NEWS IN BRIEF

PARP inhibitor pick-me-up

PARP inhibitors seemed down for the count in 2011, after Sanofi's iniparib failed in a phase III trial in triple-negative breast cancer and AstraZeneca's olaparib suffered a setback in ovarian cancer. But as drug developers realized that iniparib was not a true PARP inhibitor, and adopted a more cautious clinical trial strategy, the class mounted a comeback. In the past 5 years the FDA has approved four PARP inhibitors, from AstraZeneca, Clovis, GlaxoSmithKline and Pfizer, most notably for ovarian and breast cancers in patients with *BRCA* mutations.

Now, new data suggest that these drugs — which block DNA damage repair, leading to the accumulation of toxic insults in highly mutated cancer cells — might yet have broader applications.

In the phase III PRIMA trial, presented at the ESMO conference in September, GlaxoSmithKline tested its niraparib in platinum-based chemotherapy-responsive patients with newly diagnosed advanced ovarian cancer. In patients with DNA repair homologous-recombination deficiencies, median progression-free survival was 21.9 months on niraparib, versus 10.4 months on placebo. And patients who were homologous-recombination proficient also experienced improvements in progression-free survival, of 8.1 months on niraparib versus 5.4 months on placebo.

These data were published in the *New England Journal of Medicine*. The results from the homologous-recombination-proficient population "support the hypothesis that niraparib has mechanisms of action other than those involved in the repair of DNA damage," the authors note. These could include PARP-regulated gene transcription, ribosome biogenesis and immune activation, they speculate.

Drug development partners AstraZeneca and Merck & Co. also presented results from their phase III PAOLO-1 trial at ESMO, looking at olaparib plus bevacizumab in platinum-based chemotherapy-responsive patients with newly diagnosed advanced ovarian cancer. In homologous-recombination-deficient patients, the median progression-free survival was 37.2 months on the combination versus 17.7 months on bevacizumab alone. In homologous-recombination-proficient patients, there was no statistically significant difference in progression-free survival.

The different response profiles in homologous-recombination-proficient patients could be due to differences in clinical trial design. Or, says GlaxoSmithKline's oncology head Axel Hoos, niraparib might be able to penetrate into the tumour better than do the other PARP inhibitors. Drug developers are now working to expand the use of their PARP inhibitors into other cancers and into broader patient populations, both as monotherapies and as combination treatments.

"Over the past 10 years, the class of PD1-blocking antibodies has of course become very dominant. And that, in part, is one of the reasons why the PARP class has been underappreciated," says Hoos. "Now, people are beginning to realize that there's a lot more to PARP, that these drugs can provide a lot more benefit, and that maybe they will even play well with PD1 blockers."

Asher Mullard


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FDA approves oral version of diabetes biologic

The FDA has approved Novo Nordisk's oral semaglutide, a glucagon-like peptide 1 (GLP1) receptor agonist, for patients with type 2 diabetes.

The FDA first approved an injected formulation of semaglutide, for type 2 diabetes, in 2017. The agency has also approved five other injectable biologic GLP1 receptor agonists, all of which stimulate insulin release, suppress glucagon secretion in response to the ingestion of nutrients, delay gastric emptying and increase satiety.

The GLP1 market is already estimated to be worth around US$7.7 billion. Analysts expect Novo Nordisk's once-daily oral formulation of semaglutide to now capture a significant share of this market. Annual global sales for this formulation could reach $4.1 billion by 2025, show consensus forecasts from the Cortellis database.

The approval highlights the remaining market opportunity for oral versions of parenteral biologic drugs, many of which continue to evade reformulation into pill or capsular forms. According to Coherent Market Insights, the global oral biologics market achieved sales of $830 million in 2018, but could surpass $8 billion by 2026.

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Cancer stem cell candidate Rova-T discontinued

AbbVie has discontinued development of its rovalpituzumab tesirine, following the candidate's phase III failure as a first-line maintenance therapy for advanced small-cell lung cancer.

This discontinuation marks an expected, but nevertheless disappointing, setback for the cancer stem cell field. Rovalpituzumab tesirine is an antibody–drug conjugate against DLL3, a Notch ligand that is thought to be crucial in stem cell differentiation. The drug was developed by researchers at Stemcentrx, who reported in *Science Translational Medicine* in 2015 that the anti-DLL3 antibody component of the therapeutic could take out the cancer stem cell population, and the toxin component of the drug could kill non-stem cells that make up the bulk of a tumour. AbbVie gained access to the drug by acquiring Stemcentrx in 2016 for US$5.8 billion.

Last year, however, Abbvie reported that the drug had failed as a third-line treatment for small-cell lung cancer, casting a dark shadow over the drug's future. While cancer stem cell development has fallen out of favour, some researchers are nevertheless still trying to learn from past mistakes to revise the cancer stem cell model.

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