sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hepatocellular Carcinoma

Adam Burgoyne, MD, PhD

Assistant Clinical Professor of Medicine

UC San Diego Moores Cancer Center

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

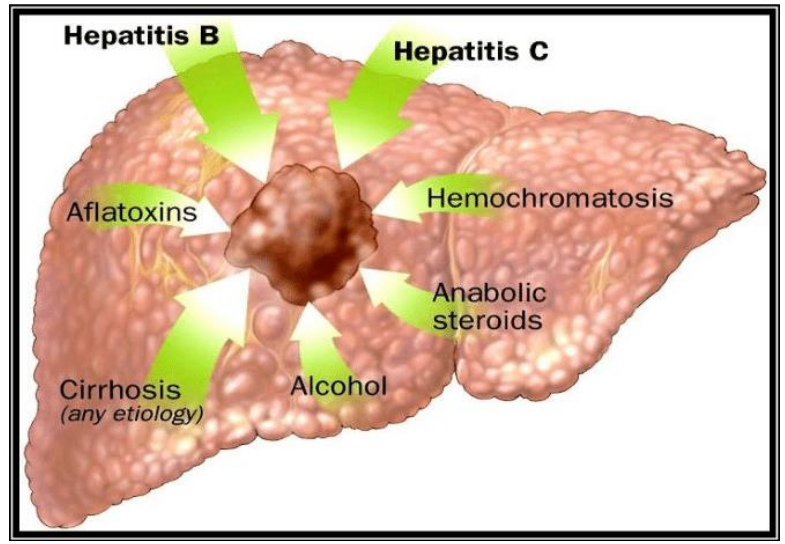
sitc Society for Immunotherapy of Cancer

Disclosures

- Within the past 12 months, I have receiving consulting fees (advisory board) from Exelixis, Eisai, and Deciphera.
- I will be discussing non-FDA approved indications during my presentation.

Background

- HCC is the most common type of primary liver cancer
- Often associated with cirrhosis (HBV or HCV, alcohol abuse)
- 3rd leading cause of cancer death worldwide
- Treatment options:
  - Curative: orthotopic liver transplantation, surgical resection
  - Chemoembolization, radiofrequency ablation, microwave ablation, radiation, chemotherapy, targeted therapy
- Many patients are ineligible for surgery/transplant – there's a need for systemic therapies in HCC



Liver Immunobiology

- The liver is densely populated with macrophages, natural killer cells, T cells, and liver sinusoidal endothelial cells.
- The liver is exposed to a flood of pathogenic and non-pathogenic antigens and hence has developed an inherent immune tolerogenicity.
- Cirrhosis results in an active inflammatory process in the liver which ultimately results in cancer.
- HCV and HBV infections also result in immune mediated inflammation which promotes cancer development.
- Analysis of HCC shows a rich immune cell infiltrate.

Liver Immunobiology

- However, the immune response is made dysfunctional by
  - expression of a greater proportion of helper T cells to cytotoxic T cells
  - hypofunctional NK cells
  - expansion of myeloid derived suppressor cells
  - secretion of immunoregulatory cytokines
  - expression of ligands that suppress immune activation and
  - downregulation of ligands that activate the immune system.

Immunotherapeutic Strategies in HCC

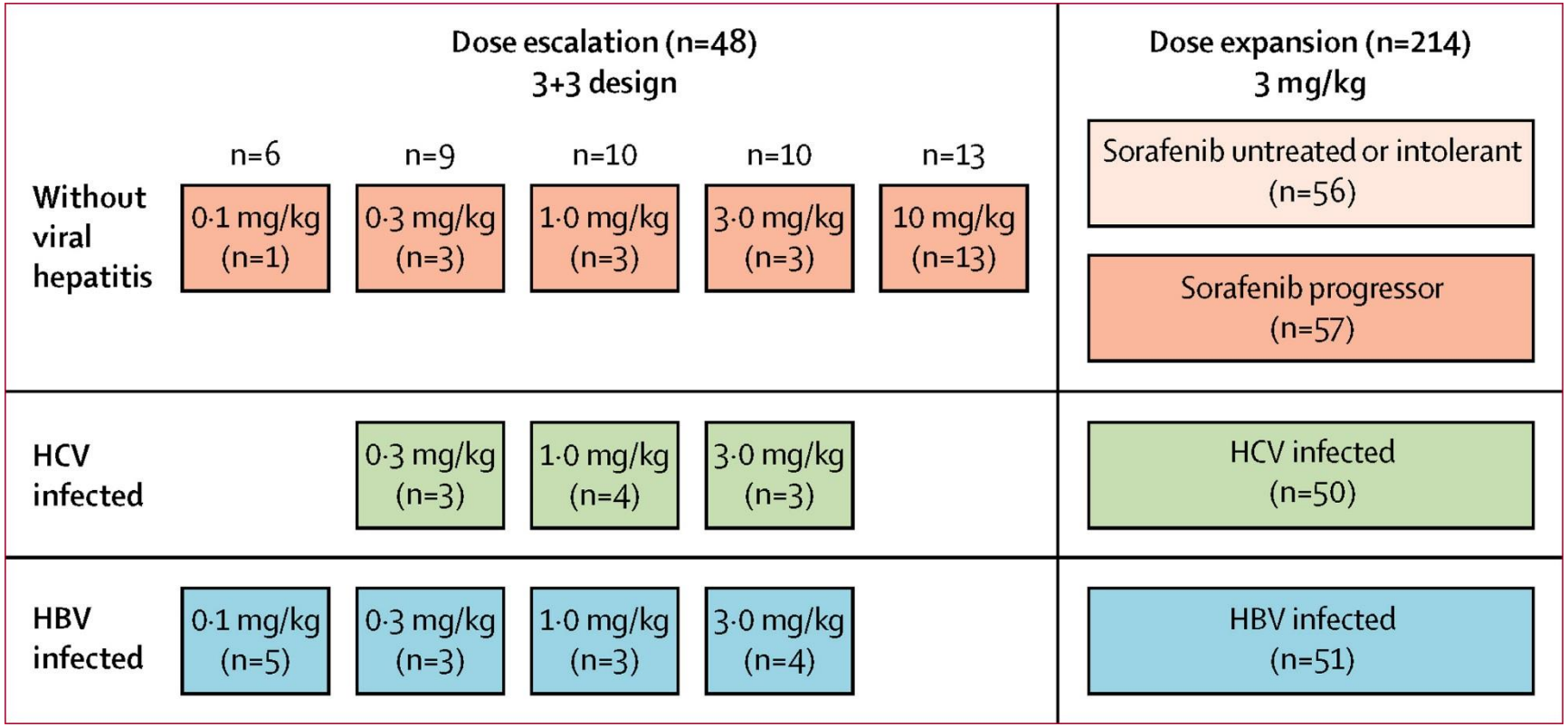
- Checkpoint inhibition
- Blocking inhibitory cytokines
- Vaccine therapies
- Oncolytic viruses
- Adoptive cell therapy

Approved checkpoint inhibitors for HCC

Drug	Approved	Indication	Dose
Nivolumab	2017	HCC with previous sorafenib	240 mg Q2W or 480 mg Q4W
Pembrolizumab	2018	HCC with previous sorafenib	200 mg Q3W
Atezolizumab + bevacizumab	*Breakthrough designation: 2018*	*1st line in advanced/metastatic HCC*	*Atezolizumab 1200 mg + bevacizumab 15mg/kg Q3W*

CheckMate 040

- Phase I/II open label study
- Child-Pugh A or B7, advanced HCC
- Previous sorafenib allowed
- Safety/tolerability for escalation; ORR for expansion



El-Khoueiry, The Lancet 2017.

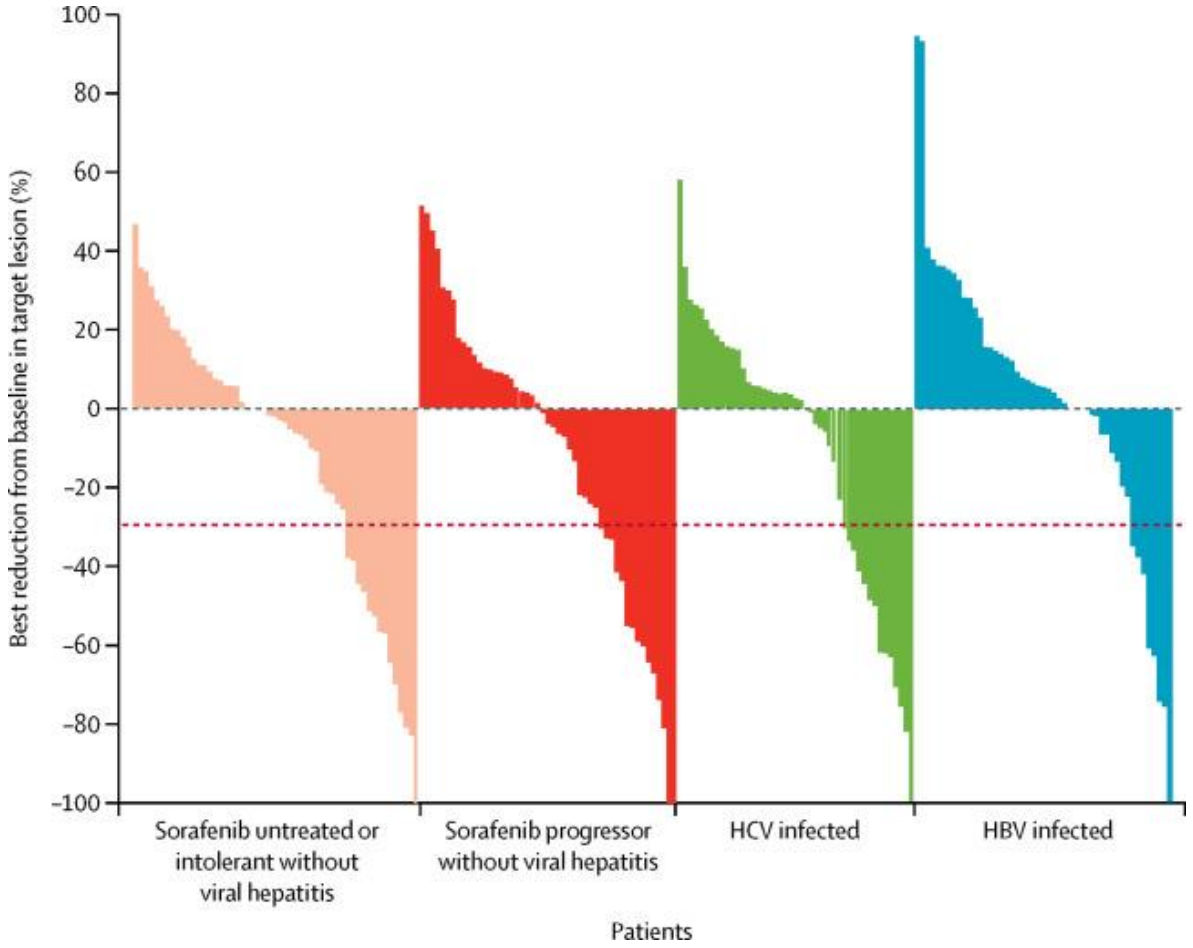
CheckMate 040

Efficacy *(by RECIST v1.1)*	Uninfected: Sorafenib Naïve OR Intolerant *(n = 56)*	Uninfected: Sorafenib Progressors *(n = 57)*	HCV *(n = 50)*	HBV *(n = 51)*	Total *(n = 214)*
Objective response, n (%)	**13 (23%)**	**12 (21%)**	**10 (20%)**	**7 (14%)**	**42 (20%)**
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
Clinical benefit, n (%)	**42 (75%)**	**35 (61%)**	**33 (66%)**	**28 (55%)**	**138 (64%)**

El-Khoueiry, The Lancet 2017.

CheckMate 040

- ORR: 20%, 3 CR, 39 PR
- @ 6 mo: OS = 83%, PFS = 37%
- @ 9 mo: OS = 74%, PFS = 28%
- No difference if previously treated with sorafenib
- No difference in AEs if HBV/HCV(+)
- Gr 3/4 TrAE: elevation of AST/ALT, elevation of bilirubin, and hepatitis



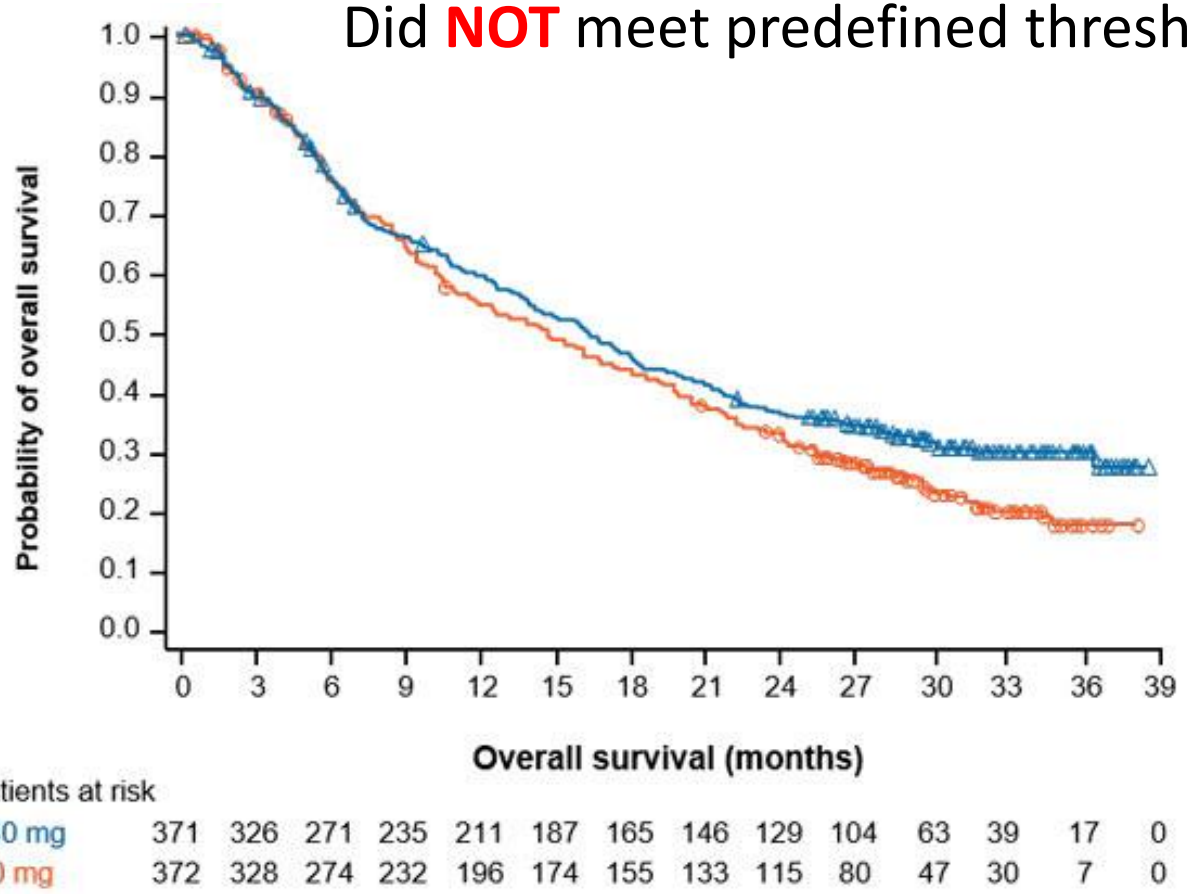
El-Khoueiry, The Lancet 2017.

CheckMate 459

- Phase 3 study results reported at ESMO 2019
- 743 patients with advanced HCC that had received no previous systemic therapy randomized 1:1 to receive:
  - Nivolumab at 240 mg IV every 2 weeks
  - Sorafenib 400 mg PO twice daily
- Primary endpoint of overall survival (OS)
- Additional endpoints:
  - Objective response rate (ORR)
  - Progression-free survival (PFS)
  - Efficacy according to tumour expression of PD-L1
  - Safety

Yau, ESMO 2019.

CheckMate 459



Did **NOT** meet predefined threshold of statistical significance (HR 0.84, P = 0.0419)

Nivolumab: mOS 16.4 mo

Sorafenib: mOS 14.7 mo

(HR 0.85, P = 0.0752)

Yau, ESMO 2019.

CheckMate 459

Endpoint	Nivolumab (n = 371)	Sorafenib (n = 372)
Median OS (95% CI), mo	16.4 (13.9–18.4)	14.7 (11.9–17.2)
12-mo OS rate, % (95% CI)	59.7 (54.4–64.6)	55.1 (49.8–60.1)
24-mo OS rate, % (95% CI)	36.8 (31.8–41.8)	33.1 (28.3–38.0)
Median PFS, mo (95% CI)	3.7 (3.1–3.9)	3.8 (3.7–4.5)
ORR, n (%)	57 (15)	26 (7)
BOR, n (%)		
Complete response	14 (4)	5 (1)
Partial response	43 (12)	21 (6)
ORR by baseline tumor PD-L1 expression, n/n (%)		
PD-L1 ≥1%	20/71 (28)	6/64 (9)
PD-L1 <1%	36/295 (12)	20/300 (7)

Yau, ESMO 2019.

CheckMate 459

- No new safety signals observed with nivolumab
- Grade 3/4 treatment-related adverse events:
  - 81 patients (22%) in the nivolumab arm
  - 179 patients (49%) in the sorafenib arm
- Treatment discontinuation due to an AE:
  - 16 (4%) in the nivolumab arm
  - 29 (8%) in the sorafenib arm

Yau, ESMO 2019.

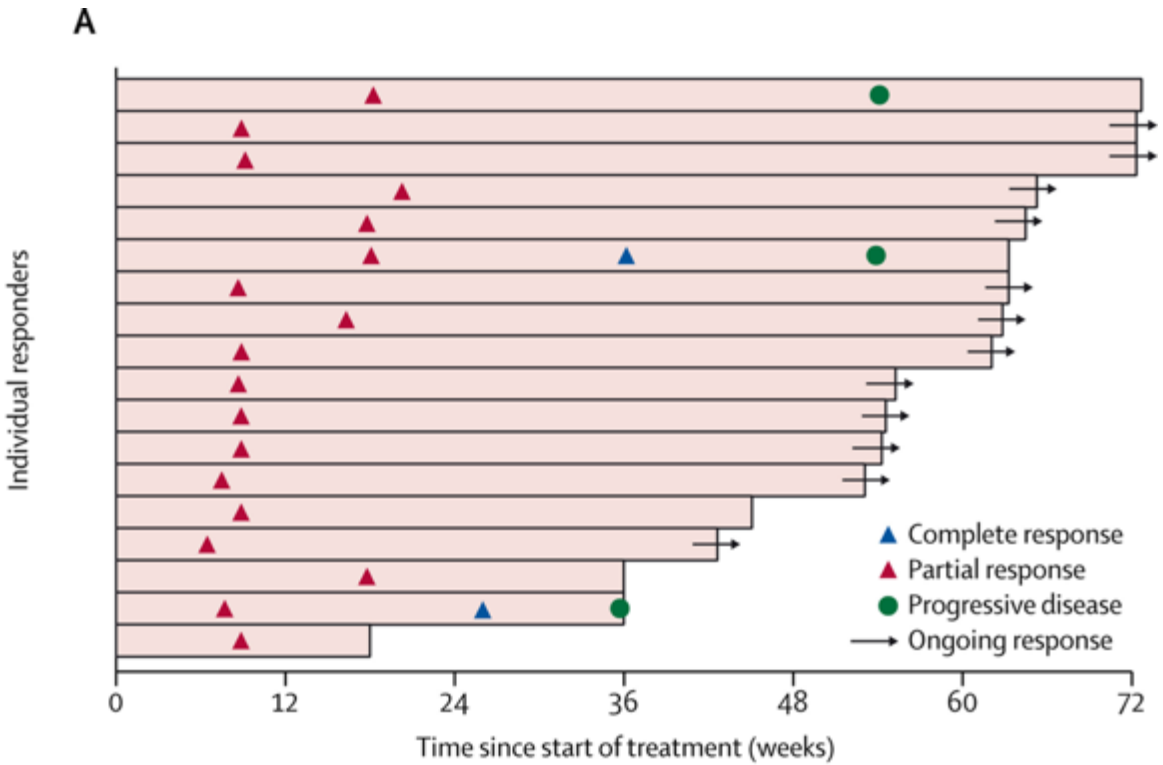
KEYNOTE-224

- Phase 2 non-randomized trial
- Previously treated with sorafenib
- Child-Pugh class A
- Pembrolizumab IV 200 mg Q3W
- Primary endpoint: objective response
- 104 patients enrolled and treated

Zhu, Lancet Oncol 2018.

KEYNOTE-224

	All treated participants (n=104)
Objective response*	18 (17%; 11–26)
Best overall response†	
Complete response	1 (1%)
Partial response	17 (16%)
Stable disease	46 (44%)
Progressive disease	34 (33%)
Not assessable‡	6 (6%)
Disease control§	64 (62%; 52–71)
Median time to response, months (IQR)¶	2·1 (2·1–4·1)
Median duration of response, months (range) ¶||	Not reached (3·1–14·6+**)
Duration of response ≥9 months¶||	12 (77%)

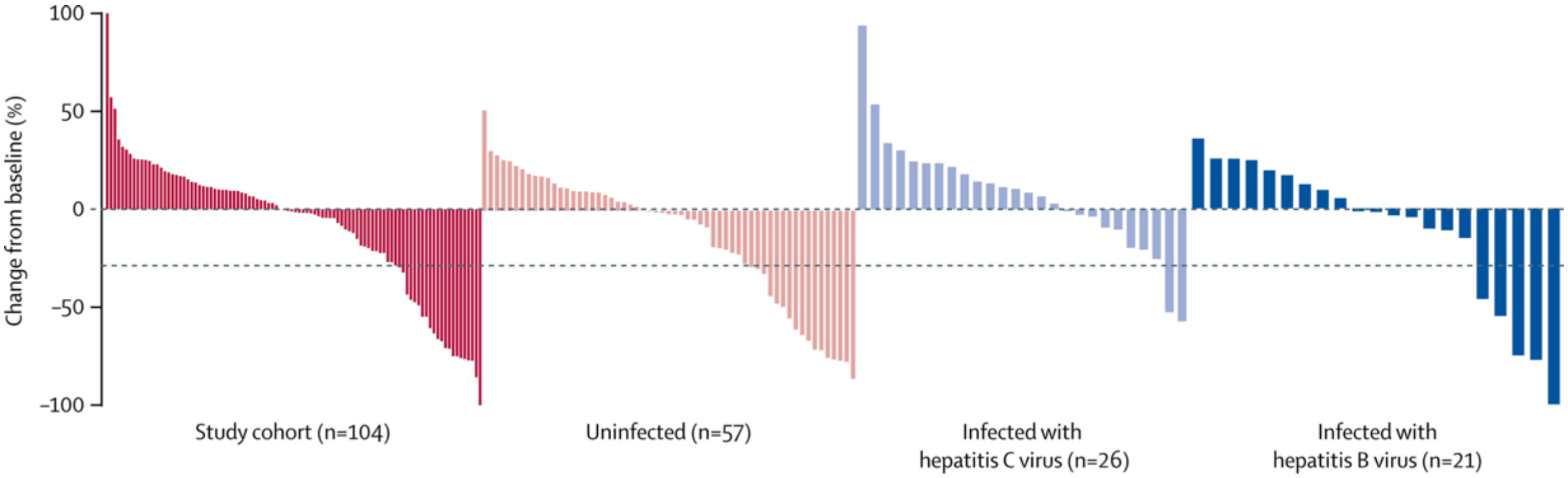


**Assessed by RECIST v1.1*

Zhu, Lancet Oncol 2018.

Zhu AX et al. Lancet Oncol. 2018 Jul;19(7):940-952.

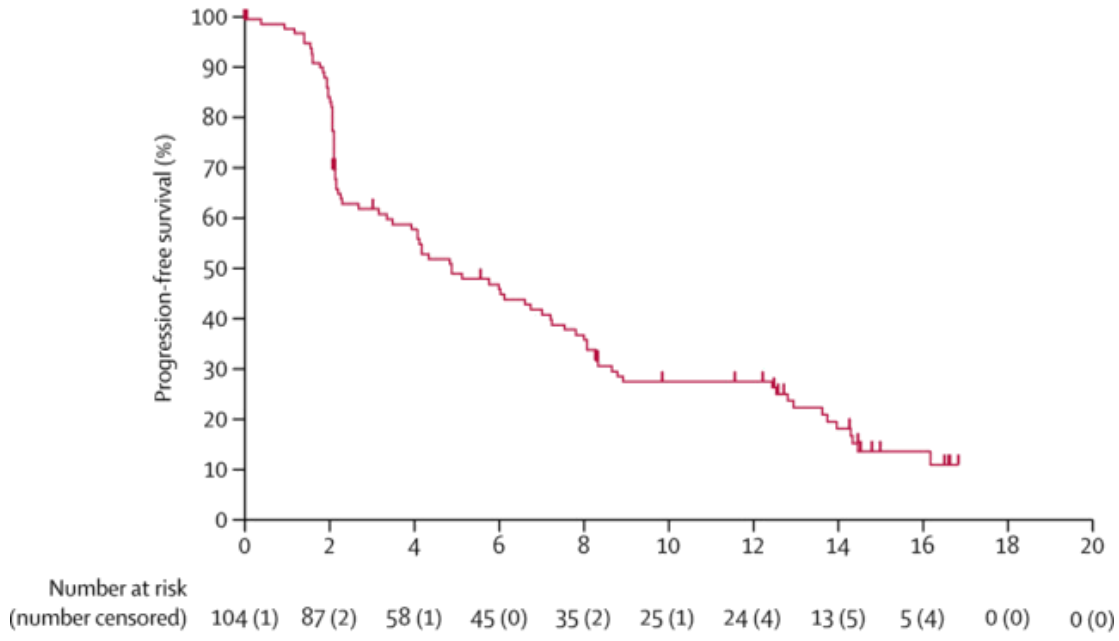
KEYNOTE-224



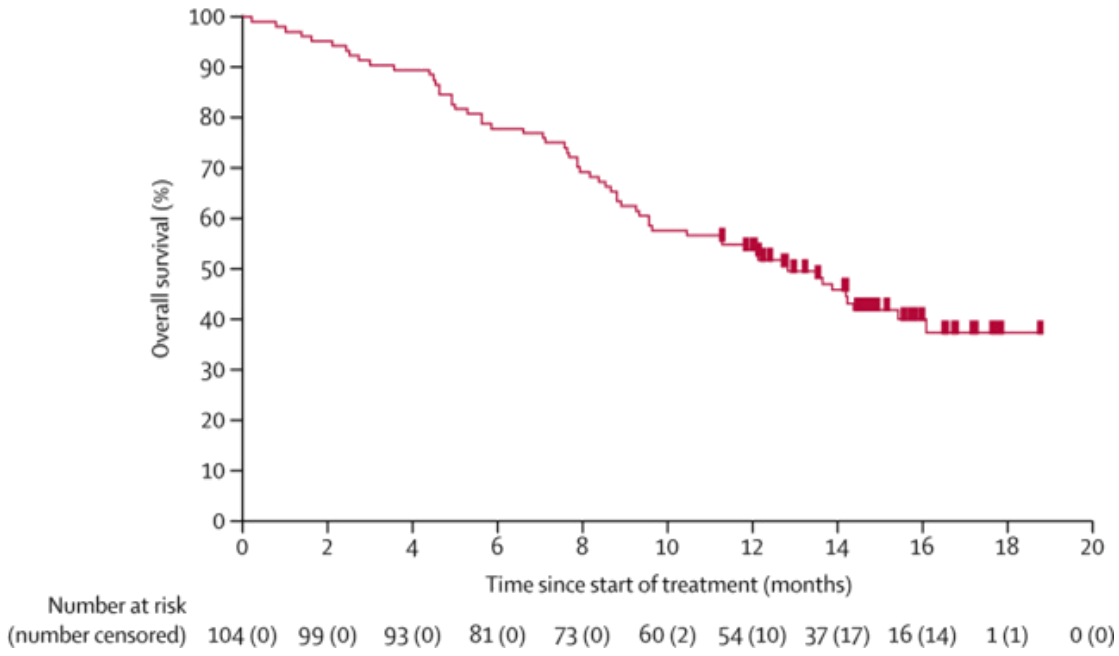
Zhu, Lancet Oncol 2018.

Zhu AX et al. Lancet Oncol. 2018 Jul;19(7):940-952.

KEYNOTE-224



mPFS: 4.9 months



mOS: 12.9 months

Zhu, Lancet Oncol 2018.

KEYNOTE-224

	Grade 1–2	Grade 3	Grade 4	Grade 5
At least 1 event	11 (11%)	4 (4%)	0	0
Hypothyroidism	8 (8%)	0	0	0
Adrenal insufficiency	1 (1%)	2 (2%)	0	0
Thyroiditis	2 (2%)	0	0	0
Severe skin reaction	0	1 (1%)	0	0
Autoimmune colitis	1 (1%)	0	0	0
Colitis	1 (1%)	0	0	0
Hyperthyroidism	1 (1%)	0	0	0
Type 1 diabetes mellitus	0	1 (1%)	0	0
At least 1 immune-mediated hepatic event*	0	3 (3%)	0	0

Zhu, Lancet Oncol 2018.

Zhu AX et al. Lancet Oncol. 2018 Jul;19(7):940-952.

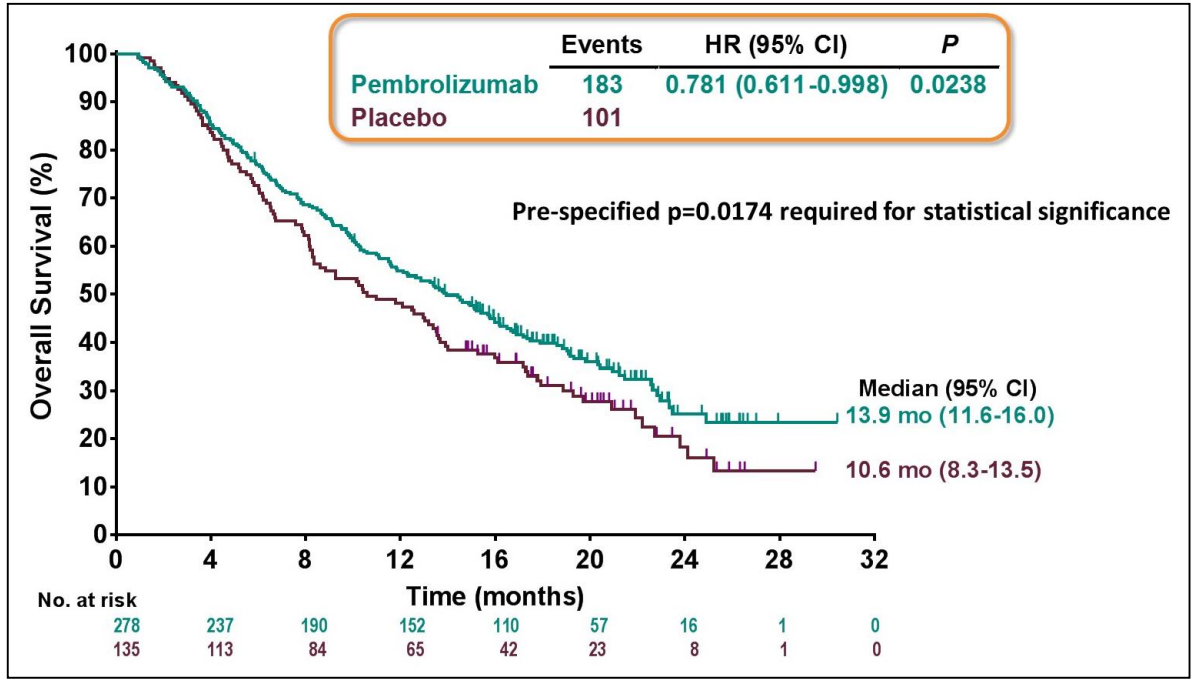
KEYNOTE-240

- Phase 3, randomized study presented at ASCO 2019
- Advanced HCC with previous systemic therapy, radiographic progression on/intolerance to sorafenib
- Child Pugh A
- Pembrolizumab 200 mg IV Q3W vs placebo
- 413 patients randomized 2:1
- Primary endpoints were OS and PFS

Finn, ASCO 2019

KEYNOTE-240

- Results: primary endpoints did **NOT** meet statistical significance.
  - OS: HR = 0.78, p = 0.0238
  - PFS: HR = 0.78, p = 0.0209
  - ORR 16.9% (95% CI 12.7-21.8) vs 2.2% (95% CI 0.5-6.4%), p = 0.00001



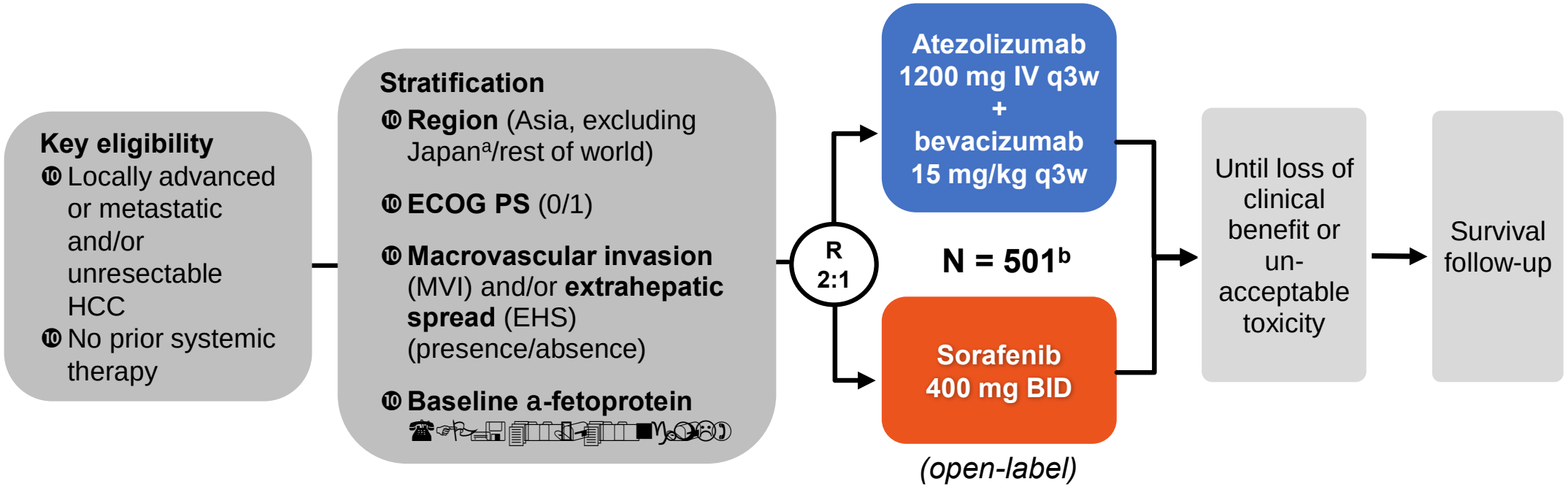
Finn, ASCO 2019

In development: Atezolizumab + bevacizumab

- Phase Ib; First line
  - Resulted in breakthrough therapy designation
- Atezolizumab 1200 mg + bevacizumab 15mg/kg Q3W
- Tolerable safety profile
- ORR 36% with mPFS of 7.3 months: *Combination has synergistic clinical activity*
- Regardless of viral infection, region, metastasis

Stein, ASCO 2018; Lee ESMO 2019

IMbrave150



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

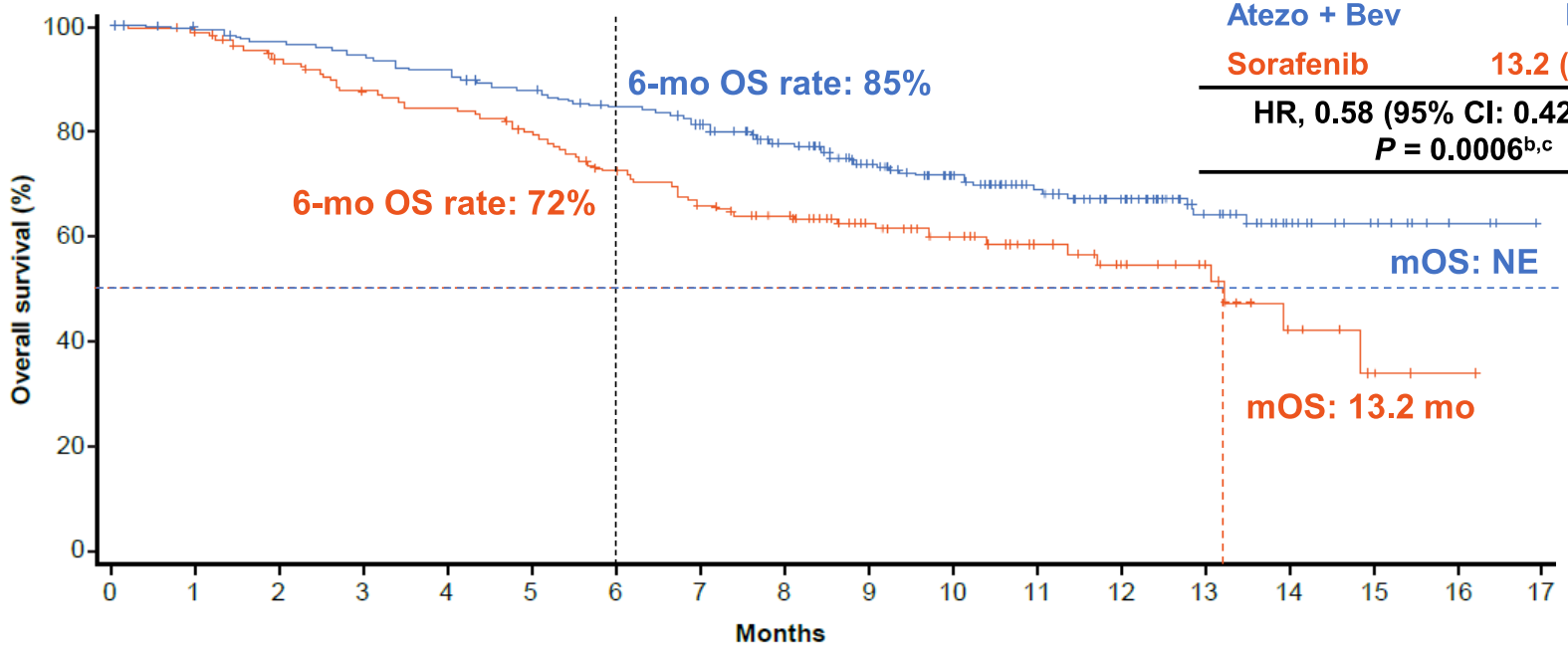
[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

Cheng, ESMO Asia 2019

IMbrave150

OS: co-primary endpoint

Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b]	
P = 0.0006[b,c]	

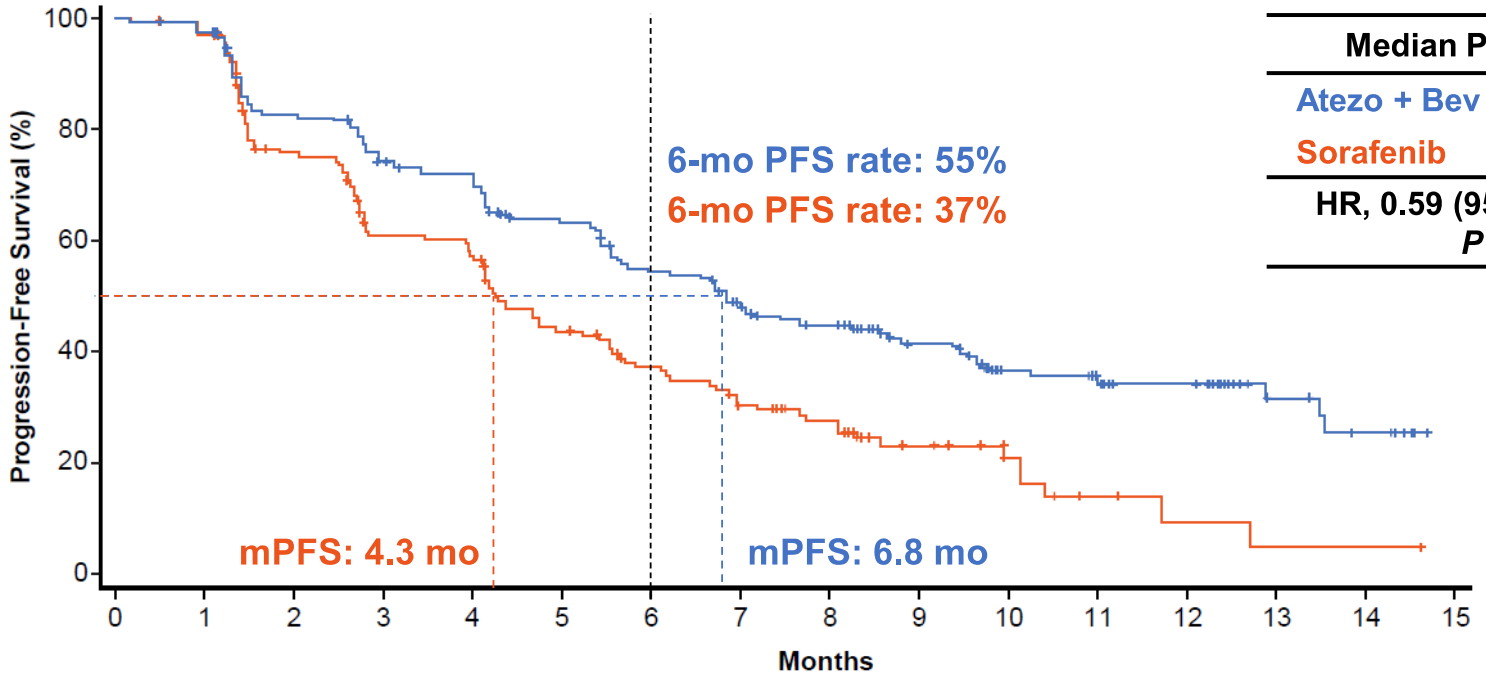


No. at risk																		
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

Cheng, ESMO Asia 2019

IMbrave150

Confirmed PFS[a]: co-primary endpoint



No. 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

Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d] *P* < 0.0001[d]	

Cheng, ESMO Asia 2019

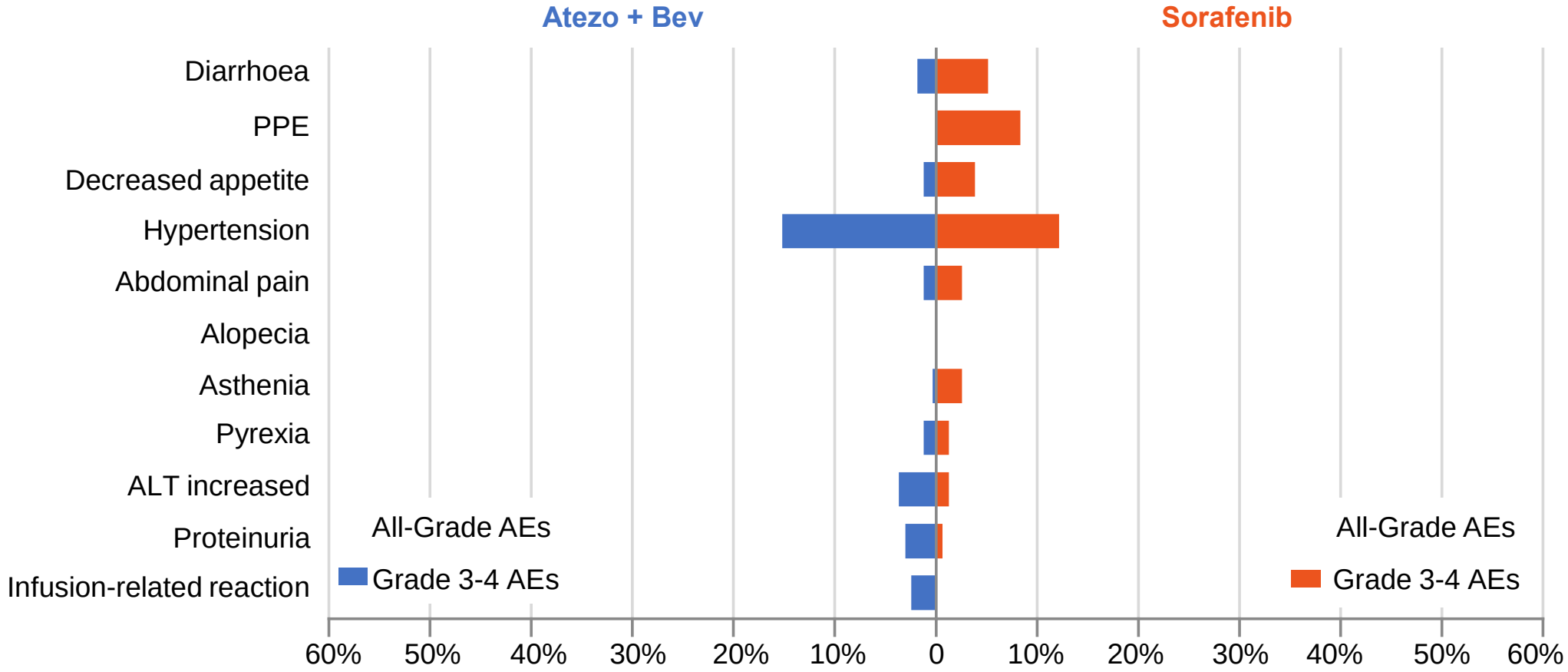
IMbrave150

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n **(%)** (95% CI)	89 **(27)** (23, 33)	19 **(12)** (7, 18)	108 **(33)** (28, 39)	21 **(13)** (8, 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 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)
Ongoing response, n (%)[c]	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)
Event-free rate at 6 months, n (%)	88	59	82	63

Cheng, ESMO Asia 2019

IMbrave150

≥ 10% frequency of AEs in either arm and > 5% difference between arms



Cheng, ESMO Asia 2019

Phase III Trials of Checkpoint Inhibitors

Trial ID	Targets	Drug arms	Status	N	Estimated completion
NCT03794440	PD-1, VEGF	• Sintilimab + bevacizumab biosimilar • Sorafenib	Recruiting	566	Dec 2022
NCT03298451	CTLA-4, PD-L1	• Tremelimumab + durvalumab • Sorafenib	Recruiting	1310	Jun 2021
NCT02576509	PD-1	• Nivolumab • Sorafenib	Active, not recruiting	726	July 2020
NCT 03755739	PD-1	• Pembrolizumab • Peripheral vs hepatic infusion after TACE	Recruiting	200	Nov 2021
NCT03062358	PD-1	• Pembrolizumab • Placebo	Recruiting	450	Jan 2022
NCT03713593	PD-1, VEGR	• Pembrolizumab + Lenvatinib • Lenvatinib	Recruiting	750	July 2022
NCT03847428	PD-L1, VEGF	• Durvalumab + bevacizumab • Combination with resection/MWA vs resection/MWA alone	Not yet recruiting	888	June 2023
NCT03764293	PD-1, TKI	• Camrelizumab + apatinib • Sorafenib	Not yet recruiting	510	Jan 2022
NCT03434379	PD-L1, VEGF	• Atezolizumab + bevacizumab • Sorafenib	Recruiting	480	June 2022

Johnston, World J Gastroenterology 2019.

Blocking Inhibitory Cytokines

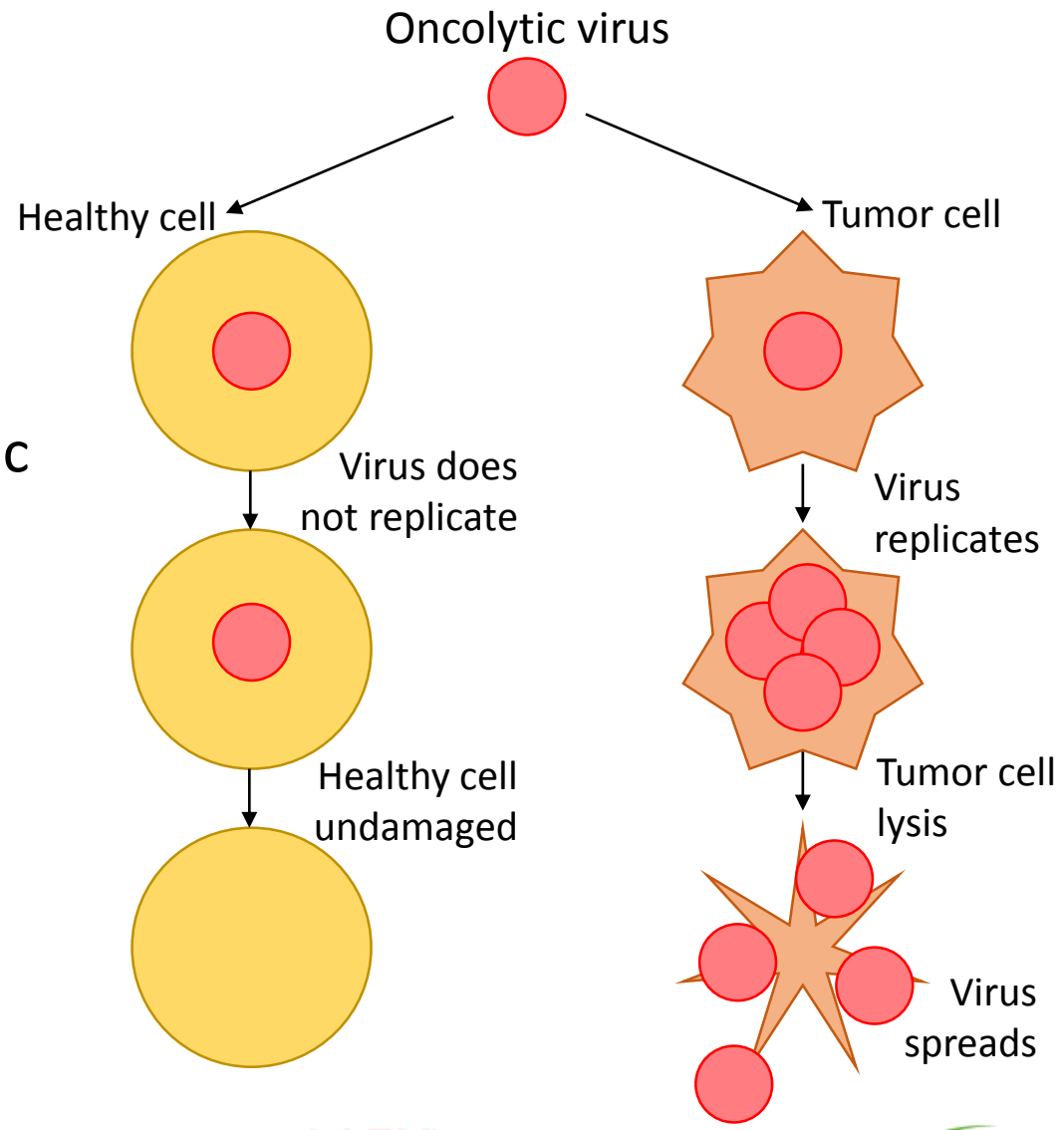
- TGF-β: a molecule that suppresses CD4+ T cell response in tumor cells thereby promoting progression of disease.
  - NCT02947165; A Phase I/Ib, Open-label, Multi-center Dose Escalation Study of NIS793 in Combination With PDR001 in Adult Patients With Advanced Malignancies
- LAG-3: a membrane protein that binds to MHC-II and suppresses T cell activity and cytokine release.
- TIM-3: transmembrane protein that is expressed on CD4 and CD8 cells that contributes to dysfunction of CD8 cells.
  - NCT03680508; Phase II Study of TSR-022 in Combination With TSR-042 for the Treatment of Advanced Hepatocellular Carcinoma

Vaccine Therapies

- Increase specific immune responses to tumor antigens
- Dendritic cells:
  - NCT01974661; Phase 1 Trial With the Cell-Based Immune Primer Ilixadencel, Alone, and Combined With Sorafenib, in Advanced Hepatocellular Carcinoma
- Peptide vaccines: another option but no trials that have shown any success yet.

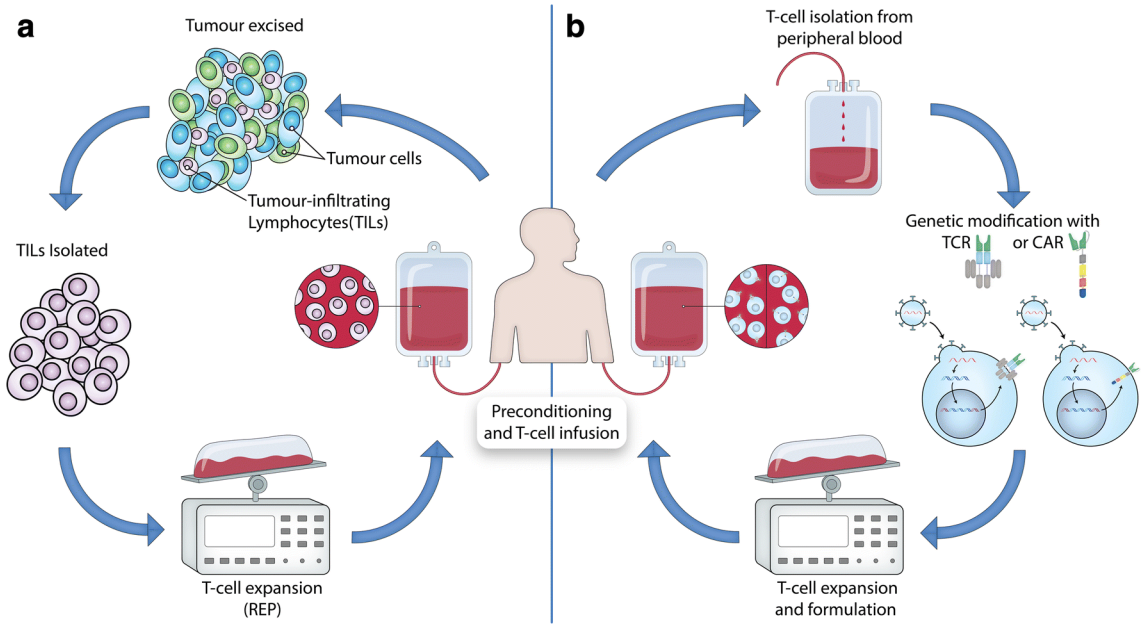
Oncolytic Viruses

- Viruses that preferentially replicate in cancer cells
  - NCT0055437; Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. Nat Med. 2013 Mar;19(3):329-36.
  - Abou-Alfa GK, et al. PHOCUS: A phase 3 randomized, open-label study comparing the oncolytic immunotherapy Pexa-Vec followed by sorafenib (SOR) vs SOR in patients with advanced hepatocellular carcinoma (HCC) without prior systemic therapy. J Clin Oncol 2016; 34: TPS4146



Adoptive Cell Transfer

- Passive administration of autologous lymphocytes following *ex vivo* cultivation
- Cell subsets that have been studied in HCC include NK cells, cytokine-induced killer (CIK) cells or TILs, and chimeric antigen receptor T cells (CAR-T cells).
  - NCT03563170; Molecularly Informed Integrated Immunotherapy Combining Innate High-affinity Natural Killer (haNK) Cell Therapy w/ Adenoviral & Yeast-based Vaccines to Induce T-cell Responses in Subjects w/ Advanced, Unresectable & Untransplantable HCC



Met *et al*, Principles of adoptive T cell therapy in cancer.

Conclusions

- Since many patients are ineligible for surgical resection/transplant, there is a great need for systemic therapies in HCC
- Recent approvals of pembrolizumab and nivolumab have moved HCC into the immunotherapy realm
- Combination treatments appear to be more successful and may be the way of the future

Case Studies

Case Study 1

- 49 y/o female with a history of obesity, hypertension, and hyperlipidemia presents with severe abdominal pain in the RUQ that has been progressing over the past several months.
- MRI of the abdomen reveals a 13cm, heterogeneous mass predominantly involving the right lobe of the liver with extension into the portal venous system; there is a large pericaval lymph node measuring 3.2 x 1.5cm. The radiologist reports this as “LIRADS-TIV, contiguous with a LIRADS-5 mass.”
- Hepatitis serologies are negative, and she denies a significant alcohol history. Her BMI is 40. Hepatology is consulted for further management of cirrhosis, which is thought to be secondary to NASH.
- CT chest and bone scan have no evidence of metastatic disease. AFP total is 65,000 with L3% of 70; DCP is 50.

Case Study 1

- Medical oncology is consulted. She is Child-Pugh A with good functional status and is motivated to pursue palliative systemic therapy. Outpatient follow-up for discussion of lenvatinib vs sorafenib is recommended. She is prescribed sorafenib 400mg PO BID with plan for follow-up in 2 months.
- Three weeks later she presents to the ER with watery diarrhea with up to 15 bowel movements per day. Her palms are erythematous with weeping blisters. She complains of weakness and fatigue. BP is 100/65 with HR of 115, and her Cr is elevated to 2 from normal baseline. She is admitted for hydration and supportive care, and sorafenib is discontinued.
- She tells you she will never take that medication again and asks if there are other options.

Case Study 1

- Given her intolerance to a tyrosine kinase inhibitor, you consider therapy with immunotherapy. What therapeutic options in this drug class are currently approved by the FDA in this setting?

  A. Nivolumab

  B. Pembrolizumab

  C. Atezolizumab

Case Study 1

- Given her intolerance to a tyrosine kinase inhibitor, you consider an immunotherapy approach. What therapeutic options in this drug class are currently approved by the FDA in this setting?

  A. Nivolumab

  B. Pembrolizumab

  C. Atezolizumab – not currently approved

- In the second-line setting for advanced or metastatic HCC, both nivolumab and pembrolizumab have been granted accelerated approval by the FDA based upon early phase clinical trial data with objective response rates of 20% and 17% respectively, with acceptable safety profiles.

Case Study 1

- She elects to pursue therapy with pembrolizumab. She asks you, will this treatment make me live longer?

  A. YES

  B. NO

Case Study 1

- She elects to pursue therapy with pembrolizumab. She asks you, will this treatment make me live longer?

  A. YES

  B. NO

  C. It's complicated…

- Both CheckMate 459 (1st line nivolumab vs sorafenib phase III) and KEYNOTE 240 (2nd line pembrolizumab vs BSC phase III) failed to meet primary endpoints of improving overall survival. Note, however, the rates of subsequent therapy in the control arms of both studies were nearly 50%.

Case Study 2

- Your patient from Case #1 elects begins therapy with pembrolizumab at standard dosing of 200mg IV q3weeks. Pre-treatment baseline labs are as follows:
  - ALT 41
  - AST 91
  - Total bilirubin 0.89
- She presents to your office prior to cycle 2. Pre-therapy labs are as follows:
  - ALT 85
  - AST 180
  - Total bilirubin 0.91
- She has no fevers, chills, abdominal pain, nausea, vomiting, or diarrhea and is otherwise feeling overall well.

Case Study 2

- What is the next best step in care?
  - A. Proceed with therapy
  - B. Hold therapy
  - C. Initiate corticosteroids
  - D. Start infliximab
  - E. Liver biopsy

Case Study 2

- What is the next best step in care?

  A. Proceed with therapy

  B. Hold therapy

  C. Initiate corticosteroids

  D. Start infliximab – contraindicated in patients with liver disease

  E. Liver biopsy

- Package label guidelines for both nivolumab and pembrolizumab have relaxed parameters for management of immune-related hepatitis in HCC patients. For pembrolizumab:
  - If baseline AST or ALT is greater than or equal to 2 times ULN, withhold pembrolizumab dose if AST or ALT rise to greater than 3 times baseline
  - Resume in HCC patients when AST or ALT recover to Grades 0-1 or to baseline

Case Study 2

- She returns to clinic prior to cycle 3 of pembrolizumab. She remains asymptomatic but has the following labs:
  - ALT 254
  - AST 386
  - Total bilirubin 0.95
- You hold therapy and repeat labs in 3 days, with the following values:
  - ALT 263
  - AST 392
  - Total bilirubin 0.94
- You elect to initiate corticosteroids with prednisone 1mg/kg/day. Daily labs continue to show no improvement for 3 days.

Case Study 2

- Which of the following options are appropriate next steps in treatment (choose all that apply)?
  - A. Admit for observation
  - B. Consult hepatology
  - C. Change route and dose of corticosteroids
  - D. Start mycophenolate
  - E. Liver biopsy

Case Study 2

- Which of the following options are appropriate next steps in treatment (choose all that apply)?

  A. Admit for observation – progressive or refractory immune-related hepatitis can rarely lead to acute liver failure and/or death so inpatient management is often warranted

  B. Consult hepatology – subspecialty care to rule out other causes of hepatitis (i.e., drug-induced liver injury, hepatitis reactivation)

  C. Change route and dose of corticosteroids – consider changing to parenteral steroids at doses up to 4mg/kg/day of prednisone equivalent

  D. Start mycophenolate – preferred over infliximab for hepatitis patients if additional immunosuppressive therapy is considered

  E. Liver biopsy – can be helpful in establishing diagnosis of immune-related hepatitis