Pioneering a new approach to treating cancer

Rakuten Medical, a clinical-stage privately funded biotechnology company, is developing first-in-class targeted cancer therapies based on Illuminox, a new platform with the potential to treat many types of solid tumor, one of the leading causes of death globally.

Rakuten Medical’s innovative platform, Illuminox, involves conjugating light-excitable non-toxic dyes to monoclonal antibodies that, when administered to patients, target and bind to a specific antigen on the surface of cancer cells. Subsequent local illumination by non-thermal red light, using a laser system and fiber optics, transiently activates the dyes, which physically disrupt the cancer cell membrane, leading to rapid cell death and tumor necrosis.

“Because the induction of cell death by Illuminox requires antibody binding to antigen-expressing tumor cells, the treatment has minimal effects on surrounding normal tissue,” explained Miguel Garcia-Guzman, Chief Scientific Officer. “The dye itself is non-toxic and, if not activated with light, does not induce pharmacological effects. This is a significant improvement over both traditional antibody–drug conjugate approaches that use cytotoxic agents, and classic photodynamic therapy that is not tumor targeted.”

A treatment cycle involves the infusion of the antibody conjugate followed, a day later, by light activation of the conjugate at the tumor site. The treatment can be applied to both superficial and large/bulky deep-seated tumors using specialized light diffusers. Repeated treatment cycles can be applied every 4–6 weeks to achieve durable disease control or even tumor eradication.

Rakuten Medical is a global company with corporate headquarters located in San Mateo, and other offices in San Diego, Germany, Taiwan, and Tokyo. The company has raised approximately $472 million in funding to date.

Rakuten Medical’s lead product ASP-1929, based on the Illuminox platform, comprises a light-activated dye conjugated to cetuximab, which specifically binds the epidermal growth factor receptor (EGFR). ASP-1929 is currently in phase 3 testing as a monotherapy to see whether it improves progression-free and overall survival of patients with recurrent head and neck squamous cell carcinoma (rHNSCC), and has received Fast Track designation from both the US Food and Drug Administration, and the Japanese Ministry of Health, Labour and Welfare. ASP-1929 is also being tested in patients with esophageal cancer and, in combination with a PD-1 inhibitor, for treating gastric cancer (Fig. 1).

Illuminox treatments can reduce tumoral immunosuppression

Rakuten Medical scientists have discovered that Illuminox treatments also induce immunogenic cell death of targeted cancer cells and activate the innate and adaptive immune response in the tumor microenvironment (TME). “Regulatory T\textsubscript{reg} cells, macrophages and other immune cells in the TME can be rapidly ablated to remove cellular immunosuppression in the TME,” explained Garcia-Guzman. “Releasing the brakes of some immune system components can activate anti-cancer immunity—localized and systemic—to treat disseminated disease. We are very excited at the possibilities this presents for successful treatment with Illuminox.”

Rakuten Medical’s candidate RM-1995, which targets the TME, is a light-excitable dye conjugated to an anti-CD25 antibody (based on basiliximab and manufactured internally). “Results from preclinical studies are promising and show that RM-1995 ablates tumoral T\textsubscript{reg} cells in the TME without impacting T\textsubscript{reg} cells in normal tissue and ignites a robust anti-cancer immune response,” said Garcia-Guzman. “In syngeneic mouse models, a single cycle of anti-CD25 Illuminox treatment induces anticancer responses similar to anti-PD-1 [immunotherapy] and is highly synergistic with combination treatments with anti-PD-1.” RM-1995 is ready for clinical trials and could be used to treat a broad range of solid tumors; a phase 1 trial is planned for launch before the end of 2020.

Advanced partnering

Rakuten Medical is already collaborating with the University of Texas MD Anderson Cancer Center to advance the development of new cancer therapies based on Illuminox, and Merck KGaA has agreed a multi-year deal to provide cetuximab for Rakuten’s ASP-1929 program. ASP-1929 is under investigation to treat local, regional and disseminated cancers from several solid tumor types, and Rakuten Medical is open to regional partnerships for co-commercializing ASP-1929 in specific countries or regions, such as Europe, China, USA and Japan. The company’s second clinical candidate, RM-1995, offers a differentiated mechanism of action and potential pan-tumor approach by targeting the TME. For this candidate, Rakuten Medical is seeking a broader partnership scope, which could include co-development or regional partnership. Furthermore, checkpoint inhibitors or other immunotherapies could be synergistic with RM-1995, and could be used to treat a broad range of local and systemic/metastatic cancers.

“We are pioneering a new approach to treating cancer by combining the targeting power of antibodies with laser-activated precision, and are keen to make this treatment available to as many people as is feasible and as soon as possible,” said Garcia-Guzman. “We hope this new, safe and effective cancer treatment option will not only give patients new hope but also transform and improve their lives.”

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Miguel Garcia-Guzman, CSO, Rakuten Medical

**Fig. 1** | Clinical trials of Illuminox-based therapies. * Investigator-initiated trials. ** Planned trials in 2020.