University of Nebraska Medical Center

Bio Ascend™

VIRTUAL CHALLENGING CASE CLINIC:

GI Cancers

Current Status: Pancreatic, Anal, and Biliary Cancers

Thursday, May 20, 2021
12:00 PM Eastern / 11:00 AM Central / 9:00 AM Pacific

Course Director

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Presenter

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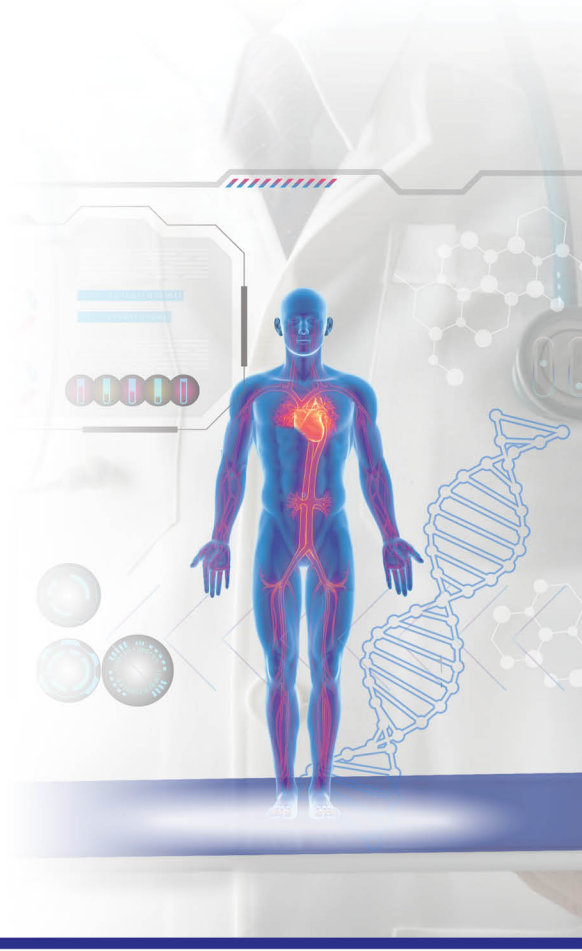

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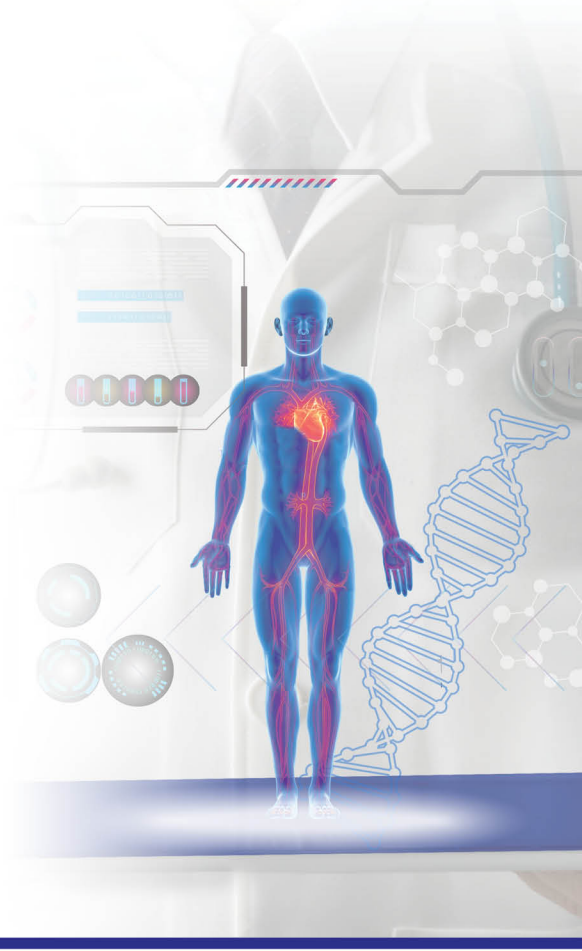

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Disclosures

Johanna Bendell, MD

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Disclosures

Andrew Ko, MD

Advisory Boards: FivePrime, Turning Point, Tyme

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IDMC Member: Erytech, Ipsen Biopharmaceuticals, Roche/Genentech, SynCore

Planning Committee

The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP

Bio Ascend: Patti Bunyasaranand, MS; Dru Dace, PhD; Lucja Grajkowska, PhD; Kraig Steubing

Learning Objectives

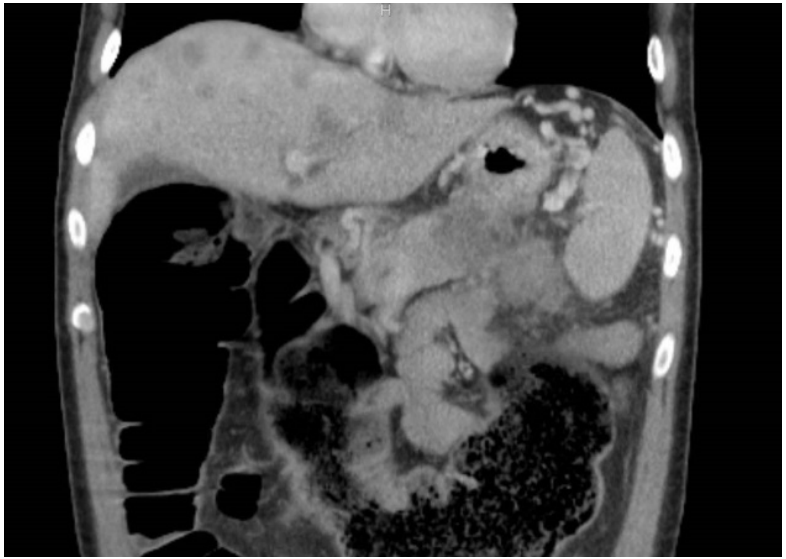
- Evaluate best available evidence regarding treatment of GI cancer
- Assess the clinical implications of emerging clinical trial data regarding treatment approaches for patients with GI cancer
- Develop strategies to address complicated GI cancer cases

Virtual Challenging Case Clinic in GI Cancers: Current Status of Pancreatic, Biliary, and Anal Cancers

Andrew H. Ko, MD, FASCO
Professor of Clinical Medicine and Chief (Interim)
Division of Hematology/Oncology
University of California San Francisco

Case 1

- Mr. Johnson is a 77 yr old man who presents with abdominal pain and progressive fatigue
- Diagnostic workup reveals the following:
  - CT: pancreatic body mass, retroperitoneal lymphadenopathy, and hepatic lesions up to 2 cm
  - Biopsy of the pancreatic mass confirms adenocarcinoma
- Genetic testing: Due to the patient's Ashkenazi Jewish heritage and family history of cancer (mother and maternal aunt with ovarian cancer), he undergoes germline testing that reveals a pathogenic *BRCA2* mutation.
- ECOG PS = 1

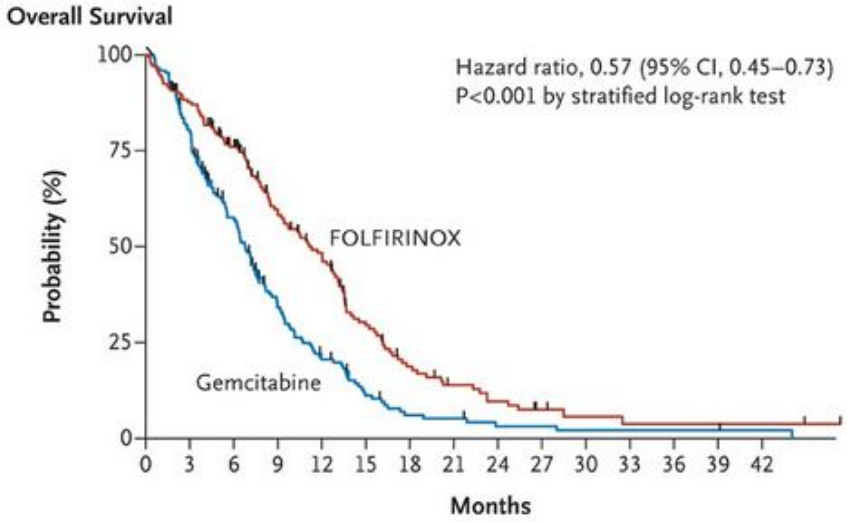


What Initial Treatment Would You Recommend for This Patient?

1. FOLFIRINOX
2. Gemcitabine plus nab-paclitaxel
3. Gemcitabine plus cisplatin
4. FOLFIRINOX + olaparib
5. Olaparib

Chemotherapy Remains the Mainstay of Treatment for Advanced/ Metastatic Pancreatic Cancer, But Survival Remains Poor

FOLFIRINOX vs gemcitabine



Conroy et al. *N Engl J Med.* 2011;364:1817-25.

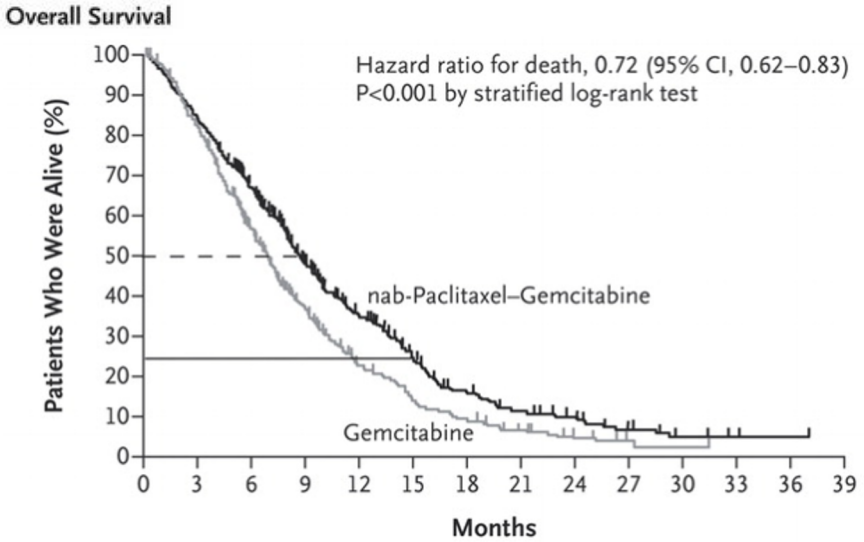
Contemporary FOLFIRINOX data for 1L met PDAC: OS = 14.4 months (SWOG 1313)

N=342	FOLFIRINOX	Gemcitabine	
ORR	31.6%	9.4%	p<0.001
Median PFS (months)	6.4	3.3	HR 0.47, p<0.001
Median survival (months)	11.1	6.8	HR 0.57, p<0.001
1 year survival	48.4%	20.6%	

Philip et al. *J Clin Oncol.* 2019;37(13):1062-1069

Chemotherapy Remains the Mainstay of Treatment for Advanced/ Metastatic Pancreatic Cancer, But Survival Remains Poor

Gemcitabine/nab-paclitaxel vs gemcitabine



Von Hoff. *N Engl J Med.* 2013;369:1691-703.

Contemporary gemcitabine/nab-paclitaxel data for 1L met PDAC: OS = 11.5 months (HALO-301)

N=861	Gemcitabine/ nab-paclitaxel	Gemcitabine	
Median OS (months)	8.5	6.7	HR 0.72 (p<0.001)
One-year survival	35%	22%	
Median PFS (months)	5.5	3.7	HR 0.69 (p<0.001)
ORR	23%	7%	p<0.001

van Cutsem et al. *J Clin Oncol.* 2020;38:3185-94.

Pushing the Envelope: New Combination Chemotherapy Regimens Under Investigation in Metastatic PDAC

- Phase Ib/II study: Frontline **NALIRIFOX** (incorporating nanoliposomal irinotecan into FOLFIRINOX regimen)
  - Dose established in phase Ib dose-exploration phase: nal-Iri 50 mg/m2, oxaliplatin 60 mg/m2, 5-FU 2400 mg/m2, LV 400 mg/m2; given every 2 weeks
  - Grade 3 or higher treatment-emergent AEs: 68%, including 12.5% FN
  - Pooled efficacy cohort (n = 32): median PFS 9.2 months, median OS: 12.6 months, ORR: 34.4%
- Basis for current phase III **NAPOLI-3 trial** [NCT04083235]
  - 1L metastatic PDAC, n=750
  - NALIRIFOX vs gemcitabine/nab-paclitaxel

Wainberg. ESMO GI 2020 Abstract LBA-001.

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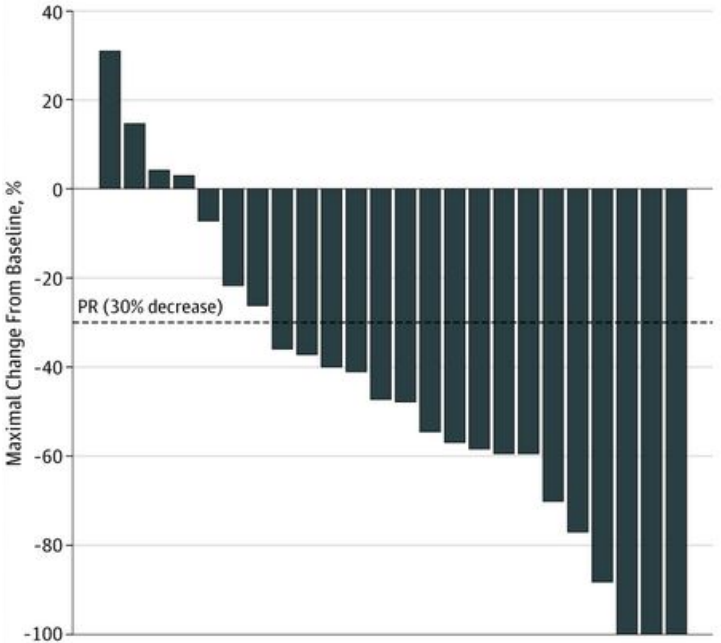
Pushing the Envelope: New Combination Chemotherapy Regimens Under Investigation in Metastatic PDAC

- Phase Ib/2 trial of nab-paclitaxel, gemcitabine, and cisplatin (NABPLAGEM) in advanced PDAC
- MTD (days 1 and 8 q21d):
  - Cisplatin 25 mg/m^2
  - Nab-paclitaxel 125 mg/m^2
  - Gemcitabine 1000 mg/m^2
- Non-biomarker selected patients (3/25 had gBRCA2 mutations)
- ORR **71%**, including 2 complete responses (8%)
- Median PFS 10.1 mos, median OS 16.4 mos



Jameson M et al. JAMA Onc. 2019; 3;6(1):125-32.

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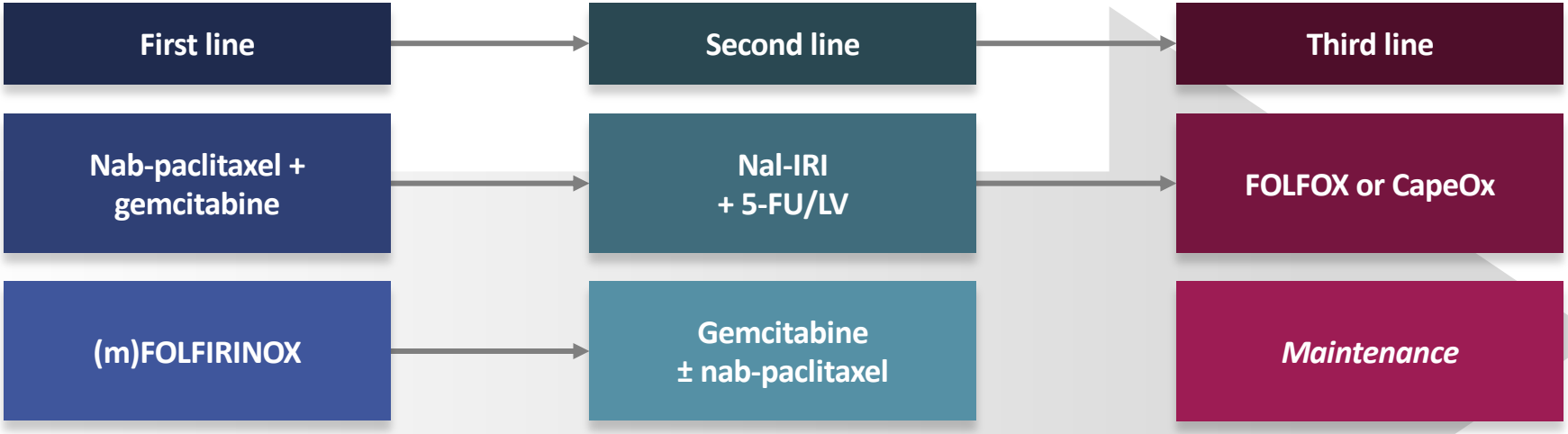
Sequencing Therapy in Advanced PDAC (2021)



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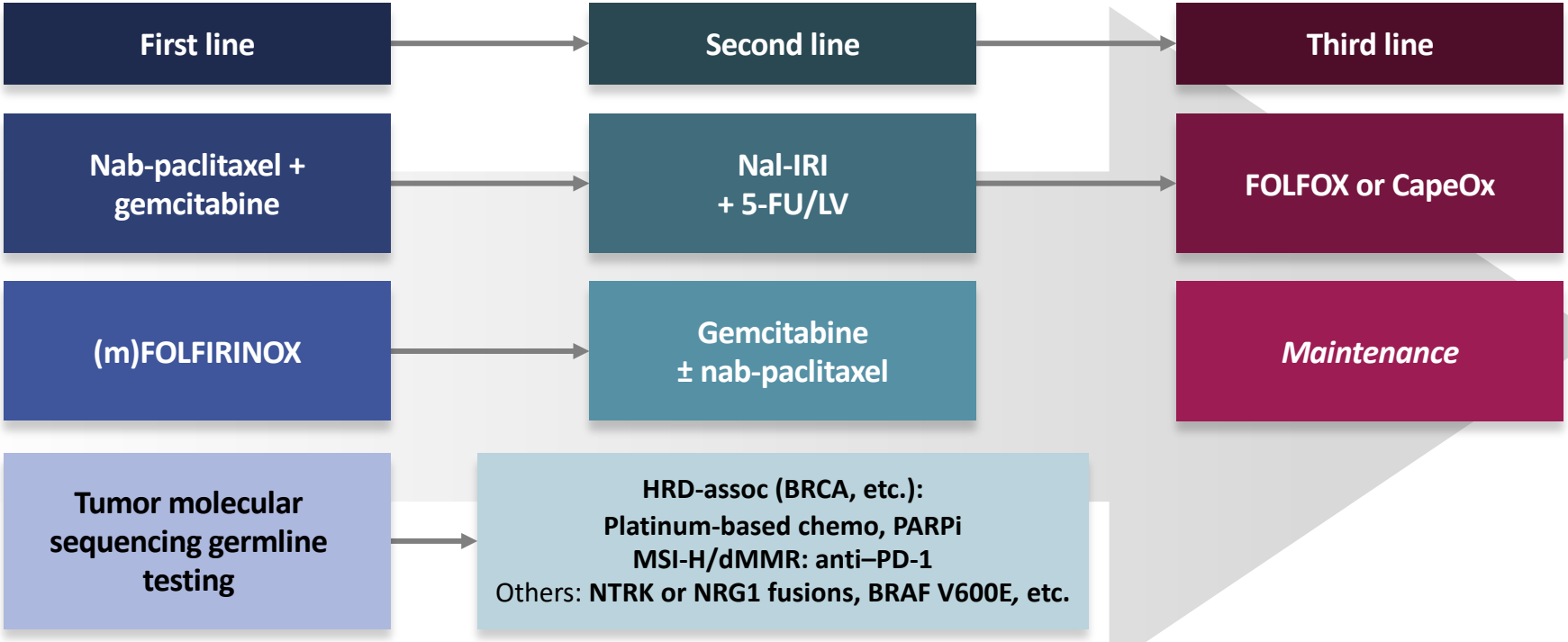

Germline and Somatic Testing in Pancreatic Cancer: Recommendations and Therapeutic Implications

- National guidelines now recommend **germline (inherited gene) testing for ALL patients** diagnosed with pancreatic cancer, regardless of family history[1]
  - A study of 3030 patients with pancreatic cancer identified **high-risk gene mutations** *BRCA1, BRCA2, CDKN2A, TP53, MLH1,* and *ATM* in **5.5% of all pancreatic cancer patients**, including 7.9% with a family history and 5.2% without a family history of pancreatic cancer[2]
- Somatic (tumor tissue) may identify potential actionable mutations -- should be considered for *all* patients with locally advanced or metastatic pancreatic cancer who are candidates for treatment

Subtype	Examples	Potential Therapy
DNA damage response (defective DNA repair)	BRCA1/2, PALB2, ATM, CHEK2 mutations	Platinum agents, PARP inhibitors
Immunogenic	MSI/MMR defects	PD-1 antibody (eg, pembrolizumab)
Rare genetic abnormalities	NTRK fusions	TRK inhibitors (eg, larotrectinib, entrectinib)

1. Stoffel. *J Clin Oncol*. 2019;37:1158. 2. Hu. *JAMA*. 2018;319:2401.

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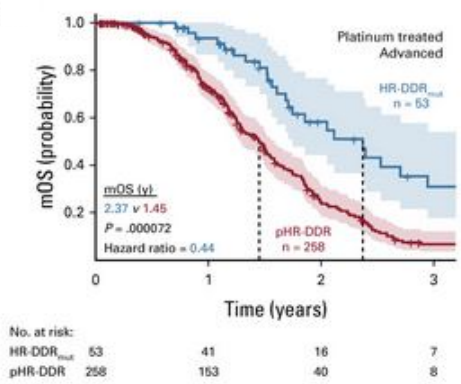
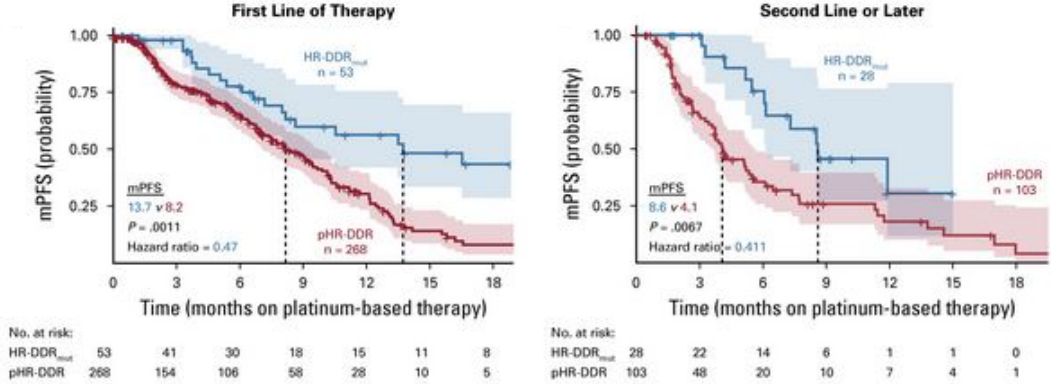
What Is the Optimal Chemotherapy Backbone for Patients with BRCA and Other HRD-Associated Pancreatic Cancer?

- Multiple lines of evidence support **platinum-based** therapies in patients with HR-deficient PDAC (improved ORR, PFS, and/or OS)

HR-DDR Deficient v HR-DDR Proficient



OS



PFS (1L and 2L+)

HRD = pathogenic mutations of somatic or germline origin in *BRCA1/2* or *PALB2* (group 1); *ATM/ATR/ATRX* (group 2); or *BAP1, BARD1, BRIP1, CHEK1/2, RAD50/51/51B, or FANCA/C/D2/E/F/G/L*
Golan et al. *Br J Cancer.* 2014; Pishvaian et al. *JCO Precision Onc.* 2019; Wattenberg et al. *Br J Cancer.* 2020; Park et al. *Clin Cancer Res.* 2020.

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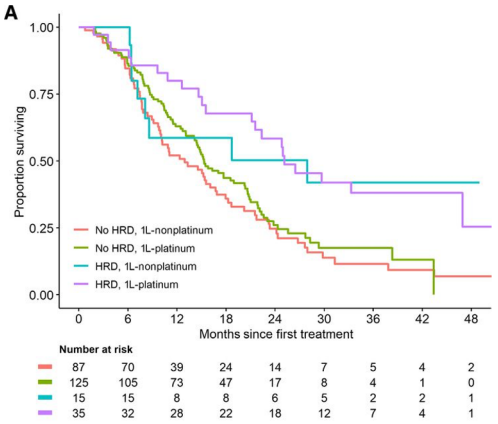
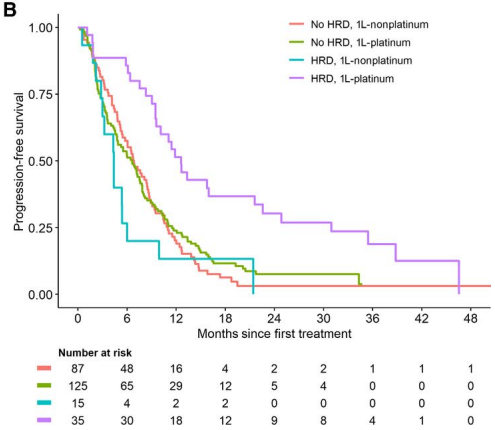




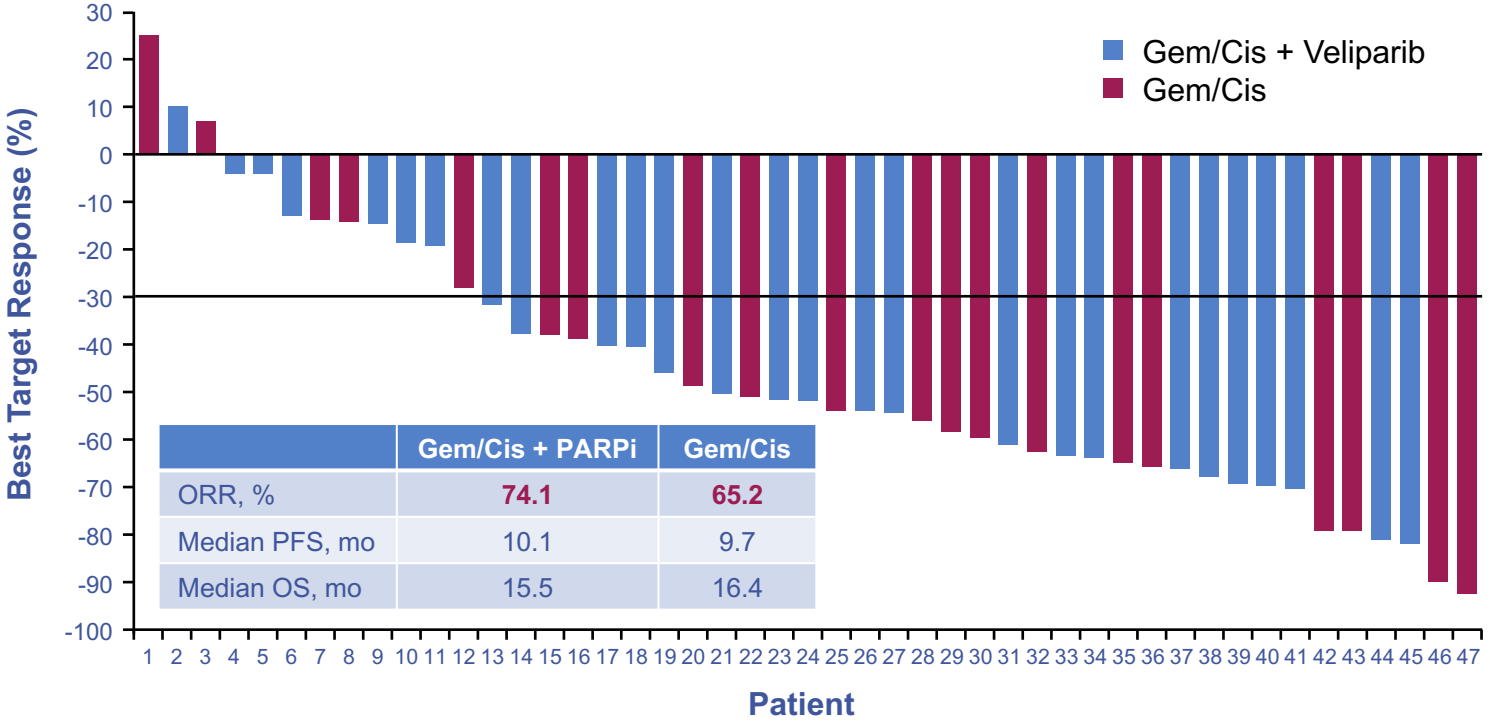
Median OS:
- HRD patients treated with 1L-platinum = 25.1 mos
- Non-HRD patients treated with or without 1L-platinum = 15.3 or 13 mos, respectively

Median PFS:
- HRD patients treated w/ 1L-platinum = 12.6 mos
- HRD patients treated w/ 1L-non-platinum = 4.4 mos

HRD = germline or somatic pathogenic alterations in: *ATM, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, PALB2, RAD50, RAD51, RAD51C,* and *RTEL1*

Golan et al. *Br J Cancer.* 2014; Pishvaian et al. *JCO Precision Onc.* 2019; Wattenberg et al. *Br J Cancer.* 2020; Park et al. *Clin Cancer Res.* 2020.

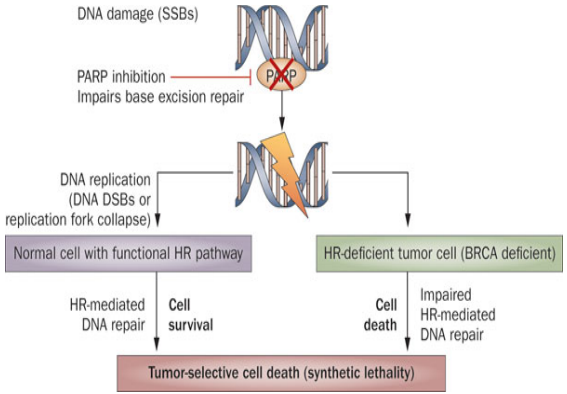
Gemcitabine/Cisplatin in Patients with Germline *BRCA/PALB2* Mutated-Associated Pancreatic Cancer: Results of a Randomized Phase II Trial



	Gem/Cis + PARPi	Gem/Cis
ORR, %	**74.1**	**65.2**
Median PFS, mo	10.1	9.7
Median OS, mo	15.5	16.4

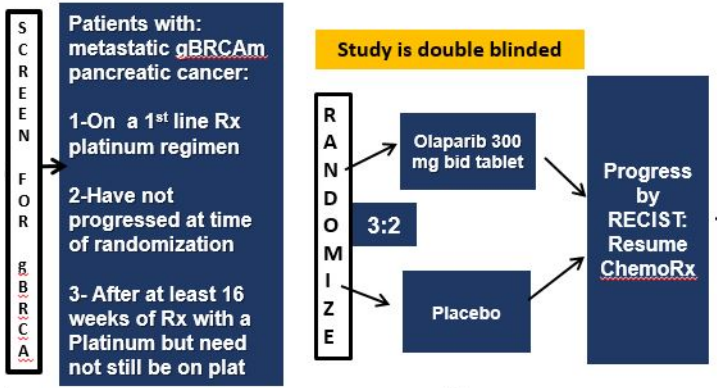
O'Reilly. *JCO*. 2020;38:1378.

The Role of PARP Inhibitors for BRCA-Associated Pancreatic Cancer



- Rationale for use of PARP inhibitors in HRD-associated cancers: Synthetic lethality
- Phase II trial of olaparib (PARP inhibitor) in patients with germline BRCA1/2 mutations and advanced solid tumors
  - Objective responses observed in 5 of 23 (21.7%) patients with pancreatic cancer

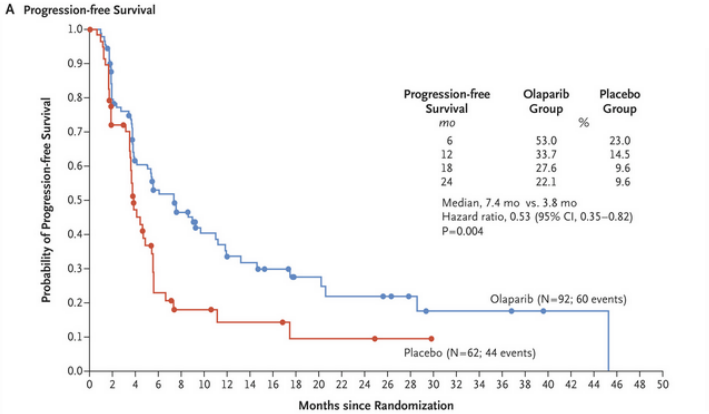
POLO-1 Trial:
Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer

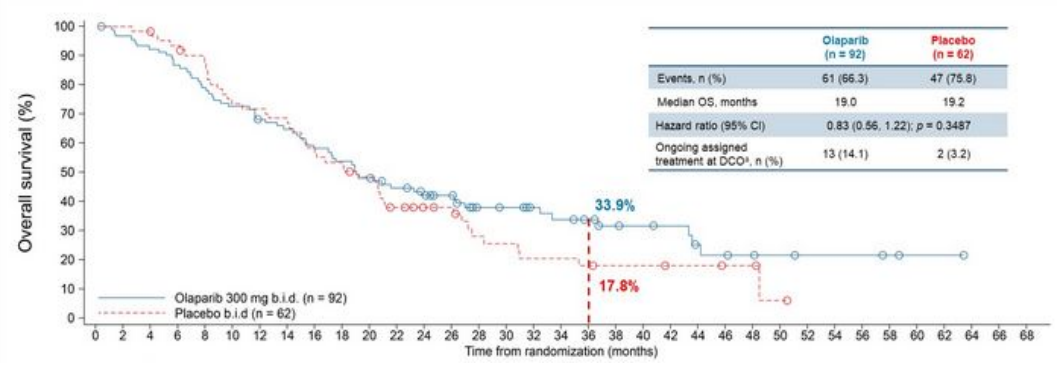


Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50.
Golan et al. *N Engl J Med*. 2019;381(4):317-327.

POLO-1 Trial Results

3315 patients screened to identify 154 eligible patients





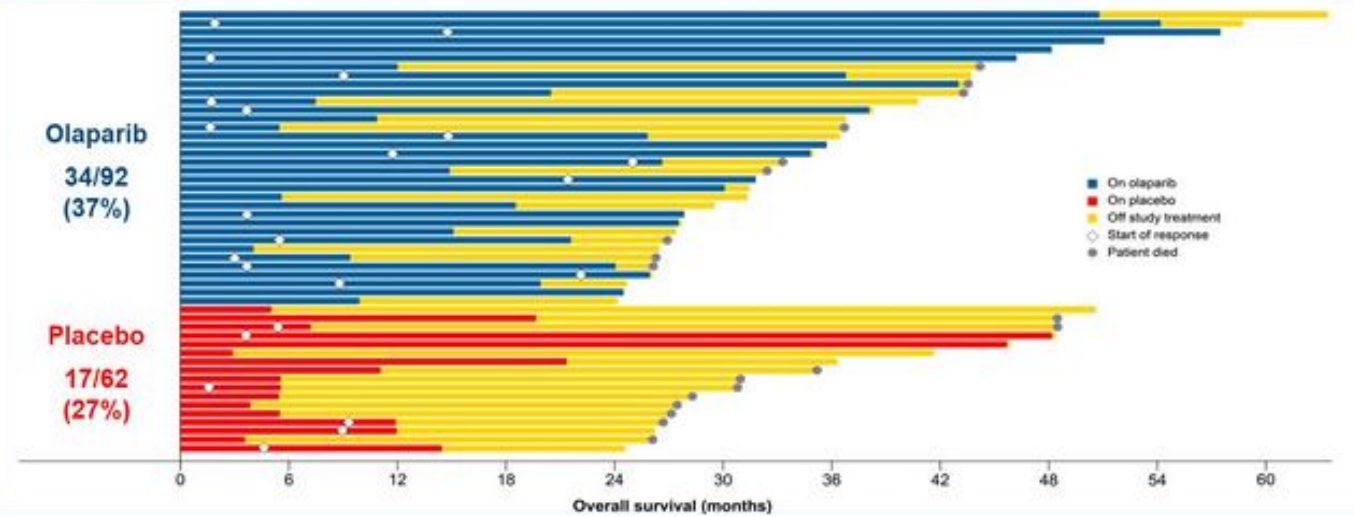
Median PFS: 7.4 vs 3.8 mos
HR: 0.53 (*P* = .004)

Median OS: 19.0 vs 19.2 months
HR: 0.83 (*P* = 0.35)

Golan et al. *N Engl J Med*. 2019;381(4):317-327.
Golan et al. *J Clin Oncol*. 39, no. 3_suppl (January 20, 2021) 378.

POLO: Long-Term Survivors (OS ≥ 2 Years)

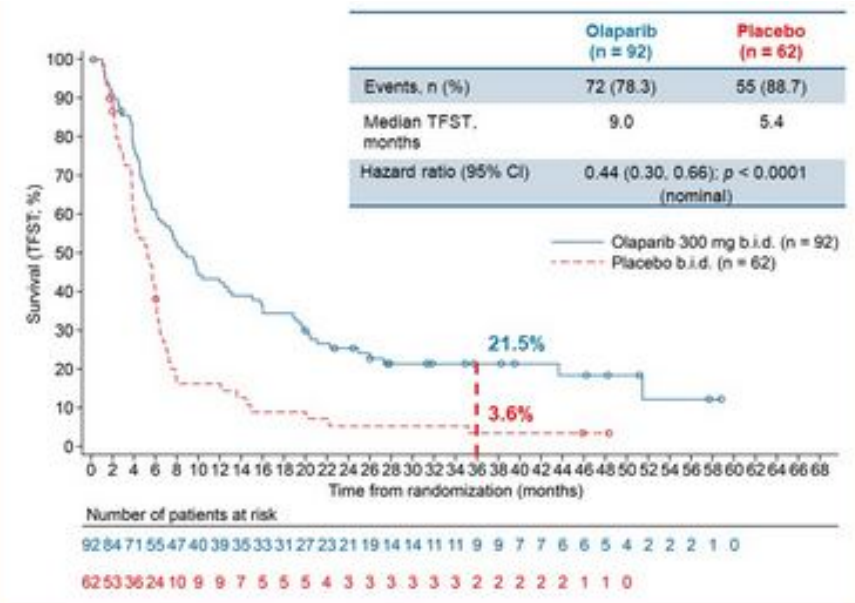
- Patients still alive at DCO: olaparib 25/34 (73.5%); placebo 7/17 (41.2%)
- CR (by investigator): olaparib 5/34 (14.7%); placebo 0/17
- Subsequent chemotherapy (≥ 2L): olaparib cohort 35.3%; placebo cohort 64.7%



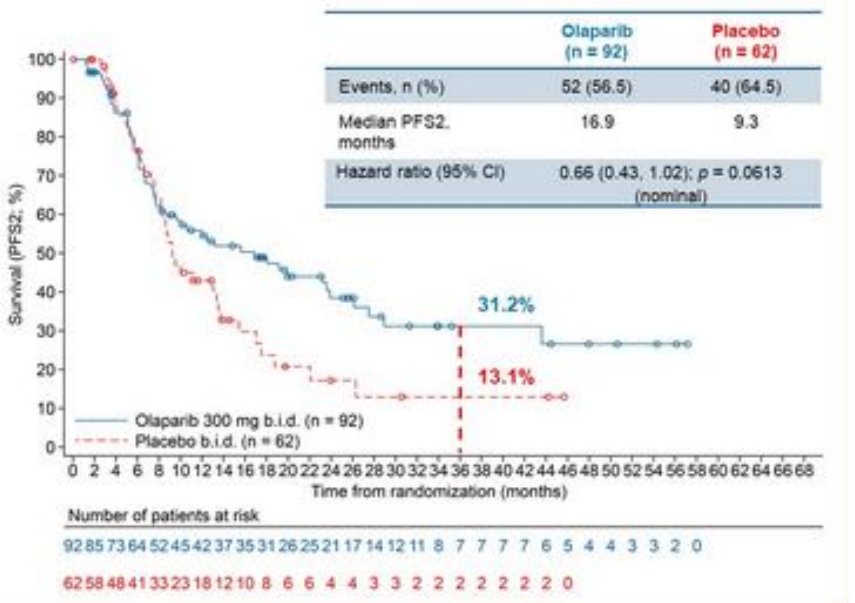
Golan et al. *J Clin Oncol*. 39, no. 3_suppl (January 20, 2021) 378.

POLO: Time to First Subsequent Therapy, and PFS2

TFST



PFS2



Golan et al. *J Clin Oncol*. 39, no. 3_suppl (January 20, 2021) 378.

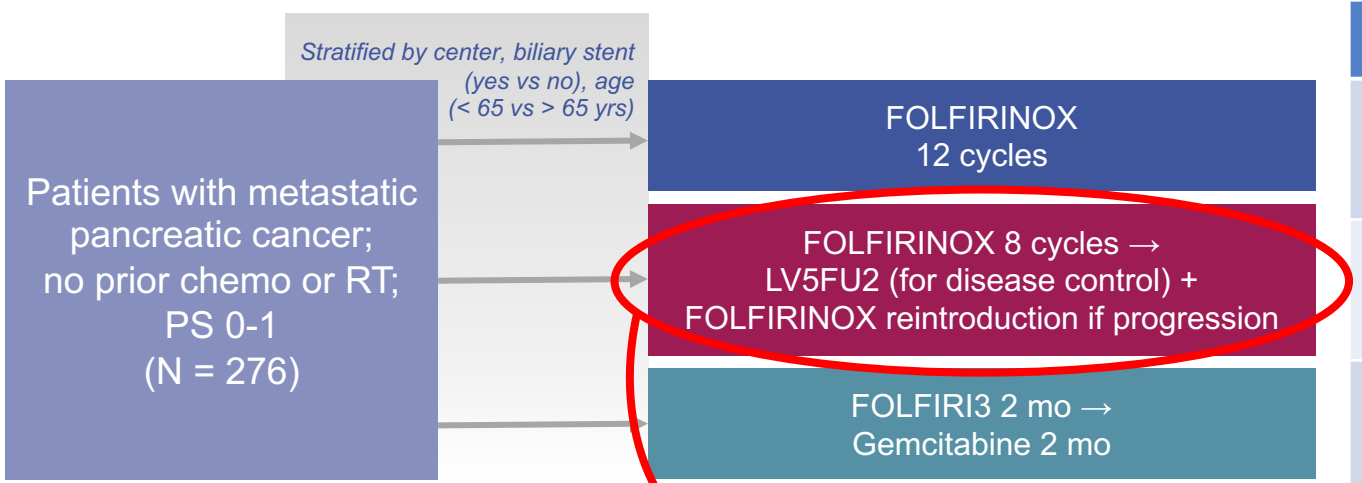
Expanding the Role for Maintenance Therapy for Patients with Advanced Pancreatic Cancer

- Patients who have response or stable disease after 4-6 mos of chemotherapy may be considered for maintenance therapy

First-line Regimen	Potential Maintenance Regimen
Platinum-based therapy and germline *BRCA1/2* mutation	• Olaparib
FOLFIRINOX	• FOLFOX • FOLFIRI • Capecitabine
Gemcitabine + nab-paclitaxel	• Modified gemcitabine + nab-paclitaxel schedule • Gemcitabine monotherapy

HU: hydroxyurea
AG: anagrelide
ASA: acetylsalicylic acid

PANOPTIMOX (PRODIGE 35): A Role for Post-FOLFIRINOX "Maintenance"?



N	6-month PFS (1o endpoint)
87	47.1%
91	44.0%
88	34.1%

FOLFIRINOX with LV/5-FU maintenance considered as effective

Dahan et al. *J Clin Oncol*. 36, no. 15_suppl, 2018: 4000.

Investigational Immunotherapies for Advanced or Metastatic Pancreatic Cancer

- Challenges include:
  - Immunosuppressive environment (eg, MDSCs, tumor-associated macrophages, lack of effector T-cells)
  - Low mutational load / rate of neoantigens
  - Low rate of DMMR/MSI-H

- Immunotherapy agents under investigation for pancreatic cancer
  - *PD-1/PD-L1 and CTLA4 antibodies:* pembrolizumab, nivolumab, durvalumab, tremelimumab
  - *IDO inhibitor*: indoximod
  - *CD40 antibodies* (agonists): selicrelumab, sotigalimab (APX-005M)
  - *CCR2 and CXCR4 antagonists*: cabiralizumab, emactuzumab
  - *CAR T-cells*: CEA targeted, mesothelin targeted
  - *Vaccines*: adenovirus, dendritic cell, peptide based (vs KRAS, other antigens)

Phase II KEYNOTE-158: Pembrolizumab in Solid Tumors (Noncolorectal) with MSI-H or dMMR

Take-home messages:

- Test all advanced pancreatic cancers for MSI/MMR status
- Do *not* use pembrolizumab as first-line treatment over chemotherapy

Tumor Type	CR/PR, n	ORR, %	Median PFS, mo	Median OS, mo	Median DOR, mo
Endometrial (n = 49)	8/20	57.1	25.7	NR	NR
Gastric (n = 24)	4/7	45.8	11.0	NR	NR
Cholangiocarcinoma (n = 22)	2/7	40.9	4.2	24.3	NR
Pancreatic (n = 22)	1/3	18.2	2.1	4.0	13.4
Small intestine (n = 19)	3/5	42.1	9.2	NR	NR
Ovarian (n = 15)	3/2	33.3	2.3	NR	NR
Brain (n = 13)	0/0	0	1.1	5.6	--

Marabelle et al. *J Clin Oncol*. 2020 Jan 1;38(1):1-10.

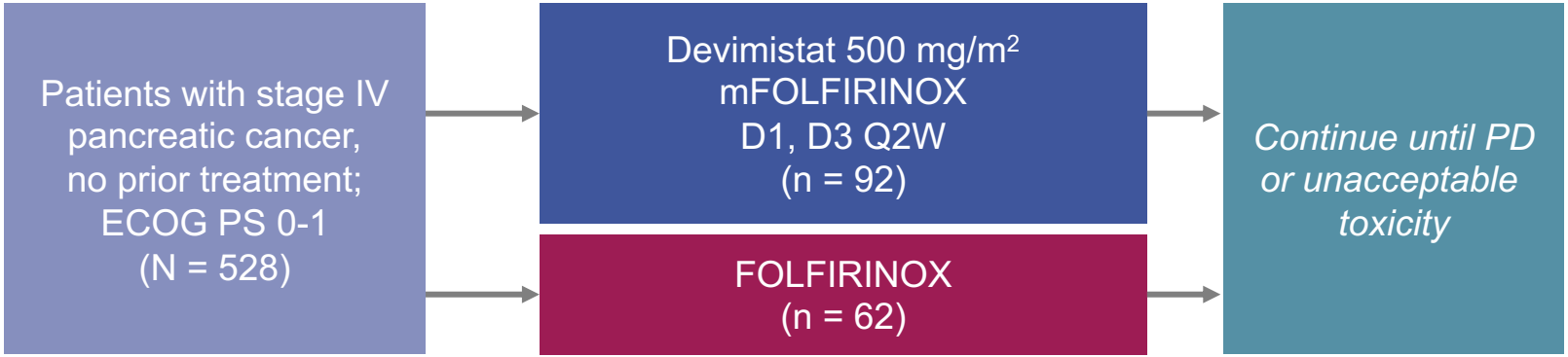
Investigational Approach: Chemotherapy + Immune Checkpoint Inhibition

Combination	N	ORR, %	Median PFS, mo	Median OS, mo
Gem/nab-P ± CD40 antibody ± nivolumab[1]	30 (24 evaluable)	58	--	--
Gem/nab-P + nivolumab[2]	50	18	5.5	9.9 • PD-L1 < 5%: 9.7 • PD-L1 ≥ 5%: 11.6
Gem/nab-P ± durvalumab/tremelimumab[3]	180 (n = 119 in combo arm)	30.3	5.5	9.8

1. O'Hara. AACR 2019. Abstract CT004. **2.** Wainberg. *Clin Cancer Res*. 2020;26:4814-22. **3.** Renouf. ESMO 2020. Abstract LBA65.

AVENGER: First-Line Devimistat + mFOLFIRINOX vs FOLFIRINOX in Metastatic Pancreatic Cancer

- Randomized phase III trial of devimistat[1], a lipoic acid analog that inhibits PDH and α-ketoglutarate dehydrogenase, thereby disrupting mitochondrial metabolism
- Phase Ib devimistat + FOLFIRINOX: 61% ORR w/median PFS of 11.5 mo[2]



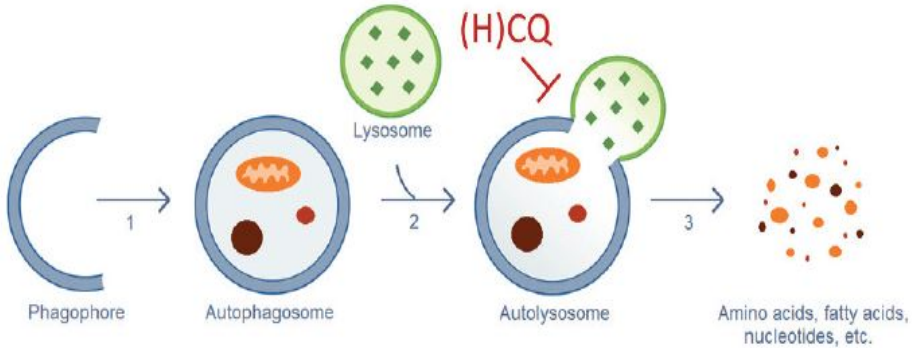
- Coprimary endpoints: ORR, PFS
- Secondary endpoint: OS, DOR

1. ClinicalTrials.gov. NCT03504423. **2.** Alistar. *Lancet Oncol*. 2017;18:770.

Autophagy Inhibition: Novel Treatment Approach

- Autophagy in pancreatic cancer, and other KRAS-driven tumor types, required to sustain metabolic needs
  - Autophagy upregulated in response to MEK/ERK inhibition (ie, MAP kinase inhibition)
  - Autophagy inhibitors include antimalarial agents like hydroxychloroquine
- Protective autophagy elicited by RAF/MEK/ERK inhibition suggests treatment approach for *RAF*-driven cancer[1]
- Combining ERK inhibition and autophagy inhibition a potential treatment approach in pancreatic cancer[2]
- Following promising preclinical results, combinations of MEK/ERK inhibitors and autophagy inhibitors are undergoing clinical investigation

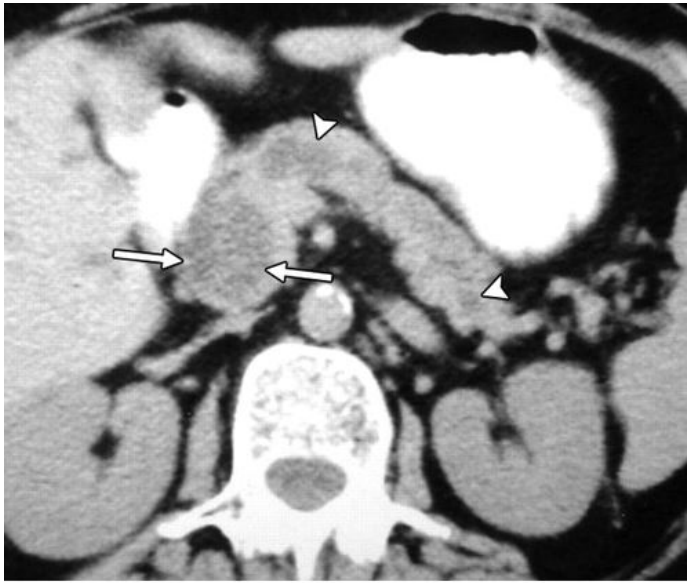
Autophagic Process



1. Kinsey. *Nat Med*. 2019;25:620. **2.** Bryant. *Nat Med*. 2019;25:628. **3.** Verbaanderd. *Ecancermedical Science*. 2017;11;781.

Case 2

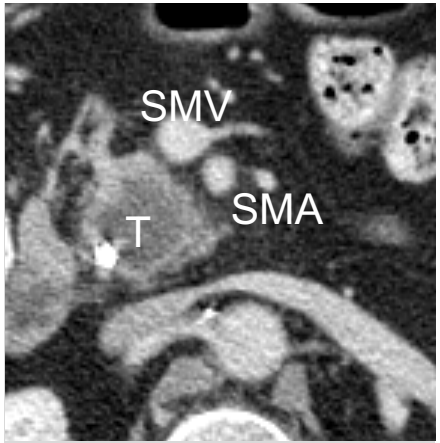
- 63 y.o. female presents with painless jaundice
- Laboratory studies reveal elevated liver function tests, including a tot bili of 5.4 mg/dL
- CT scan demonstrates a 2.6 cm pancreatic head mass with associated double-duct sign, with no evidence of vascular involvement
- She undergoes ERCP with endobiliary plastic stent placement, with normalization of liver function tests (LFTs). Simultaneous EUS-guided fine needle aspiration (FNA) of the pancreatic mass confirms adenocarcinoma



What Would You Recommend Next for This Patient?

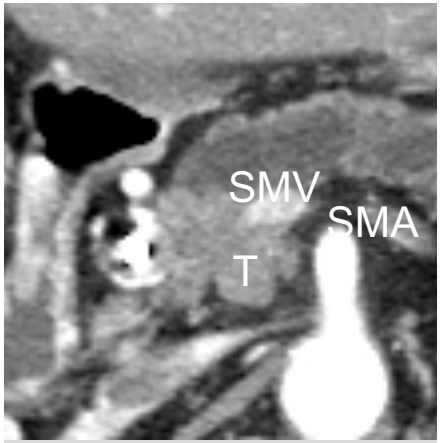
1. Whipple pancreaticoduodenectomy
2. Neoadjuvant mFOLFIRINOX
3. Neoadjuvant gemcitabine plus nab-paclitaxel
4. Capecitabine-based chemoradiation
5. Stereotactic body radiation (SBRT)

Resection Categories for Pancreatic Cancer



Resectable

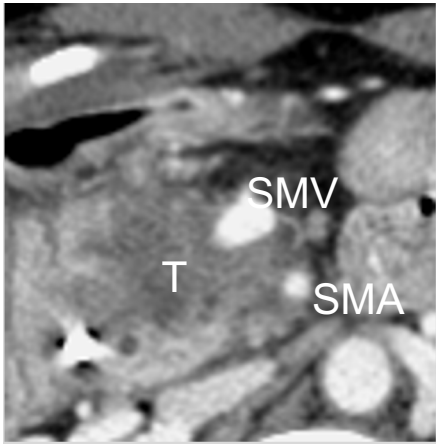
Traditionally: Up-front surgery followed by adjuvant rx



Borderline resectable

Neoadjuv rx → surgery (possibly)

- Alliance A021101, A021501
- ESPAC-5F



Locally advanced/ unresectable

Chemotherapy +/- RT

- LAP 07

Adapted from M. Katz, MD Anderson.

Neoadjuvant vs. Adjuvant Therapy for Resectable Disease

In favor of neoadjuvant rx	In favor of adjuvant rx
• Greater ability to administer systemic therapy without delay or concern re: postoperative complications • Address micrometastatic disease from the outset • Can assess drug sensitivity of tumor *in vivo* • Select patients most likely to benefit from surgical intervention	• No absolute requirement for preoperative biopsy • No need for biliary decompression/stent management; pre-emptively address any potential local obstructive complications • Avoid primary tumor seeding? • Finite window of opportunity for cure? • More level I evidence

Evolution of Adjuvant (Postop) Chemotherapy for Pancreatic Cancer

CONKO-001 (n=368)
Gemcitabine vs observation

ESPAC-3 (v2)
(n=1,088)
No difference between adjuvant gemcitabine vs 5-FU/LV!

JASPAC 01
(n=394)
Adjuvant **S-1** > gemcitabine (HR 0.57; 5-yr OS 44.1%) establishes new SOC in Asia!

ESPAC-4 (n=730)
Gemcitabine/ capecitabine vs gemcitabine

CONKO-005
(n=436)
No benefit of gemcitabine plus erlotinib in adjuvant setting

PRODIGE 24/ CCTG PA.6 (n=493)
mFOLFIRINOX vs gemcitabine

APACT
(n=866)
Adjuvant gemcitabine plus nab-paclitaxel: primary endpoint (DFS) not met

Neoptolemos. *JAMA*. 2010;304:1073-81, Uesaka et al. *Lancet*. 2016;388:248-57; Sinn et al. *J Clin Oncol*. 2017;35:3330-37; Tempero et al. *J Clin Oncol*. 2019;37(suppl 15), abstract 4000.

Mounting Evidence for *Neo*adjuvant Therapy in Patients with Resectable Disease

PREOPANC-1 (n=246; included both resectable and borderline resectable disease)

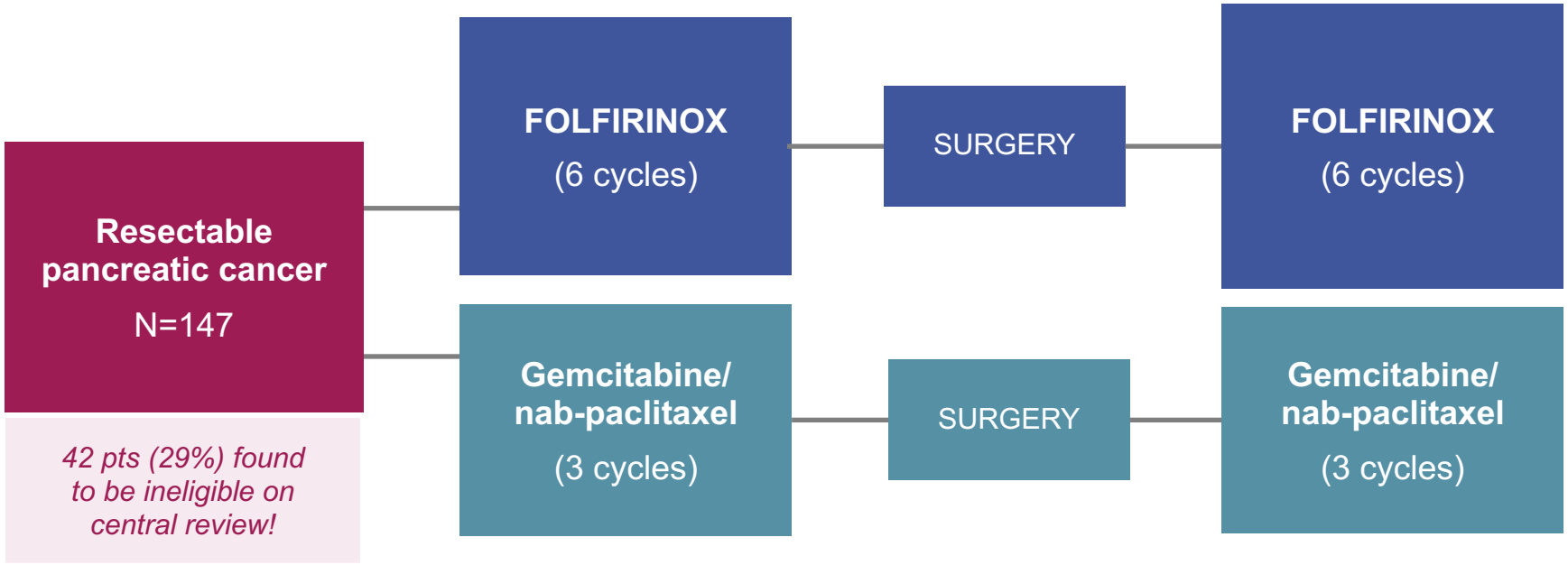
	Preop gem/gem-based RT → surg → adjuv gem	Up-front surgery → adjuv gem	
Median OS, ITT	17.1 months	13.7 months	HR 0.74, p=0.074
Median OS, pts undergoing R0/R1 resection	42.2 months	16.8 months	P<0.001

Prep-02/JSAP-05 (n=364; resectable only)

	Preop gem/S-1 → surg → adjuv S-1	Up-front surgery → adjuv S1	
Median OS	36.7 months	26.7 months	HR 0.72, log-rank p=0.015

van Tienhoven G et al. *J Clin Oncol*. 2020;38:1763-73. Unno M et al. *J Clin Oncol*. 2019;37 (suppl 4; abstr 189).

SWOG 1505: Comparison of Perioperative Chemotherapy Regimens



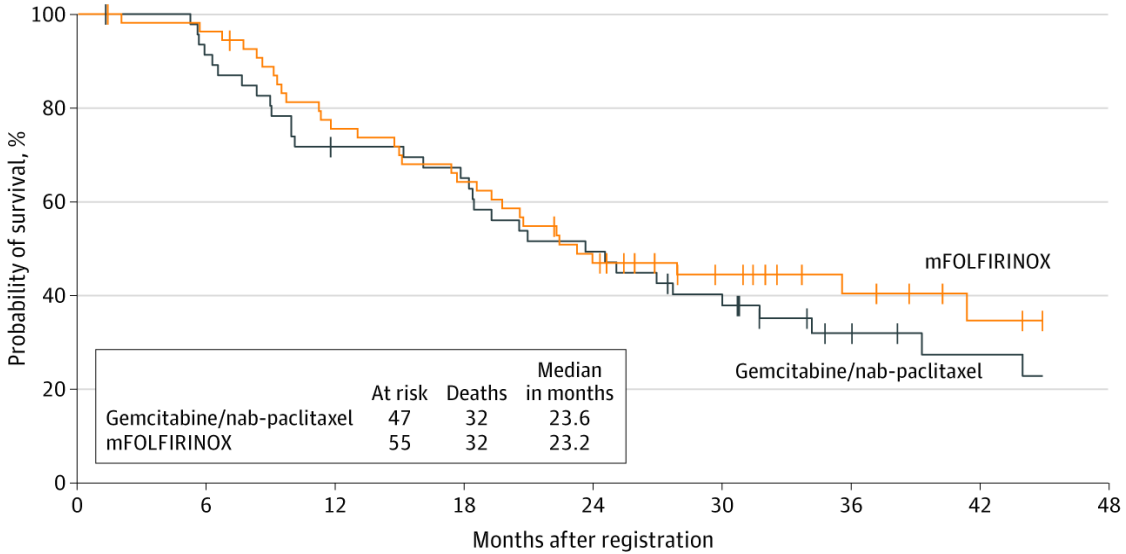
42 pts (29%) found to be ineligible on central review!

Primary endpoint = 2-year OS; "pick the winner" design

Sohal et al. *JAMA Oncol*. 2021;7(3):421-27.

SWOG 1505: Efficacy Results

On retrospective central radiology review:
43 of 147 (29%) patients did not meet imaging eligibility criteria!



Estimated 2-yr OS:
mFOLFIRINOX = 47%,
gem/nab-paclitaxel = 48%

Neither arm met study-defined positive threshold of 2-yr OS = 58%!

Sohal et al. *JAMA Oncol*. 2021;7(3):421-27.

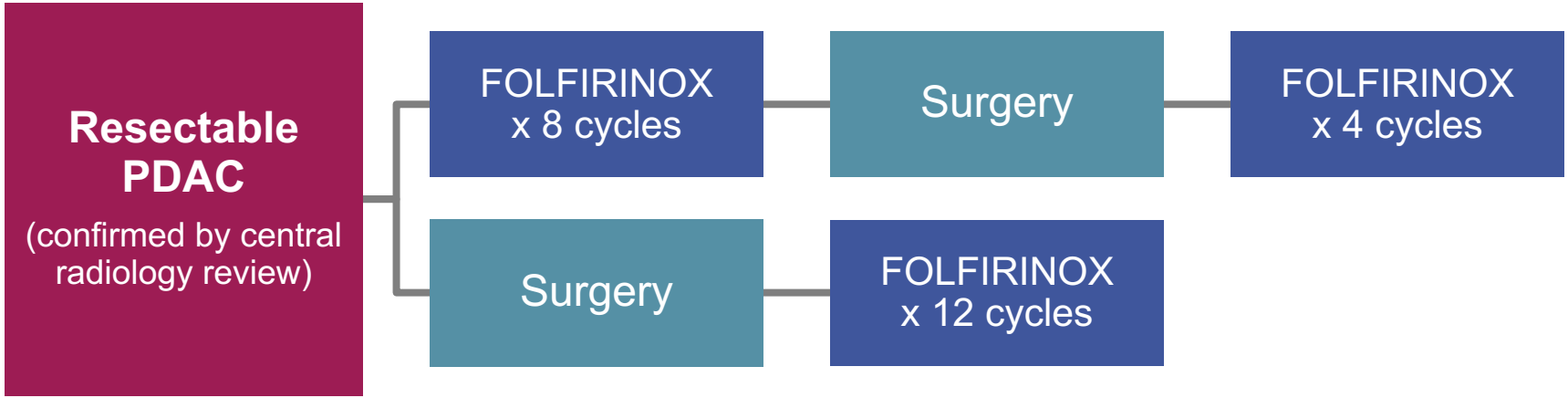
SWOG 1505: Efficacy Results

Table 2. Outcomes in Patients Undergoing Surgical Resection

Characteristic	No. (%) mFOLFIRINOX (n = 40)	No. (%) Gem/nab-P (n = 33)	*P* value (2-sided)
R0 resection	34 (85)	28 (85)	>.99
Pathologic response			
Complete	1 (3)	3 (10)	.32
Moderate	9 (22)	10 (30)	.59
Minimal	12 (30)	10 (30)	>.99
Poor or none	18 (45)	10 (30)	.23
Total nodes resected, median (range)	19 (1-56)	18 (3-45)	.64
Node-negative resection	16 (40)	15 (45)	.81
Median disease-free survival after resection, mo	10.9	14.2	.86

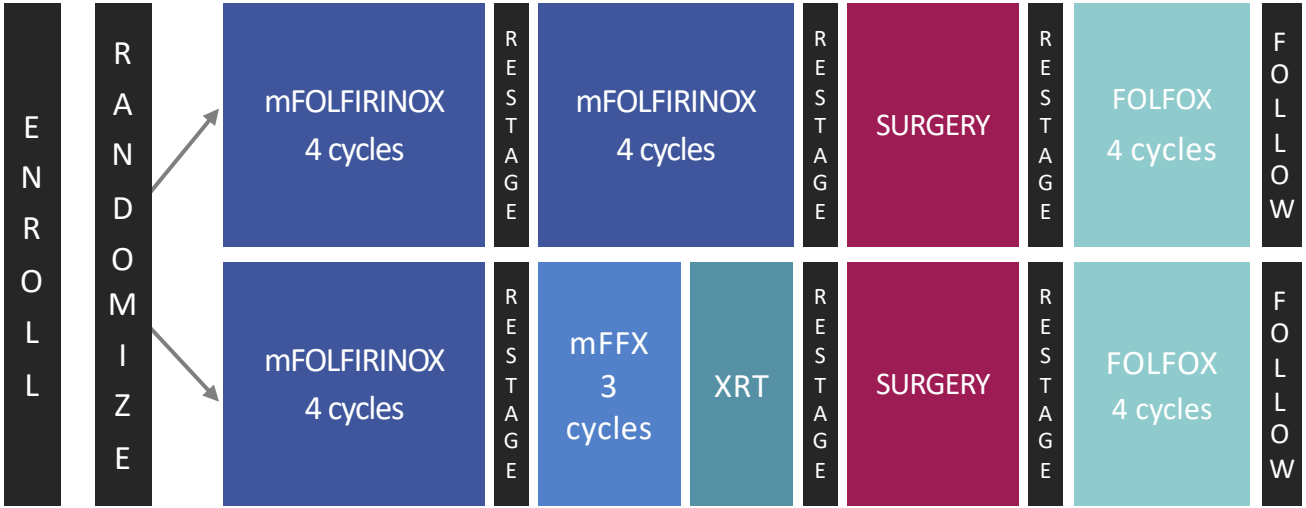
Sohal et al. *JAMA Oncol*. 2021;7(3):421-27.

Alliance A021806: Perioperative vs. Adjuvant Therapy for Resectable Pancreatic Cancer



ClinicalTrials.gov Identifier: NCT04340141

Alliance A021501 for *Borderline* Resectable Pancreatic Cancer



Primary endpoint:
18-month OS

Interim futility analysis:
closure of either arm if ≤11 of first 30 patients underwent R0 resection

- n=126
- Arm B (RT-containing arm) closed early after only 10 of first 30 pts (33%) underwent R0 resection

Katz et al. *J Clin Oncol*. 39, 2021 (suppl 3; abstr 377)

Alliance A021501 for *Borderline* Resectable Pancreatic Cancer: Key Results

Chemo-alone arm considered efficacious (39 of first 62 pts alive @ 18 months – greater than pre-specified requirement of at least 36)

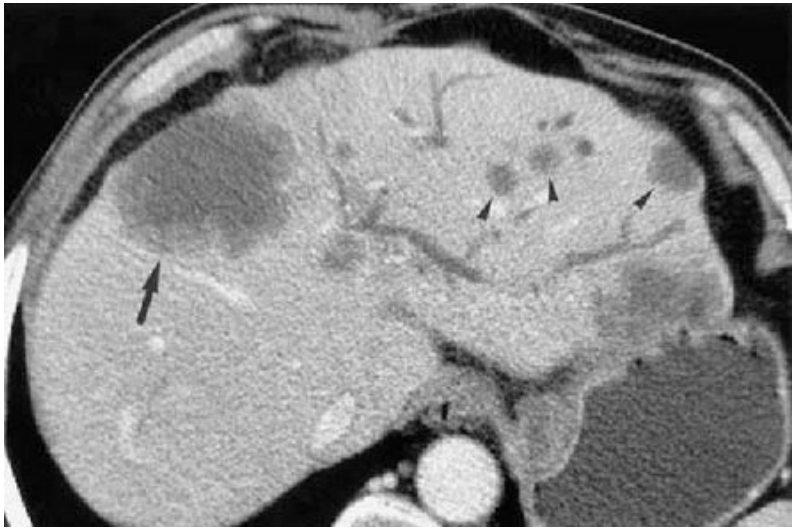
Katz et al. *J Clin Oncol*. 39, 2021 (suppl 3; abstr 377)

Shifting Gears to Cholangiocarcinoma: More Opportunities Putting Precision Medicine into Practice

Slides courtesy of Dr. Katie Kelley (UCSF), adapted for this presentation.

Case 3

- 65 y.o. woman presents with RUQ/epigastric pain and anorexia.
- Abdominal CT scan demonstrates a 6 cm in the R hepatic lobe with multiple satellite lesions.
- Percutaneous biopsy of the dominant mass demonstrates a well-differentiated adenocarcinoma, CK7-positive/CK-20 negative, c/w an intrahepatic cholangioarcinoma.
- Molecular profiling reveals a **FGFR2-BICC1** fusion, MSS, PD-L1 of 4%, and TMB of 3 muts/MB

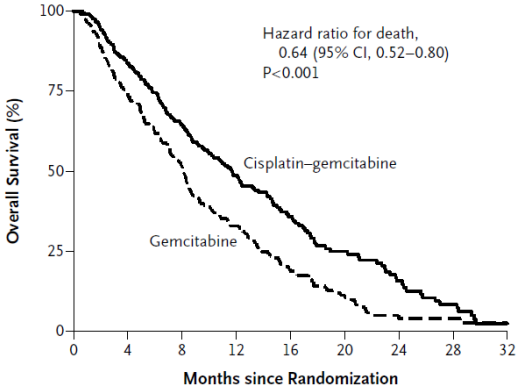


What Initial Treatment Would You Recommend for this Patient?

1. Surgical exploration
2. Gemcitabine plus cisplatin
3. FOLFOX
4. Pemigatinib (FGFR inhibitor)
5. Pembrolizumab

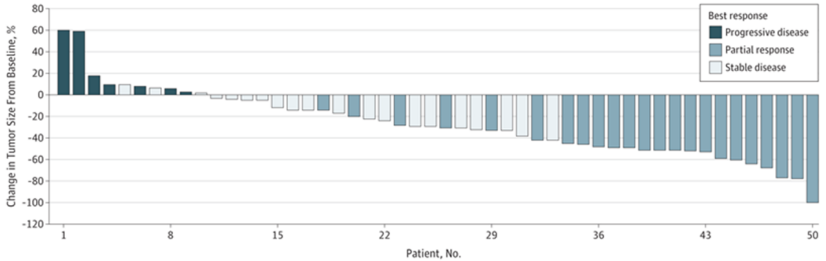
1st Line Systemic Therapy for Advanced BTC

- Gemcitabine plus cisplatin (GEMCIS) is global standard per ABC-02 trial[1]
  - mOS 11.7 mos vs 8.1 mos (p<0.001)
  - ORR 25.5% vs 14.8%



- GEMCIS plus nab-paclitaxel
  - ORR 45%, mOS 19.2 mos in phase 2 trial (n=50)[2]
  - SWOG 1815 ongoing (NCT03768414)

Phase 2 Trial of GEMCIS+nab-paclitaxel



SWOG 1815

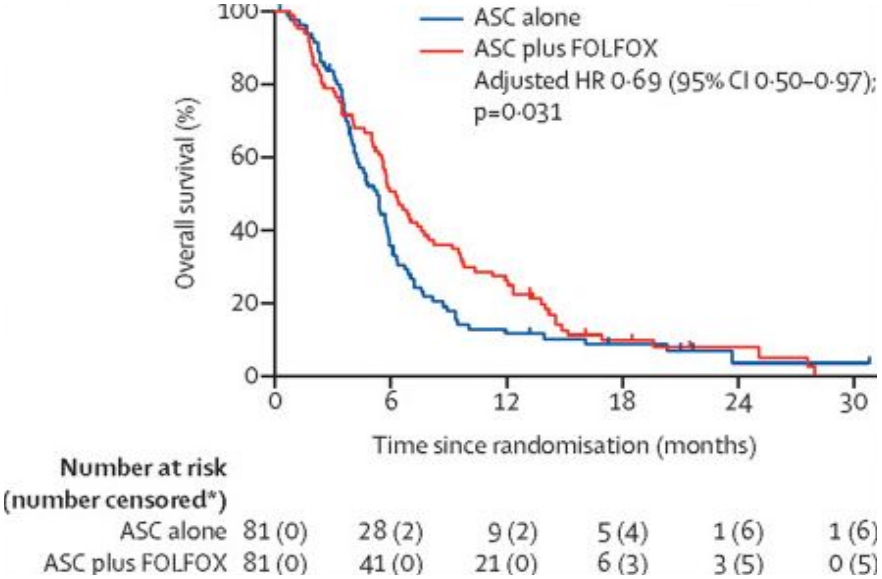
1. Valle et al, *N Eng J Med.* 2010;362(14):1273-81; **2.** Shroff et al, *JAMA Oncol.* 2019;5(6):824-30.

Advanced CCA 2L+ Systemic Therapy Options

- Before 2019: No established 2L therapy after GEMCIS
- 2019: RP3 ABC-06 trial of FOLFOX vs ASC showed improved PFS and OS for FOLFOX
  - mOS 6.2 vs. 5.3 mos for FOLFOX vs ASC
  - mPFS 4.0 months for FOLFOX
- Other regimens such as FOLFIRI, capecitabine, GEM/nab-paclitaxel are commonly used based upon phase 2 data

	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

ABC-06:
Overall survival



Lamarca et al, *Lancet Oncol*. 2021;22(5):690-701.

Beyond Standard Chemotherapy: New Therapeutic Targets in Biliary Cancers

Intrahepatic cholangiocarcinoma

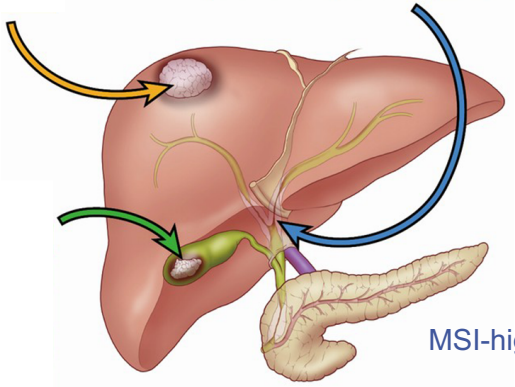
Targetable gene	Prevalence, %
FGFR2 (fusions)	10-20
IDH1/2	22-28
BAP1	15 to 25
BRAF V600 (mutation)	5-7

Gall bladder cancer

Targetable gene	Prevalence, %
EGFR	4-13
HER2/neu (amp.)	10-15
ERB3	0-12
PTEN	0-4
PIK3CA	6-13

Extrahepatic cholangiocarcinoma

Targetable gene	Prevalence, %
Her2/neu (mutation)	11-20
PRKACA and *PRKACB*	9
ARID1A	5-12

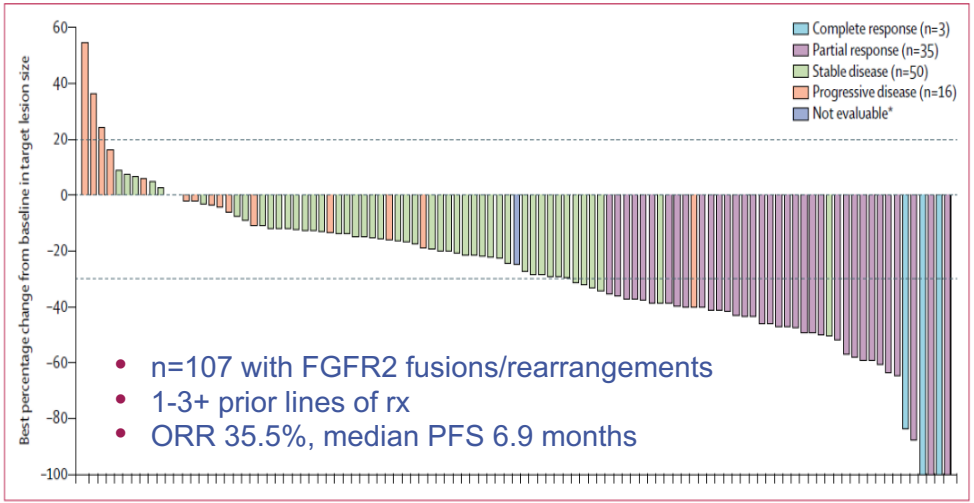


MSI-high/dMMR ~2-3%

Selected Clinical Trials of FGFR Inhibition in ICC Harboring *FGFR2* Rearrangements

- Phase 2, single arm, ≥2nd line
- ATP-competitive inhibitors of FGFR1-3>4:
  - Infigratinib
  - **Pemigatinib**
    - Approved by USFDA in 2020 for ICC with *FGFR2* rearrangement
- Covalent, irreversible FGFR 1-4 inhibitor (active against some resistance mutations)
  - Futibatinib
- Class toxicities include: Hyperphosphatemia, stomatitis, palmar-plantar erythrodysesthesia, ophthalmologic toxicities

FIGHT-202 trial of pemigatinib



Goyal et al. *Cancer Discovery*. 2019;9(8):1064-1079; Abou-Alfa et al. *Lancet Oncol*. 2020;21:671-84

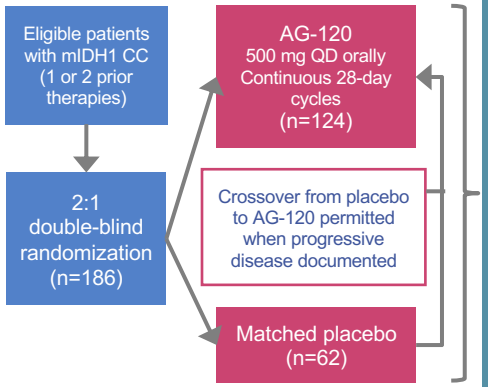
Randomized Trials of FGFR Inhibitors as First-line Therapy for *FGFR*-Rearranged ICC

FGFR Inhibitor	Control Arm	Sample Size	NCT
Infigratinib	Gemcitabine + cisplatin	384	NCT03773302
Pemigatinib		432	NCT03656536
Futibatinib		216	NCT04093362

Clinicaltrials.gov

Ivosidenib (AG-120) for *mIDH1* ICC

- Ivosidenib (AG-120) is a selective oral inhibitor of mutant IDH1
  - Showed safety and median PFS of 3.8 months in phase 1 trial



Assessments

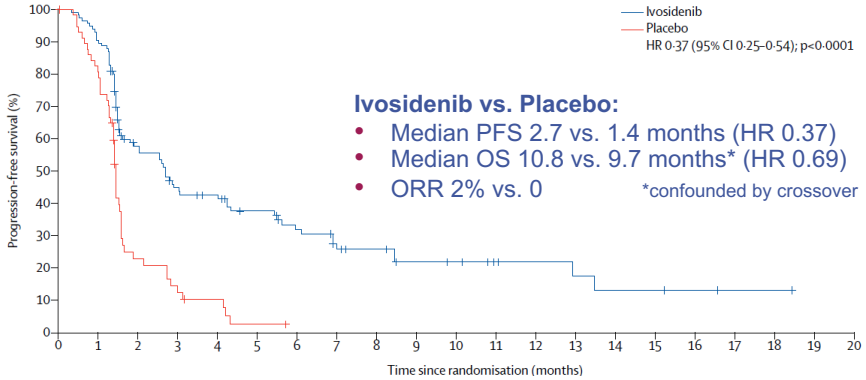
Primary
- Progression free survival (PFS), assessed by independent radiology center review

Secondary
- Safety and tolerability
- Overall response rate (ORR)
- Overall survival (OS)
- Duration of response (DOR)
- Time to response (TTR)
- Pharmacokinetic and pharmacodynamic analyses on plasma
- Quality of life as assessed by:
  - EORTC QLQ-C30
  - EORTC QLQ-BIL21
  - EQ-5D-5L

Exploratory:
- TBC

NCT02989857

- Randomized, phase 3 trial of ivosidenib vs. placebo:
  - N=185 patients, 1-2 prior therapies
  - Well-tolerated; EORTC QLQ-C30 physical functioning scores preserved in ivosidenib arm
- Ivosidenib now included in NCCN guidelines as treatment option for mIDH1 ICC (NCCN.org)



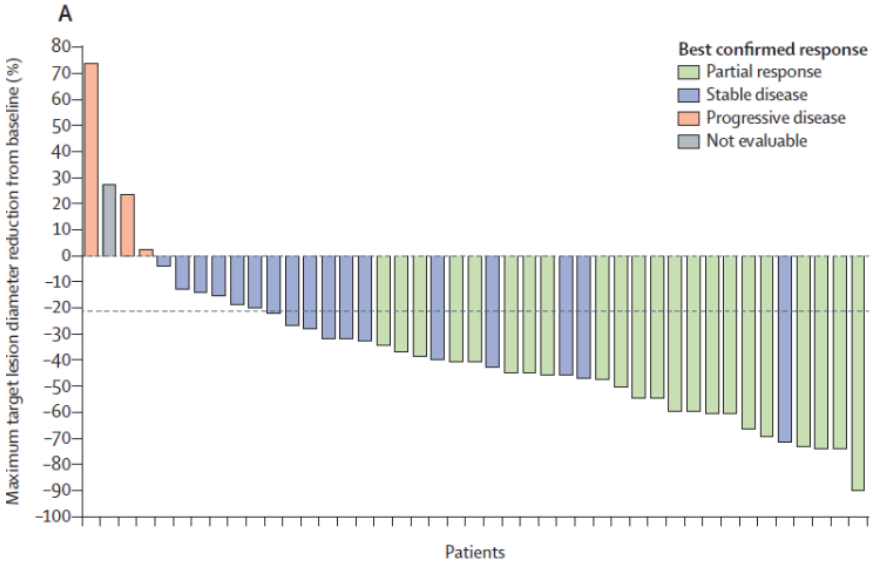
Ivosidenib vs. Placebo:
- Median PFS 2.7 vs. 1.4 months (HR 0.37)
- Median OS 10.8 vs. 9.7 months* (HR 0.69)
- ORR 2% vs. 0

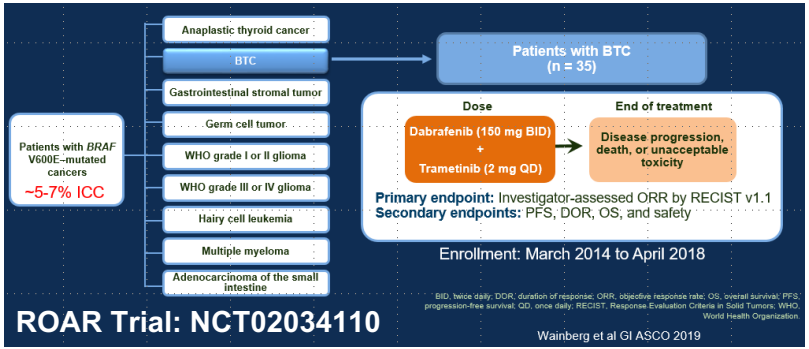
*confounded by crossover

Abou-Alfa et al. *Lancet Oncol*. 21(6) 2020

Targeting *BRAF* V600E Mutation in ICC: BRAF+MEK Inhibition

- **ROAR trial:** multicenter basket trial of dabrafenib 150 mg PO BID plus trametinib 2 mg QD





BTC cohort n=35 (91% ICC)

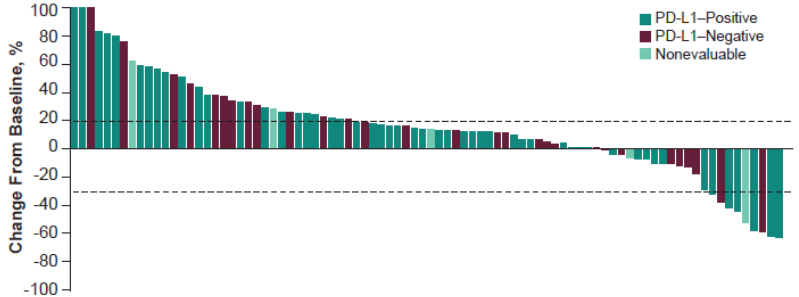
- ORR 51% (47% by central review)
- Median duration of response 9 months
- Median PFS 9 months (95% CI: 5-10)
- Median OS 14 months (95% CI: 10-33)
- Serious adverse events related to treatment in 21% (pyrexia in 19%)
  - No grade 5 related events reported

Clinicaltrials.gov; Rizzo et al. *Cancer Control.* 2020;27(1); Subbiah et al. *Lancet Oncol.* 2020;21(9):1234-43.

Are Cholangiocarcinomas Responsive to Immunotherapy?

- ~2-6% of CCA have high microsatellite instability (MSI-H)/deficiency in mismatch repair (dMMR)[1,2]
  - KEYNOTE-158[3]: (pembrolizumab 200 mg q3 weeks)
    - n=22/233 (9.4%) with CCA: **ORR 40.9%,** mOS 24.3 mos.
    - **MSI/MMR and TMB tumor testing are indicated in advanced CCA**
- What about MSS cholangiocarcinomas?
  - KEYNOTE-158[4]: (pembrolizumab 200 mg q3 weeks)
    - Biliary tract cancer cohort (n=104); median 2 prior lines of therapy, PD-L1 CPS ≥1: 59%; 99 with pMMR/5 unknown
    - Confirmed **PR = 5.8%** (6.6% for PD-L1+, 2.9% PD-L1-); median PFS and OS, 2.0 and 7.4 months
- Multicenter phase 2 trial of nivolumab (240 mg q2 weeks x16 weeks → 480 mg q4 weeks) (n=54)
  - 18/42 (43%) evaluable tumors were PD-L1+ (≥1%)
  - **ORR 11%,** median PFS = 3.7 months
  - mPFS 10.4 months vs. 2.3 mos in PDL1+ vs. PD-L1 (p<0.001)

Figure 2. Best Percentage Change From Baseline in Target Lesion Size (RECIST version 1.1 by Independent Central Review)



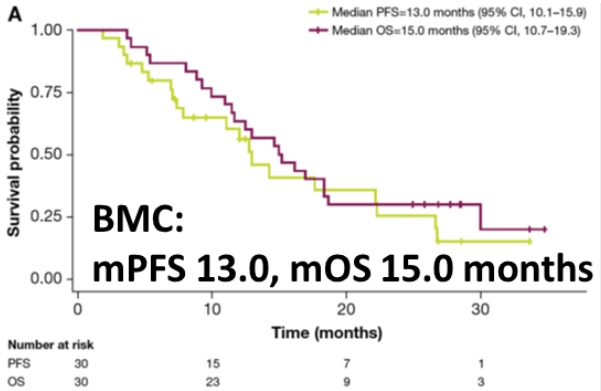
1. Le et al. *Science*. 2017;357:409-13; **2.** Ju et al. *Am J Clin Pathol*. 2020153(5):598-604; **3.** Marabelle et al. *J Clin Oncol*. 2020;38(1):1-10; **4.** Piha-Paul et al. *Int J Cancer*. 2020;147(8):2190-8; **5.** Kim et al. *JAMA Oncol*. 2020;6(6):888-94.

Phase 1 and 2 Studies of ICI + GEMCIS for 1st Line Advanced BTC

- Several small phase 1 studies showing safety of GEMCIS + nivolumab[1,2]
- Phase 2 study GEMCIS + durvalumab ± tremelimumab in 3 cohorts (N=121)[3]
  - Common treatment-related Grade 3/4 AE were neutropenia (54.5%), pruritus (55.4%)
- Favorable response rates, PFS, and OS vs. historical controls treated with GEMCIS
- Cross-study comparisons limited by uncontrolled design, unknown proportions with MSI-H/dMMR
- Phase 2/3 trials of ICI + GEMCIS now ongoing…

Table 2. Treatment response (RECIST v1.1) and survival rates.

Treatment response	BMC n=30	GemCis + D n=45	GemCis + D + T n=45
Objective response rate, % (95% CI)	50.0 (32.1–67.9)	73.4 (60.5–86.3)	73.3 (60.4–86.2)
Complete response	6.7 (0–15.6)	6.7 (0–14.0)	2.2 (0–6.5)
Partial response	43.3 (25.6–61.0)	66.7 (52.9–80.5)	71.1 (58.5–84.9)
Stable disease	46.7 (28.8–64.6)	26.7 (13.8–39.6)	24.4 (11.9–36.9)
Disease progression	3.3 (0–9.7)	0	2.2 (0–6.5)
Disease control rate, % (95% CI)	96.7 (90.3–100.0)	100.0 (100.0–100.0)	97.8 (93.5–100.0)
Median DoR, months (95% CI)	11.0 (3.9–18.1)	9.8 (8.1–11.4)	9.1 (0.0-18.8)



1. Ikeda et al. *Lancet Gastroenterol Hepatol.* 2019; 4(8): 611-21; **2.** Sahai et al. ASCO 2020 Abstr. 4582
3. Oh et al. ASCO 2020, Abstract 4520

Randomized Trials of ICI+GEMCIS in 1st Line Advanced BTC

Trial	Regimens	Sample Size	Design
NCT03875235 (TOPAZ-1)	GEMCIS ± durvalumab	757	Randomized, Phase 3
NCT04003636 (KEYNOTE-966)	GEMCIS ± pembrolizumab/placebo	1048	Randomized, Phase 3
NCT04677504	GEMCIS+atezolizumab ± bevacizumab/placebo	150	Randomized, Phase 2

Also, multiple ongoing trials evaluating combinations of ICI + locoregional therapy (RT, SIRT, ablation) in advanced BTC

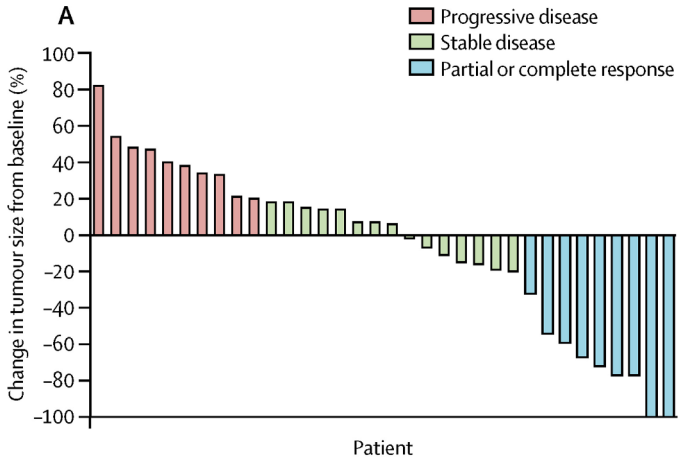
Clinicaltrials.gov

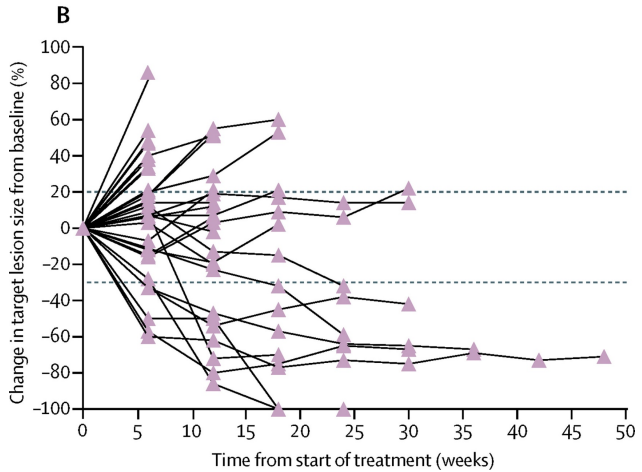
Morris et al. *Lancet Oncol.* 2017;18(4):446-53.

Last… A quick update on what's new in anal cancer

Phase II Nivolumab for Metastatic/Unresectable Anal SCC

- N= 37
  - 2 HIV (+)
  - Median prior lines of rx = 2 (range, 1-7)
- Median PFS 4.1 months, 6-month PFS = 38%

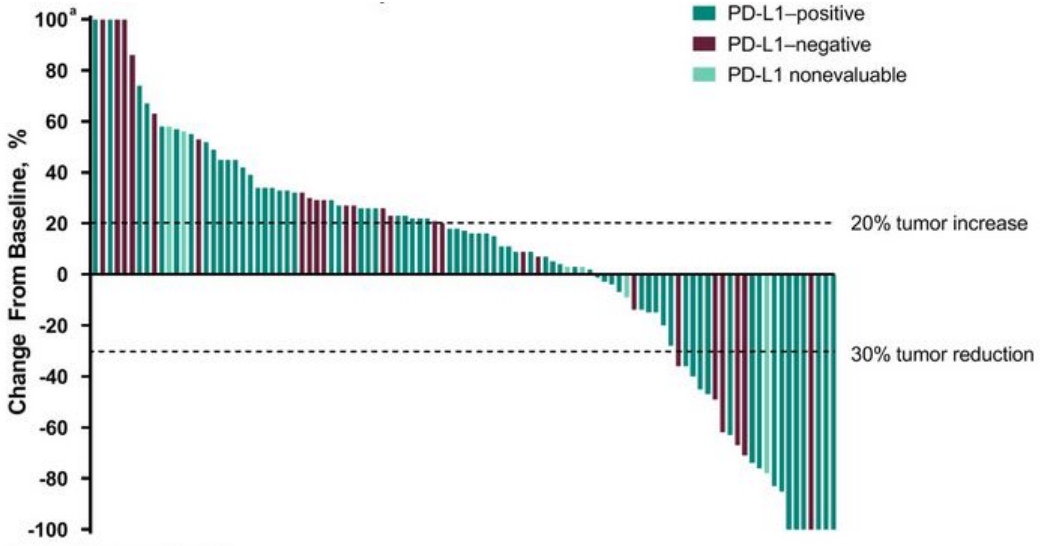




Morris et al. *Lancet Oncol.* 2017;18(4):446-53.

Pembrolizumab for Advanced Anal Squamous Cell Carcinoma: Results from the Multicohort, Phase II KEYNOTE-158 Study

- 112 pts with metastatic and/or unresectable anal SCC, prior treatment failure on or intolerance to standard first-line therapy
  - 73.2% with ≥2 prior therapies
  - 67% PD-L1 (+)
- Median OS = 12.0 mo (1-yr surv 49%)
- Median PFS = 2.0 mos (6-month PFS 18.9%)

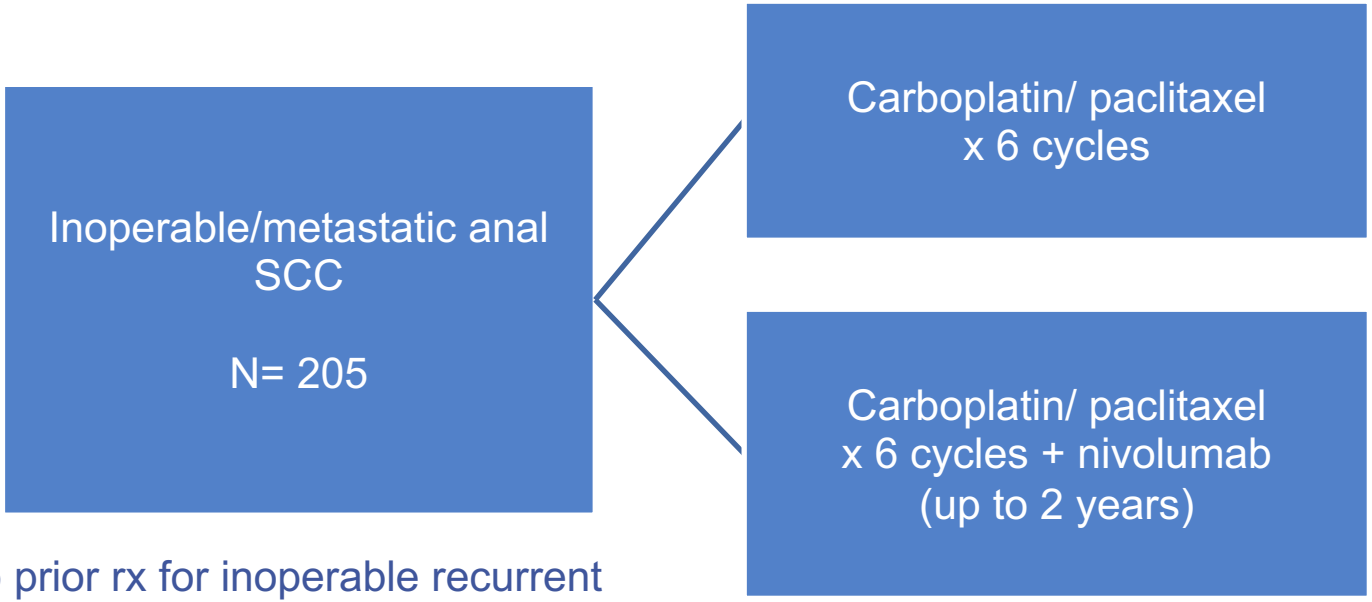


ORR = 11.6%

- PD-L1 CPS ≥1: ORR = 14.7%
- PD-L1 CPS < 1: ORR = 6.7%

Marabelle et al. *J Clin Oncol*. 38, no. 4_suppl (February 01, 2020) 1.

A Randomized Phase III Study of Immune Checkpoint Inhibition with Chemotherapy in Treatment-Naïve Metastatic Anal Cancer Patients

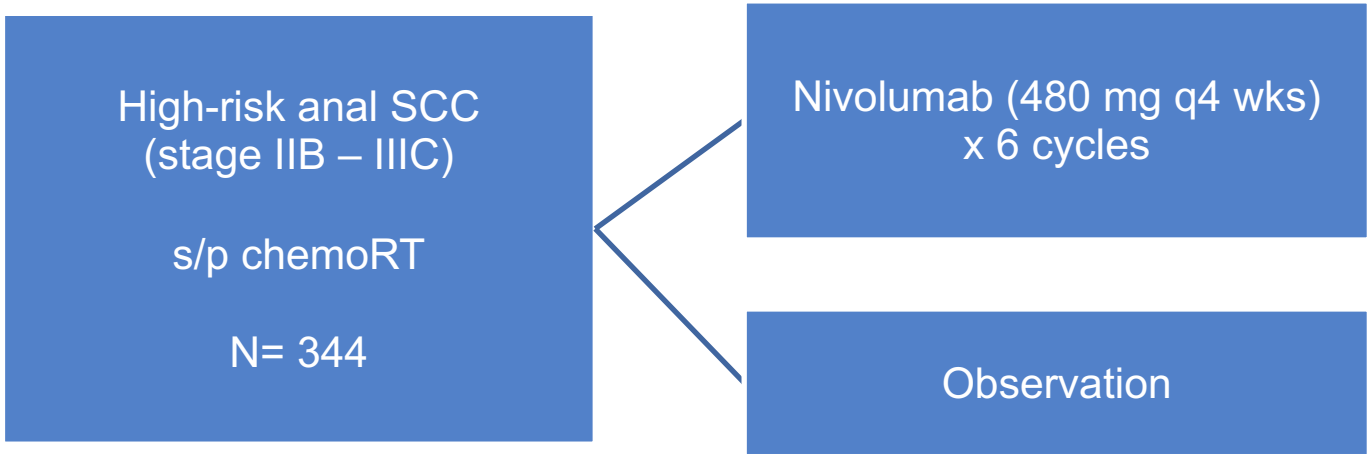


1o endpoint:
PFS

No prior rx for inoperable recurrent or metastatic anal cancer; HIV (+) OK

NCT04444921

EA2165: Nivolumab After Combined Modality Therapy in Treating Patients With High Risk Anal Cancer



1o endpoint:
DFS

Stratification by HIV+/-, clinical nodal status, registration status

NCT03233711

Thank you!

Next Presentation: Thursday, June 17

Hot Topics in Gastric and Esophageal Cancers

Presented by David Ilson, MD, PhD