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The University of New Mexico Comprehensive Cancer Center (UNMCCC) is the Official Cancer Center of New Mexico and the only National Cancer Institute (NCI) designated comprehensive cancer center in a 500-mile radius. Our 134 oncology physicians, 122 cancer research scientists, and staff focus on discovering the causes and cures for cancers disproportionately affecting the people of the American Southwest — primarily Hispanic, American Indian, and Non-Hispanic White — with strikingly different patterns of cancer incidence, mortality and disparity. In the past year, our center cared for 12,000 patients; 12 percent participated in therapeutic interventional studies and 35 percent in interventional studies. UNMCCC has outstanding programs in Cancer Control and Cancer Health Disparities; Cancer Genetics, Epigenetics, and Genomics; Cancer Cell and Systems Biology; and Cancer Therapeutics. Our research houses national centers: The Molecular Discovery and High Throughput Target Screening Center (nmmlsc.health.unm.edu), one of six Chemical Biology Consortium Centers of Excellence in The NCI NExT Program; Spatiotemporal Modeling of Cell Signaling (stmc.unm.edu), one of 13 NIH National Centers for Systems Biology; and a NIH Clinical and Translational Sciences Center. We enrich our endeavors by collaborating with Sandia and Los Alamos National Labs and Lovelace Respiratory Research Institute. Benefit from our Shared Resources including biospecimen collection and tissue analysis, genomics, biostatistics, bioinformatics, population science and behavioral interventions, and the conduct of clinical interventions. UNMCCC is the center of our statewide cancer clinical trials and health delivery research network — partly funded by a NCI NCORP Grant — and is an Oncology Research Information Exchange Network (ORIENcancer.org) member. Our center has conducted 60+ statewide community-based cancer education, prevention, screening, and behavioral intervention studies involving more than 10,000 New Mexicans. Visit cancer.unm.edu.

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Seeking experts in fundamental mechanisms of chromatin regulation and epigenetics in cancer model systems and human tissues, with interests in defining epigenetic signatures in model systems and population cohorts in response to environmental carcinogens prevalent in the American Southwest. Search chairs: Alan Tomkinson and Scott Ness
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Artificial intelligence can entrench disparities—here’s what we must do

By Kadija Ferryman
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Heinz Von Foerster, the renowned Austrian-American physicist and cybernetics scholar, declared that “information can be considered as order wrenched from disorder.” Ever-increasing amounts of digital data and new computational tools promise that technological developments such as artificial intelligence (AI) will bring order, clarity, and new solutions in multiple areas—from transportation to criminal justice.
Solutions are clearly needed in healthcare, particularly in the U.S., where high expenditures have not led to corresponding improvements in health outcomes.

Automated AI has been used in medicine since the development of computer-assisted clinical decision support tools in the 1970s, but recent advances in machine learning have produced stunning successes, such as the ability of computer programs to outperform radiologists in cancer diagnosis.2

There is growing excitement for ubiquitous healthcare, where tiny wireless sensors are able to constantly monitor, collect and transmit health data.3 And while IBM’s Watson Health has faced some challenges with implementation, there is continued optimism and investment that combining big data with advanced techniques such as machine learning will lead to improvements in cancer diagnosis and treatment.

As excitement for AI in medicine abounds, there is, at the same time, a bleak picture of health disparities in the U.S., particularly in cancer.

Racial minorities continue to have disproportionately higher incidence and mortality rates for multiple cancers, including breast, kidney, and prostate cancer.4

How can we bring together the excitement for the possibilities of AI in medicine with the sobering reality of stubborn health disparities that remain despite technological advances?

This leads to the question: As big data comes to cancer care, how can we ensure that it is addressing issues of equity, and that these new technologies will not further entrench disparities in cancer?

This is an important question to ask now, because though there is growing work on the need to understand the limits of AI in medicine—as well as its ethical implications—there is very little explicit attention on how AI can impact health disparities.

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We believe this is an important addition to the commentary on AI and health, as it incorporates both the technical and ethical challenges and extends a social justice aspect to include AI’s implications for health equity. We focus on issues of health equity in the U.S., but we hope the ideas presented here can catalyze thinking about health disparities more globally.

Today, AI looms large in both the scientific and public imaginary, and thanks to services like Netflix, many more people understand that AI is not scary science fiction, but it involves algorithms (or recipes in the most basic sense) that use data to carry out any number of actions, such as recommending and predicting entertainment choices.

In medicine, AI experienced its heyday in the 1990s with the development of automated expert systems that provided clinical advice, then a “winter” with limited development, to the latest resurgence in the last eight years with rapid advancements in techniques such as machine learning, which can be deployed on large datasets to categorize data as well as make predictions.5

Machine learning has been used to identify cancers in medical images, changes in drug treatment protocols, and predict a range of clinical outcomes. These technologies can capitalize on the availability of digital health data such as images; electronic medical records; prescription records; medical literature; and health insurance data by analyzing the information faster than humans can, and by potentially bringing these sources of data together to provide material such as previously unknown predictors of disease or adverse drug reactions.6

However, as others have pointed out, AI does have limitations. On the technical side, it is important to understand that AI is powered by data. As we know from “GIGO” (garbage in, garbage out), its applications are only as good as the data that is used to “train” the AI system.7 Incomplete and biased data will lead to incomplete and biased results.

For example, some have argued that IBM’s Watson Health system is prejudiced because it relies on data from a population of U.S.-based doctors at only one institution, and therefore reflects particular preferences rather than only expert information.8

AI models may also be accurate in predicting events, while simultaneously having inflated false negative rates. In addition, even if AI produces accurate predictions, these may seem to be er-
roneous, such as the example of an AI that predicted that patients with asthma had a lower risk of death from pneumonia than those without asthma.9

These technical limitations and possibility of “algorithmic bias” means that it is important to have “humans in the loop” in AI systems, even as they become more and more advanced and accurate. Humans are needed to check the quality of the data as well as interpret and contextualize the results.

Because of the nature of clinical care, AIs in health must have some level of transparency, and not be impenetrable “black boxes” that clinicians cannot access, understand, and explain to their patients.10

On the ethics side, we need to consider that AI in medicine has the potential to shift clinical practice, especially in those fields such as radiology and pathology that focus on categorization.

Legal scholars have also pointed out that AI has the potential to change the doctor-patient relationship, as well as the regulations around malpractice if AI systems become a major factor in making predictions and diagnoses.11

There may have to be a reconceptualization of the domains of clinician responsibility, as well as an assessment of how AIs can impact clinicians’ practices of implementing workarounds to compensate for the limitations of technological systems.12

Despite these important issues, they do not address how the increasing development of AI in medicine can affect the most vulnerable, particularly those already suffering disproportionate disease burdens.

The “GIGO” problem, for example, is troubling for everyone, but particularly concerning for some groups. It has long-been known that clinical trials data do not reflect the diversity of the U.S. population, and thus using these data in AI systems can exacerbate existing biases.

Also, the increasing use of electronic health records in AI systems favors groups who have robust health data profiles, rather than those that have limited healthcare access, discontinuous care, and more spotty and incomplete records.13

We must also pay attention to the embedded biases in health data, especially when it includes subjective assessments such as clinician’s notes. There is ample evidence that bias against demographic groups makes its way into doctor’s notes, and we must be aware of the possibility that these biases could arise due to developments such as natural language processing.

Having humans in the loop may not completely resolve this problem, particularly if the AI system’s results reinforce humans’ existing biases, such as some demographic groups are less compliant with treatment than other groups.

In addition to considering clinician bias, we must also consider that the lack of diversity in the field of AI developers and engineers impacts the systems they design. Apple designed its Health app to be a comprehensive health tracking tool, but did not include menstrual tracking until 2015, which may not be surprising considering the engineering team is predominately male.14

This is a cautionary example, but illustrates how a lack of diversity in technology development teams can lead to not recognizing the needs of specific groups. We must address the potential impacts of algorithmic bias in medicine, as well as pay special attention to how these biases may compound the exclusion and disadvantage already marginalized groups.

In addition to algorithmic bias, the ethical implications of AI in medicine such as possible changes in clinicians’ liability and obligations to explain AI systems may again have higher stakes for those who have limited access to high quality clinical care, limited health literacy, earned mistrust of medical providers, and those individuals who may be exposed to interpersonal and institutional racism and other discrimination in their health care encounters.

In this context, the dangers of ethical implications resulting in negative consequences increase the potential for reinforcing or exacerbating disparate health outcomes.

It is important to plainly state the specific challenges that AI in medicine poses to vulnerable groups, and the potential to dampen the goal of achieving health equity. Recognizing that AI in medicine can have unjust impacts across demographic groups is an important step. The following three principles comprise a framework for thinking about both the exciting possibilities for AI in medicine, as well as the potential impacts on health disparities and health equity:

1. **Prioritize health equity in AI in medicine:** Efforts should explicitly address how the development of the technology can impact health disparities. Efforts such as Google’s partnerships with major U.S. academic medical centers in developing AI health applications are promising, but do not have an explicit equity lens. Health equity should be at the forefront of AI in medicinal projects.

2. **Address algorithmic bias for health equity:** AI tools are only as powerful as the data that feeds them, so biased data will yield flawed tools (GIGO). Data must include minority and marginalized populations.
Even if datasets include adequate demographic diversity, historical biases may remain in the data. For example, a database used for AI could have an adequate amount of data from black participants, but because of historical inequities, these participants may disproportionately have cancer diagnosed at later stages.

Without attention given to the historical conditions that explain this difference, analysis of this data could lead to inaccurate conclusions about the characteristics of cancer in black populations. Stakeholders must be involved in helping to understand how big data tools can be used to empower communities of color, as well as how these same tools can perpetuate historical discrimination.

There must be a more concerted effort to increase the diversity of AI engineers so the tools that are developed do not just reflect the background, interests, and needs of select groups. Biases can make their way into AI health technologies in invisible ways that can have serious consequences for health outcomes, particularly for marginalized groups. The conversation on big data and bias in health is just beginning, and there is an opportunity to intervene before these tools are disseminated on a wide scale.

3. Collect non-biological data, too:
   With big data analysis, we have the opportunity to capture genetic, as well as non-biological, data (such as environmental records) to help us understand how multiple factors cause or prevent cancer and other diseases. Predictive analytics and AI can provide important evidence supporting the view of cancer as a disease borne from the interaction between genes and environment.

Though big data and AI pose exciting possibilities, it will likely not be the “magic bullet.” We must seriously consider not only the impacts of using big data and AI technologies but whether some of these interventions should be developed at all. It may be more effective to invest in low-tech interventions that may not be as slick and attractive as these new technologies, but are just as effective.

This editorial is our call to prioritize health equity in AI in medicine. If we are not intentional about foregrounding equity in AI in medicine (and specifically in the fight against cancer), it is likely that disparities will persist, with advantaged groups receiving the benefits and less-advantaged groups disproportionately absorbing the negative impacts.

We must keep our sights on the staggering health disparities in the U.S., as well as global health disparities between the Global North and Global South countries.

References

Trump pricing plans are pretentious, could impede access, and will not help much

By Patricia Goldsmith
Chief Executive Officer of CancerCare

Oct. 25, we heard more about President Trump’s plan to save health care dollars through a variety of Medicare pilot programs and index pricing.

One of the proposed strategies seeks to lower Medicare Part B drug prices by indexing them to the much lower prices paid by 16 countries (referred to as the International Pricing Index, or IPI). This model would be piloted in randomly selected geographic areas and would be mandatory for providers. Essentially, the price of some Part B drugs, including cancer drugs and biologics, would gradually shift to international prices.

Accompanying the IPI model, a second strategy dismantles the current buy-and-bill system, where providers purchase Part B drugs, add a handling fee, and bill their patients. In its place, private sector vendors who have contracted with the Centers of Medicare and Medicaid Services will procure drugs and distribute them to providers (who will receive a set handling fee).

CMS will then pay these vendors based on the IPI price. The proposal anticipates that these private sector vendors would drive a hard bargain with manufacturers, and compete for providers’ business.

The success of this plan depends on drug companies agreeing to sell their products at lower prices. If they aren’t willing to make these concessions, the private sector vendors may simply choose not to purchase them, resulting in patients being deprived of access to these drugs.

Since Part B coverage extends to whatever is “reasonable and necessary for the diagnosis and treatment of illness and injury,” CMS cannot refuse reimbursement based on a belief that the price for a treatment is too high. That said, however, the legal and administrative actions that could arise from disputes around these issues are mindboggling. More wheel-spinning at CMS helps no one and wastes more resources.

Two additional risks have me quite concerned:
One relates to the chaos and confusion that could arise from the introduction of “private sector vendors” to the drug distribution chain. Jeopardizing cancer patient access to life-saving treatments is simply unacceptable.

A second, longer-term risk is that pharmaceutical manufacturers take significant revenue hits that stifle their commitment to research and innovation. We all depend on drug discovery to drive better therapies and find cures. This is where hope lives.

When all is said and done, the Trump plan represents merely an advance notice of proposed rulemaking. It kicks off a long regulatory process that could last months if not years. Normally, a pre-rule precedes a proposed rule and then becomes a final rule before any changes are implemented, and the government must accept and respond to comments from the public at each stage.

To ivory tower bureaucrats and politicians, spending fewer healthcare resources may seem like the impossible dream. To those of us in the trenches who witness the delivery of healthcare services to patients every day, there are some very simple ways to make a sizable dent in spending and improve the delivery of value. Mostly, this is not about the price of drugs.

Six years ago, ASCO’s expert panel for the Choosing Wisely campaign identified use of chemotherapy in patients for whom no proven benefit existed as one of the most widespread, wasteful, and unnecessary practices in oncology.

Also, consider these studies:

• A recent study published in BMJ found the use of chemotherapy in terminally ill cancer patients in the last months of life to be associated with an increased risk of undergoing CPR, mechanical ventilation or both and of dying in an intensive care unit. BMJ. 2014 Mar 4;348:g1219. doi: 10.1136/bmj.g1219.

• A study in JAMA reported that among family members of older patients with fee-for-service Medicare who died of lung or colorectal cancer, earlier hospice enrollment, avoidance of ICU admissions within 30 days of death, and death occurring outside the hospital were associated with perceptions of better end-of-life care. JAMA. 2016 Jan;19;315(3):284-92. doi: 10.1001/ jama.2015.18604

Despite widespread awareness of this issue among cancer care providers, there continues to be vast overuse of chemotherapy among metastatic patients, driving excessive medical bills and causing physical and emotional distress among patients and families.

What’s the swift and obvious answer?

Have the tough conversations that can uncover patients’ quality of life preferences and priorities. Urge patients and families to tell their providers what really matters during and after cancer treatment—and document these conversations with Advance Directives.

Let’s think about healthcare as a true partnership between patients and providers. Instead of delivering healthcare “to patients,” treatment plans should be determined and provided “with patients.”

I know that I will.
Cornelis Melief receives 2018 ESMO Immuno-Oncology Award

Cornelis Melief received the European Society for Medical Oncology 2018 ESMO Immuno-Oncology Award in recognition of his life’s work in studying the interactions of the immune system with cancer.

The distinction will be officially presented to him at the opening keynote and award lecture of this year’s ESMO Immuno-Oncology Congress in Geneva in December.

“Professor Melief dedicated his career to understanding how the immune system, specifically cytotoxic lymphocytes, interact with cancer, and used this knowledge for the development of new therapeutic cancer vaccine strategies,” said George Coukos, a scientific co-chair of the upcoming congress.

After studying virally induced cancer in mice, he is currently involved in clinical trials with synthetic vaccines for the treatment of head and neck as well as cervical cancer associated with the human papilloma virus.

Melief’s work in developing effective immunotherapy for virus induced tumours recently led to the implementation of clinical trials to bring so-called synthetic long peptide vaccines to cancer patients worldwide.

Melief and his team were able to show the clinical effectiveness of these vaccines in treating patients with pre-malignant lesions caused by HPV type 16. They also demonstrated that in patients with cancer, in whom vaccination could not be used effectively on its own and instead should be employed in combination with other therapies.

Among the most promising results obtained to date, Melief and his team found that a combination of SLP vaccination and standard chemotherapy strengthened cervical cancer patients’ immune response and prolonged their survival.

They further discovered that a similar effect could be achieved among patients with HPV-related head and neck cancer by administering the vaccines in conjunction with immunotherapy in the form of immune system boosting monoclonal antibodies.

Melief will be the second recipient of the ESMO Immuno-Oncology Award, which was created in 2017 in commemoration of European cancer research and treatment pioneer Prof. Georges Mathé, a founding member of ESMO.

Melief is professor emeritus in tumor immunology at the Leiden University Medical Center in the Netherlands, as well as the co-founder and chief scientific officer of ISA Pharmaceuticals.

Roswell Park partners with Jagiellonian University in Kraków

Roswell Park Comprehensive Cancer Center has formed an academic cooperation with the Jagiellonian University in Kraków.

The collaboration will see the two centers exchanging staff, students and scientific resources to undertake basic, translational and clinical research in order to advance the development of cancer therapies.

The agreement grew out of a July 2018 visit by Polish Secretary of State Anna Maria Anders to Roswell Park. Four Roswell Park faculty leaders, joined by Anders, recently traveled to Kraków to initiate the collaboration: Kunle Odunsi, deputy director, chair of gynecologic oncology and executive director of the Center for Immunotherapy; Pawel Kalinski, vice chair for translational research and Rustum Family Professor for Molecular Therapeutics and Translational Research; Agnieszka Witkiewicz, director of the Center for Personalized Medicine and chief for research in the Department of Pathology; and Danuta Kozbor, associate professor of immunology and microbiology.
The agreement is effective immediately, and could see exchange of students and faculty between the two centers as early as spring 2019.

NCCS presents third annual Ellen Stovall Award to Gay Crawford and Norman Coleman

The National Coalition for Cancer Survivorship presented the third annual Ellen L. Stovall Award for Innovation in Patient-Centered Cancer Care to Gay Crawford, founding director of Cancer CAREpoint, and Norman Coleman, senior investigator at NCI.

Since her diagnosis of breast cancer at age 30, Crawford spent the last 44 years playing a leadership role in bringing patient-focused cancer care to the Silicon Valley area. She helped found and lead numerous organizations, including the non-profit organization Cancer CAREpoint, which provides a wide-range of cancer support services in Silicon Valley free of charge.

Coleman is the director of the Radiation Oncology Sciences Program. Coleman leads a laboratory at NCI focusing on radiation-induced molecular and immunotherapy targets.

Named for former NCCS CEO, Ellen Stovall, who died in 2016 due to complications from three cancer treatments, the award seeks to highlight those who continue Ellen’s work of transforming cancer care to further incorporate patients’ goals, needs, and values.

More information about Crawford, Coleman, and the Ellen Stovall Award can be found here.

IU researchers awarded $2.3 million to continue studies on CIPN

Indiana University School of Medicine cancer researchers who have been working to lessen the side effects caused by chemotherapy have been awarded $2.3 million to continue their studies.

Jill Fehrenbacher and Mark Kelley are recipients of the five-year grant (1R01CA231267) from NCI, which will enable them to continue their studies on chemotherapy-induced peripheral neuropathy.

The researchers will test the effectiveness of a small, targeted molecule called APX3330 to prevent or reverse CIPN caused by cancer drugs in tumor-bearing mice.

“For patients with CIPN, this might be an option for pain relief or neuropathic symptom relief in the future,” said Fehrenbacher, associate professor of pharmacology and toxicology at IU School of Medicine and a researcher at the IU Simon Cancer Center. “Alternatively, for patients undergoing chemotherapy treatments, it might be something we can administer alongside the chemotherapy drugs so they never develop CIPN.”

Currently, there are no effective treatments or preventive treatments against neuropathy because researchers don’t yet understand all of the mechanisms that lead to it. It is believed that neuropathy develops over time as a cumulative effect of chemotherapy that alters the function of sensory neurons, which are responsible for detecting pain and touch.

In 2017, Kelley, associate director of basic science research at the IU Simon Cancer Center, was first awarded a $2.9 million grant (1R01CA205166) from NCI to study CIPN. Fehrenbacher is also a co-principal investigator of that initial grant. That grant was awarded because Kelley, Fehrenbacher, and colleagues had previously demonstrated in the lab that increasing the repair activity of a protein called APE1/Ref-1 decreased neurotoxicity.

The aims of the 2017 grant are to study, in detail, the mechanisms by which APE1 alters the function of the sensory neurons. Interestingly, they also found that APX3330 was effective in reducing APE1’s ability to facilitate the growth and spread of tumors in mice models, therefore this new drug has the potential to block the advancement of cancer and CIPN.

APX3330 is currently in phase I trials, supported by Apexian Pharmaceuticals, to test its safety for people. Kelley is a co-founder and chief scientific officer at Apexian, which plans to advance APX3330 for phase II trials for anti-tumor and anti-CIPN studies.

APX3330 was developed based on Kelley’s nearly three decades of cancer research.

NCI awarded both grants as part of its Provocative Questions initiative, a program aimed at promoting cancer-related research on important yet understudied areas or research questions that have proven difficult to address.
UVA researchers awarded $1.8 million to test breast cancer approach

A husband-and-wife team at the University of Virginia Cancer Center have been awarded more than $1.8 million from NCI (R01 CA214594-01A1) for their effort to improve radiation therapy and breast surgery for patient with early-stage breast cancer.

Radiation oncologist Timothy Showalter and breast cancer surgeon Shayna Showalter are leading an interdisciplinary effort to evaluate a technique they have developed at UVA called Precision Breast Intraoperative radiation therapy. Precision Breast IORT seeks to improve on conventional breast IORT by making it more targeted, more powerful, more personalized and potentially more effective.

“The Precision Breast IORT program leverages UVA’s unique CT-on-rails brachytherapy suite to address the technical limitations of other IORT techniques,” said Tim Showalter, co-principal investigator. “This work represents a unique collaboration between surgery and radiation oncology, with important support from the Health System.”

Precision breast IORT adds high-powered imaging to radiation therapy to better direct the radiation, and it effectively doubles the dose patients can receive to the tumor bed when compared with conventional IORT. IORT reduces weeks of radiation treatments into a single dose given at the time of breast-preserving surgery.

The UVA doctors and their colleagues wanted to find ways to better tailor the cancer treatment to each patient, so Precision Breast IORT incorporates advanced CT image guidance to allow doctors to avoid radiation to healthy tissue and to spare the heart, lungs and other organs. The researchers hope the approach will produce improved outcomes in terms of quality of life, the effect on the immune system and the cosmetic appearance of the breast.

The researchers established the safety and feasibility of Precision Breast IORT in a phase I clinical trial. They are now conducting a phase II trial at UVA and Thomas Jefferson University Hospital in Philadelphia to evaluate the overall effectiveness of Precision Breast IORT as well as the effects on the immune system for both IORT and traditional whole-breast irradiation.

With their new, five-year grant, the Showalters plan to evaluate Precision Breast IORT in terms of:

- **Five-year breast cancer recurrence rates.** They hypothesize that those rates may be lower than with conventional IORT.
- **The effect on the immune system.** They want to see if Precision Breast IORT can avoid the immune-dampening effects of radiating the entire breast.
- **How it compares to other treatment options.** They plan to evaluate its effect on the risk of cancer recurrence, its cost effectiveness and other factors, and how those outcomes compare with existing options.

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Precision breast IORT adds high-powered imaging to radiation therapy to better direct the radiation, and it effectively doubles the dose patients can receive to the tumor bed when compared with conventional IORT. IORT reduces weeks of radiation treatments into a single dose given at the time of breast-preserving surgery.

The UVA doctors and their colleagues wanted to find ways to better tailor the cancer treatment to each patient, so Precision Breast IORT incorporates advanced CT image guidance to allow doctors to avoid radiation to healthy tissue and to spare the heart, lungs and other organs. The researchers hope the approach will produce improved outcomes in terms of quality of life, the effect on the immune system and the cosmetic appearance of the breast.

The researchers established the safety and feasibility of Precision Breast IORT in a phase I clinical trial. They are now conducting a phase II trial at UVA and Thomas Jefferson University Hospital in Philadelphia to evaluate the overall effectiveness of Precision Breast IORT as well as the effects on the immune system for both IORT and traditional whole-breast irradiation.

With their new, five-year grant, the Showalters plan to evaluate Precision Breast IORT in terms of:

- **Five-year breast cancer recurrence rates.** They hypothesize that those rates may be lower than with conventional IORT.
- **The effect on the immune system.** They want to see if Precision Breast IORT can avoid the immune-dampening effects of radiating the entire breast.
- **How it compares to other treatment options.** They plan to evaluate its effect on the risk of cancer recurrence, its cost effectiveness and other factors, and how those outcomes compare with existing options.
Deciphering genomic testing options for diverse patient populations in early-stage breast cancer

By Adam Brufsky
Associate chief, Division of Hematology/Oncology; co-director, Comprehensive Breast Cancer Center; associate director, Clinical Investigation
University of Pittsburgh Medical Center

In my twenty-two years of practicing medicine, I have observed the evolution of genomic testing and its increasing utility in oncology.

With the growing interest in precision medicine for breast cancer patients, I have found it important to decipher the differences between the two most clinically validated genomic tests, MammaPrint and Oncotype DX, and their phase III trials, MINDACT and TAILORx, respectively.

To that end, now that some time has passed since the presentation of the TAILORx findings at the American Society for Clinical Oncology Annual Meeting, I’d like to take a step back and discuss what these findings mean for patients and clinicians.

**Trial Basics**

TAILORx is one of two large prospective trials that provides evidence for the clinical utility of genomic testing in women diagnosed with early-stage breast cancer. TAILORx evaluated the Oncotype DX 21-Gene Breast Recurrence Score test in women with early-stage hormone receptor (HR)-positive, HER2-negative, lymph node-negative breast cancer.

The other prospective trial was MINDACT, which evaluated the MammaPrint 70-Gene Risk of Recurrence test in women with early-stage estrogen receptor positive, lymph-node negative breast cancer, but also included a substantial proportion of women with clinically high risk features such as lymph node positivity (48%; LN+ 1-3), higher grade (93%; II or III), and increased tumor size (58%; >2cm).

Both TAILORx and MINDACT have reported positive results supporting the utility of genomic testing in predicting distant disease recurrence for at least five years assisting personalized treatment decisions for patients.
Understanding TAILORx

The TAILORx study examined whether chemotherapy is beneficial in women with early stage HR-positive, HER2-negative, node-negative breast cancer and an Oncotype DX intermediate Recurrence Score (RS) of 11-25. In TAILORx, Oncotype recurrence scores were assigned as low (RS<11), intermediate (RS 11-25) or high risk (RS<25) scores.

Of the 9,719 eligible women enrolled in the trial, 6,711 (69%) scored in the intermediate range of 11-25 and were randomly assigned either chemoendocrine therapy or endocrine therapy alone.

Initial results from TAILORx, reported in 2015, found that women with low RS had excellent outcomes at five years when treated with endocrine therapy alone. However, at that time, the question of whether patients with an intermediate RS could benefit from chemotherapy remained unresolved.

At the 2018 ASCO meeting, TAILORx investigators reported nine-year follow up data to address this question, suggesting that 69 percent of women with an intermediate RS did not significantly benefit from adding chemotherapy to endocrine therapy after surgery.

While the new TAILORx data added to the growing knowledge around the best treatment strategies for women with early-stage breast cancer, there are still some question about the benefits of adding chemotherapy to endocrine therapy in certain groups of women with intermediate Oncotype DX scores.

In particular, women under 50 years of age with a RS 16-25, and those with a RS 21-25, appeared to have some chemotherapy benefit as evidenced by a substantial absolute improvement in the distant recurrence-free interval (6.5% in the case of RS 21-25) at 9 years of follow-up.

Additionally, women with estrogen receptor-positive, lymph node-positive disease were not evaluated in TAILORx (we await the results of the RxPONDER trial for this situation). It should also be noted that algorithms which assess histopathologic factors and immunohistochemical markers in early-stage breast cancer, such as the Magee Score, can be used to accurately estimate Oncotype DX scores and can identify women with lower-risk tumor biology who would not require chemotherapy, similar to a RS<25.

Understanding MINDACT

The MINDACT trial was designed to answer the question of whether tumor genomic profiling of women with estrogen receptor-positive breast cancer could prospectively identify those who are not likely to benefit from chemotherapy in addition to endocrine therapy.

MINDACT enrolled 6,693 women with primarily HR-positive, HER2-negative and lymph node-positive or negative early-stage breast cancer and used the MammaPrint 70-gene assay to determine whether they had a low or high genomic risk of breast cancer recurrence.

Either endocrine therapy or a combination of endocrine and chemotherapy were recommended based on a patient’s genomic or clinical risk, with clinical risk determined by tumor size, grade, and lymph node involvement.

MINDACT found that nearly half of the women who were clinically high risk and likely to be advised to receive chemotherapy based on clinical guidelines were genomically low risk and had no significant benefit from chemotherapy. These women had an excellent five-year distant disease free survival rate in excess of 94 percent without chemotherapy, despite a clinical high-risk assessment.

Findings from MINDACT are important because they suggest that many clinically high-risk patients not examined in TAILORx, such as women with lymph node-positive breast cancer, can avoid unnecessary chemotherapy without negatively affecting their outcome.

Additionally, there is no confusion about benefit to chemo (or lack thereof) in women under 50 in the MINDACT trial who received a Low Risk MammaPrint result. While MINDACT has thus far reported five-year outcomes (compared to nine-year outcomes in TAILORx), MINDACT was designed to follow patients for at least 10 years, so we can expect long-term outcome results in the near future.

What Does this Mean for Patients and Clinicians?

We now have prospective data for breast cancer genomic assays from TAILORx and MINDACT. With a growing number of treatment options for breast cancer patients, these studies highlight the utility of genomic testing for predicting patient outcomes and informing personalized treatment decisions.

The author has been a consultant for Agenda, Genomic Health, Biotheranostics, Myriad, and Bioarray Technologies.

References

Cardiovascular toxicities seen early in treatment with immune checkpoint inhibitors

In the first large-scale analysis of cardiovascular complications linked to immune checkpoint inhibitors, Vanderbilt researchers have shown that cardiovascular complications include myocarditis, pericarditis, vasculitis and arrhythmias, and that they occur early in the course of treatment.

The study, published online Nov. 12 in The Lancet Oncology, augments previous work by Vanderbilt University Medical Center researchers who first reported in 2016 rare but fatal cardiac side effects from the most widely prescribed class of immunotherapies.

The researchers used VigiBase, a global database of drug complications maintained by the World Health Organization, to track adverse cardiovascular reactions in the latest study.

"When the immune system wakes up to attack the cancer cells, in rare situations it can also attack the heart and vessels, and in some cases, this can result in fatalities," said Joe-Elie Salem, a Vanderbilt Cardio-Oncology fellow and the study’s first author.

Fatalities occurred in half of myocarditis cases (inflammation of heart muscle), 21 percent of pericardial cases (inflammation of the sac that surrounds the heart) and 6 percent of vasculitis cases (inflammation of blood vessels).

Fatalities with myocarditis occurred more often with combination therapy (65.6 percent) than monotherapy (44.4 percent). The new Vanderbilt study advises clinicians to monitor for pericardial disease and vasculitis.

Javid Moslehi, director of the Cardio-Oncology Program at VUMC and the study’s senior author, presented the study’s findings Nov. 12 at the American Heart Association Scientific Sessions 2018 in Chicago. The cardiovascular complications can also occur simultaneously with neurological complications, including myasthenia gravis, Moslehi said.

"This study suggests a role for a multi-disciplinary group that will help us characterize these novel and diverse side-effects of immunotherapies and identify those at risk," said Douglas Johnson, director of the melanoma program at Vanderbilt-Ingram Cancer Center and a study author.

Johnson, Moslehi and colleagues are forming an immuno-toxicity group with the hope of utilizing Vanderbilt resources like the REDCap database to track these toxicities. In addition, the group has established a web-based link for physicians nationally to report cases of cardiovascular complications related to immune checkpoint inhibitors, linking these cases to REDCap to collect data on the cases.

Breast screening linked to 60 percent lower risk of breast cancer death in first 10 years

Women who take part in breast screening have a significantly greater benefit from treatments than those who are not screened, according to a study of more than 50,000 women, led in the UK by Queen Mary University of London.

The research, using data from Sweden, finds that women who chose to participate in an organised breast cancer screening programme had a 60 percent lower risk of dying from breast cancer within 10 years after diagnosis, and a 47 percent lower risk of dying from breast cancer within 20 years after diagnosis.

The authors say that this benefit occurs because screening detects cancers at
The paper can be found [here].

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**Fecal transplant effective against immunotherapy-induced colitis**

For the first time, transplanting gut bacteria from healthy donors was used to successfully treat patients suffering from severe colitis caused by treatment with immune checkpoint inhibitors.

The study from MD Anderson Cancer Center, which includes two patients, suggests fecal microbiota transplantation is worth investigating in clinical trials as a therapy for this common side effect of immunotherapy.

The research, led by Yinghong Wang, assistant professor of Gastroenterology, Hepatology & Nutrition and director of Medication Induced Colitis and Enteritis, was published today in Nature Medicine.

"The resolution of colitis in these patients can be confirmed clinically and endoscopically after FMT treatment," said Wang. "Based on these results, this should be evaluated even as a first-line therapy for ICI-associated colitis because it's safe, quick, and the effect is durable - from one treatment."

Immune checkpoint inhibitors, which release a block on the immune system to attack cancer, have been successful in providing durable responses for patients with several cancer types. However, these treatments are often associated with significant immune-related toxicities.

Colitis, inflammation of the colon, is the second most common side effect from ICIs, occurring in up to 40 percent of patients, explained Wang. When ICI-associated colitis is severe, guide-lines require a patient to stop ICI treatment until the colitis is in remission.

"If the patient is a good responder to immunotherapy, that means you've taken their effective treatment away," said Wang. "We have a limited amount of time to fix the problem so they can resume ICI treatment, but I feel that we've made great progress in this area."

The researchers chose to investigate the potential for FMT as an alternative, compassionate-use therapy for patients suffering from refractory, or unresponsive, ICI-associated colitis. The two patients included in the study were treated at MD Anderson between June 2017 and January 2018.

FMT has shown promise in treating other types of gastrointestinal diseases, such as recurrent Clostridium difficile infection and inflammatory bowel disease, which shares many clinical and molecular characteristics with ICI-associated colitis.

These conditions typically are treated with steroids and targeted immunosuppressive agents, which result in additional severe side effects and can counteract the effects of immunotherapy.

Both patients in the study had a complete resolution of their colitis following treatment with FMT. The first patient's colitis resolved within two weeks following a single FMT treatment; the second patient experienced a partial recovery after the first treatment, followed by complete recovery after a second FMT.

With endoscopic evaluation before and after treatment, both patients displayed significant improvements in inflammation and ulcerations, including a reduction of inflammatory immune cells.
Pre- and post-treatment stool analyses revealed patients’ gut microbiomes to be most similar to the donor immediately after treatment, with less resemblance to the donor over time. Still, post-treatment gut bacteria remained distinct from their own pre-treatment microbiome.

Additionally, distinct new populations of bacterial species were evident in these patients following FMT compared to pre-treatment samples, including several species known to be protective or reduce inflammation.

The authors acknowledge significant limitations to this study based on the very small cohort, and they plan to pursue clinical trials to investigate the effectiveness of FMT in treating ICI-associated colitis as compared with standard immunosuppressive therapy. FMT continues to be offered to MD Anderson patients on a compassionate-use basis.

Previous MD Anderson research showed that bacteria in the gut influence patient response to ICI therapy, and other evidence suggests modifying the microbiome in mice can alter their response to immunotherapy.

The current data further suggests there is the potential for many molecular studies to better understand the role of the microbiome in driving ICI-colitis and immunotherapy response more broadly.

The study was supported by the Andrew Sabin Family Fellowship Program; the American Association for Cancer Research – Stand Up to Cancer; the National Institutes of Health (CA219896-01A1, HL124112); the Cancer Prevention & Research Institute of Texas; and the Melanoma Moon Shot, part of MD Anderson’s Moon Shots Program.

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**Biodesix test predicts response to atezolizumab in lung cancer**

Researchers with Biodesix and Genentech presented findings on a test designed to predict response to atezolizumab (Tecentriq) in patients with non-small cell lung cancer.

The blood-based test, which uses expression data from the circulating proteome to classify patients, was found to be predictive for OS and PFS between atezolizumab and docetaxel, the companies said.

Genentech is a member of the Roche Group.

These data suggest a patient’s likelihood of benefiting from PD-L1 checkpoint inhibition can be identified through circulating proteome in blood samples. Researchers presented their findings at the Society for Immunotherapy of Cancer annual meeting in Washington, D.C.

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**Keytruda significantly improved OS compared to chemotherapy in PD-L1 advanced esophageal or esophagogastric junction carcinoma**

Merck announced the phase III KEYNOTE-181 trial investigating Keytruda as monotherapy in the second-line treatment of advanced or metastatic esophageal or esophagogastric junction carcinoma has met a primary endpoint of overall survival in patients whose tumors expressed PD-L1 (Combined Positive Score ≥10).

In this pivotal study, treatment with Keytruda resulted in a statistically significant improvement in OS compared to chemotherapy (paclitaxel, docetaxel, or irinotecan) in patients with CPS ≥10, regardless of histology.

The primary endpoint of OS was also evaluated in patients with squamous cell histology and in the entire intention-to-treat study population. While directionally favorable, statistical significance for OS was not met in these two patient groups.

Per the statistical analysis plan, the key secondary endpoints of progression-free survival and objective response rate were not formally tested, as OS was not reached in the full ITT study population.

The safety profile of Keytruda in this trial was consistent with that observed in previously reported studies. Results will be presented at an upcoming medical meeting and will be submitted to regulatory authorities worldwide.

KEYNOTE-181 is a randomized, open-label, phase III trial (ClinicalTrials.gov, NCT02564263) investigating Keytruda monotherapy compared to chemotherapy in patients with advanced or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or Siewert type I adenocarcinoma of the esophagogastric junction that has progressed after first-line standard therapy.

The primary endpoint was OS (evaluated in all patients as well as in patients with PD-L1 CPS ≥10 and in patients with squamous cell carcinoma). Secondary endpoints were PFS, ORR and safety/tolerability.

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The primary endpoint was OS (evaluated in all patients as well as in patients with PD-L1 CPS ≥10 and in patients with squamous cell carcinoma). Secondary endpoints were PFS, ORR and safety/tolerability.
The study enrolled more than 600 patients who were randomized 1:1 to receive either Keytruda (200 mg fixed dose every three weeks) or investigator’s choice of any of the following chemotherapy regimens, all given intravenously: docetaxel (75 mg/m² on Day 1 of each 21-day cycle), paclitaxel (80-100 mg/m² on Days 1, 8, and 15 of each 28-day cycle), or irinotecan (80 mg/m² on Day 1 of each 14-day cycle).

Retacrit is Pfizer’s third available biosimilar in the U.S. Pfizer also has an extensive biosimilars pipeline, including three biosimilars products currently accepted for review by the FDA. Pfizer has entered into an agreement with Vifor Pharma Inc. for the commercialization of Retacrit in certain channels.

Pfizer introduces biosimilar Retacrit injection in the U.S. at a substantial discount

Pfizer Inc. announced the introduction of Retacrit (epoetin alfa-epbx) injection, the first available biosimilar to Procrit (epoetin alfa) and Epogen (epoetin alfa) in the U.S. at a substantial discount.

Pfizer began shipment of Retacrit to wholesalers in the U.S. on Nov. 12.

Retacrit will be introduced at a Wholesale Acquisition Cost of $11.03 per 1,000 units/mL, which is 57.1 percent below the WAC of Procrit (epoetin alfa) [$25.72 per 1,000 units/mL] and 33.5 percent below the WAC of Epogen (epoetin alfa) [$16.58 per 1,000 units/mL], its reference product.

WAC is not inclusive of discounts to payers, providers, distributors and other purchasing organizations.

The Centers for Medicare and Medicaid Services has granted two unique assigned Q codes for Retacrit: Q5105 for End-Stage Renal Disease on dialysis and Q5106 for non-ESRD.

Additionally, Retacrit qualifies for pass-through status under the hospital outpatient prospective payment system.

**Initial data from AMBER trial of TSR-022 + TSR-042 demonstrates clinical activity in progression following anti-PD-1 treatment**

TESARO Inc. presented initial data from the phase I AMBER trial of TSR-022 (anti-TIM-3 antibody) in combination with TSR-042 (anti-PD-1 antibody) in patients who have progressed following anti-PD-1 therapy treatment, in an oral session during the 2018 Annual Meeting of the Society for Immunotherapy of Cancer Conference in Washington, D.C.

Additionally, phase I GARNET data of TSR-042 in patients with previously treated recurrent/advanced non-small cell lung cancer and phase I monotherapy dose-escalation data for TSR-033 (anti-LAG-3 antibody) in a broad range of solid tumors were also highlighted in poster presentations.

AMBER is an ongoing, open-label, phase I study of TSR-022, an anti-TIM-3 antibody, in monotherapy or in combination with TSR-042, an anti-PD-1 antibody. The TSR-022 and TSR-042 combination portion of the study consists of dose-escalation and expansion cohorts.

Data presented at SITC included safety and efficacy data from the combination dose-escalation and two expansion cohorts: NSCLC patients that had progressed following anti-PD-1 treatment and melanoma patients that had progressed following anti-PD-1 treatment. Patients were treated with 100 milligrams or 300 milligrams of TSR-022 in combination with a fixed dose of TSR-042 (500 milligrams) every 3 weeks.

A dose response trend was observed in both the NSCLC and melanoma cohorts based on greater clinical activity observed in patients treated with a 300 milligram dose of TSR-022 as compared to a 100 milligram dose.

At the time of data cutoff, 39 patients with NSCLC who had progressed following anti-PD-1 treatment had received treatment with the TSR-022 and TSR-042 combination, including 14 patients at the 100 milligram dose and 25 patients at the 300 milligram dose of TSR-022.

Among the 11 evaluable patients treated with the 100 milligram dose of TSR-022, 1 had a confirmed partial response following anti-PD-1 treatment had received treatment with the TSR-022 and TSR-042 combination, including 14 patients at the 100 milligram dose and 25 patients at the 300 milligram dose of TSR-022.

All objective responses were in PD-L1 positive (TPS ≥ 1%) patients, indicating potential for biomarker enrichment. Sixteen patients had known PD-L1 positive tumors. Among the 12 evaluable patients with PD-L1 positive tumors treated with either the 100 or 300 milligram dose of TSR-022, 4 patients had confirmed partial responses (3 responses ongoing) and 6 had stable disease.

Preliminary safety findings indicate that the combination of TSR-022 and TSR-042 was generally well-tolerat-
Patients with NSCLC who have progressed following anti-PD-1 treatment are currently being enrolled in the NSCLC expansion cohort at the 900 milligram dose of TSR-022 in combination with TSR-042. Additional data from this cohort (900 milligram dose) and the melanoma cohort (100 and 300 milligram doses) are expected in 2019.

GARNET is an ongoing phase I study evaluating TSR-042 as a monotherapy in patients with advanced solid tumors. The ongoing cohort expansion portion of GARNET is evaluating TSR-042 at a dose of 500 milligrams every 3 weeks for the first 4 cycles and 1,000 milligrams every 6 weeks thereafter in four cohorts: MSI (microsatellite instability)-high endometrial cancer, MSI-high non-endometrial cancer, MSS (microsatellite-stable) endometrial cancer and previously treated recurrent/advanced anti-PD-1 naive NSCLC.

Data presented at SITC included safety and efficacy data from the cohort of patients with NSCLC, which is fully enrolled.

At the time of data cutoff, 67 patients with previously treated recurrent/advanced anti-PD-1 naive NSCLC had received treatment with TSR-042, and 47 patients had at least one post-baseline tumor assessment or had discontinued treatment prior to first baseline assessment.

Among these 47 patients, 15 had partial responses (including 2 unconfirmed responses that have not yet progressed) by irRECIST criteria for an overall response rate of 31.9 percent; 14 additional patients (29.8%) had stable disease. Responses were durable and nine of the 15 responses are ongoing (60%).

The majority of patients (32 of 34; 94%) with available PD-L1 status had TPS <50% and clinical activity of TSR-042 was observed across all PD-L1 TPS categories. Among the 32 patients with low PD-L1 expression, 13 patients had TPS 1-49%, of which 5 had partial responses (ORR of 38.5%; including one unconfirmed response), and 19 patients had TPS <1%, of which 3 had partial responses (ORR of 15.8%).

Preliminary safety findings indicate TSR-042 was generally well-tolerated, with a safety profile characteristic of approved anti-PD-1 inhibitors for NSCLC.

The GARNET study is intended to support a Biologics License Application submission to the FDA in 2019 for patients with recurrent endometrial cancer.

Data from the monotherapy dose-escalation portion of the CITRINO study were presented and included 30 patients treated with different doses of TSR-033. There were no Grade ≥3 treatment-related adverse events reported. Exposure and peripheral receptor occupancy increased in a dose proportional manner from 20 milligrams to 720 milligrams.

These preliminary findings indicate that TSR-033 was generally well-tolerated across multiple dose levels, with a safety profile consistent to those of other immune checkpoint inhibitors.

Enrollment is ongoing for patients treated with TSR-033 in combination with 500 milligrams of TSR-042.

Zymeworks announces updated clinical data for novel bispecific antibody, ZW25

Zymeworks Inc., announced the plenary presentation of updated ZW25 clinical data by Murali Beeram, a clinical investigator at the START Center for Cancer Care in San Antonio.

The data were presented at the Symposium on Molecular Targets and Cancer Therapeutics, sponsored by the European Organization for Research and Treatment of Cancer, NCI, and the American Association for Cancer Research. The title is “Single Agent Activity of ZW25, a HER2-Targeted Bispecific Antibody, in HER2-Expressing Gastroesophageal and Other Cancers.”

Data from Zymeworks’ ongoing multi-center phase I study showed single agent ZW25, a bispecific antibody, induced anti-tumor activity and was well tolerated in heavily pretreated patients with a variety of HER2-expressing cancers.

The plenary presentation includes all 24 gastroesophageal and other cancer patients treated at the phase II recommended dose, of which 17 were response-evaluable (defined as having measurable disease and at least one tumor restaging) at the time of data cut-off.

Of these 17 patients, eight had gastroesophageal cancers, four had colorectal cancer, and five had other HER2-expressing cancers including gallbladder, cholangiocarcinoma, cervical, fallopian tube and salivary gland. The participants in the study were heavily pretreated with a median of three prior cancer treatments.
The overall disease control rate, which includes patients with partial responses and stable disease was 82 percent. There were seven partial responses (41%), seven stable disease (41%) and three progressive disease (18%). The median progression-free survival in all 24 patients was 6.21 months (95% CI 1.94-9.33).

In the eight gastroesophageal cancer patients, who had a median of four prior systemic treatments, the response rate was 50 percent.

In the four colorectal and five other HER2-expressing cancer patients the response rate was 33 percent. Anti-tumor activity was assessed per RECIST every eight weeks.

In the study, ZW25 was well tolerated. All treatment-related adverse events were grade I or II with the exception of one patient with grade III fatigue, and no treatment-related serious adverse events were seen.

There were no grade IV or V adverse events. The most common adverse events (25% or greater) were diarrhea, infusion reaction and nausea.

“The favorable tolerability we have seen with ZW25 supports its use as both a single agent and in combination with approved anti-cancer agents,” said Diana Hausman, Zymeworks’ chief medical officer. “We are excited to be advancing ZW25’s development and have plans to explore its efficacy in a number of tumor types, including gastroesophageal and breast cancer.”

Enrollment in the first portion of the study (the dose-escalation phase) has been completed. The recommended single-agent dose was determined to be 20 mg/kg once every two weeks or 10 mg/kg weekly.

In the second part of the study (the cohort expansion phase), additional patients are being enrolled to further assess ZW25’s single-agent tolerability and anti-tumor activity against a variety of cancer types in different settings.

The third part of the study (the combination phase) is underway and is evaluating ZW25 in combination with selected chemotherapy agents in gastroesophageal and breast cancer patients with HER2 high or lower HER2 expression levels.

ZW25 is a bispecific antibody, based on Zymeworks’ Azymetric platform, that can simultaneously bind two non-overlapping epitopes of HER2, known as bisparatopic binding.

This unique design results in multiple mechanisms of action including dual HER2 signal blockade, increased binding and removal of HER2 protein from the cell surface, and potent effector function and has led to encouraging anti-tumor activity in patients.

Zymeworks is developing ZW25 as a HER2-targeted treatment option for patients with any solid tumor that expresses HER2. FDA has granted Orphan Drug Designation to ZW25 for the treatment of both gastric and ovarian cancers.

Gradalis presents initial data from phase II U.S. trial for Ewing’s sarcoma

Gradalis Inc. presented initial data from its phase II trial for Ewing’s sarcoma at the 2018 Annual Meeting of Children’s Oncology Group.

This is a two-part open-label, non-randomized, single-arm phase PP study in patients with recurrent or refractory Ewing’s Sarcoma. Part 2 of the study was established in order to assess safety and efficacy of Temozolomide / Irinotecan in combination with Vigil. All patients included in the study signed informed consent for tissue procurement treatment on the study according to the requirements of each individual institution.

As of Oct. 5, eight patients were enrolled in Part 2 of the trial, and five patients are still alive. Two patients experienced RECIST partial response and retrospectively confirmed histological complete response. Four patients had durable stable disease as best response for ≥6 months.

All eight patients had histologically confirmed Ewing’s Sarcoma. The mean age was 24 years (range: 12-46 years). All patients were heavily pretreated and failed treatment with Temozolomide and Irinotecan previously, with a mean of 5 lines of systemic treatments prior to study enrollment.

Historical progression-free survival for patients in second relapse (or greater) Ewing’s Sarcoma is 3 months or less. The median progression-free survival of the patients enrolled was 8.2 months.

The combination of Vigil, Irinotecan and Temozolomide in third-line or greater Ewing’s Sarcoma demonstrated favorable safety profile with limited treatment-related toxicities.

Phase II data demonstrates similar results from phase I trial. Previously published data of patients in second relapse (or greater) Ewing’s Sarcoma enrolled and treated with Vigil monotherapy on a phase I study revealed clinical benefit with a median survival of 2 years. While the median OS of patients in the phase II study, treated with the combination of Vigil, Irinotecan, and Temozolomide has not been reached, favorable event-free survival has been observed.

Vigil is a proprietary, investigational cellular immunotherapy technology that combines genetic engineering
with the science of immuno-oncology. Vigil is intended to stimulate and enhance the body’s natural mechanism for recognizing and killing cancer cells. It utilizes the patient’s own cancer cells to create a fully personalized cancer immunotherapy.

By utilizing the patient’s own tumor as the antigen source, Vigil is designed to elicit an immune response that is specifically targeted and broadly relevant to each patient’s unique tumor antigens. Vigil is being studied in Ewing’s sarcoma, in gynecological cancer and advanced women’s cancer in combination with PD-L1 inhibitors, and ovarian cancer as a single agent.

Using review pilot program, FDA takes two weeks to approve first-line treatment for peripheral T-cell lymphoma

FDA has expanded the approved use of Adcetris (brentuximab vedotin) injection in combination with chemotherapy by the FDA to treat adult patients with previously untreated stage III or IV classical Hodgkin lymphoma (cHL), cHL after relapse, cHL after stem cell transplant when a patient is at a high risk of relapse or progression, systemic ALCL after failure of other treatment, and primary cutaneous ALCL or CD30-expressing mycosis fungoides after failure of other treatment.

The new approval was based on a clinical trial of 452 patients with certain PTCLs who received either Adcetris plus chemotherapy or a standard chemotherapy (CHOP) as first-line treatment. Progression-free survival (the amount of time a patient stays alive without the cancer growing) was significantly longer (hazard ratio 0.71, P-value 0.01) in the Adcetris arm (median 48 months, compared to 21 months with CHOP). Overall survival and overall response rates were also significantly better in the Adcetris arm.

The most common side effects of Adcetris plus chemotherapy included nerve damage (peripheral neuropathy), nausea and vomiting, diarrhea, low white blood cell counts, fatigue, mouth sores, constipation, hair loss, fever and low red blood cell count (anemia).

Health care providers are advised to monitor patients for infusion reactions, life-threatening allergic reactions (anaphylaxis), neuropsychiatric, fever, gastrointestinal complications and infections. Patients should also be monitored for tumor lysis syndrome (a complication from many tumor cells being killed off at the same time), serious skin reactions, lung side effects (pulmonary toxicity) and liver damage (hepatotoxicity).

The prescribing information for Adcetris includes a boxed warning to advise health care professionals and patients about the risk of a fatal or life-threatening infection of the brain (progressive multifocal leukoencephalopathy) in patients receiving Adcetris.
FDA accepts novel clinical trial endpoint in approving Erleada for prostate cancer

FDA approved Erleada (apalutamide) for the treatment of non-metastatic castration-resistant prostate cancer. This is the first FDA-approved treatment for this indication.

“This approval is the first to use the endpoint of metastasis-free survival, measuring the length of time that tumors did not spread to other parts of the body or that death occurred after starting treatment,” said Richard Pazdur, director of the FDA’s Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products, said in a statement. “In the trial supporting approval, Erleada had a robust effect on this endpoint. This demonstrates the agency’s commitment to using novel endpoints to expedite important therapies to the American public.”

The FDA granted the approval of Erleada to Janssen Pharmaceutical Companies, a unit of Johnson & Johnson.

Erleada works by blocking the effect of androgens, a type of hormone, on the tumor. These androgens, such as testosterone, can promote tumor growth.

The safety and efficacy of Erleada was based on a randomized clinical trial of 1,207 patients with non-metastatic, castration-resistant prostate cancer. Patients in the trial either received Erleada or a placebo. All patients were also treated with hormone therapy, either with gonadotropin-releasing hormone (GnRH) analog therapy or surgical castration. The median metastasis-free survival for patients taking Erleada was 40.5 months compared to 16.2 months for patients taking a placebo.

Common side effects of Erleada include fatigue, high blood pressure (hypertension), rash, diarrhea, nausea, weight loss, joint pain (arthralgia), falls, hot flush, decreased appetite, fractures and swelling in the limbs (peripheral edema).

Severe side effects of Erleada include falls, fractures and seizures.

Erleada’s sponsor is the first participant in the FDA’s recently-announced Clinical Data Summary Pilot Program, an effort to provide stakeholders with more usable information on the clinical evidence supporting drug product approvals and more transparency into the FDA’s decision-making process. Soon after approval, information from the clinical summary report will post with the Erleada entry on Drugs@FDA and on the new pilot program landing page.

CHMP gives positive opinion for Kisqali combination therapy for all women with HR+/HER2- locally advanced or metastatic breast cancer

The Committee for Medicinal Products for Human Use of the European Medicines Agency has adopted a positive opinion recommending an expanded indication for Kisqali (ribociclib), the CDK4/6 inhibitor with the largest body of first-line clinical trial evidence demonstrating consistent, superior and sustained efficacy compared to endocrine therapy alone.

The drug is sponsored by Novartis.

CHMP recommended Kisqali for the treatment of women with hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) locally advanced or metastatic breast cancer in combination with fulvestrant as initial endocrine-based therapy and in women who have received prior endocrine therapy. The positive opinion also recommended approval of Kisqali in combination with endocrine therapy and a luteinising hormone-release hormone agonist (LHRH) for pre- and perimenopausal women.

This positive CHMP opinion is based on data from the Phase III MONALEESA-7 and MONALEESA-3 trials. These trials demonstrated prolonged progression-free survival (PFS) for Kisqali-based regimens compared to endocrine therapy alone and showed improvements as early as eight weeks after start of treatment with Kisqali combination therapy.

In MONALEESA-7, Kisqali plus an aromatase inhibitor and goserelin nearly doubled the median PFS compared to an aromatase inhibitor and goserelin alone in pre- or perimenopausal women (27.5 months compared to 13.8 months; HR=0.569; 95% CI: 0.436-0.743) [3]. In MONALEESA-3, Kisqali plus fulvestrant demonstrated a median PFS of 20.5 months compared to 12.8 months for fulvestrant alone (HR=0.593; 95% CI: 0.480-0.732) across the overall population of first-line and second-line postmenopausal women. Across the two trials, the most common adverse reactions (incidence >=20%) were neutropenia, nausea, infections, fatigue, diarrhea, leukopenia, vomiting, alopecia, headache, constipation, rash and cough.

The European Commission will review the CHMP recommendation and usually delivers its final decision within two months. The decision will be applicable to all 28 European Union member states plus Iceland, Norway and Liechtenstein. Additional regulatory
FDA grants priority review for Tecentriq + Abraxane for metastatic triple-negative breast cancer

FDA has granted priority review for Genentech’s supplemental Biologics License Application for Tecentriq (atezolizumab) plus chemotherapy, Abraxane (albumin-bound paclitaxel; nab-paclitaxel) for the first-line treatment of unresectable locally advanced or metastatic triple-negative breast cancer in people whose disease expresses the PD-L1 protein, as determined by PD-L1 biomarker testing.

FDA is expected to make a decision on approval by March 12, 2019. A

The sBLA is based on data from the phase III IMPassion130 study, which was presented at the European Society for Medical Oncology Congress and published in the New England Journal of Medicine in October 2018. Results demonstrate Tecentriq plus nab-paclitaxel as an first-line treatment for unresectable locally advanced or metastatic TNBC significantly reduced the risk of disease worsening or death (progression-free survival) compared with nab-paclitaxel alone in all randomized patients (intention-to-treat) (median PFS=7.2 vs. 5.5 months; hazard ratio [HR]=0.80, 95% CI: 0.69-0.92, p=0.0025) and the PD-L1-positive population (median PFS=7.5 vs. 5.0 months; HR=0.62, 95% CI: 0.49-0.78, p<0.0001), a subgroup determined by PD-L1 biomarker testing.

At this interim analysis, statistical significance was not met for overall survival in the ITT population (median OS=21.3 vs. 17.6 months; HR=0.84, 95% CI: 0.69-1.02, p=0.0840), but the combination showed a clinically meaningful OS improvement in the PD-L1-positive population (median OS=25.0 vs. 15.5 months; HR=0.62, 95% CI: 0.45-0.86).

Due to the hierarchical statistical design, results in the PD-L1-positive population were not formally tested for statistical significance. Follow-up will continue until the next planned analysis. Safety in the Tecentriq plus nab-paclitaxel arm appeared consistent with the known safety profiles of the individual medicines, and no new safety signals were identified with the combination. Serious adverse events were reported in 23 percent of people who received Tecentriq plus nab-paclitaxel compared to 18 percent of people who received nab-paclitaxel alone.

Currently, Genentech has seven ongoing phase III studies investigating Tecentriq in TNBC, including early and advanced stages of the disease. If approved, this Tecentriq combination would be the first cancer immunotherapy regimen for the treatment of PD-L1-positive, metastatic TNBC.

The IMPassion130 study is a phase III, multicenter, randomized, double-blind study evaluating the efficacy, safety and pharmacokinetics of Tecentriq plus nab-paclitaxel compared with placebo plus nab-paclitaxel in people with unresectable locally advanced or metastatic TNBC who have not received prior systemic therapy for metastatic breast cancer. The study enrolled 902 people who were randomized equally (1:1). The co-primary endpoints are PFS per investigator assessment (RECIST 1.1) and OS. PFS and OS were assessed in all randomized patients (ITT) and in the PD-L1-positive population. Secondary endpoints include objective response rate, duration of response and time to deterioration in Global Health Status/Health-Related Quality of Life.

Immunomedics expands clinical collaboration with AstraZeneca to include metastatic NSCLC

The clinical collaboration between Immunomedics Inc. and AstraZeneca and MedImmune for the development of Imfinzi (durvalumab) and sacituzumab govitac combination therapy has been broadened to include second-line metastatic non-small cell lung cancer, the companies said.

“The combination study with durvalumab, together with our internal efforts to further develop sacituzumab govitac monotherapy, will help us define the best registration strategies in NSCLC...
within accelerated timelines,” said Robert Iannone, head of research & development and chief medical officer of Immunomedics.

As CPIs increasingly move into frontline therapy, either alone or in combination with chemotherapy, treatment options for second-line and beyond are limited to single agent chemotherapies, which have only very modest activity. Thus, there is a high unmet need in NSCLC for patients who don’t respond or have progressed after treatment with CPIs.

Sacituzumab govitecan as monotherapy has produced an overall response rate of 19 percent in 47 patients with pretreated metastatic NSCLC with a duration of response of 6.0 months. In a subgroup of patients (14 of 47 patients) who had previously been treated with CPIs as their last line of therapy, ORR was 14 percent (2/14).

This open-label, multi-center phase I/II study will enroll two cohorts of patients, one in CPI primary refractory, and one in acquired resistance to CPI.

Sacituzumab govitecan, Immunomedics’ most advanced product candidate, is a novel, first-in-class antibody-drug conjugate. It is currently under priority review by the FDA for accelerated approval as a treatment of patients with metastatic triple-negative breast cancer who have received two prior therapies for metastatic disease. If approved, sacituzumab govitecan would be the first and only ADC approved for the treatment of metastatic triple-negative breast cancer.

Durvalumab is a human monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80, countering the tumor’s immune-evading tactics and releasing the inhibition of immune responses.

As part of a broad development program, durvalumab is being investigated as monotherapy and in combination with IO, small molecules, and chemotherapies across a range of tumors and stages of disease.

**Ziopharm Oncology announces Immuno-oncology Clinical Supply Agreement with Regeneron to evaluate combination therapy for brain cancer**

Ziopharm Oncology Inc., announced a clinical supply agreement with Regeneron Pharmaceuticals Inc. to evaluate Ziopharm’s Ad-RTS-hIL-12 plus veledimex in combination with Regeneron’s PD-1 antibody Libtayo (cemiplimab-rwlc) to treat patients with recurrent glioblastoma.

Ad-RTS-hIL-12 plus veledimex is an investigational gene therapy designed to induce and control the production of human interleukin 12 that activates the immune system and recruits cancer-fighting T cells into tumors.

Libtayo has been approved in the U.S. for the treatment of patients with metastatic cutaneous squamous cell carcinoma or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

Under the agreement, Ziopharm and Regeneron will initiate a phase II study in the first half of 2019 in patients with rGBM to measure preliminary safety and efficacy of Ad-RTS-hIL-12 plus veledimex in combination with Libtayo.

Ziopharm will be responsible for the conduct and costs of the clinical trial, and Regeneron will supply Libtayo for the study. The companies potential-