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Aiming for new targets in biliary tract cancer

Transcript from a touchEXPERT OPINIONS

This activity is supported by an independent educational grant from GSK and Merck KGaA, Darmstadt, Germany

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INTRODUCTION

In this activity, gastrointestinal oncology experts discuss the current unmet needs in biliary tract cancer and how the development of new treatments is driven by our understanding of the genetics and tumour microenvironment of biliary tract cancers.

Prof. Do-Youn Oh discusses the unmet needs for patients with biliary tract cancer and what the current treatment algorithm looks like. She also considers possible future treatments that may improve outcomes for these patients.

Prof. Juan Valle discusses the current genetic landscape and actionable signatures of biliary tract cancer. He also considers how this knowledge is influencing drug development.

Dr Rachna Shroff discusses new and emerging targeted therapies and immunotherapies for the treatment of biliary tract cancer. She also considers what are the implications for practice of these new agents.

LEARNING OBJECTIVES

After watching this touchEXPERT OPINIONS, you should be able to:

- Describe the unmet therapeutic needs for patients with biliary tract cancer
- Describe the genetic characteristics and tumour microenvironment of biliary tract cancers
- Explain the supporting data for new and emerging treatments for biliary tract cancers

TOPICS DISCUSSED:

- The current clinical landscape for biliary tract cancer
- How genetic alterations and the tumour microenvironment are driving the development of new therapies
- New hope from emerging therapies

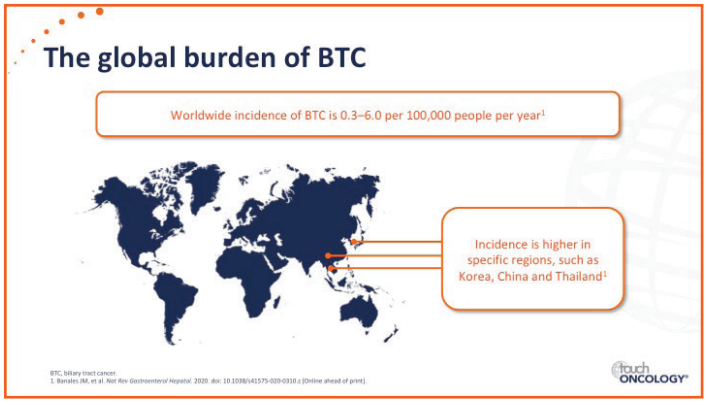
THE CURRENT CLINICAL LANDSCAPE FOR BILIARY TRACT CANCER

Prof. Do-Youn Oh:

Hello everyone. I'm Do-Youn Oh, medical oncologist, from Seoul University National Hospital. My majors are gastric, pancreatic and biliary tract cancer and phase 1 studies.

What is the global burden of biliary tract cancer?

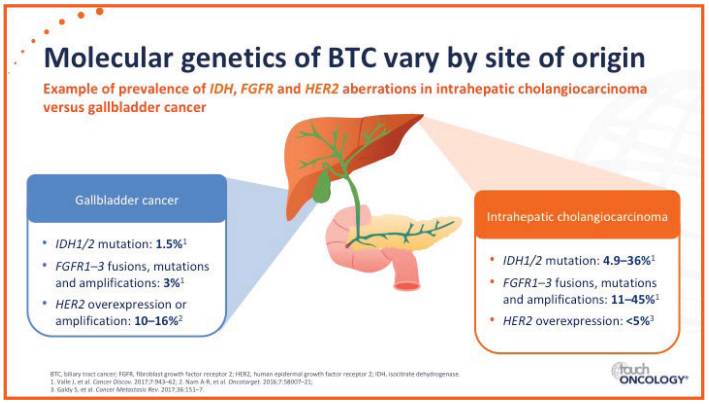
In terms of incidence of biliary tract cancer among all solid tumours, its proportion is relatively low and small. From the global point of view of incidence of biliary tract cancer, there are three hotspots across the world which show relatively high incidence. That is Korea, Southern China and Thailand. For example, in Korea the incidence of biliary tract cancer is 10 to 12 per 100,000 population. In general, in the Western countries the incidence of biliary tract cancer is around 1 to 2 per 100,000 population. The aetiology of biliary tract cancer is different across the region especially in Thailand, the majority of the biliary tract cancer aetiology is liver fluke-associated. However, except very limited regions like Thailand, the other regions' aetiology is quite similar, that means not liver fluke-associated one.



What is the heterogeneity of biliary tract cancer and how does it impact on treatment decisions?

Based on primary origins, biliary tract cancer consists of intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer and ampulla of Vater cancer. The presenting symptom and each presenting staging are a little bit different according to primary origin. Furthermore, the molecular characteristics among those subtypes are different, so genetic alteration pattern is different according to the origin. For example, IDH1 mutation or FGFR2 fusion or translocation is more predominantly observed in intrahepatic cholangiocarcinoma. Instead, HER-2 amplification or overexpression is more commonly observed in gallbladder cancer etc. So, the difference in these molecular characteristics according to the primary origin may confer the difference in the prognosis of each subtype of biliary tract cancer.

However, as I mentioned earlier, the presenting staging is also different according to the primary origin which may also impact on the prognosis. When you decide 3-month option in this advanced biliary tract cancer patient, especially in cases of cytotoxic chemotherapy, we do not consider the primary origin or the action of active cytotoxic agent. However, in cases of targeted agent, which is under clinical development, we have to consider the primary sites of biliary tract cancer for patient enrichment.

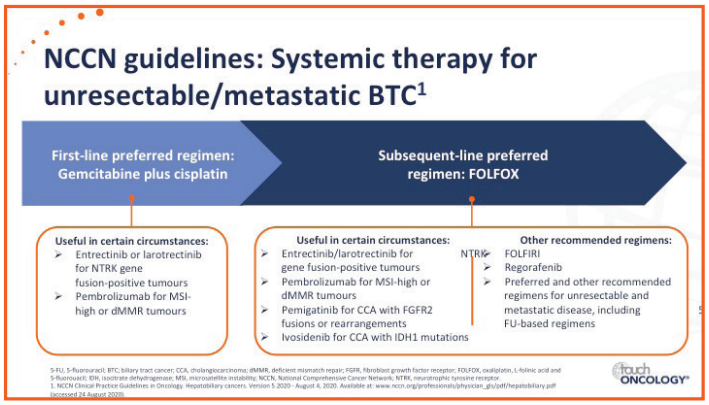


What is the current treatment algorithm for biliary tract cancer?

In the first-line setting of advanced biliary tract cancer, gemcitabine and cisplatin combination regimen is globally used if the patient performance status is good enough. After progression on this first-line gemcitabine and cisplatin, if the patient performance status still remains good, then usually a 5-FU-based regimen is commonly used. Based on the ABC-06 trial which showed the benefit of both FOLFOX regimen, compared with best supportive care in second line setting of advanced biliary tract cancer, FOLFOX regimen is one of the standards of care nowadays. But I think there is no one standard regimen in these settings still so 5-FU-based regimen is commonly used. After progression on this 5-FU-based second line regimen, then we don't have standard of care regimen to treat the cancer.

So recent studies using targeted agent have shown very promising results in those settings. One is targeting mutant IDH1.

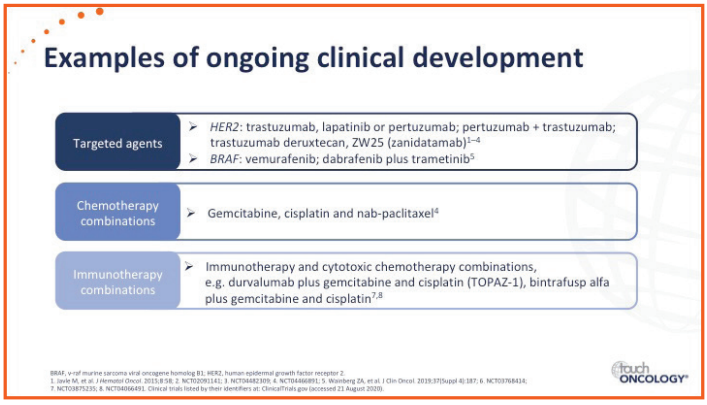
In phase II study of ivosidenib (AG-120) it improved progression free survival compared with placebo in second or third line setting of advanced biliary tract cancer with IDH1 mutation. In case of FGFR2 fusion and translocation, several FGFR inhibitors have shown very promising efficacy as monotherapy in this previously treated biliary tract cancer setting. From the tumour agnostic approach, MSI high is biomarker for a PD-1 inhibitor in all solid tumours including biliary tract cancer. The second tumour agnostic approach is for targeting NTRK fusion so even though the frequency of NTRK fusion is quite low, the majority of solid tumour types including biliary tract cancer. If the patient has an NTRK fusion, NTRK inhibitor such as larotrectinib or entrectinib is showing very good response and those responses are very durable. So therefore, in biliary tract cancer, we definitely have to investigate and as a high status, an NTRK fusion status, for selecting the patient treatment.



What is the landscape for new drug development in biliary tract cancer?

Nowadays, many interesting clinical trials are ongoing in the biliary tract cancer field. In molecular targets HER2 amplification or overexpression is one of the candidate targets and BRAF mutation is also a very interesting target. Besides those targeted therapies, in case of immunotherapy the drug development is ongoing very actively. PD-1 inhibitor monotherapy or PD-L1 inhibitor monotherapy has shown modest efficacy in general in biliary tract cancer. In some patients this PD-1 inhibitor monotherapy or PD-L1 inhibitor monotherapy shows a very good response, however, the biomarker, except MSI high that is super responder to immunotherapy, is still under investigation in biliary tract cancer.

So nowadays the drug development strategy of the immunotherapy field is to combine agents with different modes of action like immunotherapy with cytotoxic chemotherapy combinations or immunotherapy and immunotherapy combinations or something like that. For example, in the first line of biliary tract cancer, the combination of a checkpoint inhibitor and standard cytotoxic chemotherapy regimen like gemcitabine and cisplatin has been tested under the phase 3 trial design to improve survival outcome compared with cytotoxic chemotherapy alone. In case of cytotoxic regimens, more combination regimens are being tested, for example gemcitabine and cisplatin and TS-1 as your first line treatment option or gemcitabine and cisplatin and nab-paclitaxel combinations. So, we hope we can see many successes in the near future in the new drug development in this biliary tract cancer field.



HOW GENETIC ALTERATIONS AND THE TUMOUR MICROENVIRONMENT ARE DRIVING THE DEVELOPMENT OF NEW THERAPIES

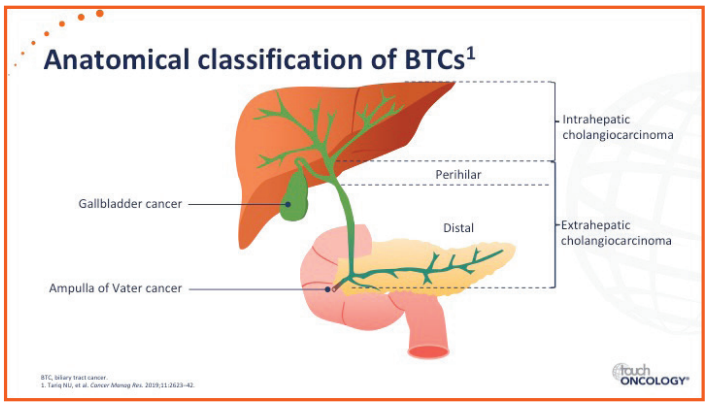
Prof. Juan Valle:

Hello my name is Juan Valle. I'm a professor and honorary consultant in medical oncology at the University of Manchester and the Christie in Manchester, UK.

Biliary tract cancers are a group of cancers with different clinical and molecular characteristics. How does this heterogeneity impact on the classification of these tumours?

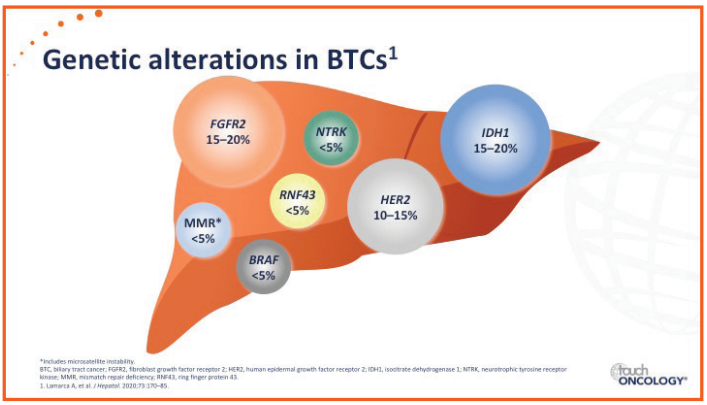
So we use the term biliary tract cancer to encompass a number of different entities including

cancers arising from the bile ducts themselves called cholangiocarcinoma which in turn can be intrahepatic, perihilar or distal as well as gallbladder cancers and cancers of the ampulla of Vater. These cancers all have very different epidemiology, risk factors and clinical management and whilst surgery is the cornerstone of cure for all of these there is an increasing understanding that molecular heterogeneity does impact on treatment options particularly in advanced disease.



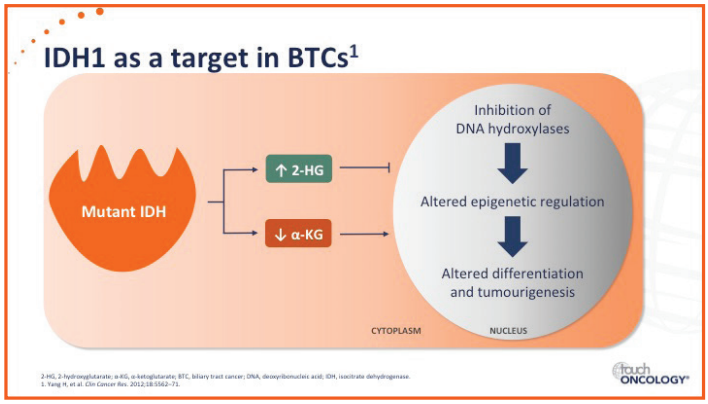
What are the most prevalent genetic subgroups of biliary tract cancer that have been identified?

And so there are now a number of studies that have looked at the molecular profiling of biliary tract cancers and what we're learning is that in fact there are a number of very discreet subgroups which go beyond the normal anatomical classification. The ones of greatest interest are those with IDH1 mutations as well as FGFR2 fusions or rearrangements but there are other smaller groups that have also got potential therapies, for example patients with BRAF mutations as well as NTRK, HER2 and patients with MSI high. These groups often go beyond the anatomical classification that we talked about previously.



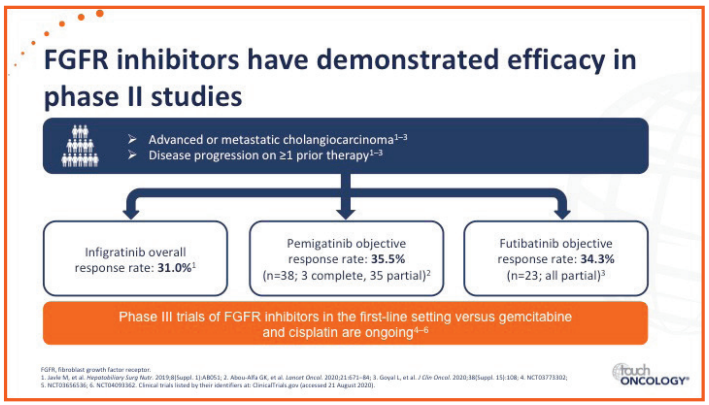
What is the role of targeting IDH1 in biliary tract cancer?

So IDH1 or isocitrate dehydrogenase 1 mutations result in a gain of function mutation and this results in an accumulation of 2-hydroxyglutarate which is an oncometabolite which is believed to drive the development of cholangiocarcinoma. Targeting mutated IDH1 with ivosidenib provided promising results in a phase one study with seventy-three patients with cholangiocarcinoma. On the basis of that a phase three study of a hundred and eighty-five patients who received either ivosidenib or a placebo in a two to one randomisation after failure of previous chemotherapy showed an improvement of the primary end point. This was progression free survival with a hazard ratio 0.37 with a modest improvement in the median overall survival from 1.4 months to 2.7 months.



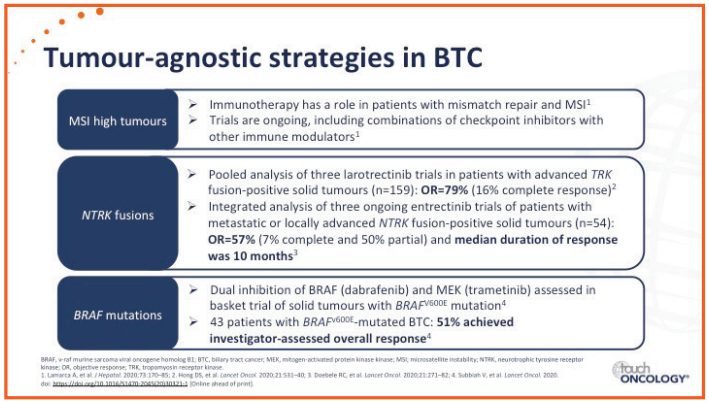
What is the role of targeting FGFR in biliary tract cancer?

So the molecular work I've talked about previously has identified activating translocation events, by which I mean fusions or rearrangements involving FGFR2. This results in upstream of the coding region which then drives cholangiocarcinoma and is relevant to around 15-20% of patients with intrahepatic cholangiocarcinoma. There are a number of phase two studies in patients who have been previously treated with chemotherapy which have shown some consistent messages. A number of patients have partial responses in the region of around 35%. Those responses are durable. A greater percentage of patients also have stable disease with only a small number of patients having disease progression as their best response. On the basis of that there are three ongoing phase three studies which are comparing FGFR inhibition against cisplatin and gemcitabine chemotherapy in the first-line setting to see whether this should be the primary treatment in patients with FGFR2 fusions or rearranged cholangiocarcinoma.



What other targets could be exploited by tumour-agnostic agents?

So we already have some evidence of tumour agnostic agents coming through which may be worth thinking about, those include patients with MSI, or microsatellite instability, high tumours for whom we think about immunotherapy. We also know that although NTRK fusions are very rare, less than 1%, treatment with NTRK targeting agents can also be of help and there's also some emerging evidence that we might be able to target BRAF as well. So I think it's important that going forward we undertake molecular profiling to see if we can uncover more of these sometimes small subgroups of patients for whom giving targeted therapy can improve patient outcomes.



NEW HOPE FROM EMERGING THERAPIES

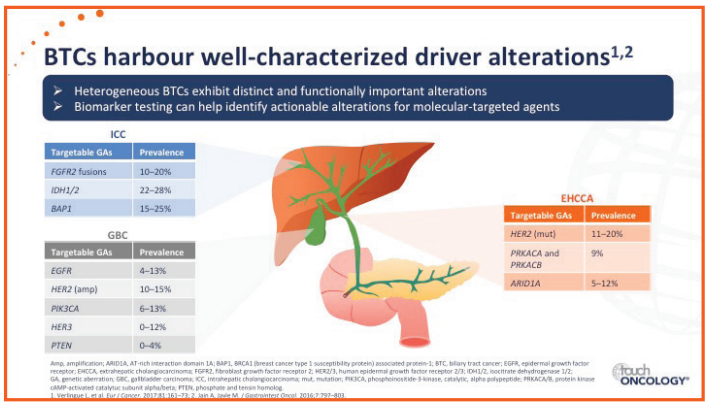
Dr Rachna Schroff:

My name is Dr Rachna Shroff. I am an associate professor and the chief of GI Medical Oncology at the University of Arizona cancer centre where I also serve as the director of the University of Arizona cancer centre clinical trials office.

Why should we molecularly profile the tumours of patients with biliary tract cancer?

So, I actually think it's very important for molecular profiling or biomarker testing to become part of the initial approach to biliary tract malignancies and it's really because there is such a heterogeneity as we have learned over time between this kind of broad category. Biliary tract cancer as you know includes intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder cancer. And, as we have done more next generation sequencing on these malignancies, we have identified that the molecular profiles of each of these three cancers are actually very distinct. And importantly, in intrahepatic cholangiocarcinoma for instance, when we do molecular profiling, in about 30 to 40% of patients we identify targetable alterations for which we have FDA-approved drugs and/or targeted therapies or even immunotherapies that are in the setting of clinical trials. It's a smaller percentage, about 15 to 20% in gallbladder cancer and extrahepatic cholangiocarcinoma but these are still very relevant.

The ideal way of doing this is doing this at the time of diagnosis with tissue. Most of the next generation sequencing platforms that are tissue based have a very broad scope in terms of mutations, fusions and alterations that are looked for. If tissue becomes an issue, as is often the case in say extrahepatic cholangiocarcinoma, then there are liquid biopsy- or ctDNA-based platforms that are now being looked at which don't have as comprehensive coverage but can still identify key alterations that could be relevant for therapeutic decisions.



How should we treat patients with FGFR-mutated biliary tract cancer?

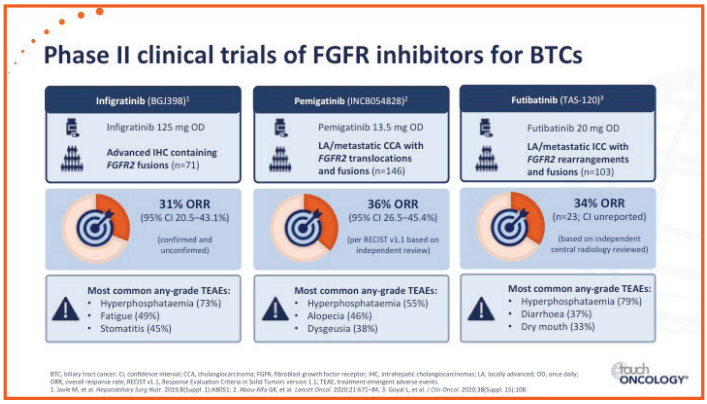
FGFR2 fusions are an incredibly relevant clinical decision-making tree when we identify them in patients typically in intrahepatic cholangiocarcinoma. So FGFR2 fusions are bound at about 15-20% of intrahepatic cholangiocarcinomas and basically these are fusions with which we can often times partner a number of other genes. So, the partner is agnostic, however, it leads to continual activation of the FGFR pathway and cancer progression. So, it is an oncogenic driver that we find early on in the disease state of intrahepatic cholangiocarcinomas, and since we have started testing a number of FGFR inhibitors in the clinic, we have identified the utility of these inhibitors for these patients. In fact, we have seen data now from 3, 4 or 5 even FGFR inhibitors at least in early phase studies and some in much larger comprehensive studies including the recent FDA approval of pemigatinib which is 1 FGFR inhibitor.

The data shows that in patients who are quite refractory, who have received at least one prior line of chemotherapy and often times two or three lines, patients with FGFR2 fusions who receive these single agent FGFR inhibitors, that include drugs like pemigatinib, infigratinib or futibatinib, those patients actually have response rates anywhere from 20 to 35% range which are response rates that are truly unheard of in a refractory cholangiocarcinoma population. Just as a benchmark, the ABC-06 data with FOLFOX in a second line setting for cholangiocarcinoma, the response rates were single digits.

So, this is a really exciting space right now, and like I mentioned, the first FDA approved drug for cholangiocarcinoma is pemigatinib, so we actually have a drug that is available to our patients and multiple clinical trials are ongoing. Importantly, some of these FGFR inhibitors are also being tested in the front-line space because the question remains; do patients with FGFR2 fusions need upfront chemotherapy like gemcitabine and cisplatin or should they be tested with these oral FGFR inhibitors? So, there are three ongoing frontline studies with infigratinib, futibatinib and pemigatinib in which patients are randomised who have FGFR2 fusions to receive either the FGFR inhibitor or gemcitabine and cisplatin.

So, this will be really important data for us to see as it reads out to demonstrate whether or not FGFR inhibitors earlier in the disease course truly provide a benefit. FGFR inhibitors because they're an oral drug are very appealing to our patients; it gives them a breakup of things like IV chemotherapy. That being said there are class effects associated with inhibiting the FGFR pathway that we did see across the board in most of these drugs and these include things like hypophosphatemia or high phosphate levels that often times require medicines to decrease the phosphorous levels as well as some ocular toxicity, some changes in terms of eyes, skin, we can sometimes see dry mucous membranes and dry skin as well as some changes in the nail beds.

So while these are different toxicities from gemcitabine and cisplatin or other chemotherapies, there are accumulative toxicities that we need to be aware of and that we are getting better about managing, and that at often times require multidisciplinary collaboration between ophthalmologists, dermatologists and such to preserve the quality of life for these patients.



How should we treat patients with IDH-mutated biliary tract cancer ?

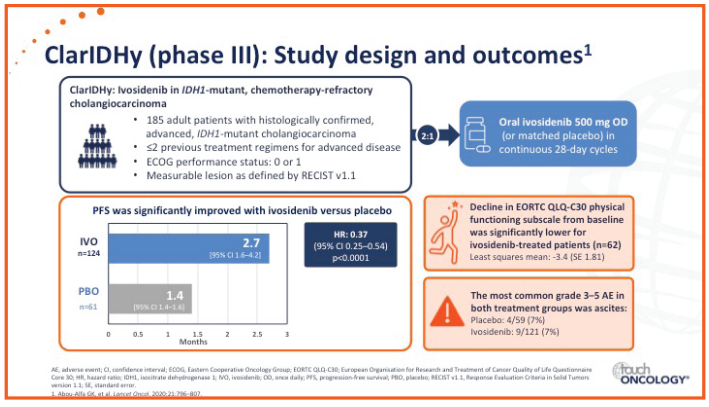
IDH mutations are again primarily seen in intrahepatic cholangiocarcinoma and in this patient population, we see it in about 20 to 25% of patients. So, this is probably the most commonly found alteration in intrahepatic cholangiocarcinoma. IDH1 mutations are more common than IDH2 mutations and this is basically a mutation that leads to dysregulation of a known metabolic pathway. We have had so far, one IDH1 inhibitor that has gone through phase three trials, and that is ivosidenib. Ivosidenib is already FDA approved in acute myeloid leukemia in patients with IDH1 mutations and has now been tested through the ClarIDHy study as a randomised based three study in patients with IDH1 mutated cholangiocarcinoma who had received at least one or two prior lines of therapy and they were randomised to receiving ivosidenib versus placebo.

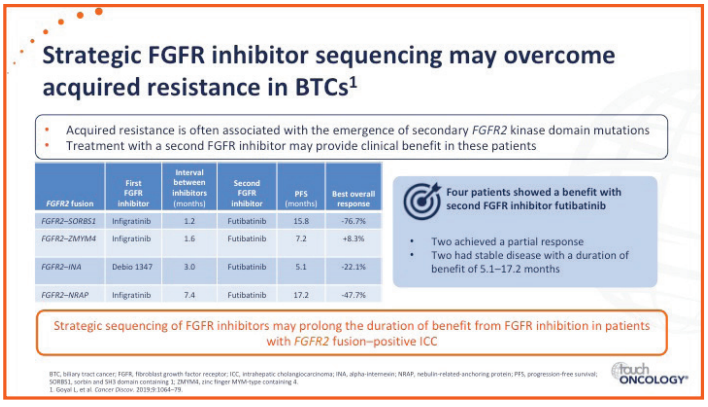
In these patients, the primary endpoint was progression free survival and there was a clinically and statistically significant improvement in medium progression free survival in the patients who received ivosidenib. Importantly, because this was a placebo-controlled study, patients were allowed to cross over, meaning if they had progression on placebo and still qualified, they could then receive ivosidenib. As a result, the median overall survival data is a little bit hard to tease out and we're still waiting for the final readout of that data and for the final determination of whether or not this will become an FDA approved drug. That being said it's a very well tolerated drug and as a result patients who demonstrate at least stability of disease demonstrated some clinical benefit and their quality of life was really well preserved and as a result I think it's really an important drug to be considered in the armamentarium for patients with IDH1 mutations. It remains to be seen how this drug will play out, both in the refractory setting based on what the FDA decides and also if there are other combinations or in combination with chemotherapy and such in which all of these questions are being studied ongoing in clinical trials.

How should we manage patients with acquired resistance to their treatment?

As is inevitable with targeted therapies, patients who are treated with drugs such as FGFR inhibitors and IDH1 inhibitors eventually develop resistance. This is still an ongoing and evolving field, what we have learned over time is that for FGFR inhibitors for instance, patients seem to develop polyclonal resistance, and this is something that was demonstrated by following ctDNA in these patients. So, patients who were treated with FGFR inhibitors had nice radiographic responses and had a decline in their ctDNA of their primary FGFR2 fusion. However, over time what was found was polyclonal resistance within the FGFR genes such as say a gatekeeper mutation which is a mutation that prevents the binding of the FGFR inhibitor to FGFR. And as this happens and as you start to see these resistant clones emerge, patients then demonstrate radiographic resistance and progression. Importantly, what has been found is that sometimes, using a different generation of FGFR inhibitors or a different type of FGFR inhibitor, after there is a break between the first FGFR inhibitor and the second one, sometimes patients still derive benefit.

So, for instance, in a really beautiful study published by Goyal et al. in Cancer Discovery, patients who were treated with infigratinib and had a nice durable response and then subsequently developed resistance were then treated later with futibatinib and still demonstrated very meaningful clinical responses and radiographic responses that appeared durable. As we get smarter about ctDNA and understanding the mechanisms of resistance, I think this will be really important for us to figure out how we could potentially sequence FGFR inhibitors given that we have so many available to us. In the IDH1 space, we're also still learning what resistance means and what it looks like. There's some early data that has come out that has suggested for instance that patients develop what's called a switch isomorph where they switch from an IDH1 mutation to an IDH2 mutation but that was a very very early study out of Memorial Sloan Kettering. I think as we get more data from the people who are





on the ClarIDHy study as well as patients who are utilising this drug in the clinic, we will hopefully better understand that resistance pattern as well.

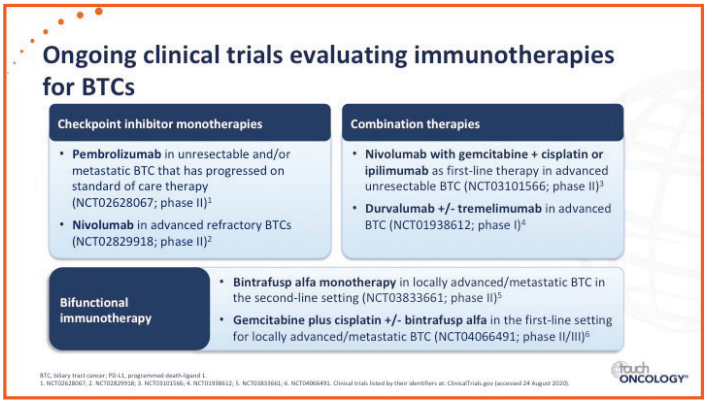
What immunotherapy agents are in development for the treatment of biliary tract cancers?

Immunotherapy is everybody's favourite topic and we of course want this to work in the biliary tract cancer space just as much as it's working in melanoma and lung cancer. The honest truth is that single agent checkpoint inhibitors such as pembrolizumab have been somewhat disappointing and frankly some of the results have been a mixed bag. Initial data was looked at specifically in the microsatellite instability high population in which we have an FDA approval and those patients of course seem to be benefitting. However, in an all-comer study, that was a single agent pembrolizumab study, response rate in the Ueno et al. study was 5.8%.

Interestingly, a multicentre study of single agent nivolumab that was published in JAMA Oncology by Kim et al. earlier this year demonstrated a higher response rate of 22% but on independent central review of radiology, it was closer to 11%. So, I think single agent checkpoint blockades still leave something to be desired. We are still on the quest for what the right biomarker is for response to immunotherapy in these patients. We know that MSI-high or tumour mutational burden high already have FDA approvals for checkpoint blockade, but I think specifically in biliary tract cancers we're still trying to understand what PD-L1 positivity could mean and what the true definition of tumour mutation burden intermediate and high could be.

That being said there are a lot of ongoing trials trying to add to the efficacy of single agent checkpoint blockade. There are gemcitabine and cisplatin plus IO combinations such as GemCis plus Nivo or GemCis plus pembrolizumab that are ongoing, and we are absolutely looking forward to the readouts of that data. Earlier this year at ASCO, there was a nivolumab plus ipilimumab study that was spearheaded by Dr Sahai at University of Michigan and in that in the frontline settings, this was a very disappointing result. So, we don't think that anti-CTLA-4 and anti-PD-1 could be beneficial in newly diagnosed patients. But there was a study out of Korea for instance that looked at durvalumab and tremelimumab in combination with gemcitabine and cisplatin and the results were certainly provocative albeit in an all-Asian population.

So, looking at the data that reads out from the gemcitabine and cisplatin plus checkpoint inhibitors that are multicentre and global studies I think will be very informative. There are also a lot of other great compounds that are being investigated that are looking at duo combination therapies or biphenotypic antibodies, for instance a TGF-β with a PD-L1 is a really interesting drug and we are actively looking at their ongoing phase 3 study in combination with gemcitabine and cisplatin. And I think there's a lot of other energy being poured into understanding how we can take what are historically called tumours and make them hot beyond just using an anti-PD-1 or -PD-L1. It'll be a really exciting time and I think in the next few years we will have readouts from these studies that will hopefully inform us about how immunotherapy can be utilised in these patients.



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Abbreviations

ASCO, American Society of Clinical Oncology; BRAF, B-Raf proto-oncogene, serine/threonine kinase; ctDNA, circulating tumor DNA; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase; PD-1, programmed cell death protein 1; MSI, microsatellite instability; NTRK, neurotrophic tropomyosin receptor kinase; TGF-β transforming growth factor beta.