Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Gastrointestinal Cancers

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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

sitc Society for Immunotherapy of Cancer

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Disclosures

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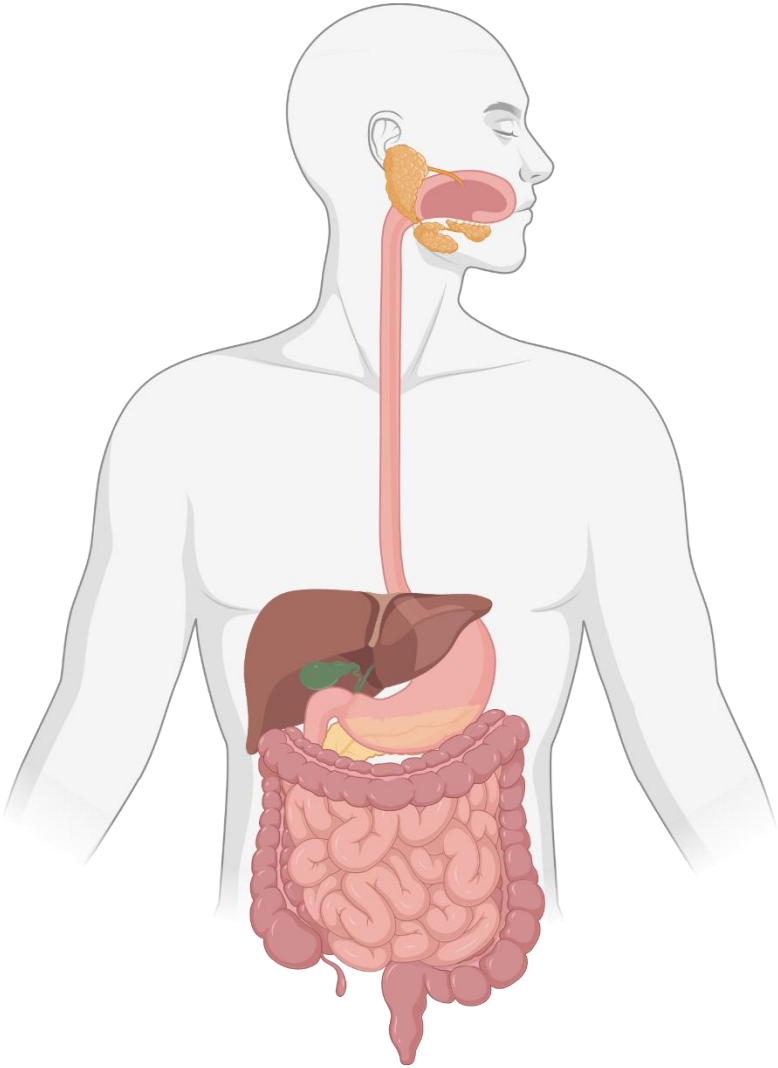
  - Consulting Fees: Genentech, AstraZeneca, Bristol Myers Squibb, Erytech, Exelixis
  - Contracted Research: Boston Biomedical Inc., Merck, Bristol Myers Squibb, IQVIA RDS Inc., Bayer, Novartis, Medimmune, Adaptimmune, Pfizer, Hoosier Cancer Research Network
- I will not be discussing non-FDA approved indications during my presentation.

Outline

- MSI High Tumors
- Hepatocellular carcinoma
- Other GI malignancies

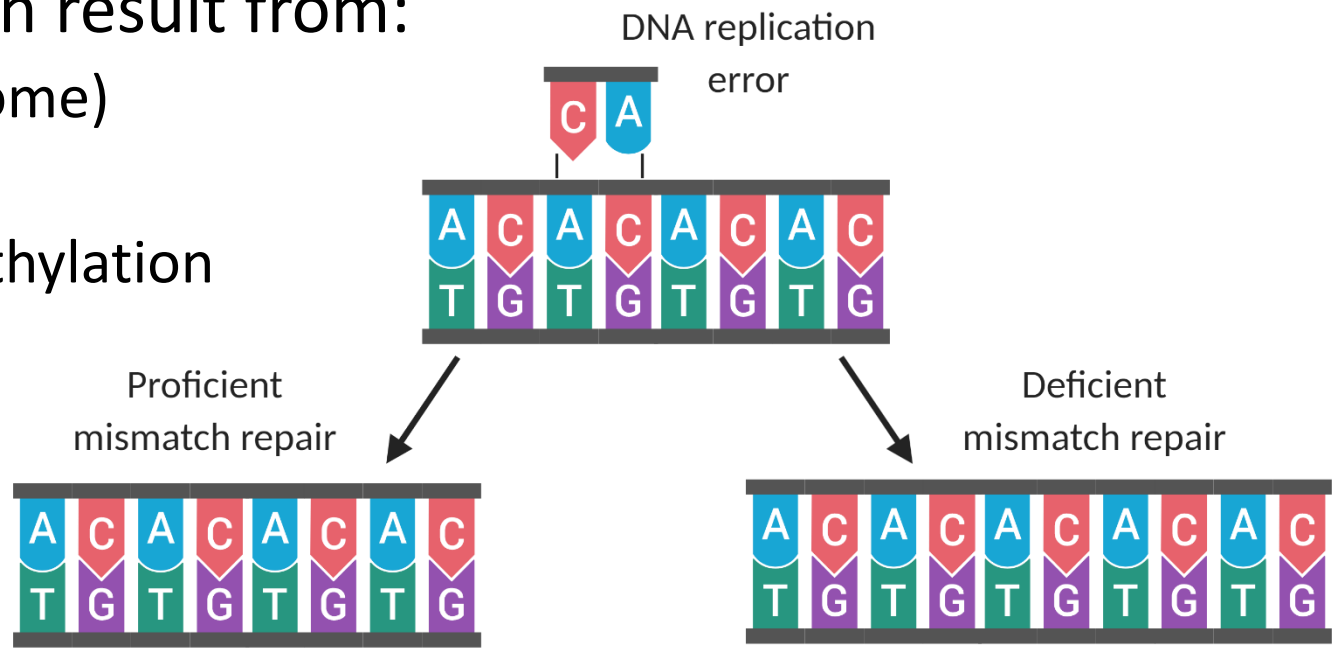


A few definitions

- **DNA mismatch repair deficiency:** Sub-optimal cell machinery for fixing mistakes made during DNA replication.
- **Tumor mutational burden:** The number of mutations in a cancer's genome.
- **Microsatellite instability:** The number of repeated DNA bases in a microsatellite changes during DNA copying. The presence of MSI is phenotypic evidence that DNA mismatch repair is not functioning properly.

DNA mismatch repair

- 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



Somatic mutation: *an alteration in DNA that occurs after birth; can occur in any non-germline cell*

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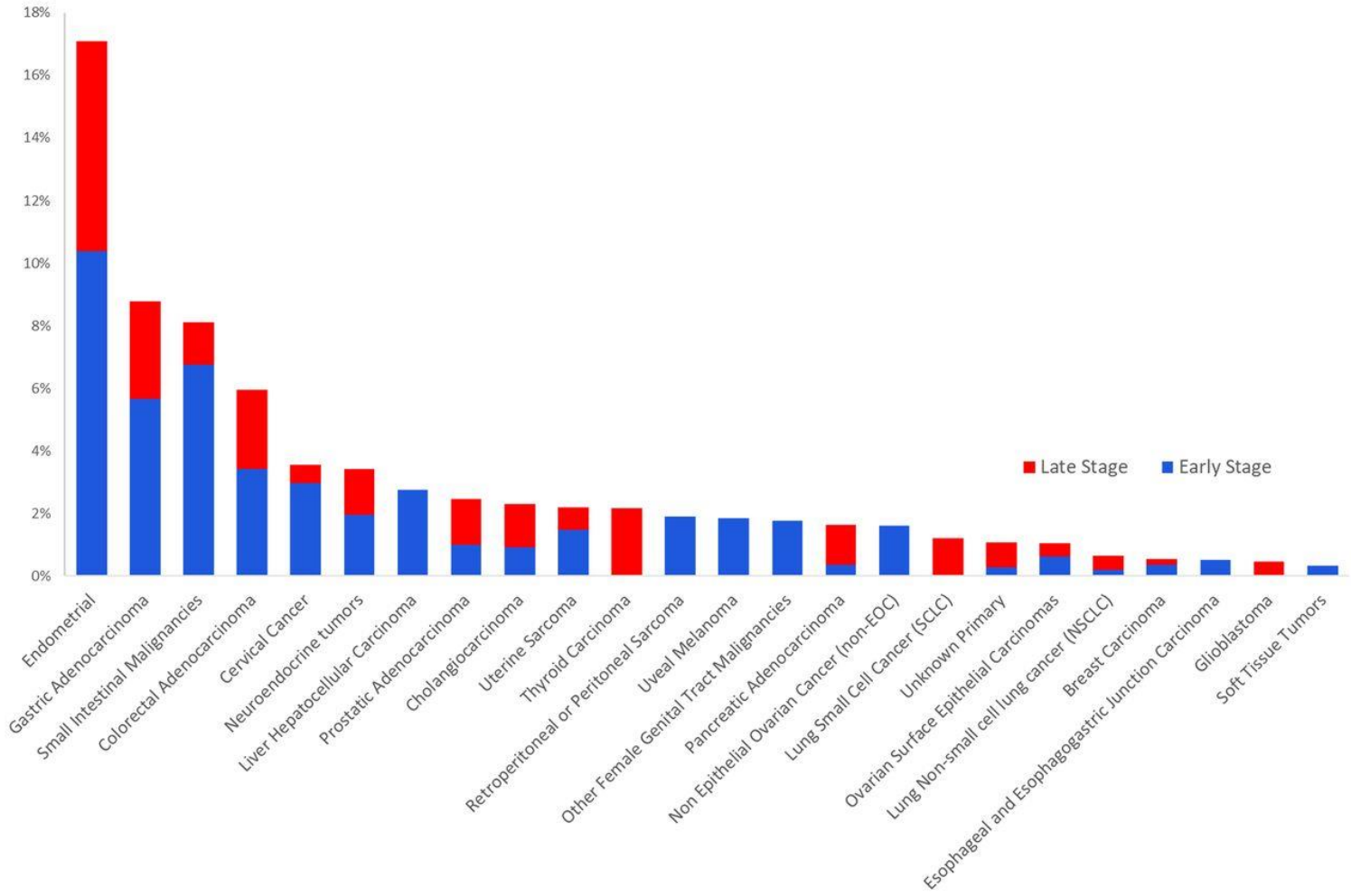
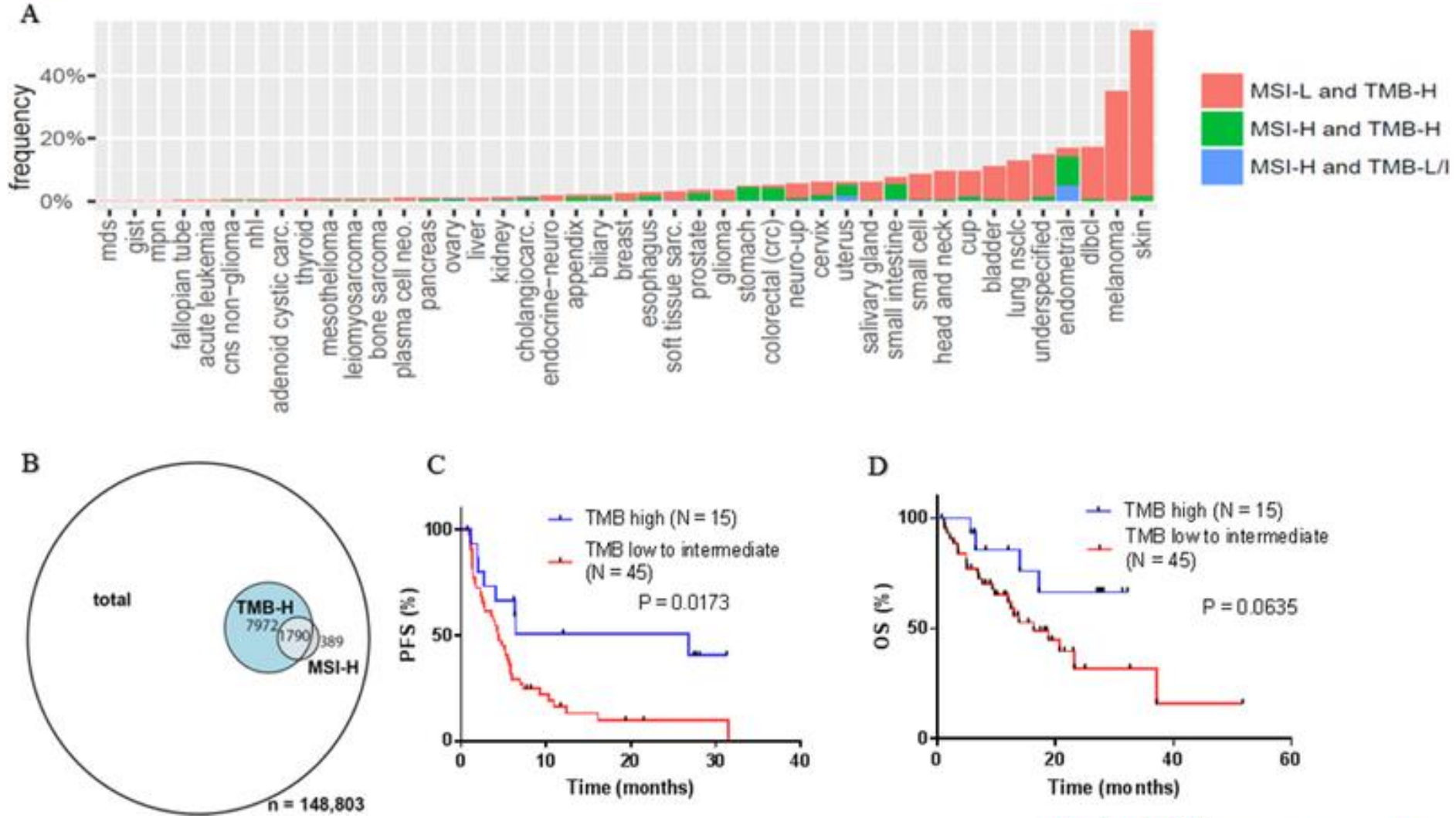
Many tumors are MSI-high or MMR-deficient



Le, Science 2017.

Relationship between TMB and MSI



Goodman, Cancer Immunol Res 2019.

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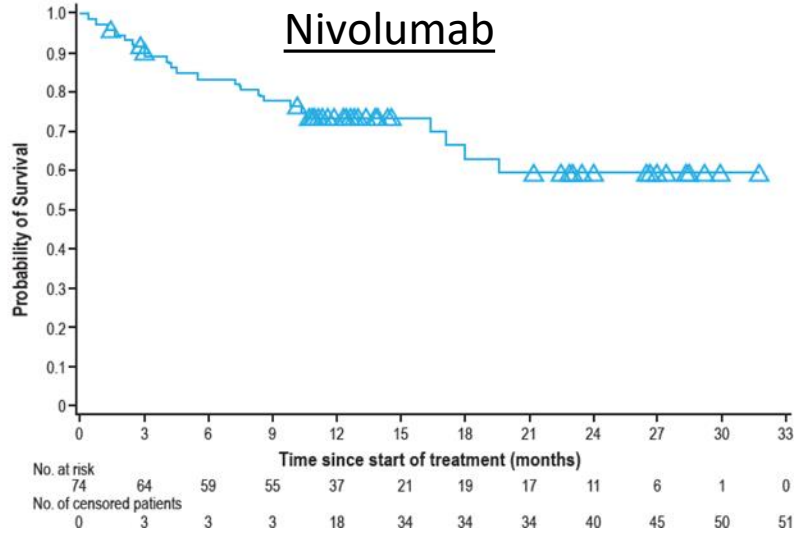
FDA-approved immunotherapies for MSI-high or TMB-high populations

	Drug	Indication	Dose
Tissue-agnostic	Pembrolizumab	Adult/pediatric patients with unresectable/metastatic **MSI-H or dMMR solid tumors** with progression on other treatment	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W
	Pembrolizumab	Adult/pediatric patients with unresectable/metastatic **TMB-high solid tumors** with progression on other treatment	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Colorectal cancer	Nivolumab	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaliplatin, and irinotecan	≥40 kg: 240 mg Q2W or 480 mg Q4W <40 kg: 3 mg/kg Q2W
	Ipilimumab + nivolumab	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaliplatin, and irinotecan	≥40 kg: 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W for 4 doses, Then nivolumab 240 mg Q2W or 480 mg Q4W
	Pembrolizumab	**MSI-H or dMMR colorectal cancer** with progression after fluoropyrimidine, oxaliplatin, and irinotecan Or First-line treatment of **MSI-H or dMMR colorectal cancer**	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W

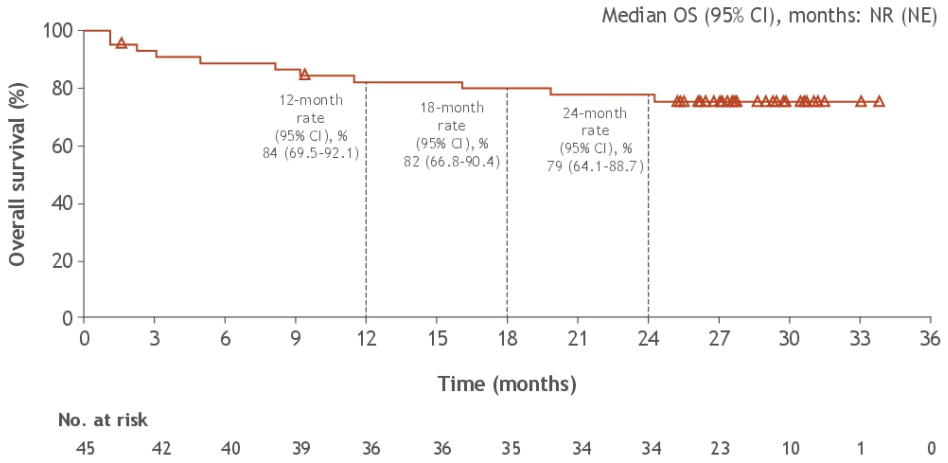
Efficacy of approved ICIs in CRC

Trial	Patient population	Treatment arm(s)	ORR	Landmark PFS	Landmark OS
CheckMate 142	MSI-H/dMMR CRC with progression on prior treatment	Nivolumab	31.1%	12-month: 50.4%	12-month: 73.4%
	MSI-H/dMMR CRC with progression on prior treatment	Nivolumab + ipilimumab	58%	24-month: 60%	24-month: 74%

Nivolumab



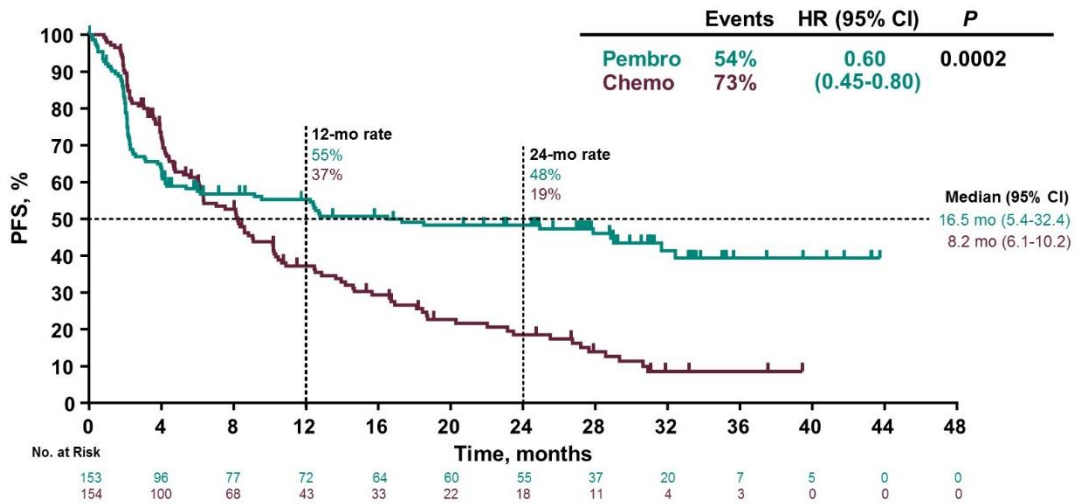
Nivolumab + ipilimumab

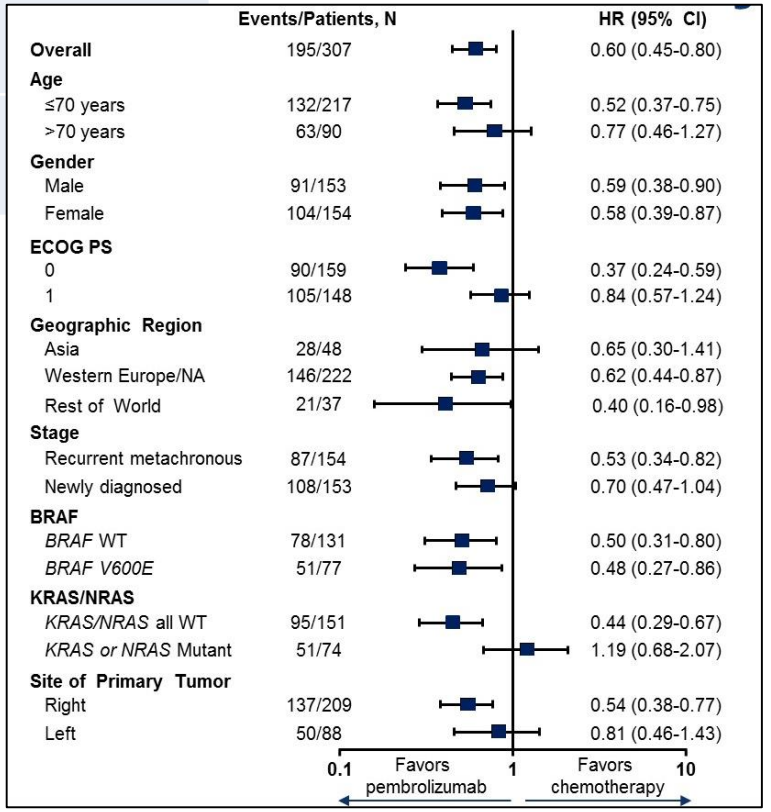


Andre, ASCO 2020; Overman, Lancet Oncol 2017; Overman, ASCO-GI 2019.

Efficacy of approved ICIs in CRC

Trial	Patient population	Treatment arm(s)	ORR	Landmark PFS	Landmark OS
KEYNOTE-177	Untreated, unresectable/metastatic MSI-H/dMMR CRC	Pembrolizumab	43.8 %	Median: 16.5 months	-
		Investigator's choice	33.1 %	Median: 8.2 months	-





Andre, ASCO 2020; Overman, Lancet Oncol 2017; Overman, ASCO-GI 2019.

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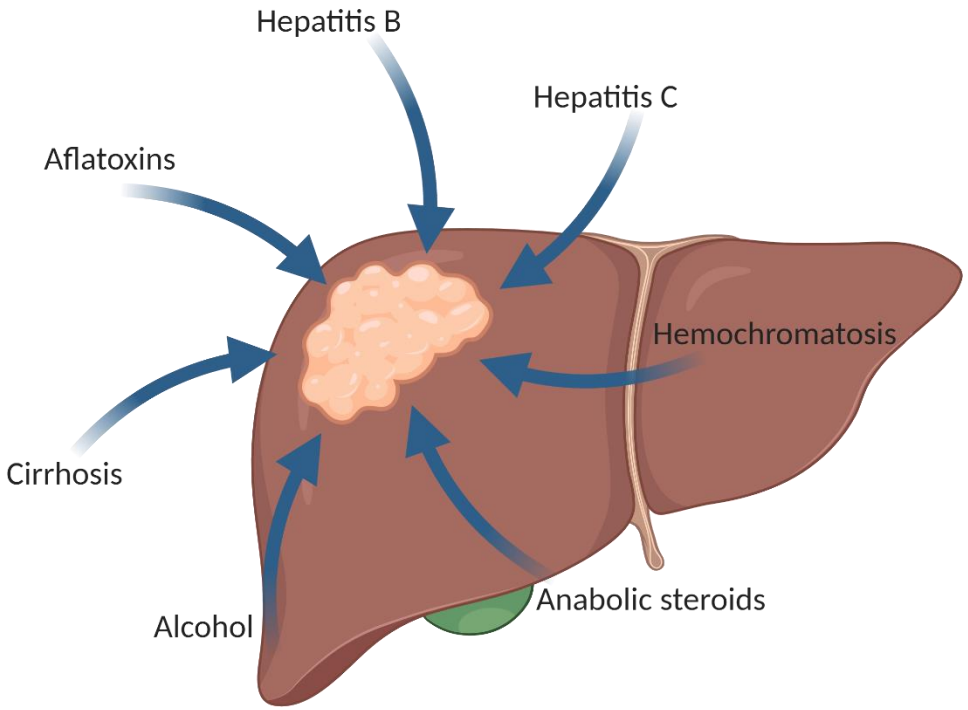
Hepatocellular carcinoma

- HCC is the most common type of primary liver cancer
- 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/RFA – there's a need for systemic therapies in HCC



Approved checkpoint inhibitors for HCC

Drug	Approved	Indication	Dose
Nivolumab	2017	Second line	240 mg Q2W or 480 mg Q4W
Pembrolizumab	2018	Second line	200 mg Q3W or 400 mg Q6W
Nivolumab + ipilimumab	2020	Second line	Nivo 1 mg/kg + Ipi 3 mg/kg for 4 doses, then nivo maintenance
Atezolizumab + bevacizumab	2020	First line	Atezolizumab 1200 mg Q3W + bevacizumab 15 mg/kg Q3W

Efficacy of ICIs in sorafenib-experienced HCC

Study	Patient population	Treatment arm(s)	ORR	Landmark OS
CheckMate 040	Advanced HCC with previous sorafenib	Nivolumab	20%	9-month: 74%
		Nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W	32%	24-month: 48%
		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W	31%	24-month: 30%
		Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W	31%	24-month: 42%
KEYNOTE-240	Advanced HCC with previous sorafenib	Pembrolizumab + BSC	18.3%	Median: 13.9 months
		Placebo + BSC	4.4%	Median: 10.6 months
Study 22	Advanced HCC with previous sorafenib	Durvalumab	10.6	Median: 13.57 months
		Tremelimumab	7.2	Median: 15.11 months
		Tremelimumab (300 mg x 1) + durvalumab 1500 mg Q4W	24.0	Median: 18.73 months
		Tremelimumab (75 mg x 4) + durvalumab 1500 mg Q4W	9.5	Median: 11.30 months

Yau, ESMO 2019; El-Khoueiry, Lancet 2017; Finn, J Clin Oncol 2020; Yau, ASCO 2019; Finn, N Engl J Med 2020; Kelley ASCO 2020.

Efficacy of ICIs in untreated HCC

Study	Patient population	Treatment arm(s)	ORR	Landmark OS
CheckMate 459	Advanced, untreated HCC	Nivolumab	57%	Median: 16.4 months
		Sorafenib	26%	Median: 14.7 months
IMbrave150	Unresectable, untreated HCC	Atezolizumab + bevacizumab	-	12-month: 67.2%
		Sorafenib	-	12-month: 54.6%

In development: Other immunotherapy strategies for HCC

- Combinations with existing immune checkpoint inhibitors
- Alternative immune checkpoints
- Cellular therapies

In development: Selected phase III trials of checkpoint inhibitors

Trial ID	Targets	Drug arms	Status	N	Estimated completion
NCT03794440 (ORIENT-32)	PD-1, VEGF	• Sintilimab + bevacizumab biosimilar • Sorafenib	Active	566	Dec 2022
NCT03298451 (HIMALAYA)	CTLA-4, PD-L1	• Tremelimumab + durvalumab • Sorafenib	Active	1310	Jun 2021
NCT02576509 (Checkmate 459)	PD-1	• Nivolumab • Sorafenib	Result pending	726	July 2020
NCT03755739	PD-1	• Pembrolizumab • Peripheral vs hepatic infusion after TACE	Active	200	Nov 2021
NCT03062358 (KEYNOTE-394)	PD-1	• Pembrolizumab • Placebo	Active	450	Jan 2022
NCT03713593 (LEAP-002)	PD-1, VEGFR	• Pembrolizumab + Lenvatinib • Lenvatinib	Active	750	July 2022
NCT03847428 (EMERALD-2)	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 (IMbrave150)	PD-L1, VEGF	• Atezolizumab + bevacizumab • Sorafenib	Active	480	June 2022

Johnston, World J Gastroenterology 2019.

Outline

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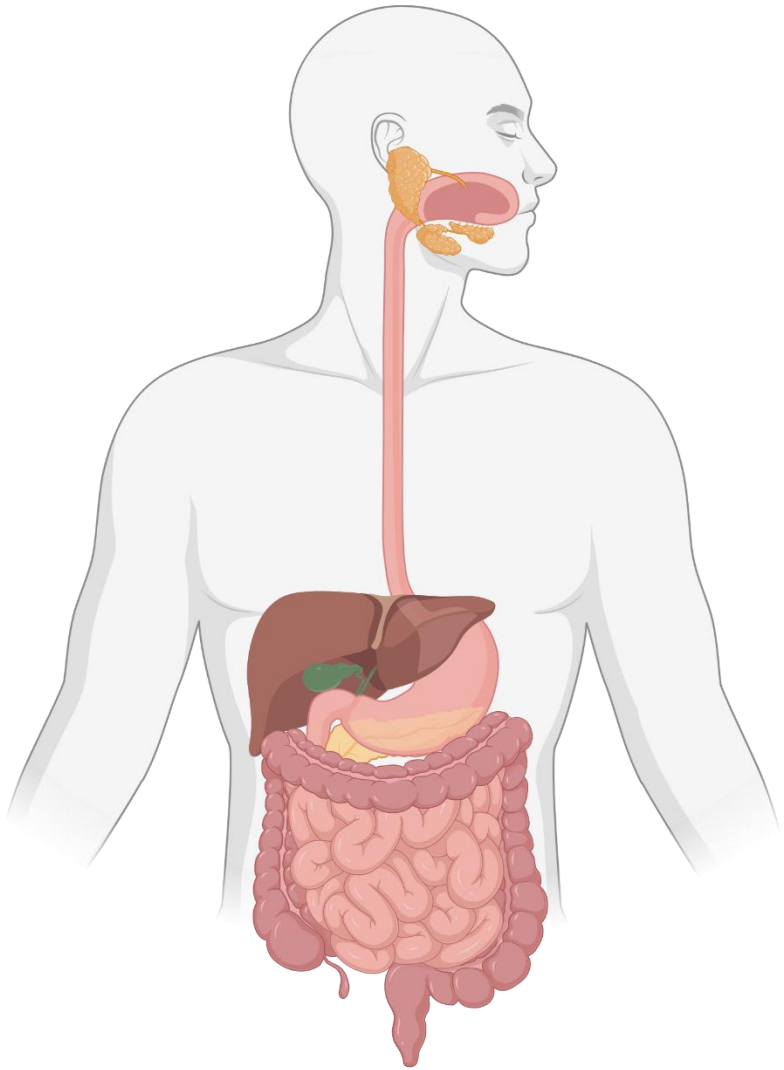
- Colorectal cancer
- Other GI malignancies



FDA approvals for other GI cancers

Drug	Approved	Indication	Dose
Pembrolizumab	2017	Previously treated PD-L1+ advanced/recurrent **gastric or gastroesophageal junction cancer**	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2019	Previously treated PD-L1+ recurrent/advanced/metastatic **squamous cell carcinoma of the esophagus**	200 mg Q3W or 400 mg Q6W
Nivolumab	2020	**Esophageal squamous cell carcinoma** after previous chemotherapy	240 mg Q2W or 480 mg Q4W

Efficacy of approved checkpoint inhibitors

Trial	Patient population	Treatment arm(s)	ORR	Median PFS (months)	Median OS (months)
KEYNOTE-059	Previously treated gastric/gastroesophageal cancer	Pembrolizumab	ITT: 11.6% PD-L1+: 15.5%	ITT: 2.0 PD-L1+: 2.1	ITT: 5.6 PD-L1+: 5.8
KEYNOTE-180	Advanced/metastatic esophageal squamous cell carcinoma after 2 prior therapies	Pembrolizumab	ITT: 14.3% PD-L1+: 20%	2.1	6.8
KEYNOTE-181	Advanced/metastatic esophageal squamous cell carcinoma after 1 prior therapy	Pembrolizumab	22%	3.2	ITT: 8.2 PD-L1+: 10.3
		Chemotherapy	7%	2.3	ITT: 7.1 PD-L1+: 6.7
ATTRACTION-3	Advanced/metastatic esophageal squamous cell carcinoma after prior therapy	Nivolumab	19.3%	HR: 1.1	10.9
		Chemotherapy	21.5%		8.4

Fuchs, JAMA Oncol 2018; Shah, JAMA Oncol 2018; Metges, ESMO GI 2019; Kato, Lancet Oncol 2019.

Conclusions

- Immune checkpoint inhibitors are beginning to fill the need for systemic therapies in hepatocellular carcinoma
- To date, only MSI-high/MMR-deficient colorectal cancers have approved immunotherapy options
- For gastric, gastroesophageal, and esophageal cancers, PD-L1 expression may be important for checkpoint inhibitor responses
- Future directions for all indications include combination therapies