2017 10th PARIS HEPATOLOGY CONFERENCE

Organised by Professor Patrick Marcellin, Chairman of the Paris Hepatitis Conference
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PRESS BOOK

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The liver, a reflection of individual health

New pathologies in hepatology

Press Contacts

LJ COMMUNICATION

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Foreword introducing the 10th PHC

The growing success of the PHC, organised by Professor Patrick Marcellin[1]* since 2004, is down to the attendance of a large number of experts from all over the world. For the past 13 years, the Conference has supported the rapid progress now being made with treatments for Hepatitis C. Thanks to the collective involvement of researchers and clinicians, today we can talk about curing this chronic disease with well-tolerated short-course oral treatments.

This year, the Paris Hepatitis Conference has been renamed the Paris Hepatology Conference in order to cover the full field of liver-related diseases that pose as yet unresolved problems. New findings in the field of viral hepatitis B and C will, of course, be on the agenda, together with metabolic liver diseases or NASH (non-alcoholic steatohepatitis) and hepatocellular carcinoma.

Accordingly, cirrhosis, which is not limited to alcohol, and cancer of the liver are the most frequent final outcomes of chronic liver diseases, which will be debated during this 10th PHC with specialists from across the world. These diseases, at once very frequent, silent and caused by three main factors (alcohol, virus and metabolic syndrome) probably affect almost one third of the world's population. The time has come to act in order to detect and prevent these diseases and to improve the early screening of cirrhosis and cancer of the liver.

First of all, for the past three years we have seen that chronic hepatitis C can easily be cured thanks to new, highly effective and well-tolerated drugs. A gradual lessening of the extent of this disease may therefore be envisaged in the short term, providing that an eradication plan for Hepatitis C is introduced in France and elsewhere. Examples of such strategies, as in Australia and Georgia, will be presented at the PHC.

Secondly, a growing number of chronic diseases and liver cancers are due to the metabolic syndrome, the prevalence of which is showing a consistent upward trend in France: the main causes are excess weight, diabetes, obesity, hypertension and dyslipidaemia. Yet prevention of the metabolic syndrome is simple, with benefits for not only the liver but also the heart and the risk of cancer. The simple solution is a balanced healthy lifestyle.

*The PHC has been organised by Professor Patrick Marcellin since 2004 under the auspices of the Hôpital Beaujon (AP-HP)/ Université Paris-Diderot/ Inserm CRI – Members of the scientific committee are Marc BOURLIERE *(France),* Massimo COLOMBO (*Italy*), Rafael ESTEBAN (*Spain*), Graham FOSTER *(UK),* Michael FRIED *(USA),* and Michael MANNS *(Germany)*

Last but not least, alcohol: over 4 million people in France drink to excess and binge-drinking is on the increase amongst teenagers and young adults. It is time to set up a policy for the prevention of alcohol-related diseases, which lead to the death of some 50,000 people in France every year.

VIRAL HEPATITIS B & C: THE NEXT STEP TOWARDS A CONCLUSION

Since 2014, we have had access to short-course treatments of 12 weeks for the Hepatitis C virus (HCV), drugs that are administered orally, well tolerated and likely to cure the majority of patients.

For the Hepatitis B virus (HBV) we have analogue treatments (entecavir or tenofovir) that help put the disease into remission with all patients. Nevertheless, this treatment cannot be halted and has to be prescribed for life. Today, clinical research is oriented towards a cure and not merely virus suppression. "HBV Cure" is a world research programme into new molecules able to act on the cccDNA (implicated in viral persistency) and lead to viral elimination. Some of these molecules today are at the very earliest stage of clinical research.

UNIVERSAL SCREENING FOR UNIVERSAL TREATMENT

In 2010, France issued a systematic screening recommendation for HIV infection amongst the general population, over and above the principal risk factors. In the same spirit, a recommendation for systematic screening for Hepatitis B & C was made in May 2014 for all males and pregnant women[1]. The simultaneous screening, at least once, of the 3 viruses - HIV, HCV, HBV - was recommended for the first time in October 2016, this being easier for physicians to propose and easier for patients to accept.(2) We now need to get this recommendation known to the general public and to physicians by way of wide-reaching awareness campaigns, during which we will also need to dwell on the efficacy and good tolerability of new treatments. The TROD programme - quick screening tests with diagnosis - (saliva or finger-prick blood testing) has led to community screening of HIV that has proven effective in France. Combined with HIV, the TROD programme for HCV would benefit the "off-premise" screening of Hepatitis C (i.e. distributed outside hospital or health professional premises) for high-exposure populations, i.e. drug-users and migrants from highly endemic regions. After a 5-year wait, the decree was recently published authorising the use of the TROD facility for Hepatitis C by association members. Associations have become organised to receive training and apply for clearance and financing for this complementary screening tool. The "Multiplot", an all-in-one device and TROD programme for HIV, HBV and HCV, should receive authorisation some time in 2017.

Universal access to treatment for Hepatitis C, recommended by all learned societies, was announced in France in May 2016. So for our country, 2017 could be the year of treatment for all, thus joining the ranks of Germany, Portugal, Georgia and Australia that have already announced the generalisation of this treatment. Two countries, Georgia and Egypt, have formulated plans to eradicate HCV infection. In Australia and Egypt, general

practitioners have been authorised to prescribe anti-HCV treatments. Owing to their high cost, a system of priority has been in place in France since January 2014 for patients suffering from severe hepatitis, extra-hepatic manifestations or co-infection with HIV.

The most serious cases have therefore received initial treatment and the percentage of cirrhosis patients has gradually dropped over the past three years. Starting in July 2016[3], the treatment can be prescribed as from the medium severity stage and at any stage of the disease in instances of genotype 3 infection, organ transplant, hemodialysis and symptoms such as, for example, intense fatigue. The treatment is authorised for all persons where there is a high risk of transmission, such as hard drug-users exchanging materials, prison inmates and women wishing to become pregnant[3]. This means that a majority of patients can now be treated pending the official text that in France would authorise treatment for all virus-affected patients, whatever the histological stage. On the 4th of January 2017, Zepatier was given marketing authorisation for the treatment of all genotype 1 and 4 patients. For 12 weeks of treatment, this association is for the time being the least expensive (€28,700) compared with Vikierax + Exviera (€41,500) and Harvoni (€46,000), but a reduction in the length of treatment from 12 to 8 weeks for naive genotype 1 patients without cirrhosis for Harvoni and Viekirax Exviera (genotype 1b) represents a significant drop in the cost of treatment[4]. Let it be said here that treatment with Zepatier cannot be reduced to 8 weeks.

Given the current momentum, wide-coverage treatment by specialists from university hospitals, general hospitals and the private sector (they being the sole authorised prescribers in France) could help cure 10,000 to 15,000 Hepatitis C sufferers in France each year. The screening and treatment of all active hard drug-users has to be organised now. Treatment for this population, recommended since May 2014, was authorised only in July 2016[3]. To achieve this goal, there has to be seamless coordination of care given in all support, welfare and addiction centres (in France - CARUD and CSAPA) and in prisons, and the doctors working in these facilities (often GPs and not specialists) must be given easier access to the prescription of direct-acting antivirals (DAAs), which is presently not the case. Treatment for active drug-users is one of the new issues involved in preventing the transmission of HCV, for it not to spread beyond that specific population. The treatment must embrace a global approach to care and support: a reduction in the excessive intake of alcohol, social support and substitute treatments. The choice of treatment must be the same as that for the population that does not use drugs. For patients in a precarious financial situation and migrants, we need to coordinate propositions for screening and care at the various centres spread across the country in France.

The general principle for the treatment of Hepatitis C lies with a combination of at least two molecules for a period of 8 to 12 weeks, with or without ribavirin according to genotype and to patient profile[5,6]. In 2016, the most frequently used combinations were Harvoni (genotype 1a and 4), Viekirax ± Exviera (genotype 1b and 4), and Sovaldi + Daklinza (genotype 2 and 3). Two new combinations will be available in 2017, Zepatier (genotype 1 and 4) and Epclusa (all genotypes).[5,6] Finally, three new pan-genotypic combinations will probably come to light in 2018: sofosbuvir combined with velpatasvir and with voxilaprevir, glecaprevir with pibrentasvir, and MK-3682 with grazoprevir (anti NS3) and with ruzasvir. These three combinations, the preliminary results of which were presented at the last AASLD Meeting (Boston 2016) are specific in that they are pan-genotypic and remain active in

the very rare case of failure using first-generation DAAs. None of them requires a combination with ribavirin.[7] Cases of HBV reactivation potentially leading to death have been reported during or after treatments for HCV with DAAs in patients suffering from HBV and HCV co-infections. As a result, systematic screening for HBV infection must be carried out before introducing treatment with DAAs.

Additionally, patients with an HBV and HCV co-infection must be observed and nursed throughout the period of treatment with DAAs to watch for the risk of B-virus reactivation.

Universal access to treatment for Hepatitis C began in France with the market authorisation granted to Zepatier on the 4th of January 2017, already cleared for all genotype 1 & 4 patients. The virtually consistent efficacy of the DAAs now available implies, in our country, more widespread screening and greater access to care and medication for patients (hard drug-users and poorer populations). Following the example set by Egypt and Georgia, a plan to eradicate HCV infection should be proposed for France, given that all the components are now in place for us to achieve this target.

THE OTHER LIVER DISEASES THAT WE ARE UNABLE TO CURE

STATE OF KNOWLEDGE, NEWS, CHALLENGES

NON-ALCOHOLIC STEATOHEPATITIS (NASH) OR FATTY LIVER: A FREQUENT DISEASE YET SELDOM MENTIONED

Slow-developing NASH has been ignored for too long. Yet it is the most frequently-occurring hepatic disease and today the prime cause of hepatic transplants in the United States. Almost 80% of cirrhoses previously considered to be idiopathic now seem to be due to NASH, especially in elderly people. NASH would seem to explain 60 to 70% of unexplained disorders seen with liver function tests. Linked to excess weight and obesity, fatty liver diseases are on the increase in industrialised countries. In the United States, NASH affects 5% of the general population, versus 1% in France. Pure steatosis (absence of inflammation, necrosis and fibrosis), a stage that precedes NASH, is said to affect 15 to 20% of the French population. In France, one third of adults are overweight ($25 \leq BMI < 30$ kg/m²) and 15% are obese ($BMI \geq 30$ kg/m²).[8] Fatty liver is the hepatic complication of the metabolic syndrome defined by 3 of the 5 following elements: diabetes, central obesity, arterial hypertension, higher levels of triglycerides, a drop in levels of HDL cholesterol. NASH is linked to an inflow of free fatty acids from adipose tissue to the liver, where they are stored in liver cells and then trigger an oxidative process and mitochondrial toxicity leading to the destruction of hepatic cells.[9] The silent nature of NASH and the absence of correlation between biology and histology have given way to non-invasive markers of fibrosis. These are still imperfect and open to discussion.[10] They reflect the severity of the affection and will justify the performing of liver biopsies, the key to diagnosis and to the treating of patients.[11,12] In terms of development, there is a distinction between low-risk patients (pure steatosis) and those with a progressive fibrosis (steatosis with inflammation, ballooning and/or fibrosis). The latter, the identification of whom is not yet optimal, require close observation for complications, particularly the existence of a hepatocellular carcinoma, which may occur even in the absence of established cirrhosis[12]. The significance of cardiac or vascular complications (20 times more frequent) justifies a regular cardiovascular evaluation with these patients[12].

Weight-loss through dieting and exercise is today the best way to treat NASH: it is now accepted that weight loss of between 5 and 7% from initial levels has an effect on steatosis and the severity of NASH[13]. The relationship between the intensity of weight loss and the resolution of NASH has been demonstrated by a Cuban prospective study that evaluated the impact of a low-calorie diet and regular physical activity over 12 months on the hepatic histology of 293 patients suffering from NASH without cirrhosis. The study confirmed the relationship between the extent of weight loss and improvement seen with NASH. The loss of 10% of initial body weight (achieved by only 10% of patients) led to the disappearance of histological signs of NASH in 90% of cases[14]. As a result, with patients suffering from NASH, weight-loss of at least 10% is the target to reach and maintain in order to hope for full resolution of the disease.

NASH is seen in around 10% of cases of severe obesity. In this situation, bariatric surgery is the most radical and the most effective treatment to achieve significant and lasting weight loss, particularly with diabetics, with an improvement seen for NASH and diabetes[15].

None of the first generation drug treatments (Metformin, Omega 3, ursodesoxycholic acid, statins, pyoglitazon) has been selected in the recommendations from learned societies with the exception of vitamin E[12]. Recommended by the EASL (European Associations for Studies of the Liver) for its anti-oxidising properties, vitamin E has so far not proven its long-term safety.

The first wave of future candidate drugs - obeticholic acid (biliary acid agonist of the FXR receptor), elafibranor (alpha PPAR and delta PPAR double agonist improving the hepatic oxidation beta) and liraglutid (agonist of Glucagon LP receptors acting on insulin secretion and insulin sensitivity) are currently under analysis in phase 3 trials. Obeticholic acid proved efficacious in an initial trial but the appearance of a pruritus-type side effect[16] in around one-third of cases resulted in the start-up of a new trial with treatment doses that were considerably lower. Elafibranor has not proven superior to the placebo with the trial's principal criterion (resolution of NASH) but has had a significant effect on the regression of fibrosis[17].

Preliminary results from the second wave of candidate drugs were presented at the AASLD Meeting in Boston.(7) These drugs specifically target the build-up of fat in the liver, fibrosis or inflammation: BMS-986036, GS-4997, Selonsertid Simtuzumab, Cenicriviroc, Semaglutide, Aramchol. None of these molecules has shown any significant efficacy with the trial's key criterion of assessment[7]. Confronted with NASH and the problems arising over its frequency, therapeutic research has mushroomed but, to date, remains inconclusive. In the absence of a miracle pill, whatever that pill may be, the bedrock for the treatment of NASH lies with hygiene and dietary measures, including a low-calorie diet (low in quickly absorbed and slowly absorbed carbo-hydrates) and the practice of a physical activity. A weight loss of between 8 and 10% is indispensable to improve the liver function and reduce cardio-vascular risks, the primary cause of mortality with these patients. Encouraging a patient to change his or her eating habits is neither simple nor easy to do but in most cases it is effective, providing the person is given individualised support and regular monitoring. Fatty liver-related diseases are now a societal problem in industrialised countries and in France the percentage of obese individuals has risen from 8% to 12% in 15 years[8]. There is a real need in our country to set up educational programmes to promote the benefits of a healthy lifestyle.

HEPATOCELLULAR CARCINOMA (HCC)

The excessive and prolonged intake of alcohol, chronic infections from the Hepatitis B and C viruses, and the metabolic syndrome that we have presented in this book are the main causes of chronic liver disease that lie at the origin of primary cancer of the liver. In the event of cirrhosis, the incidence of liver cancer is around 2% a year, meaning that any patient with cirrhosis of the liver runs a high risk of contracting cancer and so must be closely monitored.

Primary liver cancer or hepatocellular carcinoma (HCC) has the unfortunate distinction of having one of the highest mortality rates of all cancers[18,19]. **It is the main cause of death in people with cirrhosis of the liver with which it is associated in 90% of cases. Any delay in detecting and diagnosing the cancer seriously jeopardizes a patient's chances of receiving curative treatment and achieving lasting full remission.** This cancer is one of the so-called silent cancers because it remains asymptomatic until the disease has reached an advanced stage. This explains the often late diagnosis and poor prognosis.

Once symptoms have appeared, the 5-year survival rate is estimated at 10%. 75% of cancers that are detected early on can be given curative treatments and fully cured: the study by ANRS CirVir has confirmed the cost-efficiency aspect of curative treatment for small tumours. Today, methods of imagery are able to detect very small-sized nodules and allow the introduction of curative therapies such as the percutaneous destruction of nodules or hepatic transplantation, now available in addition to resections[20]. Screening for cancer with patients suffering from liver cirrhosis is now current practice in most Western countries. Based on hepatic ultrasound scanning every 6 months, it sets out to identify the cancer at the small nodule stage.[20,21,22] But in reality, patients with cirrhosis seldom have the benefit of twice-yearly monitoring. The impact of respecting recommendations for half-yearly screening for HCC has been examined with the (ANRS) CirVir prospective cohort study, which included nearly 1700 patients suffering from compensated B or C virus cirrhosis.(23) Recommendations were deemed to be respected if the mean period between two ultrasounds was less than 7 months. Respecting recommendations for screening had a significant influence on survival. Of the patients who were given half-yearly monitoring, the mean survival rate was 53.2 months, as opposed to 25.4 months in the group of patients whose ultrasound scans were performed at longer intervals. This result is explained primarily by the fact that patients given an optimal systematic screening process had access to curative treatment more often than the others, and owing to the smaller size of the tumour: 79% versus 43%.(23) The conclusions from this study therefore confirmed the necessity to conduct systematically an abdominal ultrasound every six months with patients at risk. Several leads for optimisation could improve the screening of HCC: better detection of the cirrhosis, greater awareness extended to GPs and radiologists for HCC screening, education for patients suffering from chronic liver disease and the introduction of a remember-the-date system for ultrasound scan appointments.

When the tumour cannot be given curative treatment on account of its size or spread, the sole remaining possibility is palliative therapy. The search for palliative medical treatment has long been considered a difficult task owing to the tumour's usual resistance to conventional chemotherapy. As a result, new medical treatments for advanced HCC are urgently awaited. Sorafenid, a multikinase inhibitor which reduces the proliferation and

angiogenesis of tumour cells, is the first oral treatment that has proven to be effective[24]. Nevertheless, the benefit in terms of survival is relatively low[24]. Several leads are currently being explored in order to further improve the efficacy of this molecule: a combination with other molecules, the characterisation of resistance mechanisms to sorafenib, the evidencing of factors through which to better select sensitive patients, and the combination of sorafenib with loco-regional treatments. Other antiangiogenics (sunitinib, brivanib, linifamib, erlotinib) have not proved superior to sorafenib in terms of efficacy. Ramucirumab, a new monoclonal antibody specific for VEGF-2 receptor (endothelial growth factor) is the only agent that has shown an increase in second-line survival with patients not controlled with sorafenid[25].

Immunotherapy represents a new lead to combat advanced forms of HCC. Presented at the ASCO 2016, a study tested a new immunotherapy compound, nivolumab, an anti-PD-1 antibody, with 214 patients suffering from advanced HCC. Stabilisation of the tumour was achieved in one half of patients[26]. Nivolumab will be compared with nexavar for first-line treatment of advanced HCC.

The best treatment for primary cancer of the liver would be to eradicate the cause of chronic liver disease. In cases of viral cirrhosis, antiviral treatment most likely reduces the incidence of HCC and its administration appears justified whenever possible. In 2016, a publication advanced the fact that DAAs might promote the emergence of HCC in treated patients[27]. This point will continue to fuel considerable debate in the knowledge that data from French cohorts do not confirm this tendency[28]. In instances of alcohol-related or dysmetabolic cirrhosis, complete alcohol withdrawal or a low-calorie diet combined with daily physical activity could reduce the occurrence of cancer.

Bibliographic References

1. Dhumeaux D. Prise en charge des personnes infectées par les virus de l'hépatite B ou de l'hépatite C. 2014 http://bit.ly/1HZvjzJ
2. Dhumeaux D. Prise en charge thérapeutique et suivi de l'ensemble des personnes infectées par le virus de l'hépatite C http://ww.afef.asso.fr/ckfinder/userfiles/files/recommandations-textes officiels/recommandations/rapportDhumeaux2
3. Instruction du 28 juillet 2016 relative à l'organisation de la prise en charge de l'hépatite C par les nouveaux antiviraux d'action directe http://circulaire.legifrance.gouv.fr/pdf/2016/08/cir_41219.pdf
4. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014; 370:1879-1888.
5. Recommandations AFEF sur la prise en charge des hépatites virales C http://www.afef.asso.fr/ckfinder/userfiles/files/recommandations-textes-officiels/Recoavril2016.pdf
6. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2016, http://dx.doi.org/10.1016/j.
7. The AASLD Meeting Boston November 2016. Hepatology 2016 64,
8. ObEpi.http://www.roche.fr/home/recherche/domaines_therapeutiques/cardio_metabolisme/enquete_nationale_obepi_2012.html ou http://www.lemonde.fr/vous/article/2012/10/16/les-donnees-sur-l-obesite-et-le-surpoids-en-france_1775950_3238.html
9. Neuschwander-Tetri BA. Hepatic lipotoxicity and the pathogenesis of non-alcoholic steatohepatitis: the central role of nontriglyceride fatty acid metabolites. Hepatology 2010;52:774-788
10. Nascimbeni F, Loria P, Ratziu V. Non–alcoholic fatty liver disease: diagnosis and investigations. Dig Dis Sci 2014 ;32 :586-596
11. Bedossa P, Consortium FP. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity and fibrosis (SAF) score in the evaluation of biopsies of non-alcoholic fatty liver disease. Hepatology 2014; 60: 565-575.
12. Ratziu V, Bellentani S, Cortez-Pinto H et al. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol 2010;53:372-384
13. Promrat K, Kleiner DE, Niemeier HM et al. Randomized controlled trial testing the effects of weight loss on non-alcoholic steatohepatitis. Hepatology 2010; 51:121-129.
14. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas S, Gonzalez-Fabian L, Friedman SL et al Weight Loss through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015; 149(2):367-378.
15. Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J et al. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. Gastroenterology 2015;149:379–388

16. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015; 385:956-65.

17. Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, Romero-Gomez M et al. Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-α and -δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. Gastroenterology. 2016 ; 150(5):1147-59

18. International Agency for research on Cancer. Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence worldwide in 2012. http://globocan.iarc.fr

19. Cowppli-Bony A, Uhry Z, Remontet L, Guizard AV, et al. Survie des personnes atteintes de cancer en France métropolitaine 1989-2013 - Partie 1□: tumeurs solides. 2016 Institut de veille sanitaires http://invs.santepubliquefrance.fr/fr../Publications-et-outils/Rapports-et-syntheses/Maladies-chroniques-et-traumatismes/2016/Survie-des-personnes-atteintes-de-cancer-en-France-metropolitaine-1989-2013-Partie-1-tumeurs-solides

20. Bruix J, Sherman M: Management of hepatocellular carcinoma. Hepatology 2005 ; 42 : 1208-36

21. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. European Association for Study of Liver. European Organization for Research and Treatment of Cancer. J Hepatol. 2012 Apr; 56(4):908-43.

22. Zhang BH, Yang BH, Tang ZY: Randomized controlled trial of screening for hepatocellular carcinoma. Cancer Res Clin Oncol 2004 ; 130 : 417-22

23. http://www.sfmu.org/fr/actualites/actualites-de-l-urgences/id-58162-cirrhose-virale-compensee-le-respect-du-depistage-semestriel-du-chc-ameliore-la-survie

24. Liovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF et al. Sorafenib in Advanced Hepatocellular Carcinoma N Engl J Med 2008; 359: 378-390

25. Bruix J, Merle P, Granito A, Huang YH , Bodoky G, Yokosuka et al. Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, randomized phase 3 RESORCE trial. ESMO GI 2016. Abstract LBA-03

26. El-Khoueiry LB, Sangro B, Cheung Yau T, Crocenzi TS, Welling TH, Yeo W et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): Interim analysis of the CheckMate-040 dose escalation study. ASCO 2016. Abstract 40

27. Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, et al. Unexpected early tumor recurrence in patients with Hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy. J Hepatol 2016; 65:719–726.]

28. ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol. 2016 Oct;65(4):734-40