Front-Line Management for Advanced Hepatocellular Carcinoma (HCC)

ASCO GI Satellite Symposium

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Outline

- Current standard systemic therapies in HCC
- Clinical and biologic factors affecting the selection of first-line treatment for advanced HCC
- Design of, entry criteria for and key efficacy findings from the Phase III IMbrave150 trial comparing atezolizumab/bevacizumab to sorafenib in HCC
- Spectrum, frequency and severity of treatment-related adverse events associated with atezolizumab/bevacizumab in IMbrave150
- Current clinical role of lenvatinib as first-line therapy for unresectable HCC; patient selection for its use in routine practice

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Approved HCC systemic therapies

2007
Sorafenib [6,7] 1st line

2017
Regorafenib [8] 2nd line
Nivolumab [9] 2nd line

2018
Lenvatinib [10] 1st line
Pembrolizumab [11] 2nd line

2019
Cabozantinib 2nd line
Ramucirumab 2nd line*

2020
Atezo/Bev [12] 1st line

*AFP≥400

1. Mazzaferro V et al. NEJM, 1996
2. Curley S et al. Ann Surg, 2000.
3. Livraghi T et al. Radiology, 1999.
4. Llovet JM et al. Hepatol, 2002.
5. Lo CM et al. Lancet, 2002
6. Llovet JM et al. NEJM, 2008.
7. Cheng AL et al. Lancet Oncol, 2009.
8. Bruix J, et al. Lancet, 2017
9. El-Koueiry A, et al. Lancet 2017
10. Kudo M, et al. The Lancet 2018
11. Zhu AX, et al. Lancet Oncol 2018
12. Finn RS, et al. NEJM 2020

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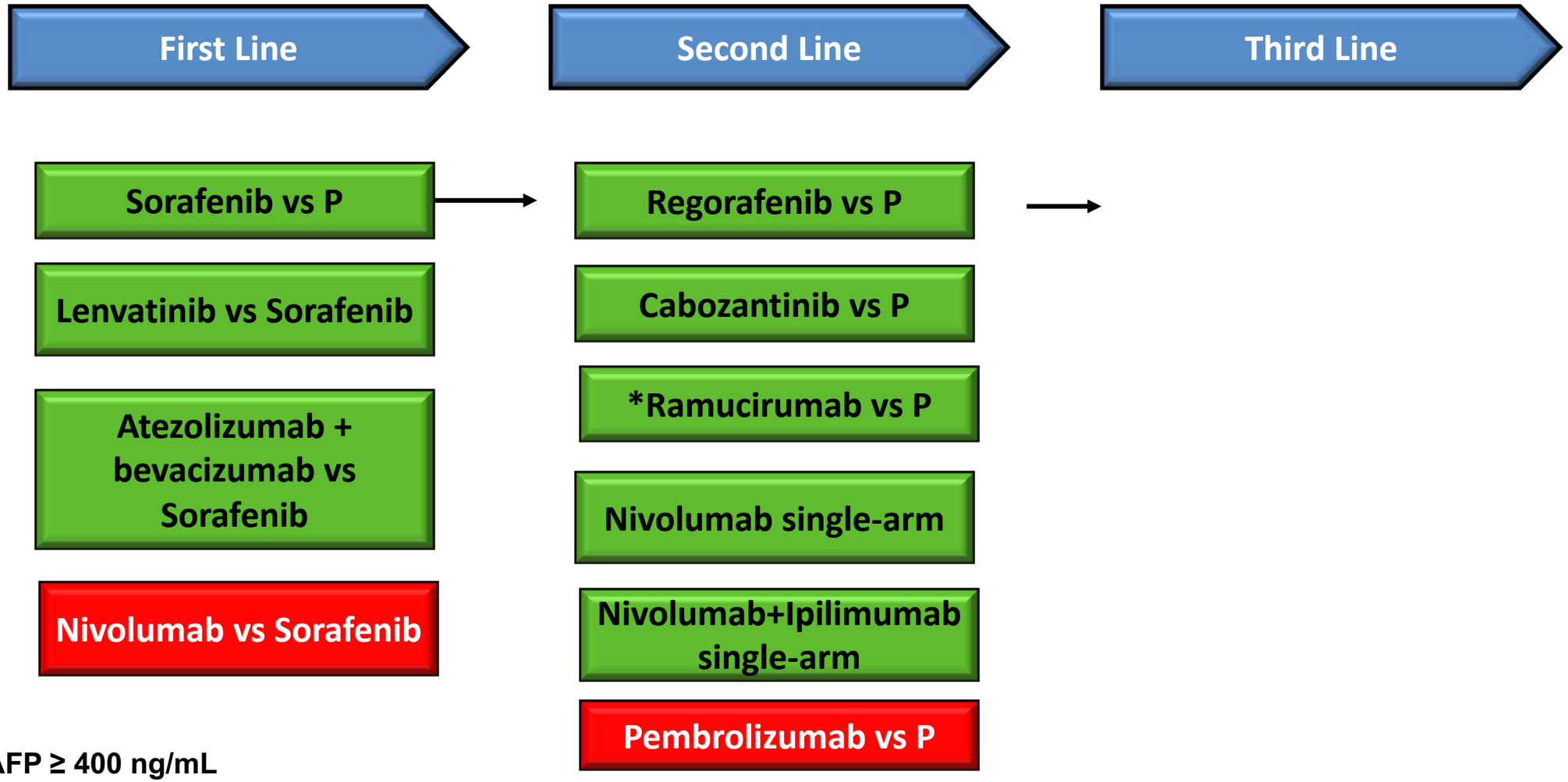
The ever-changing Landscape of Systemic Therapy in HCC



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Demographics across key frontline HCC randomized studies that could aid in patient selection

	REFLECT[1]		IMbrave150[2]	
Baseline characteristics, %	Lenvatinib (n=478)	Sorafenib (n=476)	Atezo + bev (n=336)	Sorafenib (n=165)
ECOG PS 0 | 1	64 | 36	63 | 37	| 38	| 38
Asian | Non-Asian	67 | 33	67 | 33	56 | 44	58 | 42
BCLC A | B | C	0 | 22 | 78	0 | 19 | 81	2 | 16 | 82	4 | 16 | 81
Child-Pugh class A5 | A6 | B7	77 | 32 | 1	75 | 24 | 1	72 | 28 | 0.3	73 | 27 | 0
HBV	53	48	49	46
HCV	19	26	21	22
Non-viral	29	25	30	32
MVI	23	19	38	43
EHS	61	62	63	56
MVI and/or EHS	69	71	77	73
AFP ≥200ng/mL	46	39	43	45
AFP ≥400ng/mL			38	37

- IMbrave150 study necessitated EGD within 6 months to exclude large varices at risk for bleeding
-
- REFLECT study exclusion criteria: invasion at the main portal vein; ≥50% liver occupation; invasion of bile duct

1. Kudo et al. Lancet 2018; 2. Finn et al. NEJM 2020

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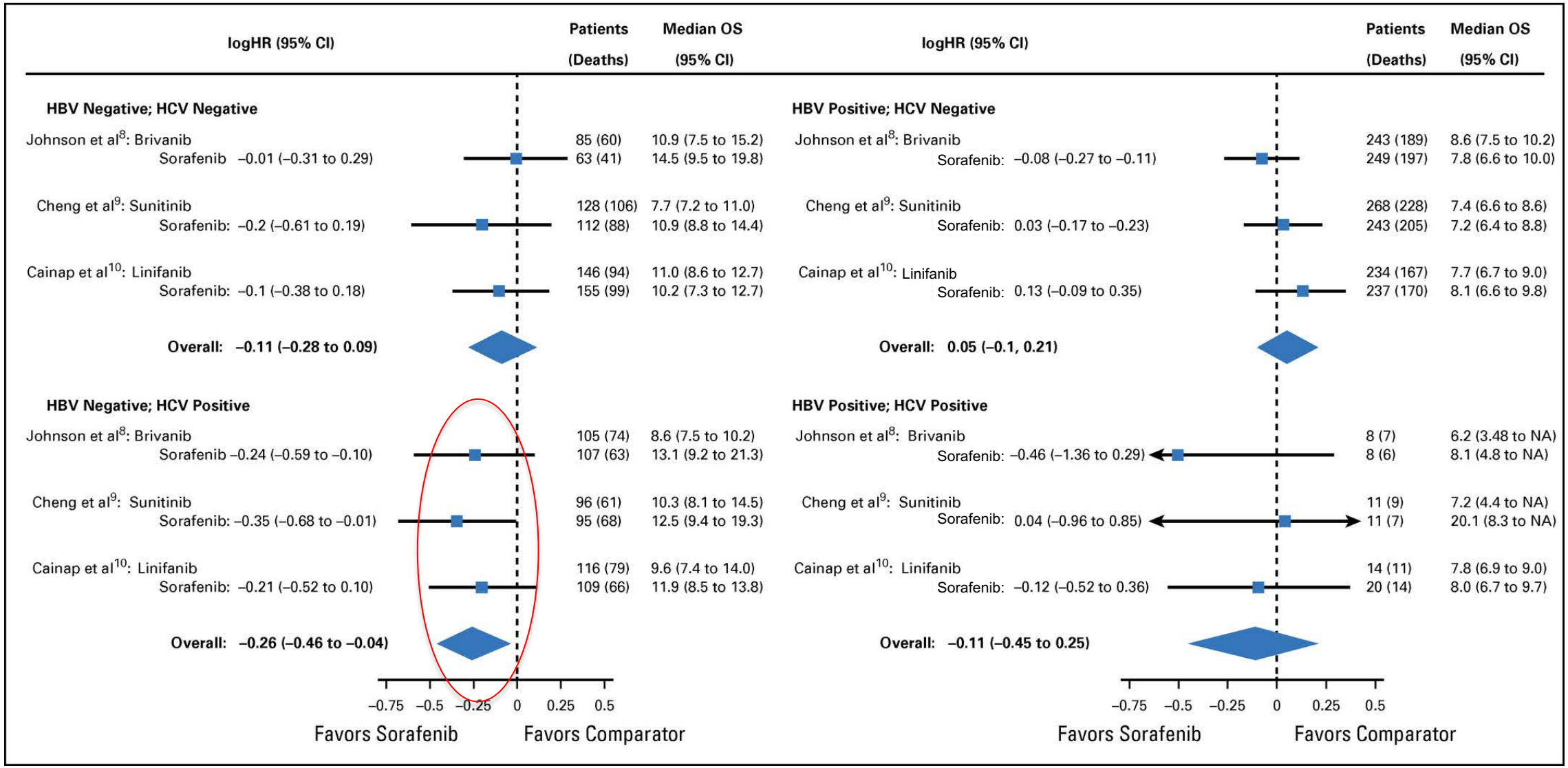
Impact of Viral Status on Survival in Patients Receiving Sorafenib for Advanced HCC: A Meta-Analysis of Randomized Phase III Trials



Jackson R, et al JCO 2017

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Summary of Recommendations – ASCO Guidelines, 2020

First-Line Therapy

Recommendation 1.1

Atezolizumab-bevacizumab may be offered as first-line treatment for most patients with advanced HCC, Child-Pugh class A, ECOG PS 0-1 and following management of esophageal varices, when present, according to institutional guidelines.

Recommendation 1.2

Where there are contraindications to atezolizumab and/or bevacizumab, tyrosine kinase inhibitors **sorafenib or lenvatinib** may be offered as first-line treatment for patients with advanced HCC, Child-Pugh class A, and ECOG PS 0-1.

ASCO Guidelines

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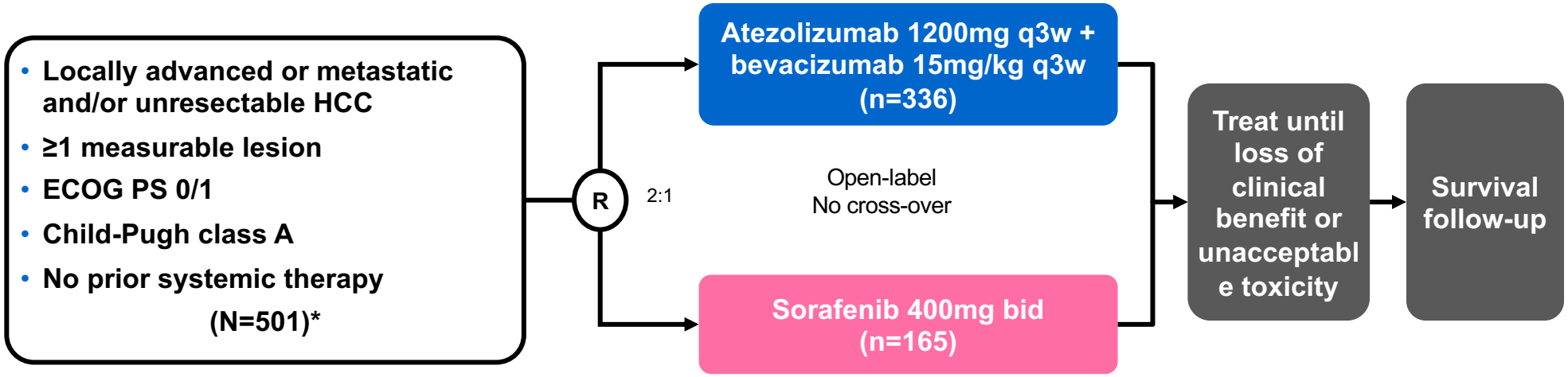
IMbrave150 Design



Stratification:
- Region (Asia excluding Japan/RoW)
- ECOG PS (0/1)
- MVI and/or EHS (presence/absence)
- Baseline AFP (<400/≥400ng/mL)

Primary endpoints
- OS
- PFS – IRF-assessed per RECIST v1.1

Secondary endpoints
- ORR, TTP and DoR (IRF-assessed RECIST v1.1)
- ORR, TTP, DoR and PFS (IRF-assessed HCC mRECIST)
- ORR, TTP, DoR and PFS (INV-assessed RECIST v1.1)
- Safety
- PROs

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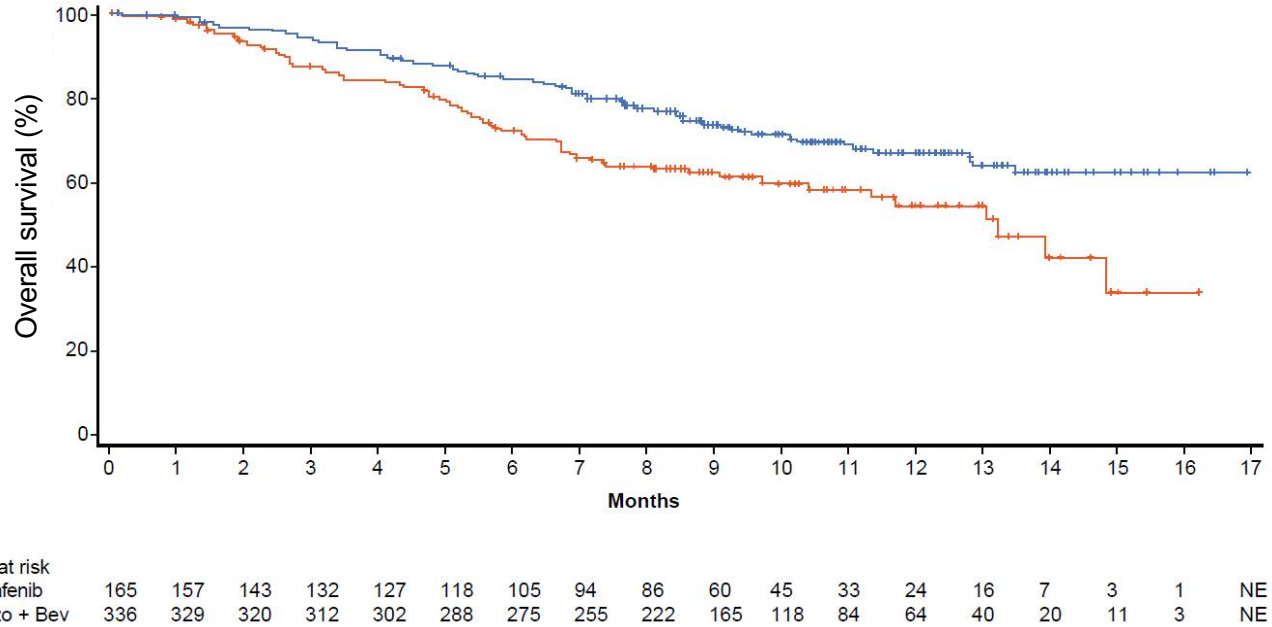
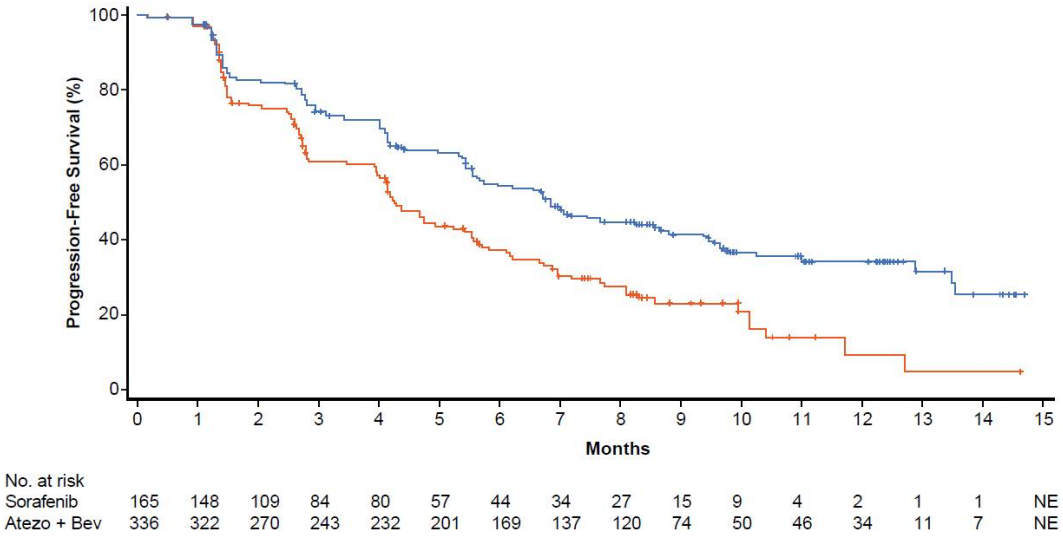
Atezolizumab + bevacizumab vs sorafenib in patients with unresectable HCC: Phase 3 results from IMbrave150

Cheng AL,[1] Qin S,[2] Ikeda M,[3] Galle PR,[4] Ducreux M,[5] Zhu AX,[6] Kim T-Y,[7] Kudo M,[8] Breder V,[9] Merle P,[10] Kaseb A,[11] Li D,[12] Verret W,[13] Xu D,[14] Hernandez S,[13] Liu J,[14] Huang C[14], Lim HY,[15] Finn RS[16]

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Events, n (%)	96 (29)	65 (39)
HR (95% CI)[a,b]	**0.58** (0.42 – 0.79)	
***P* value**[a]	0.0006	
Median OS (95% CI), mo	NE	13.2 (10.4 – NE)
6-mo OS, %	85	72



	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Events, n (%)	197 (59)	109 (66)
HR (95% CI)[b,c]	**0.59** (0.47 – 0.76)	
***P* value**[b]	< 0.0001	
Median PFS (95% CI), mo	6.8 (5.7 – 8.3)	4.3 (4.0 – 5.6)
6-mo PFS, %	55	37



Courtesy of Ahmed Omar Kaseb, MD, CMQ

Atezolizumab + bevacizumab vs sorafenib in patients with unresectable HCC: Phase 3 results from IMbrave150

Cheng AL,[1] Qin S,[2] Ikeda M,[3] Galle PR,[4] Ducreux M,[5] Zhu AX,[6] Kim T-Y,[7] Kudo M,[8] Breder V,[9] Merle P,[10] Kaseb A,[11] Li D,[12] Verret W,[13] Xu D,[14] Hernandez S,[13] Liu J,[14] Huang C[14], Lim HY,[15] Finn RS[16]

Efficacy summary

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	**Sorafenib (n = 159)**	**Atezo + Bev (n = 325)**	**Sorafenib (n = 158)**
Confirmed ORR, n (%) (95% CI)	**27** (23 – 33)	**12** (7 – 18)	**33** (28 – 39)	**13** (8 – 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified p-value[a]	**<0.0001**		**<0.0001**	
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)
DOR (n)	89	19	108	21
Ongoing response, n (%)	77 (87%)	13 (68)	84 (78)	13 (62)
Median DOR, months (95% CI)	NE	6.3 (4.7 – NE)	NE	6.3 (4.9 – NE)
Proportion of responders with DOR ≥ 6m , n (%)	88	59	82	63

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IMbrave150 Safety Data

IMbrave150 Overall safety summary

AEs, n (%)	Atezo + bev (n=329)	Sorafenib (n=156)
Any grade AEs	323 (98)	154 (99)
Treatment-related	276 (84)	147 (94)
Grade 3/4 AEs	186 (57)	86 (55)
Treatment-related Grade 3/4	117 (**36**)	71 (**46**)
Grade 5 AEs	15 (5)	9 (6)
Treatment-related Grade 5	6 (**2**)	1 (**0.6**)
Serious AEs	125 (38)	48 (31)
Treatment-related	56 (17)	24 (15)
AE leading to withdrawal from any drug	51 (16)	16 (10)
AE leading to dose interruption of any treatment	163 (50)	64 (41)
AE leading to dose modification of sorafenib	0	58 (37)

IMbrave150 Common AEs (any grade, ≥15% of patients in either arm)

	Atezo + bev (n=329)		Sorafenib (n=156)	
n (%)	All	G3/4	All	G3/4
Hypertension	98 (30)	50 (15)	38 (24)	19 (12)
Fatigue	67 (20)	8 (2)	29 (19)	5 (3)
Proteinuria	66 (20)	10 (3)	11 (7)	1 (0.6)
AST increased	64 (20)	23 (7)	26 (17)	8 (5)
Pruritus	64 (20)	0	15 (10)	0
Diarrhoea	62 (19)	6 (2)	77 (49)	8 (5)
Pyrexia	59 (18)	4 (1)	15 (10)	2 (1)
Decreased appetite	58 (18)	4 (1)	38 (24)	6 (4)
PPES	3 (1)	0	75 (48)	13 (8)
Rash	41 (13)	0	27 (17)	4 (3)
Abdominal pain	40 (12)	4 (1)	27 (17)	4 (3)
Nausea	40 (12)	1 (0.3)	25 (16)	1 (0.6)

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IMbrave150: Adverse events of Special Interests (AESI) – focus on Atezo related

AESIs, n (%)[a]	Atezo + Bev n = 329		Sor n = 156	
	All	G3-4	All	G3-4
For atezo				
Pts with ≥ 1	226 (69)	85 (26)	128 (82)	47 (30)
Hepatic events[b]	142 (43)	70 (21)	62 (40)	26 (17)
Inc AST	64 (20)	23 (7)	26 (17)	8 (5)
Inc blood bilirubin	43 (13)	8 (2)	22 (14)	10 (6)
Inc ALT	46 (14)	12 (4)	14 (9)	2 (1)
Ascites	23 (7)	6 (2)	9 (6)	2 (1)
Rash	64 (20)	2 (1)	96 (62)	21 (14)
Hypothyroidism	36 (11)	0	4 (3)	0
Infusion-related reactions	36 (11)	8 (2)	0	0
For bev				
Pts with ≥ 1	190 (58)	76 (23)	76 (49)	29 (19)
Hypertension	102 (31)	50 (15)	40 (26)	19 (12)
Bleeding/haemorrhage	83 (25)	21 (6)	27 (17)	9 (6)
Epistaxis	34 (10)	0	7 (5)	1 (1)
Upper GI bleeding[c]	24 (7)	15 (5)	8 (5)	8 (5)
Proteinuria	70 (21)	10 (3)	13 (8)	1 (1)

Inc, increased. [a] In ≥ 5% of pts. [b] ≥ 1 category possible. [c] Grouped MedDRA PT

Kudo M et al, Ann of Oncol Abstract only| Volume 31, SUPPLEMENT 6, S1304-S1305, Nov 01, 2020

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Lenvatinib Vs Sorafenib in HCC
First-Line randomized Phase III study

Outcomes	LENVATINIB	SORAFENIB	HR
Median OS, mos (95% CI)	13.6 (12.1–14.9)	12.3 (10.4–13.9)	0.92 (0.79–1.06)
Median PFS, mos (95% CI)*	7.4 (6.9–8.8)	3.7 (3.6–4.6)	0.66 (0.57–0.77)
Median TTP, mos (95% CI)*	8.9 (7.4–9.2)	3.7 (3.6–5.4)	
ORR, n (%)*	115 (24)	44 (9)	

Kudo M et al. Lancet 2018;391(10126):1163-73.

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Side-by-side summary of AEs in key frontline HCC randomized studies

	REFLECT[1]		IMbrave150[2]	
	Lenvatinib (n=476)	**Sorafenib (n=475)**	**Atezo + bev (n=329)**	**Sorafenib (n=156)**
Median follow-up, months	27.7	27.2	8.6	8.6
Median treatment duration, months	5.7	3.7	Atezo: 7.4 Bev: 6.9	2.8
Treatment-related AE, n (%)	447 (94)	452 (95)	276 (84)	147 (94)
Treatment-related SAE , n (%)	84 (18)	48 (10)	56 (17)	24 (15)
Treatment-related Grade 3/4 AE, n (%)	259 (54)*	227 (48)*	117 (36)	71 (46)
Treatment-related Grade 5 AE, n (%)	11 (2)	4 (1)	6 (2)	1 (1)
AE leading to discontinuation, n (%)	63 (13)	43 (9)	23 (7)‖	16 (10)

- 1. Kudo et al. Lancet 2018; 2. Finn et al. NEJM 2020

Courtesy of Ahmed Omar Kaseb, MD, CMQ

Case 1

- **65 y.o. female with h/o metabolic syndrome, DM-type 2, dyslipidemia, hypothyroidism**
- **Patient was in her usual state of health until 9/2018 when she developed a persistent cough prompting CXR evaluation which showed left lower lobe pneumonia. Follow-up CT Chest on 9/21/18 confirmed left lower lobe pneumonia with surrounding pleural effusion, but also incidentally showed numerous centrally necrotic masses throughout the liver.**
- **The patient underwent CT Abdomen on 9/26/18 which showed multiple bilobar liver masses, largest measuring 9.8 cm in right liver, as well as an 8.5 cm soft tissue mass in the left liver, in addition to left portal vein tumor thrombus.**
- **On 9/27/18, she underwent CT-guided liver biopsy with pathology confirming hepatocellular carcinoma.**
- **Baseline Child-Pugh score was A, HCC staging: BCLS stage C, and AFP=528**
- **Patient started on atezolizumab + bevacizumab in 10/2018 after EGD that showed no varices. Treatment was tolerated very well, except for non-significant proteinuria, and occasional fatigue**
- **Baseline scans in 10/2018 as well as follow up scans in 2/2020 are shown, indicating major tumor response. AFP normalized as well.**

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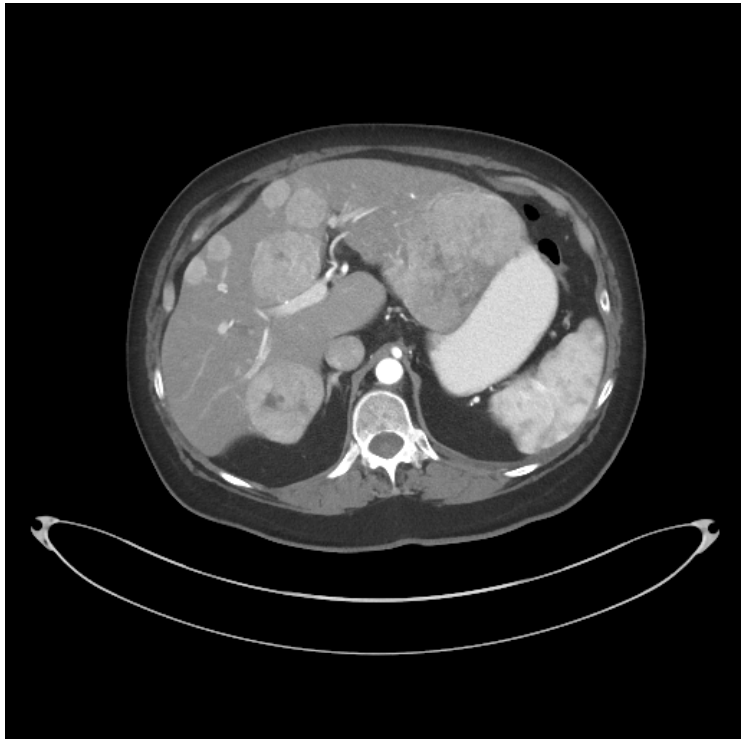
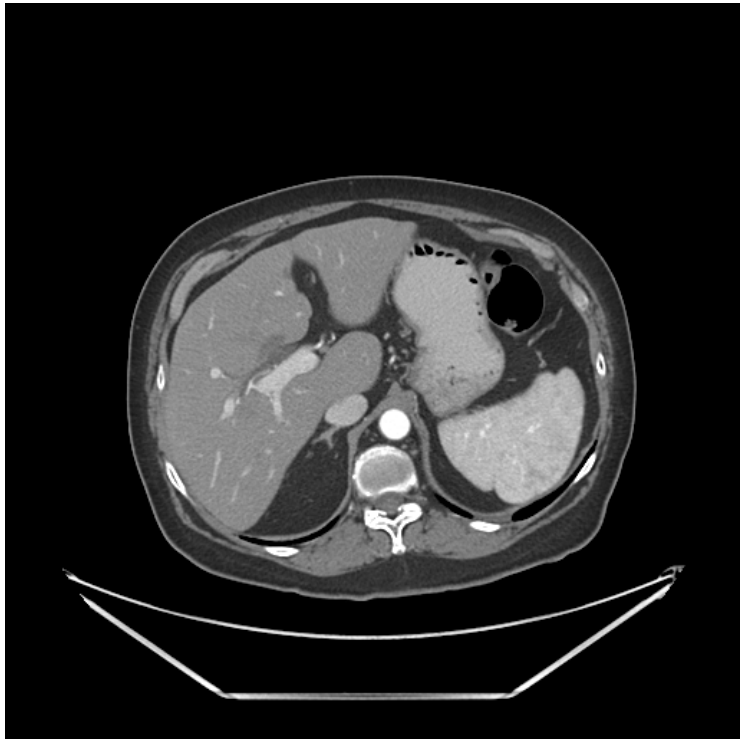
Baseline and last follow up imaging: bilobar tumors



10/2018



02/2020

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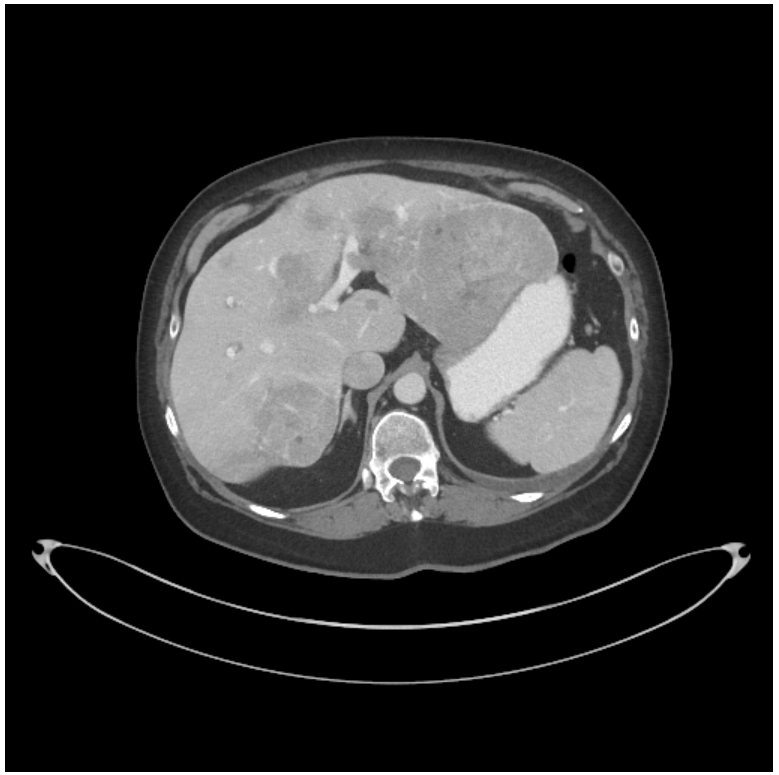
Baseline and last follow up imaging: left PV tumor thrombus



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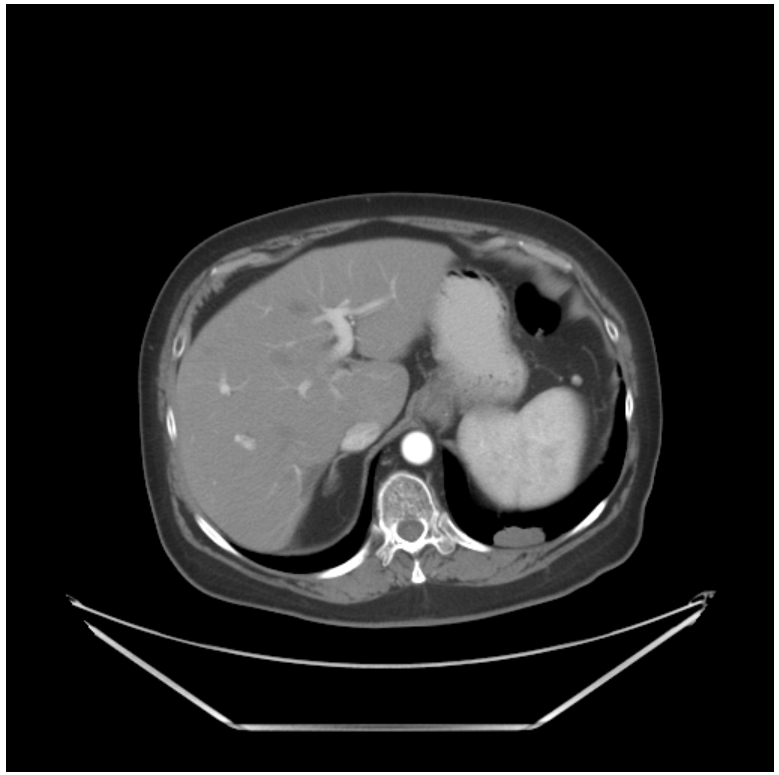

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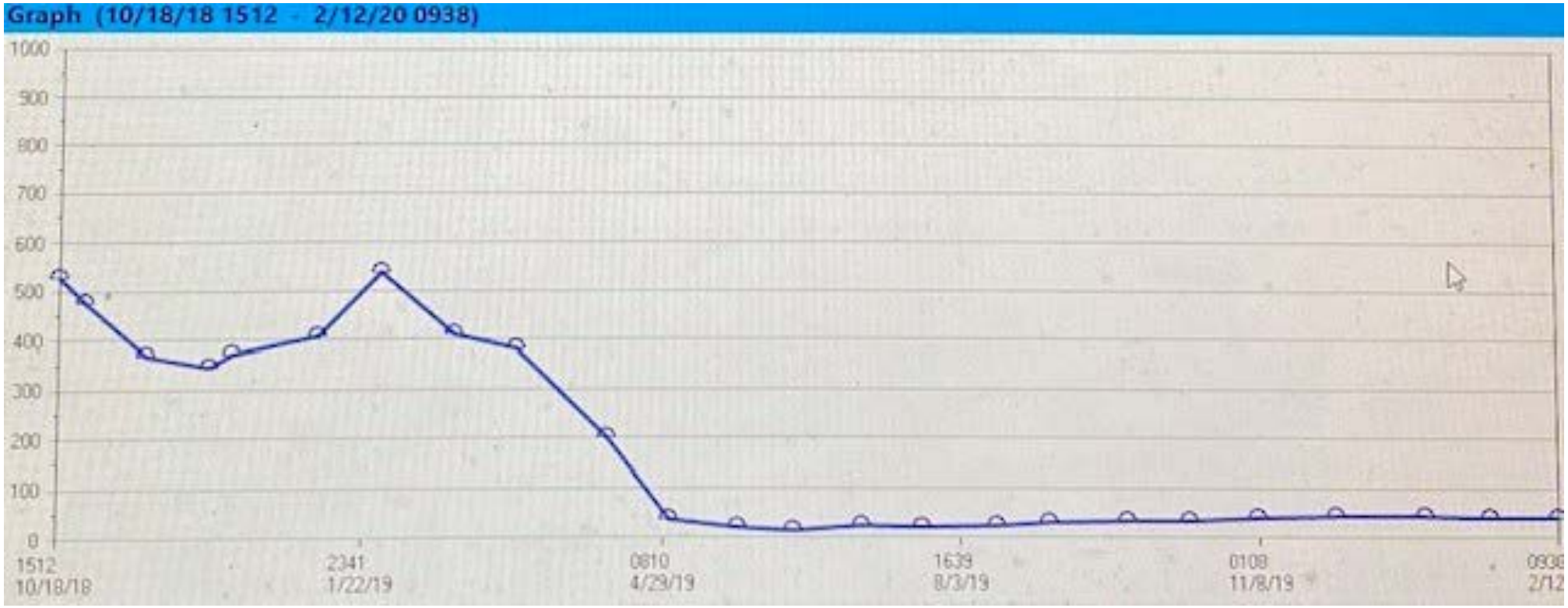
Baseline and last follow up AFP levels



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Case 2

- 60-year-old lady with h/o HTN, obesity and NASH
- She presented with right upper quadrant / flank pain in 8/2018. US and CT showed a right liver mass, interpreted as a hemangioma.
- Follow-up CT in 8/2019 showed enlargement of the segment 5/6 liver mass and a 2nd lesion in segments 4/5 and right portal vein tumor thrombus. Percutaneous biopsy showed HCC
- Baseline Child-Pugh score was A, HCC staging: BCLS stage C, and AFP=43,222
- Patient started on Lenvatinib in 08/2019 after EGD that showed no varices. Treatment was tolerated very well, except for mild increase in BP, managed by adjusting BP meds
- Baseline scans in 10/2018 as well as follow up scans in 2/2020 that showed tumor and portal vein thrombus shrinkage are shown. AFP decreased to 4,238
- Patient taken to OR for potential resection but found to have 60% macrovesicular steatosis, periportal fibrosis, and suspicious 0.5 cm left liver lesión, confirmed HCC

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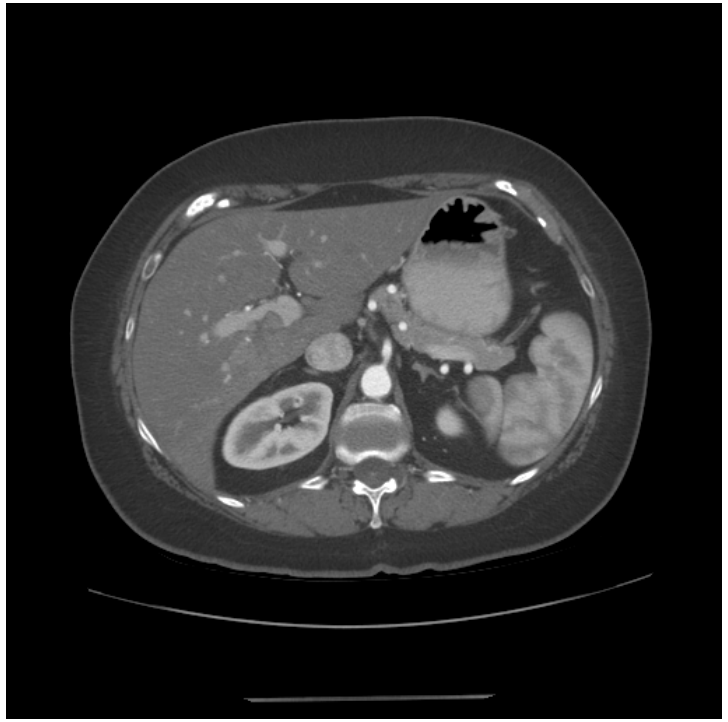
Baseline and last follow up imaging: Right PV tumor thrombus



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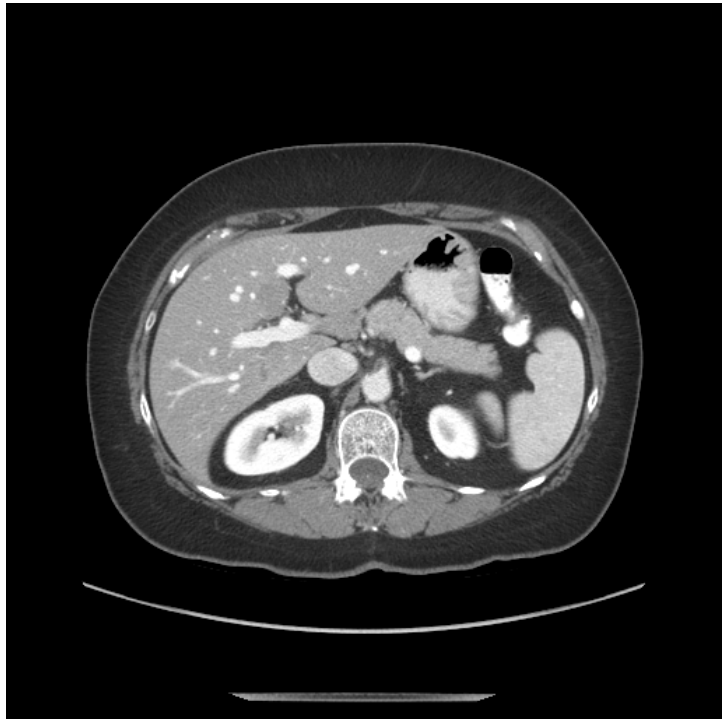

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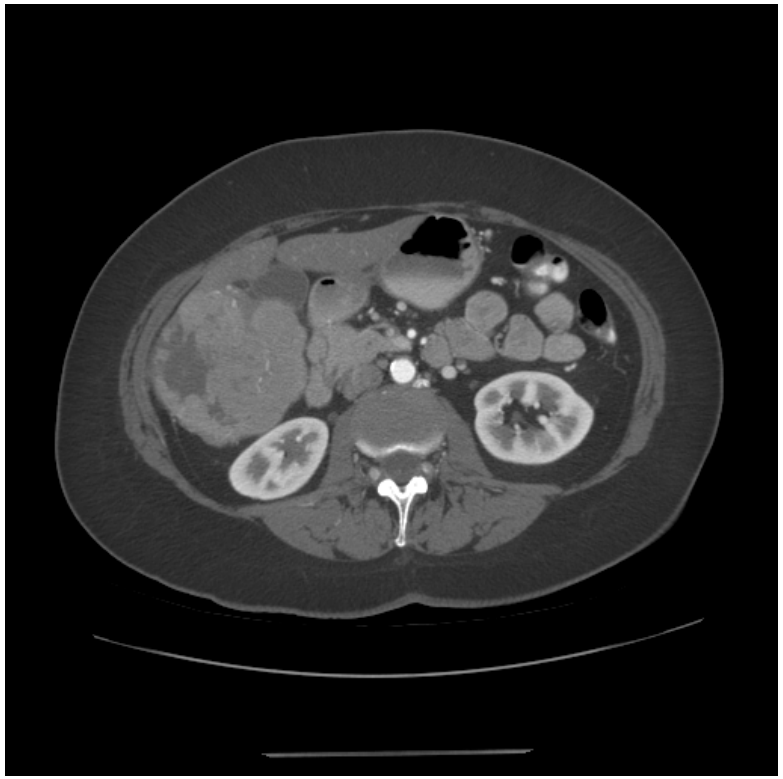
Baseline and last follow up imaging: HCC tumors



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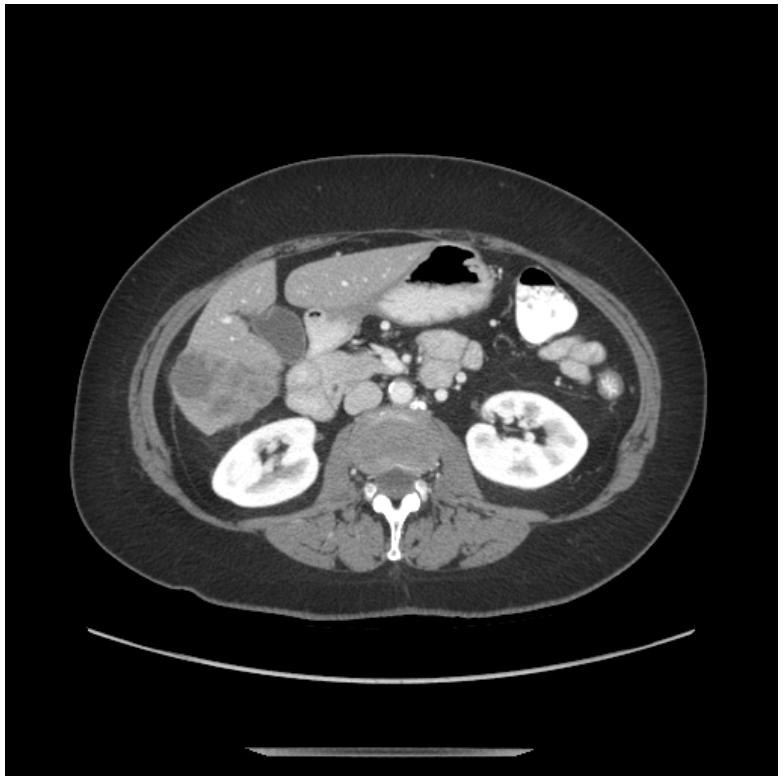

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Baseline and follow up AFP

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