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Reports from the International Liver Cancer Association (ILCA) congress 2014

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Summary

The International Liver Cancer Association (ILCA) congress took place in Kyoto, Japan, from September 4 to 7, 2014 and ranged from basic to clinical studies in the area of primary liver cancer, including hepatocellular carcinoma (HCC), but also cholangiocarcinoma. In the field of basic and translational research, several studies attempted to refine our knowledge of biological events involved in liver carcinogenesis and sought to identify new therapeutic targets for improving clinical care in the future, Fig. 1. In the present work, a subjective selection of studies among the large number of abstract available at the ILCA meeting is presented and placed into context.

From the identification of potential therapeutic targets ...

Sorafenib remains the sole approved treatment for patients with advanced HCC [1,2]. However, the efficacy of sorafenib is limited, with an increase in survival of 2.8 months compared to a placebo and median time to radiological progression of 5.5 months. Consequently, identification of the most likely responders to sorafenib and, conversely, of the mechanisms of resistance to sorafenib, is a priority, as this will help in selecting patients who will benefit from sorafenib, and in proposing combined treatments to increase its efficacy and bypass resistance.

In his lecture, Lars Zender reviewed their results, recently published in *Nature Medicine* [3]. They used RNA interference (RNAi) combined with hydrodynamic vain tail injection in a mouse model harbouring HCC in order to discover the molecular determinants of resistance to sorafenib. They identified mitogen-activated protein kinase 14 (MAPK14) (coding for p38α) as a key factor in sorafenib resistance in their mouse model. Downregulation of MAPK14 increased tumour shrinkage induced by sorafenib and consequently increased survival. In addition, phospho-Atf2 (p-Atf2), a well-known downstream target, positively regulated by MAPK14, was assessed by immunohistochemistry in tumour biopsies of patients treated with sorafenib. In addition, the authors showed that overexpression of p-Atf2 was associated with poor overall survival in patients treated by sorafenib [3].

However, we could suggest that the use of p-Atf2 as a biomarker, predictive of resistance to sorafenib, needs to be validated in a prospective cohort of patients. In addition, this type of study opens up new avenues in the treatment with second-generation MAP2K14 inhibitors (such as skepinone-L and PH-797804) to improve the efficacy of sorafenib. Ideally, this combination should be tested in patients, selected according to the p-Atf2 level of their tumours (Fig. 1).

In parallel, however, we need to go beyond a biotherapy like sorafenib for all comers, and propose different ways of managing patients with advanced HCC. Over the last few years, using next-generation sequencing, several teams have described the genetic landscape of HCC and have increased our knowledge of driver genes involved in liver carcinogenesis [4–6]. This initial step is mandatory in order to identify the main therapeutic targets of future clinical trials. However, this strategy continues to be restrained by the limited number of targeted therapies available and, consequently, by the absence of biotherapy, adapted to each therapeutic target identified by whole-exome and whole-genome sequencing. Substantial effort is being made to develop new compounds targeting the genetic drivers of liver carcinogenesis. Along this line, somatic activating mutations of *CTNNB1* (catenin beta-1) coding for beta-catenin occur in around 20% to 40% of HCCs [7]. However, until recently, no safe compounds have shown any significant activity against the Wnt/β-catenin pathway [8]. Consequently, inhibitors of Wnt/β-catenin are not used in clinical practice.

Budhu *et al.* (*A high-throughput screen identifies Wnt-beta-catenin inhibitors for a stem-like subtype of hepatocellular carcinoma*) used high through-put drug screening and identified two compounds (pimozide and fiduxosin) that inhibited the Wnt/β-catenin pathway in hepatocellular cell lines. They showed that

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Abbreviations: Ns, non-significant; Ab, antibody; D, day; M, months; PFS, progression free survival; RFS, recurrence free survival; US, ultrasonography; CEUS, contrast-enhanced ultrasonography; CholangioK, cholangiocarcinoma; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; RCT, randomized control trial; NRT-SA, non-randomized control trial, single arm.

those compounds mainly affected a subtype of HCC cell lines, harbouring stem cell markers and mutations in the Wnt-TGFβ (transforming growth factor beta) pathway, not due to *CTNNB1*-activating mutations. Interestingly, pimozide has been already tested in several clinical trials to treat psychiatric disorders with favourable safety signals [9]. However, the efficacy of such compounds against *CTNNB1* mutations, the doses required to demonstrate an anti-tumour effect in humans and their safety profile in cirrhotic patients, remain to be determined.

In addition, around 5 to 10% of HCC harbour focal amplification of the FGF19 locus that leads to constitutive activation of the FGF/FGFR (fibroblast growth factor/fibroblast growth factor receptor) pathway [10]. Hagel *et al.* (*First isoform selective inhibitor of FGFR4 for the treatment of genomically defined patients with*