Thank you very much for this opportunity and after an elaborate discussion on the five-year
update of the Crown Trial by Dr. Sudip, now it's time to reflect upon the adverse effects
that happened that were the main concern always with Laolat Nip.
And so I will be talking about this five-year follow-up, the kinetics and the management
of adverse events associated with Laolat Nip.
So Dr. Sudip has already set the stage for this.
No need to repeat.
It is a practice training trial, median follow-up of five years is there and PFS in the Laolat
Nip arm has not been reached because it is such an effective drug that we don't have
a PFS even at five years.
But it has a unique safety profile and this post-hoc analysis was done.
So five safety key takeaways that 50% of the patients were still all Laolat Nip in first
line at five years.
No new safety signals had emerged and treatment discontinuation remains low.
Permanent discontinuation overall just touched the double figures only 11%, whereas only
five percent were related to Laolat Nip.
Those reduction was seen in 49 out of 149, that is roughly you can say 33% one-third
of the patients and median time to first dose reduction was 21.6 weeks.
And it never affected the efficacy as very nicely depicted by Dr. Sudip.
So time to onset and duration of adverse effects.
First of all coming on to the hyperlipidemia, mainly hypertriglyceridemia and
hypercholesterolemia.
Both of them are the most common ones and any great adverse effect, dyslipidemia starts
within 15 days and when we look at the grade three dyslipidemia it comes at six months
and median duration was also 37 months.
When we come on to the any great edema peripheral neuropathy and CNS effects then median time
to onset was two to four months and median duration was eight to 18 months.
Weight gain was the adverse effect that had a prolonged duration that stayed for that was
more than equal to grade three and that stayed for more than three months.
So coming on to the hyperlipidemia again we are addressing hypercholesterolemia which
was seen in around 72% of the patients and hypertriglyceridemia which was there in around
69% of the patients and so it was there in majority of the patients.
90% were managed with either co-medications that in 71% of the patients or when we combined
with observation only overall there was 90% of the patients that could be easily managed only
remaining 10% required drug interruption reduction and less than 1% required drug discontinuation.
We managed them with those statins that have less interaction with CYP3CA because then
the lower level levels are not much affected and we have easily available rosoma statin which we
can always use in the setting when we are using lower tenet to control dyslipidemia.
However important thing with the treatment with lower tenetvus the many side

effects still were
unresolved like hyperlipidemia and 45% of the patients still the hyperlipidemic events were
not resolved but there was only one and only event when it required a permanent discontinuation.
Coming on to the CNS adverse effects again most of them were grade 1 of grade 2 severity only 42%
of the patients had so and out of these 42% 86% was grade 1 and grade 2 and they occur in the order of cognitive effects followed by mode effects followed by speech effects followed
by psychotic effects in incidence. Prior brain radio therapy had an effect on the CNS effects
and around there were nine patients who had received prior brain RT and around six out of
these nine patients had CNS effects when no priority was given the incidence of CNS effects reduced to
41% that was seen in 140 patients. So coming on to the incidence and the prevalence of the CNS
adverse effects it did not increase over the period of time rather when you'd see the dark
blue bars that is the incidence. So incidence was initially higher in only in the first year
and eventually it dropped down nicely and by the end of five you're probably the incidence was
quite low whereas the prevalence tend to remain stable and it never increased over a period of
time when we look at the CNS effects and these CNS effects they occurred in the incidence of most
common was a cognitive effect followed by mode effect followed by speech disorders and followed
by psychotic effects. Then we will total CNS events were 118 and more than half that is 58%
there no medical intervention was required. Out of these 58% 33% completely resolved 24%
were partially resolved and there was only 1% that did not resolve. There were 14% that
required co-medications without any interruption and out of these 14% 8% had completely resolved.
There were 14% who required those interruption alone and again 12% were completely resolved.
So once we interrupt the chances that it will be completely resolved increases significantly
and then there was a 6% who had those reduction alone and out of these 4% CNS effects were completely
resolved. So overall 60% of the CNS adverse effects resolved with management strategies only either
with co-medications or with those interruption. When we come on to the weight gain around 44% of
the patients the weight gain was seen but the significant that is grade 3, 4 weight gain was
seen in 23% of the patients and baseline weight did not have any influence on the subsequent weight
gain that is whether it was whether the patient was overweight or underweight that did not lead
the baseline weight basically did not have the future weight gain chances and also it is important
to note that the weight gain and peripheral edema it seemed to correlate only in a fraction of
patients that are only in 40% of the patients there was overlap. So probably there

is a different
mechanism whether there was a weight gain for the weight gain and for the peripheral edema.
The peripheral edema was not actually the cause of weight gain in all the patients and most of the weight gain around 95% of the weight gain did not require any medical info
intervention it was primarily managed with the lifestyle modifications 35% resolved with no
medical intervention and 11% was partially resolved 49% that is undissolved but it did not affect
their quality of life or the drug administration and there was 2% each for those reduction,
those interruption and those reduction plus those interruption. So overall it stayed there
this side effect but it was not a very worrisome side effect that interfered with the treatment.
So to conclude I would say that this was a much much needed post-talk analysis because
adverse events were always a concern when we were using low latinib initially when low latinib was
launched and we were comfortable using electinib but I think this post-talk analysis really clears
a lot given the efficacy outcomes with low latinib. Most adverse events they occur within four months
of starting treatment and more than equal to great three events occurred even within
nine months and few very few patients required permanent discontinuation. Major side effects like
hyperlipidemia easily manageable with the drugs again the incidence and prevalence of CNS effects
again it was did not increase over a period of time it was not a concern over a period of time
it remains stable only initial year showed the significant CNS effect weight gain again it was
manageable lifestyle modification. So overall I think adverse effects now we are more comfortable
dealing with them especially when we are using such an efficacious drug law latinib especially
even if the brain metastasis is there because as Dr. Sudeep has shown excellent efficacy and outcomes.
Thank you.