NEWS IN BRIEF

PARP inhibitors plough on

New clinical data for AstraZeneca's first-in-class poly(ADP-ribose) polymerase (PARP) inhibitor olaparib has raised the bar for a bevy of would-be competitors.

The FDA granted accelerated approval to olaparib in 2014 for fourth-line treatment of *BRCA*-mutated ovarian cancer, but the drug came under pressure last year when Tesaro released phase III results that suggested that its as yet unapproved PARP inhibitor niraparib might offer better efficacy.

AstraZeneca has now reclaimed centre stage, reporting that its drug provided a median progression-free survival (PFS) of 19.1 months in *BRCA*-mutated platinum-sensitive, relapsed ovarian cancer, versus 5.5 months for placebo, in a phase III trial. This is in line with Tesaro's reported 21-month median PFS in *BRCA*-mutated ovarian cancer patients treated with niraparib, compared with 5.5 months in the control arm.

These drugs act by blocking DNA damage repair, which leads to the accumulation of toxic insults in highly mutated cancer cells. Mutations in *BRCA1* and *BRCA2* also compromise DNA damage repair, and so patients with such mutations are more likely to respond to PARP inhibition.

The field almost went off track in 2011 with the late-stage failure of Sanofi's iniparib, but made a roaring comeback with the realization that the failed candidate was not a bona fide PARP inhibitor (*Nat. Rev. Drug Discov.* **12**, 725–727; 2013). The FDA approved a second PARP inhibitor, Clovis Oncology's rucaparib, late last year. Tesaro has filed its drug for approval, and is expecting a regulatory decision by the end of June. Other PARP inhibitors in phase III development include Pfizer's talazoparib and AbbVie's veliparib.

Although AstraZeneca secured the first approval in ovarian cancer, all of these companies are still chasing a first approval in other cancers. Next up is likely to be breast cancer, and so a recent study into the potential utility in this indication could be good news for the entire class. A large team of academic researchers developed an assay to detect *BRCA1*- and *BRCA2*-mutant tumours that might respond best to PARP inhibition. Whereas previous analyses estimated that ~1–5% of breast cancer patients carried these tumours, their analysis using a broader mutational signature approach estimated that up to 22% of breast cancer patients might be good candidates for treatment (*Nat. Med.*, published online March 2017).

A recent review of the field also highlighted other opportunities to expand the scope of this class (*Science* **355**, 1152–1158; 2017). Key priorities include the need to improve the understanding of who to treat, by further dissecting the mechanism by which PARP inhibition kills cancer cells, and to optimize combination therapy. "With the number of ongoing clinical trials, there is optimism that in the short term there will be additional regulatory approvals for [PARP inhibitors] in multiple cancers," the authors write.

Asher Mullard

FDA approves Novartis's CDK4/6 inhibitor

The FDA approved Novartis's ribociclib for the first-line treatment of hormone receptor (HR)$^+$/HER2$^-$ advanced breast cancer in combination with an aromatase inhibitor. This is the second approval for the cyclin-dependent kinase 4 and 6 (CDK4/6) class of kinase inhibitors.

CDKs are crucial regulatory enzymes that control cell cycle transitions and therefore cell proliferation. Although CDK inhibitors have been in development since the 1990s, drug developers struggled with efficacy and toxicity issues until they focused on selective inhibition of CDK4 and CDK6.

Pfizer was first to market, with its 2015 accelerated approval of CDK4/6 inhibitor palbociclib for HR$^+$/HER2$^-$ advanced breast cancer. Novartis now plans to compete in part by offering competitive and flexible pricing options. Analysts forecast global annual sales of up to US$1.7 billion for ribociclib, shows the Clarivate Analytics Cortellis database.

Both ribociclib and palbociclib are breakthrough therapy designees.

Despite blockbuster expectations for palbociclib and ribociclib, the development of many of the remaining CDK inhibitors appears to have stalled. One of the few remaining candidates under active development is Lilly's CDK4/6 inhibitor ademaciclib, which is in phase III trials for breast cancer and non-small-cell lung cancer and phase II trials for pancreatic cancer. Key issues holding up the field include uncertainty over how to define the tumour types that might benefit, how to optimize treatment schedules and how to combine these drugs with other therapeutics (*Nat. Rev. Drug Discov.* **14**, 130–146; 2015).

Ribociclib was discovered as part of a structure-based drug discovery collaboration between Novartis and Astex Pharmaceuticals, a fragment-based drug discovery company that is now a subsidiary of Otsuka Pharmaceutical.

Asher Mullard

TransCelerate makes progress

In 2012, ten biopharmaceutical companies joined forces to launch TransCelerate BioPharma, a non-profit organization aimed at addressing clinical trial inefficiencies (*Nat. Rev. Drug Discov.* **13**, 787–788; 2014). Five years on, with 18 companies now signed up, the precompetitive collaborative group has highlighted key progress to date.

With the Comparator Network, TransCelerate set out to address the high cost of purchasing and distributing commercially marketed products for use as comparators in clinical trials. The Comparator Network has now facilitated the purchase of more than US$120 million worth of comparator products, saving members 10–12% per transaction.

With the Placebo and Standard of Care Initiative, TransCelerate wanted to maximize the value of placebo and standard-of-care data from completed clinical trials. By sharing and pooling these data, they hoped to generate better natural histories of disease that could be incorporated into future clinical trial designs. Preliminary results suggest that these data can reduce study time and reduce the number of patients that need to be enrolled into the placebo or standard-of-care arm of a trial, they report.

TransCelerate and its subsidiary BioCelerate also disclosed their plans for the upcoming year, including the launch of a platform to share toxicology and animal control data.

Asher Mullard