# Considerations for the Treatment of HCC in Special Patient Populations

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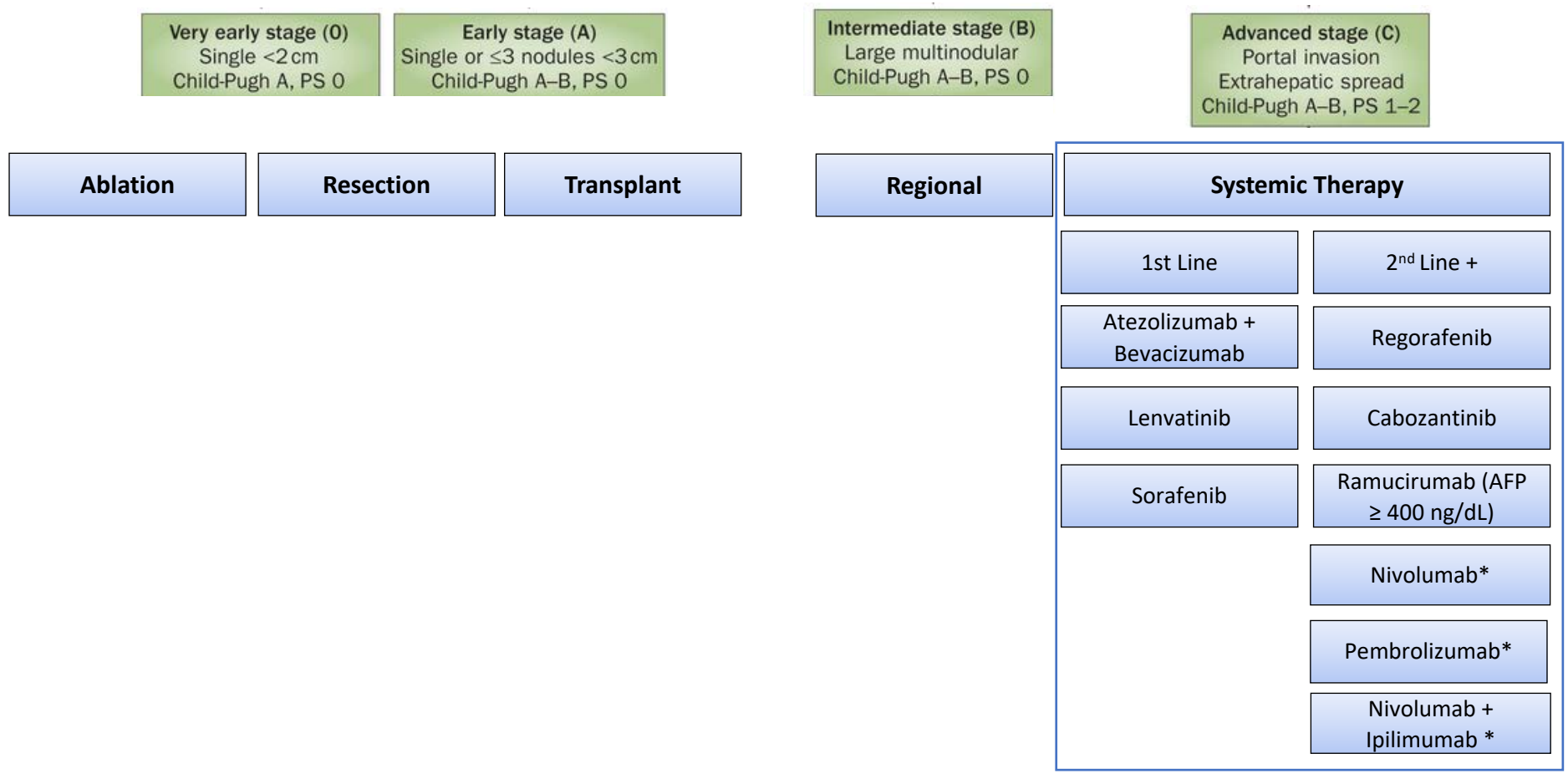
# Current Treatment Paradigm for Advanced HCC

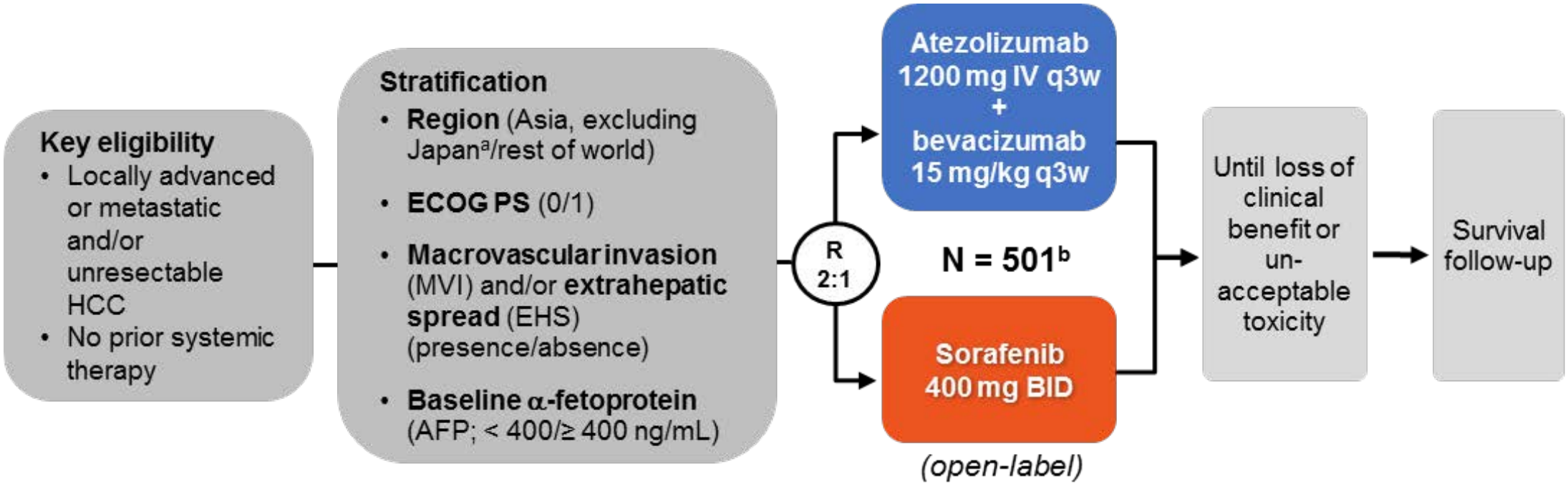
**Early Stage**
15-20%

**Advanced Stage**
75-80%




*Based on Durable objective response rate; not statistically proven OS advantage over placebo

# IMbrave150: Atezolizumab + Bevacizumab versus Sorafenib




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

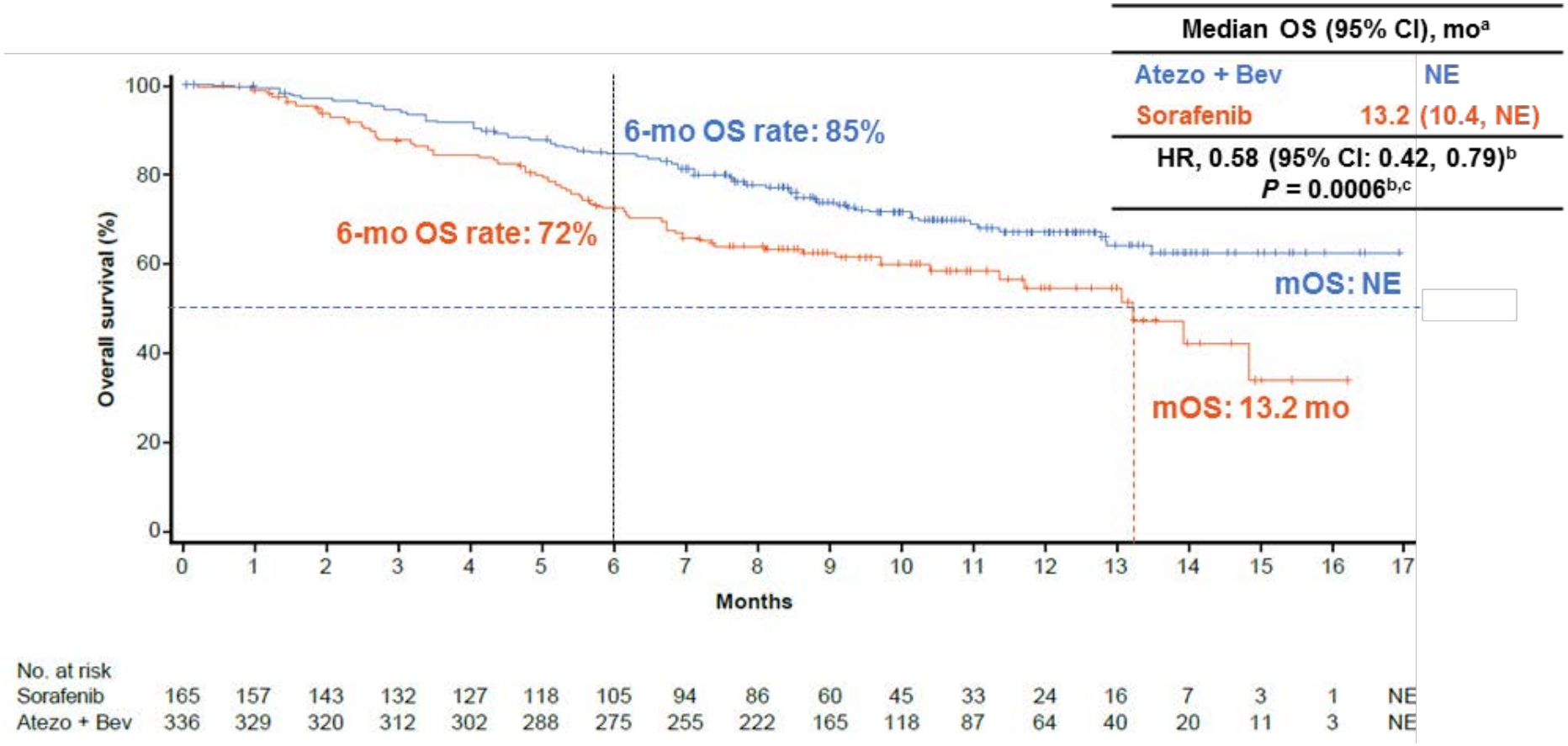
**Key secondary endpoints** (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.



Cheng et al. ESMO ASIA 2019

# IMbrave150: Atezolizumab plus Bevacizumab Improves OS Compared to Sorafenib

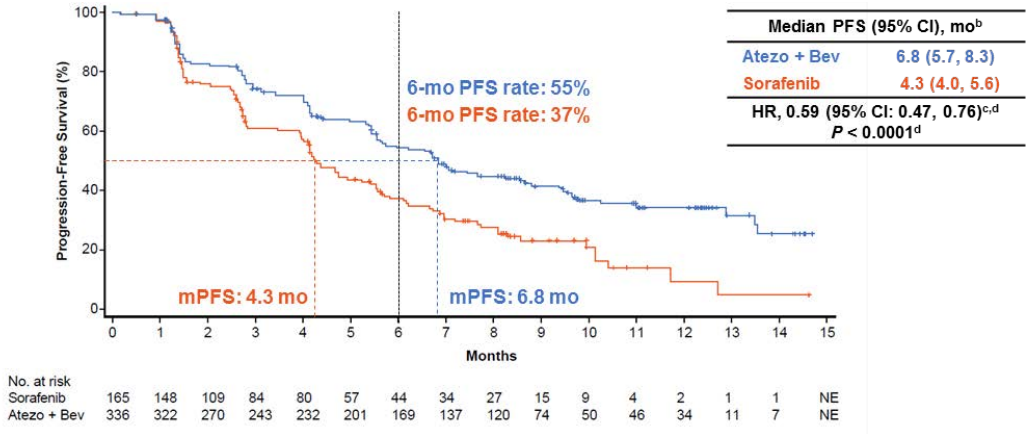



Updated data from GI ASCO 2021 indicates A + B median OS 19.2 months

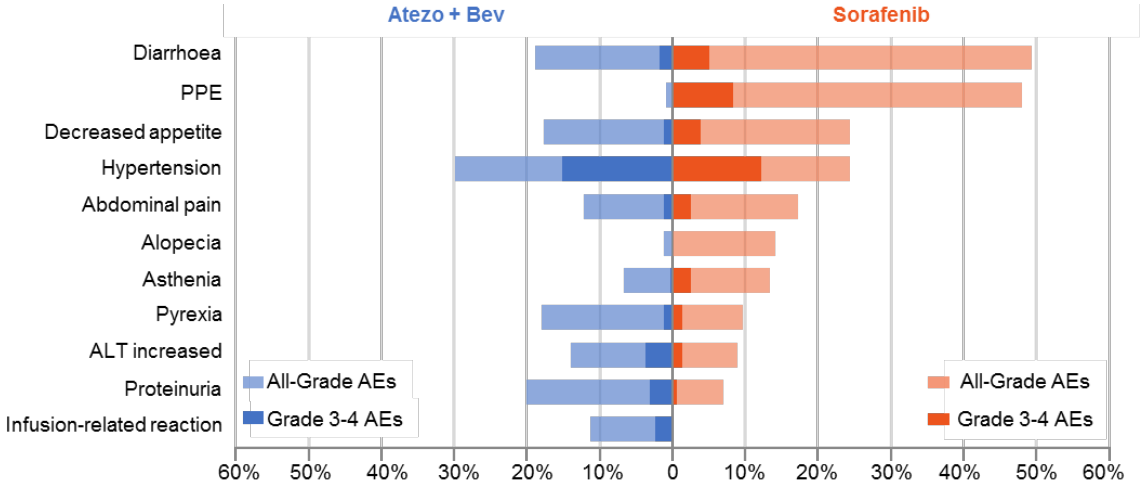
Cheng et al. ESMO ASIA 2019

# IMbrave150: Secondary Endpoints Favor Atezolizumab + Bevacizumab

## Improves PFS for Advanced Disease



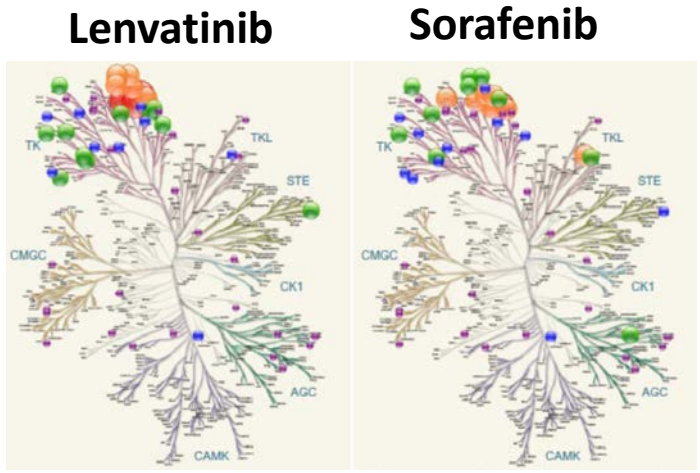

## Favorable Safety/QoL (Grade ≥ 3 AE 36% vs 46%)

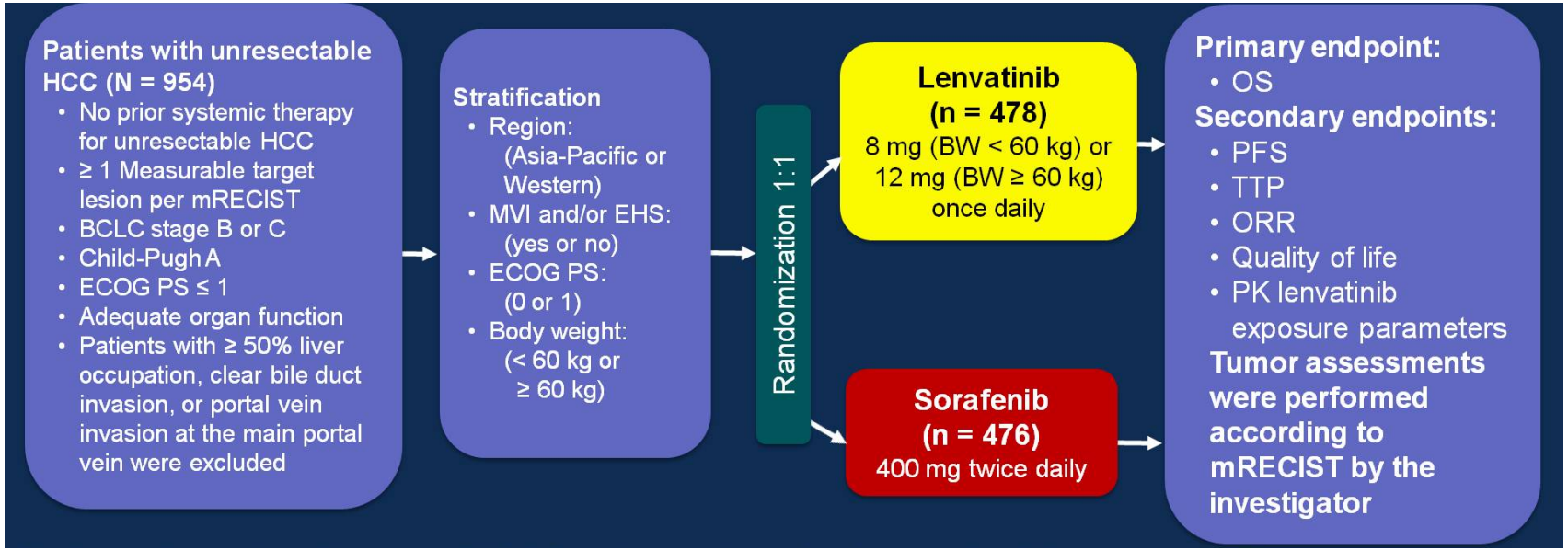



PPE, palmar-plantar erythrodysaesthesia.
[a] Safety-evaluable population.

Cheng et al. ESMO ASIA 2019

# REFLECT: Lenvatinib vs. Sorafenib




Kudo et al. Lancet 2018

# REFLECT: Lenvatinib OS is Non-Inferior to Sorafenib

| | Lenvatinib (N=478) | Sorafenib (N=476) | Effect Size | P-value |
|---|---|---|---|---|
| **OUTCOMES** | | | | |
| OS (months) | 13.6 | 12.3 | HR 0.92 (0.78-1.06) | __ |
| PFS (months) | 7.4 | 3.7 | HR 0.66 (0.57-0.77) | < 0.0001 |
| TTP (months) | 8.9 | 3.7 | HR 0.63 (0.53-0.73) | < 0.0001 |
| ORR mRECIST, Investigator | 24.1% | 9.2% | OR 3.13 (2.15-4.56) | < 0.0001 |
| ORR mRECIST, BICR (%) | 40.6% | 12.4% | OR 5.01 (3.49-7.01) | < 0.0001 |
| **ADVERSE EVENTS** | | | | |
| Related Any AEs | 94% | 99% | Grade ≥ 3 HTN, anorexia/weight loss, proteinuria numerically higher for lenvatinib<br>Grade ≥ 3 HFS higher for sorafenib | |
| Related Grade ≥3 AEs | 57% | 49% | | |

Kudo et al. Lancet 2018

# Generalizability of IMbrave150 and REFLECT?

- **Stringent selection criteria**
  - Limited the extent of liver disease
  - Exclusion of main portal vein involvement
  - Restricted to CP-A
  - Minimization of bleeding risk
- **Application to selected special population**
  - Decompensated liver function
  - Recent GI bleeding
  - Autoimmune conditions
  - Liver transplant recipient

# Child-Pugh score restricts access to pivotal clinical trials

| Pivotal Study Randomized Study | CHILD-PUGH B or worse |
|---|---|
| SHARP | Yes |
| REFLECT | NO |
| IMbrave150 | NO |
| RESORCE | NO |
| CELESTIAL | NO |
| REACH-2 | NO |
| CheckMate 459 | NO |
| KEYNOTE-240 | NO |

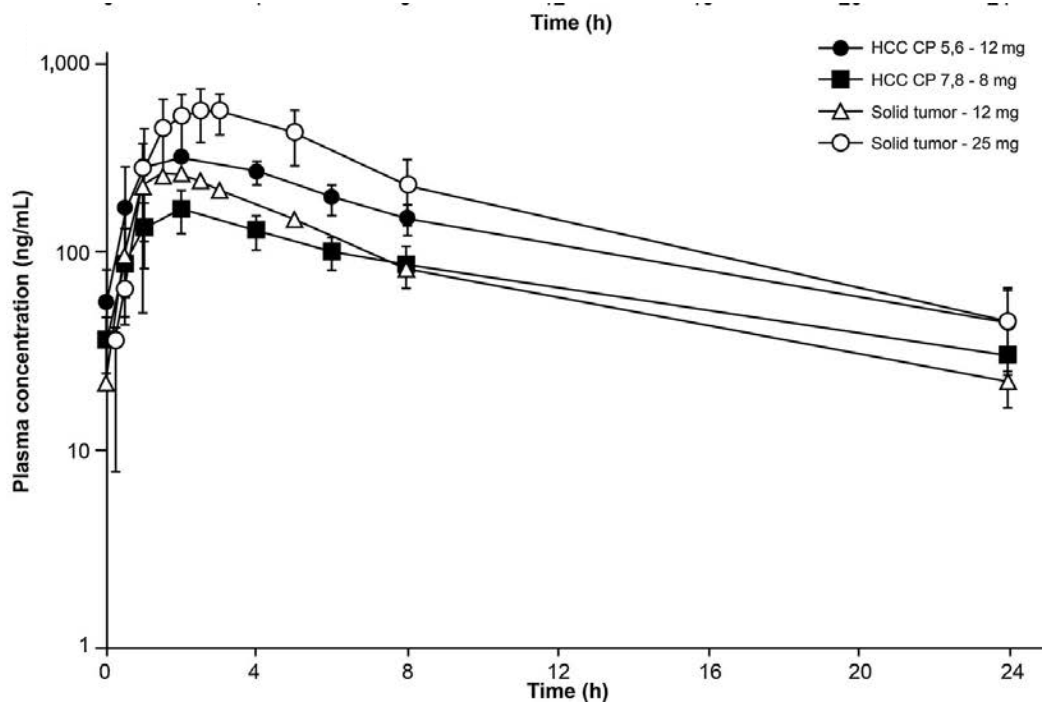
**Data with Sorafenib and decompensated liver function**

- CP-B and CP-C HCC patients are known to have worse OS on sorafenib (OS: CP-A 13.6 vs CP-B 5.2 months vs CP-C 2.6 months)
- CP-C is typically a contraindication to treatment
- A phase 1 study for sorafenib in patients with organ dysfunction indicates sorafenib dose modifications are required for CP-B or worse
- Newer TKIs and IO agents will require careful evaluation and this is ongoing

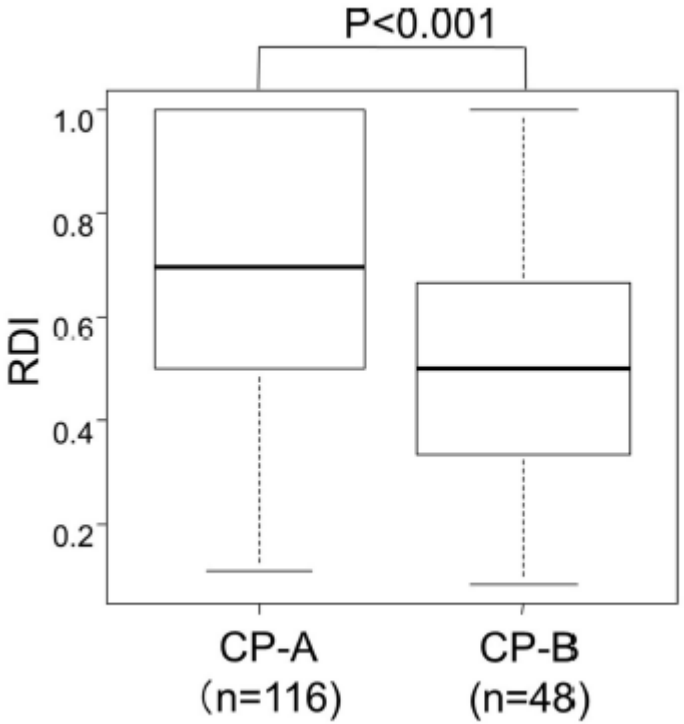
Marrero et al. J Hepatology 2016; Miler et al. JCO 2009

# Lenvatinib and CP-B liver function

Limited PK data but dose may matter relative to Liver function




Retrospective studies indicate a similar rate of AEs despite lower relative dose intensity (PDI)




Ikeda et al. CCR 2017; Ogushi et al. Clinical and Experimental Gastroenterology

# Immuno-oncology agents and decompensated liver function

| CheckMate 040 CP-B N= 49 | |
|---|---|
| ORR | 10.2% |
| DCR | 55.1% |
| mDOR | 9.9 months |
| mOS | 7.2 months |
| TEAEs | 51% |
| AEs leading to discontinuation | 4.1% |

Nivolumab in Patients With Advanced Hepatocellular Carcinoma and Child-Pugh Class B Cirrhosis: Safety and Clinical Outcomes in a Retrospective Case Series

Swetha Kambhampati, MD [1,2]; Kelly E. Bauer, AB, MSc[2]; Paige M. Bracci, PhD, MPH[3]; Bridget P. Keenan, MD, PhD[1,2]; Spencer C. Behr, MD[4]; John D. Gordan, MD, PhD[1,2,5]; and Robin K. Kelley, MD [1,2]

Post-registration experience of nivolumab in advanced hepatocellular carcinoma: an international study

Petros Fessas [1], Ahmed Kaseb,[2] Yinghong Wang [3], Anwaar Saeed,[4] David Szafron,[5] Tomi Jun,[6] Sirish Dharmapuri,[6] Abdul Rafeh Naqash,[7] Mahvish Muzaffar,[7] Musharraf Navaid,[7] Uqba Khan,[8] ChiehJu Lee,[9] Anushi Bulumulle,[7] Bo Yu,[10] Sonal Paul,[10] Neil Nimkar,[10] Dominik Bettinger,[11] Francesca Benevento,[12] Hannah Hildebrand,[4] Tiziana Pressiani,[13] Yehia I Abugabal,[2] Nicola Personeni,[13,14] Yi-Hsiang Huang [9], Lorenza Rimassa [13,14] Celina Ang,[6] Thomas Marron,[6] David J Pinato[1]

Single agent IO appears safe data are limited for new combinations

Kudo et al. JCO supplement 2019

# Bleeding risk with Atezolizumab + Bevacizumab and other agents?

**Table 2.** Major Toxicities/Adverse Effects Possibly Attributed to Bevacizumab

| Toxicity | All Grades | | Grades 3 and 4 | |
|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % |
| Hypertension | 15 | 33 | 7 | 15 |
| Proteinuria | 19 | 41 | 2 | 4 |
| Epistaxis | 5 | 11 | 0 | 0 |
| Hemorrhage | 12 | 26 | 5 | 11 |
| Arterial thrombosis | 2 | 4 | 2 | 4 |
| Venous thrombosis | 1 | 2 | 1 | 2 |
| Rash | 6 | 13 | 0 | 0 |
| Thrombocytopenia | 6 | 13 | 0 | 0 |
| Increased AST | 10 | 22 | 1 | 2 |
| Increased ALT | 9 | 20 | 1 | 2 |
| Increased alkaline phosphatase | 5 | 11 | 1 | 2 |
| Increased bilirubin | 12 | 26 | 5 | 11 |
| Ascites | 5 | 11 | 2 | 4 |
| Fatigue | 15 | 33 | 0 | 0 |
| Vomiting | 5 | 11 | 0 | 0 |
| Anorexia | 5 | 11 | 1 | 2 |
| Nausea | 5 | 11 | 0 | 0 |

Bevacizumab 5mg/kg
26% hemorrhage
11% Grade 3 or higher

| IMbrave150* | | |
|---|---|---|
| | Sorafenib | A + B |
| Any Grade Hemorrhage | 17.3% | 25.2% |
| Grade 3-4 | 5.8% | 6.4% |
| Grade 5 | <1% | 1.8% |

*EGD and primary prophylaxis were required for patient entry,
? Ablity to extrapolate to patients with portal HTN and impaired liver function

Siegel et al. JCO 2008; Finn et al NEJM 2020

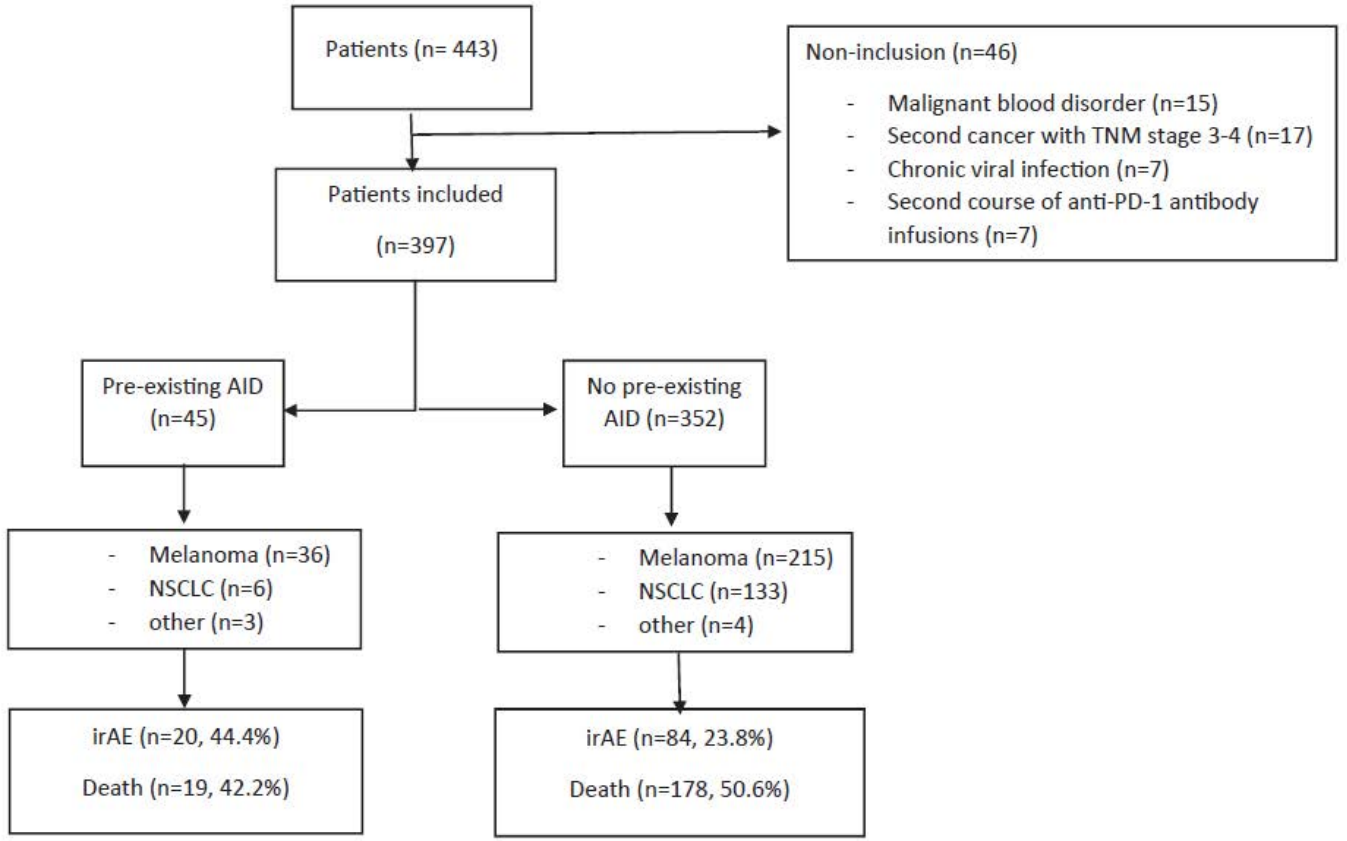
# Immunotherapy in patients with autoimmune diseases must be used with caution

HCC in the context of autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) ***Incidence 3-18 cases per 1000 patient year***

Co-occurring autoimmune disease (AID) **Incidence unknown**

All Prospective Studies in HCC and IO have excluded, thus limitation in data

REISAMIC Registry for Patient Autoimmune Disease (AID)




**irAE 44% for those with AID vs 23.8% for those without AID**

Danlos et al. European Journal of Cancer 2018

# Immunotherapy following liver transplant is contraindicated in routine practice

Change in liver function in 7 patients following IO treatment in prior liver transplant recipient

| ID | Change in Child Pugh | Change in MELD | Change in AFP (ng/mL) | Change in albumin (g/dL) | Change in Tbili (mg/dL) | Change in AST (U/L) | Change in ALT (U/L) | Change in INR |
|---|---|---|---|---|---|---|---|---|
| 1 | 0 | +5 | +1,000 | −0.3 | 0 | +162 | +84 | +0.08 |
| 2 | 0 | 0 | N/A | +0.3 | +0.1 | −4 | −7 | −0.2 |
| 3 | +1 | 0 | +214,082 | −0.1 | 0 | +3 | +26 | +0.08 |
| 4 | +1 | +1 | +8,480 | −0.3 | +0.1 | +7 | 0 | +0.08 |
| 5 | 0 | +1 | +206.1 | +1.5 | −0.1 | +11 | +1 | +0.45 |
| 6 | +2 | +5 | +64.6 | −1.1 | +0.2 | +900 | +846 | 0.18 |
| 7 | +2 | +6 | +44,767 | −0.1 | +0.8 | 169 | +151 | +0.1 |
| Median | +1 | +1 | +1,000 | −0.3 | +0.1 | +11 | +26 | +0.08 |

ID, patient identification; MELD, model for end stage liver disease; AFP, alpha-fetoprotein; Tbili, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; ng/Ml, nanograms per milliliter; g/dL, grams per deciliter; mg/dL, milligrams per deciliter; U/L, units per liter.

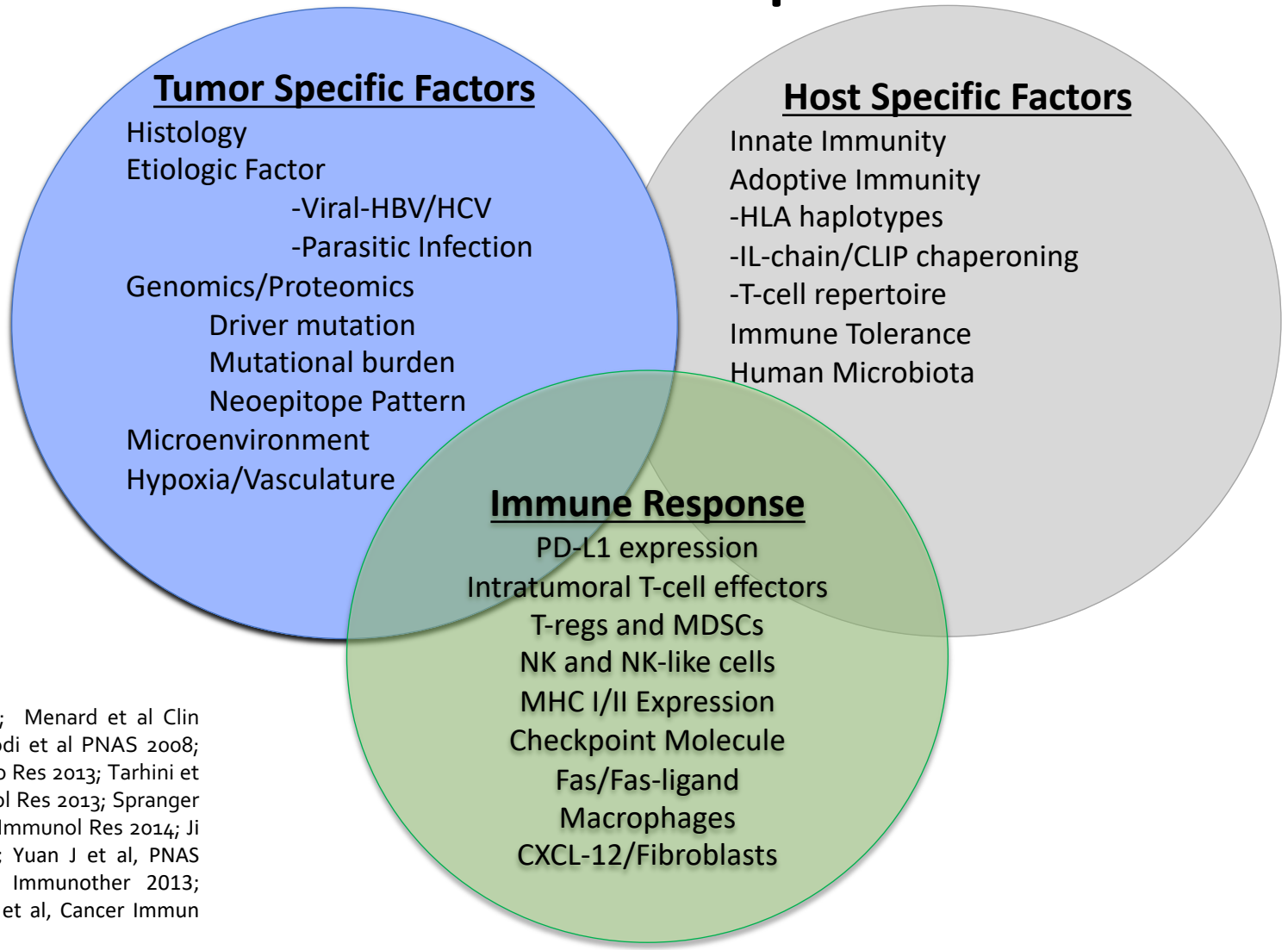
7 patients with advanced solid tumors and prior liver transplant- 5 with HCC

2 of 7 (29%) patients with prior liver transplant treated with IO developed acute rejection

0 of 5 HCC patients had clinical benefit

DeLeon et al. JGO 2018

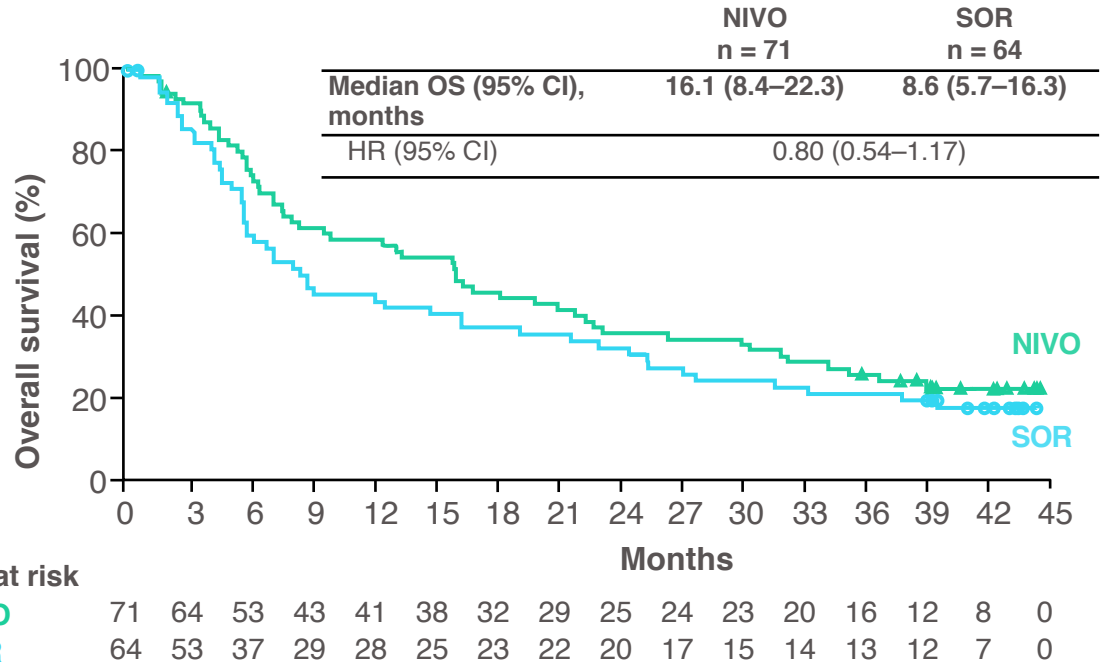
# Why do subsets of patients and tumors respond to immune checkpoint blockade?




Feig et al PNAS 2013; Ku et al Cancer 2010; Menard et al Clin Cancer Res 2008; Weber et al JCO 2009; Hodi et al PNAS 2008; Hamid et al JCO 2009; Ng et al Cancer Immuno Res 2013; Tarhini et al PLoS One 2014; Kitano et al Cancer Immunol Res 2013; Spranger et al Sci Transl Med 2013; Kitano et al Cancer Immunol Res 2014; Ji RR et al, Cancer Immunol Immunother 2012; Yuan J et al, PNAS 2011; DiGiacoa\m lo etal Cancer Immunol Immunother 2013; Queirolog et al, Cancer Invest 2013; Wolchok et al, Cancer Immun 2010.

# CheckMate 459: Overall survival by PD-L1 expression

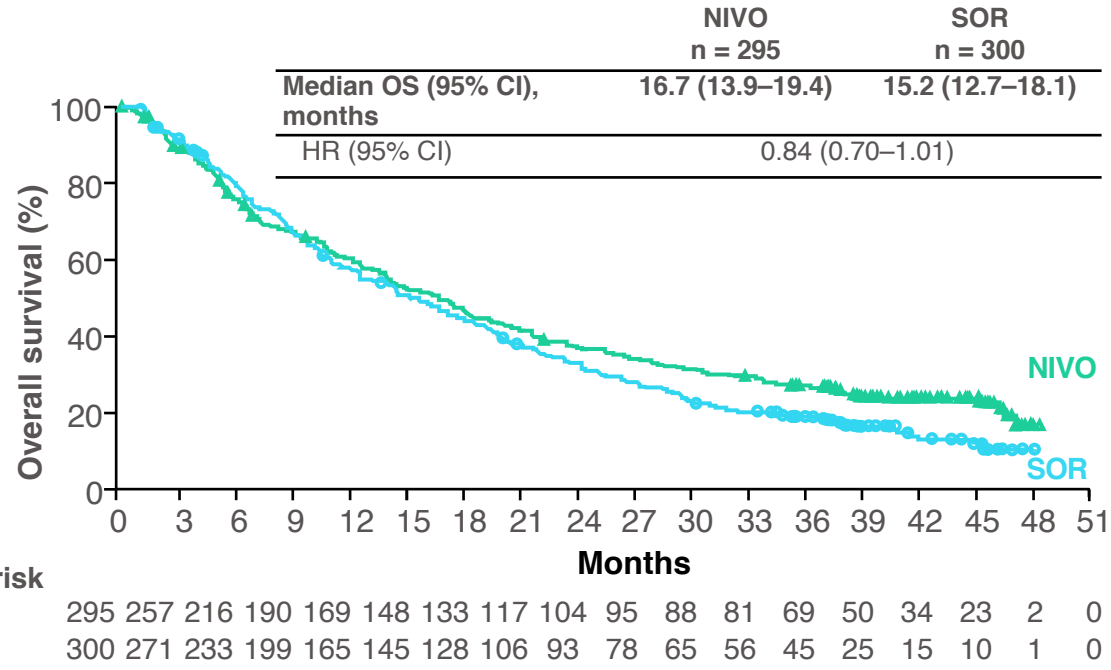
## Tumor cell PD-L1 expression ≥ 1%




No. at risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 71 | 64 | 53 | 43 | 41 | 38 | 32 | 29 | 25 | 24 | 23 | 20 | 16 | 12 | 8 | 0 |
| SOR | 64 | 53 | 37 | 29 | 28 | 25 | 23 | 22 | 20 | 17 | 15 | 14 | 13 | 12 | 7 | 0 |

## Tumor cell PD-L1 expression < 1%




No. at risk

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 295 | 257 | 216 | 190 | 169 | 148 | 133 | 117 | 104 | 95 | 88 | 81 | 69 | 50 | 34 | 23 | 2 | 0 |
| SOR | 300 | 271 | 233 | 199 | 165 | 145 | 128 | 106 | 93 | 78 | 65 | 56 | 45 | 25 | 15 | 10 | 1 | 0 |

- OS in the PD-L1 ≥ 1% group was longer in the NIVO arm compared with the SOR arm

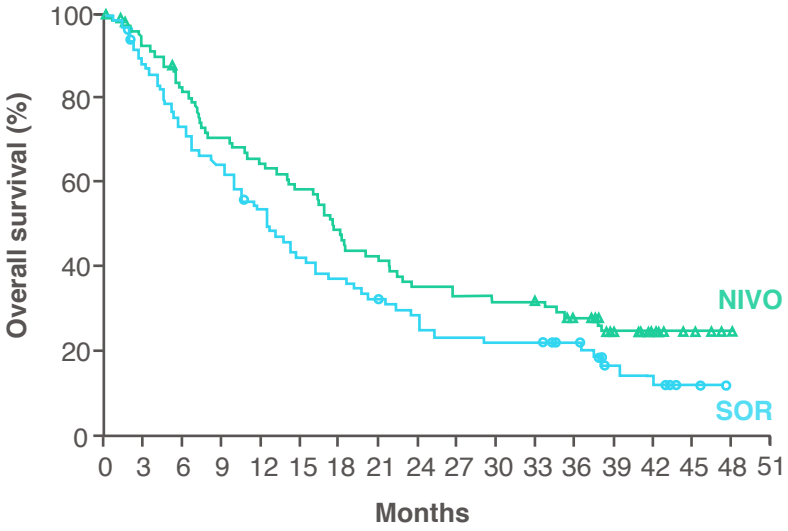


[a]IHC 28-8 pharmDx assay.
IHC, immunohistochemistry; PD-L1, programmed death ligand 1.

# CheckMate 459: Overall survival by etiology

## HCV

| | NIVO n = 87 | SOR n = 86 |
|---|---|---|
| Median OS (95% CI), months | 17.5 (13.9–21.9) | 12.7 (9.9–16.2) |
| HR (95% CI) | 0.72 (0.51–1.02) | |

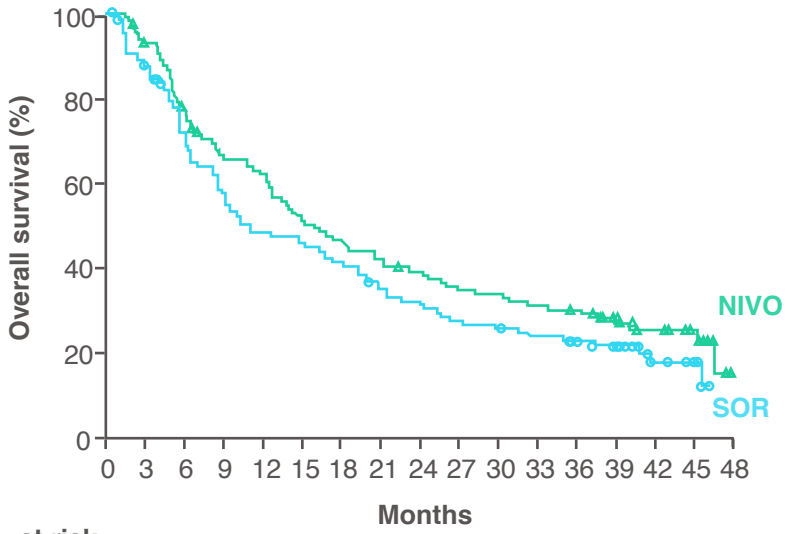



No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 87 | 77 | 67 | 58 | 53 | 48 | 40 | 34 | 29 | 27 | 26 | 25 | 20 | 13 | 8 | 4 | 1 | 0 |
| SOR | 86 | 74 | 61 | 54 | 43 | 34 | 30 | 25 | 22 | 18 | 17 | 17 | 14 | 7 | 5 | 2 | 0 | 0 |

## HBV

| | NIVO n = 116 | SOR n = 117 |
|---|---|---|
| Median OS (95% CI), months | 16.1 (12.5–21.3) | 10.4 (8.5–17.3) |
| HR (95% CI) | 0.79 (0.59–1.07) | |

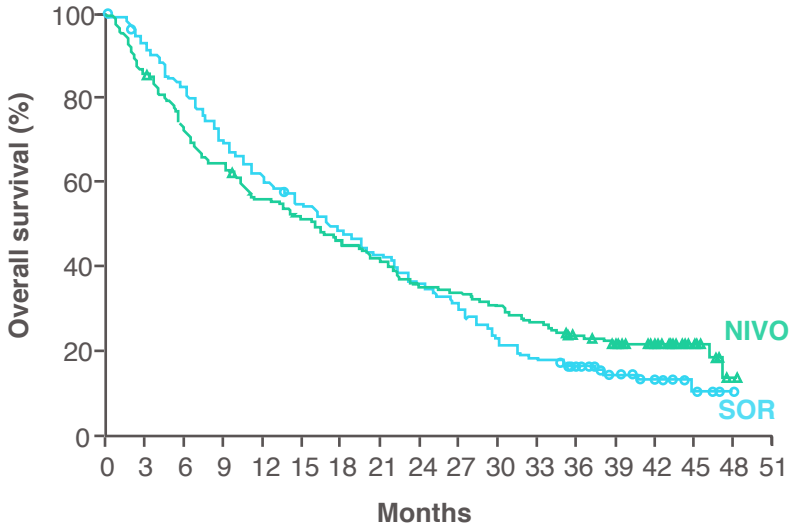



No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 116 | 106 | 86 | 72 | 68 | 56 | 51 | 46 | 42 | 37 | 36 | 33 | 31 | 21 | 14 | 9 | 0 | |
| SOR | 117 | 101 | 77 | 63 | 53 | 50 | 45 | 37 | 33 | 29 | 27 | 24 | 21 | 17 | 8 | 4 | 0 | |

## Uninfected

| | NIVO n = 168 | SOR n = 168 |
|---|---|---|
| Median OS (95% CI), months | 16.0 (10.8–20.2) | 17.4 (13.7–21.3) |
| HR (95% CI) | 0.91 (0.72–1.16) | |




No. at risk

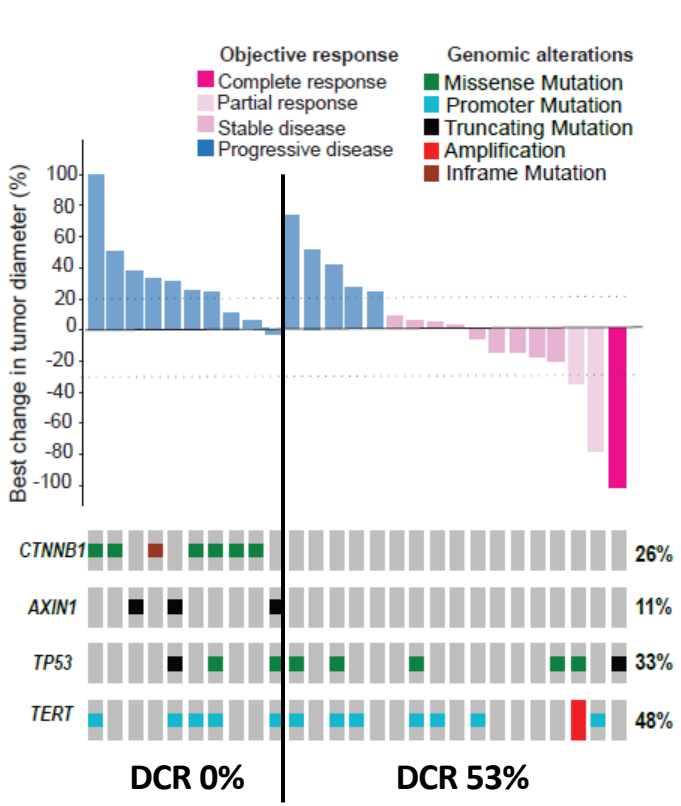
| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 168 | 143 | 120 | 107 | 92 | 85 | 76 | 68 | 59 | 56 | 50 | 44 | 35 | 29 | 20 | 10 | 1 | 0 | |
| SOR | 168 | 154 | 137 | 116 | 101 | 90 | 80 | 70 | 60 | 50 | 37 | 30 | 23 | 13 | 9 | 4 | 1 | 0 | |

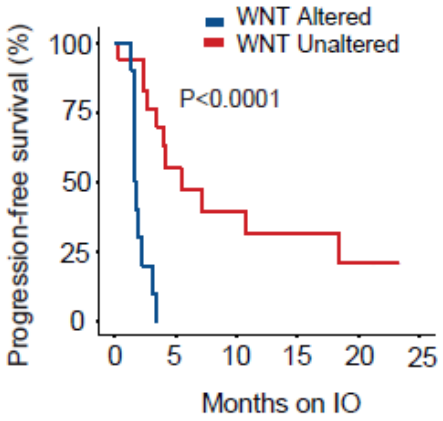
- In the HCV and HBV groups, median OS was numerically longer with NIVO versus SOR

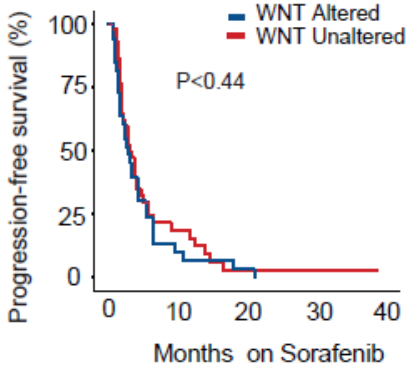
ESMO WORLD CONGRESS ON Gastrointestinal Cancer 2020 VIRTUAL

[a]Patients could have had active or resolved HBV or HCV infection as a risk factor for HCC as assessed by the investigator.

# WNT genomic alterations as a determinant of response to immune checkpoint inhibitors




Harding et al. *Clinical Cancer Research* 2018

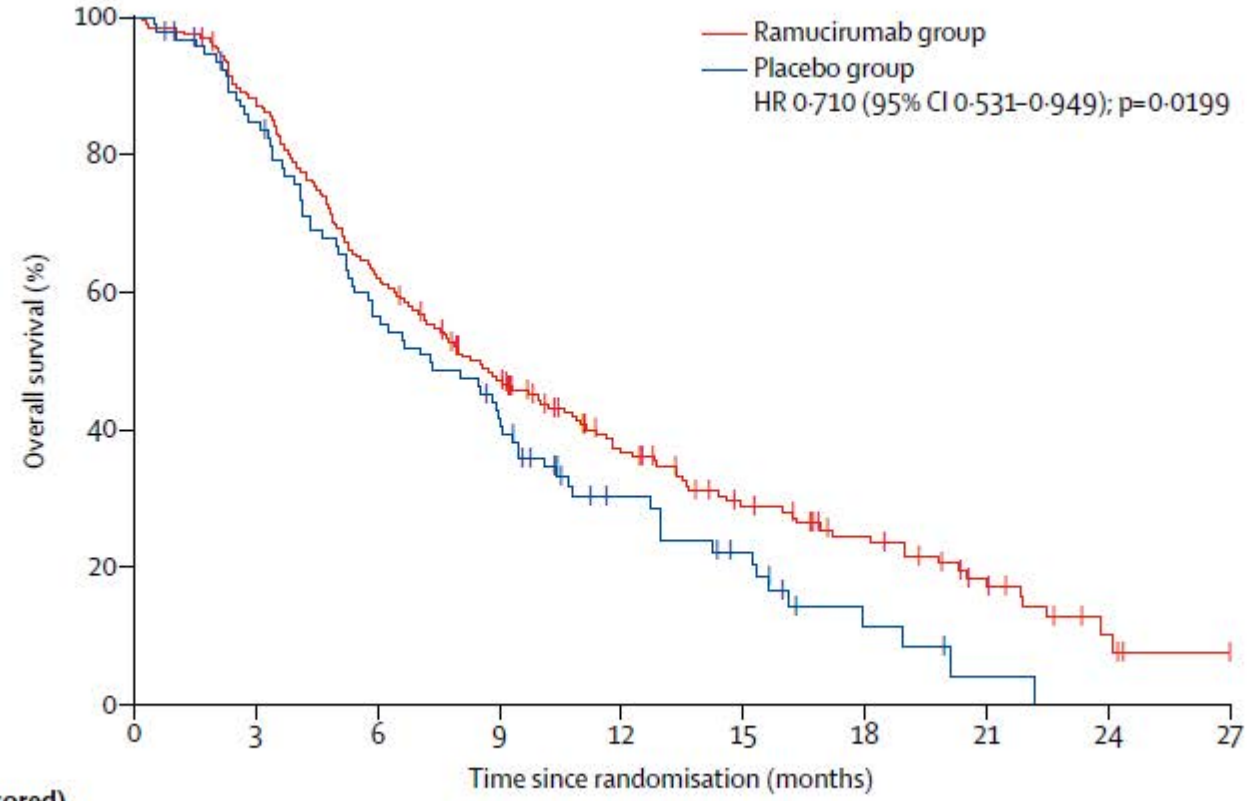
# FDA approved systemic therapies after Sorafenib Failure with overall survival advantage in HCC

| Agent | Agent | N | mOS | Absolute OS (mo) | Hazard Ratio |
|---|---|---|---|---|---|
| TKIS | **Regorafenib** | 379 | 10.6 | **2.8** | 0.63 (0.5- 0.79) |
| | Placebo | 193 | 7.8 | | |
| | **Cabozantinib** | 470 | 10.2 | **2.2** | 0.76 (0.63-0.92) |
| | Placebo | 237 | 8.0 | | |
| MoAs | **Ramucirumab** | 197 | 8.5 | **1.2** | 0.71 (0.53-0.94) |
| | Placebo | 95 | 7.3 | | |

Bruix et al. Lancet 2017; Abou-Alfa et al. NEJM 2018; Zhu et al. Lancet 2019

# REACH-2 trial and the value of AFP

**Based on the results of the REACH-2 trial, the FDA approved ramucirumab as a single agent for patients with HCC who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL and have been previously treated with sorafenib.**




| Number at risk (number censored) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ramucirumab group | 197 (0) | 172 (2) | 121 (2) | 87 (8) | 56 (22) | 37 (30) | 26 (36) | 14 (41) | 4 (47) | 0 (50) |
| Placebo group | 95 (0) | 76 (5) | 50 (6) | 36 (7) | 19 (15) | 12 (17) | 4 (20) | 1 (21) | 0 (21) | 0 (21) |

Zhu et al. Lancet 2019

# Cases

# Case 1: A 43-Year-Old Female with Stage IV HCC

- A 43-year-old female with controlled lupus and autoimmune hepatitis with AJCC Stage IV HCC
- She received lenvatinib with a partial response for 8 months and then cabozantinib with stable disease for 6 months.
- After a discussion regarding the risks and benefits of immunotherapy, the patient went on to receive a single agent anti-PD-1 therapy.
- The patient had normalization of AFP and a partial response on imaging.
- Subsequently the patient developed hypoalbuminemia, proteinuria, anasarca and hyperlipidemia and worsening liver function.
- Restaging showed continued disease control and a renal biopsy showed evidence of lupus glomerulonephritis.
- Immunotherapy was halted and the patient had improvement in her symptoms with high-dose steroids and mycophenolate.
- Restaging after 6 months showed growth of her malignancy and she has entered into a clinical trial for treatment

# Case 2: A 43-Year-Old Male with HBV-Associated HCC

- A 76-year-old male with HBV associated HCC to the LNs and adrenal gland with CP-A liver function
- Patient underwent a screening EGD that was normal, and received atezolizumab and bevacizumab
- After 9 weeks, he attained a partial response.
- The patient developed Grade 3 HTN and was treated with antihypertensives.
- After 6 months of treatment, the patient continued to have a sustained PR with well controlled blood pressure.
- The patient incidentally developed a painful inguinal hernia that required surgery.
- Bevacuzimab was held for 9 weeks while atezolizumab was continued in preparation for surgery.
- Surgery was uncomplicated and bevacizumab was resumed 9 weeks later