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Review article

Immunotherapy and Ovarian Cancer

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Abstract

Ovarian cancer is one of the leading causes of death and poses a significant health challenge worldwide. The standard therapy for ovarian cancer involving use of surgery and platinum chemotherapy had led to recurrence among majority of patients. Recent improvement in the understanding of the etiology and molecular characteritics of ovarian cancer has paved the way for exploring the utility of immunotherapy for ovarian cancer. Currently, Avastin (Bevacizumab) is the only US FDA approved immunotherapy to be used in combination with chemotherapy among women who have advanced ovarian cancer. Ongoing and planned clinical trials exploring the potential of various immunotherapy modalities will ultimately demonstrate the clinical utility of this therapeutic strategy. This article focuses on the immunotherapies that may offer therapeutic opportunities in the future.

Keywords: Ovarian cancer; Bevacizumab; Immunotherapy; Adoptive T-Cell Therapies; Therapeutic Vaccines

Abbreviations

Ad : Adenovirus serotypes ;
ADC: Antibody-Drug Conjugate;
ADCC: Antibody-dependent cellular cytotoxicity;
ALVAC (2): Replication-defective recombinant canary pox virus;
APCs: Antigen-Presenting cells;
ARID1A: AT-rich interaction domain 1A;
B7H: B7 homolog 1; programmed cell death ligand 1;
BRAF: V-Raf Murine Sarcoma Viral Oncogene Homolog B1;
CA-125: Cancer Tumor-Associated Antigen;
CDC: Complement-Dependent Cytotoxicity;
CDX2: Caudal Type Homeobox 2;
CEA: Carcinoembryonic Antigen;
chk1: checkpoint kinase 1;
CLDN6: Claudin 6;
COX: Cyclooxygenase;
CTLA4: Cytotoxic T-lymphocyte-associated antigen-4;
DC: Dendritic cells;

DLL4: Delta-like ligand 4;
DNA: Deoxyribonucleic acid;
DNP: 2,4-dinitrophenol;
EOC: Epithelial ovarian cancer;
ERBB2: Human epidermal receptor growth factor 2;
FBP: Folate binding protein;
FDA: Food and Drug Administration;
FR-alpha: Folate Receptor Alpha;
FSH: Follicle-Stimulating Hormone;
FSHR: Follicle-Stimulating Hormone Receptor;
GL-ONC: Genetically Stable Oncolytic Virus;
Hh: Hedgehog;
HLA: Human Leukocyte Antigen;
HRT: Hormone Replacement Therapy;
hTERT: human Telomerase Reverse Transcriptase;
Ig: Immunoglobulin;
KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog;
LH: Luteinizing Hormone;
MEK: Mitogen-Activated Protein Kinase;
mRNA: messenger Ribonucleic Acids;
MVA: Modified vaccinia Ankara;
MVA-h5T4: MVA viral vector encoding the 5T4 fetal oncoprotein;
NK: Natural Killer;
NY-ESO-1: New York Esophageal Squamous Cell Carcinoma 1;
p53 SLP: p53 Synthetic Long Peptide;
PARP: Poly (ADP-ribose) Polymerase;
PD-L: Programmed Death-Ligand;
PTEN: Phosphatase and tensin homolog;
rhGM-CSF: recombinant human Granulocyte Macrophage-Colony Stimulating Factor;
TAA: Tumor-Associated Antigen;
TCR: T-cell receptor;
TF: Tissue Factor;
TP53: Tumor Protein p53;
TRICOM: Triad of the Co-Stimulatory Molecules- B7-1, ICAM-1 and LFA-3;
TROP-2: Tumor-Associated Calcium Signal Transducer 2;
VEGF: Vascular Endothelial Growth Factor

Introduction/ Epidemiology

Ovarian cancer is the second most common type of gynecologic tumor in women worldwide and fifth leading cause of cancer death. In 2014, the mortality rate was estimated to be about 15,000 deaths per year worldwide [1]. Primary tumors arise from three different types of cell: epithelial, germ and sex cord stromal cell, but 90 % of the ovarian cancer accounts for the tumor of epithelial cell. Most of the malignant ovarian tumors are epithelial, but based on the morphologic classification, it is divided as serous, endometrioid, clear cell, and mucinous as well [2]. Malignant tumor shows immunogenic effect in ovarian cancer [3]. To understand the activation of immune response in ovarian cancer, there is a requirement for scheming clinically meaningful immunological strategies against ovarian cancer. The outcome of clinical trials in ovarian cancer necessitate an integrative approach in the immunotherapy of ovarian cancer [4].

Ovarian cancer is one of the leading causes of death worldwide. According to the American Cancer Society, in 2014, about 21,980 new cases of ovarian cancer were diagnosed and 14,270 women died of ovarian cancer in United States. The overall five-year survival rate is 45%, but this varies widely depending on the extent or stage of the cancer and the age of the patient. For tumors diagnosed at stage one, the five-year survival rate is 92%. However, for cancers that have spread to the surrounding organs or tissue (regional spread), the five-year survival rate is 72% and for metastatic cancer at the time of diagnosis, the five-year survival rate is 27% [5].

North American and European countries have higher incidence rates as compared to the rest of the world. The cause of ovarian cancer is not clear. Generally, it begins when a genetic mutation turns normal cells into abnormal cancer cells. [6] The incidence is higher in women, aged between 55-64 years and the median age of diagnosis is 63 years. The median age of death from ovarian cancer is 71[6].

Etiology/ Predisposing Factors

The exact cause of ovarian cancer is unknown, but several risk and contributing factors have been identified. The risk of ovarian cancer is higher in women with early menarche or late menopause. It is well known that ovarian cancer is related to ovulation. There is growing evidence that estrogen, progesterone, and other hormones also play a role in the development and progression of ovarian cancer. According to the "theory of incessant ovulation", the repeated ovarian epithelial trauma caused by follicular rupture and subsequent epithelial repair, results in genetic alterations within the surface epithelium. Additionally, the gonadotropin theory states that persistent stimulation of the ovaries by gonadotropin, coupled with local effects of endogenous hormones, increase surface epithelial proliferation and subsequent mitotic activity [7]. In ovarian cancer cell lines, both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) act by utilizing PI3K/Akt pathway to upregulate cyclooxygenase (COX-1 and COX-2), resulting in increased cell motility and invasion.The FSH receptor (FSHR) is also found in ovarian carcinomas [8].

The risk of ovarian cancer is also enhanced with hormone therapy. A nationwide prospective cohort study, conducted over 10 years that included women aged 50-79 years, stated that the risk for ovarian cancer increases with hormone therapy [9]. Incidence in current and non-users of hormones were 0.52 and 0.40 per 1000 years, respectively. It refers to approximately 1 extra ovarian cancer for approximately 8300 women taking hormone therapy, each year. Lactose intake and utilizing talcum powder on the vulva and perineum also increases the risk of ovarian cancer [9].

Predisposing Factors Which Contribute To The Progression Of The Ovarian Cancer Include: [10-12]

Age: The incidence is higher in women at the median age of 63.2 years.

Reproductive risk factors: Various pathological conditions such as nulligravidity, infertility, advanced maternal age at first childbirth, and early menarche or late menopause.

Women with endometriosis have been found to have an increased risk of developing clear cell or endometrioid ovarian cancer.

Lifestyle factors such as cigarette smoking, obesity, and unhealthy diet may increase the risk of ovarian cancer.

Family history of breast or ovarian cancer is a prominent risk factor to cause ovarian cancer, as 5–10% of ovarian cancers are due to heritable risk.

Hormone replacement therapy (HRT) increases the risk of ovarian cancer.

The availability of new technology in diagnosis may help in the early detection of ovarian cancer. Diagnostic technology will include as a primary requirement for the management of disease.

Pathophysiology and Molecular Basis

Serous cancer is divided into low and high-grade subtypes [13,14]. Low grade is characterized by mutations of Kirsten rat sarcoma viral oncogene homolog (KRAS), v-raf murine sarcoma viral oncogene homolog B1 (BRAF) and human epidermal receptor growth factor 2 (ERBB2), and high grade is characterized by tumor protein p53 (TP53) mutations and does not involve mutations of KRAS, BRAF and ERBB2 [15]. In addition to familial ovarian cancers, the histology of the patients with germline mutations in either BRCA1 or BRCA2, is mostly in the serous type. Serous type has the highest frequency of tubal cancers, and that tubal cancers are found in a higher number of patients with BRCA mutations, who undergo prophylactic salpingo-oophorectomy [16].

Another type of epithelial ovarian tumor is mucinous cancer. Metastatic ovarian cancers from the gastrointestinal tract often show mucinous architecture [17], therefore it is important to define accurately, the origin of the tumor by investigating the immunostaining patterns of cytokeratin 7, cytokeratin 20, caudal type homeobox 2 (CDX2) and some other antibodies [18]. In addition to primary ovarian mucinous cancers, mutations of KRAS were seen at higher rates (46–75%) as compared to the other types [19-21].

In endometrioid cancer, there was a genetic change in phosphatase and tensin homolog (PTEN) (20–43%) [22,23]. Mutation of β-catenin was also observed in this type of tumor (32–64%) [22,24,25]. On the other hand, the responsible genes, contributing to the carcinogenesis of clear cell cancer, are less well investigated.

In clear cell cancer, there were frequent mutations of chromatin remodeling gene AT-rich interaction domain 1A (ARID1A) (BAF250a), up to 57% and in endometrioid cancer, up to 30% [26,27].

Immunotherapy

Current immunotherapeutic modalities for ovarian cancer fall into nine broad categories: monoclonal antibodies, kinase inhibitors, check-point inhibitors, therapeutic vaccines, adoptive T cell transfer, heghog inhibitors, proteasome inhibitors, oncolytic virus therapy and chemoimmunotherapy [28].

Monoclonal Antibodies:

The Food and Drug Administration (FDA) approved Monoclonal antibodies:

Bevacizumab: [29,30] A recombinant humanized monoclonal antibody, directed against the vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab binds to VEGF and inhibits VEGF receptor binding, thereby preventing the growth and maintenance of tumor blood vessels.

Indication and uses: Bevacizumab has received FDA approval as a VEGF-specific angiogenesis inhibitor and indicated for the treatment of relapsed/refractory ovarian cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan.

PD/PK: The half-life is around 20 days and its steady state is 100 days. The males have a larger Vc (3.25 L vs. 2.66 L) and a higher clearance rate (0.262 L/day vs. 0.207 L/day) than females.

Contraindications: History of hypersensitivity to bevacizumab.

Warnings: Gastrointestinal perforations, surgical and wound healing complications, thrombosis and hemorrhage.

Adverse Events: Most common adverse events are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

Non FDA approved Monoclonal antibodies: The non-FDA approved monoclonal antibodies that are under clinical trials is given in the Table-1 below:

Farletuzumab (MORAb-003): A humanized, immunoglobulin G1 (IgG1) monoclonal antibody which targets folate receptor alpha (FR-alpha). FR-alpha is usually over-expressed by a number of epithelial-derived cancers such as ovarian,

IMAB027: A monoclonal antibody directed against the cell surface protein claudin 6 (CLDN6), with potential immunostimulating and antineoplastic activities. Upon administration, the anti-CLDN6 monoclonal antibody IMAB027 binds to CLDN-6 and may stimulate the immune system to exert both an antibody-dependent cellular cytotoxicity (ADCC) and a complement-dependent cytotoxicity (CDC)-mediated immune response against CLDN-6-expressing tumor cells. This may inhibit tumor cell growth. CLDN-6, a tight-junction protein and embryonic antigen, is expressed on a variety of tumor cells but is not expressed on normal, healthy adult cells.

Abagovomab: A murine IgG1 monoclonal anti-idiotype antibody, containing a variable antigen-binding region that functionally mimics the three-dimensional structure of a specific epitope on the ovarian cancer tumor-associated antigen CA-125, with potential antineoplastic activity.

BMS986148: An antibody-drug conjugate (ADC) composed of a monoclonal antibody directed against the cell surface glycoprotein mesothelin and conjugated to a cytotoxic drug with a potential antineoplastic activity. The monoclonal antibody moiety of anti-mesothelin ADC BMS-986148 targets and binds to the tumor-associated antigen mesothelin. Upon internalization, the cytotoxic agent kills or prevents cellular proliferation of mesothelin-expressing tumor cells through an as of yet undescribed mechanism of action.

Tisotumab Vesontin (HuMax®-TF-ADC): is an antibody-drug conjugate (ADC) targeted to Tissue Factor (TF), a protein involved in tumor signaling and angiogenesis. Based on its high expression on many solid tumors and its rapid internalization, TF is a suitable target for an ADC approach.

IMMU-132: IMMU-132 targets the tumor-associated calcium signal transducer 2 (TROP-2) antigen which is expressed on a variety of cancers. The antibody, RS7, is attached to SN38, which is the active metabolite of irinotecan.

Demcizumab: A monoclonal antibody that selectively targets Delta-like ligand 4 (DLL4), an activator of the Notch signaling pathway which is known to be important in cancer stem cells and cancer. It has been shown in preclinical studies that blocking DLL4 results in anti-tumor activity via multiple mechanisms, including inhibiting cancer stem cell growth and promoting cell differentiation, disrupting angiogenesis and potentially enhancing anti-tumor immune response.

Kinase inhibitors: The non-FDA approved kinase inhibitors that are under clinical trials is given in the Table-2 below:

Non FDA approved kinase inhibitors:

LY2606368: An inhibitor of checkpoint kinase 1 (chk1) with potential anti-neoplastic activity. Upon administration, LY2606368, selectively binds to chk1, thereby preventing activity of chk1 and abrogating the repair of damaged deoxyribonucleic acid (DNA). This may lead to an accumulation of damaged DNA and may promote genomic instability and apoptosis. LY2606368 may potentiate the cytotoxicity of DNA-damaging agents and reverse tumor cell resistance to chemotherapeutic agents. Chk1, a serine/threonine kinase, mediates cell cycle checkpoint control and is essential for DNA repair and plays a key role in resistance to chemotherapeutic agents.

Trametinib: An inhibitor of mitogen-activated protein kinase kinase (MEK MAPK/ERK kinase) and has potential neoplastic activity.

Monoclonal antibodies	Clinical trial identifier no.	Phase	Study design	Target
Farletuzumab (MORAb-003)	NCT00849667	Phase III	Randomized, Safety/Efficacy Study, Double Blind	Target at FR-alpha
IMAB027	NCT02054351	Phase I, Phase II	Safety study, open label	CLDN6
Abagovomab	NCT00058435	Phase I	Randomized, Open label	CA-125
BMS986148	NCT02341625	Phase I/IIa	Non-randomized, Open label	Cell surface glycoprotein mesothelin
Tisotumab Vesontin (HuMax®-TF-ADC)	NCT02001623	Phase I/II	Safety study, Non-randomized, Open label	Tissue factor
IMMU-132	NCT01631552	Phase I/II	Safety study, Non-randomized, Open label	TROP-2 antigen
Demcizumab	NCT01952249	Phase I/II	Safety study, Non-randomized, Open label	Delta-like ligand 4 (DLL4)

Table 1. Non FDA approved Monoclonal antibodies [31-37]

It binds to and inhibits MEK 1 and 2, thereby inhibiting the growth factor-mediated cell signaling and cellular proliferation in various cancers. MEK 1 and 2, dual specificity threonine/tyrosine kinases often upregulated in various cancer cell types, play a key role in the activation of the RAS/RAF/MEK/ERK signaling pathway that regulates cell growth.

Cediranib Maleate: Cediranib is an inhibitor of all three vascular endothelial growth factor receptor (VEGFR-1,-2,-3) tyrosine kinases resulting in blocking of VEGF-signaling, angiogenesis, and tumor cell growth. Cediranib Maleate is the maleate salt of this indole ether quinazoline derivative.

Binimetinib (MEK162): An orally available inhibitor of MEK1/2 with potential antineoplastic activity. This prevents the activation of MEK1/2-dependent effector proteins and transcription factors, thereby inhibiting growth factor-mediated cell signaling. This results in inhibition of tumor cell proliferation and an inhibition in production of various inflammatory cytokines including interleukin-1, -6 and tumor necrosis factor.

Olaparib: It is a small molecule that acts by inhibiting the nuclear enzyme poly (ADP-ribose) polymerase (PARP). This leads to inhibition of PARP-mediated repair of single strand DNA breaks; caused by increase in the cytotoxicity of DNA-damaging agents, reversing tumor cell chemoresistance and radioresistance.

Kinase Inhibitors	Clinical trial identifier no.	Phase	Study design	Target
LY2606368	NCT02203513	Phase II	Efficacy Study, open label	chk1
Trametinib	NCT02101788	Phase II/III	Efficacy Study, randomized, cross-over, open label	MEK MAPK/ERK
Cediranib Maleate	NCT02502266	Phase II/III	Efficacy Study, randomized, open label	VEGFR-1,-2,-3 tyrosine kinases
Binimetinib (MEK162)	NCT01849874	Phase III	Efficacy Study, randomized, open label	MEK1/2
Olaparib	NCT02446600	Phase III	Efficacy Study, randomized, open label	PARP

Table 2. Non FDA approved kinase inhibitors [38-42]

Checkpoint Inhibitors:

Non-FDA approved checkpoint inhibitors: The non-FDA approved checkpoint inhibitors that are under clinical trials is given in the Table-3 below:

Ipilimumab: A monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), an antigen that is expressed on activated T-cells and exhibits affinity for B7 co-stimulatory molecules. By binding CTLA4, ipilimumab enhances T-cell activation and blocks B7-1 and B7-2 T-cell co-stimulatory pathways.

Tremelimumab: A human IgG2 monoclonal antibody directed against the T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA4). Tremelimumab binds to CTLA4 and blocks the binding of the antigen-presenting cell ligands B7-1 and B7-2 to CTLA4, resulting in inhibition of B7-CTLA4-mediated downregulation of T-cell activation; subsequently, B7-1 or B7-2 may interact with another T-cell surface receptor protein, CD28, resulting in a B7-CD28-mediated T-cell activation unopposed by B7-CTLA4-mediated inhibition.

Durvalumab (MEDI4736): A monoclonal antibody directed against B7H1 (B7 homolog 1; programmed cell death ligand 1) with potential immuno-stimulating activity. Upon intravenous administration, MEDI4736 binds to the cell surface antigen B7H1, thereby blocking B7H1 signaling.

Pembrolizumab: A humanized antibody used in cancer immunotherapy. It blocks the inhibitory ligand of programmed cell death 1 receptor located on lymphocytes. This receptor is responsible for inhibiting the immune response to cancer cells which express programmed death-ligand (PD-L1 or PD-L2).

Nivolumab: A fully human immunoglobulin (Ig) G4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1,P-CD-1) with immune checkpoint inhibitory and antineoplastic activities. Nivolumab binds to and blocks the activation of PD-1, an Ig superfamily transmembrane protein, by its ligands programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on antigen-presenting cells (APCs).

Checkpoint Inhibitors	Clinical trial identifier no.	Phase	Study design	Target
Ipilimumab	NCT00039091/NCT01611558/ NCT02498600	Phase I/II	Safety study, open label	CTLA-4
Tremelimumab	NCT01975831/ NCT02485990/ NCT02658214/ NCT02571725	Phase I/II	Safety study, open label	CTLA-4
MEDI4736	NCT01975831/ NCT02484404	Phase I/II	Safety study, open label	CTLA4, PD-L1
Pembrolizumab	NCT02178722/ NCT02452424/ NCT02440425/ NCT02520154	Phase I/II	Safety study, open label	PD-L1
Nivolumab	NCT02335918/ NCT02498600	Phase I/II	Safety study, open label	PD-L1

Table 3. Non FDA approved checkpoint inhibitors [43-55]

Vaccines:

Non FDA approved Therapeutic vaccines: The therapeutic vaccines that are under clinical trials is given in the Table-4 below:

OVAX: A cancer vaccine consisting of autologous ovarian cancer cell peptide antigens conjugated to the hapten 2,4-dinitrophenol (DNP) with potential immunostimulating and antineoplastic activities.

DC-006: A cancer vaccine containing autologous dendritic cells (DCs) that are transfected with mRNAs extracted from amplified ovarian cancer stem cells, and messenger ribonucleic acids (mRNAs) of the universal tumor antigens human telomerase reverse transcriptase (hTERT) and survivin with potential immunostimulatory and anti-neoplastic activities.

E39 peptide vaccine: A cancer vaccine comprised of human leukocyte antigen (HLA) A2 restricted folate binding protein (FBP) epitope E39 (amino acids 191 to 199), with potential immunostimulatory and antineoplastic activity.

p53 SLP: A phase I and II clinical trial of Gemcitabine,with pegylated interferon alpha-2b (Peg-Intron),with and without p53 Synthetic Long Peptide (p53 SLP) vaccine, for patients with platinum-resistant ovarian cancer, is ongoing.

Ontak DC: A phase-II clinical trial of CD4+CD25+ immunoregulatory T-cells in the treatment of patients with advanced ovarian cancer, who receive dendritic cell based vaccine therapies, is going on.

FANG: Autologous tumor cells, transfected with a plasmid-expressing recombinant human granulocyte macrophage-colony stimulating factor (rhGM-CSF) and bi-functional short hairpin RNA (bi-shRNA) against furin, with potential immunostimulatory and anti-neoplastic activities.

TroVax: A cancer vaccine comprised of a recombinant modified vaccinia Ankara (MVA) viral vector encoding the 5T4 fetal oncoprotein (MVA-h5T4).

OC-DC vaccine: A Phase-1 trial of adoptive transfer of vaccine-primed CD3/CD28-co-stimulated autologous T-Cells, combined with vaccine boost and bevacizumab for recurrent ovarian fallopian tube or primary peritoneal cancer, previously vaccinated with autologous tumor vaccine,is still going on.

NY-ESO-1: A cancer vaccine consisting of an immunogenic peptide, derived from the cancer-testis antigen New York esophageal squamous cell carcinoma 1 (NY-ESO-1), an antigen found in normal testis and various tumors.

ALVAC (2)-NY-ESO-1 (M)/TRICOM vaccine: A cancer vaccine consisting of a replication-defective recombinant canary pox virus [ALVAC (2)] encoding the cancer-testis antigen NY-ESO and the Triad of the co-stimulatory molecules (B7-1, ICAM-1 and LFA-3; also called TRICOM), with potential immunostimulatory and antineoplastic activities.

Dendritic Cell/Tumor Fusion Vaccine: Dendritic cells (DCs) loaded with tumour antigens or whole tumour cell derivatives may induce immunological responses. It involves the fusion of DCs with tumor cells such that a broad array of tumor antigens are presented in the context of DC-mediated costimulation and stimulatory cytokines which results in stimulation of antitumour immunity and lysis of autologous tumour cells.

DEC-205/NY-ESO-1 fusion protein CDX-1401: A fusion protein consisting of a fully human monoclonal antibody directed against the endocytic dendritic cell (DC) receptor, DEC-205, linked to the tumor-associated antigen (TAA) NY-ESO-1 with potential immunostimulating and antineoplastic activities.

The monoclonal antibody moiety of DEC-205/NY-ESO-1 fusion protein CDX-1401 binds to the endocytic DC receptor, which may result in DC endocytic internalization of this agent, specifically delivering the NY-ESO-1 moiety. DC processing of NY-ESO-1 may boost the immune system to mount a cytotoxic T-lymphocyte response (CTL) against cancer cells expressing NY-ESO-1.

Adoptive Cell Therapy:

Non FDA approved Adoptive T-cell Transfer: The adoptive T-cells that are under clinical trials is given in the Table-5 below:

Vaccines	Clinical trial identifier no.	Phase	Study design	Target
OVAX	NCT00660101	Phase I, Phase II	Randomized, Safety/Efficacy Study, Double Blind	Cancer cells
DC-006	NCT01334047	Phase I, Phase II	Safety/Efficacy Study, open label	CTL response.
E39 peptide vaccine	NCT01580696	Phase I, Phase II	Randomized, Safety study, open label	Stimulate CTLs.
p53 SLP	NCT01639885	Phase I, Phase II	Non-Randomized, Safety/efficacy study, open label	Anti-cancer immune response.
Ontak DC	NCT00703105	Phase II	Randomized, Safety/efficacy study, open label	Acts on immune suppressing cells in the body.
FANG	NCT01309230/ NCT01551745	Phase II	Safety/efficacy study, open label	Stimulate immune response.
TroVax	NCT01556841	Phase II	Randomized, Efficacy Study, Double Blind	Helps immune system to recognize and attack cancer cells.
OC-DC vaccine	NCT01312376	Phase I	Treatment	Enhance DC cells to recognize & engulf tumor cells.
NY-ESO-1	NCT01522820	Phase I	Non-Randomized, Safety study, open label	Epithelial ovarian cancer (EOC).
ALVAC(2)-NY-ESO-1 (M)/TRICOM vaccine	NCT01536054	Phase I	Safety study, open label	Induce anti-cancer immune response.
Dendritic Cell/Tumor Fusion Vaccine	NCT01617629	Phase II	Safety study, open label	Stimulate tumour-specific immunity
DEC-205/NY-ESO-1 fusion protein CDX-1401	NCT02166905	Phase I/II	Randomized, Safety/Efficacy Study, Open label	Endocytic dendritic cell (DC) receptor

Table 4. Non FDA approved Therapeutic Vaccines [30,56-67]

Gene Modified T-cells: Phase II/Pilot Study of 2nd Generation Anti- carcinoembryonic antigen (CEA) modified T Cells in adenocarcinoma is going on.

Natural killer cells: A population of activated, immortalized, interleukin-2 (IL-2)-dependent, cytotoxic natural killer (NK) cells with potential antitumor activity.

Anti-NY ESO-1 TCR PBL: Phase II study of metastatic cancer that expresses NY-ESO-1 using lymphodepleting conditioning,followed by infusion of anti-NY ESO-1 T-cell receptor (TCR)-gene engineered lymphocytes, is going on.

NY-ESO-1 reactive TCR retroviral vector transduced autologous PBL: Human autologous peripheral blood lymphocytes (PBLs), transduced with a retroviral vector, encoding a T cell-receptor (TCR) specific for the cancer-testis antigen NY-ESO-1, with potential anti-neoplastic activity.

T-cells	Clinical trial identifier no.	Phase	Study design	Target
Gene Modified T Cells	NCT01723306	Phase II	Safety/efficacy study, open label	CEA (carcinoembryonic antigen).
Natural killer cells	NCT01105650	Phase II	Non-Randomized, Safety/efficacy study, open label	CD16.
Anti-NY ESO-1 TCR PBL	NCT00670748	Phase II	Non-Randomized, Safety/efficacy study, open label	NY-ESO1 tumor-specific antigen.
NY-ESO-1 reactive TCR retroviral vector transduced autologous PBL	NCT01697527	Phase II	Safety/efficacy study, open label	Stimulate the immune response to tumor cells.

Table-5. Non FDA approved Adoptive T cell Transfer [68-71]

Hedghog inhibitors	Clinical trial identifier no.	Phase	Study design	Target
Sonidegib	NCT02195973/ NCT01954355	Phase I	Safety/Efficacy study, open label	Hedgehog signaling pathway

Table 6. Non FDA approved Hegdhog [72,73]

Hedghog Inhibitors:

Non FDA Approved Hegdhog Inhibitors:

Sonidegib (smoothened antagonist LDE225; LDE225): An orally bioavailable small-molecule smoothened (Smo) antagonist with potential antineoplastic activity. Sonidegib selectively binds to the hedgehog (Hh)-ligand cell surface receptor Smo, which may result in the suppression of the Hh signaling pathway and, so, the inhibition of tumor cells in which this pathway is abnormally activated. The Hh signaling pathway plays an important role in cellular growth, differentiation and repair. Inappropriate activation of Hh pathway signaling and uncontrolled cellular proliferation, as is observed in a variety of cancers, may be associated with mutations in the Hh-ligand cell surface receptor Smo.

Proteasome inhibitor:

Non FDA approved proteasome inhibitor

Bortezomib: A proteasome inhibitor which inhibits 26S proteasome, a large protease complex that degrades ubiquinated proteins and affects various cell signaling pathways, leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis.

Proteasome inhibitor	Clinical trial identifier no.	Phase	Study design	Target
Bortezomib	NCT00059618/ NCT01074411	Phase I	Non-randomized, safety/efficacy study, open label	26S proteasome

Table 7. Non FDA approved Proteasome inhibitor [74,75]

Oncolytic virus therapy

Non FDA approved oncolytic virus therapy

Measles Virus: Attenuated measles virus vaccine with anti-neoplastic activity by using CD46, a regulator of complement activation that is expressed in higher abundance on human tumor cells than on their nontransformed counterparts

GL-ONC1: Genetically stable oncolytic virus based on vaccinia virus which destroys tumor cells without harming healthy tissues or organs and initiate an anti-tumor response rate.

Ad5-delta24RGD: Replication-competent adenoviruses engineered to have oncolytic properties by spreading within the tumor. It carries a cyclic Arg-Gly-Asp (RGD-4C) integrin binding motif in its fiber knob domain.

Enadenotucirev: Adenovirus serotypes Ad11/Ad3 chimeric group B that selectively destroys tumour cells and stimulates an immunological response.

Oncolytic virus	Clinical trial identifier no.	Phase	Study design	Target
Measles Virus	NCT00408590	Phase I	Safety/efficacy study, open label	Attenuated measles virus vaccine
GL-ONC1	NCT02759588	Phase I	Safety/efficacy study, open label	Vaccine targeting tumor cells and stimulating immune system
Ad5-delta24RGD	NCT00562003	Phase I	Non-randomized, safety/efficacy study, open label	Replication-competent adenoviruses
Enadenotucirev	NCT02028117	Phase I / II	Safety/efficacy study, open label	Vaccine targeting tumor cells and stimulating immune system

Table 8. Non FDA approved Oncolytic virus therapy [76-79]

Chemoimmunotherapy

Non FDA approved chemoimmunotherapy

One trial is ongoing for combination of cisplatin and the DC vaccine.

Chemoimmunotherapy	Clinical trial identifier no.	Phase	Study design	Target
Combination of cisplatin and the DC vaccine	NCT02432378	Phase I / II	Randomized, safety/efficacy study, open label	-

Table 9. Non FDA approved chemoimmunotherapy [80]

Conclusion

Immunotherapy, as a potentially promising approach for treatment of ovarian cancer, is based on several lines of evidence. Our success in treating ovarian cancer is increasing and advancing with the knowledge of the function of the immune system. Immunotherapy has achieved a promising development in the past few years. The recent activities have increased ourunderstanding of the tumor micro-environment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy). Additionally, the effects of such modalities in combination with immunotherapy,in cancer patients are still exploratory phase. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper pre-clinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients. Immunotherapy that can induce or enhance optimal immunologic conditions within ovarian cancers, may hold a great promise for extending the lives of ovarian cancer patients.

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