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MEETING SUMMARY
ESMO 2018, Munich, Germany

Dr. Changhoon Yoo

Assistant Professor, Department of Oncology, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Korea

HIGHLIGHTS ON HEPATOCELLULAR CARCINOMA

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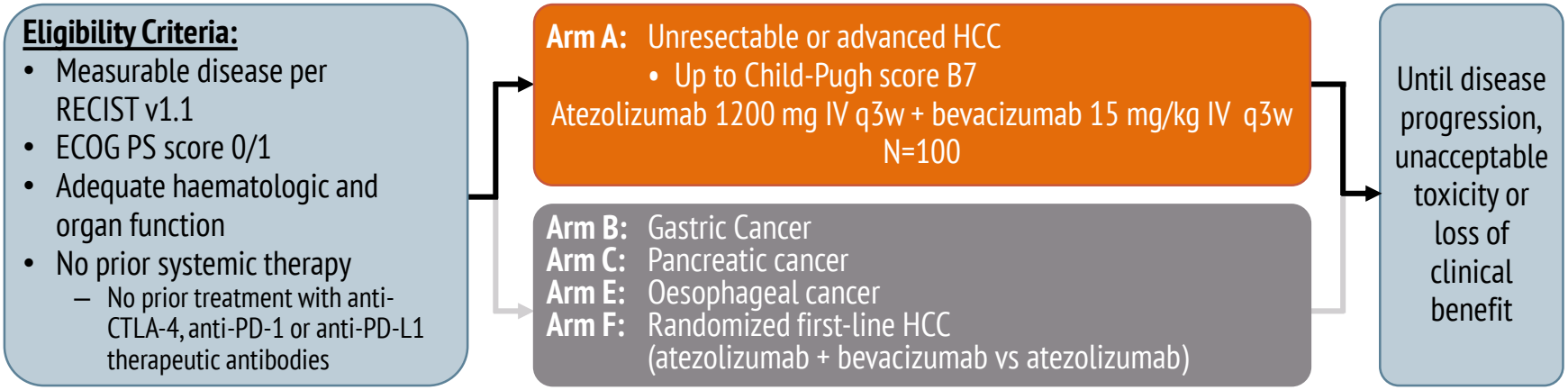
UPDATED SAFETY AND CLINICAL ACTIVITY RESULTS FROM A PHASE IB STUDY OF ATEZOLIZUMAB + BEVACIZUMAB IN HCC

M Pishvaian et al. Abst #LBA26

STUDY DESIGN



Primary endpoints[a] (Arm A)

- Safety and tolerability, investigator-assessed ORR per RECIST v1.1

Key secondary endpoints (Arm A)

- Investigator-assessed DOR, PFS and TTRP per RECIST v1.1
- IRF-assessed ORR, DOR, PFS and TTRP (all per RECIST v1.1 and HCC mRECIST)
- OS

At clinical data cut-off (26 July 2018), 103 patients with HCC treated with atezolizumab + bevacizumab were evaluable for safety and 73 patients were evaluable for efficacy with a minimum follow-up of 16 weeks

CTLA-4, cytotoxic T-lymphocyte–associated protein; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IRF, independent review facility; IV, intravenous; mRECIST, modified RECIST; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; TTRP, time to radiographic progression

[a] Endpoints per protocol version 5

Ducreux M, et al. Presented at ESMO 2018 (abstract 782TiP)

KEY EFFICACY AND SAFETY OUTCOMES

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- **Treatment-related grade 3/4 adverse events: 27%**
  - No new safety signals were identified beyond the established safety profile for each individual agent

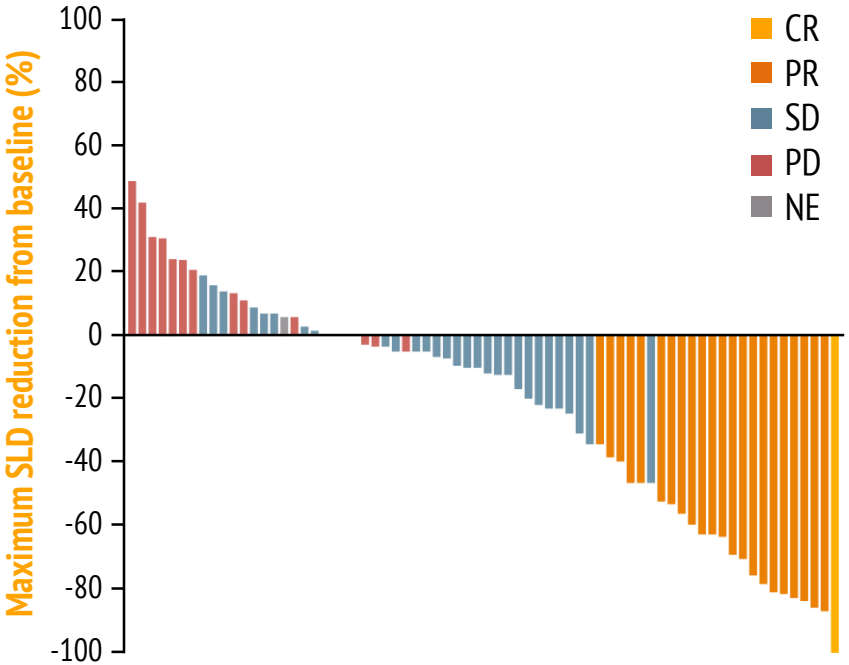
- **Best Objective Response Rates (ORR)**
  - Investigator-assessed ORR per RECIST v1.1: 32%
  - IRF-assessed ORR per mRECIST v1.1: 34%

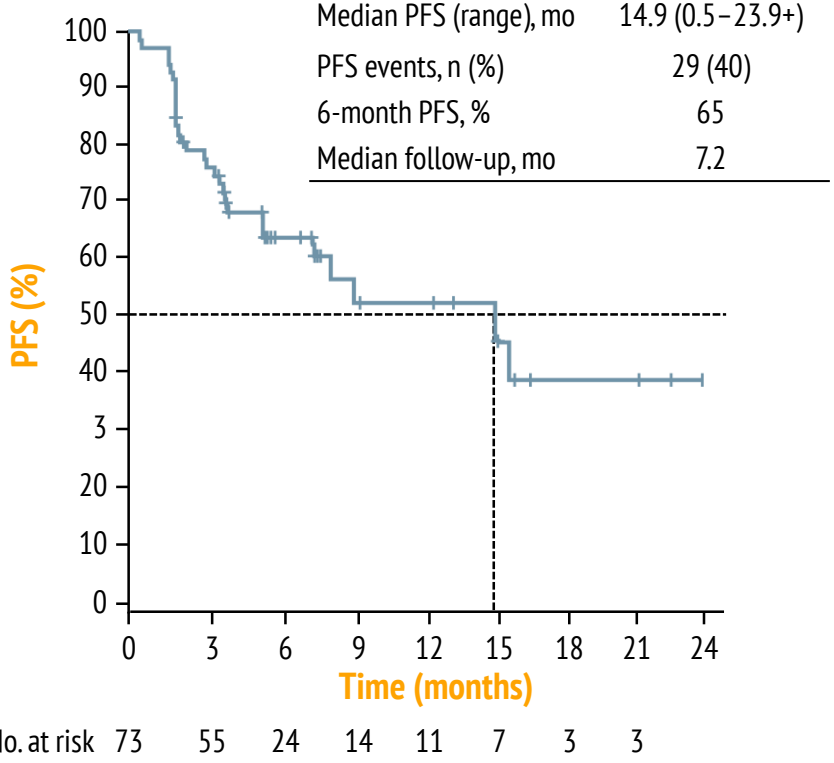
- **Progression Free Survival (PFS)**
  - Investigator-assessed per RECIST v1.1: median 14.9 months (range 0.5–23.9+)
  - IRF-assessed per RECIST v1.1: median 7.5 months (range 0.4–23.9)
  - Further follow-up is needed considering small number of events

IRF, independent review facility; mRECIST, modified RECIST; ORR, overall response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Pishvaian M, et al. Presented at: ESMO 2018 (abstr LBA26)

EFFICACY OUTCOMES: INVESTIGATOR-ASSESSED RECIST V1.1





	N=73
Median PFS (range), mo	14.9 (0.5–23.9+)
PFS events, n (%)	29 (40)
6-month PFS, %	65
Median follow-up, mo	7.2

CR, complete response; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; SLD, sum of longest diameter

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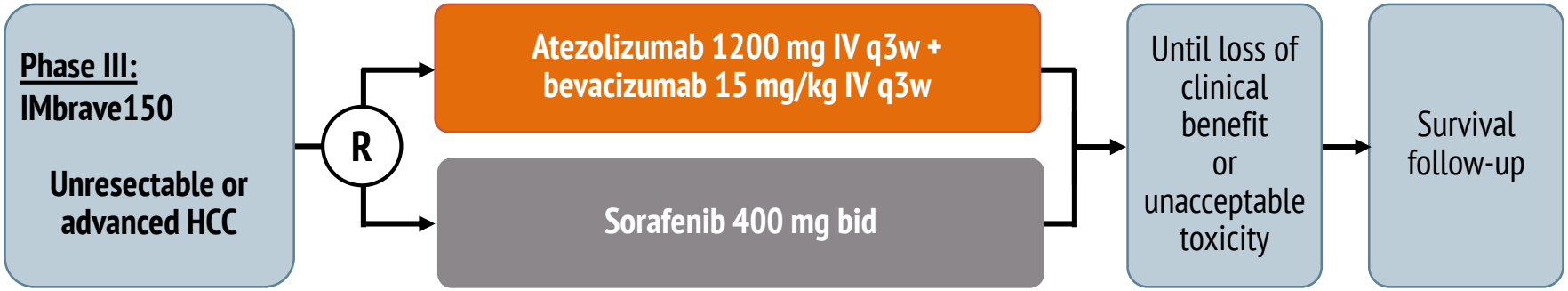
ONGOING PHASE 3 TRIALS FOR ATEZOLIZUMAB PLUS BEVACIZUMAB

- Atezolizumab + bevacizumab is being evaluated in the Phase III study IMbrave150 (NCT03434379)
  - Primary endpoint: investigator-assessed ORR per RECIST v1.1 and OS



bid, twice a day; HCC, hepatocellular carcinoma; IV, intravenous; OS, overall survival; ORR, overall response rate; q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours

Pishvaian M, et al. Presented at: ESMO 2018 (abstr LBA26)

RAMUCIRUMAB AS 2ND-LINE TREATMENT IN PATIENTS WITH ADVANCED HCC AND ELEVATED AFP FOLLOWING 1ST-LINE SORAFENIB: PATIENT REPORTED OUTCOME RESULTS ACROSS TWO PHASE III STUDIES (REACH-2 AND REACH)

A Zhu et al. Abst #622PD

AFP, alpha fetoprotein; HCC, hepatocellular carcinoma

REACH-2: RAMUCIRUMAB AS 2ND-LINE TREATMENT FOR HCC (PRESENTED AT ASCO 2018)

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- Ramucirumab significantly improved survival outcomes for patients with unresectable HCC and **AFP > 400 ng/mL** after failure of 1st-line sorafenib
  - Median **OS**: 8.5 vs 7.3 months for ramucirumab vs placebo
    - HR 0.710; 95% CI 0.531, 0.949; p=.0199
  - Median **PFS**: 2.8 vs 1.6 months for ramucirumab vs placebo
    - HR 0.452; 95% CI 0.339, 0.603; p<.0001
- **ORR:** 4.6% vs 1.1% for ramucirumab vs placebo (p=.1156)
- **DCR** (ORR + SD): 59.9% vs 38.9% for ramucirumab vs placebo (p=.0006)

AFP, alpha fetoprotein; CI, confidence interval; DCR, disease control rate; HR, hazard ratio; ORR, objective response rate; OS, overall survival; SD, stable disease

Zhu A, et al. Presented at ASCO 2018 (abstr 4003)

POOLED ANALYSIS OF REACH AND REACH-2 STUDIES FOR PROs

STUDY DESIGNS

REACH

N=250 (AFP ≥ 400 ng/mL)

- Prior sorafenib
- BCLC stage B/C
- Child-Pugh A
- ECOG PS 0 or 1

R 1:1

- Ramucirumab (8 mg/kg IV) q2w per cycle and BSC
- Placebo q2w per cycle and BSC

Treatment until disease progression or unacceptable toxiciy

Stratification factors
- Etiology (hepatitis B, hepatitis C, other)
- Geographic regions

Primary endpoint: Overall survival

Secondary endpoints include: PFS, ORR, safety

PROs

REACH-2

N=292

- Prior sorafenib
- BCLC stage B/C
- Child-Pugh A
- ECOG PS 0 or 1
- Baseline AFP ≥ 400 ng/mL

R 2:1

- Ramucirumab (8 mg/kg IV) q2w per cycle and BSC
- Placebo q2w per cycle and BSC

Treatment until disease progression or unacceptable toxiciy

Stratification factors
- Macrovascular invasion (yes vs no)
- ECOG PS (0 vs 1)
- Geographic regions

Primary endpoint: Overall survival

Secondary endpoints include: PFS, ORR, safety

PROs

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; PFS, progression-free survival; PRO, patient-reported outcome; R, randomization; q2w, every 2 weeks

ClinicalTrials.gov identifier: REACH: NCT01140347, REACH-2: NCT02435433. Zhu A, et al. Presented at ESMO 2018 (abstr 622PD)

RAMUCIRUMAB DELAYED CLINICALLY MEANINGFUL SYMPTOM DETERIORATION VS PLACEBO

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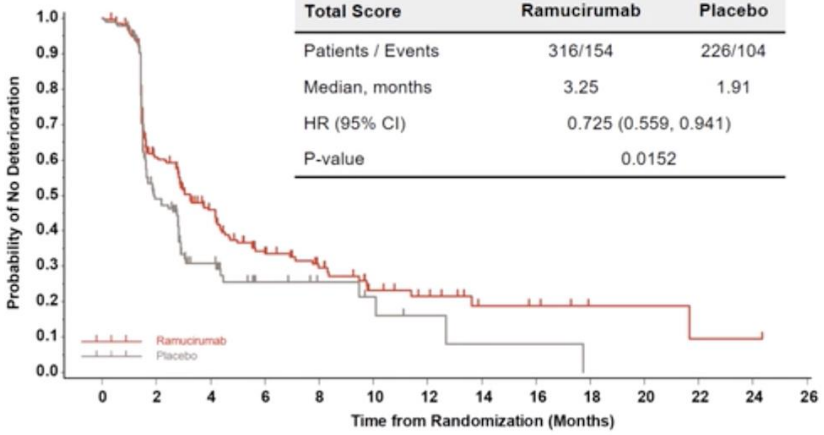
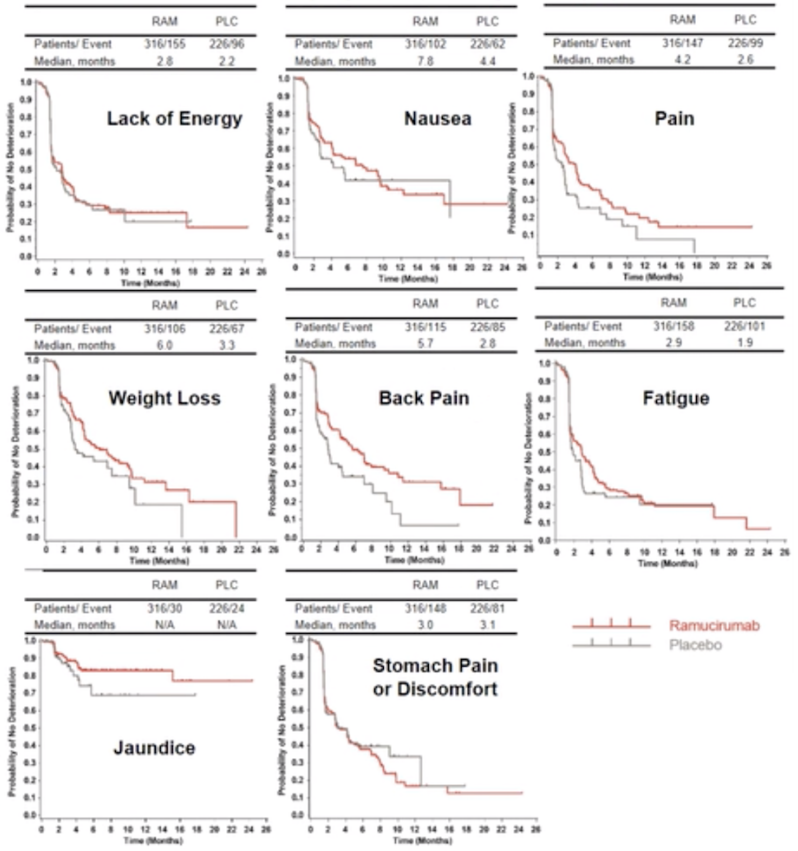
TtD in FHSI-8 total score in the pooled population

Total Score	Ramucirumab	Placebo
Patients / Events	316/154	226/104
Median, months	3.25	1.91
HR (95% CI)	0.725 (0.559, 0.941)	
P-value	0.0152	



TtD in FHSI-8 individual symptoms in the pooled population



CI, confidence interval; FHSI-8, Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index; HR, hazard ratio; N/A, not available; PLC, placebo; RAM, ramucirumab; TtD, time to deterioration

Zhu A, et al. Presented at ESMO 2018 (abstr 622PD)

IN CLINICAL PRACTICE

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- Despite promising data for immune checkpoint inhibitors in the early phase clinical trials, there are no results of randomized phase 3 trials that support the use of these agents in daily practice setting[1]
- At present, sorafenib and lenvatinib are the standard of care as first-line systemic treatment for patients with unresectable HCC[1]
- Ramucirumab demonstrated a consistent trend for a benefit in disease-related symptoms[2]
- Regorafenib is now the only globally approved agent as second-line treatment, with nivolumab approved in the USA
  - Ramucirumab and cabozantinib are awaiting approval for this indication
  - Further efforts to find the optimal subgroup of patients for each agent are needed

HCC, hepatocellular carcinoma

1. EASL. J Hepatol 2018; 69:182-236
2. Zhu A, et al. Presented at ESMO 2018 (abstr 622PD)

HCC CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

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

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