GLIPR1 Tumor Suppressor Gene Expressed by Adenoviral Vector as Neoadjuvant Intraprostatic Injection for Localized Intermediate or High-Risk Prostate Cancer Preceding Radical Prostatectomy

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Abstract

Background: GLIPR1 is upregulated by p53 in prostate cancer cells and has preclinical antitumor activity. A phase I clinical trial was conducted to evaluate the safety and activity of the neoadjuvant intraprostatic injection of GLIPR1 expressing adenovirus for intermediate or high-risk localized prostate cancer before radical prostatectomy (RP).

Methods: Eligible men had localized prostate cancer (T1-T2c) with Gleason score greater than or equal to 7 or prostate-specific antigen 10 ng/mL or more and were candidates for RP. Patients received the adenoviral vector expressing the GLIPR1 gene by a single injection into the prostate followed four weeks later by RP. Six viral particle (vp) dose levels were evaluated: 1010, 5 × 1010, 1011, 5 × 1011, 1012, and 5 × 1012 vp.

Results: Nineteen patients with a median age of 64 years were recruited. Nine men had T1c, 4 had T2a, and 3 had T2b and T2c clinical stage. Toxicities included urinary tract infection (n = 3), flu-like syndrome (n = 3), fever (n = 1), dysuria (n = 1), and photophobia (n = 1). Laboratory toxicities were grade 1 elevated AST/ALT (n = 1) and elevations of PTT (n = 3, with 1 proven to be lupus anticoagulant). No pathologic complete remission was seen. Morphologic cytotoxic activity, induction of apoptosis, and nuclear p27Kip1 upregulation were observed. Peripheral blood CD8+, CD4+, and CD3+ T-lymphocytes were increased, with upregulation of their HLA-DR expression and elevations of serum IL-12.

Conclusions: The intraprostatic administration of GLIPR1 tumor suppressor gene expressed by an adenoviral vector was safe in men, with localized intermediate or high-risk prostate cancer preceding RP. Preliminary evidence of biologic antitumor activity and systemic immune response was documented. Clin Cancer Res; 17(22); 1–9. ©2011 AACR.

Introduction

Prostate cancer is the most common solid tumor diagnosed in the United States with approximately 200,000 cases and 30,000 deaths in a year (1). Prostate cancer is commonly detected when still localized before the advent of prostate-specific antigen (PSA) screening and radical prostatectomy (RP) can improve outcomes in appropriately selected patients. Androgen deprivation therapy (ADT) is the conventional frontline systemic therapy for hormone-naive prostate cancer. However, ADT has deleterious effects on quality of life and bone health, and progression to castration-resistant prostate cancer (CRPC) is almost unavoidable in men with advanced disease. Treatment options are limited in patients with metastatic CRPC, and chemotherapy (docetaxel, cabazitaxel), immunotherapy (sipuleucel-T), and androgen synthesis inhibitors (abiraterone acetate) have shown modest extensions of survival (2–6). Clearly, there is a need for more effective and tolerable agents for prostate cancer.

Given that the vast majority of men present with localized disease, the paradigm of neoadjuvant therapy preceding RP may improve outcomes and facilitate the development of new agents for prostate cancer by providing an early signal of activity (7).
neoadjuvant therapy is justified in high-risk cases defined by high PSA, Gleason score, and clinical stage. Because pathologic and biological activity can be rapidly determined after surgery, the efficacy of a systemic regimen is evident with a relatively small number of patients before long-term follow-up. Neoadjuvant ADT followed by RP improves pathologic outcomes with no definitive evidence for improvement in long-term clinical outcomes (8). Ongoing phase III trials are evaluating the impact of combination chemotherapy and ADT on outcomes based on the suggestion of improved pathologic outcomes (9). In addition, biologic and chemotherapeutic agents have been evaluated without concomitant ADT to obtain a signal of activity and provide proof of concept (10–13). The intraprostatic delivery of genes by employing a vector has also been studied (14–16).

Because of the established association between loss of p53 function and prostate cancer metastasis, we have pursued the identification, characterization, and functional analysis of p53 target genes in prostate cancer (17–19). We identified the GLIPR1 (glioma pathogenesis related protein), previously termed RTVP-1 (related to testes specific, vespid, and pathogenesis proteins), mRNA as being upregulated by p53 in mouse prostate cancer cells. Both mouse and human GLIPR1 contain p53 binding elements in promoter and intronic sequences. GLIPR1 was shown to have proapoptotic, antiangiogenic, immunostimulatory, and metastasis-suppressing activity (20). Adenoviral vector-mediated GLIPR1 delivery in vivo was capable of eradicating micrometastatic disease (21, 22). GLIPR1 is downregulated, in part, by gene methylation in prostate cancer compared with normal prostate tissue (23). Given that GLIPR1 may confer antitumor activity, a phase I clinical trial was conducted to evaluate the safety and biologic activity of adenovirus delivered in situ GLIPR1 gene therapy for localized intermediate and high-risk prostate cancer before RP.

### Materials and Methods

#### Patient eligibility

Patients were required to have clinical stage T1c–T2cN0M0 adenocarcinoma of the prostate with a Gleason score ≥ 7 or PSA ≥ 10 ng/mL. All participants had to have a needle biopsy of the prostate (at least 12 cores) to obtain tissue for pathologic analysis. A baseline chest X-ray, bone scan, and CT scan of the abdomen and pelvis were mandated for staging. Patients were also required to be candidates for RP. Written informed consent was obtained from all of the patients.

#### Construction of adenoviral vector GLIPR1

Clinical grade replication-defective Ad5GLIPR1 viral vector was prepared in the Baylor College of Medicine (BCM) Cell and Gene Therapy GMP facility. Human GLIPR1 cDNA was PCR amplified from pcDNA3-hRTVP1 vector with specific primers that contained sequence for XbaI and KpnI restriction enzymes (underlined), respectively (upper primer: 5′-CTAGTCTAGAGCCACCAGTGCTCGACACCTGGCT-3′, lower primer: 5′-GGGGTACCTAGTGGGATCCAAAAAGAATCAAA-3′). In addition, upstream primer contained optimized Kozak sequence (GCCACC, bold font) in front of ATG codon of hRTVP-1 cDNA. The resulting 821 bp PCR fragment containing complete coding sequence of GLIPR1 was cloned into XbaI and KpnI sites of pShuttle-X (Clontech) transfer vector and sequenced. The coding sequence for GLIPR1 cDNA was not modified. Three recombinant pShuttle-hRTVPk vector clones were analyzed for hRTVP-1 expression by Western blot after transient transfection into A459 cell line. All 3 pShuttle-hRTVPk clones with modified Kozak sequence showed better expression of hRTVP-1 protein compared with the original pShuttle-hRTVP-1 vector (Fig. 1). Clone pShuttle-hRTVPk1 was used for construction of the adenoviral vector.

Clontech adeno-X expression system protocol was used and the I-Ceu/Pl-SceI fragment containing expression cassette CMV-hRTVPk1-polyA was used to generate the

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**Figure 1.** Modification of Kozak sequence of GLIPR1/RTVP-1 cDNA improves GLIPR1 protein expression. Unmodified and modified GLIPR1/RTVP-1 cDNA constructs were transfected in A459 cell line and cell lysates were analyzed by Western blot for GLIPR1 protein expression levels 48 hours after transfection. Lanes: 1, pcDNA3.1 (control vector); 2, pShuttle-hRTVP-1; 3, pSecTag-hRTVP-1; 4, pShuttle-hRTVPk1, 5, pShuttle-hRTVPk2, 6, pShuttle-hRTVPk3. All 3 pShuttle-hRTVPk clones with modified Kozak sequence (lanes 4–6) showed increased expression of GLIPR1/hRTVP-1 protein compared with the original pShuttle-hRTVP-1 vector (lane 2).
adenoviral vector. The construction of Ad5hRTVPk1 was confirmed by restriction endonuclease mapping and by conventional dideoxy nucleotide sequencing. Expression of RTVP-1 was confirmed by Western blot. For the production of recombinant adenoviruses, 293 cells were transfected with Ad5hRTVPk1. Once cytotoxic effects were observed, cells were harvested and lysed. This lysate was used for plaque purification. Further production and characterization of a clinical grade Ad5hRTVP-1 vector was done by BCM Cell and Gene Therapy GMP facility. Comprehensive information about the clinical grade vector was provided to the FDA and the vector was approved for the current IND clinical trial. According to a recent HGNC recommendation, GLIPR1 is the preferred symbol for the RTVP-1 gene. For consistency, we will use Ad5GLIPR1 symbol to indicate clinical grade vector for the remaining part of the article.

**Trial design and therapy administration**

The protocol used in our study was approved by the Biosafety Committees and the Institutional Review Boards of the participating institutions of BCM (Veterans Affairs Medical Center, Ben Taub General Hospital, St. Luke’s Episcopal Hospital), the Recombinant DNA Advisory Committee of the NIH, and the United States Food and Drug Administration. The Data and Safety Monitoring Plan was applied under an IND by the prostate cancer SPORE program at BCM.

The trial was designed as a conventional phase I trial enrolling 3 patients per cohort and evaluating 6 doses of viral particles (vp): \(10^{10}, 5 \times 10^{10}, 10^{11}, 5 \times 10^{11}, 10^{12}, \) and \(5 \times 10^{12}\) vp. On day 1, a transrectal ultrasound (TRUS) guided single intraprostatic injection of adenoviral GLIPR1 was delivered, followed by RP on day 28. Factors such as tumor size and location determined the injectable volume, which was to be no more than 2 mL split into 2 separate injections of 1 mL each into the right and left lobes. An oral, broad-spectrum antibiotic was administered the evening before and the morning of the intraprostatic injection and continued for 4 days. Following the procedure, the patients were admitted for a 23-hour observation period. They were admitted for a 23-hour observation period. They were then followed in the outpatient clinic at days 8, 15, 21, and 28, and the fourth postoperative day (±2 days at each visit). Blood was drawn at screening (days 8, 15, 21, and 28, and the fourth postoperative day (±2 days at each visit) for the following immunologic studies by ELISA: ELISPOT assay, NK activity, IL-2, IL-6, IL-12, IFN-γ, TGFβ3, and CD4/CD8 levels. The titer of serum antibodies to adenovirus was measured at baseline and day 28 (±2 days at each visit).

**Statistical considerations**

A conventional phase I trial was designed with a sample size of 3 to 6 patients for each of 6 doses of virus. The maximum tolerated dose (MTD) was the dose for which the incidence of dose limiting toxicities was lesser than 33%. Although the trial was not expected to have sufficient power to detect small differences in biomarkers, the preliminary analyses were done using all patients and stratified by dose. Numerical and graphical descriptive statistics were calculated. Paired \(t\) tests or Wilcoxon signed-rank tests were employed to evaluate the change in biomarkers from biopsy to RP. The 1-ANOVA or Kruskal–Wallis tests, followed by appropriate multiple comparisons procedures if the overall test was statistically significant at the 5% level of significance, were used to compare changes in biological markers between the dose groups to assess differences.

**Results**

**Patient characteristics**

Nineteen patients were enrolled with a median age of 64 (range 50–75; Table 1). One additional patient was accrued in the second cohort administered \(5 \times 10^{10}\) vp because a patient in this cohort withdrew consent from participation (although he did undergo therapy followed by RP). The routine pathology and toxicity data are available for the patient who withdrew consent, but correlative studies could not be done after withdrawal of consent.
Forty-seven percent of men had a clinical stage of T1c. Fifty-eight percent had a Gleason score of 7, and the remainder had a Gleason score of 8 or 9. The PSA was 10 ng/mL or less in 95% of patients. Safety and feasibility All 6 doses were feasible with no grade 4 or higher toxicities. Symptomatic toxicities included urinary tract infection (n = 3; grade 3 in 2 men), flu-like syndrome (n = 3), grade 1 fever (n = 1), and photophobia (n = 1). Asymptomatic laboratory toxicities were grade 1 elevated AST/ALT (n = 1), and elevations of PTT (n = 3; 2 were transient, 1 prolonged elevation proven to be lupus anticoagulant in the 1 × 10¹² cohort). No excess in postoperative complications was observed.

Histopathologic evaluation of radical prostatectomy specimens
Pathologic stage at RP included pT2N0 (n = 12), pT3N0 (n = 6), and pT3N1 (n = 1), with focal positive margins in 3 patients (Table 1). No pathologic complete remission (pCR) was seen, but morphologic evidence of biologic activity was observed, including cytopathic effects and inflammatory infiltrates across all doses. For example, compared with the pretreatment biopsy, H&E staining from the RP tissue from the first patient treated with the lowest dose (1 × 10¹⁰ vp) revealed extensive cytotoxic activity (Fig. 2A–D). The benign prostatic epithelium within the tumor appeared stressed but did not show the cytotoxic effect (Fig. 2C). These morphologic alterations suggest a tumor-specific cytotoxic effect of AdGLIPR1. Interestingly, a protective perineural effect was observed; the cancer cells surrounding a nerve tended to survive the AdGLIPR1-induced cytotoxic effect (Fig. 2D).

Modulation of tumor tissue biomarkers
The apoptotic activity was measured by IHC for TUNEL done in 5 patients in the first 2 cohorts (Fig. 3). The results show induction of apoptosis in these patients when pre-treatment biopsy and RP tumor specimens are compared (Fig. 3A) or when RP specimens were compared with a large number of individual RP tumor specimens (n = 464) assembled on a TMA (Fig 3B). Further evidence of AdGLIPR1 activity was documented in similar studies that showed increased levels by IHC of nuclear p27Kip1 in the same 5 patients from the first 2 cohorts (Fig. 3C). AdGLIPR1 mediated translocation of p27 to the nucleus in treated patients was shown in comparative analysis of pretreatment biopsies with RP specimens (Fig. 3C), or when RP specimens were compared with RP specimens (n = 573) assembled on a TMA (Fig. 3D).

Immunophenotyping analysis of peripheral blood lymphocytes
Cohorts 1 to 3 did not show a clear increase in CD8⁺ lymphocytes (Fig. 4A). There was moderate increase of CD8⁺ lymphocytes from 17.9%, 18.1%, and 29.2% in
cohort 4 to 6 at pretreatment to 32.4%, 29.9%, and 39.9% at 2 or 3 weeks after treatment (Fig. 4A). This increase reached statistical significance on days 21 and 28 of cohort 4 (P = 0.0012, P = 0.0440, respectively; unpaired t-test; Fig. 4A, right).

The HLA-DR marker of activation was used to double label CD4 or CD8\textsuperscript{+} lymphocytes as a relative measure of activated T cells. There was a moderate increase in the percentage of double positive CD8\textsuperscript{+} DR\textsuperscript{+} T cells for patients in cohorts 4 to 6 (Fig. 4B). The pretreatment mean percentage of CD8\textsuperscript{+} T cells positive for the HLA-DR marker of activation was 12.9%, 23.8%, and 20.8% (cohorts 4, 5, and 6). In cohort 4, for days 21 and 28 posttreatment and the fourth postoperative day, the mean percent of CD8\textsuperscript{+} DR\textsuperscript{+} T cells increased by 58.9%, 47.6%, and 34.6%, which were statistically significant (P = 0.001, P = 0.0018, and P = 0.0025, respectively; Fig. 4B, top right). In cohort 5, for days 15, 21, 28, and the fourth postoperative day, the mean percentage of CD8\textsuperscript{+} DR\textsuperscript{+} T cells significantly increased by 50.3%, 62.4%, 63.6%, and 37.9% (P = 0.0036, P = 0.0039, P = 0.0034, and P = 0.0421, respectively; Fig. 4B, bottom left). In cohort 6, on day 8, the mean percentage of CD8\textsuperscript{+} DR\textsuperscript{+} T cells was already significantly increased to 48.3% (P = 0.0107), and on day 15, the mean percent of CD8\textsuperscript{+} DR\textsuperscript{+} T cells was gradually increased to 58.6% (P = 0.0035). It reached a peak at day 21 (60.7% P = 0.0133). After that, the percent of DR\textsuperscript{+} CD8\textsuperscript{+} T cells remained high until postoperative day 4 (day 28; 58.2% P = 0.0370, fourth postoperative day: 57.8% P = 0.0280; Fig. 4B, bottom right).

In cohorts 4, 5, and 6, the posttreatment mean percentage of CD4\textsuperscript{+} T cells positive for the HLA-DR marker of activation was increased compared with pretreatment levels (Fig. 4C). The pretreatment mean percentage of CD4\textsuperscript{+} DR\textsuperscript{+} T cells was 8.6%, 10.6%, and 11.6% for cohorts 4, 5, and 6, respectively, which increased to 16.3%, 22.1%, and 20.3%, respectively. In cohorts 5 and 6, these increases were statistically significant (cohort 5: P = 0.0495, cohort 6: P = 0.0495, Mann–Whitney U test).

The posttreatment mean percentage of CD3\textsuperscript{+} T cells positive for the HLA-DR marker of activation increased compared with pretreatment for cohort 4 (Fig. 4D). The pretreatment mean percentage of CD3\textsuperscript{+} DR\textsuperscript{+} T cells was 13.3%, 11.8%, and 11.3% (cohort 4, 5, and 6, respectively), which increased to 28.0%, 21.9%, and 31.2%, respectively.
Figure 4. Flow cytometry analysis of patient samples of circulating peripheral blood lymphocytes at indicated time points. Data for each cohort are presented as mean ± SE. Values that reach statistical significance compared with the pretreatment levels are indicated by *, *P < 0.05; **, **P < 0.01. A, percent of CD8+ cells at indicated time points in cohort 1 to 6 (left). Increase in percentage of CD8+ cells in the 3 patients in cohort 4 attained statistical significance compared with pretreatment value indicated by *, *P < 0.05; **P < 0.01 at days 28 and 21, respectively. Percent of CD8+ cells for individual patients in cohort 4 (right). B, percent of CD8+DR+ cells in cohorts 1 to 6 at indicated time points during the trial (top left). Increase in percentage of CD8+DR+ cells that reach statistical significance compared with pretreatment value in cohort 4 (top right), 5 (bottom left), and 6 (bottom right) indicated. C, percent of CD4+DR+ cells at indicated time points in cohort 1 to 6 (top left). Increase in percentage of CD4+DR+ cells that reach statistical significance compared with pretreatment value in cohort 5 and 6 indicated by *, *P < 0.05. In addition, CD4+DR+ values are presented for individual patients in cohort 4 (top right) and 5, 6 (bottom left and right). D, percent of CD3+DR+ cells at indicated time points during the trial in cohorts 1-6 (left). Increase in percentage of CD3+DR+ cells that reach statistical significance compared with pretreatment value in cohort 4 indicated by *, *P < 0.05. Percent of CD3+DR+ cells for individual patients in cohort 4 is shown on right panel.
These increases attained statistical significance on day 21 of cohort 4 ($P = 0.0495$, Mann–Whitney $U$ test) and days 15 and 21 of cohort 6 ($P = 0.0495$, Mann–Whitney $U$ test).

**Analysis of serum cytokines**

The levels of serum TGFβ and IFN-$\gamma$ remained unchanged throughout the trial in all cohorts. The level of IL-6 remained at pretreatment levels and was only elevated at the fourth postoperative day, probably as a result of the surgery, in all patients regardless of treatment groups (data not shown). Serum IL-12 levels also did not show any significant changes in the majority of the patients and was less than 200 pg/mL with two exceptions. For patient #18 (cohort 5) serum IL-12 levels increased to 426 pg/mL at day 8 after treatment that gradually declined to 250 pg/mL on the fourth postoperative day (Fig. 5A). Patient #20 (cohort 6) had a moderate increase in serum IL-12 to 239 pg/mL at day 15 after treatment that declined gradually to 79 pg/mL on the fourth postoperative day (Fig. 5B).

**Discussion**

The intraprostatic administration of GLIPR1 tumor suppressor gene, expressed by an adenoaviral vector, was safe in men with localized intermediate and high-risk prostate cancer preceding RP. Preliminary evidence of local biological antitumor activity accompanied by systemic immune responses were observed. Increased levels of tumor cell TUNEL (measuring apoptosis) and nuclear p27$^{kip1}$ (a cyclin-dependent kinase inhibitor) provided corroborative evidence for biological antitumor activity. Systemic induction of an immune response was observed with an increase in serum IL-12 and circulating CD8$^+$, CD4$^+$, and CD3$^+$ T cells coupled with increased HLA-DR upregulation on these cells, a marker of activation. Indications of a dose response were observed, with serum IL-12 increases in a patient in each of the 2 highest dose cohorts and more robust increases in peripheral blood circulating activated T lymphocytes in the higher dose cohorts. In addition, the prolongation of PTT in 3 men (1 proven to be lupus anticoagulant) also suggests the generation of a systemic immune response. These data provide proof of concept and suggest a role for the further development of intraprostatic injection of adenoaviral vector-delivered GLIPR1 in the perioperative setting for prostate cancer.

Other previously reported trials have established the feasibility and biological activity (both local and systemic) of the intraprostatic delivery of favorable disease-modifying genes. INGN 201 (Ad-p53), a replication-defective adenoviral vector that encodes a wild-type p53 gene driven by the cytomegalovirus promoter, was administered in a neoadjuvant trial of patients with high-risk localized prostate cancer (14). Of 11 patients with negative baseline p53 expression, 10 had expressed p53 and 8 had an increase in apoptosis. To explore the activity of IL-2 expressing adenovirus in prostate cancer, another phase I clinical trial was conducted in patients with localized high-risk disease (15). An inflammatory response consisting predominantly of CD3$^+$CD8$^+$ T lymphocytes with areas of tumor necrosis was observed. Increases in both γ-IFN and IL-4 secreting T cells were observed. In another small neoadjuvant phase I trial, a DNA–lipid complex encoding the IL-2 gene was administered intraprostatically (16). Evidence of immune activation was observed, reflected by an increase in T-cell infiltration seen in tissue and increased proliferation of peripheral blood lymphocytes cocultured with patient serum.

A limitation of the neoadjuvant paradigm evaluating biological activity with a novel agent is that the level of biological activity that may translate to enhanced objective clinical outcomes (progression-free or overall survival) is unknown. Therefore, although our trial provides evidence of biological activity and systemic immune responses, complementary information in terms of improved clinical outcomes in the setting of a randomized trial is necessary. The pathologic stages at RP of patients enrolled on our trial are difficult to interpret in the setting of a small phase I trial. A randomized trial design employing a control arm receiving intraprostatic adenovirus vector not carrying GLIPR1 may have been more optimal but was considered impractical and beyond the scope of available resources. The evaluation of tumor tissue correlative studies was not possible in all patients due to resource constraints, although the demonstration of biological activity in the 2 lowest dose cohorts...
suggests that activity would probably have been observed in the higher dose cohorts too. Demonstration of an upregulation of GLIPR1 in tumor tissue (following therapy) correlating with biological activity may have been desirable but was considered beyond the scope of this trial. Moreover, this was a phase I trial with the primary goal of showing feasibility and biological activity, and upregulation of GLIPR1 has been shown in previous preclinical studies (20, 21). In addition, long-term follow-up with biochemical and clinical recurrence data are not available but will also probably be uninterpretable in the absence of a randomized design. Although the sparing of perineural tumor cells was based on visual interpretation and was not quantified objectively, a tumor growth promoting microenvironment provided by nerves has been previously described (24).

The appropriate dose to further develop AdGLIPR1 therapy is unclear because no MTD was established. Therefore, the optimal biological dose should be based on further analysis of correlative studies, and the study of larger doses of viral particles may be warranted. Although our study did not evaluate the potentially deleterious effects of transduction of nonmalignant prostate cells, we have previously shown substantially less preclinical proapoptotic activity of GLIPR1 delivered to nontransformed fibroblasts (20). The simultaneous induction of a suppressive immune response was not evaluated, but the overall profile strongly supports an immune stimulatory response. Although PSA changes were not monitored following the intraprostatic injection, such changes in the 4 weeks between the injection and RP are unlikely to be informative because PSA alterations are known to occur from prostatic procedures. Circulating tumor cells were not available at the time of conduct of this trial but are also unlikely to have added information because they are seldom detected in early disease. In addition, biomarkers predictive of response need to be studied; for example, tumors with p53 mutations, attenuated p53 activities, or GLIPR1 hypermethylation may preferentially respond because GLIPR1 may be expected to be downregulated.

To conclude, this phase I trial of neoadjuvant intraprostatic GLIPR1 tumor suppressor gene delivered by an adenoviral vector employed a resource-friendly and small number of patients and showed biological antitumor activity and favorable modulation of blood-based biomarkers of immune stimulation. Potentially, the biological activity of neoadjuvant adenovirus delivered GLIPR1 into early tumor tissue may translate into improved perioperative outcomes as well as activity in more advanced settings. In addition, the therapeutic index appears excellent, and combinations with other classes of tolerable and active biological agents may warrant exploration, for example, sipuleucel-T or abiraterone acetate (5, 6). The combination of adenovirus delivered GLIPR1 with conventional ADT, chemotherapy, and radiotherapy may also warrant exploration.

Disclosure of Potential Conflicts of Interest

T.C. Thompson and C. Ren are coinventors on patents involving therapeutic applications of GLIPR1. These patents are held by Baylor College of Medicine and licensed to Progression Therapeutics Inc., a private biotechnology start-up. The other authors disclosed no potential conflicts of interest.

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References


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