Results from the Phase II umbrella HUDSON study demonstrated that durvalumab, an anti-PD-L1 antibody, coupled with ceralasertib, an ATR inhibitor, boosted immune response and improved outcomes among patients with non-small cell lung cancer (NSCLC) (Nat Med 2024; https://doi.org/10.1038/s41591-024-02808-y).

"Non-small-cell lung cancer is the leading cause of cancer-related deaths," noted corresponding study author John Heymach, MD, PhD, Chair of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center. "In recent years, outcomes have improved for patients with metastatic non-small-cell lung cancer who are treated with chemotherapy and immunotherapy, which are the standard initial treatments. But, in almost all cases, tumors eventually become resistant and the available treatment options after that point have limited efficacy."

Heymach and colleagues conducted this study to address the critical need for improved combination therapies for patients whose tumors have become resistant to chemotherapy and immunotherapy, as well as to learn if genomic biomarkers could be used to tailor these treatments.

"We were interested in whether the immune system could be reactivated to fight the cancer by combining different types of targeted therapies with the standard immunotherapy drug durvalumab," he said.

Study Details
In this ongoing open-label, multicenter, umbrella Phase II trial (NCT03334617), the researchers evaluated rational combination regimens for advanced NSCLC following failure of anti-PD-(L)1-contacting immunotherapy and platinum-doublet therapy.

Study authors enrolled 268 patients with advanced NSCLC who progressed following standard-of-care therapy. The median age of participants was 63-64 years and 58 percent were male. Patients included in the trial underwent treatment with one of the following targeted therapies in combination with durvalumab: ceralasertib (ATR kinase inhibitor), olaparib (PARP inhibitor), danvatrisen (STAT3 antisense oligonucleotide), or olacrumab (anti-CD133 monoclonal antibody).

The study's primary objective is to assess the objective response rate (ORR) for each treatment combination. Secondary objectives include the following: assessment of disease control rate, progression-free survival, overall survival, and safety/tolerability.

"Exploratory objectives include investigations of cancer-relevant immune status, including biomarker analyses according to specific gene or protein expression profiles (e.g., PD-L1), and the usage of subsequent anticancer therapy," the study authors outlined.

Heymach and his team used comprehensive molecular profiling to match patients with one of the four different treatment arms based on specific biomarkers, he noted, while explaining that patients who did not have any of these biomarkers, called the "non-match" cohorts, could also be treated on the same arms.

"The study has an innovative design in that extensive molecular profiling is done at the onset and patients can be treated with specific therapies based on these biomarkers (match arms), but can also receive treatment if they don't match any arms (non-match arms)," Heymach said.

"This enables us to simultaneously investigate the effectiveness of different treatments, as well as the predictive biomarkers for tailoring therapy," he told Oncology Times. "The flexible study design also enabled investigators to test multiple combinations to find the most effective one and rapidly rule out combinations that do not appear to be effective."

"The major results of the study were that ceralasertib, a drug inhibiting the ATR kinase involved in DNA damage repair, provided the greatest clinical benefit of the four treatment arms."

—John Heymach, MD, PhD, at The University of Texas MD Anderson Cancer Center

Key Findings
The study authors evaluated the efficacy of the four rationale combinations to determine whether targeting specific pathways potentially associated with resistance could improve outcomes in this patient population. They observed notable clinical efficacy with the combination of ceralasertib and durvalumab.

"The major results of the study were that ceralasertib, a drug inhibiting the ATR kinase involved in DNA damage repair, provided the greatest clinical benefit of the four treatment arms," Heymach reported. "The progression-free survival was more than doubled at 5.8 months compared with 2.7 months for the other treatment arms.

"Furthermore, the patients who had the specific biomarker matched with this drug—alterations in the ATM gene or protein—had even greater benefit with a median progression-free survival of 8.6 months," he continued. "We also found that ceralasertib appeared to reactivate the immune system even for patients with tumors that were previously highly resistant to immunotherapy."

Data showed an objective response rate, the primary endpoint, of 13.9 percent (n=11/79) with durvalumab plus ceralasertib. In comparison, the pooled objective response rate across the other three treatment arms was 2.6 percent (n=5/189).

"All objective responses were confirmed partial responses. Disease control rates at 12 and 24 weeks, respectively, were 50.6 percent and 35.4 percent with durvalumab-ceralasertib and 32.3 percent and 15.9 percent with the pooled other regimens," the study authors stated. They also found that the benefit associated with durvalumab plus ceralasertib was consistent across known immunotherapy-refractory subgroups.

"ATM alterations confer ATR dependency in tumors. We observed an ORR of 26.1 percent (n=6/23) with durvalumab-ceralasertib in the ATM-altered biomarker-matched cohort, higher than the ORRs of 13.0 percent (n=3/23) and 6.1 percent (n=2/33) in the primary and acquired resistance biomarker-nonmatched cohorts, respectively, suggesting specific benefit of ATR inhibition in patients with ATM alterations," they noted in their recently published paper.
"Additionally, progression-free survival and overall survival appeared longer in the ATM-altered biomarker-matched cohort versus the primary and acquired resistance cohorts, respectively," they said. "Notably, while overall survival appeared longer in the acquired versus primary resistance cohorts, progression-free survival was similar."

Heymach and colleagues found that the mean durvalumab treatment duration was longer with durvalumab plus ceralasertib (8.7 months) when compared to other regimens (5.1 months). This was seen across cohorts. This analysis showed that the safety/tolerability profile for durvalumab plus ceralasertib was manageable.

"With durvalumab-ceralasertib and the other regimens, similar overall incidences of treatment-emergent adverse events (TEAEs; 93.7% and 89.9%), Grade ≥3 TEAEs (44.3% and 51.3%), treatment-related TEAEs (TRAEs; 75.9% and 71.4%), Grade ≥3 TRAEs (20.3% and 30.2%) and serious AEs (SAEs; 36.7% and 34.4%) were reported," according to the study authors, who observed a low and similar incidence of treatment-related serious adverse events and treatment discontinuation due to TRAEs with durvalumab plus ceralasertib and the other regimens.

Among patients receiving durvalumab plus ceralasertib, two (2.5%) died due to a TEAE (pneumonia and myocardial infarction, each n=1). Comparatively, five patients (2.6%) undergoing the other treatment regimens died due to a TEAE (cor pulmonale, dyspnea, sepsis, pneumonia aspiration, and renal artery thrombosis, each n=1). None were considered related to treatment, according to the study authors.

"Overall rates of TRAEs, Grade ≥3 TRAEs, and serious TRAEs were similar or numerically lower with durvalumab-ceralasertib compared with the other regimens, despite a >3-month longer mean duration of treatment," Heymach and team noted. "However, as with the efficacy data, these findings should be interpreted in the context of the limited follow-up in a number of patients receiving durvalumab-ceralasertib at data cutoff."

There are benefits to this study design, according to the study authors, who noted that modular designs make it possible to evaluate multiple combinations within a specific treatment setting simultaneously.

"Additionally, in the context of investigating molecularly targeted treatment, such study designs can encompass patients with a range of different targetable aberrations, potentially resulting in an increased proportion of screened patients meeting specific cohort eligibility requirements, in contrast to single-arm Phase II studies with a single set of eligibility criteria," they highlighted.

Heymach acknowledged there are also some limitations associated with the study. "Since biomarkers were used to guide patients into the different arms, the populations treated in the different arms are not the same and that some puts limitations in our ability to compare the results between arms."

In summary, this study showed an efficacy signal of interest with the combination of durvalumab and ceralasertib among advanced/metastatic NSCLC patients after prior failure of anti-PD-1/PD-L1 immunotherapy and platinum-doublet therapy, according to Heymach and team. "The regimen showed particular efficacy in patients with ATM alterations and biomarker-nonmatched primary and acquired resistance cohorts across various subgroups recalibrating to immune checkpoint blockade."

**Takeaways & Next Steps**
The Phase II HUDSON trial is the largest biomarker-driven study to date characterizing non-small cell lung cancer tumors that are resistant to immunotherapy, elucidating a variety of different ways that tumors can develop resistance to these drugs, according to Heymach. "It also establishes that it is feasible to use an immunotherapy-based combination to reactivate anti-tumor immunity in non-small cell lung cancer."

Based on these promising results, a Phase III study of ceralasertib and durvalumab has been launched that will definitively test whether this combination regimen is effective in patients who have progressed after platinum-doublet chemotherapy and immunotherapy. The Phase III LATIFY study (NCT05450692) compares durvalumab plus ceralasertib versus docetaxel in this patient population.