Gastrointestinal Cancer Management in North Carolina: Updates for 2020

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Learning Objectives

- Discuss optimal management for patients with advanced hepatocellular carcinoma with normal liver function
- Discuss new targeted therapy options in subsets of patients with metastatic colorectal cancer
- Discuss optimal duration and course of adjuvant therapy for stage III colon cancer

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Key updates: Focus on targeted and immune checkpoint inhibitor therapies

- Systemic therapy for metastatic gastric and esophageal cancers
- Systemic therapy for unresectable or metastatic hepatocellular carcinoma
- Systemic therapy for metastatic cholangiocarcinoma
- Adjuvant therapy for pancreatic cancer
- Biomarkers in pancreatic cancer
- Adjuvant chemotherapy duration for colon cancer
- New targeted therapy options for metastatic colorectal cancer

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Case 1

You meet a 60 year old male patient with newly diagnosed cholangiocarcinoma with bone and lung metastases. You decide to send next generation sequencing and additional molecular testing. You also start him on first-line gemcitabine + cisplatin. Unfortunately, he progresses after 6 cycles. He continues to have performance status of 1. Which of the following next line treatment options would not be indicated based on results of the biomarker testing:

A) Pembrolizumab if MSI-High
B) Pemigatinib if FGFR2 amplification
C) Pemigatinib if FGFR2 fusion
D) FOLFOX if no actionable aberration

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Case 2

You meet a 56 year old female patient who was diagnosed with resectable adenocarcinoma of pancreatic head. She underwent Whipple resection with negative margins and had pT2N0 disease. Which of the following statements about adjuvant therapy is NOT correct?

A) Adjuvant FOLFIRINOX results in superior overall survival compared to adjuvant gemcitabine
B) Adjuvant gemcitabine+nab-paclitaxel results in superior disease free survival compared to adjuvant gemcitabine
C) Adjuvant gemcitabine+capecitabine results in superior overall survival compared to adjuvant gemcitabine

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Case 3

You meet a 49 year old female patient who was diagnosed with metastatic cecal adenocarcinoma with peritoneal carcinomatosis. She received first-line FOLFOXIRI+bevacizumab before eventually progressing. She continues to have performance status of 0. Which of the following next line treatment options would be the best choice based on results of the biomarker testing:

A) Encorafenib + cetuximab if BRAF V600E mutation
B) Ipilimumab only if MSI-High
C) Irinotecan+cetuximab if BRAF V600E mutation
D) Atezolizumab + cobimetinib only if KRAS mutation

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Systemic therapies for advanced gastroesophageal cancers

Current Therapies (exclusive of immune checkpoint inhibitors)

1L	2L	3L
FOLFOX (+Trastuzumab if HER2 amp)	Paclitaxel+Ramucirumab* Irinotecan-based if neuropathy	Irinotecan Taxane Tipiracil+Trifluridine

*Ramucirumab only for adenocarcinoma

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Immune checkpoint inhibitors in metastatic gastroesophageal cancers

- 2nd-line for esophageal squamous cell carcinoma with PD-L1 CPS ≥10
- 2nd-line for any with MSI-High disease
- 3rd-line for gastroesophageal adenocarcinoma with PD-L1 CPS ≥1
  - But response rates may be more enriched with CPS ≥10

KEYNOTE-059	PD-L1 negative (n=109)	PD-L1 CPS ≥1 (n=148)	PD-L1 CPS ≥10 (n=46)
Response rate	6.4% (2.6-12.8)	15.5% (10.1-22.4)	17.4%

Fuchs CS, et al, JAMA Oncol 2018. Wainberg ZA, et al, GI ASCO 2020

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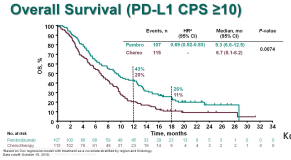
Pembrolizumab was superior to SOC chemotherapy in esophageal SCC with CPS ≥10: KEYNOTE-181

Overall Survival (PD-L1 CPS ≥10)



Kojima T, et al, GI ASCO 2019

- Among 168 PD-L1 CPS ≥10 SCC, median OS with pembrolizumab was 10.1 mo (7.0-13.4) vs 6.7 mo (4.8-8.6) with chemo (HR 0.61; 95% CI 0.44-0.85) (Shah MA, et al, ASCO 2019)
- Pembrolizumab was FDA approved in this indication in Jul 2019

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Systemic therapies for advanced gastroesophageal cancers

Current Therapies (exclusive of immune checkpoint inhibitors)

1L	2L	3L
FOLFOX (+Trastuzumab if HER2 amp)	Paclitaxel+Ramucirumab* Irinotecan-based if neuropathy Pembro (SCC w/ CPS≥10; or MSI-H)	Irinotecan Taxane Tipiracil+Trifluridine Pembro (CPS≥1)

*Ramucirumab only for adenocarcinoma

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Hepatobiliary cancers

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Current landscape of systemic therapies for HCC

First-Line Therapies	Child-Pugh	Median OS	Comparator OS
Atezolizumab + Bevacizumab	A	Not reached	13.2 mo (sorafenib)
Sorafenib	A or B7	10.7 mo	7.9 mo (placebo)
Lenvatinib	A	13.6 mo	12.3 mo (sorafenib)
Nivolumab (if not candidate for TKI)		16.4 mo (NS)	14.7 mo (sorafenib)

Second-Line Therapies	Child-Pugh	Median OS	Comparator OS
Regorafenib	A	10.6 mo	7.8 mo (placebo)
Nivolumab (acc)	A or B	ORR 20%	
Ipilimumab + Nivolumab	A	ORR 33% (16/49)	
Pembrolizumab	A	13.9 mo (NS)	10.6 mo (placebo)
Cabozantinib	A	10.2 mo	8.0 mo (placebo)
Ramucirumab for AFP≥400	A	8.5 mo	7.3 mo (placebo)

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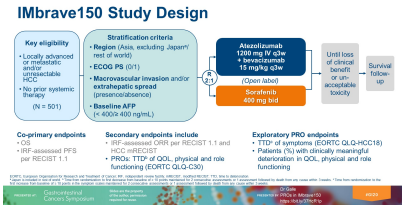
Atezolizumab + Bevacizumab compared against Sorafenib in unresectable or metastatic HCC



Galle PR, et al, GI ASCO 2020

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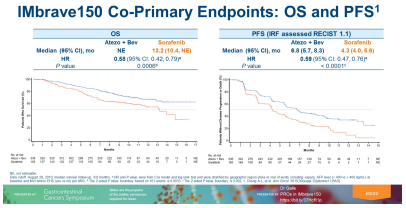
Atezolizumab + Bevacizumab improved OS and PFS compared to sorafenib



Galle PR, et al, GI ASCO 2020

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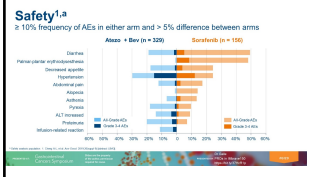

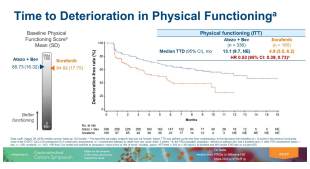

Galle PR, et al, GI ASCO 2020

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Ipilimumab + Nivolumab recently received accelerated FDA approval

- CheckMate-040

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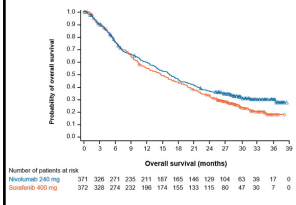
First-line nivolumab was not superior to sorafenib (CheckMate 459)



	Nivolumab (n=371)	Sorafenib (n=372)	HR
mOS	16.4 mo (13.9-18.4)	14.7 mo (11.9-17.2)	0.85 (0.72-1.02) (p=0.0752)
mPFS	3.7 mo (3.1-3.9)	3.8 mo (3.7-4.5)	

Consider if not a candidate for antiangiogenic therapy and/or TKI, but would not routinely recommend over sorafenib or lenvatinib

Yau T, et al, ESMO 2019

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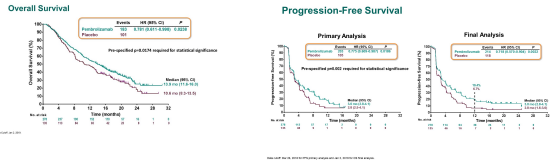
Pembrolizumab trended toward better OS and PFS than best supportive care in 2nd-line treatment

- However, based on statistical design of the KEYNOTE-240 study with dual primary endpoints, the result was not deemed statistically significant significant



Finn RS, et al, ASCO 2019

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Current landscape of systemic therapies for HCC

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Multiple ongoing questions

- Additional novel combinations of immune checkpoint inhibitors and anti-angiogenic (and other) therapies
- Identifying predictive or prognostic biomarkers
- Treatment options for Child Pugh class B patients
- Efficacy of these more effective systemic therapies in earlier stages of disease
- Emphasis on ongoing care for cirrhosis (variceal screening and treatment)

It is an exciting era for novel treatments in hepatocellular carcinoma!

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Systemic therapies in cholangiocarcinoma

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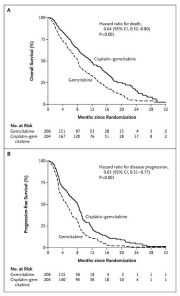
Chemotherapy for metastatic biliary tract and gallbladder cancers

- Gemcitabine/cisplatin is current standard of care and improved OS compared to gemcitabine monotherapy (ABC-02 trial)

	Gem/Cis (n=204)	Gem (n=206)	HR
mOS	11.7 mo	8.1 mo	0.64 (0.52-0.80) (p<0.001) Adjusted HR 0.67 (0.54-0.84)
mPFS	8.0 mo	5.0 mo	0.63 (0.51-0.77) (p<0.001)



Valle J, et al, NEJM 2010

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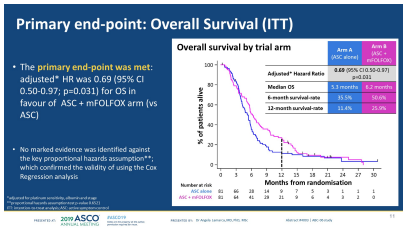
FOLFOX superior to best supportive care for 2nd-line therapy for metastatic biliary tract cancers (ABC-06)



Lamarca A, et al, ASCO 2019

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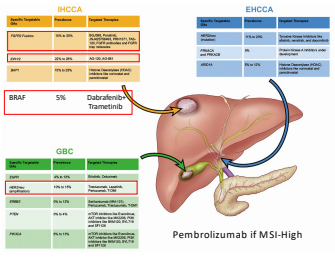
Emerging biomarkers and targeted therapies in cholangiocarcinomas

Pemigatinib received accelerated FDA approval 4/17/20



Jain A and Javle M. JGO 2016

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FGFR2 inhibitor pemigatinib is effective for cholangiocarcinoma with FGFR2 fusion/rearrangement

- 9% of screened patients had FGFR2 fusion or rearrangement
- ORR 35.5% (26.5-45.4), with 3% complete response. Median duration of response was 9.1 mo

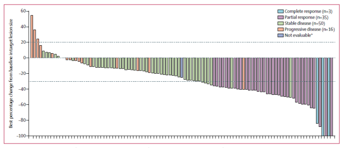

Figure 2: **Best percentage change from baseline in target lesion size for individual patients with *FGFR2* fusions or rearrangements**
Coloured bars indicate confirmed responses assessed by RECIST 1·1. FGFR=fibroblast growth factor receptor. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. *Patient had a decrease in target lesion size but was not evaluable for response using RECIST.

Abou-Alfa GK, et al. Lancet Oncol 2020

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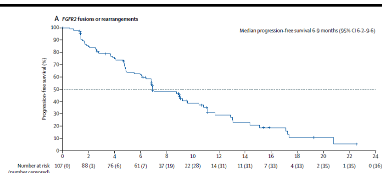

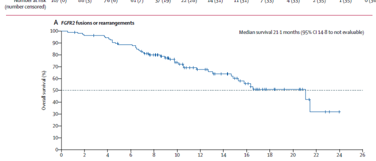

Abou-Alfa GK, et al. Lancet Oncol 2020

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Pemigatinib side effects

	Grade 1–2	Grade 3	Grade 4
Hyperphosphataemia†	81 (55%)	0	0
Alopecia	67 (46%)	0	0
Dysgeusia	55 (38%)	0	0
Diarrhoea	49 (34%)	4 (3%)	0
Fatigue	45 (31%)	2 (1%)	0
Stomatitis	39 (27%)	8 (5%)	0
Dry mouth	42 (29%)	0	0
Nausea	34 (23%)	2 (1%)	0
Decreased appetite	34 (23%)	1 (1%)	0
Dry eye	30 (21%)	1 (1%)	0
Dry skin	22 (15%)	1 (1%)	0
Arthralgia	16 (11%)	6 (4%)	0
Palmar-plantar erythrodysaesthesia	16 (11%)	6 (4%)	0
Constipation	20 (14%)	0	0
Hypophosphataemia*	8 (5%)	10 (7%)	0
Pain in extremity	15 (10%)	0	0
Vomiting	13 (9%)	1 (1%)	0
Weight decreased	13 (9%)	1 (1%)	0
Myalgia	10 (7%)	1 (1%)	0
Nail discolouration	10 (7%)	1 (1%)	0
Abdominal pain	8 (5%)	1 (1%)	0
Anaemia	8 (5%)	1 (1%)	0
Onychoclasis	8 (5%)	1 (1%)	0
Paronychia	8 (5%)	1 (1%)	0
Hyponatraemia	4 (3%)	3 (2%)	1 (1%)
Urinary tract infection	7 (5%)	1 (1%)	0
Hypercalcaemia	5 (3%)	1 (1%)	0

(Table 3 continues in next column)

	Grade 1–2	Grade 3	Grade 4
(Continued from previous column)			
Skin exfoliation	5 (3%)	1 (1%)	0
Blood alkaline phosphatase increased	2 (1%)	2 (1%)	0
Acute kidney injury	3 (2%)	1 (1%)	0
Erythema	3 (2%)	1 (1%)	0
Nail disorder	3 (2%)	1 (1%)	0
Aspartate aminotransferase increased	1 (1%)	2 (1%)	0
Alanine aminotransferase increased	2 (1%)	1 (1%)	0
Dysphagia	2 (1%)	1 (1%)	0
Keratitis	2 (1%)	1 (1%)	0
Rash pruritic	1 (1%)	1 (1%)	0
Hyperbilirubinaemia	0	1 (1%)	0
Hypokalaemia	0	1 (1%)	0
Proteinuria	0	1 (1%)	0
Skin toxicity	0	1 (1%)	0
Thrombosis	0	1 (1%)	0

Data include one patient who did not have *FGF/FGFR* status centrally confirmed and was not assigned to any cohort. FGFR=fibroblast growth factor receptor. MedDRA=Medical Dictionary for Regulatory Activities. Shown are treatment-related adverse events occurring in ≥10% of patients in the total study population of 146 patients (no grade 5 adverse events were reported in this study). Rows are ordered relative to the descending frequency of any grade treatment-related adverse events. *The following MedDRA preferred terms related to hypophosphataemia were combined: blood phosphorus decreased; and hypophosphataemia. †The following MedDRA preferred terms related to hyperphosphataemia were combined: blood phosphorus increased; and hyperphosphataemia.

Table 3: **Treatment-related adverse events***

- Hyperphosphatemia was most common side effect; usually managed with low phosphate diet, and phosphate binders

Abou-Alfa GK, et al. Lancet Oncol 2020

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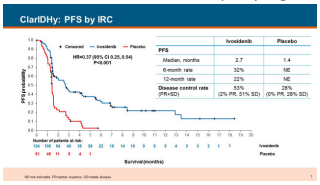
ClarIDHy trial: Ivosidenib in IDH1 mutant improved PFS

- Phase III, 2:1 randomized, double-blind trial of ivosidenib vs placebo in IDH1 mutant advanced cholangiocarcinoma with 1-2 prior treatments
- N=185
- Primary endpoint PFS; crossover was allowed upon progression



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

Abou-Alfa G, ESMO 2019

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Pancreatic cancer

- Adjuvant therapy after resection (if no neoadjuvant therapy) - depending on patient fitness
  - Modified FOLFIRINOX — MOST FIT
  - Gemcitabine + Capecitabine
  - Gemcitabine or 5-fluorouracil/leucovorin — LESS FIT

Adjuvant Chemotherapy	Median OS	Comparator OS
mFOLFIRINOX	54.4 mo	35.0 mo (gemcitabine)
Gemcitabine+Capecitabine	28.0 mo	25.5 mo (gemcitabine)

Adjuvant Chemotherapy	Median Inv Assessed DFS	Comparator DFS
mFOLFIRINOX	21.6 mo	12.8 mo (gemcitabine)
Gemcitabine+Capecitabine	13.9 mo	13.1 mo (gemcitabine)

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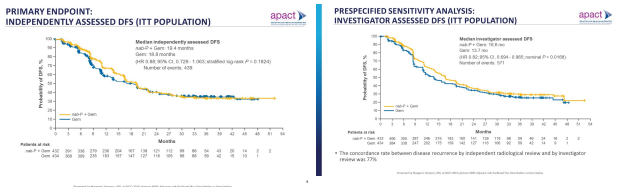
Gemcitabine + Nab-paclitaxel DID NOT improve independently assessed DFS (APACT)



- Awaiting mature OS results. However, at this time would not recommend adjuvant gemcitabine + nab-paclitaxel

Tempero MA, et al. ASCO 2019

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Pancreatic cancer: Systemic therapies for metastatic disease

First-line Chemotherapy	Median OS	Comparator OS
FOLFIRINOX	11.1 mo	6.8 mo (gemcitabine)
Gemcitabine+Nab-Paclitaxel	8.5 mo	6.7 mo (gemcitabine)
Gemcitabine+Cisplatin IF BRCA MUTANT	15.5-16.4 mo	

- Actionable biomarkers
  - MSI-High (pembrolizumab)
  - BRCA1/2 germline mutation (olaparib maintenance)

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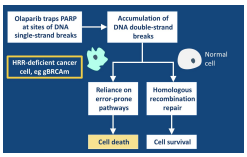
BRCA1/2 germline mutations in pancreatic cancer



Kindler HL, et al, ASCO 2019

- 5.9% in the screening population for POLO trial (Golan T, et al, JCO 2019)
  - 9.5% in U.S.
  - 10.7% in African Americans, vs 6.1% in white, 5.0% in Asian, and 1.6% in other

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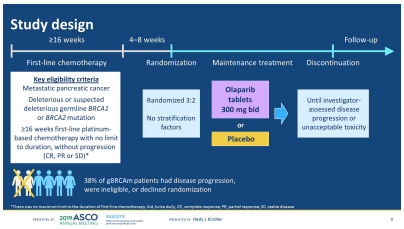
POLO: maintenance olaparib after disease stability or response after induction platinum-based chemotherapy



Kindler HL, et al, ASCO 2019

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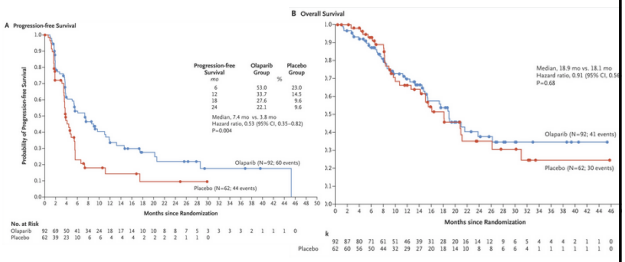
Olaparib maintenance prolonged PFS



Golan T, et al, NEJM 2019

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Table 2. Summary of Adverse Events.[a]

Variable	Olaparib (N=91)		Placebo (N=60)		Between-Group Difference (95% CI)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)				*percentage points*	
Adverse event						
Any	87 (96)	36 (40)	56 (93)	14 (23)	2 (−5 to 12)	16 (−0.02 to 31)
Fatigue or asthenia	55 (60)	5 (5)	21 (35)	1 (2)	25 (7 to 41)	4 (−4 to 11)
Nausea	41 (45)	0	14 (23)	1 (2)	22 (4 to 36)	−2 (−9 to 3)
Anemia†	25 (27)	10 (11)	10 (17)	2 (3)	11 (−3 to 24)	8 (−2 to 17)
Abdominal pain	26 (29)	2 (2)	15 (25)	1 (2)	4 (−12 to 18)	1 (−8 to 6)
Diarrhea	26 (29)	0	9 (15)	0	14 (−1 to 26)	NC
Decreased appetite	23 (25)	3 (3)	4 (7)	0	19 (5 to 30)	3 (−3 to 9)
Constipation	21 (23)	0	6 (10)	0	13 (−0.02 to 25)	NC
Vomiting	18 (20)	1 (1)	9 (15)	1 (2)	5 (−9 to 17)	−1 (−8 to 5)
Back pain	17 (19)	0	10 (17)	1 (2)	2 (−12 to 14)	−2 (−9 to 3)
Arthralgia	14 (15)	1 (1)	6 (10)	0	5 (−7 to 16)	1 (−5 to 6)
Interruption of intervention owing to adverse event	32 (35)	NA	3 (5)	NA	30 (17 to 42)	NA
Dose reduction owing to adverse event	15 (16)	NA	2 (3)	NA	13 (2 to 23)	NA
Discontinuation of intervention owing to adverse event	5 (5)	NA	1 (2)	NA	4 (−4 to 11)	NA

[a] The table includes adverse events of any grade that occurred in at least 15% of the patients in the safety population of either trial group during the trial intervention or up to 30 days after discontinuation of the trial intervention. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. NA denotes not applicable, and NC not calculated.
† The anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.

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Pancreatic cancer: Systemic therapies for metastatic disease

First-line Chemotherapy	Median OS	Comparator OS
FOLFIRINOX	11.1 mo	6.8 mo (gemcitabine)
Gemcitabine+Nab-Paclitaxel	8.5 mo	6.7 mo (gemcitabine)
Gemcitabine+Cisplatin IF BRCA MUTANT	15.5-16.4 mo	

- All patients with pancreatic cancer should be screened for BRCA1/2 germline mutations
  - Germline BRCA1/2 mutation is actionable, as olaparib maintenance therapy was FDA approved in Dec 2019
- However – we do not know if olaparib maintenance is more effective or more tolerable than maintenance with fluoropyrimidine based chemotherapy

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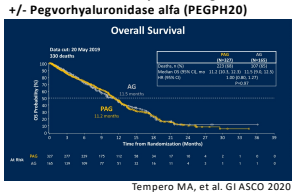
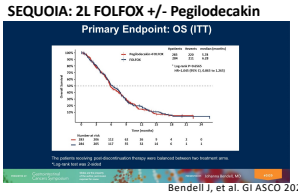
Pancreatic cancers: more negative phase III trials

HALO-109-301: 1L Nab-paclitaxel/gemcitabine +/- Pegvorhyaluronidase alfa (PEGPH20)



Tempero MA, et al. GI ASCO 2020

SEQUOIA: 2L FOLFOX +/- Pegilodecakin



Bendell J, et al. GI ASCO 2020

Also CANSTEM111P (gemcitabine+nab-paclitaxel +/- napabucasin), RESOLVE (gemcitabine+nab-paclitaxel +/- ibrutinib), and others

Novel approaches and enrollment in clinical trials are critical to move the needle in this devastating disease

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Adjuvant therapy duration in stage III colon cancer

- MOSAIC had established 6 mo duration of adjuvant fluoropyrimidine + oxaliplatin to be the standard duration of treatment
- Cumulative neurotoxicity becomes more prominent with longer duration of therapy
- The IDEA study was a preplanned, pooled analysis of 6 randomized phase III trials occurring concurrently internationally to evaluate if 3mo of either FOLFOX or CAPOX was noninferior to 6 mo, with primary endpoint of 3-yr DFS.
- In overall analysis, noninferiority of 3 mo could not be concluded. HR 1.07 (1.00-1.15). However, further subgroup analyses were done

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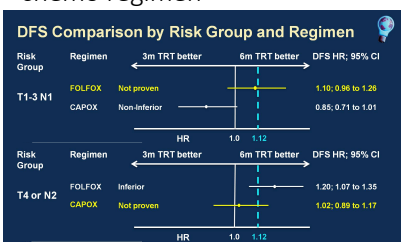
Important to consider by risk group and chemo regimen



Shi Q, et al, ASCO 2017

I recommend 3 mo of CAPOX for the low risk T1-3 N1 patients

For high risk T4 or N2 patients 6 mo of therapy has best evidence, but if giving CAPOX could consider 3 mo of therapy

I give recommendations but this does require shared decision-making.

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Updates in targeted therapy in metastatic colorectal cancer

- BRAF V600 mutations are actionable with combination targeted therapies
- MSI-High is critical to identify given susceptibility to immune checkpoint inhibitors

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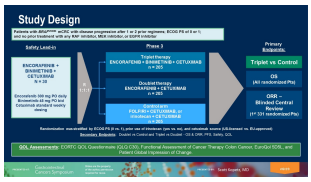
BRAF mutations confer poor prognosis

- Found in ~10% of patients with colorectal cancer
- Single-agent BRAF inhibitors were insufficient to yield responses, primarily due to feedback activation of EGFR
- Combination therapies are thus needed



Kopetz S, et al, GI ASCO 2020

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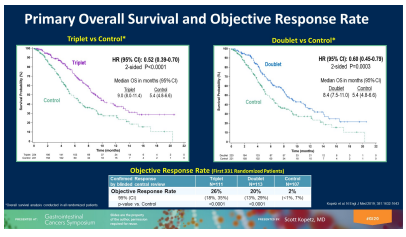
Combination therapies significantly improved overall survival compared to control



Kopetz S, et al, GI ASCO 2020

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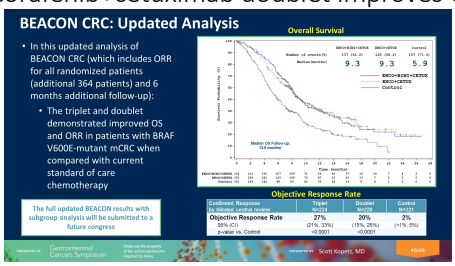
Updated survival analysis shows encorafenib+cetuximab doublet improves OS



Kopetz S, et al, GI ASCO 2020

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Microsatellite instability is predictive for response to immune checkpoint inhibitors

Immune Checkpoint Inhibitor	N	ORR	Median OS
Pembrolizumab 2L (KEYNOTE-164)	63	33% (22-46%)	NR (19.2-NR)
Pembrolizumab 3L (KEYNOTE-164)	61	33% (21-46%)	31.4 mo (21.4-NR)
Nivolumab (CheckMate-142)	74	31.1% (20.8-42.9)	NR (18.0-NR)
Ipilimumab + Nivolumab (Checkmate-142)	119	55% (45.2-63.8)	NR

Le DT, et al, J Clin Oncol 2019; Overman MJ, et al, Lancet Oncol 2017; Overman MJ, et al, J Clin Oncol 2018

- Data for use in earlier lines of therapy emerging
  - Pembrolizumab was announced in Apr 2020 to result in superior PFS compared to SOC FOLFOX or FOLFIRI based chemotherapy regimen in KEYNOTE-177. Final OS results pending
  - 1L Ipilimumabnivolumab had 60% response rate (Lenz HJ, et al, GI ASCO 2020)

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Case 1

You meet a 60 year old male patient with newly diagnosed cholangiocarcinoma with bone and lung metastases. You decide to send next generation sequencing and additional molecular testing. You also start him on first-line gemcitabine + cisplatin. Unfortunately, he progresses after 6 cycles. He continues to have performance status of 1. Which of the following next line treatment options would not be indicated based on results of the biomarker testing:

A) Pembrolizumab if MSI-High
B) Pemigatinib if FGFR2 amplification
C) Pemigatinib if FGFR2 fusion
D) FOLFOX if no actionable aberration

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Case 2

You meet a 56 year old female patient who was diagnosed with resectable adenocarcinoma of pancreatic head. She underwent Whipple resection with negative margins and had pT2N0 disease. Which of the following statements about adjuvant therapy is NOT correct?

A) Adjuvant FOLFIRINOX results in superior overall survival compared to adjuvant gemcitabine
B) Adjuvant gemcitabine+nab-paclitaxel results in superior disease free survival compared to adjuvant gemcitabine
C) Adjuvant gemcitabine+capecitabine results in superior overall survival compared to adjuvant gemcitabine

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Case 3

You meet a 49 year old female patient who was diagnosed with metastatic cecal adenocarcinoma with peritoneal carcinomatosis. She received first-line FOLFOXIRI+bevacizumab before eventually progressing. She continues to have performance status of 0. Which of the following next line treatment options would be the best choice based on results of the biomarker testing:

A) Encorafenib + cetuximab if BRAF V600E mutation
B) Ipilimumab only if MSI-High
C) Irinotecan+cetuximab if BRAF V600E mutation
D) Atezolizumab + cobimetinib only if KRAS mutation

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Questions?

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