And we have Dr. Harsh Saho, Assistant Professor from Department of Medical Anchoal of Aayu Tata Memorial Hospital with us.
Welcome Dr. Harsh.
Thank you, ma'am.
Thank you for this opportunity.
So topic that we are discussing today is emerging trend in innovation in treatment modalities
for lung cancer.
So lung cancer has evolved rapidly.
It is the one of the most rapidly evolving treatment among all of the oncology.
Detement is changing day by day.
It is mainly due to recognition of driver mutation in lung cancer.
And development of target therapy in this lung cancer which has revolutionized treatment.
Today, treatment of this target therapy driven mutation in lung cancer, it is possible
to treat the lung cancer by just oral tablet.
Immunotherapy and other paradigm, another improvement is immunotherapy.
Immunotherapy improves the survival in driver negative lung cancer.
So we are going to discuss this.
So as we know, the evolution of therapy in lung cancer has time passed.
We recognize that lung cancer is not one disease, but many disease.
Initially, the additional view was that lung cancer is a single disease.
But subsequently, we divided into small cell and non-small cell type.
And subsequently, a small cell was another, they were filled.
Subtriqually, they went to a small square mass cell, large cell, adenocarcinoma.
So, sociological breakdown.
Now we are in era where there is a molecular breakdown and breakdown on the basis of PDL1.
So for every lung cancer, we do a molecular test and divide it whether it is a driver mutation
driven lung cancer or non-river mutation driven lung cancer.
Driver mutations are like EGFR-L-C-ROS.
And if patient is non-river mutation driven, then we will divide whether it is based on
PDL1 expression.
PDL1 is a protein that predict the response to immunotherapy.
If PDL1 is less than 1%, or if it is more than 50%, or if it is between 1 and 1 to 50%.
So basically, what happens is every cell in a body has a control mechanism that prevents
its growth.
So, this is done by some genes in a body that are called tumor separation gene or proto-oncogen.
What happens is if a cell grows old, it should stop growing and it should die.
This is a normal mechanism.
But cancer cell does not do that.
There are many mechanisms that cancer cell evade this mechanism of apoptosis.
One of these mechanisms is mutation or gain of function or loss of function of cell surface
growth promoting receptor that are tyrosine kinase receptor.
It may occur due to mutation in tumor separation gene.
Tumor separation gene are the genes that should suppress the tumor that are normally active.
But they are not active.
That means they are mutated.
Then there is a loss of, that means they cannot do their function and they cannot inhibit
the cell growth.

So, subsequently, cell will start growing or mutated proto-oncogen.
So, these are inactive at baseline.
But when there is a mutation in this gene, then what will happen?
They will, there is gain of function mutation.
That means there will be a growth, the cell will grow without any growth factor or without
if, without any requirement.
So, what are these driver mutation?
Driver mutation that are recognized are EGFR.
That is epithelial growth factor receptor, Keras, Elk, Ross, Beeraf, NTRK, Mat, Exo-19,
skipping, RAD and ERB2.
What this means is these are the mutation that if present in the lung cancer, there are
other mutation also, but these mutation are targeted by the drugs.
There are many mutation that can lead to the growth of the cancer.
But if this, this set of 8-9 mutation is present, then there are drugs available that we
can target it.
So, how to recognize this mutation?
This mutation can be recognized by a test called NGS.
NGS can be done in flash frozen specimen, the biopsy specimen that we take.
We can, we send into formalin, we provide the cell block.
So, in that cell block or in that block biopsy can be done.
Or second thing we can do is that the biopsy, flash biopsy we can take.
Instead of put again formalin, we can put it in a cell line and send it directly for
an NGS testing.
So, this is sample collection.
Subsequently, there is a specific protocol process by which these are processed in labs.
And subsequently an NGS test is done.
NGS is generally a, basically DNA waste test where there are different probes are present
in which we can find out if any of these mutations are present.
So, NGS sometime will do just a limited panel NGS that will have just this 10-12 genes.
So, that it become cause effective.
Sometime will do a broad panel NGS where there are 50 genes, even those which do not
have a target therapy will analyze that also.
So, what happens that in while doing NGS, if we are doing broad panel NGS, we will have
some mutation that will be driving this cancer.
So, these are called driver mutation.
Those are clinical element we can do the therapy.
We have drugs or some prognostic value are around.
But sometime we will recognize some mutation that are not causing cancer but that naturally
occur in the cell.
Because as we grow old, due to process of aging, we naturally have some kind of mutation,
not all the mutation cause cancer.
But mutations are cause passenger.
Passenger means they are not driving the bus, but they are sitting in the bus, they are not causing cancer, but they are also present.
So, sometime we need to be careful, sometime these may be confused with a driver mutation.
Subsequently there are some germline mutation also.

That means it sometime some cancer like prostate cancer, breast cancer may be present genetically
so that can be transferred from mother to child or father to child.
And for in such mutation we need to counsel family member also, we need to do a proper
genetic counseling unit to explain risks and benefit of checking the genetic mutation.
Or sometimes there may be some error in processing, there may be artifact in the mutation.
So, in modern era around 50% of advanced non-small cell lung cancer have actionable mutation.
That means around 50% of patients will have some other kind of mutation where therapy
will be present.
The most common is EGFR mutation.
Secondly is elk mutation.
Other include met, hereto, ross, bira, fred, anti-RK, PI3, MAC1.
Another is RASG12C.
This is most common mutation, but as of now we don't have a very effective drug in this.
We have one drug which is slightly effective that is used after chemotherapy.
So, what is the general flow chart that we follow for lung cancer?
So, every patient we need to do a clinical examination.
If we are suspecting lung cancer, we need to do biopsy and process the specimen.
Or and then we will do a morphological assessment, we will see whether small cell, non-small
cell and denotes squamous, we will do a DNA extraction and analysis of NGS.
So, the tissue that could be used will maybe be a dissection, surgical specimen, maybe
a oxygen-ish-epic specimen or a tissue biopsy.
Sometimes we can use FNA for diagnosis, but this FNA cannot be used for NGS purpose.
So, that's why FNA is cytology as a sole first biopsy, we generally don't encourage.
Third is that we can do a blood and pearl fluid from this also we can do an NGS.
So, we can, NGS couldn't be done in block or slide and subsequently we can do histology,
cytology, panel diagnosis and DNA RNA protein based NGS.
So, as of now we are trying to classify lung cancer based on molecular and PDL1 testing.
So, PDL1 is an IAC molecule that is not very sensitive or specific, but if it is high,
it suggests the response to immunotherapy that we will discuss later.
So, and for NHCLC patient, even for early stage, stage 3 or an advance, we advise for
if the treatment is given before surgery, it is called new adjoint treatment.
So, in new adjoint treatment also, EGFR and ELC testing is recommended as of now with
PDL1 IAC.
For adjoint also, we need to do EGFR ELC and PDL1.
So, even as of now today there is target therapy called Osema Tenev and electenev that
are approved in adjoint setting.
If the patient is EGFR positive or ELC positive, driver mutation positive, then this treatment
do not require very well with immunotherapy.
So, that is why to spend much of the money in immunotherapy may be not beneficial on
for cost benefit ratio.

For advance, this is we generally do a broad NGS testing as we discuss earlier and PDL1
at diagnosis.
So, initially the NGS and PDL1 was relevant with stage 4 cancer only that is metastatic
disease, stage 4 cancer that lever brain or different side mass.
But as the time passes, we are recognizing that even stage 1 or stage 2 disease NGS and PDL1 testing are helpful.
There was a adora trial that is Osema Tenev.
Osema Tenev is an EGFR targeted tablet treatment that is it for one tablet only we can
treat EGFR-muted NLCLC.
So, if initially it was used in stage 4 disease, but in this trial even post surgery also
patient has received Osema Tenev.
On it has shown that after surgery also there is a survival benefit.
If we see in this graph, if we do not use Osema Tenev at 36 month that is 34% patient
would have survived.
And if we use EGFR therapy, that survival is up to 85%.
So, that means there is significant improvement by using one tablet in this day and era.
But the issue is that this tablet is costly.
It costs around 1.2 lakh rupees per month.
So, the patient we are who can do it, we are giving this tablet.
Subsequently, 5 year OS also improved to 85% for 73% in the patient who underwent surgery
in curative surgery.
Now, coming to second drug that was talking that is electenev.
Electenev is an Alc fusion positive.
Alc is used in Alc fusion positive non-small cell lung cancer.
This is a second target that target mutation that is presented in lung cancer.
And if patient has received surgery, after surgery if patient receive electenev or versus
chemotherapy.
So, patient who are Alc positive if they receive electenev, there is significant benefit
in survival.
With survival not reached so that means if there are 42 months the survival is about
80% of with electenev compared to around 52% with chemotherapy alone.
There is if the patient has not received done surgery but has received chemotherapy and
radiotherapy.
In such patient also adjuent Oseem Athenav has improved the survival.
Now, coming to immunotherapy.
What happens is that our immune system of our body fights to bacteria, fungus and virus
that we encounter daily.
But it also fights against the cancer cell.
There is almost daily some or other mutation must be happening in our body.
But this mutation are taken care about this abnormal cell.
Start performing abnormally.
These cells are killed by our immune system.
So, what happens that cancer cell figure out a way to defend themselves against the body's immune system.
So general principle is that cancer can be eradicated if immune system is instructed to
do so.

If our immune system knows it's the cancer cell and it can strain to do so it is done.
This is the concept for immunotherapy and newer genomic therapy it is done.
So what happens is that cancer cells have and immune cells have this PDL and PDL1.
PDL1 is present in cancer cell and PD1 is present in immune cell.
What happens is if they bind they will recognize that this is an abnormal cell and they will
start killing those cells.
So cancer cell find a way to escape this mechanism and there are other mechanisms also in which
cancer cell may find a way to like CTLA for this regulation and all those things.
So what happens is that if we train the if so what this is what therapy where immunotherapy
is it is PDI1 and PDL1.
So this will activate the immune cell to kill the cancer cell.
So immunotherapy advances kills the active body's immune system to kill the cancer cell.
So initially in stage 4 treatment initially there was just platinum double ed chemotherapy
in 2005 and subsequently those second line chemotherapy like dosy txl bawa sisma pami
txl carbo platin nap packli txl chem 2021 then new ajo and chemo therapy came in 2024.
Then subsequently in 2025 new lomaap came in 2026 pambalismap atisalismap these are other chemo therapy that came in 2017 we had combination of pambalismap with pami txl
and carbo platin in 2018 we had combination of pambalismap carbo platin and txl or atelizomap
carbo platin pakeli txl bawa sismap in 2019 we had 2018 we have durvalumap 2019 we had
other combination.
As the time passes the more and more immunotherapy combination are being used and are
we discover daily and added to chemotherapy daily.
So question is in curative setting why to give up pre-operioroperaate chemotherapy what
is the use of new agent therapy.
So what is the use of considering thinking of new agent immunotherapy.
So what new agent does is to treat before the surgery.
It provides the earliest opportunity to eradicate micro-matastasis.
It increases the treatment initiation rate and compliance rate.
If the patient has undergone a major surgery we don't know how well he will recover it.
So before surgery we give some chemotherapy if there is a concept that if there are some
micro-matts that may progress further in later in patient's life that are killed before
surgery also and we will have a pathological response that will guide how sensitive or
what is the biology of the tumor.
So adjuent treatment advantage it will allow the fast surgery.
So the patient has lung cancer so we will remove the lung cancer.
So pre-surgical complication is less if the new agent there is some complication the patient
cannot undergo surgery that is not the case with adjuent therapy.
It enables long treatment duration and disease control.
It has most flexible timing post surgery to provide accurate recovery of time.
So new adjuent immunotherapy that are approved include new volume app in perioperative setting

at least new periooperative means will give before also and after also the volume app
has been approved in adjuent setting, atolizumab and pembolizumab have been approved.
So what this new adjuent will does as we discussed earlier it will with immune checkpoints
inhibitor it activate the immune t cells and then will do surgical resection of the tumor and these immune t cell activation that will remain in the body and subsequently
if there is some like some remaining cells also it will kill those cells.
So this was the curative intent that is patient who had undergo surgery immunotherapy in
this setting.
Now coming to EGFR mutated and metastatic NSEL C. So there are different drugs.
So first mutation that we see so was EGFR that was Exone 19 and Exone 21 deletion that two kinds of mutation.
So that is that is best in this mutation is osymitinib.
Other combination that can be used is osymitinib with pymethyxet and carboplatin, adlothinib
afatinib jaffetinib dhakotinib ralosamab erotinib babasisamab.
These are the other drugs used in first line setting EGFR mutated center.
Even if EGFR is patient as progress on osymitinib there is option of using second line immunotherapy
there is second line targeted therapy that include avi ventamab.
In this trying they use avi ventamab less plus pym carboplatinib.
Avi ventamab has been used in first line also.
Now another mutation is HER2.
HER2 is generally seen in breast cancer values.
We use trarthosamab, TDM1 and TDX2.
There has been study to recognize whether HER2 will be useful in lung cancer also.
So basically what is HER2 is receptor thynosin kinase that is expressed in low level
epithelial cell.
Activation of HER2 receptor lead to enhanced cell proliferation via PI3K and MAP kinase
pathway.
Incidents of HER2 in lung cancer is 2 to 6%.
So what is HER2 mutation?
There is a HER2 mutation.
This broth can be recognized by NGS in metastatic non-small cell lung cancer and also for
scramacillac cancer.
HER2 amplification there is a more copy number of HER2 chromosome.
So even HER2 directed therapy have been proven to be beneficial.
Now currently they are used in second line after progression of immunotherapy but at
TMS we have a trial where HER2 directed therapy has been given in first line.
Now coming to last topic that is recent uptake.
Now recent what is is a drop to directed therapy.
Now there is an error of combining this immunotherapy.
So target therapy at target antibody with a chemotherapy.
That means there will be a drug that have antibody target with a drug that will release
in the cellular cell.
So this has not come still in lung cancer but has been studied.
The target is drop to, drop to the trans-mammary glycoprotein over experience solid tumor.
It has it is act as a decent molecule.
It has been over expressed in different cancer but it is seen up to 75% of lung

cancer.
So top two expression with prognosis very patient with low or note top two are doing better
but target is still emerging.
So antibody drug can do that.
Diaptomase, the rest can is a drop to dark and ADC.
Sectusomab, govatican that is used in drug cancer is other than drop to mutation.
So what will happen there will be a antibody.
So this is a drug.
That means there will be a chemotherapy attached to this antibody and this antibody will bind
to tumor cells.
So subsequently when this attached to tumor cell this chemotherapy instead of giving
to through vein we are directly releasing in tumor microenvironment and so it should
kill the cells effectively.
It has been approved in breast cancer and urethelial cancer.
It is still in process in lung cancer.
So to summarize the molecular testing in PDL one is required in our least stage also
and at one stage also and it is now driving the treatment of lung cancer.
Also there is a role of multi-discipline care team that will improve the health.
It provides holistic treatment to the patient including chemotherapy, including palliative
care, including nursing care, including better psychological care.
That is important for holistic treatment of the patient.
Thank you.