Good afternoon. I would be discussing on unmet needs in exone 20 EGFR insertion mutation.
It is less discussed and less studied than the common mutations which we generally see
in EGFR. So, NSCLC as we all know is not one disease. Molecular subtyping is very important
and EGFR mutations are amongst the most prevalent exenable driver mutation. All EGFR
mutations also are not same. Oncogenic mutations generally occur from exone 18 to 21 and exone
20 insertion mutation is third most common mutation after the conventional or common exone
21 L8 5 beta. So, knowing about it is important. This is the structure of exone 20
EGFR exone 20. You have a extra cellular domain then a transmembrane domain then
exone 18 19 and then 20. It is the tyrosine kinase domain. If you see exone 20 you have a C helix initially from
761 to 766 codon and then from you have a loop. It is also divided into near loop
and far loop and you see a lot of insertion mutations in the loop. So, in frame
of excitations in exone 20 of EGFR are seen in up to 12 percent of EGFR mutated
patients. So, if in absolute number we see EGFR exone 20 insertion mutation is probably somewhere close to
or Ross mutation. So, it is equally important and probably less studied. So, as discussed
you have a helical region near loop and far loop. The most common mutations occur between
761 to 775 and generally it is either duplication or insurgent mutation. You have some other
exon 20 mutations T 790M which we all are aware of. It is a resistant mutation, it is
not an insertion, it is different. The weight x is different than what we see in exon 20
insertion mutation and other uncommon exon 20 mutation is S7681. It is an activating
EGFR mutation and we see some conventional EGFR TK working in this mutation. So, what
we are talking about is exon 20 insertion mutation and not the other two exon 20 mutations.
So, again in exon 20 insertion mutation there are multiple unique variants more than 100
which was seen in this retrospective study and of which 767 and 768 mutations are more
common. So, generally in our practice we see that platinum doublet with or without immunotherapies
first line treatment in exon 20 insertion mutation. Still we do not have approval for
ami-ventum from DCGI in first line though we have data for ami-ventum I mean first line
now and the median overall survival which we expect with platinum doublet and immunotherapy
is somewhere between 6 to 28 months because this is a retrospective data you have a huge
range but in real world practice we know that generally these patients do not do well even
compared to non-driver mutation positive patients because even immunotherapy is not working
very well in this subset of patient. So, median PFS is around 3 to 7 months and for chemotherapy
based regimen and around 2 to 6 months for TKI. Initially we had TKI's posturetinib
and mobos are TINib unfortunately both of them are withdrawn now which used to work

in this kind of mutation and now probably ami-ventum is the only drug which is approved.
So this is same real world PFS in first line is 6.6 months and overall survival is 17.4 months this is with platinum based doublet and if you give IO alone probably IO alone is not the way to treat these patients even if whatever PDL1 is there because with IO alone the median PFS is 3 months only. So, in the first scan most of the time you will see a progression. If you have given platinum doublet what would be the second line treatment options. So, now the natural would be ami-ventum but initially if immunotherapy was used or other TKI's were used the median progression free survival was not more than 3 or 4 months even with TKI's you see response rate somewhere between 0 to 20 percent or 17 to 42 percent.
So, except platinum based therapy or IO alone we have already discussed even in second line they do not fare well and so largely except ami-ventum we do not have great drugs to target these patients. Ocematinib we had some data for exone 20 insertion mutation but again the median PFS was somewhere around 3 and half months. So, even ocematinib has limited activity in these patients. Mobosertinib initially we used to believe that based on far loop near loop we can decide whether TKI will work or not work and decide whether to give ami-ventum or mobosertinib. Those who have used mobosertinib in compassionate excess would have seen the toxicity that is not an easy drug to handle and eventually with longer follow up the efficacy was not superior to chemotherapy and hence the accelerated approval which was given by US FDA what the company has withdrawn the further progress of the drug. So, mobosertinib is now not available IO monotherapy is not recommended as we discussed prior because the PFS is really low. So, initially the guidelines was to give platinum doublet first and on progression you consider giving ami-ventum. Now we have data we are still awaiting DCJ recommendation but ami-ventum plus chemotherapy platinum doublet with pemeter exact is generally recommended in first line and on progression you give the next line of treatment. Real world data we all are aware that compared to conventional EGFR patients patients with exone 20 insertion mutation do worse. So, this is real world overall survival second common EGFR mutation versus EGFR exone 20 insertion mutation 25.5 versus 16.2 months and PFS 10.5 versus 2.9 months. 5 years survival rate again 8 percent. So, these patients have poorer prognosis they benefit less from TKI platinum based therapy is most commonly used regimen and there is need of more effective treatment which probably

will be discussed in next panel. Again some important points while we practice if we do PCR a lot of EGFR exone 20 insertion mutation would be missed. We have seen when we have transited from doing PCR to hotspot panels to now broad panel NGS we pick more exone 20 insertion mutation and this is true for other mutations also not only EGFR exone 20 insertion mutations. Again if you combine solid plus liquid chances of picking up actionable mutation increases. So, when feasible that is also a good way to do a combined test rather than solid alone or liquid alone. So, in PCR if you pick around 5 percent of the patients you pick 70 percent of the patients by doing NGS of the patients who are positive for exone 20 insertion mutation. So, this is data from retrospective database, US based database where PCR missed around 50 percent of the patients in both the Gini database and FMI so the message should be that broad panel NGS should be a better way to pick up exone 20 insertion mutation compared to the PCR. So, these are various studies from India where the prevalence rate of exone 20 insertion mutation is ranging from 1 percent to around 4 but 6 the highest is 8.8 percent. So, again based on time this study would have some PCR based study and some NGS based study most of them are NGS based now. So, even in our country we see around 1 to 8 percent prevalence of exone 20 insertion mutation which in absolute form is an important number. Do we have any Indian data for exone 20 insertion patients?

So, we have 2 data one is by Dr. Shruti and one by one Nita Madam this is both are retrospective studies. So, one has shown median progression free survival of 6 months and overall survival of 15.8 months and the second study has shown median overall survival of 5 months I think that was a second line study. So, there is unmet needs surrounding exone 20 insertion mutation starting from first line and even in second line the TKIs are not working platinum doublet is not working immunotherapy is not working. So, we needed better options and now we have at least option to offer to our patients I think the that part will be covered in the next panel. I think this is the last slide. Thank you.