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Cold Genesys's oncolytic virus: phase 3 ready with positive efficacy and safety data in bladder cancer

Cold Genesys is developing CG0070, a promising oncolytic virus that is proving successful in trials as a single agent, with near-term plans to develop it in combination with immuno-oncology agents.

Cold Genesys is a clinical-stage company developing an oncolytic virus (CG0070) for multiple tumor types as a single agent and in combination with immune system checkpoint inhibitors. Already with strong efficacy and safety data, CG0070 is one of the most advanced oncolytic viruses in development.

Existing phase 2 data on CG0070 in Bacillus Calmette–Guérin-unresponsive patients with nonmuscle invasive bladder cancer show a robust complete response rate, with durable responses seen in a large proportion of participants. Upon full readout and completion of the phase 2 study, Cold Genesys will initiate a registrational trial in bladder cancer in 2019.

Phase 2 efficacy details in bladder cancer

The phase 2 trial in 61 patients with bladder cancer who had failed standard-of-care treatment reported 6-month and 12-month complete response rates of 45% and 30%, respectively. No patients experienced a treatment-related grade 4 adverse event as of the 12-month cutoff, demonstrating positive safety. The 45% complete response rate exceeds those reported in other studies, and the replication competency of the virus provides an edge over the competition in the indication.

CG0070 provides a promising option for patients with bladder cancer who would otherwise require a full cystectomy, the surgical removal of the urinary bladder. Preventing or delaying cystectomy provides significant quality-of-life benefits to these patients by removing the complications and consequences of a major procedure.

> "CG0070 is one of the most advanced oncolytic viruses in development

2018–2019 milestones

Following CG0070's observed efficacy and safety in phase 2, Cold Genesys's milestones for 2018 and 2019 will include the following:

- the full readout of the ongoing phase 2 trial to assess the 24-month durability of the complete responses observed,
- enrollment of patients in a phase 3 registrational trial in bladder cancer,
- initiation of CG0070 trials in combination with checkpoint inhibitors, and
- exploration of CG0070 activity in additional tumor types beyond bladder cancer.

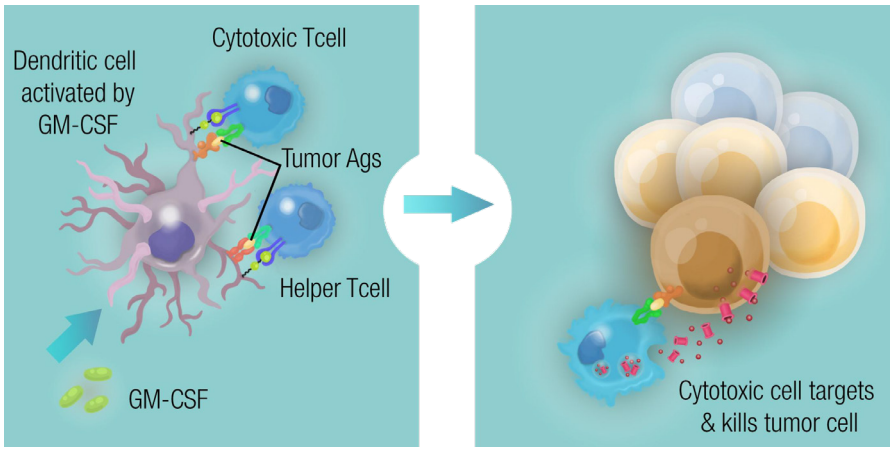

Fig. 1 | CG0070-derived GM-CSF expression induces tumor-directed immune activation. Expression and release of the immune modulator GM-CSF alongside tumor antigens occurs when CG0070 lyses a cancer cell. GM-CSF activates dendritic cells, which present tumor antigens to cytotoxic and helper T cells. As a result, T cells are trained to spot the tumor cells, then target and kill them within the body.

Background on CG0070 and its immuno-oncology mechanism of action

Oncolytic viruses were initially developed to selectively target and kill tumor cells. For CG0070, tumor specificity is achieved by placing viral replication of a wild-type adenovirus backbone under the control of E2F, a powerful transcription factor selectively active in many tumor types. E2F activity is repressed in normal noncancerous cells by the tumor suppressor retinoblastoma protein (Rb).

The Rb pathway is one of the most important tumor suppressor pathways commonly defective across many cancer types. As a result, CG0070 has built-in specificity for tumor cells that are genetically Rb-mutated or otherwise have a defective Rb pathway, enabling it to selectively lyse tumor cells without harming healthy tissues.

Direct cell lysis is one of two ways CG0070 treats cancer. The other stems from the virus's expression of granulocyte–macrophage colony-stimulating factor (GM-CSF), a powerful immune modulator. This expression results in release of the GM-CSF cytokine alongside tumor antigens when CG0070 lyses a cancer cell. The cytokine activates dendritic cells, which then present tumor antigens to cytotoxic and helper T cells. This immune system activation process trains the T cells to spot the cancer, enabling them to target and kill tumor cells throughout the body (**Fig. 1**).

When paired with CG0070's ability to lyse cancer cells, this immune activation ability gives the oncolytic virus a dual mechanism of action and unique potential to act as a powerful anticancer drug.

Summary and commercial prospects

Cold Genesys is poised to progress CG0070 to approval based on single-agent activity in patients with bladder cancer in whom other agents have failed and cystectomy is the remaining treatment option.

Beyond bladder cancer, the unique aspects of Cold Genesys's oncolytic virus, together with the proven efficacy and safety data, validate the use of CG0070 in other tumor types driven by Rb defects and in combination with other modulators of the immune response to tumors, such as recently approved programmed cell death 1/programmed cell death ligand 1 checkpoint inhibitors.

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