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A renewed push into early bladder cancer

Jacob Plieth

Ferring's Adstiladrin has joined Keytruda with a US approval, but it might not be the answer doctors are looking for.

The December US approval of Ferring's cancer gene therapy Adstiladrin probably passed unnoticed by many biotech investors; it occurred during the Christmas lull, and the beneficiary was a private European company best known for reproductive health and the microbiome.

The product's tortuous journey is the result of a renewed industry effort to tackle non-muscle invasive bladder cancer, an earlier setting than the metastatic disease that has seen several drugs approved recently. Still, Adstiladrin's long-term benefits remain elusive, and a cumbersome mechanism and use of an adenovirus vector raise questions about its viability.

The product's development history offers a lesson in tenacity. Adstiladrin was originated by Merck & Co, attracted $400m of financing from Blackstone, saw off one chief executive and survived an FDA rejection. Surprisingly, Ferring has still not launched it, and does not expect to until the second half of 2023.

One possibility is that Ferring needs a US licensee, having recently lost Blackstone as its joint-venture partner. The company does have a US commercial presence, but says it still needs to expand manufacturing capacity to be able to produce vector for oncology at commercial scale. Asked by *Evaluate Vantage*, Ferring would not comment on its commercial plans.

The vector issue

But why is Adstiladrin controversial? The product is not what many people would consider a typical gene therapy in that it does not seek to alter or correct a disease's underlying genetic defect. Rather, it merely encodes the gene for human interferon alfa-2b, and it is this cytokine, once produced locally, that exerts antitumour activity.

Potential problems extend beyond the complexity of manufacturing a gene therapy, and include Adstiladrin's use of a non-replicating adenovirus serotype 5 (Ad5) vector. Additionally, the therapy is designed to be given every three months rather than as a once-and-done procedure.

Normally, repeat dosing of an adenoviral vector would result in dangerous immunogenicity. Those with a long enough memory will recall the death of Jesse Gelsinger, attributed to his development of a severe immune reaction against a gene therapy. That gene therapy used an Ad5 vector.

"Fundamentals of virology and vaccinology tell us that repeat exposure to [Ad5] or any virus should absolutely

lead to the development of a massive neutralising antibody response against the various viral antigens," Professor Nicole Paulk, who specialises in AAV-based gene therapies at University of California San Francisco, tells *Vantage*.

However, she hastens to cite the example of Astrazeneca's Covid vaccine Vaxzevria, which also uses an adenoviral vector and is dosed two or three times. "It's clearly possible to repeat administer adenovirus," she says. "The subtleties on how Ferring is likely able to repeat administer here are important."

One possibility might be that the bladder, into which Adstiladrin is administered via a urinary catheter, is more immune privileged than thought. It should also be stressed that the Gelsinger case involved an extremely high systemic dose, and an early-generation adenovirus.

In contrast, Adstiladrin uses a "novel" Ad5 vector, says Patrick Gorman, a spokesman for Ferring, adding that therapeutic uses of adenovirus vectors have been increasingly well characterised in recent years.

"The nuance here for Adstiladrin almost certainly depends on dose, purity and route of administration," says Professor Paulk. "A combination of low dose and local delivery is likely paramount to Ferring's ability to repeat infusions."

A long history

The history of Adstiladrin, which carries the INN nadofaragene firadenovec-vncg, is long and fascinating. The therapy originated at the labs of Merck & Co, before that company sold it, along with options over gene therapies for glaucoma surgery failure and solid tumours, to a private Finnish venture called FKD Therapies in 2011.

Seven years later FKD optioned nadofaragene to Ferring, and Ferring then spun it into a new business called Fergene that it co-founded with the private equity group Blackstone Life Sciences. Blackstone was said to commit $400m to the venture, with Ferring pledging "up to $170m" and agreeing to launch and market a resulting approved product outside the US.

David Meek was appointed chief executive of Fergene, having left Ipsen after that company's disastrous $1bn takeover of Clementia. With nadofaragene reading out positively in a phase 3 trial, all seemed to be going well as the project headed to the FDA.

It was then, in mid-2020, that things started to unravel. The FDA issued Fergene a complete response letter, citing flawed manufacturing controls, a quality unit not fulfilling its responsibility to assure the identity, strength, quality and purity of nadofaragene, and inadequate responses to questions raised in an inspection report.

Mr Meek left in 2021, to take up the chief executive job at Mirati, and the Blackstone venture was officially wound up last October, with rights to nadofaragene passing back to Ferring.

But on December 16 last year the FDA approved Adstiladrin, giving it a full label for non-muscle invasive bladder cancer that is unresponsive to BCG. The setting is notable for including one approved anti-PD-1 drug, Merck & Co's Keytruda, based on results of the Keynote-057 trial.

In the single-cohort Keytruda trial 41% of patients went into complete remission, with a 16.2-month median duration of response. Adstiladrin's registrational CS-003 study was, like Keynote-057, uncontrolled, and the data it generated appear to be in line with Keytruda's. There was a 51% complete response rate, and 9.7-month median duration of response.

Is that enough?

Professor Benjamin Davies, a urologist at University of Pittsburgh Medical Center, tells *Vantage* that this looks like decent efficacy in a subset of patients, but that one-year response rates, including for Keytruda, "almost always hover at a dismal 30%".

Yet the need is clearly there. Bladder cancer, at this pre-metastatic, non-muscle invasive stage, is typically treated with BCG, but "BCG-refractory patients have limited options", says Professor Davies. Merck would not tell *Vantage* how much Keytruda sold in BCG-unresponsive non-muscle invasive bladder cancer, but back in 2019 SVB analysts said the setting represented a $250m US market opportunity.

A separate issue here is that recent years have seen a profound worldwide shortage of BCG. An alternative is gemcitabine plus docetaxel, which Professor Davies says is given instead of BCG if needed, and the two therapies are being tested head to head in the NCI's recently initiated phase 3 Bridge trial.

It is notable that the industry pipeline now includes several projects being studied on top of BCG in BCG-naive patients. These include Roche's Tecentriq, Astrazeneca's Imfinzi and Immunitybio's Anktiva/N-803, an IL-15 superagonist complex comprising IL-15N72D bound to an IL-15 receptor α/IgG1 Fc fusion protein.

Anktiva is separately awaiting US approval in Keytruda and Adstiladrin's BCG-unresponsive setting, with a May 12 FDA action date. The filing is based on a 71% complete response rate, with a median duration of 26.6 months, in the Quilt-3.032 trial.

Three other assets should be watched here: Bristol Myers Squibb's Opdivo, which should soon yield data from the recently completed Checkmate-9UT study, CG Oncology's CG0070 and Johnson & Johnson's Balversa, the last of these in FGFR-mutant disease.

Late-stage trials in high-risk, non-muscle invasive bladder cancer				
Study	**Company**	**Therapy & design**	**Setting**	**Note**
Keynote-057	Merck & Co	Keytruda, uncontrolled	BCG unresponsive	US approved
CS-003	Ferring	Adistraldin, uncontrolled	BCG unresponsive	US approved
Quilt-3.032	Immunitybio	Anktiva + BCG, uncontrolled	BCG unresponsive	US filed (12 May 2023 Pdufa)
Checkmate-9UT	Bristol Myers Squibb	Opdivo +/- BCG, uncontrolled	BCG unresponsive	Completed (no data)
Checkmate-7G8	Bristol Myers Squibb	Opdivo + BCG, vs BCG	Recurrent after BCG induction	Ends Oct 2023
Bond-003	CG Oncology	CG0070, uncontrolled	BCG unresponsive	Ends Jan 2024
NCT04172675	Johnson & Johnson	Balversa, vs chemo	BCG unresponsive, FGFRm	Ends Mar 2024
Alban	Roche	Tecentriq + BCG, vs BCG	BCG-naive	Ends Apr 2024
Crest	Pfizer	Sasanlimab + BCG, vs BCG	Recurrent after BCG induction	Ends Jun 2024
Potomoac	Astrazeneca	Imfinzi + BCG, vs BCG	BCG-naive	Ends Oct 2024
Keynote-676	Merck & Co	Keytruda + BCG, vs BCG	Recurrent after BCG induction	Ends Dec 2025
NCT02138734	Immunitybio	Anktiva + BCG, vs BCG	BCG-naive	Ends Dec 2025
Keynote-992	Merck & Co	Keytruda + chemoradio, vs chemoradio	Unclear	Ends Jun 2029
Source: clinicaltrials.gov.				

The variety of approaches is interesting, but the mechanism of Adstiladrin raises a separate consideration. On the face of it the treatment looks like a complicated way of doing something that could, in theory, be done simply by administering interferon alfa-2b directly into the bladder.

Indeed, the NCI has studied adding interferon alfa-2b to BCG in non-muscle invasive bladder cancer, and at least one hospital offers this as a treatment. A paper co-authored by Professor Davies suggests that the cytokine/BCG combo is promising.

However, interferon's effects are hampered by limited exposure and a half-life barely over two hours. In contrast, "Adstiladrin turns the patient's own bladder wall cells into interferon microfactories, enhancing interferon alfa's cytotoxicity", says Ferring's Mr Gorman. "The high local expression of interferon alfa-2b protein is sustained typically for one to two weeks."

Professor Paulk agrees: "Vectorisation here is essential to getting durable continuous expression." She also sees Adstiladrin's clinical and regulatory success as a lesson for those companies and investors who insist that systemic delivery is the only viable option for gene therapy.

"The myth of 'only systemic' is gone," she states. "I hope this ushers in a new era of low-dose, locally delivered gene therapies for indications where [this] makes sense." Pharma, however, has yet to be convinced.

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Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754