First speaker is our host, Dr. Nandini Menon.
Dr. Manu could not make it to the conference
and she'll be speaking to us on MU-Antanib plus chemo
with or without Lazar Tannib.
In Egypt, our mutated NCLC.
So good morning everyone.
I'm just filling in for Dr. Manu.
And this is the Mariposa 2 study
that I'm going to discuss in the next maybe seven to ten minutes.
So we all know that Osmatanib and now with the new data
of Laura 2 Osmatanib with chemo therapy
is considered one of the standard treatment options.
But in 2023, the Mariposa study also showed
an alternative for treatment options
using MU-Antanib which is a bi-specific monoclonal antibody
targeting EGFR and MET in combination
with a third generation TKI called Lazar Tannib.
Now we all know that once you fail an Osmatanib
in second line setting, we in the past
didn't have good drugs in the space
and this was the study which evaluated
what happens to patients who progress on Osmatanib
and how do they benefit with this regimen.
So we, as I just mentioned, EJFR and MET alterations
are known to be the major causes for resistance to Osmatanib,
especially MET amplification.
So AMI-Vantamab is a bi-specific antibody.
It binds to both the EJFR and the MET ligands.
It also has multiple other mechanisms
including immune cell directing activity
and modulating the immune responses
which lead, I mean, add to its advantage
and Lazar Tannib-like Osmatanib is a highly CNS
penetrant third generation EJFR, TKI.
So we have data from the chrysalis in the second line.
We have MET-Posa in the first line
and now we are looking at MET-Posa too.
So this study was AMI-Vantamab Lazar Tannib chemotherapy
and AMI-Vantamab chemotherapy
compared to this control arm of chemotherapy.
Now initially when the study was designed,
the AMI-Vantamab Lazar Tannib chemotherapy
and then the AMI-Vantamab chemotherapy arm
was added actually to look at what components
of this triplet or quadriplet regimen
was contributing but eventually they modified it
to allow dual primary endpoints that is to look at
comparison of AMI-Vantamab Lazar Tannib chemotherapy
versus chemotherapy and chemotherapy as a control
and AMI-Vantamab chemotherapy versus chemotherapy.
So they tested both these new combinations
with chemotherapy having a dual primary checkpoint.
So this was the primary end point of the study.
This was the same MET-Posa to which was presented
in 2023 and I'll be presenting it's another update
and this was published in 2024 in Anil's of oncology.
These were the inclusion exclusion criteria.
So advanced metastatic EGFR mutant NSCLC
with the standard EGFR mutations

exon 19 deletion or L858R.
The key criteria is they should have progressed
on Osmotanib as the most recent line
either in the first line or the second line.
Fit patients of PS0 to 1.
This study allowed brain mats if they were stable
and adequately treated, unstable untreated brain mats
were not taken but stable brain mats were allowed
and these were the stratification factors
at what line they took Osmotanib race
and presence of brain mats.
So the regimen included Osmotanib
at 1400 milligrams weekly for the first four weeks
and then 1750 every three weeks
which was the AMI-Vantamab group.
Lazar Tannib was an oral tablet
it was given at 240 milligrams.
Now initially in this arm everything was clapped together
and all were given concurrently
but they realized that Lazar Tannib and chemotherapy
toxicity is especially neurological,
vacuum elective so they then modified it
to have Lazar Tannib sequentially.
So some of the patients in this study
in the AMI-Vantamab Lazar Tannib chemotherapy arm
received Lazar Tannib sequentially.
So these were the baseline characteristics,
well balanced especially for the key stratification factors
including the brain mats and race and other things
and including for the type of EGFR mutation.
Now we look at the results.
So first we look at the objective response rates
and as you can see in the second or third line EGFR post,
EGFR mutin lung cancer post Osmotanib failure
the combination of these drugs
that is AMI-Vantamab Lazar Tannib with chemotherapy
or AMI-Vantamab plus chemotherapy
had a remarkable objective response rate
of around 64% in the second or third line setting
whereas chemotherapy only gave a objective response rate
of 36%.
So the primary endpoint was blinded central review
of these responses and if you look at it,
both AMI-Vantamab and Lazar Tannib did better than chemotherapy.
So these were dual primary endpoints.
So AMI-Vantamab Lazar Tannib and chemotherapy combination,
the quadriplet of course had a better PFS of 8.3 months.
The AMI-Vantamab chemotherapy had a 6.3 month PFS
and chemotherapy alone was 4.2.
This was something similar to the investigator
in the SSPFS.
The only difference was when the investigators assessed
they had a similar PFS for the AMI-Vantamab chemo
and the AMI-Vantamab Lazar Tannib chemo.
So again, what I wanted to highlight
is all the subgroups that they've
stratified for including brain meds,
which is one of the important prognostic factors,
the type of mutation, what line patients received

Osmotanibre's gender age.
All categories showed that whether you,
when you added AMI-Vantamab chemotherapy
or you added AMI-Vantamab Lazar Tannib to chemotherapy,
definitely there was a benefit.
Now the important thing what I want to highlight
in this Mariposa 2 study is the intracranial effect.
Now when they designed the study, AMI-Vantamab was put,
was thought that it's a monocranal antibody
does not cross the blood brain barrier
and that was a rationale of adding a CNS penetrant drug
such as Lazar Tannib to have intracranial activity.
But what you can see in this Kaplan-Mayer
is the intracranial progression survival
with AMI-Vantamab chemotherapy
and AMI-Vantamab Lazar Tannib chemotherapy was similar.
So which even the investigators proposed
that the probable reason,
which is not what they thought when they designed the study,
but the probable reason is AMI-Vantamab,
despite not probably physically crossing the blood brain
barrier, may be having effects with immune modulation,
other mechanisms other than directly targeting the EGF
and met and having an intracranial control rate
comparable to the group where AMI-Vantamab
and Lazar Tannib was combined with chemotherapy.
Again, they did a sensitivity analysis
to look at whether radiation was the reason
for these patients not progressing.
So they had a group of people who had received radiotherapy
and they had included those who did not receive radiotherapy.
And even in the group of patients
who had no prior brain artery,
there was this consistent benefit scene,
which goes to say that using AMI-Vantamab
in combination with Lazar Tannib and chemo
or AMI-Vantamab plus chemo alone,
that itself controls CNS disease irrespective
of whether the patient had received radiotherapy or not.
So this was what was the early interim
overall survival.
They seem to be a trend, but it is not significant
and that was what was published.
This is the adverse event.
We know AMI-Vantamab has significant toxicities
and like a lacan had discussed,
a sub-cute AMI-Vantamab to decrease the toxicity rate
because infusion reactions leading to issues
in more than 50% of patients
and a lot of skin toxicities which are an issue.
So that was what was the concern.
What otherwise was seen was none of the toxicities
that were compared to death,
but there was some discontinuations
of treatment in all these arms
and you know the more you combine,
the more we expect toxicities to add
and to discontinue treatment.
So if you look at the quadripletam,

there was around 10% who had to discontinue
because of toxicity.
So consistent PF is benefit across all groups,
higher objective response rate,
longer duration of response,
good intracranal PFs, excluding the fact,
I mean even if you take into consideration
for the fact of patients who have received radiotherapy,
first presentation when this paper was published
in TerimOS, we did not know
whether it was significant or not,
this seemed to be a trend.
Of course because of the hematological AEs
and the combination of AMI-Vantamab,
Lazetamab and chemotherapy having more neutropenia,
they modified it and when they presented the first data,
there was a significant number,
nearly half had received sequential Lazetanib
after completing the pemitrixet carboplatin regimen.
So that's what we need to keep in mind.
The second abstract of the presentation
is a small second interim overall survival analysis
of the same study.
Now this focused on AMI-Vantamab plus chemotherapy
versus chemotherapy and because they got that trend
when they did the initial analysis
that they might be a benefit in OS,
so they looked at for the second interim analysis
to look at the OS benefit,
when the data matured whether it really was there.
So again, if you look at this,
this is a longer follow up
and this was at 18 months landmark analysis
and you can see 50% of those who received
AMI-Vantamab plus chemotherapy,
we are not discussing the Lazetanibam here
and compared to 40% of patients who received chemotherapy
were alive at 18 months.
Again, the time to treatment discontinuation was longer
with the combination of AMI-Vantamab chemotherapy,
time to developing a symptomatic progression was longer
and time to subsequent therapy was longer.
So basically AMI-Vantamab plus chemotherapy
when you compare to chemotherapy alone
seem to have better outcomes
and this trend to overall survival seems to be sustained.
We need to see for a longer follow up for its final impact.
Here the hazard ratio was 0.73
and it was statistically significant,
but probably a longer follow up,
we also need to see what happens over time.
Now this is a diagram,
I don't want anyone to get confused
what this bar graph shows is the number of patients
who receive various therapies after failure on Mariposa 2.
That means in the third or fourth line setting
in EGFR mutated lung cancer
who progressed on Ozetanib and then progressed
on the Mariposa 2 regimens.

So in AMI-Kimo and the chemo arm
and what they showed is that of course,
fewer patients had this treatment
in their fewer patients progress so that is different,
but patients in the third line setting often we tend
to re-expose them to previously use therapies
and what they wanted to show is that
if you want to get a better survival
you should maximize the outcome in the second line setting.
So if the patient has failed on first line Ozetanib
give him the best treatment in the second line
because subsequently we may not have effective therapy.
So to conclude both the abstracts,
this was the conclusion of the second interim analysis
that Mariposa 2 is still ongoing final Ozetanib
but whatever they found on the second interim analysis
for the AMI-Ventam app chemo arm versus chemo therapy,
there was improvement in the time to symptomatic progression,
treatment, time to treatment discontinuation,
subsequent time to subsequent therapy
and maybe the trend to Ozetanib was sustained.
So probably it's a signal that that might be a promising Ozetan
and you may have a positive Oz outcome also.
So what it overall shows is that AMI-Ventam app
plus chemo therapy,
or AMI-Ventam app Lazetanib plus chemo therapy
despite the toxicity definitely has a role
in the second line or third line setting
after progression on Ozetanib.
In all parameters including progression free survival,
time to subsequent treatment, CNS disease control,
the challenge is what happens to Oz
whether it will be significant
and considering the toxicities,
especially cutaneous and infusion reaction,
what is the quality of life?
So just to summarize, this is one of the regimens
which has in a randomized study shown to be effective
in the post-Ozetanib space.
We talked about the subgroups that benefited.
We also talked about its CNS activity
even if you extruded Lazetanib
and even in patients who had not received radiotherapy
for brain meds.
After modification and making Lazetanib sequential,
the quadriplette regimen seemed to be better tolerable
but yes, toxicity is a concern
and we still need some data on the liquid biopsy
and the CTDNA in this setting.
So with this I'll conclude
and thank you for the patient here.
Thank you, Nandini.