Hi, good afternoon. I think this is one of the most talked about studies at this year's
WCLC along with the Tropian 2. And this is a molecule which is in development in China
by Akishubaya Pharma which has now been acquired by an American company. And when you see the
presentation on the 8th of September, their stocks were lying at about 43 Hong Kong dollars.
And after the presentation, it shot up to about 90 Hong Kong dollars within two days
and currently it's doing somewhere about 63 dollars for a share price. Now I didn't buy
this stock. It's not yet listed on the NSE. So this is an interesting molecule. Ak112
is a bi-specific molecule which targets the PDL1 as well as the VGF. And they looked
at going head-on with King Keteruda because we know that in October 2016, Pembroke did
get the approval in first line metastatic NSCLC both as monotherapy and in combination
with chemotherapy. So the bi-specific antibody against the PD1 and the VGF, this had shown
promising clinical efficacy. And this was in their first phase 2 study with the AK112202
study. And the Harmony study which was also known as the AK112303 was a phase 3 study
to compare the efficacy of I-O with Pembroke as first line therapy in patients with PDL1
positive advanced NSCLC. The study design looked at enrolling about 388 patients and 264 PFS
events providing a 90% power to detect a hazard ratio of 0.67. And the interim analysis for
the PFS was planned when 70% independent radiological review committee assessed PFS events occurred.
So this is the study through stage 3B, stage 4 advanced NSCLC patients who have not received
any prior systemic therapy, no EGFR or ALC mutation driven tumors patients were selected.
Patients were having good performance status of 0 or 1. And the mandatory enrollment was
at least have more than 1% PDL1 positivity. That further stratified the population into
based on stage 3B, C or 4 and histology wise whether squamous as well as non-squamous because
the phase 2 study did show that squamous population benefited with this drug much more as compared
to non-squamous. The PDL1 stratification as per TPS was more than equal to 50% versus those between
1 to 49, 3 98 patients. One is to ban randomization which is a good thing to see now. There are very
few trials which are doing this many are 2 is to 1 which can skew the statistic analysis at times.
Ivo in a standard dose of 20 milligrams per kg every three weekly, 198 patients were randomized
to this versus Pembro single agent 200 milligrams three weekly about 200 patients. The primary
endpoint being PFS, the secondary endpoint being OFS and the PFS assessed by investigators.
And both the treatments were continued until no clinical benefit or unacceptable

toxicity or up
to two years. The baseline characteristics between both these groups are well matched when we see
stage 3B, stage 3C they were about only 8% patients. So you see here that predominantly 92%
patients are stage 4, about 45% patients are squamous carcinomas and PDL1 more than or equal to 50%
forms about 42% of patients. About 12 to 14 patients had liver metastasis at baseline and about 16 to
19% patients had brain metastasis at the baseline. And when we look at the performance status,
we clearly see here that probably there is a representative population of what we see in
clinical practice with almost 85, 87% being PS1. In terms of age 65 and above we're about 50,
55%. Now this was the primary endpoint based on the independent radiology review committee.
And the I-O did score better over Pembro with an 11.1 median PFS versus 5.8 and a stratified
hazard ratio of 0.51. Initially they had started out with 0.67 in the clinical when they did the
initial statistical analysis. So this turned out to be a statistical significant improvement
and there was a difference of about 5.3 months between both these study groups.
When we look at the subgroup analysis, of course when we go by the stage first, the stage 3 BC
form only about 10% of the entire population in each arm. So that's the reason possibly that
it is crossing the midline. In stage 4 we clearly see a hazard ratio of 0.49 on the forest plot.
Squamous versus non-squamous no real difference. In terms of the TPS positivity more than 50%
hazard ratio of 0.48, 1 to 49% hazard ratio of 0.4. In terms of smoking status also not much of a
difference between both these groups. Age wise also whether patients are younger than 65 or
they are more than 65 years of age, we see a hazard ratio is almost the same.
Now when we look at the subgroup analysis based on PDL1 low and PDL1 TPS more than 50%,
these are the survival curves and of course based on the histology, the squamous as well as
non-squamous both are showing that there is a benefit of using this by specific monoclonal antibody
which is targeting PDL1 as well as VEGF. In terms of the secondary endpoints, the overall response
rate, disease control rate and duration of response, 50% ORR versus 38, 89.9% disease control rate versus
70% and median duration of response was not reached and both ORR and disease control rate
grossly higher than what single agent PEMRO does. So safety and safety summary was also
discussed about these group of patients and wherever we are using and VEGF directed therapy
in squamous carcinomas, we are all worried about the bleeding with our past experiences with
beverages in these group of patients. However when we see in the squamous subgroup more than equal
to grade 3 toxicity seen in about 22%, serious treatment related adverse events in about 18%

which is the same in both these arms and treatment discontinuation in 2% and 3% respectively.
When we look at the most common treatment related adverse event having incidence more than 10%,
we are looking at proteinuria, liver enzyme derangement, bilirubin elevation, hypertension
which are common, toxicity is related to VEGF inhibition and also related to immunotherapies.
The immune related adverse events, when we are looking at more than grade 3 events 7 and 8% in
both these groups, serious immune related adverse events are surprisingly lower with the Ivo group
in 5% and higher with the PEMRO. So I don't know what is the specific reason why this is happening
but possibly it may have to do with the selective binding of the PD-1 as well as the PD-L1.
So when we look at specifically the VEGF related adverse events proteinuria has been seen in about
31% of patients, hypertension in 15% more than grade 3 in 5%, hemorrhage in about 14% and these
as per the authors the hemorrhage grade 3 which happened in two patients they had non-scomosis, stology and was not reported in the squamous carcinoma patients.
In terms of the quality of life C30 ERTC scale there has been almost comparable time to deterioration of global health status in patients who have received both these therapies.
So in conclusion there was an improvement in the investigator,
radiological review assessed PFS in patients with advanced NSCLC and PD-L1 which was more than 1%
with the Ivo as compared to the PEMRO 11.4 versus 5.8 months. The benefit was consistent
across whether it was commerce or non-scomiss and whether the TPS was more than 50% or between
1 to 49. There was a higher rate of overall response as well as disease control with the Ivo.
Overall survival data will mature over time and the event driven overall survival analysis will
be reported. My take on this is that we are comparing a dual combination versus single drug
and we've seen the data. I know it's not a direct comparison but you have the data of A, B, C,
P versus BCP where addition of immunotherapy to the BEV and chemo combination has added another
five months of PFS in that trial. So possibly I do not know whether it is related to combining
VGF activity as well as PD-L1 and looking at two drug versus one drug here rather than just
looking at single agent PEMRO. So possibly the drug is good. We are looking at a good drug at
our hands and hopefully once we have the overall survival data this drug does have potential to change practice. There was also some criticism about using this drug only in
Chinese patients and there are more trials going on across the Caucasians and in the US also now
that this has been acquired by an American company. So they are looking at trials in different
population subsets too. So hopefully we should have more answers in another few years. Thank you.
Thank you. Thank you Dr. Litt. Two comments and I will request if you can have some opinion on

that. One is that for PD-L1 1 to 49 percent PEMRO alone is usually not the standard of care that is
discussed as a drawback of this study. Do you agree that this is drawback or this is
susceptible? What do you think? So when you look at the phase two data initially the PEMRO had
come in with all PD-L1 positivity more than 1 percent. So you do have activity of PEMRO also but when
you look at PEMRO chemo it works better. So I would have been happy looking at PEMRO and
combination for that 1 to 49 subgroup because that is the current standard of care. But obviously
the way the clinical trials are designed we all know that they are done in a particular way
with a particular intention in mind. However what is heartening to see is even in that more than
50 percent group this drug seems to be better. Seems to be better. So another point is that in
squamous we barely use Bevacizumab because of the obvious reason of hematomacizumab.
Any take on that because if you had used PEMRO plus Bevacizumab in the other arm what would
have done me the results. Because this is answer cannot be given. This answer can't be but as we
have data from the Atizobave there also we have seen that using it in non-squamous EGFR mutation
driven tumors. A BCP has not really increased the risk of hemorrhaging that subgroup of patients
when you are using it on progression. So maybe there is a trial which needs to be designed in
that way. If we have access to both the drugs I think we should be the ones to look at that as
a standalone phase 2 data. Maybe we can start as a collaborative group and collect our data to see
where we are. Thank you. Thank you.