DOSTARLIMAB – A MIRACLE DRUG RISING HOPE AGAINST ENDOMETRIAL CANCER AND MASSIVE BREAKTHROUGH IN THE FIELD OF ONCOLOGY

ABSTRACT :

Out 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 . 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. In June 2022, the clinical trial NCT04165772 ported a 100% remission rate for rectal cancer. Dostarlamib is being recommended for rectal cancer. The focus of this review is to summarize the breakthrough in medical field with the introduction of Dostarlimab.

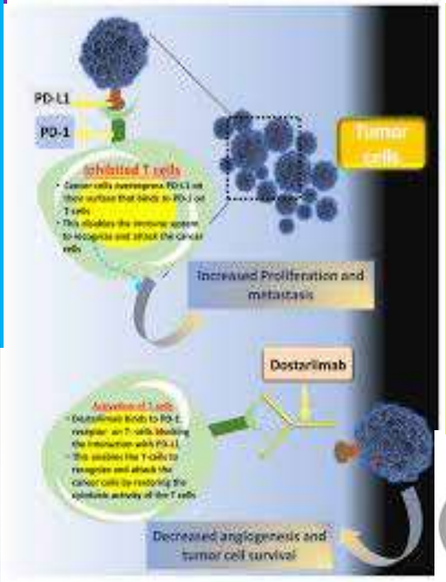
Keywords: anti-PD-1 antibody, Dostarlimab, immunotherapy, clinical trials, dMMR , Platinum containing regimen, 100% curacy rate, CRC

INTRODUCTION:

On 17 August 2021, the FDA granted accelerated approval to Dostarlimab, a monoclonal antibody, for adults with dMMR recurrent or advanced endometrial cancer that has progressed despite ongoing or prior treatment with the platinum-containing chemotherapy regimen.Tumors that exhibit the dMMR or MSI-H biomarker have an abnormal function of DNA repair mechanisms. Genes that should repair any improper activity to maintain cell health are absent in these types of cancer. Dostarlimab, an inhibitor of PD-1, demonstrated a long-lasting effect on dMMR tumors, and in 2022, reported a 100% remission rate for rectal cancer . All patients had dMMR, a mutation present in 5 and 10% of rectal cancer cases (this mutation is also present in endometrial, prostate, and bladder tumors). Lets Discuss about efficacy of Dostarlimab further,

MECHANISM OF ACTION:

PD1 is an immune checkpoint receptor found in T-cells that suppresses cancer-specific immune responses. The humanized IgG4 mAB, Dostarlimab, is derived from a **Chinese hamster** ovary cell and has a molecular weight of approx 144 kDa. A binding between the PD-1 ligands (PD-L1 and PD-L2) and the PD-1 receptor on T-cells inhibits cytokine and T-cell proliferation. In some tumors, PD-1 ligands are upregulated, and signaling through this pathway may contribute to the suppression of active T-cell immunity. This is where the drug Dostarlimab comes into the picture. It inhibits programmed cell death receptor-1 and blocks the interaction of receptors with PD-L1 and PD-L2, which in turn activates T-cells and enhances overall immunity. Studies have depicted that Dostarlimab binds with PD-1 receptors of both humans and cynomolgus monkeys with high affinity, as seen from the results obtained in flow cytometry and plasmon resonance. Moreover, a human CD4+ mixed lymphocyte reaction assay showed that Dostarlimab worked as a functional antagonist, resulting in increased IL-2 production. This assay also showed the enhanced activity of Dostarlimab when TIM3 antibodies or LAG3 antibodies were present. In the presence of antibodies, Dostarlimab exhibited increased activity, but no significant cytokine release was observed from human PBMCs (peripheral blood mononuclear cells)



RESULTS AND DISCUSSIONS:

PATIENT DISPOSITION:

At the time of analysis, 477 of 478 patients (99.8%) had at least one immunogenicity sample result and were included in the analysis of prevalence: 21 from part 1, 6 from part 2A whose Dostarlimab dosing schedule was Q3W, 7 from part 2A whose dosing schedule was Q6W, and 443 from part 2B. Out of the 444 total patients from part 2B, 1 had no immunogenicity results, 3 had no baseline results, and 126 had no post-baseline results. Of the 478 enrolled patients, 349 (73.0%) were evaluable for treatment-emergent antibodies to Dostarlimab.

DISCUSSIONS:

The CMC (Chemistry,Manufacturing and Control) process is monitored and controlled through CQAs,(Critical Quality Attributes) and batch-testing results of 11 drug substances and 17 drug products met all CQA acceptance criteria. Batch analysis and characterization studies demonstrated process consistency and no impact on potency. Overall, the data confirmed that the Dostarlimab drug substance and drug product consistently present desired product quality, with very low impurity levels, thus at low risk to elicit immunogenicity.

CONCLUSION:

Dostarlimab demonstrated a notable DCR in patients with MMRp/MSS EC, a cohort that has more patients with high-grade ECs, a characteristic associated with a worse prognosis. Further classification of the MMRp responders is ongoing and may provide useful insights on the patients who responded to dostarlimab. No new safety signals were detected, and safety profile was consistent among patients with dMMR/MSI-H and MMRp/MSS EC. Only 5.5% of patients discontinued dostarlimab because of a TRAE, and no treatment-related deaths were reported.

REFERENCES:

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