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Research Paper

Oncolytic Virus Therapy in Metastatic Breast Cancer Treatment

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Abstract— *Oncolytic viruses (OVs) are weakened viruses that can destroy cancer cells once they have become infected, changing the tumor microenvironment (TME) and triggering an immune reaction. They work by lysing cells directly and disguising the disease by immunogenic apoptosis, which enables our immune system to detect and destroy tumours. Oncolytic viruses are naturally occurring viruses that reproduce only in cancer cells and destroy them while sparing healthy cells. There are now 18 published clinical trials looking into 14 distinct kinds of viruses, and all of them are highly tolerated and safe for usage in patients. T-Vec (talimogene laherpareparevvec), the first oncolyty virus medication, has just received approval in the United States and Europe. Cancer gene treatments are often created to express tumour suppressor gene wild-type copies or to take advantage of phenotypic alterations to provide targeted cytotoxicity. Oncolytic and TME targeted gene therapy approaches have been investigated, with particular success being noted in approaches that target the cancer stroma. In this review we will discuss the therapuatic use of oncolytic virus therapy for the treatment of metastasis breast cancer and its combination with other conventional techniques used in the breast cancer treatmentsuch as chemotherapy, radiotherapy to increase efficacy of oncolytic viruses.*

Index Terms— *Metastasis, Breast Cancer, Oncolytic Viruses (OV), Therapy, Tumor Microenvironment (TME).*

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I. INTRODUCTION:

Currently, oncolytic virus (OV) therapy has been acknowledged as a new promising therapeutic strategy for the treatment of cancer.

A naturally present or genetically modified virus that can reproduce in the cancer cells and kill them are known as oncolytic viruses. When a systemic viral infection occurs naturally, tumour regression is frequently seen during or after the infection. During past years' cancer and some other diseases were tried to cure using viruses but they were not very successful because at that time no method was discovered to control virulence and enable the virus to divide in can- cer cells at the same time. With recent discoveries it is discovered that by impairing the protection strategies against the virus in most of the cancer cells can make viruses to replicate in the cancer cells. But the actual problem is that virus should not replicate in normal cells for which attempts are being made to produce cancer cell spe- cific replicating viruses. Some genetically engineered viruses are available commercially to treat cancer in different countries and some are under clinical trials (Hiroshi Fukuhara, 2016).

The purpose of oncolytic viruses is to kill cancer cells but should not affect the normal cells. The phenomenon of tumor specificity of OVs varies among the viruses. The successful oncolytic virus must be cytolytic, it should be able to destroy maximum number of cancer cells (Nikolas Tim Martin, 2018). Breast cancer is one of the most common cancer in United States. This type of cancer has relatively better prognosis than other types of cancer. Some new therapies can prolong the survival but still there is requirement for advance thera- pies. Changes in genetic and epigenetic characteristics are the two most important factors for the tumor development. The developing tumor cells should enable the cell to be destroyed by the immune system. But the cancer cells exploit the immune system to avoid the anti-tumor reaction. This exploitation makes the immune system more exposed to the viral infection. The oncolytic viruses are compe- tent for division inside the cancer cells and thus disrupt them. The combination of oncolytic therapy with immunotherapy can be a promising strategy to treat cancer. Treatment of triple-negative breast cancer (TNBC) is more difficult. A new

therapy which is based on the suppression of checkpoints (such as cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death) of immune system, can be effective. Recent studies showed the fusion of both, inhibition of checkpoints and chemotherapy, is more efficient for the treatment of metastatic and early stage TNBC (Carter ME, 2021).

Various OVs have been studied and altered for cancer therapy. Some naturally occurring OVs include Adenovirus (AdV) Herpes Simplex Virus (HSV), Vaccinia virus, Coxsackie virus, Measles, Vesicular Stomatitis Virus (VSV), and Newcastle Disease Virus (NDV) and genetically modified OVs include G47Δ, JX-594 and CG0070. The structural adaptations and mode of replication of these OVs show a drastic variation, but they share a similar and contrasting mode of action. They have the ability to destroy tumor cells without affecting healthy tissues. On the other hand, cancer cells have special features which enable them to support viral replication which include re- striction of immune responses, providing hypoxic environment for viral replication and they also expose receptors for virus attachment on their surface (Annalisa Chianese, 2021).

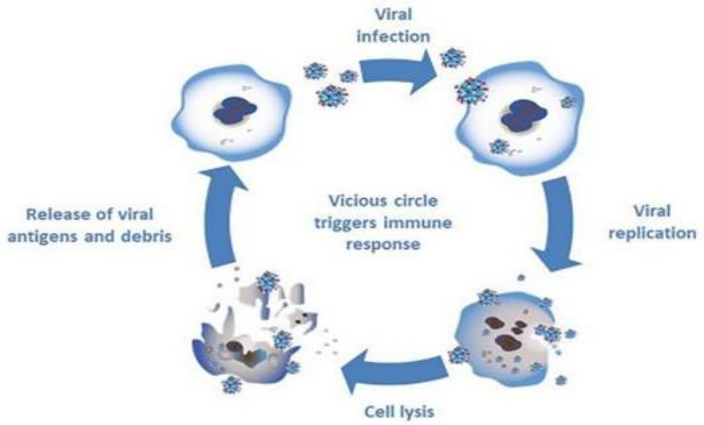

Figure 1. Triggering an immune response through infection with onco- lytic viruses. The infection of tumor cells with oncolytic viruses results inviral replication and subsequent cell lysis. The debris and new antigens that are released through cell lysis result.

II. DISCUSSION:

Oncolytic virus as cancer therapeutic:

Clinical work is being conducted on avariety of viruses with various characteristics. The size and complexity of oncolytic viruses range in different double stranded DNA viuses. Throughout their entire life cycle, oncolytic viruses lyse cells in a variety of ways, with the ex- ception of animal viruses, which can be made lytic by the production of a nephrotoxic transgene. Several wild-type viruses are now being used in medicine. Viruses with nonhuman hosts are included, Viruses which are structurally linked to polomywlities are Newcastle disease virus, coxsackievirus produces numerous signs in humans, and reovi- rus, a person's virus with minimal pathogenicity (rat), vesicular sto- matitis virus (VSV), and parvovirus H1 (avian). Contagion and on- colytic vaccinia results from vaccine strains. The reported instances of both tumour regression and infections with wild-type contagious viruses. Safety is recorded after many years of usage in individuals by using vacuum strain MVEdm and it is supported by the majority of contagion OVs. Every type of OV has a unique cellular entrance process that could affect how effective it is. For example, the polio- myelitis virus receptor CD155 helps to enter poliovirus in cells, which is seen in a variety of tumour types. Coxsackie and animal viral receptor, also known as automobile (animal virus entry recep- tor), is seen differently in tumour cells. There is increase in tumour cell binding which receive a lot of attention by retargeting cellular receptors. Many OVs are designed to improve the selectivity of tu- mour cells. Sort One of the herpes simplex virus possesses powerful lytic abilities. By eliminating the ICP34.5 neurovirulence and ICP6 (UL39) (ribonucleotide reductase) genes, many variants are com- monly created. The ester pool is essential for viral replication in healthy, dormant cells which is produced by ICP6. One of the most prevalent deficiencies in cancer, deletion ofICP6provides replicative property for cells with inactivation of the p16INK4Atumor suppres- sor. Reovirus behaves similarly to cancerous cells by activating the ras gene. In S-phase populations replication of animal viruses occurs and also safety is promoted. Additionally, supermolecule(EA1) is encoded by the wild type virus) that promotes S-phase entry via ma- lignant neoplasm signalling. Because cancer cells frequently have enriched S-phase populations and mutations in the retinoblastoma pathway, the E1A gene has been removed from the oncolytic animal virus for preventing replication in normal cells. By directly injecting high infective agent masses inside of tumours, tumour properties and potency may even be increased. However, some OVs, spread system-ically in the blood like vaccinia virus which makes treating (Sean E. Lawlerr, 2016)

Natural Occurring Oncolytic Viruses:

- **Adenovirus:**

Adenoviruses (Ad) have 38 kB of double-stranded linear DNA. The oncoloytic virus is adenovirus. Apoptosis suppression caused by adenoviruses is mostly brought on by proteins connected to the Fas ligand and TNF pathways. Adenovirus is the source of cytotoxicity. Immunological response to tumour cells that is sensitive to cytokines or that is induced by cytokine production (i.e. TNF). Adenovirus boosts the body's response to chemotherapy. Two categories of onco- lytic adenoviruses are distinguishable. Adenoviruses in the first category have genes altered to lessen infection and replication in healthy cells. Adenoviruses that have been altered to selectively target cancer cells are included in the second group. There are now 13 clinical trials testing the use of adenoviruses to treat breast cancer.

- **Herpes Virus:**

HSV is a dsDNA oncolytic virus that has been authorised for use in clinical settings. Researchers are still looking at how it might be used to treat other tumours, such breast cancer. The HSV G47 is an onco- lytic virus which contains promoter region of US11. The deletion of 47 inhibits tumour development. In vivo the survival rate of human breast cancer cells like MDA-MB-435 is increasing. A mouse model created by implanting MDA-MB-435 cells also has a higher survival rate in vivo. Target genes are introduced into HSVs to strengthen the anticancer impact. The anticancer cytokine IL-12, encoded by the HSV G471-mIL12, is developed to aid in the in vitro elimination of TNBC breast tumour cells. (Shengye Jin1, 2021)

- **Vaccinia Virus:**

The vaccine virus has dsDNA. In the cell's cytoplasm, it replicates. In the treatment of breast cancer there is lot of potential of vaccinia virus. There is clear anticancer effect of Ail-24 armed adenovirus. Il- 24 gene is present in the vaccinia virus's Guang9 (VG9). A recombi- nant virus VG9- IL-24 has no cytotoxic effects on healthy cells but can kill infected breast cancer cells. By using a mouse MDA-MB- 231 model, such as a xenograft, an in vivo anticancer effect was ob- served. Tumor growth is reduced in mice given VG9-IL-24 treatment, and longer survival periods with a higher survival rate are seen. Therefore, using the vaccine virus to treat TNBC is a possibil- ity. TNBC capability was already in place.

- **Measles Virus:**

Breast cancer can be treated with MV. Carcinoembryonic antigen which is produced by MV, which causes in vitro cell death (MV- CEA). Subcutaneous MDAMB-231 xenografts is used in vivo MV- CEA testing of the anticancer capacity led to the conclusion that both in vivo and in vitro MV-CEA demonstrated therapeutic activity against TNBC. When OVs enter cells through signalling lymphocyte activation molecule (SLAM), CD46 is expressed on nucleated cells, and many immune-associated cells are expressed. MV that is selec- tively blind to SLAM (rMV-SLAM blind) using PVRL4 as the re- ceptor.

- **New Castle Disease Virus:**

NDV is a member of the class of negative-sense ssRNA viruses. The most efficient way for NDVs to combat breast cancer is through in- ducing apoptosis in the cancer cells. TNBC cells, NDV AF2240 causes tumour regression by upregulating or downregulating several cytokines. For instance, via IL-6 excretion harm. To improve its anti- tumor effects, the NDV underwent artificial modification. Recombi- nation with other genes in the breast causes immune stimulants to express. By introducing the IL-2 gene into the NDV genome, cytotoxicity against the MDA-MB231 cell line is generated. Based on the discovery that the recombined NDV significantly suppressed 4 T1 cells and the tumour size.

- **Coxsackie virus:**

An enterovirus having positive-sense ssRNA is the coxsackievirus. It has 29 different subtypes. As a result of this virus's lower human pathogenicity, its oncolytic effect has received relatively less re- search. Genetic editing increases the viruses' tumour cell selectivity while lowering their toxicity. Coxsackievirus B3 (CV-B3) is genet- ically produced to suppress various tumour cell types which includes cancer of lungs and and endometrial. Because of its promise as a treatment, coxsackievirus for TNBC has also been confirmed.

Genetically Engineered OncolyticViruses:

- **G47Δ:**

A third-generation oncolytic HSV-1 with three mutations is called G47Δ. It is created by introducing an additional deletion mutation into the G207 genome. The Lac Z gene is inserted into the gene that is ICP6, the major subunit of ribonucleotide reductase (RR) is en- coded, a protein required for the synthesis of virus-related DNA. Compared to tissues with two mutations, such as G207 and T-Vec, G47 is safer to employ in normal tissues. G47 shows efficacy in solid tumor models when evaluated for breast cancer, prostate cancer, etc. G47 has the power to eradicate cancer stem cells. Only the third gen- eration of HSV-1 G47 has been tested on people to far.

- **JX-594:**

JX-594 is the name of the genetically altered vaccinia virus that has a TK gene mutation. Replication is granted with a preference to- wards cancer cells. Humans with the GM-CSF gene have an en- hanced immune response to tumours. The presence of the LacZ gene insertion is a marker in JX-594. When a low or high quantity of JX-594 was administered, OS was significantly longer in the high dose arm compared with the low dose arm.

- **CG0070:**

An oncolytic adenovirus is CG0070. The human gene GM-CSF is introduced with the aid of the ad5 adenovirus and is driven by the human E2F-1 promoter. The tumour suppressor protein for reti- noblastoma (Rb) controls the gene E2F-1, which is frequently altered in bladder cancer. There were no documented clinically significant adverse treatment-related events. (Fukuhara, 2016)

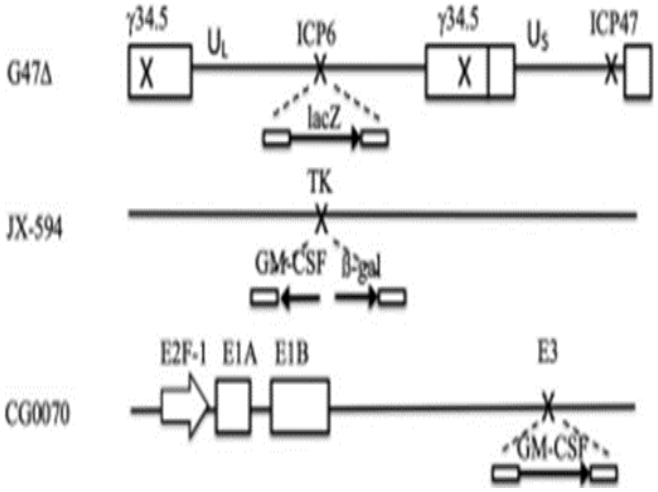

Figure 2. Major oncolytic viruses structures. In T-Vec and G47, the HSV-1DNA's long (UL) and short (US) distinctive sequences are flanked by in- verted repeat sequences. Human GM-CSF has been inserted into both copies of the c34.5 gene in T-Vec, and the a4.

OV'S combinational therapies:

Combination of OV with Chemotherapy:

In addition to deciding whether chemotherapy should be administered before the operation (neoadjuvant treatment) or after, decisions must be made regarding whether the metastasis breast cancer can be eliminated by surgery or mastectomy. For patients to survive, chemo- therapy should be customised based on their specific breast cancer subtype. Patients with breast cancer may also benefit from combina- tion medicines that reduce OV and use lower doses of chemotherapy. The majority of clinical studies have concentrated on the therapy of solid tumours since these tumours may be directly injected
with the oncolytic virus. A doxorubicin-conjugated reovirus (re-dox) was created by Berry et al. to allow for regulated drug release and viral killing of tumour cells at the same time. Results from in vitro experiments showed that the two treatments worked together to in- crease viral spread in TNBC cells. There was no change in progres- sion free survival in a trial of advanced breast cancer patients treated with pelareorep and paclitaxel, although there was a considerably longer OS (Kwan, 2021).

Combination of OV with Radiotherapy:

Oncolytic adenoviruses with radiation can be utilised to make tu- mours more responsive to radiotherapy treatment. An HSV-derived virus called T-Vec has been authorised for treatment in melanoma. There is not much clinical evidence to support the efficacy of such a therapy for breast cancer. According to certain studies, adding radia- tion to OV therapy improves viral replication, viral production, and viral release. This breach may be opened up by OV treatment in con- junction using PD-L1 or PD1 inhibitors, enabling our immune sys- tem to react to OV more forcefully. In immunocompetent mouse models, Bourgeois Daigneault et al. documented the use of a Maraba virus before the resection of breast tumours. Here, OV therapy was given for a week before to the removal of the breast tumour, and then PD1 inhibitor treatment was given as an adjuvant. Prior to surgery, the use of virotherapy made it possible to sensitise patients to im- mune checkpoint treatment that was administered concurrently, and it also ensured that the immunological effects of a subsequent chal- lenge were long-lasting. In an EMT6 immunocompetent mouse model of breast cancer, reovirus can be improved by the addition of a PD-1 inhibitor, resulting in a decrease in tumour development. This is probably because of the favourable cytotoxic adjustments in the immunological TME. Several clinical studies combining

oncolytic viruses and a checkpoint inhibitor for breast cancer are now being conducted. Currently under examination are the viral groups HSV, vaccinia, and reovirus, with the possibility that other viral groups will be (Kwan, 2021).

Combination of OV with Immunotherapy:

Prior to surgery, viral treatment enabled for immune checkpoint ther- apy to be administered adjuvantly and that the immunological effects on rechallenge were long lasting. Combining OV treatment with PD- L1 or PD1 inhibitors may help to close this gap and boost the im- mune system's response to OV. In immunocompetent mouse models, Bourgeois-Daigneault et al. documented the use of a Maraba virus before the resection of breast tumours. Prior to the removal of the breast tumour, a course of OV therapy was given, and then a course of PD1 inhibitor medication was given as an adjuvant. In an EMT6 immunocompetent mouse model of breast cancer, reovirus can be improved with the addition of a PD-1 inhibitor, resulting in a de- crease in tumour development. This is tempting for clinical trial de- signs as it can help determine if more adjuvant therapy is necessary based on how well a patient responds to neoadjuvant therapy. Cur- rently under examination are the viral groups HSV, vaccinia, and reovirus, with the possibility that new viral groups may be included as data become more complete (Kwan, 2021).

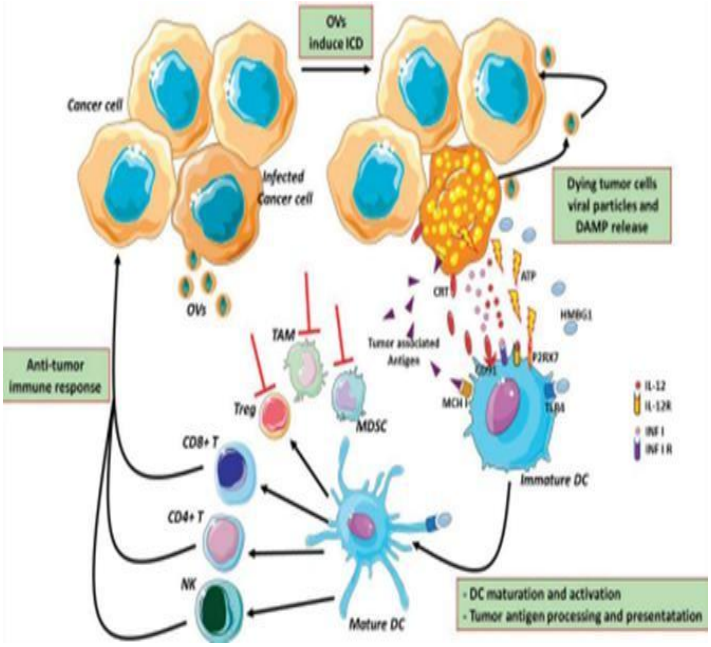

Figure 3. Mechanism of oncolytic virus immunotherapy. Oncolytic virus- es infect cancer cells and induce the immunogenic cell death and release of infectious viral progeny that infect nearby cancer cells. Tumour-associated antigens and cellular DAMPs, such as CRT, HMGB1 and cellu- lar ATP, stimulate the host antitumour immune responses. Cellular de- tection of viral infection and the products of oncolysis trigger the rapid activation of host antiviral responses and influx of immune cells that mediate the destruction of residual infected and uninfected tumour cells. The direct recognition and killing of tumour cells is primarily mediated by natural killer cells of the innate immune system and tumour antigen- specific CD8+ cytotoxic and CD4+ helper T lymphocytes of the adaptive immune system.

III. DEVELOPMENT OF OV AS DRUG:

OVs seek to specifically target and eradicate tumour cells while at- tenuating the viral pathogenesis. Some molecules, including as CD46, CD155, CD54, CD55, alfa2beta1, laminin receptor, etc., that are overexpressed on cancer cell surfaces can be exploited by OVs to recognise and enter target cells. Like the adenovirus Ad5/3 24, which was altered to attach to integrins that are significantly expressed in ovarian cancer cells, other OVs may be created to specifically target particular cell surface receptors. Natural surface molecule tropism, altered cancer cell pathways, and recombinant engineering have made it possible to investigate a number of methods to increase the potency of OVs. Because cancer cells can have viral genes inserted under active promoters, only these cells can have viral replication limited. This is the instance of a phase I study for men with prostate cancer receiving adenovirus (CV706) treatment, in which the pros- tate-specific antigen promoter was combined with the cell cycle- inhibiting E1A protein (PSA). A glioma model was used to develop this kind of construct, which demonstrated reduced viral replication in neurons that express high amounts of

miR-7 while permitting growth in glioma cells. Additionally, it has been proposed that NDV may infiltrate cells containing miRNA nearby through exosomes, inhibiting the IFN cascade and promoting viral infection(Martini, 2020).

IV. OVERCOMING STRATEGIES:

The two kinds of specific challenges that carcinoma faces can be split into two categories. 1) Host specific 2) tumour-specific. Re- search in second group is limited because it depend on data which results from immunotherapies and then it is used in the broader can- cer community. In carcinoma and malignant melanoma treatment males and females are main differences exposed in response to stop inhibition. Steroids are responsible which act as hormones on the body, possibly altering the tumour environment by fostering a tumor- igenic environment. In females cancer is diagnosed, which is due to steroids receptor upregulation so it appears as it cluster that we de- tect. , Anti-oestrogen therapy, a favourable alternative for tumours, stops inhibition in carcinoma. It appears to be serving a purpose. Clinical studies are conducted, some of which include (NCT02997995, NCT02778685, NCT03280563, NCT02990845, NCT02971748, NCT02648477, NCT02971761, NCT02997995).

These drugs, like fulvestrant or exemestane, target the steroid path- way. Inhibitors specifically target CTLA-4, PD-1, or PD-L1 check- points. By adding steroids, NV the oncolytic herpes simplex 11066 boosted the virus' lytic effect. In the absence of steroids, 95 and 97 in vitro MCF-7 cells die. This finding is beneficial for targeting addi- tional immunotherapy-resistant breast tumours that are ER+. The opposite distinction between males and females is that girls are more likely to be born with an autoimmune disease. The cancer affects older girls. Older persons are more likely to have a variety of age- related ailments. T reg cells are crucial and become more prevalent with age for hiding cancer from the host's immune system. This tran- sition is likely also reversed with FTO. Secretory changes that are tied to time are what set off immune-associated modifications. Pro- inflammatory cytokines including MCP1 and IL6 are abundant in post-menopausal girls. A few cancer patients had biological time artificially generated by LHRH antagonists. Each study shows a de- crease in CD4 T cells and B cells but an increase in peripheral CD8 T cells. The fact that each girl responds to immunotherapies is differ- ently one issue that has not been resolved. HER2+ extensive carci- noma is the cause of 15–19% of breast cancer cases. When a patient receives treatment, their body responds, and the HER2 receptor causes long-term illness freedom. The primary goal of researchers is to develop HER2 vaccines that incorporate HER2 antigens. This HER2 causes a reaction. Drugs administered to nerve cells promote immunogenic stimulation. . Short- and long-term toxicity and re- sponses are assessed after HER2 antigens are mixed with nerve fibre cells isolated from patient peripheral blood mononuclear cells. After four years of therapy, one patient developed a pneumonic lesion. After treatment, patients will live for four to five years. When HER2 is employed as the target receptor FTO is expressed. To treat HER2+ cancer, the antibody trastuzumab is used to inhibit the ERB receptor (Amy Kwan, 2021).

V. LIMITATIONS:

Oncolytic viruses must be carefully developed as therapeutic organ- isms for metastatic cancer, and proper clinical trial designs and dose regimes must be established in order to reduce any potential side effects. The requirement to improve tumour selectivity to minimize target effects following systemic transmission of the OV is the major technical problem to be solved. Another barrier is the ability of host immune system to neutralise the virus which reduces the effective use of OV therapy. Oncolytic virotherapy employs a wide variety of viral species, and the majority of the cancer patients have been al- ready exposed to the virus either by vaccination or infection. Therefore, the oncolytic virus can be blocked by circulating antibodies before it reaches to the cancer cells (Geon-Tae Park, 2016). Similar to other solid tumors, metastatic breast cancer also presents problems for virotherapy in terms of treatment efficiency as well as optimum virus delivery and propagation. Oncolytic viruses have been deter- mined to be safe for people in the majority of clinical research, alt- hough their anti-tumor efficacy has been at best mediocre. Due to production limitations, the dose-limiting toxicity has typically not been attained. To get over the manufacturing limitations, it might be possible to create oncolytic viruses with increased tumor-killing power so that a small amount of the viruses can have a significant anticancer effect (Shyambabu Chaurasiya, 2020).

VI. CONCLUSION:

Oncolytic viruses, which are evaluated against the treatment of the heterogeneous disease of cancer, are utilised in viral therapy to treat a variety of disorders. The effectiveness of naturally occurring virus- es is limited. Patients with breast cancer can be treated with a variety of medications, including atezolizumab. The main benefit of OV is that it targets tumour cells specifically and activates anti-tumor im- munity. The oncolytic virus initially kills tumours with its oncolytic capabilities, but when it is combined with other medicines, it pro- duces positive effects and enhances quality of life. There are now 18 clinical trials using 14 various oncolytic

viruses from various fami- lies. The two types of oncolytic viruses that are employed in clinical trials are 1) wildtype and 2) genetically altered for viruses that have been genetically engineered to stimulate the immune system; and 3) the replication of tumours. Particularly when used in conjunction with immunotherapies like immune checkpoint inhibitors, oncolytic viruses show that they are the most promising. There are various drawbacks to radiotherapy and chemotherapy, such as cross re- sistance and specificity. For the purpose of improving cancer treat- ment, new approaches to therapy combinations are being developed. To comprehend the mechanism of a virus's unique contributions to a treatment response, monochromatic techniques are helpful. When OV penetrates the host, it causes aggregation, which lowers the number of tumour cells. Through deliberate metabolic reprogram- ming of either immune or cancer cells, OV-induced anticancer re- sponses are also optimised. Breast cancer phase II trials have pro- duced positive findings. Oncolytic viruses are making remarkable progress toward the clinic in breast cancer treatments, but there are still many challenges. Ad vector, for instance, faces numerous diffi- culties in clinical studies due of its low potency. There are now ac- tive or completed Phase I and II clinical trials using oncolytic viruses to treat patients with breast cancer. For the most part, these combine treatments to treat tumours that are already advanced. With well- tolerated and efficient regimens, oncolytic virotherapy ushers in a new age of breast cancer treatment that enhances quality of life after treatment.

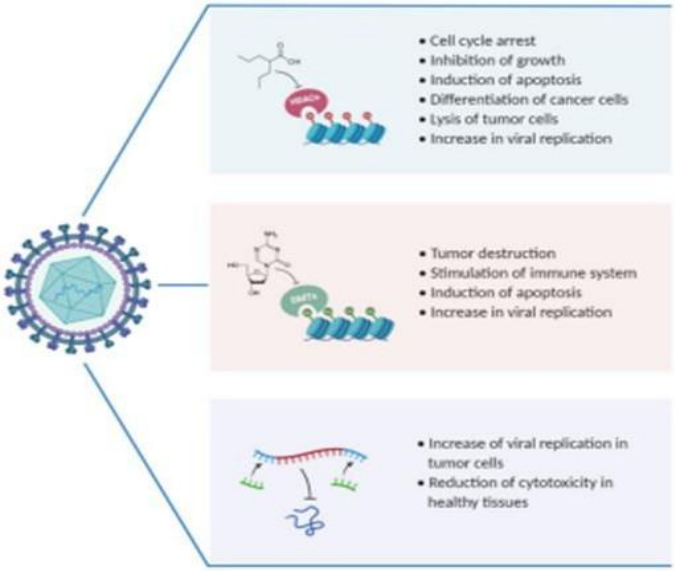

Figure 4. Summarizes the effects of combinatorial treatment by the use ofmiRNA and OV

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