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

Society for Immunotherapy of Cancer

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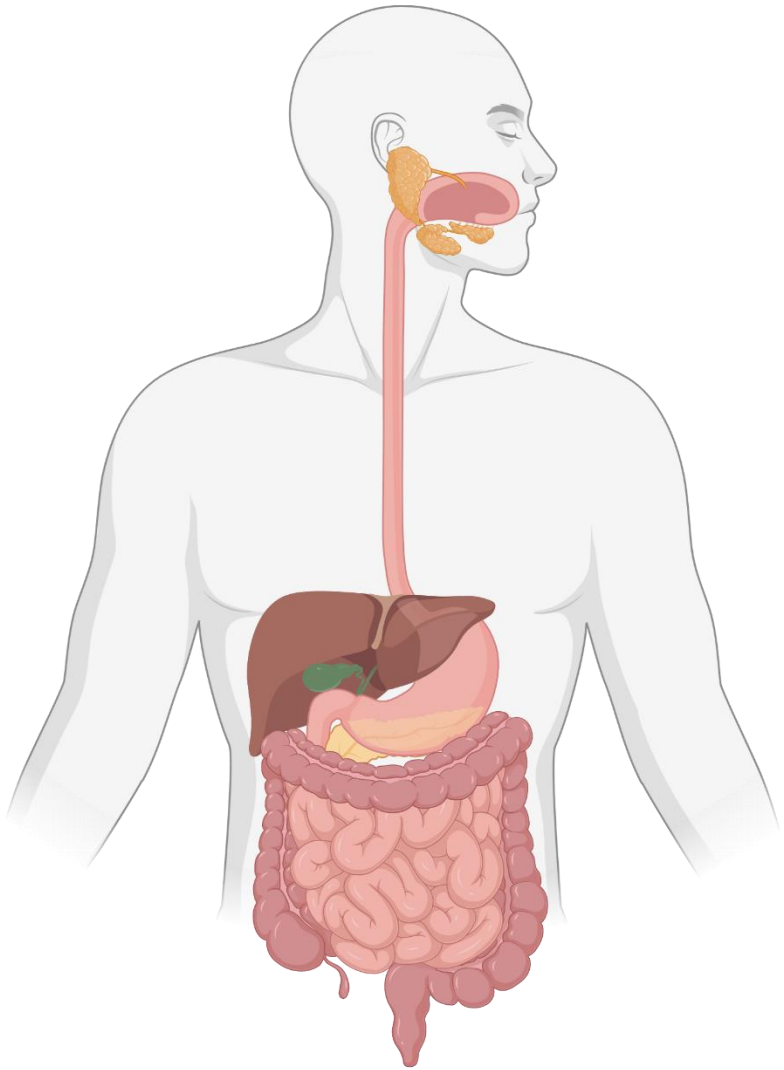
Disclosures

- Consulting Fees: Bayer, Blueprint Medicines, Caris Diagnostics, Daiichi Sankyo, Erytech, Ipsen Biopharmaceuticals, Incyte, IQVIA, Merck, Novartis, Rafael Pharmaceuticals, Syncore, Trisalus
- Contracted Research: Astellas Pharma Global Development Inc, Astra Zeneca, Bayer, BeiGene, BMS, Corcept Therapeutics, Daiichi Sankyo, Eisai, Gritstone, Incyte, IQVIA, Merck, Natera, NGM Biopharmaceuticals, Novocure, QED Therapeutics, Syncore, Taiho Oncology, Thyme, Trisalus
- I will be discussing non-FDA approved indications during my presentation.

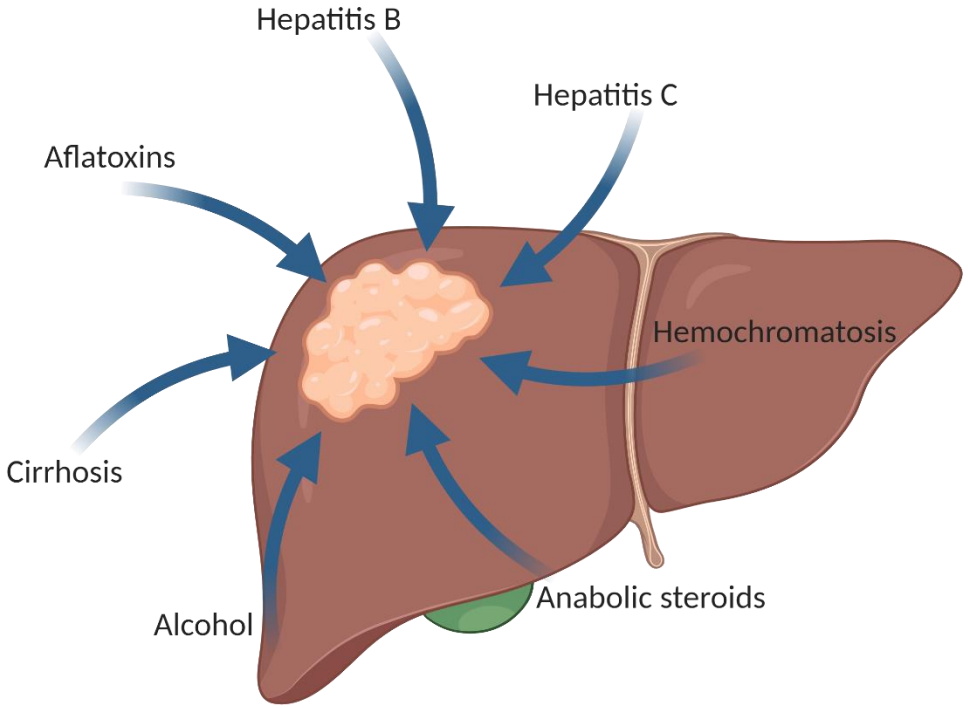
Outline

- Hepatocellular carcinoma
- Colorectal cancer
- Other GI malignancies



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: Combination therapy with ICIs in HCC

Pembrolizumab plus lenvatinib

Untreated HCC

n=100 patients

Pembro 200 mg IV Q3W plus len 12 mg (≥60 kg) or 8 mg (<60kg)

Phase 1b trial results

Median OS 22 mo

Median PFS 8.6 mo

ORR 36%

TRAEs 95% (grade ≥3 67%, grade ≥4 4%)

Phase 3 trial ongoing

FDA did not grant accelerated approval request: did not represent "meaningful advantage" over currently available options

Zhu, ASCO 2020

In development: Selected phase III trials of checkpoint inhibitors

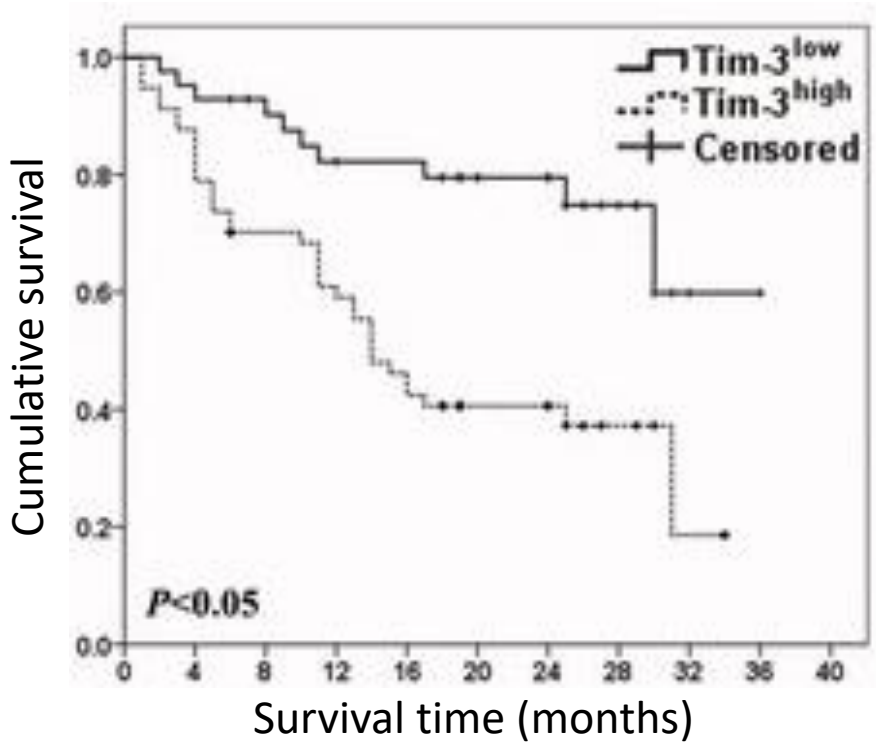
Trial ID	Targets	Drug arms	Status	N	Estimated completion
NCT03794440 (ORIENT-32)	PD-1, VEGF	• Sintilimab + bevacizumab biosimilar • Sorafenib	Active	566	Dec 2022
NCT03298451 (HIMALAYA)	CTLA-4, PD-L1	• Tremelimumab + durvalumab • Sorafenib	Active	1310	Jun 2021
NCT02576509 (Checkmate 459)	PD-1	• Nivolumab • 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.

In development: Other immunotherapy strategies for HCC

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

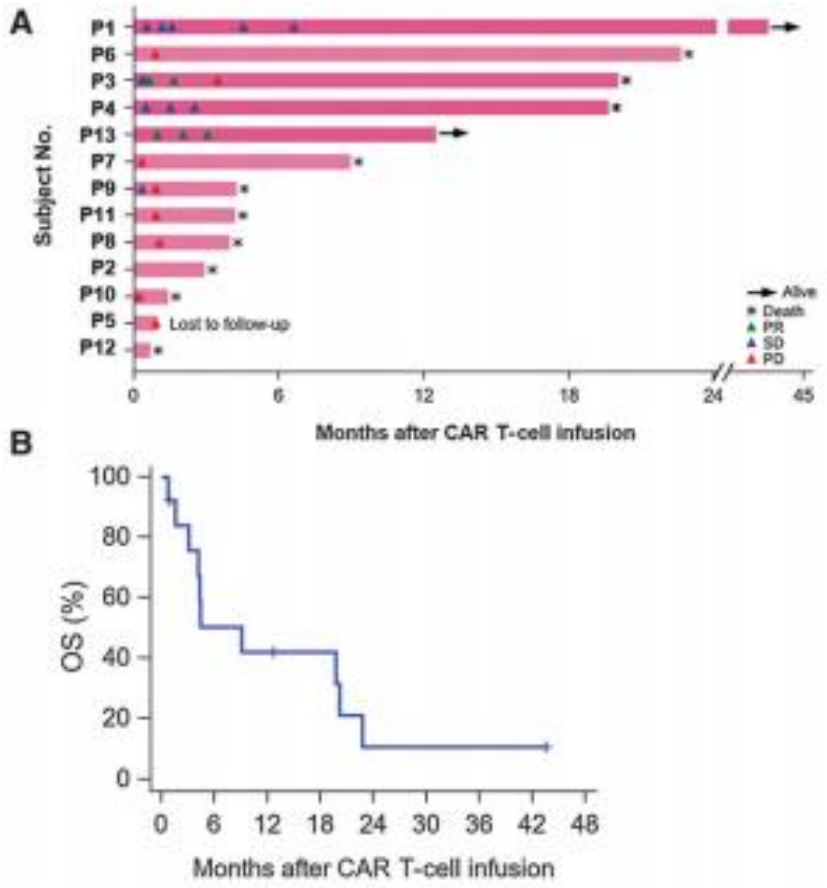
Trial	Intervention	Phase
NCT03680508	TSR-022 + TSR-042 (anti-TIM-3 + anti-PD-1)	2
NCT03652077	INCAGN02390 (anti-TIM-3)	1



Li, Hepatology 2012.

In development: Other immunotherapy strategies for HCC

- Combinations with existing immune checkpoint inhibitors
- Alternative immune checkpoints
- Cellular therapies
  - CAR-GPC3 T-cell therapy in patients with GPC+ HCC (Child Pugh A)
  - Other T-cell therapies in early phase clinical trials
    - Targeting NY-ESO-1, AFP, CD133, EpCAM, etc.



Shi, Clinical Cancer Research 2020

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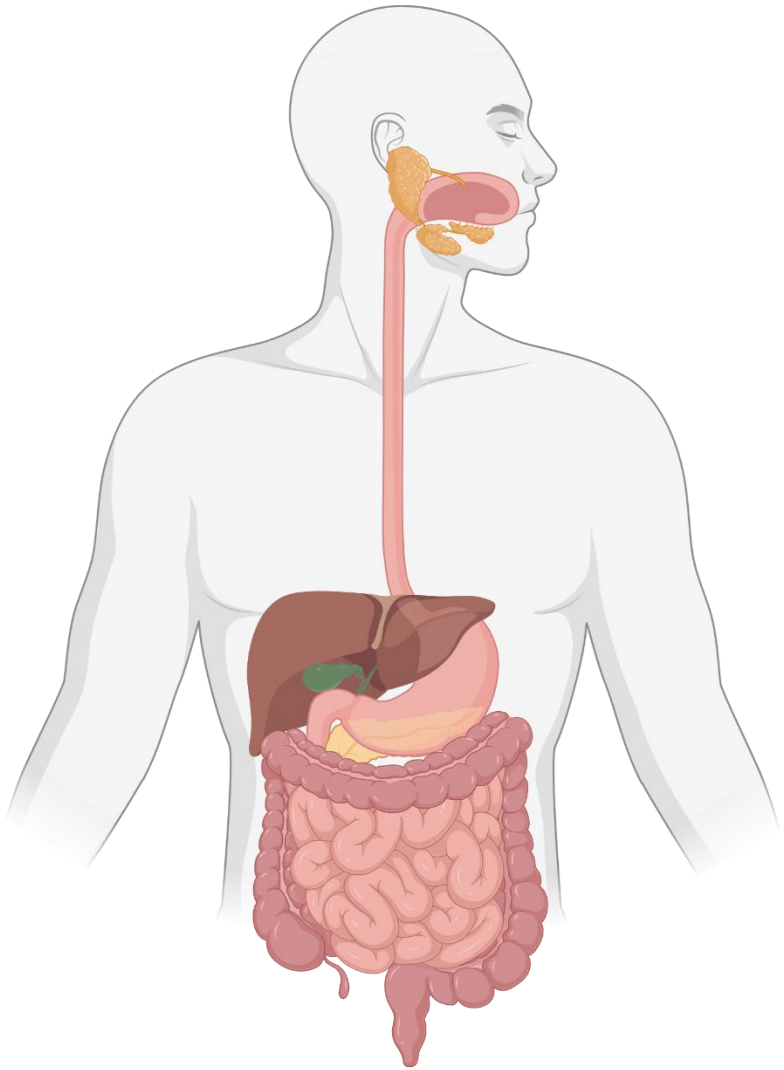
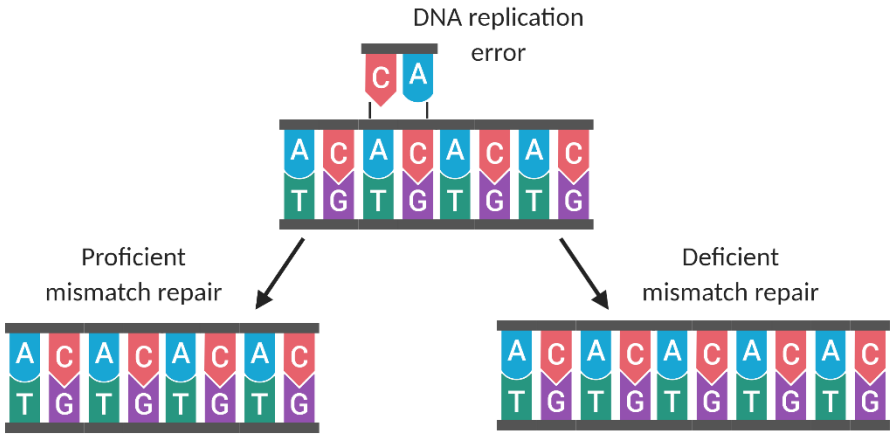
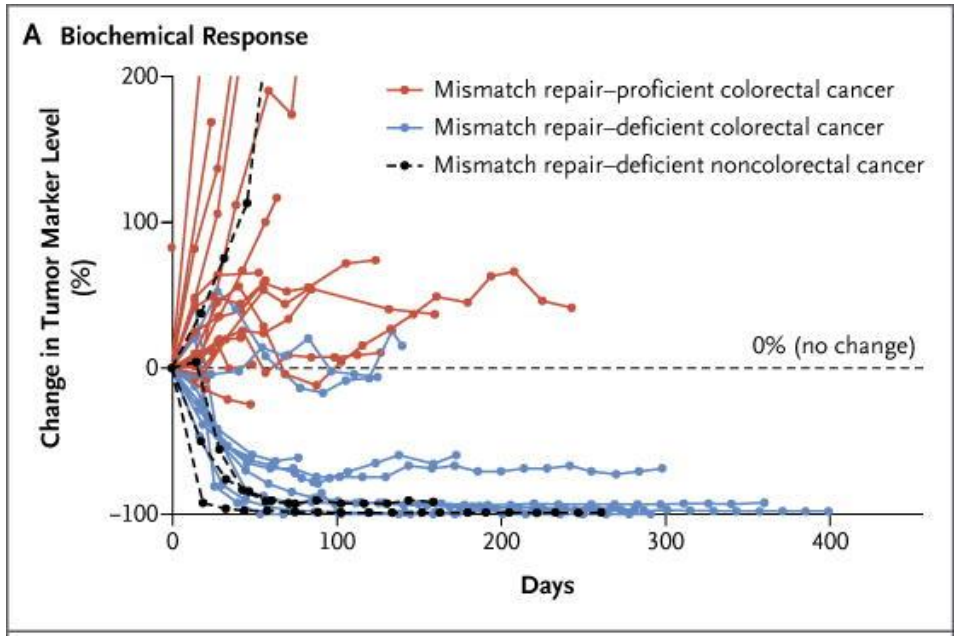


Colorectal cancer

- Categorized by microsatellite instability/mismatch repair status:
  - MSI-high/MMR-deficient: 15% (but 2-4% of metastatic CRC)
  - MSI-low/MMR-proficient: 85%





Le, N Engl J Med 2015

FDA approvals for colorectal cancer

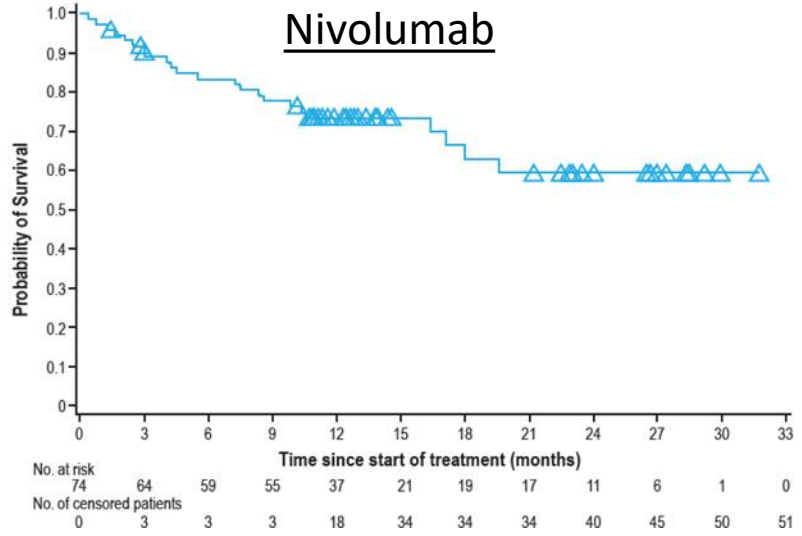
Drug	Approved	Indication	Dose
Nivolumab	2017	MSI-high/dMMR relapsed colorectal cancer following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	240 mg Q2W or 480 mg Q4W
Nivolumab + ipilimumab	2018	MSI-high/dMMR relapsed/refractory colorectal cancer following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	Nivo 3 mg/kg + ipi 1 mg/kg for 4 doses, then nivo maintenance
Pembrolizumab	2020	First-line MSI-high/dMMR colorectal cancer	200 mg Q3W or 400 mg Q6W

To date, all ICI approvals for CRC are for those with mismatch repair or microsatellite instability.

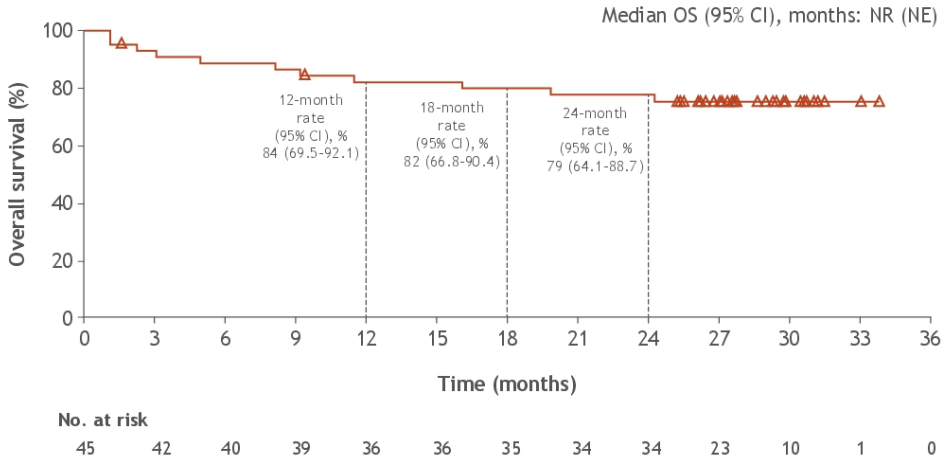
Efficacy of approved ICIs in CRC

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



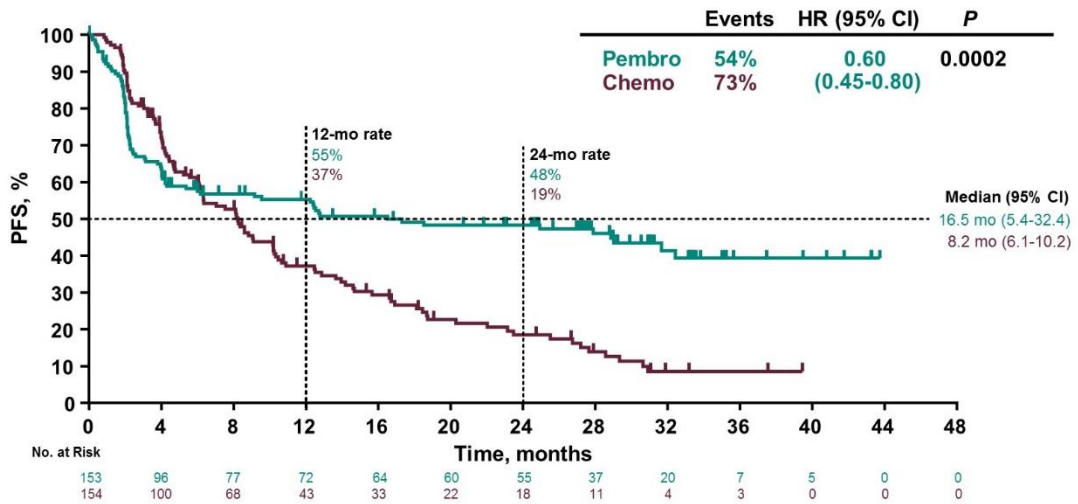
Nivolumab + ipilimumab

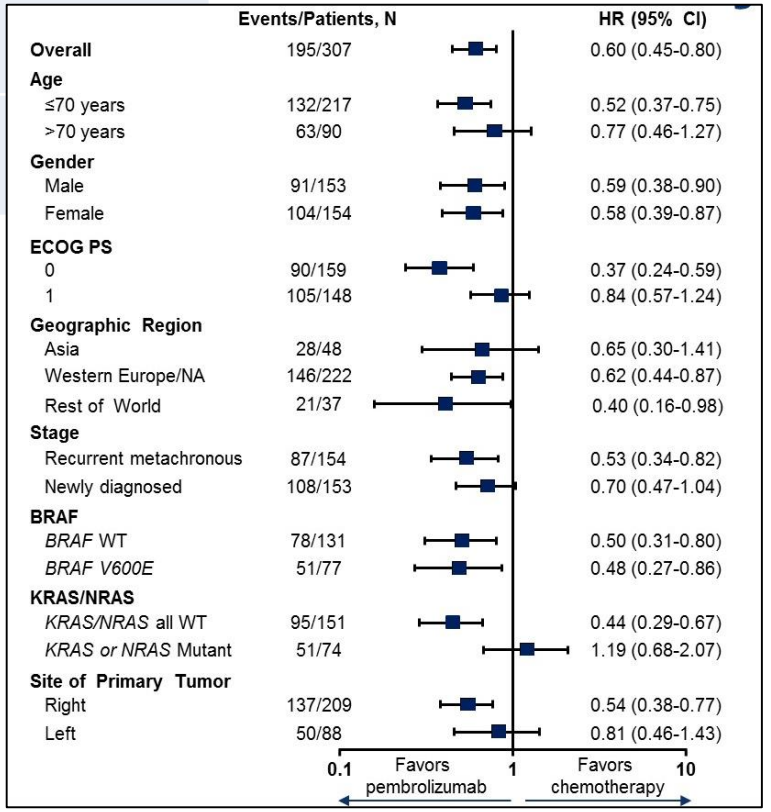


Andre, ASCO 2020; Overman, Lancet Oncol 2017; Overman, ASCO-GI 2019.

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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In development: Immunotherapy for MSS/pMMR CRC

Clinical trial number	Patient population	Treatment(s)	Treatment type(s)
NCT04262687	1st-line MSS/pMMR, high immune infiltrate, metastatic CRC	Pembrolizumab + XELOX + bevacizumab	Anti-PD-1 + chemotherapy + anti-angiogenic
NCT04108481	Liver-predominant, MSS/pMMR CRC with 2 prior therapies	Durvalumab + ^{90}Y embolization	Anti-PD-L1 + radiotherapy
NCT03832621	MSS, MGMT-silenced metastatic CRC	Nivolumab + ipilimumab + temozolamide	Anti-PD-1 + anti-CTLA-4 + chemotherapy
NCT03993626	Previously treated MSS CRC	CXD101 + nivolumab	HDAC inhibitor + anti-PD-1
NCT04044430	Previously treated MSS, BRAF V600E metastatic CRC	Nivolumab + encorafenib + binimetinib	Anti-PD-1 + MEK inhibitor + BRAF inhibitor
NCT04301011	MSS CRC with progression on prior therapies	Pembrolizumab + TBio-6517	Anti-PD-1 + oncolytic virus
NCT03639714	MSS CRC with progression on prior therapy	Nivolumab + ipilimumab + GRT-C901 + GRT-R902	Anti-PD-1 + anti-CTLA-4 + neoantigen vaccines
NCT04126733	MSS CRC with progression on prior therapy	Nivolumab + regorafenib	Anti-PD-1 + multi-kinase inhibitor

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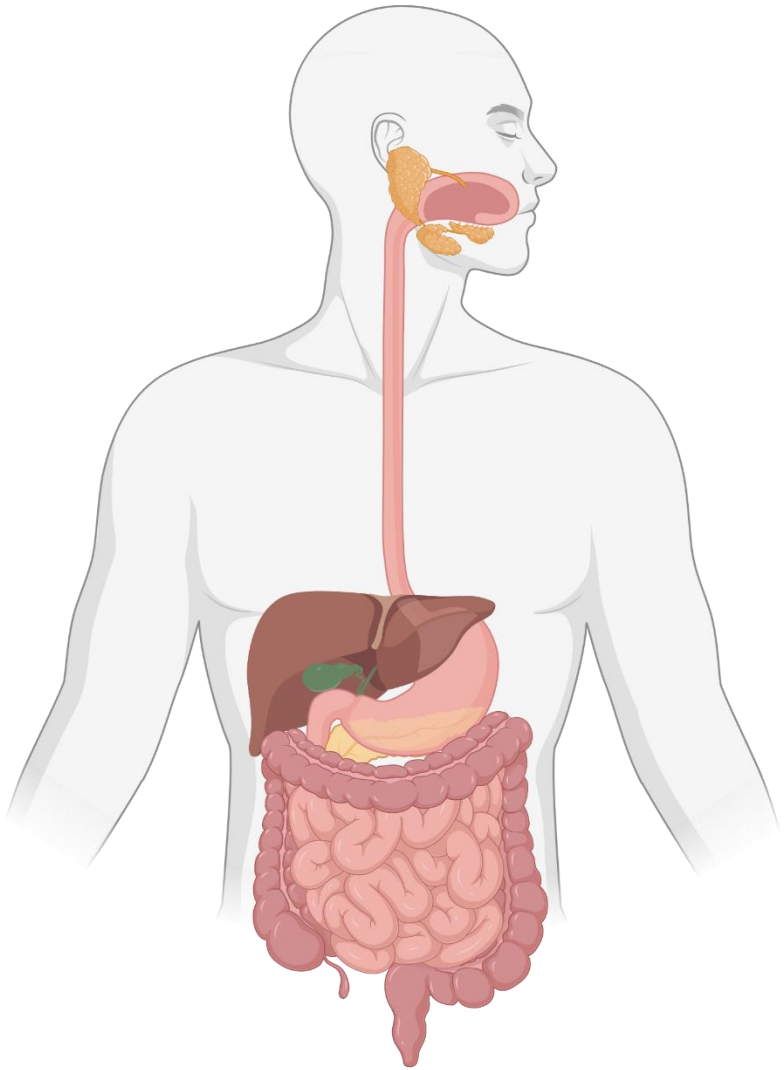


FDA approvals for other GI cancers

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
Pembrolizumab + platinum + fluoropyrimidine	2021	Metastatic or locally advanced **esophageal or gastroesophageal carcinoma** who are not candidates for surgical resection or definitive chemoradiation	200 mg Q3W or 400 mg Q6W
Nivolumab + chemotherapy	2021	First-line treatment of advanced/metastatic **gastric cancer, gastroesophageal junction cancer** and **esophageal adenocarcinoma**	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

Acknowledgements

- Some figures created using biorender.com

Case Studies

CD

- 58 year old African American woman
- Jan 2019 – appendicitis/abscess
- Feb 2019 – colonoscopy = right sided mass, poorly differentiated adenocarcinoma, signet ring and mucinous features
- Right hemicolectomy, 2/18 lymph nodes positive
- MSI-high, *MLH1* hypermethylation
- Imaging detected no metastatic disease

What would you do next?

1. No adjuvant therapy because of good prognosis being MSI-high
2. Adjuvant FOLFOX/ CAPOX for 3-6 months
3. Adjuvant PD-1/PD-L1 blocker as single agent for 12 months
4. Adjuvant PD-1/PD-L1 blocker plus FOLFOX/CAPOX for 3-6 months followed by IO to complete a whole year

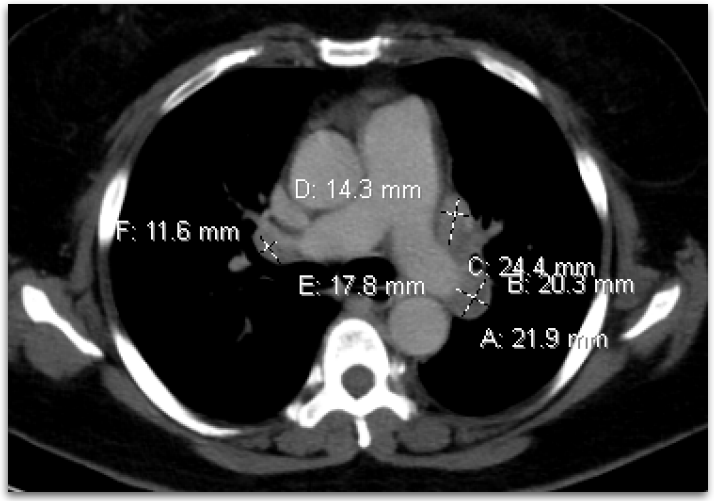
- Adjuvant mFOLFOX x 12 cycles – completed Nov 2019
- Aug 2020 – new lung/Lymph node metastases (biopsy proven)
- PS = 0
- No residual neuropathy
- *RAS/BRAF/Her-2* wild type
- MSI-high

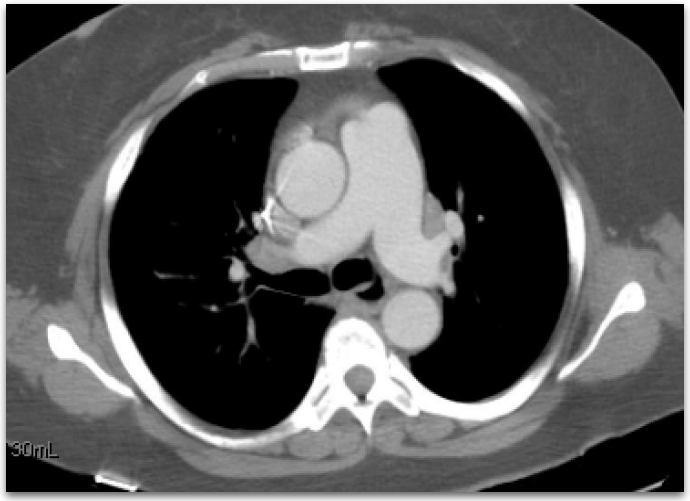
How would you manage?

1. Re-treat with FOLFOX or XELOX
2. FOLFIRI plus anti-EGFR monoclonal antibody
3. PD-I/PD-L1 blocker – single agent
4. Nivolumab + ipilimumab

Follow up

- Sept 2020 – started on pembrolizumab





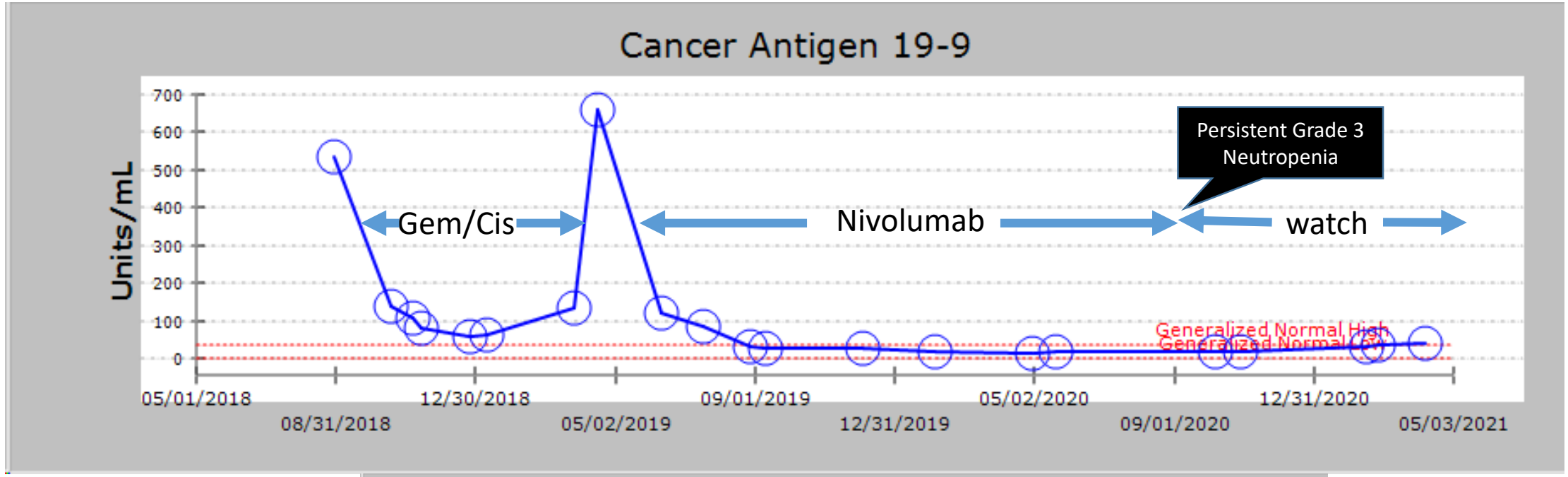
MM

- 68 year old male
- PS = 1
- Right sided abdominal pain + obstructive jaundice
- ERCP = mass in CBD + positive adenoca cells
- MRI
  - 1. Several peritoneal metastasis predominantly within the left hemiabdomen
  - 2. Diffuse intrahepatic dilatation to the right hepatic lobe. There is mass effect upon the right portal vein which is diminutive
  - 3. Osseous metastasis L5 vertebral body.
  - 4. Several metastatic periportal peripancreatic lymph nodes
- CA19-9 > 500
- MSI-high

What would you do next?

1. Gemcitabine + cisplatin
2. Gemcitabine + nabpaclitaxel + cisplatin combination
3. PD1/PD-L1 blocker as a single agent
4. Gemcitabine + cisplatin + PD1/PD-L1 blocker combination

MM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500
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100
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Nivolumab
Persistent Grade 3 Neutropenia
watch
Generalized Normal High
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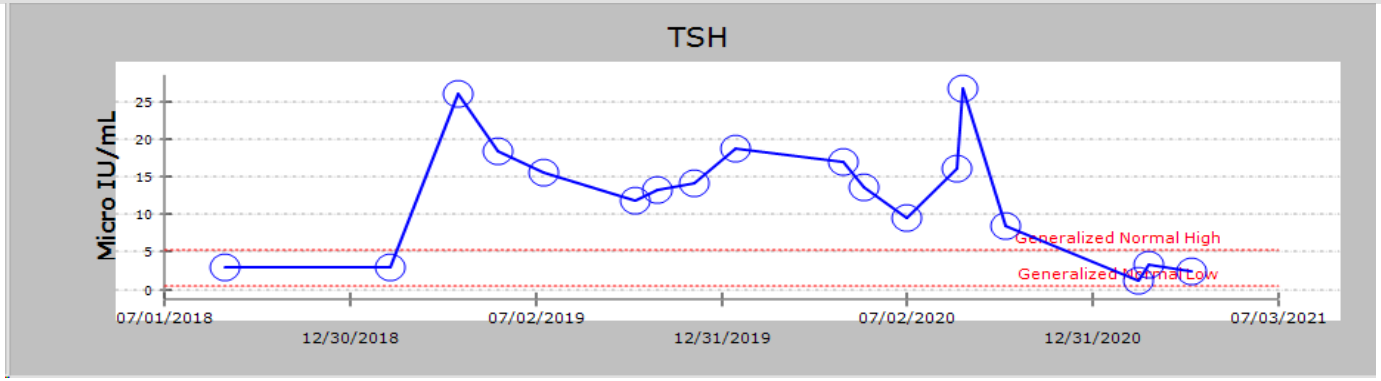
TSH
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