Review Article

An overview of gene therapy in head and neck cancer

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Gene therapy is a new treatment modality in which new gene is introduced or existing gene is manipulated to cause cancer cell death or slow the growth of the tumor. In this review, we have discussed the different treatment approaches for cancer gene therapy; gene addition therapy, immunotherapy, gene therapy using oncolytic viruses, antisense ribonucleic acid (RNA) and RNA interference-based gene therapy. Clinical trials to date in head and neck cancer have shown evidence of gene transduction and expression, mediation of apoptosis and clinical response including pathological complete responses. The objective of this article is to provide an overview of the current available gene therapies for head and neck cancer.

Key words: Gene addition therapy, gene therapy, head and neck cancer, immunotherapy, suicide gene

Introduction

Conventional treatment modalities for head and neck cancer are surgery, radiotherapy and/or chemotherapy. These treatment modalities for head and neck cancer have not greatly improved the survival rate of patients.[1] Local and/or regional recurrence develops in approximately one-third of the patients despite definite treatment.[1] In patients with distant metastasis, recurrence is often considered as incurable. The failure to conventional therapy occurs because in case of extensively large tumors it may be difficult to clear the margins or some tumors are remarkably resistant to radiotherapy or chemotherapy. Unacceptable degree of toxicity and bystander damage to normal tissue occurs if we increase the dose of radiation or chemotherapeutic drug.[2] Combinations of current treatment modalities have been moderately successful, but often these combination therapies cause unacceptable toxicity without increasing the survival rate of patients.[2] The major drawback for this conventional treatment is a lack of specificity for the tumor cells and toxicity to the normal tissues.

Recent advances in molecular biology have documented the role of gene therapy in tumorogenesis. Gene therapy has potential to target cancer cells while sparing normal cell. The clinical application of the gene therapy for the treatment of head and neck cancer will require optimization of gene delivery in conjunction with determination of transfection efficiency. Gene therapy can be defined as "gene transfer for the purpose of treating human disease, this includes the transfer of new genetic material as well as manipulation of the existing genetic material."[1] In case of malignancy, with the help of gene therapy oncogenes can be targeted without damaging the normal cells. The aim of this article is to give you an overview of the current status of the gene therapy for head and neck cancer.

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Gene Therapy Approaches for Head and Neck Cancer

Targeting the specific genetic lesions responsible for carcinogenesis and cancer progression is an attractive strategy for developing more effective anticancer therapeutics and reducing treatment related toxicity.

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Any one of a battery of known genes expressed at the right site and at appropriate levels can be very effective for selectively killing cancer cells. Although systemic administration is theoretically desirable to address metastatic disease, gene therapy has not yet been shown to be suitable for systemic delivery in cancer patients. The head and neck cancer is an appropriate target for gene therapy because primary and recurrent lesions are readily accessible for injection or application of the agent. There are several general strategies utilized in a gene therapy approach to cancer, including.

Gene addition therapy

The regulation of tumor growth is achieved in this approach by introducing tumor suppressor genes that inactivate carcinogenic cells.[3] Cancer cells generally demonstrate impaired cell cycle progression, largely due to mutation and over expression of cell cycle regulators.[4] Several genetic alterations have been reported in the head and neck cancer including mutation of P^{53}, the retinoblastoma gene (Rb1), P^{16} and P^{27}. Adult cells are normally maintained in either G_0 or G_1 stage of cell cycle by a signal from Rb pathway and P^{53} pathway.[2] The tumor suppressor genes (P^{53}, P^{16} and P^{27}) and protein products of several proto-oncogenes plays a significant role in this pathway. Mutation in some of these genes may leads to cancer by eliminating tight control of cell proliferation. The Rb protein regulate the release from G_1 phase, whereas P^{53} dictate whether cell cycle will be arrested in response to stress or deoxyribonucleic acid (DNA) damage or whether cell cycle will be directed to undergo apoptosis.[2] Since the protein P^{53} plays an important role in cell cycle and in apoptosis, it was tested in patients with squamous cell carcinoma by injecting directly into the tumor with an adenoviral vector expressing wild type P^{53}. Various randomized studies of adenoviral P^{53} are presently underway to determine its role as a surgical adjuvant and in combination with DNA damaging agents.[5-7] P^{27} gene was also found to inhibit the cell cycle of tumor cells. It acts by inducing apoptosis and triggering the suppression of tumor growth. Mutation of gene P^{27} has been demonstrated to highly related with the appearance of tongue cancer.[8-10] Other tumor suppressor gene, which were used for gene therapy are Rb gene, melanoma differentiation associated gene-7. Their anti-tumor and pro-apoptotic response is similar to those of interleukin-24 (IL-24), a Th1 cytokines that triggers an anti-tumor and pro-apoptotic response in the immune system.[1,11-13]

Cancer gene therapy using oncolytic viruses

One of the most promising gene therapy approaches is the use of viruses that replicate only in tumor cells, designated oncolytic viruses.[3] Viruses commonly used in gene therapy include, retroviruses, adenoviruses and herpes viruses.[14] The use of oncolytic viruses emerged from the discovery of adenoviruses lacking E1B, which do not grow in normal cells, but grew in cells without P^{53} gene, one of the most common characteristics of the tumor cells.[15,16]

Retroviruses are ribonucleic acid (RNA) viruses that undergo reverse transcription after infecting a cell, thereby producing double stranded DNA. DNA integrated into the host genome will pass copies of genes to all the subsequent generations.[17,18] There are strategies such as *ex vivo* transduction of leukocytes with drug resistant genes, for which retrovirus could be well suited. Large multinational glioma trials has been performed with a murine retrovirus coding for herpes simplex virus type 1 thymidine kinase (HSV-1-TK) followed by intravenous ganciclovir treatment. This treatment modality has shown some evidence of efficacy. Herpes viruses were the among the first replication competent viruses utilized for cancer treatment. Most herpes virus vectors are developed from strains of HSV-1.[19] When HSV-1 infected a cell it replicate within the cell, causes cell lyses and infection of the surrounding cells. A replication - conditional mutant of HSV has been shown to elicit anti-tumor response in preclinical models of glioma and metastatic colon cancer.[19] Two vectors, G207 and NV1020 are currently in Phase 1 and Phase 2 trials for the treatment of oral cancer. G207 is mutated so that it has attenuated neurovirulence and cannot replicate in non-dividing cells. NV1020, a derivative originally used for vaccine studies, has multiple mutations including a deletion in TK region and a deletion across the long and short component of the genome and an insertion of the TK gene under the control of the α 4 promoters.[20-23] Adenovirus is an oncolytic virus, which can be designed to replicate selectively in cancer cells and kill them by lysis.[1] The DNA of adenovirus does not integrate into the host genome and thus its effects

are transient. Therefore, multiple administrations of the vectors are usually required, in addition infection of most dividing and quiescent cell types occurs with unparalleled efficiency and the genome can accommodate relatively larger payloads.[1] The most notable adenoviral therapy is the ONYX-015 viral therapy.[24] Adenovirus ONYX-015 has been engineered to lack the viral E1B protein. In the absence of E1B protein, the virus is unable to replicate in healthy cell with a normal P^{53} pathways. Due to mutations, cancer cells often have a deficiency in P^{53} pathway and thus allow ONYX-015 to replicate and lyses the cell. ONYX-015 has been tested in Phase 1 and 2 trials on squamous cell carcinoma of head and neck that resulted in tumor regression, which correlate to the P^{53} status of the tumor. Phase 2 trials of ONYX-015 in combination with chemotherapy has demonstrated even better response and have led to a Phase 3 study.[25-29] The presence of cytokines, IL-6, tumor necrosis factor-α (TNF-α), IL-10 and interferon-gamma (IFN-ϒ) is observed at 24 h after ONYX-015 administration. IFN-ϒ level increased after 4 days while TNF-α level increased after 6 h, thereby contributing toward the appearance of immune response to the tumor.[30,31] Researchers have reported on the anti-tumor efficiency of the intravenous administration of oncolytic adenovirus OAS403. In 7-10 days, cytotoxicity appeared in tumor cells. This adenovirus is active in tumor with abnormal Rb protein and abnormality in the regulation of telomerase expression. The combination of OAS403 with conventional chemotherapeutic agent increased the anti-tumor efficacy in pre-clinical studies and Phase 3 trials are now underway.[32-35] Ongoing clinical trials on oncolytic viral therapy are given in Table 1.

Immunotherapy

In the immunotherapy either the immunogenic potential of tumor cells is increased and/or the patient's immune response to a tumor is augmented. Immunotherapy has been tried for cancer treatment for over 100 years.[1] However limited success has been achieved as cancer cells tend to evolve mechanism that evades immune detection.[36-38] Patients with head and neck squamous cell carcinoma have demonstrated functional deficiencies in several categories of immune cells including natural killer (NK) cells, T-lymphocytes and several cytokines. Animal studies have shown that IL-2 administration activate T-lymphocytes and NK cells that in turn activate TNF-α, triggered by strong tumor inhibition effect.[39] Mechanisms to increase the sensitivity of the tumor to normal therapeutic processes are under investigation. Suppression of nuclear factor kappa beta activates the anti-apoptotic proteins, TNF, TNF receptor-associated factor-1 (TRAF-1), TRAF-2, cellular inhibitor of apoptosis protein-1.[40,41] Currently, gene therapy is being used to create recombinant cancer vaccine. These vaccines are not meant to prevent disease, but cure or curtain it by training the patient's immune system to recognize the cancer cells. There are different types of cancer vaccines at the different phase of clinical trials[42] [Tables 2 and 3]. Advances in the understanding of the mechanism of action of cellular anti-tumor immune response have allowed the development of a new generation of cancer vaccines. The most immunologically active vaccine usually required costly and laborious *ex vivo* cellular cultures, whereas the cell free vaccine that can be directly administered from an easily stored and transported vials are usually less immunologically active. New advances and precise knowledge of the requirement for the generation of cellular immune response to tumor antigen will likely provide powerful, non-individualized cell free vaccine in the near future.[42-44]

Suicide gene therapy

Suicide gene therapy is also termed as gene directed enzyme pro-drug therapy and this approach has attracted increasing attention. The basic principle behind the suicide gene therapy is the selective intratumoral activation of a non-toxic drug by specific transfer of the activating transgene into tumor cells.[45] This approach encompasses several therapeutic systems, but HSV-TK is most extensively utilized. This gene encodes a viral enzyme that phosphorylates ganciclovir into a monophosphate form, which is then phosphorylated by intracellular enzyme into an active triphosphate compound that terminate DNA synthesis.[46,47] Suicide gene therapy can also use adenovirus. Adeno-associated virus (AAV) mediated delivery of the HSV-TK gene can selectively kill α-fetoprotein positive hepatocellular carcinoma cells in a mouse model and a bystander effect was demonstrated followed by the administration of the ganciclovir.[34,48] Similar *in vivo* therapeutic effect of

Table 1: Ongoing trials of oncolytic virus therapy for head and neck cancer

Study	Intervention	Phase	Study design	Investigator	Present status
A study of intra-tumoral CAVATAK in patients with Stage IIIc and Stage IV malignant melanoma	Biological: CAVATAK (Coxsackievirus A21, CVA21)	Phase 2	Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Jose Lutzky	This study is currently recruiting participants
A study of the intra-tumoural administration of CAVATAK to head and neck cancer patients	Biological: Coxsackievirus A21	Phase 1	Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Stephen Ackland David N. Dalley Jason Lickliter	This study is currently recruiting participants
GOAT; Phase 1 open label study of CGTG-102, a GM-CSF encoding oncolytic adenovirus, for advanced cancers	Biological: CGTG-102	Phase 1	Endpoint classification: Safety study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Martha M. Pritchett	This study is not yet open for participant recruitment
HSV1716 in patients with non-central nervous system solid tumors	Biological: HSV1716	Phase 1	Allocation: Non-randomized Endpoint classification: Safety study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Timothy Cripe	This study is currently recruiting participants
Parvovirus H-1 (ParvOryx) in patients with progressive primary or recurrent glioblastoma multiforme. (ParvOry×01)	Drug: H-1PV	Phase 1 Phase 2	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Andreas Unterberg	This study is currently recruiting participants
Safety study of recombinant vaccinia virus to treat refractory solid tumors in pediatric patients	Drug: Recombinant vaccinia GM-CSF; RAC VAC GM-CSF (JX-594)	Phase 1	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Timothy Cripe	This study is currently recruiting participants
Study of HF10 in patients with refractory head and neck cancer or solid tumors with cutaneous and/or superficial lesions	Drug: HF10	Phase 1	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Robert L. Ferris	This study is currently recruiting participants
Vaccine therapy with or without cyclophosphamide in treating patients with recurrent or refractory multiple myeloma	Biological: MV-NIS Drug: cyclophosphamide Other: I-123 prior MV-NIS Other: I-123 post MV-NIS Drug: Liothyronine	Phase 1	Allocation: Randomized Endpoint classification: Safety study Intervention model: Single group assignment Masking: Double-blind Primary purpose: Treatment	Angela Dispenzieri	This study is currently recruiting participants

GM-CSF: Granulocyte macrophage-colony stimulating factor, MV-NIS: Measles virus encoding the human thyroidal sodium iodide symporter

AAV-mediated delivery of HSV-TK gene has also been reported in an experimental glioma model and a human squamous cell carcinoma.[49,50] Considerable knowledge is now available on genes that contribute toward resistance against chemotherapy, including multidrug resistance protein 1 (MDR1), multidrug related protein, dihydrofolate reductase.[35] MDR is associated with over expression of the P-glycoprotein. It is a 170-kDa transmembrane ATPase that export chemotherapeutic drug from cells.[51,52] Li *et al.* has used self-complementary vectors scAAV to successfully deliver hairpin small interfering RNA (siRNA) into

Table 2: Ongoing trials of gene immunotherapy for head and neck cancer

Study	Intervention	Phase	Study design	Investigators	Present status
Allogeneic tumor cell vaccination with oral metronomic cytoxan in patients with high-risk neuroblastoma (ATOMIC)	Biological: Neuroblastoma vaccine Drug: Cytoxan	Phase 1 Phase 2	Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Charystal Louis and Malcolm Brenner	Recruiting participants
Gene therapy in treating patients with unresectable, recurrent, or refractory head and neck cancer	Biological: IL-12 gene	Phase 1 Phase 2	Primary purpose: Treatment	Dimitrios Colevas	
IL-2 gene or methotrexate in treating patients with recurrent or refractory Stage III or Stage IV head and neck cancer	Biological: Gene therapy Biological: IL-2 gene Drug: Methotrexate	Phase 2	Primary purpose: Treatment	Thomas V. McCaffrey	
A Phase 2 clinical trial of the effectiveness of IRX-2 in treating patients with operable head and neck cancer	Drug: IRX-2 Drug: Cyclophosphamide Drug: Indomethacin Drug: Zinc Drug: Omeprazole	Phase 2	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Jeffrey S. Moyer	-
A Phase 2 study of EBV-specific immunotherapy for nasopharyngeal carcinoma	Biological: Epstein-Barr virus specific immunotherapy	Phase 2	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Marshall Posner	Recruiting participants
A study of adoptive immunotherapy with autologous tumor infiltrating lymphocytes in solid tumors	Biological: Tumor infiltrating lymphocytes, IL-2	Phase 1	Endpoint classification: Safety study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Yi-Xin Zeng	Recruiting participants
Induction chemotherapy prior to radio-immunotherapy in head and neck cancer stage III/IV-a methodical trial (ASOG-HNO1)	Procedure: Radio-immunotherapy	-	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Felix Keil	
LMP1- and LMP2-specific CTLs to patients with EBV-positive NPC (NATELLA)	Procedure: CTLs	Phase 1	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Stephen Gottschalk	Recruiting participants
MAGE-A3/HPV 16 vaccine for squamous cell carcinoma of the head and neck	Biological: MAGE-A3 Biological: HPV-16 vaccine	Phase 1	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Martin J. Edelman	
Safety study of HPV DNA vaccine to treat head and neck cancer patients	Biological: pNGVL-4a-CRT/E7 (detox) DNA vaccine	Phase 1	Allocation: Non-randomized Endpoint classification: Safety study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Sara I Pai	Not yet open for participant recruitment
Study of chemo-immunotherapy in head and neck cancer patients	Biological: Cyclophosphamide, docetaxel, dendritic cells, OK-432	Phase 1	Allocation: Non-randomized Endpoint classification: Safety study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Hiroki Ishii	Recruiting participants

IL: Interleukin, HPV: Human papillomavirus, DNA: Deoxyribonucleic acid, CTLs: Cytotoxic T- lymphocytes, LMP: Latent membrane protein, NPC: Nasopharyngeal carcinoma, ASOG-HNO1: It is a study ID number- Austrian south oncology group-HNO1, IRX: Iroquois

MDR human breast cancer and oral cancer cells.[52] It dramatically reduces P-glycoprotein expression levels resulting in substantial reversal of the MDR phenotype in the cells. One of the major drawbacks of the suicide gene therapy is transfection efficiency.[1] However, a high percentage of transfected cells do not appear to be required *in vivo* due to the ability of transfected tumor cells to induce cell death in neighboring transfected

Table 3: Cancer vaccines

Type of vaccines
In vivo APC based vaccines
Intratumoral BCG
Intratumoral HLA-B7
Whole-cell tumor vaccine
Gene-modified tumor vaccine
Heat shock protein
Peptide-based vaccine
Naked DNA
The primary – boost strategy
Bacterial vectors
Augmentation of the number of APCs
Viral vectors
Ex vivo APC-based vaccines
Dendritic cells
Exosomes
Stimulation of effector cells
Non-specific immunologic stimulant
Intra-tumoral plasmid injection
Immunocytokines
Adoptive transfer of tumor -specific T-cell effectors
Negative regulatory pathway blockade
Blockade of tumor -derived immune suppressive molecules
Non-T-cell directed cancer vaccine

APC: Antigen presenting cell, BCG: Bacillus Calmette-Guerin, HLA-B7: Human leukocyte antigen, DNA: Deoxyribonucleic acid

cells (bystander effect).[1] Ongoing clinical trials on suicide gene therapy are given in Table 4.

Antisense RNA

The activity of several known oncogenes including myc, fos and ras and certain viruses such as HSV-1, human papillomavirus and human T-lymphotropic virus type I can be inhibited by antisense RNA.[3] Antisense RNA is a complimentary strand of the DNA. Gene expression can usually be inhibited by the RNA.[1] Inhibition of expression of theses oncogenes may alter the phenotype, thus abrogating tumor growth.[1] Conventional use of this technique is limited by the difficulty of introducing a sufficient quantity of antisense molecules to inhibit tumor growth. To overcome this drawback, powerful promoters are being used.[53] Preclinical studies using antisense RNA promoters demonstrated a powerful anti-tumor effect with minimal toxicity.[54] A phase-1 study in patients with advanced oral cancer is underway to determine the safety and biological effect of liposome mediated intratumoral epidermal growth factor receptor antisense gene therapy. Results have been positive, showing a low toxicity and high efficacy.[54]

RNA Interference (RNAi)-Based Gene Therapy

siRNA are mainly involved in guiding messenger RNA degradation. RNAi-based gene therapy consist of two approaches: Plasmid or viral vector mediated delivery of short hairpin RNA precursors and direct delivery of siRNAs or siRNA precursors to target cells.[55] RNAi-based gene therapy has been used to treat age related molecular degeneration and respiratory syncytial viral infection.[55] The application of RNAi-based gene therapy for cancer is in the preclinical stage. Although RNAi-based gene therapy has been confirmed efficacious, improvements are required and a number of challenges must be addressed to realize its full potential.

Conclusion

As shown in this review, cancer gene therapy has been shown to be effective in initial clinical trials. As our understanding of the molecular mechanism of cancer increases, it is possible to exploit these principles to target tumor cells selectively. Very soon it may contribute a definitive treatment for head and neck cancers that will offer great effectiveness compared with current therapies and will markedly reduce the high mortality associated with these lesions. Gene therapy is now moving from Phase 1 and 2 trials to the next level of Phase 3 and 4 trials, but it will take considerable time and require a large number of patients to demonstrate the true efficacy of the therapies. Moreover, gene therapy is likely to be very effective in combination with pre-existing clinical regimen such as radiotherapy, chemotherapy and surgery. A large number of studies are now showing great potential for combining gene therapy and chemotherapeutic, immunological and radiotherapeutic approaches to kill cells more effectively and in greater numbers. The field of cancer gene therapy is rapidly maturing and will definitely be part of the future cancer therapeutics. While not all the current trials will lead to a variable therapeutic agent, there is greater hope that these advances will help to treat cancer patients without offering suffering and death.

Table 4: Ongoing trials of suicide gene therapy for head and neck cancer

Study	Intervention	Phase	Study design	Investigators	Present status
A study of an infectivity enhanced suicide gene expressing adenovirus for ovarian cancer in patients with recurrent ovarian and other selected gynecologic cancers	Genetic: Ad5.SSTR/TK.RGD Drug: Ganciclovir (GCV)	Phase 1	Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Ronald D. Alvarez	This study is ongoing, but not recruiting participants
Administration of Donor T cells with the Caspase-9 suicide gene (DOTTI)	Drug: AP1903	Phase 1	Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Malcolm K. Brenner	This study is not yet open for participant recruitment
CASPALLO: Allodepleted T cells transduced with inducible Caspase 9 suicide gene	Biological: Allodepleted T cells	Phase 1	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Malcolm Brenner	This study is currently recruiting participants
Infusion of Donor lymphocytes transduced with the suicide gene HSV-TK in patients with hematological malignancies	Genetic: HSV-TK	Phase 1 and Phase 2	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Fabio Ciceri	This study is ongoing, but not recruiting participants
Randomized trial of suicide gene therapy and prostate cancer (ReCAP)	Biological: Ad5-yCD/mutTKSR39rep-ADP Radiation: IMRT	Phase 2 Phase 3	Allocation: Randomized Endpoint classification: Safety/efficacy study Intervention model: Parallel assignment Masking: Open label Primary purpose: Treatment	Benjamin Movsas	This study is ongoing, but not recruiting participants
Suicide gene therapy for Donor lymphocytes infusion after allogeneic hematopoietic stem cell transplantation (ILD-TK01)	Biological: Donor lymphocyte infusion	Phase 2 Phase 3	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single group assignment Masking: Open label Primary purpose: Treatment	Sébastien Maury	This study is currently recruiting participants
Suicide gene therapy trial	Biological: HSVTK retrovirally-transduced donor T lymphocytes	Phase 1 Phase 2	Allocation: Non-randomized Endpoint classification: Safety/efficacy study Intervention model: Single Group assignment Masking: Open label Primary purpose: Treatment	Anne-Marie McNicol	This study is currently recruiting participants

HSV: Herpes simplex virus-thymidine kinase, IMRT: Intensity-modulated radiation therapy

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