Clinical Trial Protocol

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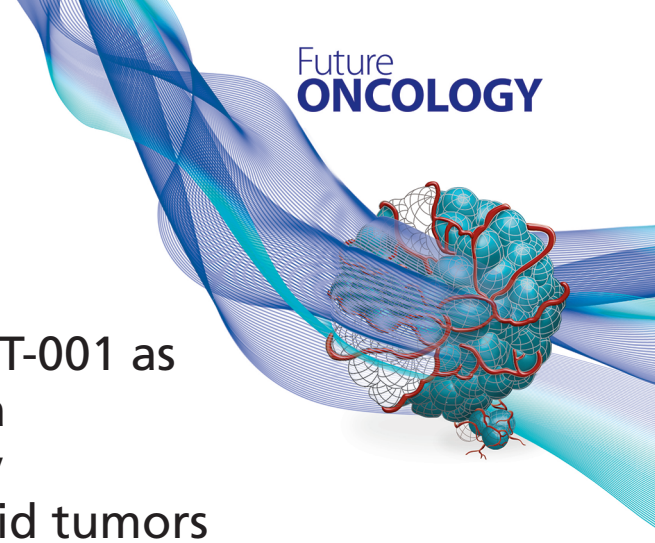

BETA PRIME: Phase I study of AdAPT-001 as monotherapy and combined with a checkpoint inhibitor in superficially accessible, treatment-refractory solid tumors

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AdAPT-001 is an investigational therapy consisting of a replicative type 5 adenovirus armed with a TGF-β receptor-immunoglobulin Fc fusion trap, designed to neutralize isoforms 1 and 3 of the profibrotic and immunosuppressive cytokine, TGF-β. In preclinical studies with an immunocompetent mouse model, AdAPT-001 eradicated directly treated 'cold' tumors as well as distant untreated tumors, and, from its induction of systemic $CD8^+$ T cell-mediated antitumor immunity, protected the mice from rechallenge with tumor cells. AdAPT-001 also sensitized resistant tumors to checkpoint blockade. This manuscript describes the rationale and design of the first-in-human phase I, dose-escalation and dose-expansion study of AdAPT-001 alone and in combination with a checkpoint inhibitor in adults with treatment-refractory superficially accessible solid tumors.

Plain language summary: The purpose of this study is to find out more about the experimental oncolytic virus called AdAPT-001 that has been designed to selectively eliminate cancer cells. The virus is also designed to make a particular protein called a TGF-β trap, which neutralizes TGF-β, an overproduced chemical in cancer cells that puts the immune system into a comatose state. This article discusses a clinical trial called BETA PRIME for patients with no other standard treatment options. The trial will explore different doses of AdAPT-001 both alone and in combination with an approved checkpoint inhibitor or another immunotherapy, which blocks the 'off' signal on immune cells, to determine the safest and best dose.

Clinical Trial Registration: NCT04673942 (ClinicalTrials.gov)

Twitter abstract: BETA PRIME, a phase I clinical trial, will study AdAPT-001, an oncolytic adenovirus that carries a TGF-β 'trap' +/- a checkpoint inhibitor with the ultimate objective to turn 'cold' tumors 'hot' and increase response rates.

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Keywords: abscopal effect • AdAPT-001 • BETA PRIME • oncolytic adenovirus • solid tumors • study protocol • TGF-β trap

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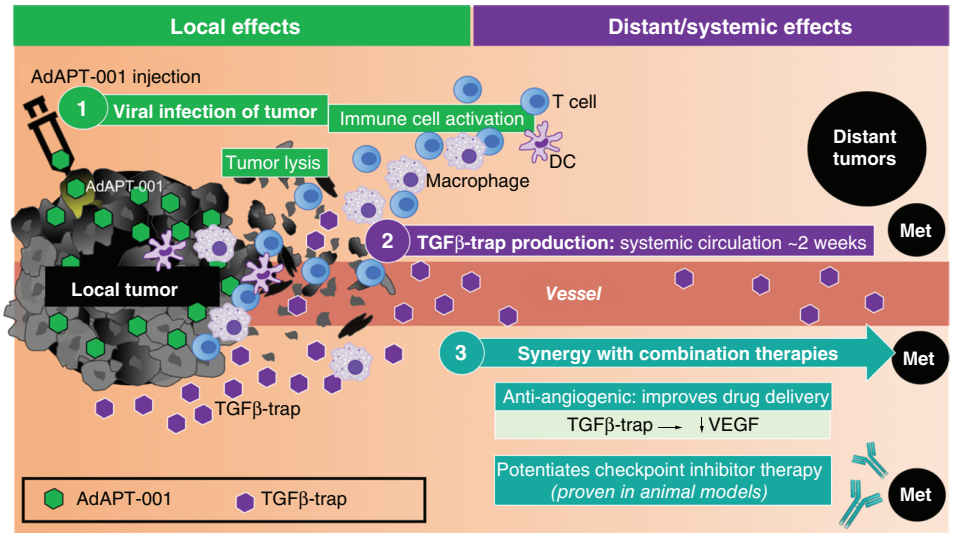
Graphical abstract:



The term 'oncolytic virotherapy' refers to the administration of replication-competent viruses, a kind of 'living drug', that specifically targets and eliminates cancer cells and that, hopefully, in the process, through the release of progeny virions, danger signals, tumor associated antigens and proinflammatory cytokines induces a robust systemic antitumor response.

Adenoviruses (Ad), discovered in the 1950s, and associated in humans with mild 'common cold' upper respiratory infections, informally enjoy 'most favored status' among oncolytic viruses because of their many practical advantages including high stability, ease of manufacture, the lack of host genome integration, large packaging capacity of approximately 35 kb and favorable safety profile in multiple phase I and phase II trials [1,2]. While to date only one oncolytic virus therapy, a genetically modified variant of herpes simplex virus (HSV), Talimogene herparepvec (T-VEC), which carries a granulocyte-macrophage colony-stimulating factor (GM-CSF) cistron, has received an US FDA approval, the first commercialized oncolytic virus product (in China only) was a type 5 oncolytic Ad (OAV) called Oncorine for the treatment of head and neck cancers [3]. Second- and third-generation Ad, which followed Oncorine, have been modified to deliver an immunostimulatory 'payload' with the added potential to reverse tolerance within the tumor microenvironment.

OAVs are a natural complement to checkpoint inhibitors (CI) whose relative success is tempered by the non responsiveness of immunologically cold tumors, which are either devoid of immune cell infiltration (an 'immune desert') or predominantly infiltrated by suppressive regulatory cell subtypes such as Tregs, regulatory B cells and myeloid-derived suppressor cells [4] that overelaborate immunosuppressive cytokines like IL-10 and TGF-β.

In addition to OAVs, HSV-1, a neurotropic DNA virus, has also been a widely studied and used OV. However, unlike Ad type 5, which is responsible mostly for benign respiratory tract infections, genetically modified oncolytic HSV (oHSV) theoretically carries higher safety risks including reversion of neurovirulence activity from recombination with wild type HSV-1 strain *in vivo* and the risk of latency, since latent infection is a feature for herpes viruses, and hence oHSV may enter a latent phase and reactivate later [5].

The oHSV-1, T-VEC (talimogene laherparepvec), which, as discussed above, encodes for the immune regulatory cytokine, GM-CSF, was the first OV approved for the treatment of inoperable melanoma by the FDA in October 2015, followed by EMA, based on the promising results of a phase III randomized clinical trial called OPTiM [6]. However, it has recently been discovered that GM-CSF overexpression paradoxically drives tumor-related immunosuppression via the induction of monocyte derived suppressor cells, which release the anti-inflammatory cytokine IL-10, impair both $CD4^+$ T cells and NK cell responses and contribute to the expansion of Tregs and protumorigenic M2-like macrophages [7]. In addition, GM-CSF is endogenously produced during viral expression, which possibly renders its incorporation as a transgene redundant and superfluous. All of this may explain why in the phase III MASTERKEY-265 study in 692 patients with advanced melanoma, the combination of T-VEC with pembrolizumab failed to meet its progression-free survival primary end point [8].

As immunologically foreign pathogens, which the immune system has evolved over millions of years to sense and to eliminate, OVs can catalyze strong immune responses; these responses have the potential to convert 'cold' (very low T-cell infiltration and non inflamed) tumors that are non responsive to CIs to 'hot' (highly T-cell infiltrated and inflamed) ones that are much more likely to respond.

Tumors develop from initially normal cells and overexpress self-antigens or slightly modified self-antigens, to which the immune system responds weakly or not at all. The challenge, like a game of immunological hide and seek, is to expose downregulated non self tumor-associated antigens and tumor-specific antigens such that the immune system can locate them and go on the offensive; this 'unveiling' may result from viral replication in cancer cells, followed by lysis, with release of tumor-specific antigens and tumor-associated antigens and subsequent uptake by antigen presenting cells, essential for the generation of $CD8^+$ T-cell responses.

Cancer not only hides away from the immune system but actively suppresses it by means of an 'Iron Curtain' of macrophages and neutrophils, fibroblasts, anti-inflammatory cytokines, abnormal blood vessels and extracellular matrix [9], behind which the tumor is safely ensconced; hence, the rationale in BETA PRIME to combine the virus with a TGF-β trap, which, through its proinflammatory, antifibrotic, anti-angiogenic and anti-immunosuppression properties, may lift or remove this Iron Curtain-like divide and thus potentially sensitize once-resistant tumors to immune checkpoint blockade. Of the many TGF-β pathway-targeting agents in development, the most notable is perhaps bintrafusp alfa, a bifunctional antibody against TGF-β and PD-L1, the development of which has reportedly been discontinued after disappointing data across several clinical trials in non-small-cell lung cancer, esophageal, gastric and biliary tract cancers [10].

The multiple clinical trial failures of bintrafusp alfa notwithstanding, dual TGF-β and PD-L1 inhibition makes rational sense, especially in fibrous or desmoplastic tumors such as pancreatic cancer or the consensus molecular subtype 4 of colorectal cancer where hyperactive TGF-β signaling has been implicated. Unlike AdAPT-001, which, as an intratumorally injected virus, induces direct immunogenic tumor cell death (ICD), bintrafusp alfa is not an ICD inducer, since antibodies that block immune checkpoints target lymphocyte receptors or their ligands rather than the tumor cells themselves. ICD involves the release of highly immunostimulatory damage-associated molecular patterns from dying tumor cells [11]. Since the efficacy of CIs is primarily limited to hot tumors already infiltrated by T cells (TILs), bintrafusp alfa may have benefited (and may yet benefit) from combination with a *bona fide* ICD inducer, like AdAPT-001, with the potential to prime, boost and recruit effector T cells into the tumor microenvironment, where checkpoint blockade may broadly enhance/sustain the antitumor response through the removal of inhibitory signals [12].

Another possible explanation for the failure of bintrafusp alfa is the dual or simultaneous, rather than sequential, administration of the anti-TGF-β and anti-PD-L1, on the premise that it takes time for the aberrant tumor microenvironment to normalize; hence, administration of a TGF-β inhibitor prior to that of the CIs may 'prepare the terrain' for CI activity. In addition, given the multitudinous physical and physiological barriers imposed by the tumor microenvironment, which impede drug delivery, it is possible that the large size (kilodaltons) of the bifunctional antibody prevented adequate tumor penetration and distribution.

TGF-β

The scientific literature extensively implicates the three mammalian isoforms of TGF-β (TGF-β1, -β2 and -β3), as key drivers of malignant transformation, neoangiogenesis, metastasis [13] and therapeutic resistance. The primary physiologic role of TGF-β is to suppress inflammation and the development of autoimmunity [14]. Many cells carry TGF-β receptors, including platelets and bone cells and besides the mediation of immunosuppression, the cytokine positively and negatively regulates a suite of homeostatic functions such as proliferation, differentiation, adhesion and migration [15]. In response to TGF-β binding, TGF-β receptors type I and II form tight complexes that phosphorylate Smad2 and Smad3, members of the Smad protein family, which partner with Smad4 and translocate to the nucleus to activate the transcription of target genes [16,17].

Although TGF-β acts as a growth suppressor to inhibit the early stages of carcinogenesis, cancers eventually develop resistance to TGF-β's growth inhibitory effects and the tumor microenvironment [18] constitutively overexpresses TGF-β to mediate immunosuppression, cancer invasiveness and neovascularization. Through this overexpression of TGF-β as well as multiple other immunosuppressive mechanisms including the release and secretion of IL-10 [19], IL-35 and indoleamine 2,3-dioxygenase (IDO [20]), and the upregulation of inhibitory molecules such as CTLA-4 and PD-1, the tumor weaves a tangled tolerogenic web that interferes with the activation and

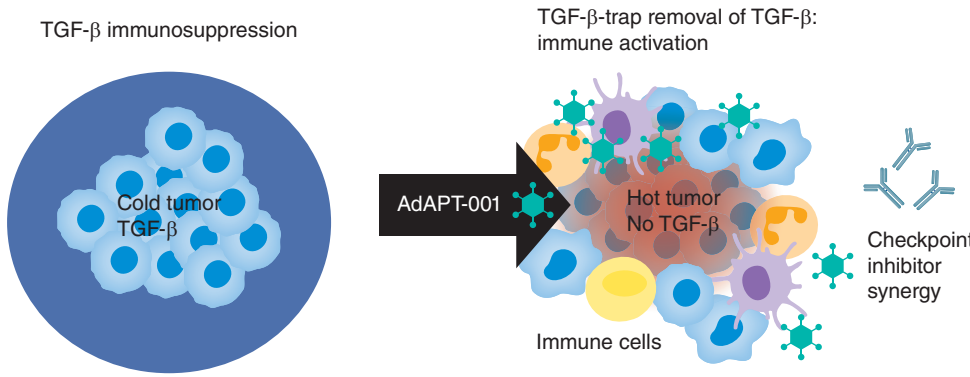


Figure 1. Mechanism of action of AdAPT-001.

effector functions of T cells [21]. Given the centrality of TGF-β to the maintenance of T-cell suppression, TGF-β ligand trapping constitutes an attractive strategy to heighten the immune response.

Despite a theoretical risk for the development of autoimmunity/immunopathologic reactions with TGF-β blockade due to stimulation of T-cell activity, clinical experience with GC-1008 (fresolimumab), a pan-specific monoclonal antibody that binds to and inhibits the biological activity of all three TGF-β isoforms, suggests otherwise [22]. In clinical trials, fresolimumab was safe and well tolerated with no dose-limiting toxicities.

The AdAPT-001-mediated delivery of a neutralizing TGF-β ligand 'trap' that consists of the extracellular domain of TGFβRII linked to the human IgG1 Fc domain directly to the tumor may focally reverse the local immunosuppression and in combination with the protective effect of anti-adenoviral neutralizing antibodies prevent 'spillover' of any toxicity to normal tissues.

In summary, elevated TGF-β-mediated immunosuppression leads to a microenvironment permissive for tumor growth. Since the concerted activities of multiple mechanisms are necessary for the tumor to escape immune surveillance, the combination of direct viral oncolysis to increase antigen release or antigen presentation and induce cytotoxicity via immune effectors, and the removal of local TGF-β-mediated immunosuppression may synergize to induce a concerted antitumor response with profound improvements in clinical outcomes.

AdAPT-001

AdAPT-001 is a type 5 conditionally replicative Ad [23] that carries an immunomodulatory TGF-β trap. This trap is a fusion protein of soluble TGF-β receptor II and the Fc portion of human IgG1, which binds to, sequesters and; hence, neutralizes the activity of isoforms 1 and 3 of TGF-β. A multifunctional cytokine, TGF-β wears many hats in the tumor microenvironment through its regulation of immune tolerance, inflammation, angiogenesis and fibrosis. The viral vector into which the TGF-β trap has been inserted carries a small 50 bp deletion in the E1A promoter region, which limits lytic viral replication to cancer cells only. In non transformed cells, infection is abortive, indicating that any early genes such as transgenes, which the virus carries, are expressed, but late-gene expression is reduced to the extent that subsequent virion assembly and cell lysis never occurs. In BETA PRIME, AdAPT-001 is injected intratumorally, on the expectation that high concentrations of virus *in situ* will recruit the appropriate immune cells and cytokines for generation of a systemic antitumor response. However, the long circulating half-life of the TGF-β trap during biodistribution studies suggests that AdAPT-001 is also amenable to intravenous administration, since comparatively higher levels of the TGF-β trap are seen in the serum from iv. rather than intratumoral dosing (Figure 1) [24].

In vitro, AdAPT-001 has been shown to block the TGF-β downstream signaling molecules Smad2 and Smad3, which is important for its activity [25].

In an immunocompetent syngeneic mouse model with anti-PD-1 resistant *KRAS*-mutant lung adenocarcinoma tumors, mice 6–8 weeks old of either gender were injected subcutaneously with one million ADS-12 cells and allowed to form tumors until they reached >50 mm^3 in size. When the average tumor size reached >50 mm^3, mice were randomized into treatment groups, ten mice per group. Treatment involved intratumoral injections of either viral storage buffer or mouse-AdAPT-001 at 10^9 PFU/dose on days 0, 4 and 8, plus intraperitoneal injections of either phosphate-buffered saline or 200 µg anti-PD-L1 antibody (clone 10F.9G2, BioXcell, NH, USA) diluted

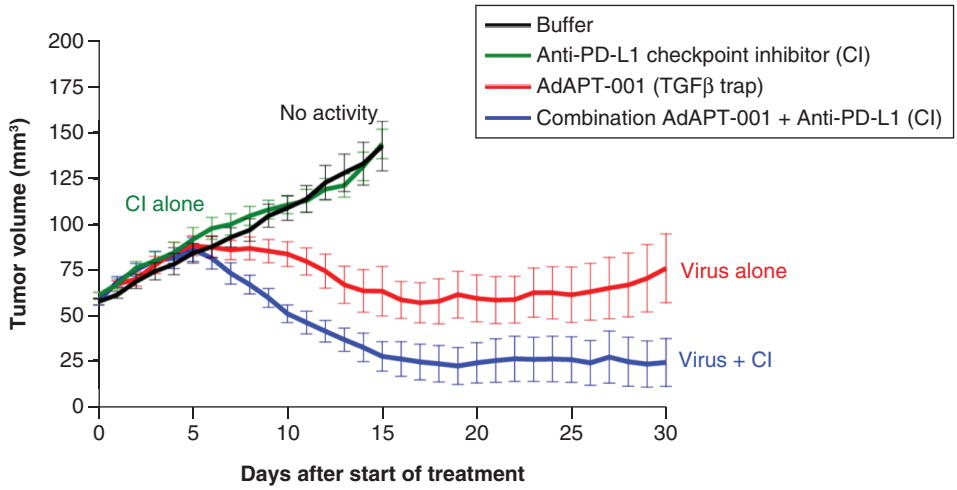


Figure 2. AdAPT-001 sensitizes PD-L1-resistant tumors to checkpoint inhibitor blockade.
CI: Checkpoint inhibitor.

in phosphate buffered saline on days 1, 5, 9 and 13. Treatment with the mouse version of AdAPT-001 induced $CD8^+$ T-cell infiltration and sensitized the tumors to CI blockade, as shown in Figure 2.

Further, local intratumoral injection of AdAPT-001 led to eradication of untreated, 'anamnestic' tumors indicative of activation of a systemic antitumor immune response and significantly improved survival compared with control or virus alone without the TGF-β. The TGF-β trap is also anticipated to disrupt the collagen network in tumors and increase the distribution of the virus and infiltration of $CD8^+$ T cells since the TGF-β trap on its own inhibits collagen I production by carcinoma-associated fibroblasts isolated from xenograft models.

Taken together, these observations warrant the clinical investigation of AdAPT-001 either as a single agent therapy or in combination with a CI to evaluate its safety and efficacy in patients with treatment-refractory solid tumors.

AdAPT-001 phase I trial

We report the design and methods for an ongoing phase I study of AdAPT-001 as monotherapy and in combination with a CI (NCT04673942). This study began enrollment in March 2021 with up to six sites in the USA.

Study design

This is an open label single-arm interventional phase I study using a 3 + 3 Dose escalation safety run-in (PART 1), followed by a Dose expansion single-agent (PART 2) and trailed by a Combination expansion (PART 3). The study is designed to define a maximal tolerated dose/recommended dose (MTD/RD) and regimen; to assess safety and tolerability; to assess immunogenicity; and to assess potential anti-tumor activity of AdAPT-001 in subjects with selected advanced solid tumors. All eligible subjects will have relapsed or refractory disease after standard therapy. The study design is illustrated in Figure 3.

PART 1: Dose escalation safety run-in cohort levels were (this part is completed):

- Cohort level 1: 2.5×10^{11} viral particles: three subjects
- Cohort level 2: 5.0×10^{11} viral particles: three subjects
- Cohort level 3: 1.0×10^{12} viral particles: three subjects

PART 2: Dose expansion single-agent:

- MTD run-in continuous assessment cohort: six subjects
- MTD expansion cohort: Up to 19 subjects

PART 3: Combination expansion:

- AdAPT-001 plus CI: number of subjects to be determined

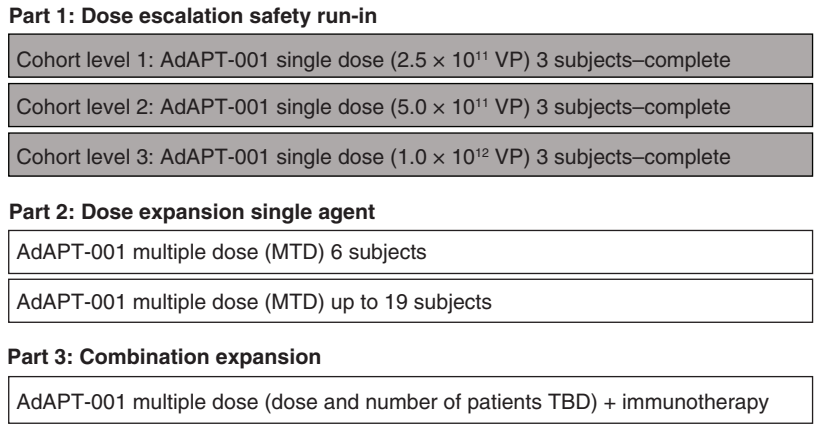


Figure 3. Three-part study design.

PART 1 Dose-escalation plan: Subjects were enrolled in each Dose Escalation Safety Run-In Cohort for which no dose limiting toxicities were observed and no MTD was reached. AdAPT-001 administration was performed by intratumoral injection in a volume of 2 ml, according to the specified dose level and each patient received one dose. A fan-shape injection technique was emphasized for better diffusion of/exposure to AdAPT-001 in the tumor lesion(s). All superficial, easily accessible tumors were injectable regardless of size, which ranged from millimeters to centimeters.

PART 2 Dose expansion: Six subjects will be enrolled in the lead-in cohort. The recommended dose of AdAPT-001 is based on the MTD/highest dose received in Part 1, 1.0×10^{12} VP. A safety analysis by the Data Review Committee will be performed after six subjects have received at least two doses, following which an additional 19 subjects may be enrolled. All subjects in PART 2 will receive injections of AdAPT-001 on Days 1 and 15 of 28-day cycles for a maximum of 12 injections.

PART 3 Combination expansion with a CI will begin following a safety review of Part 2.

All subjects will remain on trial until confirmed disease progression, unacceptable toxicity, clinically assessed symptomatic deterioration, achievement of maximal response, loss to follow-up, withdrawal of consent, subject or physician's decision, EpicentRx or FDA terminates the study or death. Treatment may continue beyond investigator-assessed radiographic progression of disease if evidence of clinical benefit, absence of rapid progression and stable performance status are present.

Eligibility criteria

This study includes general eligibility criteria for all tumor types. Eligible patients must be aged ≥18 years and have superficially accessible, relapsed/refractory solid tumors with documented disease progression on or after their last regimen, and an Eastern Cooperative Oncology Group performance status of ≤2. Participants with an autoimmune disease, prior adenoviral therapy excluding AdAPT-001 or chemotherapy or immunotherapy within 14 days of initiating study drug are ineligible. A full list of eligibility criteria is shown in Box 1.

Tumor assessments using CT scans will be performed at screening and after 28 days in Part 1, and every 8 weeks in Parts 2 and 3 until the specified ontrial treatment terminates, the patient withdraws consent or starts a new antineoplastic regimen. RECIST version 1.1 and immune RECIST (iRECIST) will be performed to evaluate disease status. Radiographic assessments and efficacy analyses will be conducted by the investigator's site. Pharmacodynamic analyses will also be performed to assess the effects of AdAPT-001 on cytokine levels including TGF-β and tumor biomarkers, as appropriate. Buccal and skin swabs will be collected to assess for viral shedding. Quantitative PCR will be used to assess virus biodistribution and vector shedding.

Outcome measures/end points

The primary objective of the Part 1 dose-escalation phase is to evaluate the safety, tolerability, MTD and recommended dose of single dose, single-agent AdAPT-001. The primary objective of the dose-expansion phase is to evaluate the safety and tolerability of multiple doses of AdAPT-001 monotherapy. Secondary objectives are to assess the anti-tumor activity of AdAPT-001 by objective response rates and best overall response rates per response eval-

Box 1. Inclusion/exclusion criteria.

Inclusion criteria:
- Subject can understand the purpose and risks of the study and is able to provide written informed consent
- Subject is male or female, aged at least 18 years
- Subject has a histologically or cytologically confirmed diagnosis of an advanced malignant solid tumor(s) who have exhausted all standard curative therapies and have a tumor that is easily accessible for treatment
- Subject's Eastern Cooperative Group performance status is 0–2 at screening
- Subject has acceptable liver function at screening, as evidenced by:
  - Bilirubin <1.2 x ULN
  - AST (SGOT), ALT (SGPT) and alkaline phosphatase <2.5 x ULN
- Subject has a serum creatinine <1.5 x ULN
- Subject has acceptable hematologic status at Screening, as evidenced by:
  - Absolute neutrophil count >1500 cells/mm^3; >1.5 $\times$ 10^9/l, and
  - Platelet count >75,000/mm^3; >75.0 $\times$ 10^9/l and
  - Hemoglobin >10.0 g/dl; >6.2 mmol/l
- Subject has an INR <1.2
- Have available archival formalin-fixed paraffin-embedded block(s) or previously cut archival tissue for at least five unstained slides
- Female subjects of childbearing potential (i.e., women who have not been surgically sterilized or have not been postmenopausal for at least 1 year), and male subjects with partners of childbearing potential, must agree to use medically acceptable methods of contraception beginning on study day 1 and continuing until at least four weeks after administration of the subject's final dose of AIM-001. Medically acceptable contraception is defined as either: usage by at least one of the partners of a barrier method of contraception, together with usage by the female partner, commencing at least 3 months prior to study day 1, of a stable regimen of any form of hormonal contraception or an intrauterine device; or usage by the couple of a double-barrier method of contraception. Use of a single–barrier method alone or abstinence alone is not considered adequate
- Subject is willing and able to comply with all protocol procedures, evaluations and rescue measures.

Exclusion criteria:
- Presence of a serious comorbid medical condition, or a clinically significant laboratory finding(s) that, in the opinion of the investigator, suggests the presence of an infectious, endocrine and/or other inadequately treated systemic disorder
- A known active bacterial, fungal or viral infection
- Known positive HIV
- Known history of hepatitis. If history of hepatitis or liver risks, negative results for hepatitis C virus, hepatitis B surface antigen and hepatitis B core antibody must be obtained.
- If female, subject is pregnant and/or breastfeeding.
- Subjects with active autoimmune disease or history of autoimmune disease that might recur and may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded Note: Subjects having a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study agent administration. Treatment with NSAIDs is allowed
- Prior adenovirotherapy for any indication
- Chemotherapy or immunotherapy within 14 days of study treatment. Hormonal therapy (including tamoxifen, aromatase inhibitors and gonadotropin releasing hormone agonists) is allowed.

INR: International Normalized Ratio; ULN: Upper limit of normal.

uation criteria outlined in Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1), as well as progression-free survival and duration of response. The primary objective of the combination immunotherapy phase is to evaluate the safety and tolerability of multiple doses of AdAPT-001 monotherapy in combination with a CI. Secondary objectives are to assess the objective response rate and pharmacodynamics of multiple doses of AdAPT-001 in combination with a CI.

Statistics

Nine patients were enrolled in the single dose-escalation phase, the purpose of which was to determine the MTD or a recommended dose for the multiple dose-expansion phase. Approximately 25 patients will be enrolled to the multiple dose-expansion phase. For the combination with a CI, the number of enrolled patients is currently undetermined. Populations for analysis include: the response-evaluable population, which is defined as all enrolled patients that receive at least one dose of AdAPT-001, have measurable disease at baseline and at least one post baseline

planned response assessment; and the safety population, which is defined as all enrolled patients that receive at least one dose (or partial dose) of AdAPT-001. The evaluation of efficacy, which is based on the response-evaluable population, will include overall response rate, complete response rate and partial response rate; these measures will be summarized using the 95% CI from the Clopper–Pearson exact method for binomial distribution.

Conclusion

This phase I trial is the first to investigate the safety and efficacy of AdAPT-001 in humans. The primary goal is to determine the safety and tolerability, MTD and recommended dose of AdAPT-001 plus/minus a CI in the setting of relapsed/refractory solid tumors. Results from this trial will serve to guide and inform the future development of AdAPT-001. Hopefully, as a strategy to target malignant immunosuppression, AdAPT-001, which directly stimulates and mobilizes an immune response against tumor cells, will meet the urgent unmet need as monotherapy or in combination with CIs to improve quantity and quality of life for cancer patients.

Executive summary

Background & rationale

- Next generation immunotherapeutic strategies depend on the conversion of immune 'cold' tumors with low level or lack of T-cell infiltration, insufficient tumor neoantigen burden and overtly immunosuppressive microenvironments, which are in the majority, into 'hot', treatment-responsive tumors.
- TGF-β is a versatile cytokine whose neutralization with a TGF-β trap has the potential to enhance the antitumor response based on the well-established profibrotic, proangiogenic and immunosuppressive properties of TGF-β.
- Infection with an oncolytic virus also has the potential by itself to lift the cloak of immunologic invisibility from tumors and render them susceptible to T cell-mediated clearance.

AdAPT-001

- AdAPT-001 is an investigational 2-in-1 therapy which combines a replication-competent, tumor-tropic type 5 adenovirus (Ad) with a TGF-β receptor-immunoglobulin Fc fusion trap, designed to sequester and neutralize isoforms 1 and 3 of TGF-β.
- The copy number of the TGF-β trap increases significantly from replication of viral genome in the AdAPT-001 infected cancer cells.
- AdAPT-001 demonstrated potent oncolytic properties across a broad spectrum of human and murine cancer cell lines.
- In an immunocompetent mouse model with bilaterally implanted tumors, AdAPT-001 induced a potent anamnestic response with regression of injected and uninjected tumors and significantly improved survival compared with control or virus alone without the TGF-β transgene. In addition, the accumulation of T cells was demonstrated within both injected and uninjected lesions, suggesting the elicitation of a systemic antitumoral immunity.
- Studies have also shown that AdAPT-001 synergizes with a checkpoint inhibitor (CI) to which the syngeneic mouse tumors were previously resistant.

AdAPT-001 phase I trial

- This is a phase I, open-label, multicenter, dose-escalation and dose-expansion study of AdAPT-001 alone or in combination with a CI in adult subjects having previously received all available treatment options, an Eastern Cooperative Oncology Group performance status of $\leq$2 and acceptable biochemical and hematologic status.
- The primary objective of the dose-escalation phase is to evaluate the safety, tolerability, maximum tolerated dose and recommended Phase II dose of single dose, single-agent AdAPT-001.
- The primary objective of the dose-expansion phase is to evaluate the safety and tolerability of multiple dose AdAPT-001.
- Approximately 9 and 25 patients will be enrolled in the dose-escalation (Part 1) and dose-expansion (Part 2) phases, respectively. Parts I and 2 are followed by combination dosing with a CI with the number of patients and the specific CI to be determined.
- Results from this study will inform the optimal dose for future studies of AdAPT-001 and may provide an initial indication of whether AdAPT-001, either as monotherapy or in combination with a CI, has the potential to convert immune cold into immune hot tumors.
- This trial is expected to enroll at approximately six sites in the USA; for participating trial sites, please visit: https://clinicaltrials.gov and search NCT04673942.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: https://www.futuremedicine.com/doi/suppl/10.2217/FON-2022-0481

Author contributions

All authors drafted, critically reviewed or revised the manuscript for important intellectual content. All authors reviewed the final version and agreed with the content and approved of the decision to submit.

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Financial & competing interests disclosure

EpicentRx, Inc. is the clinical trial sponsor. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, informed consent has been obtained from the participants involved.

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