Thank you sir for the opportunity. So today I will be discussing immunotherapy related
pneumonitis risk factors and predictors. Although Dr. Preetam gave us a shot and obsessed in one of the slides and just expand on it. So what we will be covering today, we will be covering the mechanisms of how these immunotherapies work which are the FDA approved immunotherapy agents, new targets and pipeline, the mechanism of immune checkpoint inhibitor related pneumonitis, grades of pneumonitis, incidence and onset of duration, risk factors and predictors and tickle. So the mechanism of PD1 and PDL1 block it is such that PD1 is a protein on the T cells which inhibit and suppress the function of telemfluid, controlling its autoimmune response. PDL1 is a ligand on the tumor cells and PDL1 and PD1 bind together and they reduce the effectivity of T cells causing tumor immune escape. How the ICIs work is by binding to the PD1 inhibiting the PDL1 and PD1 to mate, reactivating the T cell function by blocking the signal that suppresses them. This causes the killing of the tumor cells. The mechanism of cytotoxic T cell antigen inhibitors is such that CTLA4 is a transmembrane protein on CD4 and CD8 T cells. Their primary role is to inhibit the T cell priming. How the ICIs work is by targeting these proteins, stopping them from suppressing the T cells and causing new T cell clones. While PD1 block it causes expansion and recruitment of the existing T cells, CTLA4 block it causes new T cell clones. So why this is important is because one of the important trials has caused that CTLA4 inhibitors and PDL1 PD1 inhibitors can be synergistically used because they have different mechanisms to activate the T cells. So these are the next-generation ICIs as of 2021 in approved by FDA. We need to know these subgroups because they kind of affect the incidence of immunitis. CTLA4 has IMPLIMAP, PD1 has semi PILAM, nebulamab and pembrolyzumab, PDL1 has avalumab, duralumab and atazolezumab. In the pipeline there are many new immunotherapy agents coming. As we can see that there are lots of new targets, lymphocyte activation gene, T cell immunoglobulin, natural killer group routine etc. So lot of phase 1 and phase 2 trials are ongoing and I assume that there's going to be a robust boost in immunotherapy agents. So why does ICI in induced immunitis occur? As the tumor cells require checkpoints even normal cells rely on checkpoints and then nonspecific block it can result in variety of autoimmune toxicities, the term which we call as immune-related adverse events. Whereas CTLA4 inhibitors enhance T cell lymphocyte and antigen-ridden presenting cell interaction, PD1 and PDN1 inhibitors enhance T lymphocyte and tumor cell interaction. In general CTLA4 inhibitors cause much more nonspecific activation of T cells causing overall more toxicities compared to PD1 and PDL1 inhibitors. But interestingly the rates of immunitis incidence of immunitis is more with PD1 and PDL1 inhibitors. The mechanism of immune checkpoint inhibitors there are various hypothesis such as hypersensitivity and related immunological reactions, increased level of inflammatory cytokines, upregulation of pre-existing and autoantibodies. So this kind of underscores that we need to check for each patient whether they are having any
underlying autoimmune disease as well. Also the theory suggests that on target pharmacology such as toxicity related to action on the intended receptor certain anti-CTLA4
antibodies can cause hypophysitis that is inflammation of the pituitary gland. And off-target pharmacology that is activated T cells across antigens shared between tumors
and normal lung tissue. This is important because this is also one of the reasons why
limonitis occurs in lung cancer, more in lung cancer than other cancers. And also biological
activation of the drug by liver to form toxic metabolites. The grading of immunotherapy related
limonitis grades from one being asymptomatic to grade 4 being severely symptomatic. Usually

with one we discontinue the drug grade 3 and above we permanently stop the drug. So the real world incidence is varied from various studies as low as 1.4% to as high as 21.78%.
And as we see that major studies are done in lung cancer patients and most of these patients
have received anti-PD1 inhibitors. The onset of occurrence of pneumonitis in immunotherapy
patients ranges from few weeks to few months depending on the type of therapy and also the
type of cancer they are being used for. So it is about 2.3 months earlier in lung cancer patients
and more longer in melanoma patients. So we'll go over the risk factors and predictors and
each risk factor how it affects the pneumonitis association with the type of malignancy.
As I mentioned earlier the incidence of pneumonitis is much more in lung cancer. As we see out of 26
studies with 5,000 patients the incidence was higher for all grade limonitis in lung cancer
patients and for grade 3 or higher especially in lung cancer patients. Association of the type
of ICI and combination therapies. Another paper with 19 trials and 5,000 patients showed that
PD1 inhibitors had statistically significant higher incidence for any grade limonitis as compared to
PD-L1 inhibitors. 35% of this pneumonitis cases were severe and also very interesting to note that
treatment knife patients had a higher incidence of all grade limonitis as compared to patients who
had received immunotherapy earlier. All in all we must remember that the incidence is higher in
PD1 inhibitors than PD-L1 inhibitors than CTLA4 inhibitors. The checkmate trial which had nevolumab
and epilium mumbam in lung cancer showed that the pulmonary side effects were higher in the
dual group. Out of that the grade 3 and 4 were also higher as compared to when devolumab was
given alone. So this underscores that patients receiving concomitant or 2 immunotherapy agents
are likely to develop pneumonitis than in individual agent. Another interesting study which studied
peripheral blood biomarkers for early diagnosis severity in immunotherapy related pneumonitis
patients showed that about 10% of their patients developed pneumonitis out of which the histological
subtype was quamisyl carcinoma which was most associated with immunotherapy related pneumonitis
and also patients who were previously related had a higher frequency of pneumonitis. Another interesting
study was that ICM monotherapy was associated with a higher risk of pneumonitis and compared
to patients who were receiving immunotherapy and chemotherapy concomitantly. Another interesting
study in which the role of the safety and toxicity profile of SBRT and concurrent immunotherapy
was studied. 54 patients received SBRT and concurrent either single or dual immunotherapy versus 63
who received SBRT alone. The risk of grade 3 pneumonitis was higher in the SBRT and immunotherapy group

and risk of any grade pneumonitis appeared higher in SBRT and either dual or monotherapy with
immunotherapy. All in all even if patients are receiving SBRT we must keep a very close clinical
watch. Association with pre-existing lung and autoimmune diseases and smoking.
A trial of 10 studies, a systemic review of 10 studies with 179 patients showed that immunotherapy
was not inferior in patients with pre-existing ILD and overall response rate was higher in
these ILD patients. However the incidence of pneumonitis was more in those with ILD and even
the incidence of more than grade 3 pneumonitis was higher in patients with pre-existing ILD.
Here again where pre-existing ILD and the risk of pneumonitis was assessed.
The median onset was much lesser 1.3 months to develop immunotherapy reduced pneumonitis versus
patients who did not have pre-existing ILD. Another study, single institute study, where
about out of 102 patients, 19 patients developed immunotherapy in lung cancer. We see that there
is a really strong association in heavy smokers and in those who had a poor performance scale
for all grades of ILD, all grades of immunotherapy and for those with having a poor performance
scale they had a higher chance of having grade 3 immunotherapy related pneumonitis.
So smoking and ICHs, there's some good news and some bad news. Heavy smokers because of the DNA
damage, they have a better response to ICH treatment. Heavy smokers are also with the same virtue at
having an increased risk of immunotherapy related pneumonitis. Greater incidence of
pneumonitis in immunotherapy is also noted in asthma and COPD patients. This was noted in the
keynote trial with Pembroly zoom app. We shouldn't forget that greater incidence of
pneumonitis is also seen in pre-existing auto-antibodies, autoimmune diseases. These may appear as
atypical radiological presentations on CT and hence we must keep an open eye and low threshold
for testing antibodies in suspected cases. Risk factors and predictors in association with blood
indices. So this study which we covered earlier which had about 10% of patients having pneumonitis
in advanced lung cancer showed that high IL-6 levels were associated with severe grade and a poor
prognostic marker. Also studies have shown that elevated neutrophil to lymphocyte ratio have
been linked to development of particularly pneumonitis and interesting for all of us
pulmonologists to note that absolute ear-sennofil count has also been noted higher in pneumonitis
patients. So the absolute ear-sennofil count can work as a predictor marker prior to the
development of symptoms although more studies are needed to establish the causative role and relation.
Association with radiology patterns see multiple patterns are seen. We see organizing pneumonia,
ground glass opacities, reticular patterns, hypersensitivity like pneumonia,
pneumonitis, N-SIP pattern, even sacroidlytic reaction, plural effusions. But none of these
patterns are associated with the clinical outcomes or the severity other than just

acute
interstitial pneumonia which is frequently seen in grade 3, pneumonitis. So I'll sum it up that
the onset of symptoms may vary from one month to five months. Nimonitis occurs more commonly
in lung cancer patients especially the squamous histological subtype, more with PD1 inhibitors
than CTLFO inhibitors, also more with contourmital or dual use of immunotherapy in previously
related individuals including those who have received SBRT. In pulmonary comorbidities,
preexisting ILD heavy smokers are at higher risk and even those with e-coxcal of 2 or more.
Increased incidence is also noted in patients with obstructive air disease. There are biomarkers
like IL6, new TOFL2 lymphocyte ratio, absolute use of OFL count which in the future may help us
determine in predicting and helping determine the severity. All in all, we need to check all the
patients before they receive immunotherapy and sequentially monitor them during the therapy by
clinical assessment, pulmonary function test and radiology in tandem with the oncologist.
Thank you. Thanks a lot. Thanks again.