Recent Updates on the Management of Unresectable Hepatocellular Carcinoma

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Disclosure

- I have no conflict of interest to report

Objectives

1. Evaluate literature on the emerging systemic therapies in the management of unresectable hepatocellular carcinoma (uHCC)
2. Apply the safety and efficacy data of emerging systemic therapies in the management of uHCC

Hepatocellular Carcinoma

- Estimated > 41,000 new diagnosis in the US in 2022
- Prognosis is poor, with ~ 3% survival rate in distant stage
- Sorafenib has been the standard of care for advanced disease in the first-line setting since 2008
  - Median OS: 10-12 M
- Monotherapy with PD-1 inhibitors have not shown to improved overall survival
  - VEGF inhibition is believed to reverse VEGF-mediated immunosuppression and promote T-cell infiltration in tumors, thereby enhancing activity of PD-1 inhibitors

VEGF=vascular endothelial growth factor

Siegel RL, et al. CA Cancer J Clin. 2022;72(1):7-33.; Johnson PJ, et al, Philip PA, et al. J Clin Oncol. 2013;31:3517–3524.; Kudo M, et al, Piscaglia F, et al. Lancet. 2018;391:1163–1173.; Llovet JM, et al. N Engl J Med. 2008;359:378–390.; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatocellular Carcinoma. V.2.2022

IMbrave150 - Background

Multicenter, randomized, open-label, phase 3 trial

Patients with **advanced and/or unresectable HCC**, who had not previously received systemic therapy
- Child–Pugh class A

Atezolizumab 1200 mg IV
plus bevacizumab 15 mg/kg IV every 3 weeks*

Until POD or unacceptable toxicity

Sorafenib 400 mg PO BID

Stratified by
- Geographic region (Asia excluding Japan vs. the rest of the world)
- Macrovascular invasion or extrahepatic spread of disease
- Baseline alpha-fetoprotein level (<400 vs. ≥400 ng per milliliter)
- ECOG PS (0 vs. 1)

*Single-agent therapy was allowed if patient experienced toxicity with dual therapy

ECOG PS=Eastern Cooperative Oncology Group Performance Status; GEJ=gastroesophageal junction; HCC=hepatocellular carcinoma; PD-L1= programmed death ligand 1

Finn RS, et al. N Engl J Med. 2020;382(20):1894-1905.;
Cheng AL, et al. J Hepatol. 2022;76(4):862-873.

IMbrave150 - Baseline Characteristics

	Atezolizumab/bevacizumab (n=336)	Sorafenib (n=165)
Age, median, years	64	66
ECOG PS, n (%)		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
BCLC Stage, n (%)		
B	52 (15)	26 (16)
C	276 (82)	133 (81)
Alpha-fetoprotein ≥400 ng/mL, n (%)	126 (38)	61 (37)
Macrovascular invasion, n (%)	129 (38)	71 (43)
Extrahepatic spread, n (%)	212 (63)	93 (56)
Varices present at baseline, n (%)	88 (26)	43 (26)

BCLC=Barcelona clinic liver cancer; ECOG PS=Eastern Cooperative Oncology Group Performance Status;

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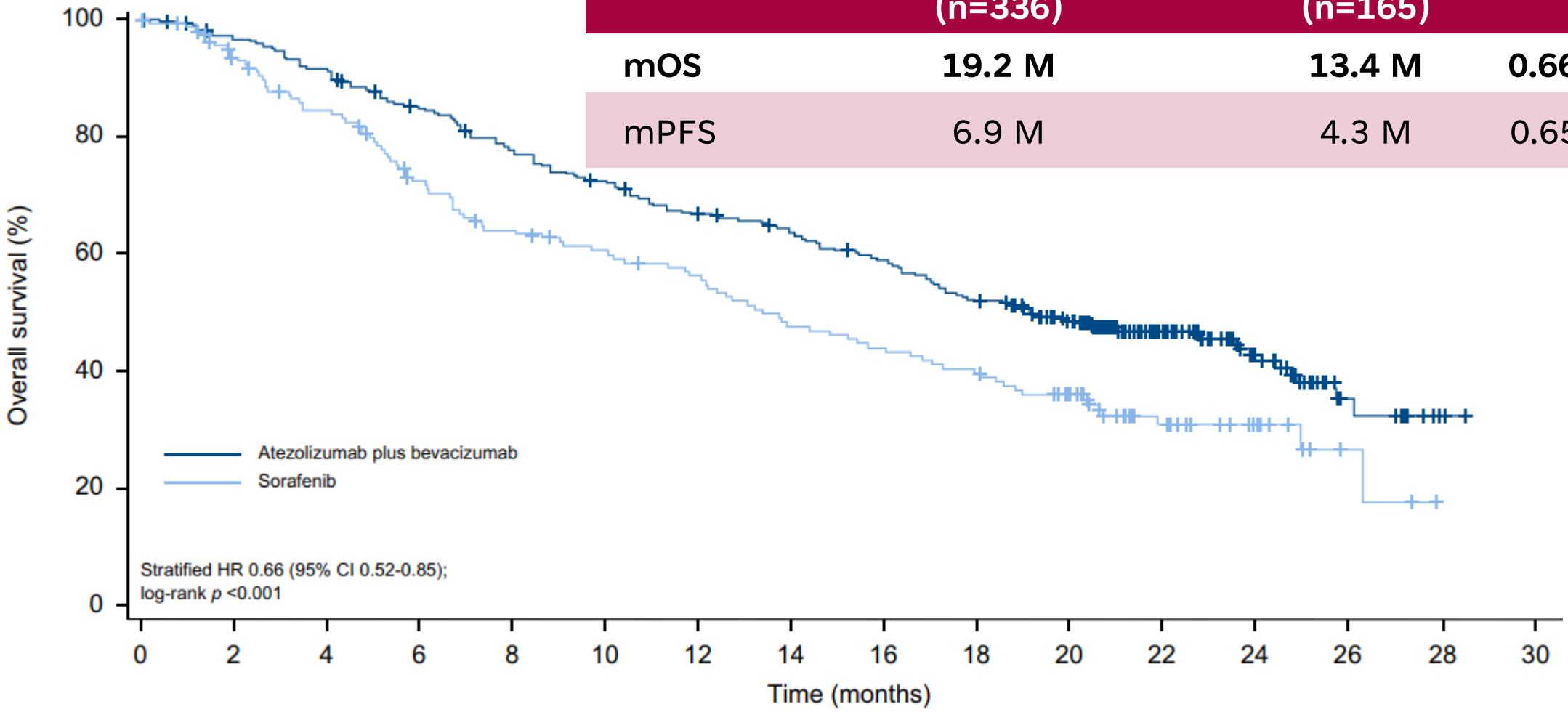
IMbrave150 - Results (12 M after Primary Analysis)

	Atezolizumab/bevacizumab (n=336)	Sorafenib (n=165)	Hazard ratio (95% CI)
mOS	**19.2 M**	**13.4 M**	**0.66 (0.52-0.85)**
mPFS	6.9 M	4.3 M	0.65 (0.53-0.81)



ORR=overall response rate; OS=overall survival; PFS=progression free survival; TrAEs= treatment-related adverse events

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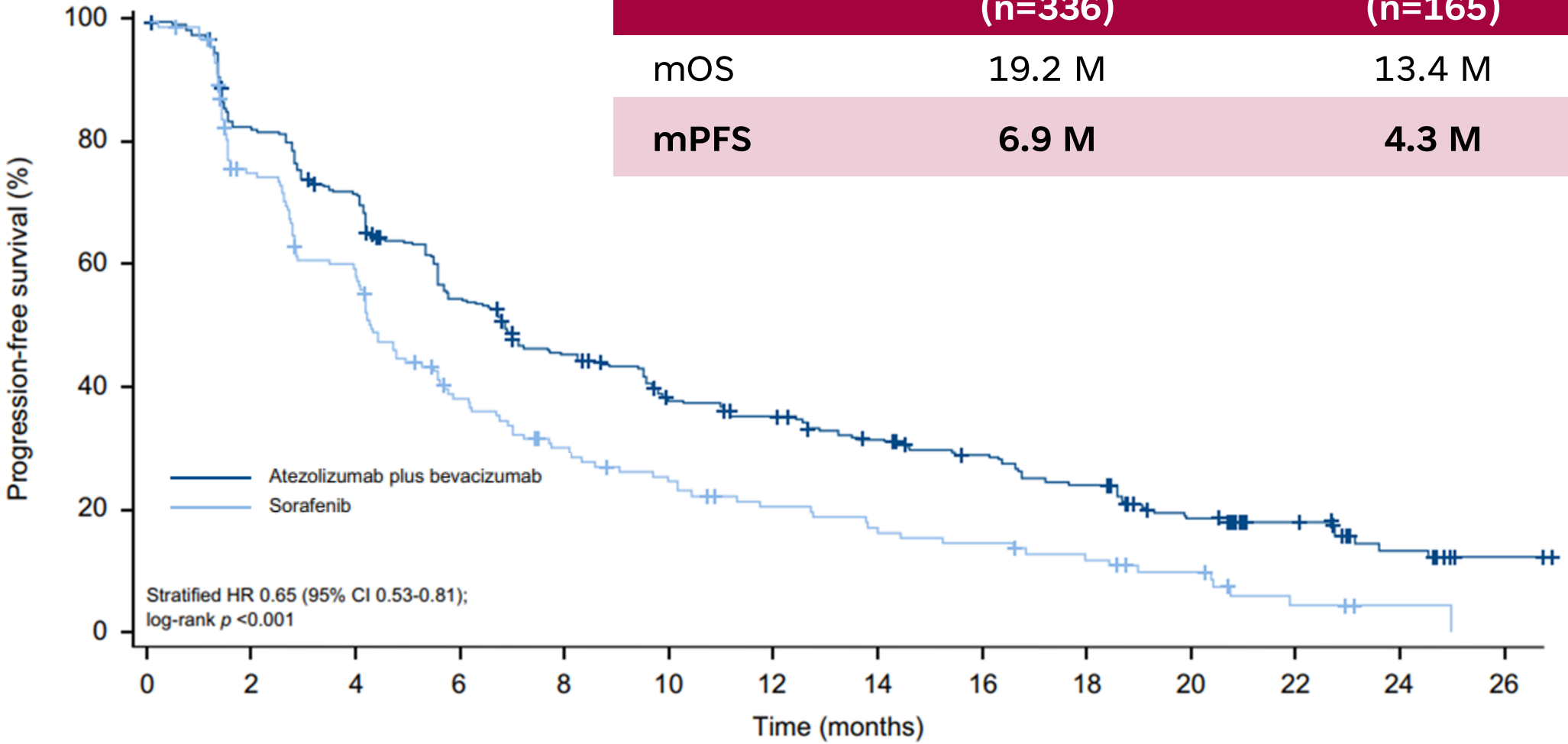

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IMbrave150 - Results (12 M after Primary Analysis)

	Atezolizumab/bevacizumab (n=336)	Sorafenib (n=159)	Hazard ratio (95% CI)
ORR, n (%)	97 (30)	18 (11)	
Complete response	25 (8)	1 (<1)	-
Partial response	72 (22)	17 (11)	
Stable disease, n (%)	144 (44)	69 (43)	-
AEs leading to withdrawal, n (%)	72 (22)	18 (12)	
Grade ≥3 TrAEs, n (%)	143 (43)	72 (46)	-
Hepatitis, n (%)			
All grade	175 (53)	62 (40)	-
Grade 3 or 4	83 (25)	28 (18)	

ORR=overall response rate; OS=overall survival; PFS=progression free survival; TrAEs= treatment-related adverse events

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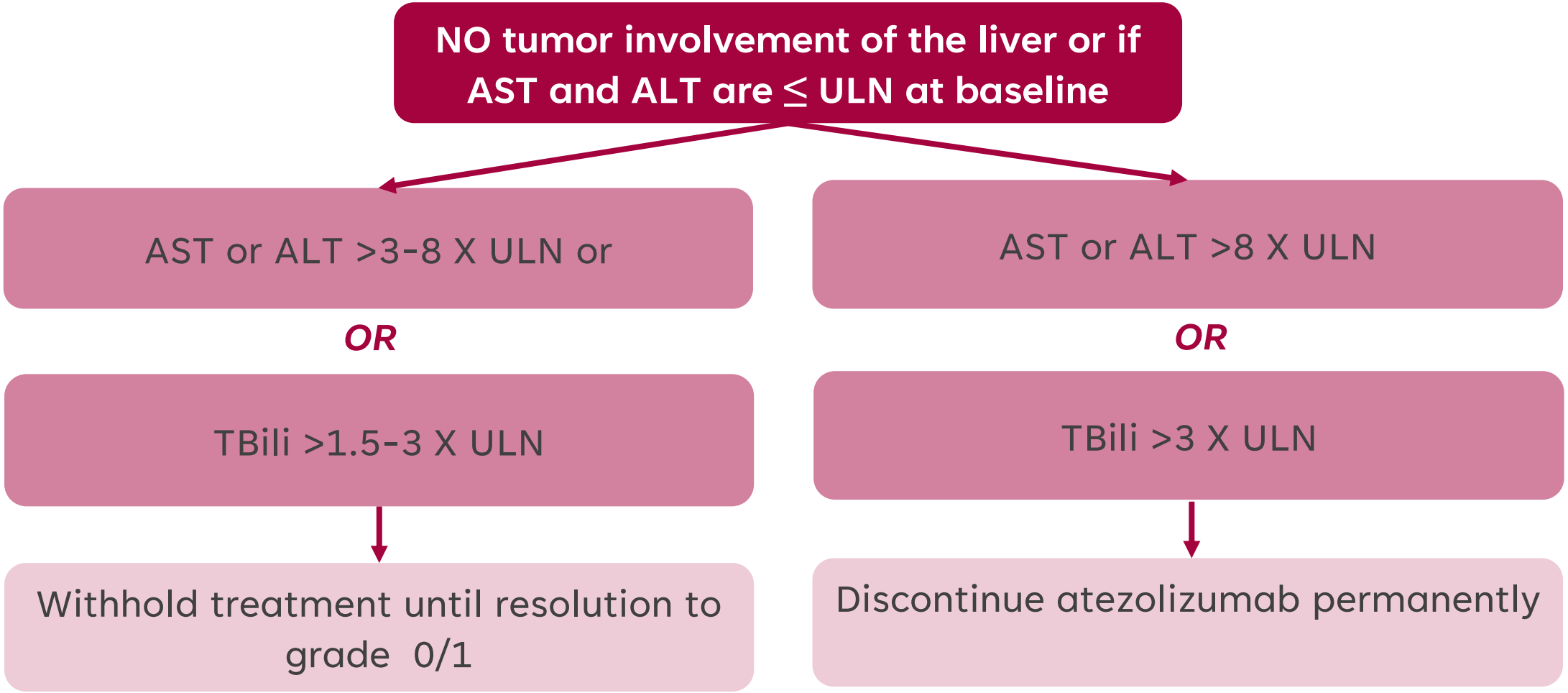
Atezolizumab (Tecentriq®)

Anti-programmed death-ligand 1 (PD-L1) antibody

- **Dosing:** 1200 mg IV in combination with bevacizumab every 3 weeks
  - Single-agent dosing (if discontinue bevacizumab due to toxicity):
    - 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks
- **Dosage forms:** 100 mg/50 mL & 200 mg/100 mL IV solution
- Immune-mediated hepatitis ?
  - Dose modification based on tumor involvement of the liver

TECENTRIQ® (atezolizumab) injection. [package insert] January 2022

Immune-mediated Hepatitis in Patients with HCC



TECENTRIQ® (atezolizumab) injection. [package insert] January 2022
IMFINZI® (durvalumab) injection. [package insert] October 2022

Immune-mediated Hepatitis in Patients with HCC

WITH tumor involvement of the liver

Baseline AST or ALT >1-3 X ULN and increases to >5-10 times ULN

OR

Baseline AST or ALT >3-5 X ULN and increases to >8-10 X ULN

→ Withhold treatment until resolution to grade 0/1

AST or ALT increases to >10 X ULN or Tbili increases to >3 X ULN

→ Discontinue atezolizumab permanently

TECENTRIQ® (atezolizumab) injection. [package insert] January 2022
IMFINZI® (durvalumab) injection. [package insert] October 2022

Bevacizumab (Avastin®)

Vascular endothelial growth factor (VEGF) inhibitor

- **Dosing:** 15 mg/kg in combination with atezolizumab every 3 weeks
- **Dosage forms:** 840 mg/14 mL & 1200 mg/20 mL IV solution

AVASTINâ (bevacizumab) injection. [package insert] September 2022

Bevacizumab (Avastin®)

Vascular endothelial growth factor (VEGF) inhibitor

- **Special considerations:**
  - Hypertension
    - Goal SBP <150 mmHg and DBP < 90 mmHg
  - Proteinuria
    - Withhold until proteinuria < 2 g/24 hr
  - Impaired wound healing
    - Withhold for ≥ 28 days prior to elective surgery and ≥ 28 days following major surgery and until adequate wound healing
  - Hemorrhage or thromboembolic events
  - Gastrointestinal perforations and fistulae
    - Adequate endoscopic evaluation and management for esophageal varices within 6 months prior

AVASTINâ (bevacizumab) injection. [package insert] September 2022

HIMALAYA - Background

Multicenter, randomized, open-label, phase 3 trial

Patients with **advanced and/or unresectable HCC**, who had not previously received systemic therapy
- Child–Pugh class A

→ **Tremelimumab** 300 mg IV **plus Durvalumab** 1500 mg IV on C1D1 only → **Durvalumab** 1500 mg IV **monotherapy** every 4 weeks

→ **Durvalumab** 1500 mg IV **monotherapy** every 4 weeks

→ **Sorafenib** 400 mg PO BID

Stratified by
- Macrovascular invasion or extrahepatic spread of disease
- Etiology of liver disease (hepatitis B or C virus or other/nonviral)
- ECOG PS (0 vs. 1)

ECOG PS=Eastern Cooperative Oncology Group Performance Status; HCC=hepatocellular carcinoma
Kelley RK, et al. J Clin Oncol. 2021;39(27):2991-3001.; Abou-Alfa GK, et al. NEJM Evid 2022; 1 (8)

HIMALAYA - Background

	T300 + D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Age, median, years	65	64	64
ECOG PS, n (%)			
0	244 (62)	237 (61)	241 (62)
1	148 (38)	150 (39)	147 (38)
BCLC Stage, n (%)			
B	77 (20)	80 (21)	66 (17)
C	316 (81)	309 (79)	323 (83)
PD-L1 $\geq$ 1%	148 (38)	154 (40)	148 (38)
AFP $\geq$400 ng/mL, n (%)	145 (37)	137 (35)	124 (32)
Macrovascular invasion, n (%)	103 (26)	94 (24)	100 (26)
Extrahepatic spread, n (%)	209 (53)	212 (55)	203 (52)

AFP=alpha-fetoprotein; BCLC=Barcelona clinic liver cancer; ECOG PS=Eastern Cooperative Oncology Group Performance Status;

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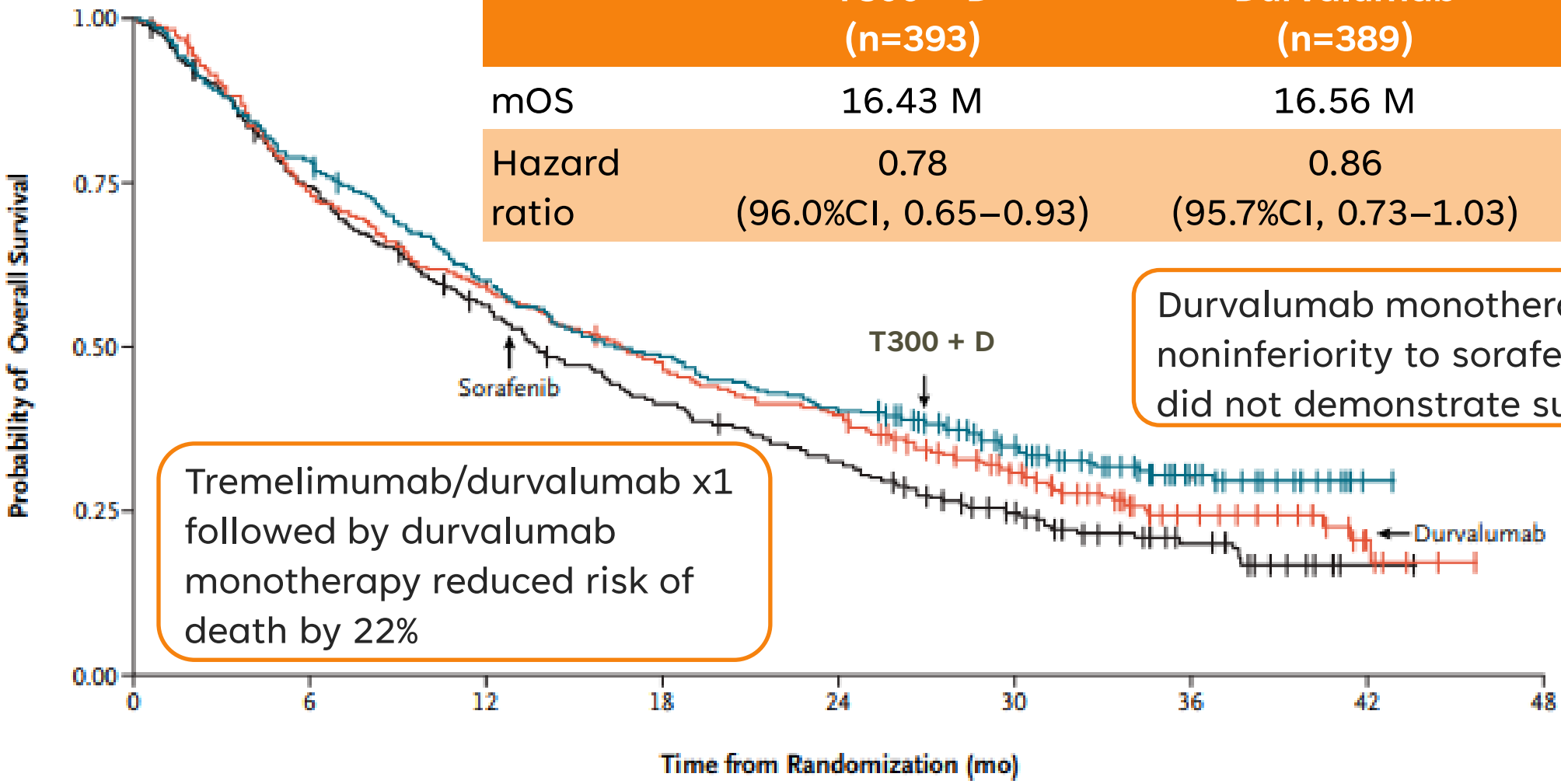
Abou-Alfa GK, et al. NEJM Evid 2022; 1 (8)

HIMALAYA - Results

	T300 + D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
mOS	16.43 M	16.56 M	13.77 M
Hazard ratio	0.78 (96.0%CI, 0.65–0.93)	0.86 (95.7%CI, 0.73–1.03)	



Durvalumab monotherapy is noninferiority to sorafenib but did not demonstrate superiority

Tremelimumab/durvalumab x1 followed by durvalumab monotherapy reduced risk of death by 22%

OS=overall survival

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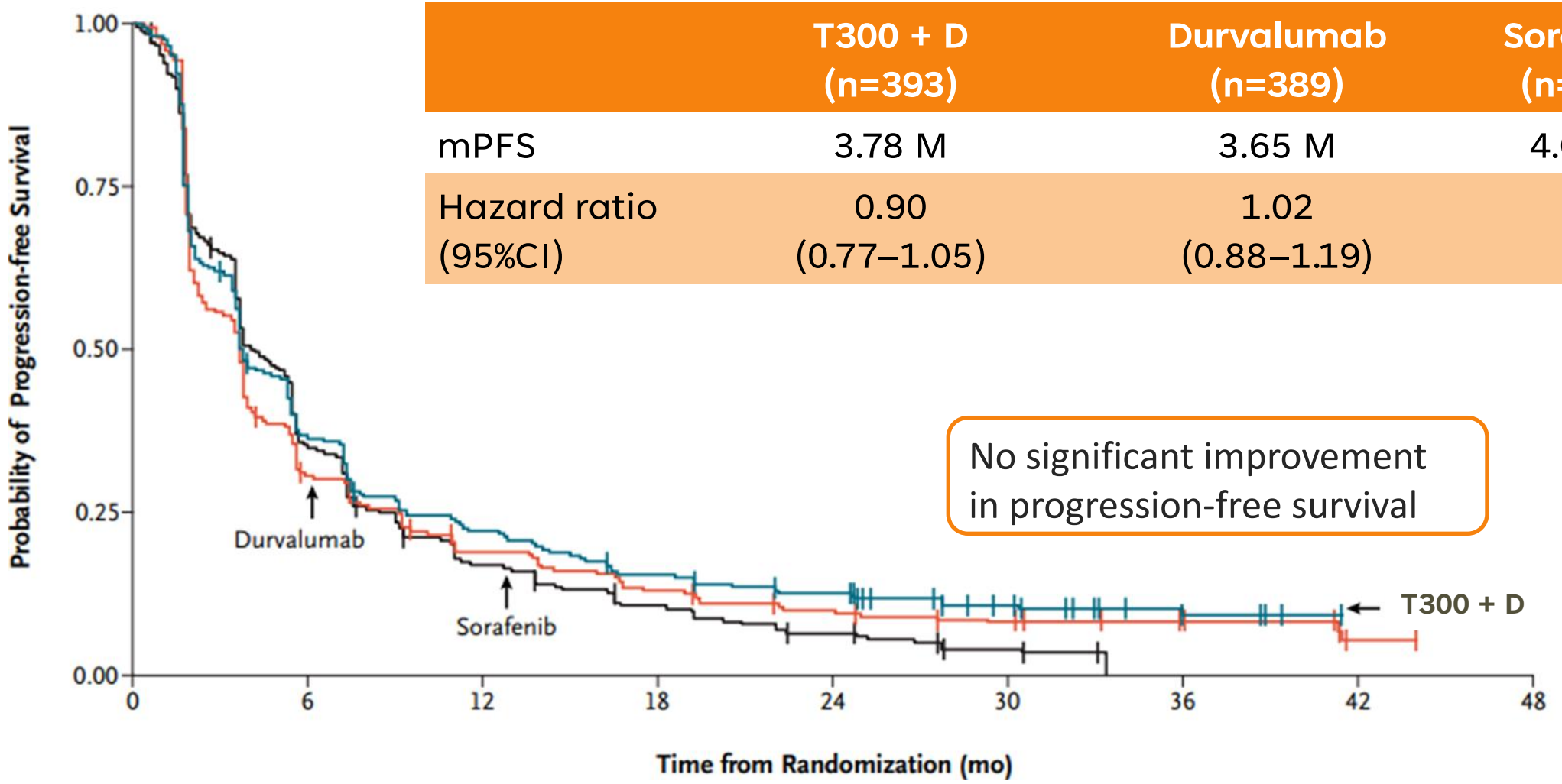
HIMALAYA - Results

	T300 + D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
mPFS	3.78 M	3.65 M	4.07 M
Hazard ratio (95%CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	



No significant improvement in progression-free survival

PFS=progression-free survival

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HIMALAYA – Results

	T300 + D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR, n (%)	79 (20)	66 (17)	20 (5)
Complete response	12 (3)	6 (1.5)	0
Partial response	67 (17)	60 (15)	20 (5)
Stable disease, n (%)	157 (40)	147 (38)	216 (56)
AEs leading to discontinuation, n (%)	53 (14)	32 (8)	63 (17)
Grade ≥3 TrAEs	100 (26)	50 (13)	138 (37)
Grade ≥3 IrAEs	49 (13)	25 (6)	30 (8)
Any hepatic AEs	144 (37)	129 (33)	121 (32)
Grade 3 or 4	54 (14)	54 (14)	39 (10)
Immune-mediated hepatitis	4 (1)	0	-

HCC=hepatocellular carcinoma; NCCN=National Comprehensive Cancer Network; OS=overall survival

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatocellular Carcinoma. V.4.2022
US Food and Drug Administration (FDA). Drug Approvals and Databases. https://www.fda.gov/drugs/resources-information-approved-drugs

Summary

Both atezolizumab/bevacizumab and tremelimumab/durvalumab are NCCN category 1 preferred first-line systemic therapy for advanced HCC

- **No head-to-head comparison**

Atezolizumab/bevacizumab

- Preferred category 1 for patients with Child-Pugh Class A only
- HTN, GI perforations, bleeding/DVT/PE
- High rate of immune-mediated hepatitis reported in the trial

Tremelimumab/durvalumab

- Lower rate of hepatic AEs reported in ~ 1.5yr f/u

HCC=hepatocellular carcinoma; NCCN=National Comprehensive Cancer Network

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