Role of Tecentriq® (Atezolizumab)+ Avastin™ (Bevacizumab) as 1L in Unresectable HCC

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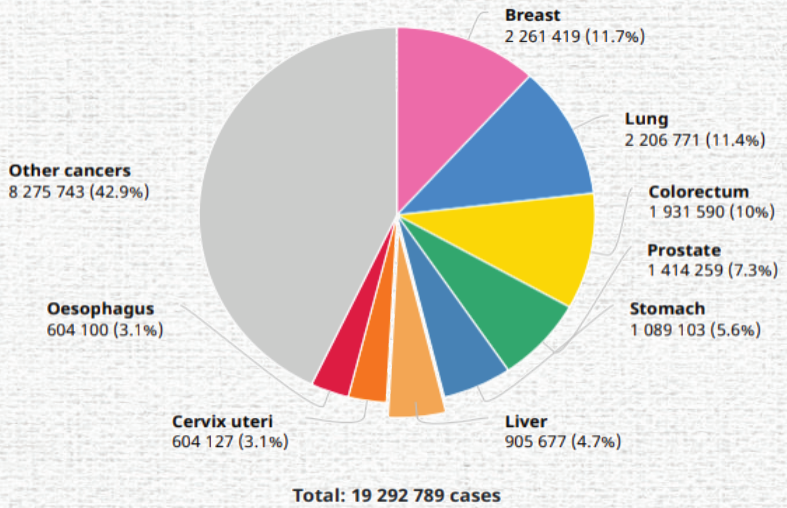
Liver cancer global incidence and mortality

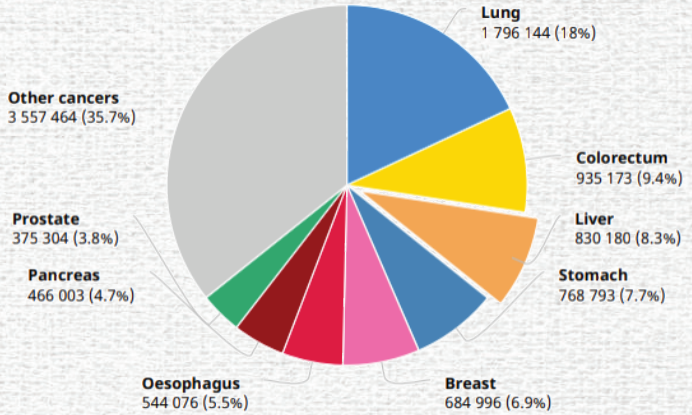
Incidence	Mortality
Liver cancer represents 4.7% of all cancer diagnosis, 6th most common cancer overall	Liver cancer is the third leading cause of global cancer mortality, accounting for 8.3% of all cancer deaths
3 times more common in males than females	

Number of new cases in 2020, both sexes, all ages



Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages



Total: 9 958 133 deaths

WHO. Liver-The Global Cancer Observatory. December 2020. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf . Accessed on Aug 2021

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Rationale for the combination of Atezolizumab and Bevacizumab for the treatment of patients with HCC

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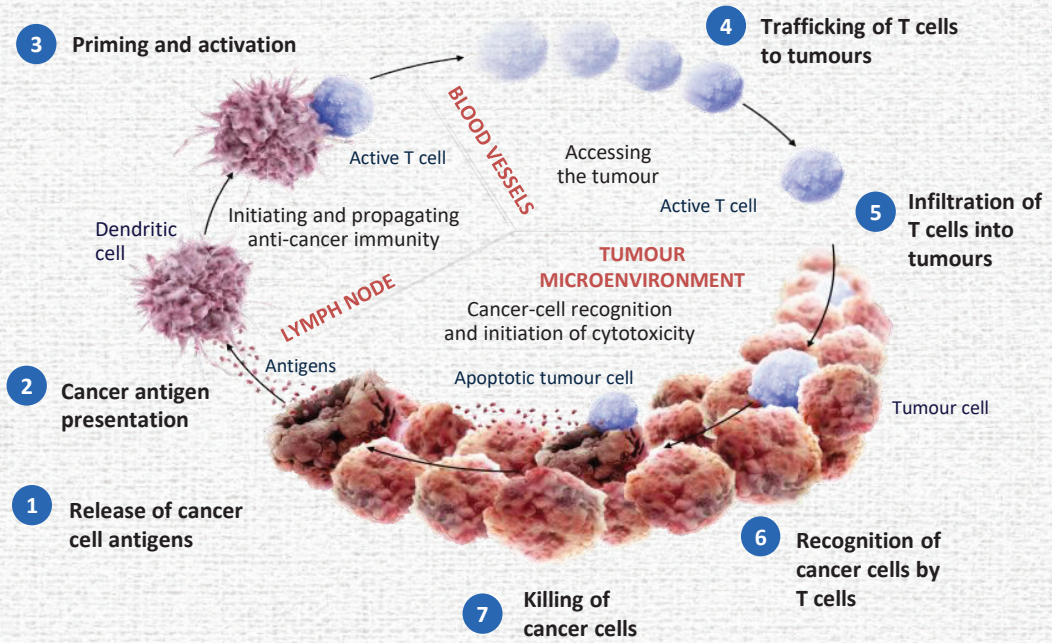
Available evidence implicates mechanisms of immune escape in HCC tumours

The cancer immunity cycle[1]



- Spontaneous regression of tumours has been observed in HCC, suggesting the presence of immune system-mediated anti-tumour activity[2]
- Tumour-infiltrating T cells are found in >50% of HCC patients[2,3]
  - Presence of tumour-infiltrating cells has been shown to correlate with PFS[2,3]
- HCC may evade immune checkpoint inhibitors by expressing PD-1/PD-L1, CTLA-4, TIM-3 and LAG-3[2]

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LAG3, lymphocyte activation gene-3; PD-1, programmed cell death protein-1
PD-L1, programmed death-ligand 1; PFS, progression-free survival; TIM-3, T-cell immunoglobulin and mucin-domain containing-3

1.Chen et al. Immunity 2013
2.Hato et al. Immunotherapy 2016
3.Flecken et al. Hepatology 2014

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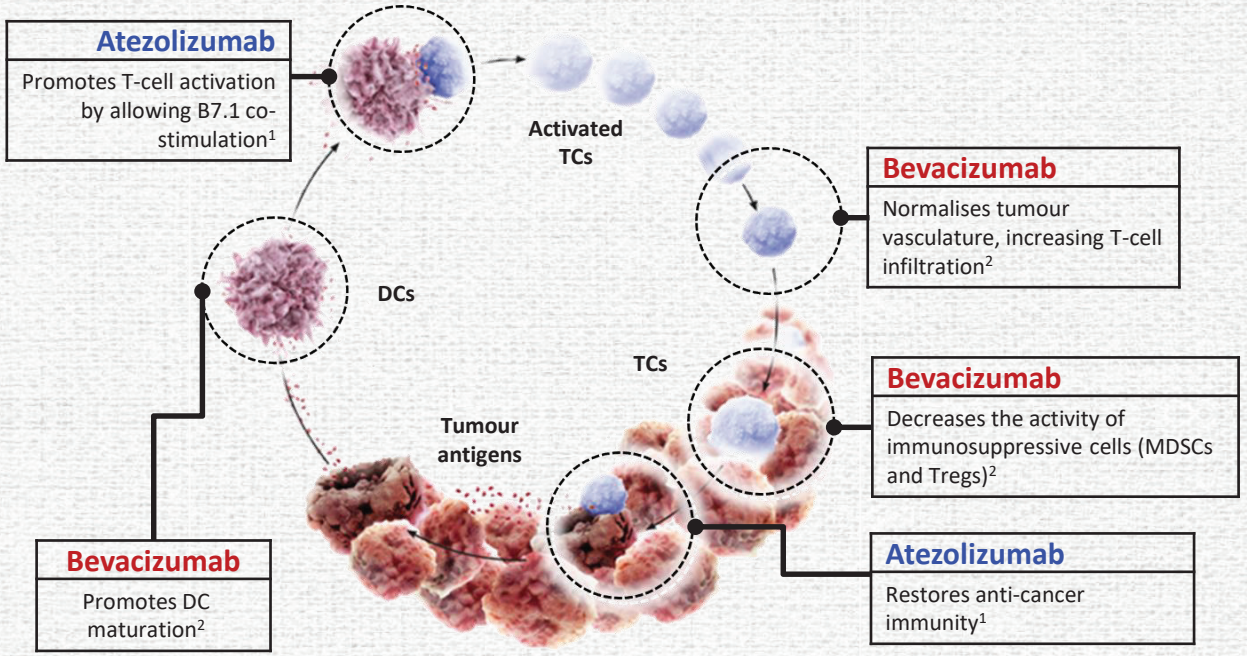
Combining checkpoint inhibition with VEGF blockade targets multiple steps of the cancer immunity cycle



Bevacizumab (anti-VEGF) is an anti-angiogenic agent with additional immunomodulatory effects

In combination, Bevacizumab may enhance Atezolizumab's efficacy by reversing VEGF-mediated immunosuppression to promote anti-cancer T-cell activity

DC, dendritic cell; MDSC, myeloid-derived suppressor cell TC, T cell; Treg, regulatory T cell

1.Chen et al. Immunity 2013
2.Hato et al. Immunotherapy 2016

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IMBrave 150: Phase III trial of 1L Atezolizumab + Bevacizumab in patients with unresectable HCC

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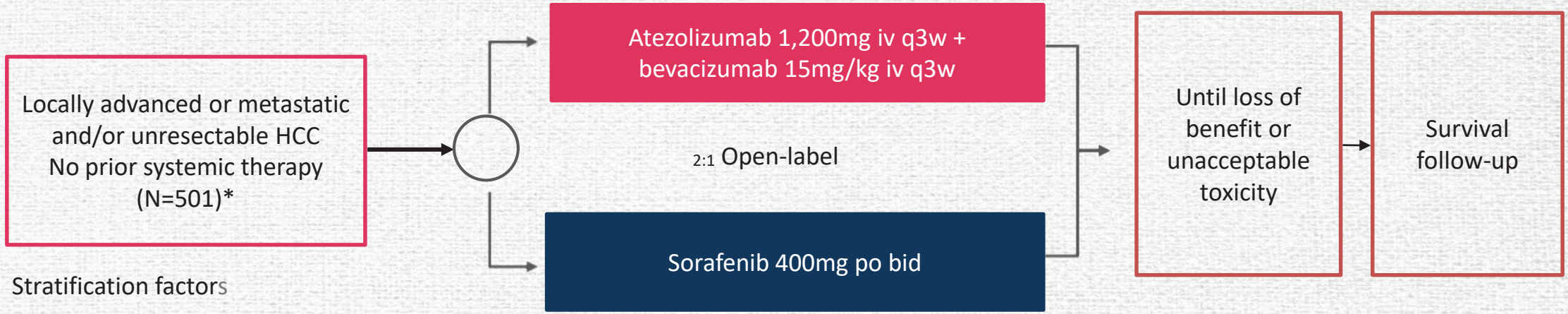
IMbrave150 is a phase III trial of 1L Atezolizumab + Bevacizumab in patients with unresectable HCC[1]



Stratification factors

- **Region** (Asia excluding Japan‡/Rest of World)
- **ECOG PS** (0/1)
- **MVI and/or EHS (presence/absence)**
- **Baseline AFP** (<400/≥400ng/mL)

Included high risk patients (20%): Invasion of main portal vein, bile duct, >50% liver occupying tumor

Co-primary endpoints: OS and PFS IRF-assessed per RECIST v1.1

Key secondary endpoints (in testing strategy): ORR IRF-assessed per RECIST v1.1 and HCC mRECIST

*There were an additional 57 Chinese patients in the China extension cohort who were not included in the global population/analysis[2] ‡Japan is included in Rest of World

AFP, alpha-fetoprotein; bid, twice daily; EHS, extrahepatic spread; IRF, independent review facility; (m)RECIST, (modified) Response Evaluation Criteria in Solid Tumors; MVI, macrovascular invasion; ORR, objective response rate; PFS, progression-free survival; R, randomisation

1. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745.
2. Cheng A-L, Qin S, Ikeda M, et al. IMbrave150: efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol. 2019;30(suppl 9) [abst.

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IMbrave150: baseline characteristics (ITT)

Characteristic	Atezo + bev (n=336)	Sorafenib (n=165)
Median age, (IQR) years	64 (56–71)	66 (59–71)
Sex, male, n (%)	277 (82)	137 (83)
Region, n (%)		
Asia (excluding Japan*)	133 (40)	68 (41)
Rest of World	203 (60)	97 (59)
ECOG PS, n (%)		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child-Pugh class, n (%)		
A5	239/333 (72)	121/165 (73)
A6	94/333 (28)	44/165 (27)
BCLC stage at study entry, n (%)		
A	8 (2)	6 (4)
B	52 (16)	26 (16)
C	276 (82)	133 (80)

Characteristic	Atezo + bev (n=336)	Sorafenib (n=165)
Aetiology of HCC, n (%)		
HBV	164 (49)	76 (46)
HCV	72 (21)	36 (22)
Non-viral‡	100 (30)	53 (32)
AFP ≥400ng/mL, n (%)	126 (38)	61 (37)
Disease burden, n (%)		
EHS	212 (63)	93 (56)
MVI	129 (37)	71 (44)
EHS and/or MVI	**258 (77)**	120 (73)
Prior local therapy for HCC, n (%)	161 (48)	85 (52)

*Japan is included in Rest of World; ‡Non-viral causes include alcohol, other, and unknown HBV and HCV causes; ITT, intention to treat; IQR, interquartile range

Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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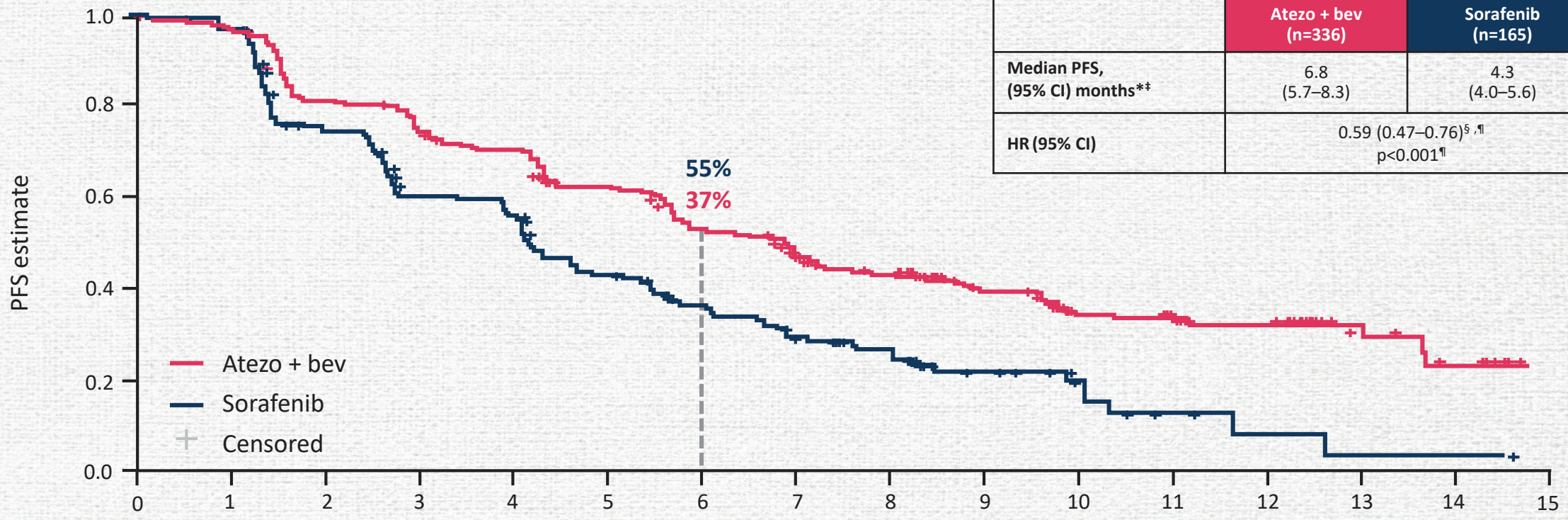
IMbrave150: PFS (co-primary endpoint)

	Atezo + bev (n=336)	Sorafenib (n=165)
Median PFS, (95% CI) months*‡	6.8 (5.7–8.3)	4.3 (4.0–5.6)
HR (95% CI)	0.59 (0.47–0.76)§,¶ p<0.001¶	



Patients at risk

Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

Clinical cut-off date: 29 Aug 2019; median survival follow-up, 8.6 months; *Assessed by IRF per RECIST v1.1; ‡197 patients (59%) in the atezo + bev arm vs 109 (66%) in the sorafenib arm had an event; §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 ≥400ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS; ¶The 2-sided p-value boundary is 0.002

Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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Follow-up systemic therapy for HCC

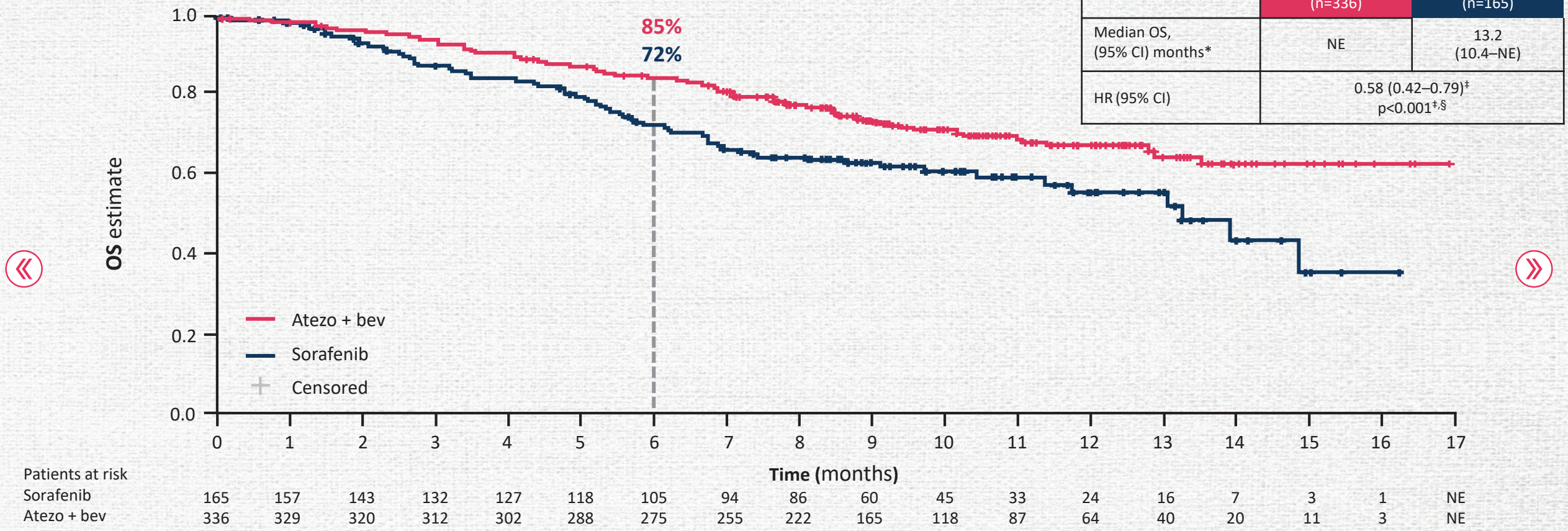
	Updated analysis	
	Atezo + Bev (n = 336)	Sorafenib (n = 165)
≥ 1 systemic treatment, n (%)[a]	120 (36)	86 (52)
2L therapy	102 (30)	81 (49)
3L therapy	33 (10)	39 (24)
Type of therapy, n (%)		
Tyrosine kinase inhibitors	108 (32)	54 (33)
Immunotherapy	11 (3)	43 (26)
Chemotherapy	11 (3)	15 (9)
Angiogenesis inhibitors[b]	6 (2)	10 (6)
Others	6 (2)	6 (4)

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. 2L, second line; 3L, third line; 4L, fourth line.[a] ≥ 4L therapies are not included in table. [b]Monoclonal antibodies

Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

IMbrave150: OS (co-primary endpoint)

	Atezo + bev (n=336)	Sorafenib (n=165)
Median OS, (95% CI) months*	NE	13.2 (10.4–NE)
HR (95% CI)	0.58 (0.42–0.79)‡ p<0.001‡,§	



Clinical cut-off date: 29 Aug 2019; median survival follow-up, 8.6 months

*96 patients (29%) in the atezo + bev arm vs 65 (39%) in the sorafenib arm had an event; ‡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 ≥400ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS; §The 2-sided p-value boundary based on 161 deaths is 0.0033. NE, not estimable; IxRS, interactive voice/web response system

Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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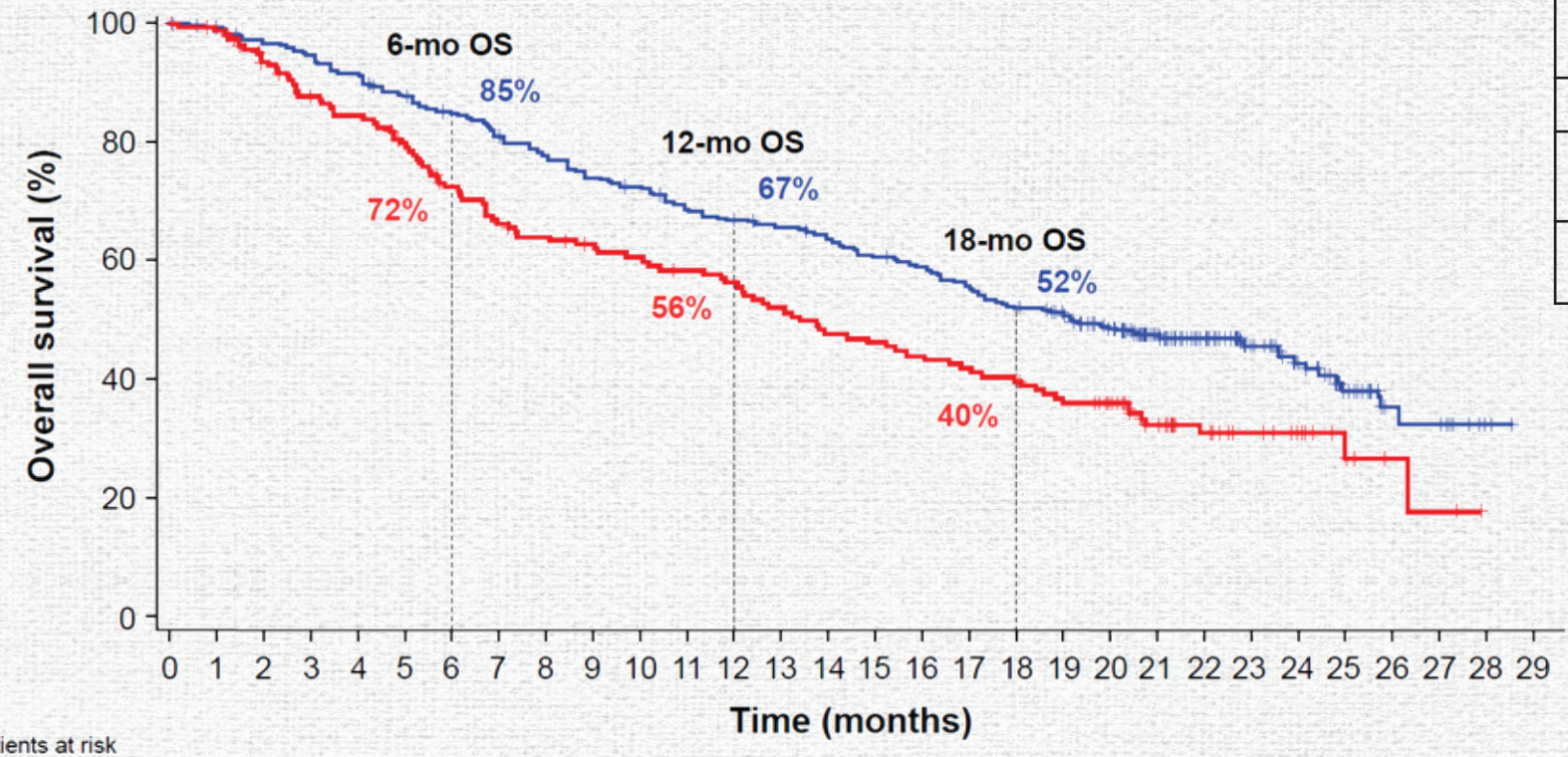
Updated OS



No. of patients at risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. [a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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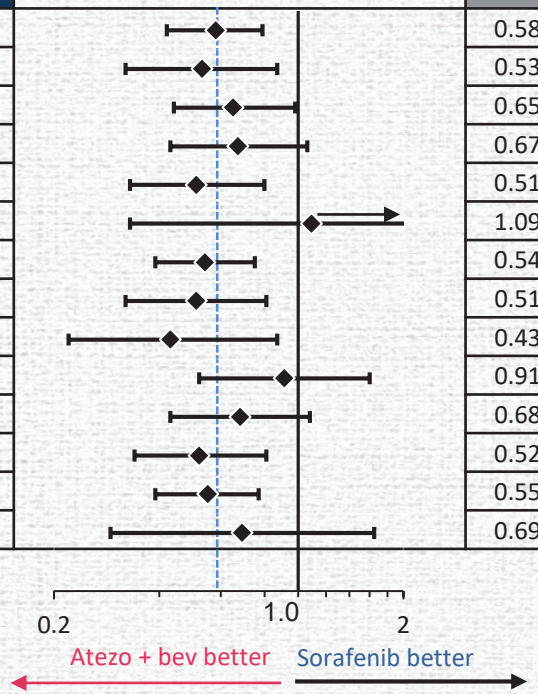
IMbrave150:OS and PFS according to baseline characteristics[1,2]

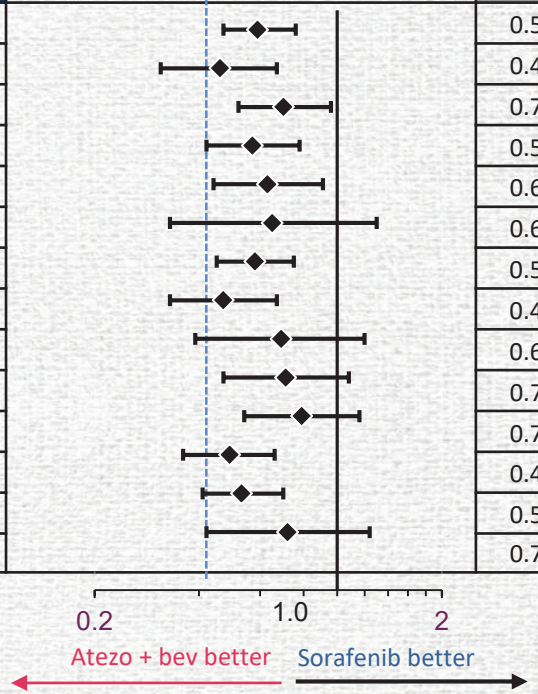
OS subgroup analysis

	Atezo + bev mOS, mo (n=336)	Sorafenib mOS, mo (n=165)	OS HR (95% CI)*
All patients	NE	13.2	0.58 (0.42–0.79)
Asia (excluding Japan‡)	NE	13.1	0.53 (0.32–0.87)
Rest of World	NE	13.2	0.65 (0.44–0.98)
ECOG PS 0	NE	13.9	0.67 (0.43–1.06)
ECOG PS 1	NE	7.4	0.51 (0.33–0.80)
BCLC stage B	NE	14.9	1.09 (0.33–3.53)
BCLC stage C	NE	11.4	0.54 (0.39–0.75)
HBV HCC	NE	13.9	0.51 (0.32–0.81)
HCV HCC	NE	13.1	0.43 (0.22–0.87)
Non-viral HCC	NE	14.9	0.91 (0.52–1.60)
AFP ≥400ng/mL	12.8	9.1	0.68 (0.43–1.08)
AFP <400ng/mL	NE	13.9	0.52 (0.34–0.81)
EHS and/or MVI (yes)	NE	10.4	0.55 (0.39–0.77)
EHS and MVI (no)	NE	14.9	0.69 (0.29–1.65)



PFS subgroup analysis

Atezo + bev mPFS, mo (n=336)	Sorafenib mPFS, mo (n=165)	PFS HR (95% CI)*
6.8	4.3	0.59 (0.47–0.76)
7.7	2.8	0.46 (0.31–0.67)
6.7	4.9	0.70 (0.52–0.96)
7.9	4.8	0.57 (0.42–0.78)
5.6	4.0	0.63 (0.44–0.91)
NE	8.6	0.65 (0.33–1.30)
6.4	4.1	0.58 (0.45–0.75)
6.7	2.8	0.47 (0.33–0.67)
8.3	5.8	0.69 (0.39–1.20)
7.1	5.6	0.71 (0.47–1.08)
5.2	4.1	0.79 (0.54–1.16)
8.3	4.4	0.49 (0.36–0.66)
6.1	4.0	0.53 (0.41–0.70)
9.9	8.6	0.72 (0.42–1.24)



Clinical cut-off date: 29 August 2019, median survival follow-up: 8.6 months *Unstratified HR shown for all characteristics except for 'All patients', where stratified HR is shown
‡Japan is included in Rest of World

1. Cheng A-L, Qin S, Ikeda M, et al. IMbrave150: efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol. 2019;30(suppl 9) [abstract LBA3].
2. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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IMbrave150: response rates[1,2]

Doubling of response

	IRF RECIST v1.1		IRF HCC mRECIST	
	Atezo + bev (n=326)	Sorafenib (n=159)	Atezo + bev (n=325)*	Sorafenib (n=158)
Confirmed ORR, % (95% CI)	27 (23–33)	12 (7–18)	33 (28–39)	13 (8–20)
CR, n (%)	18 (6)	0	33 (10)	3 (2)
PR, n (%)	71 (22)	19 (12)	75 (23)	18 (11)
Stratified p-value	<0.001		<0.001	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Median DoR, (95% CI) months	NE	6.3 (4.7–NE)	NE	6.3 (4.9–NE)
Event-free rate at 6 months, %	88	59	82	63

Clinical cut-off date: 29 August 2019, median survival follow-up: 8.6 months , *IRF HCC mRECIST-evaluable population is based on patients who presented with measurable disease at baseline per HCC mRECIST criteria

1. Cheng A-L, Qin S, Ikeda M, et al. IMbrave150: efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol. 2019;30(suppl 9) [abstract LBA3].
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Updated response and duration of response

	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. DCR, disease control rate. [a] Only patients with measurable disease at baseline were included in the analysis of ORR. [b] Only confirmed responders were included in the analysis of ORR and DOR.

Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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IMbrave150: safety summary[1,2]*

AEs	Atezo + bev (n=329)	Sorafenib (n=156)
Median treatment duration, months	Atezo = 7.4; bev = 6.9	2.8
Any-grade AEs, %	98	99
Treatment related	84	94
Grade 3/4 AEs, %‡	57	55
Treatment related‡	36	46
SAE, %	38	31
Treatment related	17	15
Grade 5 AE, %	5	6
Treatment related	2	0.6
AE leading to withdrawal from any component, %	16	10
Both components	7	N/A
AE leading to dose interruption of any study treatment, %	50	41
AE leading to dose modification of sorafenib, %§	N/A	37

*Safety-evaluable population; ‡Highest grade experienced §No dose modification allowed for atezolizumab + bevacizumab arm, SAE, serious adverse event

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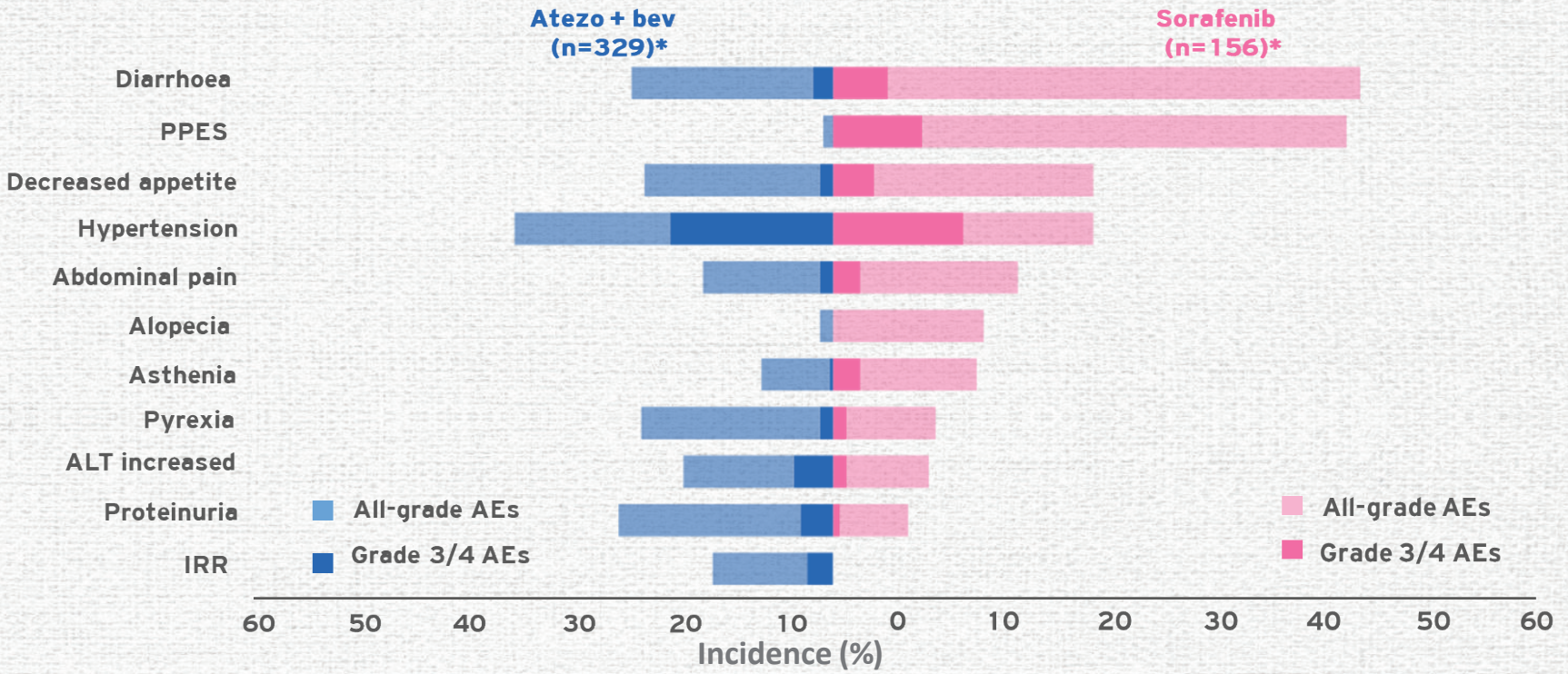
IMbrave150 illustrated some typical differences in safety profiles between TKIs and cancer immunotherapy-based regimens[1]



≥10% frequency of AEs in either arm and >5% difference between arms, *Safety evaluable population, AE, adverse event; ALT, alanine aminotransferase; IRR, infusion-related reaction; PPES, palmar plantar erythrodysaesthesia

1. Cheng A-L, Qin S, Ikeda M, et al. IMbrave150: efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol. 2019;30(suppl 9.

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The rate and grades of bleeding events in IMbrave150 were similar between treatment arms

	REFLECT[1]		IMbrave150[3]	
	Lenvatinib (n=476)	**Sorafenib (n=475)**	**Sorafenib (n=165)**	**Atezo + bev (n=336)**
Key exclusion criteria	• Oesophageal/gastric varices that require treatment • ≥50% liver occupation • Invasion of bile duct or main portal vein (Vp4)		• Untreated or incompletely treated oesophageal/gastric varices with bleeding or high risk for bleeding	
Median duration of treatment, months	2.8	5.7	3.7	7.4 (atezo) 6.9 (bev)
All-grade bleeding/ haemorrhage events, %[2]	23	15	17	25
Grade 3/4	4	4	6	6

1. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018 Mar 24;391(10126):1163-1173. doi: 10.1016/S0140-6736(18)30207-1.
2. Lenvatinib prescribing information. February 2020
3. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular

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This slide is not intended for cross-trial comparisons

Bleeding events with systemic therapies were typically low in grade and unrelated to varices

IMbrave150[1]

%	Atezo + bev (n=336)		Sorafenib (n=165)	
	Any grade	Grade 3/4*	Any grade	Grade 3/4*
Varices at baseline	**26**		26	
Treated at baseline	11		14	
All-grade bleeding/ haemorrhage events	**25**		17	
Epistaxis	10.3	0	4.5	0.6
Oesophageal varices haemorrhage	2.4	1.8	0.6	0.6
GI haemorrhage	2.4	1.2	1.9	1.9
Upper GI bleeding	1.2	0.6	1.3	1.3

Varices activity assessed before therapy

*Highest grade assigned, GI, gastrointestinal

1. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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Hepatitis occurred at similar rates between treatment arms in IMbrave150

IMbrave150

Atezolizumab AESIs occurring in ≥10 of patients, %	Atezo + bev (n=329)		Sorafenib (n=156)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hepatitis (diagnosis, lab abnormality)*	43	21	40	17
Hepatitis (lab abnormality)*	38	17	35	14
Hepatitis (diagnosis)*	13	7	13	5
Rash	20	0.6	62	14
Hypothyroidism	11	0	3	0
IRR	11	2	0	0

*Hepatitis (diagnosis; eg hepatic failure, liver injury, etc) and hepatitis (lab abnormality; eg ALT increase, blood bilirubin increase, etc) were grouped per MedDRA preferred terms based on AE terms reported by the investigators

1. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

IMbrave150 PRO: assessment[1,2]

Key aspects of the patient experience were evaluated in patients receiving atezolizumab + bevacizumab vs sorafenib in patients with HCC

Quality of life

Functioning: physical, role

Symptoms: fatigue, pain, appetite loss, diarrhoea, jaundice

Patients completed the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires every 3 weeks while on treatment until treatment discontinuation or progression, and every 3 months thereafter for 1 year questionnaire completion rates were ≥93% until treatment cycle 17 and ≥80 thereafter until treatment was discontinued

EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire PRO, patient-reported outcome

1. Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes (PROs) from the phase III IMbrave150 trial of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol*. 2020;38(suppl 4):Abstract 4762.

2. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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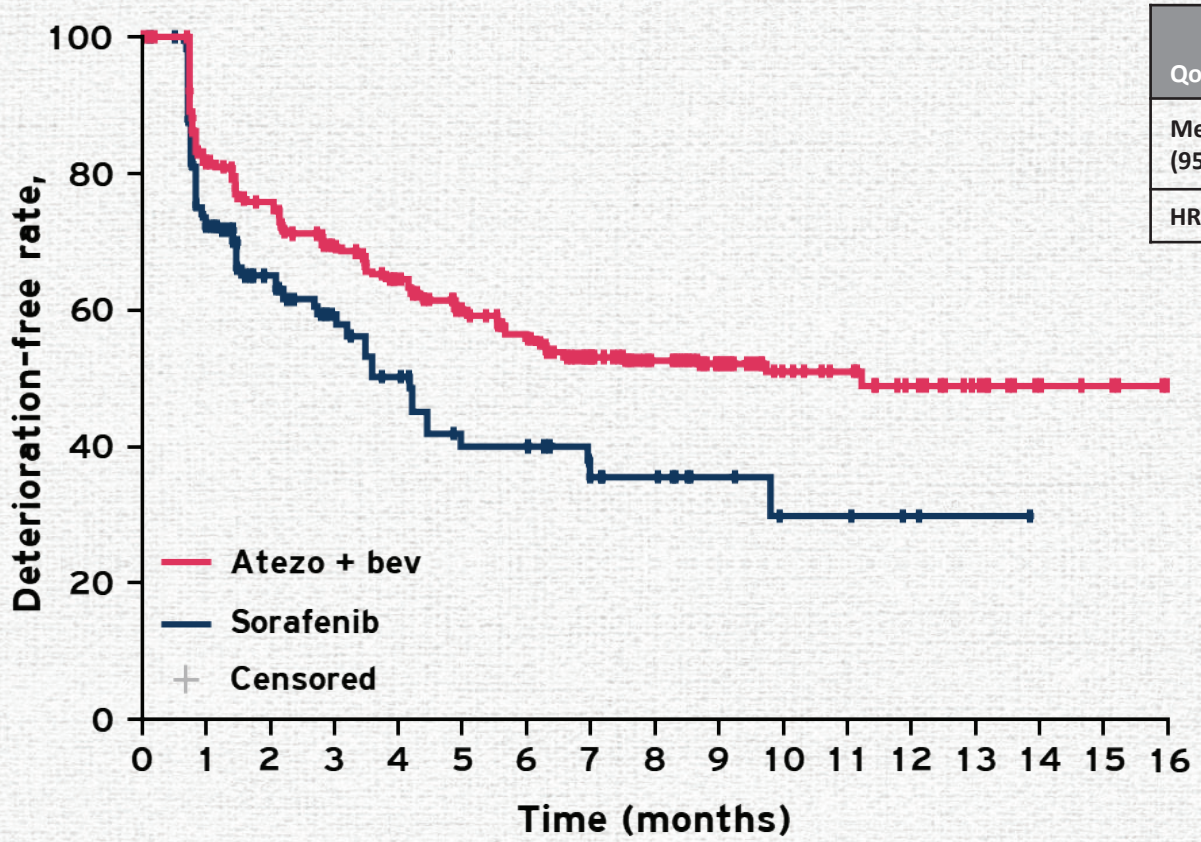
IMbrave150 PRO: time to deterioration in patient-reported QoL[1,2]

QoL	Atezo + bev (n=336)	Sorafenib (n=165)
Median TTD, (95% CI) months*	11.2 (6.0–NE)	3.6 (3.0–7.0)
HR (95% CI)	0.63 (0.46–0.85)	



Patients at risk

Sorafenib	165	93	60	39	31	22	22	14	12	7	4	4	2	1	NE	NE	NE
Atezo + bev	336	239	208	181	157	134	121	99	78	58	40	32	20	14	7	5	NE

Clinical cut-off date: 29 Aug 2019; median survival follow-up, 8.6 months, *The events for 'time to deterioration' were defined as a ≥10 points decrease from baseline[3] in the GHS/QoL scale of the EORTC QLQ-C30 questionnaire maintained for two consecutive assessments or one assessment followed by death from any cause within 3 weeks

GHS, Global Health Scale; QoL, quality of life; TTD, time to deterioration

1. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745
2. Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes (PROs) from the phase III IMbrave150 trial of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol*. 2020;38(suppl 4):Abstract 4762.
3. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44. doi: 10.1200/JCO.1998.16.1.139.

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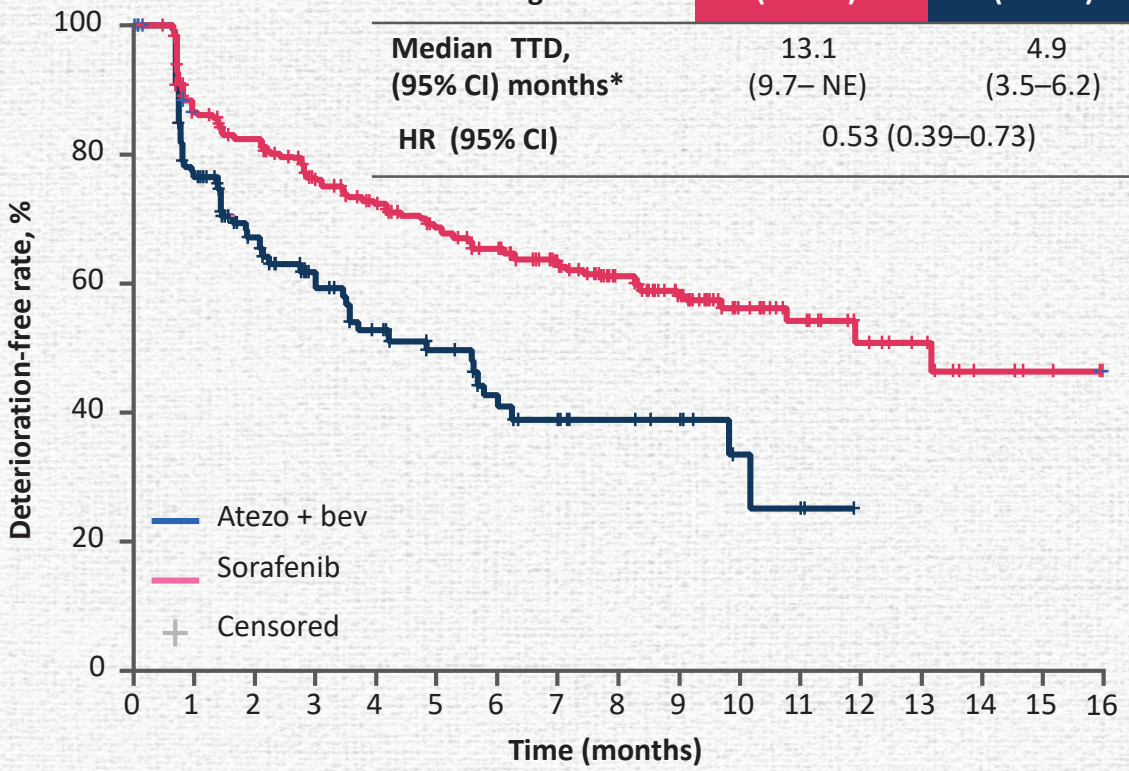
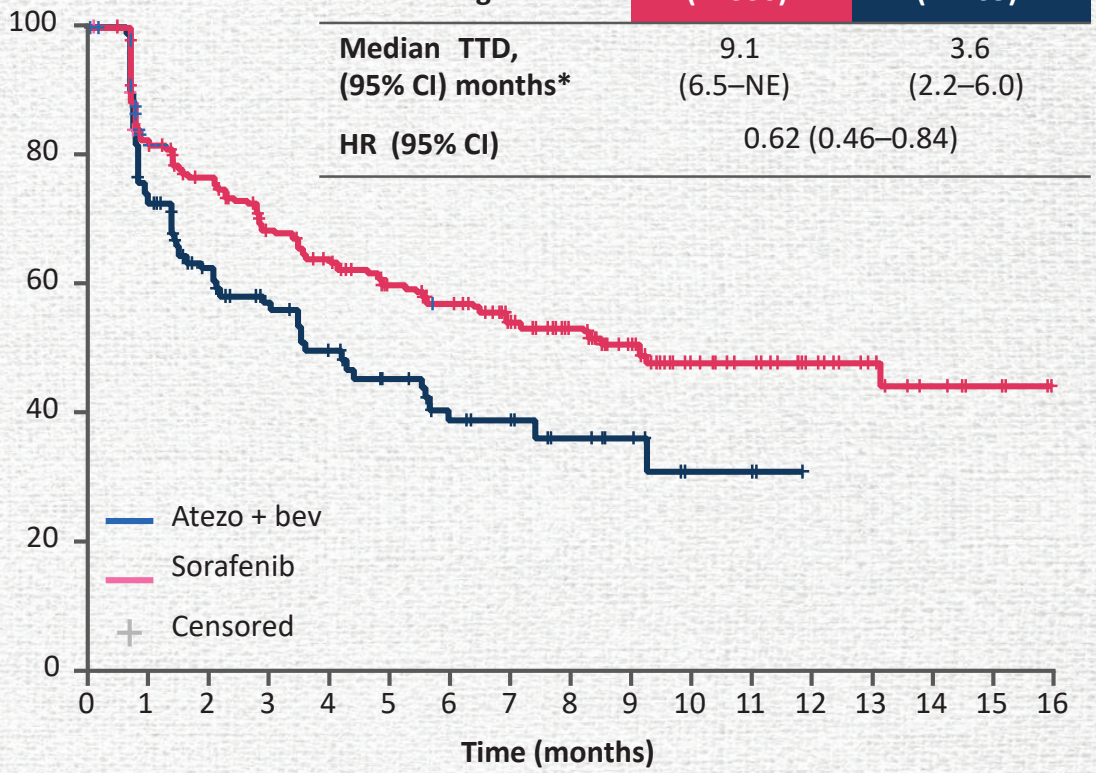
QoL must be considered when choosing a regimen – side effects can affect a patient's perception of their well-being[1,2]

Physical functioning	Atezo + bev (n=336)	Sorafenib (n=165)
Median TTD, (95% CI) months*	13.1 (9.7– NE)	4.9 (3.5–6.2)
HR (95% CI)	0.53 (0.39–0.73)	



Role functioning	Atezo + bev (n=336)	Sorafenib (n=165)
Median TTD, (95% CI) months*	9.1 (6.5–NE)	3.6 (2.2–6.0)
HR (95% CI)	0.62 (0.46–0.84)	



*The events for 'time to deterioration' were defined as a ≥10-point decrease from baseline[3] in the physical/role functioning scales of the EORTC QLQ-C30 questionnaire maintained for two consecutive assessments or one assessment followed by death from any cause within 3 weeks

1. Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes (PROs) from the phase III IMbrave150 trial of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol*. 2020;38(suppl 4):Abstract 4762. 2. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745
3.Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44. doi: 10.1200/JCO.1998.16.1.139.

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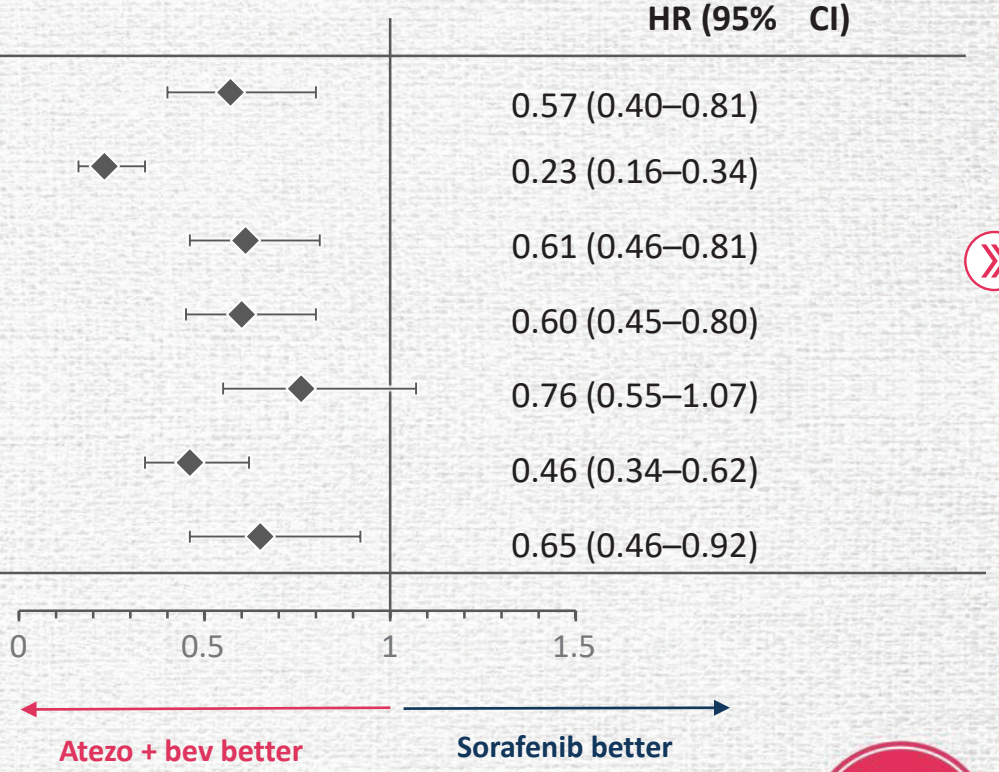
Deterioration of symptoms can also affect a patient's QoL

Scale (questionnaire)	Median time to event, (95% CI) months: Atezo + bev (n=336)	Sorafenib (n=165)	HR (95% CI)
Appetite loss	NE	7.62 (3.48–NE)	0.57 (0.40–0.81)
Diarrhoea	NE	4.44 (3.48–5.59)	0.23 (0.16–0.34)
Fatigue (QLQ-C30)	5.68 (4.30–7.10)	2.10 (1.45–4.83)	0.61 (0.46–0.81)
Fatigue (QLQ-HCC18)	5.65 (4.30–9.03)	2.14 (1.64–2.83)	0.60 (0.45–0.80)
Jaundice	10.55 (6.93–NE)	6.47 (5.55–NE)	0.76 (0.55–1.07)
Pain (QLQ-C30)	9.72 (7.16–NE)	2.79 (2.14–4.30)	0.46 (0.34–0.62)
Pain (QLQ-HCC18)	NE	9.82 (4.27–NE)	0.65 (0.46–0.92)



1. Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes (PROs) from the phase III IMbrave150 trial of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol*. 2020;38(suppl 4):Abstract 4762.

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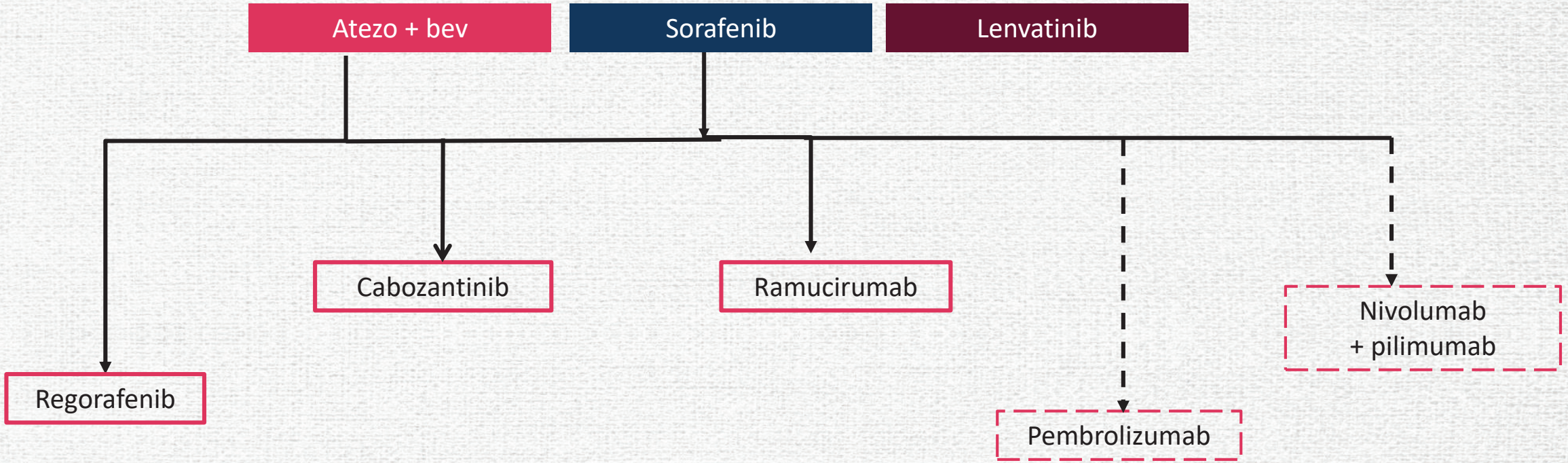
Systemic Therapy for HCC in 2021



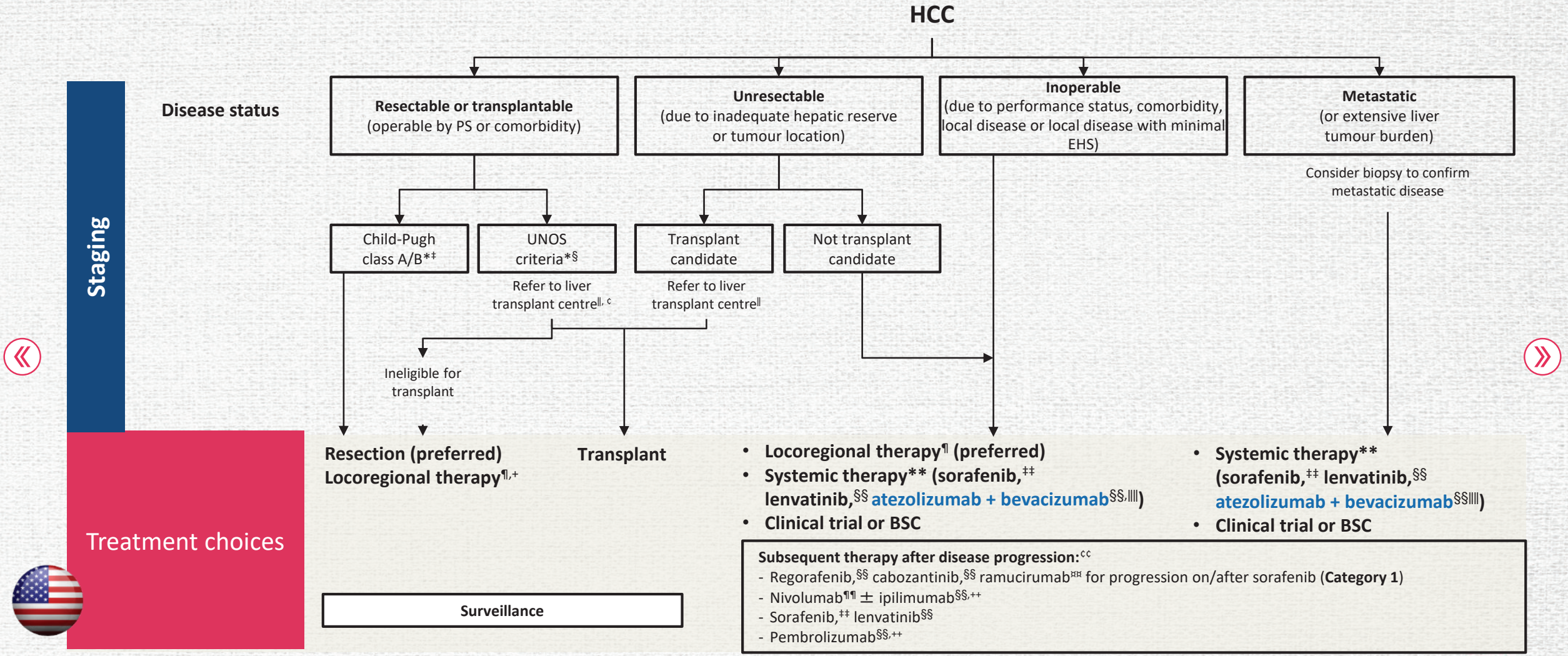
Based on RCTs

Based on non-randomized trials

Slide credit: clinicaloptions.com

ExpressPoints: Critical Advances in Systemic Therapy for HCC: Building on Recent Progress for Community Practices. Available on : https://www.clinicaloptions.com/oncology/programs/hcc-advances-2020/downloadable-slidesets/slideset-ep. Accessed on Aug 2021

US: NCCN guidelines for HCC



Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate; Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. Footnotes included in the slide notes. Added in v1.2020 update and confirmed as Category 1 recommendation in v4.2020 update. PS, performance status; UNOS, United Network for Organ Sharing

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. Version 4.2020. https://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf. Accessed on Aug 2021.

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Systemic Therapy for Advanced HCC

First-line systemic therapy options

For patients with advanced HCC, Child-Pugh class A, and ECOG PS 0-1, treatments discussed in the guideline include

- Atezolizumab + Bevacizumab
- Tyrosine Kinase Inhibitor (TKIs) (Sorafenib or Lenvatinib)

Second-line systemic therapy options

Depending on the first-line therapy received, treatments discussed in the guideline include

Following first-line treatment with atezolizumab + bevacizumab,

- TKIs (Sorafenib, Cabozantinib, or Regorafenib)

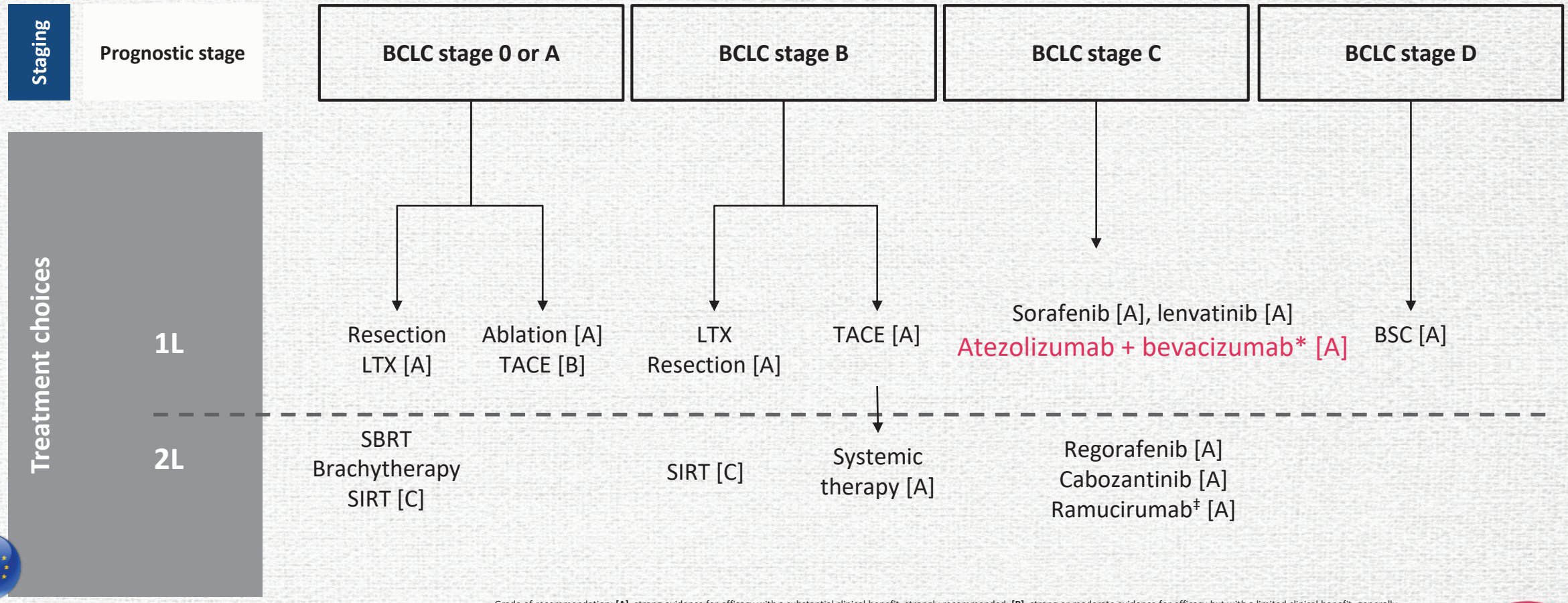
Following first-line treatment with sorafenib or lenvatinib,

- Another TKIs (Cabozantinib, Regorafenib)
- Atezolizumab+ Bevacizumab (if not given first-line)
- Ramucirumab (AFP ≥ 400ng/mL)
- Immune checkpoint inhibitors (pembrolizumab, nivolumab, ± ipilimumab)

ASCO® Guidelines

Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, Goff L, Gupta S, Guy J, Harris WP, Iyer R, Jaiyesimi I, Jhawer M, Karippot A, Kaseb AO, Kelley RK, Knox JJ, Kortmansky J, Leaf A, Remak WM, Shroff RT, Sohal DPS, Taddei TH, Venepalli NK, Wilson A, Zhu AX, Rose MG. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. J Clin Oncol. 2020 Dec 20;38(36):4317-4345. doi: 10.1200/JCO.20.02672. Epub 2020 Nov 16. PMID: 33197225.

Europe: ESMO guidelines for HCC



Grade of recommendation: **[A]**, strong evidence for efficacy with a substantial clinical benefit, strongly recommended; **[B]**, strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended; **[C]**, insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (AEs, costs), optional**Added in 19 June 2020 eUpdate;** *Not EMA-approved; ‡AFP-high (≥400ng/mL); LTX, liver transplantation; SBRT, stereotactic body radiation therapy

1. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, Nault JC, Neumann U, Ricke J, Sangro B, Schirmacher P, Verslype C, Zech CJ, Arnold D, Martinelli E; ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv238-iv255. doi: 10.1093/annonc/mdy308. Erratum in: Ann Oncol. 2019 May 1;30(5):871-873. Erratum in: Ann Oncol. 2019 May;30(5):871-873.

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Conclusions

- The combination of atezolizumab + bevacizumab has demonstrated efficacy in patients with unresectable HCC in the phase III trial, IMbrave150
  - Atezolizumab + bevacizumab demonstrated a statistically significant and clinically meaningful improvement in OS and PFS compared with sorafenib
  - Atezolizumab + bevacizumab resulted in a clinically meaningful delay in deterioration of patient-reported QoL, physical functioning, role functioning and key symptoms compared with sorafenib
- The positive phase III data for atezolizumab + bevacizumab highlights the benefit of targeting multiple steps in the cancer immunity cycle and has the potential to transform the current treatment paradigm for 1L unresectable HCC

Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745

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