IN brief

PARP inhibitors' revival

Drug developers are mounting a poly(ADP-ribose) polymerase (PARP) inhibitor comeback, and a few are now experimenting with a more comprehensive companion diagnostic to smooth the way. BioMarin, of San Rafael, California, announced in November that it will use Myriad Genetics' novel homologous recombination deficiency (HRD) diagnostic to identify likely responders to its experimental PARP inhibitor BMN 673, currently in phase 3. Clovis Oncology, of Boulder, Colorado, is working on a similar strategy with diagnostic firm Foundation Medicine, of Cambridge, Massachusetts, to develop a PARP inhibitor. "For the pharmaceutical industry, these HRD tests could provide an opportunity to expand the market and license of their drugs," says Jonathan Ledermann, an oncologist at University College London, who has collaborated on PARP inhibitor trials. PARP inhibitors block DNA repair enzymes used by cancer cells to repair themselves. For years PARP inhibitor developers have used *BRCA1* and *BRCA2* assays to identify tumors with dysfunctional DNA repair pathways that are likely to respond to the therapy. BioMarin and four other companies—AstraZeneca of London; Tesaro of Waltham, Massachusetts; AbbVie of North Chicago, Illinois; and Teva of Petach Tikva, Israel—have incorporated Salt Lake City, Utah-based Myriad's older BRACAnalysis test into the clinical development programs of their experimental PARP inhibitors. Myriad's HRD test is a gene-agnostic assay that looks at 50,000 SNPs to look for evidence of genomic disrepair. Early data suggest that the broad HRD approach could capture twice as many responders as a *BRCA*-specific analysis, adds Ledermann.

Asher Mullard

IN their words

"This could only happen because Mandela was a pioneer in using research to transform a country."

Jean Lebel, president of the International Development Research Centre, Canada, speaking of Mandela's promotion of democracy through

supporting research by South Africa's brightest minds. (*SciDevNet*, 19 December 2013)

"We think we are the right one that can address a lot of the limitations that have kept [clinical genetics] from turning into reality before."

George Yancopoulos, CSO of Regeneron in Tarrytown, New York, on his company's program to sequence 100,000 volunteers in collaboration with the Geisinger Health System in Pennsylvania. (*New York Times*, 13 January 2014)

activity in CLL in terms of response rates was comparable, she says, although median duration of response is not yet known. Response rate data so far with ONO-4059 appear to be very strong in CLL, but the phase 1 trial is still ongoing. David Nierengarten and Gregory Wade, analysts at Wedbush Securities, however, believe that drug development in previously treated CLL will be difficult following positive phase 3 data of Imbruvica, and the FDA may require a demonstration of superiority to Imbruvica or establishment of the unmet medical need in Imbruvica-failed patients.

More imminent competition to Imbruvica seems more likely to come from newer, targeted agents in late-stage development, especially in CLL. One class is the PI3 kinase inhibitors, including Gilead's PI3 δ inhibitor idelalisib, which is in phase 3 trials. The Foster City, California-based biotech filed idelalisib with FDA in September for the treatment of refractory indolent non-Hodgkin's lymphoma, and the drug was also awarded a breakthrough therapy designation for CLL in relapsed patients. Another rival compound is Cambridge, Massachusetts-based Infinity Pharmaceuticals' IPI-145, a PI3K δ and PI3K-gamma inhibitor, also

in phase 3 development in CLL. PI3K δ is equally essential for BCR signal transduction as BTK, and links this pathway to the kinases AKT and mTOR, which govern cancer cell metabolism and survival. Doctors view the class as having promising activity in CLL, although some say that side effects, which include colitis, may be less benign than Imbruvica's. Another class of targeted agents are the BCL-2 inhibitors, BCL-2 being an anti-apoptotic protein that is commonly overexpressed in CLL and MCL. North Chicago, Illinois-based AbbVie partnered with Basel-based Roche, has recently entered phase 3 development in CLL with ABT-199/GDC-0199. Activity again has been strong, but a troubling side-effect has been tumor lysis syndrome in some patients.

It is also possible that eventually these drugs will be combined with BTK inhibitors, given that the combinations may more effectively prevent drug resistance from developing. In some diseases like CLL, where chemotherapy is not curative, combinations of targeted agents may one day replace it. "Treatment of CLL will move from chemotherapy to targeted, kinase-directed therapy, and Imbruvica will be a big part of this," predicts Byrd.

Malini Guha *Freehold, New Jersey*

Illumina claims \$1,000 genome win

Illumina, of San Diego, California, has laid claim to a coveted prize in DNA sequencing technology: the \$1,000 genome. The economics of the HiSeq X Ten system, which the company unveiled on 14 January and expected to begin shipping in March, only work for population-scale, whole-genome sequencing initiatives, however. Access to the technology requires an initial outlay of \$10 million, as Illumina is only accepting orders for a minimum of ten systems. Its \$1,000-per-genome calculation is based on the use of ten systems over four years, which represents the equivalent of over 72,000 genomes—or about \$82 million in total capital and running costs. The new system offers a tenfold performance improvement over the company's current high-end HiSeq 2500 systems, which can sequence 600 gigabases (Gb) in ten days. A single run, which costs \$12,750, yields 16 Gb of data. An array of ten HiSeq X sequencers can sequence 1.8 terabases (1,800 Gb) in three days. The performance improvement, says Joel Fellis, senior manager in product marketing at Illumina, is due to an increase in data output—"The big driver there is a new type of sequencing flow cell," he says—and to a faster run time, which he attributes to a redesigned optical system and to faster oligonucleotide incorporation into Illumina's core sequencing-by-synthesis process.

Newscom.com/Alex Wong/Getty Images

The Archon Genomics X Prize which had a goal of \$1000 a genome, was cancelled last year due to a lack of interest from entrants in meeting the competition's accuracy goal of one error per million DNA bases.

Cormac Sheridan