Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hepatocellular Carcinoma

Osama Rahma, MD
Assistant Professor of Medicine, Harvard Medical School
Center for Immuno-Oncology, Gastrointestinal Cancer
Dana-Farber Cancer Institute

AAEM American Academy of Emergency Medicine — Champion of the Emergency Physician

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Research support from Merck
- Speaker for activities supported by educational grants from BMS and Merck
- Consultant for Merck, Celgene, Five Prime, Roche/Genentech, GSK, GFK, Defined Health INC, Puretech, Leerink and PRMA Consulting
- I will be discussing non-FDA approved indications during my presentation.

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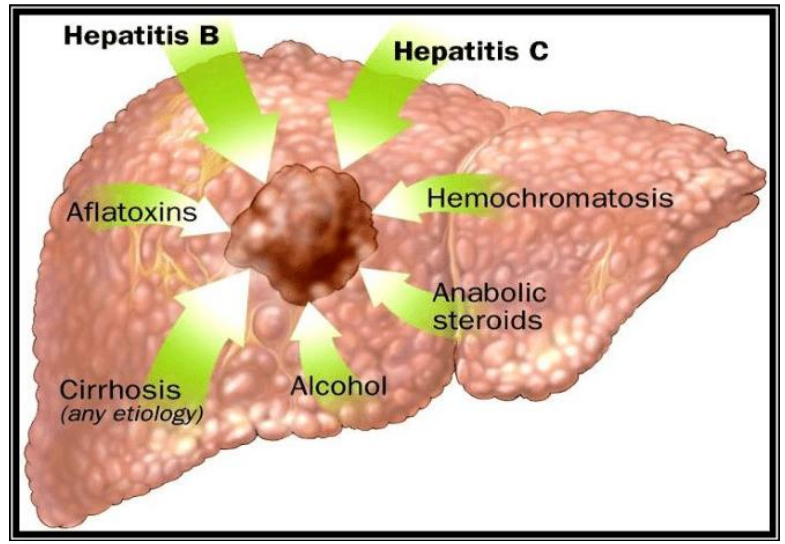
Background

- 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



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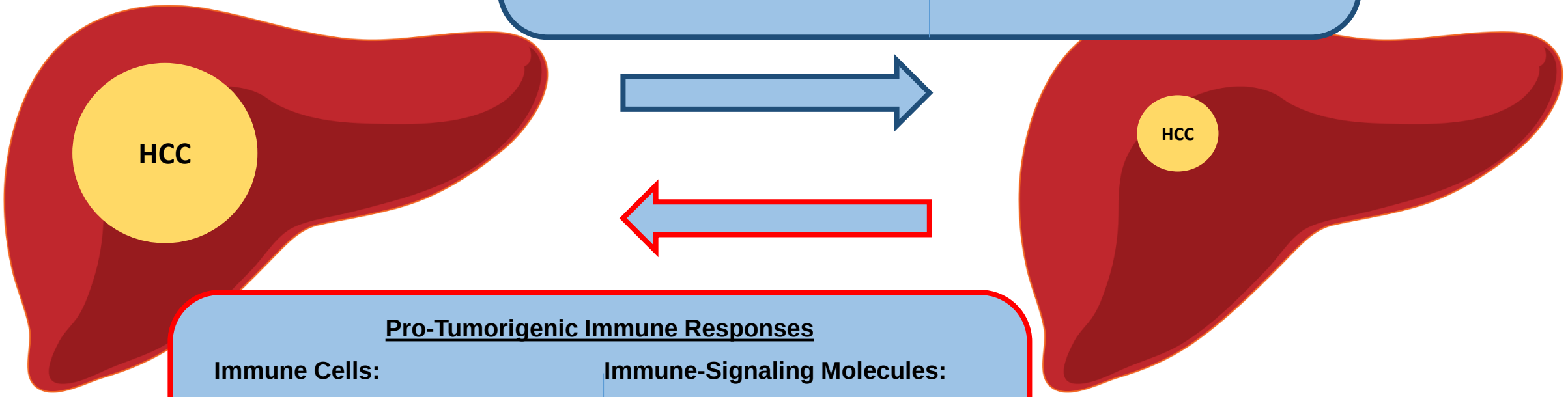
Anti-Tumorigenic Immune Responses

Immune Cells:

- CD8⁺ Effector T-Cells
- CD4⁺ Helper T-Cells
- Dendritic Cells
- NK Cells

Immune-Signaling Molecules:

- 4-1BB
- STAT4
- CXCL10, CCL2/5, CCR2
- OX40



Pro-Tumorigenic Immune Responses

Immune Cells:

- FoxP3⁺ Regulatory T-Cells
- MDSCs
- Kupffer Cells
- NKT Cells
- Neutrophils

Immune-Signaling Molecules:

- PD-1/PD-L1
- CTLA-4
- TIM-3
- LAG-3

Obeid, Rahma et al, CII 2018

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Liver Immunobiology

- 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

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Liver Immunobiology

- However, the immune response is made dysfunctional by
  - Expression of a greater proportion of **T-regulatory/cytotoxic T cells**
  - **Hypofunctional NK cells**
  - **Expansion of MDSCs**
  - secretion of **immunoregulatory cytokines**
  - **Expression of inhibitory ligands** that suppress immune activation and
  - **Downregulation of stimulatory ligands** that activate the immune system.

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Immunotherapeutic Strategies in HCC

A. Vaccines:

- Dendritic cells
- Viral vectors
- Peptide vaccines

Shared Targets:

- AFP
- hTERT
- NY-ESO-1
- Glypican 3
- SSX2
- Tumor lysate (cell line)

Personalized Targets:

- Autologous tumor cell lysate
- Mutated antigens
- In situ vaccination

B. Adoptive Cell Therapies:

- Expanded TILs
- Antigen specific T-cells
- Chimeric antigen receptor T-cells
- Cytokine induced killer cells

C. Immune Checkpoint Blocking Antibodies:

- Anti CTLA-4
- Anti PD-1
- Anti PD-L1
- Anti TGF-β receptor

D. Potential Combinations of Immunotherapies:

- Within and between groups A,B and C
- With chemotherapy (tyrosine kinase inhibitors)
- With locoregional therapies (TACE and/or radiotherapy)

Obeid, Rahma et al, CII 2018

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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

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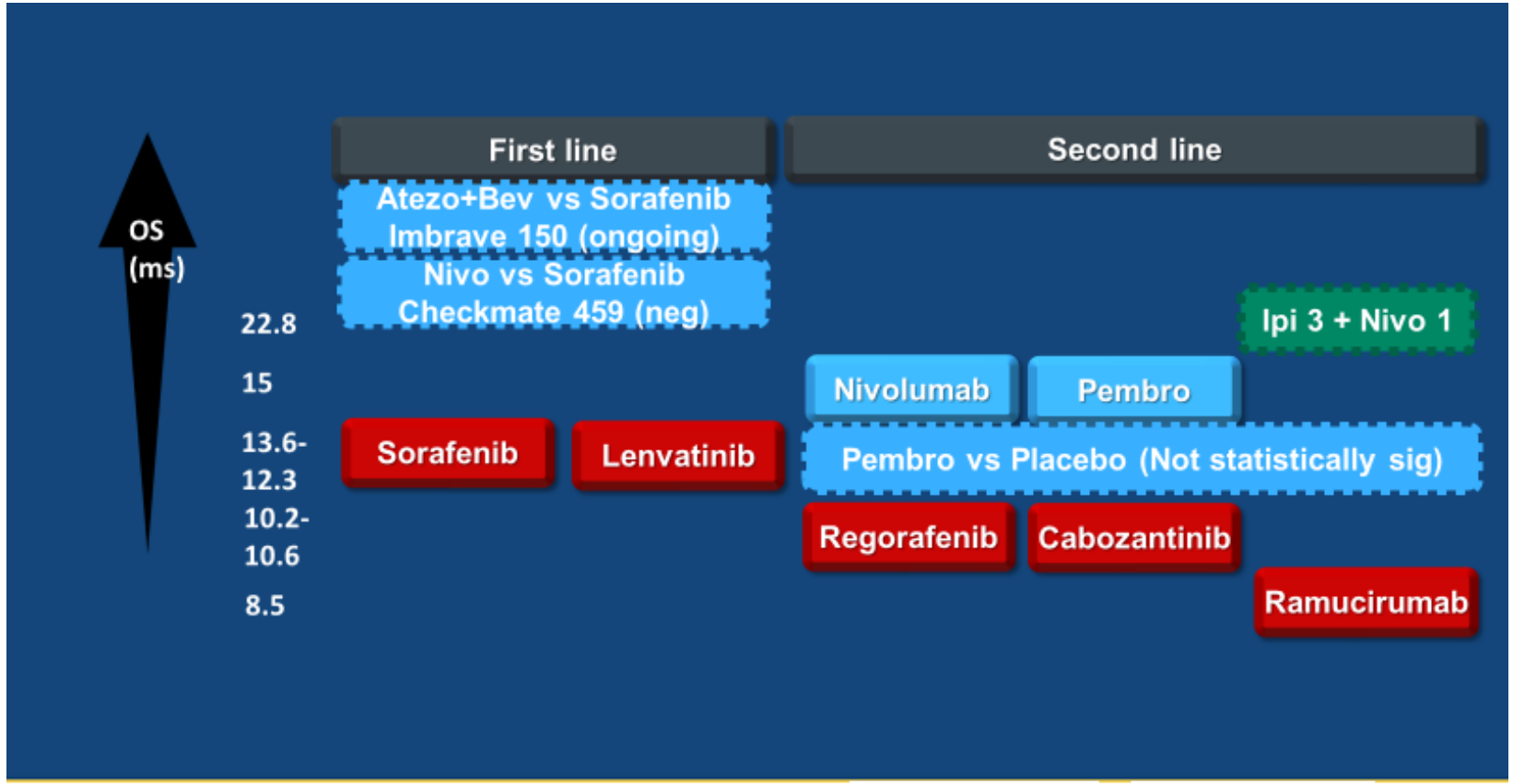
Current Treatment Paradigm in HCC



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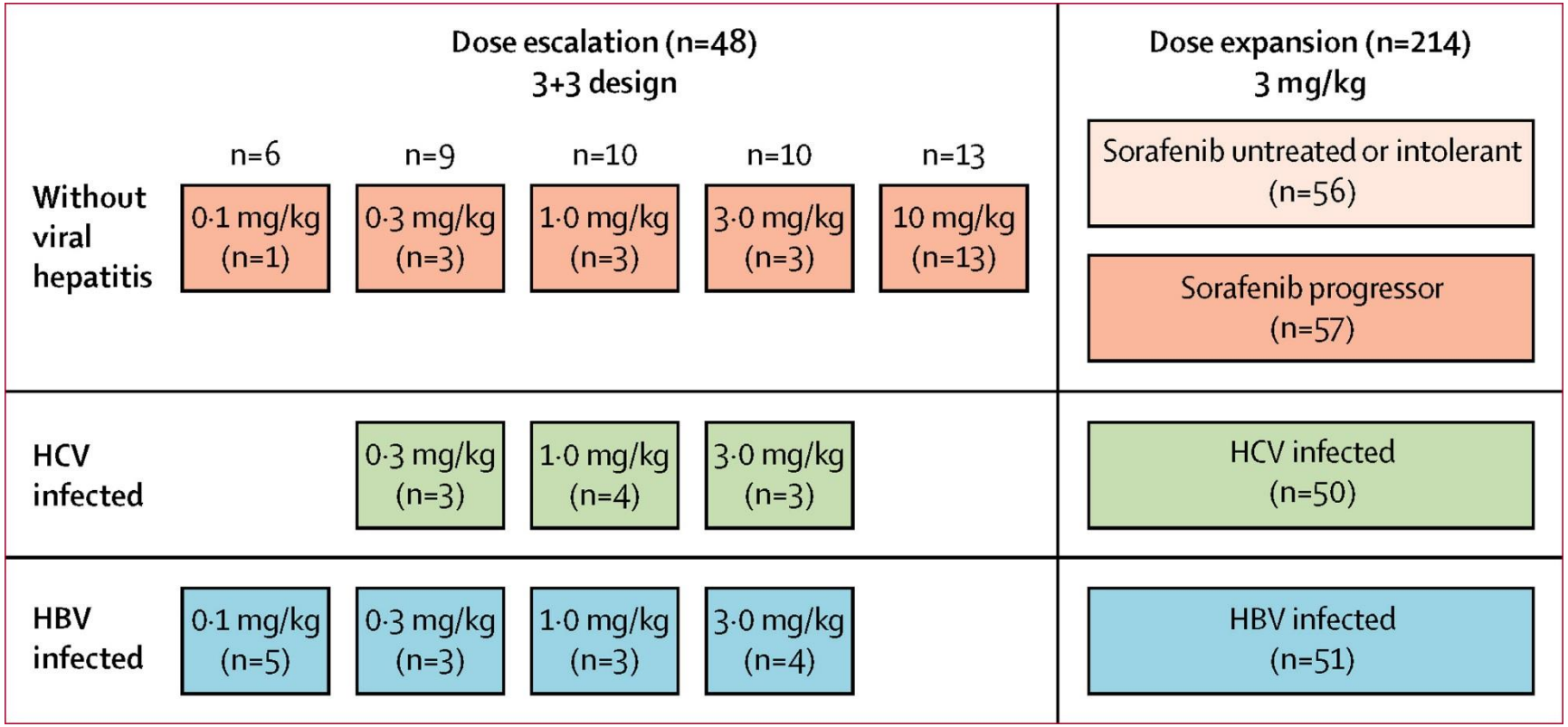
CheckMate 040

- 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.

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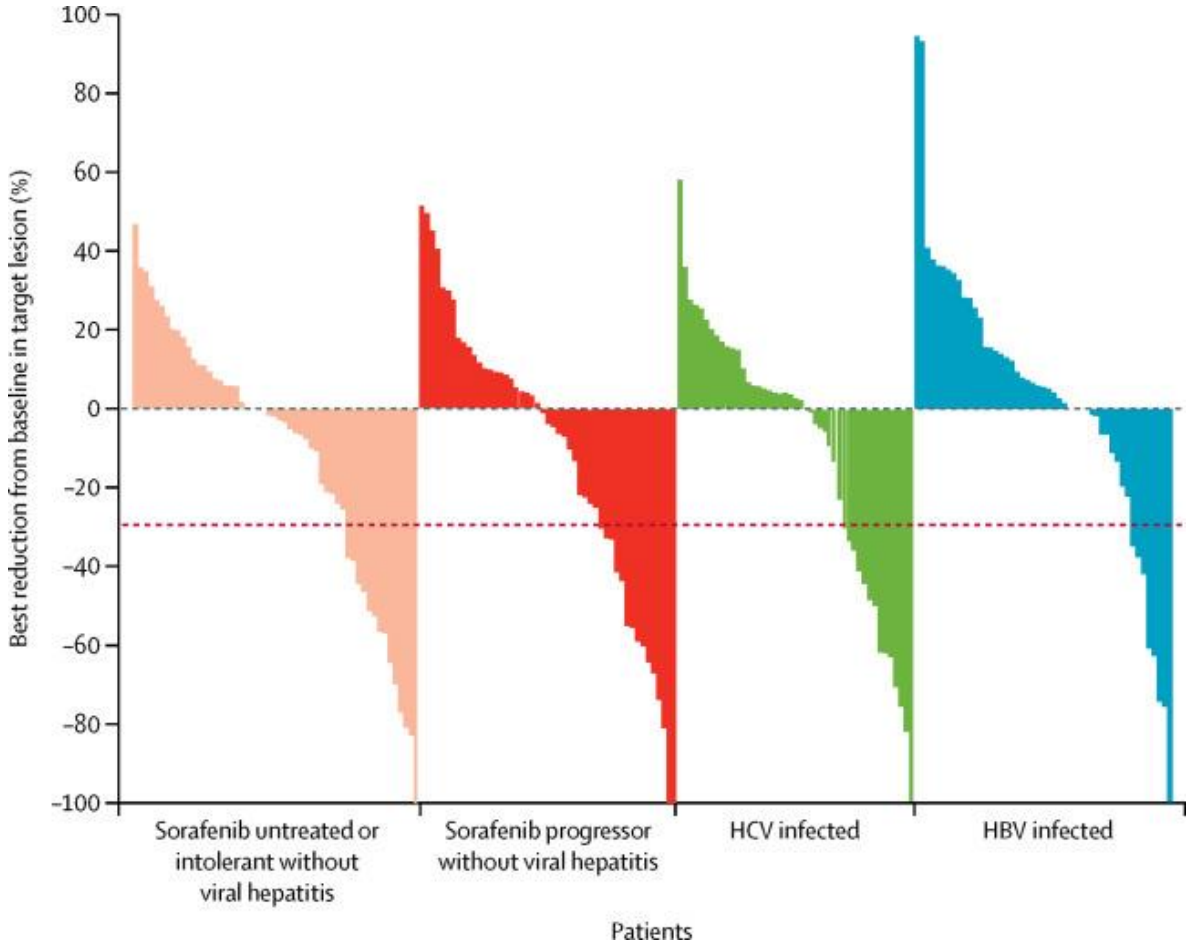
CheckMate 040

- 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.

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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.

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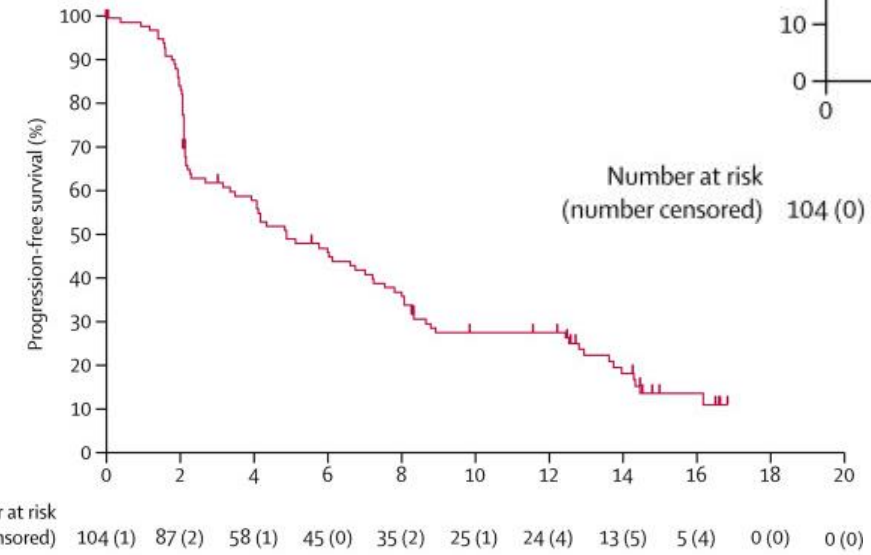
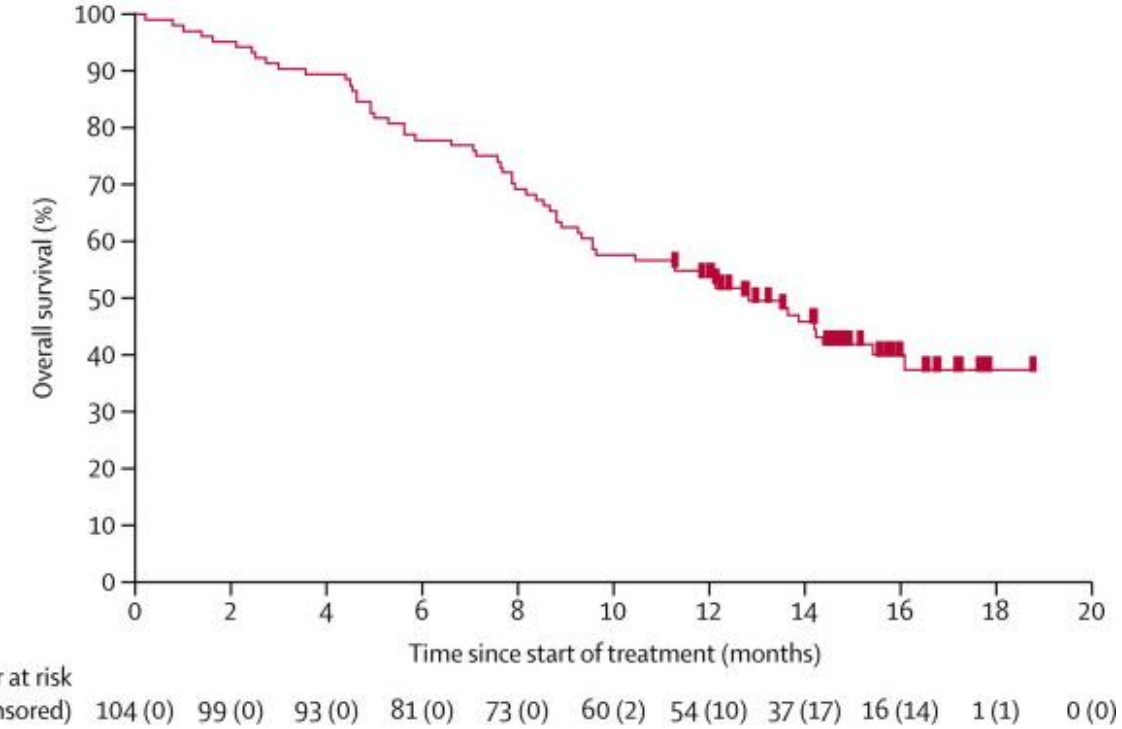
KEYNOTE-224

- 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.

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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

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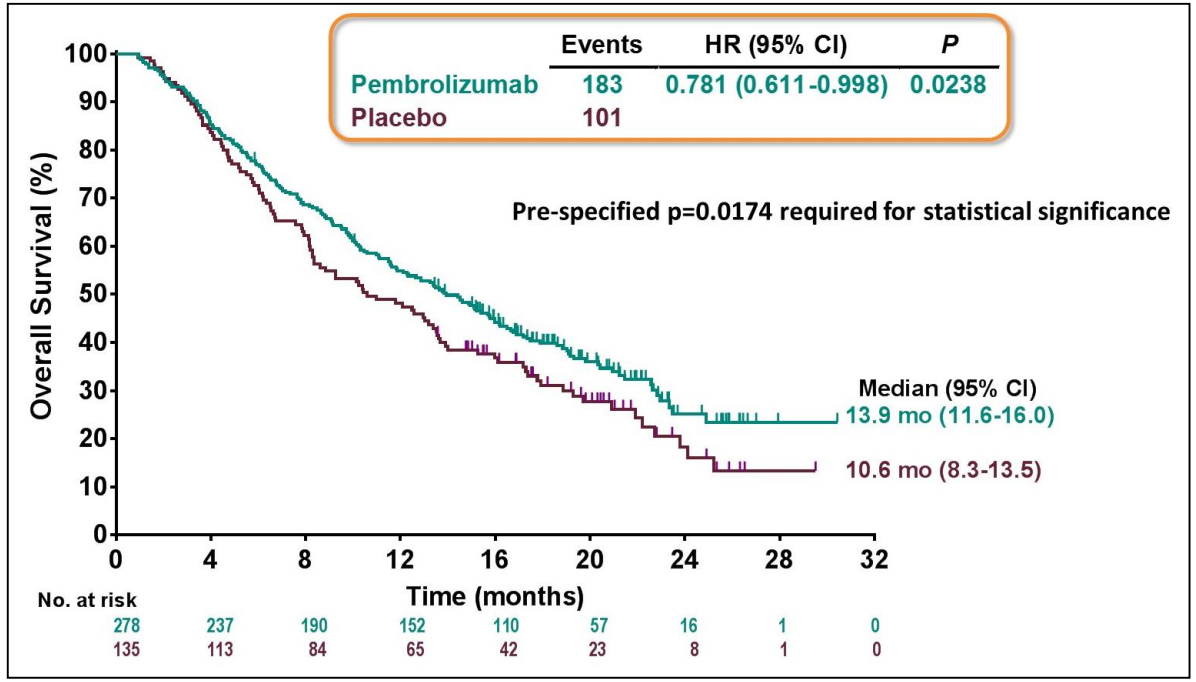
KEYNOTE-240

- 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

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In development: Atezolizumab + bevacizumab

- Phase Ib; First line
  - Resulted in breakthrough therapy designation
- Atezolizumab 1200 mg + bevacizumab 15mg/kg Q3W
- 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
- Gr 3/4 TRAE in 35% of patients – hypertension, autoimmune encephalitis, mental status change and intra-abdominal hemorrhage

Stein, ASCO 2018

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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	Negative study (Press release)	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.

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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

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Vaccine Therapies

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

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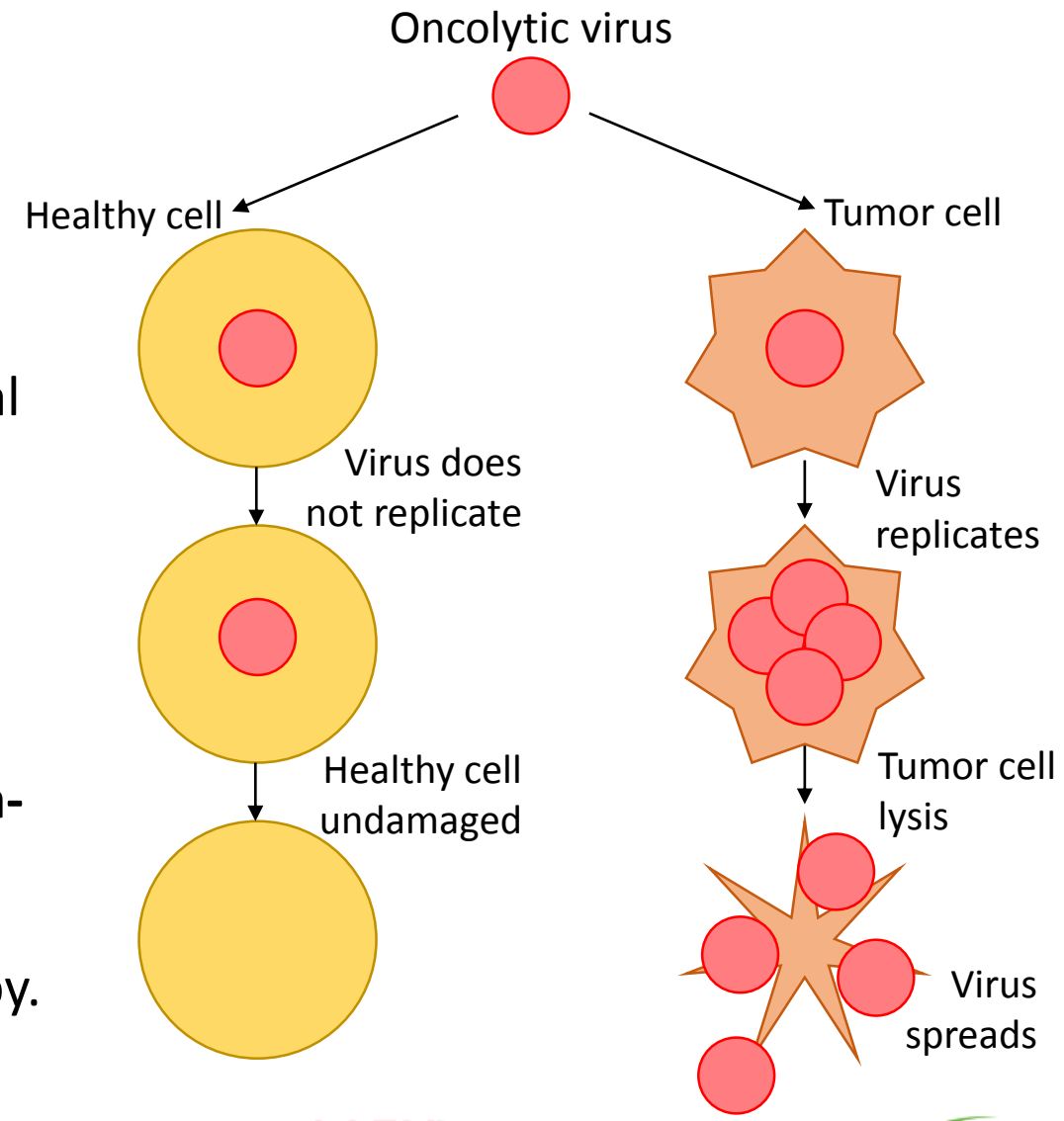
Oncolytic Viruses

- 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.
  - 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



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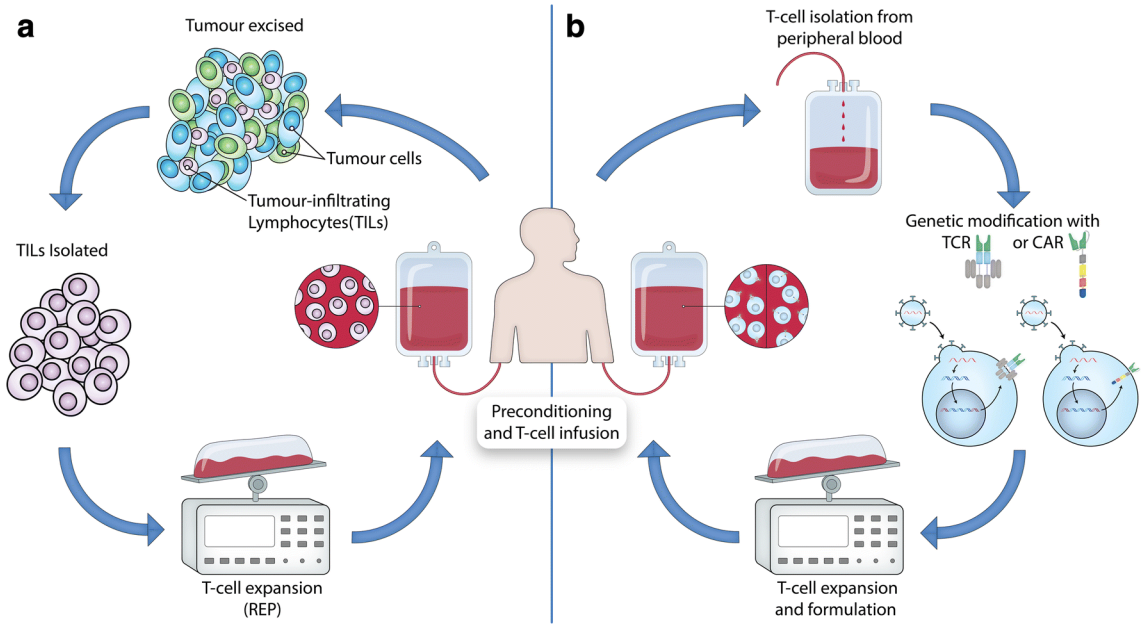
Adoptive Cell Transfer

- 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.

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Conclusions

- Since many patients are ineligible for surgical resection/transplant, there is a great need for systemic therapies in HCC
- Currently both pembrolizumab and nivolumab are considered standard of care as a second line post-sorafenib
- Many ongoing trials with combinations of immunotherapies or targeted therapies (anti-angiogenesis) in HCC

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Case Studies

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Case Study 1

Mr. AB is a 65 yo male with h/o liver cirrhosis who was found to have 2 liver lesions during routine US. Further workup including chest/abd and pelvic ctscan revealed a lung lesion with a biopsy consistent with metastatic HCC. The patient has a Child Pugh of A. He presented to your office to explore treatment options.

1. The next treatment option for this patient is:

   A. Start Nivolumab 240mg every 2 weeks.

   B. Start Sorafenib 400mg daily.

   C. Strat combination of Sorafenib and nivolumab.

   D. Strat combination of atezolizumab and bevacizumab.

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Case Study 1

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1. The next treatment option for this patient is:

   A. Start Nivolumab 240mg every 2 weeks. Nivolumab has not shown better activity compared to sorafenib in the first line setting.

   B. Start Sorafenib 400mg daily. Sorafenib remains the first line option in HCC.

   C. Strat combination of Sorafenib and nivolumab. This combination has not been tested in clinical trials.

   D. Strat combination of atezolizumab and bevacizumab. The preliminary result of Phase IB of this combination is promising, however, the phase III of the combination vs sorafenib will not be released until 2022.

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Case Study 1

- The patient was started on sorafenib 400 mg daily which he tolerated well beside developing rash and intermittent diarrhea. However, his 9-months restaging scan showed increase size and number of liver lesions consistent with progression of disease.

- Your next step is:

A. Strat nivolumab 240mg every 2 weeks.

B. Start pembrolizumab 200mg every 3 weeks.

C. A or B.

A. Refer the patient to clinical trial.

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Case Study 1

- The patient was started on sorafenib 400 mg daily which he tolerated well beside developing rash and intermittent diarrhea. However, his 9 months restaging scan showed increase size and number of liver lesions consistent with progression of disease.

- Your next step is:

A. Strat nivolumab 240mg every 2 weeks.

B. Start pembrolizumab 200mg every 3 weeks.

C. A or B. Both nivolumab and pembrolizumab have similar activity and are considered second line options in HCC.

D. Refer the patient to clinical trial. This is a possibility, however, this could be offered when patient progresses on nivolumab

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Case Study 1

- The patient was started on nivolumab and had stable disease so far for the past 6 months.

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Case Study 2

Mr. NL is a 55 yo male with h/o liver cirrhosis due to hepatitis C and large HCC liver mass with multiple satellite lesions which was not amendable to surgical resection or liver transplant. He recently developed a progression of disease while on sorafenib. He is Child Pugh A. His AST is 60, ALT 75 and ALP 100. Hepatitis C viral load is 10,000.

The next treatment option for this patient is:

A. Refer the patient to GI to start treatment for hepatitis C before considering treatment with nivolumab.

B. Start TKIs (levatinib or cabozantinib) since PD-1 inhibitors are contraindicated due to hepatitis C.

A. Start TKIs (levatinib or cabozantinib) since PD-1 inhibitors are contraindicated due to elevated LFTs.

B. Start nivolumab 240mg every 2 weeks.

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Case Study 2

Mr. NL is a 55 yo male with h/o liver cirrhosis due to hepatitis C and large HCC liver mass with multiple satellite lesions which was not amendable to surgical resection or liver transplant. He recently developed a progression of disease while on sorafenib. He is Child Pugh A. His AST is 60, ALT 75 and ALP 100. Hepatitis C viral load is 10,000.

The next treatment option for this patient is:

A. Refer the patient to GI to start treatment for hepatitis C before considering treatment with nivolumab. Nivolumab could be started safely in patients with hepatitis C based on Checkmate-240.

B. Start TKIs (levatinib or cabozantinib) since PD-1 inhibitors are contraindicated due to hepatitis C. Nivolumab could be started safely in patients with hepatitis C based on Checkmate-240.

A. Start TKIs (levatinib or cabozantinib) since PD-1 inhibitors are contraindicated due to elevated LFTs. Nivolumab could be started safely in patients with elevated LFTs.

B. Start nivolumab 240mg every 2 weeks. Nivolumab is considered second line in HCC.

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Case Study 2

- The patient was started on nivolumab 240mg every 2 weeks. He returned for a follow up 8 weeks after starting nivolumab. His LFTs were as follow: AST 500, ALT 750 and ALP 110.

- Your next step is:

  A. Hold nivolumab.

  B. Obtain restaging scan.

  C. Continue Nivolumab and obtain restaging scan as planned before the next cycle.

  D. A and B

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Case Study 2

- The patient was started on nivolumab 240mg every 2 weeks. He returned for a follow up 8 weeks after starting nivolumab. His LFTs were as follow: AST 500, ALT 750 and ALP 110.

- Your next step is:

  A. Hold nivolumab. Immune hepatitis is a know adverse event of nivolumab. Therefore treatment should be held.

  B. Obtain restaging scan. Increased LFTs could be due to progression of disease which should be ruled out.

  C. Continue Nivolumab and obtain restaging scan as planned before the next cycle. Both immune hepatitis and progression of disease should be ruled out as above.

  D. A and B

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Case Study 2

The patient underwent a restaging scan and was found to have progression of disease. He eventually deteriorated and was placed on hospice.

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