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Dostarlimab & its Herbal Analogues: Review

[1]Sumit U. Devkar , [2]Piyush N. Jangam, [3]Naziya F. Pathan , [4]Onkar M. Gade, [5]Unnati N. Shetiya,
[1] Student* , [2]Associate Professor , [3]Student , [4]Student , [5]Student
Department of Pharmacology
Arihant College of Pharmacy,Kedgaon, Ahmednagar, Maharashtra,India, 414005.

Abstract: Dostarlimab (Jemperli™ , dostarlimab-gxly; TSR-042) is an approved, humanized, Programmed Death – 1 (PD-1) inhibiting monoclonal antibody that has proven efficient in multiple kinds of solid tumors particularly for Endometrial cancer. Monoclonal antibodies that plays important role in blocking the interaction between programmed cell death 1 (PD-1) receptor and its ligand (PD-L1) have revolutionized most of the cancers immunotherapy(1). dostarlimab was proven significant and long lasting clinical activity with an acceptable safety profile. (2). Rhus Verniciflua Stokes , Quercetin , Liquoritegenin , Glyasperin c , Ellagic acid , Caffeoxylquinic acid derivatives are Dostarlimab analogues which shows antineoplastic activity by blocking programmed cell death 1 receptor. The focus of the present study is to summarize the present expertise related to dostarlimab with its herbal analogues and discover the probabilities of mono and combination therapies.

Keywords : **Dostarlimab, Endometrial cancer, Ellagic acid , Jemperli , Immune checkpoint Inhibitor , Rhus verniciflua Stokes, Quercetin , anti PD-1.**

I. INTRODUCTION:

Apart from Cardiovascular diseases, Cancer is the second most essential cause of mortality and morbidity worldwide. Uncontrolled development and proliferation of modified cells is the key feature of this aggressive disease (3). Each year, thousands and thousands of peoples are recognized with cancer, whereas nearly 35 lakh cancer-related deaths are yearly recorded globally (4,5). Particularly, solely in Europe, about 3.45 million new instances of cancer had been reported in 2012, apart from non-melanoma pores and skin cancer, whereas about 1.75 million deaths took place (6). Endometrial cancer is also the most common class of uterine cancer, and is commonly referred as uterine cancer. About 50,000 women are recognized with the disease every year only in America (7).

Now coming to the treatment of Cancers, Cancer is mostly treated by the ways like Chemotherapy, Immunotherapy, Hormone therapy, Hyperthermia, Photodynamic therapy, Radiation therapy, Stem cell transplant, Surgery, Etc. There are, in total, five types of immunotherapy, including checkpoint inhibitors, antibody-based targeted therapies, cancer vaccines, antigenic receptor T-cells, and finally oncolytic viruses [8–9]. Recent studies have shown that immune checkpoint blockades have beneficial effects with conventional cancer therapies, such as chemotherapy and radiation therapy [10]. Immune checkpoint blockades are recognized to activate T cell, whereas the traditional cancer treatment options promote antigen launch and presentation. Dostarlimab one of the recent Immune checkpoint inhibitor helps in effective prevention of the endometrial cancer.

ENDOMETRIAL CANCER:

Endometrial cancer is a type of cancer which deals with high rates of the microsatellite instability–severe condition and DNA Mismatch repair–deficiency (MSI-H/dMMR)(11).It is a 6th most occurring cancer in Women. Endometrial cancer most commonly develops in post-menopausal women . The common age of women recognized with endometrial hyperplasia is 60. It is rarely found in female below the age of 45 (7). Endometrial cancer begins in the lining of the uterus i.e. the endometrium.

The precise reason of endometrial cancer is now not known. However, medical practitioner believes that avoiding the known risk factors when possible, the use of oral contraceptives or different types of hormonal birth control, treating obesity and controlling diabetes are the excellent approaches to lower the risk of developing endometrial cancer (7). Being obese has a great impact which increases a woman's danger of endometrial cancer. Other danger factors which serves in development of endometrial cancer are age, family history, a analysis of polycystic ovary syndrome and prior use of the breast cancer treatment with drug tamoxifen.

Symptoms include peculiar vaginal bleeding, ache throughout intercourse, difficult or painful urination, and pain in the pelvic region. Endometrial cancer is particularly treatable when diagnosed early. This type of cancer is greatly common in Black ladies than white women, and Black women are more prone to death due to endometrial cancer (7).

II. DOSTARLIMAB:

Dostarlimab is an approved monoclonal antibody which inhibit Programmed cell death (PD-1) receptor in humans. Dostarlimab is sold under the Brand name Jemperli. It serves best in condition of Mismatch repair–deficiency (MSI-H/dMMR) .Research and Development of Dostarlimab was started in the year 2018.Commencement of Phase 1 GARNET study was started in 2018.Further major milestones in development of dostarlimab are shown graphically in Figure (Fig.-F.1).

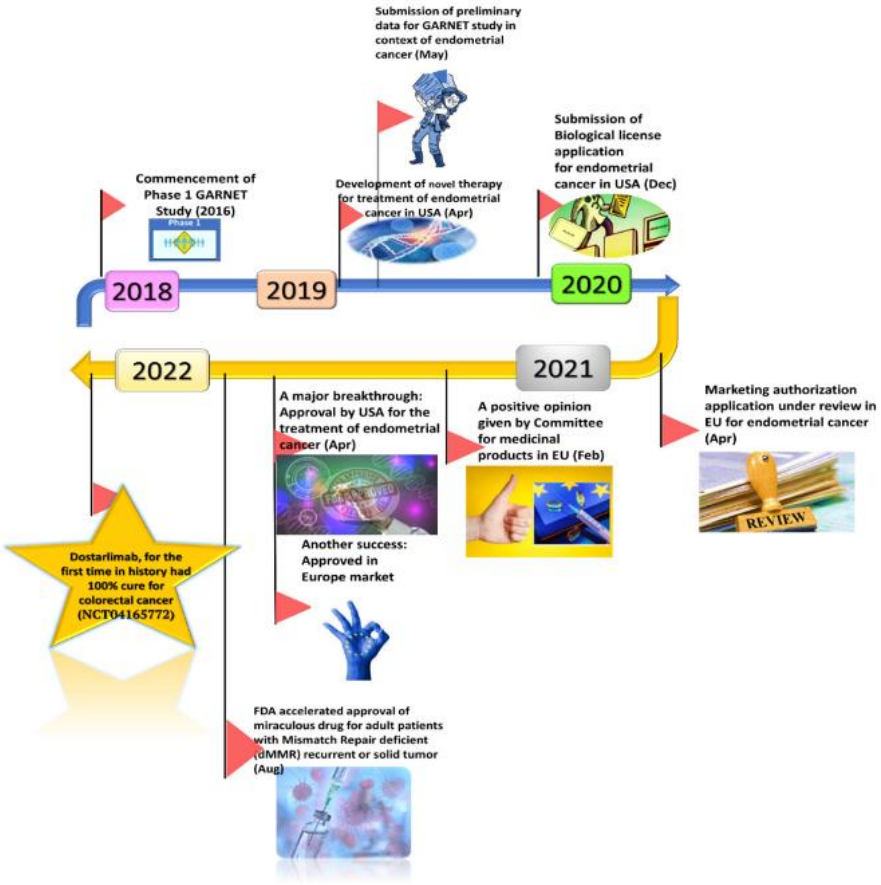

Fig.F-1 : Major milestones in the Research and Development of Dostarlimab.

Dostarlimab as a recent Immune checkpoint inhibitor helps in effective prevention of the endometrial cancer by acting in following manner.

MECHANISM OF ACTION OF DOSTARLIMAB :

Heavy chain of Dostarlimab participates in the interaction between PD-1 and Dostarlimab, the light chain is predominantly considered for steric blockage of PD-L1 binding. To acquire excessive affinity, Dostarlimab causes conformational modifications in the BC, C'D, and FG loops of PD-1. By occupying the concave surface on the heavy chain with the aid of several interactions, the residue R86 inside the C'D loop of PD-1 performs a quintessential position in Dostarlimab binding. This high-resolution shape ought to be beneficial in developing better anti-PD-1 biologics or high-quality cancer immunotherapy aggregate methods [12]. (Fig.–F.2).

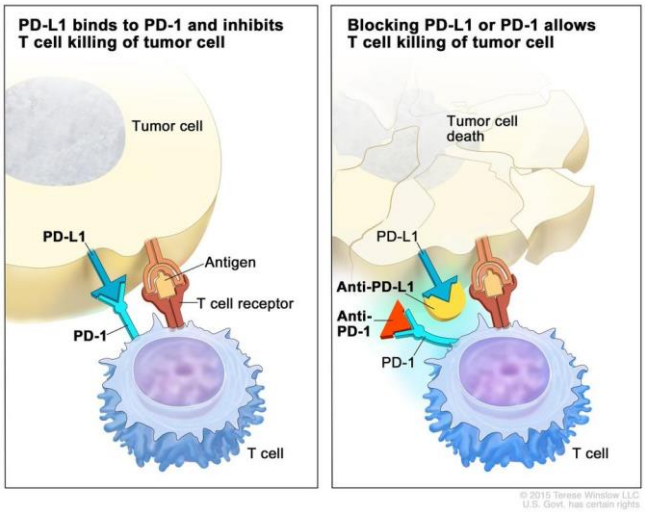

Fig.-F.2 : Mechanism of action of Dostarlimab.

Dostarlimab has a KD value of 0.3 nM for human PD-1, with an affiliation fee of 5.7105 (M−1s−1) and a dissociation rate of 1.7 104 (s−1), indicating quickly target association and delayed dissociation [13]. Apc and complement-dependent cytotoxicity (CDC), Dostarlimab was designed to avoid tumor-reactive T cell depletion.

III. DOSTARLIMAB ANALOGUES:

Throughout history, plant extracts and their isolated purified active components have found to be backbone of cancer chemotherapeutics (14). It is estimated that over 70% of anticancer compounds are either natural products, or herbal product-derived resources (15). Rhus verniciflua Stokes , Quercetin , Liquoritegenin , Glyasperin c , Ellagic acid , Caffeoxylquinic acid derivatives are examples of herbal immune checkpoint inhibitors i.e. Programmed cell death 1 (PD-1) receptor blockers , in other words Dostarlimab analogues

1). RHUS VERNICIFLUA STOKES :

The bark of Rhus verniciflua Stokes (RVS) (belonging to family Anacardiaceae) has been used in treatment of cancer. From nearly 800 natural plant derived extracts with the help of competitive Enzyme-Linked Immunosorbent Assay (ELISA), it is observed that RVS inhibited both the PD-1/PD-L1 and the CTLA-4/CD80 interactions. RVS inhibited 29.9% of CTLA-4/CD80 interaction at 5μg/mL and the EtOAc fraction has found to be the most fantastic blockading activity on CTLA-4/CD80 binding (10). Eriodictyol and fisetin had been the secondary metabolites found in EtOAc fraction of RVS exhibited strongest blockading effects. RVS have been additionally used as herbal medicine to treat a range of conditions, such as gastrointestinal inflammation, arthritis, hypertension, diabetes, heart stroke, and chronic fatigue disease (10).

2). QUERCETIN :

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) belongs to polyphenolic flavonoids which are found in apples in sufficient amount. We can extract quercetin from red grapes, onions, raspberries, honey, cherries, citrus fruits and green leafy vegetables also, studies have proven that extract of grape stem have an potential to inhibit the uncontrolled growth of colon cells(HT29), breast cells(MCF-7), kidney cells (Caki-1) and thyroid cells (K1) most cancers cell lines (16,17). These extracts contains flavonols, specifically quercetin and rutin in very high amount (17). And exerts a range of beneficial effects to health, such as antioxidant, anticancer, antiviral, apoptosis-inducing, protein kinase C-inhibitory, cell cycle modulatory and angiogenesis inhibitory effects. quercetin dihydrate was once screened and proved its potential to inhibit the PD-1/PD-L1 interaction. Treatment with quercetin dihydrate promoted the cytotoxic activity of T cells on MDA-MB-231 and NCI-H460 most cancers cells. Experiments conducted with the help of xenograft mouse model showed that the increasing rate of tumor volumes and masses in the quercetin dihydrate-treated mice had been decreased significantly. Indeed, quercetin is a specialized compound due to its capacity to fight against cancer-related diseases in a multi-targeted manner (18–19). Plenty of researches have investigated the anticancer activity of quercetin (20–21).

3).ELLAGIC ACID FROM BLACK RASPBERRY (*RUBUS COREANUS* MIQUEL) EXTRACT:

Rubus coreanus Miquel (R. coreanus) is a species of genus Rubus belonging to eastern Asia. Its common name in Korean is black raspberry referred to as “bokbunja”. The unriped fruits of R. coreanus have been used as typical medicine for centuries [22].ellagic acid is a chief phenolic constituent found in black raspberry fruit recognized to have a potent antioxidant and anti-tumor potential [23].To check out impact of RCE on the interaction between PD-1 and PD-L1, competitive ELISA tests had been carried out [24] and also pull down assays were performed to elucidate the binding efficiency of RCE in vitro. Cellular PD-1/PD-L1 blocker activities have been measured with the help of T cell receptor (TCR)-induced nuclear factor of activated T cells-luciferase activity in co-cultured cell models along with PD-1/NFAT Jurkat and PD-L1/aAPC CHO-K1 cells. The in vivo efficacy of RCE was once established in humanized PD-1 mice containingMC38 colorectal tumor. RCE and ellagic acid dose-dependently inhibited the binding of PD-1 to PD-L1. However, oral administration of RCE showed the potent anti-tumor property similar to anti-PD-1 antibody. The results validated that RCE interfered the binding of PD-1 and PD-L1 dose respectively at an indicated concentration in range from 25 to 800 μg/mL. The half maximal inhibitory concentration (IC50) value of RCE was once round to be 83.8 ± 4.7 μg/mL. Antagonist antibody to PD-L1 (αPD-L1) were used as a superb positive control, with IC50 value with 1.69 ± 0.8 μg/mL.Hence ellagic acid from RCE possesses powerful anti-tumor effect by means of PD-1/PD-L1 inhibitor. (24)

4). CAFFEOYLQUINIC ACID DERIVATIVES:

Derivatives of Caffeoylquinic acid and itself with a caffeoyl group connected to the − 3, − 4, and − 5 position of quinic acid, respectively, had been recognized as PD-1/PD-L1 inhibitors with the usage of SPR spectroscopic technique [25].Surface Plasmon Resonance (SPR) technology was used to assess the affinity and competitive blockade of 9 caffeoylquinic acid compounds (CQAs) towards PD-1/PD-L1.As a result, four small molecules which include 1-CQA, 3-CQA, 4-CQA and 5-CQA had found to be as inhibitor of PD-1/PD-L1 interaction (26).The KD values of caffeoylquinic acid and its derivatives on PD-1 and PD-L1 receptor , ranged from 0.507 × 10–5 to 1.68 × 10–5 M and from 1.71 × 10–5 to 8.13 × 10–5 M, respectively, found in SPR. In addition, a competitive SPR assay was once used to compare the binding affinity between quinic acid derivatives with one or two caffeoyl group(s) and PD-1. It was concluded that, as in contrast to dicaffeoylquinic acids, mono-caffeoylquinic acid derivatives had a improved stronger binding capacity with PD-1 and PD-L1.

5). APIGENIN & COSMOSIIN FROM *SALVIA PLEBEIAN:*

Salvia plebeian R. Br. (SP) fits for human consumption the plant extensively found in many countries, such as Korea, India, and China and has been used as potent medicine to deal with common cold, diarrhea, and hepatitis (27, 28) SPE and its derivative cosmosiin efficiently inhibited the molecular interaction between PD-1 and PD-L1 receptor. (29) it inhibited tumor growth via upregulating availability of CD8 T-cells in the tumor through the activation of tumor-specific T-cells in a humanized PD-1 mouse model having hPD-L1 knock-in MC38 in cancer .To assess the selective PD-1/PD-L1 inhibitory property of SPE, test was conducted in which competitive PD-1/PD-L1 ELISA-binding assays were done. As a positive control, PD-L1-blocking antibody was once used, which acknowledges the extracellular domain of hPD-L1 blocks the binding of PD-L1 to PD-1 .SPE 50 μg/mL gave relatable inhibitory effect compared to that of PD-L1-blocking antibody 10 μg/mL. Result suggests that SPE particularly blocks the PD-1/PD-L1, Test additionally validated that SPE (50 μg/mL) and SPE-EA (50 μg/mL) inhibited the PD-1/PD-L1 interaction at rate of 41.93 and 62.89%, respectively.

6). ISOLIQUIRITIGENIN:

Isoliquiritigenin (2′,4′,4-trihydroxychalcone, ISL), one of the most significant bioactive substance with a chalcone structure, is derivative of liquorice root. Liquorice is many times recognised as Glycyrrhiza, including Glycyrrhiza uralensis, Glycyrrhiza radix, and Glycyrrhiza glabra, which are commonly accessible in common ingredients and Chinese natural medicines based totally on a large range of biological functions and pharmacological effects(30). ISL stimulated intrinsic apoptosis, inhibits cell proliferation and induces cell cycle arrest (30).

IV. CONCLUSION:

Preliminary findings from the GARNET trial dMMR EC cleared that dostarlimab monotherapy was proven significant and long lasting clinical activity with an acceptable safety profile. Considering these results, the protocol was been amended to continue enrolling patients with dMMR EC (11). There is a need of novel work on the activity of herbal analogues of dostarlimab as they can be used in combination with other drugs

V. RESULT:

In MMR-deficient instances, Dostarlimab has tested for its promising benefits, Treatments such as Dostarlimab have to come extensively available, for treatment as well as access to a clinical group who will assist reveal patients like in the trial NCT04165772 and intervene if the tumor comes back. Rhus verniciflua stockes kill tumor cells and then promote antigen presentation. In addition, RVS, which can block PD-1/PD-L1 and CTLA-4/CD80 checkpoints, would stimulate the sustained activation of T cells.

VI. ABBREVIATIONS:

ADCC	Antibody-Dependent Cellular Cytotoxicity.
APC	Antigen-Presenting Cells.
ELISA	Enzyme-Linked Immunosorbent Assay.
EC	Endometrial cancer.
MSIh	Microsatellite Instability.
CTLA	Cytotoxic T Lymphocyte Associted Protein4
CDC	Complement-Dependent Cytotoxicity.
IgG4	Immunoglobuline G4.
CHO	Chinese Hamster Ovary.
RVS	Rhus Verniciflua Stokes.
CQAs	Caffeoylquinic Acid Compounds.
SPE	Salvia Plebeian Extract.
RCE	Rubus Coreanus Extract.
ISL	Isoliquiritigenin.
TCR	T Cell Receptor.
EtOAc	Ethyl Acetate.

VII. CONFICT OF INTEREST:

Authors declare no conflict of interest.

VIII. ACKNOWLEDGEMENT:

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