cancer:- In this, the earliest stage of colorectal cancer (also called carcinoma in situ or intramucosal carcinoma), the cancer cells are contained to the rectum's or colon's inner lining. This stage is also marked by this characteristic: Abnormal cells are found in the innermost layer (mucosa) that lines the colon or rectum, but these cells have not become cancerous.
B. Stage 1 of colorectal cancer:- In stage 1, colorectal cancer cells are found in deeper layers of the colon or rectum wall, but they haven't spread beyond the wall. This stage is also marked by these specific characteristics: Cancer cells are found in the innermost layer lining the colon or rectum, and they have grown into the second layer of tissue (the submucosa).The cancer may have also spread to a nearby muscle layer (muscularis propria) but hasn't reached nearby lymph nodes.
C. Stage 2 colorectal cancer:- Stage 2 colorectal cancers have not spread to the lymph nodes, but some may have spread through and beyond the wall of the colon or rectum, sometimes into nearby tissues or organs. They are also marked by these specific characteristics:.
    i. Stage 2A: The cancer has spread through the layers of the colon or rectum wall and has reached the outermost layer, but no farther.
    ii. Stage 2B: The cancer has grown past the outermost layer of the colon or rectum wall but hasn't spread to nearby tissues or organs.
    iii. Stage 2C: The cancer has spread past the outermost layer of the colon or rectum wall and has grown into nearby tissues or organs, but it hasn't spread to lymph nodes or distant organs.
D. Stage 3 colorectal cancer: - In stage 3, colorectal cancer cells have spread to one or more nearby lymph nodes, but they have not grown beyond the lymph nodes and colon or rectum wall to other parts of the body. They are also marked by these specific characteristics:
    i. Stage 3A: The cancer has spread through the first two inner layers of the colon or rectum wall (mucosa and submucosa) and may have also reached the third layer (muscularis propria).
    ii. Stage 3B: The cancer has reached the outermost layer (serosa) of the colon or rectum wall.
    iii. Stage 3C: The cancer has grown past the colon or rectum wall and has spread to the tissue that lines the abdominal organs, but it has not spread to nearby organs.
E. Stage 4 colorectal cancer: - Stage 4 colorectal cancer have spread beyond the colon or rectum to distant areas of the body, including tissues and/or organs. They are also marked by these specific characteristics:
    i. Stage 4A: The cancer has reached one area or organ that isn't near the colon or rectum (such as the liver, lung, ovary or a faraway lymph node).
    ii. Stage 4B: The cancer has reached more than one area or organ that isn't near the colon or rectum.
    iii. Stage 4C: The cancer has spread to distant parts of the tissue that lines the abdominal wall and may have reached other areas or organs. [11]

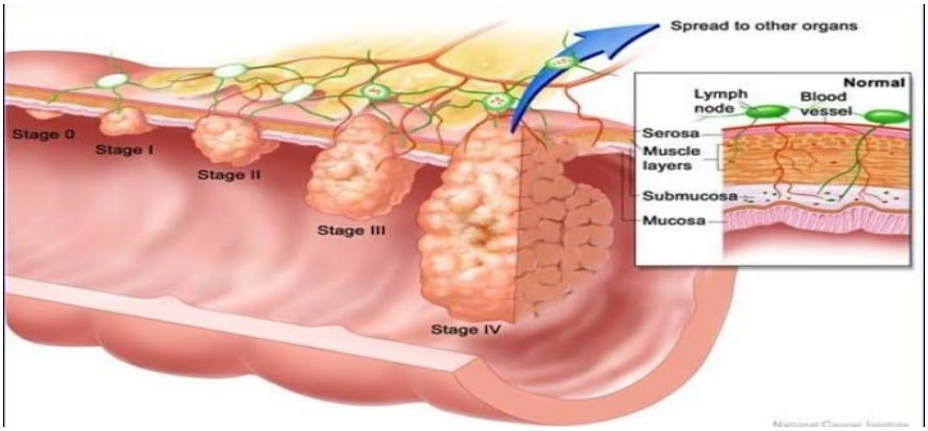

Fig.3 Stages of CRC
(Source: https://www.ccalliance.org/colorectal-cancer-information/stage-of-diagnosis)

6.About Dostarlimab

Dostarlimab, also known by the brand name JEMPERLI, is a group of synthetic compounds that can replace human antibodies.[11]. Dostarlimab is an anti-programmed cell death receptor-1 (PD-1) antibody used to treat adult patients with recurrent or progressed solid tumours that are mismatch repair-deficient (dMMR) as well as endometrial cancer that is dMMR-recurrent or advanced. [12] JEMPERLI binds to PD-1, which is located on the surface of T lymphocytes. When T cells are healthy, PD-1 serves as a brake to stop them from launching an unrestrained immune response. T lymphocytes in tumours, however, can become inactive and unable to kill cancer cells due to PD-1. Inside the tumour mass, the number of PD-L1 and PD-L2 molecules that bind to PD-1 on the surfaces of cancer cells and normal cells is enhanced. When these two molecules (PD-L1 and PD-L2) bind to the T cell's PD-1 receptor, the T cell becomes inactive and unable to destroy the cancer cells. PD-L1 and PD-L2 cannot bind to the PD-1 receptor because of the way JEMPERLI interacts to it. The PD-1 blockage permits.[13]

Dostarlimab

Generic name: dostarlimab [dos-TAR-li-mab]
Brand name: Jemperli
Dosage form: intravenous solution (gxly 500 mg/10 mL)
Drug class: Anti-PD-1 monoclonal antibodies

Fig.4 Marketed preparation of Dostarlimab
(Source: https://www.empr.com/drug/jemperli/)

Table 1. Overview on Jemperli

Type	Whole Antibody
Source	Humanized
Target	PDCD1
Trade name	Jemperli
Other name	TSR-042, WBP-285, dostarlimab-gxly
Route of administration	Intravenous
Drug class	Antineoplastic
Formula	C6420H9832N1690O2014S44
Molar Mass	144325.73 g·mol−1

A small group of colorectal patients (18 individuals) just witnessed something no short of a scientific miracle, their sickness reduced completely after experimental treatment undertaken by a group of experts at Memorial Sloan Kettering Cancer Center, New York. The trial's outcome was unexpected because every patient was entirely cured, without exception. According to several specialists, these new findings are unexpected in the field of cancer research.[14]

These individuals underwent life-altering surgery that could affect bowel, urinary, and sexual functions, as well as treatments including chemotherapy and radiation. Dr. Diaz's 2017 clinical trial design served as the study's primary source of inspiration. 86 people with metastatic cancer that had spread throughout their bodies were included. Unfortunately, a gene mutation present in every tumour rendered cells incapable of repairing DNA damage. 4% of cancer patients have these mutations. Patients in that study received pembrolizumab, a checkpoint inhibitor from Merck, for up to two years. Tumors decreased in size or stabilized in roughly one-third to one-half of the patients, prolonging their survival. 100% of participants who took part in the trial had their tumours removed. The investigation must.[15] Dostarlimab (JEMPERLI) is a PD-1 monoclonal antibody for the treatment of adult patients, with mismatch repair deficient (dMMR), recurrent or advanced endometrial cancer that has progressed on or following prior therapy with a platinum-containing regimen. As determined by an FDA-approved test this indication was granted rapid approval based on the rate of tumor response and the duration of the response. Continued approval for this indication is conditioned on further confirmatory trials demonstrating and documenting clinical benefit. In June 2022, the clinical trial NCT04165772 reported a 100% remission rate for rectal cancer. This clinical trial brought proof that we can match a tumor and the genetics of what is driving it, with therapy. This clinical trial continues to enroll patient and is currently enrolling patients with gastric, prostate, and pancreatic cancers. Dostarlamib is being recommended for rectal cancer. The focus of this review is to summarize the existing knowledge regarding Dostarlimab and explore the possibilities of mono- and combination therapies. A humanized mAB called dostarlimab (JemperliTM) or dostarlimab-gxly functions as an antagonist for programmed death-1 (PD-1) receptors. For the treatment of various cancers, including endometrial cancer, colorectal cancer, ovarian cancer, cancer of the head and neck, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), squamous cell cancer (SCC), fallopian tube cancer, pancreatic cancer, and many more, it is being developed by GlaxoSmithKline (GSK) under a licence from AnaptysBio Inc. Dostarlimab was only just approved (22 April 2021) for persons with advanced or recurrent

advanced mismatch repair deficient endometrial cancer (dMMR), according to early results from the GARNET trial. Dostarlimab is often prescribed at a dose of 500 mg every three weeks (during the first four weeks).[16][17]

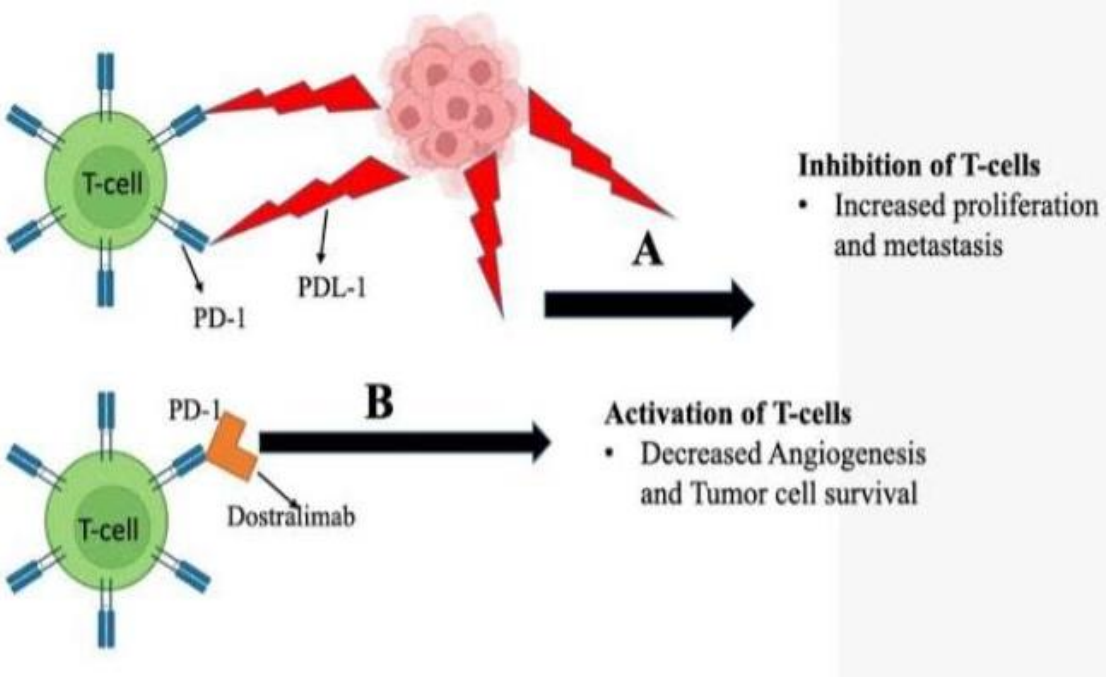

Fig 5. Mechanism of action of Dostarlimab
(Source: https://www.mdpi.com/1648-9144/58/11/1572)

7.Background:

Dostarlimab is a programmed death receptor-1 (PD-1) blocking antibody that has been given approval in the US as a monotherapy for adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer that has progressed during or after prior treatment with a platinum-containing regimen, as well as dMMR recurrent or advanced solid tumours that have progressed during or after prior treatment and for whom there are no other acceptable treatment options. Here, we provide the results of a post-hoc subgroup analysis of cohort F of the GARNET trial on the antitumor activity and safety of dostarlimab monotherapy in patients with dMMR colorectal cancer.

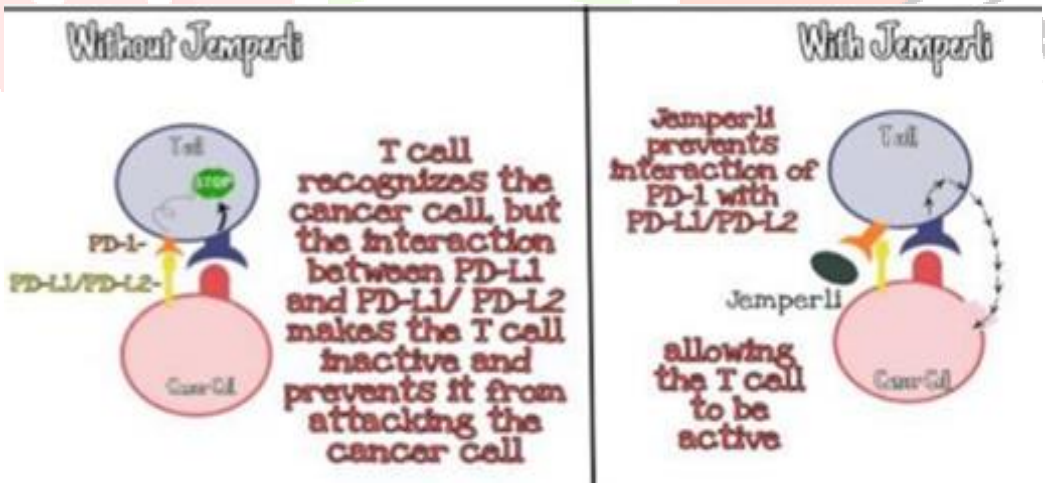

Fig 6. (Source: https://www.ucir.org/immunotherapy-drugs/dostarlimab-gxly)

8.Methods:

The GARNET study uses dostarlimab monotherapy in patients with advanced or recurrent solid tumours. It is a phase 1, multicenter, open-label, single-arm study. Patients with dMMR/MSI-H or POL mutant non-endometrial solid tumours, including patients with CRC, were enrolled in Cohort F of the GARNET expansion cohorts. After receiving prior systemic therapy for advanced illness, patients had to have advanced according to a blinded independent central review (BICR). Patients with CRC had to be intolerant to fluoropyrimidine, oxaliplatin, or irinotecan or had progressing illness. Patients were given 500 mg of intravenous dostarlimab every three weeks for four cycles, then 1000 mg every six weeks until the medication was stopped. Objective response rate (ORR) and duration of response by BICR per RECIST v1.1 were the main objectives. If a patient received 1 dose, they were included in the efficacy analysis.

9.Results:

141 patients with dMMR non-endometrial solid tumours were included in the safety analysis as of the interim analysis data cut on March 1, 2020, and 106 patients were included in the efficacy analysis. 69 (65.1%) of the patients in the efficacy analysis had CRC. In patients with dMMR CRC, the confirmed ORR by BICR according to RECIST v1.1 was 36.2% (95% CI, 25.0%-48.7%). 22 partial responses out of 3 total responses were given. 23 patients (92%) were still receiving care as of the data cut. For pts with CRC, the median response time had not been attained. Treatment-related adverse events (TRAEs) were observed in 68.1% of patients with dMMR non-endometrial solid tumours, with 8.5% of patients reporting at least one grade 3 TRAE. The typical grade 3 TRAE.

10.Conclusions:

Dostarlimab demonstrated durable clinically meaningful antitumor activity in pts with dMMR CRC, which was consistent with that seen in patients with dMMR non-CRC solid tumors. No new safety signals were detected in patients with dMMR non-endometrial solid tumors. Clinical trial information: NCT02715284.

11.References:

1) Kuipers EJ, Rösch T, Bretthauer M. Colorectal cancer screening—optimizing current strategies and new directions. Nat Rev Clin Oncol. 2013; 10:130–42. Review of current state of art of colorectal cancer screening. [PubMed] [Google Scholar] [Ref list]
2) Warthin AS. Heredity with reference to carcinoma: as shown by the study of the cases examined in the pathological laboratory of the University of Michigan. Arch Intern Med. 1913; 12:546–55. [PubMed] [Google Scholar] [Ref list]
3) Vasen HFA, Tomlinson I, Castells A. Clinical management of hereditary colorectal cancer syndromes. Nat Rev Gastroenterol Hepatol. 2015; 12:88–97. [PubMed] [Google Scholar] [Ref list]
4) https://www.cdc.gov/cancer/colorectal/basic_info/what-is-colorectal-cancer.htm
5) https://www.cancercenter.com/cancer-types/colorectal-cancer/risk-factors
6) Adelstein BA, Macaskill P, Chan SF, Katelaris PH, Irwig L. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. BMC Gastroenterol 2011; 11:65. [PMC free article] [PubMed]
7) Jellema P, van der Windt DA, Bruinvels DJ, Mallen CD, van Weyenberg SJ, Mulder CJ et al. Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis. BMJ 2010; 340: c1269. [PMC free article] [PubMed]
8) Xiao JB, Leng AM, Zhang YQ, Wen Z, He J, Ye GN. CUEDC2: multifunctional roles in carcinogenesis. Front Biosci (Landmark Ed). 2019 Mar 01;24(5):935-946. [PubMed] [Ref list]
9) Gajendran M, Loganathan P, Jimenez G, Catinella AP, Ng N, Umapathy C, Ziade N, Hashash JG. A comprehensive review and update on ulcerative colitis. Dis Mon. 2019 Dec;65(12):100851. [PubMed] [Ref list]
10) Colorectal cancer: epidemiology, risk factors, and protective factors – UpToDate. https://www.uptodate.com/contents/colorectal-cancer-epidemiology-risk-factors-and-protective-factors [Ref list]
11) Miracle" A drug trial erases cancer from every patient's body – first time in history, Econ. Times. https://economictimes.indiatimes.com/industry/healthcare/biotech/miracle-a-drug-trial-erases-cancer-from-every-patients-body/first-time-in-history/slideshow/92083596.cms [Ref list]
12) Jemperli (dostarlimab-gxly) to treat advanced solid tumours. https://www.clinicaltrialsarena.com/projects/jemperli-dostarlimab-gxly/ [Ref list]
13) Dostarlimab-gxly (Jemperli) drug information. https://www.ucir.org/immunotherapy-drugs/dostarlimab-gxly [Ref list]
14) Cancer drug had 100% success rate : NPR. https://www.npr.org/2022/06/07/1103545361/cancer-drug-experimental-rectal-chemotherapy-surgery-treatment-immunotherapy [Ref list]
15) A cancer trial's unexpected result: remission in every patient | Business Standard News. https://www.business-standard.com/article/current-affairs/a-cancer-trial-s-unexpected-result-remission-in-every-patient-122060701128_1.html [Ref list]
16) FDA; CDER. Highlights of Prescribing Information Tissue, Including the Following: Immune-Mediated Pneumonitis, (n
17) Jemperli | European Medicines Agency, (n.d.). Available online https://www.ema.europa.eu/en/medicines/human/EPAR/jemperli (accessed on 16 June 2022
18)) https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.4_suppl.201