Good afternoon. Thanks to the organizers and the slides have been provided by Novartis.
We will be talking about serotonin and the line management of first line advanced IL-positive
NSCLC. This is a disclaimer. So, as we all know the NSCLC is heterogeneous and we are
getting more and more mutations which are positive in NSCLC. So, and IL-positiveity the
range is 7 to 8 percent. I think in the T-MH data also it is around 7 to 8 percent in NSCLC
and it is one of the important mutations. Now molecular technology preference testing basically
varies and for IL-positiveity we have essentially three methods. You have the IHC. For example,
the crown study used IHC monoster chemistry as the test to determine IL-positive status. You
have the fish which was the classical break apart fish and you have the NGS panel which not only
tests for IL but also others. Essentially we require DNA and RNA based testing in NGS to
determine fusions. And multiple genetic tests required last issue volumes and sequential testing
for EJFR, IL-CROSS and if it negative then further testing is almost. Nowadays never done
because we have moved to NGS as the test of choice. SMO as well as NCC and recommended NGS
testing and what are the benefits of NGS testing is you have a reliable detection of
signed off care mutations with good sensitivity specificity, accurate identification of up to
three times more clinically actionable alterations. NGS testing panels may provide data for all
known mutations. So you have co-mutations like D53 which actually impact the outcome in EJFR as
well as IL-positive NSCLCs and nowadays the turnaround time is also acceptable. So overall NGS is the
way to go. Also what is more important nowadays is that you have cost effective NGS so you have
these 12 or 15 gene panels which please note that they also contain other co-mutations like
TP53 which has been shown to have a negative outcome in EJFR as well as IL-positive patients.
And this noattis does support testing and also period when testing is combined with NGS in sort
of this service provided by noattis. Now we come to serotonin first line serotonin versus chemotherapy
in patients with IL-positive lung cancer. SN4 was the study. It is sometime back so it is comparing
IL-positive metastatic NSCLC in the first line setting no prior treatment,
stratified by performance status, brain meds and prior new adjoint adrant therapy randomized in
a 1 is to 1 passion. Please note the dose of serotonin which was 750 milligram once a day versus
pam platinum based chemotherapy. So either pamsis or pam cargo and patients who received chemotherapy
also received pametex and maintenance. And there was an option to crossover later on 80
patients to crossover to serotonin. So serotonin double the median PFS as compared to chemotherapy.

So the median PFS was 16.6 months versus 8.1 months hazard ratio of 0.55 plus a 45% risk reduction
of death or progression as with compared to chemotherapy. Overall response rate was impressive
72.5% duration of response around 2 years and 24 month overall survival rate 70.6%.
In the Asian subset also serotonin did have an impact or the septation of the curve is slightly
later but again the median PFS is 26.3 months versus 10.6 months hazard ratio of 0.66 34%
reduction in progression or death even though the confidence interval is slightly crossing one.
What is interesting is this with no artist is that this study was conducted because usually we
sort of once the dose is established 750 milligram you don't week around with the dose and especially
you don't reduce the dose. But in this assign 8 study you actually had three types of dozing.
So one was serotonin 450 milligram with meal, serotonin 600 milligram with meal and serotonin
750 milligram fasting which was the dose used in assign 4 study. And the primary end point in
this study was not clinical it was a study PK of serotonin in all these with all these doses and
most clinically meaningful difference was seen in the pharmacokinetics studies with all these
three doses. But what is important is if you look at the secondary clinical endpoints the dark red
is the 450 milligram fed state dose the orange is the 600 milligram fed and the dotted blue line
is the standard dose which was used in assign 4 which is the 750 milligram in fast red. You
actually are seeing as far as the duration of a response the PFS and the OS the 450 milligram
with meal dose is doing better. And if you look at the overall response rate it is around 80% for
all these three. But if you look at duration of response 68 versus 44 versus 20 if you look at
PFS rate at 24 months 58 versus 37 versus 22. So definitely 450 milligram fed state dose probably
was the way to go and that is the standard dose. So on 50 milligram pill three pills taken with
meal is the is the standard dose which has been approved. So it saves on cost and also this dose
has lesser side effects. So lesser GIS side effects as opposed to the 750 milligram fasting dose.
Now brain meds are an important issue with positive NSCLC and you have 30% of patients might have
brain meds at baseline 70% will not have. So patients who have brain meds you require a TK
which penetrates the blood brain barrier and serotonin does penetrate the blood brain barrier
and has a good intracranial efficacy. In patients who do not have a brain med at baseline prevention
of progression in the CNS is also very important and again serotonin being effective in the CNS
has that impact also. So if we look at a site of metastasis in alkenibita naive patients
if we use the first generation thirzotenin CNS was the primary site of relapse in almost half the

patients 46% of patients and next generation alkenibita with increased blood weight penetration may have
high volume in the first line setting. Not only to control the CNS meds in patients 30% of patients
who have brain meds at baseline but to prevent the development of brain meds in the 70% who do
not have brain meds. So again in patients who had brain meds the PFS was 10.7 months versus 6.7
months in patients who did not have brain meds the PFS was 26.3 months that is more than two years
as opposed to 8.3 months thus reflecting the intracranial efficacy of serotonin.
If you look at the intracranial response rate so again so if you look at the overall
intracranial response rate 72.7% versus 27% so 45% delta and you have a reasonable duration
of intracranial response 16 months and again if you look at the best overall intracranial response
rate with serotonin there is a high intracranial response rate 44% versus 22% systemic
whole body efficacy is 65 versus 29 but intracranial response rate is also significantly better
with serotonin. Now if you look at the comparative efficacy of serotonin and chryzotenib so there
is no direct comparison serotonin has been compared with chemotherapy chryzotenib also has been
compared with chemotherapy. Lottetenib and electinib have been compared with chryzotenib but
if you look at the PFS as so 10.9 months with chryzotenib versus 7 months with chemotherapy
if you look at SN4 16.6 months versus 8 months overall survival data because of crossover we
cannot comment but there is a reasonable overall survival data for both of them. If you look at
the safety profile serotonin acts fast also there is a good response rate and you see that the time
to definitive deterioration is also significantly prolonged with serotonin 23.6 months versus 12.6
months and there is a early separation of curve thus reflecting that not only is there is a good
response but there is a early response also on the right you are seeing that there is a treatment
difference in lung cancer specific scores like dyspnea pain and other parameters in symptoms
related to lung cancer and serotonin does significantly improve the quality of life and significantly
prolong the time to deterioration of lung cancer specific symptoms as opposed to chemotherapy.
Now what are the side effects of serotonin? So serotonin main side effects which we should be
aware of is diarrhea, nausea, vomiting, abdominal pain and hepatotoxicity. If you look at the label
there are other side events like pancreatitis, serotonin does cause 2t prolongation and I think
baseline ECG something which is warranted. So here what you are seeing with serotonin is 5%
to 5% diarrhea grade 3 grade 4, vomiting grade 3 grade 4 and hepatotoxicity you are seeing around
around 20 to 30% grade 4. So this is what is important but with proper management so with

proper considering the patient giving profileactic anti-emetics properly for the first 1 to 2 months
of treatment and using the proper dose that is 450 milligram in effect say these GSI effects
are manageable. You have lot of options for alpositive NSCLC you have lollatinib, resotinib, serotonin, electinib, bragatinib now and how do we choose them is a question and the
first drug to be effective was resotinib followed by that serotonin electinib, bragatinib came and
nowadays there is a lot of discussion on the crown study data. Rolatinib is one of the drugs
which we consider especially because of the increased intracranial penetration.
So what are the options? So if you look at the NCCN guidelines you have all these options in
the first line if at all chemotherapy is started there is an option of completing that and switching
over to alkinibiter but what is practically possible in India? Practically serotonin remains the most
cost effective treatment for alpositive patients in India. The cost of monthly treatment is around
45,000 and practically speaking this is one drug which has intracranial penetration it is cost
effective and the GSI effects etc are manageable overall this is probably the most feasible to
be given in India as of now and thus maybe most of the patients might receive serotonin as opposed
to electinib or lollatinib if we talk about cost. Also if we look at the sequencing there is data
that serotonin followed by electinib or lollatinib may have a comparable efficacy but now the updated
crown study shows 60% PFS at five years so 60% at 60 months that is impressive but again it is
there are two issues one is that how many patients will actually afford a lollatinib.
Secondary second issue is the lollatinib is associated with some CNS related side effects etc and also
we need to sort of be become better at managing them. Obviously if the patient can afford
lollatinib is a good drug as of now but serotoninib is probably the most affordable feasible drug
in Indian setting. Now points to consider while using an ALT care so periodificacy in the first
line so basically if you want a drug which will penetrate the blood brain barrier have intracranial
penetration because many patients may not receive a second line. If there are no brain
mitts at baseline we need to use a drug which prevent the brain metastasis and serotonin
sort of fulfills that requirement. If there are brain mitts at baseline 30% of patients we require
a drug which will cross the blood brain barrier and have a good intracranial response that again
serotonin will fulfill. Symptomatic disease again you saw the quality of life curve you saw the
response rate of around about 70% and you saw the rapidity of response so again serotonin fulfills
that requirement also and do we have a second line post serotoninib? Yes we can use drugs like
lollatinib post serotoninib also and if we are using the frontline lollatinib we

probably don't
have clear cut evidence that what is the second line we can use. So again serotonin fulfills most
of these requirements in treating ALT positive advanced NSCLC and to conclude in asin force study
alkinibiter, nive patients, first line setting serotonin versus hemotherapine serotoninib
showed significantly improved PFS, numerically improved OS. PFS benefit was also seen regardless
of the presence of brain metastasis. Castorin terrestrial and adverse events were prominent,
nausea, vomiting, diarrhea and heppetal toxicity but were manageable and 450 milligram dose was
then sort of the dose to to finally sort of settle the issue that 750 milligram is fasting is inferior to 450 milligram with meals so that is the dose we give and efficacy and
safety of serotonin was also established in Asian patient population with ALT positive NSCLC.
I have come to the end of my talk thank you.