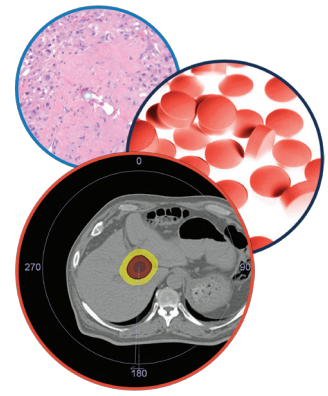
CONFERENCE REPORT



Hepatic Oncology

The 9th Annual Conference of the International Liver Cancer Association (ILCA) 2015

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The 9th International Liver Cancer Association Annual Conference was held from 4th to 6th September 2015 in Paris, France, and attracted a record breaking 900 participants from 51 different countries and 386 submitted abstracts from scientists around the globe. The congress provided a comprehensive overview of current developments in primary liver cancers (i.e., hepatocellular carcinoma and cholangiocarcinoma) and covered a broad range of topics from basic science to clinical studies. Following the success of immunotherapies in recent years, a preconference workshop on immunopathogenesis and immunotherapy in hepatocellular carcinoma also took place. This report will provide a subjective summary of selected abstracts presented at the conference.

KEYWORDS
• cholangiocellular carcinoma • heptatocellular carcinoma • ILCA 2015 • primary liver cancer

The crucial role of the chronically altered inflammatory microenvironment for liver cancer initiation and progression is increasingly recognized [1]. In this context, the cross-talk between tumor cells and cells in the surrounding microenvironment is a field of intense research and possesses significant impact on the development of novel therapeutic strategies [2]. Given the recent success of immunotherapies in many solid tumors the preconference workshop on immunopathogenesis and immunotherapy focused on a hot topic in translational research of hepatocellular carcinoma (HCC). The workshop provided a comprehensive and interactive summary on the conflicting roles of the different involved immune cells and their potential as novel therapeutic targets in HCC. Besides application of checkpoint inhibitors (i.e., PD1/PD-L1 and CTLA4) to induce an antitumor T-cell response in HCC, the future of oncolytic vaccinia viruses after the recent failure of the Pexa-Vec (pexastimogene devacirepvec; JX–594) Phase IIB trial in advanced HCC was discussed. In continuation of this trial, a first-line Phase III trial comparing the combination of JX–594 and sorafenib versus sorafenib alone is now planned in advanced HCCs [3]. Further, promising antitumorigenic effects from preclinical investigations on immunotoxin-based inhibition of GPC3, a frequently upregulated onco-fetal protein in HCC, using an antibody-toxin/drug conjugate with subsequent inactivation of Wnt/Yap signaling pathways were summarized [4]. Overall, the workshop clearly delineated the considerable capacity and potential pitfalls of immune-based therapeutic approaches in liver cancer.

The conference opened with a symposium on emerging trends in translational research on primary liver cancer (PLC). In a state-of-the-art lecture, Prof Schwabe then outlined the critical importance of the bacterial microbiota in the regulation of our immune system and promotion of chronic disease as well as carcinogenesis [5]. The recent developments in molecular hepatocarcinogenesis were presented in the first plenary session. Given the recent advances in next-generation sequencing (NGS), these technologies were increasingly applied to delineate the spectrum of molecular alterations

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in PLCs over the last years [6,7]. Most common genetic alterations were subsequently identified in key pro-oncogenic molecules such as, TP53, WNT–CTNNB1 and cell cycle related genes [8]. Other frequent changes were found in telomere maintenance (TERT), chromatin modifiers and inflammatory pathways [9]. Later during the conference, the validity of these findings was confirmed by Dr Luis Roberts, who presented preliminary results of the comprehensive and multilevel TCGA project on HCC (http://cancergenome.nih.gov). Letouzé *et al.* analyzed mutational signatures of hepatocellular tumors (adenoma and HCC) using whole exome and genome sequencing of 330 patients [6]. They applied the Wellcome Trust Sanger Institute mutational signatures framework1, to dissect the predominant mutational signature of each sample, and subsequently correlated the identified signatures with clinical and molecular tumor characteristics. A total of eight signatures were identified from which six have been already described in liver or other cancers and correlated with specific tumor or clinical characteristics. However, one of the newly identified signatures (signature 16) was characterized by T>C mutations with a strong transcriptional strand bias and potentially corresponded to a new mutagenic process operative in rare HCC cases and the other signature (signature 24) was predominantly seen in African cases with HBV infection and mutation in R249S TP53 characteristic of aflatoxin B1 exposure. Together, the authors suggest that the distinct landscape of mutational signatures might be a helpful tool to reveal new etiological factors that promote liver cancer development. While the majority of HCCs develop on the basis of a predisposing chronic liver disease and/or cirrhosis, Nault and colleagues now present a potentially important alternative route of liver cancer development by mutational insertion of AAV2 with subsequent activation of key oncogenes such as TERT, CCNA2, CCNE1 and TNFS10 [10]. From a cohort of 150 HCC patients, the authors could detect recurrent somatic integration of the virus in a total of seven cases (5%) without predisposing risk factors. The presented new mechanistic insights from the mentioned studies clearly confirm the considerable molecular heterogeneity and low frequency of oncogene addiction loops in primary liver cancer that hamper therapeutic progress [8]. Nepal *et al.* queried publicly available and newly generated large-scale NGS data for novel therapeutic options in intrahepatic cholangiocellular carcinoma (CCA) [11]. Overall, a range of 20–170 somatic deleterious mutations per patient in a cohort of 142 CCA patients was identified. Besides known hotspot mutations in KRAS(G12D) and IDH1(R132G), the investigators identified novel aberrations in genes, for example, CDC27, PABPC3, BCLAF1, KIR2DL3, POTEF, FRG1 and CCR5, with no prior association to CCA. Additionally, novel recurrent hotspot mutations were found in BCLAF1(N627S), FRG1(K258R) and KIR2DL3(C270S). Clustering of patients with KRASG12D and IDH1R132G mutations indicated a set of mutated genes and downstream-associated pathways to each of these driver mutations, which could be used to distinguish different subsets of CCA patients. The authors conclude that association of 'passenger' genes with a known disease causing genetic alteration could be used in novel therapeutic approaches for CCA patients. Schalm *et al.* computationally screened RNA seq data of rare fibrolamellar HCC (FL-HCC) samples from the TCGA database for kinase fusion, followed by functional validation of each candidate in liver cancer cells. The authors confirmed the distinct genetic profile of FL-HCC and a high prevalence of previously identified DNAJB1–PRKACA fusion as a driving oncogenic mechanism in FL-HCC [12]. Consistently, expression of DNAJB1–PRKACA activated PKA signaling and increased proliferative capacity of liver cancer cells. Notably, DNAJB1–PRKACA fusion displayed similar levels of kinase activity as well as sensitivity to targeted small molecules in comparison with wild-type PRKACA. Therefore, the authors suggest that inhibition of the fusion gene might offer unique opportunity for targeted approaches in FL-HCC. Tovar *et al.* used xenograft mouse models to explore the role of tumor-initiating cells for the development of resistance to sorafenib. By using a variety of functional and molecular approaches, the authors confirm recent notion that tumor-initiating cells play a critical role in the acquisition of a resistant phenotype [13]. Mechanistically, activation of IGF and FGF signaling was detected and could be a promising therapeutic target for patients with progression on sorafenib treatment. After these interesting translational studies, the first day concluded by a pro and con discussion on current controversies in staging and management of HCC.

New insights into epidemiology, staging and prognosis were discussed in the first clinical session. In a prospective multicenter study from France, Ganne *et al.* followed a cohort of 601 patients with compensated alcoholic cirrhosis to determine the incidence of HCC and other associated hepatic complications. While only 25% of the detected lesions were confirmed as HCC, minimal annual incidence of HCC was 1.6%. Additionally, they could show that a third of all deaths could be attributed to liver-related mortality. Another French study by the same group prospectively investigated 1323 patients with HCV-related compensated cirrhosis to develop a scoring system, which estimates the risk of HCC development in these patients. During a mean follow-up of 51 months, 11–14% of the patients in the training and validation cohort developed HCCs. Further, a new score consisting of four baseline variables (age, past excessive alcohol consumption, platelets count, GGT serum level) and qualitative HCV RNA was generated that accurately predicted the individual risk of patients with or without sustained virologic response (SVR) for the development of HCC. Nahon *et al.* could further show that patients with HCV-related compensated cirrhosis with SVR display a fivefold reduction in HCC incidence compared with non-SVR patients. Moreover, SVR reduced the annual incidence to <1%. Additionally, the investigators could show that risk factors and prognosis of SVR patients are distinct from viremic patients. Noteworthy, Singal *et al.* showed that only a third of patients with cirrhosis receive HCC surveillance in the USA, despite high levels of knowledge about the disease. The interesting study by Nahon *et al.*, therefore, has major implications for the surveillance and management of HCV patients in the context of recent developments of HCV therapies that overall achieve viral clearance in >95% of patients [14]. During lunch time, the ILCA special interest groups presented the latest developments in hot topics of liver cancer. A premier at this year's ILCA was the ILCA luncheon workshop: Egypt meets ILCA. The well attended workshop outlined common approaches and regional differences in the management of HCC, thereby paving the way for the establishment of new collaborative efforts.

Since the majority of HCC develop on the bases of chronic liver diseases, identification of novel targets for chemoprevention might be a promising strategy to reduce the incidence of liver cancer [15]. While overexpression of cyclooxygenase–2 (COX–2) was recently demonstrated to be prevalent in HCC [16], Takami *et al.* now show that inhibition of COX–2 by meloxicam did not result in a clinical benefit with regards to overall survival (OS) or disease-free survival rates. However, for patients with nonviral-related HCC, significant differences in disease-free survival were revealed suggesting that meloxicam may suppress recurrence after initial curative treatments in these patients. Llovet and colleagues evaluated the efficacy of living donor liver transplantation for HCC patients exceeding currently used Milan criteria. In a cohort of 22 patients, 1, 3, 5 and 10-year survival rate were encouraging with 95, 84, 77 and 69%, respectively. Perioperative mortality and complication rate were quite low confirming the feasibility of this approach. De Martin *et al.* compared the outcome of liver transplantation versus resection in small PLCs (intrahepatic CCA and HCC) in a cohort of 60 patients. Overall, a good long-term survival and significantly lower recurrence rate was shown after liver transplantation, which suggests that this might be a good therapeutic strategy in patients with cirrhosis and small PLCs.

Sunday morning session traditionally includes results from ongoing clinical trials. Given the failure of recent Phase III clinical trials in advanced HCC, the pursuit for novel biomarker-driven trials is demanding [17]. Lorenza Rimassa presented the tumor and plasma biomarker analysis from the recently concluded Tivantinib Phase II clinical trials [18]. Interestingly, MET was found to be highly expressed in 40% of biopsies taken before and in 82% of biopsies taken after sorafenib. A good association between treatment and tumor MET levels in OS could be demonstrated indicating its potential use for response prediction. While circulating baseline MET, alpha-fetoprotein (AFP) and hepatocyte growth factor (HGF) levels were prognostic, no marker other than tumor MET was predictive of response to the treatment. The ongoing METIV-HCC Phase III trial will further elucidate the role of MET inhibition in MET high tumors. Hoeflich and colleagues further showed that around 23% of HCC patients show aberrant expression of FGF19, and may respond to specific FGFR4 inhibition. Promising *in vitro* and *in vivo* data provide further evidence that stratification of patients based on FGF19 and subsequent targeting of the signaling using BLU–554 might be a promising therapeutic approach and will be evaluated in a clinical trial soon. Results from

a Japanese cohort of patients from the REACH trial [19] were presented by Hatano *et al.* In this subgroup, Ramucirumab did improved OS, PFS, as well as overall response rate, and demonstrated an acceptable safety profile. In concordance with the observation from other patients in the trial, even greater benefit was present for patients with AFP ≥400 ng/ml. Further evaluation of the drug and dissection of the clinical as well as molecular features of the Japanese patients is warranted. Finally, results from two Phase II trials using different immunotherapies (i.e., oncolytic viral therapy (JX–594) and immunomodulation with Tasquinimod) were presented by Moehler *et al.* and Edeline *et al.*. Despite modest antitumor activity, both trials showed acceptable safety profiles, which provide important basis for subsequent clinical applications.

Overall, the annual ILCA meeting in Paris nicely reflected the vibrant and growing scientific community in PLCs. Significant achievements in both clinical and translational science delineated a bright path for the future. We are looking forward to the 2016 meeting in Vancover, Canada.

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