2019 Emerging Topic Conference:

ADVANCES IN HCC THERAPIES AND TRIAL DESIGN

March 22–23, 2019
Atlanta, GA

Program Chairs:
Josep M. Llovet, MD, FAASLD
Lewis R. Roberts, MBChB, PhD, FAASLD

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Schedule-at-a-Glance and Meeting Locations

Wi-Fi Network: WESTIN-MEETING

Wi-Fi Password: AASLD19

Friday, March 22, 2019

6:30 AM – 4:15 PM	Registration	GRAND BALLROOM PREFUNCTION
7 AM – 8 AM	Breakfast	GRAND BALLROOM C
8 AM – 4:15 PM	General Session	GRAND BALLROOM AB
9:40 AM – 10 AM	Break	GRAND BALLROOM PREFUNCTION
11:45 AM – 12:45 PM	Lunch	GRAND BALLROOM C
2:15 PM – 2:30 PM	Break	GRAND BALLROOM PREFUNCTION

Saturday, March 23, 2019

6:30 AM – 11:30 AM	Registration	GRAND BALLROOM PREFUNCTION
7 AM – 8 AM	Breakfast	GRAND BALLROOM C
8 AM – 11:30 AM	General Session	GRAND BALLROOM AB
9:20 AM – 9:40 AM	Break	GRAND BALLROOM PREFUNCTION

– Notice –

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TABLE OF CONTENTS

General Information.....1
Disclosures…….....2
Conference Agenda…….....7
Speaker Summaries ……..10
Oral Abstract Summaries…….....49

Current HCC Molecular Classification
David Wheeler, PhD ……..…….11

Clinical Trial Designs Incorporating Predictive Biomarkers
Sumithra J. Mandrekar, PhD ……..……..…….13

Design and End-point Considerations in HCC Trials
Timothy Meyer, MD, PhD ……..….15

Summary of AASLD Guidelines on Management of HCC
Jorge A. Marrero, MD.....17

Design and End-Points in Trials for HCC - Neo-Adjuvant and Adjuvant Trials
Peter R. Galle, MD ……..……..….19

Next Steps in Intermediate Stage HCC
Riad Salem, MD ……..…..20

Advanced HCC, First, Second Line and Beyond
Josep M. Llovet, MD, FAASLD ……..…21

Radiologic Assessment of Response
Riccardo Lencioni, MD ……..24

Checkpoint Inhibitors and Related Strategies
Anthony B. El-Khouiery, MD ……..27

Oncolytic and Immunovirotherapy
Mitesh Borad, MD ……..…….29

Is there a Role for CAR-T and Cell Therapies in HCC?
Tim Greten, MD ……..……..…….30

Design of Clinical Trials in the Setting of Liver Transplantation
Myron E. Schwartz, MD ……..……..….32

Recent Results from Phase II-III Studies Testing SBRT (Stereotactic Body Radiation)
Laura Dawson, MD, FRCPC ……..….33

Tumor Biopsy in Trials for Advanced HCC
Lorenza Rimassa, MD ……..……..…….35

What Really Matters: Optimizing Quality of Life
Neehar Parikh, MD, MS ……..……..……..….38

Side Effect Response in Assessing Efficacy
Maria Reig, MD ……41

Biomarker Response in Assessing Efficacy
Richard Finn, MD ……44

Liquid Biopsy: Diagnosis, Prognosis and Prediction
Augusto Villanueva, MD, PhD ……45

The View from Industry
Gerold Meinhardt, MD ……47

Challenges in Trial Design in HCC and How to Solve Them.
Andrew X. Zhu, MD, PhD ……48

2019 Emerging Topic Conference
Advances in HCC Therapies and Trial Design
March 22 – 23, 2019
The Westin Buckhead Atlanta
Atlanta, GA

Program Chairs**:** Josep M. Llovet, MD, PhD, FAASLD and Lewis R. Roberts, MBChB, PhD, FAASLD

Learning Objectives:
Upon completion of this activity, participants will be able to:

- Review novel strategies for biomarker based clinical trial designs and articulate new approaches including the role of tumor biopsies and circulating cell-free based assays in guiding therapeutic decision-making.
- Understand recent advances in integrated molecular classification of HCC and their application to improved treatment of HCC.
- Review recently approved molecular therapies and anticipated novel immune-based, cellular, and oncolytic virus therapies for HCC and effectively manage the common side effects of these therapies

This activity was planned in the context of the following ACGME/IOM/IPEC competencies: Patient Care and Procedural Skills, Medical Knowledge Practice-based Learning and Improvement, Systems-based Practice, Provide Patient-centered Care, Work in Interdisciplinary Teams, Roles/Responsibilities Interprofessional Communication, Apply Quality Improvement and Teams and Teamwork Utilize Informatics

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The American Association for the Study of Liver Diseases (AASLD) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. AASLD designates this live activity for a maximum of 9.00 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Maintenance of Certification (MOC)
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 9.00 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for granting ABIM MOC points.

CME Credits
Physicians and other health care professionals seeking 9.00 *AMA PRA Category 1 Credits*™ for this live continuing medical education activity must complete an evaluation by **Tuesday, April 23, 2019**. A link to the CME and MOC evaluation will be emailed to attendees after the conference.

Certificates will only be issued to those who complete an evaluation by the deadline. CME certificates will be emailed upon successful completion of the evaluation.

ABIM MOC Points
Physicians seeking ABIM MOC points must complete the CME evaluation and the MOC evaluation by **Tuesday, April 23, 2019**. Requests for MOC after this date will not be honored. The MOC evaluation is included in the CME evaluation that will be emailed to all attendees and will remain live until the deadline.

MOC points will be reported to the ABIM by the end of April 2019 for attendees who successfully complete the MOC evaluation.

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As an accredited provider, AASLD requires individuals involved in the planning of continuing medical education (CME) activities to disclose all financial relationships, including those of their spouse or partner, with a commercial interest within the past 12 months. A commercial interest is defined as any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. All conflicts of interest are resolved prior to participation.

Statement on off-label and investigational use: Speakers are asked to make a reasonable effort to identify during their presentation any discussion of off-label or investigative use or application of a product or device.

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Nothing to disclose

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Grant/Research Support: Merck

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Conference Agenda

Friday, March 22, 2019

7 am	**Breakfast**
8 am – 8:05 am	Introduction and Scope of the Emerging Topic Conference *Lewis R. Roberts, MBChB, PhD, FAASLD and* *Josep M. Llovet, MD, FAASLD*
Session I: Overview of End-Points and New Trial Designs in Cancer *Moderators: Lewis R. Roberts, MBChB, PhD, FAASLD and Timothy Meyer, MD, PhD*	
8:05 am – 8:25 am	Current HCC Molecular Classification *David Wheeler, PhD*
8:25 am – 8:45 am	Clinical Trial Designs Incorporating Predictive Biomarkers *Sumithra J. Mandrekar, PhD*
8:45 am – 9:05 am	Design and End-point Considerations in HCC Trials *Timothy Meyer, MD, PhD*
9:05 am – 9:25 am	Summary of AASLD Guidelines on Management of HCC *Jorge A. Marrero, MD*
9:25 am – 9:40 am	Panel Discussion/Q&A
9:40 am – 10 am	**Break**
Session II: Design and End-Points in Trials for HCC *Moderators: Josep M. Llovet, MD, FAASLD and Riccardo Lencioni, MD*	
10 am – 10:20 am	Design and End-Points in Trials for HCC - Neo-Adjuvant and Adjuvant Trials *Peter R. Galle, MD*
10:20 am – 10:40 am	Next Steps in Intermediate Stage HCC *Riad Salem, MD*
10:40 am – 11 am	Advanced HCC, First, Second Line and Beyond *Josep M. Llovet, MD, FAASLD*
11 am – 11:20 am	Radiologic Assessment of Response *Riccardo Lencioni, MD*
11:20 am – 11:40 am	Panel Discussion/Q&A
11:45 am – 12:45 pm	**Lunch**
Session III: Incorporating Immune Therapies into Trial Designs *Moderators: Anthony B. El-Khouiery, MD and Mitesh Borad, MD*	
12:45 pm – 1:05 pm	Checkpoint Inhibitors and Related Strategies *Anthony B. El-Khouiery, MD*
1:05 pm – 1:25 pm	Oncolytic and Immunovirotherapy *Mitesh Borad, MD*
1:25 pm – 1:45 pm	Is there a Role for CAR-T and Cell Therapies in HCC? *Tim Greten, MD*
1:45 pm – 2:15 pm	Panel Discussion / Q&A
2:15 pm – 2:30 pm	**Break**

Session IV: Emerging Topics in Trial Design *Moderators: Tim Greten, MD and Myron E. Schwartz, MD*	
2:30 pm – 2:50 pm	Design of Clinical Trials in the Setting of Liver Transplantation *Myron E. Schwartz, MD*
2:50 pm – 3:10 pm	Recent Results from Phase II-III Studies Testing SBRT (Stereotactic Body Radiation) *Laura Dawson, MD, FRCPC*
3:10 pm – 3:30 pm	Tumor Biopsy in Trials for Advanced HCC *Lorenza Rimassa, MD*
3:30 pm – 3:50 pm	What Really Matters: Optimizing Quality of Life *Neehar Parikh, MD, MS*
3:50 pm – 4:15 pm	Panel Discussion/Q&A

Saturday, March 23, 2019

7:00 am	**Breakfast**
Session V: Assessing Predictions of Response and Therapies *Moderators: Richard Finn, MD and Maria Reig, MD*	
8 am – 8:20 am	Side Effect Response in Assessing Efficacy *Maria Reig, MD*
8:20 am – 8:40 am	Biomarker Response in Assessing Efficacy *Richard Finn, MD*
8:40 am – 9 am	Liquid Biopsy: Diagnosis, Prognosis and Prediction *Augusto Villanueva, MD, PhD*
9 am – 9:20 am	Panel Discussion/Q&A
9:20 am – 9:40 am	**Break**
Session VI: Novel Concepts and Challenges *Moderators: Peter R. Galle, MD and Andrew X. Zhu, MD, PhD*	
9:40 am – 10 am	The View from Industry *Gerold Meinhardt, MD*
10 am – 10:20 am	Challenges in Trial Design in HCC and How to Solve Them *Andrew X. Zhu, MD, PhD*
10:20 am – 10:45 am	Panel Discussion/Q&A
10:45 am – 11 am	Abstract Presentation A MULTIDISCIPLINARY APPROACH FOR HCC RISK PREDICTION IN A DIVERSE CIRRHOTIC POPULATION UTILIZING ELASTOGRAPHY, IMAGING, CIRCULATING TUMOR CELLS AND GENOMICS *Emmanuel Thomas, MD, PhD, FAASLD*
11 am – 11:15 am	Abstract Presentation CHECKMATE-040: NIVOLUMAB (NIVO) IN PATIENTS (PTS) WITH ADVANCED HEPATOCELLULAR CARCINOMA (AHCC) AND CHILD-PUGH B (CPB) STATUS *Frank DeRosa, MD*
11:15 am – 11:30 am	Wrap-up *Lewis R. Roberts, MBChB, PhD, FAASLD*

11:30 am	**Adjourn**

SPEAKER SUMMARIES

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Current HCC Molecular Classification

Classifying hepatocellular carcinoma into clinically homogenous subgroups would be highly advantageous as a strategy for improving outcomes in this disease. In recent years, pathologic and histologic stratification has given way to molecular subtyping with somewhat improved correlation with outcomes but not definitive indications for therapy. This is partly due to the heterogeneity of cancer in general, and HCC in particular, which leads to variable results across different cohorts confounding the discovery of a robust classification system. Nevertheless, current clustering strategies have contributed important insights into the biology of the disease (1, 2, 3).

The Cancer Genome Atlas project used five genomic platforms to characterize molecularly the tumors of nearly 400 subjects and produce the most comprehensive catalogue of molecular variation in HCC to date (4). Using this data set we took the approach of clustering all data-types together at once using the 'iCluster' (5). This approach grouped patients into three clusters, with significantly differing survival. The survival outcomes of the iCluster groups were replicated across three independent studies.

Novel transcriptional classifications based on distinctive mutational features continue to yield insight into the biology of the disease that may lead to new therapeutic approaches (3,4). Rare mutation of IDH1 in HCC is associated with a stem-cell expression phenotype that can be identified in 5-10% of patients in each of five different HCC cohorts. The signature is much more common than the IDH1 mutation itself in HCC, and supports an underlying link of HCC to cholangiocarcinoma where IDH1 mutation is relatively more common (6).

Similarly mutation of TP53, which occurs in about a third of HCC tumors, was also shown to be associated with a transcriptional signature with stem-cell features (7). TP53 mutation is correlated with poor survival compared to the wild-type in some HCC cohorts but not others. In the TCGA cohort we found a more robust signature of TP53 mutation, which, owing to non-mutational modes of TP53 inactivation, can also be observed in patients who are wild-type. The TP53 mutant transcriptional signature exhibits significant correlation with outcomes across multiple HCC cohorts. Interestingly this mutant signature includes the Patched D4 gene, which is down regulated, providing suggestive evidence for activation of hedgehog signaling in TP53 mutants in HCC (8). The hedgehog pathway plays a critical role in stem-cell maintenance and proliferation in adult tissues.

Limited studies in cell culture suggested a possible role for activation of hedgehog signaling in HCC (9) and the multiple ‘omic’ platforms of TCGA lend support to this notion. In addition to Patched down-regulation, transcription of hedgehog interacting protein is frequently inactivated by methylation; whereas Gli2, the proximal transcriptional activator of the hedgehog program, was observed to be dramatically up-regulated by an integration of HBV. In cancers such as medulloblastoma and basal cell carcinoma where hedgehog signaling plays an established role, components of the pathway are mutated. Thus, activation of the pathway in HCC is mechanistically very different from other cancers and may be under-appreciated as a result.

These results suggest that hedgehog signaling may play an important role in as many as one third of patients.

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1. Hoshida, Y, et al. Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. Cancer Res 69, 7385-7392 (2009).
2. Kim, S., et al. Sixty-five gene-based risk score classifier predicts overall survival in hepatocellular carcinoma. Hepatology 55, 1443-1452 (2012).
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9. Zheng, X et al. Role of the Hedgehog pathway in hepatocellular carcinoma (review). Oncol. Rep. 30, 2020–2026 (2013).ale for targeting SHH instead.

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Clinical Trial Designs Incorporating Predictive Biomarkers

Clinical trial design strategies have evolved as a means to accelerate the drug development process so that the right therapies can be delivered to the right patients. Predictive biomarker validation, both in an initial (i.e., phase II) and in a definitive (i.e., phase III) setting, is complex and requires the same level of evidence (for definitive validation) as is needed to adopt a new therapeutic intervention [1, 2]. This implies that a predictive marker validation is prospective in nature, and the obvious strategy is to conduct an appropriately designed prospective randomized controlled trial (RCT). Several designs have been proposed and utilized in the field of cancer biomarkers for the prospective validation of predictive markers [1, 2]. Briefly, these designs can be classified as A) Enrichment Designs; B) All-Comers Designs, which are further classified as Hybrid Designs, Marker by Treatment Interaction Designs or Sequential Testing Strategy Designs; and C) Adaptive Analysis Designs. The choice of a biomarker design depends on the study objectives, strength of preliminary evidence, assay performance, marker prevalence, and assay turnaround times.

Basket, umbrella, and adaptive enrichment strategies represent a class of novel designs for testing targeted therapeutics in oncology. Umbrella trials include a central infrastructure for screening and identification of patients, and focus on a single tumor type or histology with multiple sub trials, each testing a targeted therapy within a molecularly defined subset. These trials may include phase II or phase II/III trials, wherein the individual marker-specific sub-trials or cohorts may be either single-arm studies of paired targeted agents, or randomized studies comparing targeted agents versus placebo or standard of care [4]. Basket trial designs offer the possibility to include multiple molecularly defined subpopulations, often across histology or tumor types, but included in one cohesive design to evaluate the targeted therapy in question. They are typically early stage, single-arm, phase II, proof-of-concept trials where in each basket or cohort is itself a single-arm trial studying a preliminary target-response hypothesis. Such cohorts are generally small (about 20-30 patients) and only powered to detect strong signals of activity meant to motivate further study in a randomized context. Sometime adverse event profile is a key secondary endpoint in these sub-studies where drug tolerability is not yet well understood [4].

This talk will aim to discuss the fundamentals of these design strategies, the underlying framework, and the logistics of implementation, using case studies and examples such as trials from the National Cancer Institute's precision medicine initiative trials (NCI- MATCH, and ALCHEMIST) [5, 6].

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Design and End-point Considerations in HCC Trials

The initial, single-arm phase II trial of sorafenib for HCC demonstrated a low response rate by conventional RECIST criteria, but drug activity was suggested by a reduction in tumor arterialization and delay in radiological progression[1]. The subsequent phase III SHARP trial confirmed that sorafenib delayed progression and improved survival despite the low response rate[2]. Consequently, sorafenib became the first drug to be approved for advanced HCC and the SHARP trial established some important principals for trial design which were enshrined in a guideline published by an international panel of experts in 2008[3]. Time to progression (TTP) was recommended as the endpoint for randomized phase II trials and overall survival (OS) as the primary endpoint for phase three trials. A modification of RECIST (mRECIST) was proposed based on arterialized tumor diameter and mRECIST was further defined in a subsequent publication[4]. The composite endpoint, progression free survival (PFS) was discouraged because of concerns that death from liver disease was a confounder. One of the most important recommendations was that trial patients should have well compensated liver disease as defined by Child Pugh A class, and this has largely obviated some of the original concerns about PFS.

The therapeutic landscaped has been transformed in the past 10 years and whilst there have been many failed trials, there have been notable successes resulting in FDA approval of five new agents, four of which are in second-line, post-sorafenib. Given the wealth of data that has accrued from these trials, it is timely to revisit the guidelines for the design of clinical trials in HCC. The first observation is that the original guidelines have been variably adopted; of 17 phase three trials of systemic therapy published since 2008, RECIST was reported in 14, mRECIST in four and only two reported both. TTP was reported in 14, PFS in 12 and both in nine. In those studies that report both RECIST and mRECIST[5,6], the response rates have been higher for mRECIST but there is no evidence that mRECIST is a superior surrogate for survival compared to RECIST. Data from the BRISK PS study support the role of mRECIST but there is no comparison with RECIST[7]. The only study to date that directly compared mRECIST with RECIST was an analysis of combined data from two randomized phase II trials of sorafenib versus nintedanib[8]. This demonstrated that response by both criteria was an independent predictor of survival outcome and no advantage for the use of mRECIST was demonstrated. The reproducibility of mRECIST has also been questioned by the significant discrepancy between investigator and central review reported in the REFLECT trial in which the partial response rate for lenvatinib according to mRECIST was 23% by investigator and 38% by central review[6]. The reliability of response as a surrogate for survival benefit is also questioned by the fact that the overall response rate for lenvatinib by mRECIST was 40.6% compared with 12.4% for sorafenib, yet despite the dramatic improvement in response, lenvatinib was not superior for survival. Finally, in recent studies incorporating PD-1/PD-L1 inhibitors, the difference between mRECIST and RECIST is negligible[9] and response by RECIST was very clearly associated with extraordinary survival benefit in patients treated with nivolumab. In sum, the case for mRECIST in favor of RECIST has yet to be made and more data is required to define the role of mRECIST.

The approval of second line therapies has improved the survival for patients with advanced disease but creates challenges for trial design. Overall survival as an endpoint now demands larger trials with longer follow-up both of which impact on cost. Moreover the use of second and third line agents may confound the outcome from first line trials. Surrogate markers for

survival provide a potential means to increase the speed and lower the cost of drug approval. The initial enthusiasm for TTP has been tempered by the observation that both BRISK-PS and REACH achieved a HR for TTP of 0.56 and 0.59 yet both failed to meet their primary OS endpoint[10,11]. Meanwhile the original concerns for PFS have proved unfounded in the presence of appropriate selection criteria and for many investigators, the inclusion of death as part of the composite endpoint is viewed as extremely important. In fact the correlation between PFS and TTP is remarkably high and all of the five trials that met their superior survival endpoint had a HR for TTP or PFS which was less than 6. By contrast, all trials that missed this endpoint had a PFS of >6. Whilst this suggests a potential threshold for surrogacy in superiority trials, we do not have such data for non-inferiority trials nor for those including checkpoint inhibitors.

In summary, RECIST should continue to be reported as a standard response criterion while mRECIST needs further evaluation. Overall survival remains the most robust endpoint for phase III trials but the possibility of PFS as a surrogate endpoint is worthy of further consideration.

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Summary of the AASLD Guidelines on Management of Hepatocellular Carcinoma

The American Association for the Study of Liver Diseases (AASLD) commission an update on Guidelines for the Management of Hepatocellular Carcinoma (HCC). Unlike previous AASLD practice guidelines, this guideline was developed in compliance with the Institute of Medicine standards for trustworthy practice guidelines and uses the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach (1). Multiple systematic reviews of the literature were conducted to support the recommendations in this practice guideline. The guideline developers from the AASLD identified key questions that physicians are faced with frequently in the evaluation and management of patients with HCC. The questions pertaining to management were:

1. **Should adults with Child class A cirrhosis and early stage HCC (T1 or T2) be treated with resection or loco-regional therapy?**

2. **Should adults with cirrhosis and HCC that has been resected or ablated successfully undergo adjuvant therapy or not?**

3. **Should adults with cirrhosis awaiting liver transplantation and HCC (T1) be treated or undergo observation?**

4. **Should adults with cirrhosis awaiting liver transplantation and HCC (T2) undergo transplant alone or transplant with bridging therapy while waiting?**

5. **Should adults with cirrhosis awaiting liver transplantation and HCC beyond Milan criteria (T3) be transplanted without downstaging or be transplanted following downstaging to within Milan criteria?**

6. **Should adults with cirrhosis and HCC (T2 or T3, no vascular involvement) not candidates for resection or transplantation be treated with transarterial chemoembolization, transarterial radioembolization, or external radiation?**

7. **Should adults with Childs A/B cirrhosis and advanced HCC with macrovascular invasion be treated with systemic or locoregional therapies?**

8. **Should adults with Childs A/B cirrhosis and advanced HCC with metastatic disease be treated with systemic or locoregional therapies?**

Importantly, AASLD recommend to develop a Guidance document on HCC (2). This document provides a data-supported approach to the diagnosis, staging, and treatment of patients diagnosed with hepatocellular carcinoma HCC. A guidance document is different from a guideline. Guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE). A guidance document is developed by a panel of experts in the topic, and guidance statements, not

recommendations, are put forward to help clinicians understand and implement the most recent evidence.

In this conference a summary of the AASLD Guidelines and Guidance on the management of HCC will be provided.

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Design and End-Points in Trials for HCC - Neo-Adjuvant and Adjuvant Trials

Introduction

In patients with hepatocellular carcinoma (HCC) in very early and early stage disease (BCLC O/A) surgical intervention (resection, transplantation) and local ablation are performed in curative intent. However, tumor recurrence is common, reaching 70% at 5 years and impacting the long-term prognosis. Furthermore, underlying liver disease contributes to poor prognosis, both as a confounding factor and as “cancer-prone-field” with a high risk of de novo tumor development. In this setting (neo-) adjuvant treatments are needed and are conceivably useful to control minimal residual disease and/or act as chemo-preventive measure.

Resection/Ablation

Several strategies to prevent recurrence have been tested in proof-of-concept and in randomized studies. This includes treatment with interferon, chemotherapy, chemoembolisation, internal radiation and retinoids. No convincing benefit in terms of prevention of relapse was observed. A randomized controlled trial (RCT) testing sorafenib vs. placebo as adjuvant therapy after LR or ablation failed to demonstrate any positive effect. In view of these findings neoadjuvant or adjuvant therapies are not recommended by EASL because they have not been proven to improve the outcome of patients treated with resection (evidence high; recommendation strong) or local ablation.

Liver Transplantation

Liver transplantation (LT) candidates with HCC are inherently at risk of cancer progression while waiting. Several studies and meta-analyses on locoregional treatment have demonstrated significant advantages of neoadjuvant therapies in reducing the drop-out risk due to tumor progression. Neoadjuvant protocols are very heterogeneous among centers, but hierarchic use of ablation and transarterial therapies in various combinations is almost universal. RCT data are lacking and are unlikely to be produced in the future. In LT candidates with HCC, the use of pre-transplant (neoadjuvant) loco-regional therapies is recommended by EASL if feasible, as it reduces the risk of pre-LT drop-out and aims at lowering post-LT recurrence (evidence low; recommendation strong).

Future Development

Several small trials demonstrated the potential of adoptive immunotherapy to reduced HCC recurrence and to increase recurrence-free survival. This is of interest in light of future studies on modern therapies with immune checkpoint inhibitors, including the CTLA-4, PD-1, and PD-L1 inhibitory pathways and other checkpoint proteins. Several prospective studies in this setting are ongoing. Time to recurrence (TTR) and recurrence-free survival (RFS) are recommended as primary endpoints for HCC phase 2 and 3 studies assessing adjuvant therapies after resection or local ablation.

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Next Steps in Intermediate Stage HCC

In the last decade, there have been 2 major areas of scientific interest and investigation in locoregional therapies (LRTs), particularly intermediate stage. The first was prompted by the reporting of SHARP, where sorafenib was shown to improve survival in advanced disease SHARP. In particular, the observation of longer TTP in the sorafenib arm was postulated to be directly responsible for the improved survival observation. As a result, investigators sought to add sorafenib to intermediate stage HCC, hoping that survival would similarly be prolonged. Unfortunately, many studies testing this hypothesis failed to show that the combination with LRT would delay progression and/or improve survival. More recently, progression-free survival was positively shown to be improved with the combination; long-term survival outcomes are awaited. That study demonstrated longer time to un-embolizable progression, an attempt to match a study endpoint with actual clinical practice. Relative to radioembolization, a recent study reported no increase in survival compared to sorafenib arm when adding Y90; a subset of non-cirrhotics and non-alcohol related cirrhosis did demonstrate a hypothesis-generating improved survival. Other studies with Y90 have demonstrated its superiority compared to chemoembolization in early disease, and has been implemented as first-line arterial therapy in many centers. Currently, we await the reporting of STOP-HCC (NCT01556490), a 526 patient study comparing Y90 + sorafenib versus sorafenib. The second main area of interest includes the concepts of LRT (early/intermediate) and immunotherapy. Preclinical and early clinical studies have suggested the possibility of synergies between immunogenic locoregional treatments and systemic checkpoint inhibition. Ablative treatments with checkpoint inhibition have been shown to exhibit superior outcomes in murine models and human studies. T cell populations have also been shown to be altered following embolization. As a result of these early studies, there has been growing interest in checkpoint inhibitor immunotherapy for hepatocellular carcinoma, with CHECKMATE-040 and KEYNOTE-224 resulting in accelerated Federal Drug Administration approvals of nivolumab and pembrolizumab for HCC previously exposed to sorafenib. Clearly and reproducibly identifying the abscopal effect remains the panacea of combination locoregional and systemic immunotherapy. While case reports have described radiologic responses in lesions not treated by LRT in metastatic tumours, there are limited formal reports of this phenomenon in the HCC literature. There are currently several studies combining Y90 or other external radiotherapies with immunotherapies (NCT02837029). These will report in the upcoming years.

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Advanced HCC, First, Second Line and Beyond

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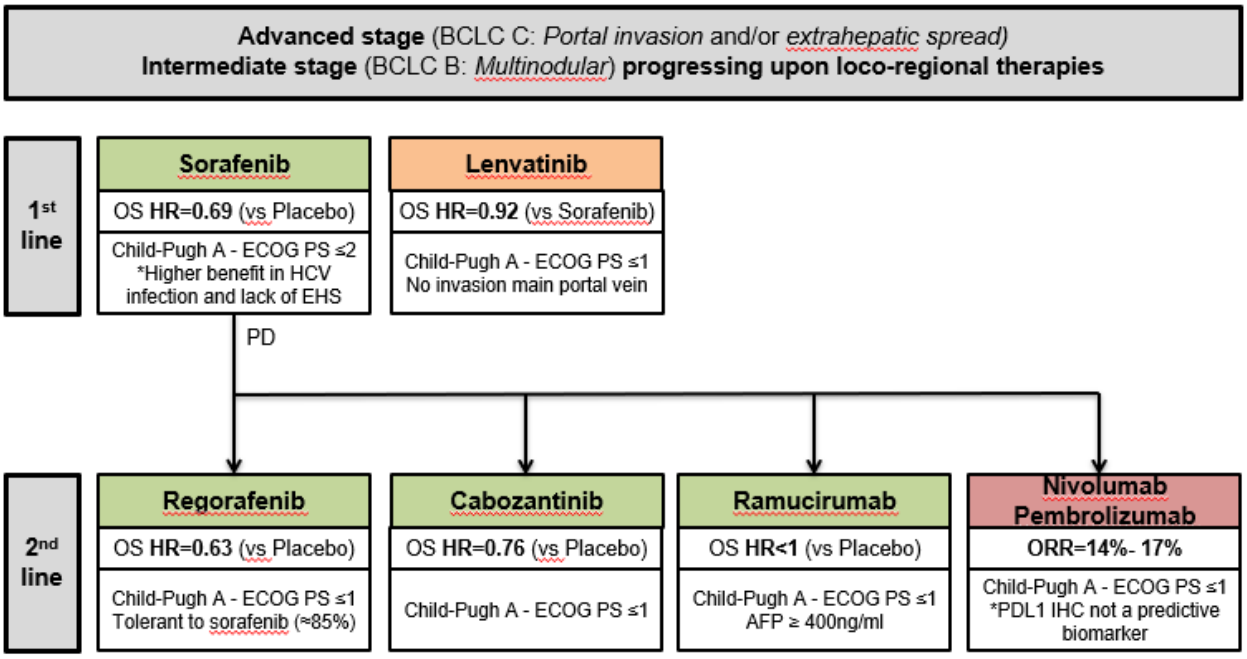
The incidence of hepatocellular carcinoma (HCC) is increasing globally and is estimated to surpass one million annual cases worldwide[1]. It is estimated that 50% of patients will receive systemic therapies at one time point of the natural course of the disease[2,3]. In 2008, the landmark SHARP trial assessing the multi-tyrosine kinase inhibitor sorafenib (VEGFRs, PDGFRs, RAF and KIT) was the first study to significantly expand survival for 3 months with manageable adverse events in patients with advanced HCC[4]. The success of this trial established contemporary concepts in trial design that have been implemented in phase III studies over the past decade.

After several failures with molecular therapies in phase III, regorafenib (VEGFRs, PDGFRs, KIT and Tie2) demonstrated survival benefits in second-line in patients that were tolerant to sorafenib and progressed after this front-line treatment, with an improvement in median overall survival from 7.8 months with placebo to 10.6 months [5]. Other phase III clinical trials have recently improved survival in second-line when compared to placebo: The CELESTIAL study, showing median OS of 10.2 months with cabozantinib (VEGFRs, MET and AXL)[6]; and the REACH-2 study, demonstrating median OS of 8.5 months with the monoclonal antibody ramucirumab (VEGFR2) in the specific population of patients with alpha-fetoprotein (AFP) higher than 400ng/ml[7], traditionally known for its poor prognosis[2]. Thereby, this becomes the first positive phase III trial for a biomarker-driven population in HCC. In parallel, lenvatinib (VEGFRs, FGFRs, RET, KIT and PDGFRA) has become an option for the first-line setting after the positive result of the non-inferiority REFLECT trial against sorafenib[8].

Finally, the FDA has granted accelerated approval to the PD1 immune checkpoint inhibitors nivolumab and pembrolizumab in the second-line setting as a result of promising objective response rates of 14% and 17% by RECIST, respectively, in phase II single arm trials[9,10]. The revolution of immune therapies that has changed the paradigm of treatment in oncology is now finding its way in HCC, with ongoing phase III studies in both first-line (NCT02576509, NCT03298451, NCT03434379) and second-line (NCT02702401) assessing PD1, PDL1 and CTLA4 inhibitors, alone or in combination with kinase inhibitors. In this regard, early clinical trials in advanced HCC are showing promising results with combinations of checkpoint inhibitors and targeted therapies, with ORR of 46% by mRECIST with Lenvatinib plus pembrolizumab (NCT03006926) and 27% by RECIST with atezolizumab plus bevacizumab (NCT02715531). In fact, the later combination was granted breakthrough therapy designation by the FDA. Overall, the results of these studies provide clinicians with an abundance of treatment options for the management of advanced HCC. Upcoming clinical trials should clarify the treatment

allocation process for the optimal use of current and future effective drugs in this still challenging disease.

Figure 1: Treatment strategy for advanced hepatocellular carcinoma.
Adapted from Llovet JM, et al. Nat Rev Clin Oncol 2018[3]. Drugs in green have positive results from phase III trials with a superiority design. Drugs in orange have positive results from phase III trials with a non-inferiority design. Drugs in red have received accelerated approval from the FDA on the basis of promising efficacy results in phase II trials.



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Radiologic Assessment of Response

The standard imaging approach for the assessment of tumor response in oncology is the use of RECIST. Nevertheless, the RECIST expert panel acknowledged that amendments to the general RECIST guideline could be needed for tumors presenting unique complexities and for the evaluation of anticancer therapies other than cytotoxic drugs. Both these issues are highly relevant for hepatocellular carcinoma (HCC):

1. The common association of HCC with an underlying chronic liver disease creates a very challenging scenario for imaging assessment, since pathologic and hemodynamic changes inherent in the cirrhotic process and extrahepatic manifestations of the chronic liver disease may mimic tumor progression.
2. Nonsurgical treatments for HCC, including loco-regional therapies and systemic targeted agents, often fail to induce sizeable tumor shrinkage despite the reported improvements in survival, frustrating attempts to capture tumor response by using standard RECIST metrics.

In 2010, modified RECIST (mRECIST) criteria for HCC were proposed (1), following the guidelines for the design of HCC clinical trials issued by a group of experts convened by the AASLD (2). In mRECIST for HCC, the first issue was addressed by producing specific amendments for the assessment of lymph nodes, ascites, portal vein thrombosis, and newly detected hepatic nodules, aimed at preventing overcalls of progressive disease. The second issue was addressed by introducing into the standard RECIST model the concept of “viable tumor” in the measurement and assessment of intrahepatic HCC lesions, with the intent to enable the detection of objective responses in patients who develop substantial intratumoral necrosis as a result of the treatment in the absence of significant changes in overall tumor diameter.

During the past decade, mRECIST for HCC has been used at a level far beyond expectations in HCC clinical research, collecting more than 1,400 citations in the scientific literature. Over the years, the proposed mRECIST refinements concerning the assessment of lymph nodes, ascites, portal vein thrombosis, and newly detected hepatic nodules, were progressively incorporated into radiology charters of HCC clinical trials, even when the criteria were formally named RECIST or RECIST 1.1 (3). This process had the benefit to homogenize radiologic interpretation of these complex findings across the criteria, improving consistency and reliability in the assessment of tumor progression. In fact, recent studies reported similar results for standard RECIST 1.1 and mRECIST in the assessment of progression-driven endpoints, such as PFS and TTP (4, 5). Currently, the main difference between standard RECIST and mRECIST is in the approach to the measurement and assessment of intrahepatic lesions, which primarily affects the ability to capture an objective response (OR). The use of the mRECIST concept of viable tumor has been shown to result in the identification of 2-3 times more responders than standard RECIST, not only in patients treated by loco-regional treatments but also in those receiving systemic therapies (5, 6).

The AASLD guidelines for the design of HCC clinical trials proposed to investigate TTP as potential surrogate endpoint of OS (2). However, data correlating TTP and OS has been controversial. A meta-analysis including 9 RCTs reported medium strength of correlation

between treatment effects on TTP and OS in patients with advanced HCC, and showed that the minimum TTP effect to predict a treatment effect on OS was a HR of 0.63 (7). Other analyses suggested that TTP may capture heterogeneous features, and that the pattern of tumor progression may be relevant to predict post-progression survival (8). The use of PFS was discouraged in the AASLD guidelines due to the competitive risk effect of dying due to the natural history of cirrhosis despite a relevant anti-tumoral benefit (2). However, a careful selection of patients with well-preserved liver function allows to minimize the impact of death unrelated to tumor progression.

Several clinical investigations have shown that OR measured by mRECIST predicts survival in patients treated by loco-regional therapies. A meta-analysis including 7 trials and 1,357 patients reported a HR for OS (responders versus non responders) of 0.39 (95% CI, 0.26–0.61; p<0.0001) (9). Recently, data from randomized trials confirmed that OR by mRECIST predicts survival in patients with advanced-stage HCC receiving systemic therapies (Table), and suggested that OR by mRECIST can be considered as a candidate surrogate endpoint of OS, although further research is needed to support this finding (6, 10, 11).

Table. OR by mRECIST and OS in Advanced-Stage HCC Patients Treated by Systemic Therapies: Analysis of RCTs.

	Lencioni et al. (10)	**Meyer et al. (6)**	**Kudo et al. (11)**
Agents	Brivanib vs Placebo	Nintedanib vs Sorafenib	Lenvatinib vs Sorafenib
Study Design	Phase 3 RCT, 2nd Line	Phase 2 RCT, 1st Line	Phase 3 RCT, 1st Line
No. of Subjects	226 (brivanib arm)	180 (both arms combined)	954 (both arms combined)
OR by mRECIST	11.5%	15.6%	16.6%
Median OS: R vs NR * (mos)	14.3 vs 9.4	16.7 vs 10.9	22.4 vs 11.4
HR (95% CI)	0.31 (0.16-0.60)	0.54 (0.33-0.88)	0.61 (0.49-0.76)
P value	< 0.001	0.0122	< 0.001

* R, responders (CR + PR). NR, non-responders (SD + PD).

With the advent of immune checkpoint inhibitors, the basic structure of the RECIST model might require further changes. In fact, response to immunotherapy can manifest after imaging features that meet the current RECIST criteria for progression. Immune-related response criteria have been developed, that address this issues by including a confirmation of progression, similar to the concept of confirmed response, and incorporate new lesions into the “total tumor burden”. Investigation of these approaches in the setting of HCC clinical trials is clearly a priority.

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Checkpoint Inhibitors and Related Strategies

The evaluation of immunotherapy to improve outcomes and survival of patients with hepatocellular carcinoma (HCC) is an area of active investigation. Evidence of anti-tumor immunity has been reported in patients with HCC; patients whose tumors harbor a pro-inflammatory infiltrate with a high CD4:CD8 ratio have a reduced risk of tumor recurrence following liver transplantation (1). Similarly, the presence of low intra-tumoral T-regulatory lymphocytes in combination with high intra-tumoral activated CD8+ cytotoxic T cells has been associated with improved disease-free survival and overall survival (2). These immunogenic effects are counteracted by several tolerance inducing mechanisms that suppress effective antitumor response. These mechanisms of immune tolerance include the production of immunosuppressive cytokines (IL-10, TGF-β, IDO, and others) (3), the presence of myeloid derived suppressor cells (MDSCs) (4), and the upregulation of immune checkpoints such as PD-L1 and CTLA-4 (5).

The evaluation of the clinical efficacy of checkpoint inhibitors began with a small phase 2 study that assessed the safety and anti-tumor activity of tremelimumab, an IgG2 anti-CTLA-4 monoclonal antibody in patients with hepatitis C related HCC with child pugh A or B liver cirrhosis (6). The most common treatment-related grade 3 or higher adverse events included AST and ALT elevation in 45% and 25% respectively, total bilirubin in 10%, followed by neutropenia, diarrhea and rash in 5% each (6). The objective response rate was 17.6% and 59% of patients had stable disease. This was followed by the evaluation of anti-PD-1 directed therapy in at least 3 separate phase I/II trials: nivolumab in checkmate 040, pembrolizumab in keynote 224, and camrelizumab (7-9). All three agents were shown to have a manageable safety profile in HCC with the adverse events being consistent with the safety profile in other solid tumors. In checkmate 040, nivolumab had an overall response rate of 20% by RECIST 1.1 across all study cohorts, and a response rate of 14.5% in patients with prior sorafenib exposure. The responses were seen across all cohorts independent of etiology. Of note, the responses were durable with a median duration of response of about 17 months. Similar efficacy was noted in keynote 224 with a response rate of 16.3% for pembrolizumab. Camrelizumab had an overall response rate of 13.8%. These preliminary findings are awaiting validation in two phase 3 trials: checkmate 459 which compares nivolumab to sorafenib in first line HCC treatment and keynote 240 which compares pembrolizumab to placebo in patients who had prior sorafenib therapy. In a recent press release about keynote 240, it was noted that the trial did not reach statistical significance in improving overall survival compared to placebo and additional details are awaited. Biomarkers for improved patient selection are needed and being actively evaluated.

Based on the preliminary signals of activity noted, there is a large number of ongoing combination trials. These include trials combining anti PD-1 or anti PD-L-1 therapy with tyrosine kinase inhibitors such as lenvatinib, sorafenib, regorefanib and cabozantinib or with the anti-VEGF antibody bevacizumab. In a phase Ib study of 26 patients, the confirmed ORR for pembrolizumab and lenvatinib was 27% by mRECIST (10). A phase Ib of atezolizumab and bevacizumab had an ORR of 27% by independent radiology review (11). Another area of active investigation is the combination of immune-oncology agents such as anti PD-1 or anti PD-L-1

with anti CTLA-4. Such combinations may hold the promise of higher response rates but it remains to be determined whether this will translate into clinically meaningful improvements in survival with manageable toxicities.

In conclusion, checkpoint directed therapies have shown consistent signals of early activity in HCC with a manageable safety profile. Results of ongoing phase 3 trials are awaited to verify whether there is an impact on survival with single agent anti-PD-1 therapy. The evaluation of several combinations involving checkpoint inhibitors is ongoing along with extensive biomarker research for improved patient selection. Several trials evaluating the potential role of checkpoint inhibitors in earlier stages of disease have been launched. These include a randomized phase 3 trial of nivolumab versus placebo as adjuvant therapy with patients with resected HCC and multiple smaller trials to assess the addition of checkpoint therapy to locoregional treatment such as ablation, trans-arterial chemoembolization and radio-embolization in patients with intermediate stage HCC.

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Oncolytic and Immunovirotherapy

Recombinant therapeutic viruses represent an emerging therapeutic platform in oncology. Vector design had initially focused on attenuating wild type viral pathogenicity and leveraging their oncolytic potential. More recent understanding of the mechanisms of action of these agents has centered around exploiting their immunomodulatory properties, and evaluating combination therapies with established immunotherapeutics such as immune checkpoint inhibitors. We will review the history of oncolytic viruses in cancer and pay particular attention to a number of key barriers in the field. These include: drug delivery, lack of tumor specificity, neutralization by anti-bodies and by activation of anti-viral pathways. Recombinant vesicular stomatitis viruses will be used as a model system for patients with liver cancers to describe pre-clinical evaluations to ascertain suitability towards advancement into human studies. We will also review trial design and translational assessment opportunities in the context of early phase human studies. We will review strategies to mitigate toxicity and biomarker development to identify patients at risk for toxicity, and also who might have highest potential for therapeutic benefit. Finally, we will explore opportunities in the current clinical paradigm for the treatment of patients with liver cancers, particular combinations with immune checkpoint inhibitors.

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Is There a Role for CAR-T and Cell Therapies in HCC?

Immunotherapy has gained a lot of interest in the context of hepatocellular carcinoma (HCC), which is the sixth most frequent neoplasm and the second leading cause of cancer-related deaths worldwide (1). HCC typically arises in the context of liver cirrhosis, which adds a certain level of complexity in terms of treatment. In the past few years a number of new drugs have been approved for patients with HCC including immune checkpoint inhibitors (2) and there is an increasing interest in immune based treatments for patients with HCC. Apart from immune checkpoint blockade cell-based therapies represent an interesting alternate option. As a matter of fact, one of the first positive cell-based trials in HCC was already published in 2000. A group from Japan tested the effect of adoptive immunotherapy in the adjuvant setting using autologous, in vitro activated lymphocytes and observed an increase in recurrence free survival (3). Most experience exist for the treatment with cytokine induced killer cells (CIK). CIK are characterized by the co-expression of CD3 and CD56. They can be generated by expanding human peripheral blood mononuclear cells in the presence of interferon- □□(IFN-□□, anti-CD3 and IL-2. Lee and colleagues from Seoul, demonstrated the efficacy of cytokine induced killer cells in the adjuvants setting in a randomized phase III study in 2015 (4). There are also currently a number of studies ongoing in which antigen-specific cell-based approaches are being tested in patients with HCC. Two different approaches are currently being developed for patients with HCC. Autologous T cells are either being transduced with a chimeric antigen receptor (CAR) or T cell receptor (TCR) (5). In either cases T cells recognize specific antigens to be expressed on tumors but not on healthy tissue. CARs enable highly specific targeting of antigen in an MHC-independent fashion. CARs are formed from a combination of antibody-derived or ligand- derived domains and TCR domains. In contrast TCR transduced T cells, which also recognize a specific antigenic peptide, are MHC restricted (6). Glypican 3 is a target frequently used for antigen specific responses in HCC (7). Preclinical data using a CAR T cells against Glypican 3 have been published (8) and clinical trials using Glypican 3 targeting CAR T cell approaches are under way. A few investigators also test AFP directed therapies (9), also one needs to point out that AFP can also be expressed on healthy tissue and it is not clear how tumor specific such therapy will be. In summary the field of cancer immunotherapy for HCC has never been as exciting as it is now. Apart from studies evaluating the efficacy immune checkpoint blockade, there are a number of cell-based therapies, which are currently being evaluated and novel cell-based therapies will hopefully be effective in this difficult to treat disease.

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Design of Clinical Trials in the Setting of Liver Transplantation

Key questions:

1. Candidate selection
    a. Who is too early? Single tumor, preserved liver function; salvage transplantation
    b. Who is too late? Extended criteria, downstaging
    c. How does effective HCV therapy alter the choice of transplant vs alternatives?
    d. Role of biomarkers
2. Donor source: living vs deceased
    a. Are there relevant biological differences?
    b. Is waiting good or bad?
3. Organ allocation
    a. How should patients with HCC be prioritized
        i. Among themselves- are some more urgent than others?
        ii. Vis-s-vis other candidates?
4. HCC treatment while awaiting transplant
    a. Does it improve results? Should it be done even if there is no need to wait?
    b. Can locoregional treatment cause tumor spread?
    c. Which modalities in which situations?
    d. Is there a role for systemic therapy? Immunotherapy?
    e. What is the target endpoint? Milan criteria? Complete necrosis?
5. Intraoperative factors
    a. Alternative techniques, e.g.caval preservation
    b. Role of blood loss / transfusion in promoting recurrence
6. Posttransplant immunosuppression
    a. Does routine immunosuppression (tacrolimus) promote HCC recurrence?
    b. Are there strategies, e.g everolimus, that can reduce risk of recurrence?
7. Treatment of HCC recurrence after transplant
    a. Existing date heavily affected by case selection bias
    b. Transplant patients routinely excluded from systemic therapy trials

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Recent Results from Phase II-III Studies Testing SBRT (Stereotactic Body Radiation)

Radiation treatment has been used to treat cancers since the early 20th century. Ionizing radiation therapy (most often delivered as high energy photons or protons) produces double strand DNA breaks directly in cancer cells from ionizations or through free radical generation, leading to mutations impairing DNA replication and mitotic cell death. The potential for radiation therapy to control HCC was documented as early as 1960 (1); however early investigations were limited to low dose whole liver radiation, due to technical challenges in imaging liver tumors, and delivering focused radiation therapy safely. Over the past few decades, an evolution in technical advances in imaging, computer-controlled radiation therapy planning, delivery and image guidance have enabled the safe delivery of ablative doses of conformal radiation therapy to HCC (2). The fear of radiation induced liver toxicity (which can now be avoided in the great majority of patients), resulted in a delay in investigations of radiation therapy to treat HCC, compared to other cancers where radiation therapy now has an established role.

Stereotactic body radiation therapy (SBRT) refers to the use of highly precise radiation therapy, delivered in fewer high dose radiation fractions (generally 1-5) with rapid fall off in dose around targets. SBRT is associated with additional mechanisms of cell kill, including microvascular dysfunction and tumor antigen specific immune response (3). Liver HCC SBRT presents unique challenges in tumor visualization/targeting and motion management throughout radiation. With modern technologies and careful patient selection (e.g. Child Pugh A or B7), SBRT may be used to treat HCC safely. While fiducial placement is used in some centers, non-invasive image guidance techniques are now being used in routine, further increasing the safety and feasibility for patients with comorbidities.

SBRT has generally been reserved for HCC patients with less favorable prognosis, with worse performance status, more comorbidities and larger, multifocal, advanced tumors, compared patients treated with other therapies. Compared to RFA, SBRT has the advantage of accessing hard-to-reach tumors, e.g. in peri-ampullary, peri-hilar or subcapsular locations. SBRT also has less limitations regarding tumor size. In contrast, tumors adjacent to the stomach or bowel are less well suited for SBRT due to potential risk of gastrointestinal track toxicity.

There are an increasing number of phase II studies of radiation therapy for HCC. It is now established that HCC is more sensitive to radiation than many other solid malignancies. SBRT has led to sustained local control in ~ 85% of patients 1- 3 years post treatment in patients with HCC of varying stage and volume (4). Radiation therapy has also been used to treat HCC with microvascular invasion in phase II studies (5) and multi-center registries (6), with ~85% one year local control and recanalization of the portal vein in the majority of patients. In a recent review of 128 patients with HCC and macrovascular invasion, median survival was 21.4 months in patients with distal portal vein involvement and 18.1 months in patients with main portal or IVC invasion (7). Liver SBRT has been shown to impact positively on patient's quality of life (8). Overall prognosis post SBRT is related to standard HCC, liver and patient prognostic factors including baseline liver function and performance status.

Two randomized studies of radiation therapy for HCC have been published. The first randomized study was an interim analysis of 69 patients with early stage HCC randomized to proton radiation therapy versus TACE in patients planned for liver transplant (9). Overall survival was the same in both arms (59% at 2 years). There were trends for improvement in 2 year local control and progression free survival (PFS) with radiation therapy versus TACE (local control 88% vs. 45%, p=0.06; 2 year PFS 48% vs. 31%, p=0.06 respectively). In transplanted patients, the complete pathological response rate was 25% post radiation therapy and 10% post TACE. A second randomized phase II trial randomized 90 patients with HCC with macroscopic vascular invasion to radiation therapy and TACE versus sorafenib alone. The experimental arm of radiation therapy and TACE was associated with improved PFS (12 week PFS 87% vs. 34%, p< 0.001) and overall survival (55 vs. 43 weeks, p=0.04) (10), compared to sorafenib, presenting a potential new combined modality treatment for HCC.

Randomized phase III trials of SBRT for HCC are needed. RTOG1112 is an open phase III study randomizing patients with HCC (up to 20 cm, unsuitable for or refractory to TACE) to sorafenib or SBRT followed by sorafenib (clintrial.gov NCT01730937). Other randomized trials comparing TACE and SBRT are ongoing. A particularly exciting area of research is the study of how SBRT may improve the efficacy of immunotherapy. Trials of SBRT and PD1 inhibitors are ongoing in HCC patients (clintrial.gov NCT03316872) to establish safety and best timing of radiation therapy with immunotherapy. The potential for SBRT to improve the efficacy of systemic response to immunotherapy in HCC patients is strong and worthy of investigation in phase III studies.

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Tumor Biopsy in Trials for Advanced HCC

The current landscape of treatment of advanced HCC is going to expand and become more articulated, based on the positive results of the phase 3 trials of targeted agents published in the last 2 years. Also, great expectations come from the ongoing phase 3 trials of checkpoint inhibitors, and new key signaling pathways, molecular mechanisms, and oncogenic addiction loops are being studied as further promising targets.

However, while prognostic and predictive molecular biomarkers have already been clinically validated and are used for other solid tumors in clinical practice, biomarker research has not yet produced conclusive results for HCC, and there is an urgent need to identify predictive molecular biomarkers, which allow to define, stratify, select different subgroups of patients. Therefore, it is intuitive that in clinical trials, collection of tumor samples should be mandatory to identify and validate prospectively prognostic and predictive biomarkers [1].

In fact, tumor biopsies may help identify the patient populations who would most benefit from target-driven treatments, in order to improve the clinical benefit rate and spare adverse events to patients who are not likely to benefit from the experimental drug. Also, analyzing tumor specimens is essential to improve the knowledge about the biology underpinning progression and treatment of HCC. Particularly, clarifying tumor biology may in turn lead to identify prognostic and predictive biomarkers [1]. Biological understanding of the treated population can be relevant even in trials where the target expression is not used as an entry criterion, providing key information to design subsequent target-selected studies. Of note, in the advanced setting, the risks associated with biopsy are minimal, seeding is rare, and its consequences are irrelevant given the overall dismal prognosis, while bleeding is extremely rare, especially if biopsy is conducted at expert centers [1]. In the METIV-HCC trial (see below) only four serious adverse events caused by bleeding were reported on more than 1,100 biopsies [2].

Recently, clinical trials have included exploratory biomarker endpoints and collected tumor tissue from enrolled patients, although, given the optional nature of tumor biopsies in almost all the trials, the number of collected samples and the achieved results have been of limited relevance. Furthermore, the adequacy of tumor samples represents a practical problem as frequently the provided material is not quantitatively and qualitatively adequate for running of comprehensive biological analyses [1]. In the first-line phase 3 REFLECT trial of lenvatinib versus sorafenib, out of 954 randomized patients, 119 tumor tissue samples were obtained, 61 samples were not tested due to lack of sufficient available tumor, and eventually only 58 samples could be tested [3,4]. Similarly, in the second-line phase 3 RESORCE trial of regorafenib, out of 573 randomized patients, 68 archival tumor samples were available, and 46 passed quality control [5,6].

A different story comes from two second-line phase 3 trials of tivantinib, a MET-inhibitor, in patients with high tumor MET expression [2,7]. In fact, based on the positive efficacy [8] and biomarker results [9] in MET-high patients in a previous randomized phase 2 study, which showed the prognostic and predictive role of MET expression, tivantinib was further tested in two phase 3 studies selecting only MET-high patients, one in western countries (METIV-HCC)

[2] and the other in Japan (JET-HCC) [7]. Importantly, METIV-HCC was the first phase 3 study in patients with advanced HCC to select the patient population on the basis of biomarker analysis at screening. Although the results of both trials were negative, these studies demonstrated the feasibility of doing integral tissue biomarker studies, which could be a requirement for enrollment in future trials to stratify patients and improve clinical outcomes. In METIV-HCC, 53% of the 1,125 tested tumor samples expressed high MET levels at baseline. Of note, this percentage was 35% in samples taken before sorafenib treatment, and 69% in tumor tissues collected after sorafenib. Also, 61% of MET-low patients with available paired biopsies converted to MET-high after sorafenib therapy, and a statistically significant correlation was demonstrated between MET-high status and previous sorafenib treatment [2]. These results highlight biomarker plasticity and the need to biopsy and collect tumor tissue allowing for molecular profiling of the disease at different time points, as tumors accumulate genetic alterations over time developing heterogeneity and drug resistance [10].

While only tivantinib has been tested in a tumor biomarker-selected patient population in phase 3 studies, other trials are collecting tumor tissue for biomarker analyses as secondary / exploratory endpoints, emphasizing the importance of tumor tissue biopsies for patients enrolled in clinical trials.

In conclusion, as more targeted therapies are developed, hopefully the biological characteristics of tumors, including specific molecular markers, will be evaluated in the therapeutic decision process for HCC patients as currently occurs for other tumor types. In the event that in the future any molecular classifiers will be found to have an impact in the clinical decision-making process, then routine biopsy should become part of the standard of care.

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What Really Matters: Optimizing Quality of Life

In its broadest sense, quality of life (QOL) can be defined as “an overall sense of well-being, including aspects of happiness and satisfaction with life as a whole.”(1) This definition, includes specific, measurable concepts such as mental well-being, physical functioning, and overall health status, which may be influenced by multiple factors, such as occupational and marital status.(1) QOL data serve as a complementary endpoint in hepatocellular carcinoma (HCC) clinical trials that can help contextualize medical outcomes such as survival, drug related adverse events, and medical morbidity. There is a clear relationship between the patient’s biological and physiological variables and their QOL, however several other factors may play a role including symptom status, functional status, and general health perceptions, which makes measurement of QOL a distinct outcome of importance.(2)

Quality of Life Measurement in Clinical Trials

Guidance from the National Cancer Institute and Food and Drug Administration have recommended inclusion of quality of life in clinical trial design and can be a central component of the drug approval process. QOL data can be a technically demanding endpoint to collect due to patient effort and time required to collect complete serial data, however careful planning for QOL measurement can yield vital information about the overall efficacy of a drug or intervention.(3) QOL in a clinical trial setting requires measurement at pre-specified clinically relevant time points and use of an appropriate instrument for measurement. This must be balanced by patient questionnaire fatigue (e.g. time to completion and number of assessments) that can limit compliance with data collection.

Timing of measurement in HCC trials generally should start prior to initiation of therapy (baseline assessment) and subsequent, longitudinal measurements coincide with treatment related milestones, such as assessment of disease progression. The most efficient methods of in clinic ascertainment of QOL is with electronic devices (i.e. tablets computers) while paper-based or post-visit QOL measurements for patients can lead to inefficiencies with data entry or lead to lower completion rates, respectively.(4)

Measurement Instruments

There are two main categories of quality of life instruments, generic and disease specific. Generic instruments, such as the SF-36 and EQ5D, are widely used and well validated, however fail to account disease specific symptoms. This may be particularly relevant in patient with HCC, who often have underlying cirrhosis that may uniquely impact their QOL. There are primarily two disease-specific quality of life instruments for patients with HCC/hepatobiliary malignancies:

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire HCC 18 (EORTC-QLQ HCC 18)(5)
- Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire (FACT-Hep)(6, 7)

Both scales have associated generic QOL measures (EORTC QLQ 30 and FACT-G) that are general administered with disease specific modules developed from patient interviews and

standardized methodology (item generation, item reduction, scale construction, and validity and reliability testing). The scales have been used in several contemporary clinical trials in HCC therapy, including the RESORCE(8) and REFLECT(9) studies.

Questionnaire completion rates is always the first step in analyzing quality of life as missing data can lead to significant bias and difficulty in interpreting the results. When analyzing QOL data there are two main approaches: analysis of longitudinal changes in individual patient QOL over time and between group differences in clinically meaningful changes in QOL from baseline. Individual patient changes can allow for understanding of temporal relationships related to clinically meaningful events during the trial (e.g. disease progression and adverse events). Clinically meaningful changes (minimally important difference) in QOL are critical to contextualizing if an observed difference is meaningful even if there is a statistical difference between comparison groups. Thresholds for minimally important differences are typically established using anchor-based methods or distribution based methods or some combination thereof.(10)

Summary

QOL is an important complementary endpoint when considering trial design and highly relevant in the context of HCC clinical trials given the varying adverse event profiles of many of the medications and interventions under investigation. Careful planning and integration of QOL measurement in clinical trial design with appropriate instruments allows for the highest likelihood of obtaining meaningful, interpretable QOL data. Future research into expansion of QOL measurement into routine clinical practice of HCC care is needed for better understanding of QOL in populations outside of clinical trials.

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Side Effect Response in Assessing Efficacy

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Historically, side effects (SE) were seen as a negative issue in the management of patients with cancer under chemotherapy due to the link between severe hematology and/or cardiology toxicity and risk of SE-related death. However, the incorporation of target therapies such as tyrosine kinase inhibitors or immunotherapy has modified the profile of SEs. Nowadays the development of specific SEs is associated with better outcome and opens up a new approach towards the impact of SEs on patient outcome. The absence of SEs however, does not mean that the treatment is not working. Thus, the SE response in assessing efficacy should be seen as an umbrella of multiples factors that should be analyzed simultaneously.

In the setting of hepatocellular carcinoma (HCC) patients under sorafenib treatment, Ponziani et al demonstrated that the development of SE ≥ grade II was associated with better overall survival (OS)[1]. Similarly, Iavarone et al. analyzed the OS according to the cause of sorafenib discontinuation[2] and as was expected, patients who discontinued due to tumor progression or liver decompensation presented worse OS. Thus, patients who discontinued due to sorafenib-related SEs presented longer OS than those patients who discontinued due to other causes.

SEs are evolutionary events and the longer the treatment the greater the risk of developing SEs. Thus, analyzing the SEs without establishing a specific time-point could lead to an overestimation of the positive impact of the SEs on patient outcome. For this reason, in 2014 we evaluated the impact of early adverse events appearing within the first 2 months of treatment and which were associated with sorafenib dose modification[3]. We analyzed 147 HCC sorafenib-treated patients and only the early dermatologic SEs (eDSE) were associated to better outcome. The median OS of patients with and without eDSEs were 18.2 and 10.1 respectively. Additionally, the time to progression (TTP) was also longer in patients who developed eDSEs (8.1 and 3.9, respectively). This data was externally validated by Branco et al[4] and the RESORCE trial (multicenter and randomized trials which compared regorafenib vs. placebo in second-line HCC treatment)[5]. Additionally, a recent meta-analysis[6], which included 2035 patients, showed that 1370 would be necessary to rule out the positive impact that was observed in that meta-analysis.

In addition, in a Spanish multicenter study that included 1119 HCC patients treated with sorafenib, 91.7% of patients who achieved complete radiological response (according to RECIST v1.1 criteria) presented eDSEs[7]. This information showed for the first time in HCC patients the link between outcome and SEs. Nevertheless, due to the retrospective nature of that study, at that time we only raised the hypothesis that the development of eDSEs could be related to a specific immune- profile that was triggered by sorafenib in a population with a specific make-up. This hypothesis was demonstrated in a prospective pilot cohort of 30 patients in which patients who developed eDSEs presented an increased number of T cytotoxic cells and Natural Killer cells in comparison with those who did not present these

SEs[8].

In this regard, PFS is presented as an alternative end-point to select the best drug when more than one drug may improve the OS of patients. However, PFS is defined as the time from randomization until objective tumor progression or death, whichever occurs first. In the REFLECT trial[9] (a multicenter, randomized and double blind trial which compared the impact of sorafenib and levantinib as a first line treatment in patients with HCC) the primary end-point was OS. TTP, progression free survival (PFS) and treatment duration (TD) were the secondary end-points but safety was not considered as an end-point of the trial. In this regard, the REFLECT[9] trial was the first positive trial after the SHARP[10] and Asia-Pacific[11] trial publications and demonstrated that both treatments improve OS in HCC patients. However, the median TTP, PFS and TD were longer in the lenvatinb treated patients than in the sorafenib patients. How do we explain the discrepancy between OS, PFS and TTP in the REFLECT trial? If sorafenib treated patients presented similar OS to lenvatinib treated patients but shorter TTP, PFS and TD this means that these patients are still alive despite developing tumor progression. In addition, the median TTP and PFS in the sorafenib arm were 3.7 months but in lenvatinib arm the median TTP was 8.9 months and PFS 7.4 months. This could mean that the PFS in the sorafenib arm was due to tumor progression but in the lenvatinib arm it was due to reasons other than tumor progression such as death. It is important to highlight that PFS was shorter than TTP in the lenvatinib arm. How do we interpret death before tumor progression? Could it be considered as a SE-related death? Is PFS due to death a predictor of safety profile? All these questions could be answered if we set aside dogmas and start using composite end-points, which include SEs. Unfortunately, the safety profile was not considered as an end-point in the REFLECT trial and the direct comparison between the arms is not reliable. Nevertheless, the lenvatinib arm presented 18% of severe drug-related SEs and 10% in the sorafenib arm. In addition, the rate of severe hand-foot reaction in the sorafenib arm seems to be higher than in the lenvatinib arm (11 % and 3%, respectively). Thus, if we combine the already known data regarding the outcome according to the eDSEs and the potential role of combined PFS due to death or tumor progression, we can analyze the current clinical trials from another perspective. However, we should consider the patients as a whole and the analysis also needs to consider the tumor burden evaluation and confounding factors such as genetic make-up and serum biomarkers. Finally, all these assumptions are also applicable to the second-line trials analysis.

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Biomarker Response in Assessing Efficacy

The NCI defines a biomarker as: “A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition”. The use of biomarkers have had a significant impact in cancer medicine as both prognostic and predictive markers. In HCC, many studies have identified various biomarkers that are associated with better or worse prognosis (i.e AFP). Unlike other cancers, the use of biomarkers to predict response to treatment have generally not been used. We did see negative data with the use of c-MET expression in the context of tivantinib and recently we saw positive data with the use of AFP to identify patients that respond to ramucirumab. These studies raise important challenges to biomarker development including assay development, validation, and incorporation into trial design. In addition, biomarkers can be assessed over the course of a study to evaluate the pharmacodynamics effects of a given agent. While these studies are not necessarily a strategy for registration they can inform the development of a given therapeutic by answering important questions in regards to mechanism of action and anti-tumor effects. In the lecture we will review these concepts and emerging data from clinical studies and how we can incorporate biomarkers in clinical research.

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Liquid Biopsy: Diagnosis, Prognosis and Prediction

The concept of “liquid biopsy” refers to the analysis of molecular components (e.g., nucleic acids, circulating tumor cells (CTC)) released by tumor cells to the bloodstream[1]. The presence of circulating tumor DNA (ctDNA) in plasma of cancer patients has been known for decades, but its application to address clinical problems significantly increased over the last 5 years. In 2016, the FDA approved the first diagnostic tool to detect druggable EGFR mutations in plasma of lung cancer patients, which underscores the clinical impact of this technology. Recently, a composite panel of blood markers including ctDNA sequencing (i.e. cancerSEEK), showed promising results for the diagnosis of various types of cancer[2]. Despite this study also included patients with hepatocellular carcinoma (HCC), only a few of them were at early stages. Thus, there are limited data on the performance of ctDNA analysis for the detection of early stage HCC. This is of particular relevance in HCC since, unlike most solid tumors, there is a well-defined population of patients at high risk of HCC development (i.e., cirrhotic patients), who benefit from surveillance programs and early diagnosis. Recent studies on mutation profiling[3] and methylation analysis of ctDNA[4] suggest that ctDNA could be a good source for novel early detection biomarkers in HCC.

Circulating tumor cells (CTCs) are frequently detected in patients with HCC and their number correlates with clinical outcomes. These are the cellular substrate of distant metastasis, despite that not all CTCs will ultimately originate a metastatic deposit. Most studies focused on the enumeration of CTCs using a small set of surface markers (e.g., EpCAM, ASGPR1, pan-Cytokeratin, etc.), but few have provided a thorough molecular characterization of CTCs. It is critical to obtain molecular data from CTCs in HCC as these patients are frequently diagnosed with imaging techniques, which limits access to tissue for biomarker studies. Recent studies have provided additional molecular information of CTCs: 1) the use of imaging flow cytometry (Imagestream) helped visualize CTCs and document their heterogeneity[5]; and 2) the application of RNA-based digital PCR has helped deriving CTC-specific gene signatures[6]. The use of single-cell RNA sequencing technologies has expanded the quantity of molecular information obtained from CTCs[7]. The application of these technologies to analyze CTCs helped revealed heterogeneity in signaling pathways in prostate cancer patients, which contributed to treatment failure. It also allowed the identification of known driver mutations in breast cancer.

When HCC patients are diagnosed at advanced stages, available treatment options offer a limited survival benefit. Despite recent advancements with new targeted therapies approved by the FDA, patients at advanced stages live less than 30 months on average. Two phase 2 single-arm clinical trials have shown promising results with the PD-1 inhibitors nivolumab[8] and pembrolizumab[9]. Response rate is approximately 18%, but more importantly, duration of response is significant with both drugs (i.e., more than 9 months in 50% of responders). This has spurred extensive research to identify tissue-based predictive biomarkers of response to these therapies. So far, PD-1 staining[8] and tumor mutational burden[10] have shown suboptimal predictive performance in HCC. There are few studies on the role of liquid biopsy to predict response to these therapies. However, considering the limited access to tissue biopsies in patients at advanced stages, liquid biopsy could have a major role as a novel source of predictive biomarkers in this setting. In summary, tumor cells release components to the bloodstream (DNA, RNA, CTCs), which can be isolated and analyzed. Analysis of ctDNA allows detecting tissue mutations, tracing minimal residual disease after resection

and facilitates molecular monitoring. Thus, liquid biopsy as emerged as promising and very convenient tool for biomarker development in HCC.

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The View from Industry

Syllabus summary not available at time of print

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Challenges in Trial Design in HCC and How to Solve Them

Recent development of molecularly targeted agents and immune checkpoint inhibitors in advanced hepatocellular carcinoma (HCC) has generated renewed interests in drug development in this disease. However, with the evolving treatment landscape, clinical trial design in HCC has encountered new challenges. The author will discuss some of the major challenges in HCC trials design including the use of surrogate endpoints (PFS or responses), how to optimize the stratification in trial design, and how to select the right population for clinical trial design in the adjuvant setting and advanced stage. In the era of personalized cancer medicine and the increased recognition of HCC heterogeneity, there is an unmet need for developing biomarkers for predicting survival and treatment response for HCC. Despite the latest progress on the identification of many tissue-based biomarkers and genomic signatures in predicting the recurrence and overall survival, there is a paucity of data how to apply these signature and biomarkers in clinical trials design in advanced HCC. The author will discuss the lasted efforts and challenges in this direction.

ORAL ABSTRACT PRESENTATIONS

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A MULTIDISCIPLINARY APPROACH FOR HCC RISK PREDICTION IN A DIVERSE CIRRHOTIC POPULATION UTILIZING ELASTOGRAPHY, IMAGING, CIRCULATING TUMOR CELLS AND GENOMICS

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Background: HCV and NASH induced HCC is increasing in the United States. Therefore, it is imperative that we understand the genetic and cellular based mechanisms underpinning the linkages between HCV/NASH and HCC and the impact of race/ethnicity on the development of this deadly tumor. The aims of our study were to assess changes in transient elastography (TE) and fibrosis-4 (FIB-4) score in a large cohort of patients and identify risk based on race/ethnicity. Patients were also stratified for HCC risk based on the Toronto HCC Risk Index (THRI), genomics, imaging data with inclusion of screening for circulating tumor cells.

Methods: Our cohort included 1,943 patients with liver disease, including HCV, HBV, NASH, etc., were assessed by Fibroscan and comparisons made with clinical parameters of liver disease. Approximately 750 patients had liver biopsies. Statistical analysis with Kruskal-Wallis and Chi-Square tests was carried out. Values reported are mean ± standard deviation. The estimated stage of liver fibrosis based on TE was categorized as F0-F2 (<9.4kpa), or F3 (9.5 – 12.4 Kpa), or F4/cirrhotics (TE >12.5 kpa).

Results: In our cohort, African Americans (AAs) had higher BMIs (27.8±5.2, p<0.01) and lower albumin levels (4.2±0.5 g/dl, p=0.01). Platelet (p=0.79) and AST values (p=0.17) were comparable between races; however, ALT was highest among non-Hispanic whites (67±68, p=0.02). TE measurement was highest in AAs and Hispanics (12.2±12 and 12.2±12 kPa, respectively) and lowest in non-Hispanic whites (12.2±12 kPa) (p<0.01), while FIB4 Index was not statistically different (p=0.23). Risk of developing HCC, as measured by THRI, was highest in AAs (234±65) and lowest in Hispanics (214±68, p<0.01). Stratifying by Hepatitis C (HCV) status, the majority of non-Hispanics had HCV, whereas most Hispanics had non-HCV liver disease (p<0.01). HCV positive patients were older (59±11 vs 54±14 years, p<0.01), had higher AST (60±71 vs 45±58, p<0.01), ALT (67±67 vs 55±75, p<0.01), THRI (238±64 vs 189±68, p<0.01), TE scores (12.4±11.6 vs 10.6±11.5 kPa, p<0.01), and FIB4 (3.0±3.2 vs 2.0±1.7, p<0.01), but lower BMI (26.4±4.5 vs 27.4±4.9, p<0.01), platelets (187.0±72 vs 204.1±74 109/L, p<0.01), and albumin (4.2±0.5 vs 4.4±2.3 g/dl, p<0.01).

Conclusion: Liver fibrosis stage, as determined by TE, increased with HCC risk as determined by THRI. THRI identified the subpopulation of African Americans as having generally greater risk of HCC, despite comparable platelet and FIB4 levels. Hispanics had similarly high TE scores as AAs, but lower risk of developing HCC. The patients who remain at risk for HCC will be further stratified for increased propensity to develop HCC utilizing

genomics, advanced imaging and screening for circulating tumor cells. These results suggest the need for enhanced investigation of key drivers of HCC, with particular attention to racial/ethnic disparities.

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Disclosure: Nothing to disclose.

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CHECKMATE-040: NIVOLUMAB (NIVO) IN PATIENTS (PTS) WITH ADVANCED HEPATOCELLULAR CARCINOMA (AHCC) AND CHILD-PUGH B (CPB) STATUS

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Background: Pts with aHCC and CPB liver status are often excluded from clinical trials of novel therapies due to their poor prognosis (Greten British J Cancer 2005). Historical overall survival (OS) for these pts when treated with sorafenib (SOR) has ranged ≈3–5 mo in retrospective or descriptive studies (Abou-Alfa Gastrointest Cancer Res 2011; Da Fonseca Mol Clin Oncol 2015; Pressiani Ann Oncol 2013; Chiu Cancer 2012); thus, novel treatment options are needed for these pts. The PD-1 inhibitor NIVO is approved in the US, Canada, and elsewhere, most recently Australia, for SOR-treated pts with aHCC based on results from CheckMate-040 (NCT01658878) (El-Khoueiry Lancet 2017). Here we report data from the CPB cohort of CheckMate-040, the first prospective study of immunotherapy in this pt group.

Methods: Pts with CPB (B7–B8) aHCC who were SOR-naïve (n=25) or -experienced (n=24) received NIVO 240 mg IV for 30 min Q2W until unacceptable toxicity or disease progression. Primary endpoints were objective response rate (ORR) (investigator assessed [INV], RECIST v1.1) and duration of response (DOR). Safety was assessed in all treated pts using NCI CTCAE v4.0.

Results: Of 49 analyzed pts, 28 (57.1%) had vascular invasion or extrahepatic spread. During a follow-up range of 6–18 mo, INV ORR was 10.2% with 5 pts responding; disease control rate (DCR) was 55.1%. Median (m) time to response was 2.7 mo and mDOR was 9.9 mo; 2 pts had ongoing responses at data cutoff. The mOS was 7.6 mo (mOS follow-up was 7.4 mo); mOS in SOR-naïve and -treated pts was 9.8 and 7.3 mo, respectively. Treatment-related adverse events (TRAEs) were reported in 25 (51%) pts; 4 (8.2%) pts had select hepatic TRAEs. TRAEs led to discontinuation in 2 pts (4.1%). NIVO safety profile in these pts appeared comparable to cohorts of pts with CPA aHCC. Comparison data for pts with CPA aHCC and extended follow-up for pts with CPB aHCC will be presented.

Conclusion: Encouraging DCR and durable responses were observed in pts with CPB aHCC treated with NIVO. AEs were manageable and did not lead to higher discontinuation compared with pts with CPA aHCC. NIVO showed promising efficacy and tolerability compared with

historical data, supporting further investigation.

Original publication by Kudo M, et al., ASCO Gastrointestinal Cancers Symposium 2019, abstract 327.

Disclosure: Nothing to disclose.

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