



Long Term Survival Following DeltaRex-G/DeltaVax Tumor-Targeted Gene Therapy for Advanced Chemotherapy-Resistant Malignancies: An Academic Milestone

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Abstract

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Background and Purpose: DeltaRex-G is a tumor-targeted retrovector (1) displaying a Signature (SIG)-decapeptide for binding to anaplastic SIG proteins that are abnormally exposed in the tumor microenvironment, and (2) encoding a cytotoxic CCNG1 inhibitor gene for killing rapidly dividing cells such as cancer cells. DeltaVax is a tumor-targeted retrovector encoding two genes, (1) a GM-CSF gene for *in situ* autovaccination, and (2) the HSVtk gene for regulating GM-CSF expression in cancer cells. This case series reports on the long-term survival of patients who participated in five Phase 1/2 and Phase 2 US-based and one Phase 1/2 Philippine-based clinical trials using intravenous DeltaRex-G, with or without DeltaVax, for locally advanced or metastatic cancer.

Methods and Patients: The case report forms of patients enrolled in the above-mentioned FDA and IRB approved clinical trials were reviewed and survival data documented.

Results: Ninety-eight patients with advanced chemo-resistant solid malignancies received >5,000 intravenous infusions of DeltaRex-G. Another 16 patients received 288 intravenous infusions of DeltaRex-G with 96 infusions of DeltaVax followed by valacyclovir orally. Cancer types include pancreatic adenocarcinoma (n=1), osteosarcoma (n=3), MPNST (n=1), invasive breast carcinoma (n=2), and B-cell lymphoma (n=1). The median estimated tumor burden was 29.1×10^9 (range: 6.2 to 75.5×10^9) cancer cells, median duration of treatment was 20 (range: 6 to 28) months, and median duration of survival was 12 (range: 10 to 12) years from DeltaRex-G treatment initiation. Survival analysis showed 5 of 98 (5.1%) 10 to 12-year survival rate for patients who received DeltaRex-G alone, 3 of 22 (13.6%) for osteosarcoma patients receiving DeltaRex-G alone or with DeltaVax, and 4 of 16 (25%) for DeltaRex-G + DeltaVax combination.

Conclusion: Taken together, these data suggest that DeltaRex-G, with or without DeltaVax, may induce prolonged survival in advanced chemo-resistant solid malignancies and B-cell lymphoma. Points to consider going forward with the next phase 2 and phase 3 clinical trials using DeltaRex-G include patient's (1) estimated tumor burden (2) risk of recurrence/disease progression after standard therapy, (3) molecular profile of tumor, and (4) CCNG1 expression levels in tumors and circulating tumor cells, to identify patients who will benefit the most with DeltaRex-G/DeltaVax therapy.

Keywords: Tumor-targeted cancer gene therapy; Cell cycle control; CCNG1; Metastatic cancer; Chemotherapy resistant cancer; Pancreatic cancer; Sarcoma; Osteosarcoma; Breast cancer; B-cell lymphoma

Introduction

Metastatic cancer is associated with, hitherto, an invariably fatal outcome. While neoadjuvant and/or adjuvant chemotherapies have been effective in treating, and even curing some resectable cancers, the development of metastasis and multi-drug resistance spell therapeutic failure [1]. From 2004 to 2020, the safety and efficacy of a pathotropic (disease-seeking) tumoricidal retroviral vector, DeltaRex-G (Former names: Regin-G, Mx-dnG1) in stage 4 chemo-resistant cancers have been reported, gaining USFDA orphan drug designation for pancreatic cancer in 2003 and for soft tissue sarcoma and osteosarcoma in 2008 [2,3], fast track status for pancreatic cancer in 2009 [4,5], Philippine FDA accelerated approval for all chemotherapy-resistant solid malignancies in 2007 [4,5] and US FDA authorization for expanded access to DeltaRex-G for an intermediate size population in 2020 [6-8].

Long term survival outcomes of stage 4 cancer patients following treatment with DeltaRex-G were initially reported by Kim et al. [9] and Al-Shihabi et al. [10]. In 2018, Ignacio et al. [8] reported on the safety and efficacy of the GeneVieve Protocol, a dual targeted approach to cancer gene therapy using cytotoxic DeltaRex-G followed by DeltaVax for tumor eradication and *in situ* vaccination, respectively (Figure 1). Here, we report a detailed updated long-term survival data of 8 stage 4 chemo-resistant cancer patients who were treated with DeltaRex-G, with or without DeltaVax, and outline "Points to Consider" in planning the next phase 2 and phase 3 clinical trials for pancreatic adenocarcinoma, osteosarcoma, breast carcinoma and B-cell lymphoma.

Patients and Methods

Case report forms and survival data of 98 patients who participated in U.S. FDA and IRB-approved Phase 1/2 and phase 2 clinical trials using DeltaRex-G monotherapy conducted at the Cancer Center of Southern California/Sarcoma Oncology Center, Santa Monica, CA, Bruckner Oncology, New York, NY, USA, Duke University Medical Center, Durham, NC, USA, and 16 patients who participated in a Philippine FDA and IRB-approved Phase 1/2 clinical trial using DeltaRex-G plus DeltaVax (The GeneVieve Protocol) conducted at Asian Hospital and Medical Center/Civic Place, Ayala Alabang, Metro Manila, Philippines, were reviewed. Investigational new drug applications were reviewed and authorized by the USFDA or the Philippine FDA. The patients were recruited on a first-come first-serve basis and a written informed consent was obtained from each patient at the time of enrollment. All personnel who handled and disposed of the gene therapy products observed BSL 2 compliance in accordance with the NIH guidelines for research involving recombinant DNA molecules.

The US-based phase 1/2 clinical trials using DeltaRex-G monotherapy consisted of escalating doses of DeltaRex-G, 1 to 3 × 10¹¹ cfu three times a week for 4 weeks with a two-week rest period (one treatment cycle). Treatment cycles were repeated if there was stable disease and grade 1 or less toxicity. Surgical resection of residual tumor was done at the discretion of the principal investigator/s [6,7,11].

The GeneVieve protocol (DeltaRex-G + DeltaVax) is a phase 1/2

open label study, single center, single arm, DeltaVax dose-seeking study that incorporates a modification of the standard cohort of 3 design combined with a phase II efficacy component by adaptive design [8]. For the phase I part of the study, treatment with DeltaRex-G was administered at a previously confirmed effective and safe dosage (2.0 × 10¹¹ cfu, i.v.) on days 1, 3, and 5, followed by DeltaVax at three escalating doses (0.5, 1.0, 2.0 × 10¹⁰ cfu i.v.) on day 3. Valacyclovir, 3 grams/day orally was given on days 6 to 19 comprising one treatment cycle. For the phase II part, patients who had grade 1 or less toxicity received additional cycles of DeltaRex-G and DeltaVax for a total of 6 months.

Evaluation of tumor burden: Estimated Tumor Burden (ETB) was determined for each patient using the following formula:

$$\text{ETB (\# cancer cells)} = [\text{Sum of Target Lesions (cm)} + (\text{No. of Non-Target Lesions} + (20^*))] \times 10^9 \text{ (Assumption: 1 cm} = 1 \times 10^9 \text{ cancer cells).}$$

*Note: 20 × 10⁹ cancer cells for each occurrence of ascites, pleural effusion, and/or 'too many to count' non-target lesions [11].

Results

Ninety-eight patients with chemotherapy-failed metastatic solid tumors received DeltaRex-G and 16 patients with advanced solid tumors and B-cell lymphoma received DeltaRex-G + DeltaVax. Table 1 shows the characteristics of these long-term cancer survivors, clinical trial number or name, diagnoses, baseline Estimated Tumor Burden (ETB), investigational products used, treatment duration, and duration of survival. The median ETB was 29.1 × 10⁹ (range 6.2 to 75.5 × 10⁹) cancer cells, median duration of treatment was 20 (range 6 to 28) months, median duration of survival was >12 (range >10 to 12) years from DeltaRex-G treatment initiation. Survival analysis showed 5 of 98 (5.1%) 10 to 12 year survival rates for patients who received DeltaRex-G alone, 3 of 22 (13.6%) for osteosarcoma, and 4 of 16 (25%) for DeltaRex-G + DeltaVax combination. Additionally, we describe the individual clinical features of the 8 long term cancer survivors [3,4,6-8,11-14].

Case 1: Pancreatic adenocarcinoma metastatic to lymph node, liver, and peritoneum (NCT00504998)

This patient is an 84-year-old white female who was initially diagnosed with non-metastatic, poorly differentiated adenocarcinoma of the pancreas, underwent a Whipple's resection with postoperative radiation therapy, and received chemotherapy with 5-Fluorouracil (5FU) and gemcitabine for one year. A year later, she presented with hepatic and lymph node metastases and peritoneal carcinomatosis with an elevated serum CA19-9 level of 76 units/mL (normal <37 U/mL). At age 72 years, she participated in a Phase I/II study using DeltaRex-G, with an ETB of 25 × 10⁹ cancer cells [11]. The patient completed a total of 18 months of therapy with DeltaRex-G and achieved a complete remission after week 36 of treatment. The patient received no additional cancer therapy and is alive with no evidence of cancer or late onset adverse effects.

Case 2: Osteosarcoma metastatic to lung (NCT00572130 phase 2)

This is 51-year-old female with osteosarcoma, left fibula, metastatic to lung. Previous therapy included neoadjuvant therapy

Table 1: Characteristics of long-term cancer survivors with DeltaRex-G +/- DeltaVax.

Patient #	NCT #	Diagnosis	Estimated Tumor Burden, × 10 ⁹ cancer cells	Products Used	Treatment Duration, months	Late Adverse Events	Duration of Survival, years
1	504998	Pancreatic cancer	25	DeltaRex-G	18	none	>12
2	571030	Osteosarcoma	42.2	DeltaRex-G	8	none	>12
3	505713	MPNST	64.8	DeltaRex-G	28	none	>12
4	GeneVieve Protocol	B-cell lymphoma	33.2	DeltaRex-G + DeltaVax	6	none	>11
5	00505271 + GeneVieve Protocol	Breast carcinoma	20	DeltaRex-G + DeltaVax	18	none	>12
6	572130	Osteosarcoma	75.5	DeltaRex-G	12	none	>10
7	GeneVieve Protocol	Osteosarcoma	6.2	DeltaRex-G + DeltaVax	6	none	>12
8	GeneVieve Protocol	Breast carcinoma	20	DeltaRexG + DeltaVax	12	none	>10

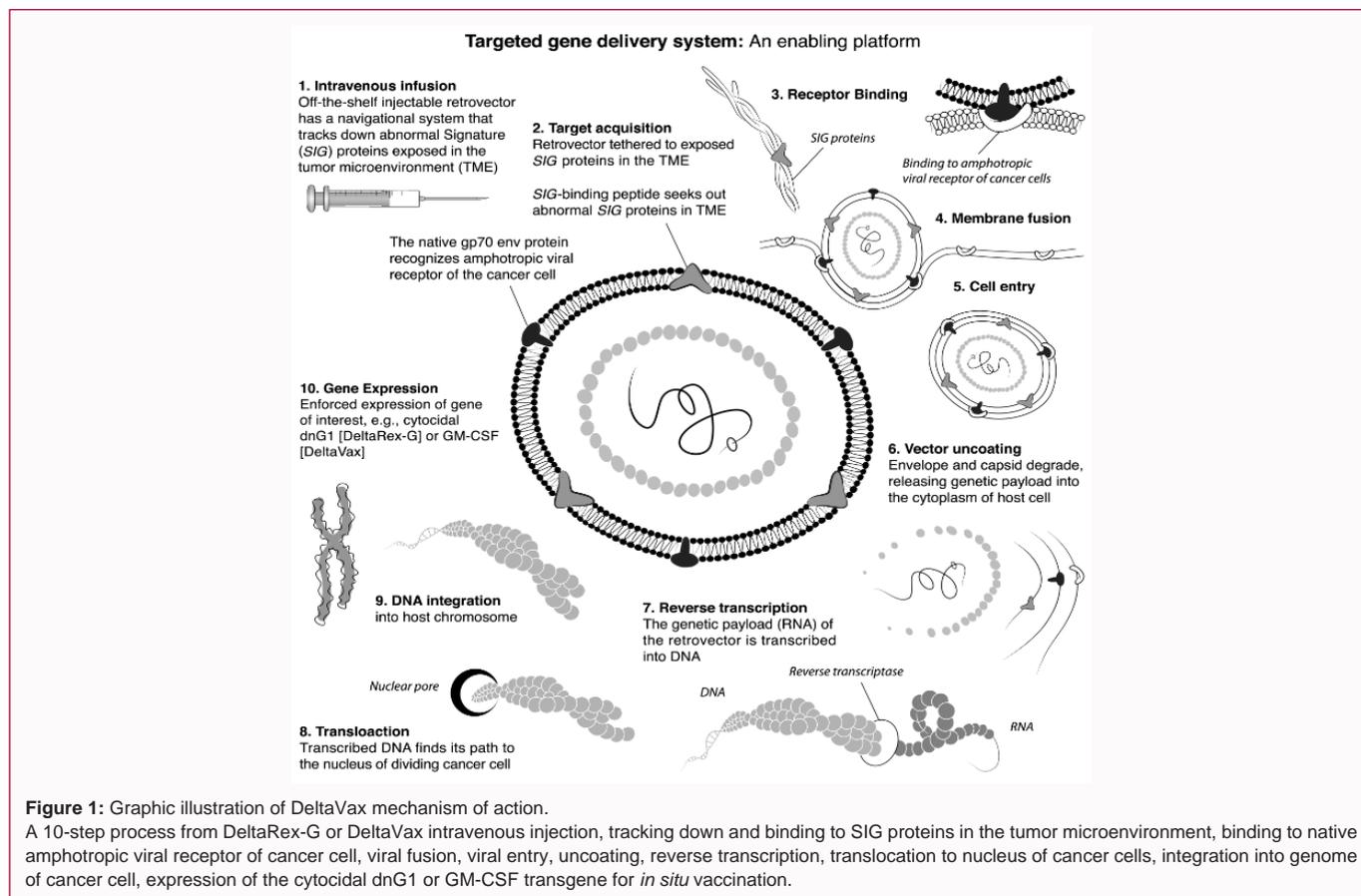


Figure 1: Graphic illustration of DeltaVax mechanism of action.

A 10-step process from DeltaRex-G or DeltaVax intravenous injection, tracking down and binding to SIG proteins in the tumor microenvironment, binding to native amphotropic viral receptor of cancer cell, viral fusion, viral entry, uncoating, reverse transcription, translocation to nucleus of cancer cells, integration into genome of cancer cell, expression of the cytotoxic dnG1 or GM-CSF transgene for *in situ* vaccination.

with methotrexate, ifosfamide, cisplatin, doxorubicin, followed by limb salvage, and adjuvant chemotherapy with methotrexate, ifosfamide, cisplatin, and doxorubicin. Four years later, the patient developed lung metastases and was treated with various combinations of the above-mentioned 4 drugs plus alpha interferon. After failing these regimens, at age 39 years, the baseline ETB was 42.2 cm. She was treated with DeltaRex-G, 2×10^{11} cfu three times a week for 4 months, followed by resection of 2 residual lung tumors, and then given another 4 months of DeltaRex-G therapy [3,6]. Twelve years later, the most recent CT scan showed no evidence of osteosarcoma and the patient enjoys sustained remission with no delayed treatment related adverse events [10,14].

Case 3: Malignant Peripheral Nerve Sheath Tumor (MPNST) of parotid gland, metastatic to lung, chemotherapy

resistant (NCT00505713)

This 27-year-old white female with advanced chemotherapy resistant MPNST participated, at 15 years of age, in a phase 1/2 clinical trial using i.v. DeltaRex-G for advanced bone and tissue sarcoma in March 2008. Prior to enrollment, the patient underwent parotidectomy and received various chemotherapy treatments such as doxorubicin, ifosfamide, and temozolomide, sorafenib, and Interleukin-2 (IL-2) immunologic therapy. These treatments were unsuccessful and subsequently discontinued, with severe toxicity due to IL-2 therapy and further progression of the patient’s lung metastases. With an ETB of 64.8 cm, the patient received intravenous DeltaRex-G, 3×10^{11} cfu three times weekly [9]. The patient experienced minimal, if any, treatment related adverse events toxicity, had sustained disease control (stable disease) by RECIST v1 for 28 months while receiving

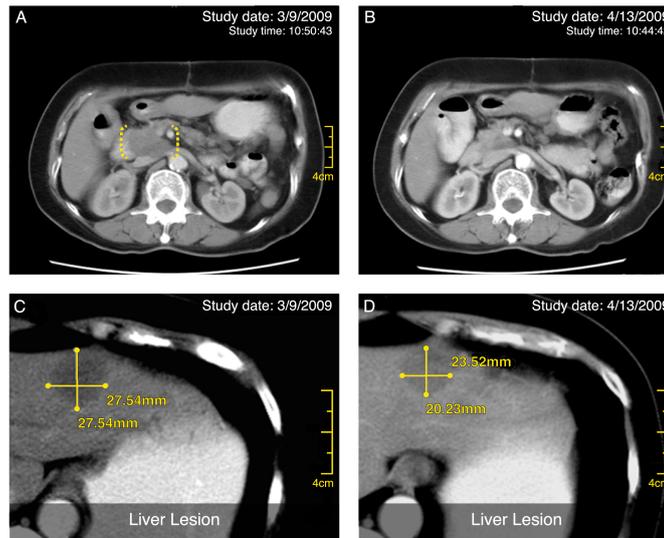


Figure 2: Complete resolution of pancreatic mass and shrinkage of liver lesion. CT scan was obtained after one treatment cycle of DeltaRex-G, 2×10^{11} cfu/dose i.v. three times a week for 4 weeks. (A, C) Before treatment; (B, D) After treatment.

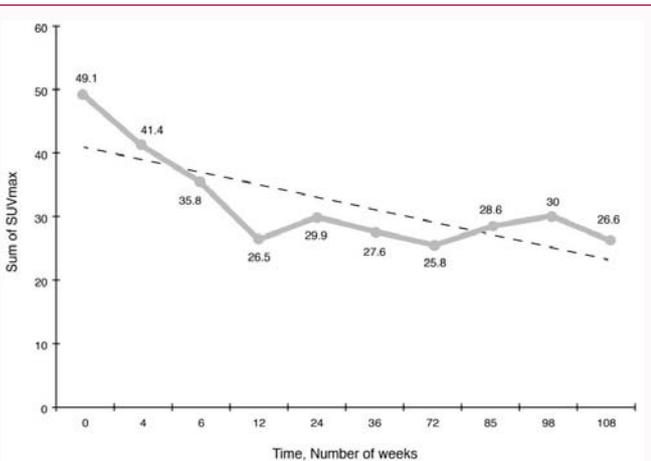


Figure 3A: Improvement in bone metastases by PET scan during treatment with DeltaRex-G. The sum of SUV/max, is plotted on the vertical axis, as a function of time, plotted on the horizontal axis.

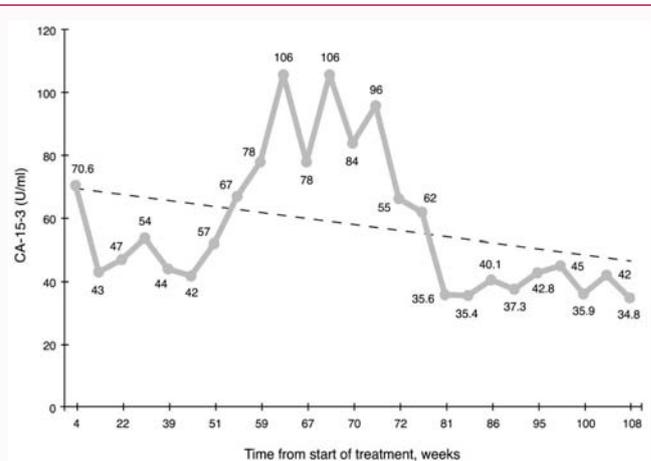


Figure 3B: Reduction in serum CA15.3 levels during treatment with DeltaRex-G and GeneVieve (DeltaRex-G+DeltaVax). The CA15.3 levels are plotted on the vertical axis, as a function of time, plotted on the horizontal axis. The spike in serum CA15.3 level was during a period when patient was not receiving any treatment while waiting to begin the GeneVieve Protocol.

a total of 205 DeltaRex-G vector infusions. At the end of treatment, a PET/CT scan demonstrated overall improvement compared to that at DeltaRex-G treatment initiation. The patient’s pulmonary metastases improved dramatically in size, and the right pleural effusion and significant ascites also resolved. Twelve years later, the patient has no evidence of active disease, on no further cancer therapy.

Case 4: Pancreatic B-cell lymphoma metastatic to liver, lung, mesentery and cervical lymph node (GeneVieve Protocol)

This 72-year-old female was diagnosed in January 2009 with pancreatic adenocarcinoma, metastatic to the mesentery, liver, and lungs. The patient underwent a biliary bypass and was treated with standard chemotherapy, gemcitabine 1000 mg/m² for 4 weeks, which failed and resulting in disease progression. In April 2009 (at age 60 years), with a baseline ETB of 33.2 cm, she started treatment with DeltaRex-G i.v. at 2×10^{11} cfu per dose, given three times a week for

4 weeks. Follow-up CT scan at the end of 4 weeks showed complete regression of the pancreatic tumor and significant reduction in the size of the liver metastasis (Figure 2). After a 4-week treatment with DeltaRex-G, the patient was enrolled in the GeneVieve Protocol, consisting of DeltaRex-G plus DeltaVax (tumor targeted GM-CSF) personalized vaccine therapy [8]. She completed the 6-month treatment with DeltaRex-G + DeltaVax without event. Of note, further immunohistochemical staining of her original archived tumor showed CD20+ B cells which led to a revised diagnosis of pancreatic B cell lymphoma. She completed treatment with R-CHOP and the patient currently has no evidence of disease 12 years later. Given the patient’s favorable response to DeltaRex-G with complete disappearance of the pancreatic tumor and reduction of liver lesion by CT scan, these findings indicate that DeltaRex-G may be an effective treatment for B-cell lymphoma.

Case 5: Breast carcinoma metastatic to bone (NCT00505271; GeneVieve Protocol)

This is a 60-year-old white female with poorly differentiated ductal carcinoma of breast and extensive bone metastases involving ribs, thoracic and lumbar vertebrae, and right femoral head. Previous chemotherapy consisted of doxorubicin, paclitaxel and cyclophosphamide. Patient was treated, at age 49 years with a baseline ETB of 20 cm. and received DeltaRex-G 3×10^{11} cfu i.v. three times a week for 4 weeks followed by a two-week rest period (one treatment cycle) for 17 months at Bruckner Oncology Clinic. Subsequently, she was treated in Manila with DeltaRex-G and DeltaVax for an additional 6 months [8]. Figure 3 shows improved tumor responses by International PET criteria (Figure 3A) and CA15.3 levels during treatment with DeltaRex-G + DeltaVax respectively (Figure 3B). Patient is alive 12 years later with metastases to liver and is on capecitabine therapy.

Case 6: Chondroblastic osteosarcoma metastatic to lungs (NCT00572130 phase 2)

This is a 37-year-old male with chemotherapy resistant osteosarcoma of left hip, metastatic to lungs, left inguinal lymph node, left femoral neck, left public bone, and left supracetabular region. Previous chemotherapy included doxorubicin, methotrexate, cisplatin, ifosfamide and alpha interferon. At age 25 years, his baseline ETB was 75.5 cm. He received DeltaRex-G, 2×10^{11} cfu three times a week for 18 months, followed by resection of the pelvic mass which showed no residual disease [3,6]. Twelve years later, the patient is still alive with no evidence of active disease and no late adverse event except for cisplatin-induced chronic renal failure requiring hemodialysis [10,14].

Case 7: Chondroblastic osteosarcoma, locally advanced, unresectable, mandible (GeneVieve Protocol)

This 37-year-old male with recurrent unresectable chondroblastic osteosarcoma of left mandible (previous therapy: 3 surgical resections), was treated, at 26 years of age (baseline ETB of 6.2 cm), with 2×10^{11} cfu per dose, given three times a week for 4 weeks. After one cycle of DeltaRex-G, the patient was enrolled in the GeneVieve Protocol, consisting of DeltaRex-G plus DeltaVax vaccine therapy [8]. After 6 months, the patient received four doses of doxorubicin

60 mg/m² i.v. every 3 weeks which resulted in a dramatic shrinkage (50%) of his mandibular tumor, indicating that DeltaRex-G could be used to prime a tumor to respond to chemotherapy. Twelve years later, the patient is alive today with no evidence of active disease or late adverse events.

Case 8: Intraductal carcinoma of breast metastatic to bone, chemotherapy resistant (GeneVieve Protocol)

This 65-year-old white female with poorly differentiated invasive ductal carcinoma of breast and extensive bone metastases (previous chemotherapy: docetaxel and carboplatin; cyclophosphamide, methotrexate, 5FU, zometa) was treated, at 54 years of age (baseline ETB of 20 cm.), with 2×10^{11} cfu per dose, given three times a week for 4 weeks. After one cycle of DeltaRex-G, the patient was enrolled in the GeneVieve Protocol, consisting of DeltaRex-G plus DeltaVax [8]. Figure 4 shows reduction in bone metastases during treatment with DeltaRex-G + DeltaVax. Ten years later, the patient is alive with no active disease, on no further cancer therapy, and no late vector related adverse events.

Discussion

In an era of precision medicine, the successful treatment of 8 long term survivors with tumor-targeted DeltaRex-G, with or without DeltaVax, after failing standard therapy encourages the rapid clinical development of these cancer therapies for effecting long term survival/possibly cure. The initial phase 1 and phase 2 studies broadened our understanding of the mechanisms of action of DeltaRex-G and DeltaVax [2-8]. We learned that while patients with large tumor burdens may respond favorably to DeltaRex-G/DeltaVax therapy, the median ETB of long-term survivors is 29.1×10^9 cancer cells or 29.1 cm sum of longest diameters of target lesions (ΣLD) by CT scan. Further, DeltaRex-G is cytotoxic not only to cancer cells, but also to Tumor Associated Microvasculature (TAMs) and Tumor Associated Fibroblasts (TAFs), thus, promoting enhanced immune cell trafficking in the Tumor Microenvironment (TME). This phenomenon can make tumors appear larger and occult tumors to become visible on CT scan. Hence the International PET criteria would be a more appropriate imaging study for evaluating tumor responses to DeltaRex-G and DeltaVax, as in the case of immune checkpoint inhibitor therapies/immunotherapies [2-8,11-13]. We

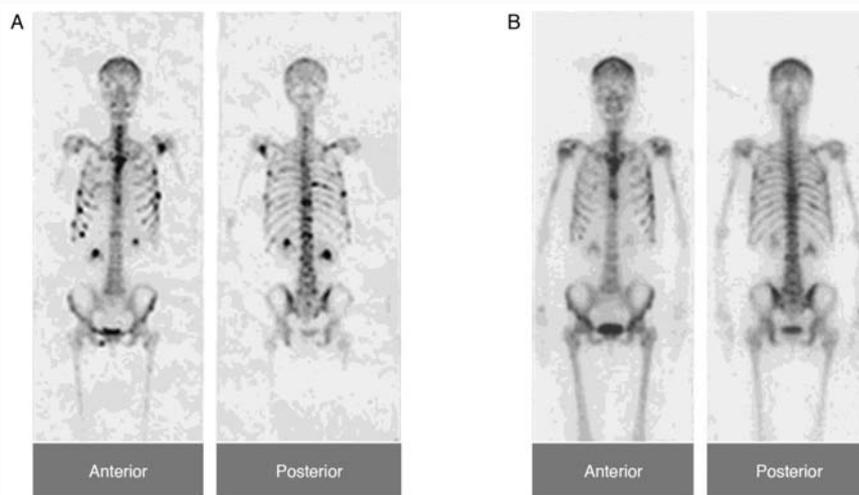


Figure 4: Improvement of bone metastases during treatment with DeltaRex-G and the GeneVieve Protocol (DeltaRex-G+DeltaVax) (A) Before treatment; (B) After treatment with GeneVieve Protocol (DeltaRex-G + DeltaVax)

also noted that some long-term survivors achieved a complete remission after prolonged DeltaRex-G treatment or after surgical resection of residual tumors [11-14]. An interesting concept would be to use DeltaRex-G/DeltaVax as adjuvant therapy or follow-on therapy for cancers that have high recurrence risk. Recent advances in molecular profiling and functional genomics identified cyclin G1 (CCNG1 gene) as a critical element of the cyclin G1/Mdm2/p53 axis and a strategic locus for re-establishing cell cycle control via cancer gene therapy [15]. Recently, Ravicz et al. [16] reported enhanced CCNG1 gene expression in over 50% of tumors tested by RNA sequence analysis, indicating that CCNG1 is a molecular target for DeltaRex-G, a CCNG1 inhibitor. Taken together, these data indicate that there are "Points to Consider" going forward with the next phase 2 and phase 3 clinical trials as follows: (1) Inclusion criteria would include patients with baseline Estimated Tumor Burden (ETB) of less than 30 billion cancer cells or Σ LD of less than 30 cm by CT scan. Rationale: DeltaRex-G is a replication incompetent retroviral based vector that delivers only one or two copies DNA per cancer cell. Using the calculus of parity published by Gordon et al. [17] in 2006: ETB \times Multiplicity of Infection (MOI) of 100 represents the total dose of DeltaRex-G, in colony forming units (cfu), that would be needed to overcome the tumor burden in a reasonable period of time, (2) Criteria for continuing therapy in the presence of radiologic progression. Rationale: DeltaRex-G does not suppress the immune system, may evoke enhanced immune cell trafficking in the TME causing an increase in the size of target lesions and/or non-target lesions or causing occult lesions to become more apparent by CT/MRI [13]. In a previous study [4,6], a number of patients subsequently achieved either a Complete Response (CR), Partial Response (PR) or Stable Disease (SD) with continued DeltaRex-G treatment [5,7,11,12]. Therefore, the conditions for continuing therapy in the presence of radiographic progression will include clinical benefit, grade 1 or less toxicity, and patient consent to continue therapy with DeltaRex-G and/or DeltaVax, (3) Adjuvant therapy or follow-on therapy with DeltaRex-G and/or DeltaVax after standard adjuvant therapy for cancer types with high risk of recurrence, e.g., pancreatic cancer, osteosarcoma, soft tissue sarcoma. Rationale: Chemotherapy is limited by unacceptable toxicity while DeltaRex-G has minimal, if any, toxicity and can be given repeatedly for an extended period of time (2 years or more) to prevent recurrence, eradicate cancer stem cells and evoke long term survival/cure, (4) The use of DeltaRex-G as a primer to targeted therapies, chemotherapy or immunotherapy. Rationale: DeltaRex-G may serve as an immune modulator and could prime the tumor to respond better to other targeted therapies, chemotherapy or immunotherapy [3], (5) Development of novel biomarkers, such as CCNG1 and oncogenic drivers along the CCNG1 pathway to identify patients who will benefit most from DeltaRex-G therapy, and (6) Identification of cancer stem cell markers, i.e., myc, TP53 in patient's tumor, and first line use of DeltaRex-G in patients whose tumor molecular profiles indicate resistance to chemotherapy.

Currently, there is an USFDA authorized protocol known as "Blessed: Expanded access for DeltaRex-G for an intermediate size population with advanced pancreatic cancer and sarcoma" (NCT04091295; [18]). Single patient use protocols using DeltaRex-G for stage 4 cholangiocarcinoma, non-small cell lung cancer, and prostate cancer and as adjuvant therapy for triple receptor positive early-stage breast cancer have also been authorized by the USFDA (IND# 19130). The results of these FDA sanctioned protocols are hypothesis generating and will also be used in planning the next

Phase 2/3 clinical trials for these cancer types.

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