Good morning. We all know that we are entering an era of precision medicine in last decade and you can see through this timeline of events where initially we were subtracting it as a small cell versus non-small cell later after all these molecular events. Now in 2024 we have plethora of things to understand and subtract. We all know that lung cancer mortality is decreasing and survival are increasing due to multiple factors. One of the factors is subtracting a disease properly and understanding its biology. So delivering targeted therapy to biomarker patients as we can see whether they are oncogenic drivers versus non-oncogenic drivers when the driver targeted therapies have resulted in better survival. Now how NGS is directly impacting the survival like we can go through the further slides where we can delineate each subtype where we have a better survival compared to traditional chemotherapy resimens. So in this slide you can see in flora trial however, SMART NF has improved median overall survival to 38.6 when compared to conventional chemotherapy which is 8 to 10 months alone and we all know in profile trial where cresotenib has improved along with the nrytenib to 50 months and all. So all these oncogenic drivers are bit costly but still they are definitely worthy improving the survival of patients with less toxicity or specified toxicities rather than complicated toxicities which we see with traditional chemotherapies. So we have a lot of things to identify coming from PDL1, EGFR, ALCROS, RAB, BRAP, NTRK, RED, MAT, HERDOO and MAT amplification now KRAS and other immuno oncology biomarkers we have to identify tumor mutation burden, inflammation and a lot of things. The problem is there is more complexity in testing, standardization and understanding the reports and we have to identify a clinical need and patient wishes and what is the accessibility to this drug whether they are available in India or we have to import access or what is the knowledge and awareness and how much experience we have to deal with these drugs and their related toxicities and reimbursement issues and there are plethora of NGS platforms available in the country which creates much more confusion.

So coming to CAP or ISLC or EMP guidelines we have a lot of guidelines which says that the treatment patterns are different when the patient has expression of PDL1. The whole treatment pattern is different in stage 4 NSCLC where PDL1 more than 50% versus PDL1 less than 50% in diagnosis and decision making and survival patterns and counseling. Everything relies on this stratification. So even in squamous cell carcinoma PDL1.ioc testing is a routine and we also know that 3 to 5% of squamous cell carcinomas are oncogenic driven. So we have a small guidelines where it

mandates that testing is required because every stratification is based on whether patient is
having this specified mutation or not. So primarily we subtype as small cell versus non-small cell then squamous versus defective adenocharzoma then PDL1.ioc testing is a mandate
then again whether it is NGSLC platform or ISLC platform we test for EJPR, ALCROS, BRAF, India, K-Metra, TEN, HER2. Then determining on biology and this biomarker findings we can
divide them into oncogenic driven versus non-driven and tiler our therapies accordingly.
So coming to WHO lung classification and it is extensive depending on morphological type versus
oncogenic type. So and by using earlier methods of ISLC we could rarely subtype these NSCLC.
Now we can better subtype NSCLC and the rates of NSCLC and OS is less than 10%.
So what it will provide whether this biomarker testing is like it will stratify the patient and
indicates where the probable drugs can be used and also it is also based on decision making of
stage of the disease and performance status of the patient. So whether we should test every
lung cancer sample for everything. So fixation and processing and handling and storage issues like
initial biopsies when we are going to process it after two years or three years the quality of
DNA and quality of nucleic acid in the sample is a very big problem. And sometimes the newer
metastatic sites are not amenable for biopsy or patient is not convinced about re-biopsies
because it is invasive quite. So processing, fixing and preserving samples is also an issue.
So initially we are so simple we can diagnose morphologically then we are not bothered but
nowadays with each recurrence we should test again and again and we should take decisions
based on real-time monitoring of this tissue evolutions. So coming to dual-track testing when
European Union where they do biomarker testing parallely with the NGS based testing on DNA or
RNA extraction samples where multiple mutations and fusion genes can be found parallely along with morphological testings. So ideally we should test for everything
if affordable and possible otherwise a few like at least EGFR-AL cross PDL1 is a must.
So PDL1 ISC testings is now a routine standard. So in SP263SA which states only 50 cells are
required but majorly we assess on bases of 100 accessible tumor cells and the report is
stratified as less than 1% 1 to 49% and greater than 50% to base clinical indications and also
prognosticate the people. So again as we discussed earlier that tumor is present or not how much the
lab knows how to process it whether nuclear percentage in the sample is adequate or not
and quality of RNA or DNA in the sample and whether it is adequately tested in PCR methods
by NGS or not these needs to be identified and has to be matched with controls to understand
the report comprehensively. So current diagnostic standards on which gene

alteration should be
tested for we have standard EGFR exone 18 to 21, B-RAF, Keras met her too and gene fusions like
IL-PROS, RAT and NTRK. So as sent sensitivity and specificity we should know at least 20% of
tumor content is needed to get an ideal report. So and we also know once testing it is not adequate
when patient progresses again we need to know why the progression has occurred. Sometimes in
baseline samples we can see the primary mechanisms of resistance then we can prognosticate the patient
to go for either clinical trials or other alternative therapies which are available at
better places. When patient is acquiring a second resistance over the time of treatment
then we can know what are the interventions which can be done. Like if patient has transformed
to small cell lung cancer when he is primary adeno carcinoma then chemotherapy is one of the option.
So multiplex testing is certainly way to go but the thing is cost and the reliability is
standardization of the techniques and reports how validate they are and understanding detail
about coverage of engineers and also multiple ISC biomarkers with validations and parallel
testings is an issue. So multiplex parallel testing of all required biomarkers is generally
ideal especially IL-CROS, NTRK, RAT, fusions or EGFRK-RAS mutations are mainly tested.
So reflex versus B-spoke on demanding testing generally reflex testing is preferred when
patient is aware and you have an MDT generally that is the way in good centers we have MDTs,
molecular MDTs and their reflex testing is automatically practiced but in some centers in
peripheries where you do not have many of the options or treatment access abilities and
availabilities then we should go for B-spoke testing then depending on triage of patient and
condition we can discuss in MDT and review the test. So if something is good and cheap it can be
fast if something is fast and good it can't be cheap so we need to understand all these things
while cancelling the patient and inform choice making on discussion with the patient is the key
because patient will be on so much hope when he is spending so much amount on these multiplex
testing he thinks some magic is going to happen to him depending on this result.
Sometimes we don't get result on DNA sample then we need to run it on another RNA sample
and again it's a time consuming process. So most of the turnaround time recommendations are different
in clinical practice many NCLC patients are not tested for all actionable biomarkers even in
best of the best countries. So evidence suggests that testing is frequently less than recommended
guidelines that is quite true in India and other South Asian countries. So mainly the communication
is vital whether it is on discussion with the patient or in the MDT or your quite

frequent
interactions with the molecular lab to understand this testing and nuances in your updates is must.
Biomarker selected therapies definitely work that's why we do have not lot of precision on
call weekly next nowadays and testing guidelines and multiple recommendations exist we need to
Tyler according to your pattern of practice and definitely recommendations get updated we need
to also get updated with that recommendations and we need to update it in the community is also a must.
Thank you.
Thank you very much for the talk.