[MUSIC PLAYING]

NATHAN BAHARY: Happy to get the chance to talk about the non colorectal GI cancers. Dr. Earle and I split them with-- I'm going to do the pancreaticobiliary. He'll do the gastroesophageal. Here, oh wait a second, that button. There we go. There are my conflicts of interest, just to be out there.

And I want to talk about some objectives within the biliary cancer field first. So the first objective is to understand the utility of adjuvant capecitabine to reduce the risk of relapse and improve overall survival in biliary cancers. That's the BILCAP study. And then I'm going to go on to a number of posters. A couple of them were presented in discussion in the post or abstract session. And we'll just do a slide or two each so just to go through some of the molecularly targeted therapies.

Within the pancreatic cancer world we're going to talk about adjuvant therapy for pancreatic cancer. And once agai, to nail home, [INAUDIBLE] has no role in the adjuvant setting and has minimal role in the metastatic setting. And that's going to come from the RTOG 0848 study. Talk about targeted therapy for PDAC, targeted in the sense this is targeting the stroma not necessarily a molecular target. And then to go on to a question about germline genetic testing and unselected pancreatic ductal adenocarcinomas.

So this is the first study, the BILCAP study. Adjuvant capecitabine for biliary tract cancers. And here's a little bit of overview for it. So the incidence is not terrifically high. It's about 15,000 per year towards cholangiocarcinomas over gallbladders. Gallbladders are often found incidentally which is a whole other talk. And the overall survival is variable, it's between 20% and 40% if you integrate, intrahepatic, and carry hilar cholangiocarcinomas. Have a-- let's see if I can get this-- there we go-- response rate in the proximately-- I mean the overall survival rate in about the three year range.

Gallbladders is very variable depending upon whether you look at those that are incidentally found versus not in distals and extrahepatic cholangiocarninoma probably do the best. OK. So what are the NCCN guidelines currently state for adjuvant? Well it's all over the place. So if you take a look at R0 node-negative you can observe these patients. You can give him chemotherapy or you can give them chemoradiation therapy. Not really certain exactly what the other options might be.

Same thing for intrahepatic and as well as for extrahepatic and perihilars. Node-positive, pretty much everybody will want to utilize radiation, although the data is scant to say that it is helpful. Chemotherapy. Pretty much everybody will get and there's all sorts of combinations. Chemo upfront, radiation upfront, followed by chemotherapy.

So what are the questions? Is chemotherapy necessary? Chemoradiation therapy necessary? Here what's going back. Adjuvant RT did not seem to improve survival in those patients who had perihilar cholangiocarcinoma In a recent paper that was an Oncotargets you have to go way back in time at least about 15 years or so to look at adjuvant chemotherapy for gallbladder cancer. And the problem with even if there is a survival benefit here is that staging is completely different. And I don't know if this is applicable anymore.

And is adjuvant chemo-- might be a small benefit in biliary tract cancer is also from the ESPAC-3 study which you might remember was actually a pancreatic trial but some of them had extrahepatic cholangiocarninoma. Instead distinction can be difficult. And it was observation versus 5-FU and gemcitabine. And there was a slight improvement of overall survival in those patients who got chemotherapy.

S0809 was a study that we participated in. It was a phase 2 single arm study that was part of SWOG, ECOG, and the Alliance and gemcitabine and capecitabin upfront. For those people extrahepatic angiocarcinomas, all gallbladder cancers, distals and perihilar's were allowed. And it was gem-cape for three months, followed by capecitabine RT. And it was a single arm study and you can see that the median overall survival is 35 months, the two year survival 65%. This was presented a couple of years ago at ASCO and published in 2015.

If you take a look, the majority of these people have extra Hiler-- cholangiocarcinomas in the early stages. In the later stages were the perihilar and gallbladders. So this was a GIASCO, a trial that came out looking at biliary tract cancers as the PRODIGE study ACCORD 18, it was GEMOX versus observation. As we well know the either GEMOX or GEMCIS is considered the current standard of care in the first line metastatic setting. Though data for GEMOX although not randomizes probably equivalent.

So biliary tract cancers with R0 or R1 so you could have positive or negative margins. ECOG performance status 0 to 2 adequate liver function and randomisation with three months. They either got GEMOX which was gemcitabine and oxaliplatin. Notice they give day one and day two, even though when I've given it, I usually give them on the same day. This is the European way of giving it or surveillance only. And what they've found of 196 patients-- this was powered now for relapse free survival not overall survival. It was to improve it from 18 to 30 months and you can see, even though that there is a slight difference between the GEMOX and surveillance this didn't reach statistical significance. So the GEMOX [INAUDIBLE] was 30 months, surveillance was 22 months, the four year relapse survival not much different.

So this brings us to the BILCAP study now that we know the background. Adjuvant capecitabine for biliary tract cancers. The BILCAP study overview looks like this. Resection and then a 1 to 1 randomisation, the capecitabine or observation. This is a two on one, off cycle of the capecitabine so a total of six months. And outcome measures was overall survival secondary looking at relapse free survival toxicity quality of life. And it was par here to see a two year overall survival benefit of 60% to 71%.

So this is the overall survival intention to treat population the capecitabine arm hit 51.1 months, the observation arm 38.4 months, and it just missed statistical significance for the overall. But they went through and matched everybody in the two arms for a nodal status and disease grade which we know actually does influence survival. And when we do that the p-Value becomes highly statistically significant.

So what's the difference between these two trials? The BILCAP study used capecitabine alone the PRODIGE study GEMOX, capecitabine 223 patients versus observation 224. So it's a much larger population than the GEMOX trial, median relapse free survival was 24.6 months in the capecitabine arm and 17.6 months in the observation arm which was statistically significant. It was not in the GEMOX trial. Median overall survival wasn't looked at in the PRODIGE study but you can see it was statistically significant in the BILCAP study.

So this is the largest phase 3 trial ever done in biliary cancers. The primary endpoint was met and the intention to treat population after adjustment for nodal status and grade. There's a 15 month overall improvement and the final thing is capecitabine should be considered the new standard of care and should become the future control arm in all trials or so. So what's ongoing right now? Two large trials of GEMCIS trial versus observation in biliary tract cancers in Germany, UK Netherlands, Australia. It's not likely to give us data until 2022 and has a much larger end than the GEMOX trial did. And GEMOX versus cape for intrahepatic in China, which we may get in the next year or so some of the data.

So I want to look on to genetic targets and this came from a paper in Nature Communications. Just about a couple of years ago and looking at a lot of biliary tract cancers and seeing what you can find in terms of targeted agents. A lot of FGFR translocations, you can see KRAS. You could see IDH1 mutations as well. And I didn't get to show you but there were a number of vascular abnormalities, KDR receptors that were also altered in these tumors.

So the first study that I wanted to just talk about briefly was-- came from our institution. Was an intent-- it was an IIT from Dr. [INAUDIBLE] looking at biliary cancers and second line therapy and metastatic biliary tract cancers. The primary objective was to evaluate the progression free survival of patients with advanced biliary tract cancers who had failed standard chemotherapy. And the second one to look at overall response rates and survival or so.

So this was a single arm study and so was going to have the strengths and weaknesses of a single arm study. To the right is the survival curve and that doesn't really help us a whole lot but what's interesting is there was a PR and stable disease rate that approach 75%. And some of these are actually still ongoing after a total of eight-- some of them up to 18, 20 months or so. So it's intriguing. It was alcomers, there's tissue collected. There's no secondary analysis done but this will likely lead to a randomized trial on the second line setting in the relatively near future.

So what about other truly collectedly molecularly target therapies? This is a trial of a pan-fibroblast growth factor inhibitor. There were 35 patients, 18 positive by FISH, 17 by next generation sequencing. So there were fusions and mutations that activated. It was ARQ 087 at 300 milligrams. Many of these were very heavily pretreated and I didn't show you, I just stuck in there. There was an impressive burden disease in many of these patients. And it had a stable disease activity rate of about 62% PR rate of 17%, reasonable tolerability, similar than activity reported with other Pan-FGFR receptors.

And there's a registration trial and refractory intrahepatic cholangiocarcinoma that's being planned to open then which we will participate in. And this is an IDH inhibitor and this is a phase one study of AG-120 and IDH mutant tumors. There are cholangiocarcinoma patients in that arm, 73 of them treated. Most were intrahepatic and they had the canonical R132C activation mutation. It was reasonably tolerable. It had relatively high stable disease rate, very few responses actually.

And there's a placebo controlled global phase 3 trial of this with an arm not only in glioblastoma. But which is another place we see a lot of IDH mutants with cholangiocarcinomas also. And the low PR rate is going to be interesting. Whether there's going to be some secondary analysis able to be done in that randomized trial to figure out why they become resistant to it.

And the last one. Just to show you some of the pitfalls of it. This is a randomized phase 2 trial of a single arm MEK inhibitor, trametinib, and the reason why that this was done was because preliminary data showed a very impressive stable disease in response rate in a single arm study and aberrant Ras signaling reported in cholangioscopy carcinomas. Trametinib is a MEK inhibitor, currently approved for melanomas. And so it was a randomized phase 2 trial of a MEK inhibitor alone versus 5-FU capecitabine.

Second line therapy refractory to a Gem based regimen and the PR rate you can see was 8% versus 10% for chemotherapy. The disease control rate was far better in the chemotherapy and it led to early closure. And so it's unquestionable why is there an activity? Perhaps they weren't selected for the proper thing? Maybe we should be looking at possible ERK or other MEK activation. But there's a lesson here is that randomized trials are still the gold standard and we shouldn't necessarily practice based upon non randomized phase two data.

So I'm going to turn to pancreatic cancer and talk about the results of partial or the results of the RTG 0848 study. It's a randomized trial evaluating the addition of erlotinib to adjuvant capecitabine for patients with receptive pancreatic adenocarcinomas. And just to go through the summary again of what we know about adjuvant chemotherapy post resection for pancreatic cancer.

ESPAC-1 had a median survival of about two years. The CONKO-001 trial also about two years. ESPAC-3 was 5-FU gemcitabine also about two years. And at GIASCO and at ASCO last year the discussion of the ESPAC-4 study which was gem-cape versus gemcitabine showed an improvement of about three to four months in overall survival. And RTOG 0848 has been ongoing for as long as I can remember and it's gemcitabine plus or minus orlotabine and plus or minus radiation.

And to give you a-- deal the current schema. It's, what we're doing is that there's a first-- is our first randomization either get erlotinib or not and then the second randomisation to radiation or not. Because it's still the question about definitive radiation. And here is the overall survival treatment for the first portion of it looking at gemcitabin versus gem erlotinib. It would be hard to actually see two overall survival curves that overlap more than this.

The trial is probably in trouble I don't think that it's going to actually reach accruals. It currently is supposed to reach accrual by 2029 which means your grandchildren might actually get it. And by then no one's going to be doing this anyway. So it's ongoing because a lot of results have been pushed into it but I don't think it's going to actually give us any more data. So of benefit we have in the adjuvant setting gemcitabine we have 5-FU, gemcitabine. Capecitabine is now the standard of care from previous ASCO. There's no benefit for erlotinib in addition to gemcitabine.

But you know the interesting thing was if you notice there's in these adjuvant trial they're-- probably because we're getting better at picking out patients who shouldn't have gone to surgery in the first place. There's a median overall survival creep of just a gemcitabine alone of many months. So it's actually the random-- non randomized phase two studies become harder and harder to actually utilize their data.

So what's pending? We have the gemcitabine plus or minus nab paclitaxel. The so-called 8-patch trial. Hopefully data within the year and in Europe they're doing modified fulfill announced versus gemcitabine which is where all the non industry related trials get done in this space.

So then I'd like to turn to this so-called targeted therapy. It's a randomized phase 2 trial of PEGPH20, nab paclitaxel which is Abraxane/Gemcitadine versus the combination of AG alone. It's a study that we participated in and put quite a number of patients on. So just to give you a little bit better. Pancreatic cancer has-- one of the issues is getting treatment responses and pancreatic cancer probably deals with the stroma that surrounds it. It's a hilar, there's hyaline and a number of other stromal components that actually wrap around that that make it relatively anoxic and make it very difficult for chemotherapy to get in.

If you actually put in little electrodes into these things and you're asked what's the pressure? The pressure inside the tumors about 70 or 80 millimeters of oxygen, which means you sort of have to hook the pancreatic cancer up to the right-- the left ventricle in order to pump chemotherapy through this barrier or so. So the idea was hyaluronan is the-- HA is the primary component of the stroma. And the thought was that HA accumulation increases tumor. Interstitial pressures makes it difficult to get chemotherapy in, that if you could break down this barrier you might actually allow the chemotherapy to get in better.

PEGPH20 is a pegylated form of recombinant human hyaluronan days which degrades HA and remodels the tumor stroma. This was the overview of the trial which took stage for pancreatic adenocarcinomas never been treated. You got randomized to either PAG or AG primary endpoints for progression free survival and thromboembolic events. And we'll talk about why that happened. Secondary events progression free survival and exploratory overall survival by HA level.

So there are two stages to this and the reason why it turned into a two stage trial is originally everybody was randomized 1 to 1 to receive either the triplet or the doublet. And the problem was there was a large number of clots, much higher than expected even for pancreatic cancer in the hyaluronan case arm. So actually treatment was stopped for a number of months while they decided what to do the thought was to actually in the future not allow anybody with a clot on to trial. And to give everybody prophylaxis with Lovenox originally once a day and then twice a day.

So in the second stage when it reopened in order to move things they randomized people 2 to 1 to the PEG versus the AG and there was also a companion diagnostic to decide how much hyaluroan was in the tumor itself. So this is the primary efficacy endpoint for the combined stages. And it was looking at progression free survival with the triplet versus the doublet and met its primary endpoint with a p-value of 0.045. More interesting though is if you take a look at the secondary endpoints by what was considered the HA high in the companion diagnostics and there you see a much larger difference in progression free survival.

Here's the waterfall plot to take a look at the HAI patients with a post baseline CT scan. You can see that is a much different waterfall plot than we normally would see with Abraxane gemcitabine alone. So this is the ongoing trial that we have open here. It is UPCI protocol 17065. It is a worldwide protocol. HALO 301 What it requires us to do is to have metastatic pancreatic adenocarcinoma you're actually biopsied and if you are the HA high group from the companion diagnostic which is about 40% of the patients you get randomized 2 to 1 to either the triplet combination or the doublet combination.

Primary endpoints, there's two co-primary endpoints in this progression free survival and overall survival. And secondary would be our overall survival and safety of the combination. So I turn to just interesting things about genetic testing, unselected pancreatic adenocarcinomas. This came out of the work from Randy Brand here and it was a tri-institution collaboration or so. Just to plug Randy Brand and his group, they put on 220 of the 300 patients because we have one of our highest volume pancreatic centers around.

And the idea was to use a prospective study at three academic medical centers, consecutive unselected newly diagnosed PDAC patients and they were accrued over an approximately one year period. They had to have PDAC of any stage so it could be early stage resectable. It could be metastatic disease, had to be diagnosed within 12 weeks and they use the Ambry genetics cancer next panel, which has 32 genes. And some of them are known to have PDAC associations such as BRCA-1, BRCA-2, EPCAM, microsatellite instability, STK, APC, and those who had known association with other cancer types. But not necessarily pancreatic cancer, including a CHEK and a number of other-- CHEK 2 here and some of the other enzymes involved in DNA repair.

So these are the mutations that were identified 6.7% of them had at APC, BRCA-1 and 2 Again, these are unselected. So if they come in and they say that they've had ovarian cancer, breast cancer and their cousin had ovarian cancer. You kind of know what you're dealing with. But this is just consecutive pick patients, unselected patients. What was interesting was it was a very high rate or a relatively high rate of 4% of CHEK 2 mutations that previously had not been associated with PDAC risk.

So there were 239 unselected patients in the abstract. There's 300 patients total. There will be an updated GIASCO. A number of them tested positive for germline mutations, 22% of the mutation carries criteria for genetic testing, which was interesting. And so tells us there's probably some sort of refinement of the genetic testing guidelines and because we do have therapies that can help some of these patients. It's going to be interesting of whether we want to try to adopt this as a standard of care. But this does not support it quite yet.

Just to show there was a poster this was a talk at ASCO. There was a poster from Memorial Sloan Kettering which showed very similar data with their genetic panel. So there's a lot of interesting data still to be explored to CHEK 2 mutations. Hopefully within the next year or so there'll be overall survival response to treatment by mutation status will be available also. And regarding communications and how you deal with dealing with germline mutations with families will be available as well.