00:17 -- 00:40 – Lorenza Rimassa
Hello, my name is Lorenza Rimassa. I am associate professor of medical oncology at Humanitas University and Humanitas research hospital in Milan, Italy. It is my great pleasure to be here with Alejandro Forner to summarize the abstracts presented during general session four therapy and clinical trials in 2021 at the ILCA annual conference 2021.

00:41 -- 01:05 – Alejandro Forner
Hi to everyone. I am Alejandro Forner from the BCLC group Hospital Clinic of Barcelona, and it is a great pleasure to stay here with Lorenza and Lorenza, I would like to know your comments regarding the abstract presented by Trojan and colleagues, and was entitled nivolumab in sorafenib-naïve and sorafenib-experienced patients with advanced HCC. And this is the five year follow up from the CheckMate 040 cohorts 1 and 2.

01:06 -- 02:46 – Lorenza Rimassa
Yes, Alejandro. We know that nivolumab monotherapy demonstrated a clinical activity in patients with advanced HCC previously treated or not previously treated with sorafenib based on the published results of the Check-Mate 040 study in this presentation, the authors report safety and efficacy data with five years of follow up. And they analyzed patients according to prior sorafenib treatment. They confirmed the efficacy and safety data already published with a longer follow up. In particular, the in sorafenib-naïve patients, objective response rate was 20% and median overall survival was 26.6 months. So very long survival, and in sorafenib-experienced patients, the overall response rate was 14% and the median overall survival was 15.2 months. The author evaluated also the efficacy of nivolumab, according to etiology (uninfected patients, HCV infected, HBV infected), and according to PDL-1 expression and the efficacy of nivolumab was confirmed regardless of the baseline characteristics. In terms of safety, grade 3 and 4 treatment-related adverse events were observed in a 33% of the patients previously untreated with sorafenib and in 21% of sorafenib-experienced patients, and treatment related adverse events leading to discontinuation occurred approximately in 3 to 6% of the patients.

02:47 -- 03:38 – Lorenza Rimassa
So, I think that this abstract is really important because it confirmed the efficacy and safety of nivolumab with a very long follow up, as I said, five years. And so it is something that is important for clinical practice, even if we don't have nivolumab, at least in European clinical practice and also as a single agent it is no longer available in the US, but I think this data confirmed, as I said, the efficacy safety profile of this drug, and Alejandro would you like to comment on the abstract about the third dose cohort and expansion phase of the phase 1 trial of ADP-A2AFP spear T-cells for patients with HCC or other cancer types expressing AFP presented by Bruno colleagues?
Yes Lorenza. In this study, the author described the data from the third dose cohort and expansion phase of an ongoing phase 1, first in human trial, evaluating the safety and antitumoral activity of autologus T cells genetically modified to target AFP expression or secreting tumors in the context of specific HLA expression in patients with HCC or other cancer types that express AFP. In this cohort, the authors included 10 patients and the treatment was really very well tolerated, just only the common side effects. They also reported leukopenia, neutropenia lymphopenia, increase of transaminases, pyrexia and thrombocytopenia. And just only in two patients reported a total of three treatment-related serious adverse events that included cytokine release syndrome grade 1, infusion related reaction grade 2, and just only neutropenia grade 3. Regarding the tumor response from 10 patients, one experience a complete response, four stable disease, and the complete response was associated with a rapid and sustained decrease of the AFP levels.

Also 20% of patients, two patients, have shown durable stable disease, and three patients have shown greater than 75% of decrease on AFP. Accordingly, it seems that this study demonstrates good safety profile of this treatment approach, and the authors suggest that we have to follow and to continue with the investigation. And this is all that we wanted to comment, and Lorenza, I would like to know your opinion regarding the paper presented by David Pinto, that was entitled treatment related toxicity and improved outcome with immune checkpoint inhibitors in patients with HCC.

Yes Alejandro. We know that the development of a treatment related adverse event correlates clinical outcomes in multiple studies of patients receiving immune checkpoint inhibitors. But this relationship is a still undefining in patients with HCC. And in this presentation, the authors reported the results of a retrospective international multicenter study, including 357 patients, with the aim to assess the relationship between clinically significant treatment related adverse events defined as grade higher than 2 treatment-related adverse events. And to define that if this adverse events correlate with the prognosis in HCC. And subsequently the authors validated the results in a separate cohort of 406 patients receiving ICI therapy in international clinical trials submitted to the US FDA in support of marketing applications. And the authors demonstrated the correlation, so the development of a clinically significant treatment-related adverse event was associated with a longer overall survival and progression free survival, even after adjusting for baseline characteristics and steroid therapy.

And also the adverse events correlate not only with overall survival and progression free survival, but also with the overall response rate. And this association was confirmed in the FDA cohort and also confirmed in a landmark and adjusted analysis. So, in conclusion, the development of a clinical significant treatment related adverse events may correlate with the response and survival in patients with HCC receiving ICI and prospective studies aimed at better understanding this relationship are warranted to identify predictive biomarkers of toxicity and response. So I think these are very interesting data that should be prospectively confirmed. And Alejandro, there is another abstract that is entitled tailored approach for the treatment of HCC within Milan criteria developed on advanced fibrosis or cirrhosis by multibipolar radiofrequency ablation or liver resection. This is a retrospective, very large retrospective French study. And would you like to summarize or comment on this?

Yes, this is a multicenter retrospective analysis that the authors included 620 patient treated with multibipolar radiofrequency and 440 HCC treated with liver resection. In most cases, the tumor was
uninodular, and in most cases, the patients had a cirrhosis, and as expected, the patients treated with RFA were older and had worse liver function compared with those that were treated with liver resection, and after adjustments in the analysis, the overall survival, the recurrence free survival was significantly superior in patient treated with liver resection compared with frequency, but without statistical differences in terms of transplantation free survival. As expected, the morbidity and the mortality were lower after radiofrequency. The authors tried to subanalyze the data. And for instance, the main conclusion that had the authors was that for unique tumors, less than 3 cm and for multinodular tumors, the outcome were identical with radiofrequency or surgery. However, in patients with single tumors between three and five centimeter, the outcome, according to the overall survival and recurrence-free survival was a superior after liver resection.

09:27 --> 10:30 – Alejandro Forner

Also, additional data was that the tumors that were located in, in the left lobe had a better survival with liver resection. And finally, and this is a very interesting finding, the overall survival benefit was obvious when the patients were resected with laparoscopic approach. However, the difference were not there when the, resection was done in an open laparotomy. Accordingly, the authors consider that we may tailor the therapy according to some tumour characteristics like the size or the localization, or the number of nodules, but also to the ability to perform an laparoscopic resection approach. And this is everything I wanted to comment, but Lorenza, I would like to know your comments or your opinion regarding the paper reported by Dr. Lim colleagues that they explored regorafenib in patients with unresectable HCC in the routine clinical practice; Updated interim analysis of the prospective observational REFINE trial.

10:31 --> 11:43 – Lorenza Rimassa

Yes, this is an updated analysis, and as you all know, a previous interim analysis of the first 500 patients enrolled in the REFINE study, that is a prospective observational multicenter study of regorafenib in unresectable HCC in a real world setting showed that this trial had more viral patient population compared with the phase 3 RESOURCE trial as expected. And importantly, in this presentation, the authors report an interim analysis of all patients enrolled in REFINE, and all patients are 1031 patients, large number of patients. And 1008 were available for analysis. Baseline characteristics were the baseline characteristics of patients that we see every day in the clinic. So most of patients were male, were BCLC C, CHILD-PUGH A if we decide to treat them, and ECOG-performance status 0-1, and had received the one prior line of systemic therapy in most of cases, sorafenib, but importantly, this trial included also patients from Asia, and in particular, 55% of patients were from Asia.

11:44 --> 13:18 – Lorenza Rimassa

So we had both Eastern and Western patients included in this trial among the other baseline characteristics, approximately 60% of the patients had extrahepatic spread or metastasis, and 34% had vascular invasion. Less than 50% of the patients, 47%, started sorafenib at the approved dose over 160 milligrams. 91% of the patients experienced treatment-emergent, adverse events, and 44% treatment-emergent adverse events leading to those modification. The most frequently reported treatment-emergent adverse events were, as expected, hand skin reaction diarrhea, fatigue, decreased appetite, abdominal pain, hypertension, and asthenia. Overall survival was 12.9 months, and median progression free survival was 3.8 months. So, in conclusion, the authors concluded, and I totally agree, that the results of this interim analysis, which included 1031 patients, are consistent with the results of the RESOURCE phase 3 trial and support the real world efficacy and safety of regorafenib in a broad population of patients with a unresectable HCC. Alejandro, there is another important abstract entitled systematic review and metaanalysis of randomized control trials: Is etiology relevant for immunotherapies presented by Philipp Haber.
13:19 --> 14:43 – Alejandro Forner

Yes, Lorenza in this presentation, the authors report results of a systematic review and analysis of 49 high quality phase 3 randomized trials conducted in HCC across the disease stage during the last 18 years. And the aim was to check the relationship between etiology and outcome after systemic therapies with either tyrosin kinase inhibitors, antiangiogenic agents, or immune checkpoint inhibitor therapy. The metaanalysis including eight trials with 3,739 patients revealed that immune checkpoint inhibitor therapy is significantly more effective in patient with viral hepatitis compared with non-viral related HCC. However, there were no differences related to etiology when the patients were treated with tyrosin kinase inhibitors or anti PDGF antiangiogenic agents, and the conclusion of the authors was that this results should be taking into account when interpreting the immune checkpoint inhibitor data in HCC, and probably we have to keep in mind this information for designing future clinical trials in this field. And this is a study that provides very interesting information and will have impact in the trial design, and in the data interpretation of the new trials that are ongoing.

14:44 --> 14:46 – Lorenza Rimassa

Thank Alejandro and thank you for listening.