Thank you to the organizers for the opportunity. The slides have been provided by AstraZeneca.
I welcome all my panelists. So, we will be talking about TKIS plus something in EJAPR
and Rookton at once in a CLC, what works well. So, as we all know that with the first generation TKIS
F10A bar lot in EJAPF, we get a PFS of around 10 to 12 months with second generation ones like
Dachometinib around 15 months and Osmutinib in Flora 18.9 months. But why is there a need for
combinations because very few patients remain on treatment for after two years. If you are
seeing here with Osmutinib at three years, 54% patients are remaining on treatment. So, 28% on
treatment, the overall survival is 54%. With the first generation TKIS, 9% on treatment overall
survival is 44%. So, we studied this combination of TKIS plus chemotherapy. We have the TMS study
showing the PFS of 16 months overall survival of not reach was 17 months and also there was
the Japanese study. So, first question to Dr. Bhaavish experience because this study was in TMS,
for generation TKIS combination with chemotherapy. What is your experience? And most of our patients
will not be affording Osmutinib. So, do you think in all comers we can use this combination?
Yes, I think it is doable for all comers. Only thing we have to keep are monitoring and patient
education is again important because what we want to look for is the toxicity. So, we are obviously
happy with the efficacy, but toxicity is something what we have to keep it in our mind.
Okay, and in your experience, what is the toxicity which sort of we face?
So, I think GI toxicities, mucocytis, this is something what I have worried and another is the
hematological toxicities. So, both things I will keep a close watch. I am not worried about skin
reactions because usually they are a great one, great two and quite easily manageable.
Alright, so, Dr. Sathvik you are opinion on this study also. The TMS study also included patients
brain meds etc. So, your opinion, if the patient is not affording Osmutinib, should everyone
receive the first gen TK with you? Almost all comers except the poor PS or somebody who frail
elderly, I would avoid chemotherapy. If the patient is not affording Osmutinib, otherwise,
almost all I would advise chemo plus and Jeff combination or chemo plus first generation TK.
So, do you think plain chemotherapy works in brain meds? So, Dr. Vijay was just saying that even
Otherapinio EP, you prime the immune cells, they reach the brain. Normal PEM, platinum does it,
does it work in brain meds? Yes, to some extent, it does work because we have been seeing
and the patients who are driver negative and those who cannot take immunotherapy,
we are giving post W, we are TKMO only and obviously it won't work as good as TKI,
but yeah, they do work.
So, definitely chemo adds to intracranial control, even with the first generation

TK, fine, fair enough.
So, what is Dr. Darshana, your experience in using something other than chemo therapy,
like anti-angiogenics with combination with TK?
So, the BEVAS is a map with something that we use, but yes, the patient selection is important
and like the outcome compared to the TKI is not that great in my practice.
Okay, Dr. Monica, any experience of using BEV or anything like that in combination with TK?
Never used, but maybe I would use it if the patient is not fit for chemotherapy and I want to add on something else
more than TKI would want to use, but I have never used so far. It's not something that I usually do in my practice.
Okay, because BEV also make pinnettate with the brain, you have BEV second line in glau plasma, it can actually have some effect,
but not very commonly used.
So, if you can just comment, use of anti-angiogenics or something else with TKI, perjurition TKI.
I think I must say that I have not never used it.
Yes, and some other, I think that data is early there where they have shown that addition of the neurosis map makes a difference.
Thank you, sir.
So, in your combination therapy, so you have essentially two studies, you have this floratoo study which combined patina-based chemotherapy with osmotenib, four cycles followed by pemetric segmentinins and osmotenib versus osmotenib alone.
And you have mariposa trial which you looked at, amnomertenib, lazotenib versus osmotenib versus lazotenib alone,
but essentially we compared amylazor with osmotenib.
And floratoo, there was a PFS benefit. If we looked at the PFS was 25 months versus 16 months,
the independent central PFS 29 versus 19 months, hazard ratio 0.62 in both, and mariposa also showed PFS 23 months versus 16 months.
So, Dr. Monika, starting with you, do you consider this clinically significant and you are happy to use PFS data or you want to wait for OS?
I am happy to go with the PFS data.
You are happy to go with the PFS data and why are you happy? Because you will require, you will get sequencing.
So, in your practice, how many patients will receive a second line? In EJFR, we have ten NSCLs, advanced.
Maybe about 30, 30% one-third of the patients who are on first line will go on to receive second line.
So, classical teaching is second line lung cancer 30% will go to a second line, but does it hold true even now in actual clinical practice?
Now, we are probably seeing a much more larger percentage of patients going for second line because with the first line treatments that are becoming more and more effective,
their performance status is also very well preserved even by the time they have progression.
So, we see more and more patients going on to second, even third line also probably.
So, maybe that numbers are slightly bigger now, but as far as this is concerned, PFS is something which I am okay with.
It will come subsequently OS data, but PFS maintaining them progression-free is also an important parameter.
So, traditionally, second line usually 70% patients will go according to most of the data, but in practice, I think it is improving because we monitor the patient quite well.
And we do keep a very low threshold of changing the therapy or switch the therapy when the patient starts progressing.

So, I think most patients will receive second line now unless and until their PFS is deteriorated very bad, it has become PS4 or PS3 and you are not able to offer anything.
So, that will be a very small, the percentage is becoming smaller.
Most of them will go on second line.
So, many of them will receive a second line.
Yes. Okay. Fair enough.
So, what about brain metastasis?
So, both the trials very interestingly had around 40% patients with brain metastasis and Laura 2, median PFS 24.9 months versus 13.8,
and we laser 18.3 versus 13.
So, again, the hazard ratio is 0.474, Laura 2.69 for the manicosa.
And the CNS responses were also breakthrough.
So, higher risk to solve complete responses were also seen with the combination of ocemetinic platinum pemetric state.
So, Dr. Sathvik MRI is in all cameras nowadays, advanced NACLC.
Yes. So, ideally we should do MRI brain all cameras, but most of the time in practice we are doing PET-CT along with CCT brain for the convenience of the patient.
But ideally we should do MRI.
Dr. Darshana?
So, I am doing PET-CT and MRI for all patients.
So, I think the guidelines also are pretty clear that MRI is a part of mandatory part of workup and if there are no brain meds at baseline,
do you consider MRI for monitoring later on?
No. No, unless he is symptomatic, I would have-
No, just monitoring. If there are no symptoms.
And if there are brain meds at baseline, what is your surveillance protocol?
Then, yes, we do do the follow-up, like post whatever the treatment we start.
Suppose we do the radiation, then post three months, and if at all the treatment is started,
then again after three months we do try to evaluate the lesion status and take it from there, like based on the response.
Yeah, no, I think if we had baseline MRI, which is showing brain meds, you have given some treatment.
I think later we don't do MRI brain. We are happy with the PET.
Unless and until patients start symptomatically, I mean showing that probably there is a brain meds again or increasing brain meds or any kind of edema,
which is increasing, that will warrant an MRI again. But till that point of time, I am happy with PET scan because it will include the CCT brain also.
Okay, but Dr. Mavish, if you are only treated as symptomatic brain meds with TK, no CNS directed treatment, would you still be comfortable in just continuing PET scan only, no MRI?
Yes, I will still continue. If patient is asymptomatic and I have already decided that I am not going to do anything for the brain as of now, I will still wait till the patient becomes symptomatic.
Okay, Dr. Monika, your opinion on this CNS data, do you feel that having brain meds warrants use of chemotherapy with osmotenia?
Osmotenia single agent is also fine, but now it's more of osmotenia plus beyond that something else also we want to add for given the PFS benefit as per flora too.
So the presence or absence of brain meds won't dictate my addition of chemotherapy, but mainly the fitness of the patient and the disease burden.
In most of the patients, we are adding chemotherapy to osmotenia. So it's rather in whom we omit is what is important.
We would omit in patients who are not having that fitness, then osmotenia single agent.
And Mariposa and flora too, both of them show that those who have brain metastasis, the combination did better, but it's not correct probably to do the cross trial comparison and compare the absolute numbers of the PFS, but both of them, because

lazotenib also has very good CNS penetration, although amoevantamab doesn't have at all.
In the flora too combination, osmotenib and carboplatin, both of them have good CNS activity. So both the regimens are fine as far as patients with brain meds are concerned.
All right. And how do you manage a CNS patients with EGFR mutation, symptomatic patient?
A symptomatic patient will just give TKA probably and symptomatic SRS neurosurgery depends on size.
It depends on the size, side, the fitness of the patient. SRS is something which we're commonly doing multiple symptomatic brain meds. We are going for whole brain, and we're going to be doing it differently.
Whenever they come for their first follow-up and thereafter, maybe once in six months, we are doing MRI brain for surveillance to look for progression, even if they're not symptomatic, although there's no definite guideline as such, but we are doing it.
Yeah. So what I can understand is in general, asymptomatic brain meds, you have a driver mutation, you are avoiding RT.
That's what the panelists told me. If is there any situation of brain meds that you would give RT, even though you're planning for maybe Oc-Murtinib, multiple brain meds, cerebellar, is there any situation?
If they're symptomatic, definitely not. If they're asymptomatic, maybe something which is very close to the cortex can precipitate a seizure.
These are the patients where I would probably give RT just to have an immediate disease control, because any time, even if a few millimeters increase in size might cause a seizure to the patient.
So 10 lesions asymptomatic?
Still, we would not prefer whole-brain RT, because these patients live long enough to survive the effects of whole-brain RT and to experience the long-term effects of cognitive impairment, because they're usually there there for four or five years at least, many of them.
So that's why we are trying to avoid if it's absolutely asymptomatic, small, even the number is not an absolute, we don't have an absolute cut-off as far as the number is concerned.
So is that the practice with everybody?
So multiple lesions, and we see this not frequently, but we do see it when we are doing a routine baseline MRI. There are multiple lesions.
Sometimes there's a lesion in the cerebellum, you're worried that there's no space for that.
So at least in my practice, my posterior, for solisions, if there are multiple lesions, etc., I do consider it a WBRT or some SANA-directed treatment.
So that was the point I was trying to make. So if there is a situation that you see something radiologically on the MRI, which will warrant RT, which can still be asymptomatic, then probably we should be doing surveillance MRIs if we are not giving them RT. I think that was the point I wanted to make.
Because ma'am, that can happen back.
Thank you. Thank you ma'am.
So outcome as far as the mutation type is concerned, floratoo, exon-19, as well as exon-21 L8 firetard, did show PFS benefit.
Exon-21 in the subgroup analysis of florra-1, did not show benefit.
So what is your opinion on this Dr. Havish?
Exon-21 does poorly in your practice as compared to exon-19, and does exon-21 warrant addition of chemotherapy if you are considering or submitted?
Actually, it does make a difference, but if you are using, I mean, ocementinipilous chemo, floratoo, then I think it is taken care of. Both the things can be taken care of.
Okay. If you had enough, any other opinion?
Almost same.
But do you think that exon-21 has poor outcome as compared to exon-19 in today's

day and age and age and age, if you noticed that probably you can change your therapy.
If you are just going to go for TKI. So you can choose your TKI depending upon that, like, recommend any of these little better.
So you can choose according to that, but if not, then it is okay.
So Asian subgroup also did not per se show, the hazaj show was again unity in florra, but again, this addition of chemo therapy does seem to show benefit as in Asian sub-set patients also.
And regarding adverse events. So Dr. Monika, when you talk about Jeff Dinep plus more floratoo, you are essentially giving you an interconnection in the clinic chemo therapy.
Right. If you consider Pemitek said maintenance. So how does that conversation take place?
So essentially the first question they ask is how much time will I be on chemo therapy? Right.
So what is your opinion on this?
We counsel the patient that they will need chemotherapy indefinitely and we do give them a choice.
It's better to continue Pemitek's it, but if by choice they are not very keen, then we do omit and continue also mutinit, but we try to convince them.
In general, it's a very well tolerated drug. We do monitor the RFT before every dose.
So that's not an issue and all the other precautions. We do tell them to maintain good hydration, avoid other nephrotoxic drugs.
We give them a list of drugs which are potentially nephrotoxic, which they should use with caution.
And with this kind of a monitoring and counseling, I don't think the toxicity of chemo therapy with EJFR TKI is that unmanageable.
We can still continue to give Pemitek's it. We have patients who've been on Pemitek's it for almost two years now, along with TKI and they are tolerating it quite well.
So experience with this combination has been quite fine. I've hardly had patients.
In few I had to omit Pemitek's it because of a slowly climbing creatinine.
I had to omit it, but most of the patients were managing to continue.
Do patients agree for indefinite chemotherapy?
Do you give Pemitek's it once a month rather than once in three weeks? Something of that sort?
Because in the end it's a clinic visit. In the end the patient probably has to have a day goes for infusion so as to speak.
Usually it depends upon how you're counseling the patient. So if your counseling is good enough and they are convinced you can continue.
But many a times later it becomes like subticu to chalrya. So let us increase it.
So that will be something which comes from the patient, not from you.
So if patient asks for it or if he is not ready to come every three weeks he wants some leisure time extra, then probably you can exercise that after maybe at least two years of therapy.
Then you can try to exercise it. But I think in the first two years you should be very vigilant enough to not stop the therapy number one, not to increase the duration.
So something two years good control after that you can try to experiment, not before that.
So in the two studies if you look at the serious adverse events, adverse events lead to death 2% and flora 2% with Mariposa amylazole.
And treatment discontinations 10% with amylazole and 3% with osmotinib. So essentially more of hematological adverse events with Ossipem, carbo or pem platinum.
And Mariposa, hepatic derangements, infusion related reactions which always happen for the first cycle with amylazole and also some amount of venous thromboembolism.
Advanteis are your opinions on the adverse event profile of osmotinib plus pem,

carbo and pem platinum.
And how do the patient's take pemetric state maintenance compliance, etc.?
I think everything depends upon how you can't counsel.
According to me, that's the only factor. It's not the patient's factor.
It's how clinicians are able to convince the patient that this is good.
And of course, you know something which bothers me always that you tell the patient you have to take for life long.
That's not necessary to tell them. Life long means also as long as there's a progression you will stop it.
So you don't say that life long. Life long means that thing, but till I die, this treatment will go.
This treatment may not go. After two years, if you have a progression of the disease, the treatment may change.
So I think how you play around with the words and how you react.
Now what I do is almost all of our patients continue the pemitax.
Everybody, three weeks, if they say 21 days is from another 25 days,
nobody knows whether 21 days or 25 days there's any difference.
So you have to play around that. And sometimes they say, 28 days. So it's okay.
But I think it's good to convince the patient and we have a patient.
They are taking it for five years. They take it for five years also.
So I think that's a very important factor that we must follow and we have seen the disease remaining under control.
The side effects of the combination are always much more than the side effects of the single agents.
But I think Emma went in a little more. You have to be careful about the doses.
Some of the other doses which are written in the books that you give, 1,150 and 350, that sometimes causes a lot of problems.
And so if a patient once he gave the problem that he has to go to the ICU and all, I think after that you have to either abandon that or you have to be very, very careful.
Thank you so.
So side effects, so we have spoken and this may be the newer treatment option paradigm.
So what I would come to now is biomarker testing and commutation.
So how much is the usual panel nowadays we do? Dr. Hawesh?
Only 12 gene with coupon without coupon.
Most patient 12 gene with coupon because that is financially affordable for almost everybody.
Okay. Dr. Sathvik?
Yes, most of the patients, we do counsel for broad based NGOs but most of the patients end up getting the coupon based NGOs.
So presence of commutations has been shown to have an inferior outcome.
And what are the mutations which we are actually looking at?
So we have, so this is TP53 which has shown a poor outcome.
What are the TP53C, etc.
So Dr. Vijay, sir, is there or Dr. Akil?
Comments on commutations?
What sort of commutations are we actually looking at?
So I think TP53 has been highlighted.
It is definitely one of the most important mutation which we always want to look.
Met alteration is useful sometimes to select the treatment between the two regiments that is one of the best possible which we can get.
And the most important thing is that we first, on progression, if we are doing in the second line setting,
we must rule out his allergic transformations. That is the most important part.
Which is actually more with Osmoteing if than with the...
Yeah.
So...
Yes.

Yes.
And obviously we know that not TPFR, even in ALK.
If there are mutations like TP53 which are there, they are associated with poor prognosis.
So in this patient, it would be worthwhile to consider either a florida to like regimen or a MIPO.
Like when the data clearly shows that. So I think this is time we start refining our first line EGFR mutation saying that it is only EGFR positive
or it has a co-mutation. This decision now needs to be taken by the physician while treating this patient.
Absolutely.
I think this comes when you are trying to do CGP. But when we do a 12 gene or a select panel.
We don't get to...
We don't even get that information.
We come to know only in practice that how the patient is responded. Patient is not responding.
There is unexpected response, lesser response. Then we try to focus on something else is there which we have missed.
Thankfully TP53 is in the actual Belgian panel. Thankfully.
Yes.
So I think we should end now. I think there are those two.
So basically you have combination regimens which are I think the way to go nowadays.
Flora to PEM platinum plus ocemetinib is one of them which is possibly better tolerated in terms of side effect profile also.
Advani such as said that counseling the patient is important. PEMETIC set maintenance is also reasonably well tolerated.
And I think exon 21 patients, patient with home mutations, patient with brain meds may do better with this combination than with others.
Thank you so much. I have come to the end. Thank you.
Thank you, Dr. Rohit for the great panel discussion and thank you to all the panelists.