Case Studies in Immunotherapy for the Treatment of Hepatocellular Carcinoma

January 10, 2021

6:30 – 7:30 p.m. EST

Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

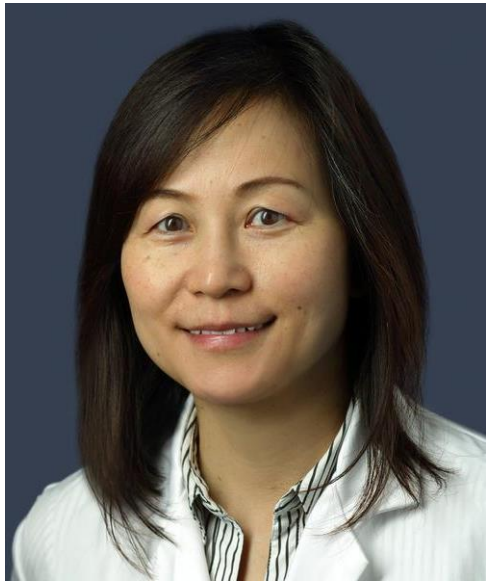
The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)

Webinar faculty

Tim F. Greten, MD

Expert Panel Chair

Ahmed O. Kaseb, MD – *The University of Texas MD Anderson Cancer Center*



Aiwu Ruth He, MD, PhD *– Medstar Georgetown University Hospital*

Anthony B. El-Khoueiry, MD – *USC Norris Cancer Hospital*

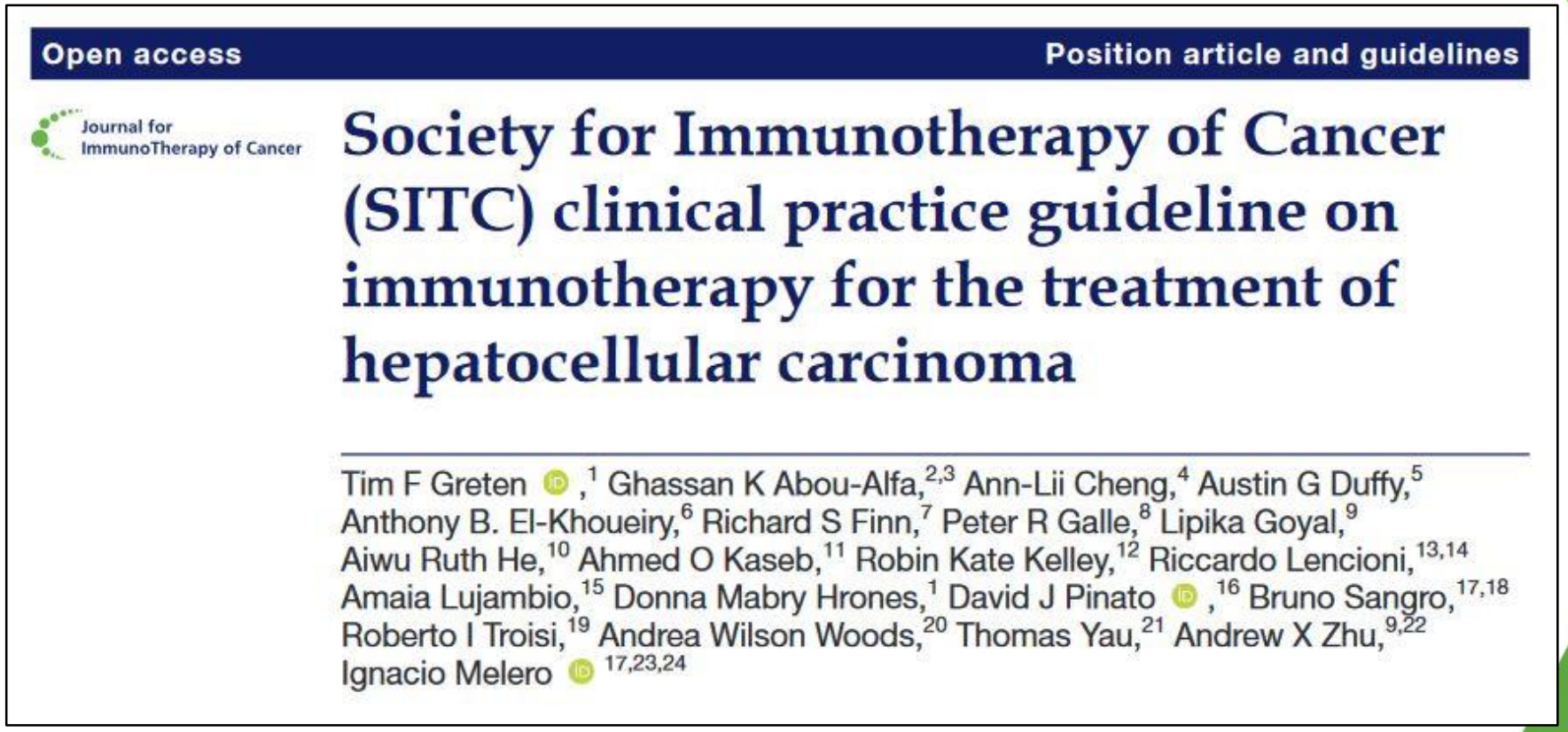
Learning objectives

- Plan immunotherapy treatment regimens for challenging patient populations
- Identify management strategies for uncommon and/or atypically responsive toxicities
- Select appropriate treatment strategies for patients with relapsed and/or unresponsive disease
- Articulate the potential risks and benefits for proceeding with any other possible interventions specific to a given disease setting in the context of an immunotherapy treatment plan

Webinar outline

- Development of the guideline
- Case 1: First-line therapy with atezo and bevo
- Case 2: IO-IO combination therapy in second-line
- Case 3: Single agent PD-1 Child Pugh B score
- Key takeaways

Development of the guideline



Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma

Tim F Greten ,[1] Ghassan K Abou-Alfa,[2,3] Ann-Lii Cheng,[4] Austin G Duffy,[5] Anthony B. El-Khoueiry,[6] Richard S Finn,[7] Peter R Galle,[8] Lipika Goyal,[9] Aiwu Ruth He,[10] Ahmed O Kaseb,[11] Robin Kate Kelley,[12] Riccardo Lencioni,[13,14] Amaia Lujambio,[15] Donna Mabry Hrones,[1] David J Pinato ,[16] Bruno Sangro,[17,18] Roberto I Troisi,[19] Andrea Wilson Woods,[20] Thomas Yau,[21] Andrew X Zhu,[9,22] Ignacio Melero [17,23,24]

Development of the guideline

- Developed according to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Panel consisted of 21 experts in the field
- Recommendations are based upon published literature evidence, or clinical evidence where appropriate
- Consensus was defined at 75% approval among voting members

Webinar outline

- Development of the guideline
- Case 1: First-line therapy with atezo and bevo
  - Highlight patent selection, including EGD
  - Potential complications
  - Discussion of other front-line options
- Case 2: IO-IO combination therapy in second-line
- Case 3: Single agent PD-1 Child Pugh B score
- Key takeaways

Front-Line Management for Advanced Hepatocellular Carcinoma (HCC)

SITC Case Series– January, 2022

Ahmed O Kaseb, MD

Professor and Director, HCC Program

Director, MD Anderson HCC SPORE

Department of GI Medical Oncology, MD Anderson

Editor-in-Chief: Journal of Hepatocellular Carcinoma

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Disclosure

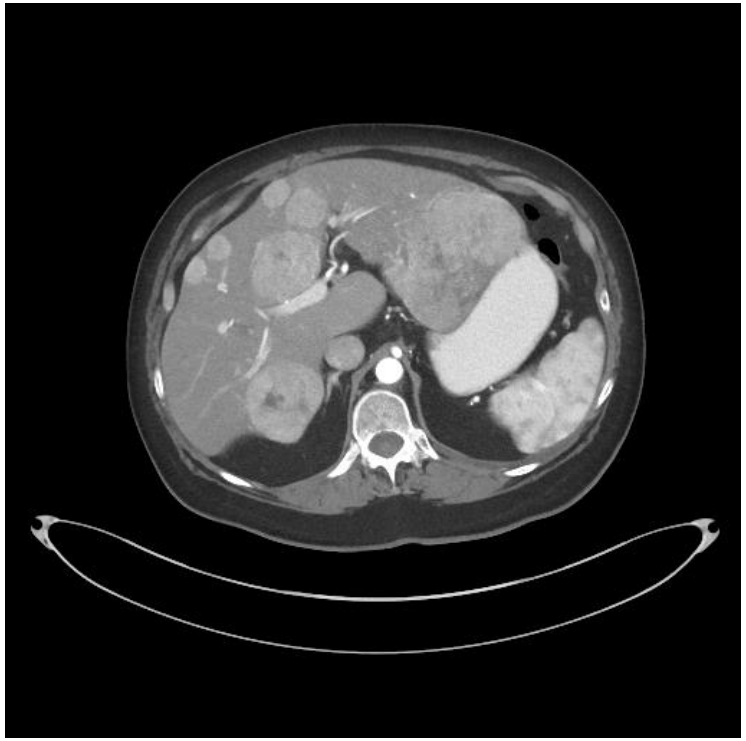
Research Support:

NCI, Merck, BMS, MedImmune, Immatics, Bayer/Onux, Amgen, Pfizer, Eisai, Roche / Genentech, Tracon, and Hengrui Therapeutics

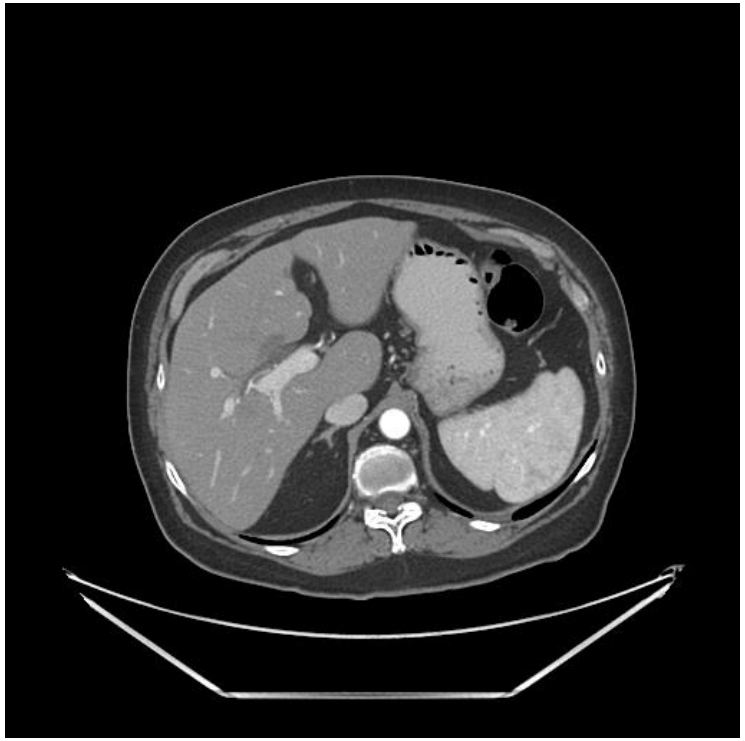
Case 1

- **65 y.o. female with h/o metabolic syndrome, DM-type 2, dyslipidemia, hypothyroidism**
- **Patient was incidentally found to have numerous centrally necrotic masses throughout the liver per imaging done during work up for pneumonia.**
- **CT Abdomen in 10/2018 showed multiple liver masses, largest was 9.8 cm in right liver and 8.5 cm in the left liver, with left portal vein tumor thrombus.**
- **Bx: mod-diff HCC, Child-Pugh 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 significant proteinuria that led to discontinuing bevacizumab (continued Atezolizumab), and occasional fatigue**
- **Baseline scans in 2018 as well as subsequent follow up scans in 2020 are shown, indicating major tumor response. AFP normalized as well.**

Baseline and last follow up imaging: bilobar tumors

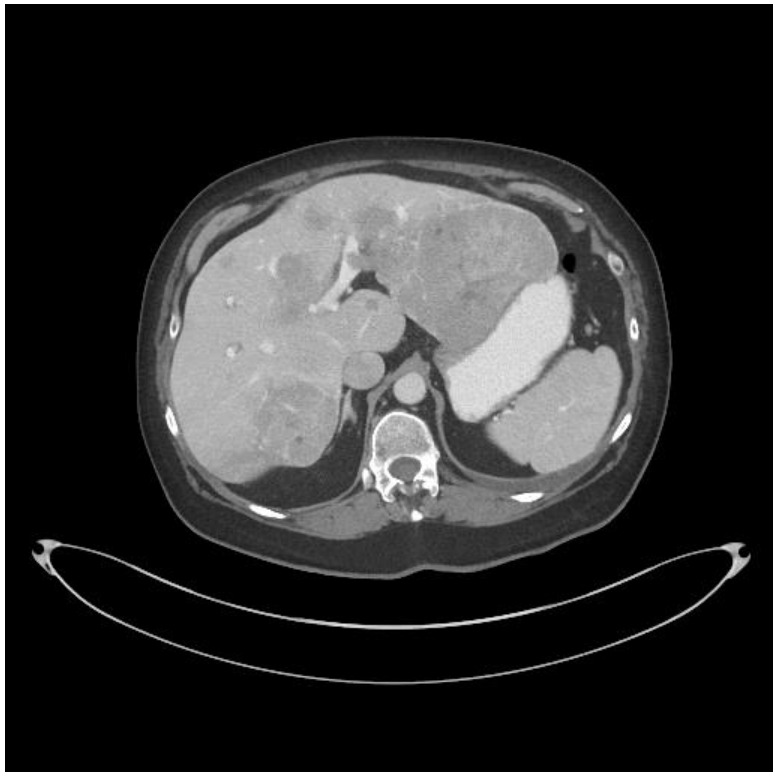


10/2018



02/2020

Baseline and last follow up imaging: left PV tumor thrombus



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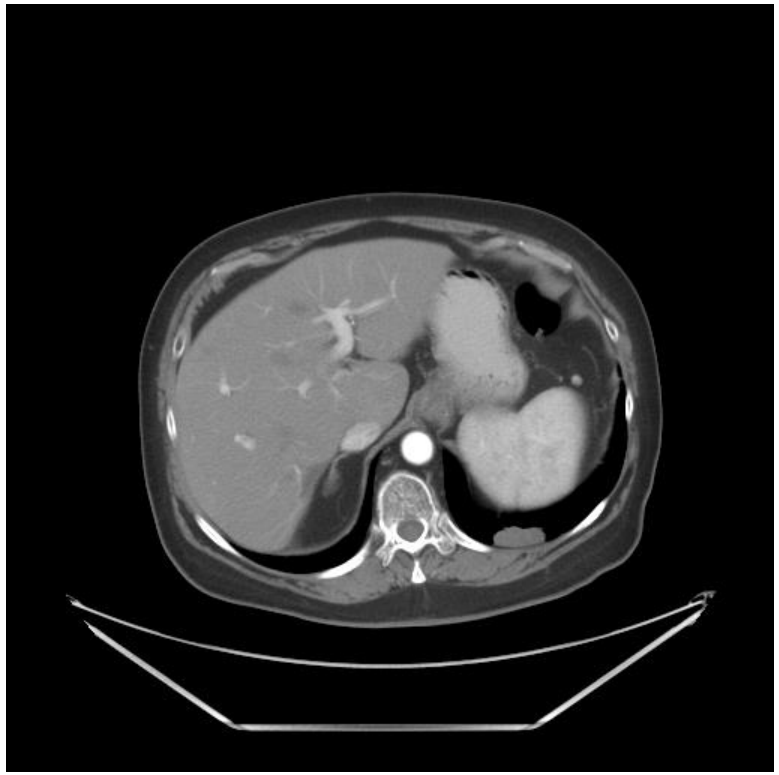

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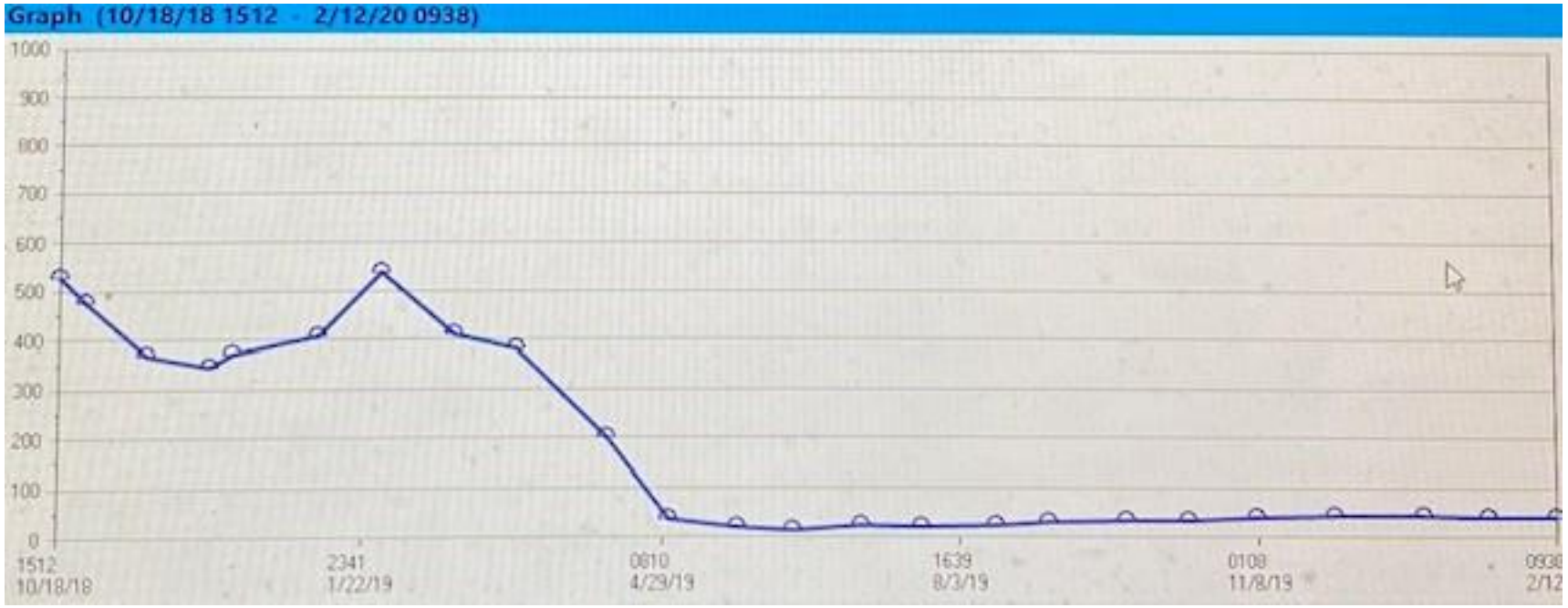
Baseline and last follow up AFP levels



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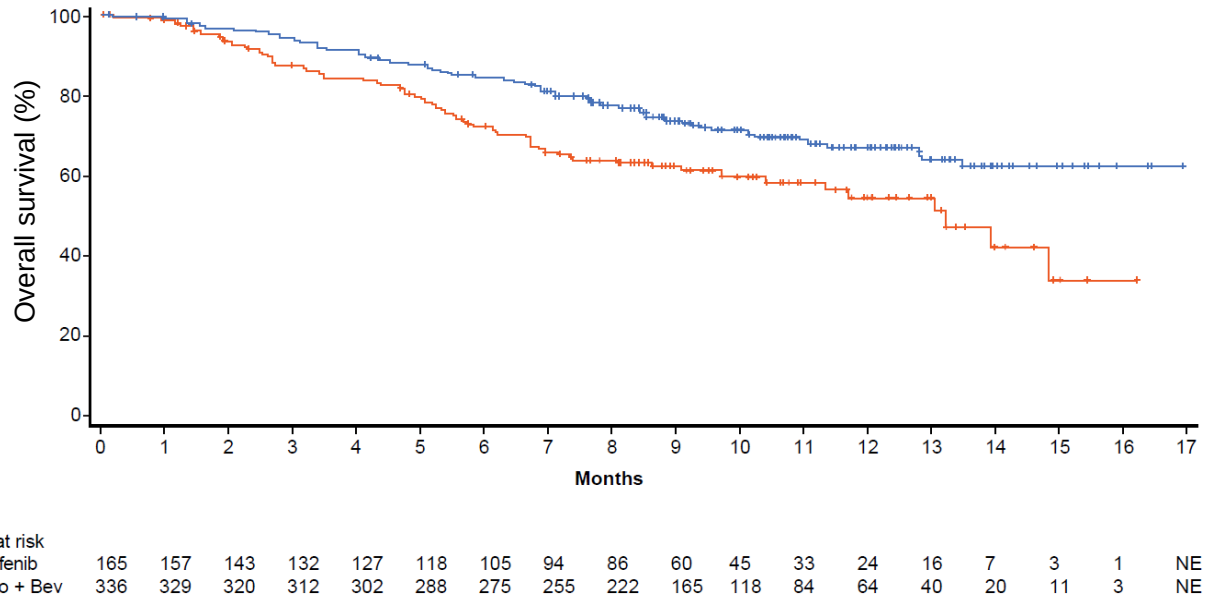
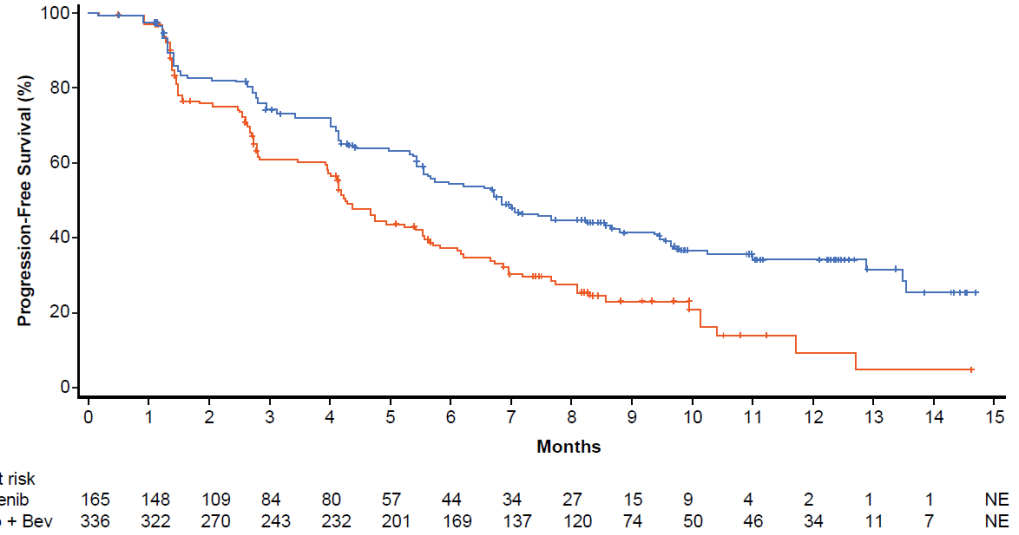
Atezolizumab + bevacizumab vs sorafenib in patients with unresectable HCC: Phase 3 results from IMbrave150

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



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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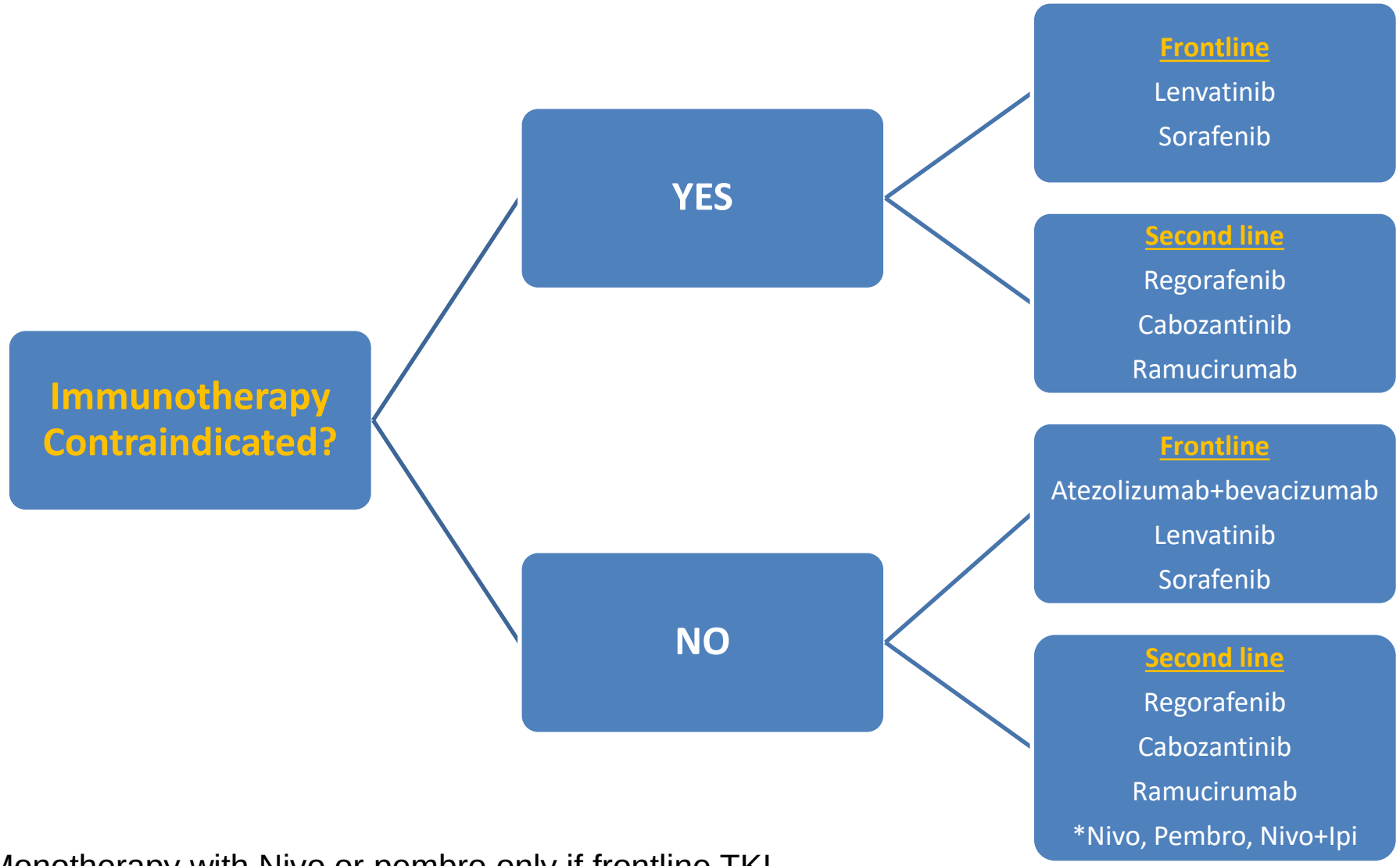
Sequencing Systemic Therapy in 2021 (approved therapy)



* Monotherapy with Nivo or pembro only if frontline TKI

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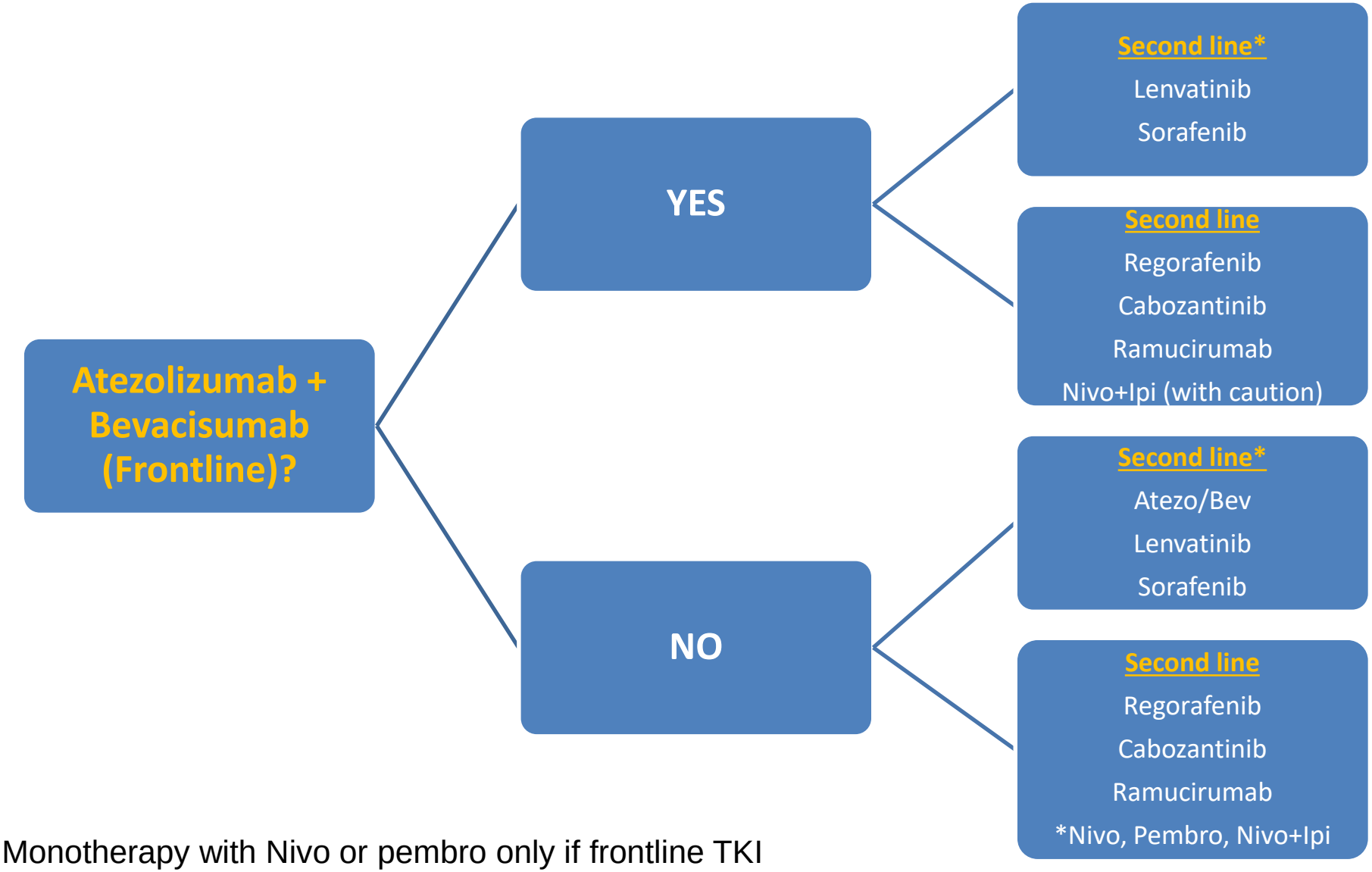
Sequencing Systemic Therapy in 2021 (Approved therapy)



* Monotherapy with Nivo or pembro only if frontline TKI

Webinar outline

- Development of the guideline
- Case 1: First-line therapy with atezo and bevo
- Case 2: IO-IO combination therapy in second-line
  - Patient selection
  - Illustrate immune-management
  - Discuss data gaps – activity of combinations post-first-line IO
- Case 3: Single agent PD-1 Child Pugh B score
- Key takeaways

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COMPREHENSIVE CANCER CENTER

PATIENT CARE
RESEARCH
EDUCATION
COMMUNITY

IO-IO combination therapy in second-line treatment of HCC

Aiwu Ruth He, MD, PhD
Lombardi Comprehensive Cancer Center
Georgetown University
Washington DC

NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

FDA grants accelerated approval to nivolumab and ipilimumab combination for hepatocellular carcinoma

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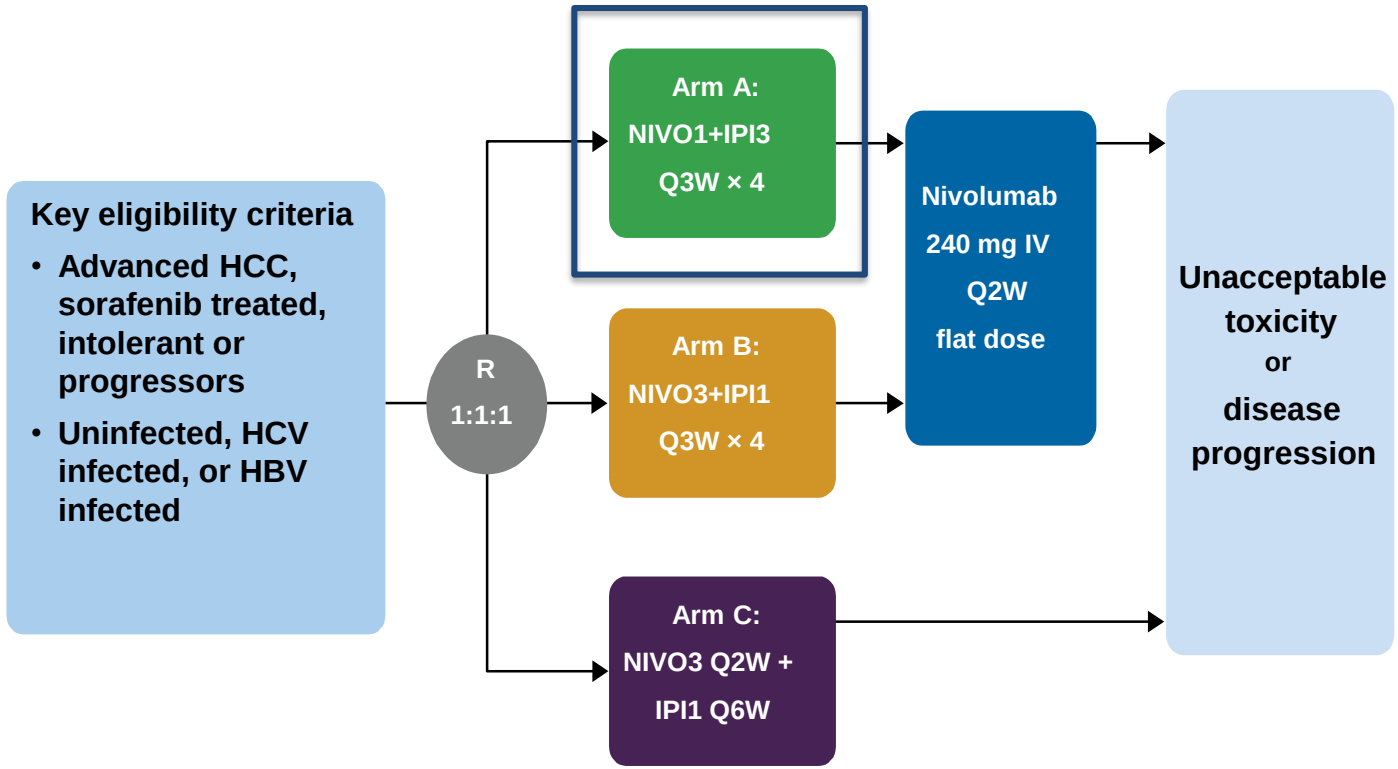
On March 10, 2020, the Food and Drug Administration granted accelerated approval to the combination of nivolumab and ipilimumab (OPDIVO and YERVOY, Bristol-Myers Squibb Co.) for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

CheckMate 040 NIVO+IPI combination cohort study design (NCT01658878)



Primary endpoints

- Safety and tolerability using NCI CTCAE v4.0
- ORR and DOR based on investigator assessment[a]

Secondary endpoints

- DCR
- PFS
- OS
- TTP
- TTR

Other key endpoints

- BOR and ORR based on BICR-assessed tumor response[a]

[a]Using RECIST v1.1.
Minimum follow-up at time of data cutoff: 28 months.

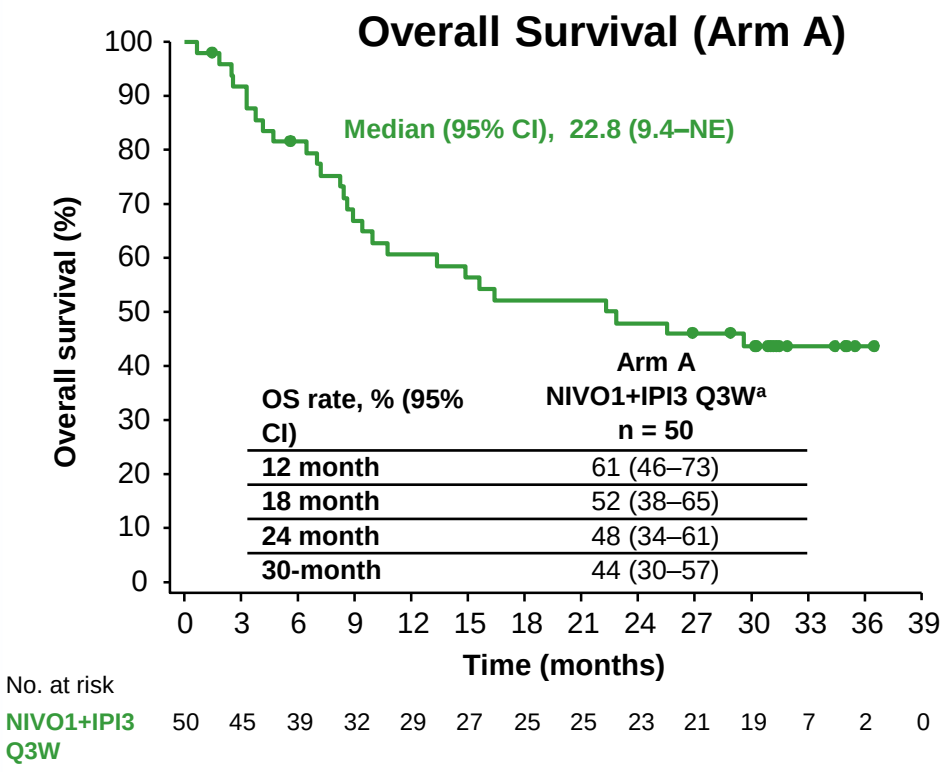
Response, Disease Control, and Durability

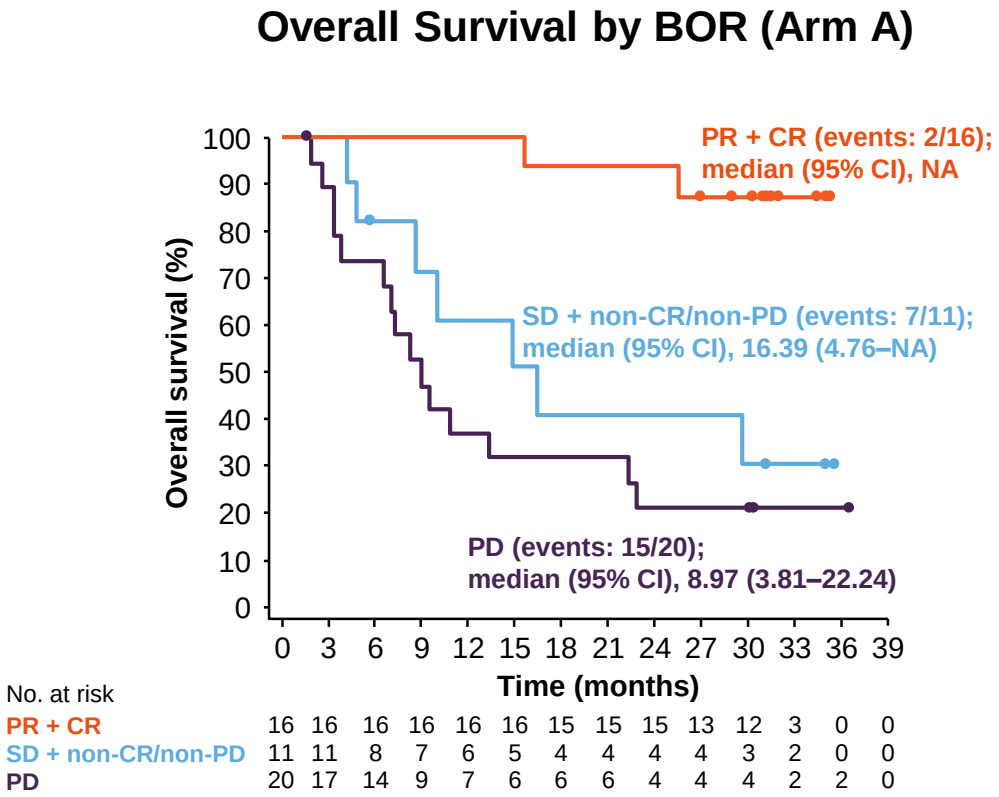
	Arm A NIVO1+IPI3 Q3W n = 50[a]
ORR by BICR using RECIST v1.1,[b] n (%)	16 (32)
BOR, n (%)	
CR	4 (8)
PR	12 (24)
SD	9 (18)
PD	20 (40)
Unable to determine	3 (6)
DCR,[c] n (%)	27 (54)
Median TTR (range),[d] months	2.0 (1.1–12.8)
Median DOR (range), [d] months	17.5 (4.6 to 30.5+)

- Four patients had a CR and the DCR (CR + PR + SD + non-CR/non-PD) was >50%

[a]NIVO1/ IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose;.

Overall Survival





- Median OS was 22.8 months, with an OS rate of 44% through 30 months
- Median OS for patients with PR + CR (2/16 events) was not reached

Summary of IMAEs

n (%)	Arm A NIVO1+IPI3 Q3W n = 49[a]	
	Any grade	Grade 3–4
Rash	17 (35)	3 (6)
Hepatitis	10 (20)	10 (20)
Adrenal insufficiency	9 (18)	2 (4)
Diarrhea/colitis	5 (10)	3 (6)
Pneumonitis	5 (10)	3 (6)
Nephritis/renal dysfunction	0	0
Hypersensitivity	0	0
Hypophysitis	1 (2)	0
Hyperthyroidism	0	0
Hypothyroidism/thyroiditis	0	0
Diabetes mellitus	0	0

- Most common IMAEs were rash, hepatitis, and adrenal insufficiency

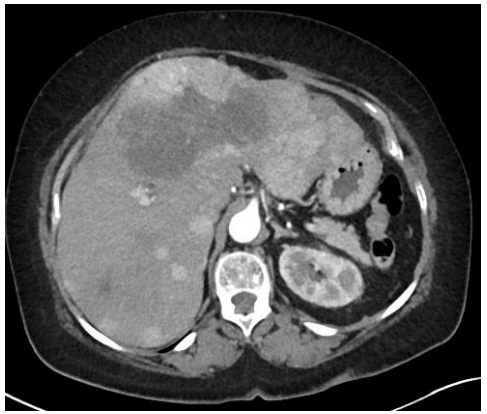
IMAEs are specific events considered as potential immune-mediated events by investigator, regardless of causality, and treated with immune-modulating medication.

Yau T, et al. JAMA Oncol. 2020 Nov 1;6(11):e204564. doi: 10.1001/jamaoncol.2020.4564. Epub 2020 Nov 12.PMID: 33001135.

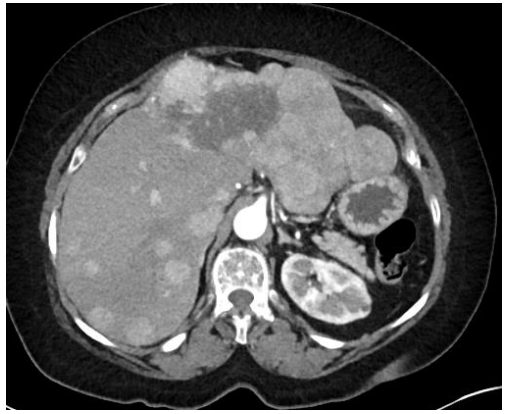
Case History

- 69 year old Hispanic female without history of HCV or HBV infection, has a history of type II diabetes, developed right upper quadrant pain in October of 2018.
- Abdominal ultrasound showed a liver mass, CT scan on 1/18/2019 showed a large exophytic heterogeneously enhancing hepatic mass. Biopsy on 1/13/2019 showed hepatocellular carcinoma.
- Patient had Y90 TARE on 07/11/2019, DEB-TACEs on 12/9/2019, 12/30/2019.
- CT scan showed disease progression with the increase in size and number of HCC lesions.
- Patient started sorafenib at 400mg bid on 2/26/2020. Treatment was held for 2 weeks for grade 3 hand and foot reaction. The dose of sorafenib was reduced to 400mg daily.
- CT scan on 5/18/2020 showed disease progression.

2/4/2020



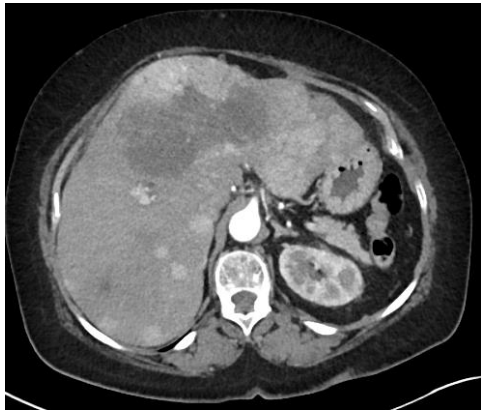
5/15/2020



Effect of Treatment on Tumor

Sorafenib 400mg bid → **Nivolumab + Ipilimumab x 3 cycles followed by Nivolumab** →

2/4/2020



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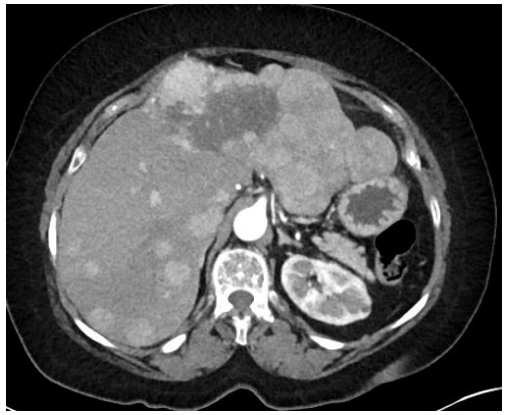
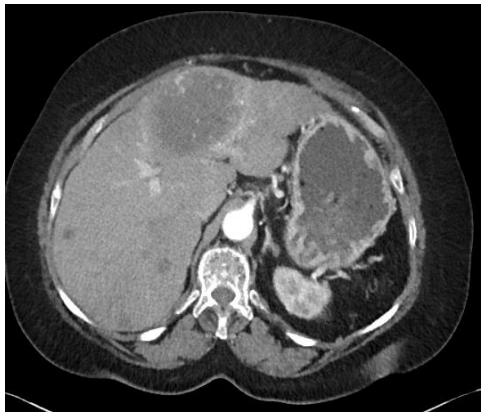
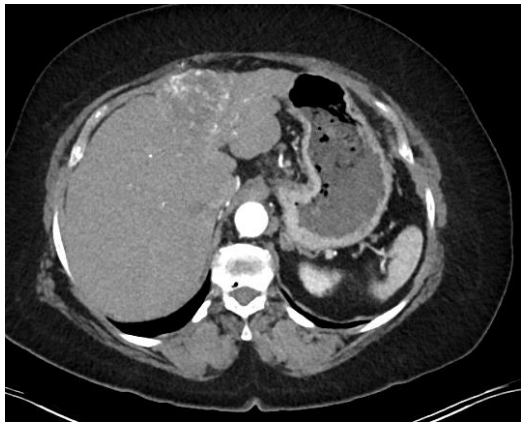


9/14/2020



9/21/2021



2nd Line IO-IO Treatment Course:

Patient started on nivolumab and ipilimumab on 06/01, 2020, she received 3 cycles of the combination therapy on 6/1/2020, 6/22/2020, 7/13/2020.

She developed immune mediated hepatitis on Aug 3, 2020, was treated with prednisone at 1mg/kg daily, tapered off prednisone on 9/7/2020.

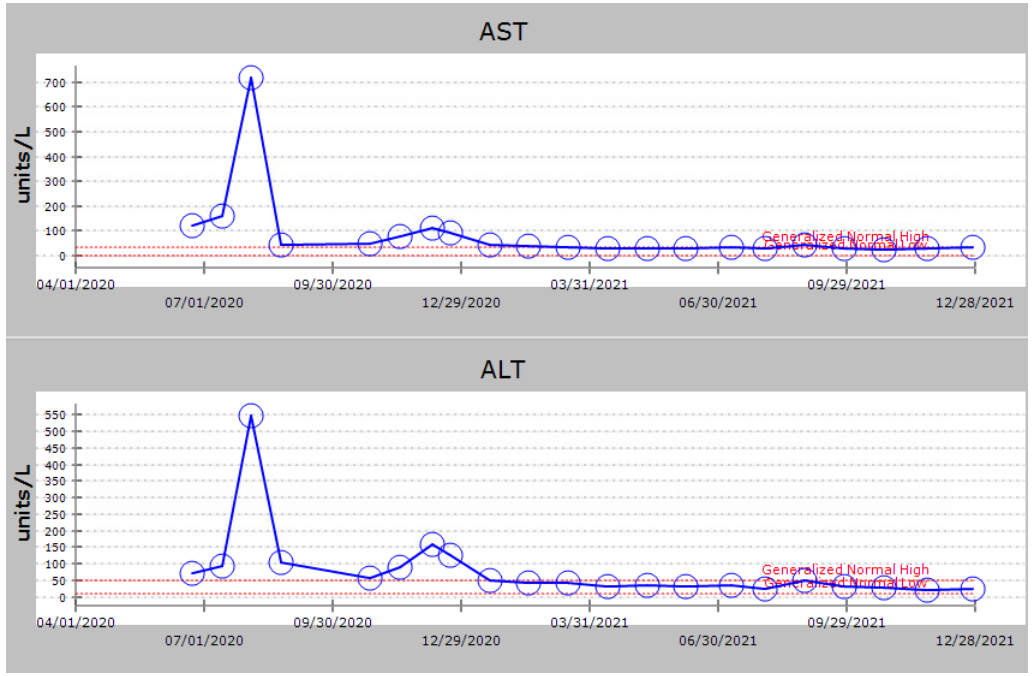
Repeat scan on 9/14/2020 showed tumor shrinkage (RECIST PR, 37% tumor shrinkage).

Patient resumed nivolumab monotherapy on 10/26/2020.

Repeat CT scans showed decrease in the size and arterial enhancement of the liver lesions

Nivolumab treatment was discontinued on 9/21/2021.

Change in Transaminases



Patient Selection:

1. Patients with HCC who progressed on or were intolerant to sorafenib.
2. Patient with good liver reserve, prefer patient with Child Pugh A score.
3. Patient who has no autoimmune disease.

Manage Immune-mediated side effects

For grade 3 or 4 side effects:

1. Steroid 1-2mg/kg daily, when the side effects improved to grade 1 or baseline, taper the steroid off in 3-4 weeks.
2. Steroid sparing treatment: a) Mycophenolic acid (Cellcept) (1000mg bid followed by tapering over 3-4 weeks); b) TNFα-blocking agent infliximab (Initial dosing with 5 mg/kg was given for 3 doses and then a maintenance therapy was installed (100 mg).)

Data gaps

Activity of combinations post-first-line IO (bevacizumab + atezolizumab)

Activities of combination post-first line Lenvatinib treatment.

Safety in patients with Child Pugh B liver function.

Webinar outline

- Development of the guideline
- Case 1: First-line therapy with atezo and bevo
- Case 2: IO-IO combination therapy in second-line
- Case 3: Single agent PD-1 Child Pugh B score
  - Patient selection
  - Review available safety and efficacy data
- Key takeaways

USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Immunotherapy for HCC with Child Pugh B Cirrhosis

Anthony El-Khoueiry, MD

USC Norris Comprehensive Cancer Center

Los Angeles, CA

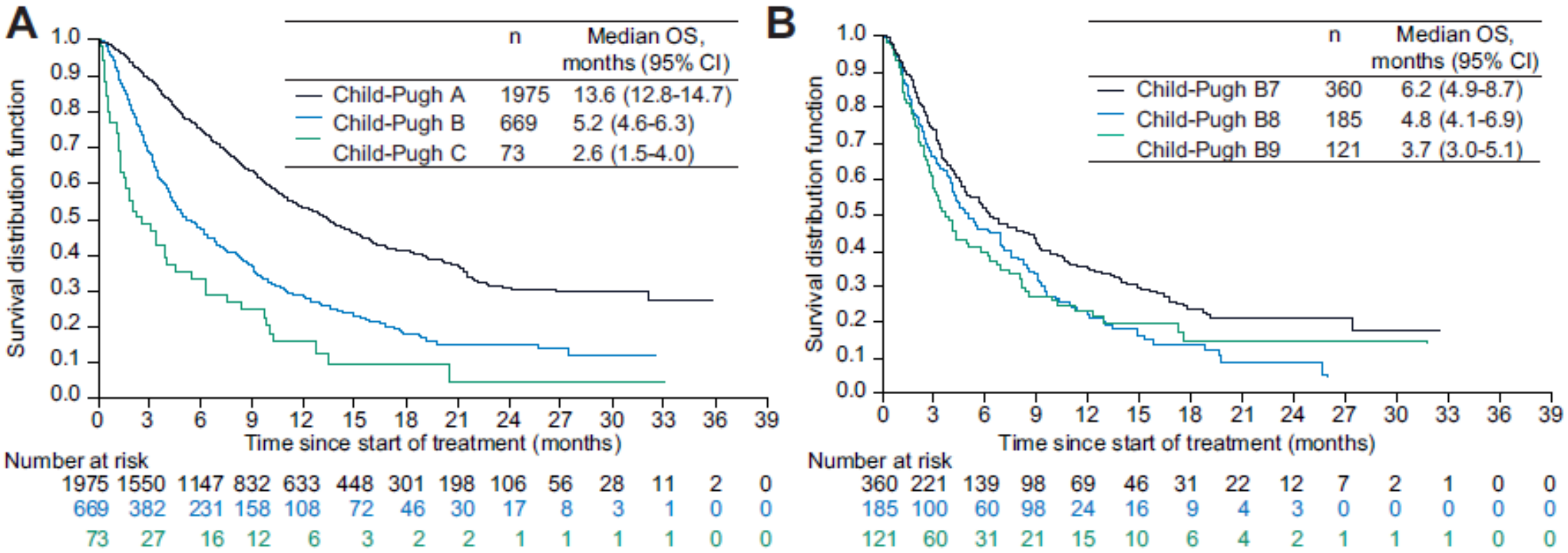
Single agent anti PD-1 therapy in setting of Child Pugh B cirrhosis

- 69-year-old Hispanic male with alcoholic liver cirrhosis
  - Past history significant for esophageal varices bleeding, last in January 2020
- 1/6/2020: single phase CT scan noted a 6.6 cm left lobe hypodense mass
- 4/15/2020: CT scan noted a left lobe 3.4 cm mass with arterial enhancement and venous wash out and a right hepatic dome 1.6 cm mass with arterial enhancement and venous wash out
  - Child Pugh A to B7
  - AFP 1055
- 6/17/2020: DEB-TACE to both lesions
- 7/24/2020: CT scan shows significant progression; left lobe 10.3 cm mass, 3 masses in right hepatic lobe ranging between 1.1 and 2.1 cm all consistent with HCC
  - AFP > 60,000
  - Child Pugh B8: albumin 2.5; total bilirubin 2.5; INR 1.6; platelets 54,000

Single agent anti PD-1 therapy in setting of Child Pugh B cirrhosis

- 8/6/2020: Started Nivolumab
- 9/28/2020: CT scan shows response
  - Left hepatic lobe mass 7.4 cm from 10.3 cm previously
  - 2 right hepatic lobe masses 1.5 cm from 2.1 cm previously
  - 1 hepatic lobe mass not visible versus 1.1 cm previously
  - AFP 4026
- Serial CT scans show progressive response with resolution of left hepatic lobe mass and stability of right hepatic lobe masses at 1 to 2 cm; AFP normalized
- Last Nivolumab dose 12/27/2021
  - Child Pugh A to B7

The challenge of underlying liver cirrhosis



Marrero J, J of Hepatology 65, 2016

Sorafenib in setting of liver dysfunction

Table 3. Overall safety profile of sorafenib by Child-Pugh score.

n (%)	Child-Pugh score[a,b]					
	A (<7) (n = 1968)	B7 (n = 359)	B8 (n = 182)	B9 (n = 122)	B (7-9)[c] (n = 666)	C (>9) (n = 74)
AEs (all grades)	1653 (84)	313 (87)	166 (91)	109 (89)	590 (89)	68 (92)
Drug-related AEs (all grades)	1349 (69)	240 (67)	114 (63)	74 (61)	429 (64)	29 (39)
Serious AEs[d]	708 (36)	192 (54)	126 (69)	82 (67)	402 (60)	52 (70)
Drug-related serious AEs	174 (9)	48 (13)	28 (15)	18 (15)	94 (14)	2 (3)
All grade 3 or 4 AEs	638 (33)	109 (30)	57 (31)	44 (36)	210 (32)	13 (18)
Drug-related grade 3 or 4 AEs	503 (26)	79 (22)	41 (23)	26 (21)	146 (22)	8 (11)
Deaths[e]	349 (18)	113 (31)	78 (43)	46 (38)	239 (36)	38 (51)

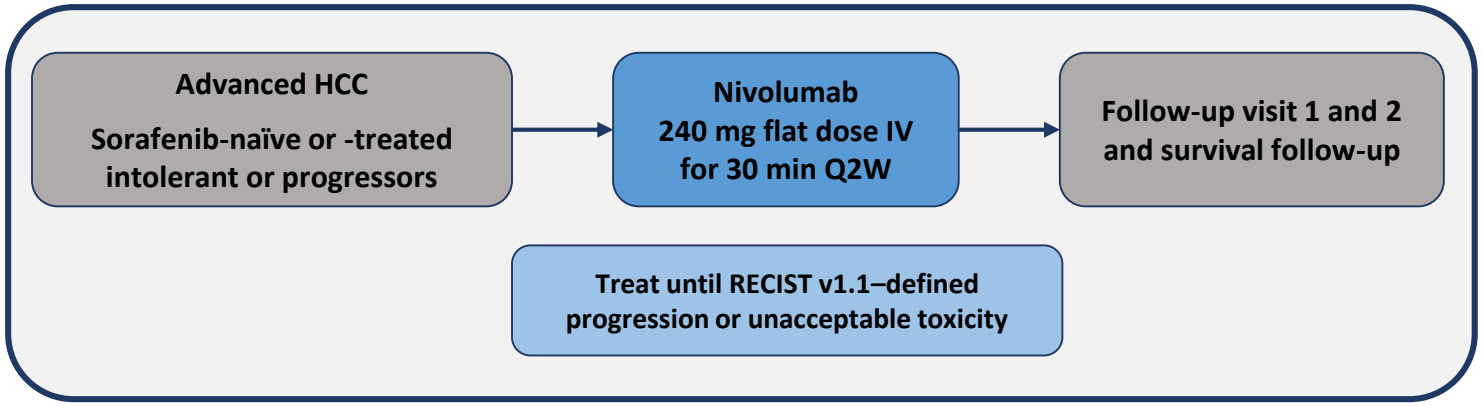
Table 4. Incidence of adverse events and drug-related adverse events occurring in ⩾10% of patients by Child-Pugh score.

n (%)	Child-Pugh score[a,b]											
	A (<7) (n = 1968)		B7 (n = 359)		B8 (n = 182)		B9 (n = 122)		B (7-9)[c] (n = 666)		C (>9) (n = 74)	
	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE
Diarrhea	616 (31)	556 (28)	112 (31)	98 (27)	52 (29)	48 (26)	31 (25)	23 (19)	196 (29)	170 (26)	13 (18)	8 (11)
Hand-foot skin reaction	636 (32)	626 (32)	70 (20)	70 (20)	29 (16)	29 (16)	14 (11)	14 (11)	116 (17)	113 (17)	4 (5)	4 (5)
Fatigue	440 (22)	311 (16)	98 (27)	56 (16)	43 (24)	22 (12)	30 (25)	17 (14)	171 (26)	95 (14)	15 (20)	10 (14)
Anorexia	285 (15)	209 (11)	57 (16)	30 (8)	29 (16)	11 (6)	14 (11)	8 (7)	100 (15)	49 (7)	10 (14)	5 (7)
Abdomen pain	224 (11)	62 (3)	63 (18)	26 (7)	31 (17)	8 (4)	23 (19)	6 (5)	118 (18)	24 (4)	13 (18)	4 (5)
Liver dysfunction[d]	203 (10)	36 (2)	46 (13)	10 (3)	43 (24)	7 (4)	30 (25)	2 (2)	120 (18)	19 (3)	16 (22)	0
Rash/desquamation	258 (13)	238 (12)	41 (11)	35 (10)	17 (9)	15 (8)	8 (7)	7 (6)	66 (10)	57 (9)	4 (5)	3 (4)
Nausea	167 (8)	106 (5)	42 (12)	28 (8)	19 (10)	8 (4)	9 (7)	5 (4)	70 (11)	41 (6)	9 (12)	7 (9)
Hypertension	243 (12)	215 (11)	21 (6)	18 (5)	7 (4)	7 (4)	3 (2)	3 (2)	31 (5)	28 (4)	0	0

Marrero J, J of Hepatology 65, 2016

CheckMate 040 Child-Pugh B Cohort Study Design

Child-Pugh B7–B8 Cohort (N = 50)



Median follow-up: 11.8 months (range, 6.4–18.0 months)

Study Endpoints

Primary

- ORR based on investigator assessment[a]

Secondary

- Disease control rate
- Duration of response
- Time to response
- Time to progression
- Progression-free survival
- Overall survival

Other

- BOR and ORR based on BICR-assessed tumor response[a]

[a]Using RECIST 1.1.

BICR, blinded independent central review; BOR, best overall response; HCC, hepatocellular carcinoma; IV, intravenous; ORR, objective response rate; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Key Eligibility Criteria

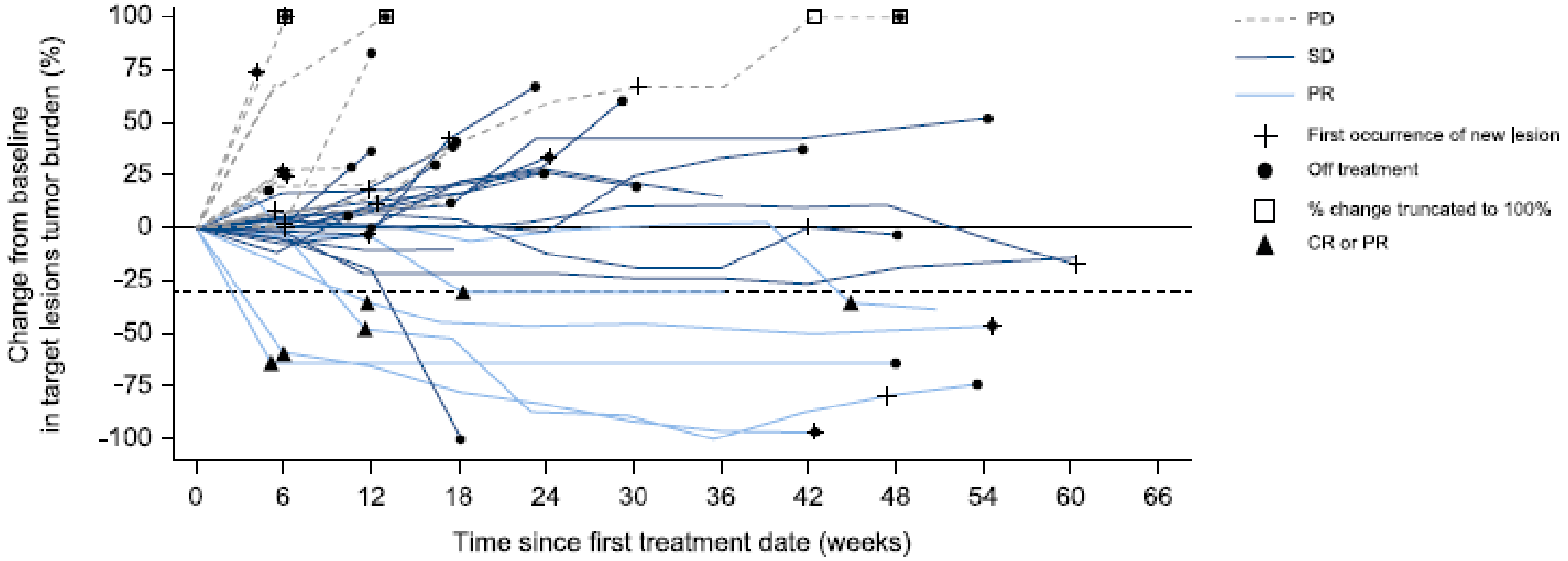
Key Inclusion Criteria
Histologically confirmed advanced HCC not eligible for surgical and/or locoregional therapy
≥ 1 untreated lesion measurable by RECIST v1.1
HBV-HCC, HCV-HCC, or non–viral-related HCC
No prior sorafenib treatment, or documented radiographic progression on or intolerance to sorafenib
Child-Pugh score of B7 or B8
No ascites (1 point) or mild ascites (2 points)
Eastern Cooperative Oncology Group performance status of 0 or 1
Key Exclusion Criteria
Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
Active brain metastases or leptomeningeal metastases
Active co-infection with both HBV and HCV
History of hepatic encephalopathy within 6 months of screening
History of hepatorenal syndrome
Paracentesis for treatment of ascites within 3 months of screening
Prior liver transplant

Best overall response: primary analysis

	Sorafenib naive (n = 25)	Sorafenib treated (n = 24)	All patients (N = 49)
Objective response (investigator assessed; RECIST v1.1, n (%)	3 (12)	3 (13)	6 (12)
95% CI	3–31	3–32	5–25
BOR			
Complete response, n (%) [95% CI]	0 [0–14]	0 [0–14]	0 [0–7]
Partial response, n (%) [95% CI]	3 (12) [3–31]	3 (13) [3–32]	6 (12) [5–25]
Stable disease, n (%)	12 (48)	9 (38)	21 (43)
Progressive disease, n (%)	7 (28)	8 (33)	15 (31)
Unable to determine, n (%)	3 (12)	4 (17)	7 (14)

1. Kudo M, et al. *J Hepatol* 2021.

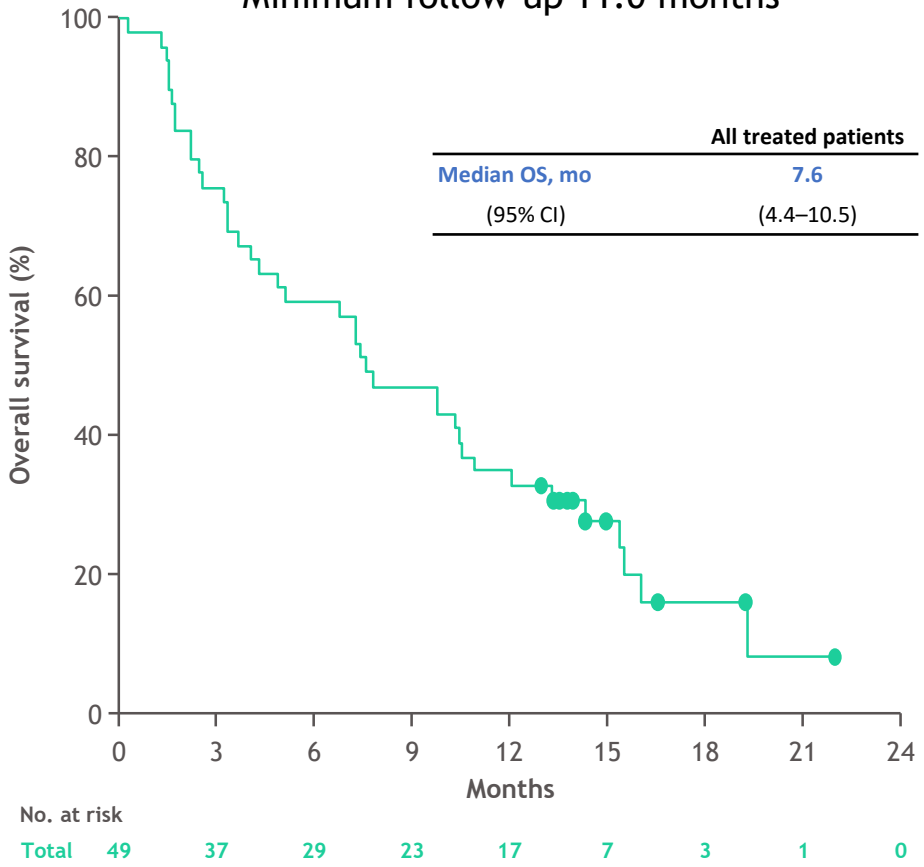
Durable Responses Noted



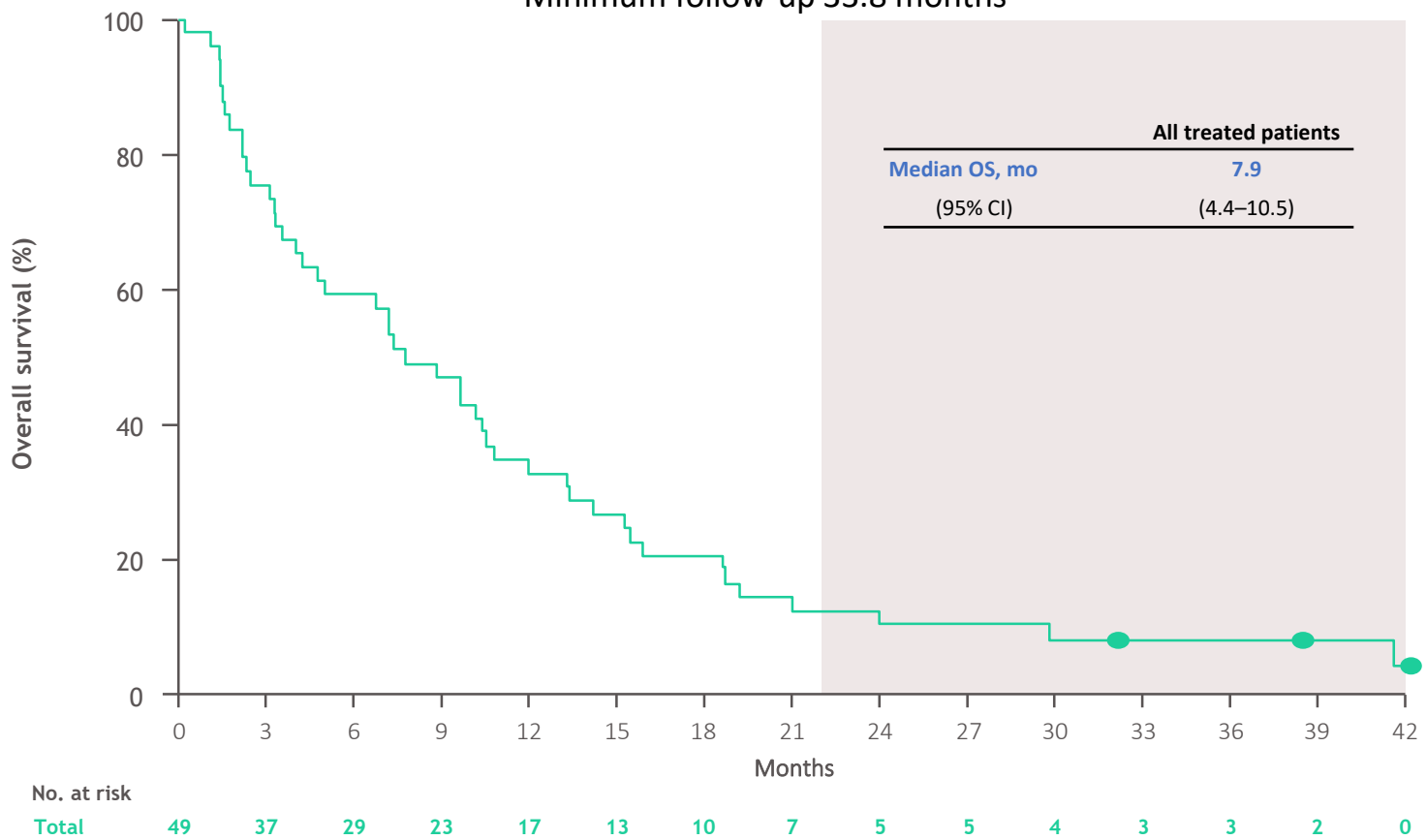
Kudo M, et al. J Hepatol 2021; Matilla A et al; EASL 2021 abstract 295

Overall survival: all treated patients

Primary analysis (November 2018 DBL)
Minimum follow-up 11.0 months



Long-term follow-up (September 2020 DBL)
Minimum follow-up 33.8 months



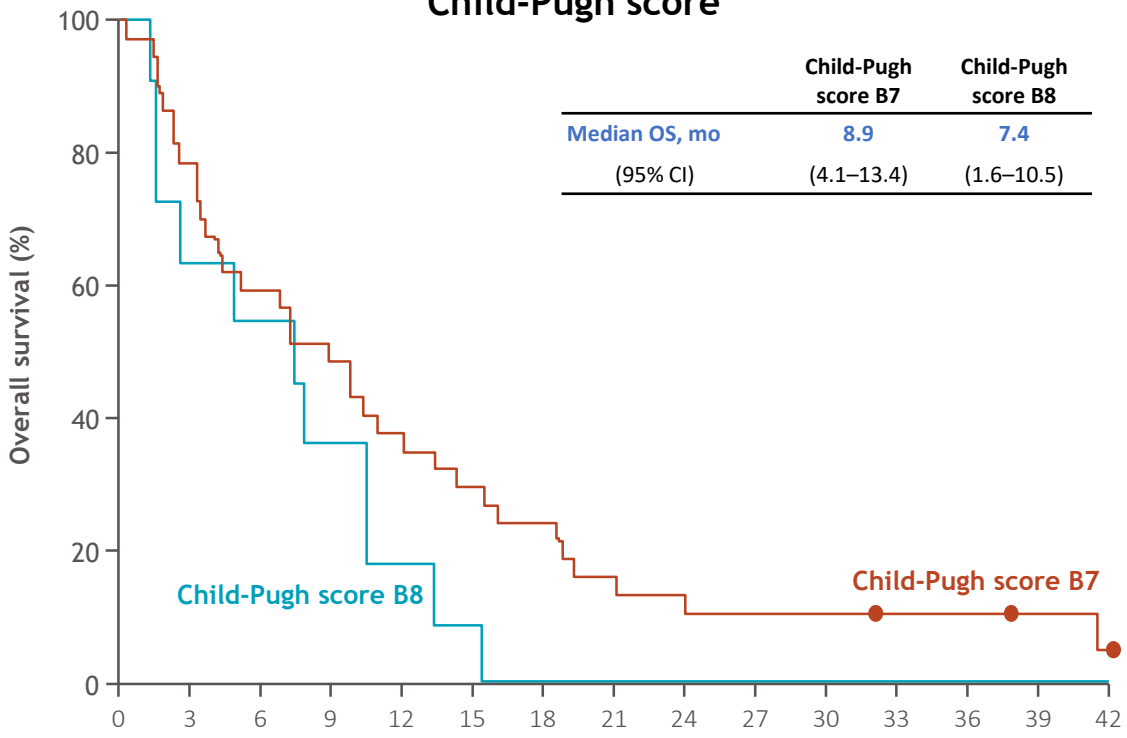
- At long-term follow-up, median OS was 7.9 months for all treated patients
- OS rates (95% CI) were 34.7% (21.8–47.9) at 12 months and 10.2% (3.7–20.5) at 24 months

Symbols represent censored observations.

Kudo M, et al. J Hepatol 2021; Matilla A et al; EASL 2021 abstract 295

Overall survival by Child-Pugh score and by ALBI grade

Child-Pugh score

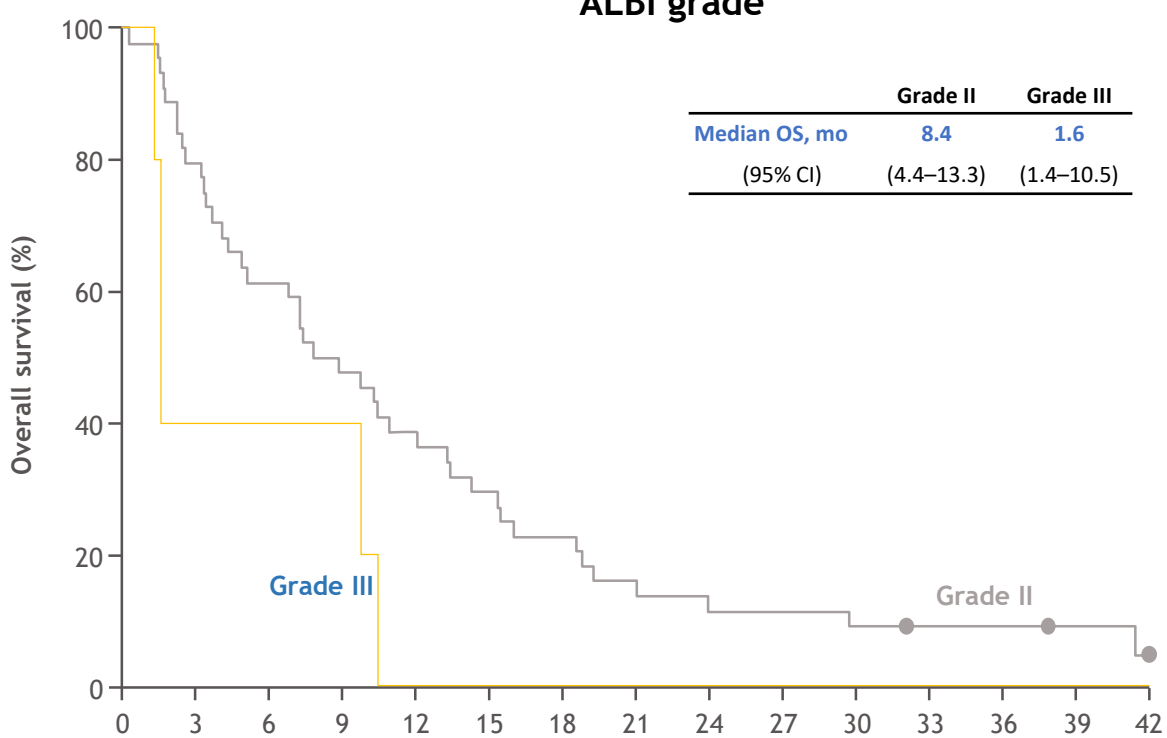


	Child-Pugh score B7	Child-Pugh score B8
Median OS, mo	8.9	7.4
(95% CI)	(4.1–13.4)	(1.6–10.5)

No. at risk

Child-Pugh score B7	37	29	22	18	14	11	9	6	4	4	4	3	3	2	0
Child-Pugh score B8	11	7	6	4	2	1	0	0	0	0	0	0	0	0	0

ALBI grade



	Grade II	Grade III
Median OS, mo	8.4	1.6
(95% CI)	(4.4–13.3)	(1.4–10.5)

No. at risk

Grade II	44	35	27	21	17	13	10	7	5	5	4	3	3	2	0
Grade III	5	2	2	2	0	0	0	0	0	0	0	0	0	0	0

- Median OS was 8.9 months and 7.4 months, respectively, in CPB subgroups B7 and B8
  - 1 patient with CPA had OS of 29.7 months and was excluded from the analysis
- Median OS was 8.4 months and 1.6 months, respectively, for ALBI grades II and III

Symbols represent censored observations.

Kudo M, et al. J Hepatol 2021; Matilla A et al; EASL 2021 abstract 295

TRAEs in ≥ 2 patients

	Child-Pugh B (n = 49)	
	Any grade	Grade 3–4
Any TRAE, n (%)	24 (49)	12 (24)
Pruritus	7 (14)	0
Amylase increased	3 (6)	2 (4)
Asthenia	3 (6)	0
Dysgeusia	3 (6)	0
Fatigue	3 (6)	0
Lipase increased	3 (6)	2 (4)
Anemia	2 (4)	0
Aspartate aminotransferase increased	2 (4)	2 (4)
Diarrhea	2 (4)	1 (2)
Hypertransaminasemia	2 (4)	2 (4)
Rash, erythematous	2 (4)	0
Stomatitis	2 (4)	0
Any TRAE leading to discontinuation, n (%)	3 (6)	3 (6)

- The most common TRAE of any grade was pruritus (14% of patients), which was consistent with prior clinical experience[1,2]
- No new safety signals were observed
- 46 patients (94%) died, primarily as a result of disease progression (78%); no deaths were due to study drug toxicity
- The most common TRAEs of any grade leading to discontinuation were hypertransaminasemia (n = 2; 4%), abnormal hepatic function (n = 1, 2%), and hyperbilirubinemia (n = 1, 2%)

1. Kudo M, et al. *J Hepatol* 2021 [accepted for publication]; 2. El-Khoueiry AB, et al. *Lancet* 2017;389:2492–2502.

Summary and Conclusions

- Compromised liver function presents a challenge in the treatment of advanced HCC
- Careful selection and consideration warranted to decide if a patient with child pugh B cirrhosis should undergo anti-cancer therapy
  - Performance status
  - Degree of decompensation (poorly manageable ascites and hepatic encephalopathy)
- Nivolumab evaluated in Child Pugh B cohort in Checkmate 040 with manageable toxicity profile and promising efficacy

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