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Remedial Magic of Dostarlimab in Endometrium Cancer

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Abstract: ***Endometrial cancer can be cured if we can diagnosed it early, even after that 0.88 million cases were found in India with an incident rate of 105.5 per 100, 000 in women. Immunotherapy is one of the most effective and convenient method used in the treatment of cancer. It includes immune checkpoint inhibitors therapy, monoclonal antibody therapy for example anti-programmed cell death proteinPD-1 receptor monoclonal antibody (Dostarlimab), antigen T-cell therapy. Immunotherapy works on the cancer cells by making their progression decline and controls the growth of cells. In this review, we discussed the mechanism of Dostarlimab in the endometrial cancer mainly. We also discussed the different trials that were going out with the drug Dostarlimab and the pharmacokinetic and pharmacodynamic of the drug which helps in the better understanding of the drug in terms of its evolution after the large number of trials in humans and other living organism also.***

Keywords: Immunotherapy, Programmed cell death protein receptor, Endometrial cancer

1. Introduction

Cancer is the most diagnosed disease in India now (9%) that shows high mortality rate in non-communicable diseases (NCDs) and leading to increased death rate globally. The majority of the patients with cancer were diagnosed as locally/ advanced/ locoregional for breast cancer ([4]) (50.8%), lung cancer (69%) (18). GLOBOCAN estimates of the worldwide incidence and mortality for 36 cancers in185 countries reported 382, 069 new cases of endometrial carcinoma (EC) and 89, 929 deaths due to this cancer in 2018. EC has long been subdivided into two main categories termed type I endometrioid carcinoma and type II non-endometrioid carcinoma, but this dualistic model does not take into account the molecular, biological and pathological heterogeneity among each category. On the basis of integrated genomic, transcriptomic and (3)Cancer Genome Atlas Research Network (TCGA) has proposed a novel classification into four categories termed polymerase " (POLE) ultramutated, microsatellite instability (MSI) hypermutated, copy number low (endometrioid) and copy number high (serous-like) have suggested a simplified, pragmatic, clinically applicable molecular based classification system termed Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) which does not require the expensive genomic methodology and that is applicable to formalin-fixed paraffin-embedded samples. This system based on mismatch repair (MMR) protein immunohistochemistry, POLE mutational analysis and p53 immunohistochemistry identifies four molecular subtypes that are similar but not identical to genomic TCGA subtypes. Endometrial cancer was gradually increased from past 3-4 years, since 2020 it is the 6th most common cancer diagnosed in women, and it was increases to 18.3% in India (18). The mortality rate is projected to rise by 19% between 2014 and 2035, and to 9 deaths per 100, 000 females by 2035. Endometrium cancer begins in the cells of the lining (endometrium) of the uterus, also known as womb/uterus/cervix uteri cancer. Patients with intermittent endometrial cancer (EC) are not suitable for surgery or radiotherapy is patients for pharmacological treatment frequently with unsatisfactory clinical results (6).

Dostarlimab is a monoclonal antibody that blocks programmed cell death receptor-1 (PD-1) and has shown positive results in the treatment of endometrial cancer. It is indicated as monotherapy for the treatment of patients with relapsed or advanced endometrial cancer (EC) with maladjustment repair deficiency (dMMR) / microsatellite instability (MSI-H) who have continued or after treatment with a platinum-containing regimen (cisplatin, carboplatin). Programmed cell death-1 (PD-1) is an immune checkpoint receptor expressed on antigen-activated and dissipated T cells that releases inhibitory signals to control local inflammation response and maintains self-tolerance. When the PD-1 receptor binds to tumor-expressed PD-L1 and PD-L2 ligands, it inhibits T cell proliferation and cytokine production (15). Stimulation of PD-L1 by many tumors creates agitation of PD-1 / PD-L1 pathway, sufficient to attenuate the cytotoxic T cell response in the tumor microenvironment and has been associated with misdiagnosis. Blocking the PD-1/PD-L1 binding reversed immune evasion and restored the adaptive immune response in opposition to the tumor. Additionally, PD-(L)1 monoclonal antibodies (mAbs) have demonstrated antitumor activity in patients with various solid tumors (10).

In Phase I/II of the GARNET study, 104 women with MSI and 143 women with advanced/relapsed CE MSS received dostarlimab 500 mg every 3 weeks (once every 3 weeks) for 4 doses, then 1000 mg every 6 weeks (once every 6 weeks). The primary endpoint was ORR (overall response rate); DCR (disease control rate) and DOR (duration of response) were secondary endpoints.

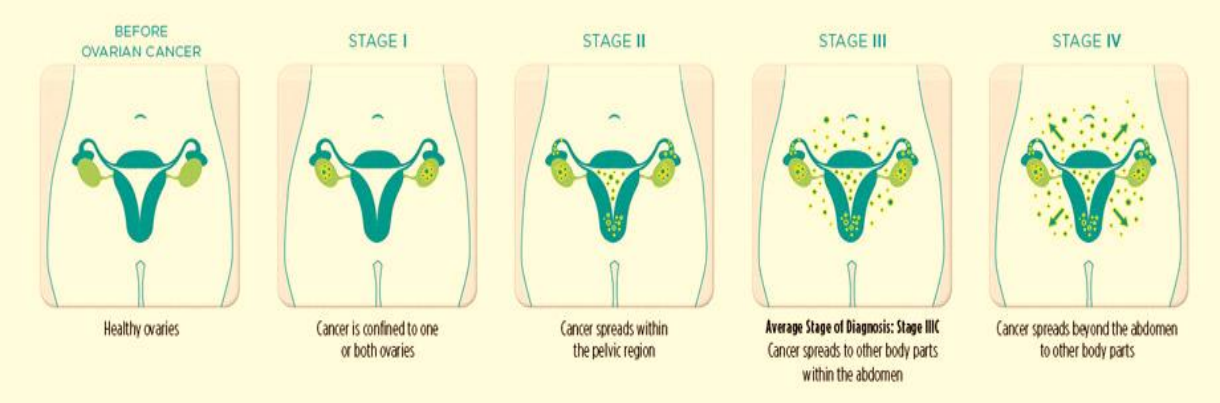

Figure 1: Stages of Endometrial Cancer

Dostarlimab has shown significant clinical benefit, with an ORR of 44.8% (96% CI, 34.9%-54.8%) in MSI, and 13.5% (95% CI, 8.4%-20.5%) in MSS women. DCR was 57.8% and 35.6% in the MSI and MSS groups, respectively. 63.8% MSI and 71.9% MSS patients developed TRAEs (number and grade of treatment related adverse events), of which 13.8% and 19.8% were serious AEs (13). Dostarlimab is currently being studied in a phase III clinical study (RUBY) in combination with standard chemotherapy in patients with recurrent or predominantly advanced endometrial cancer [44]. Another PD-1 inhibitor, pembrolizumab, is also being studied in another phase III clinical trial (NRG GY-018) [45]. The NRG GY-018 study aimed to determine the efficacy of pembrolizumab in combination with paclitaxel and carboplatin in patients with advanced disease (stage III or measurable IVA, stage IVB and stratified recurrent endometrial cancer depending on ROR status). A clinical trial with a PD-L1 inhibitor is also underway. AtTENd/ENGOT-en7 is a Phase III, multicenter, double-blind, randomized, controlled study of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/relapsed endometrial cancer (3).

How Dostarlimab Works

PD-1 iPD1 is an immune checkpoint receptor found in T cells that suppresses cancer-specific immune responses. The humanized IgG4 mAb, dostarlimab, is derived from Chinese hamster ovary cells and has a molecular weight of approximately 144 kDa. Binding between 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 signalling through this pathway may contribute to the suppression of active T-cell immunity. This is where the drug dostarlimab comes in. It inhibits programmed cell death receptor-1 (PD-1) and blocks the receptor interaction with PD-L1 and PD-L2, which in turn activates T cells and enhances overall immunity (14). Studies have shown that dostarlimab binds with high affinity to human and cynomolgus monkey PD-1 receptors as indicated by flow cytometry and plasmon resonance results. . Additionally, a human CD4+ lymphocyte response assay demonstrated that dostarlimab acted as a functional antagonist, resulting in increased IL-2 production. This test also demonstrated the increased activity of dostarlimab in the presence of TIM3 antibodies or LAG3 antibodies. In the presence of antibodies, dostarlimab showed increased activity, but no significant cytokine release from human PBMCs (peripheral blood mononuclear cells), a cell surface protein encoded by the PDCD1 gene and expressed specifically on the surface of lymphocytes B and T activated, was observed (1).

The PD-1 pathway is a negative feedback system that controls the cytotoxic activity of lymphocytes to prevent autoimmune reactions. Its main ligand PD-L1 is constitutively expressed at low levels on antigen-presenting cells (dendritic cells, macrophages and B cells) and is upregulated in these cells after their activation, as well as in activated T cells and in various cancer cells.

PD-L1 is regulated by many inflammatory cytokines including IFNγ, GM-CSF, LPS, IL-4 and IL-10 [11, 12]. PD-L1 expression has been amply demonstrated in tumors and is often associated with poor prognosis.

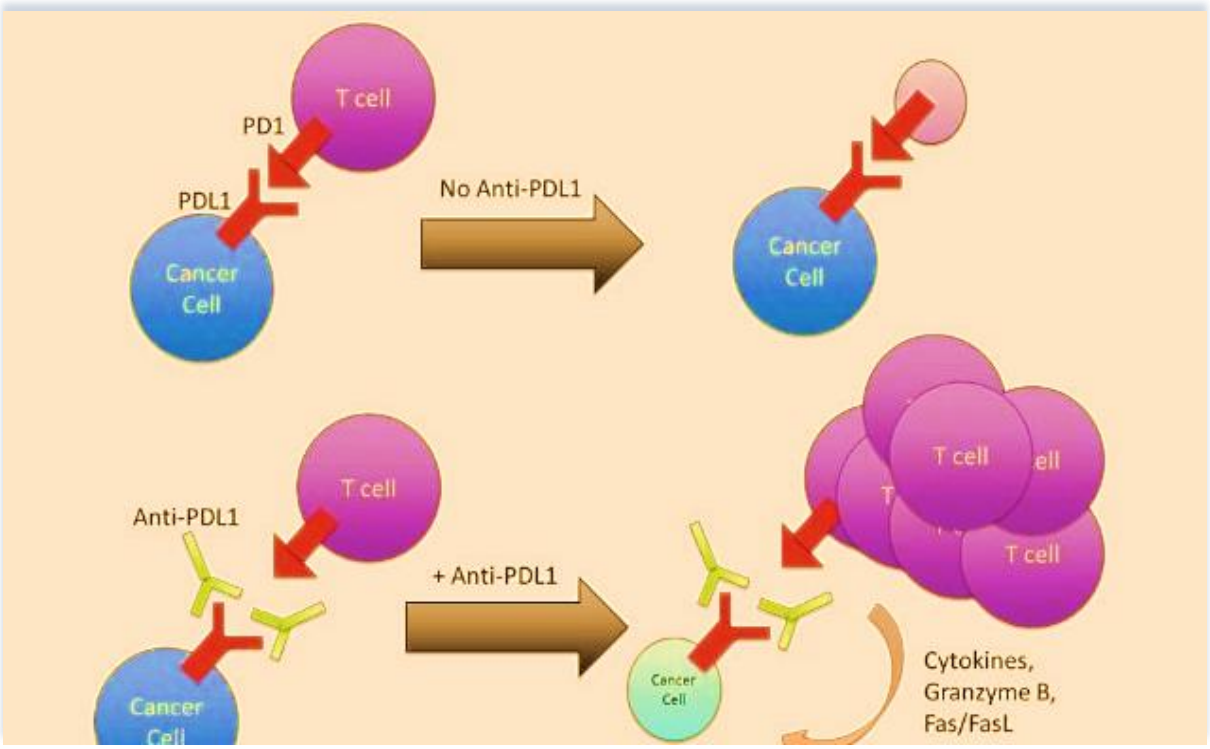

Figure 2: It shows the mechanism of PDL1 Receptor on Cancer cells

Its main ligand PD-L1 is constitutively expressed at low levels on antigen-presenting cells (dendritic cells, macrophages and B cells) and is upregulated in these cells after their activation, as well as in activated T cells and in various cancer cells. PD-L1 is regulated by many inflammatory cytokines, including IFN, GM-CSF, LPS, IL-4, and IL-10. PD-L1 expression has been amply demonstrated in tumors and is often associated with poor prognosis. PD-L1 upregulation is modulated by CD8 + T cells and IFN. Therefore, PD-L1 expression could be viewed as a negative feedback loop dependent on an infiltrating immune response. PD-L1 is expressed in 92% of endometrial cancers. High PD-L1 expression is associated with advanced tumor stage and poor tumor differentiation. PD-L1 is expressed in92% of endometrial cancers. High PD-L1 expression is associated with advanced tumor stage and poor tumor differentiation; however, unlike what is usually observed in other solid tumors, PD-L1 does not appear as a prognostic factor in endometrial cancers. (6)

On the other hand, the PD-L2 expression is much more restricted. It is mainly expressed on antigen presenting cells but expression can be induced on several other immune and non-immune cells depending on environmental stimuli. PD-L2 has moderate to-high expression in triple negative breast cancer and gastric cancer and low expression in renal carcinoma. PD-L2 is expressed at low levels within endometrial tumors, but at higher rates in serous tumors. More data are needed to better understand its role in immune response before confirming it can be considered a good candidate to target in this tumor type. Modulation of the immune response thus appears to be different within molecular subtypes. Willvonseder et al. demonstrated greater infiltration by TILs in high-grade tumors compared to low-grade tumors, as well as in the POLE and MSI-H subgroups. The greater infiltration of ultramutated POLE and MSI-H tumors is accompanied by over expression of PD-1 and PD-L1. Likewise, the immune microenvironment of MSIH endometrial tumors harbors more activated CD8 + T-cells and PD-L1 + cells in MSI-H vs. MSS. In a large cohort of 183 EC, Kim et al. showed that a high level of PD-L1 + T-cells was significantly associated with a shorter PFS predominantly in MSS tumors (2).

Pharmacokinetic and Pharmacodynamic of the Drug

The blood sampling schedule is detailed in the supplement methods. Dostarlimab serum concentrations were quantified using the enzyme immunoassay (supplementary methods). PK analysis was performed with (WinNonlin Version 8.0, Phasight, Mountain View, CA)and 2-compartment analysis methods (NONMEM, ICON Development Solutions, Ellicott City, MD). Maximum (Cmax) and trough serum concentrations (Ctrough) of dostarlimab and time to Cmax (Tmax) were the observed values. In total Systemic exposure to dostarlimab was estimated by calculation area under dostarlimab serum concentration - time Curve (AUC) according to the linear trapezoidal method (linear upwards, Sign out). The terminal elimination half-life was calculated as ln (2)/k. Body weight was assessed as a covariate for clearance of dostarlimab before studying the fixed-dose strategy in Part 2A and further analysis of the combined data both parts 1 and 2A. (10) Also a preliminary population The PK model was developed based on available data from weight-based doses in 17 patients. The preliminary model was developed to describe PK properties in general terms of dostarlimab and to assess the effect of body weight on exposure to pharmacokinetics to support the search for a fixed dose of Dostarlimab future cohorts. Multi-compartment mode structures have been sought. Given the purpose of body modeling only Weight was determined as a covariate for drug clearance. Based 1000 patients under dosage were simulated on this model Schemes with 500 mg

Q3W or 1000 mg Q6W. Trust & Prediction intervals around minimum concentrations Calculated and reported at the end of the dosing interval (16). To analyze PDy, flow cytometry was used to evaluate: direct occupation of the PD-1 receptor (RO) of Dostarlimab on CD3 + mononuclear cells circulating in peripheral blood [14, 15]. The functional RO grade of dostarlimab was further determined by measuring interleukin-2 (IL-2) concentrations. After ex vivo stimulation of T lymphocytes. Whole blood collected from patients was incubated with superantigenstaphylococcal enterotoxin B in the presence of saturation concentrations of dostarlimab or isotype control to be increased IL-2 production. The ratio of IL-2 to saturation with dostarlimab versus isotype control is an RO measure of of which 1 reflects the maximum and therefore complete stimulation a pharmacokinetic study for dostarlimab-gxly was performed on patients with solid tumors which included 150 endometrial cancer patients. It was noted that there was a proportionate increase in mean Cmax, AUC0□inf and AUC0□_ over the dose range of1.0-10 mg/kg. Moreover, the mean cycles of Cmax and AUC0□_ after the administration of 500 mg dostarlimab once every 3 weeks was reported to be in the range of 171 _g/Ml and 35, 730 _g_h/mL, respectively, and 309 _g/mL and 95, 820 _g_h/mL, respectively, at a dose of 1000 mg administered once every 6 weeks. Similarly, the study also evidenced the mean steady-state volume of the distribution of dostarlimab to be around 5.3 L, and the mean steady-state clearance to be in the range of 0.007 L/h. There were no clinically significant differences observed in the pharmacokinetics characteristics of Dostarlimab based on gender, age, ethnicity, tumor type, or renal or hepatic impairment. Although, there are no studies conducted to determine whether dostarlimab-gxly is carcinogenic orgenotoxic. Fertility studies have been performed for this drug on monkeys which, after repeating doses for one and three months, found no significant effects on male or female reproductive organs, although most animals in these studies were not sexually mature by the time of study (11).

The first human study, 4010-01-001, also known as the GARNET study (NCT02715284), evaluated the pharmacokinetics (PK), pharmacodynamics (PD), tolerability, clinical activity and safety of dostarlimab in several solid cancers, including endometrial cancer, NSCL, and ovarian and fallopian tube cancer. A modified 3+3 design was used to evaluate three weight-based doses (1, 3, and 10 mg/kg) each administered2 weeks intravenously in Part 1. Part 2A used two fixed dosage regimens, 500 mg intravenously every 3 weeks and 1000 mg intravenously every 6 weeks in Part 2B. Part 1 data showed maximal receptor occupancy at serum dostarlimab concentrations of 2.4 g/mL. Additionally, a PK model was constructed using the PK data from Part 1 to predict dostarlimab concentrations that would exceed them resulting in maximum receptor occupancy at fixed doses. Similarly, Part 2A demonstrated dose-proportional pharmacokinetics and median trough serum concentrations to be approximately40 and 50 ng/mL after a single dose of 500 mg and 1000 mg, respectively (1).

Dostarlimab and Other Combination Therapies under Trial

There are several other immune checkpoint inhibitors such as nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab that are used to treat cancer. Since dostarlimab is an mAB and not a drug transporter substrate or cytokine modulator, drug interactions are unlikely. However, a comparison of dostarlimab is based on its pharmacodynamic and pharmacokinetic properties should be performed with other immune checkpoint inhibitor therapies for a clear and optimal understanding. Similar to nivolumab and pembrolizumab, dostarlimab acts specifically on anti-PD-1 receptors, while atezolizumab, durvalumab and avelumab act not only via anti-PD-1 receptors, but also interact with anti-PD-1 receptors. PD-1 and B7.1 blockers. Similarly, the mean peak occupancy is ~90% for dostarlimab and ~85% (70-97%) for nivolumab. The cumulative dose has also been recorded forthese drugs: approximately 2-fold for dostarlimab, 3.7-fold for nivolumab, 2.2 times for pembrolizumab, approximately 1.91 times for atezolizumab and 4.3 times and 1.25 times for durvalumab and avelumab, respectively. The three-week dosing regimen is similar for the pembrolizumab and nivolumab dosing regimens and provides closer monitoring of patients when initiating new treatment. A dose of 500 mg i. v. every 3 weeks followed by 1000 mg IV every 6 weeks is usually given as a safety regimen for dostarlimab, whereas this one is 240 mg i. v. 2 weeks and 200 mg IV every 3 weeks for nivolumab or pembrolizumab. Similarly, the administered dose of atezolizumab is 1200 mg or 15 mg/kg i. v. every 3 weeks; to Durvalumab is 1500 mg i. v. every 4 weeks and for ICI avelumab 10 mg/kg i. v. every 2 weeks. (8).

Dostarlimab is also being studied for activity with one or more chemotherapy drugs Drugs like niraparib, pembrolizumab, bevacizumab, cobolimab and many more. Most of these studies, which have been conducted for different types of cancers, are still in the experimental phase.

The following data refers to some of these ongoing investigations. A combined study looked at the drug PARPi niraparib and the anti-PD-1 Mab dostarlimab, given to patients with advanced squamous cell carcinoma of the head and neck (HNSCC). Niraparib is a type of targeted therapy that inhibits polyadenosine diphosphate ribose polymerase (PARP), an enzyme that repairs DNA when it is damaged. Blocking this PARP can prevent DNA repair in cancer cells, causing them to die. This phase II study with 49 patients was initiated on February 8, 2021. Researchers speculate that combinatorial immunotherapy may lead to a reduction in the number of locoregional relapses (LRR) and distant metastases (DM) in high-risk patients. by HNSCC. Similarly, a phase III study has been designed to investigate the effects of dostarlimab and niraparib to investigate their effects in the treatment of small cell lung cancer and other high-risk neuroendocrine cancers. This open-label one-group study began on February 1, 2021, with an estimated enrolment of 48 patients. Different Phase II studies are currently underway for this combination therapy (dostarlimab and niraparib) in patients with BRCA1 / 2 and PALB2 mutated germline cancer or somatic pancreatic

cancer, for breast cancer in patients with BRCA mutations, pediatric solid tumors, mesothelium NSCLC and pancreas, endometrial and ovarian cancer. (10)

Besides these, other combinations such as cobolimab, docetaxel and dostarlimab, dostarlimab and pembrolizumab; feladilimab, dostarlimab and cobolimab; bevacizumab, carboplatin, cobolimab, dostarlimab, niraparib, paclitaxel and pemetrexed; and dostarlimab, niraparib and pembrolizumab are currently being studied for NSCLC (1). Additionally, dostarlimab, cobolimab, nivolumab, encelimab and docetaxel; B intrafusp alpha, cobolimab, dostarlimab, feladilimab, GSK 3174998 and pembrolizumab; and Dostarlimab and encelimab are being studied for other collateral and solid tumors. (9)

2. Conclusion

The T-cell often becomes "on" after a virus enters the body or when a given stimulus fails to have an effect, activating the body's immune system to defend itself. Immune checkpoint proteins are present on the surface of these T-cells. The majority of cancer cells over express certain proteins that deactivate T-cells, which ought to be present to fight cancer cells as they grow and multiply. The immune response button of T-cells is thus "turned off" by cancer cells, preventing them from detecting and suppressing the cancer cells. As a result, immunotherapy targets tumours and prevents them from acting on T cells. T-cells are then compelled to combat them right away as a result of this. One immune checkpoint inhibitor, dostarlimab, prevents the PD-1 protein from binding.

References

[1] Singh, V.; Sheikh, A.; Abourehab, M. A. S.; Kesharwani, P. Dostarlimab as a Miracle Drug: Rising Hope against Cancer Treatment. Biosensors **2022**.
[2] Rousset-Rouviere, S.; Rochigneux, P.; Chrétien, A. -S.; Fattori, S.; Gorvel, L.; Provansal, M.; Lambaudie, E.; Olive, D.; Sabatier, R. Endometrial Carcinoma: Immune Microenvironment and Emerging Treatments in Immuno-Oncology. Biomedicines **2021**, 9, 632
[3] J Gynecol Oncol. 2022 Mar; 33 (2): e43 pISSN 2005-0380·eISSN 2005-0399
[4] Gadducci, A.; Cosio, S. Pharmacological Treatment of Advanced, Persistent or Metastatic Endometrial Cancer: State of the Art and Perspectives of Clinical Research
[5] for the Special Issue “Diagnosis and Management of Endometrial Cancer”. Cancers **2021**, 13, 6155.
[6] Maiorano BA, Maiorano MFP, Cormio G, Maglione A, Lorusso D and Maiello E (2022) How Immunotherapy Modified the Therapeutic Scenario of Endometrial Cancer: A Systematic Review. Front. Oncol.12: 844801. doi: 10.3389/fonc.2022.844801
[7] Gadducci, A.; Cosio, S. Pharmacological Treatment of Advanced, Persistent or Metastatic Endometrial Cancer: State of the Art and Perspectives of Clinical Researchfor the Special Issue “Diagnosis and Management of Endometrial Cancer”. Cancers 2021, 13, 6155.
[8] Ilia N. Buhtoiarov, Paul M. Sondel, Jon M. Wigginton, Tatiana N. Buhtoiarova, Eric M. Yanke, David A. Mahvi and Alexander L. Rakhmilevich Anti-tumour synergy of cytotoxic chemotherapy and anti-CD40plus CpG-ODN immunotherapy through repolarization of tumour associated macrophages 2010.
[9] Francesco Passiglia, Paolo Bironzo, Luisella Righi, Angela Listì, Francesca Arizio, Silvia Novello, Marco Volante, Giorgio Vittorio ScagliottiA Prospective Phase II Single-arm Study ofNiraparib Plus Dostarlimab in Patients With Advanced None small-cell Lung Cancer and/or Malignant Pleural Mesothelioma, Positive forPD-L1 Expression and Germline or Somatic Mutations in the DNA Repair Genes: Rationaleand Study Design, Clinical Lung Cancer, Vol. 22
[10] Islam, M. R.; Awal, M. A.; Khames, A.; Abourehab, M. A. S.; Samad, A.; Hassan, W. M. I.; Alam, R.; Osman, O. I.; Nur, S. M.; Molla, M. H. R.; et al. ComputationalIdentification of Druggable Bioactive Compounds from Catharanthus roseus and Avicennia marina against Colorectal Cancer by Targeting Thymidylate Synthase. Molecules 2022, 27.
[11] Amita Patnaik1 · Glen J. Weiss2, 6 · Drew W. Rasco1 · Lisa Blaydorn2 · Amy Mirabella3 · Murali Beeram1 · Wei Guo4 ·Sharon Lu4 · Hadi Danaee4, 7 · Kristen McEachern5 · Ellie Im4 · Jasgit C. Sachdev3Safety, antitumor activity, and pharmacokinetics of dostarlimab, an anti-PD-1, in patients with advanced solid tumors: a dose-escalation phase 1 trial, 2021/09.
[12] Prashant Mathur, DNB, PhD1; Krishnan Sathishkumar, MSc1; Meesha Chaturvedi, MBBS1; Priyanka Das, B-Level1; Kondalli Lakshminarayana Sudarshan, MSc1; Stephen Santhappan, MSc, MPhil1; Vinodh Nallasamy, MSc, MPhil1; Anish John, BE1; Sandeep Narasimhan, MSc1; and Francis Selvaraj Roselind, MSc1Cancer Statistics, 2020: Report From National Cancer Registry Programme, India, 2020.
[13] Peyraud F, Italiano A. Combined PARP inhibition and immune checkpointtherapy in solid tumors. Cancers (Basel) 2020; 12: 1502.
[14] Rahiman, N.; Markina, Y. V.; Kesharwani, P.; Johnston, T. P.; Sahebkar, A. Curcumin-based nanotechnology approaches andtherapeutics in restoration of autoimmune diseases. J. Control. Release 2022, 348, 264-286
[15] Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R. L.; Torre, L. A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.
[16] CA Cancer J. Clin. 2018, 68, 394-424. 2. Siegel, R. L.; Miller, K. D.; Jemal, A. Cancer statistics, 2020. CA Cancer J. Clin. 2020, 70, 7-30.
[17] Rizvi NA, Hellmann MD, Snyder A, et al. Mutational landscape determinessensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348 124-8.
[18] National Centre for Disease Informatics and Research: Time trends in cancer incidence rates, 1982-2010, Bangalore: National Cancer Registry Programme (NCRP-ICMR), 2013.
[19] Takiar R: Status of breast and cervix cancer in selected registries of India. Ann Women’s Health 2: 1012, 2018.