Incyte-sponsored ILCA symposium: Personalised Approaches in Cholangiocarcinoma

What is the best way to navigate the genomic diversity of cholangiocarcinoma (CCA)? How do clinicians ensure patients with CCA receive the most appropriate treatment tailored to their individual needs?

These were the key questions addressed by four leading CCA experts, as they shared experiences and practical guidance on a precision medicine-based approach during the Incyte-sponsored educational symposium **'Personalised Approaches in Cholangiocarcinoma'**, chaired by Professor Bruno Sangro**. Watch the full symposium here.**

Chair: Prof Bruno Sangro
(Clinica Universidad de Navarra, Spain)

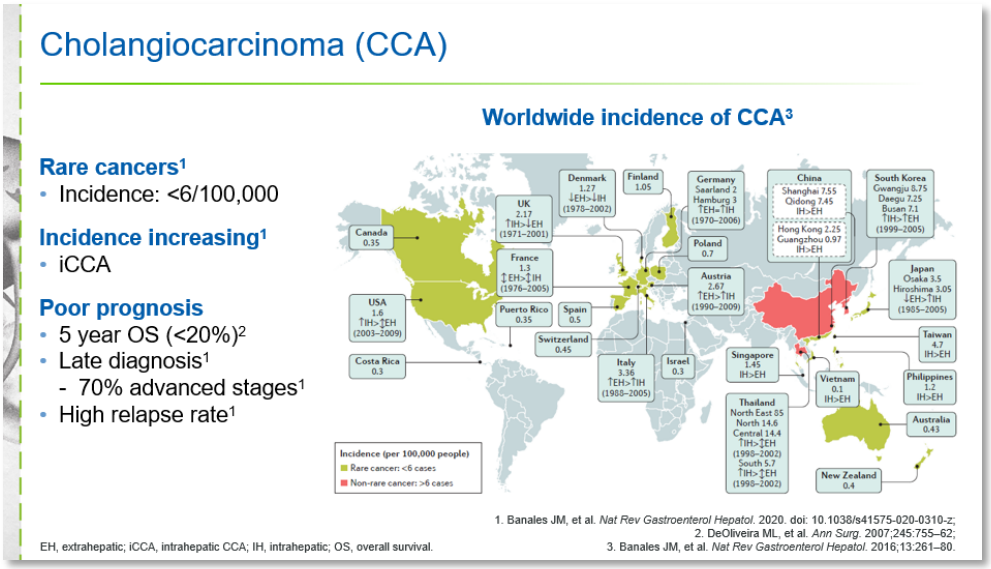
Dr Harpreet Wasan
(Imperial College London, UK)

Dr Ana Vivancos
(Vall d'Hebron Institute of Oncology, Spain)

Dr Joachim Mertens
(University Hospital Zurich, Switzerland)

Professor Bruno Sangro – Welcome and introduction

Professor Sangro opened the meeting by highlighting that, although a rare cancer, the incidence of CCA, in particular intrahepatic CCA (iCCA), is generally increasing worldwide.[1] CCAs are usually asymptomatic in their early stages.[1] Therefore, ~70% of patients are diagnosed with advanced disease, which compromises therapeutic options and leads to a poor prognosis (5-year overall survival <20%).[1,2] Further, a lack of adequate screening means the population at risk is poorly defined.[1] Genomic characterisation of CCA has enabled the evaluation of potential new treatments that target specific molecular alterations,[3] with Professor Sangro concluding that "this is the time of personalised therapy for CCA".

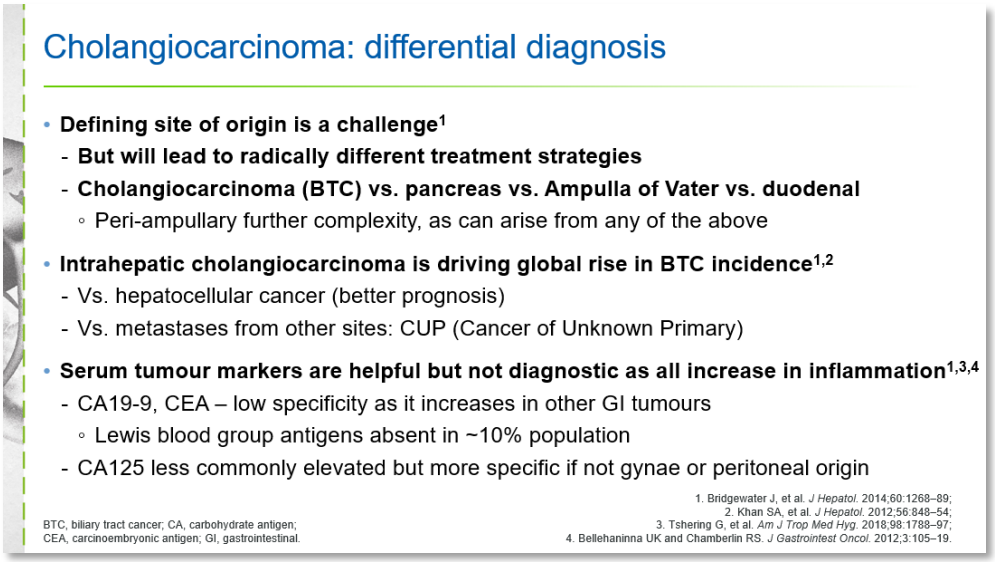


SOLVE ON.

Date of preparation: September 2020
BE/OTHR/M/20/0022

Dr Harpreet Wasan – Cholangiocarcinoma: Not a single disease

Dr Wasan discussed how CCA has major anatomical complexity leading to clinical and genetic heterogeneity, and provided his expert insights on the potential relevance of this heterogeneity to optimised disease management. As CCA has many differential diagnoses (eg, hepatocellular carcinoma and cancers of unknown primary), defining the site of origin is a challenging but critical step for the multidisciplinary team, as this will lead to radically different treatment strategies.[4] While serum tumour markers (eg, carbohydrate antigen 19-9 and cancer antigen 125) are helpful, they cannot be considered diagnostic as their low specificity/sensitivity limits their clinical application.[4,5] Pathology cannot clearly differentiate CCA from other upper gastrointestinal/hepato-pancreato-biliary adenocarcinomas, and mixed hepatocellular CCA tumours remain a diagnostic challenge.[4] There is no clear evidence from randomised clinical trials of a differential treatment effect of cytotoxic chemotherapy between different anatomical sites of origin within the biliary tract; however, patients with gallbladder cancer have been shown to have worse overall survival compared with tumours with other anatomic biliary tract sites of origin.[6] Dr Wasan concluded that a multidisciplinary approach is crucial for diagnosis and optimising personalised management of patients with CCA.

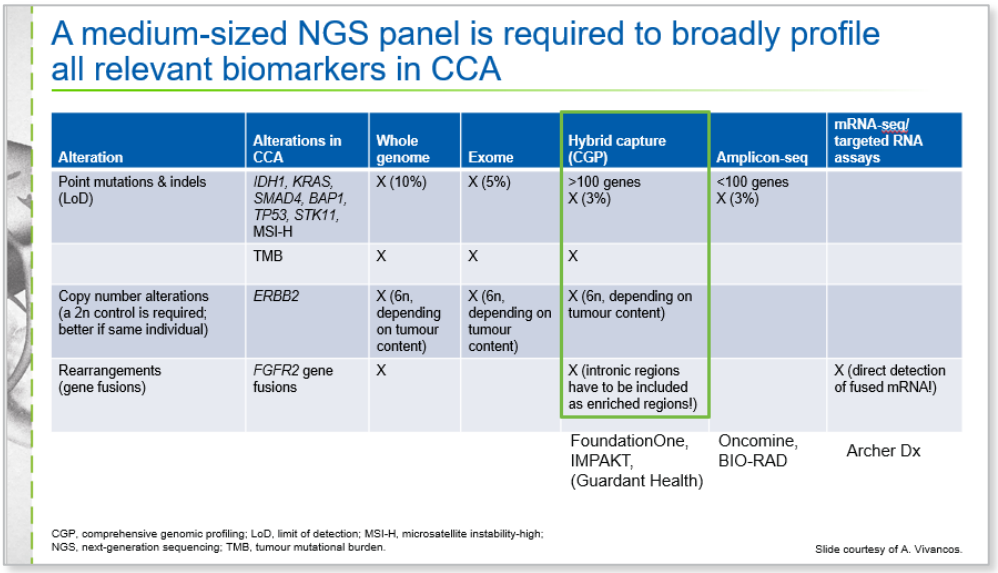


Dr Ana Vivancos – Cholangiocarcinoma molecular characterisation: Challenges and opportunities

Dr Vivancos explored the evolving role of molecular profiling in CCA and shared her perspectives on the key considerations, challenges and opportunities associated with the different technologies used. Potentially actionable genomic alterations have been identified in ~47.6% of patients with CCA,[7] highlighting the importance of routine comprehensive genomic profiling to inform treatment strategy. Dr Vivancos commented that multi-gene, DNA-based, next-generation sequencing (NGS) is the best approach for thorough molecular profiling of CCA biomarkers, due to its ability to identify gene fusions, single nucleotide variants, indels and copy number alterations; the importance of a high-quality tumour sample of sufficient quantity was highlighted. Fibroblast growth factor receptor 2 (FGFR2) gene fusions were identified by Dr Vivancos "as of now, **the** biomarker to test in iCCA". With regard to testing for FGFR2 fusions, in contrast to fluorescence *in situ* hybridisation (in which fusion status is determined by the uncoupling of collocated probes), NGS allows for precise identification of the

Date of preparation: September 2020
BE/OTHR/M/20/0022

underlying genomic breakpoint and identification of the fusion partner.[8] Dr Vivancos concluded by highlighting that liquid biopsy offers a non-invasive assessment of the tumour-specific mutational profile for patients for whom a tissue biopsy is not available and can help identify resistance mechanisms; however, not all patients shed circulating tumour DNA into the blood, which may limit the clinical application of this technique.[9,10]



A medium-sized NGS panel is required to broadly profile all relevant biomarkers in CCA

Alteration	Alterations in CCA	Whole genome	Exome	Hybrid capture (CGP)	Amplicon-seq	mRNA-seq/ targeted RNA assays
Point mutations & indels (LoD)	*IDH1, KRAS, SMAD4, BAP1, TP53, STK11,* MSI-H	X (10%)	X (5%)	>100 genes X (3%)	<100 genes X (3%)	
	TMB	X	X	X		
Copy number alterations (a 2n control is required; better if same individual)	*ERBB2*	X (6n, depending on tumour content)	X (6n, depending on tumour content)	X (6n, depending on tumour content)		
Rearrangements (gene fusions)	*FGFR2* gene fusions	X		X (intronic regions have to be included as enriched regions!)		X (direct detection of fused mRNA!)
				FoundationOne, IMPAKT, (Guardant Health)	Oncomine, BIO-RAD	Archer Dx

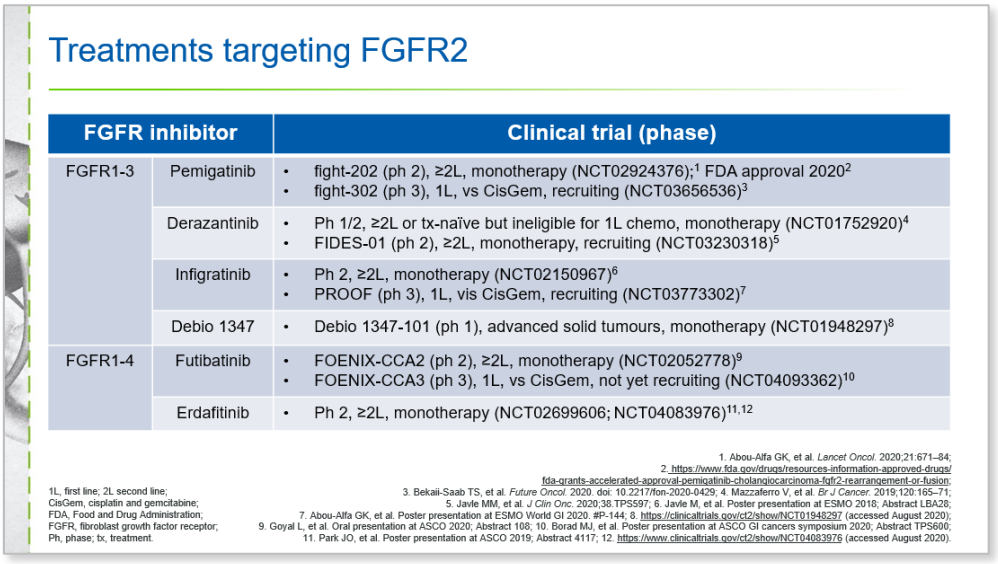
CGP, comprehensive genomic profiling; LoD, limit of detection; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; TMB, tumour mutational burden.

Slide courtesy of A. Vivancos.

Dr Joachim Mertens – Cholangiocarcinoma clinical research: What's new?

Dr Mertens gave an overview of evolving treatment strategies in CCA. Surgery remains the only potential curative option for patients with resectable disease; however, relapse rates are high (~60%).[1] Based on the results of the Phase 3 BILCAP study, adjuvant capecitabine is considered standard of care following surgery.[11] For patients with unresectable disease, gemcitabine plus cisplatin remains standard of care for first-line treatment.[12] Therapeutic options are limited in the second line; however, the Phase 3 ABC-06 trial supports the use of modified 5-fluorouracil, leucovorin and oxaliplatin (mFOLFOX) plus active symptom control in this setting.[13] Liver transplantation in unresectable cases has been explored; however, this remains investigational and rigorous patient selection is key.[14] Dr Mertens highlighted three key targets of molecularly driven therapies under investigation: FGFR2,[15] isocitrate dehydrogenase 1 (IDH1)[16] and neurotrophic receptor tyrosine kinase (NTRK).[17,18] With regards to immunotherapy, Dr Mertens commented that there are no convincing data to date for monotherapy; however, combination trials are ongoing. He concluded by highlighting that future directions should focus on molecular testing, targeting the tumour stroma and combination therapies.

Date of preparation: September 2020
BE/OTHR/M/20/0022



Treatments targeting FGFR2

FGFR inhibitor		Clinical trial (phase)
FGFR1-3	Pemigatinib	• fight-202 (ph 2), ≥2L, monotherapy (NCT02924376);[1] FDA approval 2020[2] • fight-302 (ph 3), 1L, vs CisGem, recruiting (NCT03656536)[3]
	Derazantinib	• Ph 1/2, ≥2L or tx-naïve but ineligible for 1L chemo, monotherapy (NCT01752920)[4] • FIDES-01 (ph 2), ≥2L, monotherapy, recruiting (NCT03230318)[5]
	Infigratinib	• Ph 2, ≥2L, monotherapy (NCT02150967)[6] • PROOF (ph 3), 1L, vis CisGem, recruiting (NCT03773302)[7]
	Debio 1347	• Debio 1347-101 (ph 1), advanced solid tumours, monotherapy (NCT01948297)[8]
FGFR1-4	Futibatinib	• FOENIX-CCA2 (ph 2), ≥2L, monotherapy (NCT02052778)[9] • FOENIX-CCA3 (ph 3), 1L, vs CisGem, not yet recruiting (NCT04093362)[10]
	Erdafitinib	• Ph 2, ≥2L, monotherapy (NCT02699606; NCT04083976)[11,12]

1L, first line; 2L second line; CisGem, cisplatin and gemcitabine; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; Ph, phase; tx, treatment.

1. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21:671–84; 2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pemigatinib-cholangiocarcinoma-fgfr2-rearrangement-or-fusion; 3. Bekaii-Saab TS, et al. *Future Oncol.* 2020. doi: 10.2217/fon-2020-0429; 4. Mazzaferro V, et al. *Br J Cancer.* 2019;120:165–71; 5. Javle MM, et al. *J Clin Onc.* 2020;38.TPS597; 6. Javle M, et al. Poster presentation at ESMO 2018; Abstract LBA28; 7. Abou-Alfa GK, et al. Poster presentation at ESMO World GI 2020. #P-144; 8. https://clinicaltrials.gov/ct2/show/NCT01948297 (accessed August 2020); 9. Goyal L, et al. Oral presentation at ASCO 2020; Abstract 108; 10. Borad MJ, et al. Poster presentation at ASCO GI cancers symposium 2020; Abstract TPS600; 11. Park JO, et al. Poster presentation at ASCO 2019; Abstract 4117; 12. https://www.clinicaltrials.gov/ct2/show/NCT04083976 (accessed August 2020).

References

1. Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17:557–88.
2. DeOliveira ML, et al. *Ann Surg*. 2007;245:755–62.
3. Braconi C, et al. *Liver Int.* 2019;39(Suppl 1):32–42.
4. Bridgewater J, et al. *J Hepatol*. 2014;60:1268–89.
5. Tshering G, et al. *Am J Trop Med Hyg*. 2018;98:1788–97.
6. McNamara MG, et al. *J Hepatol*. 2020. doi:10.1016/j.jhep.2020.05.014.
7. Lowery MA, et al. *Clin Cancer Res.* 2018;24:4154–61.
8. Bekaii-Saab TS, et al. *Future Oncol*. 2020; doi: 10.2217/fon-2020-0429.
9. Crowley E, et al. *Nat Rev Clin Oncol.* 2013;10:472–84.
10. Ettrich TJ, et al. *Sci Rep.* 2019;9:13261.
11. Primrose JN, et al. *Lancet Oncol.* 2019;20:663–73.
12. Valle J, et al. *New Engl J Med*. 2010;362:1273–81.
13. Lamarca A, et al. Oral presentation at ASCO 2019. Abstract 4003.
14. Darwish Murad S, et al. *Gastroenterology.* 2012;143:88–98.
15. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671–84.
16. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:796–807.
17. Drilon A, et al. *N Engl J Med*. 2018;378:731–9.
18. Doebele RC, et al. *Lancet Oncol*. 2020;21:271–82.

A virtual educational event organised and sponsored by Incyte Biosciences International.

Date of preparation: September 2020
BE/OTHR/M/20/0022