TRENDS-in-MEDICINE

BULLETIN:

EORTC-NCI-AACR SYMPOSIUM ON MOLECULAR TARGETS AND CANCER THERAPEUTICS

November 30, 2016
by Lynne Peterson

In a teleconference with reporters, European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI), and American Association for Cancer Research (AACR) officials, speaking from the Molecular Targets and Cancer Therapeutics meeting in Munich, issued a joint statement on the need for improved partnerships and funding for cancer research, offered some thoughts on oncology drug development, and highlighted a few abstracts being presented at the meeting (November 29 - December 2, 2016). Both drugs that got a mention target the same cancers, and liquid biopsies were described as transformative technology but not yet ready for prime time.

Trial design changes

Denis Lacombe, MD, director general of EORTC, called for a change in the way oncology trials are conducted, away from the traditional "silo" approach to a patient-centered approach.

Dr. Lacombe said the field is facing challenges, "We are seeing in oncology a number of innovations, but this doesn't go without some challenges…We are in an era of molecular biology and immunotherapy…But there are some challenges like high priced drugs and economic constraints…Today we see a number of new drugs…sometimes we don't know how to combine them, how long to give them, and what may be the best patient population…The fact that industry works in silos doesn't make it [easy] to understand this."

He described the solution EORTC is proposing: "Instead of writing protocols to try to identify optimal patients suitable [for a trial]…I think we should completely invert the process and put the patient in the center…so, that instead of writing a protocol for a drug that is seeking patients to match [the protocol]…I think we should put patients in the center, with maximum information on the patient, and then match the protocols to the patient. This requires re-engineering clinical research pathways…different types of partnerships, and different types of collaboration with industry."

Dr. Lacombe said EORTC has been discussing this approach at a high level with regulators, with the European Commission, and with the pharmaceutical industry, "There is an active dialog on how new partnerships could reposition the patient…looking at our infrastructure and having prospective platforms to follow patients longitudinally, with data annotated and curated."

U.S. funding

Margaret Foti, MD, PhD, the CEO of AACR, expressed hope that National Institutes of Health (NIH) funding will not be either stagnant or cut under President Trump. She noted that there currently is "uncertainty about cancer research funding" in the U.S. Among her comments were:

- "We really need to advocate for more funding for cancer research."

- Extending the continuing resolution from December 9, 2016, to March 31, 2017, would freeze NIH and NCI budgets, and she said this "would be devastating."
- "We hope for passage of 21st Century Cures bill…which, if passed, will give $1.8 billion over 5 years for the Cancer Moonshot.
- "Now is the time for policymakers and the public to prioritize and invest in lifesaving cancer research."

Asked about the possible effect of a repeal of the Affordable Care Act, Dr. Foti said, "We are concerned about just about everything on the table for discussion and repeal…and what could be considered a regressive approach to biomedical research."

George Demetri, MD, director of the Center for Sarcoma and Bone Oncology and senior vice president for Experimental Therapeutics at Dana-Farber Cancer Institute – and an AACR board member – added, "Citizens of the U.S. are concerned that we have a plan to cover the health of our citizens…I am an optimist…I think it is promising that Dr. Price [Rep. Tom Price, R-GA, an orthopedic surgeon] was nominated to head the Department of Health and Human Services…and he has always put forward at least some other plans [in lieu of Obamacare]."

Asked how innovation is suboptimal in Europe, where there are ~600 drugs in late-stage development:

- Dr. Lacombe said, "It is not innovation but access to innovation, optimal innovation [that is the issue]…We are still developing drugs in the traditional way. At this point in time, we do not have optimal infrastructure for patient access to treatment and research."
- Jean-Charles Soria, MD, PhD, chair of the meeting's executive science committee, a medical oncologist from Institut Gustave Roussy in Paris, and editor-in-chief of the ***Annals of Oncology***, said, "One of the concerns of EORTC is that the price that is paid by countries for innovative drugs is inversely related to the wealth of the country. The stronger the country, the stronger the negotiating, and the lower the price…The U.K., France, and Germany get good prices…while Bosnia, Romania, etc., pay much higher prices…That is an area of concern…We have EMA [the European Medicines Agency] for approvals but no central mechanism for negotiation of price, which is an area of concern."

Asked about the affordability of 803 trials of immunotherapy combinations, an expert said, "That is the reason for the need for a different approach. We can't do all those trials. We need to find different models." Dr. Demetri added, "Every patient we see these days asks for an immunotherapy trial…This is No. 1 on the hit list that people are asking for…803 sounds massive, but there are literally millions of patients around the globe with cancer…Our community could do better with pharma in a rational way that is more efficient."

HIGHLIGHTED STUDIES

BLUEPRINT MEDICINES' BLU-285

Researchers are reporting on the first 36 patients from an ongoing Phase I study in gastrointestinal stromal tumors (GISTs) with mutations in either KIT or PDGFR in patients who had failed at least 2 prior TKIs. The principal investigator, Michael Heinrich, MD, a hematologist from Oregon Health and Science University, said:

- BLU-285 has shown remarkable anti-tumor activity, with a response seen at the lowest dose level.
- CT and MRI scans showed that tumors shrank in 14 of 15 evaluable PDGFR patients and 5 of 13 evaluable KIT patients.
- There was a >10-fold reduction in levels of PDGFR-mutated DNA circulating in the blood. This was seen as early as 2 weeks, even before the imaging scans confirmed that tumors were shrinking.
- The treatment has been well tolerated so far, and 27 patients continue to be treated, with 9 discontinuing for progression.

Dr. Soria commented, "What I find very interesting is this is a first-in-class drug against very specific mutations that drive GIST…Clinical efficacy was seen at very low doses. This clinical efficacy is very impressive, even in extremely heavily pre-treated patients. There was also a reduction in circulating DNA that can be seen at 2 weeks."

Kapil Dhingra, MBBS, MD, PhD, a member of the meeting's executive committee – former head of oncology drug development at Roche, and now a pharmaceutical consultant with KAPital Consulting – said, "The data from this study to date show that GISTs with

PDGFR and KIT mutations, including activation loop mutations, are sensitive to BLU-285, a potent and highly selective tyrosine kinase inhibitor [TKI]. Preliminary clinical efficacy has been seen, even at very low doses, and it is active in patients with advanced disease, many of whom had disease that had progressed on previous treatments. Liquid biopsies showed a large reduction in circulating tumor DNA and within two weeks of starting treatment."

DECIPHERA PHARMACEUTICALS' DCC-2618 in GIST and glioblastoma

Researchers are reporting on the first 25 patients in a Phase I trial in GIST patients with mutations in either KIT or PDGFR and in other advanced cancers. The principal investigator, Filip Janku, MD, PhD, a medical oncologist and researcher in the Department of Investigational Cancer Therapeutics at MD Anderson Cancer Center, reported:

- "While it is early, we observed signs of benefit in the GIST patients treated whose disease had progressed despite multiple previous treatments. Early partial metabolic responses, a sign of reduced tumor metabolic activity, were observed in 14 of the 15 patients evaluated with KIT-mutant GIST.
- "In this study, we also employed a novel next-generation sequencing technology to identify and dynamically track molecular alterations in tumor-derived circulating cell-free DNA [cfDNA] isolated from blood of treated patients in order to understand the molecular basis of response and intrinsic or adaptive resistance to DCC-2618."
- A patient with glioblastoma multiforme (GBM) demonstrated improvements early in treatment, with slow but steady tumor shrinkage, and that patient is continuing to do well at Month 12.

Dr. Soria commented, "This is also a first-in-class drug…even though Phase I dose escalation is ongoing, we see very impressive responses in difficult to treat situations. Here again, liquid biopsies reveal, in near real time, the presence of multiple mutations that reflect tumor heterogeneity even more than an invasive tissue biopsy."

Dr. Dhingra commented, "DCC-2618 is one of the most active compounds I have seen in the Phase I setting in my career…Impressive activity [was] seen in GIST patients and a patient with brain cancer."

Asked if this and the Blueprint drug are competitive, Dr. Heinrich said, "Both treated resistant tumors. Both showed activity. Neither reached MTD [maximum tolerated dose]. Ultimately, they could be used in sequence…or replace other drugs…they have different chemical structures…There likely can be resistance to these drugs as well…but in the future it is likely combinations could be more effective than what we have currently."

Liquid biopsies

A study being presented by researchers from Massachusetts General Hospital successfully identified molecular alterations driving drug resistance in nearly 80% of patients studied (all MGH patients). The liquid biopsies used in this study were mostly the Guardant Health's Guardant360 assay, but some of the liquid biopsies used an academic panel (an IRCC target panel) by Alberto Bardelli, PhD, in Torino, Italy.

The principal investigator, Ryan Corcoran, MD, PhD, Translational Research Director at the Tucker Gosnell Center for Gastrointestinal Cancers at Massachusetts General Hospital Cancer Center, explained, "We employed a systematic 'liquid biopsy' program…by which blood was collected at the time that a patient's disease stopped responding to treatment and the disease started to progress. Circulating tumor DNA was analyzed by next-generation sequencing to identify mutations that emerged during therapy to drive resistance to treatment."

- In 31 patients, this liquid biopsy program identified a molecular alteration driving resistance in nearly 80% of patients, and half of these patients were found to have multiple alterations detectable in the blood.
- In patients in whom biopsies of the tumor had also been taken at the time of progression, liquid biopsy identified additional alterations 62% of the time.
- Systematic liquid biopsy also led to the discovery of several novel mechanisms of resistance, "which can help guide the development of therapeutic strategies to overcome resistance."

Dr. Corcoran added, "Overall, these data show how routine clinical implementation of liquid biopsy at the time of disease progression on targeted therapy can effectively identify important mechanisms of resistance and may offer certain advantages relative to tumor biopsies."

Dr. Soria commented, "This shows clearly how liquid biopsy can change treatment…Mutations are not often detected in tissue biopsies or would require multiple invasive biopsies."

Asked if liquid biopsies are affordable or viable:

- *Dr. Lacombe:* "They are very much affordable…A tumor biopsy is expensive, especially in the U.S. but even in the EU…[They can] just piggyback on blood draws…So, it is a very cost competitive approach."
- *Another expert:* "When we look at the cost of trials which mandate on-treatment biopsies, it is always the most expensive part of the study…We hope liquid biopsies will give us a broader read because one of the things that dogs our current ability to use targeted therapies is we know that when we do a biopsy, it could be different depending on where we biopsy…It should not be more expensive."
- *Dr. Demetri:* "We need to think about what it could replace…Right now, it is expensive, but it will be a commodity…And you have to consider…that it will spare use of wrong therapies."

Asked how liquid biopsies will evolve in clinical practice and how they will be combined with targeted exome sequencing:

- *Lee Helman, MD, a pediatric oncologist and head of the molecular oncology section at NCI:* "You have to be careful with liquid biopsies…One is cell-free, and the other is circulating tumor cells, and they are complementary…cfDNA is clearly making an impact on following the course of disease, early disease, early detection of recurrence that allow earlier intervention…The technology is getting to where you can do single-cell RNA [testing]…but the technology is still evolving."
- *Dr. Demetri:* "We are still seeing the early days…Much of the liquid biopsy world has to be validated, but in 2-5 years a patient might have a blood test, find a pattern in cfDNA, and be given a drug. If it works, you should know in a few weeks from another blood test…Perhaps the impact on practice would be we don't do the next CT scan for 4-6 months…Gene expression is the next level of complexity…That will require some significant pattern recognition research, which companies like Google are investing in heavily…and new players coming in."
- *Another expert said it is more than just eliminating some CT scans:* "Sometimes it is three months before we can see if a disease is progressing on a scan. If we could find that out earlier and save a month or two of treatment that is costly and not helping, that would be big savings…We are not there, but it is where the field could go."
- *Dr. Soria:* "Liquid biopsy is the most transformative thing I've seen in years…This will completely change the rules of engagement…With liquid biopsy, patients might not even need to come see us…We can tell local doctors we are looking for certain types of patients…So, only patients who are positive will need to travel…I am really ready to bet this is the most transformative thing in oncology."