The Changing Treatment Landscape of Unresectable Hepatocellular Carcinoma

Associate Professor Simone Strasser
Senior Staff Specialist,
AW Morrow Gastroenterology and Liver Centre and Australian National Liver Transplant Unit,
Royal Prince Alfred Hospital, Sydney
University of Sydney
President, Gastroenterological Society of Australia
Dr Strasser has received honoraria for advisory boards or speaking from:

- Bayer Healthcare
- Sirtex
- Gilead
- BMS
- MSD
- AbbVie
- Norgine
- Astellas
- Novartis
- Eisai
- Ipsen
- Pfizer
Trends in Liver Cancer incidence rates in Asia and Oceania 1990-2030

Observed age-standardized rates per 100,000 (solid lines) versus Predicted rates (dashed lines), by region and by sex (age-standardized rates per 100,000 men/women)

Increasing rates of nonviral liver disease (alcohol and NAFLD) in Australia and NZ accounting for rising rates of liver cancer

Valery PC et al. HEPATOLOGY 2018;67:600-611
New Zealand cancer survival overview

Relative survival for all cancers, 1994–2011

Published: April 14 2015

5-year survival
14.7%
2010-2011

5-year survival
9.8% in Maori Population
2010-2011
Risk factors for HCC in NZ

**Figure 2: Age standardised percentage of patients with viral hepatitis.**

**Table 1: Characteristics of 97 Māori and 92 non-Māori liver cancer patients.**

<table>
<thead>
<tr>
<th>Comorbid conditions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>30</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>22</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>103</td>
</tr>
<tr>
<td>CPD</td>
<td>24</td>
</tr>
<tr>
<td>Diabetes</td>
<td>64</td>
</tr>
<tr>
<td>Heavy alcohol usea</td>
<td>74</td>
</tr>
<tr>
<td>Other primary cancer</td>
<td>19</td>
</tr>
<tr>
<td>Renal disease</td>
<td>10</td>
</tr>
</tbody>
</table>

According to 2007 statistics from the World Health Organization (WHO), New Zealand has the second-highest prevalence of overweight adults in the English-speaking world.

Prevalence of overweight people in the Anglosphere

2,613,000 (67%) overweight or obese in 2017/2018
Indicator: Hazardous drinkers (AUDIT score ≥8, among total population)

The prevalence was 19.8%, which is an estimated 775,000 adults 2017/18

- Men vs women: Adjusted ratio 2.11*
- Māori vs non-Māori: Adjusted ratio 1.62*
- Pacific vs non-Pacific: Adjusted ratio 0.88
- Asian vs non-Asian: Adjusted ratio 0.26*
- Most vs least deprived: Adjusted ratio 1.30*

An asterisk indicates that the adjusted ratio is statistically significant.

Advanced HBV-related HCC in New Zealand
No improvement in survival from 2003 to 2017

New Zealand Liver Unit HCC multidisciplinary meeting,

Incidence of advanced HBV-related HCC increased:

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Incidence Rate/million</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-2007</td>
<td>4.5</td>
</tr>
<tr>
<td>2008-2012</td>
<td>6.0</td>
</tr>
<tr>
<td>2012-2017</td>
<td>6.3</td>
</tr>
</tbody>
</table>

A: No previous diagnosis of HBV
B: Known HBV but no HCC surveillance for ≥ 2 yrs
C: Known HBV but suboptimal HCC surveillance
D: Known HBV and optimal HCC surveillance

Median survival 138 days

Overall | Group A | Group B | Group C | Group D
---      | ---     | ---     | ---     | ---
Median survival (days) | 138 | 90 | 145 | 152 | 469


HBV and optimal surveillance

Poor survival
BCLC B
Not suitable for further LRT

BCLC C
Extrahepatic Disease

BCLC C
Vacular Invasion

Peritoneal metastases

Pulmonary metastases
Endpoints in Clinical Trials in HCC

• **Primary Endpoint**
  • Overall survival

• **Secondary Endpoints**
  • Response (PD, SD, PR, CR) (determined by RECIST or mRECIST)
  • Time to progression
  • Progression free survival
  • Objective Response Rate (ORR) (PR + CR)
  • Disease Control Rate (DCR) (SD + PR + CR)
# Response Evaluation Criteria In Solid Tumors

## Total diameter

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>RECIST</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response category</td>
<td>Diameter of arterial enhancement</td>
<td>Diameter of arterial enhancement</td>
</tr>
<tr>
<td>CR</td>
<td>Disappearance of all target lesions</td>
<td>Disappearance of any intratumoral arterial enhancement in all target lesions</td>
</tr>
<tr>
<td>PR</td>
<td>At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions</td>
<td>At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions</td>
</tr>
<tr>
<td>SD</td>
<td>Any cases that do not qualify for either PR or PD</td>
<td>Any cases that do not qualify for either PR or PD</td>
</tr>
<tr>
<td>PD</td>
<td>An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started</td>
<td>An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started</td>
</tr>
</tbody>
</table>

## Non-target lesions

<table>
<thead>
<tr>
<th>Response category</th>
<th>RECIST</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all non-target lesions</td>
<td>Disappearance of any intratumoral arterial enhancement in all non-target lesions</td>
</tr>
<tr>
<td>IR/SD</td>
<td>Persistence of one or more non-target lesions</td>
<td>Persistence of intratumoral arterial enhancement in one or more non-target lesions</td>
</tr>
<tr>
<td>PD</td>
<td>Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions</td>
<td>Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions</td>
</tr>
</tbody>
</table>

## mRECIST recommendations

- **Pleural effusion and ascites:** Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.
- **Porta hepatitis lymph node:** Lymph nodes detected at the porta hepatitis can be considered malignant if the lymph node short axis is at least 2 cm.
- **Portal vein thrombosis:** Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group.
- **New lesion:** A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.
Systemic Therapies for HCC in Australia

- **Sorafenib** TGA approved and PBS listed for first line systemic therapy HCC
- **Lenvatinib** TGA approved and PBS listed for first line systemic therapy HCC
- **Regorafenib** TGA approved for second line systemic therapy HCC (no PBS)
- **Carbozantinib** TGA approved for second line systemic therapy HCC (no PBS)
- **Nivolumab** TGA approved for second line systemic therapy HCC (no PBS)
Systemic Therapies for HCC in New Zealand

General Principles of Systemic Therapy

- Decisions to initiate systemic therapy should occur in an MDT
- Patients should be CP A and ECOG 0 or 1
- Treatment should be supervised by an experienced clinician
- A toxicity management plan should be in place before commencing systemic therapy
- First line systemic therapy should be stopped when there is radiological progression and if patient eligible for second-line therapy
Clinical Trial Development in Advanced HCC

- Stat sig in Non-Inferiority trial
- Stat sig in Superiority trial

All negative trials

* Stat sig in Non-Inferiority trial  ** Stat sig in Superiority trial
Improving Survival in Sorafenib arm of Clinical Trials

* Stat sig in Non-Inferiority trial  ** Stat sig in Superiority trial

T Meyer
Sorafenib

- Approved in Australia 2008
- On PBS (Auth) Feb 2009
- Must be the sole PBS-subsidised therapy, for HCC BCLC B or C
- Child Pugh class A, WHO performance status ≤ 2
- Patient must not have received prior treatment with a VEGF-TKI for this condition; OR Patient must have developed intolerance to a VEGF-TKI of a severity necessitating permanent treatment withdrawal.
- Not PBS-subsidised as adjunctive treatment after resection, ablation or TACE
- Not PBS-subsidised for maintenance therapy after disease progression

Updated criteria 2019
The SHARP trial
Sorafenib 400mg bd vs placebo in advanced HCC

Overall Survival

Not eligible for or had disease progression after surgical or locoregional therapies

- Sorafenib
  Median: 10.7 months
  (95% CI: 9.4-13.3)
- Placebo
  Median: 7.9 months
  (95% CI: 6.8-9.1)

HR (S/P): 0.69 (95% CI: 0.55-0.87)
P < .001
SORAFENIB

Predictive factors

1. Extrahepatic spread (EHS)

2. Hepatitis C Virus (HCV)

3. Neutrophil to lymphocyte ratio (NLR)

4. Tumour Burden

Bruix J., et al. J Hepatol 2017, 67 (5), 999-1008 Published under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/3.0/
Tolerability of oral sorafenib (SOR) in patients with advanced HCC in the SHARP trial.

- Prior to commencement of sorafenib
  - Check hands and feet
  - Start emollients/moisturisers
  - Podiatrist review
  - Optimise antihypertensives
  - Educate patient

- Regular monitoring and management
  - Hands and feet
  - Blood pressure management
  - Diarrhoea management

- Dose reduction
  - Try to avoid dose cessation

* $p = 0.04$, ** $p = 0.007$, *** $p < 0.001$ vs PL.
Lenvatinib

• Approved in Australia 2018
• On PBS (Streamlined Authority) March 1 2019
• Advanced (unresectable) BCLC Stage B or Stage C HCC
• The treatment must be the sole PBS-subsidised therapy for this condition
• Child Pugh class A; PS ≤2
• Patient must not have received prior treatment with a VEGF-TKI for this condition; OR must have developed intolerance to a VEGF-TKI of a severity necessitating permanent treatment withdrawal.
REFLECT: Study 304: Phase 3 Study to Compare the Efficacy and Safety of Lenvatinib vs Sorafenib in First-line Treatment of Patients with uHCC

NCT01761266: Study Design: Global, Randomised, Open-label, Phase 3 Non-inferiority Study

Patients with unresectable HCC (N=954)
- No prior systemic therapy for unresectable HCC
- ≥1 measurable target lesion per mRECIST
- BCLC-B (not applicable for TACE) or BCLC-C
- Child-Pugh A
- ECOG-PS ≤1
- Adequate organ function
- Patients with ≥50% liver occupation, clear bile duct invasion, or portal vein invasion at the main portal vein (Vp4)* were excluded²

Stratification:
- Region: Asia-Pacific or Western
- MVI and/or EHS: Yes or no
- ECOG-PS: 0 or 1
- Body weight: <60 kg or ≥60 kg

Lenvatinib (N=478)
- 8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) once daily

Sorafenib (N=476)
- 400 mg twice daily

Primary endpoint:
- OS

Secondary endpoints:
- PFS
- TTP
- ORR
- Quality of life
- Safety & tolerability
- PK lenvatinib exposure parameters

* Tumor assessments were performed according to mRECIST by the investigator

Designed as a NON-INFERIORITY trial

BCLC = Barcelona Clinic Liver Cancer; BW = body weight; ECOG-PS = Eastern Cooperative Oncology Group performance status; EHS = extrahepatic spread; HCC = hepatocellular carcinoma; MVI = macroscopic portal vein invasion; mRECIST = modified Response Evaluation Criteria In Solid Tumours; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumours; TACE = trans-catheter arterial chemoembolisation; TTP = time to progression; uHCC = unresectable hepatocellular carcinoma.

REFLECT: Study 304: Phase 3 Study to Compare the Efficacy and Safety of Lenvatinib vs Sorafenib in First-line Treatment of Patients with uHCC

Primary Endpoint: Kaplan-Meier Estimate of Overall Survival

<table>
<thead>
<tr>
<th>Deaths %</th>
<th>Median OS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=478</td>
<td>N=476</td>
<td>N=478</td>
</tr>
<tr>
<td>73%</td>
<td>13.6</td>
<td>0.92</td>
</tr>
<tr>
<td>(351)</td>
<td>(12.1, 14.9)</td>
<td>(0.79, 1.06)</td>
</tr>
</tbody>
</table>

a. Based on stratified Cox-model. Non-inferiority margin for HR (lenvatinib vs sorafenib) is 1.08.

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib (N=478)</th>
<th>Sorafenib (N=476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>73%</td>
<td>74%</td>
</tr>
<tr>
<td>(n)</td>
<td>(351)</td>
<td>(350)</td>
</tr>
<tr>
<td>Deaths</td>
<td>73%</td>
<td>74%</td>
</tr>
<tr>
<td>(n)</td>
<td>(351)</td>
<td>(350)</td>
</tr>
<tr>
<td>Median OS</td>
<td>13.6</td>
<td>12.3</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(12.1, 14.9)</td>
<td>(10.4, 13.9)</td>
</tr>
<tr>
<td>HR</td>
<td>0.92</td>
<td>0.79, 1.06</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.79, 1.06)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; OS = overall survival; uHCC = unresectable hepatocellular carcinoma.
REFLECT: Study 304: Phase 3 Study to Compare the Efficacy and Safety of Lenvatinib vs Sorafenib in First-line Treatment of Patients with uHCC

Secondary Endpoint: Objective Response Rate

Investigator-assessed by mRECIST

<table>
<thead>
<tr>
<th>Objective Response, n, %</th>
<th>Lenvatinib(^1) (N=478)</th>
<th>Sorafenib(^1) (N=476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>115 (24.1% (20.2, 27.9))</td>
<td>44 (9.2% (6.6, 11.8))</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>3.13 (2.15, 4.56)</td>
<td>3.13 (2.15, 4.56)</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>CR</td>
<td>6 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>PR</td>
<td>109 (23%)</td>
<td>42 (9%)</td>
</tr>
<tr>
<td>SD</td>
<td>246 (51%)</td>
<td>244 (51%)</td>
</tr>
<tr>
<td>SD ≥23 weeks</td>
<td>167 (35%)</td>
<td>139 (29%)</td>
</tr>
<tr>
<td>PD</td>
<td>71 (15%)</td>
<td>147 (31%)</td>
</tr>
<tr>
<td>Unknown/NE</td>
<td>46 (10%)</td>
<td>41 (9%)</td>
</tr>
<tr>
<td>DCR (95% CI)</td>
<td>361 (75.5% (71.7, 79.4))</td>
<td>288 (60.5% (56.1, 64.9))</td>
</tr>
</tbody>
</table>

- Percentage increase in tumour size was truncated at 100% (rectangles)\(^2\)

Cl = confidence interval; CR = complete response; DCR = disease control rate; mRECIST = modified Response Evaluation Criteria in Solid Tumours; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; uHCC = unresectable hepatocellular carcinoma.

REFLECT: Study 304: Phase 3 Study to Compare the Efficacy and Safety of Lenvatinib vs Sorafenib in First-line Treatment of Patients with uHCC

Patients with radiologic response to Lenvatinib or Sorafenib have a survival advantage!
Note:
Levatinib or sorafenib were not the final treatments in many patients

- 156 (33%) patients in the levatinib arm and 184 (39%) in the sorafenib arm received post-study anticancer medication (including investigational therapy).

- Of these patients, 121 (25%) in the levatinib arm and 56 (12%) in the sorafenib arm received sorafenib during survival follow-up.

Keypoints

- First positive trial in front-line: non-inferior to sorafenib
- Mainly AP population
- Excluded main PVI and less 50% liver involvement Improved secondary endpoints
- Different toxicity profile to sorafenib – more HT and hypothyroidism, less HFSR

Second Line Therapies in Advanced HCC – Phase 3

**Regorafenib vs Placebo**

- Median OS mo (95% CI)
  - Regorafenib (N=379): 10.6 (9.1-12.1)
  - Placebo (N=194): 7.8 (6.3-8.8)

- Hazard ratio 0.63 (95% CI 0.50-0.79), P<0.0001

**Cabozantinib vs Placebo**

- Median OS mo (95% CI)
  - Cabozantinib (N=470): 10.2 (9.1-12.0)
  - Placebo (N=237): 8.0 (6.8-9.4)

- Hazard ratio 0.76 (95% CI 0.63-0.92), P=0.0049*


57 year old man with CTP A cirrhosis secondary to HCV and alcohol
57 year old man with CTP A cirrhosis secondary to HCV and alcohol
57 year old man with CTP A cirrhosis secondary to HCV and alcohol

Locoregional Therapies

Start Sorafenib July 2017

Start Regorafenib April 2018

Patient feeling well!

AFP normal for 12 mths Remains well on treatment
Selective Internal Radiation Therapy (SIRT)

• **Selectively target** a very high radiation dose to all tumours within the liver, regardless of their cell of origin or location, while at the same time maintaining a low radiation dose to the normal liver tissue

• Delivery via hepatic artery, using differential blood supply to liver tumours thereby preferentially targeting tumours

• Uses yttrium-90 ($^{90}\text{Y}$) labelled microspheres
  • Diameter approx. 32 µm (microns)
  • Half life: 64.1 hours
  • Pure Beta emission @ 0.93 MeV
  • Penetrates mean 2.5 mm tissue; max 11 mm

Common Terminology
- Interv Rad -> “radioembolization”
- Rad Onc -> “microsphere brachytherapy”
- Nuc Med, Med Onc -> “SIRT”
2 RCTs of Sorafenib vs SIRT in Advanced HCC - Both negative studies (superiority design)
Addition of selective internal radiation therapy does not significantly improve overall survival compared to sorafenib alone.

RCT of patients with advanced HCC ineligible for TACE

11:10 ratio combo vs SOR alone

NS in PP and ITT analyses
Efficacy and Safety of TACE plus External Beam RT vs Sorafenib in HCC with macroscopic vascular invasion: An RCT

**Table 1. Baseline Characteristics of the Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 90)</th>
<th>Sorafenib Group (n = 45)</th>
<th>TACE-RT Group (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral PV</td>
<td>53 (58.9)</td>
<td>27 (60.0)</td>
<td>26 (57.8)</td>
</tr>
<tr>
<td>Bilateral or main PV</td>
<td>33 (36.7)</td>
<td>16 (35.6)</td>
<td>17 (37.8)</td>
</tr>
<tr>
<td>Unilateral PV + HV or IVC</td>
<td>2 (2.2)</td>
<td>1 (2.2)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Bilateral PV + HV or IVC</td>
<td>2 (2.2)</td>
<td>1 (2.2)</td>
<td>1 (2.2)</td>
</tr>
</tbody>
</table>

**TACE (every 6 weeks) plus RT (within 3 weeks after the first TACE)**

<table>
<thead>
<tr>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.27</td>
<td>(0.17-0.44)</td>
</tr>
<tr>
<td>TTP</td>
<td>0.28</td>
<td>(0.17-0.46)</td>
</tr>
<tr>
<td>OS</td>
<td>0.61</td>
<td>(0.38-0.98)</td>
</tr>
</tbody>
</table>

Median OS 55.0 vs 43.0 weeks; P = .04

Curative surgical resection in 5 patients (11.1%)
Overcoming adaptive immune resistance with checkpoint inhibitors.

Cancers develop multiple strategies to evade and suppress antitumour immune response. Checkpoint inhibitors block inhibitory molecules to drive CTL killing of cancer cells expressing escape neoantigens.
CheckMate 459: A Randomized, Multi-Center Phase 3 Study of Nivolumab vs Sorafenib as First-Line Treatment in Patients With Advanced Hepatocellular Carcinoma

Thomas Yau,1 Joong-Won Park,2 Richard S. Finn,3 Ann-Lii Cheng,4 Philippe Mathurin,5 Julien Edeline,6 Masatoshi Kudo,7 Kwang-Hyub Han,8 James J. Harding,9 Philippe Merle,10 Oliver Rosmorduc,11 Lucjan Wyrwicz,12 Eckart Schott,13 Su Pin Choo,14 Robin Kate Kelley,15 Damir Begic,16 Gong Chen,16 Jaclyn Neely,16 Jeffrey Anderson,16 Bruno Sangro17

1University of Hong Kong, Hong Kong, China; 2Center for Liver Cancer, National Cancer Center, Goyang, South Korea; 3Geffen School of Medicine, UCLA, Los Angeles, CA, USA; 4National Taiwan University Hospital, Taipei, Taiwan; 5Centre Hospitalo-Universitaire Claude Huriez, Service d'Hépatologie, Lille, France; 6Medical Oncology, Centre Eugène Marquis, Rennes, France; 7Kindai University Faculty of Medicine, Osaka, Japan; 8Severance Hospital, Yonsei University, Seoul, South Korea; 9Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 10Hepatology Unit, Croix-Rousse Hospital, Lyon, France; 11Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière – Université Pierre et Marie Curie, Paris, France; 12M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; 13Helios Klinikum Emil von Behring GmbH, Klinik für Innere Medizin II, Berlin, Germany; 14National Cancer Centre Singapore, Singapore; 15UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 16Bristol-Myers Squibb, Princeton, NJ, USA; 17Clinica Universidad de Navarra and CIBEREHD, Pamplona, Spain
Checkmate 459 Study Design
NCT02576509

Key eligibility criteria
- Histologically confirmed advanced HCC not eligible for surgical and/or LRT; or progressive disease after surgical and/or LRT
- Child-Pugh class A
- ECOG PS 0 or 1
- Systemic therapy naive

Objectives
- Primary – OS
- Secondary – ORR, PFS, efficacy by PD-L1 status
- Exploratory – HRQoL using FACT-Hep

Stratification factors
- Etiology (HCV vs non-HCV)
- Vascular invasion and/or extrahepatic spread (present vs absent)
- Geography (Asia vs non-Asia)

Patient randomization:
- January 2016–May 2017
- Database lock: June 2019

Designed as a SUPERIORITY trial

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; FACT-Hep, Functional Assessment of Cancer Therapy - Hepatobiliary Cancer; HCV, hepatitis C virus; HRQoL, health-related quality of life; IV, intravenous; LRT, loco-regional therapy; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; po, oral; R, randomization.
Overall Survival

**The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit.**

<table>
<thead>
<tr>
<th>Months</th>
<th>Nivolumab (n = 371)</th>
<th>Sorafenib (n = 372)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12mo</td>
<td>Median OS</td>
<td>16.4 (13.9–18.4)</td>
<td>0.85</td>
<td>0.0752</td>
</tr>
<tr>
<td>12-24mo</td>
<td></td>
<td>14.7 (11.9–17.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on Kaplan–Meier estimates; *b*Stratified Cox proportional hazards model. HR is nivolumab over sorafenib; *c*P value from log-rank test; final OS boundary: 0.0419 for a 2-sided nominal P value.

HR, hazard ratio.
Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

IMbrave150 study design

Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

Atezolizumab (anti–PD-L1) + Bevacizumab (anti-VEGF)

---

*Japan is included in rest of world.
*An additional 57 Chinese patients in the China extension cohort were not included in the global population analysis.
OS: co-primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), mo(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab + Bevacizumab</td>
<td>NE</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>13.2 (10.4, NE)</td>
</tr>
</tbody>
</table>

HR, 0.58 (95% CI: 0.42, 0.79)\(^b\)

\(P = 0.0006^{b,c}\)

6-mo OS rate: 85%
6-mo OS rate: 72%

mOS: NE
mOS: 13.2 mo

NE, not estimable. \(^a\) 96 patients (29%) in the Atezolizumab + Bevacizumab arm vs 65 (38%) in the sorafenib arm had an event. \(^b\) HR and \(P\) value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per RxRS. \(^c\) The 2-sided \(P\) value boundary based on 181 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.8 mo.
Authors Conclusion:

Atezolizumab + bevacizumab should be considered a practice-changing treatment for patients with unresectable HCC who have not received prior systemic therapy
### Many immunotherapy combinations are under investigation

**Monotherapy (checkpoint inhibitors – mostly in 2L)**

- **Atezolizumab** (phase Ib)  
  *Anti-PD-L1*  
  *NEG*

- **Pembrolizumab** (phase I/II)  
  *Anti-PD-1*  
  *NEG*

- **Cemiplimab** (phase I)  
  *Anti-PD-L1*  
  *NEG*

- **Nivolumab** (phase III)  
  *Anti-PD-1*  
  *NEG*

- **Durvalumab** (phase I/II)  
  *Anti-PD-L1*  
  *NEG*

- **Spartalizumab** (phase Ib/II)  
  *Anti-PD-1*  
  *NEG*

- **Camrelizumab** (phase II)  
  *Anti-PD-1*  
  *NEG*

- **Avelumab** (phase II)  
  *Anti-PD-L1*  
  *NEG*

- **Tiseliuzumab** (phase III)  
  *Anti-PD-1*  
  *NEG*

**Combinations of checkpoint inhibitors + anti-VEGF**

- **Atezolizumab + bevacizumab** (phase III)  
  *Anti-PD-L1 + anti-VEGF*  
  *POS*

- **Pembrolizumab + lenvatinib** (phase III)  
  *Anti-PD-1 + TKI*  
  *NEG*

- **Atezolizumab + cabozantinib** (phase III)  
  *Anti-PD-L1 + TKI*  
  *NEG*

- **Pembrolizumab + regorafenib** (phase Ib)  
  *Anti-PD-1 + TKI*  
  *NEG*

- **Nivolumab + bevacizumab** (phase I)  
  *Anti-PD-1 + anti-VEGF*  
  *NEG*

- **Nivolumab + sorafenib** (phase III)  
  *Anti-PD-1 + TKI*  
  *NEG*

- **Nivolumab + lenvatinib** (phase Ib)  
  *Anti-PD-1 + TKI*  
  *NEG*

- **Camrelizumab + apatinib** (phase II)  
  *Anti-PD-1 + TKI*  
  *NEG*

- **Avelumab + axitinib** (phase Ib)  
  *Anti-PD-L1 + TKI*  
  *NEG*

- **Spartalizumab + sorafenib** (phase II)  
  *Anti-PD-1 + TKI*  
  *NEG*

**Combinations of two checkpoint inhibitors**

- **Durvalumab + tremelimumab** (phase III)  
  *Anti-PD-L1 + anti-CTLA4*  
  *NEG*

- **Nivolumab + relatilimab** (phase I/II)  
  *Anti-PD-1 + anti-LAG3*  
  *NEG*

- **Nivolumab + ipilimumab** (phase II)  
  *Anti-PD-1 + anti-CTLA4*  
  *NEG*

---

> ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the regulatory authorities in your country according to your national requirements.
The changing landscape of advanced HCC

- 2008-2017: Sorafenib

- 2018:
  - Lenvatinib
  - Regorafenib
  - Cabozantinib
  - Ramicirumab
  - Nivolumab
  - Pembrolizumab

- BSC: 8 m
- Sorafenib: 11 m
- Sorafenib and second-line therapy: 26 m

Atezolizumab + Bevacizumab and future IOs
Challenges

• Increasing burden of hepatocellular carcinoma

• How do we ensure access to new therapies with proven benefit in randomised-controlled trials? How do we afford them?

• How do these agents perform in real-world settings? Is toxicity manageable?

• Who should care for patients with advanced HCC? Liver disease, HCC progression, AEs, - Hepatologists or Oncologists?

• Systems impact – Capacity to deliver therapies in multiple settings for long durations
Thank you

WELCOME TO AGW 2020 in MELBOURNE

AGW 2020

When and Where
Sunday 30 August – Tuesday 1 September 2020
Melbourne Convention Centre, Melbourne

Bushell Lecturer
Professor Jonel Trebicka
Goethe-Universität Frankfurt am Main
Medical Clinic I, Faculty of Medicine
Niederrad Campus

Sponsorship, Exhibition and Advertising
Check back for more details

Opportunities
We are hoping to arrange opportunities to visit the new world-leading Melbourne medical precinct.

More Information
agw@gesa.org.au or mobile/sms: 0466 574 002