Good morning, good afternoon everyone. So this is a new Arizona in the lung cancer treatment that is analyzing the MRD, that is molecular residual analysis, that is from the ADORA trial by Thomas John et al. It was an oral abstract which was presented in ASCO this year. So just refreshing the ADORA phase 3 study design. So patients with completely resected stage 1b to 3a NACLC with or without adjuvant chemotherapy with EGFR exon 19 deletion and AL858R

They are randomized either to osimertinib 80 mg OD for 3 years versus placebo. So the 5-year updated analysis is the DFS with the Azar ratio of 0.27 and the 5-year OS was 88% versus 78% with the Azar ratio of 0.49. So what they did in this study is the main endpoint was whether they evaluated the feasibility of the ctDNA-based MRD detection, whether it is going to predict the disease recurrence either during adjuvant osimertinib treatment

or in the post-treatment fallout. So how they analyzed this? So they collected samples, that is the blood samples, plasma samples, the CT DNA samples were collected, one at the baseline, that is either during post-surgery or plus or minus adjuvant chemotherapy, that is at baseline. Then during adjuvant treatment, that is for the three years, every 12 weeks it has been collected. Then from three years to five years, first week 12 and 24, and then every 24 weeks. Then after five years, every 52 weeks, the sample has been collected.

So whether this tumor-informed MRD can be a biomarker for disease recurrence? Because in early stage NSLC and in adjuvant settings, detecting a ctDNA can be challenging because of the low tumor burden. And there are studies in early stage disease which support that the use of tumor-informed MRD assays can be done using an high-depth NGS.

So, when MRD is detected in plasma, that means that you are detecting clinically undetected cancer cells. So, it can be used as a biomarker for early disease recurrence and could inform the treatment and prognosis. In this study, how they did using a RADRR platform, that is from the tumor sample, all exam sequencing has been done, then from tumor specific CT DNA panel design has been created and then germline DNA panel validation has been done so that they are excluding the germline and chip variants.

And they analyzed the plasma longitudinal MRD monitoring via the NGS. So some definitions for this is, one is the MRD undetected at baseline, that is during randomization. The second is MRD detected at baseline. So even if detected at baseline, during treatment, that is the MRD clearance. That is, it is undetected within the first two time points. And the last one is MRD detected during study.

How the MRD detected means the plasma ctDNA becomes positive for one or more mutations in tumor-informed patients. And by analyzing this, they have assessed in relation with the DFS events. So MRD positive, it has been assessed in relation with the DFS events, that is the clinical recurrence or death in both arms. So in ADORA trial, total 682 patients were randomized, but

Tumor plus DNA samples were analyzed in 242 patients. Out of this 220 patients, the MRD analysis set was analyzed. 112 in the osimertrinib and 108 in the placebo arm. So baseline characteristics, they are almost similar in both arms. So as we know that because osimertrinib has been given, so MRD events were detected in 49% in the placebo group versus 13% in the osimertrinib group.

By doing surgery followed by plus or minus adjuvant chemotherapy, at baseline MRD was undetected in almost 92% of the patients, whereas 8% had MRD positivity. That is most common in the stage 2 and stage 3A patients.

Those patients who had MRD detected at baseline, they were associated with poor outcomes. So total number of patients were 18. Out of 18 patients, 5 patients were in the osmolitinib group. So here you can see the blue color is the osmolitinib. But even though MRD detected at baseline, in the first 3 patients you can see MRD clearance has been done. And they have completed 3 years of adjuvant osmolitinib. But after stopping the osmolitinib, the disease has recurred.

And the fourth and fifth patient, in the fourth patient MRD cleared but again it recurred and the disease has recurred. But the fifth patient there is no clearance. So out of five patients, three patients completed three years of adjuvant osmotonib and after stopping the disease again recurred. So a patient becoming MRD positivity, whether it is correlating with the DFS events, that is clinical recurrence or death, yes it has a mid-late time of around 4.7 months.

So after the completion of 3 years of adjuvant osmertinib, 86% of the patients in the osmertinib arm, they were DFS and MRD even free. Overall, that is 3 years of adjuvant osmertinib and 2 years of post-treatment follow-up, 75% of the population in the osmertinib arm, they were MRD negative or DFS even free.

and the rest 25% in that 25, 8% they recurred during the treatment and the rest 17% they recurred post treatment and that too if we dissect that 17% in the first one year post completion 58% recurred so within two years post treatment discontinuation almost 95% of the patients recurred so they have analyzed still further that is post three years of adjuvant osmolipidinib two years of follow-up

So two months, two years post-osmaltinib discontinuation 66% of the patient they had MRD or DFS even free. That means there is a group of population who is going to recur post stopping of adjuvant osmaltinib. So it has to be taken with a pinch of salt whether

Just like the Laura trial as Cyrus mentioned, post CTRT continuing the osmaritinib till progression or as per the ADORA, we have to stop it because still we don't have a data at present whether post surgery we have to continue more than three years or not. But this MRD, it will be in the future become a both prognostic and predictive marker whether to continue the treatment or to stop there.

So, coming to the conclusion, so in ADORA, we have three years of adjuvant osmertinib. It showed a statistically significant and clinically meaningful DFS and OS. And the tumor-informed MRD in ADORA, it was feasible. It identified recurrence with a mid-let time of around 4.7 months in this study. So, MRD analysis, it demonstrated the maintenance of both DFS and MRD even-free status for most patients during and also after osmertinib treatment.

and it was able to identify the molecular occurrence prior to the DFS events. As mentioned, the mid-late time of around 4.7 months, it highlights the potential to monitor and personalize patient care in the setting. So this is the more way forward. Thank you.