



Short Communication

Dostarlimab: A breakthrough in the field of oncology

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ABSTRACT

Of the 19 million cancer cases reported worldwide in 2020, colorectal cancer (CRC) has a 10% prevalence and 9.4% mortality. A critical lack of cancer treatment facilities in third-world countries like Pakistan where a significant prevalence of CRC has been detected. The five FDA-approved drugs used for CCR therapy (Durvalumab, Atezolizumab, Nivolumab, Pembrolizumab, and Avelumab) have been associated with a high occurrence of grade 3-4 adverse side effects. Dostarlimab is a new drug previously used to treat endometrial cancers and has a mechanism of action that is in accordance with other PD-1/PD-L1 inhibitors. A recent clinical trial has found Dostarlimab to cure 100% of the CRC patients who were given this drug while also showing no adverse events of grade 3 or higher in any patient. The recent clinical trial has opened up doors for future clinical trials perhaps with bigger sample sizes and ones that also include CRC patients belonging to wider geo-economic backgrounds such as those of Pakistan and other Asian countries.

1. Background

Cancer/Tumour is an uncontrollable cell growth at a specific body region that can metastasize to other body parts consisting of trillions of cells. Tumors are classified into cancerous (malignant tumors) and non-cancerous (benign tumors) depending on their ability to metastasize [1]. Cancer, being one of the lethal diseases of the 20th Century has alarmingly increased during the 21st century so much so that every fourth person is likely to develop it [2]. There have been 19 million new malignancy cases and approximately 10 million mortalities due to cancer worldwide in 2020, according to GLOBOCAN 2020. Breast cancers (11.7%) have the highest incidence rates, followed by lung cancers (11.4%) and colorectal cancers (CRCs) (10%). While in terms of mortality, lung cancers (18%) are topping the list, followed by colorectal (9.4%) and liver (8.3%) malignancies in both the sexes of all ages [3].

Pakistan being one of the developing countries with mere advancements in cancer research, reported having 14,694 prevalent cases (5-year) and 4557 deaths by CRC as per GLOBOCAN 2020 [4]. The third

most prevalent cause of cancer deaths worldwide, CRC, shows ethnic-/racial disparity in a study by Obrochta et al. who reported that patients with lower neighbourhood socioeconomic status (nSES) were at high risk of treatment delay or not getting treatment at all, making them more prone to CRC mortality [5]. This puts the Pakistani population at a higher risk since it is a third-world country and still undergoing development with a substantial number of people with low socioeconomic status.

In a meta-analysis that aimed to evaluate the occurrence of different types of cancers in Pakistan, CRC was found to have an overall prevalence of 5%; the p-value was <0.001 which was markedly statistically significant; I² value was 85.4% indicating a very high heterogeneity [6]. With an annual cancer incidence of 0.17 million, Pakistan faces multiple challenges in the field of oncology [4]. As of 2014, Pakistan's total expenditure on health as a percentage of GDP was only 2.6% [7]. The human development index for Pakistan was 0.562 in 2017, ranking it at 150 out of 189 countries [8]. These grim figures do not bode well for Pakistan, a lower middle-income country (LMIC) with grossly

Abbreviations: CRC, colorectal cancer; LMIC, lower-middle-income country; GDP, gross domestic product; MMRd, mismatch repair-deficiency; FDA, Food and Drug Administration; PD-L1, programmed death 1 ligand 1; SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; MRI, magnetic resonance imaging; PET, positron emission tomography; PD-1, programmed death 1.

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unavailable facilities for cancer care amidst an increasing cancer burden. Pakistan faces a dearth of adequate facilities for both diagnosis and treatment of cancer, let alone palliative and hospice care [6].

2. Pathophysiology of CRC

Mismatch repair-deficiency (MMRd) is a genetic mutation that interferes with the correction of mistakes during DNA replication. MMRd is most frequently seen in CRCs [9]. Additionally, T-cells express an important immune-checkpoint receptor called Programmed death 1 (PD-1) which plays a pivotal role in immunosuppression specific to cancerous cells. CRCs with MMRd are found to be sensitive to the blocking of PD-1 immune-checkpoint receptors with antibodies [10,11]. Hence, programmed death 1 ligand 1 (PD-L1) binds to PD-1 receptors on T-cells to inhibit/kill them hence inhibiting immunosuppression [11–13].

3. PD-1/PD-L1 antagonists currently in use

The following five PD-1/PD-L1 inhibitors for CRC therapy have currently been approved by the US Food and Drug Administration (FDA): Durvalumab; atezolizumab; nivolumab; pembrolizumab; avelumab [14].

- **Durvalumab:** In a study conducted by Oh et al., the median duration of response was not reached and the progression-free survival rate of 12 months was only 52.2% (95% confidence interval [CI]: 39.0–73.1) [15].
- **Atezolizumab:** Median overall survival was 7.10 months (6.05–10.05) [16].
- **Nivolumab:** In a phase 1 study of nivolumab in 39 patients with treatment-refractory solid tumors, only one metastatic colorectal cancer (mCRC) patient (1/14; 17%) achieved a lasting complete response for 6 months [17]. Similarly, in another phase 1 study of nivolumab (n = 296), objective responses were observed only in patients with non-small cell lung cancer, melanoma, or renal cell carcinoma, and not in the mCRC population (0/19, 0%) [13].
- **Pembrolizumab:** Median progression-free survival was reported as 16.5 months (95% CI: 5.4–32.4) in a study published in the New England Journal of Medicine [18].
- **Avelumab:** Median progression-free survival and overall survival was reported as 3.9 and 13.2 months respectively in a phase 2 study of avelumab monotherapy [19].

According to National Cancer Institute, numerous drugs other than PD-1/PD-L1 inhibitors like oxaliplatin, regorafenib, and capecitabine are also being used as cancer therapeutics [20].

4. Dostarlimab as a neoadjuvant therapy

Despite the high efficacy and safety of the above-mentioned drugs, none of them were able to portray promising results by utterly terminating the tumors. However, recently a phase 2 open-label clinical trial experimented with Dostarlimab as single neoadjuvant therapy for CRC. The trial was conducted on stage 2 or 3 CRC patients with MMRd [11]. For the first time in history, a clinical trial reported 100% eradication of tumors with no recurrence of cancerous cells [11,21]. A positive response was seen in 12/12 patients (100%) (95% CI: 74–100), with complete elimination of the locally advanced tumor. This trial was very recently conducted at Memorial Sloan Kettering Cancer Center in Manhattan, US [22].

5. Recommended dosage and side effects of dostarlimab

Dostarlimab (Jemperli™, dostarlimab-gxly) is an anti-PD-1, monoclonal IgG4 antibody that is produced from a mouse hybridoma that

blocks the antigen-receptor activity of PD-L1 and PD-L2 hence normalizing the immune response. Its mechanism of action is in accordance with other PD-1/PD-L1 inhibitors. It got approved on April 22, 2021 for the treatment of endometrial cancer [23] and came in the limelight as a viable treatment for CRC after this trial was conducted. Further usage of this drug includes the treatment of numerous cancers including pancreatic cancer, ovarian cancer, fallopian tube cancer, non-small cell lung cancer (NSCLC), and small-cell lung cancer (SCLC) [24].

A pharmaceutical company, GlaxoSmithKline's (GSK) recommended dosage for Dostarlimab is four doses of 500 mg each after every 3 weeks, followed by doses of 1000 mg each after every 6 weeks until intolerable toxicity [25]. The drug was administered to 16 patients according to the recommended dosage with a follow-up period of six months and the malignancy was astonishingly undetected through ¹⁸F-fluorodeoxyglucose-positron-emission tomography (PET) scans, endoscopies, biopsies, digital rectal examinations, and Magnetic resonance imaging (MRI) scans [11]. The percentage of patients with a complete response was 100% (95% CI: 74–100) in 12 consecutive patients who have completed 6 months of therapy [11]. Table 1 further compares the complications and side effects of Dostarlimab with other PD-1/PD-L1 inhibitors.

6. Future prospect

Until the recent trial, cancer was considered an incurable malady causing millions of mortalities globally. Although the trial conducted by Cercek et al. is a paramount breakthrough in the field of oncology, its sample size was extremely small, making it less reliable in spite of all the authentic manoeuvres performed throughout the trial [11]. Moreover, the period of follow-up was not adequately long. Hence, further trials with longer follow-up periods for assessment of tumor recurrence and drug response duration are required. Furthermore, there is a dire need to

Table 1

Comparison of adverse effects/complications with Dostarlimab versus other PD-1/PD-L1 inhibitors.

Trial author	Phase of trial	ClinicalTrials.gov Identifier	Drug	Complications/ Adverse effects
Oh et al. [15]	2	NCT03435107	Durvalumab	Grade 3 TRAE ^a occurred in 36.4% of the patients
Eng et al. [16]	3	NCT02788279	Atezolizumab	Grade 3 and 4 adverse outcomes reported were 28 of 90 (31%), and serious adverse events were reported in 15 of 90 (17%) patients
Brahmer et al. [17]	1	–	Nivolumab	One TRAE ¹ , inflammatory colitis was reported in patient of melanoma
André et al. [18]	3	NCT02563002	Pembrolizumab	56 out of 307 (18.2%) patients are dead within 2 years of drug administration
Kim et al. [19]	2	NCT0315-0706	Avelumab	Grade 3 or 4 TRAEs ^a occurred in six out of 33 patients (18.2%)
Cercek et al. [11]	2	NCT04165772	Dostarlimab	No adverse events of grade 3 or higher were reported in any patient. No patients have had disease progression or recurrence, and all 12 patients are alive

^a TRAE – Treatment-related adverse event.

conduct such trials in Asian countries specially Pakistan where CRCs constitute about 4.8–5.8% of all cancer cases [4] as regional differences play a significant role in drug efficacy and safety [26].

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Author contribution

Syeda Tayyaba Rehan: Conceptualization, Writing – original draft.
Hassan ul Hussain: Writing – original draft. **Muhammad Husban Burney:** Writing – original draft. **Mohammad Mehedi Hasan:** Conceptualization, Writing - review & editing.

Trial register number

- 1 Name of the registry: NA
- 2 Unique Identifying number or registration ID: NA
- 3 Hyperlink to your specific registration (must be publicly accessible and will be checked): NA

Guarantor

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Consent

NA.

Conflicts of interest

NA.

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Not applicable.

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