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2024 YEAR IN REVIEW

NON-SMALL CELL LUNG CANCER

This year in review of 2024 milestones in non-small cell lung cancer (NSCLC) features coverage of the LAURA trial presented in June at the American Society of Clinical Oncology meeting in Chicago, Illinois, and the EMPOWER-Lung 1 and the Beamion LUNG-1 studies presented in September at the World Conference on Lung Cancer in San Diego, California. It includes updated data from Beamion LUNG-1 shared at the European Society for Medical Oncology (ESMO) Asia meeting held in Singapore in December, as well as an interview with Edgardo Santos Castillero, MD, FACP, on the significance of the Beamion LUNG-1 results. This phase 1a/b dose escalation study examined zongertinib in patients with *HER2* mutation-positive NSCLC.

Updated Data Show Zongertinib Yields Responses in 71% With Previously Treated *HER2*-Mutated NSCLC

MARY CAFFREY | DECEMBER 13, 2024

Data presented December 6, 2024, show that zongertinib, an investigational oral *HER2*-specific tyrosine kinase inhibitor (TKI), produced responses in 71% of patients in a phase 1b study of previously treated patients with advanced non-small cell lung cancer (NSCLC).¹

Results for Beamion LUNG-1 (NCT04886804), presented at the European Society for Medical Oncology (ESMO) Asia conference in Singapore, are updated from data seen at the World Conference on Lung Cancer in September.²

Zongertinib, being developed by Boehringer Ingelheim, is a highly selective oral TKI that promises potent responses with a favorable safety profile. The oral administration

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would fill an unmet need for patients with *HER2*-mutated NSCLC.

In his presentation in Singapore, Noboru Yamamoto, MD, PhD, deputy director of the National Cancer Center Hospital of Japan and chief of the Department of Experimental Therapeutics, explained that *HER2* mutations are seen in 2% to 4% of all patients with NSCLC, and these patients are more likely to have brain metastases and poor outcomes than other patients with the disease.

Approximately 48% of *HER2* mutations are in exon 20, the active site of the tyrosine kinase domain, Yamamoto said. Zongertinib, he explained, is an irreversible TKI that selectively inhibits *HER2* while sparing *EGFR*, “thereby avoiding associated toxicities.”

Zongertinib has been studied at doses of 120 mg/d and 240 mg/d. The results shared at ESMO Asia involve 75 patients who were given a 120-mg dose of zongertinib once daily. These patients had a median age of 62 years; 68% of the group was female, 53% were Asian, 32% were White, and investigators did not have a race recorded for 15%.¹

Among the patients, 35% were former or current smokers, while 65% had never smoked. A little more than half (56%) had 1 prior line of systemic therapy, 16% had 2 lines, and 28% had 3 or more lines of treatment.

Results were as follows¹:

- Zongertinib at 120 mg/d yielded a confirmed overall response rate by central review of 71% (95% CI, 60%-80%; $P < .0001$), with a disease control rate of 93%.
- At 6 months, the time-to-event data show progression-free survival of 69% and duration of response at 73%, which investigators said suggest responses are durable. Data are not yet mature.
- At the time of data cutoff, 55% of patients remained on treatment.

“This data update adds to the body of evidence indicating that zongertinib could be a future option for patients with

[NSCLC] who have activating *HER2* mutations, a patient population for which targeted treatment options are currently severely limited,” Yamamoto said in a statement.³ “These data demonstrate the potential of zongertinib and support the long-term vision to change the benchmark for *HER2* mutation–driven cancers.”

Zongertinib was granted FDA fast track designation in 2023 and received breakthrough status earlier in 2024.

Safety data were highly favorable, with only 4 patients of the 75 (5%) requiring a dose reduction and only 2 patients (3%) stopping the drug due to adverse events (AEs). Most treatment-related AEs were manageable; only 1 patient had grade 3 diarrhea, and no patients had interstitial lung disease.

Zongertinib was granted FDA fast track designation in 2023 and received breakthrough therapy designation earlier in 2024.³ A phase 3 study, Beamion LUNG-2 (NCT06151574), plans to enroll 270 patients with unresectable or metastatic nonsquamous NSCLC harboring *HER2* tyrosine kinase domain mutations to compare zongertinib with standard of care. ●

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Osimertinib Offers 84% Improvement in PFS Over Standard of Care in Stage III Unresectable *EGFR*-Driven NSCLC

MARY CAFFREY | JUNE 2, 2024

The targeted therapy osimertinib (Tagrisso; AstraZeneca) improved progression-free survival (PFS) by a whopping 84% over the current standard of care in patients with *EGFR*-mutated non–small cell lung cancer (NSCLC) who are not eligible for surgery, according to findings from the phase 3 LAURA trial (NCT03521154).

The findings were presented during a plenary session at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting.¹ The results seem certain to lead to this patient population being treated with the third-generation tyrosine kinase inhibitor. Osimertinib is already approved for patients with *EGFR*-mutated stage IV NSCLC and as adjuvant therapy for those with stage IB to IIIA disease.¹

The immune checkpoint inhibitor durvalumab (Imfinzi, AstraZeneca) has been the current standard of care for patients with unresectable NSCLC following chemoradiotherapy. “While this has been used routinely for the past few years, whether this benefits patients with *EGFR* mutation has not been clear,” Suresh S. Ramalingam, MD, FACP, FASCO, said during a press briefing. “In fact, a subset analysis of the pivotal PACIFIC study that showed durvalumab is the new standard of care failed to show a difference in outcomes for patients with *EGFR* mutation between durvalumab and placebo.” Ramalingam is executive director of Winship Cancer Institute of Emory University in Atlanta, Georgia.

The international LAURA trial enrolled patients with unresectable stage III NSCLC with *EGFR* mutations whose disease had not progressed during or after treatment with definitive platinum-based chemoradiotherapy. Patients were randomly assigned 2:1 to receive osimertinib (n=143) or placebo (n=73). Disease progression was verified with CT scans and MRI at baseline and intervals.

The median age of the participants was 62 years in the osimertinib group and 64 years in the placebo group; the osimertinib group was 63% women, and the placebo group was 58% women. Most patients were Asian (81% in the osimertinib arm, 85% in the placebo arm) and had never smoked (71% in the osimertinib arm, 67% in the placebo arm).

FINDINGS. Results overwhelmingly favored osimertinib. The median PFS for patients taking osimertinib was 39 months compared with less than 6 months for those taking placebo. Patients whose cancer progressed while on placebo could switch to osimertinib, and 81% did, Ramalingam said.

Detailed results showed the following²:

- Osimertinib significantly improved PFS by blinded independent central review compared with placebo (HR, 0.16; 95% CI, 0.10-0.24; $P < .001$).
- Interim overall survival (OS) analysis (20% maturity) showed a trend in favor of osimertinib (HR 0.81; 95% CI, 0.42-1.56; $P = .530$).
- Median PFS in the osimertinib group was 39.1 months (95% CI, 31.5-not calculable) compared with 5.6 months (95% CI, 3.7-7.4) for the placebo group.
- The 12-month PFS rate was 74% for osimertinib vs 22% for placebo; the 24-month rate was 65% vs 13% favoring osimertinib.
- All-causality adverse events (AEs) were reported in 98% of the osimertinib patients vs 88% of those on placebo; grade 3 or higher events affected 35% vs 12% of patients, respectively, and serious AEs were seen in 38% vs 15%, respectively. AEs leading to discontinuation were reported in 13% vs 5%, respectively.
- Pneumonitis was the most common AE, Ramalingam said. He noted that the duration of treatment for osimertinib patients was almost 4 times higher, so this group was more likely to report AEs.

Based on these results, Ramalingam said, osimertinib will become the new standard of care “for patients with locally advanced non–small cell lung cancer following definitive chemoradiation, and *EGFR* mutation testing should be conducted for patients.”

David R. Spigel, MD, chief scientific officer at Sarah Cannon Research Institute in Nashville, Tennessee, who also spoke at the press briefing, noted the significance of the findings for patients and their physicians. He praised the study team for offering patients in the placebo arm the opportunity to cross over into the osimertinib arm.

“We don’t always do that, because we’re trying to find an overall survival benefit. But in this case, it was the right thing to do,” he said. “When patients progress, they don’t always get a chance to get that crossover therapy or their next line of therapy. In fact, in lung cancer, about 40% of patients will never make it to the next line of therapy.” Spigel said the findings would be “practice changing” as soon as there is new indication.

The results were published simultaneously in the *New England Journal of Medicine*.³

NEED FOR TESTING. In response to a question from *The American Journal of Managed Care*[®], Ramalingam addressed barriers to

next-generation sequencing or *EGFR* testing required to access osimertinib, which several physicians at the press briefing said falls short of where it should be.

“There are some practical barriers. And then there are some other barriers that we continue to face, such as insurance coverage being an issue [or] patients not having access to dedicated teams that can provide the sort of expertise that is needed. We see that specifically in the underrepresented minority patients, where the gap for not undergoing testing is even wider,” Ramalingam said. He also noted problems such as insufficient tissue being collected for testing, which may someday be solved with the use of liquid biopsy.

“Still, sometimes you have to go back for the second biopsy,” he said. “There is still an awareness issue. I don’t think everybody is fully aware of the implications of the value of molecular testing and how critical it is to make treatment decisions for patients.”

ADRIATIC Findings in LS-SCLC

Consolidation therapy with durvalumab, given after chemoradiotherapy, allowed patients with limited-stage small-cell lung cancer (LS-SCLC) to live almost 2 years longer than patients who received chemoradiotherapy alone, according to results presented at ASCO.⁴ Spigel presented results from the phase 3 ADRIATIC trial (NCT03703297) during the plenary session, after others called the findings “practice changing” during a press briefing.

“There really have not been any major advances in the treatment of limited-stage small cell lung cancer for several decades,” Spigel said. “The standard of care is concurrent chemoradiotherapy, but despite that, most patients will have relapsed within 2 years, and a minority of patients will survive 5 years.”

Lauren Byers, MD, a professor and chief of the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, agreed that ADRIATIC is a landmark trial.

“In this trial, patients with this cancer who received the addition of immunotherapy after traditional chemotherapy and radiation lived longer and were less likely to have their cancer recur,” said Byers, who is well known for identifying 4 subtypes of SCLC. “It’s also an important study because of the magnitude of benefit that patients receive for the addition of durvalumab consolidation, with the average improvement in overall survival around 2 years. This is in contrast to many clinical trials in small cell lung cancer, where often the benefit may only be measured in months.”

The trial enrolled 730 patients with LS-SCLC who had finished their course of chemoradiotherapy within the past 6 weeks. The results presented at ASCO showed that 264 patients were randomly assigned to receive durvalumab, a PD-L1 antibody, and 266 received placebo. An additional cohort received a combination of durvalumab and a CTLA-4 inhibitor, tremelimumab (Imjudo; AstraZeneca), but Spigel explained those results were not ready.

Spigel explained the ADRIATIC trial’s rationale was based on earlier trials in NSCLC: the phase 3 PACIFIC2 trial (NCT03519971) evaluated durvalumab after chemoradiotherapy in stage III NSCLC, and the phase 3 CASPIAN trial (NCT03043872) looked at durvalumab with or without tremelimumab following chemotherapy in extensive-stage SCLC.

Detailed findings include the following⁴:

- At the data cutoff of January 15, 2024, the median OS was 55.9 months for patients who received durvalumab vs 33.4 months for those who received placebo, for an HR of 0.73 (95% CI, 0.57-0.93; *P* = .0104).
- Median PFS was 17 months for patients who received durvalumab vs 9 months for patients who received the placebo, for an HR of 0.76 (95% CI, 0.61-0.95; *P* = .0161).
- The 36-month OS rate was 56.5% in the durvalumab group and 47.6% in the placebo group. The 24-month PFS rate was 46.2% in the durvalumab group and 34.2% in the placebo group.
- Rates of severe AEs were 24% in both groups. Approximately 16% of the patients in the durvalumab group stopped treatment due to AEs, compared with 11% in the placebo group.
- Pneumonitis was seen in 38% of participants in the durvalumab group, compared with 30% in the placebo group. Grade 3 or 4 pneumonitis was similar between the groups (3.1% in the durvalumab group and 2.6% in the placebo group).

FDA UPDATES

On June 10, 2024, FDA accepted AstraZeneca’s supplemental new drug application for osimertinib and granted a breakthrough therapy designation for the treatment of certain adult patients with stage III *EGFR*-mutated non-small cell lung cancer (NSCLC) after chemoradiotherapy, based on results of phase 3 LAURA trial (NCT03521154).

On September 25, 2024, FDA approved osimertinib for adult patients with locally advanced, unresectable, stage III NSCLC whose disease has not progressed during or following chemoradiotherapy and whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.⁵ ●

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New Hope for Rare but Challenging *HER2* Mutations in NSCLC

CHRISTINA MATTINA | SEPTEMBER 9, 2024

Novel targeted therapies show promising signs of treating *HER2*-mutated non–small cell lung cancer (NSCLC), according to new results presented in the second Presidential Symposium at the 2024 World Conference on Lung Cancer (WCLC).

About 1 in 5 patients with breast cancer carry the *HER2* mutation,¹ but it is much rarer in lung cancer, seen in approximately 2% to 4% of patients with NSCLC.² There is also a great unmet need for these patients, considering the poor prognosis driven by brain metastases and that current treatment options are limited to chemotherapy and antibody-drug conjugates. Abstracts detailing the results of novel agents were selected for the WCLC symposium on September 9, 2024, in San Diego, California.

SOHO-01: BAY 2927088

Xiuning Le, MD, PhD, of The University of Texas MD Anderson Cancer Center, presented findings from the phase 1/2 SOHO-01 study (NCT05099172) of BAY 2927088, a novel oral tyrosine kinase inhibitor (TKI), in patients with *HER2*-mutant NSCLC.² These data focused on a cohort of patients who had received chemotherapy but no prior targeted therapy. Of these 44 patients, 63.6% were female and 18.2% had brain metastases at baseline.

Investigator assessment by RECIST 1.1 criteria revealed a 72.1% overall response rate (ORR) and 83.7% disease control rate (DCR), with tumor shrinkage observed regardless of *HER2* alteration subtype and presence of brain metastases. Le described the good tolerability and manageable adverse events (AEs) observed with BAY 2927088, with no new safety signals seen.

“These data support ongoing investigation of BAY 2927088 in patients with *HER2*-mutated non–small cell lung cancer,” Le said. In a press briefing following the symposium, she confirmed that the phase 3 SOHO-02 trial (NCT06452277) is ongoing in hopes of providing further evidence. She also noted that if oral TKIs can move into the frontline setting, their convenience and tolerability compared with those of chemotherapy could improve quality of life for patients and allow them to stay on the treatment for a longer duration.

Beamion LUNG-1: Zongertinib

Data from the phase 1b Beamion LUNG-1 trial (NCT04886804) of zongertinib were presented by Gerrina Ruiter, MD, PhD, of Netherlands Cancer Institute.³ These results focused on 2 dosages of the novel oral *HER2*-directed TKI in patients with pretreated NSCLC with a *HER2* mutation in the tyrosine kinase domain. Of the 132 patients, 75 received 120 mg and 57 received 240 mg daily; the proportions with brain metastases were high, at 37% and 46%, respectively.

Tumor shrinkage was observed in 94% of patients; the ORR was 72.4% in the 120-mg group and 78.2% in the 240-mg

group, and the DCR was 94.8% and 100.0%, respectively. Data on progression-free survival and duration of response were immature, as two-thirds of patients were still receiving treatment as of the data cutoff in May; however, in the press briefing, Ruiter said those data should be available by the end of this year. Most treatment-related AEs were manageable, and zongertinib also showed encouraging preliminary intracranial activity.

“Zongertinib demonstrated significant and clinically meaningful activity in patients with pretreated NSCLC with a *HER2* tyrosine kinase domain mutation, including in those with brain metastases,” Ruiter said. The agent has been granted a breakthrough therapy designation by the FDA, and investigators are now enrolling for the Beamion LUNG-2 phase 3 trial.

A Patient Perspective on the Findings

At the press briefing, patient advocate Angus Pratt took to the podium to share what these findings mean to him. When he was diagnosed with breast cancer in 2018 followed by a diagnosis of lung cancer, he heard a lot of discussion of *HER2* as it relates to breast cancer, but not as much about its role in lung cancer, so he is excited that “we’re starting to understand that some of these genetic drivers cross over between the solid tumors.”

There is still work to do to get these advances into the hands of patients who will benefit, Pratt said. Approximately 43% of patients do not receive biomarker testing before treatment, and considering that all the work presented here was based on biomarker data, “it is so critical that we advocate and make sure that patients have biomarker testing done before they begin treatment.” He also praised the emerging focus on central nervous system progression in this research, as the brain is often the first place that lung cancer spreads to.

“I’m really excited as I sit here and think about the variety of treatments that have been presented here today. The options for [patients with] lung cancer are growing, and we’re seeing so many exciting, new, novel treatments. Yes, these are probably 3, 4, 5 years from market and availability to patients, but those who are coming behind me will need these. It’s just an exciting moment to be involved,” Pratt concluded. ●

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Emerging Therapies in *HER2*-Mutant NSCLC: Expert Insights

From John Heymach, MD, PhD

KYLE MUNZ | SEPTEMBER 10, 2024

The opening day of the 2024 World Conference on Lung Cancer in September included a session that shined a spotlight on novel therapies being developed for clinical use. Speakers discussed unmet needs in lung cancer, future treatment perspectives, emerging therapies, and the selective targeting of *HER2* in non-small cell lung cancer (NSCLC).

Following his *HER2* presentation, John Heymach, MD, PhD, chair of the Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, spoke with *The American Journal of Managed Care (AJMC)* on current advancements in this field, important considerations for patient selection, the safety and tolerability of *HER2*-targeting therapies, future research efforts, and more.

“There are still a lot of patients who don't get appropriate [next generation sequencing] testing. This is an important need in this field....”

AJMC: What are the latest advancements in selectively targeting *HER2* in NSCLC, and do these approaches differ from traditional *HER2*-targeted therapies used in other cancers?

HEYMACH: Currently, we don't have any oral agents approved for *HER2*-mutant lung cancer. The only approved targeted treatment for these patients is the antibody-drug conjugate [ADC] trastuzumab deruxtecan, which is a drug that has activity but comes with significant toxicities, and the duration of responses is modest.

Earlier oral medications—earlier tyrosine kinase inhibitors [TKIs]—had been tested for these patients, but the drugs carried substantial toxicities and treatments were not highly effective. So, in light of that background, our results were very encouraging because we sorted 2 TKIs: zongertinib [BI 1810631; Boehringer Ingelheim] and the Bayer BAY 2927088 compound.

Both were highly effective in terms of inducing responses, each with response rates around 70%. Now, the data are still early, and we don't yet have this whole set of data available, but given the high response rate, I think it seems likely that

in the near future we're going to have an oral medication that's highly effective in patients with this disease.

AJMC: In your opinion, what are the most critical factors in identifying patients who would benefit most from *HER2*-targeted therapies?

HEYMACH: In recent years, we've seen an increase in the number of patients who are receiving what we call next-generation sequencing [NGS], and this is critical because patients with *HER2* mutations can have a wide variety of different mutations. There isn't one single mutation that you can run a test for. For that reason, it's critical that NGS or a similar approach be taken.

It's worth noting that tests used for breast cancer—for example, *HER2* amplification or *HER2* immunohistochemistry—are not relevant to this population in lung cancer. It's *HER2* mutations that we're targeting that can only be discovered with sequencing. NGS was not widely used until the last couple of years for lung cancer, and it still has not been implemented at the levels that are needed for the population. So, there are still a lot of patients who don't get appropriate NGS testing. This is an important need in this field: to make sure that all patients with NSCLC get appropriate NGS testing, and that includes *HER2* as part of that testing.

AJMC: What are the common mechanisms of resistance observed in patients receiving *HER2*-targeted therapies in NSCLC, and how can these be managed?

HEYMACH: That's a great question. The data are still too early at this point, so we have not identified common mechanisms of resistance. We know from similar types of drugs with *EGFR*, which is a related gene, that resistance can arise through multiple mechanisms. You can get additional mutations in the gene itself, or you could turn on other pathways, and we assume similar things will occur with *HER2*. But none of that data has been reported yet because it's still too early, and we don't have a big enough experience with patients with resistance.

AJMC: Are there ongoing studies exploring combination therapies or novel agents to address resistance?

HEYMACH: I think combination studies are just being started now. I am particularly enthusiastic about combinations of these oral medications with ADCs like trastuzumab deruxtecan or other similar drugs because we see each of those drugs works by a



different mechanism. And, so, we expect that by putting the 2 drugs together, we may be able to really target a drug resistance or prevent it from emerging more effectively. It's also worth noting that because these are different types of drugs, antibodies of conjugates like trastuzumab deruxtecan and the TKIs, the data we have so far suggest that resistance to the ADCs won't mean resistance to the TKIs, and you can still treat patients after they've progressed on the ADCs effectively with a TKI.

AJMC: How do the safety and tolerability profiles of selective HER2-targeted therapies in NSCLC compare with other targeted therapies or standard chemotherapy? Are there any unique adverse events associated with HER2 inhibition that clinicians should be aware of?

HEYMACH: The advantage of oral TKIs, or HER2-specific TKIs, is that they don't carry with them the toxicities associated with chemotherapy, like hair loss, significant nausea, or immune suppression. There are some toxicities observed, but, overall, they are much milder and much more easily managed. For zongertinib, there was, in some patients, diarrhea observed or mild rash. But this was always grade 1 or 2 and was easily managed. Very rarely did patients have to have a dose reduction. So, overall, it had a very favorable safety profile. In addition, occasionally patients had an elevation of their liver enzymes. But, again, this rarely required dose reduction.

For BAY 2927088, there was a higher rate of diarrhea, including grade 3 diarrhea, which is more serious. So it may require prophylactic management, where patients are given medications ahead of time to prevent it from occurring. ●

EMPOWER-Lung 1 Data Showcase Promise of Cemiplimab in NSCLC

KYLE MUNZ | SEPTEMBER 9, 2024

The use of immunotherapy in lung cancer was a theme throughout the 2024 World Conference on Lung Cancer, as seen in a presentation led by Ana Baramidze, MD, PhD. Baramidze provided insights into the phase 3 EMPOWER-Lung 1 trial (NCT03088540) and presented 5-year outcomes associated with cemiplimab monotherapy in patients with non–small cell lung cancer (NSCLC) with lower expression of PD-L1.

In this interview with *The American Journal of Managed Care* (AJMC), Baramidze elaborates on the study's key findings and outlines the patient characteristics most important for a clinician to consider ahead of initiating treatment with this PD-L1 inhibitor. Baramidze is head of the Department of Clinical Research at Todua Clinic in Tbilisi, Georgia.

This transcript has been lightly edited for clarity.

AJMC: What do the 5-year outcomes of the EMPOWER-Lung 1 trial reveal about the long-term efficacy and safety of cemiplimab (Libtayo; Regeneron) monotherapy? Are there any new insights or unexpected findings from this extended follow-up?

BARAMIDZE: EMPOWER-Lung 1 is a trial that investigated the efficacy and safety of the PD-L1 inhibitor in patients with advanced non–small cell lung cancer. Five-year outcomes provide valuable insight into the long-term effects of the treatment, and the 5-year follow-up data generally showed that cemiplimab monotherapy continues to provide significant long-term survival benefits. In terms of safety profile, cemiplimab still remains consistent

with earlier reporting, and the new treatment-related adverse events are generally manageable. The key findings were that we have seen the durability of response, and the patients who initially responded well to cemiplimab often continued to benefit from the treatment.

In summary, I can say that the 5-year outcomes from the EMPOWER-Lung 1 trial reinforce the long-term efficacy of cemiplimab monotherapy, and it highlighted its potential for durable responses and manageable long-term safety. This finding further supports the availability of this treatment for non–small cell lung cancer, advanced or metastatic.

AJMC: How should clinicians select patients for cemiplimab monotherapy in advanced NSCLC? Are there additional biomarkers or patient characteristics that could further refine eligibility or predict response?

BARAMIDZE: Based on the outcomes of EMPOWER-Lung 1, clinicians should consider several key factors when selecting the patient for the cemiplimab monotherapy in advanced non–small cell lung cancer. But the key biomarker is PD-L1 expression for predicting the response. Higher PD-L1 expression levels in tumor cells correlate with better response to cemiplimab. ●

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Zongertinib Offers “The Best Toxicity Profile I Have Ever Seen,” Santos Says

INTERVIEW BY MARY CAFFREY | DECEMBER 2024

Updated data for Beamion LUNG-1 (NCT04886804) for zongertinib, the investigational oral *HER2*-specific tyrosine kinase inhibitor (TKI) for patients with *HER2*-mutated non–small cell lung cancer (NSCLC), were presented at the European Society for Medical Oncology (ESMO) Asia conference in Singapore on December 6, 2024.¹ Following the release of these updated data, *The American Journal of Managed Care (AJMC)* sought insight on the results from Edgardo S. Santos Castellero, MD, FACP, FASCO, who practices with The Oncology Institute (TOI) of Hope and Innovation in Broward County, Florida.

Santos is a clinical associate professor at the Charles E. Schmidt College of Medicine at Florida Atlantic University; medical director at Broward County, Florida, for TOI; vice president of the Florida Society of Clinical Oncology (FLASCO); and president of the FLASCO Foundation. He is also a member of the Membership Committee and an editorial group member of the International Association for the Study of Lung Cancer, a member of its Evidence-Based Medicine Committee and Head and Neck Guideline Advisory Group, and a member of the 2023–2024 ASCO–SEP Item Writing Task Force for the American Society of Clinical Oncology (ASCO).

This interview has been edited for length and clarity.

AJMC: Could you characterize the unmet need of patients with *HER2*-mutated NSCLC who have exhausted current therapies?

SANTOS: First, I want to thank *AJMC* for having this important discussion on *HER2*-mutated [NSCLC]. In my opinion, there are unmet needs that we have here today. Even though *HER2* has shown to be a driver mutation in lung cancer, we still don't have a medication that is approved by the FDA as a frontline [therapy]. We have an approval...[for] a medication called trastuzumab deruxtecan [Enhertu; AstraZeneca], which is an ADC [antibody-drug conjugate] in second line or beyond.² It's a great medication with good results, but we still have a lot of room for improvement.

An ADC is an [intravenous (IV)] medication, and certainly, in the target therapy arena, most of our targeted therapies are oral medications. So, we still don't have [an approval] in lung cancer for these particular agents.... That is an unmet need because, at the end of the day, we have to have an active drug that also [ensures] the quality of life for all our patients, so the patient can take a medication with good efficacy and stay at home, and they don't have to go to the clinic and receive an IV medication. That would have a major impact [on] our patients' quality of life.

AJMC: Besides the need for an oral medication, are there other features you would be looking for

in a highly selective *HER2*-targeted TKI compared with therapies available today?

SANTOS: We have struggled for so many years trying to get targeted therapy in the *HER2* space until trastuzumab deruxtecan came along. We have many other kinase inhibitors approved by the FDA in other diseases, and we have tried to bring them to the lung cancer space as well, specifically the [NSCLC] population. We have medications such as afatinib [Gilotrif]...which is a pan-*HER* inhibitor—a TKI that is approved by the FDA for *EGFR*, which is *HER1* but not for *HER2*. Have we used it in the past in clinical practice? Yes, because of the lack of medication. We also have other medications, [such as] lapatinib [Tykerb], another TKI in the lung cancer space, as the same thing applied for furmonertinib [Ivesa] and erlotinib [Tarceva]. Dacomitinib [Vizimpro] is another example. All those kinase inhibitor oral therapies are approved by [the] FDA. But again, for these 2%, 3%, [or] 4% of [patients with NSCLC] who have *HER2* mutation, we don't have any yet in terms of oral...kinase inhibitors. So, certainly, we are looking for that opportunity.

The question is: Can we bring patients an agent that is truly a targeted therapy? When we talk about targeted therapy—first line or sometimes second line—we expect to have an overall response rate [of] at least above 50% to 60% that can translate into a meaningful progression-free survival [PFS], duration of response, and, ultimately, overall survival. That's exactly what we are looking [at] in thoracic oncology for our patients [with] *HER2* mutations, to have truly targeted therapy, and we are [still] waiting for that.

AJMC: We're looking at new data presented at ESMO Asia for zongertinib, and some of the newer data points shared were a PFS rate of 69% over 6 months and a duration of response of 73%. With the caveat that these data are not yet mature, do you believe these results will generate interest among physicians who treat patients with *HER2*-mutated NSCLC?

SANTOS: I started looking at data on this therapy when it was in development in phase 1 dose escalation, either once or twice a day. I have seen the transition from phase 1a to phase 1b, and prior to phase 1b...the sponsor decided to pursue 120 mg per day, which was presented at ESMO Asia.

As we have seen the transition from the phase 1a optimization to phase 1b, especially in cohort 1, which is the previously treated [NSCLC] population, we see how this agent has been very well tolerated. Again, with a targeted therapy, in the efficacy in the



Edgardo S. Santos Castellero, MD, FACP, FASCO

overall response rate that this agent has shown—especially with a very high 6-month [PFS] rate at 69% [and] a duration of response at 6 months of 73%, which is very high in a previously treated population—zongertinib looks very promising. There is no question that this agent will catch the attention of the thoracic oncologist.

AJMC: Let's turn to the safety data, which are very important for managed care. Of the 75 patients whose data were reported at ESMO Asia, 4 had adverse events requiring dose reductions, 2 required discontinuation, 1 had interstitial lung disease, and 1 patient had grade 3 diarrhea. Of these data, what impresses you as making a difference in the quality of life for your patients?

SANTOS: To be honest with you, zongertinib has the best toxicity profile that I have seen on any HER2 TKI. Most of the toxicity seen is grade 1; as you mentioned, there is only 1 case of grade 3 diarrhea. This is excellent, because [TKI] medication in other spaces gives us a lot of problems with our patients with grade 3 gastrointestinal [GI] toxicity. This medication at that level of GI toxicity seems to be very well tolerated because this is a very selective HER2 TKI. When we look these molecules, they basically spare everything that has to do with the EGFR, [or] the HER1. That's why there is no report on grade 3 rash or skin toxicity, which is very critical for our patients.

And...you just mentioned that dose reduction only occurred in 4 patients of the 75—that is only 5% dose reduction, [which] is [a] very low mean dose reduction.... In other medications for breast cancer that we have tried [moving] to the lung cancer [space], we have been unable to do it because of the dose reduction and...discontinuation, which was only 2 patients, [or] 3%, who discontinued [in this case]. This drug has a very good toxicity profile, and that's why I think the sponsor has filed this medication with the FDA for fast track designation and breakthrough therapy in lung cancer.³

We are very enthusiastic when we see this efficacy. The overall response rate for [these] particular 75 patients is 71%...in previously treated patients. This is truly targeted therapy, and having this toxicity profile, which looks very good, there is no question that we will be paying attention to this agent. Hopefully, we can have something for our patients in the near future.

AJMC: The investigators concluded by saying they will report more data at an upcoming conference. What will you want to see when the next round of data appear?

SANTOS: There is no question [that] these data from ESMO Asia are encouraging. In this cohort in phase 1b—to get any 75 patients with *HER2* mutations who have been previously treated with this great overall response rate—I don't know [whether]

we can get better than 71%. It has a great toxicity profile. The PFS is still not mature, but that rate at 6 months looks very good, as well as the duration of response. So, what I expect to see in the future—which could be either [the American Association for Cancer Research] or ASCO in Chicago in June—are the final results [of] PFS in these 75 patients.

Now, we didn't mention that zongertinib made a lot of noise at the World Conference on Lung Cancer in San Diego, [California, in 2024]. The investigators also reported on the [central nervous system] activity. The overall response rate on a patient [with] a brain lesion was 33%. But [what's] also very important [is that] there was a 74% disease control rate in the brain.⁴ So, what we want to see in the next presentation will be more mature data in these efficacy points, the [final] overall response rate...the final PFS, [and] the final duration of response.

As you know, the FDA, in this particular scenario, will likely approve the agent based on overall response rate and duration of response. I think this is moving in that direction. The next question will be [a] confirmatory trial; the sponsor is [already] moving on and developing Beamion LUNG-2 [NCT06151574], which will be first line vs standard of care for our patients with [a] *HER2* mutation in [NSCLC].

“...It is great to have this overall response rate in pretreated patients and to have a great toxicity profile. No interstitial lung disease has been reported....”

AJMC: Is there anything else you would like to add?

SANTOS: As I mentioned, the *HER2* mutation does not have anything approved in first line in lung cancer, and we need that. A lot of clinical trials are moving in that direction. Zongertinib is not an exception. Trastuzumab deruxtecan also has a first-line clinical trial [NCT05048797]. There is another agent—[an oral] TKI from Bayer—with a first-line trial [NCT06452277].

First line is an unmet need for all our patients with adenocarcinoma having a *HER2* mutation in the tyrosine kinase domain. It is our responsibility, as researchers and clinicians, to deliver to our patients the best therapy available in the frontline setting. We'll see what will happen. But certainly, in this particular case...it is great to have this overall response rate in pretreated patients and have a great toxicity profile. No interstitial lung disease has been reported on this, which has been the issue for other TKIs. As you know, a lot of our [patients with] lung cancer have received prior radiation therapy to the lung; many are heavy

smokers. Sometimes they are not, but at the end of the day, the disease is in the lung, so if we can avoid this interstitial lung disease...that will be great. ●

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