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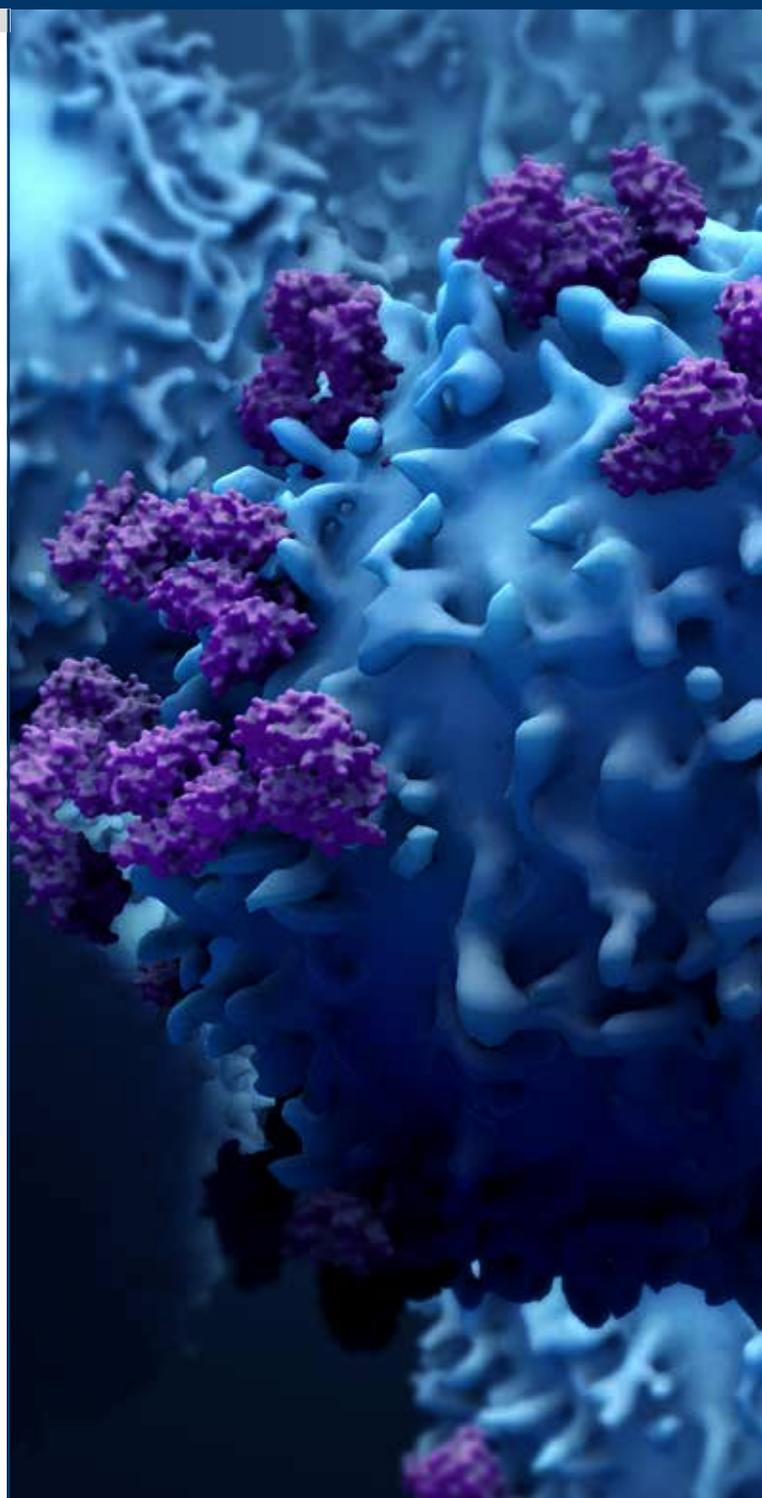
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Emerging Targeted Therapies Continue to Shift Paradigm in EGFR Exon 20–Mutated NSCLC

Ryan Scott

AMIVANTAMAB-VMJW (RYBREVANT) and mobocertinib (Exkivity) have been integrated into treatment for patients with non-small cell lung cancer (NSCLC) harboring *EGFR* exon 20 mutations in the metastatic setting. As these agents continue to be explored, moving them into earlier lines of treatment could provide more benefits for this patient population, according to Edward Kim, MD, MBA.

“Targeted therapy has been a true renaissance in lung cancer. I still remember the days when we used doublet chemotherapy and were arguing about which adverse effects were better or worse, and in which patients. You would feel so helpless as a practitioner if that’s the only thing you were really discussing [instead of treatments] with greater efficacy. Now though we have made some incremental progress. Precision medicine [has led to] this integration of targeted therapy,” Kim said in an interview with *OncLive*® following an Institutional Perspectives in Cancer (IPC) webinar on lung cancer.

In the interview, Kim, the chair of the IPC meeting, discussed the facets of each presentation from the meeting, featuring other emerging targeted therapies in NSCLC, biomarker testing in the space, frontline immunotherapy in NSCLC, and the current management of small cell lung cancer (SCLC). Kim is the physician-in-chief at City of Hope Orange County, and vice physician-in-chief at the City of Hope National Medical Center.

***OncLive*®: What are some of the exciting emerging areas for targeted therapy in NSCLC?**

Kim: I had the pleasure to speak about several emerging areas in lung cancer. The first one is *EGFR* exon 20 [mutations]. We know that *EGFR* is expanding as far as the types of mutations that we’re finding, and now we have more drugs that are inclusive in this area that are FDA approved, including osimertinib [Tagrisso], amivantamab, and mobocertinib. These are drugs that are being implemented when we find these *EGFR* exon 20 mutations and have now become part of the armamentarium in lung cancer. [We are also aware that we] have to make sure we get comprehensive [genomic] testing in each patient.

I also covered osimertinib and its approval in the frontline setting and how it has changed targeted therapies. It is a drug that has high potency and high penetration into the central nervous system and is now being implemented in earlier-stage, surgically resectable disease. That excites me because this means we’re taking our wisdom, our

scientific knowledge [that has been utilized] in the metastatic setting and moving it to the early-stage setting. We are following [the trend of] the breast cancer paradigm, which is exciting.

Finally, [I discussed] *KRAS* mutations. *KRAS* was something that, if you asked [clinicians] in the early 2000s, we would have assumed that this was the first biomarker that would have been relevant clinically. It hasn’t been until recently that we finally have a drug that’s FDA approved for *KRAS* G12C–mutated lung cancer [in sotorasib (Lumakras)], and that’s an exciting area. We expect other [mutations] to follow suit.

Given the exponential growth we’ve seen with targeted therapy, where do you see the field headed?

We want to measure the genomics of each individual’s cancer to see what comes up. Our menu of drugs that we can offer for specific targets has greatly expanded, and that’s exciting. However, it’s also daunting because there are so many targets and so many drugs now. Lung cancer is still in the middle of this change where we will continue to find more targets and more drugs. We have been a poster child for precision medicine.

Could you expand on the importance of genomic testing and the timing of that testing?

I consider genomic testing of one’s cancer essential, and I wish we would [include it] as part of the staging process. When you hear staging, you think of what CAT scans, PET scans, or MRIs you have to conduct in order to stage [the cancer]. Then you think of what the diagnosis is, and the diagnosis is a histological diagnosis of NSCLC or SCLC and whatever subtype it is.

Biomarkers is a third bucket, but I would hope that we could put biomarkers and genomic testing in one of those two areas, as either part of staging or part of histological diagnosis. If you think of breast cancer, when patients get a diagnosis, it is not complete until you have the hormone markers, the HER2 status, and now other markers.

I hope lung cancer now shifts in that direction that it [would be considered] incomplete staging or an incomplete diagnosis unless you have these genomic findings.

What options are currently available for patients with *KRAS* G12C–mutated NSCLC?

KRAS G12C mutations are a new area. It’s a subset of

the *KRAS* gene, so it does not make up the entire 25% to 30% of lung cancer that harbors *KRAS* mutations. [*KRAS*] has multiple subtypes as well.

We have identified treatments that target *KRAS* G12C. The first agent is sotorasib. That is a drug that has been FDA approved and is utilized in previously treated patients based on the phase 1/2 CodeBreak 100 trial [NCT03600883]. I'm glad we have a treatment, and we have other treatments down the road that are coming.

I also mentioned the phase 1/2 KRYSTAL-1 trial [NCT03785249] that evaluated adagrasib, which is coming as well. We're hopeful that other drugs in the pipeline will cover some of these other *KRAS* subtypes down the road.

Your colleague, Michelle Afkhami, MD, of City of Hope, spoke on biomarker testing in lung cancer. How has this testing evolved over time?

Dr Afkhami gave an elegant talk on the perspective from pathology on the importance of biomarker testing. The things we always focus on are the technology platforms and how much tissue or blood we need, how quickly we can run the markers, and how many markers we can run. [The speed of these tests has been] increasing, and [the amount of blood or tissue needed has been] decreasing. It's a rapidly changing area. The technology continues to improve. The types of specimens we are testing are changing, and the number of markers that we as clinicians want to have, not only to treat our patients in the clinic, but also to measure for research purposes, [are changing, too].

It is like a microcosm of what we're doing with telescopes in space. We have a great telescope, we launch it, we can see things we've never seen before, but then we need a new one to see deeper and find other things. This is a similar type of paradigm, except we're moving faster.

[Genomic testing] is of the utmost importance. We're still trying to emphasize to our clinical colleagues that you have to do this up front. There's still data that's being reported that [genomic testing rates are] no [higher] than 90%, and that needs to change. We also understand that we have to make it easier to do this testing. There are hurdles in some rural areas, community-based areas, and even metropolitan areas where it is challenging to get this done. We need to work on both sides: the attitudes and beliefs [on genomic testing] and the processes. We need to make it all better.

Erminia Massarelli, MD, PhD, of City of Hope, spoke on frontline immunotherapy. How has immunotherapy changed historical approaches to treatment?

Dr Massarelli is the section head of lung cancer at City of Hope, and she talked about frontline immunotherapy,

another great frontier that has been crossed in patients who we are treating for lung cancer. She talked specifically about the phase 3 CheckMate 277 trial [NCT02477826] and the phase 3 CheckMate 9LA trial [NCT03215706], as well as the phase 3 EMPOWER-Lung 1 trial [NCT03088540]. We know that the established frontline regimen is a combination of chemotherapy and immunotherapy. We have multiple options on the table. We still use the phase 3 KEYNOTE-189 trial [NCT02578680] regimen of pembrolizumab [Keytruda] plus chemotherapy; that's the most popular. But [these trials] have advanced the options of what we had with doublet chemotherapy or even with bevacizumab [Avastin] in previous iterations.

We're now at a point where immunotherapy has completely changed not only how we treat patients but what our expectations of their outcomes are. I love the fact that we can use lesser toxic chemotherapies but also empower [a patient's] immune system to help battle the cancer. This has changed the paradigm of our treatment approach.

Nishan Tchekmedyian, MD, of City of Hope, gave a presentation on targeted therapy. Are there any other key areas of targeted therapy that you want to highlight?

Dr Tchekmedyian has worked in a community-based system and is now one of our faculty members at City of Hope. He and his group previously have done a lot of research in a regional-based setting. Additionally, he has recently [coauthored] the *Journal of Clinical Oncology* publication on poziotinib [in the phase 2 ZENITH20 trial (NCT03318939)] in patients with NSCLC harboring *HER2* exon 20 insertion mutations.

He gave us an update on *RET* and *ALK*. *ALK* was the second targeted therapy class in lung cancer, but now it has multiple generations of drugs. Most recently, the phase 3 CROWN trial [NCT03052608] was reported, and [lorlatinib (Lorbrena)] is being integrated into our treatment paradigms.

He discussed *RET*, which is an area that is new for lung cancer, and it is exciting as well. It is another marker that we're measuring so that we can implement the appropriate treatments. There are a lot of changes, even in these rarer markers. There are more drugs and more options, which leads us down the road of how we sequence these drugs in patients who have this biomarker. What works best first? What works best in overcoming resistance? These are the questions that we're now asking, whether it's with targeted therapies or immunotherapies because we want to be able to treat patients as long as possible and overcome resistance mechanisms that the cancers are constantly trying to fight us with.

Lastly, Jyoti Malhotra, MD, MPH, of City of Hope, spoke about current management of SCLC. What recent updates in this field have been exciting to hear?

Dr Malhotra has now joined us at City of Hope to be our lung lead in our Orange County Campus. She spoke on SCLC, and we should not forget SCLC and leave it behind. For years, NSCLC and SCLC were equally frustrating in the treatments that we would offer with doublet chemotherapy. Just because one of our areas has advanced a lot, which is NSCLC, we shouldn't leave the other behind.

SCLC is getting the attention that it deserves. We're trying to find biomarkers and targeted therapies. You'll hear people say that we're not going to find [these biomarkers and targeted therapies], but we said that about NSCLC for many decades. It finally happened [in NSCLC], and I believe it will happen in SCLC as well.

Dr Malhotra gave a nice overview of the phase 3 CASPIAN trial [NCT03043872], the phase 3 IMpower133 trial [NCT02763579], as well as what we do in the second-line setting of SCLC. It's important to continue to include SCLC in our dialogues, discussions, and research because it constitutes about 15% of lung cancer. That puts it in line with an *EGFR* incidence or some of these other markers,

such as *KRAS* G12C. This is an equally important population, and we need to continue to pursue and find the best treatment options because our patients are still being diagnosed with SCLC, and SCLC can tend to be more aggressive. We urgently need to find these therapies.

What do you believe is the biggest highlight to come out of the IPC meeting?

These meetings are great. They provide a great service to people who are trying to keep up with all the data. These days, everyone's so busy, but over a 2-hour period, you can get updated with all the latest and the greatest in a particular disease type. These types of formats are great for learners, and great for folks who are busy.

I really enjoy the fact that we can cover so many topics from pathology and biomarkers all the way through the different treatments for lung cancer right now. The format is great. I do believe that the right messages are being taken home. It's like a summary of what the current state of the data is, and that's why you continue to see a lot of participation and a lot of interest by experts in the field who want to use this type of format to convey this important information and timely updates for the community at large. ■

HER2 Expression Is a Key Determinant of Trastuzumab Deruxtecan Activity

Jason Harris

HER2 EXPRESSION APPEARED to be a significant predictor for response to fam-trastuzumab deruxtecan-xki (Enhertu), according to findings from a biomarker analysis of patients with metastatic breast cancer in the phase 2 DAISY trial (NCT04132960) presented during the European Society for Medical Oncology Breast Cancer Congress 2022.¹

Investigators in DAISY assigned 186 patients with metastatic breast cancer to 1 of 3 cohorts based on HER2 immunohistochemistry (IHC) expression: IHC3+ or IHC2+/in situ hybridization (ISH)+ (cohort 1; n = 68); IHC2+/ISH- or IHC1+ (cohort 2; n = 72); and IHC0+ (cohort 3; n = 37). All patients received 5.4 mg/kg trastuzumab deruxtecan intravenously on day 1 of 21-day cycles.

Patients in cohort 1 were resistant to trastuzumab (Herceptin) and ado-trastuzumab emtansine (T-DM1; Kadcyla). Those in cohorts 2 and 3 were resistant to anthracyclines and taxanes, and to inhibitors of CDK4/6 inhibitors if they had hormone receptor-positive disease. Mosele noted that this population was heavily pretreated,

with 53.1% of patients receiving at least 5 prior lines of treatment.

Best objective response (BOR) favored cohort 1 (71.0%; 95% CI, 58.3%-81.0%) compared with cohort 2 (37.5%; 95% CI, 26.4%-50.0%) and cohort 3 (30.0%; 95% CI, 16.0%-47.0%). Mosele added that the difference between the 3 groups was statistically significant ($P < .0001$).

"Antitumor activity [with trastuzumab deruxtecan] was associated with levels of HER2 [expression], even if we observe a 30% of response in the cohort of patients with no detection of HER2," Maria Fernanda Mosele, MD, a clinical oncologist and translational researcher at Gustave Roussy Cancer Center in Villejuif, France, said in a presentation. "There was a moderate correlation between trastuzumab deruxtecan distribution and HER2 expression. A decrease in PD-L1 was observed only in the cohort of patients with HER2 overexpressing breast cancer."

In an exploratory analysis, investigators sought to further explore the mechanism of action of trastuzumab deruxtecan through evaluation of the agent's distribution, modulation of immune cells, and dynamic HER2 expression

before and after administration. Additionally, investigators sought to develop predictors of response and identify mechanisms of primary and secondary resistance.

To conduct these analyses, tumor biopsy and whole blood samples of 5 mL were mandatory of all cohorts at baseline. Additional tumor biopsies were optional on days 2 and 4 of all cohorts with mandatory biopsy required between day 22 and 43 for patients in cohort one after cycle ¹.

Ten paired samples at baseline and between days 2 and 4 were stained for trastuzumab deruxtecan distribution including 2 from cohort 1, 3 from cohort 2, and 5 from cohort 3. Distribution was lower in the cells that did not express HER2 compared with cells with higher HER2 expression.

Investigators assessed trastuzumab deruxtecan for modulation of immune cells. Among patients with HER2 IHC3+ or HER2 IHC2+/ISH+ disease (n = 18), Mosele and colleagues observed a significant decrease in PD-L1 expression ($P = .002$). She noted there was no such decline observed in patients with IHC1+ or IHC2+/ISH-negative (n = 10) or HER-IHC 0 (n = 3) disease.

In terms of secondary resistance, Mosele and colleagues used IHC to assess HER2 staining at baseline and at progression. Investigators noted that among 20 analyzed tumor samples, 65% (95% CI, 40.8%-84.6%) of patients demonstrated a decline in HER2 expression at progression.

She added that investigators are further assessing HER2 expression levels in baseline samples from patients in cohort 3 with no detection of HER2 by standard methods of immunohistochemistry. Trials assessing trastuzumab deruxtecan distribution at progression are also ongoing.

In findings first presented at the 2021 San Antonio

Breast Cancer Symposium evaluating progression-free survival (PFS) by HER2 expression, investigators found that those in cohort 1 had the longest median PFS at 11.1 months (95% CI, 8.5-14.4) compared with 6.7 months (95% CI, 4.4-8.3) in cohort 2 (HR, 0.53; 95% CI, 0.34-0.84). In cohort 3, the median PFS was 4.2 months compared with cohort 2 (HR, 1.96; 95% CI, 1.21-3.15).²

On May 4, the FDA approved trastuzumab deruxtecan for adults with unresectable or metastatic HER2-positive breast cancer who have previously received an anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within 6 months of therapy completion.

Data from the multicenter, open-label, DESTINY-Breast03 trial (NCT03529110) showed that trastuzumab deruxtecan improved median PFS compared with T-DM1 (not reached vs 6.8 months; HR, 0.28; 95% CI, 0.22-0.37; $P < .0001$).³ ■

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Biomarker Testing Will Fuel Next Wave of Treatment Innovations in Breast Cancer

Chris Ryan

SIGNIFICANT PROGRESS HAS shifted the treatment paradigm in various spaces within breast cancer, including therapy options for patients with HER2-positive metastatic breast cancer, hormone receptor (HR)-positive, HER2-negative breast cancer, and triple-negative breast cancer (TNBC). However, further advancements in treatment will derive from increased knowledge surrounding biomarkers in breast cancer, according to Christos Vaklavas, MD.

“We are increasingly recognizing that we have to understand the biology [of breast cancer] better. Our approaches have to be tailored to the biology of the cancer. Right now,

we are using crude biomarkers, like PD-L1, or even before that, [estrogen receptor (ER) and] HER2,” Vaklavas said in an interview with *OncLive*[®] following an Institutional Perspectives in Cancer (IPC) webinar on breast cancer, which he chaired.

In the interview, Vaklavas discussed highlights from the meeting, including an increased emphasis on investigating tumor biology in breast cancer, plus the evolving treatment landscapes in HER2-positive breast cancer, HR-positive, HER2-negative breast cancer, and TNBC. He is the physician leader in breast cancer at the

Huntsman Cancer Institute and an associate professor in internal medicine in the Division of Oncology at the University of Utah.

OncLive®: Your presentation focused on HR-positive, HER2-negative breast cancer. What are the pertinent updates in this space?

Vaklavas: The addition of CDK4/6 inhibitors to a backbone of endocrine therapy, whether it is letrozole, anastrozole, or potentially exemestane, has been associated with equal magnitude of benefit in progression-free survival. We have started seeing benefit in overall survival [OS], specifically with ribociclib [Kisqali]. We do not know what the pharmacologic underpinning of this benefit is specifically with ribociclib. Whether this is practice changing, or whether we should start prescribing ribociclib, we do not know yet. [These developments] are giving us confidence that the CDK4/6 inhibitors are associated with benefits in OS, although perhaps not all to the same extent.

The second takeaway [involves] oral selective ER degraders [SERDs], a new class of drugs coming around. The phase 3 EMERALD trial [NCT03778931] was positive with elacestrant, but we found that a second study, the phase 2 AMEERA-3 trial [NCT04059484] with amcenes-trant was negative. This new generation of SERDs may be effective in patients who have *ESR1* mutations, whether they arise [at diagnosis] or they arise as a consequence [of treatment], and [the latter] is considerably more frequent. Those mutations [tend] to arise because of therapeutic pressure with first-line therapy.

The third point [relates] to what is coming [down the pipeline]: a series of agents for patients [who] progress on 1, 2 or, even 3 lines of endocrine therapy. There are novel antibody-drug conjugates [that are being studied in] HER2-positive and HER2-low breast cancer. In the next few months with the announcements of those results, [treatment options] will settle.

Mei Wei, MD, of the University of Utah, spoke about early-stage and metastatic HER2-positive breast cancer. What are some of the updates we have seen there?

[New] HER2[-targeted agents] are moving [into the] second-line [setting]. Recently in the *New England Journal of Medicine*, we saw [updated data the phase 3 DESTINY-Breast03 trial [NCT03529110] with fam-trastuzumab derux-tecan-nxki [Enhertu] vs ado-trastuzumab emtansine [Kadcyla; T-DM1] in patients with HER2-positive breast cancer. [Trastuzumab derux-tecan] has been incorporated in the National Comprehensive Cancer Network guidelines, and, [potentially] soon, the FDA is going to approve trastuzumab derux-tecan as a second-line therapy in the metastatic setting.

Treatment in the third line and thereafter are still in flux right now. We know that tucatinib [Tukysa] probably has a leading edge in [patients] with brain metastases, but there is some emerging evidence that [trastuzumab derux-tecan] may be efficacious in patients with active brain metastases, as well. It has not been specifically looked at, but there are studies that are looking into it right now. [This could be] practice changing.

Right now, a taxane, trastuzumab [Herceptin], and pertuzumab [Perjeta] is the preferred first-line therapy in the metastatic setting. [There have been] no changes in the adjuvant or neoadjuvant setting yet. In the first-line metastatic setting, a taxane, pertuzumab, and trastuzumab have been associated with benefits in OS. However, a lot of studies are ongoing in [the first-line] space to challenge the dogma of a taxane, trastuzumab, and pertuzumab.

In DESTINY-Breast03, the rate of interstitial lung disease (ILD) was lower than it was in the phase 2 DESTINY-Breast01 trial (NCT03248492). What are some of the interventional and management strategies that led to that reduction?

Early recognition [was key]. An algorithm for the management [of ILD] and the aggressive discontinuation of [trastuzumab derux-tecan] with grade 2 or greater ILD brought the rate down to around 10%, which is not significantly different from [the rate in DESTINY-Breast01 of] about 13%. There is still a lot to be learned about ILD and [our management] algorithm. There is still a lot to learn about the natural history. [Does increased exposure to the drug] increase the risk of ILD? Is there something idiosyncratic, something special with those patients that they are developing ILD?

We need to understand it, and I do have patients that have ILD or lymphocytic carcinomatosis of the lung. At least up until recently, we were appalled at the idea of giving those patients HER2[-targeted therapy]. Now, I am a little bit bolder and give those patients HER2[-targeted therapy] with the idea that the disease will go into remission, and [we can] worry about ILD later.

Namita Chittoria, MBBS, of the University of Utah, focused on TNBC. What is important for practicing oncologists to know about advancements in this space?

The biggest advance in recent years is the approval of sacituzumab govitecan-hziy [Trodelvy] as a third-line therapy [for patients with unresectable locally advanced or metastatic TNBC who received 2 or more prior systemic therapies, with at least 1 of prior therapy for metastatic disease]. The data are compelling to use this drug in patients with metastatic breast cancer.

The second biggest advance or practice-changing development was the approval of pembrolizumab [Keytruda] in the adjuvant setting alongside carboplatin plus paclitaxel, followed by epirubicin and cyclophosphamide in patients with stage II or III, early-stage, nonmetastatic, TNBC. There are some developments in terms of the adjuvant setting, such as the phase 3 OlympiA trial [NCT02032823], which evaluated [adjuvant] olaparib [Lynparza] in patients with a germline *BRCA1/2* mutation.

Moving to the presentation by Cristina DeCesaris, MD, of the University of Utah, on novel and de-escalation radiotherapeutic regimens in breast cancer, what would you say has emerged in this space?

The techniques are getting better, and they are getting safer. The biggest advance is that there are many clinical trials whose results are going to be practice-changing, because they're incorporating biologic features of the disease captured with [the Oncotype DX test], primarily to escalate or de-escalate radiation therapy. [The field is] moving away from the one-size-fits-all [treatment approach] and is looking into the biology of the disease and accordingly tailoring [a patient's] radiotherapeutic approach.

Do you have any anecdotal experiences with de-escalated therapy?

Our institution participates in the phase 2 I-SPY trial [NCT01042379]. Up until recently, the dogma was to complete a set of agents in the preoperative setting. I-SPY has pushed the envelope a little further, and with the use of MRI and biopsies, we get what is called a pre-residual cancer burden [RCB]. Pre-RCB [gives] the probability of having achieved complete pathologic response [pCR] based on the MRI and the tumor biopsy.

If the pre-RCB is high, the patient has a high likelihood of having achieved a pCR. Then they do not need to receive epirubicin and cyclophosphamide, the second half of the treatment. Thus far, with all the patients that we have subjected to pre-RCB, their pre-RCB [result] was consistent with [their achieving] a complete response. [In those cases,] we omitted the epirubicin and cyclophosphamide, and the patients underwent surgery.

Is there any ongoing or planned research at Huntsman Cancer Institute that you wanted to highlight?

The FORESEE trial [NCT04450706] that we are doing integrates the development of patient-derived xenografts and patient-derived organoids in patients with HR-negative breast cancer. [The study is examining] newly diagnosed

patients with metastatic breast cancer—either TNBC [in the] first line or HR-positive, HER2-negative breast cancer that has exhausted endocrine options. We take a biopsy, and we generate patient-derived organoids. Those organoids are miniature reflections of the patient's cancer, and we leverage those organoids to conduct medium-throughput drug screens.

We integrate the information we collect from those medium-throughput drug screens, [along] with circulating tumor DNA and tumor tissue DNA testing and compile a report that we share with the patient, with the most likely drugs that the patient will respond [to] as a second-line therapy.

We would like to foresee what the optimal treatment is for patients in the second line in metastatic TNBC or metastatic HR-positive, HER2-negative breast cancer that has exhausted all endocrine options, because right now, the choice of second-line therapy comes down to a little bit of guessing work. We [usually] give patients chemotherapy that the cancer has not seen before, assuming that these chemotherapies will have the best benefit. However, we call it functional precision oncology, because essentially, we move it one step further. We don't look at the DNA and the RNA right now. We take snapshots of the genomic composition of the cancer. But we leverage those organoids to do medium-throughput drug screens.

What other questions are trying to be answered in clinical research in breast cancer?

Some of the questions have to do with what the future will bring and how all those novel therapies are going to be integrated. The phase 3 KEYNOTE-355 trial [NCT02819518] led to the current standard of care of chemotherapy with pembrolizumab. The key question that I have is whether we need to treat everybody with this intensive regimen vs spreading a few agents, spreading a few cycles, or spreading certain toxicities [over time] in patients who are going to do well either way. We as a scientific community are doing clinical trials to understand [that and] de-escalate therapy. We are not there yet, but hopefully we are going to get there.

How would you summarize all the advances that we have seen in breast cancer recently, where the field is now, and potentially where it is heading?

Now we are [relying more on] MammaPrint, OncotypeDX, next-generation sequencing, *PIK3CA* [mutation status], mutational burden, and mismatch repair proficiency or deficiency. All those biomarkers are increasingly having therapeutic implications. Advances in understanding the biology of breast cancer bring more biomarkers and more biomarker-driven therapeutic interventions [to patients]. ■

Gene Expression Model Predicts PFS in Follicular Lymphoma

Jason Harris

A “ROBUST” 23-GENE expression-based model successfully predicted progression-free survival (PFS) for patients with follicular lymphoma enrolled in the phase III randomized PRIMA trial.

Investigators identified 395 genes that were associated with the risk for progression, 23 of which were included in a predictive model based on both B-cell biology and tumor microenvironment. In a multivariate Cox model for PFS adjusted on rituximab (Rituxan) maintenance treatment and Follicular Lymphoma International Prognostic Index 1 (FLIPI-1) score, the model independently identified patients at high risk for progression compared with those at low risk (adjusted HR [aHR], 3.68; 95% CI, 2.19-6.17; $P < .0001$). The 5-year PFS was 26% (95% CI, 16-43) in the high-risk group and 73% (95% CI, 64-83) in the low-risk group.

The predictor performances were confirmed in each of 3 individual validation cohorts. The aHR comparing high-risk to low-risk groups was 2.57 (95% CI, 1.65-4.01) in cohort 1, 2.12 (95% CI, 1.32-3.39) in cohort 2, and 2.11 (95% CI, 1.01-4.41) in cohort 3.

The median PFS was 3.1 years (95% CI, 2.4-4.8) for the high-risk group and 10.8 years (95% CI, 10.1-not reached) for the low-risk group ($P < .0001$) in the combined validation cohort. The risk for lymphoma progression at 2 years was 38% (95% CI, 29-46) in the high-risk group and 19% (95% CI, 15-24) in the low-risk group. In a multivariate analysis, the score predicted PFS independently of anti-CD20 maintenance treatment and of the FLIPI score (HR, 2.30; 95% CI, 1.72-3.07).

“This predictor can be used in routine practice and captures multiple aspects of the biology of the tumor and the heterogeneous composition of the tumor microenvironment,” Gilles Salles, MD, Service d’Hématologie Clinique, Centre Hospitalier Lyon Sud, Pierre-Bénite Cedex, France, and colleagues wrote.

“Together with clinical parameters such as the FLIPI index, this score might allow clinicians to better adjust existing therapeutic options according to the patient risk category. For patients at low risk of progression, short treatments with a low toxicity profile should be considered. For patients with high-risk FLIPI and 23-gene scores, having a 50% risk estimate of lymphoma progression at 2 years, new treatment options should be developed,” added Salles et al.

Salles and colleagues collected fresh-frozen tumor biopsies from 160 treatment-naïve patients participating in the PRIMA trial evaluating rituximab maintenance following

rituximab plus chemotherapy induction in patients with high-tumor-burden follicular lymphoma.

Patients were first treated with 1 of 3 regimens: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), or R-FCM (rituximab, fludarabine, cyclophosphamide, and mitoxantrone). After this induction phase, patients with a complete or partial response were randomly assigned to observation or rituximab maintenance for 2 years.

Investigators collected RNA from 150 patients. Formalin-fixed, paraffin-embedded biopsies were also available for 53 patients for the technical validation of gene-expression quantification on fixed tissue.

As mentioned above, the model generated from the training cohort was further evaluated in 3 independent validation cohorts of patients for whom formalin-fixed, paraffin-embedded biopsies obtained at diagnosis were available, including a distinct validation set of patients in PRIMA who were not part of the training cohort (cohort 1; $n = 178$), 201 patients from the University of Iowa/Mayo Clinic Lymphoma SPORE trial (cohort 2), and 109 patients from the Hospital Clinic University of Barcelona (cohort 3). Cohorts 2 and 3 consisted of newly diagnosed patients who were prospectively recruited in observational studies.

When investigators tested the 23-gene expression model in the independent cohorts, the digital gene-expression data met quality criteria for 460 (94%) of 488 formalin-fixed, paraffin-embedded samples, with performances ranging from 93% to 97% across the 3 cohorts.

“Despite recent progress in the stratification and management of patients with follicular lymphoma, a substantial proportion of patients are still underserved by existing standard treatment and have rapid progression of their disease,” wrote Salles et al. “Our gene-expression predictor could be valuable in the clinical setting to identify patients at high risk or low risk of progression so as to adjust the therapeutic strategy and enrollment for innovative treatments.” ■

REFERENCE

Huet S, Tesson B, Jais JP, et al. A gene-expression profiling score for prediction of outcome in patients with follicular lymphoma: a retrospective training and validation analysis in three international cohorts [published online February 20, 2018]. *Lancet Oncol*. doi: 10.1016/S1470-2045(18)30102-5.