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ASCO 2019: POLO trial brings PARP to pancreas

By Anette Breindl,
Senior Science Editor

CHICAGO – Results from the phase III POLO trial presented at the 2019 American Society of Clinical Oncology's (ASCO's) 2019 annual meeting on Sunday showed that treatment with Lynparza (olaparib, Astrazeneca plc/Merck & Co Inc.) after platinum chemotherapy nearly doubled the progression-free interval (progression-free survival, PFS) in a group of 154 metastatic pancreatic cancer patients with germline BRCA mutations, from 3.8 to 7.4 months.

Also roughly doubled was the proportion of patients who had not progressed after two years, from 9.6% to 22.1%.

Overall survival (OS), remarkably, is not yet mature. It does not differ between the two groups at this point, though in a *New England Journal of Medicine* paper published concurrently with the ASCO presentation, the authors noted that OS "may be confounded by subsequent therapies," since 15% of patients who progressed in the placebo arm went on to receive PARP inhibitors.

Study lead and University of Chicago professor of medicine Hedy Kindler, who presented the data at a press conference Sunday, called the results "truly remarkable for metastatic pancreatic cancer" and said the study "should lead to a new standard of care" for metastatic pancreatic cancer patients with BRCA mutations.

The results, Olivier Nataf told *BioWorld*, bring new options to a patient group that has "an incredible need… When you look at the overall survival curves, it's abysmal." Nataf is vice president, U.S. oncology, at Astrazeneca plc.

With the POLO trial, pancreatic cancer joins the list of tumor types where BRCA mutations confer sensitivity to PARP inhibitors. In a press release, Astrazeneca stated that it plans to "discuss these results with global health authorities as soon as possible."

Myriad Genetics Inc. announced that it has developed a companion diagnostic test, BRACAnalysis CDx, for identifying pancreatic cancer patients with BRCA1 and BRCA2 mutations.

The same sensitivity has been demonstrated in patients with breast, ovarian and prostate cancers. How broadly PARP inhibition might be useful in different anatomical sites remains to be fully explored. Nataf said that "we have tested the activity in many types of tumors" and also have seen signs of activity in several other tumor types, including gastric, colorectal and non-small-cell lung tumors.

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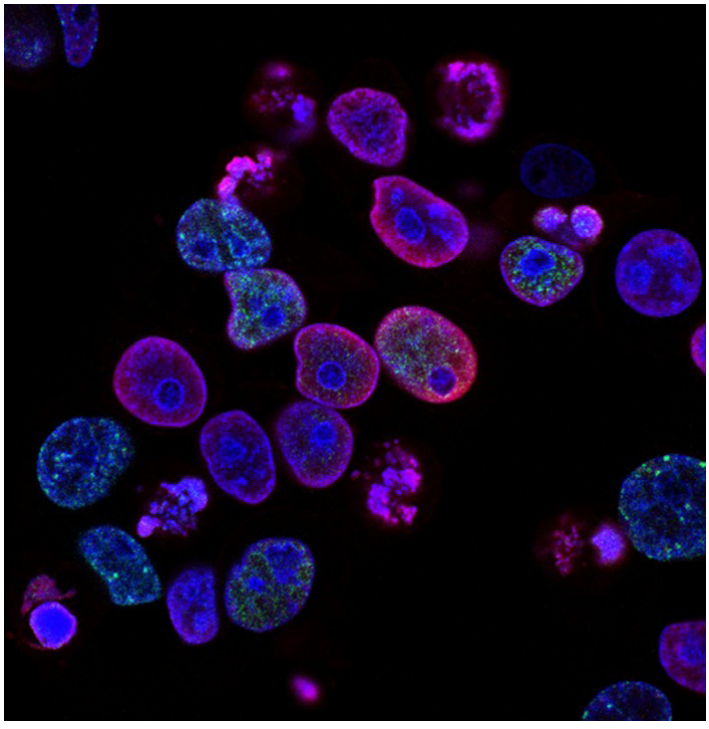
Left: Hedy Kindler, FASCO, presenting POLO trial data (LBA4) at ASCO. Credit: © ASCO/Luke Franke 2019



Below: Human colorectal cancer cells treated with a topoisomerase inhibitor and an inhibitor of the protein kinase ATR (ataxia telangiectasia and Rad3 related). Cell nuclei are stained blue; the chromosomal protein histone gamma-H2AX marks DNA damage in red and foci of DNA replication in green. Credit: Yves Pommier & Rozenn Josse, NCI Center for Cancer Research

Continued from previous page

Beyond POLO, several hundred posters and oral sessions at the ASCO meeting are attesting to the fact that PARP inhibition, with four approved agents and at least 10 more in clinical trials, has become a major success story of targeted therapy.

Many of those presentations were about combination treatments, and at a Friday education session, Timothy Yap, of the MD Anderson Cancer Center, gave a broad overview of combinatorial categories for the class, as well as predictions for how those categories are likely to shift in the next few years.

One combination that has yielded an unexpected amount of benefit is the combination of PARP inhibitors and VEGF inhibitors. In a combination trial of experimental VEGF blocker cediranib (Astrazeneca plc) and Lynparza, the combination significantly improved PFS compared to Lynparza alone. Surprisingly, that benefit appeared to be driven by a benefit for patients without BRCA mutations – a subgroup that also showed a significant benefit in overall survival in the most recent interim analysis, which was published in February.

'Chemical BRCAness'

In a paper published in the May 15, 2019, issue of *Science Translational Medicine*, researchers from Yale University reported that cediranib suppressed the expression of BRCA1 and BRCA2 as well as another DNA repair gene, RAD51. That suppression occurred partly as a result of the hypoxia induced by angiogenesis inhibition, but also because the drug directly affected the signaling of platelet-derived growth factor (PDGFR).

In doing so, cediranib induced a form of what has been termed "chemical BRCAness" – depriving cells of working BRCA. Furthermore, the researchers showed that this effect occurred in tumor cells but not in bone marrow cells, avoiding the synergistic myeloid toxicity that has been an issue for DDR targeting. The results suggest that at least in some cases, synthetic lethality could be used even against tumor types that lack a BRCA mutation.

Another class of combination trials where Yap predicted growth was combination trials with checkpoint inhibitors. Five phase III trials combining PARP and PD-1/PD-L1 inhibition are currently ongoing.

Yap dryly noted that this is in part because combination trials with Keytruda (pembrolizumab, Merck & Co. Inc.) and its ilk have become "the chili of oncology – everyone thinks chili makes everything hotter."

But there are also reasons to think that damaging DNA repair, which increases the mutational load of tumors, could make them more sensitive to immune-oncology approaches, and that such immune stimulation may be behind some of the long-term responses seen in the SOLO-1 trial data presented at the European Society of Medical Oncology last fall. (See *BioWorld*, Oct. 23, 2018.) ♦

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On the EVe of big change in urothelial, Seagen ADC nets response rate of 44%

By Randy Osborne, Staff Writer

CHICAGO – Seattle Genetics Inc. (Seagen) and Tokyo-based partner Astellas Pharma Inc. saw their antibody-drug conjugate (ADC) enfortumab vedotin (EV) highlighted at the American Society of Clinical Oncology (ASCO) annual meeting by way of the abstract for data from a single-arm phase II trial in 125 patients with locally advanced or metastatic urothelial cancer.

The Nectin-4-targeting ADC, which takes on a protein found in 97% of urothelial tumors, produced responses in 44% of patients with locally advanced or metastatic disease. Subjects had previously been treated with platinum-based chemotherapy and a PD-1 or PD-L1 immune checkpoint inhibitor, but the cancer had progressed anyway.

Made of an anti-Nectin-4 monoclonal antibody attached to the microtubule-disrupting agent monomethyl auristatin E using Seagen's linker technology, the ADC resulted in either no growth or shrinkage in patients' tumors, and 12% turned up a complete response with no detectable sign of cancer. The median overall survival time was 11.7 months. Among those patients with cancer who had not responded to a checkpoint inhibitor, 41% got better with EV, and 38% of people with cancer that had metastasized to the liver responded to the drug. EV was well-tolerated, with the most common side effects including fatigue (50%), alopecia (49%), rash (48%), and decreased appetite (44%).

In group one of the study, 70% of enrollees were male and the median age was 69; 35% of people had cancers in their upper urinary tract, a relatively uncommon site; and enrollees had a median of three prior systemic treatments but had not received treatment for at least two weeks prior to enrolling. The results "confirmed our observations in the phase I trial," said lead study author Daniel Petrylak during an ASCO session. "We feel that both of these trials support the submission to the FDA for accelerated approval." As for the side effects, "all of these were pretty much reversible," said Petrylak, a professor of medicine in oncology and urology at Yale Cancer Center in New Haven, Conn.

Urothelial cancer includes cancer of the bladder (90% of cases), the urethra, ureters, renal pelvis, and other adjacent organs. Cases occur more frequently in men in the U.S., and this year an estimated 80,470 new cases of bladder cancer (61,700 men and 18,770 women) will arise, causing 17,670 deaths (12,870 men and 4,800 women).

After diagnosis, patients are usually treated first with platinum chemo. Second-line efforts involve a checkpoint inhibitor, but the disease still advances in 75% to 80% of patients. After that, nothing is left – until now. ASCO expert Robert Dreicer welcomed the data with EV, noting the low response rate with checkpoint drugs. Recently approved erdafitinib (Balversa, Johnson & Johnson) is meant only with tumors bearing susceptible FGFR3 or FGFR2 genetic alterations. The drug is "useful, however it only impacts about one out of five patients," he said. "I would support accelerated approval. I hope the FDA shares that [view]." (See *BioWorld*, April 15, 2019.)

Discovered in the past five years or so, Nectin-4 is found mostly in cancer cells and not in normal ones, Petrylak said, and EV is under investigation for a handful of other tumor types. Meanwhile, along with the phase III study to confirm the latest findings, a second group is enrolling in the trial that created the ASCO buzz. There's also an experiment in progress to measure the benefits of providing EV for people newly diagnosed with advanced urothelial disease, specifically studying EV in combination with pembrolizumab (Keytruda, Merck & Co. Inc.) and when paired with platinum chemo.

Seagen, of Bothell, Wash., also disclosed at ASCO more analyses of results from the phase III trials called Echelon-1 and Echelon-2 with the CD30-directed ADC Adcetris (brentuximab vedotin). The former consisted of a three-year update of the test evaluating Adcetris in combination with AVD (adriamycin, vinblastine and dacarbazine) compared to ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) in stage III or IV frontline classical Hodgkin lymphoma patients, including analyses by cycle 2 positron emission tomography status and in patients less than 60 years old. Two poster presentations evaluated CD30 expression and response to Adcetris treatment in Echelon-2, which took aim at peripheral T-cell lymphomas, and an analysis of five more trials in T-cell and B-cell non-Hodgkin lymphomas. ♦

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Lung story short: Merck's Keytruda guts, glory story offers hope on two fronts

By Randy Osborne, Staff Writer

CHICAGO – Merck & Co. Inc.'s Keytruda (pembrolizumab) gained still more laurels at the American Society of Clinical Oncology (ASCO) meeting, where attendees learned of two victorious experiments with the anti-PD-1 immunotherapy.

Gaining the most air time for Kenilworth, N.J.-based Merck with Keytruda was the win achieved in five-year data from the phase Ib Keynote-001 trial, an experiment that showed the drug was safe, effective and substantially increased overall survival (OS) for advanced non-small cell lung cancer (NSCLC). In the findings, 23.2% of people who had not previously been treated with chemotherapy and 15.5% of previously-treated patients were alive after five years, with the greatest benefit observed in patients with higher PD-L1 expression.

In times before immunotherapies took center stage, five-year survival rates averaged 5.5% in the disease. Investigators at ASCO popped the lid off the longest follow-up study to date of people with advance NSCLC treated with Keytruda. When the study began enrollment in 2011, most participants had previously been treated with systemic medicines or targeted therapies. The trial enrolled 550 people with advanced NSCLC – 101 who had not previously received any treatment and 449 who had. All were given 2 mg/kg of their body weight of Keytruda every 3 weeks or 10 mg/kg every two or three weeks. In recent years, investigators changed the protocol to a single dose of 200 mg regardless of body weight every 3 weeks, the typical regimen in clinical practice.

Patients were followed for a median of 60.6 months, or about five years. At that point, 18% of enrollees (100 participants) were still alive. Of those who had not received prior treatment, 23% were still alive after five years compared with 15.5% of those who did; higher levels of PD-L1 expression predicted longest survival. In previously untreated people, 29.6% with PD-L1 expression of 50% or more were alive after five years compared with 15.7% with expression levels below 50%. In those previously treated, 25% who had PD-L1 expression levels of 50% or more were alive after five years compared with 12.6% with expression levels between 1 to 49%. Only 3.5% of people with expression levels below 1% were alive after five years.

Among patients given Keytruda after undergoing previous treatment, 42% had responses that lasted for a median of 16.8 months. For those who received Keytruda as their initial therapy, 23% had responses that lasted a median of 38.9 months. Immune-related toxic side effects occurred in 17% of enrollees. The most common was hypothyroidism, and the most serious was pneumonitis, an inflation of lung tissue, but that was uncommon.

Next, investigators plan to drill down further, discovering which patients received the most benefit from Keytruda and why, as well as to identify impediments that may prevent the immune system from destroying tumors. Combo therapies marrying Keytruda with conventional or other immunotherapies will be probed.

'Open question' in gastric

Keytruda first gained clearance by the FDA for advanced melanoma in September 2014; the advanced NSCLC label followed in October 2015. In October of the next year, U.S. regulators greenlighted the compound as a first-line treatment for advanced NSCLC tumors that do not have EGFR or ALK gene mutations but that express PD-L1 on 50% or more of their cells. In April of this year, the drug won another expanded approval for front-line treatment of patients with stage III NSCLC who could not have the tumors surgically removed or irradiated, or advanced NSCLC with PD-L1 expression levels over 1% and no EGFR or ALK mutations. (See *BioWorld*, May 25, 2017.)

Although the NSCLC results were loudly trumpeted, Keytruda also turned up efficacy in another challenging tumor type. The phase III study known as Keynote-062 nailed its primary endpoint, showing that for patients with PD-L1-positive, HER2-negative, advanced gastric or gastroesophageal junction (G/GEJ) cancer, initial therapy with the Merck compound resulted in comparable (non-inferior) OS as standard chemo. Keytruda yielded clinically meaningful improvement in OS among patients with tumors that had high levels of PD-L1 expression. At two years, 39% of patients (all of whom had high PD-L1 levels) given Keytruda monotherapy were alive, compared with 22% of those on standard chemo. The trial also evaluated Keytruda when paired with chemo but the regimen did not improve survival relative to chemo alone.

About 27,510 new gastric (stomach) cancers and 11,140 deaths from the disease are expected to occur in the U.S. this year. It's the fifth most frequently diagnosed tumor type worldwide. GEJ, a less common cancer, occurs where the esophagus and stomach meet. Incidence rates have been on the rise during the present decade, especially in Western nations.

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"This is a tough disease to treat," said ASCO chief medical officer Richard Schilsky, a gastrointestinal oncologist for about 30 years at the University of Chicago. "The patients are often older, often frail, and often malnourished." Until recently, chemo was the only option, though there was a "glimmer of hope some years ago when it became clear that about 15% of patients with gastric cancer had amplification of the HER2 gene," and could be treated with chemo and Herceptin (trastuzumab, Roche AG).

Schilsky also addressed the non-inferiority concept with respect to Keynote-062. "In essence, at the beginning of the study, the investigators declared that they were willing to accept the possibility that Keytruda could be at least 20% worse than chemotherapy and still be considered non-inferior," he said. "That's a clinical assessment, not really a statistical assessment. Does [the non-inferiority result] that mean it's better than chemotherapy? No, but it certainly seems to meet the prespecified definition of not being worse and, together with the substantially improved safety profile, I think it would be pretty clear to me that this would be a preferred treatment for this patient population." Keytruda, he said, "should in many cases replace chemo as a first-line treatment," although "it's an open question as to why there was no additive benefit" by combining Keytruda with chemo. ♦

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Hail fellow well Enzamet: Xtandi shines, with J&J's Erleada drawing eyes, too

By Randy Osborne, Staff Writer

An appreciative audience at the American Society of Clinical Oncology (ASCO) heard details of two important prostate cancer trials, including an interim analysis of the international randomized, phase III Enzamet study finding that 80% of men with metastatic hormone-sensitive prostate cancer (mHSPC) were alive after three years when given the non-steroidal anti-androgen (NSAA) drug Xtandi (enzalutamide) from New York-based Pfizer Inc. and Astellas Pharma Inc., of Tokyo, along with standard of care therapy. That number compared with 72% of men who received other NSAAs along with the typical treatment.

Metastatic HSPC typically is treated first with surgical removal of the testes or injection with a hormone analog to reduce the blood levels of androgens. Other treatments can be added, including abiraterone (Zytiga, Johnson & Johnson) or docetaxel chemotherapy. If the cancer doesn't back off, doctors will try more hormone treatments and chemo.

Xtandi won FDA approval in 2012, based on data showing it extended survival in men who had been treated with docetaxel for prostate cancer that grew despite low testosterone. In 2014, it was approved for the same indication in men who had not previously been treated with docetaxel. Now, the Enzamet effort has determined that Xtandi works better on the androgen receptor than bicalutamide, nilutamide, or flutamide, the comparison standard NSAAs used in the trial, though it can also bring side effects that differ from those drugs.

In the study, men with mHSPC were randomly assigned between March 2014 and March 2017 to receive an injection of a testosterone-suppressing medicine such as goserelin, leuprolide, or degarelix with either a 160-mg Xtandi pill daily or one of the three standard NSAAs. Of 1,125 men enrolled, 503 received early doses of docetaxel and 602 did not. Patients were followed for a median of 34 months.

Led by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group, Enzamet showed that, at the three-year mark, of 596 men with a higher amount of disease on imaging scans, 71% taking Xtandi were alive compared with 64% taking another NSAA. Of 529 men with a low amount of disease on imaging scans, 90% on Xtandi were alive compared with 82% taking another NSAA. The increase in survival with Xtandi was most obvious in men who did not receive docetaxel; among patients who received enzalutamide without docetaxel, 83% were alive compared with 70% taking another NSAA. Sixty-four percent of men were still taking Xtandi compared with 36% of men taking another NSAA at the time of the first analysis of the data, said study co-chair Christopher Sweeney, cancer specialist at the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute in Boston. Serious adverse events turned up in 42% of men taking Xtandi vs. 34% of the men taking one of the other NSAAs. No survival benefit emerged with docetaxel in men with a low volume of disease, but Xtandi did boost survival in that segment.

The results from Enzamet are being put together with outcomes from similar experiments so that researchers can accumulate a data set that includes over 10,000 men, an arsenal of info that will enable comparisons between therapies and target them to specific subgroups where upside is the strongest. "The story is yet to be told in full," Sweeney reminded listeners at a briefing session on the interim results.

'All options on table,' including chemo

Other prostate cancer news at ASCO spotlighted Whitehouse Station, N.J.-based Johnson & Johnson's Erleada (apalutamide). Data from the investigational phase III study called Titan proved that adding the androgen receptor inhibitor to androgen deprivation therapy (ADT) compared with placebo plus ADT significantly improved the dual primary endpoints of overall survival (OS) and radiographic progression-free survival in patients with metastatic castration-sensitive prostate cancer (mCSPC). The project included patients with mCSPC regardless of extent of disease or prior docetaxel treatment history. Results were also published online in *The New England Journal of Medicine*.

Specifically, Erleada plus ADT added to OS compared to placebo plus ADT with a 33% reduction in the risk of death (HR=0.67; 95 percent CI, 0.51-0.89; p=0.0053). The drug plus ADT also significantly improved rPFS compared to placebo plus ADT, with a 52% reduction in risk of radiographic progression or death compared to placebo plus ADT (HR=0.48; 95% CI, 0.39-0.60; p<0.0001). The two-year OS rates, after a median follow-up of 22.7 months, were 82% for Erleada plus ADT compared to 74% for placebo plus ADT.

The data formed the basis of a supplemental NDA to the FDA seeking approval of a new indication for Erleada for the treatment of patients with mCSPC, currently under review.

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In February 2018, ahead of its assigned PDUFA date, Erleada became the first therapy cleared by U.S. regulators to treat patients with non-metastatic CRPC, those whose disease has quit responding to medical or surgical treatments that lower testosterone but has yet to spread. The go-ahead, which followed a priority review at the agency, was based on pivotal data showing that the drug decreased the risk of distant metastasis or death by 72 percent vs. placebo while extending median metastasis-free survival by 24.3 months in such patients. (See *BioWorld*, Feb. 15, 2018.)

"Of course one positive study is encouraging, but two large studies demonstrating similar findings is even better," ASCO expert Neeraj Agarwal said. "I have very few patients who are enthusiastic about chemotherapy." But how do patients, with their doctors' help, choose between the two new compounds? Sweeney pointed out that chemo must be "in the mix as well, as much as you could possibly do for patients who are fit" for the regimen and bear a high disease burden. Men might undergo chemo, "be on a treatment break and come back to these hormones," he said.

Otherwise, he predicted a Pepsi vs. Coke style matchup between Xtandi and Erleada, priced similarly. Among afflicted men "there's a bit of chemophobia," he noted. "All options have to be on the table." ♦

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Genomic Dx sweep ASCO as tumor and liquid biopsy redefine cancer treatment parameters

By Stacy Lawrence, Staff Writer

Genomic diagnostic tests that help to guide toward personalized treatment for cancer patients seized the stage at this year's American Society of Clinical Oncology (ASCO) conference in Chicago. Most prominently, a study of more than 10,000 women funded by the NIH's National Cancer Institute that reported results at last year's conference now offered the basis of dramatically revised ASCO guidelines limiting the use of chemotherapy in early stage breast cancer.

Based on the use of the 21-tumor gene expression assay Oncotype Dx Breast Recurrence Score test from Redwood City, Calif.-based Genomic Health Inc., the new guideline for node-negative breast cancer means that most of these women, roughly 70% to 80% of them, will not require chemotherapy alongside hormone therapy after surgery. That's roughly an inversion of prior ratios and redefines the appropriate treatment for a large group of patients.

Chemo-sparing

"The new guidelines for the first time established the TAILORx-defined Oncotype Dx Breast Recurrence Score cutoffs to guide chemotherapy use. The implication of that is that it's going to greatly increase the proportion of women who can be effectively treated with hormone therapy alone, without chemotherapy," Genomic Health founder and chief science officer Steven Shak told *BioWorld*.

"Before Oncotype Dx, when decisions were being made based just on what we knew about tumor size and grade as well as age, probably north of 70% to 80% of patients with node negative, ER-positive breast cancer were being treated with chemotherapy," he continued. "Based on these new TAILORx-defined cutoffs, it's going to completely flip it around to north of 70% to 80% of patients can be treated without chemotherapy. It's an important minority that can only be defined by the recurrence score that actually can have potentially lifesaving treatment with chemotherapy."

The new ASCO guidelines indicate that patients with a Oncotype DX Breast Recurrence Score of 25 or less, up to 80% of women with node-negative early breast cancer, may be spared chemotherapy, while those with a score of 26 to 100 should receive chemotherapy. The test has also been validated in node-positive breast cancer for patients with micromets and up to three positive lymph nodes.

Genomic Health is partnered with Mechelen, Belgium-based Biocartis Group NV to develop the Idylla platform to run an in vitro diagnostic (IVD) version of Oncotype Dx tests, including in breast cancer recurrence. That desktop-based test is slated to be in use at clinical validation sites in France and Germany during the second half of this year. An IVD version is expected to drive adoption of the breast cancer recurrence test globally.

"We're working together to develop a desktop system to perform Oncotype Dx, delivering similar results that we can deliver in our very large laboratory in California," said Shak. "This provides the opportunity, especially important outside the United States, to allow pathology labs to run the essay locally in order to even deliver more timely results to their patients. In some of those countries where local performance of the lab is important. That's going to make a big difference in many countries, including China."

An IVD version will allow hospital labs to conduct these tests on their own, without sending it to a central lab at Genomic Health. The company expects to launch an IVD Oncotype Dx Breast Recurrence Score test around the end of 2020, while an IVD version of its Oncotype Dx Genomic Prostate Score test is slated for 2022.

Genomic Health also markets Oncotype Dx AR-V7 Nucleus Detect to identify metastatic castration-resistant prostate cancer (mCRPC) patients, who are resistant to androgen receptor (AR)-targeted therapies. Oncotype Dx tests have been used in more than 1 million patients in over 90 countries, with the breast cancer test being the primary adoption driver.

Liquid biopsy predictions

Liquid biopsy test providers also rolled out further data to establish their usefulness in guiding cancer treatment. Prenatal testing player Natera supported its efforts to move into cancer with data on its Signatera test that showed it's effective in monitoring patient response to immunotherapy across several metastatic cancer types.

In the 70-patient INSPIRE study, the researchers found that changes to circulating tumor DNA correlated with overall survival, progression-free survival and clinical response rate in these solid tumor patients who were treated with immune checkpoint inhibitor pembrolizumab.

Researchers at The Institute of Cancer Research in London

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also used liquid biopsy as part of a clinical trial for Pfizer's palbociclib and fulvestrant to treat advanced breast cancer in estrogen receptor positive disease. Of the 310 clinical trial subjects, 131 (42%) of them had one of more than three changes to circulating tumor DNA that was associated with early relapse.

Specifically, women whose ctDNA contained changes in gene p53 saw a recurrence after only 3.7 months, as compared to 12.7 months on average for those without p53 changes. In addition, an increased number of FGFR1 gene copies and a high level of tumor DNA also shortened the average time to cancer's return. These changes in ctDNA indicated an average time to relapse of 3.9 months, as compared to 12 months for women without them.

"Exciting new targeted treatments like palbociclib are beginning to have a real impact on survival for women with breast cancer, but unfortunately many tumors which initially respond will later develop resistance and come back," said Nicholas Turner, professor of molecular oncology at the Institute of Cancer Research (ICR) and consultant medical oncologist at The Royal Marsden.

"Our study found that a new genetic test could detect right at the start of treatment those women whose cancers were most likely to develop resistance quickly to palbociclib," he concluded. "We could then adjust their treatment plan accordingly, trialing additional treatments from the outset to try and prevent resistance, or planning for a switch to another treatment as soon as resistance develops. We now need to assess in a clinical trial whether helping direct women's care with this new test can offer improved survival and quality of life." ♦

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Cancer research: Investors remain bullish about its progress

By Peter Winter, BioWorld Insight Editor

The American Society of Clinical Oncology (ASCO) annual meeting, which closed last week, had fewer standout presentations than in previous years but the many hundreds of studies that were described did serve to demonstrate the sheer volume of clinical cancer research that is currently underway.

The price-weighted BioWorld Cancer Index, which comprises 21 biotech companies developing cancer therapies, increased in value a modest 4% during the conference period showing that investors are still bullish about the space. The second part of this feature reports on how the equities of public biopharmaceutical companies that are developing cancer therapies performed during the week of the event.

The BioWorld Cancer Index does not include big pharmaceutical companies such as Bristol-Myers Squibb Co., Pfizer Inc. and Merck & Co. Inc.; rather, the main selection criterion is that a firm's pipeline must consist mainly of candidate cancer therapies that are under development.

By market close Thursday, the index was trading up 12% year-to-date in line with the general markets where the Nasdaq Composite index is up almost 15% and the Dow Jones Industrial Average up over 10% in the same period. (See BioWorld Cancer Index, below.)

Leading gainers

Cambridge, Mass.-based Blueprint Medicines Corp. was the leading gainer in the group with its shares (NASDAQ:BPMC) jumping 19% thanks to a strong showing at ASCO. The precision therapy company focused on genomically-defined cancers, rare diseases and cancer immunotherapy, reported updated data from an ongoing registration-enabling ARROW trial of BLU-667 in patients with RET (rearranged during transfection)-altered cancers. The data show durable clinical activity in patients with RET-altered non-small-cell lung cancer (NSCLC), medullary thyroid cancer (MTC) and other cancers. BLU-667 is a potent and highly selective oral inhibitor of RET fusions and mutations, including predicted resistance mutations.

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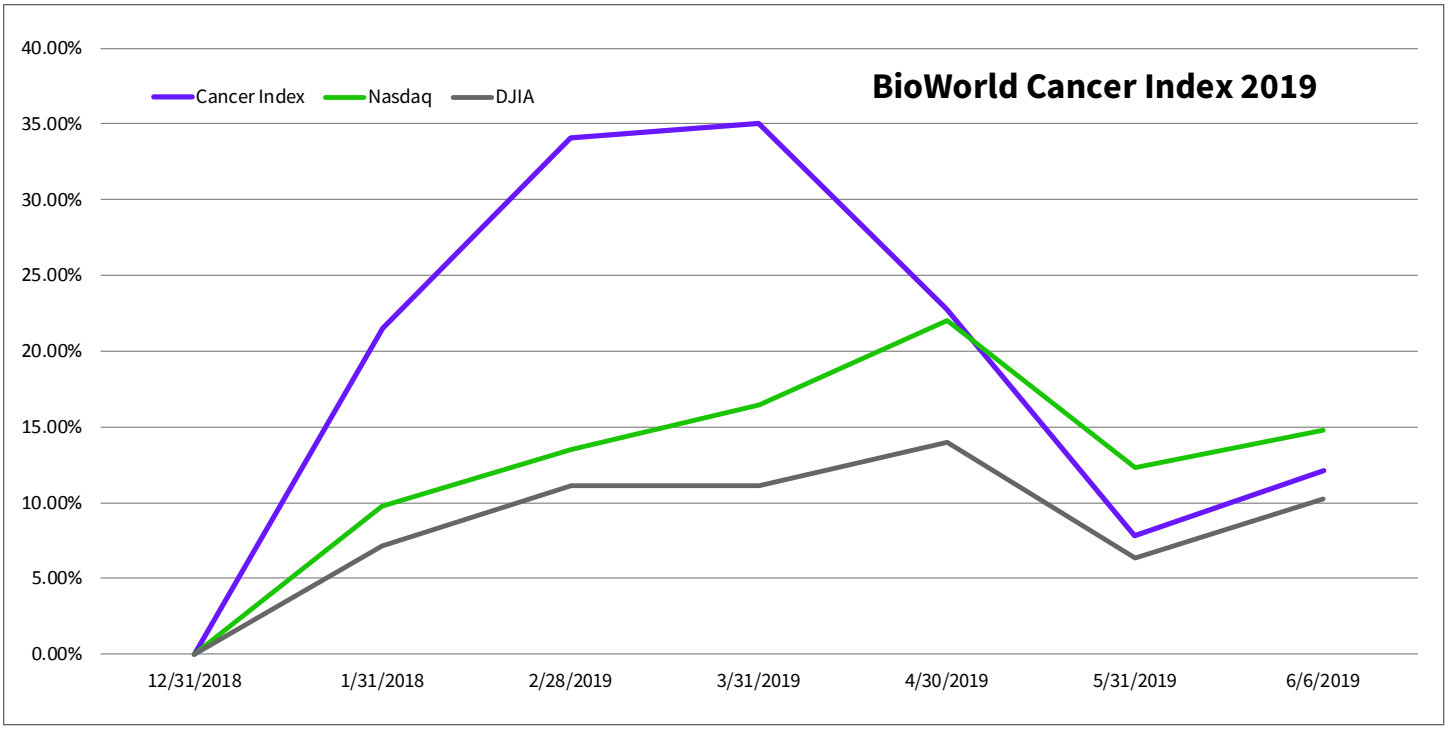

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The new results, the company said, support their plans to submit an initial new drug application (NDA) to the FDA for BLU-667 for the treatment of patients with RET-fusion NSCLC previously treated with platinum-based chemotherapy in the first quarter of 2020, and an NDA for the treatment of patients with RET-mutant MTC previously treated with an approved multi-kinase inhibitor (MKI) in the first half of next year.

"Importantly, the company indicated that BLU-667 is active in patients failing LOXO-292, with a 50% response rate (2/4 partial responses)," noted SVB Leerink analyst Andrew Berens. "This finding is important because it expands the overall opportunity for both drugs, and also lessens the urgency that BLU-667 needs to be superior to LOXO-292 to have a meaningful market presence."

The presented data included 120 patients with RET-fusion NSCLC, 64 patients with RET-mutant MTC and 12 patients with other RET-altered cancers (nine papillary thyroid cancer [PTC], two pancreatic cancer and one intrahepatic bile duct carcinoma) enrolled in the ARROW trial as of a data cutoff date of April 28, 2019. The patients with RET-fusion NSCLC and RET-mutant MTC received a starting dose of 400 mg once daily (QD), which is the recommended phase 2 dose (RP2D). Patients with other RET-altered cancers were included regardless of starting dose.

At the meeting, the company also reported data demonstrating clinical activity and favorable tolerability from the registration-enabling NAVIGATOR trial of avapritinib in patients with PDGFRA Exon 18 mutant gastrointestinal stromal tumors (GIST) and fourth-line GIST. Data from the program showed that patients with PDGFRA Exon 18 mutant GIST achieved an objective response rate (ORR) of 86% while the median duration of response (DOR) was not reached. Meanwhile, patients with fourth-line GIST had an ORR of 22% while the median DOR was 10.2 months.

The company said it plans to submit an NDA for avapritinib later this month and subsequently, file a regulatory application in Europe during third-quarter.

TG Therapeutics Inc. also saw it shares climb (NASDAQ:TGTX) 12%. It presented positive interim data from an ongoing single-arm marginal zone lymphoma (MZL) cohort of its phase IIb UNITY-NHL trial currently evaluating umbralisib as a single agent in patients with relapsed/refractory MZL. Umbralisib is an oral, once-daily PI3K delta inhibitor currently under development for the treatment of non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia.

The MZL cohort of UNITY-NHL enrolled patients with relapsed or refractory MZL who had received prior treatment with one or more lines of therapy including at least one anti-CD20 regimen. In August 2018, the trial completed enrollment with 69 treated patients. The interim data included safety and tolerability data on all 69 treated patients (safety population) and efficacy data on 42 patients who were enrolled at least 9 cycles (28-days) prior to the data cutoff date. It was found that the ORR was 52% (n=42), with complete response (CR) rate of 19%, by central independent review committee (IRC).

Disappointing results

Rockville, Md.-based Macrogenics Inc. saw its shares (NASDAQ:MGNX), swoon 20%. At ASCO the company reported the results from the phase III SOPHIA study of margetuximab in patients with HER2-positive metastatic breast cancer who had previously been treated with anti-HER2-targeted therapies.

The study met its first sequential primary endpoint of progression-free survival (PFS). The median PFS of patients treated with margetuximab and chemotherapy was 5.8 months compared to 4.9 months in patients treated with trastuzumab and chemotherapy (hazard ratio [HR]=0.76; 95% CI: 0.59-0.98; p=0.033). Among the approximately 85% of patients carrying the CD16A 158F allele, a pre-specified exploratory subpopulation in the study, PFS was prolonged by 1.8 months in the margetuximab arm compared to the trastuzumab arm (6.9 months versus 5.1 months; HR=0.68; 95% CI: 0.52-0.90; p=0.005). The ORR, a secondary outcome measure in the SOPHIA study, was 22% in the margetuximab arm (95% CI: 17.3-27.7%) compared to 16% in the trastuzumab arm (95% CI: 11.8-21.0%).

Jonathan Chang, an analyst at SVB Leerink said that, "We believe the stock reaction reflected disappointment in the OS data although the data are not yet mature. Management expressed confidence in achieving a survival benefit as the data mature despite the modest PFS benefit based on the immune-based mechanism of margetuximab." ♦