Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

# Immunotherapy for the Treatment of Microsatellite Instability – High Cancers

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# Disclosures

- None
- I will be discussing non-FDA approved indications during my presentation.

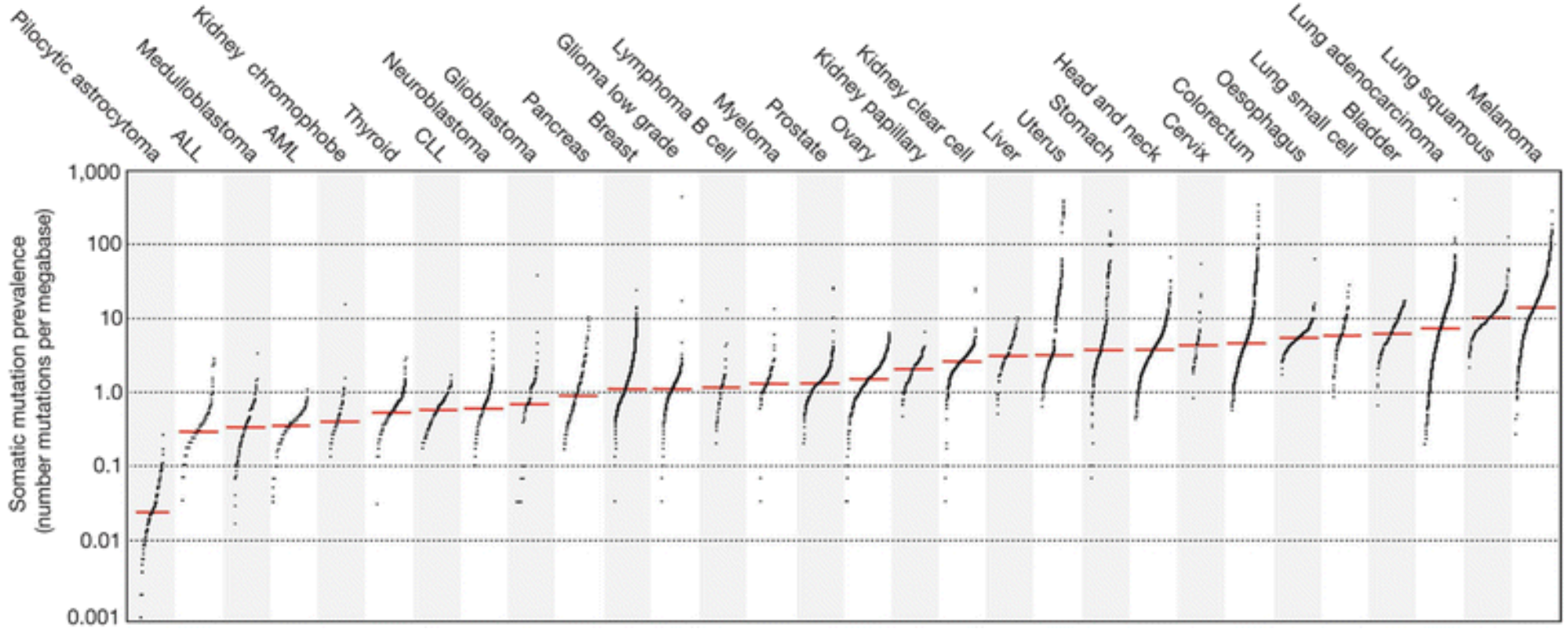
# DNA Mismatch Repair

- The presence of microsatellite instability (MSI) represents phenotypic evidence of mismatch repair (MMR) dysfunction.
- MMR dysfunction can be caused by mutations in genes that code for MMR proteins (MLH1, MSH2, MSH6, PMS2)
- Mutations in MMR proteins can result from:
  - Hereditary causes (Lynch syndrome)
  - Somatic mutations
  - Silencing through promoter methylation

# Microsatellite Instability

- Microsatellites are stretches of DNA with a repetitive sequence of nucleotides and are susceptible to acquiring errors when defective MMR genes are present.
- MSI is a condition in genetic hypermutability
- Increased somatic mutations → increased neoantigen numbers
- Patients with MSI-H tumors responding to immune checkpoint inhibitors develop rapid expansion of neoantigen-specific T cell clones that are reactive to tumor neoantigens
- The 1997 NCI consensus meeting recommended testing a core panel of five microstatellite markers for MSI (BAT25, BAT26, D2S123, D5S346, and D17S250). MSI-high is defined as 2/5 microsatellite markers that are mutated

# Somatic mutations by cancer type

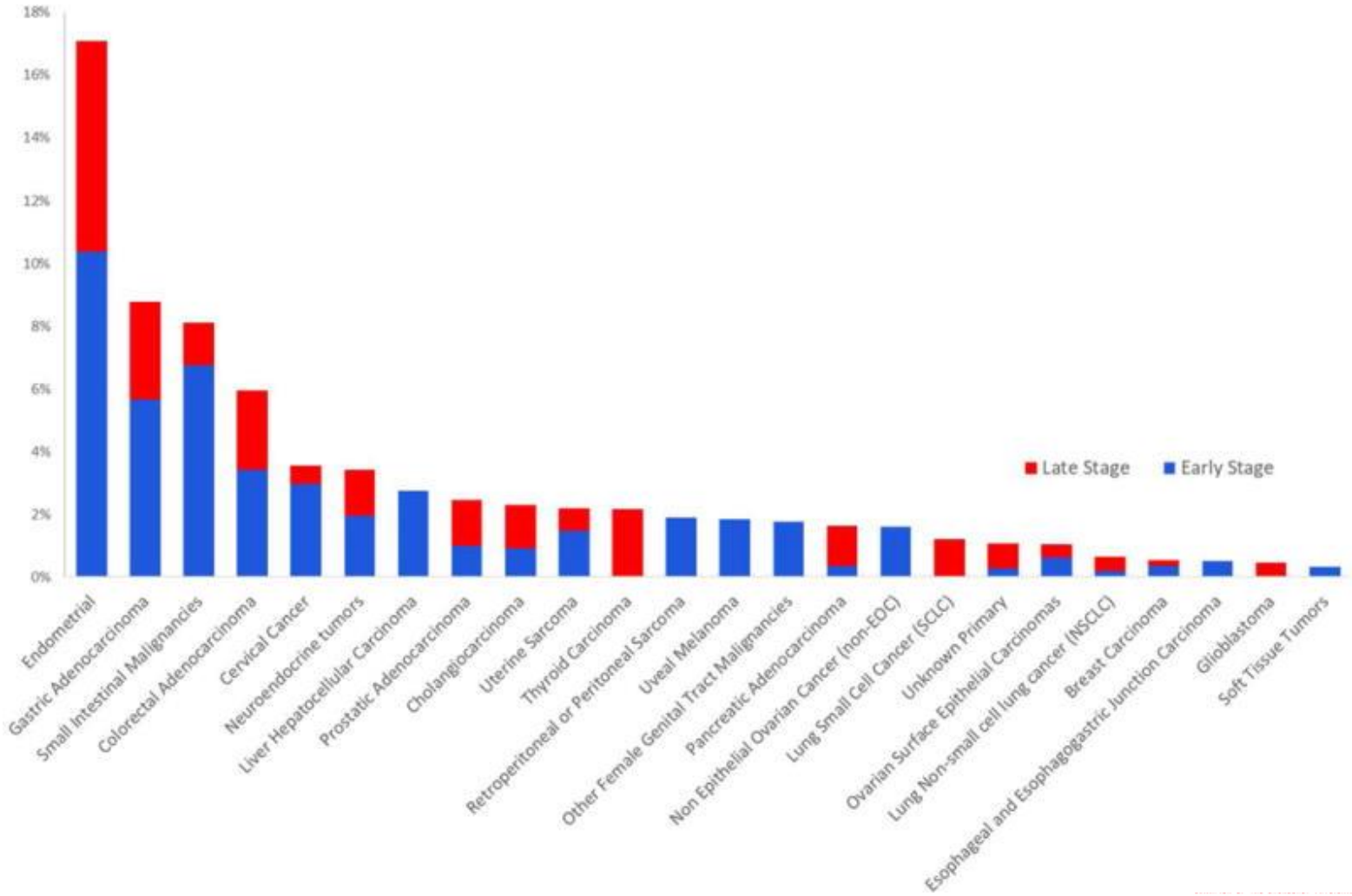



Alexandrov, Nature 2013.

# Many tumors are MSI-high or MMR-deficient

- Endometrial cancer (30%)
- Colorectal/gastric cancer (20%, up to 5% of metastatic patients)
- Genitourinary, breast, thyroid, others (<5%)
- Also share histopathological characteristics, like immune cell infiltration, medullary histology, poorly differentiated
- Prognosis with MSI-H appears to be stage-specific
  - Localized, surgically-resected is favorable
  - Metastatic = not favorable

# Many tumors are MSI-high or MMR-deficient



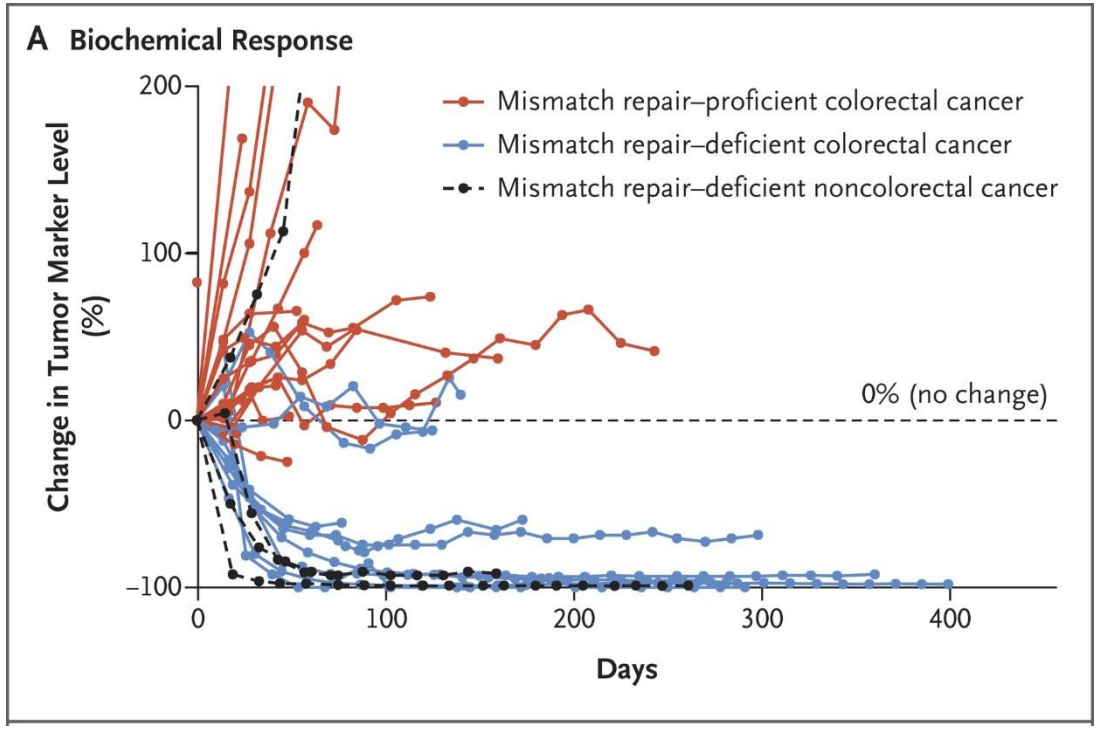

Le, Science 2017.

# FDA-approved immunotherapies for MSI-high populations

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Pembrolizumab | 2017 | Adult/pediatric patients with unresectable/metastatic **MSI-H or dMMR solid tumors** with progression on other treatment<br>**MSI-H or dMMR colorectal cancer** with progression after a fluoropyrimidine, oxaplatin, and irinotecan | Adults: 200 mg Q3W<br>Pediatric: 2 mg/kg (up to 200 mg) Q3W |
| Nivolumab | 2017 | Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaplatin, and irinotecan | ≥40 kg: 240 mg Q2W or 480 mg Q4W<br><40 kg: 3 mg/kg Q2W |
| Ipilimumab + nivolumab | 2018 | Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaplatin, and irinotecan | ≥40 kg: 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W for 4 doses,<br>Then nivolumab 240 mg Q2W or 480 mg Q4W |

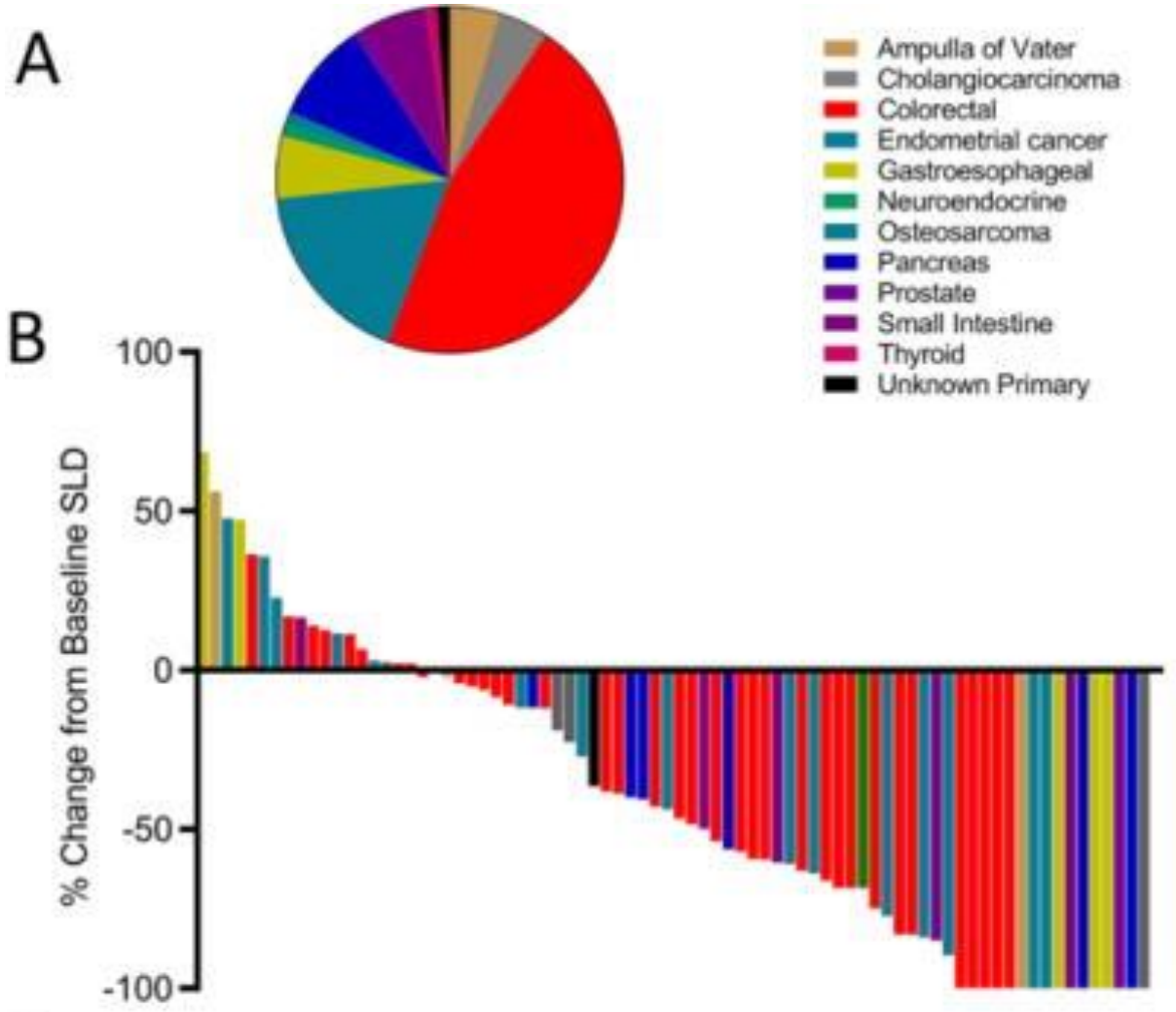
# Clinical Data – pembrolizumab studies

- KEYNOTE-016: CRC only
  - no CR in MMR-proficient, 40% in dMMR
- KEYNOTE-164 and 158
  - ORR:
    - 27.9% for MSI-H CRC
    - 37.7% for MSI-H non-CRC
  - At 6 months OS:
    - 87% CRC
    - 73% non-CRC




Le, NEJM 2015.

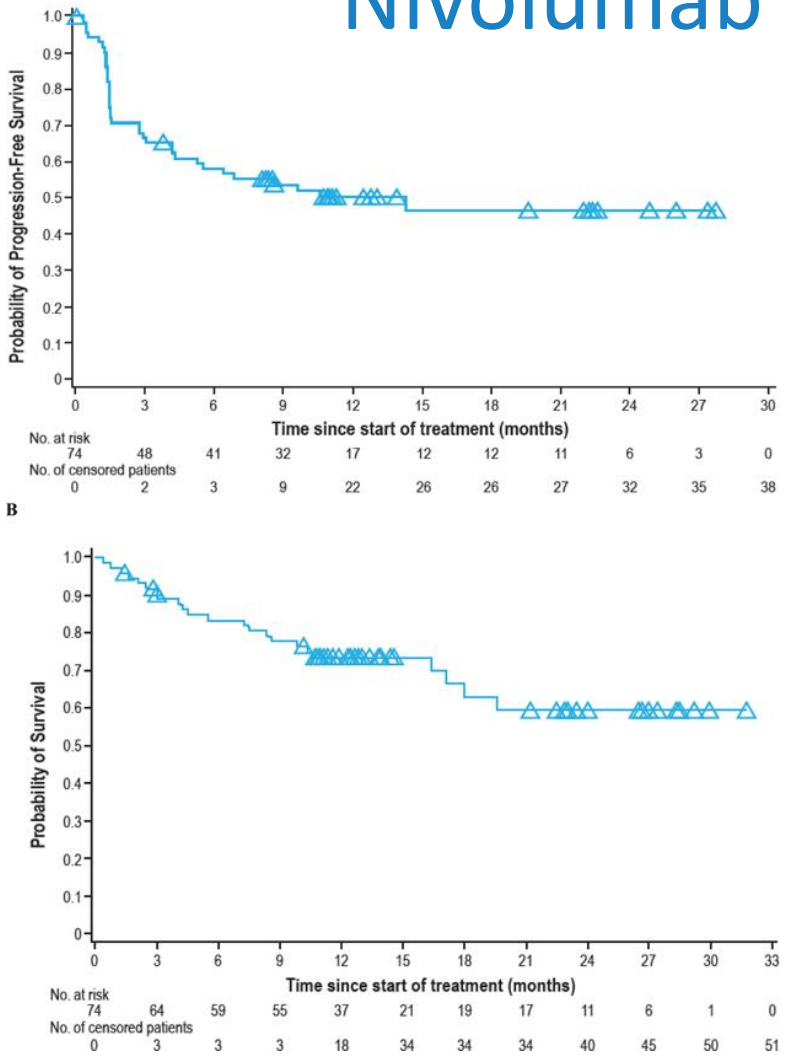
# Clinical Data – pembrolizumab studies




- NCT01876511
- 12 cancer types with dMMR
- ORR: 53%
- CR: 21%

Le, Science 2017.

# Clinical Data – CheckMate 142
## Nivolumab monotherapy



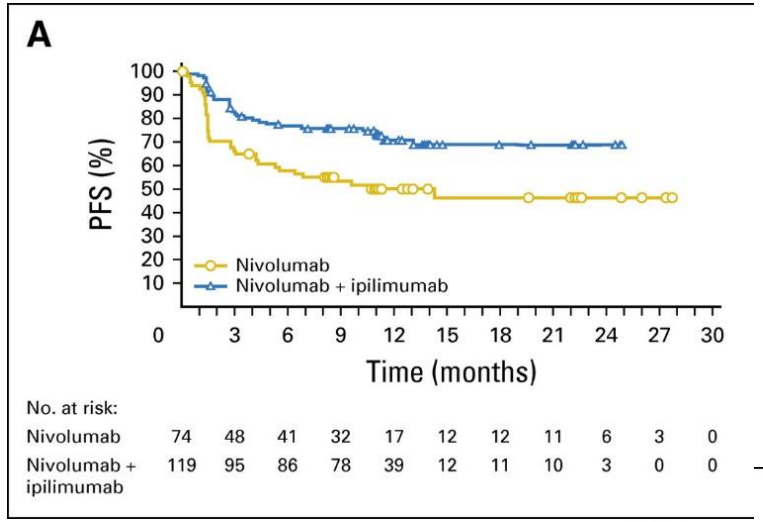

- mCRC with MSI-H, progressed after ≥1 therapy
- Nivolumab 3 mg/kg Q2W
- At 12 months: 31% ORR
- 68.9% disease control >12 weeks
- Median DOR not reached

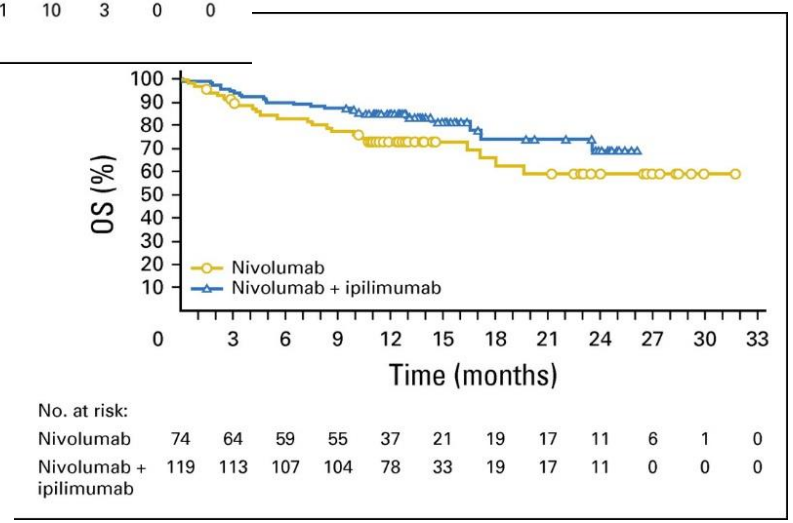
Overman, Lancet Oncol 2017.

# Clinical Data – CheckMate 142

## Nivolumab + Ipilimumab

- MSI-H/dMMR mCRC
- Nivolumab 3mg/kg + ipilimumab 1 mg/kg Q3W (4 doses), then nivolumab 3 mg/kg Q2W
- At 13.4 months: 55% ORR
- PFS: 76% (9 months); 71% (12 months)




Overman, J Clin Oncol 2018.

# In development for MSI-high

- Potential for immunotherapy to impact new disease states
  - Prostate (~3%), pancreatic (~1%)
- Other tissue-agnostic markers:
  - Microbiome
  - POLE mutation
  - Mutational signatures beyond TMB

# Resistance in MSI-H tumors

- Loss of β2 Microglobulin, a critical component of the antigen presentation machinery and MHC class I expression.
  - Gurjao C, Liu D, Hofree M, et al. Intrinsic Resistance to Immune Checkpoint Blockade in a Mismatch Repair Deficient Colorectal Cancer. Cancer Immunol Res. 2019 Jun 19. pii: canimm.0683.2018. doi: 10.1158/2326-6066.CIR-18-0683. [Epub ahead of print]
- Other mechanisms are similar to causes of resistance to ICI in any cancer type

# Future Directions

- No standard companion diagnostic test yet approved – subjectivity of interpreting results; lack of consistency
- Not every clinic has access to these resources for measuring MSI/MMR (PCR, IHC, NGS) – may limit who can use the treatment
- Laid the groundwork for future biomarker-related drug approvals

# References for T-cell clonality


- Fehlings M, Simoni Y, Penny HL, Becht E, Loh CY, Gubin MM, Ward JP, Wong SC, Schreiber RD, Newell EW. Checkpoint blockade immunotherapy reshapes the high-dimensional phenotypic heterogeneity of murine intratumoural neoantigen-specific CD8+ T cells. Nat Commun. 2017 Sep 15;8(1):562. doi: 10.1038/s41467-017-00627-z.
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- Riaz N, Havel JJ, Makarov V, et al. Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab. Cell. 2017 Nov 2;171(4):934-949.e16. doi: 10.1016/j.cell.2017.09.028. Epub 2017 Oct 12.
- van Rooij N, van Buuren MM, Philips D, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol. 2013 Nov 10;31(32):e439-42. doi: 10.1200/JCO.2012.47.7521. Epub 2013 Sep 16.

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# Immunotherapy for the Treatment of Hepatocellular Carcinoma

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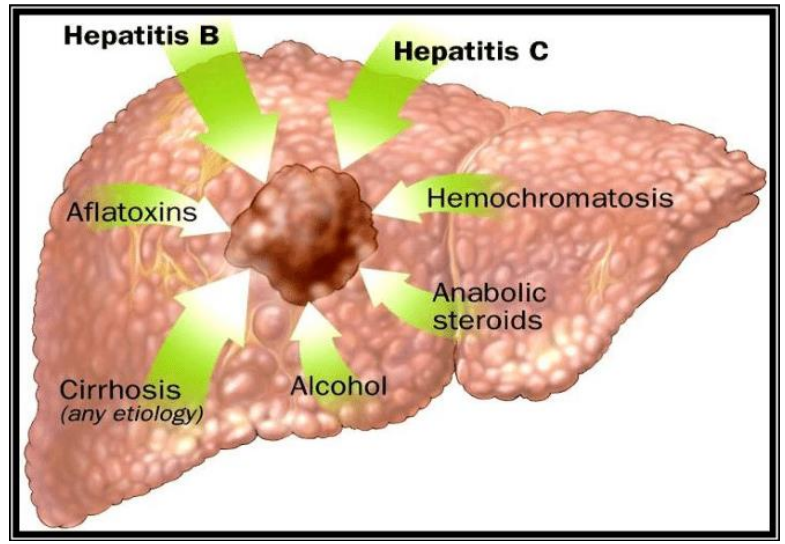
# Background

- HCC is the most common type of primary liver cancer
- Often associated with cirrhosis (HBV or HCV, NASH, 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

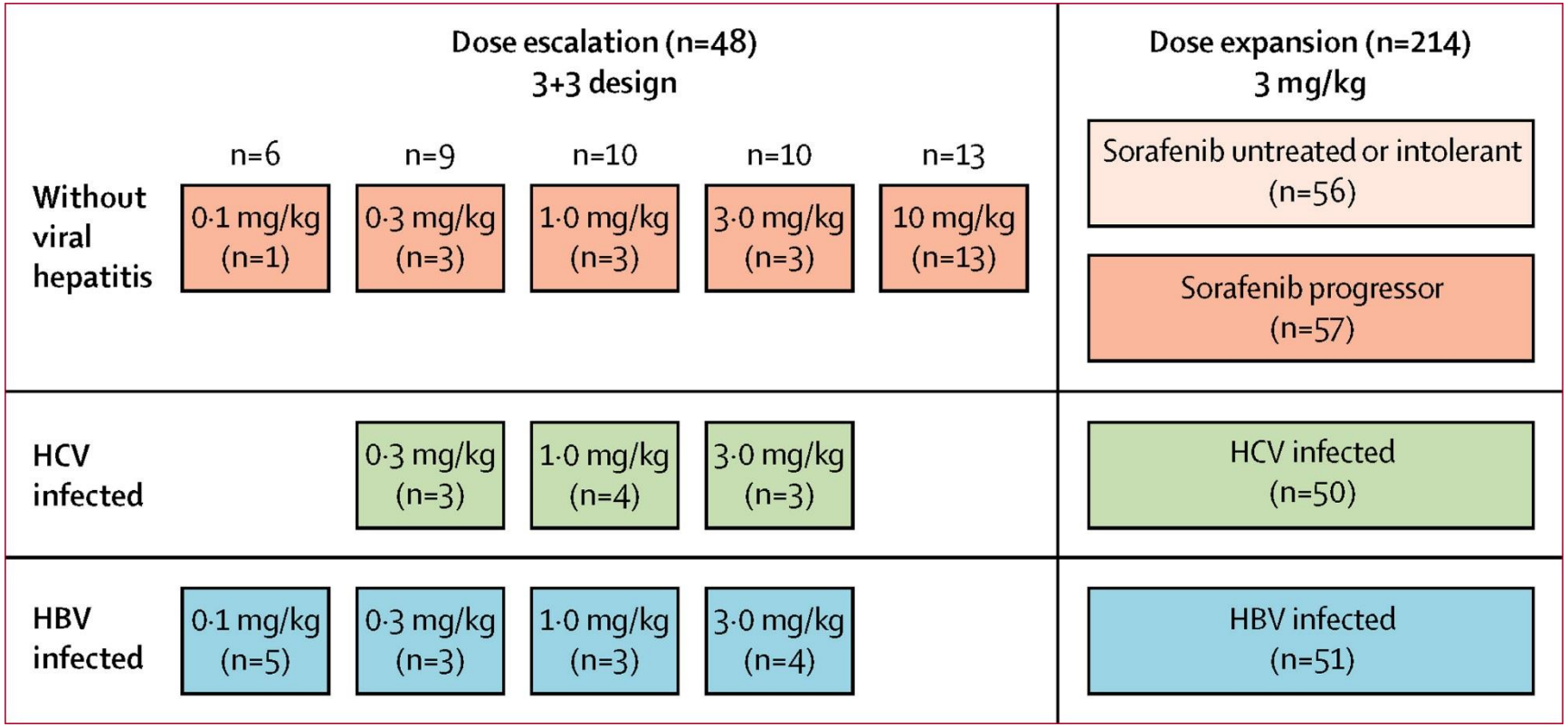
- Checkpoint  inhibition
- Blocking inhibitory cytokines
- Vaccine therapies
- Oncolytic viruses
- Adoptive cell therapy

# 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

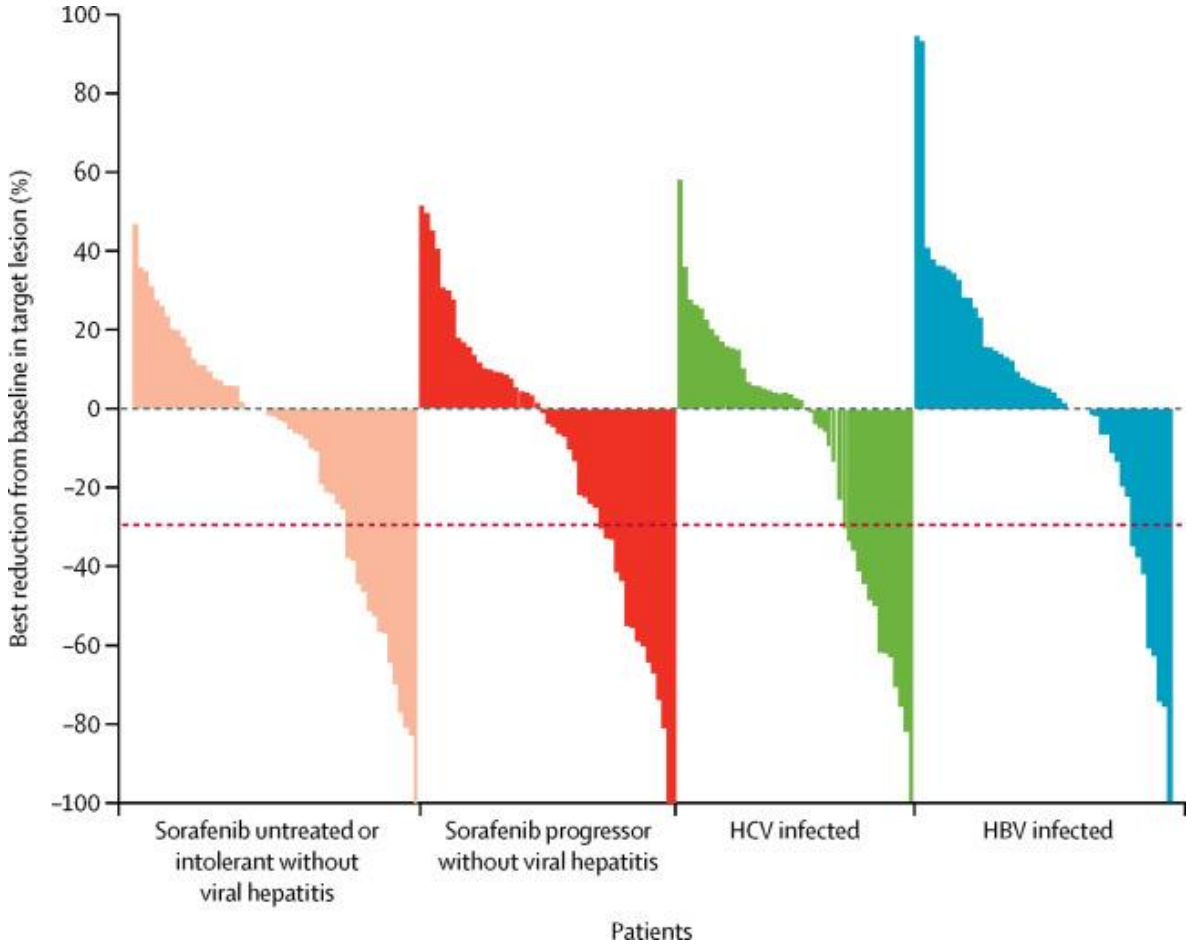
- Phase I/II open label study
- Child-Pugh A or B7, advanced HCC
- Previous sorafenib allowed
- Safety/tolerability for escalation; ORR for expansion




El-Khoueiry, The Lancet 2017.

# CheckMate 040

- 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.

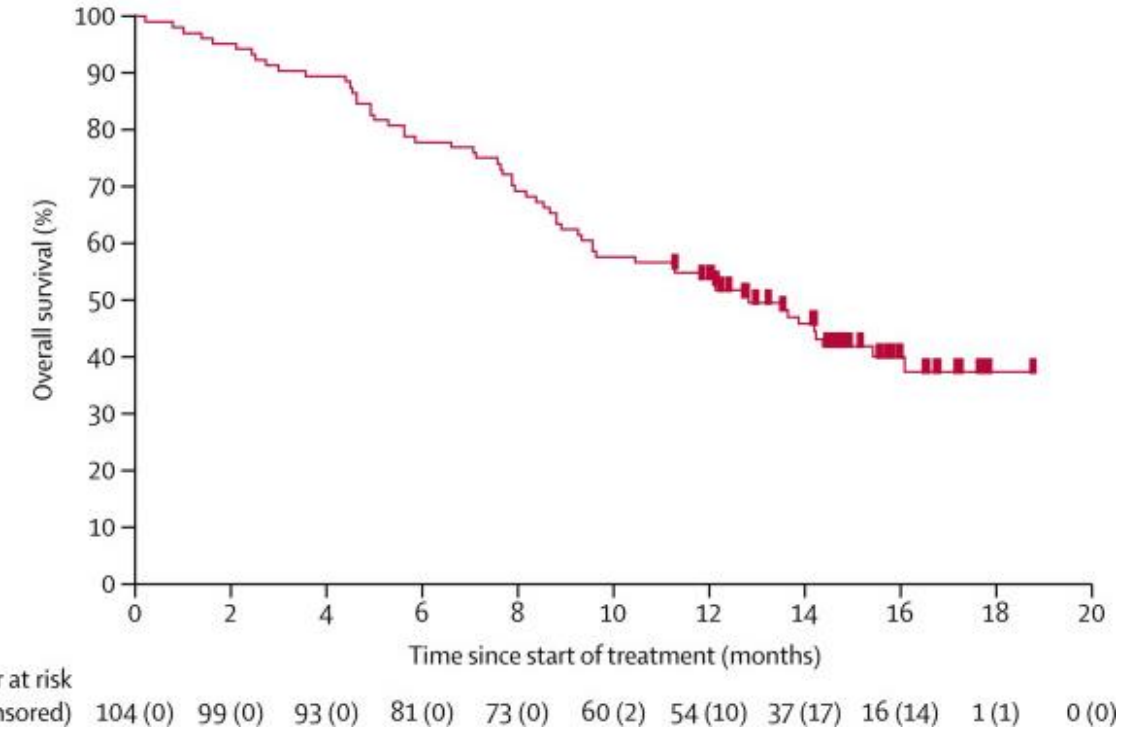
# KEYNOTE-224

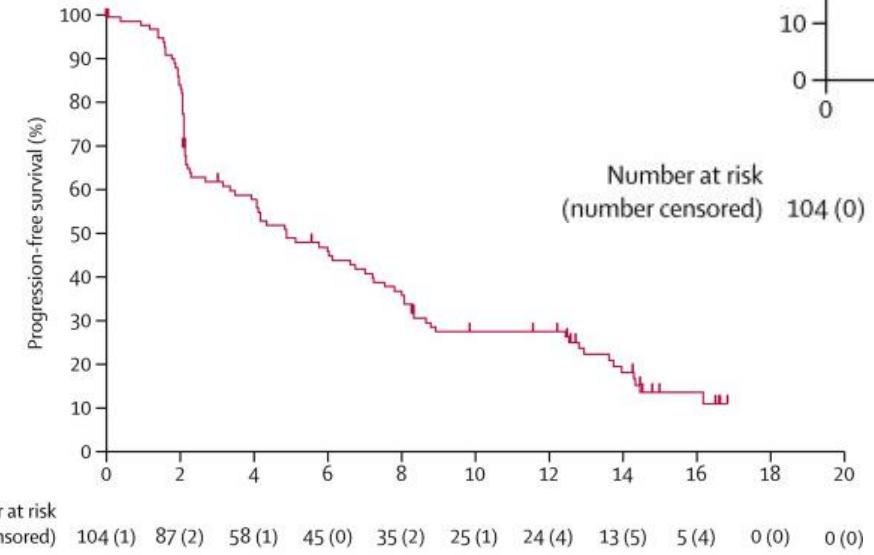
- Phase 2 non-randomized trial
- Previously treated with sorafenib
- Child-Pugh class A
- Pembrolizumab IV 200 mg Q3W
- Primary endpoint: objective response
- 104 patients enrolled and treated

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.

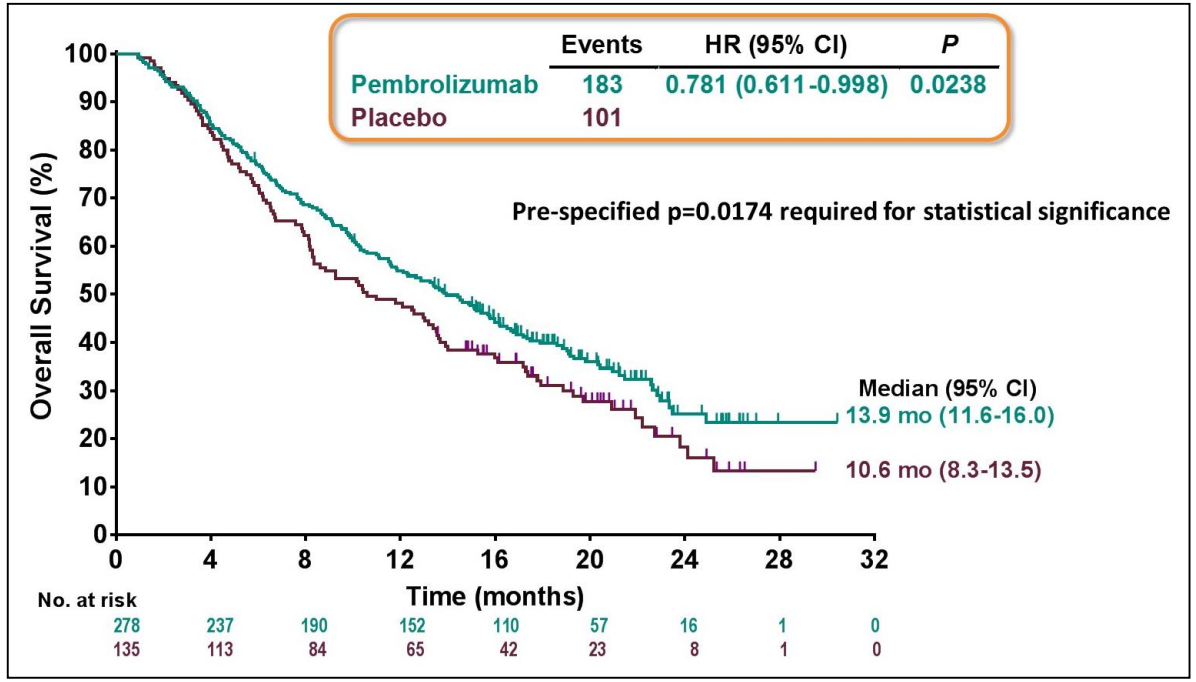
# KEYNOTE-240

- 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

# **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 + bevacizumab/IMbrave150

- Media release: Atezolizumab/Bevacizumab improved OS and PFS in patients with unresectable liver cancer (October 21, 2019)
- No new safety signals
- Further data to be presented at upcoming major medical meeting

# Nivolumab vs Sorafenib as First-line Therapy for Advanced HCC (CheckMate 459)

- International, open-label, randomized phase III trial (minimum follow-up: 22.8 mos)

*Stratified by etiology, vascular invasion and/or hepatic spread, geography*

Adults with histologically confirmed advanced HCC; ineligible for or PD after surgical and/or locoregional therapies; Child-Pugh class A; ECOG PS 0/1; no prior systemic therapy for HCC; no prior liver transplant; no known fibrolamellar or sarcomatoid HCC or mixed cholangiocarcinoma and HCC; no autoimmune disease
(N = 743)

**Nivolumab** 240 mg IV Q2W
(n = 371)

**Sorafenib** 400 mg PO BID
(n = 372)

***Until PD, unacceptable toxicity, consent withdrawal, or end of study***

- Primary endpoint: OS
  - Predefined threshold for statistical significance: HR of 0.84 (*P* = .0419)
- Secondary endpoints: PFS, ORR, association between PD-L1 expression and efficacy

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

Slide credit: clinicaloptions.com

# CheckMate 459: Conclusions

- In this randomized phase III trial, first-line treatment with nivolumab did not demonstrate significantly improved OS vs sorafenib in patients with advanced HCC, but investigators note longer OS with nivolumab
  - Median OS: nivolumab, 16.4 mos; sorafenib, 14.7 mos (HR: 0.85; 95% CI: 0.72-1.02; *P* = .0752)
  - Median OS prolonged with nivolumab vs sorafenib in those with PD-L1 ≥ 1% (16.1 vs 8.6 mos, respectively)
- ORR favored nivolumab vs sorafenib (15% vs 7%; odds ratio: 2.41; 95% CI: 1.48-3.92)
  - ORR higher in those with PD-L1 ≥ 1% (28% vs 9%)
- No new safety signals observed with nivolumab, which was associated with lower rates of grade 3/4 TRAEs and related discontinuations
- Improved QoL was reported using FACT-Hep QoL scores
- Investigators concluded that first-line treatment with nivolumab demonstrated clinically meaningful improvement in survival and response, along with a favorable safety profile, in advanced HCC

Yau. ESMO 2019. Abstr LBA38_PR.

# Phase III Trials of Checkpoint Inhibitors

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

Johnston, World J Gastroenterology 2019.

# Blocking Inhibitory Cytokines

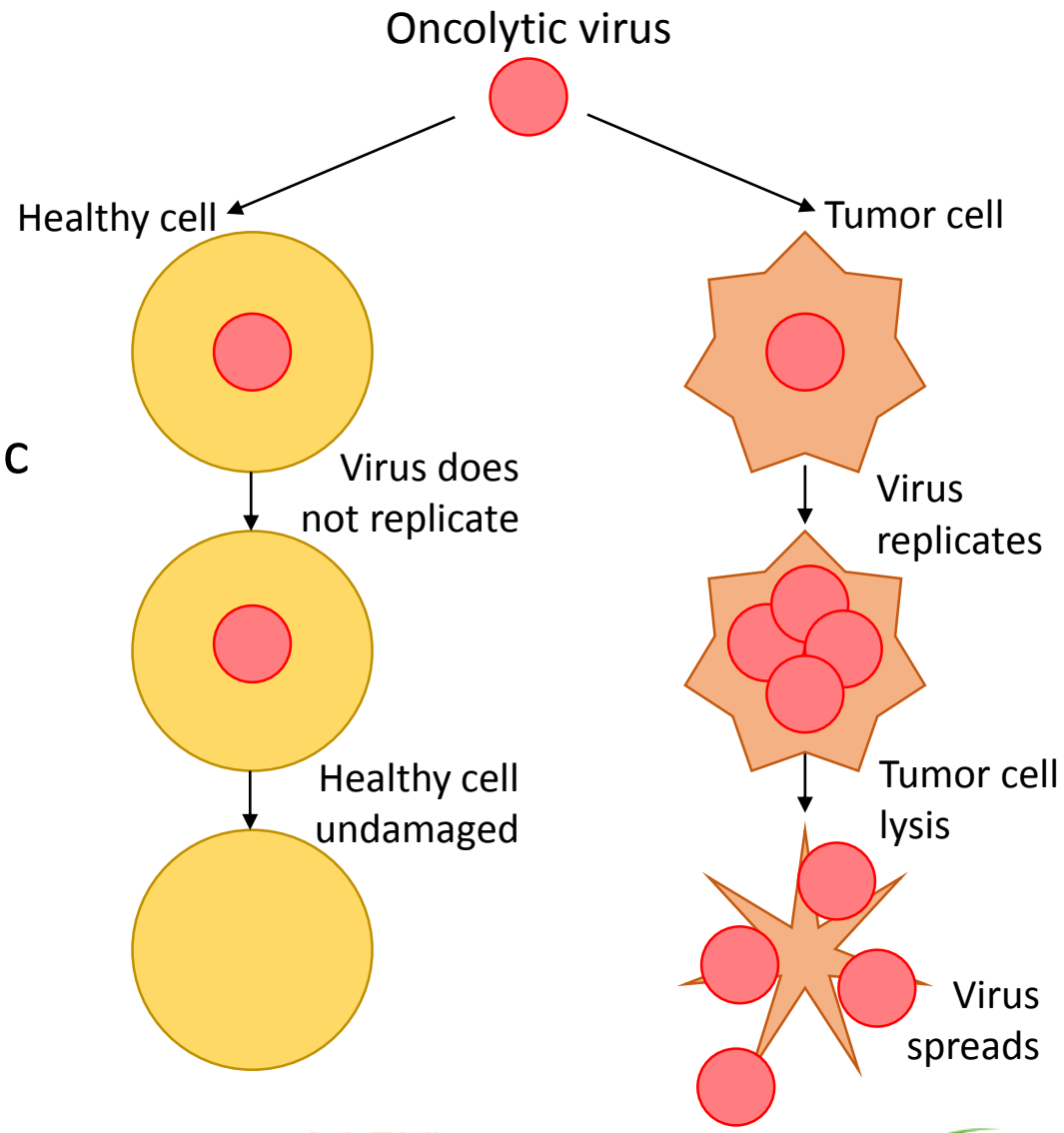
- TGF-β: a molecule that suppresses CD4+ T cell response in tumor cells thereby promoting progression of disease.
  - NCT02947165; A Phase I/Ib, Open-label, Multi-center Dose Escalation Study of NIS793 in Combination With PDR001 in Adult Patients With Advanced Malignancies
- LAG-3: a membrane protein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

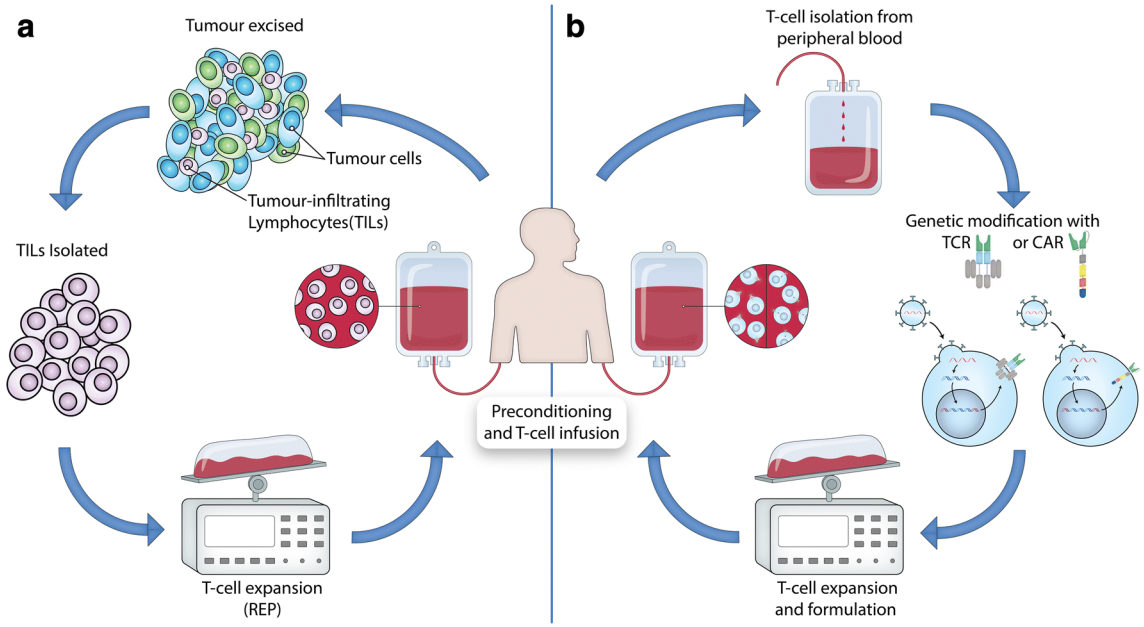
# Oncolytic Viruses

- 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

- A 62-year-old gentleman with a history of nonalcoholic steatohepatitis with cirrhosis is diagnosed with multifocal hepatocellular carcinoma with the largest liver lesion 7 cm in size. He has progressed after local regional therapy with Y 90 embolization and most recently received systemic therapy with sorafenib. He has started Nivolumab 2 weeks ago, and presented to the office today with intractable diarrhea, noticing up to 7 loose bowel movements per day and is found to be orthostatic.
- Based on these findings you recommend:

  A. Loperamide and a one week delay in treatment

  B. Dose reduction of Nivolumab without interruption in treatment

  C. Prednisone 1 mg/kg/day followed by colonoscopy

  D. Metronidazole

# Case Study 1

- He does have he continues to have significant diarrhea for 4 more days and remains hospitalized receiving IV hydration. His bowels are moving up to 8 times per day. Colonoscopy suggests a colitis on the basis of Nivolumab. The next medication in his management should be:
  - A. Pembrolizumab
  - B. Infliximab
  - C. Rituximab
  - D. Ipilimumab

# Case Study 1

- Six weeks after initiating Infliximab, he has normal bowel function and has completed his corticosteroids. PS is 1 and he desires further therapy. You recommend:
  - A. Nivolumab with 50% dose reduction
  - B. Pembrolizumab 200 mg
  - C. Regorafenib 160 mg daily
  - D. Hospice

# Case Study 2

- A 53-year-old gentleman underwent his first colonoscopy after learning that his 45-year-old sister was diagnosed with colon cancer. He was found to have a right colon mass that was a high-grade adenocarcinoma. He had no other medical problems and his staging work-up was negative. He underwent a right hemicolectomy and was found to have a T3 N1a M0 stage IIIB colon cancer. He was found on immunohistochemistry to have an MSI high tumor consistent with a inherited susceptibility. Neither he nor his sister have yet to have genetic testing performed. You recommend:

  **A. Observation**

  **B. Capecitabine**

  **C. FOLFOX**

  **D. Nivolumab**

# Case Study 2

- Because of neuropathy he discontinued therapy after 8 cycles of treatment. He did not return for intended assessments. Approximately 18 months later he was seen in the emergency room with abdominal pain and was found to have multiple bi-lobar liver metastases as well as retroperitoneal adenopathy. CT of the chest showed no disease above the diaphragm. His performance status is 1. A liver biopsy confirms that this is metastatic colorectal cancer. His tumor is mutated for K-RAS. Outside of a clinical trial, you recommend:

  A. FOLFOX with Panitumumab

  B. FOLFIRI with bevacizumab

  C. Pembrolizumab

  D. Nivolumab and ipilimumab

# Case Study 2

- He had several months of symptomatic improvement but about 4 months into treatment he noticed increasing right upper quadrant pain. On imaging he had multiple new liver metastases and several small lung nodules. He had no symptomatic toxicity of treatment. His liver function test were within normal limits and there remains grade 1 neuropathy from the prior adjuvant oxaliplatin. He desires further treatment Outside of a clinical trial, you recommend:

  A. Evaluation by interventional radiology for local regional therapy.

  B. Regorafenib

  C. Nivolumab and ipilimumab

  D. Referral for hospice