25th Multidisciplinary Management of Cancers: A Case-based Approach

Gastrointestinal Tumor Board

March 9, 2025 and 8:30 am

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25th Multidisciplinary Management of Cancers: A Case-based Approach

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Panelists

Lipika Goyal, MD, MPhil, *Stanford*- Chair
Pamela Basto, MD, PhD, *Stanford*- Fellow, Case Presenter

Medical Oncology
Karen Chee, MD, *UCSF*
Steven Corsello, MD, *Stanford*
Andrew Ko, MD, *UCSF*
Zach Koontz, MD, *Pacific Cancer Care*
Steven Lee, MD, *TPMG*

Surgical Oncology
Cameron Gaskill, MD, MPH, *UCSF*
Ajay Maker, MD, *UCSF*
Ankit Sarin, MD, MHA, *UC Davis*
Brendan Visser, MD, *Stanford*

Radiation Oncology
Erqi Pollom, MD, *Stanford*

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Disclosures

Faculty Name	Role	Type of Financial Relationship	Company
Lipika Goyal	**Chair**	Advisory Board or Panel	AbbVie, Agenus, AstraZeneca (DSMB), Boehringer Ingelheim, Compass Therapeutics, Exelixis, Kinnate Biopharma, Merck, Relay Therapeutics, Servier, Surface Oncology, Taiho, and TransThera
		Grants/Research Support	Alyssum Therapeutics, Boehringer Ingelheim, Genentech, AstraZeneca, Cogent, and Tyra Biosciences.
Pamela Basto	**Fellow**	Disclosed Patents	Cartesian Therapeutics, Stem Cell Technologies
Karen Chee	Panelist	Disclosed no relevant financial relationships.	
Steven Corsello	Panelist	Grants/Research Support	Past lab research funding from Bayer and Calico
		Other Financial or Material Support (royalties, patents, etc.)	Past lecture honorarium from Genentech.
Cameron Gaskill	Panelist	Disclosed no relevant financial relationships.	
Andrew Ko	Panelist	Advisory Board or Panel	Arcus, Astellas, Corcept Therapeutics, Eisai, Fibrogen, Lenovo, Merus, Renovo, and Tango Therapeutics
		Grants/Research Support	Abgenomics, Apexigen/Pyxis, Astellas, Biomedical Valley Discoveries, Bristol-Myers Squibb, Genentech/Roche, LEAP Therapeutics, and Verastem
		Salary/Contractual Services	Roche/Genentech, Ipsen, and Grail
Zach Koontz	Panelist	Stock/Shareholder (excluding diversified mutual funds)	Merck <$50k
Steve Lee	Panelist	Disclosed no relevant financial relationships.	
Ajay Maker	Panelist	Grants/Research Support	Shannon Biosciences
Erqi Liu Pollom	Panelist	Advisory Board or Panel	Vysioneer, GT Medical Technologies, and Castle Biosciences
		Speaker's Bureau	Varian; Salary/Contractual Services: Stanford
Ankit Sarin	Panelist	Consultant	Noah Medical, Averto medical, and Intuitive Surgical
Brendan C Visser	Panelist	Disclosed no relevant financial relationships.	

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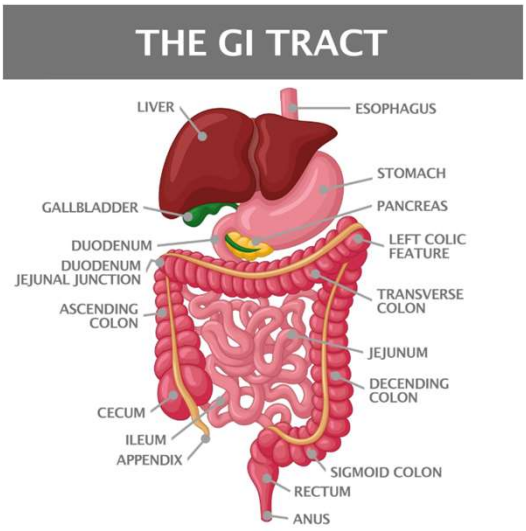
Outline

Case 1: Pancreatic Cancer
Case 2: Hepatocellular Cancer
Case 3: Gastric Cancer
Case 4: Rectal Cancer
Case 5: Biliary Tract Cancer

Biomarkers discussed:
HER2, KRAS, Claudin 18.2



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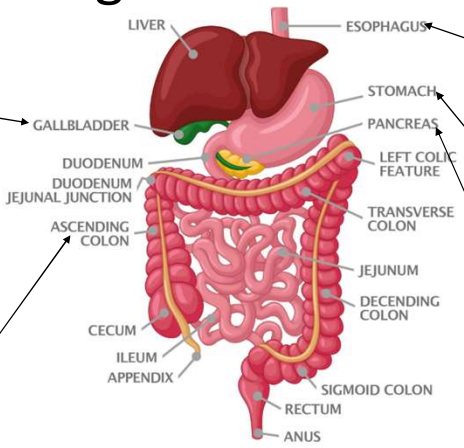
Recent FDA Approvals for unresectable or metastatic gastrointestinal cancers

BILIARY
1. Zanidatamab:
refractory HER2+ (IHC 3+)

COLON
2. Adagrasib + cetuximab:
refractory KRAS G12C mutated
3. Sotorasib+panitumumab:
refractory KRAS G12C mutated
4. Encorafenib + cetuximab + mFOLFOX6:
BRAFV600E mutated



ESOPHAGEAL SQUAMOUS
5. Tislelizumab
2nd+ line treatment

GASTRIC AND GE JUNCTION ADENO
6. Zolbetuximab + chemotherapy:
1st line treatment of Claudin 18.2+, HER2-
7. Tislelizumab + chemotherapy:
1st line treatment of PD-L1 (≥1), HER2-

PANCREAS
8. Zenocutuzumab
refractory NRG1 gene fusion+

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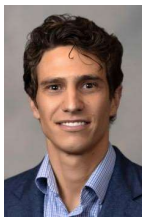
Case 1 – Pancreatic Cancer

1. **Role of radiation in borderline resectable PDAC?**
2. Role of neoadjuvant chemotherapy in resectable PDAC?
3. Management of oligometastatic PDAC?

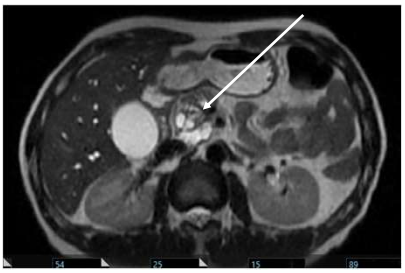


Case 1 – Pancreatic Cancer

49 y.o. male presents with one week of jaundice and diarrhea

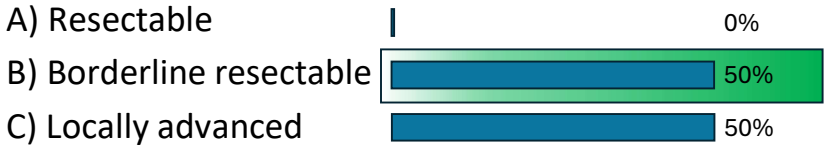
- ECOG PS 1, **Tbili 15, ALT 443, AST 172, Alk Phos 741, CA19-9 244**

- Radiology
  - MRI Abdomen: 2 cm mass in the pancreatic neck with obstruction of the main pancreatic duct. **Encasement and constriction of the portal confluence**. SMA <180
  - EUS: 2.2 cm mass at the pancreatic head and bile duct dilation, cT2N0M0
- Pathology: pMMR adenocarcinoma



Case 1 – Pancreatic Cancer Audience Questions

Question 1.1 How would you define the resectability of this tumor?



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Case 1 – Pancreatic Cancer Panel Discussion

How do you define borderline resectable?

Do you give neoadjuvant chemotherapy for borderline resectable, and why?

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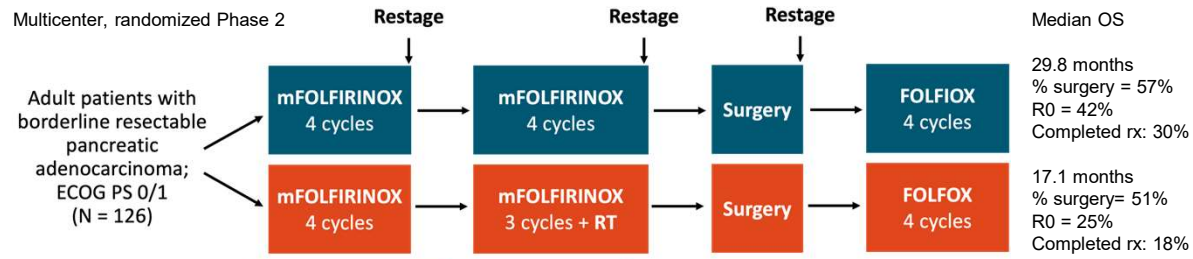
What about neoadjuvant XRT for borderline resectable PDAC?

Alliance A021501: Neoadjuvant mFOLFIRINOX +/- RT



Median OS

29.8 months
% surgery = 57%
R0 = 42%
Completed rx: 30%

17.1 months
% surgery= 51%
R0 = 25%
Completed rx: 18%

Outcome	mFOLFIRINOX (n = 65)	mFOLFIRINOX + RT (n = 55)
OS		
▪ Events	35	40
▪ Median OS, mos	29.8	17.1
▪ 18-mo OS rate, %	66.4	47.3

35 treated with SBRT and 5 treated with HIGRT
Median CA19-9 171 U/mL (Chemo only) vs. 248 U/mL (RT)

Katz et al. *ASCO GI*. 2021. Clinicaloptions.com

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Case 1 – Pancreatic Cancer Panel Discussion

When do you consider giving radiation for borderline resectable PDAC? What about extranodal irradiation?

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Case 1 – Pancreatic Cancer

After 4 doses of FOLFIRINOX:

- CA19-9 down from 423 to 170
- CT: shrinkage of the primary mass

After 8 doses FOLFIRINOX:

- **CA19-9 up from 170 to 271**
- CT: New enlarging tumor involving the upstream pancreatic body/tail with suspected stomach invasion. cT3N0. Unchanged vascular involvement.

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Case 1 – Patient Case

Molecular Profiling:

GENOMIC VARIANTS

Biologically Relevant		Variant Allele Fraction
KRAS	p.G12V Missense variant (exon 2) - GOF	5.3%
GNAS	p.R201C Missense variant - GOF	2.7%

pMMR intact, Claudin 18.2 & Her2 negative, TMB 2.6 mut/MB

- Not eligible for any clinical trials
- Treated with gemcitabine/nab-paclitaxel for 3 months
- CA19-9 decreased to 102
- Planned pre-operative SBRT +/- extranodal irradiation, followed by surgery.

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Case 1 – Pancreatic Cancer

1. Role of radiation in borderline resectable PDAC?
2. **Role of neoadjuvant chemotherapy in resectable PDAC?**
3. Management of oligometastatic PDAC?

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Case 1 – Pancreatic Cancer Audience Questions

Question 1.2 What if the patient had a 2 cm pancreatic neck mass with no vascular involvement or enlarged lymph nodes?

A) Upfront surgery — 50%

B) Neoadjuvant mFOLFIRINOX x 4-6 months — 46%

C) Neoadjuvant gemcitabine/Nab-paclitaxel x 4-6 months — 0%

D) Neoadjuvant mFOLFIRINOX + Radiation — 4%

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Does **neoadjuvant** chemotherapy prolong survival in patients with *resectable* pancreas cancer?

	Patient Population	Arms for Randomization	# of Pts	Pts completing neoadjuvant chemo by ITT	Median OS (mo)	HR /p- value
Pre—02/JSAP-05	Resectable & Borderline Resectable	Neoadjuvant gemcitabine plus S-1 vs. upfront surgery	182 vs. 180	Not reported	36.7 vs. 26.6	HR 0.72, p=0.015
NEONAX	Resectable	Neoadjuvant gemcitabine and Abraxane vs. upfront surgery	59 vs. 59	53 (90%)	25.5 vs. 16.7	Not reported
PREOPANC1	Resectable & Borderline resectable	Neoadjuvant gemcitabine and radiotherapy vs. upfront surgery	119 vs. 127	81 (68%)	15.7 vs. 14	HR: 0.78 p= 0.096
PANACHE01 PRODIGE48	Resectable	Neoadjuvant mFOLFIRINOX vs. neoadjuvant FOLFOX vs. upfront surgery	70 vs. 50 vs. 26	62 (88%) vs. 42 (84%)	30.6 vs. 31.3 vs. >36	Not reported
PREOPANC2	Resectable & Borderline resectable	Neoadjuvant mFOLFIRINOX vs. neoadjuvant FOLFOX (closed) vs. upfront surgery	185 vs. 184	115 (62%) vs. 149 (81%)	21.9 vs. 21.3	HR 0.87 P= 0.28
SWOG1505	Resectable	Neoadjuvant mFOLFIRINOX vs. gemcitabine and Abraxane	55 vs. 47	46 (84%) vs. 40 (85%)	22.4 vs. 23.6	Not reported

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Adapted from Henault et al. *The Lancet Gastroenterology & Hepatology*. 2024

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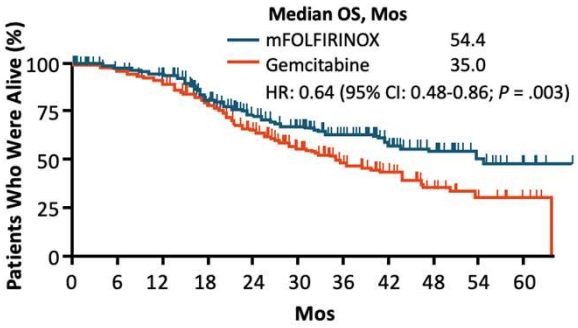
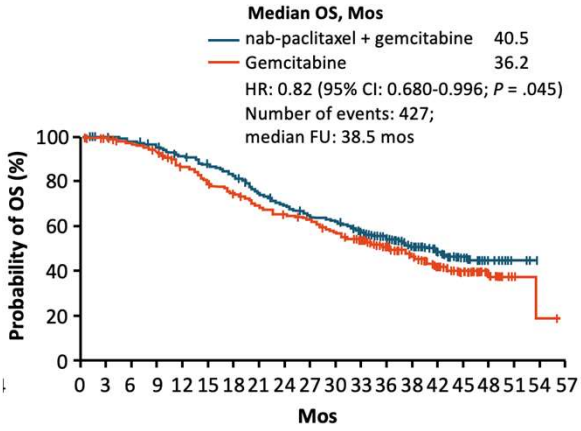
Does **adjuvant** chemotherapy prolong survival in patients with *resectable* pancreas cancer?

PRODIGE 24/ CCTG PA-6



Survival Outcome	mFOLFIRINOX (n = 247)	Gemcitabine (n = 246)
3-yr OS, %	63.4 (55.7-70.1)	48.6 (40.9-55.8)

APACT



Conroy et al. *NEJM*. 2018
Tempero et al. *ASCO*. 2019

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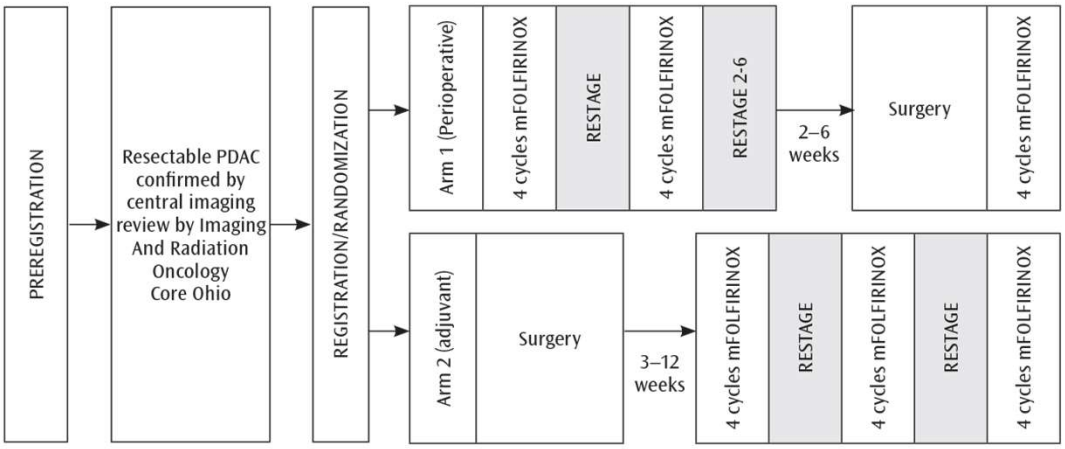
What about perioperative vs. adjuvant chemotherapy in *resectable* pancreatic cancer?

Alliance A021806



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Case 1 – Pancreatic Cancer Panel Discussion

Do you give neoadjuvant chemotherapy for resectable disease and for which subset of patients?

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Case 1 – Pancreatic Cancer

1. Role of radiation in borderline resectable PDAC?
2. Role of neoadjuvant chemotherapy in resectable PDAC?
3. **Management of oligometastatic PDAC?**

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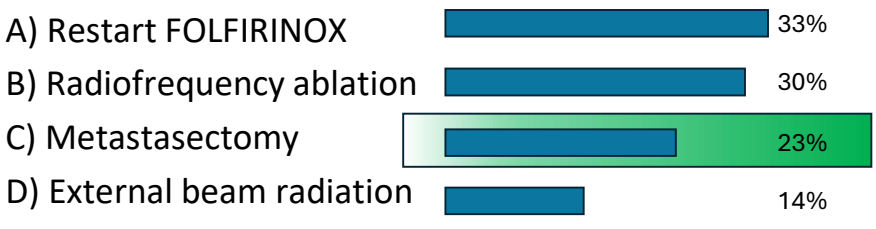
Case 1 – Pancreatic Cancer Audience Questions

Question 1.3 47 y.o. woman s/p Whipple for T2N0 PDAC and 6 months of adjuvant FOLFIRINOX. At 18 months, the patient develops an isolated 2.5 cm segment 8 liver lesion.

What would you do?



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Case 1 – Pancreatic Cancer Panel Discussion

Oligometastatic Disease:

- How do you treat synchronous oligometastatic disease with a CA19-9<500?
  - 1 liver lesions?
  - 1 lung nodule?
  - >1 liver or lung nodule?
- How long do you wait for stability metachronous oligometastatic disease before deciding to definitively treat?

Springfield et al. *Nature Reviews Clinical Oncology*. 2023

Case 1 – Summary for Pancreatic Cancer

- No definitive improvement of OS with neoadjuvant chemotherapy in *resectable* cancers
- Neoadjuvant chemotherapy for *borderline resectable* pancreatic cancer is standard of care
- Pre-operative SBRT can improve R0 resection but has not demonstrated improvement of overall survival
- Targeted therapies have yet to be integrated in the perioperative setting

Pancreatic Cancer Trials

Current Trials
Future Trials

Kaiser Permanente

- Perioperative/Adjuvant: ALLIANCE study of FOLFIRINOX before/after PDAC surgery vs adjuvant

Stanford

- Perioperative/Adjuvant: ALLIANCE study of FOLFIRINOX before/after PDAC surgery vs adjuvant
- 1st line: AZD0901 Claudin 18.2 ADC + chemo
- 2nd+ line: AZD0022 (KRAS G12D inhibitor) +/- chemo
- 2nd+ line: INCB161734 (KRAS G12D inhibitor) +/- chemo

UC Davis

- Neoadjuvant Phase 1/2 Study of M3814 (Peposertib) + Hypofractionated Radiotherapy for Locally Advanced Pancreatic Adenocarcinoma
- 1st line: Nab-Paclitaxel and Gemcitabine plus/minus VCN-01 in Patients with Metastatic Pancreatic Cancer

UCSF

- Adjuvant Autogene Cevumeran + Atezolizumab + mFOLFIRINOX vs mFOLFIRINOX in Resected PDAC
- 1st Line : Gemcitabine and Nab-paclitaxel in Combination with VS-6766 and Defactinib
- 1st Line: Quemliclustat and Chemotherapy Versus Placebo and Chemotherapy in Patients for newly metastatic PDAC not previously treated
- 2nd Line: Maintenance Ivaltinostat + Capecitabine or Capecitabine in Patients with mPDAC With No Progression on First Line FOLFIRINOX
- 2nd Line: Nabplagem Vs. Nab-Paclitaxel/Gemcitabine in BRCA1/2 or PALB2 Mutant Metastatic Pancreatic Ductal Adenocarcinoma (PLATINUM)
- 2nd+ Line: RMC-6236 versus Investigator's Choice of Standard of Care Therapy in Patients with mPDAC
- 3+ line: Phase 1/2 : 177Lu-FAP-2286 in Patients With an Advanced Solid Tumors

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Case 2 – Hepatocellular Carcinoma

1. How do we choose between the multiple first line options for advanced HCC?
2. How do anti-PD-1 and anti-CTLA-4 antibodies work?

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Case 2 – Patient Case

44 y.o. male h/o chronic hepatitis B

- Presents to PCP with daily low grade fevers/chills, 2 months of progressive SOB, and 2 weeks of nausea/vomiting
- Exam: Abdominal distention, RUQ pain and lower extremity swelling
- WBC 11.3, Hgb 10.3, Plt 115K, Tbili 1.3, AST 72, ALT 51, Alk Phos 176, AFP 5, INR 1.4, Alb 3.6
- **BCLC-C, Child Pugh A6**

Abd US: gallstones sludge and possible liver mass

Sent to the Emergency room

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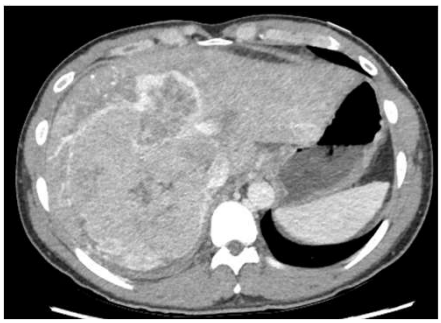
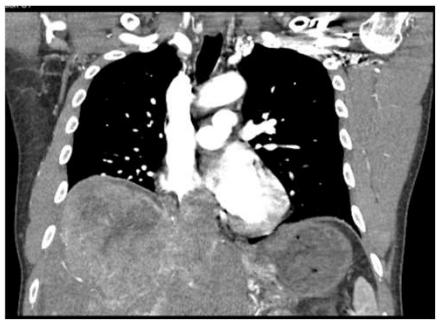
Case 2 – Patient Case

In the ED, CT A/P: extensive HCC of right lobe, tumor thrombus in the inferior cavoatrial junction/ right atrium

CT Chest Angiogram: no pulmonary embolism





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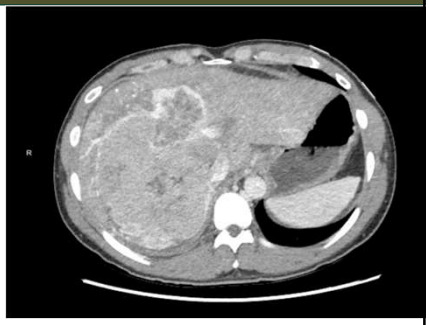
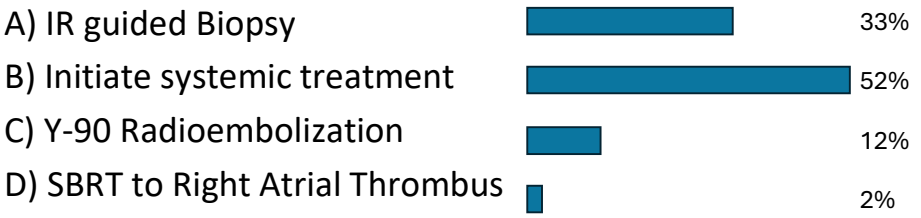
Case 2 – Audience Question



44 y.o. with chronic HBV, Child Pugh A6, Tbili 1.3, Plts 115KI CT with large liver mass and tumor thrombus at IVC/RA junction

Question 2.1 What would you do next?



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Case 2 – HCC Audience Question

Tumor Board: 14 cm liver mass with extensive tumor in vein at portal venous confluence causing cavernous transformation. Raised concern for shunting with Y90. Recommended systemic therapy.

EGD: Grade 1 esophageal varices

Question 2.2. Which 1L systemic treatment would you choose?

A) Atezolizumab/bevacizumab
B) Durvalumab/tremelimumab
C) Nivolumab/ipilimumab
D) Lenvatinib

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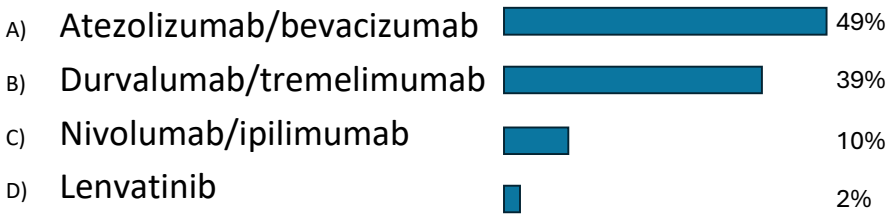

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Case 2 – 1L Unresectable HCC Rx Options

	Study	Ph	Patient #	BCLC Stage C	Etiology Hep B/HepC	ORR (95% CI)	Median PFS (months)	Median OS (months)
Atezolizumab + Bevacizumab vs. sorafenib	IMBrave 050	3	501	82% vs. 81%	49%/21% vs. 46%/23%	30% vs. 11% 5.5% CR	6.9 vs. 4.3 HR 0.65 (0.53-0.81)	19.2 vs. 13.4 HR 0.66 (0.53-0.85)
Durvalumab + Tremelimumab vs. sorafenib	HIMALAYA	3	388	80.4% vs. 79.4%	31%/ 28% vs. 30.6%/ 27.5%	20.1% vs. 5.1% 3.1% CR	3.78 vs. 4.07 HR 0.9 (0.77-1.05)	16.4 vs. 13.8 HR 0.78 (0.65-0.92)
Nivolumab + Ipilimumab vs. Lenvatinib/sorafenib	Checkmate 9DW	3	530	73% vs. 73%	34%/27% vs. 35%/29%	36% vs. 13% 7% CR	9.1 vs. 9.2 HR 0.87 (0.72-1.06)	23.7 vs. 20.6 HR 0.79 (0.65-0.96)

Finn et al. *NEJM.* 2020
Abou-Alfa et al. *NEJM Evidence* 2022
Galle et al. *JCO* 2024

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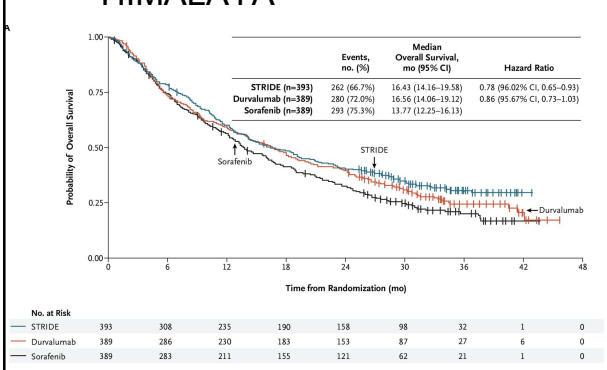
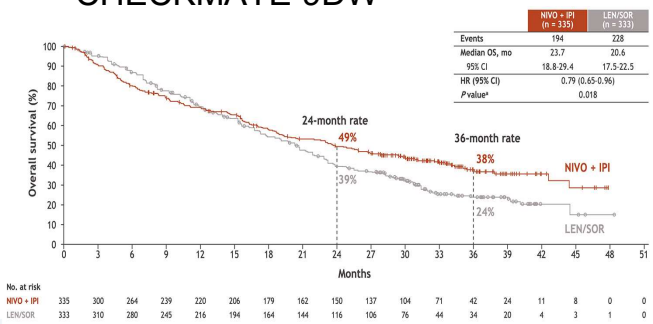
Comparison of HCC 1L CTLA4+PD(L)1 combination

HIMALAYA



STRIDE: tremelimumab 300 x1C + durvalumumab 1500 mg q4w
4 year survival: 25.2% with STRIDE vs. 15.1% sorafenib
Median OS 16.43 vs. 16.56 vs. 13.77; HR 0.78, p=0.0008
ORR: 20% vs. 17% vs. 5.1%
DOR: 22.3 mo vs. 16.8 mo vs. 18.4 mo
Steroid use: 20% vs. 10% vs. 2%

CHECKMATE 9DW



9DW: ipilimumab 3mg/kg x4C + nivolumab 1mg/kg q3w
85% received Lenvatinib
Median OS: 23.7 vs. 20.6 mo, HR 0.79, p=0.018
ORR: 36% vs. 13%
DOR: 30.4 mo vs. 12.9 mo
Steroid use: 29% vs. NR

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Abou-Alfa et al. *NEJM Evidence*. 2022; Galle et al. *JCO* 2024; Sangro et al. *Annals of Oncology*. 2024

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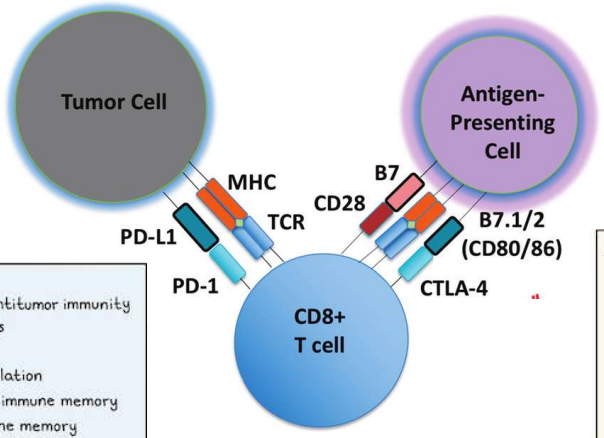
25th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 2 – Immune Checkpoint Inhibition



anti-PD-1
- weaker memory response/antitumor immunity
- fewer antigen-specific T cells
- ↑ TCF-1$^-$TOX$^+$ T cells
- less IFNγ upon *ex vivo* stimulation
- CD4$^+$ T cells not required for immune memory
- TCF-1 not required for immune memory
- TOX not required for immune memory

anti-CTLA-4
- stronger memory response/antitumor immunity
- more antigen-specific T cells
- ↑ TCF-1$^+$TOX$^-$ T cells
- more IFNγ upon *ex vivo* stimulation
- ↑CXCR3
- CD4$^+$ T cells required for immune memory
- TCF-1 required for immune memory
- TOX not required for immune memory

Wang et al. *Cancer Cell*. 2024
Aref et al. *Lab on a Chip*. 2018
Mok et al. *PNAS*. 2025

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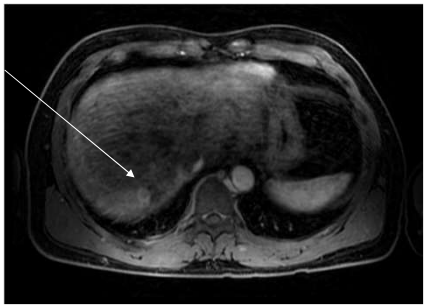
25th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 2 – Hepatocellular carcinoma

Patient received 3 cycles of atezolizumab + bevacizumab
- presented to ED with melena
- EGD with 5 moderate/large esophageal varices s/p banding with eradication

From Cycle 4 to Cycle 29, only received single agent atezolizumab



MRI A/P: (18 mo later)
- 1.3 cm and 1.1 cm residual foci in segment 7
- Similar necrotic tumor thrombus in the hepatic IVC and inferior atriocaval junction
- Similar burden of bland thrombus in portal veins and proximal splenic vein
- Cirrhotic liver morphology

Abou-Alfa et al. *NEJM Evidence* 2022
Galle et al. *JCO* 2024

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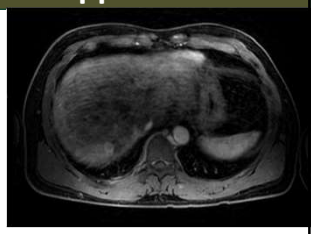
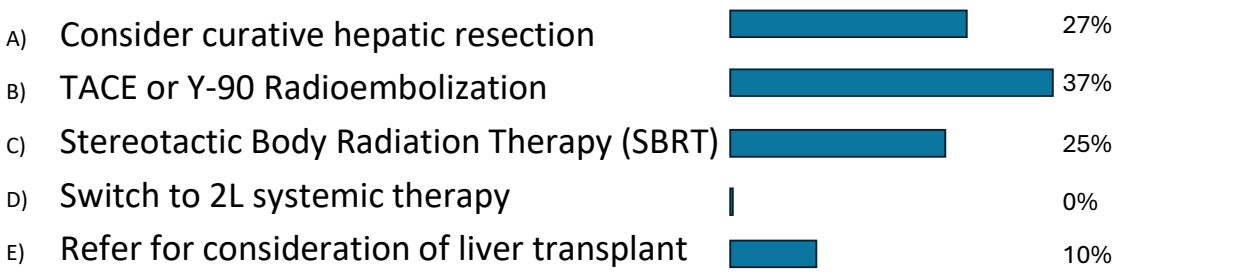
25th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 2 – HCC Audience Question



- 1.3 cm and 1.1 cm residual foci in segment 7 after atezo/bev
- Similar necrotic tumor thrombus in the hepatic IVC and inferior atriocaval junction

Question 2.3. What would be your next step?



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Case 2 – HCC Panel Discussion

1. When would you use atezolizumab/bevacizumab vs. durvalumab/tremelimumab vs. ipilimumab/nivolumab for 1L?
    a. Efficacy: Does median OS or landmark analysis matter more?
    b. Safety: Does rate of immune-related toxicities requiring steroids factor into your decision?
2. What are the indications for SBRT vs. liver directed therapies by IR for BCLC stage C HCC with vascular invasion?

Case 2 – Summary for Hepatocellular Carcinoma

1. Multiple 1L treatment options for unresectable HCC, perhaps reserve nivo/ipi (higher CTLA4 dose 3 mg/kg and 4 doses) for more robust patients
2. In preclinical models, CTLA4 inhibition improves tumor specific memory response over PD-1 inhibition, which may explain synergy in combination.
3. Triplet combinations are now being evaluated in for frontline treatment of advanced HCC

Hepatocellular Carcinoma Trials

Current Trials
Future Trials

Stanford

- 1st line: Atezo/Bev/Tiragolumab (anti-TIGIT) vs Atezo/Bev (Child Pugh A)
- 1st line: Atezo/Bev or Atezo alone (Child Pugh B)
- 2nd+ line: Phase 1 TYRA-430 in HCC and Other Solid Tumors with Activating FGF/FGFR pathway aberrations (SURF-431)

UCSF

- 2nd + line: Durvalumab (MEDI4736) +/- Tremelimumab for Advanced Hepatocellular Carcinoma after Palliative Hypofractionated Radiotherapy
- Umbrella Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients with Advanced Liver Cancers (Morpheus-Liver)
- 2nd+ line: A Phase I/II Study to Evaluate AZD5851 in GPC3+ Advanced/Recurrent Hepatocellular Carcinoma (ATHENA)
- 1st line: TheraSphere™ Followed by Durvalumab with Tremelimumab for HCC (ROWAN)
- 2nd+ line: Phase 1 TYRA-430 in HCC and Other Solid Tumors with Activating FGF/FGFR pathway aberrations (SURF-431)

UCDavis

- 1st line: Atezo/Bev or Atezo alone (Child Pugh B)

Case 3 – Gastric Cancer

1. How do we integrate local and systemic therapy for patients with GEJ or gastric cancer?
2. What are the FDA approved immunotherapies for 1L advanced GEJ and gastric cancer?
3. What is all the noise about Claudin 18.2?

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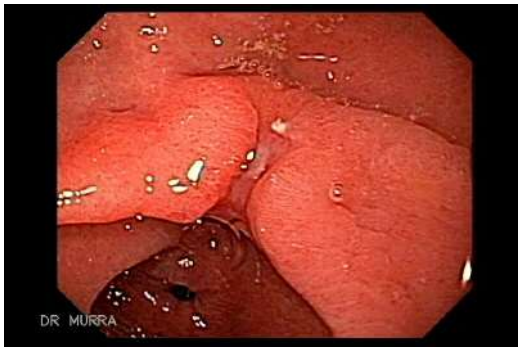
Case 3 – Gastric Cancer

58 y.o. male, h/o H. Pylori, who presents with 1 year of progressive epigastric pain, weight loss and decreased satiety, ECOG 1

EGD: normal esophagus and large circumferential mass in the distal stomach without bleeding at the pylorus, negative for H. Pylori.

Biopsy: poorly differentiated adenocarcinoma



www.gastrointestinalatlas.com

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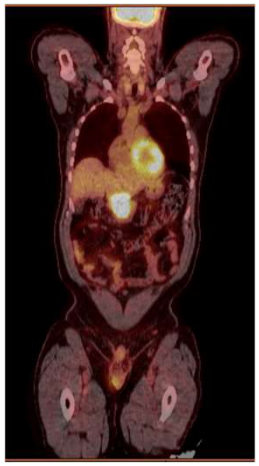
Case 3 – Gastric Cancer



CT CAP:

- Nodular or irregular wall thickening of the distal stomach extending into the gastroduodenal junction
- Several LN in the perigastric region are concerning for local regional lymphadenopathy.

PET/CT:

- Hypermetabolic gastric mass
- No FDG adenopathy or metastatic disease

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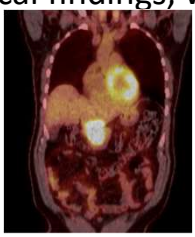
Case 3 – Gastric Cancer Audience Question

Given MRI and clinical findings, what would be next course of action?



- Hypermetabolic distal gastric mass
- No FDG-avid adenopathy or metastatic disease

A) Await IHC- MMR, PDL1 CPS, HER2 — 44%
B) 5-FU, oxaliplatin, taxol (FLOT) — 33%
C) Paclitaxel, carboplatin -> radiation (CROSS) — 0%
D) 5-FU, oxaliplatin, taxol (FLOT) + pembrolizumab — 21%
E) Definitive chemoradiation — 3%

Resectable Gastric Cancer

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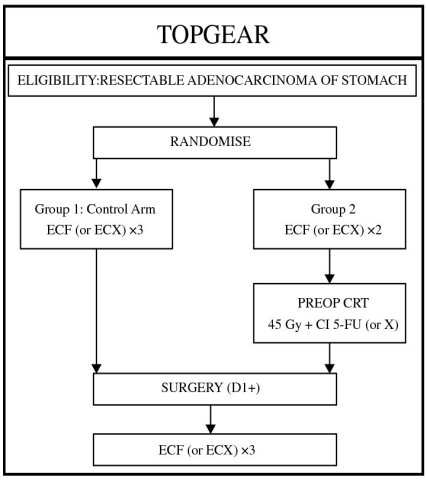
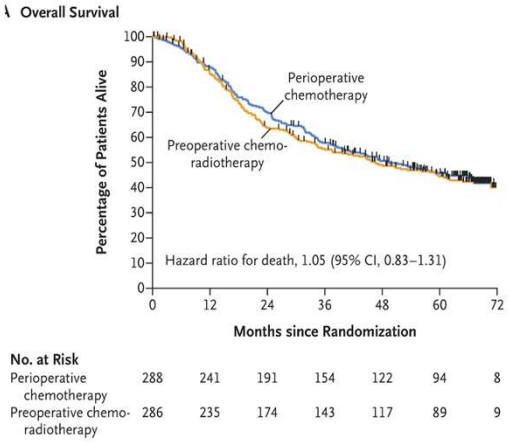
TOPGEAR: chemotherapy +/- XRT for resectable gastric cancer





- pCR in chemoXRT 17% vs. 8% chemo alone
- No difference in mOS (46 vs. 49 mo) or mPFS (31 vs 32 mo)
- Chemotherapy regimen: ECF/ECX 67%, FLOT 33%
- Chemo alone preferred for lower 1/3 of stomach (HR 1.17, 95%CI 1.05-2.77)
- G3+AE: 66 vs 61%

Leong et al. *NEJM* 2024

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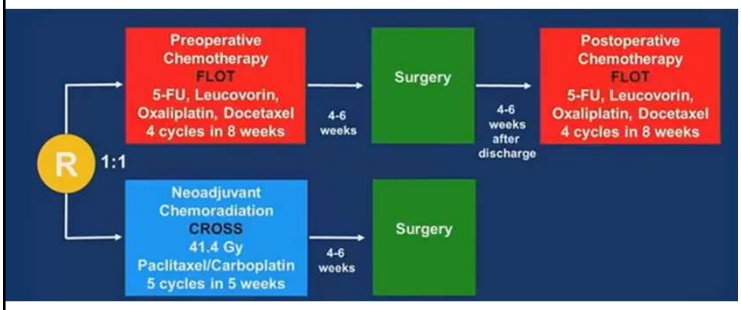
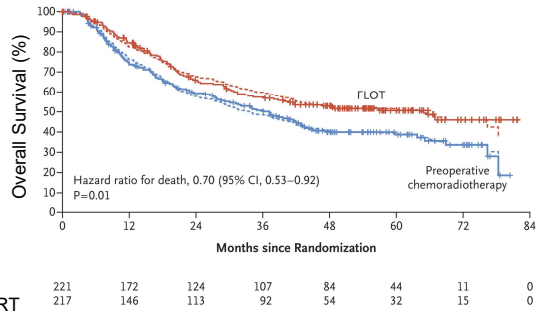
ESOPEC: CROSS vs FLOT for resectable esophageal cancer





mOS @ 3 years:
FLOT 57.4% vs. CROSS 50.7% HR 0.71, p=0.01
G3+ AE: 58% vs. 50%

Hoeppner et al. *NEJM* 2025

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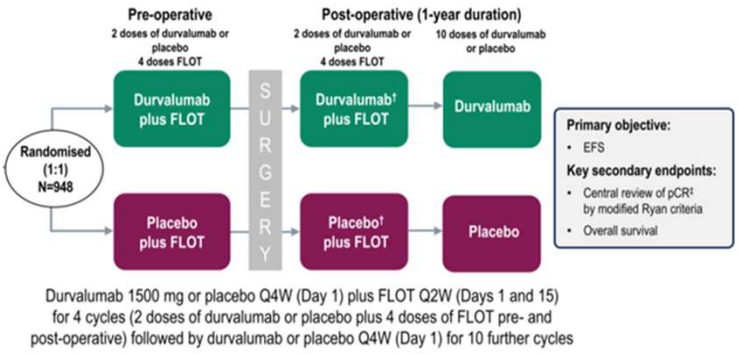
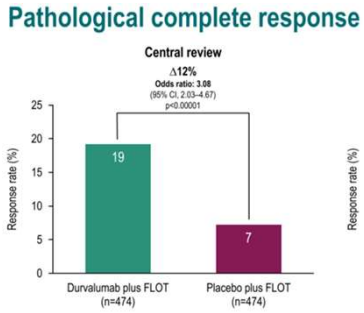
Matterhorn: FLOT+/- durvalumab in resectable gastric and GEJ adenocarcinoma



Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative) followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles



Jangigian et al. *ASCO GI.* 2024

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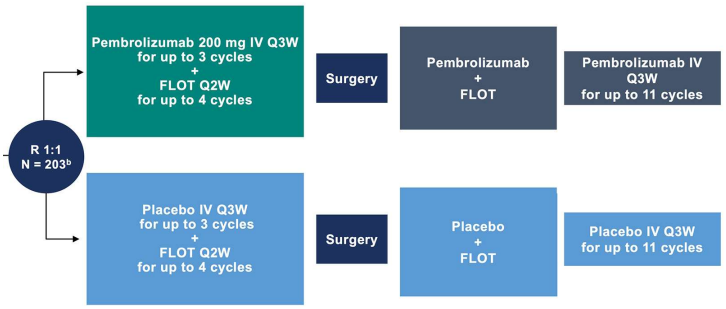
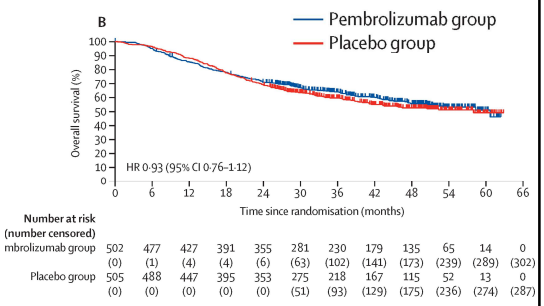
Keynote 585: FLOT+/-pembro for locally advanced, resectable gastric or GEJ





mOS 60.7 mo vs. 58.0 mo *HR* 0.90, p=0.174
FLOT + pembro: R0 resection rate 79% and 80%
pCR 17.0% versus 7.0%

Shitara et al. *Lancet.* 2024

25th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 3 – Gastric Cancer

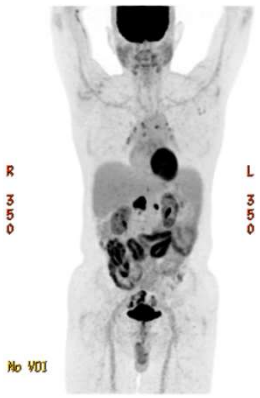
PLAN: 4 cycles of FLOT → distal gastrectomy + D2 LN dissection

HIS COURSE:

- 1 cycle of FLOT -> presented to ED 5 days later with abdominal pain
- CT with pneumoperitoneum secondary to a microperforation of tumor.
- Patient underwent emergent distal gastrectomy with Roux-en-Y reconstruction, D2 lymphadenectomy, and hyperthermic intraperitoneal chemotherapy (HIPEC), complicated by acute tubular necrosis requiring hemodialysis.
- Pathology: 4.5 cm tumor, 1/23 nodes, pT3N1, R0 resection, G3 poorly differentiated, LVI positive

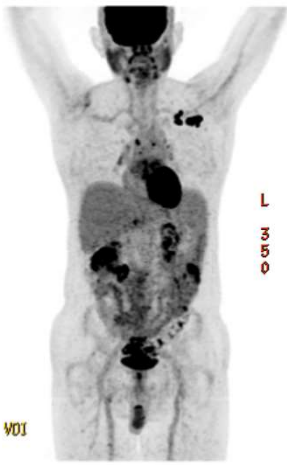
Case 3 – Patient Case

- POD 32, developed SBO followed by pericarditis requiring treatment by steroids, new Cr 3.44 requiring hemodialysis
- PET/CT (3 mo post-op): Two new hypermetabolic retroperitoneal LNs
- Proceeded with 5 –FU single agent x 3 months
- PET (6 mo post-op)- Increased hypermetabolic activity of nodes within the central mesentery and retrocaval region
- Tumor board recommended: SBR 4500 Gy in 5 fractions to perigastric nodes



25th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 3 – Patient Case



- PET/CT (12 months post-op):
  - Enlarged intensely hypermetabolic left retropectoral and axillary lymph nodes consistent with metastatic involvement.
- Axillary LN Biopsy: Metastatic gastric adenocarcinoma
- Now off hemodialysis, Cr 2.20-2.44
- No PMH of autoimmunity
- Molecular profiling: **MLH1 and PMS2 mutated, MLH1 hypermethylated, PDL1 CPS score 100**, HER2 negative, Claudin TBD, no other actionable alterations

25th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 3 – Audience Question

Question 3.2 What would you recommend as next line?

A) Radiation to retropectoral and axillary LN — 4%
B) Pembrolizumab single agent — 71%
C) Oxaliplatin + oral capecitabine+ tislelizumab (Rationale 305) — 4%
D) Oxaliplatin+ oral capecitabine + pembrolizumab (KEYNOTE 859) — 20%

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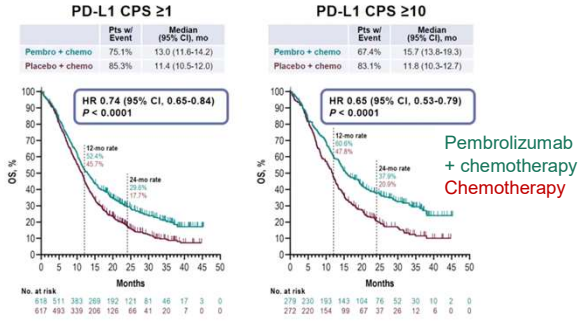
25th Multidisciplinary Management of Cancers: A Case-Based Approach

FDA Approved 1L ICI for HER2- Gastric/GEJ Cancer

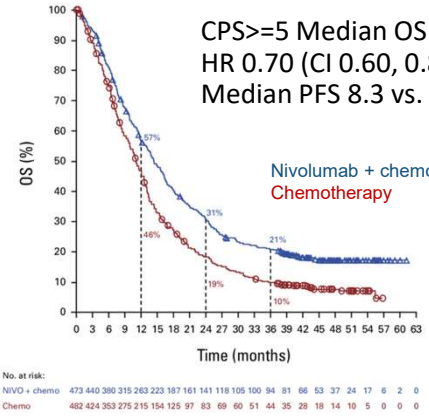
KEYNOTE 859 - pembrolizumab



Pembrolizumab + chemotherapy
Chemotherapy

CPS>=1 Median OS 13.0 vs. 11.4 mo
HR 0.74 (CI 0.65, 0.84)
Median PFS 6.9 vs. 5.6 mo
Grade 3+ SAE: 59% vs. 51%

Checkmate 649- nivolumab



CPS>=5 Median OS 14.4 vs. 11.1 mo
HR 0.70 (CI 0.60, 0.81)
Median PFS 8.3 vs. 6.1 mo

Nivolumab + chemotherapy
Chemotherapy

Rha et al. *The Lancet.* 2023
Janjangan et al. *JCO. 2024*
Qiu et al. *BMJ.* 2024

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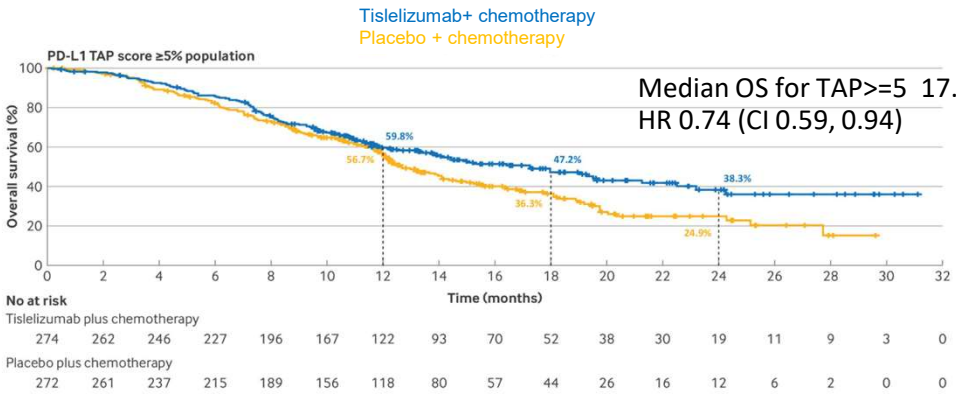
FDA Approved 1L ICI for HER2- Gastric/GEJ Cancer



Median OS for TAP>=5 17.2 vs. 12.6 mo
HR 0.74 (CI 0.59, 0.94)

Median PFS for TAP>=5 7.2 vs. 5.9 mo
Grade 3 + SAE: 54% vs. 50%

Rha et al. *The Lancet.* 2023
Qiu et al. *BMJ.* 2024

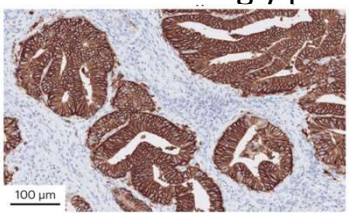
25th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 3 – Gastric Cancer Patient Case

Patient received 1.5 years of single agent pembrolizumab every 2 weeks, c/b Grade 2 pruritis alleviated with topical ointment. Recently completed 4 years of remission.

Case 3 – Audience Question

Question 3.3 What would you do if his tumor was CPS <1, HER2 negative, Claudin 18.2 positive (moderate to strongly positive staining in ≥75% cells)?



A) Radiation to the LN — 5%

B) 5-FU, leuocovorin, oxaliplatin, taxol — 10%

C) Zolbetuximab, CAPOX (GLOW) — 38%

D) Zolbetuximab, mFOLFOX (SPOTLIGHT) — 48%

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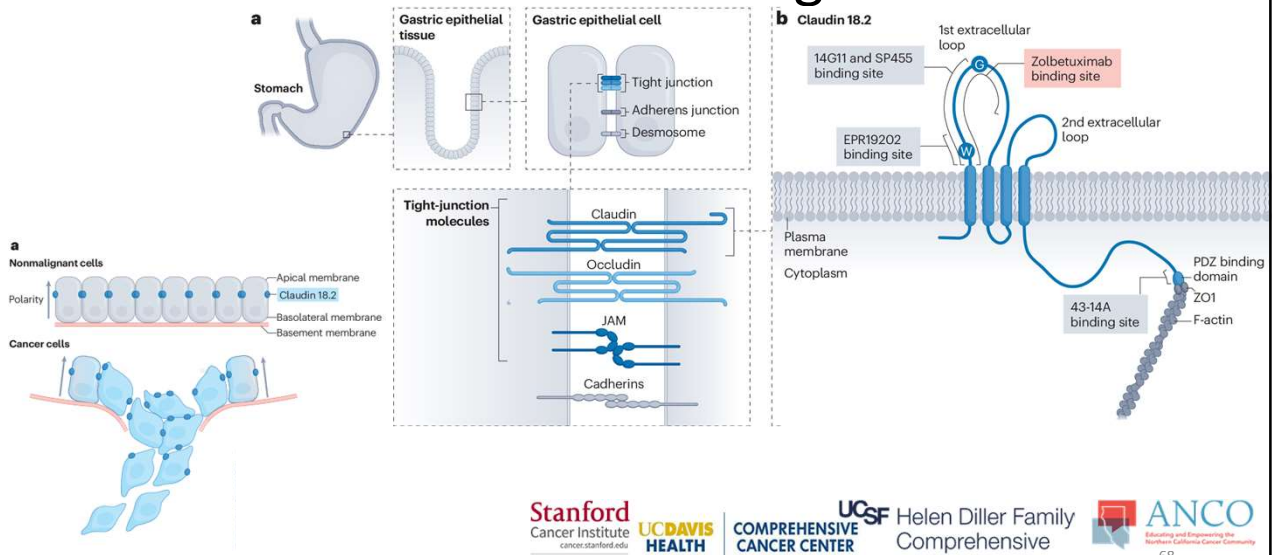
Case 3 – Claudin 18.2 Background



Nakayama et al. *Nature Reviews Clinical Oncology*. 2024

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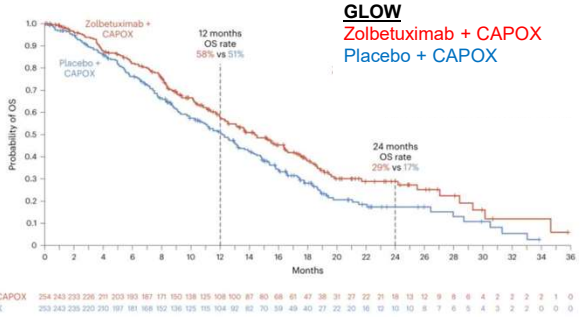
25th Multidisciplinary Management of Cancers: A Case-Based Approach

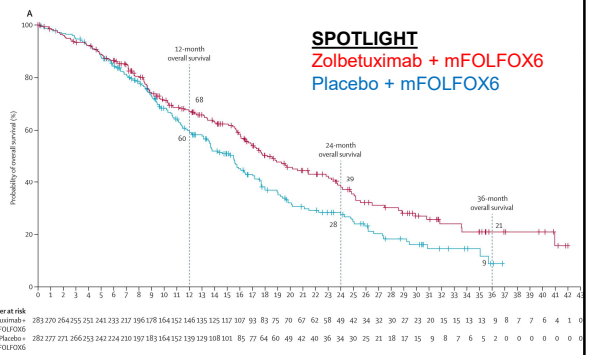
Claudin 18.2 Targeted Clinical Trials

25th Multidisciplinary Management of Cancers: A Case-Based Approach

Comparison of 1L Claudin 18.2+ trials for Gastric and GEJ



GLOW
Zolbetuximab + CAPOX
Placebo + CAPOX



SPOTLIGHT
Zolbetuximab + mFOLFOX6
Placebo + mFOLFOX6

Median OS 14.4 vs. 12.2 mo
HR 0.771 (CI 0.6195, 0.965)

Median OS 18.2 vs. 15.2 mo
HR 0.7501 (CI 0.601, 0.936)

Notable adverse side effects: nausea, vomiting

Shahi et al.*Nature Medicine.* 2023
Shitara et al. *The Lancet.* 2023

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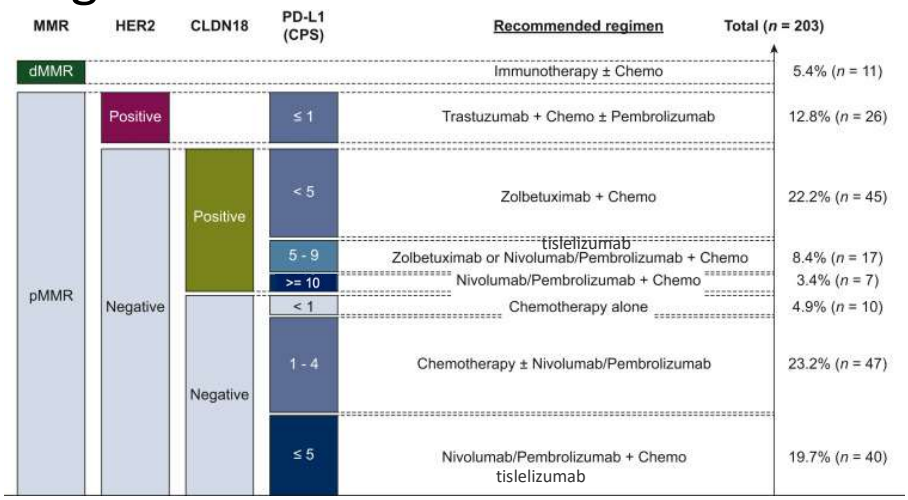
Algorithm for GEJ Cancer Treatment



Modified Okazaki et al. *ESMO Gastrointestinal Oncology*. 2024

Case 3 – Gastric Cancer Panel Discussion

1. In the setting of a local recurrence, what factors impact your choice of local vs systemic therapy?
2. How do you choose from pembrolizumab, nivolumab, and tislelizumab for 1L?
3. For CPS 1-5, Claudin 18.2 +, would you choose IO vs. zolbetuximab to use first?

Case 3 – Summary for Gastric and GEJ tumors

1. With triple biomarker disease (HER2, CPS, Claudin 18.2), we have multiple frontline combination regimens.
2. If HER2 negative and high PDL1 CPS, chemotherapy + ICI is first line, but can consider single agent ICI if concerns about chemotherapy toxicity
3. Zolbetuximab + chemotherapy is now standard of care for Claudin 18.2+ tumors, but slow translation due to side effect profile and practicality (infusion times)

Gastroesophageal Cancer Trials

Current Trials
Future Trials

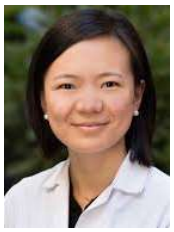
Kaiser Permanente
- 2nd +line Nivolumab/paclitaxel/ramucirumab vs. paclitaxel/ramucirumab with PD-L1 CPS>=1 (Alliance A022102)
- 1st line: mFOLFIRINOX +/- nivolumab vs. FOLFOX+/- nivolumab for HER2 negative GEJ

Stanford
- 2nd+ line: Neratinib/Trastuzumab-deruxtecan for HER2+ GI cancers
- 2nd+ line: AZD0901 Claudin 18.2 ADC
- 2nd+ line: INCB161734 (KRAS G12D inhibitor) +/- chemo

UC Davis
- 2nd +line: Nivolumab/paclitaxel/ramucirumab vs. paclitaxel/ramucirumab with PD-L1 CPS>=1 (Alliance A022102)
- 2nd +Line: M6620 + Irinotecan with Progressive TP53 mutant GEJ cancers

Case 4- Rectal Cancer

1. What is the incidence and biology of KRAS mutations in colorectal cancer?
2. What are the data for the FDA approvals of KRAS G12C inhibitors in CRC?


Case 4 – Patient Case

65 y.o. male, FIT test positive

- Colonoscopy showed a 2 cm, fungating, non-circumferential, non-obstructing mass in the distal rectum, 3-6 cm proximal to the anus, ECOG 0
- Pathology Biopsy: tubulovillous adenoma

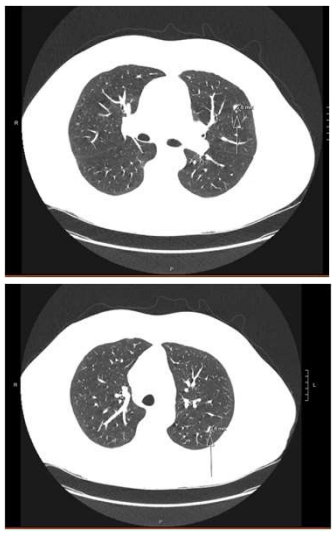
Case 4 – Patient Case

Flexible sigmoidoscopy: 3 cm lesion in the rectum removed by endoscopic submucosal dissection

Pathology: 2.5 cm pT1 invasive adenocarcinoma R0 resection

- G1 well differentiated, LVI+, PNI+
- pMMR, Molecular profiling pending

CT Chest: Seven pulmonary nodules are indeterminate however at least two appear spiculated



Case 4 – Rectal Cancer Audience Question

Question 4.1. What is your next recommended course of treatment?

A) Await molecular profiling results — 14%

B) Start FOLFOX — 7%

C) Start course of definitive chemoradiation — 19%

D) Biopsy/Lobectomy for confirmation of metastatic disease — 60%

Case 4 – Patient Case

- PFTs within normal limits
- Wedge resections of the left lower lobe performed
- Pathology: 1.1 and 1.2 cm foci of HER2- metastatic colorectal adenocarcinoma

SUMMARY OF FINDINGS	
APC R283* (Pathogenic)	*KRAS* G12C (Pathogenic)
Estimated tumor mutation burden: 5.0 mut/Mb†	
The following variants are not known to be clinically relevant at this time:	
CASP8 T407M (Unknown significance)	*POLE* M1769V (Unknown significance)
Please see the following pages for variant annotations.	

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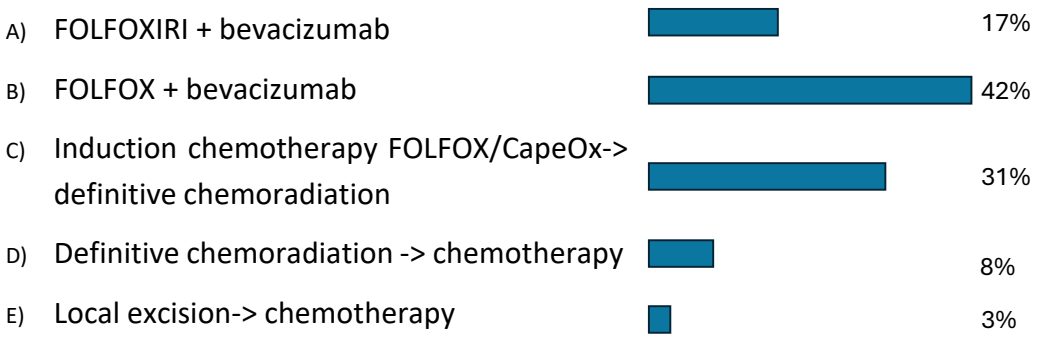
Case 4 – Audience Question

Question 4.2. In a T1NXM1, high risk pt, how would you would treat next?



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Case 4 – Patient Case

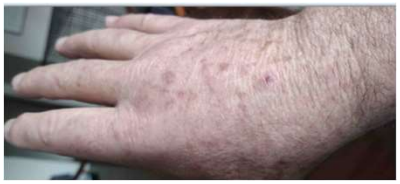
Received 1 cycle of CAPEOX c/b Grade 1 hand and foot syndrome,

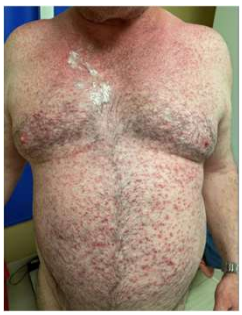
2 additional cycles of oxaliplatin. Severe brain fog led to patient preference for discontinuance.

Switched to adagrasib + cetuximab and completed 6 cycles c/b Grade 2 EGFR inhibitor rash Grade 1 arthralgias

CT CAP: no evidence of metastatic disease

MRI Abd/Pelvis: no evidence of residual or recurrent rectal tumor





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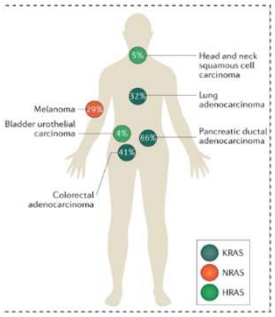
Case 4 – Prevalence of KRAS mutations



% total disease	KRAS	KRAS G12D	KRAS G12V	KRAS G12C	KRAS G13D
CRC	>40	15	9	3	7
PDAC	>85	37	28	1	1
NSCLC	>30	4	6	12	1

Moore et al. *Nature Reviews Drug Discovery*. 2020
Nassar et al. *NEJM*. 2021

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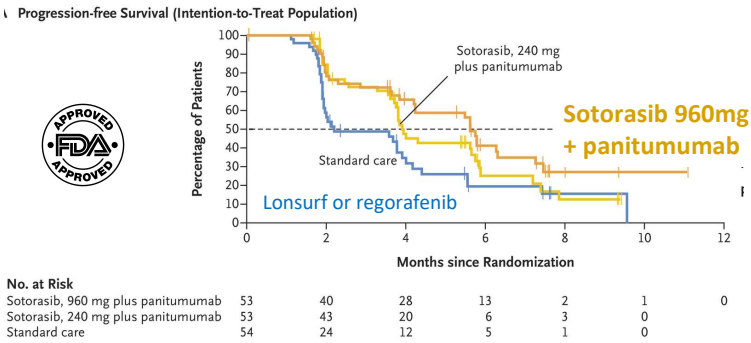
FDA Approved 2L+ KRAS G12C Inhibitors for mCRC

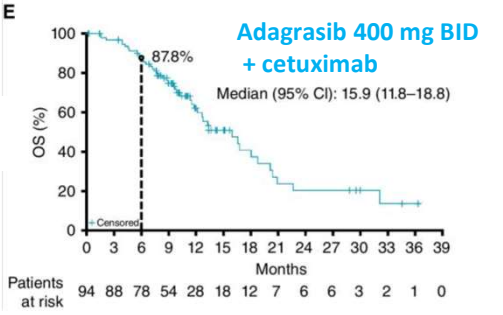
CodeBreaK300- sotorasib



mPFS 5.6 mo vs. 2 mo
ORR 26% vs. 0 %, mDOR 4.4 mo
Not powered for OS, mOS (mo): NR vs. 10.3
HR 0.7 (960mg) p<0.0001

Fakih et al. *NEJM .2023*
Yaeger et al. *Cancer Discovery* 2024

KRYSTAL-1- adagrasib



mPFS 6.9 mo, ORR 34% mDOR 5.8 mo
Median follow-up 11.9 mo:
Median OS (mo): 15.9 (11.8-18.8)

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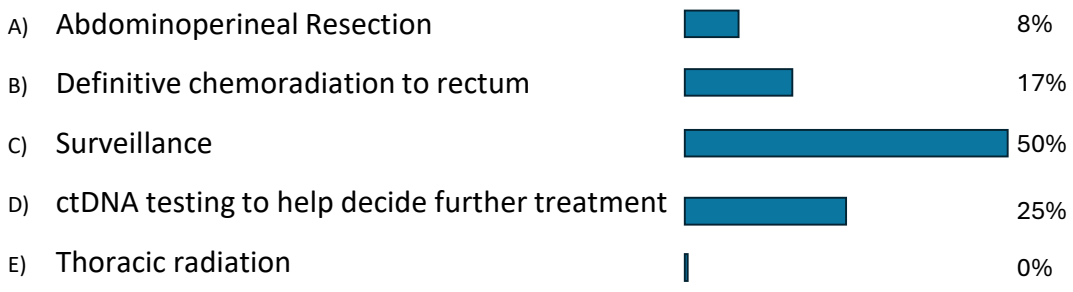
Case 4 – Audience Question

Question 4.3. What would be your next step?



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Case 4 – Gastric Cancer Panel Discussion

- Do you have preference for adagrasib vs. sotorasib and why?
- When would you consider chemoradiation and surgery for the primary tumor in the setting of metastatic rectal cancer?

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Case 4 – Rectal Cancer

Patient is currently completing long course chemoradiation and referred to Phase 1 clinic for consideration for KRASg12C trials.

Plan for restaging and discussion of definitive ablation or resection of lung lesions vs. continuing systemic therapy with adagrasib + cetuximab.

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Case 4 –Summary for Rectal Cancer

1. Two newly FDA approved KRAS inhibitors for KRAS G12C mutated tumors as second line with many ongoing and future trials moving to first line and others focusing on more prevalent KRAS G12D KRAS G12V mutations.
2. Can consider induction chemotherapy for patients with oligometastatic disease, but TNT approach can still be pursued.

Colorectal Cancer Trials

Current Trials
Future Trials

Kaiser Permanente

- Adjuvant Chemotherapy Based on Evaluation of Residual Disease (CIRCULATE-US)

Stanford

- 2nd+ line: Neratinib/Trastuzumab-deruxtecan for HER2+ GI cancers
- 2nd+ line: AZD0022 (KRAS G12D inhibitor) +/- chemo
- 2nd+ line: INCB161734 (KRAS G12D inhibitor) +/- chemo

UCSF

- A Phase II Study of Preoperative Immunotherapy in Patients With Colorectal Cancer and Resectable Hepatic Metastases
- Phase 1 Multicenter Study Evaluating the Safety and Tolerability of GCC19CART for Subjects With Relapsed or Refractory Metastatic Colorectal Cancer

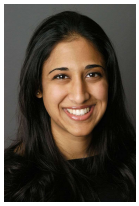
UC Davis

- Adjuvant Chemotherapy Based on Evaluation of Residual Disease (CIRCULATE-US)

25th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 5 – Biliary Tract Cancer

1. How common is HER2+ in cholangiocarcinoma and gallbladder cancer and what is the biology?
2. What are the data for FDA approved HER2-directed therapies in biliary tract cancers?



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Case 5 – Biliary Tract Cancer

70 y.o. female with PMH of post-COVID bronchiolitis obliterans organizing pneumonia, dx 2023, now off immunosuppression, presents to pulmonology clinic with mild abdominal discomfort. ECOG 1

Tbili 4/ AST 1779/ ALT 671/ Alk Phos 1198

Abdomen US: No bile duct dilation. Gallbladder sludge and small stones without definitive evidence of acute cholecystitis.

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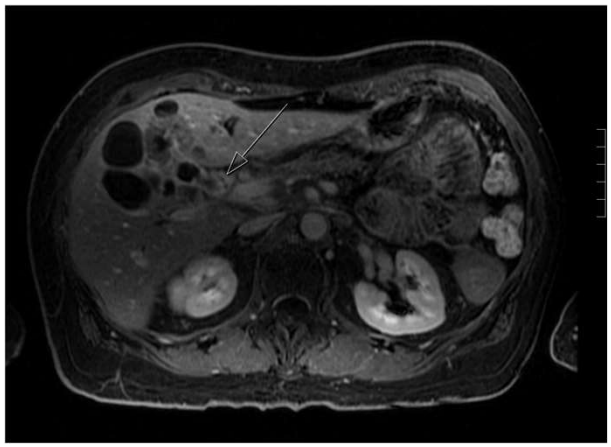
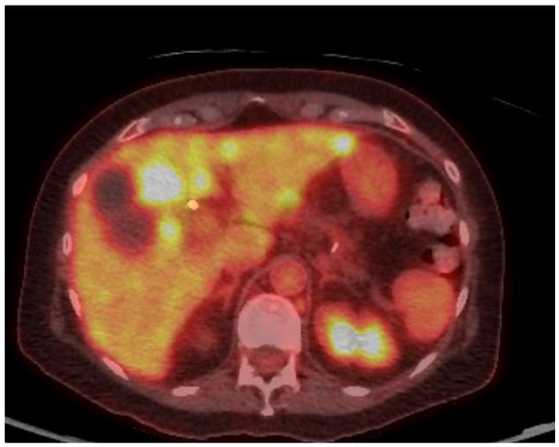
Case 5 – Patient Case





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Case 5 – Patient Case

ERCP: single biliary stricture in the common hepatic duct. A biliary sphincterotomy performed. One plastic stent placed into the common hepatic duct.

Porta Hepatis LN biopsy: Involved by adenocarcinoma, pMMR, **HER2 by IHC 3+,** CK7 +, CK20 +, PAX8-, TTF-1-

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Case 5 – Audience Question

Question 5.1 What would you do as next step?

A)	Expedite molecular profiling	0%
B)	Initiate first line systemic treatment	0%
C)	Enroll in clinical trial	0%

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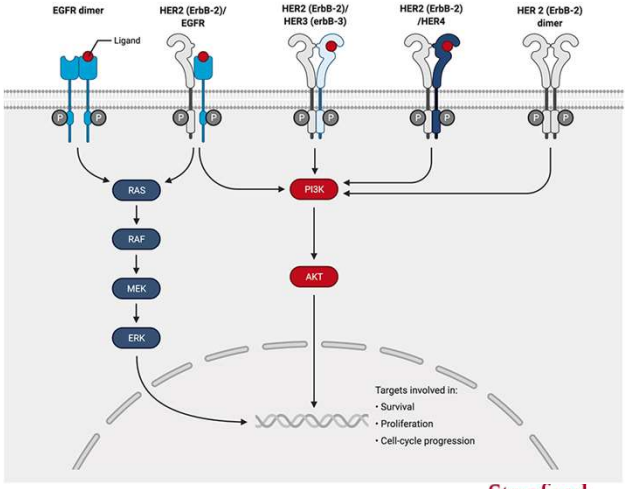
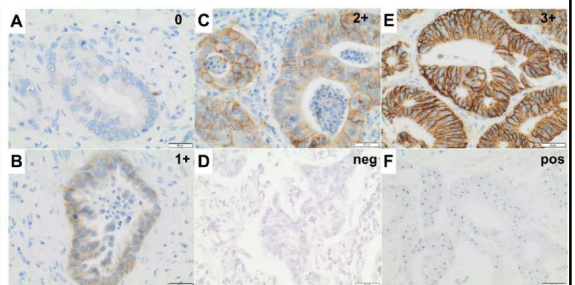
HER2 in Biliary Tract Cancers



Primary Tumor Site	Frequency of HER2 Alteration (S. Korea)	Frequency of HER2 Alteration (Europe)
Intrahepatic Cholangiocarcinoma	5.8%	4.2%
Extrahepatic Cholangiocarcinoma	13.9%	9.7%
Gallbladder Cancer	36.4%	
Ampulla of Vater	18.2%	



Rockland.com
Ayasun et al. *Cancers* 2023
Albrecht et al. *BMC Cancer* 2019

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Case 5 – Audience Question

Question 5.2 What would you use for first line treatment?

A. Gemcitabine/Cisplatin/Durvalumab or pembrolizumab 0%
B. Gemcitabine/Cisplatin/Trastuzumab 0%
C. Gemcitabine/Cisplatin/Trastuzumab/Pembrolizumab 0%
D. FOLFOX/Trastuzumab 0%
E. 5-FU/Cisplatin/Trastuzumab/Pembrolizumab (KEYNOTE-811 from gastric) 0%

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Case 5 – Patient Case

- Gemcitabine/cisplatin/trastuzumab sent for authorization, trastuzumab denied and sent for appeal
- Sent to ED for episode of cholangitis with Enterobacter cloaca bacteremia and stent migration given i.v. antibiotics + bilateral PE requiring therapeutic anticoagulation
- Gemcitabine/cisplatin for two cycles, Trastuzumab approved and added during Cycle 2
- Patient was admitted for second episode of cholangitis with Serratia maraceans and given i.v. antibiotics

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Case 5 – Panel Discussion

Question 5.3 What would you use for second line treatment?

A) Trastuzumab-deruxtecan (Enhertu)	0%
B) Perjeta/Trastuzumab	0%
C) Zanidatamab	0%
D) FOLFOX/Trastuzumab	0%
E) Ado-trastuzumab (T-DM1)	0%

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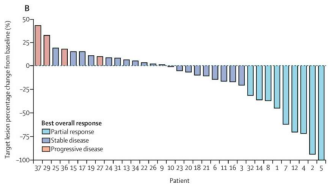
HER2 Overexpression and/or Amplifications seen in 10-15% of Biliary Tract Cancers

Trastuzumab/Pertuzumab
(2 monoclonal antibodies)

MyPathway (N=39)
HER2 3+ by IHC, *HER2:CEP17* >2.0 or HER2 CN>6.0 by FISH/CISH, or HER2 amp by NGS

ORR: 23%
DoR: 10.8 months

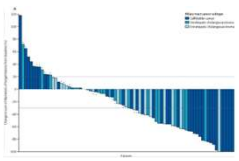


Javle, et al. *Lancet Onc*, 2021

Zanidatimab
(bi-specific antibody)

HERIZON-BTC-01 (n=80)
HER2 2+ or 3+ by IHC

ORR: 41.3%
DoR: 12.9 months
ORR 51.6%/5.6% for IHC 3+/2+

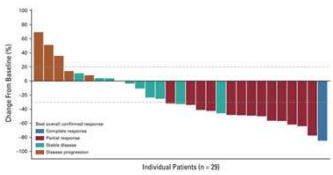


Harding, et al. *Lancet Onc*, 2023

Trastuzumab/Tucatinib
(monoclonal Ab/small molecule)

SGNTUC-019 (n=30)
HER2 3+ by IHC, *HER2:CEP17* >2.0 or HER2 CN>6.0 by FISH/CISH, or HER2 amp by NGS

ORR: 46.7%
DoR: 6.0 months

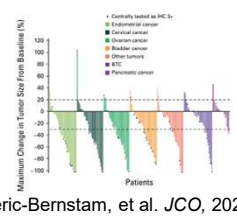


Nakamura, et al. *JCO*, 2023

Trastuzumab-deruxtecan
(antibody drug conjugate)

DESTINY-PanTumor 02
(n=41 with BTC)
HER2 2+ or 3+ by IHC

ORR 22%
DOR 8.6 months
ORR 56.3%/0% for IHC 3+/2+



Meric-Bernstam, et al. *JCO*, 2024

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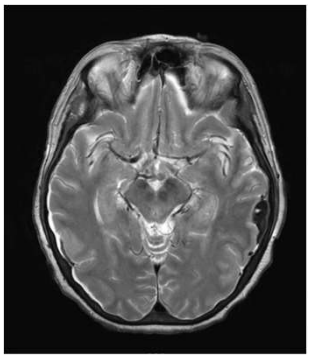
Case 5 – Patient Case

Received second dose of trastuzumab, chemotherapy held due to ongoing antibiotic treatment. Pertuzumab appealed for authorization.

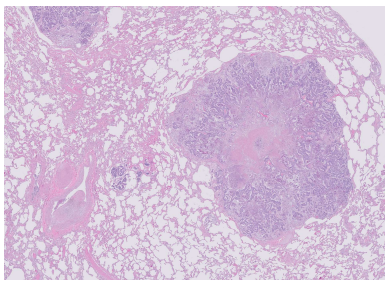
Within 2 weeks, presented with a nosebleed, word finding difficulties

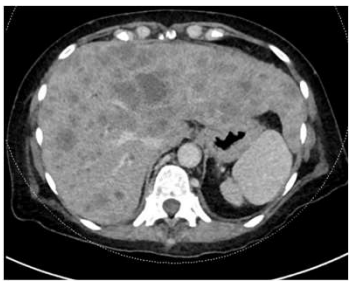
- CT Head: bilateral subdural hematomas secondary to therapeutic anticoagulation
- Septic shock and admitted to the neuro ICU
- Not a surgical candidate
- Transitioned to inpatient hospice-> passed on Day 9 of admission.
- 5 months survival since diagnosis



Case 5 – Patient Case

Patient gifted her body to science for the rapid autopsy program and on gross review: the entire liver replaced by tumor, mostly necrotic, with innumerable small metastatic lung lesions (image)





Case 5 – Summary for Biliary Tract Cancer

1. HER2 staining should be conducted at time of initial pathology diagnosis on all GI tumor tissues
2. HER2 targeted treatment approved in the 2L, would consider fam-trastuzumab deruxtecan (Enhertu)
3. There are increasing numbers of HER2 targeted options and would consider 1L HER2 BTC clinical trials

Cholangiocarcinoma Trials

Current Trials
Future Trials

Stanford

- Neoadjuvant/Perioperative: OPT-IN chemotherapy around re-resection for incidental gallbladder cancer
- Adjuvant: Rilvegostomig (bispecific Ab against PD-1 / TIGIT) + chemo vs chemo
- 2nd+ line: Neratinib/Trastuzumab-deruxtecan for HER2+ GI cancers
- 2nd+ line: AZD0901 Claudin 18.2 antibody drug conjugate
- 2nd+ line: CGT4859 (FGFR2/3 inhibitor) for FGFR-altered tumors
- 2nd+ line: INCB161734 (KRAS G12D inhibitor) +/- chemo
- 3rd+ line: Tinengotinib (FGFR inhibitor) in FGFR-fusion+ cholangiocarcinoma

UCSF

- 1st line: T-DXd and Rilvegostomig versus Gemcitabine, Cisplatin, and Durvalumab for Advanced HER2+ BTC
- 3rd + line: TYRA-200 in Intrahepatic Cholangiocarcinoma and Other Solid Tumors with FGFR2 Alterations (SURF-201)

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GI Multi-Histology Trials

Current Trials
Future Trials

Stanford

- 2nd+ line: CGT4859 (FGFR2/3 inhibitor) for FGFR-altered tumors
- 2nd+ line: Neratinib/Trastuzumab-deruxtecan for HER2+ GI cancers
- 2nd+ line: AZD0901 Claudin 18.2 antibody drug conjugate
- 2nd+ line: AZD0022 (KRAS G12D inhibitor) +/- chemo
- 2nd+ line: INCB161734 (KRAS G12D inhibitor) +/- chemo
- 2nd+ line: Phase 1 TYRA-430 in HCC and Other Solid Tumors with Activating FGF/FGFR pathway aberrations (SURF-431)

UCSF

- Phase II Study of Hypofractionated Radiation Therapy to Augment Immune Response in Patients With Metastatic Gastrointestinal Malignancies Progressing on Immune Therapy (ARM-GI)
- Phase I/II FMC-376 in Participants with KRAS G12C Mutated Locally Advanced Unresectable or Metastatic Solid Tumors
- Phase I Dose Escalation and Expanded Cohort Study of P-MUC1C-ALLO1 in Adult Subjects With Advanced or Metastatic Solid Tumors
- Phase I of AZD3470, a PRMT5 Inhibitor, in Patients With MTAP Deficient Advanced/Metastatic Solid Tumors (PRIMROSE)
- Phase I Study of Autologous CD8+ and CD4+ Engineered T Cell Receptor T Cells in Subjects With KRASG12V Advanced or Metastatic Solid Tumor

UCDavis

- 2nd + Line: Phase 1 ceraleserib + trastuzumab deruxtecan for HER2+ cancers

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