Northern California Society for Clinical Gastroenterology

NEWSLETTER

ISSUE NO. 10 | September 2022

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Dear Colleague,

The NCSCG Board and Meeting Planning Committee are proud to announce the 8th Annual NCSCG hybrid Liver Symposium, being held Saturday, January 21, 2023, both online and in-person at the Hotel Nia in Menlo Park, CA!

The symposium will provide a unique opportunity to receive a comprehensive update in chronic liver disease from nationally renowned faculty. The educational lectures at this symposium will focus on important advances presented at the annual American Association for the Study of Liver Disease (AASLD) Meeting and/or in recent publications. You will also have ample opportunity to interact with colleagues, our expert faculty members, and industry representatives.

As a NCSCG member you will receive:
20% discounted registration for the 2023 NCSCG Liver Symposium.
Discounted registrations for other 2023 events.

Sincerely,

The 2023 NCSCG Liver Planning Committee
Robert Wong, MD, MS; NCSCG Vice President
Mikhail Alper, PA-C; NCSCG APP Committee Member
Nghiem Ha, MD; NCSCG Lead Fellow
Allison Kwong, MD; Board Member
Marina Roytman, MD, FACP; Board Member
Kidist Yimam, MD; Board Member

CALL FOR ABSTRACTS AND CASE VIGNETTES

ABOUT

The Northern California Society for Clinical Gastroenterology (NCSCG) invites the submission of abstracts and case vignettes describing clinical, basic science, and/or psychosocial research in the fields of endoscopy, gastroenterology, gastrointestinal surgery, and hepatology. Our goal is to promote research among trainees in the field, stimulate collaboration, and foster the development of ideas for future studies. Authors may submit abstracts and case vignettes of completed work, work in progress, or work presented elsewhere within the past 12 months. All submissions will be peer reviewed, and all that meet the specifications below will be selected for an in person poster presentation.
If you don't have a printed poster from this year, or printing your poster is not financially feasible for this event, please let us know as these will be reviewed on a case by case basis.

WHO SHOULD SUBMIT?

Postgraduate trainees at all levels – including residents, fellows and advanced fellows, faculty members, practicing physicians and Advanced Practice Providers.
TOP THREE CHOSEN SUBMISSIONS WILL BE AWARDED A GIFT CARD.

ABSTRACT SUBMISSION DEADLINE

The deadline for receipt of abstract is 11:59 PM PT on January 3, 2023.

FIND OUT MORE ABOUT SUBMISSION

SAD ANNOUNCEMENT

Dear NCSCG community,

It is with great sadness that we inform you that Dr. Vinay Sundaram passed away on July 14, 2022. Many of you may have known Vinay well. Vinay was an accomplished, committed and compassionate hepatologist, who practiced at Cedars Sinai Medical Center in Los Angeles. In addition to his clinical work, he was passionate about his research in advancing the field of acute on chronic liver failure and liver transplantation outcomes. He was an enthusiastic advocate for trainees and served as the Chair of the AASLD Membership and Mentorship Committee. He was an active board member of our sister organization - the Southern California Society of Gastroenterology (SCSG) - and was instrumental on the planning committee of the 2022-2023 NCSCG-SCSG webinar series. He was a well respected and loved member of our hepatology community, and he will be dearly missed. He is survived by his wife Ashwini and his daughter Divya. You can access his obituary by clicking here.

FELLOWS CORNER

Nathan Kim, MD
University of California San Francisco
Fellow Representative, Northern California

Any personal background you would like to share

I grew up in South Korea, Puerto Rico, southern California, and Michigan. I attended college at Harvard, medical school at Stanford, internal medicine residency at UCLA, and now am in gastroenterology fellowship at UCSF.

Clinical and/or research interests

My interests are in hepatocellular carcinoma and transplant hepatology, looking at outcomes research.

Your involvement with SCSG/NCSCG and why did you decide to join SCSG/NCSCG?

I learned about NCSCG through my co-fellows with the monthly webinar series, and joined to connect with local gastroenterologists and hepatologists and to gain exposure to different aspects of practice.

What most excites you about GI/Hepatology in in the next 2-3 years

I am most excited by improved locoregional and systemic treatments for hepatocellular carcinoma, as well as changing trends in chronic liver disease and advances in transplant outcomes.

Other interesting facts you would like to share about yourself.

I am a big fan of the NBA, and enjoy rooting for the Los Angeles Lakers.

Farah Shirazi, MD
California Pacific Medical Center
Fellow Representative, Northern California

Any personal background you would like to share

I was born and raised in Los Angeles, where I received my bachelor's degree from Occidental College. I obtained a masters in public health from Tufts University in Boston before moving to New York for medical school at New York Medical College. I completed my residency at California Pacific Medical Center, where I have stayed for fellowship.

Clinical and/or research interests

My clinical interests are primarily in general gastroenterology. I also have particular clinical and research interests in obesity medicine and bariatric endoscopy.

Your involvement with SCSG/NCSCG and why did you decide to join SCSG?/NCSCG?

I attended my first NCSCG Liver Symposium as a 3rd year medicine resident, and since then have attended many of the monthly webinars/lectures. One of my favorite aspects has been connecting with my peers in the area and learning from this fantastic community in Northern California.

What most excites you about GI/Hepatology in in the next 2-3 years

I am very excited about applications of artificial intelligence in endoscopy, as well as more widespread use and greater understanding of outcomes of endoscopic bariatric therapies for management of obesity.

Other interesting facts you would like to share about yourself.

I enjoy spending time with my family, especially going on adventures with my 1-year-old and 3-year-old sons. I really enjoy hiking all over the Northern California Coast. In my free time I also love photography and cooking.

APP CORNER

Maribel Torres, MSN, FNP-C
Adventist Health-Hanford, CA
NCSCG APP Committee Member

Any personal background you would like to share

I am from Visalia, first generation, and first in my family to receive a Master's Degree. I received my master's in nursing, and Nurse Practitioner through Fresno Pacific University. My clinical background experience includes Internal Medicine, Nephrology, and most recently working with an underserved community of GI/Hep patients.

Clinical and/or research interests

I have a wide variety of clinical experience which includes: Colon screening, IBS, IBD, Hepatitis, Cirrhosis, Nash, fatty liver, GERD, functional disorders, and Motility disorders, all in a short amount of time.

Your involvement with the NCSCG and why did you decide to join the NCSCG?

I learned about NCSCG in 2021 through Mikhail Alper and became involved immediately. I began working in this specialty field the same year, and I joined as an APP committee member in 2021.

I decided to join NCSCG because I knew it would be great to network with other professionals. I am happy to have met many amazing, and intelligent providers. I also wanted to continue growing and learning about the different disease processes.

What most excites you about GI/Hepatology in in the next 2-3 years

What most excites me about GI/Hepatology are the advances and development in medication and treatment for our patients. Also knowing I can make a difference in my community, knowing that the population is growing day by day of newly diagnosed patients. I have grown up knowing I want to give back to my community. Currently the location I practice in is considered a rural area of the Central Valley. I plan in the future to learn more about research, and become involved.

Other interesting facts you would like to share about yourself.

Interesting fact is that I am a busy wife, daughter, and mother of 4 beautiful girls (Yes I said 4), I recently welcomed twin girls. I also enjoy music, dancing, and traveling.

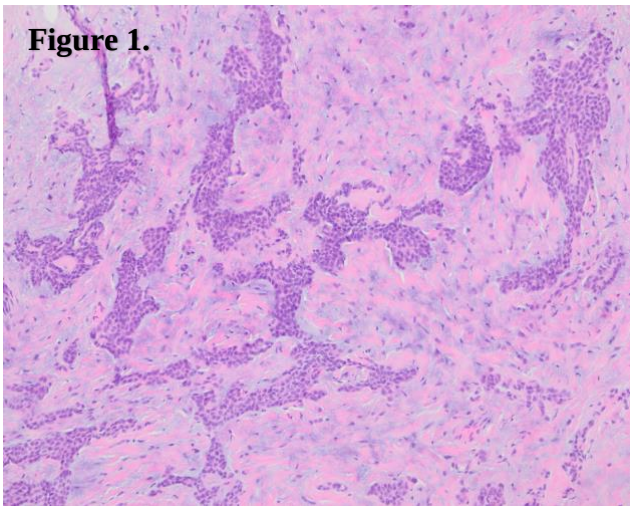
Images in Clinical GI

Can you solve the case?

Welcome to Images in Clinical GI, where we present images from interesting cases submitted by some of our members! This quarter, we present a case from Dr. Ofer Fass, a GI fellow at Stanford. ***Answers and discussion on this case can be found on page 11.*** *We hope you enjoy!*

A 78-year-old gentleman with a history of coronary artery disease, benign prostatic hyperplasia, and depression, presents with new onset large-volume ascites. The patient reports that he started noticing abdominal swelling beginning 5 months ago. Associated symptoms include a 30 lbs weight loss and bilateral leg edema. The patient has never experienced this swelling before and denies any history of alcohol abuse or liver disease. He does not have any family history of liver cirrhosis or malignancy. His home medications include aspirin, tamsulosin, quetiapine, and escitalopram. Physical examination demonstrates a large, distended abdomen and +2 pitting edema of his bilateral lower extremities. There are no spider angiomas, palmar erythema, or jaundice.

Initial laboratory studies show normal blood counts, metabolic panel, and liver chemistries. Serum albumin is 4.0. A CT abdomen reveals large volume ascites, right pleural effusion, and mild splenomegaly. A paracentesis is performed with 15L of hazy, yellow ascites removed. Initial fluid studies show albumin 2.6, total protein 3.7, adenosine deaminase 21.5, triglyceride 15, no neutrophils, negative gram stain, and negative culture growth (aerobe, anaerobe, fungal, and acid-fast bacilli). An echocardiogram demonstrates normal heart function. A transjugular liver biopsy is performed, which shows non-specific changes not compatible with fibrosis or cirrhosis, which is confirmed on Fibroscan (F0 - F1). A repeat paracentesis is performed with a negative tuberculosis PCR. Cytology shows scattered mesothelial cells and histiocytes, but no evidence of malignancy. EGD/Colonoscopy finds no significant findings. A PET-CT scan displays stable right-sided pleural effusion, ascites, and uptake in the peritoneum with greatest intensity in the perihepatic region. A peritoneal biopsy is obtained via surgical laparoscopy, and pathology is shown below:



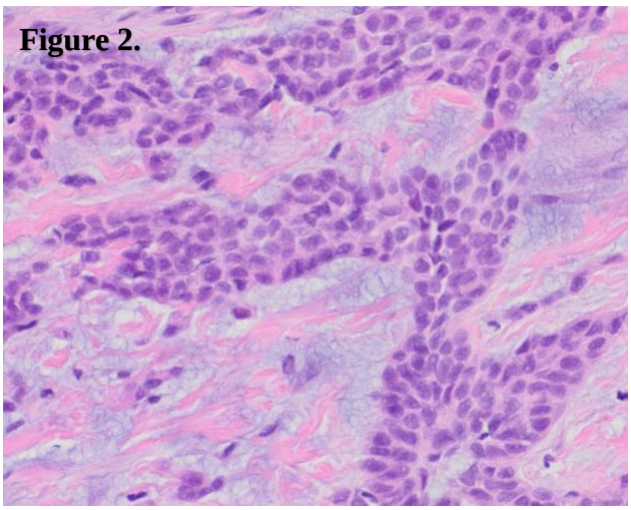


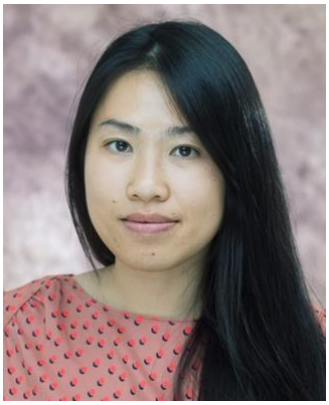
Figure 1. Peritoneal biopsy (low power). Cells demonstrating an architectural growth pattern of infiltrative sheets with associated greyish desmoplastic stroma. **Figure 2.** Peritoneal biopsy (high power). Higher power of magnification redemonstrates an infiltrative growth pattern and desmoplastic stroma. The cells are overall extremely bland cytologically.

What is the etiology of the patient's cryptogenic ascites?

If you have any interesting cases you would like to share or suggestions for this section, please contact us at: NCSCG@pacemedcom.com

SYSTEMIC THERAPY FOR HCC

Liver cancer remains a global health challenge and its incidence is growing worldwide. The landscape of systemic treatment for patients with advanced HCC has changed significantly in the past decade with the approval of many TKIs, immunotherapy (especially checkpoint inhibitors) and combination of both. In this article, we aim to briefly review the most updated recommendations for the systemic treatment of advanced, unresectable HCC.
Please scroll down to the end of the newsletter, page 12, to access the full practical review or click here.



An Uche MD, is a full time Hematology/Oncology faculty at Highland Hospital, part of Alameda Health System. Her clinical interests include GI cancers, sarcoma, medical education, and making clinical trials more accessible for underserved patients. During her free time, she enjoys hiking, reading and spending time with her family.

Dear Colleague,

The NCSCG Education and Trainee Committee is pleased to announce the CME Accredited NCSCG and SCSG Education and Trainee Committee 2022-2023 Webinar Series. This year we are excited to collaborate with the Southern California Society of Gastroenterology (SCSG)!

About the NCSCG Webinar Series

The NCSCG Education and Trainee Committee Webinar Series aims to provide an education and career development focused resource for our GI community. Our series has been developed with gastroenterology and hepatology fellows from training programs in Northern California and incorporates sessions specifically focused on important aspects of career development and the job search process. In addition, our series will also include high yield and hot topics in clinical gastroenterology and hepatology. We offer these sessions as a free resource to anyone interested in participating.

To replicate a meal we would have together, the NCSCG would like to offer all NCSCG and SCSG fellows who attend the webinars a meal up to the value of $30 to be eaten at the time of the webinar.

To receive your free meal during the webinar follow these easy steps:

1. Register for the event
2. Ensure that you are an NCSCG or SCSG fellow. You may register as a member or renew your membership by clicking here
3. Attend the webinar (attendance is monitored)
4. Order your meal for the time of the webinar up to the value of $30 and save the receipt!
5. Please turn on your webcam so that we can connect as we dine, converse, collaborate and learn together during this program
6. Fill in an expense reimbursement form sent after each webinar and submit this, along with your receipt to Dani Smith: dsmith@pacemedcom.com
7. Receive a check for the value of your meal, up to $30, mailed to you shortly after the event.

Sincerely,
The NCSCG Education and Trainee Committee

SEPTEMBER 8, 2022
6PM – 7PM PT
GI Emergencies
Rika Mallepally, MD; USC
Nghiem Ha, MD; UCSF

SEPTEMBER 27, 2022
6PM – 7PM PT
Career Development Webinar #1: Hepatology
Courtney Sherman, MD, UCSF
Kali Zhou, MD, USC
Nizar Mukhtar, MD, Kaiser Permanente

OCTOBER 6, 2022
6PM – 7PM PT
Career Development Webinar #2: GI/Advanced
Berkeley Limketkai, MD, UCLA
Abdul Kouanda, MD, UCSF
Ryan McConnell, MD, Palo Alto Foundation Medical Group

NOVEMBER 2022
6PM – 7PM PT
Career Development Webinar #3: Contract Negotiation
Patrick McCabe, MD, GI Consultants SF
Gavin Park, MD, Queens Health System Honolulu

DECEMBER 2022
6PM – 7PM PT
Research Seminar #1

TO REGISTER FOR THE ENTIRE SERIES AND FOR MORE INFORMATION, VISIT:
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REGISTRATION FEES
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View Past Recorded Webinars Now!

RECRUITMENT

ALAMEDA HEALTH SYSTEM

ADULT GASTROENTEROLOGIST PHYSICIAN: Oakland, California

The East Bay Medical Group (EBMG) is currently seeking a 6th full-time BC/BE adult Gastroenterologist to join the Division of Gastroenterology and Hepatology at Alameda Health System. This 1.0 FTE position is charged with serving the clinical and academic mission of the Division, the Department of Medicine, and Alameda Health System.

Alameda Health System (AHS) is a major public health system and medical training institution based in Oakland, CA (Alameda County). The system encompasses 3 hospitals – Highland Hospital (Level 1 Trauma Center), Alameda Hospital (Community Hospital), and San Leandro Hospital (Community Hospital) – and includes residency training programs in Surgery, Emergency Medicine, and Internal Medicine. East Bay Medical Group (EBMG) is a subsidiary of Alameda Health System and is the primary contracting entity for physicians.

The primary role of this position is to provide high-quality GI/Liver care to the underserved patients of Alameda County in both the hospital and ambulatory setting. Academic responsibilities are embedded within this role and include active participation in all teaching programs related to the Division and the Department. Teaching responsibilities include oversight of medical students, Highland Hospital Internal Medicine residents, and GI fellows who rotate from California Pacific Medical Center.

We are seeking candidates who:

- Are committed to AHS' safety-net mission of providing high quality care to the underserved.
- Are interested in being on a team that prioritizes a culture of continuous improvement, collegiality, respect, and support for one another.
- Are capable managing full spectrum GI and liver cases in both the ambulatory and hospital setting.
- Are proficient in both acute and outpatient endoscopy.
- Are capable and interested clinical educators and role models for trainees.

The ideal candidate would have proficiency in ERCP and EUS.

Compensation and benefits package is competitive for the San Francisco Bay Area.

For more information about the Division of Gastroenterology and Hepatology at Alameda Health System, please visit the Division website at: https://sites.google.com/view/highlandgi/about-us

If you are interested, please submit your CV and statement of interest to Dr. Taft Bhuket, Division Chief of Gastroenterology & Hepatology. tbhuket@alamedahealthsystem.org
Dr. Benny Liu, Associate Division Chief of Gastroenterology & Hepatology
beliu@alamedahealthsystem.org

PEDIATRIC GASTROENTEROLOGIST OPPORTUNITY - Fresno, California

The Permanente Medical Group, Inc. is currently seeking a 0.6 FTE outpatient BC/BE Pediatric Gastroenterologist to join our Pediatric Group in Fresno, California. This is a purely clinical and procedural position as we have no pediatric inpatient ward. Duties would include consultation, evaluation, and management of common gastroenterology concerns. You will also be able to perform lactose and fructose breath testing, endoscopies, and colonoscopies.

The California Central Valley offers

- A location nestled between the Cascade, Sierra Nevada, and Tehachapi mountains to the east and the San Francisco Bay Area and Pacific Coast to the west
- Mild winters, warm summers, and close to some of our state's most popular recreation destinations, including biking, kayaking, and boarding
- Nearby California State and National Parks offer great hiking trails, camping, and fishing in pristine lakes and rivers
- High quality and attractive lifestyle, including affordable housing costs, shorter commutes, and great schools
- Enjoyable community activities, a vibrant arts scene (including lively theater and music performances), sporting events, museums, family and gourmet eateries, fashion malls, and universities

EXTRAORDINARY BENEFITS:

- Competitive compensation and benefits package
- Moving allowance and home loan assistance - up to $200,000 (approval required)
- Malpractice and tail insurance
- Paid holidays, sick leave, education leave
- Shareholder track
- Three retirement plans, including pension

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For more information or to apply, please visit: **tpmg.permanente.org**

You may also contact and/or send CV to Judy Padilla at: **Judy.G.Padilla@kp.org** or call: 510-625-5915.

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Images in Clinical GI
(Solution and Discussion)

Solution

Malignant peritoneal mesothelioma

Discussion

Mesothelioma is a rare malignancy of the serosal membranes arising within the pleura, peritoneum, pericardium, or tunica vaginalis testes.[1] Of the approximately 3,300 annual diagnoses in the United States, 10-15% affect the peritoneum.[2] Carcinogenesis is strongly associated with industrial exposure to asbestos, although other pollutants may be implicated as well (erionite, fluoro-edenite, Thorotrast).[3-5] There are also reports of prior abdominal radiation increasing the risk for peritoneal mesothelioma.[6] Patient later recalled a history of asbestos exposure from his work.

The most common presenting symptoms include abdominal pain, distension, weight loss, dyspnea, and chest pain, with the average time between symptom onset and diagnosis being 5 months.[7] In general, cytologic evaluation of ascites fluid has low diagnostic yield as it does not allow for assessment of stromal invasion into the peritoneum. Additionally, differentiating between benign and malignant mesothelial cells is challenging as the cells are often cytologically "bland".[8] A peritoneal biopsy is typically required for a definitive diagnosis.[9,10]

Disease extent is described as diffuse or localized. Diffuse disease appears as peritoneal carcinomatosis and bowel obstruction (advanced disease). Localized disease appears as a well circumscribed mass. Diffuse disease carries a poor prognosis whereas localized disease carries a more favorable prognosis following complete tumor excision.[11,12]

Our patient was confirmed to have malignant mesothelioma involving his peritoneum and pleura. He was started on immunotherapy with nivolumab and ipilimumab and continues therapy currently with close oncology follow-up. This case highlights a classic presentation of peritoneal mesothelioma. The presence of abdominal ascites and concurrent pleural effusion in the absence of hepatic, cardiac, or renal disease, should raise suspicion for malignant mesothelioma.

References

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Acknowledgements
Thanks to Dr. Christine Louie from VA Palo Alto GI Pathology for providing the images used for Figures 1 and 2.

SYSTEMIC TREATMENTS FOR HEPATOCELLULAR CARCINOMA – A PRACTICAL REVIEW

Adam Mortimer[1], Maria Avenido[1], and An Uche[2]

[1] Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, California

[2] Division of Hematology and Oncology, Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, California.

Introduction:

Liver cancer remains a global health challenge and its incidence is growing worldwide.[1,2] It is estimated that, by 2025, more than 1 million individuals will be affected by liver cancer annually.[3] Hepatocellular carcinoma (HCC) is the most common form of liver cancer and accounts for ~90% of cases. Risk factors for HCC include but are not limited to hepatitis B virus (HBV), hepatitis C virus (HCV), aflatoxin-contaminated foods, excessive and chronic alcohol intake, excess body weight, type 2 diabetes, and smoking.

With screening and early detection, patients with early-stage HCC might be cured with liver transplant or surgical resection. Locoregional treatments, such as transarterial chemoembolization (TACE), microwave ablation or cryotherapy can also be curative in selected patients (tumor < 3 cm). For the patients who are not candidate for these treatment options, systemic therapy might provide palliative benefits, such as reduced complications from the cancer and prolonged survival. In this article, we aim to briefly review the most updated recommendations for the systemic treatment of advanced, unresectable HCC.

First Line Therapy:

1. *Atezolizumab and Bevacizumab (Atezo/Bev) is the most efficacy treatment combination for unresectable HCC*

It is consistent across the guidelines (National Comprehensive Cancer Network, American Society of Clinical Oncology, and European Society for Medical Oncology) that atezo/bev should be utilized as the first line therapy for the selected patients with unresectable or non-transplantable HCC. In the IMbrave150 trial, 336 patients were randomized to receive the combination treatment, while 165 patients were randomized to receive sorafenib. The results showed that the combination of atezo/bev significantly improved outcomes compared to sorafenib, with 12-month overall survival (OS) (67.2% vs 54.6%, HR 0.58, $P < 0.001$) and median progression free survival (PFS) (6.8 months vs 4.3 months, HR 0.59).[4] It is important to note that the IMbrave150 trial only included patients with compensated liver cirrhosis, as defined by the classification Child-Pugh Score class A. This is due to concern of higher prevalence of portal hypertension in patients with decompensated liver failure that could translate into higher risk of bleeding with bevacizumab, a monoclonal antibody against VEGF. In addition, all the patients participated in the trial were required to undergo evaluation for esophageal varices with upper endoscopy within 6 months prior to enrolling. The guidelines uniformly recommend that upper endoscopy should be performed prior to starting atezo/bev. Finally, the trial also excluded patients who are on treatment dose of anticoagulation. Patients with HCC can often have portal vein thrombosis – either due to tumor invasion (tumor thrombus) or true thrombus. We do not usually recommend anticoagulation for patients who have tumor thrombus. Thus, careful review of images such as CT triple phase or MRI

liver to determine the nature of portal vein thrombosis is important so that patients are not unnecessarily excluded from this effective combination.

2. <u>When Atezo/Bev is Not an Option, Sorafenib or Lenvatinib Should Be Offered As First Line Therapy</u>

When atezo/bev is not an option, guidelines recommend that sorafenib or lenvatinib should be offered as first line therapy. Sorafenib received its approval from the U.S Food and Drug Association (FDA) as treatment for HCC in 2008 based on the results of the SHARP trial, which showed improved OS of patients with HCC treated with sorafenib compared to those treated with placebo (10.7 months vs 7.9 months; HR 0.69, 95% CI 0.55-0.87, P < 0.001).[5] It remained as the only choice for first line treatment for advanced, inoperable hepatocellular carcinoma until 2018, until the REFLECT trial showed that lenvatinib is noninferior to sorafenib with median OS of 13.6 months vs. 12.3 months (HR 0.92, 95% CI 0.79-1.06) respectively.[6]

In practice, the decision to choose between sorafenib or lenvatinib is often made based on the side effects profile of each drug, patients' characteristics and preferences and cost. The underlying viral etiology of HCC can also be a helpful consideration in choosing between sorafenib or lenvatinib. In the SHARP trial, HCV was the most common cause of chronic liver disease (28%), followed by alcohol (26%) and HBV (19%). In contrast, HBV was the most common cause of chronic liver disease in the REFLECT trial (53% vs 48%, for the lenvatinib and sorafenib group respectively). Several meta-analyses of RCTs have shown sorafenib to be more beneficial in patients with HCV, especially as compared with patients with HBV.[7-9] In the REFLECT trial there was a trend toward improvements across endpoints for lenvatinib over sorafenib in the HBV subgroup, though it was not significant. A recent meta-analysis by Casadei et al showed that for HBV-positive patients, there was a clear trend in favor of lenvatinib over sorafenib (HR 0.82, 95% CI 0.60-1.15).[10]

Second Line Therapy:

It is important to note that all of the second line therapy options for HCC have only been evaluated in the settings of progression after or intolerant to sorafenib; no second line therapy options have been evaluated following treatment with lenvatinib or atezo/bev. The guidelines recommend that that data for treatment options following sorafenib may be cautiously extrapolated to the population that has received first-line therapy with lenvatinib, as both agents are TKIs. The guidelines also recommend that due to their differing mechanisms of action, second line treatment with a TKI may offer clinical benefit following treatment with atezo/bev. The options for second line therapy are:

- *<u>Regorafenib:</u>* an oral multi-kinase inhibitor with activity against VEGFR1-3, PDGFRB, KIT, RET, RAF-1, and other growth signaling kinases. It was approved in 2017 as a second line treatment option for patients with unresectable HCC who progressed on sorafenib based on the results of the RESORCE trial. Compared to the placebo, regorafenib improved median OS (10.6 months vs. 7.8 months, respectively; HR 0.63, 95% CI 0.50-0.79; *P* < 0.001).[11]
- *<u>Cabozantinib:</u>* an oral multikinase inhibitor with potent activity against VEGFR1-3 and MET among other targets, was assessed in the phase III randomized CELESTIAL trial including 707 patients with advanced HCC who have progressed on or after sorafenib. Median OS and PFS were significantly greater in patients randomized to receive cabozantinib (10.2 months and 5.2 months, respectively), compared to patients randomized to receive a placebo (8.0 and 1.9 months, respectively) (HR 0.76, 95% CI 0.63-0.92, *P* = 0.005 for OS; HR 0.44, 95% CI 0.36-0.52, *P* < 0.001 for PFS).[12]
- *<u>Ramucirumab:</u>* the monoclonal antibody against VEGFR2 is approved for use as second line therapy for patients with advanced HCC who progressed on prior therapy and who has AFP level of ≥ 400 ng/mL.

This is based on the results of REACH-2 trial which showed OS and PFS were greater in patients who received ramucirumab, compared to patients randomized to receive a placebo (median OS 8.5 months vs. 7.3 months, respectively; HR 0.71, 95% CI 0.53-0.95, $P = 0.0199$).[13]

- *Pembrolizumab:* a monoclonal antibody against PD-L1, has an accelerated approval from the FDA as second line therapy for patients with advanced HCC who has received sorafenib. This is based on results the phase 3 KEYNOTE-240 trial. Even though the trial did not meet its primary endpoints (OS and PFS) based on the rigorous statistical plan, updated data published in an abstract, showed that the median OS with pembrolizumab versus placebo was 13.9 vs. 10.6 months, respectively (HR 0.77) and the median PFS was 3.3 vs. 2.8 months, respectively (HR 0.70).[14,]

Patients with Child-Pugh Class B Liver Function

Since all the clinical trials studying systemic therapy for HCC included mostly patients with Child-Pugh class A liver function and Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, there continues to be a large unmet need for data to support treatment benefit in patients with decreased functional status and decompensated liver disease. All major guidelines do specify that most systemic therapy options are limited to the Child-Pugh Class A population, with the exception of nivolumab.

In 2017, the FDA gave accelerated approval for nivolumab as second line treatment for patients with HCC who progressed on sorafenib. This was based on results from the CheckMate-040 trial, which showed an overall response rate (ORR) of 14.3%, with 3 complete responses (CRs) and 19 partial responses (PRs). Duration of response (DOR) ranged from 3.2 to 38.2 months; 91% of responders had responses lasting 6 months or longer and 55% had responses lasting 12 months or longer.[16] However, the confirmatory randomized phase III trial, CheckMate-459, comparing nivolumab vs sorafenib, did not meet its primary or secondary endpoints.[17] In 2021, nivolumab was withdrawn from the U.S marker as a single agent for patients with HCC who were previously treated with sorafenib.

However, the phase I/II CheckMate-040 trial did include 49 patients with Child-Pugh Class B (25 patients who were sorafenib-naïve and 24 patients who received sorafenib prior). Subgroup analysis of this cohort showed an ORR of 12% (95% CI 5-25%) with 6 patients had response. Median time to response was 2.7 months, and median DOR was 9.9 months (95% CI 9.7-9.9). Treatment-related adverse events were reported in 25 patients (51%) and led to discontinuation in 2 patients (4%). The safety of nivolumab was comparable to that in patients with Child-Pugh class A liver function.[18] Based on this, even though the National Comprehensive Cancer Network guideline removed its recommendation of nivolumab as a subsequent-line treatment option for patients with Child-Pugh class A liver function, it does maintain the recommendation for nivolumab as an option for patients with Child-Pugh Class B liver function, as treatment options are limited for these patients.

Summary

The landscape of systemic treatment for patients with advanced HCC has changed significantly in the past decade with the approval of many TKIs, immunotherapy (especially checkpoint inhibitors) and combination of both. Currently, atezolizumab plus bevacizumab is considered the most effective regimen and standard of care for patients with advanced HCC who

are treatment naïve. Sorafenib, lenvatinib, regorafenib, and cabozantinib are TKIs that have activity in first and second line settings. Ramucirumab has unique indication for patients with advanced HCC who progressed on prior therapy and have high AFP levels. Finally, nivolumab can be considered for patients with Child-Pugh class B liver function.

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