

City of Hope Claims Victory After Updated CROWN Presentation Data in NSCLC

At the 25th Annual International Lung Cancer Congress hosted by Physicians' Education Resource[®], experts in non-small cell lung cancer (NSCLC) met to debate the latest advances and treatment options and the hottest topics in the space. The competitors were City of Hope and the University of California San Diego (UCSD). The 3 rounds focused on top presentations in NSCLC over the past year. Read on for key insights from both teams.

Judges



Edward S. Kim, MD, MBA
City of Hope



Misako Nagasaka, MD
University of California, Irvine



Terence T. Sio, MD, MS
Mayo Clinic

University of California San Diego Team



Sandip P. Patel, MD



Karen Yun, MD



Amanda Herrmann, MD

City of Hope Team



Jyoti Malhotra, MD, MPH



**Erminia Massarelli,
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What Is Face-Off?

An educational program designed as a competition for teams to present to and against each other.

How Does It Work?

There are 3 rounds: data presentations, patient cases, and hot topics. During each round, both teams will have the chance to present and defend their ideas but also challenge the other team. The judges will be there to determine who will be worthy of the top prize.

Round 1: Data Presentation

Team City of Hope and 5-Year Updated CROWN Data

Presented by Erminia Massarelli, MD, PhD, MS

Investigators presented 5-year efficacy data from the phase 3 CROWN trial (NCT03052608) at the 2024 American Society of Clinical Oncology Annual Meeting.¹ The trial assessed patients with *ALK*-positive NSCLC being treated with lorlatinib (Lorbrena) at 100 mg once daily (n = 149) or crizotinib (Xalkori) at 250 mg twice daily (n = 147).

The current analysis data cutoff was October 31, 2023. Investigator-assessed end points included progression-free survival (PFS), objective response rate, duration of response (DOR), safety, and biomarker analyses.

The median follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm. At the median follow-up, the median PFS was not reached (NR) in the lorlatinib arm (95% CI, 64.3-NR) and 9.1 months (95% CI, 7.4-10.9) in the crizotinib arm (HR, 0.19; 95% CI, 0.13-0.27).

Investigators noted the overall survival (OS) at the time of the second interim analysis had not been reached and that follow-up is still ongoing.

For patients with baseline brain metastases, the median PFS was NR in the lorlatinib arm (95% CI, 32.9-NR) and 6.0 months (95% CI, 3.7-7.6) in the crizotinib arm (HR, 0.08; 95% CI, 0.04-0.19). For participants without brain metastases, the median PFS was NR (95% CI, 64.3-NR) and 10.8 months (95% CI, 9.0-12.8) in both groups, respectively (HR, 0.24; 95% CI, 0.16-0.36).

The time to intracranial progression was NR in the lorlatinib arm (95% CI, NR-NR) and 16.4 months (95% CI, 12.7-21.9) in the crizotinib arm (HR, 0.06; 95% CI, 0.03-0.12). For participants with brain metastases, time to progression was NR in the lorlatinib arm (95% CI, NR-NR) and 7.2 months (95% CI, 3.7-11.0) in the crizotinib arm (HR, 0.03; 95% CI, 0.01-0.13). For participants without brain metastases, rates were NR (95% CI, NR-NR) and 23.9 months (95% CI, 16.4-30.8) between both arms (HR, 0.05; 95% CI, 0.02-0.13).

Adverse effects (AEs) of any grade occurred in 100% of patients, with 77% experiencing grade 3/4 AEs and 44% experiencing serious AEs.

Investigators found that a dose reduction did not impact the efficacy of lorlatinib treatment if they had it within the first 16 weeks.

Patel / If the PFS is so good and we are at 5 years, why haven't we heard about OS yet, which is probably what matters most to this patient [population]?

Massarelli / First of all, we don't have mature data for OS

because these patients are surviving longer. If a patient is tolerating lorlatinib, [and surviving longer instead] of progressing after 5 years or 6 years, this is a golden point.

Patel / You nailed the question. I'm advocating alectinib [Alecensa] and brigatinib [Alunbrig] until lorlatinib. They're still getting lorlatinib. A plus B is always greater than A [alone]. The only way to disprove that is OS, and I haven't seen any OS data yet. How can I tell a patient that I'm going to use your best gun first, but after lorlatinib, [we don't have anything to use]?

Massarelli / After lorlatinib there are chemotherapy options.

Patel / If I use alectinib and brigatinib, I can use lorlatinib.

Massarelli / You don't [always] save for the best for last.

Patel / How can I know that without OS data?

Massarelli / They don't want to progress. It's scary.

Patel / That's scary, but not having a plan B...after drugs is equally scary for patients.

Team UCSD on 5-Year CheckMate 9LA Data

Presented by Amanda Herrmann, MD

The phase 3 CheckMate 9LA trial (NCT03215706) assessed nivolumab (Opdivo) at 360 mg every 3 weeks plus ipilimumab (Yervoy) at 1 mg/kg every 6 weeks plus chemotherapy every 3 weeks for 2 cycles of chemotherapy every 3 weeks for 4 cycles in patients with treatment-naïve stage IV/recurrent NSCLC and *EGFR/ALK* wild-type disease.²

The median follow-up for OS was 57.3 months in the combination arm and 64.5 months in the chemotherapy arm. All patients who had been randomly assigned had a median OS of 15.8 months in the combination arm and 11.0 months in the chemotherapy arm (HR, 0.73; 95% CI, 0.62-0.85).

For patients with PD-L1 expression of 1% or less, the median OS was 17.7 months vs 9.8 months in the chemotherapy arm (HR, 0.63; 95% CI, 0.49-0.83), and for those with PD-L1 expression of 1% or more, the median OS was 15.8 months vs 10.9 months (HR, 0.73; 95% CI, 0.59-0.90).

The median PFS for all randomly assigned patients was 6.7 months (95% CI, 5.6-8.0) vs 5.3 months (95% CI, 4.4-5.6) in both arms (HR, 0.70; 95% CI, 0.60-0.83). The 5-year PFS rates were 10% (95% CI, 7%-13%) and 4% (95% CI, 2%-8%). The ORR was 38% (95% CI, 33%-43%) vs 25% (95% CI, 21%-30%), and the median DOR was 12.4 months (95% CI, 8.7-20.2) vs 5.6 months (95% CI, 4.4-7.1). At 5 years, an ongoing response was observed in 19% (95% CI, 11%-27%) and 8% (95% CI, 2%-18%) of patients, respectively.

For patients with PD-L1 expression of 1% or less, the median PFS in the nivolumab arm was 5.8 months (95% CI, 4.4-7.7) and 5.0 months (95% CI, 4.2-5.8) in the chemotherapy arm (HR, 0.71; 95% CI, 0.54-0.93). The 5-year PFS rates were 9% (95% CI, 4%-15%) and 3% (95% CI, less than 1%-8%),

respectively. The ORR was 31% (95% CI, 23%-40%) and 20% (95% CI, 14%-28%), and the median DOR was 17.5 months (95% CI, 6.9-37.8) and 4.3 months (95% CI, 2.8-7.1). The ongoing response at 5 years was 25% (95% CI, 12%-40%) and 0%.

For patients with PD-L1 expression of 1% or higher, the median PFS was 6.9 months (95% CI, 5.6-8.9) in the combination arm and 4.7 months (95% CI, 4.2-5.6) in the chemotherapy arm (HR, 0.70; 95% CI, 0.56-0.87). The 5-year PFS rates were 10% (95% CI, 6%-16%) and 5% (95% CI, 2%-10%), respectively. The ORR was 43% (95% CI, 36%-50%) vs 28% (95% CI, 22%-35%), and the median DOR was 11.8 months (95% CI, 8.6-20.3) vs 5.6 months (95% CI, 4.3-8.0). At 5 years, ongoing responses were observed in 15% (95% CI, 6%-28%) and 10% (95% CI, 3%-23%) of patients.

For patients who discontinued the combination because of treatment-related AEs, the median OS was 27.5 months.

In the combination arm, the 5-year PFS was NR (95% CI, 44.8-NR) vs 16.8 months (95% CI, 7.1-NR) in the chemotherapy arm (HR, 0.52; 95% CI, 0.26-1.02). The 5-year PFS rates were 55% (95% CI, 39%-69%) and 38% (95% CI, 19%-58%), respectively. The ORR was 73% (95% CI, 58%-85%) vs 60% (95% CI, 41%-77%), and the median DOR was 59% (95% CI, 35%-76%) vs 46% (95% CI, 20%-69%).

The safety results were consistent with previously reported results.

Malhotra / Are you offering this regimen to all your patients with PD-L1 expression less than 1% or squamous histology?

Hermann / If they have PD-L1 expression less than 1%, this is a regimen that I would recommend to them. Squamous histology is something that I would think more about. The data were not quite as strong for that as for PD-L1. If they have *STK11/KEAP1* mutations or other high-risk features, this is a regimen that I'm recommending.

Malhotra / What do you do about maintenance? The maintenance is nivolumab and ipilimumab, but we know from the data that patients on average got only 4 to 5 cycles of ipilimumab before they discontinued it, so why even bother giving ipilimumab as maintenance while per the phase 3 POSEIDON trial [NCT03164616], you can offer them pemetrexed and durvalumab [Imfinzi], which was tested in the trial?

Patel / When you think about the goal of the dual immunotherapy maintenance, the ipilimumab, one thing to point out is it's 1 mg/kg every 6 weeks, so this is different from the "induction ipilimumab" that's used in melanoma and renal cell carcinoma. We use it in mesothelioma, as well, based on the phase 3 CheckMate 743 trial [NCT02899299]. This dose has a reasonable AE profile in terms of gastrointestinal toxicity while maintaining efficacy. We have data here already with CheckMate 9LA, and I have to make decisions in the clinic based on the data that are in

front of me, and between CheckMate 227 [NCT02477826] and CheckMate 9LA, it's a robust data set for that cohort as well.

Round 2: Case Presentation

Team UCSD on Metastatic *ROS1* Fusion-Positive NSCLC

Presented by Karen Yun, MD

- A 65-year-old woman with a history of tobacco use and no past medical history presented to the emergency department with 6 weeks of progressive cough, shortness of breath, and intermittent episodes of confusion
- CT scan of the chest, abdomen, and pelvis showed a right upper lobe consolidative mass, right hilar and mediastinal lymphadenopathy (LAD), subcranial LAD, moderate right pleural effusion, a 2.8-cm left retroperitoneal mass, and multiple bone lesions.
- Brain MRI found multiple small enhancing lesions in the supratentorial brain consistent with intracranial metastases and a 1.1-cm lesion in the right parietal calvarium.
- Pathology
 - Right thoracentesis with cytology positive for adenocarcinoma, CLDN4 positive, TTF1 positive
 - Bronchoscopy with endobronchial ultrasound. Fine needle aspiration of station 7 and 11L lymph nodes showed adenocarcinoma, TTF1 positive, PD-L1 TPS 90%.
- Treatment
 - Carboplatin at the area under the curve of 5 and pemetrexed given at 500 mg/m² for 1 cycle in the hospital given her burden of disease and symptoms
 - The patient decided to pursue comfort care, but after her liquid biopsy results were positive for an *EZR::ROS1* fusion, she was started on entrectinib (Rozlytrek) at 600 mg daily.
- Molecular testing
 - Liquid biopsy showed *EZR::ROS1* rearrangement, *TP53* p.Q331*, *BRCA2* loss (single copy deletion)
 - Tempus tissue next-generation sequencing (NGS) showed *EZR::ROS1* rearrangement, *TP53* p.Q331*, tumor mutational burden of 3.2 mut/Mb

Yun posed the question, "Would you treat this patient differently?"

Massarelli / At that time, because crizotinib doesn't have any brain penetration, it's excluded. It's a matter of entrectinib

or repotrectinib (Augtyro). I don't know whether you had the approval for repotrectinib at that time, but even if you had, repotrectinib does have problems with symptoms of dizziness and ataxia. We know repotrectinib has a very high penetrance and efficacy above 90% intracranial response. Eventually, it's to keep in mind. Entrectinib also has a difficult toxicity profile, though. I'm curious about whether your patient had neuropathy or any other issue.

Yun / She tolerated entrectinib well. She had only grade 1 dysgeusia and dizziness but otherwise has been doing well on the full dose of entrectinib.

City of Hope on Osimertinib for EGFR-Mutated Disease

Presented by Ramya Muddasani, DO, MS

- A 65-year-old woman, never smoker, presented in October 2022 with right upper quadrant abdominal pain.
- A biopsy confirmed she had *EGFR*-mutated exon 19 deletion, *MET*-amplified left lung stage IV NSCLC, and poorly differentiated sarcoma with focal squamous differentiation involving bone, thorax, and bilateral adrenal glands.
- She began osimertinib (Tagrisso) 80 mg once a day and preferred to defer chemotherapy.
- She has received multiple courses of radiation to her lung primary, right rib metastasis, right adrenal gland, and right parietal bone metastasis.
- In August 2023, she presented with *MET* amplification and began tepotinib (Tepmetko) in addition to osimertinib.
- In December 2023, she began a break of treatment for a parietal bone x-ray.
- A March 2023 CT scan of the chest, abdomen, and pelvis showed reduction in the size of the left upper quadrant mass and both adrenal metastases with no new sites of disease.

Muddasani asked, "What would you have done for this patient?"

Patel / If I saw this patient in my clinic, I would lean toward osimertinib. I congratulate you on getting NGS outside nonsquamous [disease] because a lot of [physicians] think it's just for squamous. In my clinic, I would offer osimertinib to this patient. I don't have a good sense of the burden of the disease and whether this patient has a high [rate] of brain metastasis where one may consider a phase 3 FLORA2 [of osimertinib plus chemotherapy] type of regimen [NCT04035486]. Without further details, my initial gestalt would be osimertinib monotherapy here.

Muddasani / I kept it simple because this is a basic case. What

would you do when the patient progresses after 11 months?

Yun / Given her repeat molecular testing, and especially in light of the *MET* amplification, the phase 3 MARIPOSA-2 trial [NCT04988295] regimen [of amivantamab-vmjw (Rybrent) plus chemotherapy with or without lazertinib (Lazcluze)] would be a good one in this case with amivantamab, which is targeting both *EGFR* and *MET*.

Muddasani / That is a very valid option. Given the *MET* amplification and the fact that the patient tolerated osimertinib well, we decided to add tepotinib. We added tepotinib at 225 mg once daily. As you can see, about 7 months later, the patient had a very good response to the right adrenal gland. I focused on that lesion because that was the largest site of progression. To this day, they continue to respond.

Round 3: Hot Topics

UCSD on Neoadjuvant Chemoimmunotherapy for Resectable NSCLC

Presented by Karen Yun, MD

Yun / I'll start this debate by arguing in favor of neoadjuvant therapy for resectable lung cancer. For years our standard-of-care treatment for resectable lung cancer has been up-front treatment, surgery followed by adjuvant radiation for positive margins, and/or chemotherapy for large tumors or positive nodes. The efficacy of adjuvant chemotherapy has shown only a modest benefit in improvement in survival. With the demonstration of immunotherapy and its efficacy in the metastatic setting, the idea here is whether we can move or use immunotherapy in the earlier-stage lung cancers in combination with chemotherapy, as this could be an opportunity to eliminate micrometastatic disease and increase the chance for curative surgery. Also, with the presence of the tumor antigen and with the bulk of the tumor still there, this could be an opportunity to enhance tumor response.

CheckMate 816 [NCT02998528] was the phase 3 clinical trial that looked at neoadjuvant nivolumab plus chemotherapy vs chemotherapy alone in patients with resectable lung cancer.³ This trial did exclude patients with *EGFR* and *ALK* alterations. This is the 4-year analysis that showed that neoadjuvant nivolumab plus chemotherapy was superior in terms of event-free survival [EFS] vs chemotherapy alone. The HR was 0.66. The other end point was looking at pathologic complete response [pCR]. CheckMate 816 showed an improvement in pCR with neoadjuvant chemoimmunotherapy vs chemotherapy alone. That's important because the investigators also looked at the association between pCR and EFS and showed that patients who were able to achieve pCR did have an improvement in EFS vs those who did not.

In terms of OS at the 4-year analysis, survival was not reached in either treatment arm. However, we can see here a trend toward

OS benefit in those patients who had received neoadjuvant chemotherapy with immunotherapy. This trial also looked at circulating tumor DNA [ctDNA] clearance, and they found that in patients who had received nivolumab plus chemotherapy, there was a higher rate of ctDNA clearance, and the HR for ctDNA clearance was higher in the chemoimmunotherapy arm vs those who had received chemotherapy alone.

City of Hope on Why Neoadjuvant Therapies Will Not Replace Adjuvant Treatment

Presented by Joyti Malhotra, MD, MPH

Malhotra / Neoadjuvant immunotherapy has now become the standard of care to be used before surgery for many patients. If we look at all the different neoadjuvant chemoimmunotherapy trials that have been reported for lung cancer, it does not help every single patient. We still are seeing many patients progress after nivolumab and chemotherapy, for example in CheckMate 816. We are also seeing now, for example, patients who do not show any response or do not have a pCR or major pathologic response after neoadjuvant treatment, and patients who have high-risk features on surgical pathology N2 disease, to name a few.

What do we do with these patients? Do we just say, “You got neoadjuvant treatment,” and that’s it? What neoadjuvant treatment is not good for is diplomatic relations between thoracic surgery and radiation oncology. Before neoadjuvant treatment, it was clear—resectable and unresectable. Since neoadjuvant treatments were approved, the consensus, or what we hear from a lot of our colleagues, is just to give neoadjuvant treatment and then we’ll see whether the patient [has] resectable [disease]. When we come to adjuvant therapy, that’s like the model of world peace. Both radiation oncology and thoracic surgery notes say the same thing. Follow up with medical oncology for adjuvant treatment. No discussions there. It’s completely clear. Now we have started seeing more data come out. We still do not have trials that are doing in-depth comparisons between what adjuvant treatment is adding in perioperative regimens to neoadjuvant, and now it’s a requirement in future trials per the FDA.

In the phase 3 CheckMate 77T [NCT04025879] trial, for example, we did see a signal.⁴ Patients who got

chemoimmunotherapy followed by nivolumab maintenance for a year and did not have a pCR did the same, as well as patients who got only chemotherapy and had a pCR. That shows that adjuvant treatment is adding something in addition to neoadjuvant treatment for N2 disease. There’s useful information we learn at the time of surgery. We can learn from serial ctDNA assessments even after surgery, which can only be incorporated in an adjuvant treatment plan and cannot be incorporated in neoadjuvant treatment. We haven’t started talking about *EGFR*-mutated NSCLC, where adjuvant osimertinib has hit the ball out of the park and neoadjuvant osimertinib did not meet the primary end point. It does make me think that neoadjuvant treatments are great, but they can be used for only 2 to 3 months. There’s a limited amount of time where neoadjuvant treatment needs to get to the maximal response before surgery is done. Maybe that’s not possible with some therapies. Sometimes you need longer than that, but you do not have the luxury of waiting for months and months to get to the maximal response or a pCR before surgery planning. In conclusion, adjuvant treatment is here to stay. Neoadjuvant treatments are not going to replace adjuvant treatment. They may work very well hand in hand. We have a difficult disease to treat. We have to use all the tools that we have and use biomarkers to decide which patient gets neoadjuvant, which patient gets adjuvant, and which patient gets both.

Kim / I am going to announce by split decision that the winner of tonight’s trophy face-off for the International Lung Cancer Conference 2024 is Team City of Hope! ■

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WINNERS

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