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Immunotherapy for the Treatment of Hepatocellular Carcinoma

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

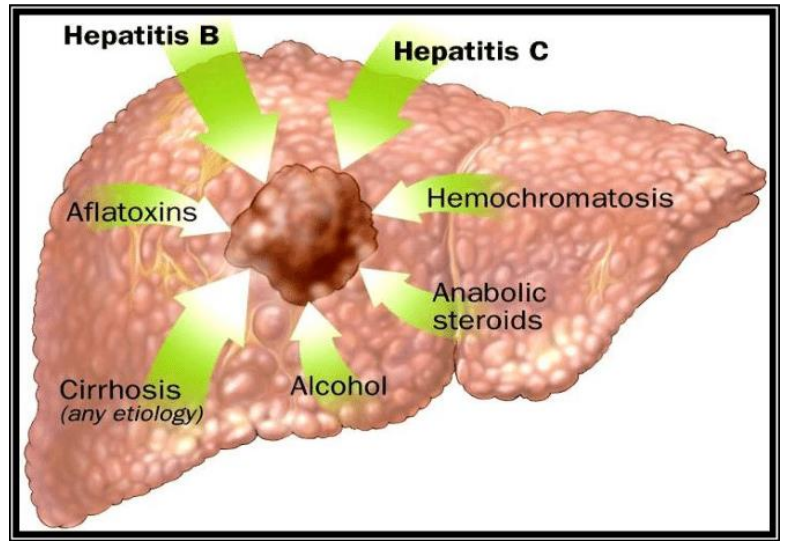
Society for Immunotherapy of Cancer

Disclosures

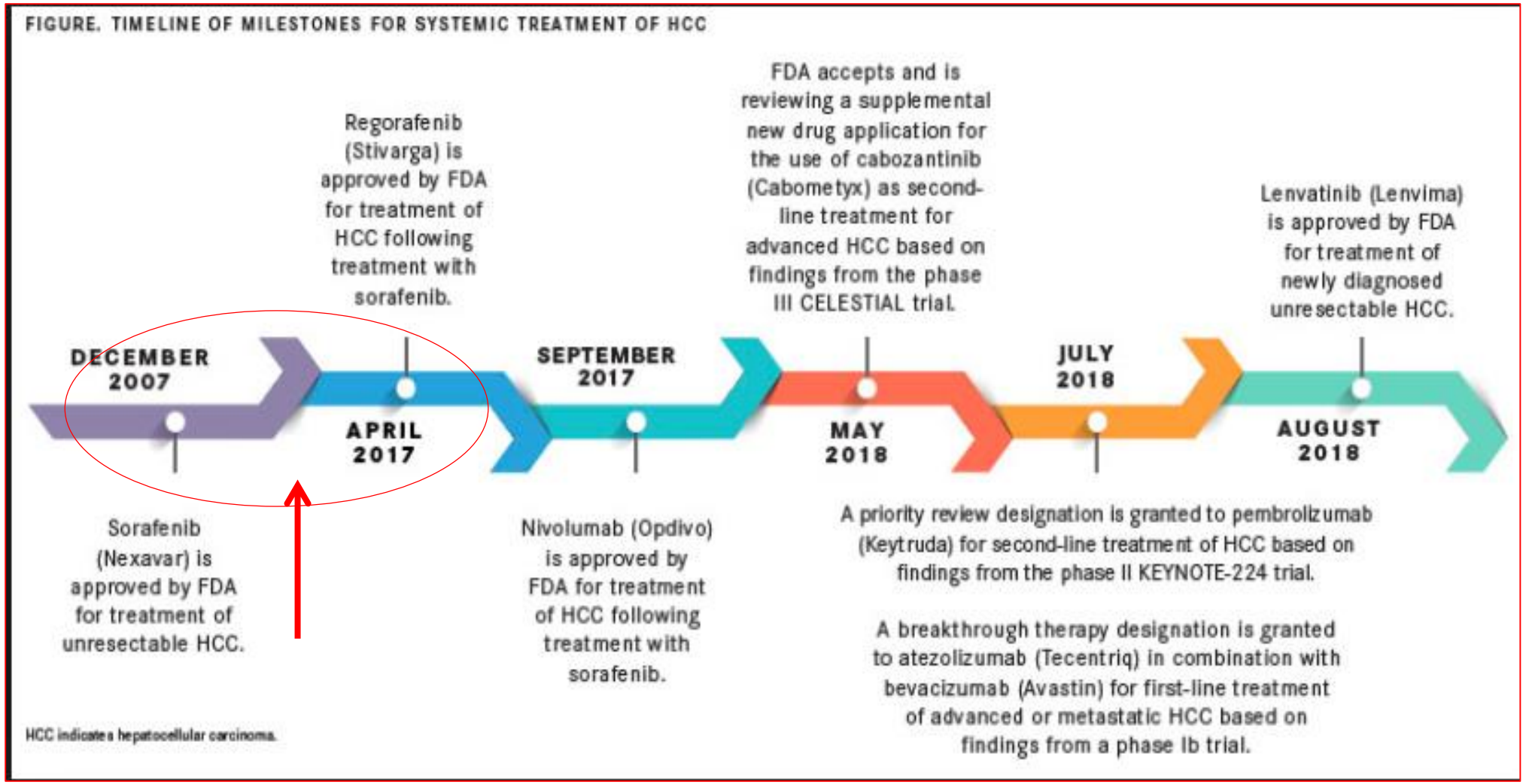
- Consulting/Advisory board: Bristol Myers Squibb , Eisai, Exelixis, Ipsen, BTG
- Speaker – Exelixis
- Research funding – BMS, Exelixis

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



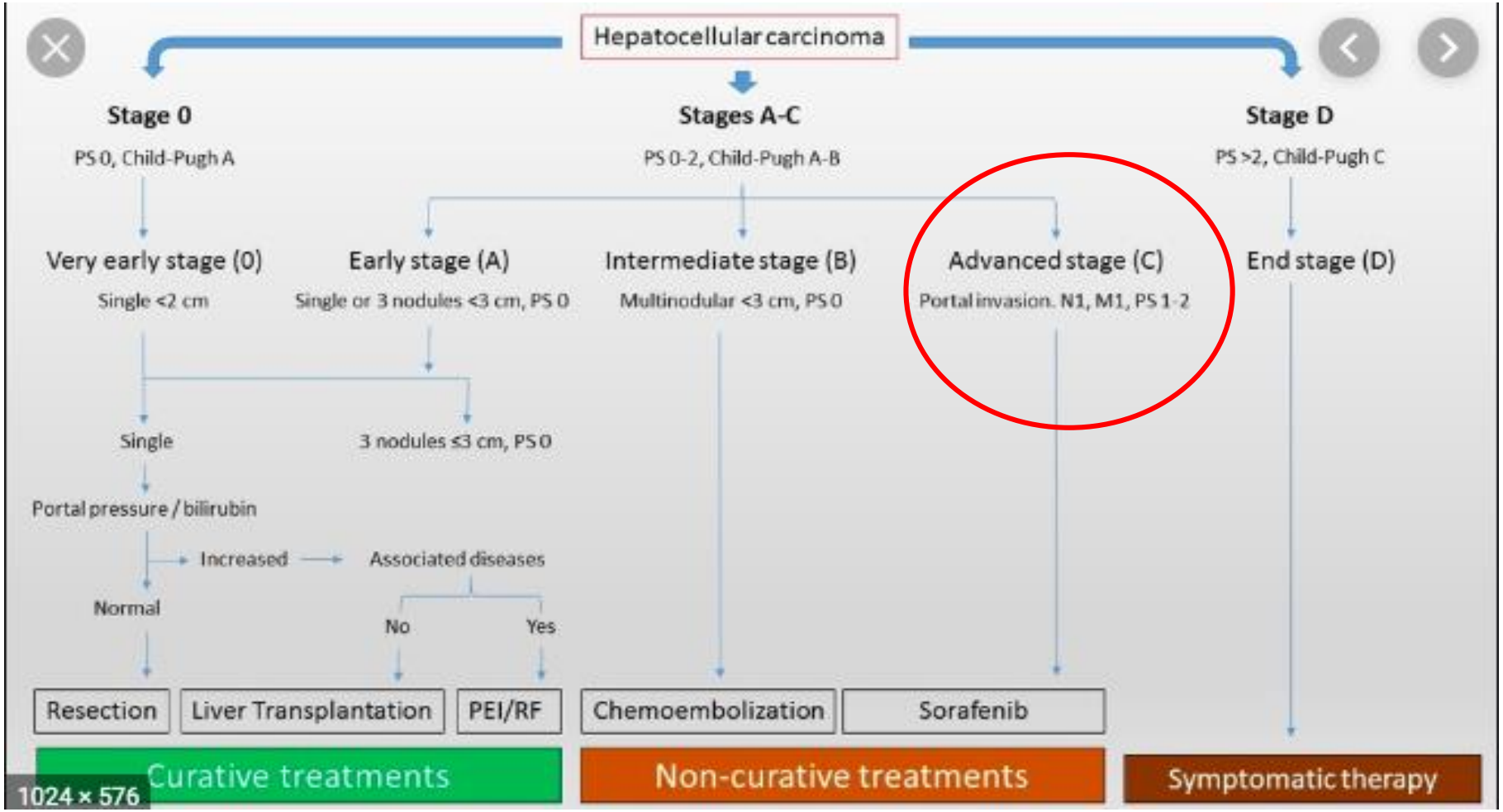
Treatment Paradigm Shift in HCC



Child Pugh Score

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
or			
International normalized ratio	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

BCLC score - Prognostic



Prognostic and Treatment directive

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

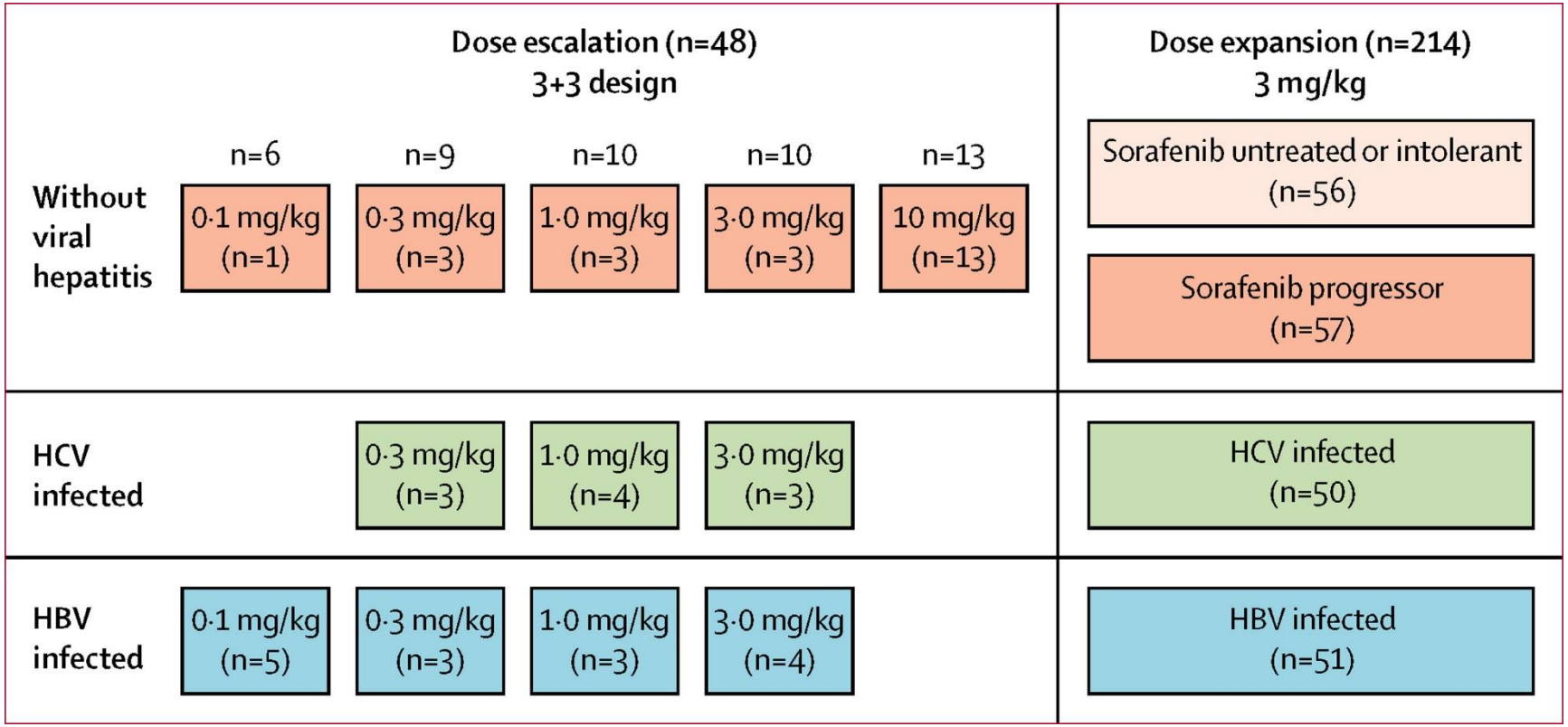
- Checkpoint inhibition
- Blocking inhibitory cytokines
- Vaccine therapies
- Oncolytic viruses
- Adoptive cell therapy

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

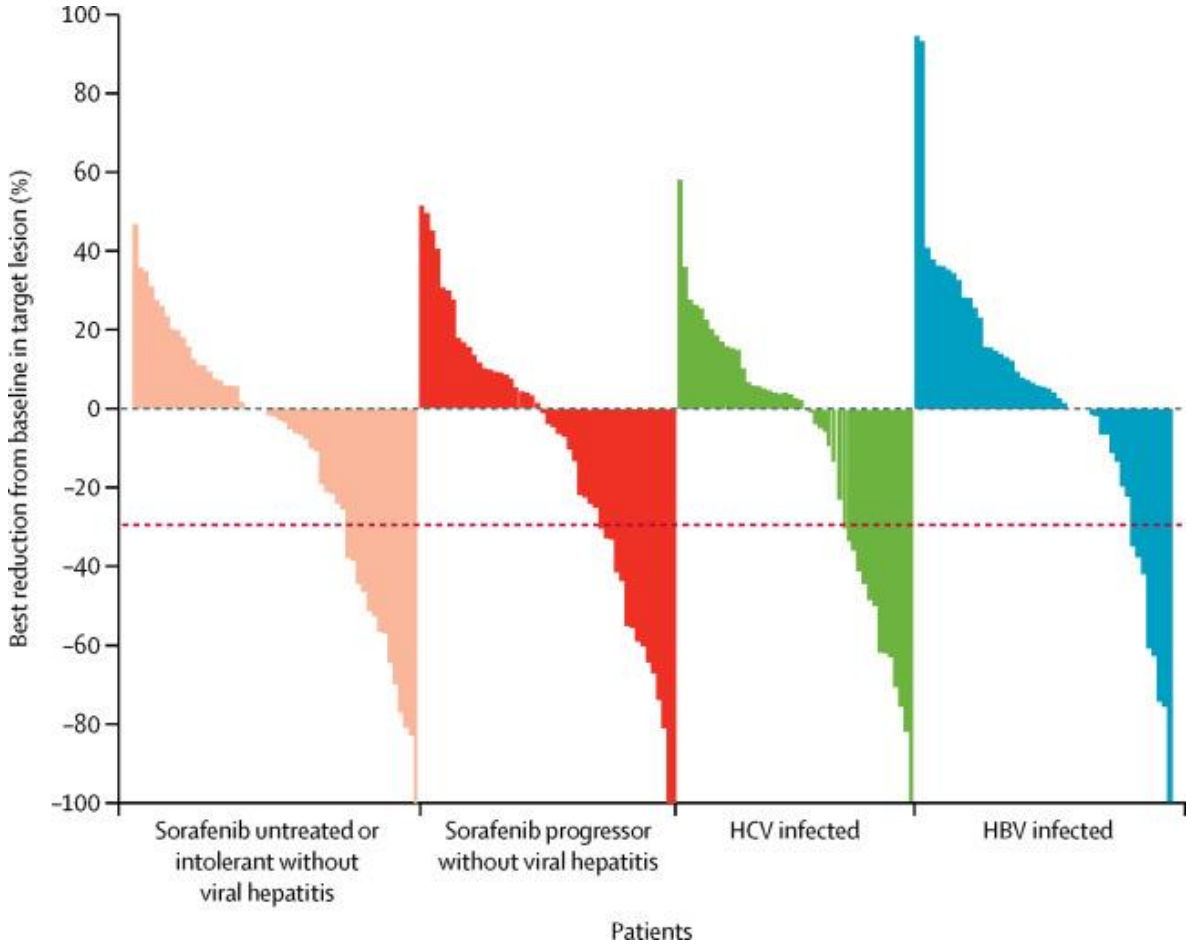
- Phase I/II open label study
- Child-Pugh A or B7, advanced HCC
- Previous sorafenib allowed
- Safety/tolerability for escalation; ORR for expansion



El-Khoueiry, The Lancet 2017.

CheckMate 040

- 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.

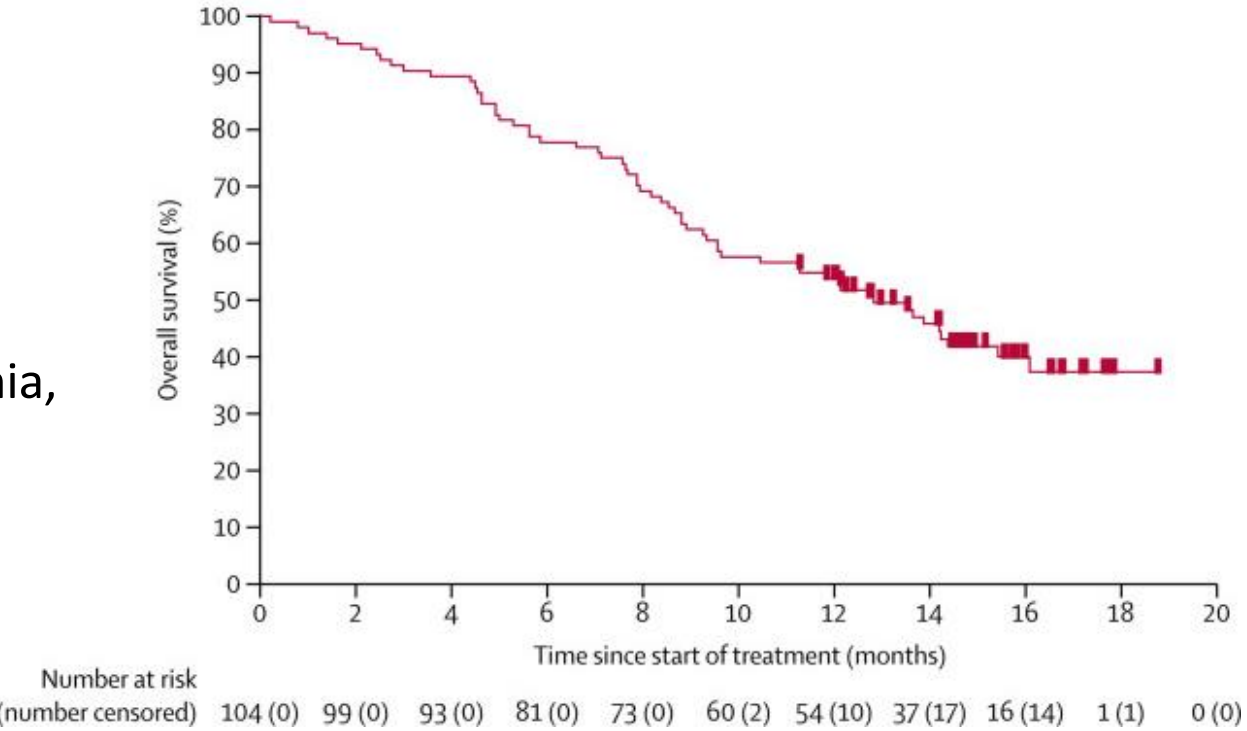
KEYNOTE-224

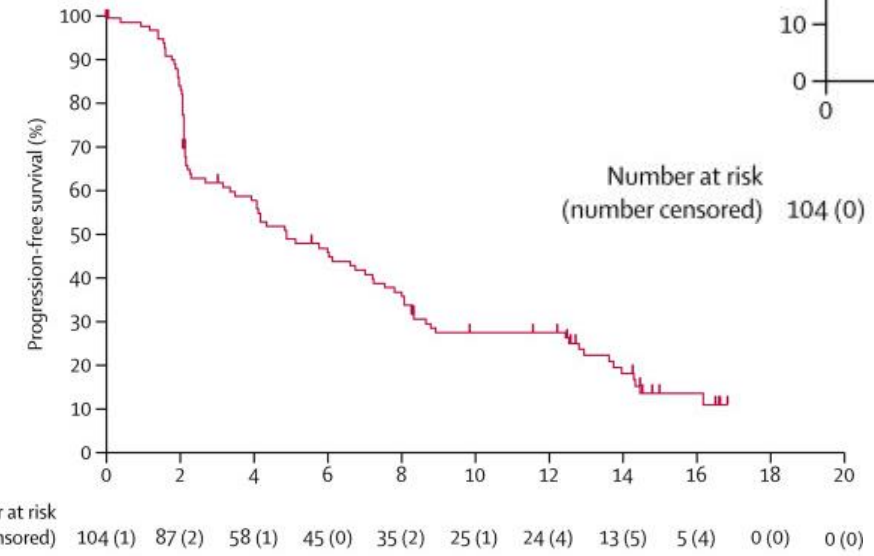
- Phase 2 non-randomized trial
- Previously treated with sorafenib
- Child-Pugh class A
- Pembrolizumab IV 200 mg Q3W
- Primary endpoint: objective response
- 104 patients enrolled and treated

Zhu, Lancet Oncol 2018.

KEYNOTE-224

- ORR: 17%, 1 CR, 17 PR
- mPFS: 4.9 months
- mOS: 12.9 months
- G 3/4 treatment-related adverse events: Increased ALT, AST, fatigue, hyperbilirubinemia, ulcerative esophagitis, and hepatitis





Zhu, Lancet Oncol 2018.

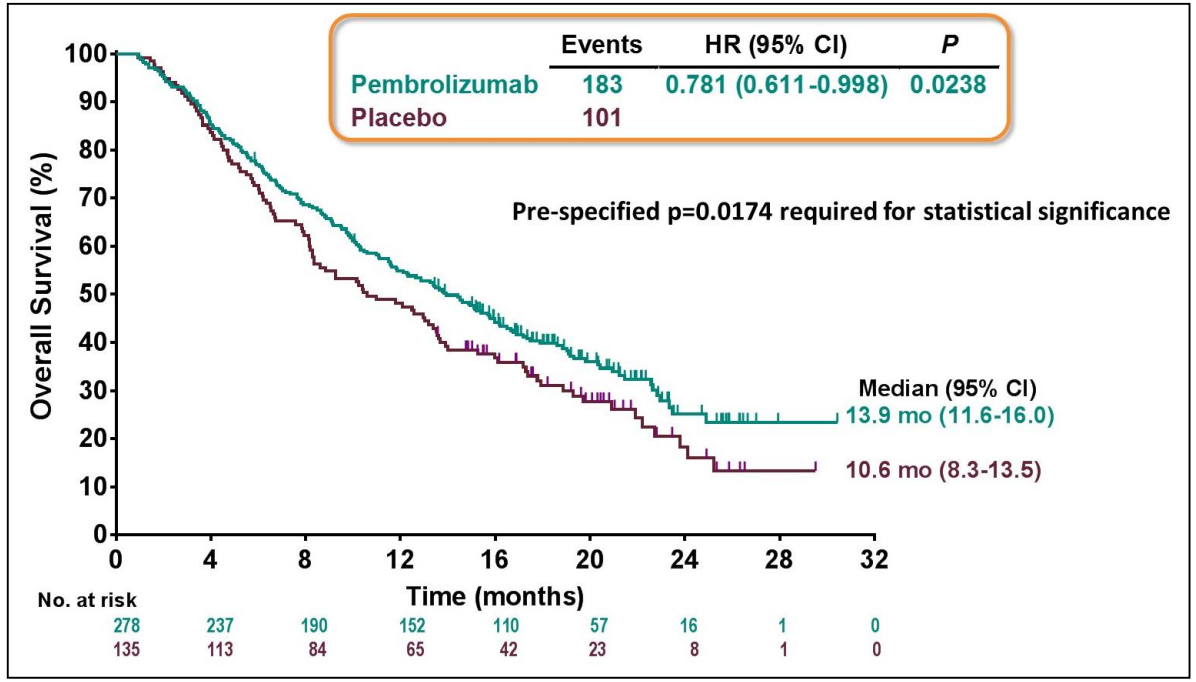
KEYNOTE-240

- Ph III, randomized
- 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

NCCN guidelines.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Hepatocellular Carcinoma

PRINCIPLES OF SYSTEMIC THERAPY

- **First-line systemic therapy**
  - **Preferred**
    - **Sorafenib (Child-Pugh Class A [category 1] or B7)[a,b,1,2]**
    - **Lenvatinib (Child-Pugh Class A only)[3]**
  - **Other Recommended**
    - **Systemic Chemotherapy (category 2B)[c]**

- **Subsequent-line therapy if disease progression:**
  - **Regorafenib (Child-Pugh Class A only) (category 1)[d,4]**
  - **Cabozantinib (Child- Pugh Class A only) (category 1)[d,5]**
  - **Ramucirumab (AFP ≥ 400 ng/mL only) (category 1)[d,6]**
  - **Nivolumab (Child-Pugh Class A or B7)[7]**
  - **Sorafenib (Child-Pugh Class A or B7)[a,b] (after first-line lenvatinib[e])**
  - **Pembrolizumab (Child-Pugh Class A only)[8] (category 2B)**

Checkmate 459

CheckMate-459: Nivolumab vs Sorafenib as First-line Treatment in Advanced HCC

- Randomized, open-label, multicenter phase III trial

Stratified by etiology, vascular invasion and/or extrahepatic spread, and geography

Advanced HCC; no prior systemic therapy; not eligible for/progressed after locoregional therapy; C-P A; ECOG PS 0-1 (planned N = 726)

Nivolumab
30 min IV Q2W

Sorafenib
PO BID

All pts treated until PD, unacceptable toxicity, or withdrawal of consent

*Nonviral HCC, HBV-HCC (HBV infection resolved or controlled), or HCV-HCC (resolved or active HCV infection)

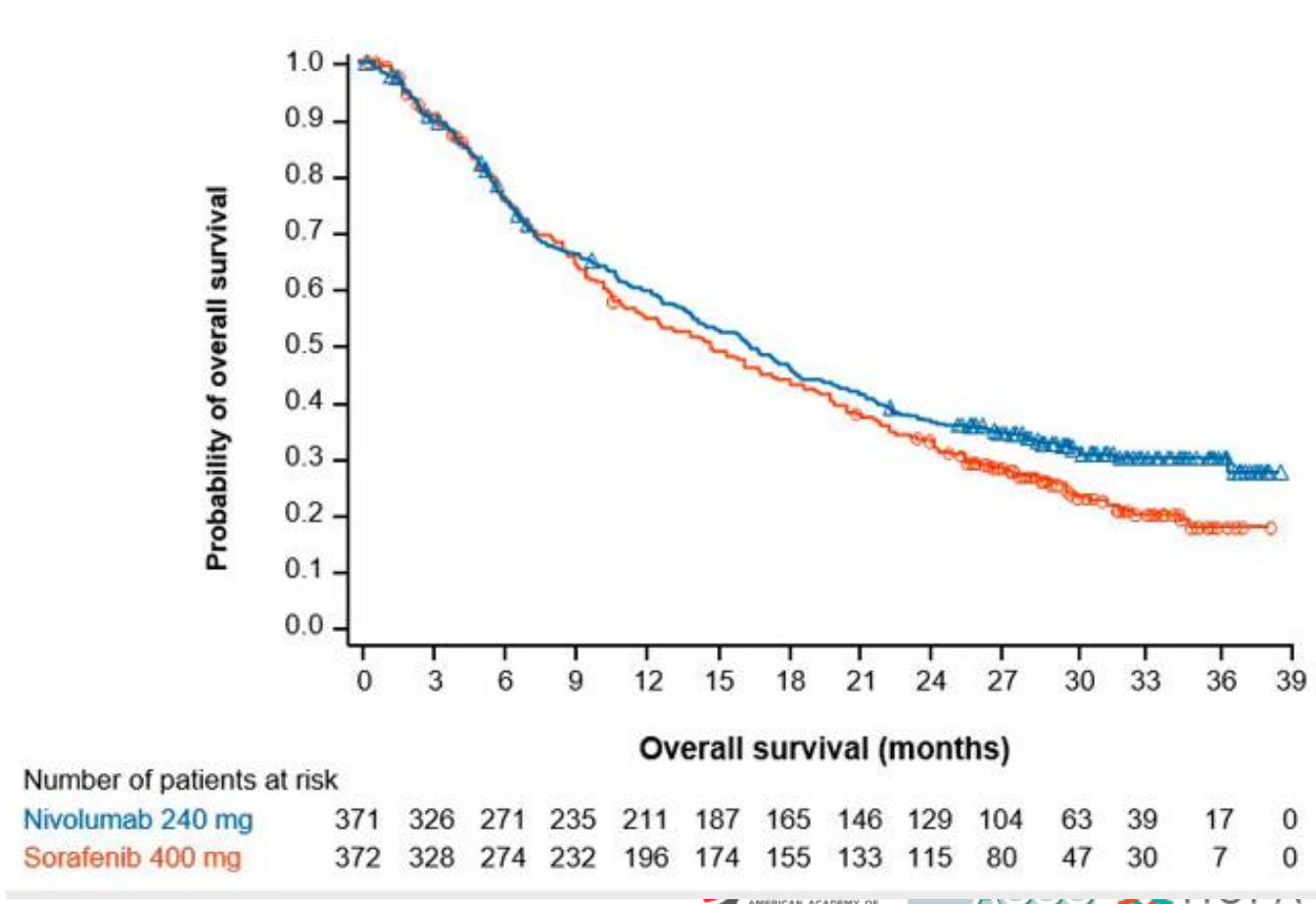
- Primary endpoint: time to progression, OS
- Secondary endpoints: ORR, PFS, PD-L1 expression

Sangro B, et al. ASCO 2016. Abstract TPS4147.
ClinicalTrials.gov. NCT02576509.

Slide credit: clinicaloptions.com

Checkmate 459

- At minimum follow-up of 22.8 months, the OS analysis showed that it did not meet the predefined threshold of statistical significance (p = 0.0419).

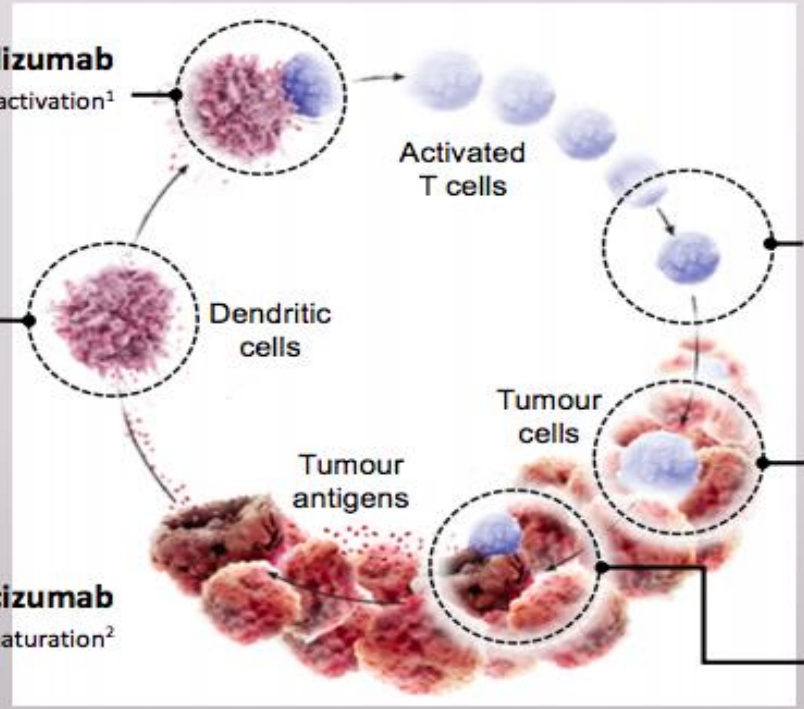


In development: Atezolizumab + bevacizumab

- Phase Ib; First line
  - Resulted in breakthrough therapy designation
- Atezolizumab 1200 mg + bevacizumab 15mg/kg Q3W
- Gr 3/4 TRAE in 35% of patients – hypertension, autoimmune encephalitis, mental status change and intra-abdominal hemorrhage
- Partial responses in 62% of patients: *Combination has synergistic clinical activity*
- Regardless of viral infection, region, metastasis
- mPFS, DOR, and OS not reached at 10.3 months

Stein, ASCO 2018

Atezolizumab and Bevacizumab - Mechanism of Action



Bevacizumab
Normalises the tumour vasculature, increasing T-cell infiltration[2]

Bevacizumab
Decreases the activity of immunosuppressive cells (MDSCs and Tregs)[2]

Atezolizumab
Restores anti-cancer immunity[1] with activity further enhanced through VEGF-mediated immunomodulatory effects

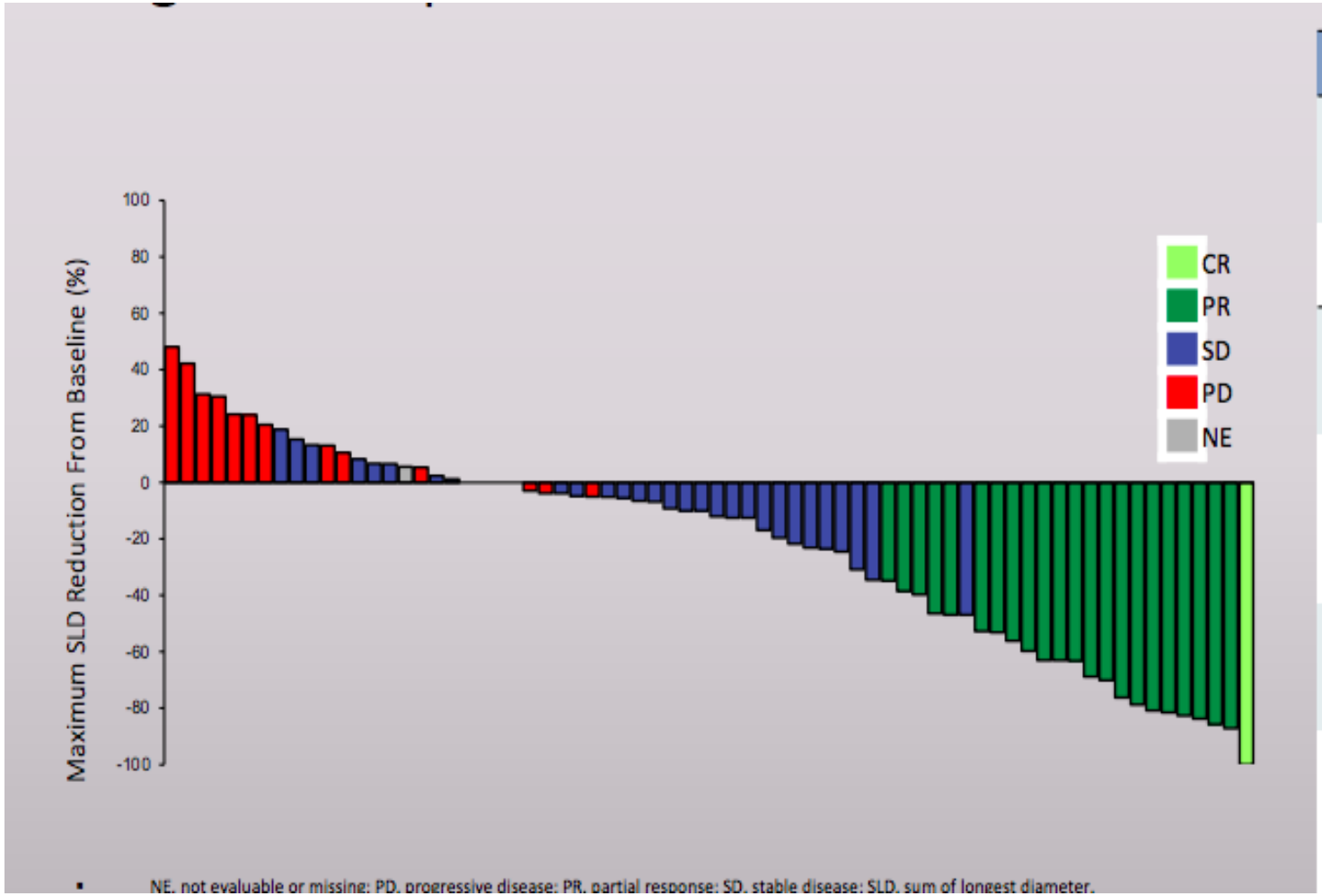
- Bevacizumab (anti-VEGF) is an anti-angiogenic agent with additional immunomodulatory effects
- In combination, bevacizumab may further enhance atezolizumab's efficacy by reversing VEGF-mediated immunosuppression to promote T-cell infiltration into the tumour

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

References: 1. Chen, Mellman. *Immunity*. 2013. 2. Chen, Hurwitz. *Cancer J*. 2018.

Hsu et al: Atezolizumab + bevacizumab in HCC

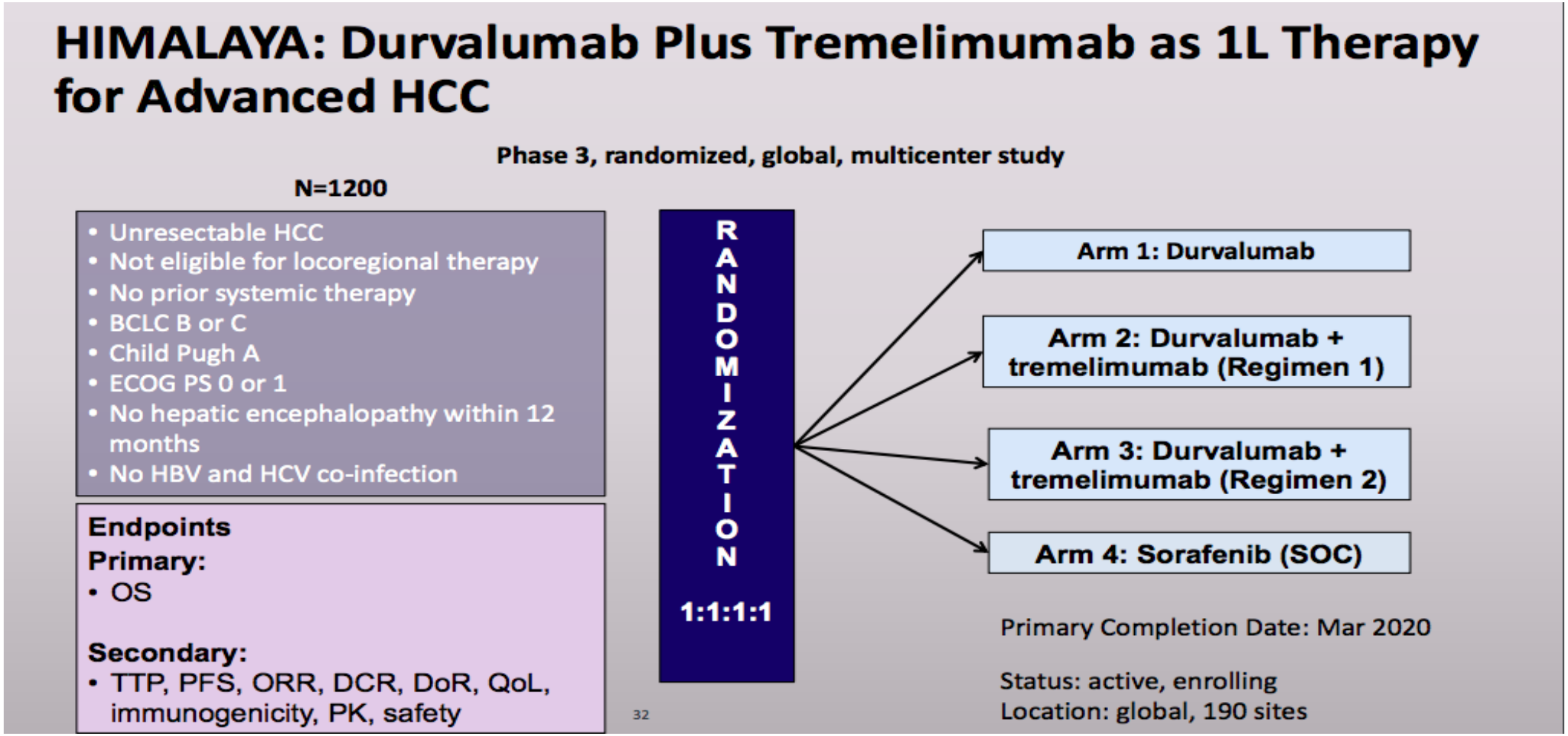
Atezo + Avastin



NE, not evaluable or missing; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameter.

ORR	
Overall, n (%)[a]	**23/73 (32)**
CR	1/73 (1)
PR	22/73 (30)
SD	33/73 (45)
PD	13/73 (18)
By region, n/n (%)[b]	
Asia excluding Japan	12/41 (29)
Japan/USA	10/31 (32)
By aetiology, n/n (%)	
HBV	11/36 (31)
HCV	10/23 (43)
Non-viral	2/14 (14)
By baseline AFP, n/n (%)[c]	
< 400 ng/mL	12/41 (29)
≥ 400 ng/mL	11/27 (41)
By EHS/MVI, n/n (%)[d]	
EHS and/or MVI	18/64 (28)
MVI negative	13/32 (41)
EHS negative	9/22 (41)

Upcoming trials.



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

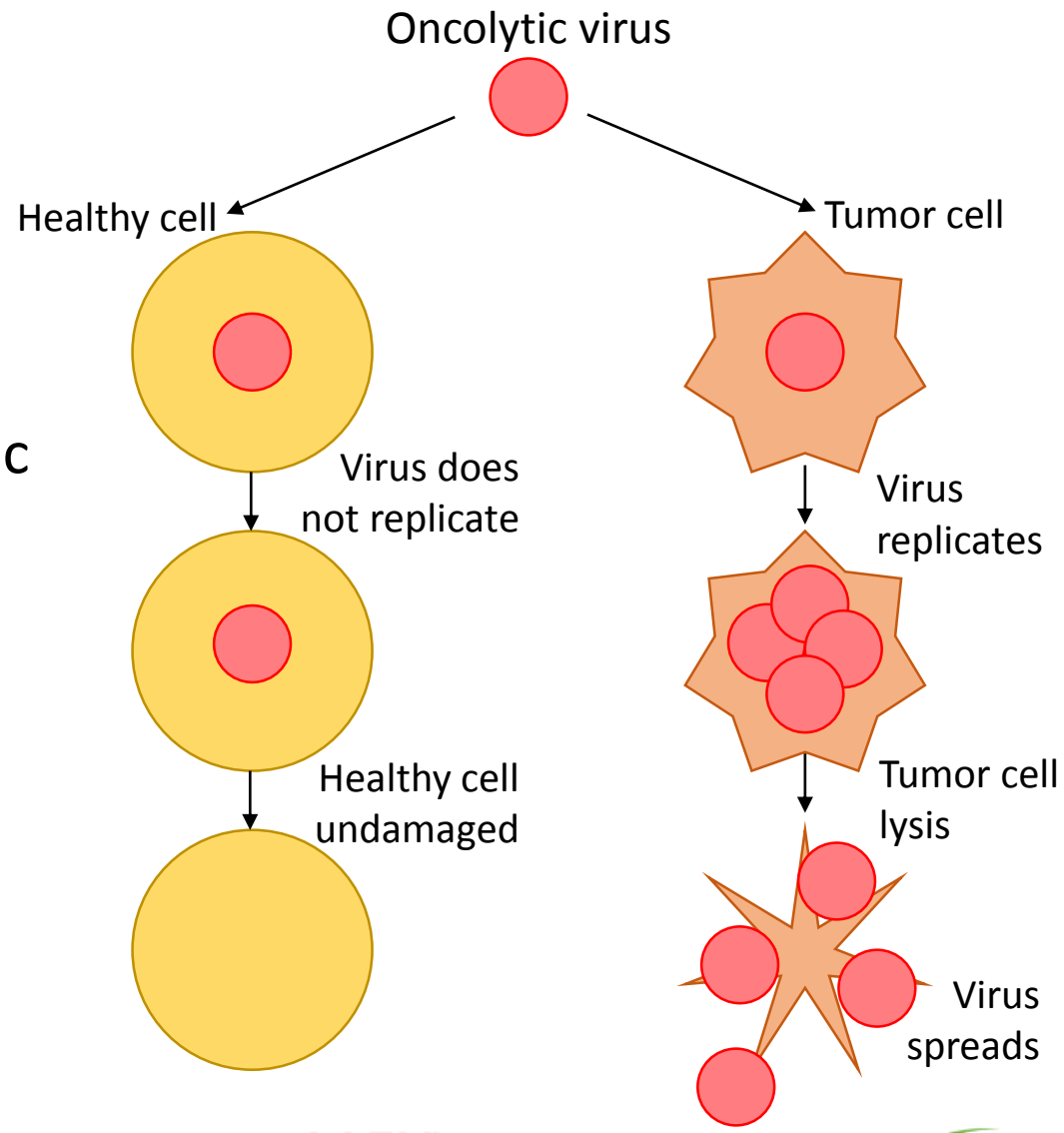
- TGF-β: a molecule that suppresses CD4+ T cell response in tumor cells thereby promoting progression of disease.
  - NCT02947165; A Phase I/Ib, Open-label, Multi-center Dose Escalation Study of NIS793 in Combination With PDR001 in Adult Patients With Advanced Malignancies
- LAG-3: a membrane protein 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.

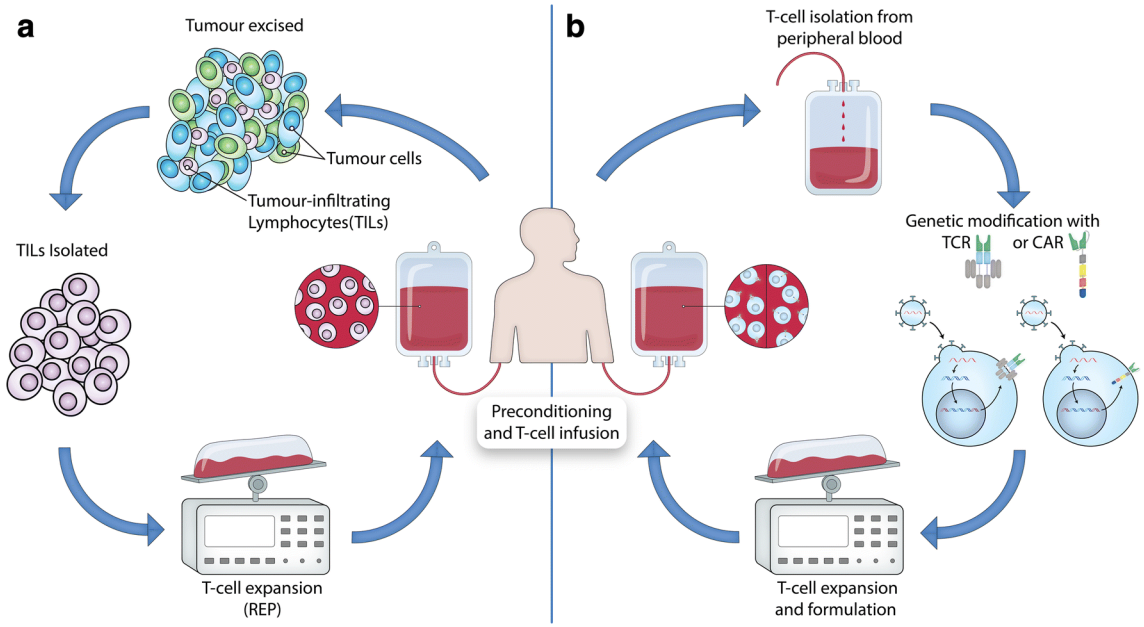
Oncolytic Viruses

- 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

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Case Studies

Case Study 1

- 34yo female presented with abdominal pain and found to have a ruptured abdominal mass.
- No hx of hepatitis. Liver did not appear cirrhotic on imaging.
- No Past Medical history apart from depression
- Underwent surgical resection of this with final pathology c/w HCC.
- Post resection she was enrolled in a clinical trial for adjuvant therapy. (Nivo vs. placebo, double blind). 8 months of being on trial, imaging with new RP nodes and liver lesion c/w POD.
- Taken off clinical trial. Found to have been randomized to placebo.
- ECOG PS 1. LFTs were in the normal range, TB 0.6

- What would be the next treatment option.

(1) Start patient on Sorafenib

(2) Start patient on Nivolumab

(3) Liver directed Therapy with Y90

Case Study 1

- She is now metastatic and treatment with systemic therapy is appropriate. First line options at this stage are Sorafenib and Lenvatinib. Either of these options are appropriate and decision would be based on side effect profile. First line Nivolumab on its own is not appropriate based on results of the CM 459 study that was recently released. At the time patient was treated, nivo was not available as a 1st option.
- She was treated on a clinical trial with Immunotherapy and LDT (with Y90). Rationale for this was to try to extract abscopal effect.

Case Study 1

- She responded on this treatment for another 8 months with stable disease and ultimately had to be taken off therapy for progression of disease
- She then was treated with 2nd line therapy with Cabozantinib. She opted to not try sorafenib for fear of side effects
- Has remained on this therapy for about 4 months with normalization of her AFP

Case Study 2

- 56 yo male with hx of Alcohol related cirrhosis developed HCC.
- He was treated with y90 x 2 initially. He was considered for liver transplantation and while waiting for transplant, his disease unfortunately progressed and became metastatic with large porta hepatis LN.
- Clinical decline with worsening ascites requiring paracentesis every week.
- He was started on Sorafenib . Unfortunately did not tolerate Sorafenib due to side effects (significant fatigue and HFS).
- ECOG PS about 2, TB 1.1, transaminases in the normal range

- What would be the next treatment option

1. Cabozantinib
2. Nivolumab
3. Lenvatinib

Case Study 2

- He was treated with Nivolumab every 2 weeks with excellent response. His paracentesis improved and he stopped requiring them all together about 4 months into therapy. His scans had significant improvement with complete resolution of his extra-hepatic disease. He only has a liver lesion now that is visible on scans.
- He is now 2 years from having started treatment. After lengthy decision, we opted to stop his nivolumab all together. His scans continued to remain stable.
- Main side effect from therapy remains that of hypothyroidism from the Nivo.

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Thank you