
HCC
connect
POWERED BY COR2ED

EXPERTS KNOWLEDGE SHARE:

UNDERSTANDING THE CHANGING TREATMENT LANDSCAPE IN HCC AND OPTIMISING THERAPY FOR THE INDIVIDUAL PATIENT

Dr. Richard Finn, Dr. Catherine Frenette and Dr. Amit Singal

Sunday November 11th 2018

San Francisco, USA

DISCLAIMER

Please note:

The views expressed within this presentation are the personal opinions of the authors. They do not necessarily represent the views of the author's academic institution or the rest of the HCC CONNECT group.

This meeting is supported by an Independent Educational Grant from Bayer.

EXPERTS KNOWLEDGE SHARE

HCC connect
POWERED BY COR2ED

THE OBJECTIVE OF THIS MEETING IS TO DISCUSS THE TOPIC 'UNDERSTANDING THE CHANGING TREATMENT LANDSCAPE IN HCC AND OPTIMISING THERAPY FOR THE INDIVIDUAL PATIENT'

- Your opportunity to **discuss and share learnings on a challenging topic** within the area of liver oncology
- A chance to hear **the views of our Experts** and allow them to answer the questions that are important to you
- Review and discuss **Patient Case Studies**, using the questions that you have sent in advance of this evening

HCC, hepatocellular carcinoma

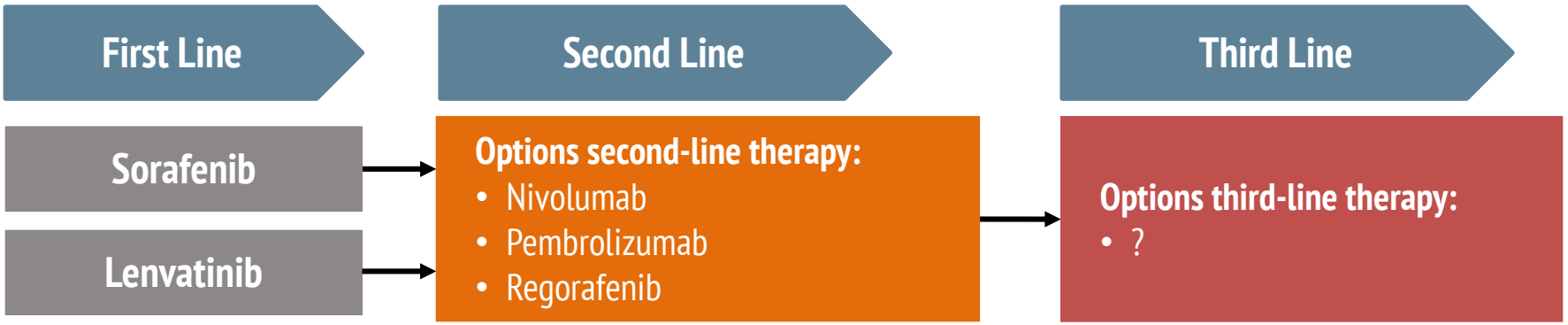
OVERVIEW AND SCENE-SETTING

Dr. Richard Finn
UCLA Geffen School of Medicine, USA

CURRENT SYSTEMIC THERAPY SEQUENCES IN ADVANCED HCC

HCC connect
POWERED BY COR2ED

FDA approved in the US



Positive data from randomized phase III studies, under FDA review in the US, pending approval

HCC, hepatocellular carcinoma; FDA, Food and Drug Administration; ILCA, International Liver Cancer Association; US, United States

PRE-MEETING SURVEY AMONG DELEGATES

HCC connect
POWERED BY COR2ED

- **At what point do you transition from loco-regional to systemic therapy?**
  - Disease stage and treatment response were the most important indicators for transitioning from loco-regional to systemic therapy
- **What role does treatment sequencing play in your therapeutic decision making?**
  - For most delegates, treatment sequencing plays a (very) important role in daily practice
- **Do you prescribe immunotherapy?**
  - Not all delegates prescribe immunotherapy themselves
  - Some collaborate with their oncologist to treat patients with immunotherapy
  - In some countries immunotherapy is not yet available for the treatment of HCC

CASE STUDY 1

Dr. Amit Singal

UT Southwestern Medical Center, USA

PATIENT CASE #1
INITIAL PRESENTATION

HCC connect
POWERED BY COR2ED

History

- 57-year old male
- History of obesity, diabetes, and **hepatitis C**, diagnosed by PCP during routine "baby-boomer" screening
- Asymptomatic and actively working
- Presents for consideration of hepatitis-C treatment

AFP, alpha-fetoprotein; HCC, hepatocelluar carcinoma; INR, international normalized ratio; MRI, magnetic resonance imaging; PCP, primary-care provider

PATIENT CASE #1
INITIAL PRESENTATION

- **History**
  - 57-year old male
  - History of obesity, diabetes, and **hepatitis C**, diagnosed by PCP during routine "baby-boomer" screening
  - Asymptomatic and actively working
  - Presents for consideration of hepatitis-C treatment
- **Examination**
  - Compensated cirrhosis
  - No ascites or encephalopathy
  - HCC **screening ultrasound** was read as **US-3** (≥ 1 observation ≥ 1 cm)
  - **MRI** shows **multifocal, bilobar HCC (LR-5)**
    - 4 lesions, largest 6 cm
    - No evidence of vascular invasion or distant metastases
- **Status**
  - Child-Pugh score A – bilirubin 0.6, albumin 3.4, INR 1.1, platelets 87
  - AFP 427 ng/mL

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; INR, international normalized ratio; MRI, magnetic resonance imaging; PCP, primary-care provider

PATIENT CASE #1
INITIAL TREATMENT

HCC connect
POWERED BY COR2ED

WHAT WOULD YOU CONSIDER FOR INITIAL TREATMENT IN THIS PATIENT?

PATIENT CASE #1
INITIAL TREATMENT

HCC connect
POWERED BY COR2ED

WHAT WOULD YOU CONSIDER FOR INITIAL TREATMENT IN THIS PATIENT?

The PREMIERE trial of transarterial radioembolization (TARE) versus conventional transarterial chemoembolization (TACE) showed:

Time to progression	Survival
• > 26 months for TARE • 6.8 months for TACE • HR 0.12, 95% CI 0.03–0.56	• 18.6 months for TARE • 17.7 months for TACE • P = 0.99

CI, confidence interval; HR, hazard ratio.
Salem R, et al. *Gastroenterology.* 2016;151:1155-1163.e2.

PATIENT CASE #1
INITIAL TREATMENT

HCC connect
POWERED BY COR2ED

IS THERE ANY ROLE FOR A COMBINATION OF LOCOREGIONAL AND SYSTEMIC THERAPY?

PATIENT CASE #1
INITIAL TREATMENT

HCC connect
POWERED BY COR2ED

IS THERE ANY ROLE FOR A COMBINATION OF LOCOREGIONAL AND SYSTEMIC THERAPY?

SPACE[1] **TTP**	TACE-2[2] **PFS**	TACTICS[3] **PFS**	SORAMIC[4] **OS**
• 169 days for TACE + sorafenib • 166 for TACE • HR 0.80, p = 0.07	• 238 days for TACE + sorafenib • 235 days for TACE • HR 0.99 95% CI 0.77–1.27	• 25.2 months for TACE + sorafenib • 13.5 months for TACE • HR 0.59 95% CI 0.41–0.87 • Treated until unTACEable progression (other studies treated until radiologic progression)	• 12.1 months for SIRT + sorafenib • 11.5 months for sorafenib • HR 1.01 95% CI 0.82–1.25

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization; TTP, time to progression

1. Lencioni R, et al. *J Hepatol.* 2016;64:1090-1098. 2. Meyer T, et al. *Lancet Gastroenterol Hepatol.* 2017;2:565-575. 3. Kudo M, et al. *J Clin Oncol.* 2018;36:Suppl. Abstract 206. 4. Ricke J, et al. *Liver Int.* 2015;35:620-626.

PATIENT CASE #1
FOLLOW-UP PRESENTATION

- **Diagnosis**
  - Multifocal HCC
- **Initial treatment**
  - TARE to both right and left lobes
- **Follow-up MRI** after 3 months
  - Evidence of progression
  - Left portal-vein tumor thrombus
- **Status**
  - Child-Pugh score A – bilirubin 0.7, albumin 3.2, INR 1.1
  - ECOG-PS score 0
  - AFP 1,274 ng/mL

AFP, alpha-fetoprotein; ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocelluar carcinoma; INR, international normalized ratio; MRI, magnetic resonance imaging; TARE, transarterial radioembolization

PATIENT CASE #1
TREATMENT

HCC connect
POWERED BY COR2ED

WHAT TREATMENT WOULD YOU CONSIDER IN THIS PATIENT?

PATIENT CASE #1
TREATMENT

HCC connect
POWERED BY COR2ED

WHAT TREATMENT WOULD YOU CONSIDER IN THIS PATIENT?

SARAH[1] OS	SINveNIB[2] OS	SHARP[3] OS	Asia-Pacific[4] OS	REFLECT[5] OS	CHECKMATE 459
• 8.0 months for SIRT • 9.9 months for sorafenib • HR 1.15 95% CI 0.94–1.41	• 8.8 months for SIRT • 10.0 months for sorafenib • HR 1.1 95% CI 0.9–1.4	• 10.7 months for sorafenib • 7.9 months for placebo • HR 0.69 95% CI 0.55–0.87	• 6.5 months for sorafenib • 4.2 months for placebo • HR 0.68 95% CI 0.50–0.93	• 13.6 months for lenvatinib • 12.3 months for sorafenib • HR 0.92 95% CI 0.79–1.06 • Secondary endpoints: • PFS 7.3 vs. 3.6 months for lenvatinib vs. sorafenib • ORR 41% vs. 12% for lenvatinib vs. sorafenib	• Results for nivolumab versus sorafenib are pending

CI, confidence interval; HR, hazard ratio; ORR, overall respsonse rate; OS, overall survival; PFS, progression-free survival; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization

1. Vilgrain V, et al. *Lancet Oncol.* 2017;18:1624-1636. 2. Chow PHW, et al. *J Clin Oncol.* 2018; 36:1913-1921. 3. Llovet JM, et al. *N Engl J Med.* 2008;359:378-390. 4. Cheng AL, et al. *Lancet Oncol.* 2009;10:25-34. 5. Kudo M, et al. *Lancet.* 2018;391:1163-1173.

PATIENT CASE #1
SYSTEMIC TREATMENT

HCC connect
POWERED BY COR2ED

WOULD YOU STILL PURSUE SYSTEMIC THERAPY IF THE PATIENT HAD PROGRESSION BUT HAD NOT YET DEVELOPED VASCULAR INVASION?

INR, international normalized ratio

PATIENT CASE #1
SYSTEMIC TREATMENT

HCC connect
POWERED BY COR2ED

WOULD YOU STILL PURSUE SYSTEMIC THERAPY IF THE PATIENT HAD PROGRESSION BUT HAD NOT YET DEVELOPED VASCULAR INVASION?

What if:

- The patient was **Child-Pugh B** – bilirubin 2.1, albumin 2.9, INR 1.2?
- Bilirubin was 1.5 but the patient had developed **mild ascites**?

INR, international normalized ratio

CASE STUDY 2

Dr. Catherine Frenette

Scripps Green Hospital, La Jolla, CA, USA

PATIENT CASE #2
INITIAL PRESENTATION

- **History**
  - 74-year old woman
  - Hepatitis C
    - Contracted from her husband
    - Never been treated
- Presents with a **new diagnosis of HCC** to pursue treatment

PATIENT CASE #2
EXAMINATION

- **Ultrasound**
  - 4.5-cm mass in her liver
- **CT-liver**
  - Solitary 6.3-cm lesion in segment 4 consistent with HCC, with tumor thrombus in the middle hepatic vein
- **CT-chest**
  - Multiple lung lesions concerning for metastatic disease, all < 1cm
  - Multiple small peripheral pulmonary emboli
  - 3-cm destructive lesion in left 7th rib, consistent with bony metastasis

CT, computerized tomography; HCC, hepatocellular carcinoma

PATIENT CASE #2
ANAMNESIS AND LAB RESULTS

HCC connect
POWERED BY COR2ED

- **Anamnesis**
  - She denies any history of decompensating events
  - Feeling well, except for some mild discomfort in her ribs on the left side that she had attributed to a fall
- **Lab results**
  - Normal basic metabolic panel
  - CBC notable for platelets 145, otherwise normal
  - AST 90
  - ALT 113
  - Bilirubin 0.4
  - Albumin 4.1
  - AFP 2982
- **Status**
  - Child-Pugh score A
  - Cirrhotic, CTP score 5
  - ECOG-PS score 0
  - BCLC stage C

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CBC, complete blood count; CTP, Child-Turcotte-Pugh; ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocelluar carcinoma

PATIENT CASE #2
INITIAL TREATMENT

HCC connect
POWERED BY COR2ED

IS THERE A ROLE FOR LOCOREGIONAL THERAPY IN A PATIENT WITH METASTATIC DISEASE?

PATIENT CASE #2
INITIAL TREATMENT

HCC connect
POWERED BY COR2ED

IS THERE A ROLE FOR LOCOREGIONAL THERAPY IN A PATIENT WITH METASTATIC DISEASE?

SHOULD HER RIB LESION BE RADIATED?

PATIENT CASE #2
INITIAL TREATMENT

HCC connect
POWERED BY COR2ED

- The patient was started on **sorafenib** 200 mg twice daily, and titrated based on side effects to total dose of 400 mg in morning and 200 mg in evening
  - Full dose had resulted in significant all-over body rash and diarrhea
- She also underwent **radiation** to the rib lesion and the tumor thrombus to attempt to decrease further risk of a pulmonary embolism

PATIENT CASE #2
FOLLOW UP – 3 MONTHS

- **Restaging** after radiation and three months of sorafenib therapy
  - AFP 15
  - Rib lesion without enhancement and with 30% shrinkage
  - Liver lesion without enhancement, tumor thrombus resolved
  - Pulmonary metastatic disease stable

- She **remained on sorafenib therapy** for the next 20 months

AFP, alpha-fetoprotein

PATIENT CASE #2
FOLLOW UP – 20 MONTHS

- At her **20 month visit**
  - CT-liver stable without enhancement in primary lesion
  - CT-lungs stable
  - Rib lesion with **local recurrence** of 2.8 cm lesion
  - **AFP increased** from 20 to 862

AFP, alpha-fetoprotein; CT, computerized tomography

PATIENT CASE #2
SECOND-LINE TREATMENT

HCC connect
POWERED BY COR2ED

WHAT SECOND-LINE THERAPY WOULD YOU CONSIDER FOR THIS PATIENT?

PATIENT CASE #2
SECOND-LINE TREATMENT

HCC connect
POWERED BY COR2ED

WHAT SECOND-LINE THERAPY WOULD YOU CONSIDER FOR THIS PATIENT?

Would your therapy be different:

- If her AFP had increased but **no progressive disease** was evident on **imaging**?
- If she had **not tolerated sorafenib**?

PATIENT CASE #2
SECOND-LINE TREATMENT

HCC connect
POWERED BY COR2ED

SHOULD TYROSINE KINASE INHIBITORS BE STARTED AT FULL DOSE INITIALLY AND TITRATED DOWN, OR LOW DOSE AND TITRATED UP?

PATIENT CASE #2
SECOND-LINE TREATMENT OPTIONS

HCC connect
POWERED BY COR2ED

Tyrosine kinase inhibitors

Regorafenib[1]
- Phase-3 RESORCE study in patients who tolerated sorafenib ⩾ 400 mg daily for 20 of prior 28 days
- OS: 10.6 months vs 7.8 months with placebo (HR 0.63)

Cabozantinib[2]
- Phase-3 CELESTIAL study
- OS: 10.2 months vs 8.0 months with placebo (HR 0.76)

Immunotherapy

Nivolumab[3]
- Phase-2 CHECKMATE-040 study
- ORR (mRECIST): 19%
- OS: 15.6 months

Pembrolizumab[4]
- Phase-2 KEYNOTE-224 study
- ORR (mRECIST): 15%
- OS: 12.9 months

Anti-VEGF

Ramucirumab[5]
- Phase-3 REACH-2 study in patients with AFP > 400
- OS: 8.5 months vs 7.3 months with placebo (HR 0.71)

HR, hazard ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, overall response rate; OS, overall survival

1. Bruix J, et al. *Lancet.* 2017;389:56-66. 2. Abou-Alfa GK, et al. *N Engl J Med.* 2018;379:54-63. 3. El-Khoueiry AB, et al. *Lancet.* 2017;389:2492-2502. 4. Zhu AX, et al. *Lancet Oncol* 2018;9:940-952. 5. Zhu AX, et al. *J Clin Oncol.* 2018;36:Suppl:4003

PATIENT CASE #2
SECOND-LINE TREATMENT

HCC connect
POWERED BY COR2ED

- The patient was started on **regorafenib** at 160 mg daily, three weeks on and one week off (prior to the approval and availability of immunotherapy)
  - The dose was titrated for side effects of diarrhea, and she was able to maintain 120 mg daily
- The rib lesion was again **radiated** for symptoms
- **Three months** after starting regorafenib she had **stable disease** on imaging and her AFP had decreased to 26
- She **continued regorafenib** for the next 18 months
- Most recent imaging shows **stable disease**, but **AFP** has started to creep **upwards**, latest value 79

AFP, alpha-fetoprotein

PATIENT CASE #2
THIRD-LINE TREATMENT

WHAT ARE THE THIRD-LINE TREATMENT OPTIONS?

PATIENT CASE #2
THIRD-LINE TREATMENT

WHAT ARE THE THIRD-LINE TREATMENT OPTIONS?

Cabozantinib	Immunotherapy
• 27% of patients in the CELESTIAL trial had 2 prior systemic therapies • Subgroup analysis of patients receiving 2 prior systemic therapies HR 0.90 (NS)	• No data on third-line immunotherapy

HR, hazard ratio; NS, not significant

Abou-Alfa GK, et al. *N Engl J Med.* 2018;379:54-63

PATIENT CASE #2
THIRD-LINE TREATMENT

HCC connect
POWERED BY COR2ED

SHOULD HER HEPATITIS C BE TREATED?
IF YES, WHEN?

Are you interested in finding out more about HCC CONNECT and our educational programmes?

Visit our website
at www.hccconnect.info

Follow us on Twitter
@hccconnectinfo

Join the
HCC CONNECT
group on LinkedIn

HCC CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.co

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com