

Health & Science

Drug developers take fresh aim at 'guided-missile' cancer drugs

FRANKFURT/ZURICH: Dozens of drugmakers are conducting human trials for a record 89 therapies that pair antibodies with toxic agents to fight cancer, evidence of renewed confidence in an approach that has long fallen short of its promise, an analysis compiled for Reuters shows.

These antibody-drug conjugates, or ADCs, from companies including AstraZeneca and GlaxoSmithKline, are described by researchers as "guided missiles" packing a powerful anti-cancer punch.

They are engineered to zero in on tumours and then release cytotoxins that deliver up to 10,000 times the potency of standard chemotherapy, while minimizing damage to healthy tissue.

The approach has for decades been a major biotech industry focus. Many experimental ADCs, however, failed due to the complexity of pairing the right antibody with the appropriate toxic agent. Some were abandoned as too weak; others were too harmful.

From 2000 to 2018, only five ADCs won approval. Just one, Roche's Kadcyla, approved in 2013 for breast cancer, has surpassed \$1 billion in annual sales after data last year showed it boosted disease-free survival for some patients compared with the standard treatment, Roche's Herceptin.

Over time, however, scientists devised better ways to connect payloads and antibodies and more precisely reach tumours. There is a growing understanding, too, of how to design ADCs to kill even surrounding cancer cells that previously evaded destruction.

"What we're seeing now are the benefits of the science becoming mature," said ADC pioneer Chris Martin, CEO of Switzerland's ADC Therapeutics. "It took at least a decade, probably more like 15 years, to really begin to turn the art into a science."

In 2019, U.S. regulators approved three ADCs, the most ever in a single year, as last-ditch treatments based on studies showing they helped patients whose survival outlook was bleak.

They include AstraZeneca's and Daiichi Sankyo's breast cancer drug, Enhertu, which was shown to help patients who had failed numerous previous treatments survive a median of more than 16 months before their disease worsened.

Astellas' and Seattle Genetics' bladder cancer drug, Padcev, also received expedited approval in December, based on evidence that 44% of patients who had failed immunotherapy showed improvement, and in some cases, no evidence of cancer, when they were assessed after treatment.

Roche's Polivy was green-lighted against lymphoma in June after producing complete response rates, with no signs of disease, in 40% of patients when combined with two other therapies.

NEW RECORD

While all three drugs must prove their mettle in further studies, the industry is growing optimistic that ADCs' time may have arrived.



STEVENAGE: File photo shows a scientist studies cancer cells inside white blood cells through a microscope at the GSK research centre in Stevenage.

The number of ADC drug candidates is at unprecedented levels, according to data from consultancy Beacon Targeted Therapies compiled for Reuters, based on a review of companies' pipelines. Dozens more ADC prospects are in pre-clinical review.

London-based Beacon advises drugmakers on targeted therapies, helping them decide whether to pursue prospective drugs or redirect efforts, based on industry trends.

Current ADC projects include GlaxoSmithKline testing its belantamab mafodotin against multiple myeloma.

ADC Therapeutics, part-owned by private equity firm Auen Therapeutics, has several studies on experimental drugs, including with Danish partner Genmab, on blood cancers and solid tumours.

U.S. biotech Immunomedics' market capitalization gained more than 60% to \$4.3 billion in the last six months, ahead of the U.S. Food and Drug Administration's late-December decision to review its ADC against triple-negative breast cancer, which is hard to treat and has poor prognosis.

Massachusetts-based ImmunoGen, hit by past trial failures, got a lift in December for its ADC against ovarian cancer when the FDA indicated it may become a candidate for accelerated approval.

The surge in ADC investment has been fueled, in part, by improvements in the so-called "linker" technology that binds the antibody to its cancer-killing toxins, keeping them stable in the circulatory system until the poison can

be unleashed on the targeted tumour.

ADCs are generally delivered via repeated infusions, similar to chemotherapy.

"There is a revival again because there is a new generation of molecules in which the linker is more efficient," Giuseppe Curigliano, clinical director of early drug development at Milan's European Institute of Oncology, told Reuters.

BETTING ON GROWTH

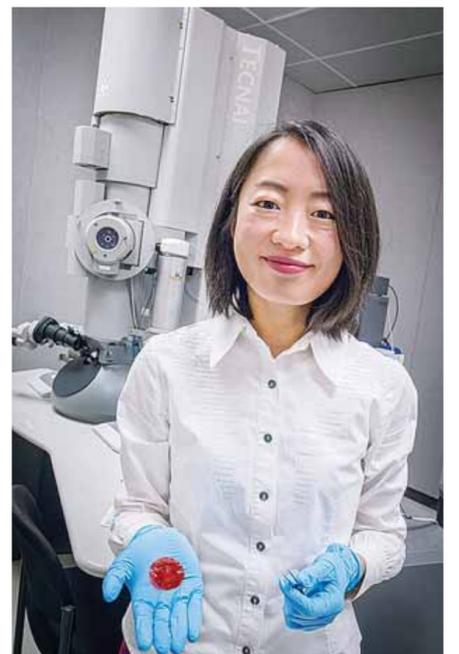
This optimism has contract manufacturers like Merck KGaA and Lonza ramping up facilities, in hopes drugmakers will farm out complex ADC production.

Merck expects the overall ADC market to grow by more than 20% in coming years, boosting its business, which includes manufacturing of monoclonal antibodies, linkers and cytotoxic agents.

Rival Lonza, which helps make Roche's two ADCs and sees annual 9% growth for the so-called bioconjugates market, is investing millions of dollars in its Swiss site, where it produces ADCs for other drugmakers.

"What we see over time at Lonza is a good request for capacity," said Iwan Bertholjotti, Lonza's bioconjugate commercial development head. "That's a good sign that the market is booming." Still, enthusiasm is not universal.

AbbVie in August abandoned its ADC candidate Rovala-T after flunking a lung cancer trial and wrote off most of the \$5.8 billion it paid for the drug's developer, Stemcentrx, in 2016.



BERKELEY: Chelsea Chen, a postdoctoral researcher at Berkeley Lab, holds a sample of a polymer membrane material that turned red when it soaked up a chemotherapy drug. The material is designed to bind the drug, based on its electric charge, after the drug targets tumors and before it circulates throughout the body.

Roche, which helped pioneer ADCs with Kadcyla and Polivy, has also backed off. In 2013, the Basel-based company had about a dozen experimental ADCs. Today, only one remains, and it is being developed for Staph infections, not cancer.

"We have shifted our technology priorities," Roche CEO Severin Schwan told Reuters. "Maybe others will be luckier, but we failed to master the complexity." AstraZeneca aims to do just that.

In March, the Cambridge, England-based drugmaker struck a \$7 billion deal with Japan's Daiichi Sankyo for rights to Enhertu, getting \$1.35 billion up-front, and more if it challenges Roche drugs' dominance in breast cancer.

Some industry analysts see Enhertu sales eventually reaching up to \$7 billion annually.

"Our plan is to expand the number of studies in different tumour types," said Gilles Gallant, head of oncology R&D at Daiichi Sankyo. "This agent has potential." —Reuters

Switzerland grapples with assisted suicide for prisoners

GENEVA: A request by a convict behind bars for life is testing Switzerland's support for assisted suicide, raising complex questions over whether ill prisoners can seek help to end their own lives.

The unprecedented case has exposed a legal vacuum in the country which has long been at the forefront of the global right-to-die debate and an official decision is due in the coming months.

"It is natural that one would rather commit suicide than be buried alive for years to come," prisoner Peter Vogt said, in a written response to questions submitted by AFP.

The 69-year-old, convicted for sexual assault and rape against multiple girls and women ranging in age from 10 to 56, says he is suffering from serious kidney and heart conditions, among other ailments.

He has also been diagnosed with several psychological disorders.

Although Vogt's most recent sentence was a 10-year term handed down in 1996, he is imprisoned for life at Bostadel prison in northern Switzerland as he is still considered dangerous.

This follows a decision in 2004 when Swiss voters approved a popular initia-

tive allowing the indefinite detention of people with established sexual delinquencies who posed a public risk.

The authorities have repeatedly determined that Vogt remains a threat despite years of treatment.

"It would be better to be dead than to be left to vegetate behind these walls," he said. In July 2018, Vogt contacted Exit Switzerland, an organisation that supports assisted suicide under specific conditions. He argues that he should be able to benefit from Switzerland's liberal assisted suicide laws too.

"We told him that his particular case needed to be clarified," Juerg Wiler, its vice president, told AFP.

'Unbearable suffering'

Swiss law generally allows assisted suicide if the person commits the lethal act themselves — meaning doctors cannot administer deadly injections, for example — and the person consistently and independently articulates a wish to die.

Organisations that support assisted suicide also apply their own procedures, which are more robust than the legal requirements.

The authorities, aiming to take a position on the matter in the coming months, have asked the Swiss Centre of Expertise in Prison and Probation, a publicly funded foundation, to provide guidance following Vogt's request.

In October, the experts at the foundation advised that assisted suicide rights should apply to prisoners under certain conditions, noting that in cases of mental

illness two independent specialists should be consulted.

Any detainee possessing discernment should, in principle, have assisted suicide rights if they have "a physical or mental illness resulting in unbearable suffering," Barbara Rohner, lead author of the foundation's report, told AFP.

The foundation also recommended that authorities responsible for the prisoner's welfare must ensure the suicide request is not the result of a short-term emotional crisis.

Vogt insisted that he wanted to die because of the "unbearable" deterioration in his quality of life, along with the fact that he can no longer see his gravely ill mother, who lives in Austria.

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Prisoner Peter Vogt



Barbara Rohner



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More requests coming?

Rohner said that while Vogt's case

may be exceptional, similar situations could increasingly arise.

"There will be more and more elderly and sick prisoners in detention because of the ageing of the prison population," she said.

According to the Swiss National Science Foundation, a research institute, the number of prisoners over 50 years old doubled to 600 between 2005 and 2016.

Vogt told AFP that he knows of another inmate interested in assisted suicide, adding: "Nobody should have to commit suicide in his cell alone."

Some have raised concern that assisted suicide requests could be used by convicts as a negotiating tactic to demand better conditions in prison.

For Christine Bussat, founder of the Swiss chapter of the Marche Blanche victims' rights groups, decisions on a convict's right to die should rest with their victims. —AFP

Years of drought threaten S Africa's wildlife industry

STRYDENBURG/GROBLERSHOOP: A severe drought is threatening South Africa's wildlife industry, with game farmers keeping fewer animals and tourists visiting game lodges in smaller numbers.

Parts of the country have been affected by consecutive years of abnormally hot weather and below average rainfall that have scorched grazing lands and dried up watering holes since 2015, the driest year on record. Industry body Wildlife Ranching South Africa (WRSA) estimates the Northern Cape province

has lost more than two-thirds of its game over the last three years. It is conducting a nationwide survey to determine the scale of animal losses and the financial impact on the country's more than 9,000 wildlife ranches.

"It's been an extraordinary drought," said WRSA chief Adri Kitshoff-Botha. "It's not a one-year or two-year drought. In some areas we've seen it has been going now for six years."

The wildlife industry generates revenue for South Africa through tourism, hunting, breeding and meat production. Trophy hunting alone generated 2 billion rand (\$140 million) in 2016, according to research carried out for the environment ministry.

Southern Africa's temperatures are rising at twice the global average rate, according to the International Panel on

Climate Change, and in much of South Africa the level of water in reservoirs is dwindling. For Burger Schoeman, manager at Northern Cape game farm Thuru Lodge, the withered vegetation and parched ground are a serious concern for the sector.

Once home to around 4,500 wild animals - including 35 different species, from antelope to rhino - the lodge has lost around 1,000 animals due to drought. Carcasses are piling up in abandoned mines on the edge of the property. "At this stage we are quite stretched. All the money you get from selling the animals, meat and all of that, gets put straight back into the property to look after the rest of the animals," Schoeman said.

The lodge has seen costs rise as it buys in additional feed for the animals,

but hunters are paying less and fewer tourists are coming as the animals are in worse condition.

At the 48,000-hectare Karreekloof Safari Lodge in the same province, rangers come across carcasses every week.

"Nobody wants to buy the game, because they also (are experiencing) ... the same drought," said farm manager Gideon Watts, adding that his farm received a quarter of its usual rainfall this season.

The industry has seen a decline of around 20% in tourist numbers over the past year, said WRSA's Kitshoff-Botha.

The drought has also hit the rest of the region, with Botswana, home to almost a third of Africa's elephants, seeing more than 100 of the creatures die in two months last year. —Reuters

Water harvesting has added benefit for Kenya

MUKURWEINI: In parts of Kenya along the Tana River, heavy rainfall has long brought inundation, landslides and losses of homes and property.

But last year's heavy rains brought less destruction for an unexpected reason: Drought-hit areas further upstream have improved their water storage capacity, and are now capturing more of what once rushed downstream.

"Water harvesting actually helps reduce the impacts of flooding, saving the communities from unexpected risks," said Hussein Idhoro, drought coordinator for upstream Tharaka Nithi County.

In the catchment of the Tana River, the partially government-funded Upper Tana Natural Resources Management Project has since 2012 given financial and technical support for the construction of rain-water harvesting dams that today hold up to 100 million litres of water.

The project also has established nearly 325 roof-top water harvesting systems at schools and farms within the catchment, said James Maina, a sub-regional manager at the national Water Resources Management Authority.

The Mukurweini Technical Training Institute, for instance, in early 2019 constructed a small reservoir capable of storing 3,000 cubic metres of water for sanitary use and for irrigation of farm plots on its campus. In past years, "we had constant conflicts with our neighbours living downstream as the floodwaters swept their homes and property", said the institution's principal, Patrick Muchemi.

But these days the school's water storage capacity has reduced that problem, and also cut erosion from flowing water on the campus' own land.

Fredrick Wamae, a neighbour of the school, said he now sleeps in peace during heavy downpours, confident the area won't flood. "Most of my fears have now been eroded and every time we experience heavy downpours I get to relax," he said.

The school has almost halved its water costs by using its own harvested water for many purposes, though it still buys drinking water and top-up water from the local utility, Muchemi said.

Solar panels power the harvested water through a piping system, "saving the institution much in terms of cost", the principal said. Farmers in the area also have constructed small reservoirs to catch excess rain and hold it to irrigate crops through drought periods. Terra Mathenge Nderitu, 70, of Nyeri County, even has rigged a system to direct water from his home's roof to a water pan he constructed. —Reuters