ESMO Annual Meeting 2022

Consultant Responses to Selected Abstracts and Posters

EXECUTIVE SUMMARY

Data presented at the ESMO Annual Meeting on September 9-13, 2022 was discussed by hematology/oncology physicians at a two-session meeting, October 18 and October 25, 2022. During these sessions, the moderator and oncologists discussed several clinical trials, posters, and abstracts to assess state-of-the-art information on drug development for the treatment of non-small cell lung cancer (NSCLC). Key points are summarized here.

Attendees

Moderator

Bruna Pellini, MD
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Faculty

Manojna Konda, MD Oncology Fellow University of Arkansas for Medical Sciences Little Rock, AR	**Matthew Hadfield, MD** Hematology & Medical Oncology Fellow Brown University Providence, RI
Aakash Desai, MD Hematology & Medical Oncology Fellow Mayo Clinic Rochester, NY	**Jaclyn LoPiccolo, PhD, MD** Clinical Fellow, Hematology/Oncology Dana-Farber Cancer Institute Boston, MA
Salman Punekar, MD Thoracic Medical Oncologist NYU Langone Health New York, NY	**Samuel Geurkink, MD** Oncology Fellow University of Arkansas for Medical Sciences Little Rock, AR
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KEY TAKEAWAYS

- The anti-PD-L1 monoclonal antibody (mAb) durvalumab has been FDA-approved for PD-L1+ non-small cell lung cancer since 2016 and continues to be studied in numerous disease subgroups and in combination with other agents.

- Durvalumab + concurrent radiotherapy in unresectable locally advanced PD-L1+ NSCLC may be an option for patients unable to undergo the standard of durva + chemotherapy.

- Pembrolizumab in combination with chemo continues to be a standard of care in metastatic NSCLC and prolongs OS and PFS compared to chemo alone. Exploratory analyses of multiple trials utilizing pembrolizumab support its use as 2L therapy if patients responded to it as 1L therapy.

- Data from trials examining the anti-PD-L1 mAbs atezolimumab and avelumab, as well as those examining anti-PD-1 mAbs nivolumab and sintilimab, have not yet yielded practice-changing data in the minds of the panelists.

- The anti-KRAS-G1C agent sotorasib has significant toxicities, but may be a viable option over chemo in the setting of NSCLC with progression on prior platinum-based chemotherapy with a checkpoint inhibitor.

- Follow-up data of the TKI osimertinib confirms its efficacy in the EGFR+ NSCLC setting despite some concern that the drug may not be killing cancer cells, but merely putting them in a latent state.

SUMMARY POINTS

Immunotherapy (IO) with targeted immune checkpoint inhibitors (ICIs) is standard treatment for non-small cell lung cancer (NSCLC) and is the subject of several trials examining these agents in combination with each other and in conjunction with chemotherapy (chemo; CT) and radiotherapy (RT).

Durvalumab, an anti-PD-L1 mAb, has been FDA-approved for PD-L1+ NSCLC since 2016 and continues to be studied in various regimens, disease subgroups, and in combination with other agents.

- A follow-up of overall survival (OS) data from the POSEIDON trial of the anti-PD-L1 mAb **durvalumab** ± the anti-CTLA-4 mAb tremelimumab + chemotherapy in first-line (1L) metastatic non-small cell lung cancer (mNSCLC) demonstrated durable long-term OS benefit of the durvalumab + tremelimumab + chemo regimen vs durvalumab + chemo, and supports the use of this regimen as a first line treatment option for mNSCLC.
    - Participants were encouraged by the OS benefit from doublet IO + chemo but were hesitant to call it practice-changing and were wary of the possible added toxicity risks.
        - Desai: *"It's good to know that there is overall survival benefit. It is potentially providing more basis and more evidence for chemoimmunotherapy and dual immunotherapy with chemo, but I don't think that just based on this abstract I think there is a lot of practice change, at least at our institution and for me personally."*
        - Kim: *"We see a positive outcome demonstrating that probably the combination of chemo and doublet IO is something that could potentially be used but I don't know if it would really change practice in a way where we would choose this regimen over something that we're all comfortable with already."*
        - Desai: *"I don't really think that I would expose the patient to additional toxicity with an agent like tremelimumab just knowing the fact that the dual immune therapy blockade has a higher frequency of immune related adverse events. Especially because I think if we are trying to up by treatment and the patient ends up having an immune-related adverse event I think it really kind of hampers their treatment algorithm going forward."*

- An exploratory analysis of survival outcomes in the POSEIDON trial (above) according to KRAS, STK11, and KEAP1 mutational status postulated that the triplet regimen (dual IO + chemo) may improve clinical outcomes for these hard-to-treat subgroups with co-mutations.
    - Hazard ratios for OS favored triplet vs single-agent chemotherapy irrespective of STK11 or KEAP1 mutational status, consistent with results in the intention to treat population, and OS rates were higher again with the triplet therapy across all subgroups suggesting sustained benefit at two years with the triplet regimen.
    - There is support for the triplet regimen as a potential 1L treatment option, including those patients with KRAS mutation, STK11 mutation, or KEAP1 mutated tumors.
    - Again, participants were wary of clinical use due to risk of added toxicities from two IO agents.

        - Desai: *"I would personally think these data are great and these are hypothesis generating but I don't think that I'm going to change my practice until I see a randomized trial particularly in these subgroups showing benefit of what I'm calling the triplet regimen which is two immunotherapies plus chemotherapy versus something like KEYNOTE-189. If there is evidence from that randomized trial then I think obviously this is definitely practice changing but I think just as of yet I would potentially not just based on this data… I wouldn't feel comfortable in terms of benefit/risk ratio. I think there's still a higher risk than benefit for a patient of mine that I have and seeing [sic] in the clinic who has an STK11 mutation."*

- The DURATION phase 2 study examined an older, more frail population of patients with advanced NSCLC, comparing 4 cycles chemo vs 2 cycles chemo + consecutive **durvalumab**, stratified into fit or unfit groups. Median PFS, OS, and included endpoints were relatively equal.
    - Panelists found the data a bit confusing with too many comparisons and were unsure how to apply it the results to clinical practice.
        - Kim: "*I think what it's doing is it's comparing, like two cycles of chemo followed by durva versus just chemotherapy alone. There's no immunotherapy in that arm but that's not standard of care right now. So, I think if for frail patient, I would even think about, you know, just IO alone, like immunotherapy alone rather than just four cycles of double chemo. So, I'm just not sure how this applies what we're practicing in the clinic right now."*
        - Pellini: "*I think there were too many comparisons, which makes a little confusing. But I think for our reality in the US, the most interesting data would be to focus in this group of frail patients with 0% PD-L1. Those are the ones that we are not sure what to do. I mean, we know what we shouldn't do, and we know what we will give, it will be just like placebo. But I think if I could see the data of that patient population, which is really what will immediately affect my clinical decision-making tomorrow, maybe even if it's a phase two, because this is like real world, like problems that we have to solve."*

- The DOLPHIN phase 2 study examined **durvalumab** + concurrent radiotherapy in unresectable locally advanced PD-L1+ NSCLC. The standard of care for Stage 3 NSCLC is durvalumab consolidation post concurrent chemoradiotherapy; some patients can't receive this combination, so it was postulated that perhaps RT + ICI would have a synergistic effect.
    - This trial was similar to PACIFIC (concurrent immunotherapy + RT with consolidation immunotherapy + chemo) minus the chemo.
    - The study was felt to be promising as the primary endpoint of 12-month PFS rate was met (72%) and was expected to be 50%; in comparison, the 12-month PFS rate in PACIFIC was 55%.
    - Panelists felt that this regimen may be appropriate for patients who cannot take or refuse chemo.
        - Pellini: *"The reality is you will see that if you haven't seen, there are patients that they do not want chemo. Doesn't matter if they have stage 3 disease, they just*

don't want it or they're unfit, so I think it's good to have some data to try to guide decisions because if you're not going to give that, then what are you going to give them? You're going to treat them with an intention to palliate their disease. Then you're going to give us stage 4 disease regimen or you may want to try just the immunotherapy and then you could do sequential radiotherapy but then the question is, is the outcome going to be the same? The answer is probably not because we know they're giving those things together tends to be better."

- The phase 2 ORION study examined **durvalumab** + the PARP inhibitor olaparib vs durvalumab alone in adv/mNSCLC without EGFR mutations to evaluate whether tumor immunogenicity might be modified with the addition of a PARPi to maintenance immunotherapy. The primary endpoint was investigator-assessed PFS, with secondary endpoints of OS, PFS in patients with homologous recombinant repair mutations (HRR) and safety. PFS was not improved with the addition of olaparib, even in the HHR mutation cohort. Data did not support the addition of olaparib to maintenance durvalumab.
    - Panelists wondered if PARPi might be useful as 2L therapy; as platinum chemo uses the same DNA mismatch repair pathway mechanism to PARPi, using PARPi immediately after platinum may not be beneficial.
        - Pellini: *"It was a little bit disappointing because at least we expected the signal from that [HHR] subgroup and we know it's only 10% of patients, but still, the numbers don't look promising."*
        - Pellini: *"The conclusion is maybe there's some interest in exploring this in lines beyond maintenance, which is obviously first-line, but this data, it's not promising the way it is. You wouldn't proceed with a phase 3 trial because it's basically a negative study."*
        - Kim: *"Is there a subset of patients where we can identify those at high risk of recurrence? Maybe they might benefit from PARP inhibitors because at least in the breast cancer setting, olaparib can be used in kind of the maintenance setting for BRCA1 and BRCA2 in patients, but it's not for everybody. It's for patients who meet a specific criterion of just high risk of recurrence. Maybe that's a subset of patients that we might need to identify and who might see a benefit."*
        - Desai: *"Mechanistically, if we are taking subset of population which has homologous repair deficiency, hypothetically, these tumors potentially because they have a DNA mismatch repaired deficiency probably have higher tumor mutation burden or acquire more defects. While you have patients on immunotherapy, theoretically your immune system can kill those tumors. That's maybe the reason why PARP inhibitors are not doing much with IO combinations compared to what we saw in other tumor types because the tumors are already kind of with high tumor mutation burden and things which will be recognized by the immune system, especially with Durva that perhaps PARP is not adding much. That may be another kind of mechanistic hypothetical scenario that's going on."*

- HUDSON was a phase 2 open-label umbrella study of **durvalumab** in advanced NSCLC, no driver mutations, after progression on ICI, consisting of two groups. Group 1 (biomarker match group)

received durvalumab + PARPi (olaparib, ceralasertib, olecumab, or trastuzumab deruxtecan [TDxD]). HHR mutant LKB1 received olaparib; ATM, ceralasertib; CD73, oleclumab; and HER2, TDxD. Group 2 (biomarker non-matched cohorts) received the same therapies. Patients either had primary resistance (disease progression after 24 weeks on 1L traditional chemoimmunotherapy or acquired resistance (progression after 24 weeks).

- Durvalumab + ceralasertib yielded an ORR of 16%, with very minimal response rates with all other combinations. Disease control rate was highest with durvalumab + ceralasertib arms; PFS was also numerically higher, with the longest PFS being six months.
  - Punekar: *"This definitely supports the use of ATR inhibitors, which is the ceralasertib in combination with durva and it can be used as a biomarker-specific strategy or even a non-specific strategy based on overall response rates in both of these cohorts. The remainder of the drugs, they're all drugs that at least have some theoretical benefit in lung cancer after progression on checkpoint inhibitors. It just shows that that doesn't necessarily mean that they'll pan out into anything. Similar to the previous abstract where we discussed that maybe PARP inhibitors don't have as much efficacy as suggested in the lab."*
  - Pellini: *"The other thing is a little disappointing looking at the table like the other groups because the PFSs are so low which it's similar to giving a single agent chemo almost or even worse if you compare cross trials that we really shouldn't, but we all do… But based on this data, and again, there's a subgroup of a subgroup analysis, so it's hard to make major conclusions. The PFS is still disappointing, much lower than what we would expect."*

The anti-PD-L1 mAb pembrolizumab (pembro) is approved as a single agent and in combination therapy for advanced/metastatic NSCLC in multiple disease populations. Pembro in combination with chemo has been the standard of care for several years and it prolongs OS and PFS compared to chemo alone.

- An exploratory pooled analysis of outcomes with 2L **pembrolizumab** across five phase 3 studies of NSCLC (KEYNOTE-024, KEYNOTE-042, KEYNOTE-598, KEYNOTE-189, KEYNOTE-407) was performed to ascertain whether patients responding to 1L pembro might respond to 2L pembro. Authors concluded that when patients have achieved a response with 1L pembro, a second course of pembro is feasible; some activity was shown and the safety profile is very manageable.
  - Guerkink: "*I'm encouraged that people still can respond to immunotherapy because that's the big fear and the big question that patients have each time is if I stop it, is it going to work again if we use it again? I think that the results are encouraging. At least some patients are responding… It's also great to have this data to show insurance companies because they don't like to approve pembrolizumab after the patient's already been on it. Actually, been a big problem for my practice."*
  - Kim: *"The other thing I think would be interesting to look at is I guess trying to understand is there a timeline of how many months it's OK to restart pembro because the range is pretty wide. As you mentioned, it's between four months to 35 months. Maybe I would feel comfortable re-challenging with pembro. Potentially is it more than six months from the last dose? Is it one year from the last dose? I would feel less comfortable about*

rechallenging with pembro if they've progressed like four months ago since that's so close to kind of their last treatment dose and their progression."

- The TROPION-Lung-02 phase 1B study of the antibody-drug conjugate datopotamab deruxtecan (Dato-DXd) + **pembro** + chemo in advNSCLC had 6 cohorts. Patients in cohorts 1-2 (prior chemo) received the doublet regimen dato-DXd + pembro. Patients in cohorts 3-6 (treatment naïve) received the triplet regimen of dato-DXd + pembro + platinum-based chemo (carboplatin or cisplatin). The primary objective was to assess tolerability and safety and the secondary objectives were to evaluate efficacy, pharmacokinetics, and anti-drug antibodies.
    - ORR in all comers was 39%, and disease control rate (dCR) was 82%. In 1L patients, ORR was 69% and dCR was 100%. The triplet combination of dato-DXd + pembro + chemo as 1L therapy achieved an ORR of 50% and dCR 90%. With doublet treatment, the ORR was 62% and dCR 100%. As 2L therapy, the doublet and triplet regimens produced ORRs of 24% and 29%. ORR for both regimens was 84%. Authors stated that dato-DXd had a good safety profile and was efficacious, warranting phase 2 and phase 3 studies.
    - Participants expressed concern that the treatment discontinuation rate of 43% was too high and that the median treatment duration of 2.7 months was short.
        - Kim: *"It would be interesting to see how long patients respond. I think they just looked at – they said the median treatment duration was only about 2.7 months so it's still early on. Even though they report a disease control rate of a hundred percent in the first-line setting, how long these patients respond I think would be interesting to look at, especially given that there might be higher percentage toxicity with the 43% of patients discontinuing treatment due to AEs."*

Anti-PD-L1 mAbs atezolimumab (atezo) and avelumab were evaluated as alternative treatment regimens to chemo in 1L adv/mNSCLC. Atezo was also studied as additional therapy after tumor resection.

- A phase 3 study examined the feasibility of 1L **atezolimumab** vs single agent chemo in locally adv mNSCLC without driver mutations, ineligible for first line platinum-based chemo either due to their poor performance status or comorbidities. The study was not stratified for PD-L1 subgroup status.
    - Atezo group performed better than chemo. At median follow up of 41 months, atezo significantly improved OS compared to chemo (HR 0.78) with ORR 16.9% vs 7.9%, and median OS of 10.3 vs 9.2. But the duration of response was 14 months for atezo vs 7.8 months for chemo, suggesting that if patients responded, they responded well and also for a longer period of time.
    - Twice as many patients were alive at two years when treated with atezo (24.3%) vs chemo (12.4%). Consistent benefit was noted across p-subgroups including PD-L1 expression, performance status, and histology. The atezo group also had less grade 3-5 AEs compared to chemo, and no new or unexpected safety concerns were seen in this group.
        - Konda: *"So one of the biggest trends of the study I think is the study population. It enrolled patient population, which is usually excluded from clinical trials. And yet these patients are what make it to our clinic. So, it's – I think the trial did a*

great job by trying to incorporate such an underrepresented population. This trial also, you know, showed survival benefit and overall response, and almost double the overall response and median duration of response with less toxic and function in medically limited patients. So, I think that that is also a great thing. However, this is not PDL biased – Pd-L1 stratified study, the benefit was seen across all histologies in PD-L1 expression. I would like to see the subgroup breakdown, especially PD-L1 to know the magnitude of benefit."

- Kim: *"I think there are still big questions on for example, if you are never smoker or light smoker, would you see benefit in this? Could you even consider like single agent Abraxane instead if someone had rapidly progressive disease versus a single agent and atezolizumab, so I think it's great. I think it supports the idea that we can use single agent immunotherapy in older patients as well. But I think if someone presented with the low PD-L1 score, I would still be wary about using a single agent immunotherapy."*

- Panelists discussed an updated OS analysis of the phase 3 EMPOWER-010 study of **atezolimumab** which demonstrated DFS benefit with adjuvant atezo compared to best supportive care after resection in NSCLC following platinum-based chemotherapy. Based on the study results, atezo was approved for use after resection and after adjuvant chemo for patients with a PD-L1 >1% in stage 2/3A settings.
    - At median follow-up of 45 months, there was an OS trend in favor of atezo for PD-L1 >1% in stage 2/3A. In all randomized patients regardless of PD-L1 status, and in the ITT population (Stage 1B-4A), there was no difference in OS for atezo vs best supportive care.
        - Kim: *"A lot of clinicians speak about DFS is important, but does it really translate into OS? And I think the study, given that there's a trend towards OS benefit, I think we will probably possibly see OS benefit maybe in the longer setting. So, what would we do in clinic? I would continue to offer I think atezo for anyone who received upfront resection followed by adjuvant chemotherapy. As far as which patients, would I give it to someone with PD-L1 one to 49 versus greater than 50%? I'll probably lean favor in giving it definitely for patients with greater than 50%. For the one to 49, I think there's still a question. But I think I would still offer it given that the benefit probably outweighs the risks of giving IO. For stage 1… I probably would favor on not potentially giving it because I think stage 1 in general with resection followed by adjuvant – for 1B especially, even with the adjuvant chemo for the 1B patients, the benefit from the meta-analysis, it's very minimal actually. Even the benefit of adjuvant chemo is just five percent. So, with those stage 1B patients, I think I'd probably hold off on maybe saving IO for when they recur, potentially in more advanced setting."*
        - Pellini: "*But then the question that you may be asking yourself is well, with all the stage 4 data that we see, we know that chemo with*

immunotherapy is better than just giving the immunotherapy in patients that are candidates for that. And it kind of makes the tumor microenvironment more responsive. Will I add anything if I just give the immunotherapy? I don't know. I don't think anyone knows. And I think it has to be a discussion with the patient's preference, and just disclose this is the data. This is what we have. Would you like to try this or not? And I kind – the way I phrase is if your cancer comes back, will you regret not getting this? Will you blame yourself? If the answer is yes, then maybe you should. If you think that no, doesn't matter and I just want to be treated when I have to, then we don't need to treat because we don't have data."

- The phase 1 JAVELIN Lung-100 trial examined **avelumab** vs platinum-based chemo as 1L in treatment-naïve advanced PD-L1+ NSCLC, with primary endpoints of OS and PFS.
    - There was no statistically significant difference in OS or PFS between each of the avelumab arms and the chemotherapy arm. The incidence of treatment related AEs was the same regardless of therapy type, 95-97%, with grade 3 TEAEs of 60%. The trial did not meet its primary objectives or endpoints, and the safety profile of avelumab was consistent with the prior phase 1 trials and also consistent with other studies including GU cancers.
    - Panelists felt the changes in avelumab dosing during the trial may have hindered the results and it may not have been a statistically sound study.
        - Punekar: *"Mechanistically, the different targets seem to have at least similar profiles in terms of efficacy, as well as tolerability and toxicity. I think in this trial, it's a little bit hard to tell what's going on in part because there were all of these kind of weird protocol amendments; there were delays… I'm still unclear if avelumab is useful in non-small-cell lung cancer. Like, theoretically, I want to say that, I mean, it should work like any other PD1, PD-L1 inhibitor. But like, why is this data so lukewarm?... But this is an example of what happens when you wait – oh, you sorry, you don't wait until one trial is completed and then you already initiate the next trial. And then you're a little bit stuck saying like, well, we don't actually know what the optimal dosing strategy is, and you tried to add it on. But to answer your question, like you know, I cannot imagine that avelumab is that different than any other PD1 or PD-L1 antibody. And thus, like it should retain efficacy, just if it's in a better clinical trial."*

Anti-PD-1 mAbs nivolumab and sintilimab were evaluated as treatments versus chemotherapy in phase 2 studies.

- NADIM-2 was an open label, 2 arm multicenter trial of stage 3 NSCLC without EGFR/ALK mutations of carbo-taxol chemo + **nivolumab** vs carbo-taxol only, with a primary endpoint of pathological complete response (path CR) and secondary endpoints of PFS and OS.
    - Path CR was 36.2% in the experimental arm vs 6.8% control arm. PFS at 24 months was 67% experimental arm vs 52% control arm. OS at 24 months was 85% experimental arm,

64.8% control arm. In the experimental arm, patients with PD-L1 >1% showed a greater PFS than those with an undetectable PD-L1 (HR 0.26).

- Geurkink: *"This study kind of makes us think of the CheckMate 816, which was published earlier this year. I was confused, I thought I was almost reading the same trial whenever I was looking at it. But they're very similar trials, with the exception that these patients got adjuvant nivolumab following surgery. I think that this kind of creates a space for adjuvant immunotherapy in this setting. Potentially, you're looking at doing neoadjuvant immunotherapy and adjuvant immunotherapy and patients benefiting from it… It's encouraging that we're now looking at this surrogate marker of path CR in lung cancer with both the CheckMate 816 and with this trial to determine how well people are going to continue to respond. In that data, you know being a year and a half out without, with no patients having any disease progression is an encouraging sign. And it seems like path CR really is something that we should continue to pursue. I think it would have been interesting to stratify the patients who did not have a path CR, to look at their PD-L1 status and see if they do benefit from adjuvant nivolumab versus just watching them. But really the main thing is that, kind of like I mentioned earlier, I just think it provides a niche to give adjuvant immunotherapy in these patients."*

- A "chemotherapy-free" strategy for mNSCLC was investigated in a phase 2 study of the anti-PD-1 mAb **sintilimab** + anlotinib, a small-molecule TKI targeting VEGFR, FGFR, PDGFR and c-kit, vs platinum-based doublet chemo as 1L therapy in Stage 4 EGFR/ALK/ROS1-negative treatment-naïve disease.
  - Primary endpoint was ORR, and secondary endpoints were PFS, disease control rate, OS, and safety. Data suggested a trend towards improved response and survival with the use of sintilimab + anlotinib compared to chemotherapy in treatment-naïve mNSCLC.
  - The trial was compared to KEYNOTE-024 (single-agent pembro vs doublet chemo) and EMPOWER (atezolimumab)
  - Panelists were unsure that the data were practice-changing given that pembrolizumab is widely used in this setting, and adding a TKI to this type of IO regimen could increase toxicities and cost, but there may be a patient population that could benefit from it.
    - Desai: *"I think until we see data with single agent immunotherapy seeing that immunotherapy plus TKI, I don't really think this is going to impact my practice."*
    - Punekar: *"For whatever reason, we see a lot of patients who are very much adamant against chemotherapy. Regardless of whether they truly understand its benefits or its actual toxicities, they may have friends or family who have undergone other types of chemotherapy for different diseases and that's in their heads. And so, I think for chemotherapy free regimens, we're actually pretty lacking in terms of immunotherapy monotherapy or immunotherapy dual checkpoint inhibition so any form of chemo free synergies could be beneficial."*

Tyrosine kinase inhibitors (TKIs) sotorasib, which targets KRAS-G12C mutations, and osimertinib, which targets EGFR mutations, were evaluated for their efficacy in the advanced/metastatic NSCLC space.

- CodeBreak 100 examined the safety and efficacy of **sotorasib** in combination with pembro or atezo in advanced KRAS-G12C NSCLC, based on preclinical evidence of sotorasib having increased CD8 for T-cell infiltration and tumors with the addition of a PD-L1 inhibitor.
    - Sotorasib is the first FDA approved KRAS-G12C target therapy, approved in the 2L setting of NSCLC based on trial findings of durable ORR of 41% and OS of 33%.
    - The multiple cohort dose exploration trial yielded durable clinical activity with lower rates of grade 3-4 TRAEs compared to patients receiving these therapies concurrently, yet significant hepatoxicity was noted in several of the cohorts.
        - Hadfield: *"If you're having a significant proportion of patients develop immune checkpoint inhibitor hepatotoxicity, that's going to make it a very poorly tolerated treatment in the future. Given that we don't have any predicted biomarkers to determine who's going to develop these toxicities, I think it's going to have to be very, very convincing efficacy data that's going to change your practice in the future, which it does, it's trending that way, but it's certainly a toxicity that you're going to have to deal with very, very commonly since all cohorts showed that."*
        - Pellini: *"The other thing is obviously when we have grade three or four toxicities, we're holding therapy and we have to treat the side effects. You are giving less drug to that patient because of the AE that has been incurred onto them. Looking at the numbers, we know that sotorasib does cause hepatotoxicity. All these drugs in this class like KRAS-G12C inhibitors, they cause that. I think what concerns me the most is doubling the side effect. Then you have the majority of patients that I'm not treating them because I incur the side effect."*

- CodeBreak 200 was a phase 3 global, open-label study of **sotorasib** vs docetaxel in NSCLC patients with KRAS-G12C mutations who progressed on prior platinum-based chemotherapy with a checkpoint inhibitor.
    - The primary endpoint was PFS, and secondary endpoints were ORR, disease control rate, OS, and safety. It was demonstrated that oral sotorasib compared to docetaxel had a superior PFS and ORR compared to docetaxel alone, with a more favorable safety profile.
    - Panelists felt that sotorasib may be a viable option over chemo in this setting given the myelosuppression and fatigue seen with docetaxel.
        - Pellini: "I*t does not change what we were doing because probably most of us were already giving sotorasib in the second line setting, but at least this shows us, well, it's not inferior and it's a little bit better than chemo that has a lot of toxicities."*
        - *Desai: "I think this does give proof in a randomized phase 3 setting that sotorasib at least is slightly better if not in the PFS setting than docetaxel alone… I think the CodeBreak 100, most of us were starting to use second line sotorasib but for me, I think this is practice-changing if you're really truly thinking of phase 3 trials as kind of the gold standard of evidence to change your practice."*

- Two-year added follow-up data from the ADAURA trial of **osimertinib**, a 3rd generation TKI selectively inhibiting EGFR-TKI sensitizing mutations, vs placebo, was discussed. The original ADAURA data was presented at ASCO in 2020 and then subsequently published.
    - Follow-up data yielded a DFS of 84% with osimertinib vs 34% with placebo. In the osimertinib arm, fewer patients experienced local, regional, and distant recurrence vs placebo. Safety toxicities were very consistent with previous reported data and there were no new safety signals that were concerning.
        - Hadfield: *"I think everyone's mostly doing adjuvant osimertinib already based on the 2020 data. It's nice to have the increased follow-up for an additional two years but just a real win of a trial overall… You don't typically see hazard ratios to this degree and 84% of disease-free survival down from 99%. It's very, very compelling to use this in the adjuvant setting."*
        - Pellini: *"Some say that this drug is not really killing cancer cells. It's just putting them in a latent state and that perhaps giving that when the disease actually become microscopic will not change the overall outcome of the patient because we're not really curing the disease, rather just putting it to sleep. At the time that we stop the drug, it's going to come up."*
        - Desai: *I think that's a realistic concern because we don't have overall survival data… but the real question is are we curing patients by giving them three years of adjuvant osimertinib? Also, the side effects and the long-term toxicity, not to mention the financial toxicity of it. I think those are really good relevant points, but I just feel like right now with the DFS benefit, until the OS is read out, if you're not giving our patients adjuvant osimertinib I think we may be potentially giving them suboptimal treatment."*
        - Kim: *"I guess what's also interesting is that I think when they presented this data, the hazard ratios are extremely low but if you really follow the whole trend, I think they actually come together at the end. Some clinicians are questioning, are we preventing recurrence or are we just delaying recurrence. I think that's a really good question to see. Then the other thing though is even though it's only DFS, there was a big difference in CNS DFS and CNS disease. I think even if it doesn't affect survival if it does recur, it does tend to affect quality of life. I think in that case, giving adjuvant osimertinib I think is clinically efficacious, especially in this really preventing CNS recurrence."*