Oncolytics Biotech® Inc.: REOLYSIN® for melanoma therapy

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Practice points

- Oncolytics Biotech® Inc. is focused on the development of oncolytic viruses for use as cancer therapeutics. The Company's lead product, REOLYSIN®, a proprietary formulation of the human reovirus, is in late-stage clinical testing in a range of cancers.
- REOLYSIN preferentially replicates in cancer cells that have an 'activated Ras pathway', while sparing normal cells. This makes it intrinsically tumor selective without the need for any genetic manipulation of the agent.
- Clinical trials of Oncolytics Biotech's proprietary variant of the reovirus (REOLYSIN) are now underway to evaluate the use of reoviruses in a wide variety of cancers, including ovarian, pancreatic, prostate, colorectal, nonsmall cell lung and breast cancers.
- Oncolytics is collaborating with researchers to assess the potential of REOLYSIN to increase the therapeutic activity of anti-PD-1 checkpoint inhibitors.
- At the December 2014 American Association for Cancer Research (AACR) Tumor Immunology and Immunotherapy Conference in Orlando (FL, USA), researchers presented preclinical data demonstrating that provision of systemic anti-PD-1 antibody along with intratumoral reovirus, significantly enhanced survival compared with intratumoral reovirus alone, and led to more than 40% of mice being cured long term.
- Immune analysis suggests that the enhanced therapeutic benefit of reovirus plus checkpoint inhibition is contributed by at least two factors. Thus, blockade of PD-1 significantly enhanced the ability of NK cells to recognize (TNF- α secretion), and kill reovirus-infected target tumor cells. Second, anti-PD-1 antibody led to a significant reduction in Treg activity in reovirus-treated mice, with the overall effect of increasing the adaptive CD8⁺ antitumor T-cell response.
- These data suggest that combination of checkpoint inhibition therapy with reovirus oncolytic/immunotherapy represents a readily translatable method to enhance the therapeutic value of either alone.
- Two factors seem to contribute to the possibility that metastatic disease, including metastatic melanoma, would be susceptible to treatment with REOLYSIN. First, REOLYSIN appears to distribute preferentially to organs where metastasis is common, so the agent can be concentrated in those regions of the body. And second, a growing body of literature suggests Ras pathway activation is common in metastatic lesions.

SUMMARY Oncolytics Biotech® Inc. is focused on the development of oncolytic viruses for use as cancer therapeutics. The Company's lead product, REOLYSIN®, a proprietary formulation of the human reovirus, is in late-stage clinical testing in a range of cancers. REOLYSIN has been utilized in nearly 30 clinical trials including translational, Phase I, Phase II (single arm and randomized) and Phase III studies in a broad range of cancer indications. To date, Oncolytics has been issued more than 370 patents worldwide and has more than 230 pending applications. Issued patent claims pertaining to the reovirus cover: compositions of matter comprising reovirus; pharmaceutical use of reoviruses to treat neoplasia and cellular proliferative diseases and combination therapy with radiation, chemotherapy and/or immune suppressants.

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KEYWORDS

• anti-PD-1 • combination therapy • introduction • melanoma • oncolytic virus • REOLYSIN® • reovirus

Company

Oncolytics Biotech Inc. was founded in Calgary in 1998 based on discoveries made at the University of Calgary regarding the oncolytic potential of the reovirus. From 1999 to 2000, the company transitioned from private to public ownership. Its shares began trading on the Toronto Stock Exchange (TSX) in June 2000 and on the NASDAQ in October 2001. Since its inception, Oncolytics has worked to develop REOLYSIN®, its proprietary formulation of the human reovirus, as a potential cancer therapeutic. In 2000, Oncolytics Biotech Inc. received permission to conduct its first Phase I clinical trial, which was designed to test the safety of REOLYSIN in human patients. The positive results of this first study led to the rapid and continuous expansion of Oncolytics' clinical trial program, with Phase II studies beginning in Canada in 2001, USA and subsequent cross-border studies beginning in 2002, and enrollment in a multicenter Phase III trial beginning in 2010.

Reoviruses in cancer treatment

The reovirus is a form of oncolytic virus. It is a nonenveloped virus with a double-stranded (ds), segmented RNA genome. The reovirus preferentially replicates in cancer cells that have an 'activated Ras pathway', which is caused by mutations in genes including *KRAS*, *BRAF* and *EGFR*. The reovirus leaves normal cells unharmed. This makes it intrinsically tumor selective without the need for any genetic manipulation [1].

The reovirus is a virus with no known associated disease. It replicates in the cytoplasm and therefore does not integrate into the cell's DNA. The reovirus is found commonly in nature and has been isolated from untreated sewage, river and stagnant waters. Exposure to the reovirus is common in humans, with half of all children by the age of 12 years having been exposed and up to 100% testing positive by adulthood [2].

Tumors bearing an activated Ras pathway cannot activate an anti-ds-RNA viral response mediated by the host cellular protein, PKR. Studies have shown that the reovirus actively replicates in transformed cell lines with an active Ras signaling pathway, eventually killing the host cell and freeing the viral progeny contained within, which in turn go on to infect and kill more tumor cells. When normal cells are infected with the reovirus, the normal anti-ds-RNA viral response can neutralize the virus.

Approximately two-thirds of cancer cells have an activated Ras signaling pathway [3].

Company technology

Clinical trials of Oncolytics Biotech's proprietary variant of the reovirus (REOLYSIN) are now underway to evaluate the use of REOLYSIN as a treatment for a wide variety of cancers, including ovarian, pancreatic, prostate, colorectal, nonsmall cell lung and breast cancers. For example, a US Phase II single-arm clinical trial in patients with squamous cell carcinoma of the lung using intravenous administration of REOLYSIN in combination with carboplatin and paclitaxel recently reported that, of the evaluable patients who had received more than one cycle of therapy, 92% exhibited overall tumor shrinkage [4]. Separately, data from a US Phase II study examining the use of REOLYSIN in combination with carboplatin and paclitaxel in patients with stage IV nonsmall cell lung cancer reported that 20 of 36 evaluable patients survived a year or more [5].

• REOLYSIN as companion therapy to anti-PD-1 drugs in melanoma treatment

On 4 September 2014, the US FDA approved Merck & Co.'s highly anticipated immunoncology drug, KEYTRUDA® (pembrolizumab), as a treatment for melanoma. The drug is the first in a promising new class designed to help the body's own immune system fend off cancer by blocking a protein called PD-1, used by tumors to evade disease-fighting cells. PD-1 effectively acts as an 'off switch', shutting down the immune system's ability to detect and eliminate cancer cells. Many researchers are trying to find a way to block the activity of PD-1. If successful, this would unleash the immune system's T cells that target cancer, essentially releasing a natural brake on the immune system and 'training' it to attack tumors. It is believed, however, that the majority of patients with metastatic melanoma exhibit no response to the form of anti-PD-1 immunotherapy that Merck is developing. This has led some experts to suggest that anti-PD-1 therapy should be combined with other forms of immunotherapy to improve outcomes further [6].

Oncolytics is collaborating with researchers to assess the potential of REOLYSIN to increase the therapeutic activity of anti-PD-1 checkpoint inhibitors. At the December 2014 American Association for Cancer Research (AACR)

Tumor Immunology and Immunotherapy Conference in Orlando (FL, USA), researchers presented preclinical data demonstrating REOLYSIN's abilities in this area. The research was designed to exploit the immune components of reovirus therapy by testing REOLYSIN in combination with systemic checkpoint inhibition (using anti-PD-1 antibodies), which increases the immune system's ability to recognize and attack cancer cells.

The combination was tested in immune-competent mice with established B16 melanomas. The investigators concluded that in this model, provision of systemic anti-PD-1 antibody along with intratumoral reovirus significantly enhanced survival compared with intratumoral reovirus alone ($p < 0.01$) and led to more than 40% of mice being cured long term. Immune analysis suggests that the enhanced therapeutic benefit of reovirus plus checkpoint inhibition is contributed by at least two factors. Thus, blockade of PD-1 significantly enhanced the ability of NK cells to recognize (TNF- α secretion), and kill reovirus-infected target tumor cells. Second, anti-PD-1 antibody led to a significant reduction in Treg activity in reovirus-treated mice, with the overall effect of increasing the adaptive CD8⁺ antitumor T-cell response. The researchers also showed that timing of the checkpoint inhibitor antibody was significant in balancing toxicity with anti-tumor therapy. These data suggest that combination of checkpoint inhibition therapy with oncolytic immunotherapy using REOLYSIN represents a readily translatable method to enhance the therapeutic value of either alone [7].

Future perspective

Much research remains to be done on the ability of REOLYSIN, alone or in combination with anti-PD-1 therapies, to impact melanoma and other cancers. However, two factors seem to contribute to the possibility that metastatic disease, including metastatic melanoma, would be receptive to treatment with reovirus. First, REOLYSIN appears to distribute preferentially to organs where metastasis is common, including the lungs, liver, lymph nodes and the peritoneal cavity, so the agent can concentrate in those regions of the body. And second, a growing body of literature suggests Ras pathway activation is common in metastatic lesions. If positive, future studies will provide an even clearer perspective on whether REOLYSIN offers an effective avenue toward a reliable and commercially viable complement to existing therapies for oncologists and their patients with metastatic (and localized) melanoma and other cancers. There may be new hope on the horizon for these patients – a hope coming from within the human body itself.

Financial & competing interests disclosure

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