

THE REVOLUTIONARY IMPACT OF DOSTARLIMAB IN TREATING dMMR/MSI-H RECTAL CANCER: A COMPREHENSIVE REVIEW

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Abstract: This article reviews the groundbreaking results of Dostarlimab, a PD-1 inhibitor, in the treatment of dMMR/MSI-H rectal cancer, a rare and difficult-to-treat subtype of colorectal cancer. Dostarlimab has demonstrated unprecedented efficacy, achieving a 100% clinical response rate in patients undergoing treatment, with no recurrence or metastasis observed. These promising results were observed in a pivotal clinical trial where patients who were previously facing limited treatment options showed complete remission after receiving Dostarlimab as a monotherapy. The article delves into the mechanisms of action of Dostarlimab, its role in immunotherapy, and its potential as a future standard of care for dMMR/MSI-H rectal cancer. Additionally, the article explores the ongoing clinical trials and FDA approval, highlighting the significant hope this treatment brings to patients and oncologists alike. The potential long-term impacts of Dostarlimab on the oncology landscape are also discussed, focusing on its ability to revolutionize cancer treatment paradigms.

Keywords: Dostarlimab, PD-1 Inhibitor, dMMR/MSI-H, Rectal Cancer, Clinical Trials, FDA Approval, Oncology, Cancer Treatment.

Dostarlimabning dMMR/MSI-H to'g'ri ichak saratoni davolanishidagi inqilobiy ta'siri: Batafsil tahlil

Annotatsiya: Ushbu maqola dostarlimab, PD-1 ingibitorining dMMR/MSI-H to'g'ri ichak saratoni bo'yicha inqilobiy natijalarini ko'rib chiqadi. Dostarlimab bemorlarda 100% klinik javobni taqdim etgan, takrorlanish va metastazlar kabi holat kuzatilmagan. Ushbu ishda, ilgari davolash variantlari cheklangan bemorlar, dostarlimab bilan monoterapiya olganidan keyin to'liq tiklangani kuzatilgan. Maqolada dostarlimabning harakat mexanizmlari, immunoterapiya va kelajakda dMMR/MSI-H to'g'ri ichak saratoni uchun standart davolash usuli sifatida qanday o'rni borligi ko'rib chiqiladi. Shuningdek, FDA tomonidan tasdiqlangan va joriy klinik tadqiqotlar davomida bemorlar va onkologlar uchun katta umidni ko'rsatayotgan natijalar ham yoritilgan. Dostarlimabning onkologik davolash yondoshuvlarida uzoq muddatli inqilobiy

o'zgarishlarga olib kelishi mumkinligi ham tahlil qilinadi.

Kalit so'zlar: Dostarlimab, PD-1 ingibitori, dMMR/MSI-H, to'g'ri ichak saratoni, klinik sinovlar, FDA tasdiqlash, onkologiya, saraton davolash.

Революционное влияние достарлимаба на лечение рака прямой кишки с dMMR/MSI-H: Комплексный обзор

Аннотация: Эта статья рассматривает революционные результаты препарата достарлимаб, ингибитора PD-1, в лечении dMMR/MSI-H рака прямой кишки, редкой и трудно поддающейся лечению подтипа колоректального рака. Достарлимаб продемонстрировал беспрецедентную эффективность, достигнув 100% клинического ответа у пациентов, прошедших лечение, при этом не было зафиксировано рецидивов или метастазов. Эти обнадеживающие результаты были получены в ходе ключевого клинического исследования, где пациенты, ранее имеющие ограниченные варианты лечения, полностью выздоровели после применения достарлимаба в качестве монотерапии. В статье рассматриваются механизмы действия достарлимаба, его роль в иммунотерапии и потенциал в качестве будущего стандарта лечения для dMMR/MSI-H рака прямой кишки. Также в статье обсуждаются продолжающиеся клинические исследования и одобрение FDA, подчеркивая значительную надежду, которую этот препарат дает пациентам и онкологам. Обсуждаются возможные долгосрочные последствия применения достарлимаба для онкологии и его способность революционизировать подходы к лечению рака.

Ключевые слова: Достарлимаб, ингибитор PD-1, dMMR/MSI-H, рак прямой кишки, клинические испытания, одобрение FDA, онкология, лечение рака.

INTRODUCTION

Rectal cancer is a major contributor to cancer-related deaths around the world, and this underscores the urgent need for new treatments. According to Cercek et al. (2022), deficiencies in DNA mismatch repair (MMR), as seen in more than 10% of rectal cancers, are known to confer resistance to conventional therapies, offering an alternative target for physicians to pursue [1]. MMR-deficient (or dMMR) tumours are biomarker-rich and immunogenic (or immune system-targetable), allowing us to approach them as a surgical strike on the disease pathway rather than collateral damage. The advent of dostarlimab, a programmed cell death protein 1 (PD-1) inhibitor, represents a transformative development in this domain.

Figure 1. Adapted from Drug Discovery Today (2023), illustrates the mechanism by which Dostarlimab works. Dostarlimab interacts with the PD-1 receptor to inhibit its binding with PD-L1 and PD-L2 pathway. This action restores T-cell activity, enabling the immune system to

recognize and destroy cancer cells[3].

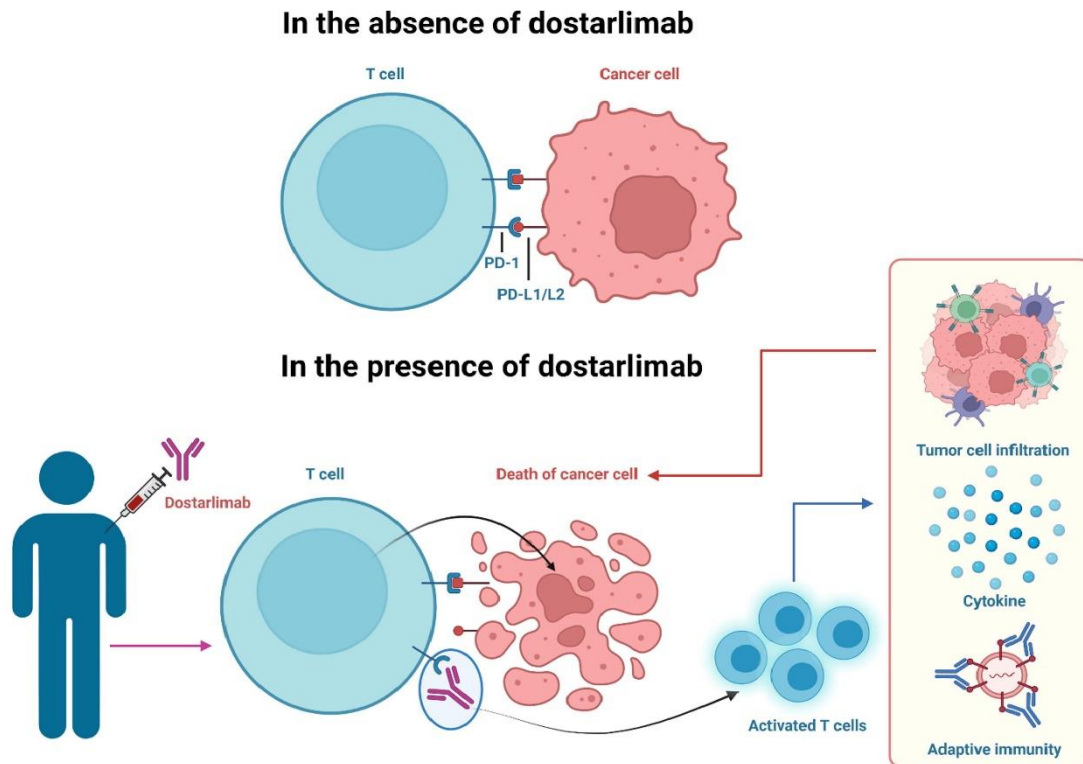


Figure 1. Binding of dostarlimab to PD-1 and the initiation of T-cell activation. T cells [2] recognize cancer cells and the interaction between PD-L1/PD-L2 and PD-1 causes the inactivation of T cells, which prevents them from attacking cancer cells. On the other hand, dostarlimab prevents PD-L1/PD-L2 and PD-1 interaction, which allows activation of T cells followed by attacking of cancer cells[3].

This mechanism explains the remarkable outcomes observed in clinical trials, with Dostarlimab demonstrating a 100% response rate in patients with dMMR/MSI-H rectal cancer, including no recurrence or metastasis. The effectiveness of this treatment represents a major breakthrough in immuno-oncology and highlights the potential of PD-1 inhibitors like Dostarlimab in cancer therapy.

METHODS

This review includes an analysis of recent clinical trials that evaluated the effectiveness of Dostarlimab in treating dMMR/MSI-H rectal cancer. Patients with mismatch repair deficiency and stage II or III colorectal cancer (CRC) was selected for phase 2 of the trial(Author: Cercek et al., ClinicalTrials.gov Identifier NCT04165772)[1]. Dostarlimab, an anti-PD-1 monoclonal antibody, was administered at a dose of 500 mg every 3 weeks for 6 months. Patients with a clinical complete response after this therapy could avoid standart chemoradiotherapy and surgery. The primary endpoints were sustained clinical complete response after 12 months from

the ending of dostarlimab therapy or pathological complete response with or without chemoradiotherapy, and overall response to neoadjuvant dostarlimab measured the therapy’s success[1].

RESULTS

According to a pharmaceutical company called GlaxoSmithKline’s (GSK), the clinical trial data for Dostarlimab in dMMR/MSI-H rectal cancer demonstrate a 100% clinical response rate, with tumor elimination in all participants and no evidence of metastasis during the follow-up period.

The New England Journal of Medicine published the results of the trial in June 5 2022 and according to it all of 12 patients had a clinical complete response. There was no evidence of cancer on magnetic resonance imaging(MRI), positron emission tomography(PET), endoscopic and digital rectal examination, or biopsy. Also no patients had received chemotherapy/surgery and no adverse effects of grade 3 or higher have been reported[1].

However, dostarlimab is not approved anywhere in the world for the frontline treatment of locally advanced dMMR/MSI-H rectal cancer.

DISCUSSION

The results of the Dostarlimab trials represent a monumental shift in the treatment of dMMR/MSI-H rectal cancer. The drug’s 100% response rate in clinical trials is unprecedented in oncology[4].In comparison to standart therapies, Dostarlimab exhibits superior response rates, reduced adverse effects, and a non-invasive treatment pathway. While these results are promising, long-term follow-up data is needed to determine the durability of the response. Additionally, the cost and accessibility of Dostarlimab may limit its widespread use. Future studies should focus on expanding the patient population and exploring combination therapies.

Table 1 Comparison of Dostarlimab and Traditional Treatment Methods for dMMR/MSI-H Rectal Cancer

Aspect	Dostarlimab	Traditional Treatment (Chemotherapy/Surgery)
Treatment Method	PD-1 Inhibitor (Immunotherapy)	Chemotherapy or Surgical Resection
Complete Response Rate	100% (in dMMR/MSI-H colorectal cancer trials)	20-30% (varies by cancer type)
Common Side Effects	Mild (e.g., fatigue, rash)	Severe (e.g., nausea, hair loss, infection)
Cost per Patient (Approx.)	\$11,000 per dose	\$5,000-\$20,000 (depending on regimen)
Invasiveness	Non-invasive (IV infusion)	Invasive (e.g., surgery, catheter use)

CONCLUSION

Dostarlimab marks a significant advancement in oncology, providing an effective and well-tolerated therapeutic option for individuals with dMMR/MSI-H rectal cancer. While the current clinical data is highly promising, continued research is needed to further establish its long-term efficacy and safety. As more data becomes available, Dostarlimab may become the new standard of care in oncology.

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