to 2 study presented in ASCO 24 and this I will be talking about in brief. Additionally, several questions remain unanswered and in fact, this is the unmet need that what are the further prognostic stratification factors, what is the optimal time to include this local consolidated therapy, what about genomic characterization of the residual lesions and is there any value of post local consolidated therapy CTDNA analysis.

So as I have spoken about, there are varying definitions of oligometacetic disease that have been used over the years but the most common is the ERTC isro consensus guideline definition. So maximum number of Metz 5, maximum number of organ systems involved 3, maximum number of Metz per organ 2, but diffuse serosal disease of the meninges pericardium, pluramisentry, bone marrow are usually excluded.

There are few important terminologies that are restricted only to oligometacetic NSCLC, I will not be covering all but what is important to know is that there is something known as Genuine or Deno oligometacetic disease and induced oligometacetic disease. So Genuine or Deno means they are oligometacetic from the start. Induced oligometacetic disease is they were polymetacetic at baseline that is more than 5 meds at baseline, they were given systemic treatment and then now their current state is often oligometacetic disease.

Another term that I would like to talk about is oligo persistence or oligo residual disease is that the oligo residual disease that is the disease which persists after initial treatment. What is important is that oligo progression is a different topic but what we will be dealing today is oligo persistence, oligo residual disease and induced oligometacetic disease.

So this has been the traditional teaching. So and this is the data from the MD Anderson group they had initially done this study in 2016 and they published the long-term data in 2019 and this was prior to the immunotherap era. So this is the only when chemotherapy was present or being used. So when they added local consolidated therapy to patients who had not progressed on systemic therapy there was a survival benefit. So here they added local therapy at three months. When they did a long-term follow-up in 2019 the only factor that was significant on multivariate analysis was the presence of the was actually giving local consolidated therapy even for molecular positive disease.

So this was prior to the Ose-Mertin-Nabira and they were using or giving local consolidated therapy early on in the treatment. So what they found is that this is a single arm study there was a significant prolongation of the PFS and OS. So median PFS of 17 months just with first and second generation EGFR TKI and a median OS of 55 months. But in the immunotherapy and targeted therapy era these concepts are evolving and being challenged.

So the NRGLU 002 study actually said which was published which was actually presented in ASCO 2024 that local consolidated therapy added to systemic therapy which includes immunotherapy.

Does not produce a significant benefit. Reducing toxicity and increasing biologically driven patient selection may actually optimize the therapeutic ratio. On the other hand there was one data presented in WCLC 2024 which said that ablation to all who residual disease in patients been treated with chemo and immunotherapy actually improved survival. So we have data on both the sides where local consolidated therapy did not improve survival and on the other hand local consolidated therapy did improve survival. So what is this study?

So this was a prospective real world observational study enrolling NSCLC patients with systemic therapy induced oligometacetic disease.

So not polymetaceticate means polymetaceticate baseline and they were having induced oligometacetic disease. There were two cohorts. So this flow chart is important. So there was one group which was given local consolidated therapy. One group that was not given local consolidated therapy.

In this group which was given local consolidated therapy they did a CTDNA analysis prior to giving local consolidated therapy to find out whether

these patients were actually in molecular remission or no.
So let's see what is the results. So they validated all the tools that they used. They checked CTDNA, MRDE sequencing depth of 30,000.
They validated the tools that they used. They even biopsied. So they even did a genomic analysis of the resected oligo the residual disease. They did a genomic analysis. So what are the results? So main the main thing I'll focus on. So 60 to 65 percent of these patients were EGFR mutant positive.
Overall driver mutant positive was 70 to 75. So this data was primarily for driver mutant positive and targeted therapy was given to 75 percent of patients. So what is MOD? MOD means primarily is they entered into molecular remission that is MRDE prior to giving local therapy. So there were two groups. One which achieved an MRDE, one which did not achieve an MRDE. So patients who achieved an MRDE had higher proportion of intra-thoracic disease. They had oligopressistence and in the resected specimen they achieved a major pathological response. Also this MOD group had lower tumor mutational burden, tumor neo antigen burden, lower HRD score and lower intra-tumoral heterogeneity. And this is the survival outcome. So if you look on the left, the PFS 1 and 2 is significantly improved with additional local consolidated therapy. But if we see on the curve on the right, primarily this improvement is driven by that cohort which has achieved an MRDE negativity and not by that cohort which has not achieved an MRDE negativity. What about factors that predict prognosis? The only factor that predicted long-term survival is those who achieved an MRDE negative.
None of the other factors actually predicted for long-term survival in this cohort. Another important question they asked, how long should you give systemic therapy prior to giving local consolidated therapy and that is always a question. So here they found out that you should give systemic therapy more than the median PFS of the regimen that you are giving. So the blue curve represents those patients who were given systemic therapy prior to local consolidated therapy and that systemic therapy was longer than the median PFS of that particular regimen. So they concluded that three factors are very important, radiological criterion of oligometastatic disease, pre-local therapy, the CTDNA status and the systemic treatment duration.
They also did a genomic analysis of the residual disease that they resected. What they found out was if there was resistant disease picked up in this genomic sequencing, the survival was actually inferior. There was also value for CTDNA monitoring, post-receiving local consolidated therapy and if there was resistant mutations that were picked up, this resistant mutation preceded radiological progression by an average of five months and in some cases 13 months. So this is a take-home message that molecular remission indicates a subgroup of patients with a good prognosis and should be strongly recommended prior to local consolidated therapy.
Three factors should be considered. Does it fulfill the criterion of an radiological oligometastatic disease? What is the CTDNA status prior to local consolidated therapy and what is the duration of systemic treatment that was given? Patients with potential resistant mutations detected in the residual lesion tend to have a worse prognosis and dynamic post-local treatment CTDNA monitoring may be important for decision-making and there were similar studies that were done before. Thank you.