CHRISTOS FOUNTZILAS: You have to the whole GI tract, so we rely a lot on anatomy. And we have a few molecular targets, but anatomy is important in GI malignancies. So I have no disclosures. And we're going to start from the upper, go down to lower, and talk about the neuroendocrine cancers at the end.

So starting with gastric and esophageal cancer, the first study is the KEYNOTE-181 study presented in ASCO GI this year-- a study of pembrolizumab versus chemotherapy as second-line treatment in advanced esophageal cancer. So this study is a study for above-the-diaphragm patients.

Patients who have received one prior line of therapy-- platinum based-- with either adenocarcinoma or squamous carcinoma were randomized pembrolizumab-- the FDA approved those-- versus taxane or irinotecan monotherapy.

The study had three co-primary endpoints that were tested hierarchically. The first one was the overall survival in the PD-L1 population with a CPS more than 10. So just to differentiate from Dr. Yao's presentation, CPS is a combined proportional score, meaning that we count both tumor cells and immune cells to stay in positive for PD-L1, and we use the 22C3 assay as the companion diagnostic.

So for the first co-primary endpoint, overall survival in the CPS more than 10 population, pembrolizumab, outperformed chemotherapy, with an improvement in 18-month overall survival-- 26% versus 11%-- and a hazard ratio of 0.69. The p-value was 0.007. The goal was to be less than 0.008, and that is because they had three co-primary endpoints, so they had to split their p-value.

The second co-primary endpoint was the overall survival in squamous population. Again, the benefit at 18 months is almost similar to the CPS more than 10, but the study was not positive for that endpoint, because it was more than 0.007. So very low p-values in negative studies-- that's a common theme for this year-- in the checkpoint inhibitor, at least. And then [INAUDIBLE] population-- again, though there was a little bit of a benefit at 18 months, the study was negative for the overall [INAUDIBLE] population.

Patients with either squamous carcinoma or PD-L1 more than 10 had a significant improvement in overall response rate, and based on that data, the FDA approved pembrolizumab for squamous carcinoma of the esophagus with CPS more than 10-- so more than 10 CPS, counting both the immune cells, and the tumor cells, and disease above the diaphragm. So for whatever reason, checkpoint inhibitors work well for this above the diaphragm, but not below the diaphragm. It's unclear why that is. So lung cancer, the same thing. Esophageal, the same thing.

Now moving at the junction, or below the diaphragm-- so pembrolizumab with or without chemotherapy for advanced gastric and GE junction adenocarcinoma-- that's the Keynote-062 study. That study randomized patients in three groups-- pembrolizumab monotherapy, pembrolizumab plus chemotherapy, chemotherapy plus placebo-- with many co-primary endpoints.

So the first one that had to be tested was a non-inferiority between the pembrolizumab arm and the chemotherapy alone arm in the CPS more than 1. And that study was positive for that endpoint, since the non-inferiority margin was not crossed. But as you see here, the target non-inferiority margin was 1.2, and the upper limit went up to 1.18.

That means, really, that yes, it's not inferior, but if your patient is to survive with chemotherapy for 10 months, immunotherapy might mean that they will survive for eight months. Of course, chemotherapy has more side effects compared to pembrolizumab, but if you see your overall survival curve, you have within the first 12 months a lot of patients on the pembro arm not surviving.

Since that was a positive endpoint, they moved to test overall survival in the chemotherapy plus pembro arm versus chemotherapy arm for both CPS more than 10 and CPS more than 1 population. Definitely, there was no benefit for the more than 10 population. There was a slight benefit for more than 1-- again, don't ask me why, nobody knows that-- but both endpoints were negative. So some data were presented for superiority for CPS more than 10 pembro versus chemotherapy, but technically, you're not supposed to put a lot on that, because everything else was negative.

Going into all the new biomarkers for upper GI cancers-- so the first one, HER2, we all know from [INAUDIBLE] study that for patients with HER2 positive, gastroesophageal cancer addition Herceptin to platinum plus fluroropyrimidine therapy improves overall survival. At this year's GI ASCO, we had a small study presented from Memorial from Dr. Janjigian, where patients with gastric and GE junction cancer PD treatment-naive with any PD-L1 expression and HER2 positive were treated with trastuzumab, pembrolizumab, and platinum fluroropyrimidine.

Overall response rate was 83%, median PFS was 11 months-- that is based on close to 30 patients. There is a big study now-- one of the keynote studies-- that is ongoing, the 811 study. The second study that an update was presented in this year's ASCO GI was the zolbetuximab-- a study for patients who have Claudin positive, gastric and gastroesophageal cancer.

So Claudin 18.2 is a tight-junction protein, and 18.2 is a mutated variant that is expressed in about 30% of gastric and gastroesophageal cancers-- in more than 75%. So the first study that compared mainly in Europe EOX to EOX plus zolbetuximab. In the [INAUDIBLE] population, overall survival was superior in the zolbetuximab arm, with Claudin +2 expression more than 40%. In an exploratory analysis, the outcomes were even better in patients who had more than 70% Claudin expression.

There is an ongoing phase 3 study-- the spotlight study, that we actually have opened here at Roswell-- that is looking into-- it's a registration study-- it's looking into Claudin more than 75%. So if you have have any patients with gastric and gastroesophageal cancer who is treatment-naive, please refer the patient for the study.

The TAGS study is a study for patients with gastric or gastroesophageal cancer. Patients with advanced disease who had received at least two prior lines of therapy were randomized 2 to 1 to trifluridine/tipiracil-- that's Lonsurf-- versus placebo. And there was a significant benefit, statistically, with a hazard ratio of 0.69. Again, if you look at the median, it's four to six months, but it is approved by the FDA, actually, for patients who have received at least two prior lines of therapy.

So where are we with gastric and esophageal cancer in 2019? So the FDA approved pembrolizumab for patients with squamous cell carcinoma and CPS more than 10 who have received at least one prior line of therapy. The sibling of KEYNOTE-062 has completed accrual we participated here at Roswell that compares chemo plus pembrolizumab to chemo alone. We'll see if that is similar to the lung studies, versus it's more similar to the gastric studies-- so we will see.

For HER2 positive disease, the KEYNOTE-811 that compares chemotherapy plus trastuzumab to chemotherapy plus trastuzumab plus pembrolizumab-- that's also in progress, and still accruing. And Spotlight for Claudin 18.2 positive patients is in progress. We have the study open, please refer patients.

For gastric patients, pembrolizumab is still approved in the third line setting for patients h a CPS more than 1, and trifluridine/tipiracil launch was also approved this year. So which one to use? I have to say, technically, trifluridine/tipiracil has not been tested in fourth line, and pembrolizumab-- the more lines of chemotherapy they had before, the less the efficacy. But it can be a discussion with the patient. The median overall survival is more or less the same with checkpoint inhibitors, and trifluridine/tipiracil-- I tend to discuss with the patient. If the patient is in a good shape in the fourth line setting, I use whatever I haven't used before.

Moving to pancreatic cancer, the first study is a study presented at ASCO this year-- the APACT study. Adjuvant gemcitabine plus nab paclitaxel versus gemcitabine alone. A large study-- close to 900 patients-- with an R1 resection allowed, and actually, 25% of the patients had an R1 resection.

For enrollment, the CA19.9 had to be less than 100, and that enrollment was allowed for up to 12 weeks from surgery. So the primary endpoint for that study was the relapse-free survival based on central review, that was proven not a very good endpoint for a study. It was negative, with a hazard ratio of 0.88. As everybody understands, for patients who had a Whipple and have a lot of post-op changes to surgical bed, whether the patient is relapsing or not is not only the radiologist's determination-- it's mostly a clinical determination.

You might have a patient who has a soft tissue mass at the surgical bed, but that mass is not really compressing the mesenteric vessels, and the patient is doing great-- gaining weight, they look like a peach-- and you have a patient who has some indeterminate findings, with stranding in the peritoneum, and they're losing weight-- so the radiologist shouldn't be the one who's determining, really, whether a patient relapsed or not. But for whatever reason, they picked that as their primary endpoint, and they failed.

In terms of overall survival, that was one of the key secondary endpoints, with close to 70% mature data. Gemcitabine nab paclitaxel was superior to gemcitabine with a hazard ratio of 0.82.

So in 2019, we have several options for adjuvant treatment. Observation based on the old CONKO-001 data has a median overall survival of 20 months. When you use single-agent gemcitabine, you see, miraculously, that over the years, your median survival improves. And of course, that's not gemcitabine is getting better over time, but surgeons are getting better over time, and they select patients who will benefit from surgery more.

And when you use multi-agent therapy, no matter if you use a three drug regimen as in the PRODIGE study for FOLFIRINOX, modified FOLFIRINOX, or doublets gemcitabine/capecitabine as in ESPAC-4, or gemcitabine nab paclitaxel as in APACT study-- you see an improvement in overall survival.

If you look at the hazard ratios, the best hazard ratio was achieved with the modified FOLFIRINOX regimen. The APACT and ESPAC have a similar hazard ratio. Usually, I reserve modified FOLFIRINOX for patients who have phenomenal recovery after their surgery, with [INAUDIBLE] and not a lot of gastrointestinal sequelae from their surgery.

Moving to have a biomarker-based therapy for pancreatic cancer, pancreatic cancer tends to be a target-poor disease, but looking a bit more carefully, we see that about 15% of the patients, no matter what database you look at, have abnormalities in the homologous recombination deficient and DNA damage response pathway, most common mutations being ATM and BRCA2 mutations.

And for patients who have [INAUDIBLE] pancreatic cancer, using platinum at some point might be improving outcomes. The p is not significant, but if you look at the numbers, only about 20% of the patients had an abnormality, with some improvement in the median overall survival. But if you take the patients who have advanced disease, definitely giving them platinum at some point in their disease course is going to be beneficial in terms of overall survival.

So homologous recombination deficiency may be a biomarker for potential benefit of platinum. Definitely, it looks like germline mutations is a biomarker for benefit from PARP inhibitors. So I think that's the first pancreatic study that made it to-- oh, and I'm stuck. It was presented in ASCO last year, and published at the same time in the New England Journal of Medicine.

Olaparib as maintenance therapy for patients with germline-mutated pancreatic cancer after benefit on a first-line platinum-based therapy. Patients were randomized. [INAUDIBLE] at least received 16 weeks of platinum-based therapy for FOLFIRINOX, or gemcitabine cisplatin with no progression. Then they were randomized, 3 to 2, to olaparib versus placebo, and continued treatment until disease progression or an acceptable toxicity.

About 40% of the patients were not eligible, and most of them, really, had disease progression. The study was benefit for the primary endpoint of progression-free survival. It cut the risk of progression by half-- improved from median close to four months to 7 and 1/2 months.

The study, really, was criticized for the lack of active chemotherapy in the comparator arm. We from the PANOPTIMOX study that after 16 weeks of FOLFIRINOX, you can de-escalate treatment to 5FU maintenance without losing much in terms of overall survival. So nobody really knows how olaparib would have performed if the patients had received maintenance capecitabine or 5FU.

With less than 50% maturity overall survival, there was no benefit in overall survival. So the question is, do we give PARP inhibitors as maintenance therapy after benefit on platinum-based therapy only for germline mutated patients? We don't know yet.

There is a smaller study that was presented in AACR 2019 by Binder and colleagues that actually accrued patients with somatic BRCA and PALB2 mutations. So far, the data-- they had only one patient with somatic BRCA2 mutation who had a response. This study used rucaparib as maintenance, so a different PARC inhibitor. In 50% accrual, overall response rate was close to 35%, with a median PFS of 9 months.

PARC inhibitors-- there are many out there, and not all of them are the same-- they differ in terms of their catalytic activity, they differ in terms of the trapping activity. So which PARC inhibitor to use is unclear, but for the terms of our discussion, alaparib is endorsed in the national guidelines for treatment of patients with germline mutations after benefit with platinum-based therapy.

So we talked a lot about genotype-- how about phenotype? COMPASS is a big study that is ongoing in Canada. It's a prospective retrospective evaluation of an RNAseq platform. And really, what they came up to-- they were able to differentiate pancreatic cancer to two different subtypes-- basal versus classical subtype.

And they saw, really, that the basal subtype tends to be more chemo-resistant, and that patients who have the basal subtype should not receive any FOLFIRINOX. So patients with classical who received FOLFIRINOX-- 10 months. Patients with either classical or basal [INAUDIBLE] gemcitabine abraxane median about eight months, and basal with FOLFIRINOX, five months. Again, this is perspective retrospective. The treatment was not selected based on the RNAseq, but this study is ongoing, and we will try to validate their biomarker prospectively.

When they looked at their whole-exome sequencing data, they found approximately 40% of the patients had an actionable mutation, but a really actionable mutation is either really an NTRK fusion or an FGFR amplification. In patients who have a wild-type pancreatic cancer-- that's less than 10% of the patients-- germline BRCA mutations that again are targetable with a PARC inhibitor-- 6% of the patients.

So really, when we are sequencing our pancreatic patients, we need to tell them that, really, we're looking into whether you're going to be in those 15% of the patients who have an either KRAS wild-type cancer with a targetable fusion, or a germline BRCA mutation.

So where are we in pancreatic adenocarcinoma in 2019? For localized disease, even though the APACT study was a negative study, it might be an option for adjuvant therapy for patients who are not candidates for FOLFIRINOX chemotherapy. For those patients, I tend to use mostly gemcitabine and capecitabine-- I think it's less toxic than gemcitabine nab paclitaxel-- but it can be an option. And germline testing is recommended for patients with localized disease.

For patients with advanced disease, both germline testing and somatic mutation testing is recommended for patients who are ineligible for systemic therapy. And for patients with pathogenic BRCA mutation, platinum-based therapy followed by PARC inhibitor-- olaparib or rucaparib-- can be another treatment option.

Moving to hepatobiliary cancers, the first study is the KEYNOTE-240 study. It is a study that compared pembrolizumab to best supported care as second-line therapy patients with advanced hepatocellular carcinoma. Patients with preserved liver function and measurable disease were randomized 2 to 1 to pembrolizumab or placebo.

The study, even though the p-value was less than 0.05, and the median was superior-- 14 months to 10.5 months-- was negative. Because again, as we discussed in the other KEYNOTE studies, they had multiple co-primary endpoints-- they had to split their p-value-- so the p specified was 0.01.

At the same time the study was ongoing, nivolumab was also approved in second-line, so how much the approval of all those new medications in hepatocellular carcinoma have affected. There are also other studies to be determined.

Earlier this year, there was a press release from Bristol-Meyers-- the CheckMate-459 study that compared nivolumab to sorafenib in first line-- was a negative study. The study was presented, actually, last week in ASCO. Yes, the study was a negative study, but there is definitely a signal with nivolumab with superior median overall survival. Not statistically significant, but meaningful, I think.

Again, nobody knows how the approval of nivolumab in second-line and pembrolizumab in second-line may have affected the results of the study, along with all the other TKIs and VEGF based treatments that have been approved over the past two years.

Biliary cancer, from all GI cancers-- probably, this is the most target-rich tumor, mainly the intrahepatic cholangiocarcinomas. You see about 25% of the patients with intrahepatic cholangiocarcinomas have IDH mutations, and actually, in ASCO last week, there was a study with refractory patients with IDH inhibitors versus standard of care that saw benefit of the IDH inhibitor.

FGFR fusions are also present in about 20% of the patients. We have a study here with FGFR positive patients with cholangiocarcinomas. With the extrahepatic cholangiocarcinomas, it appears more that HER2 mutations are the most prevalent, and gall bladder cancers tend to be the less target-rich tumors.

So the study that came up this year at GI ASCO is the ROAR study. That's a basket study for BRAF V600 patients-- that's about 5% of all cholangiocarcinomas-- that tested the double MEK BRAF treatment dabrafenib/trametinib. About 3/4 of the patients had two or more prior lines of therapy. The overall response rate was very promising-- 41%-- with a PFS of seven months and an overall survival of 11 months. That's pretty good for that patient population.

And this is the waterfall plot-- not that impressive, like the osimertinib waterfall plots, but less patients-- but it looks good. It looks good. Definitely looks good.

So for hepatobiliary cancers in 2019, the first-line options-- we have lenvatinib or sorafenib, with lenvatinib being non-inferior to sorafenib. Second-line options remain, in my opinion-- and the FDA has the same opinion, actually-- checkpoint inhibitor, despite the negative studies, or regorafenib for patients who did tolerate sorafenib first-line, or cabozantinib or ramucirumab for patients who had an AFB more than 400.

All second-line agents-- that's important-- have been tested after first-line sorafenib, so we don't really know what the benefit of second-generation VEGF inhibitors, or ramucirumab or a checkpoint inhibitor can be after Anyway Regorafenib is not tested in sorafenib-intolerant direct patients. Cabozantinib is tested in third-line-- about a third of the patients in the CELESTIAL study had received two prior lines of therapy.

And what about checkpoint inhibitors plus TKIs? Dr. [INAUDIBLE] has very interesting translational data for the [INAUDIBLE] effect of sorafenib, and we have a study, actually, with sorafenib and pembrolizumab ongoing. It's about to close shortly, so please refer patients, but we have another study with tivozanib and durvalumab coming up, so please refer patients.

Cholangiocarcinoma multiple targetable alterations-- it makes sense to sequence all patients with cholangio. University of Pittsburgh has IDH inhibitor, we have an FGFR inhibitor-- please consider patients for clinical trials for those very tough diseases.

Now going to colorectal cancer, the main thing that came up this year is really, do we escalate treatment for all patients by doing a triplet therapy with FOLFOXIRI? And there were two studies that were presented in this year's ASCO from Europe. One was this one, that compared FOLFOXIRI-bev to FOLFOX-bev in patients with more than three circulating tumor cells, and TRIBE-2 from Italy-- FOLFOXIRI plus bev versus sequential FOLFOX-bev FOLFIRI-bev. Of

The VISNU had as primary endpoint progression free survival. This is a Spanish study, and their data pointed out that patients with more than three circulating tumor cells get a worse prognosis. That's why they targeted this patient population. There was a benefit in terms of progression-free survival by about three months, with a hazard ratio of 0.64-- that was statistically significant.

There was an incremental benefit in PFS. There was a benefit in OS that was not statistically significant, and a slight improvement in response rate. Again, we cannot really target patients based on the circulating tumor cells-- it's prognostic, it's not predictive, and it's not really recommended for standard of care.

The TRIBE-2 took patients with metastatic and [INAUDIBLE] colorectal cancer younger than 75 years, with a performance status 0 to 1, or 0 if they were 70 to 75 who have not received any adjuvant oxaliplatin. Randomized 1 to 1 to FOLFOX-bev followed by 5FU-bev maintenance, and upon progression, switched to FOLFIRI-bev followed by 5FU-bev maintenance, or FOLFOXIRI-bev followed by bev 5FU maintenance, and upon progression, reintroduction of the same regimen.

The primary endpoint was the PFS2 tool-- that really captures the effect of both induction regimens. And there was, again, a slight incremental benefit of about two months in median overall survival-- less than 0.42 hazard ratio.

If you look at the second-line PFS, the benefit of reintroducing the quite toxic triplet was not great. So when your patient progresses after 5FU bev, do you really need to do all three again, or can you go along by just getting the [INAUDIBLE] back on? That's probably safer to do. Definitely less toxic-- better for the patient's quality of life.

Important-- for patients who were treated with the FOLFOXIRI regimen in both studies, no patient had prior adjuvant oxaliplatin, so for patients who had prior oxaliplatin, it's unclear what the benefit is going to be from intensification of treatment. Again, the treatment regimen is way more toxic than the doublet, and for the actual minor incremental benefit, you really need to discuss with your patients whether it really matters.

Now, going to the BEACON study. BEACON was a randomized 3-arm phase 3 study of threefold treatment with BRAF inhibitor, MEK inhibitor, and EGFR inhibitor, versus either FOLFIRI or irinotecan plus cetuximab in BRAF V600E mutated advanced colorectal cancers who had received at least one prior line of therapy.

Again, in contrast to lung cancer and melanoma, double treatment with BRAF inhibitors and MEK inhibitors does not work. There are a lot of feedback loops that get reactivated, so you really need to block it EGFR at the same time. So the BEACON regimen with MEK inhibitor, BRAF inhibitor, and FGFR inhibitor was superior in terms of overall response rate. About a quarter of the patients had an objective response, and the median overall survival was significantly improved.

Going to another small patient subgroup, they had two amplified patients. This year in *Lancet Oncology,* the results of MyPathway cohort for colorectal cancer were published. Patients with HER2 amplified colorectal cancer, either increase the chemistry or NGS or [INAUDIBLE] were treated with trastuzumab plus pertuzumab. The overall response rate was 30%, and it appears the outcomes appear to be better for patients with KRAS wild-type tumors, patients with PI3K wild-type tumors, and with no prior EGFR-based therapy.

So for patients with advanced disease, do we really need to intensify treatment with FOLFOXIRI? Yes, for BRAF V600 patients, subgroup analysis from TRIBE-1 study showed benefit with V600, and that's because most of those patients are not going to do well if you put them on FOLFIRI second-line.

It is unclear, if you need treatment intensification in first-line, if they don't have a BRAF V600 mutation-- maybe for patients who are borderline resectable in terms of their liver burden. If the patient is very symptomatic and they have a right-sided tumor, and you really need to get the best response ever, maybe, but for patients with not as much tumor burden-- patients who had prior oxaliplatin in the adjuvant setting-- I would go with our usual treatment with doublet, some maintenance therapy, switching to the alternative upon progression.

Triplet therapy with BRAF, MEK, and EGFR inhibitor-- yes, definitely, for patients with BRAF V600 mutation who have progressed in first-line treatment. And for the triple negative colorectal patients-- meaning patients with wild-type KRAF, NRAS, and BRAF-- think HER2, test for HER2.

Single-agent HER2 does not work-- you need dual HER2 treatment. The data are out there for lapatinib herceptin, for pertuzumab herceptin, and we do have a study with tucatinib herceptin-- [INAUDIBLE] and new study So if you have a HER2 amplified patient who has received oxaliplatin and [INAUDIBLE] please refer to the patient.

And last but not least, neuroendocrine tumors. This is a study done by Alliance, present in ASCO this year. A randomized phase 2 study of pazopanib versus placebo in patients with progressive non-pancreatic enteric neuroendocrine tumors. Patients were randomized 1 to 1 to pazopanib versus placebo, and they would cross over upon progression [INAUDIBLE] placebo to pazopanib. Actually, I had a patient on that study as a fellow. The study was positive in terms of the primary endpoint of progression-free survival, with a hazard ratio of 0.53.

So based on that study, we know that VEGF inhibitors might be beneficial in patients with enteric nets. We don't know whether VEGF inhibitors should be used before everolimus or after everolimus. We have a study with cabozantinib for patients have progressed under everolimus, so please refer patients for the study.

So it went quickly, I think-- I didn't expect it to be that fast. But anyway, so questions. A 55-year-old man with metastatic famous carcinoma of the esophagus with a performance status 1 who progressed after cisplatin/5FU. The combined proportion score was 5, and the patient is microsatellite-stable. What are your options for second-line-- Pembrolizumab, paclitaxel, paclitaxel/ramucirumab, irinotecan, or options 2 and 4?

So technically, pembrolizumab does not have approval for CPS less than 10, but the data are not that dissimilar to the chemotherapy. Paclitaxel/ramucirumab is not approved for squamous carcinoma of the esophagus. This is approved for adenocarcinoma of the stomach or the GE junction. So technically, the right answer is 2 and 4, but pembrolizumab can definitely be used after a discussion with the patient.

So question number 2-- a 55-year-old man with metastatic adenocarcinoma of the GE junction, HER2 negative, with a performance status of 1, who progressed after FOLFOX and paclitaxel/ramucirumab. CPS is 5, and the patient is macrosatellite-stable. What's your option for third-line-- pembrolizumab, irinotecan, trifluridine/tipiracil, or epirubicin, or 1, 2, and 3?

And the right answer is 1, 2, and 3. Irinotecan, actually, is a very good medication-- causes no neuropathy-- so sometimes we can use it second-line if the patient has significant neuropathy from oxaliplatin. But definitely, all of pembrolizumab, irinotecan, and Lonsurf are approved in third-line setting.

Question number 3-- a 55-year-old man with metastatic pancreas adenocarcinoma with performance status of 0-- he gets FOLFIRINOX for four months with partial response, and maintains performance status. You do a germline testing, and the patient has a variant of a non-significant for BRCA1, and you do somatic testing and they're microsatellite-stable.

They have mutant G12D mutation-- we don't have many 12Cs, unfortunately, in the GI world, and a P16 mutation. What are your next steps-- do you continue with FOLFIRINOX, you continue with 5FU maintenance, or olaparib maintenance, or palbocyclib, or options 1 and 2?

Yeah, so you can continue for FOLFIRINOX-- that's appropriate-- but based on the PANOPTIMOX data presented in ASCO last year, you can definitely deintensify treatment to 5FU maintenance. And olaparib maintenance-- or rucaparib, based on the data-- can be another option. Actually, no, I'll take that back. If you've noticed the patient had a BRCA1 VUS, technically you are not supposed to use a PARC inhibitor, so the options are 1 and 2.

Question number 4-- a 55-year-old woman, metastatic hepatocellular carcinoma related to hepatitis C, received sorafenib as first-line for six months with poor tolerance-- a bad fatigue and hand-foot syndrome, requiring multiple dose reductions and delays. Finally, the patient progresses. Performance status is 1, Child-Pugh score is 6, and the AFP is more than 1,500. Appropriate options for her-- nivolumab, pembrolizumab, regorafenib, ramucirumab, or 1, 2, and 4?

Yes, so it's 1, 2, and 4. Nivolumab and pembrolizumab are both approved. Regorafenib is approved, but I wouldn't use it on this patient, who was intolerant to first-line sorafenib. Ramucirumab is approved in second-line for patients who have an AFP more than 400, so 1, 2, and 4 is the right answer.

Question number 5-- you have a patient who is 55-year-old woman, metastatic colorectal cancer, wild-type for KRAS, NRAS, BRAF, and amplified for HER2 by FISH, performance status 1, progressed on fluroropyrimidine, oxaliplatin, irinotecan, bevacizumab. What are appropriate options for her-- irinotecan/cetuximab, referral for dual HER2 study, regorafenib, or Lonsurf, or options 1 and 2?

Yeah, so 1 and 2. You can definitely use irinotecan/cetuximab, but definitely, the data for dual HER2 therapy are very promising.