Iowa Oncology Society

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IOWA | Carver College of Medicine

Upper GI Malignancies

NAOMI FEI MD, MS
8/24/24

Disclosure

- I have no relevant financial relationships with ineligible companies to disclose.

Outline

- Esophageal/Gastric Cancer
  - ESOPEC
  - ARMANI
- Pancreatic Cancer
  - RTOG 0848
  - GIANT
- Cholangiocarcinoma
  - ABC-07

2024 ASCO ANNUAL MEETING

Perioperative Chemotherapy (FLOT) versus Neoadjuvant Chemoradiotherapy (CROSS) for Resectable Esophageal Adenocarcinoma

The ESOPEC Trial (NCT02509286)

J Hoeppner, F Lordick, T Brunner, C Schmoor, B Kulemann, UP Neumann, G Folprecht, T Keck, F Benedix, M Schmeding, E Reitsamer, CJ Bruns, JF Lock, B Reichert, M Ghadimi, K Wille, I Gockel, JR Izbicki, S Utzolino, P Grimminger

PRESENTED BY: Jens Hoeppner MD FACS FEBS

Treatment for Resectable Esophageal Adenocarcinoma

- cT2-4a,cN+/-: **Neoadjuvant chemoradiation** plus surgery
- cT2-4a,cN+/-: **Perioperative chemotherapy** plus surgery

	CROSS (2012)	FLOT (2017)
Treatment Arms	Surgery vs. 41.4 Gy + 5C Carbo/Taxol => Surgery	Peri-operative ECF/ECX vs. Peri-operative FLOT
Inclusion	Esophageal and GEJ Adenocarcinoma (75%) and SCC (25%)	Gastric and GEJ Adenocarcinoma
pCR	--- vs. **23%**	6% vs. **16%**
mOS	27.1m vs. **43.2m**	35 m v. **50m**
5yr OS	34% vs. **43%**	36% vs. **45%**

•Eyck et al. *JCO* 39, 1995-2004(2021)
•Al-Batran et al. Lancet, 2019.

FLOT v. CROSS? NEOAEGIS (2023)

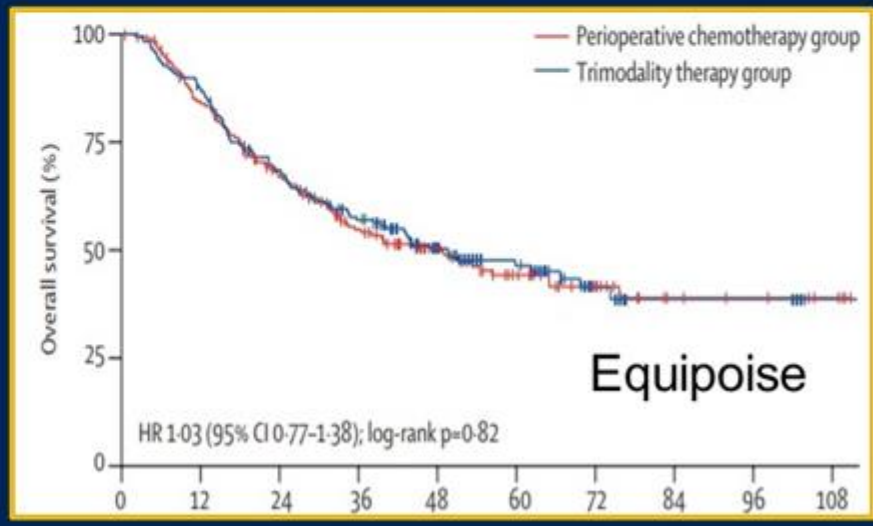
- Esophageal and GEJ Adenocarcinoma, Siewert I-III
- cT2-3, N0-3, M0
- N = 377
- **Non-Inferiority**

R 1:1

EC(O)F(X) or FLOT → Surgery → EC(O)F(X) or FLOT

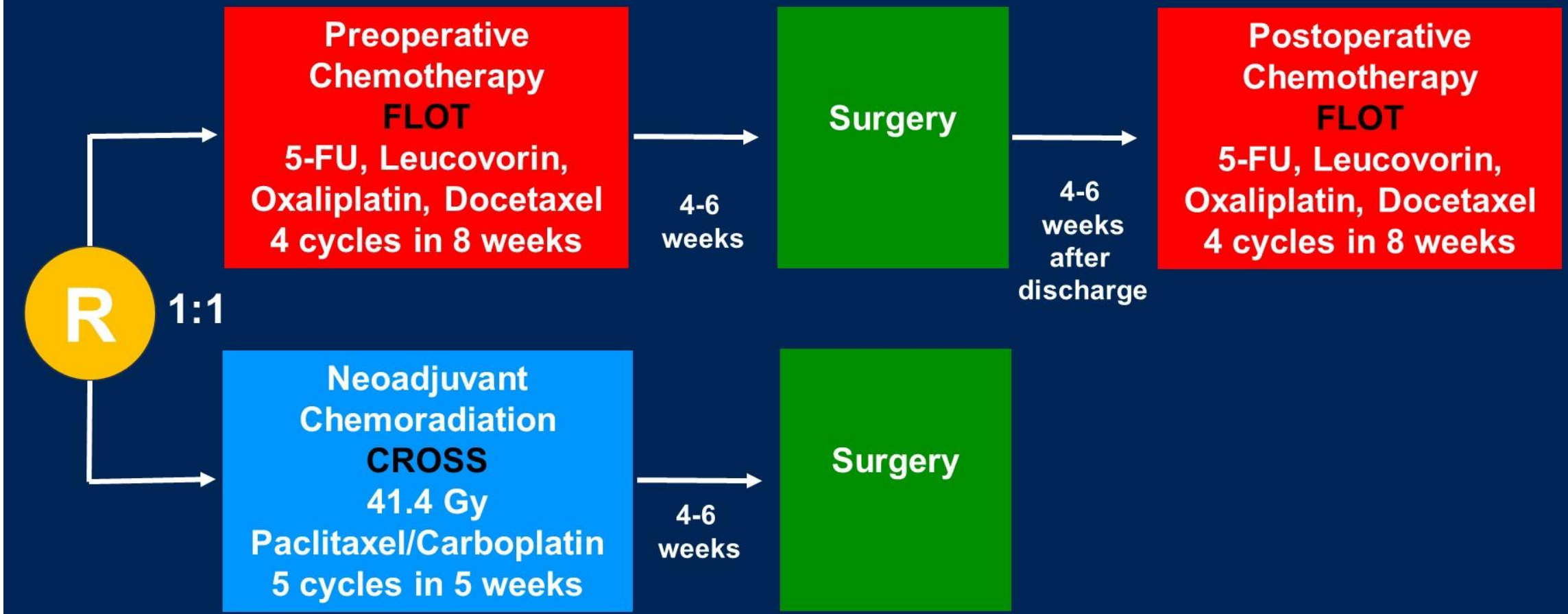
41.4 Gy+ Carboplatin/Paclitaxel → Surgery

No significant difference in severity of complications or post-op mortality, no negative effects of pre-op chemoradiation



Reynolds JV, Lancet Gastroenterol Hepatol, 2023

ESOPEC Trial Scheme



Main Eligibility Criteria

Inclusion Criteria

- Histology: Adenocarcinoma
- Esophageal cancer according UICC (TNM7)[1,*]
- Clinical stage cT1N+ or cT2-4a, cN0/+, cM0

Exclusion Criteria

- Squamous or other non-adenocarcinoma histology
- Gastric cancer
- Clinical Stage cT1cN0 and cT4b
- Metastatic disease

*Tumors of the esophagus and tumors of which the epicenter is within 5 cm of the esophagogastric junction and also extend into the esophagus.

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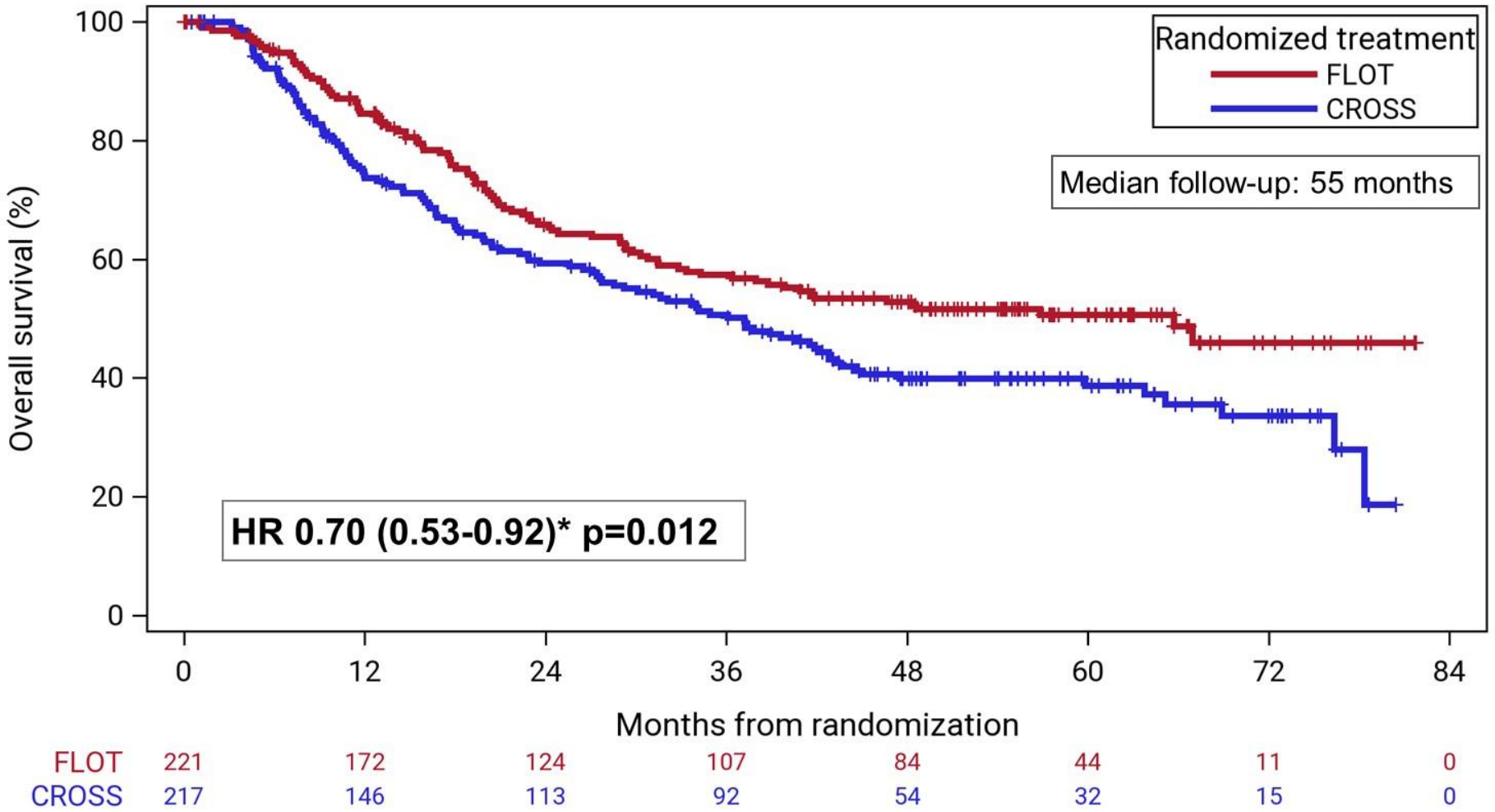
1. Sobin LH UICC TNM 7th edition 2009

Characteristics of ESOPEC Trial Patients

	FLOT Group	CROSS Group
N	221	217
Age mean (SD) in years	63.1 (8.6)	62.6 (9.8)
Sex male	89.1 %	89.4 %
ECOG		
> 0	26.7%	28.1%
Clinical T-stage		
cT1-2	19.5%	17.1%
cT3-4	79.1%	81.9%
Clinical N-stage		
cN0	22.2%	18.4%
cN+	77.8%	81.6%

1. Missing: 2 patients
2. Siewert BJS 1998
3. Tx:5 patients; Missing 2 patients

Overall Survival - ITT Population



	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

*Two-sided 95% confidence interval; Cox regression adjusted for N stage and age, stratified for trial site

Treatment Exposure

	FLOT Group	CROSS Group
N	221	217
Started neoadjuvant treatment (PP population*)	**93.7 %**	**90.3 %**
Completed neoadjuvant treatment ★	**87.3 %**	**67.7 %#**
Received neoadjuvant treatment plus surgery	**86.0 %**	**82.9 %**
Received adjuvant treatment ★	**63.3 %**	
Completed adjuvant treatment ★	**52.5 %**	

*Per protocol population according to Clinical Trial Protocol and Statistical Analysis Plan

#Completion rate (41.4Gy) of radiotherapy **98%**

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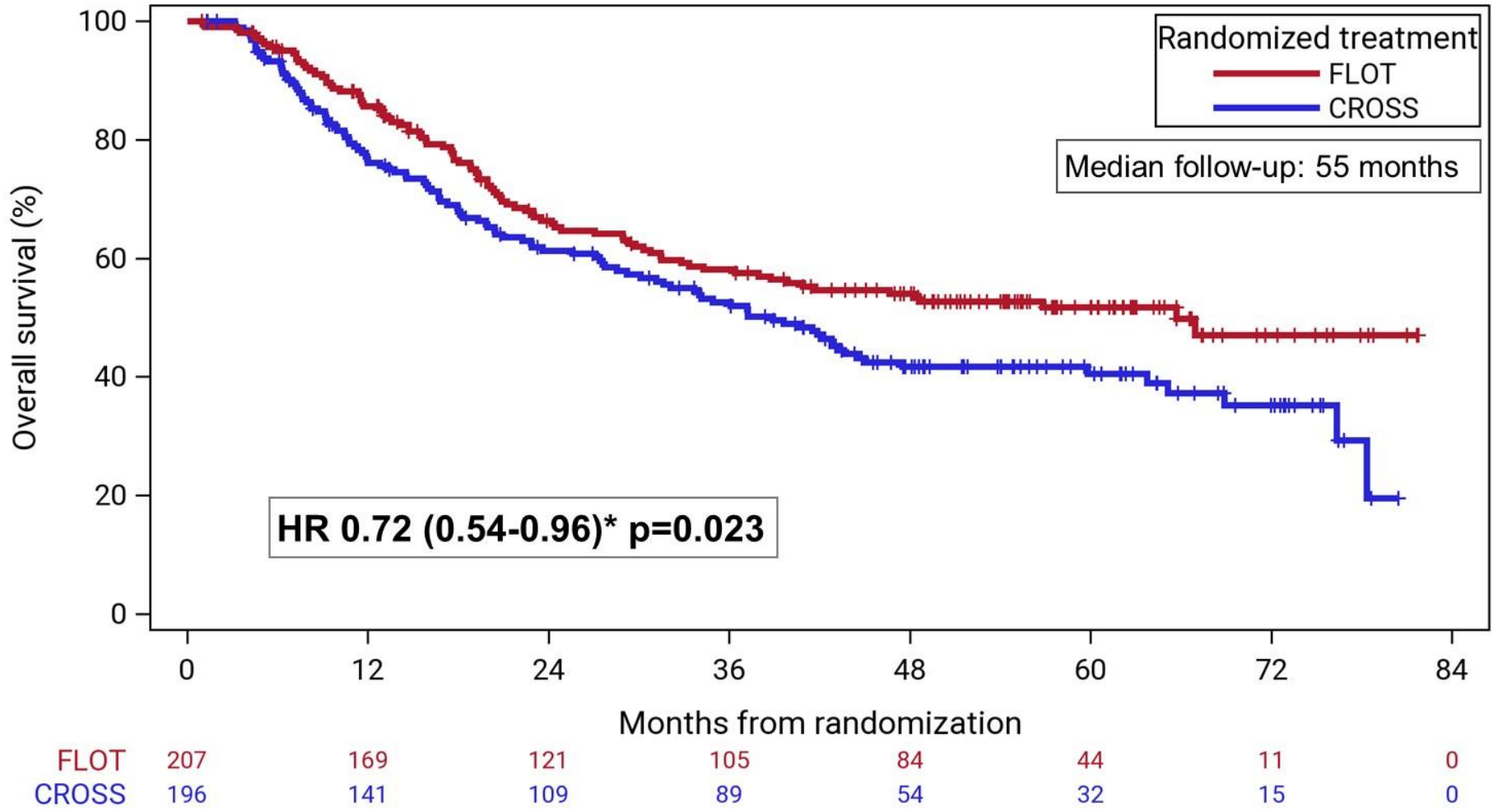
Overall Survival – PP Population



	FLOT	CROSS
Events	92	110
Median OS time (months)	66 95% CI 38 – n.e	39 95% CI 29 – 45
3-year OS rate	58.1%	52.6%
5-year OS rate	51.8%	40.5%

*Two-sided 95% confidence interval; Cox regression adjusted for N stage and age, stratified for trial site

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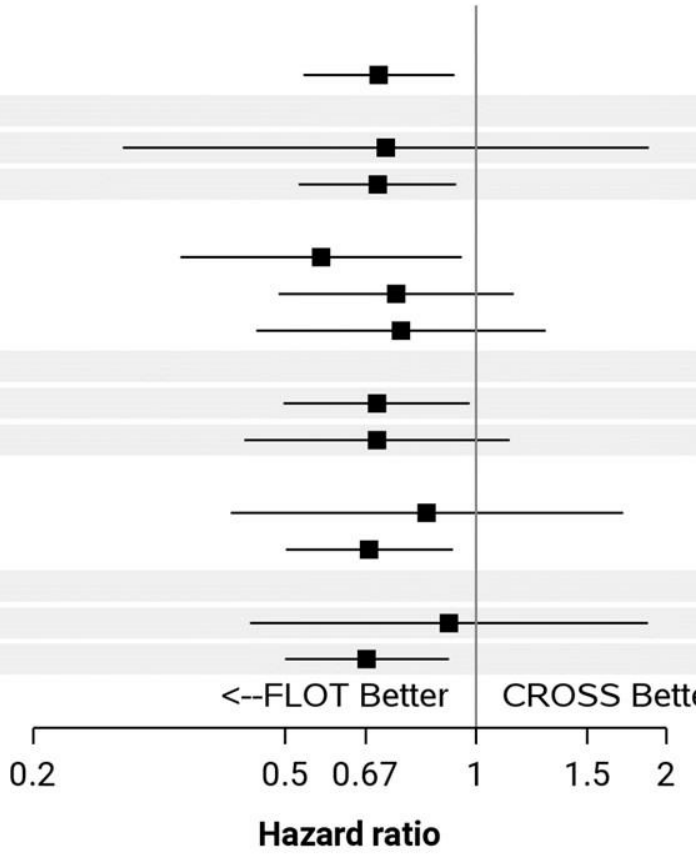
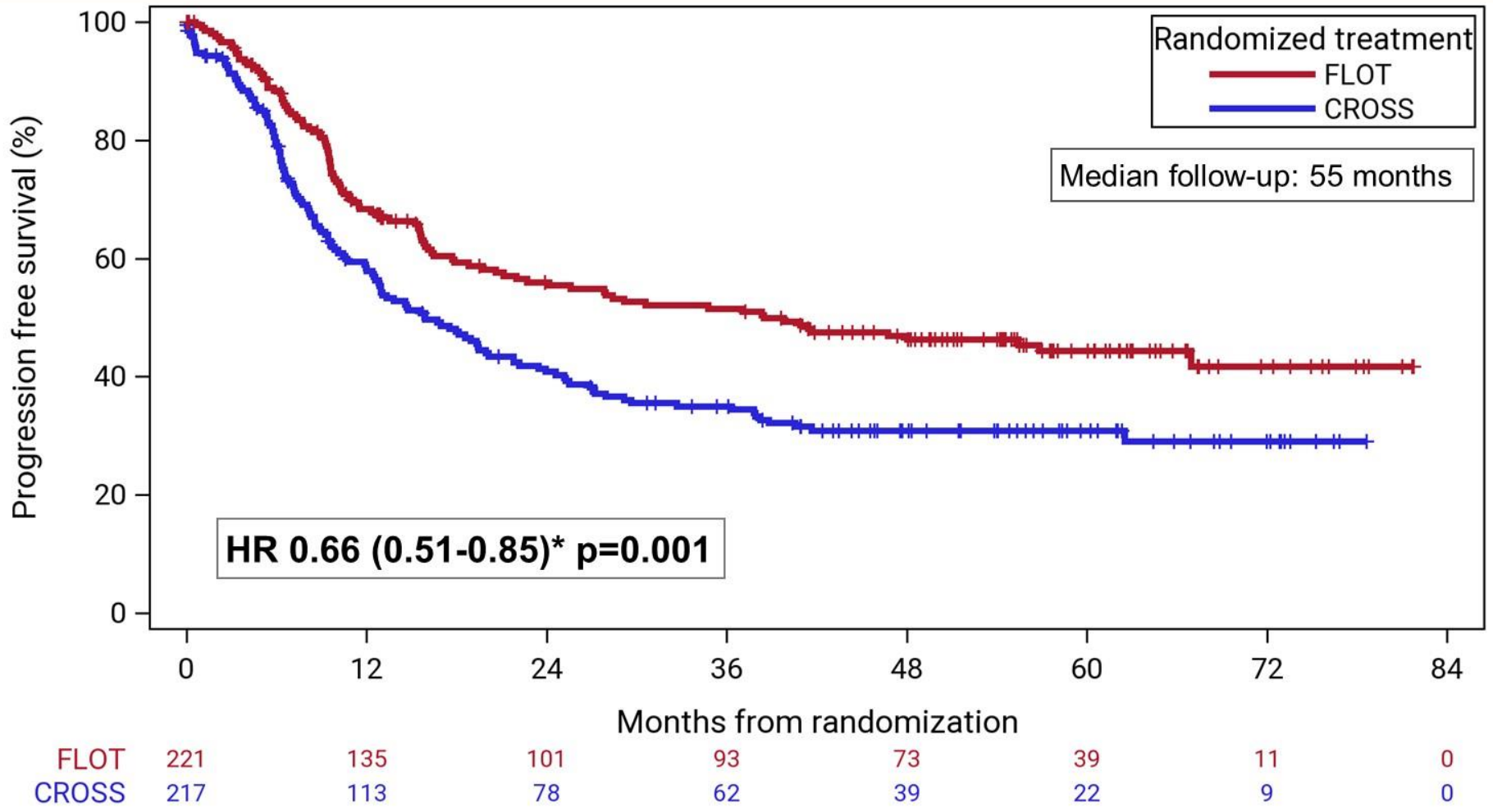
Overall Survival in Exploratory Subgroups

Subgroup	% of patients	Hazard ratio (95% CI)	p-value for interaction
Overall	100%	0.70 (0.53, 0.92)	
Sex			0.95
female	10.7%	0.72 (0.28, 1.88)	
male	89.3%	0.70 (0.53, 0.93)	
Age			0.67
<60 years	36.3%	0.57 (0.34, 0.95)	
60-69 years	38.1%	0.75 (0.49, 1.15)	
>=70 years	25.6%	0.76 (0.45, 1.29)	
ECOG			1.00
0	72.6%	0.70 (0.50, 0.98)	
>0	27.4%	0.70 (0.43, 1.13)	
Clinical T-stage			0.60
T1-2	18.3%	0.84 (0.41, 1.71)	
T3-4	80.5%	0.68 (0.50, 0.92)	
Clinical N-stage			0.45
N0	20.3%	0.91 (0.44, 1.87)	
N+	79.7%	0.67 (0.50, 0.91)	



Progression Free Survival – ITT Population



	FLOT	CROSS
Events	107	137
Median PFS time (months)	38 95% CI 21 – n.e.	16 95% CI 12 – 22
3-year PFS rate	51.6%	35.0%
5-year PFS rate	44.4%	30.9%

*Two-sided 95% confidence interval; Cox regression adjusted for N stage and age, stratified for trial site

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Pathology Results – Surgery Population

	FLOT Group	CROSS Group
N	191	180
Resection status		
No resection	0.5%	1.1%
R0	94.2%	95.0%
R1	5.2%	3.9%
Postoperative N-Stage		
ypN-	50.8%	54.4%
ypN+	48.7%	44.4%
Pathological complete remission		
ypT0 ypN0	16.8%	10.0%
Tumor regression grade (Becker[1])		
Complete regression	18.3%	13.3%
Near complete regression (<10% vital tumor)	25.1%	39.4%

per local pathology assessment

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1. Becker K Cancers 2003

Postoperative Complications – Surgery Population

	FLOT Group	CROSS Group
N	191	180
Postoperative morbidity		
Clavien Dindo I	20.9%	20.0%
Clavien Dindo II	13.6%	15.0%
Clavien Dindo III	23.0%	23.3%
Clavien Dindo IV	6.8%	4.4%
Postoperative mortality		
30-days	1.0%	1.7%
90-days	3.2%	5.6%

Conclusion:

- Peri-operative FLOT improves overall survival compared to neoadjuvant chemoradiation (CROSS) in resectable esophageal adenocarcinoma.

Discussion: Comparing aCROSS trials

	ESOPEC Trial				
	FLOT Group	CROSS Group	CROSS Trial (CRT Group - AC)	Neo-AEGIS Trial (CRT Group)	FLOT-4 (FLOT Group)
Completed **pre-op** treatment	87.3%	**67.7%**	92%	87% (RT - 99%)	90%
Completed **post-op** treatment	52.5%				46%
★ pCR	16.8%	**10%**	23%	12%	16%
★ Median OS	66 mos	**39 mos**	43 mos	49 mos	50 mos
3-year OS	57.4%	50.7%	54%	57%	57%

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

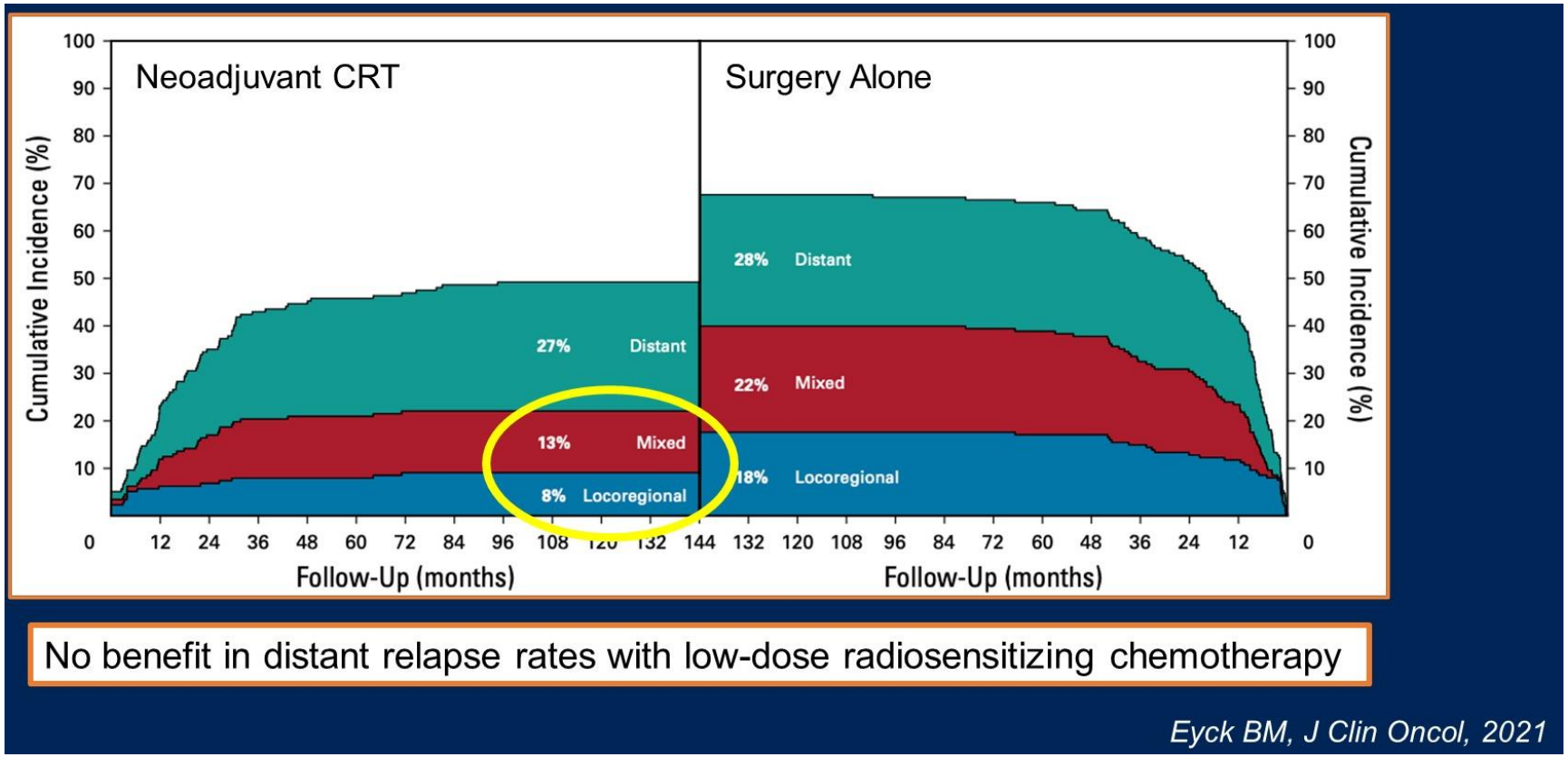
- Only 67.7% of patients on CROSS arm completed neoadjuvant regimen
- Time to surgery after RT was 4-6 wks vs. 6-8 wks in OG CROSS trial

Discussion: Considerations for CROSS

- Benefit of FLOT was lesser in patients with T1-2 and N0 disease.
- Some patients are able to pursue organ preservation and active surveillance if clinical complete response after chemoRT

★In patients not candidates for FLOT, CROSS is reasonable given equipoise from Neo-AEGIS.

Discussion: Incorporating Immunotherapy



Checkmate 577

- Since ESOPEC did not incorporate adjuvant IO, we cannot conclude perioperative FLOT is better than CROSS + adjuvant nivolumab.

Discussion: Incorporating Immunotherapy

- Existing trials have not reliably demonstrated improvement with IO to peri-operative chemotherapy.

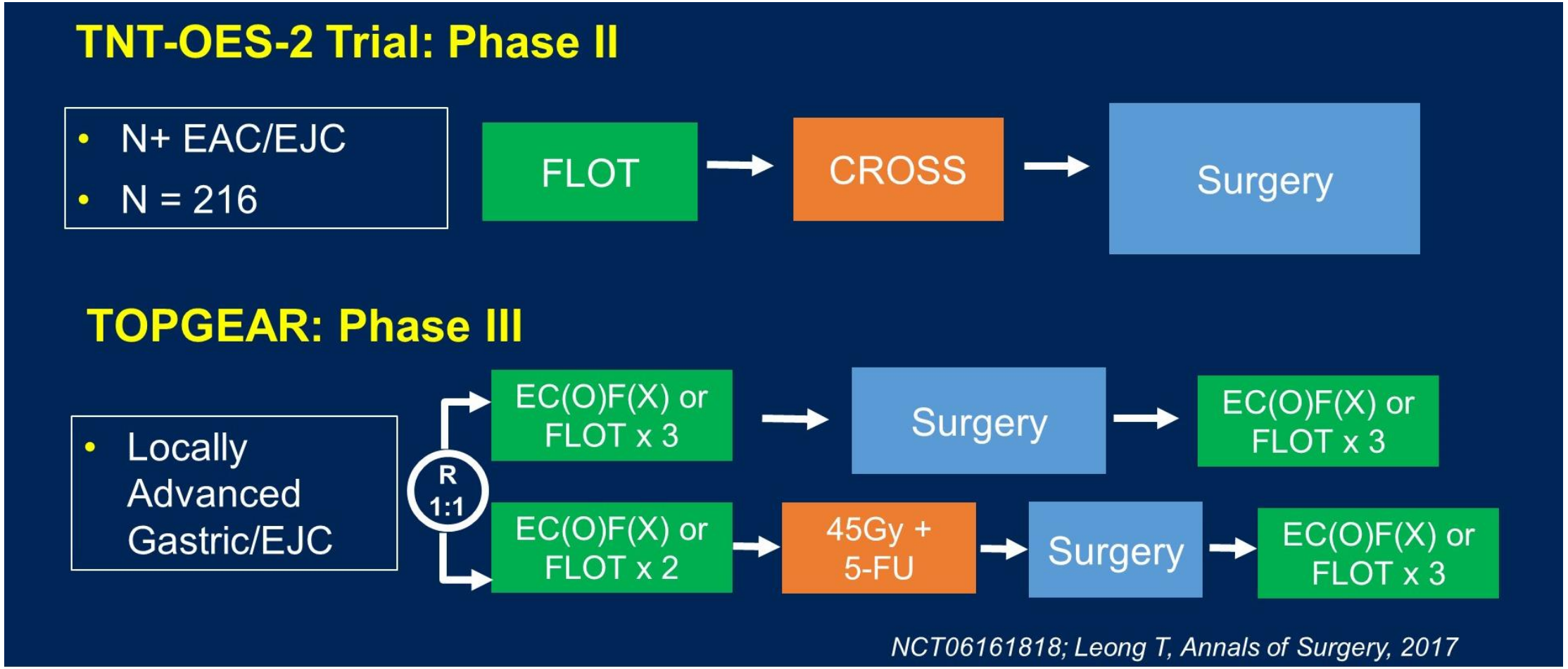
KEYNOTE 585
No improvement in EFS or OS with addition of concurrent Pembrolizumb to peri-op Cis/5-FU or FLOT

ATTRACTION-5
No improvement in RFS with addition of Nivolumab to post-operative chemo (S-1 or CAPEOX)

MATTERHORN/DANTE Phase 2
Durvalumab or Atezolizumab to peri-op FLOT
increased pCR rates DFS + OS data pending

- It may be that radiation improves response to the addition of IO
- Consider: Induction chemo => Chemo RT => Surgery => IO

Upcoming Trials to Watch:



Ramucirumab plus paclitaxel as switch maintenance versus continuation of oxaliplatin-based chemotherapy in patients with advanced HER2-negative gastric or gastroesophageal junction cancer: the ARMANI phase III trial

*Filippo Pietrantonio**, *Giovanni Randon, Sara Lonardi, Silvio Ken Garattini, Stefano Tamberi, Elisa Giommoni, Samantha Di Donato, Lorenzo Fornaro, Oronzo Brunetti, Ferdinando De Vita, Giovanni Luca Frassineti, Claudio Chini, Andrea Spallanzani, Valerie Bethaz, Antonia Strippoli, Tiziana Latiano, Giovanni Gerardo Cardellino, Federica Palermo, Rosalba Miceli, Maria Di Bartolomeo*

*GI Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

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PRESENTED BY: Filippo Pietrantonio

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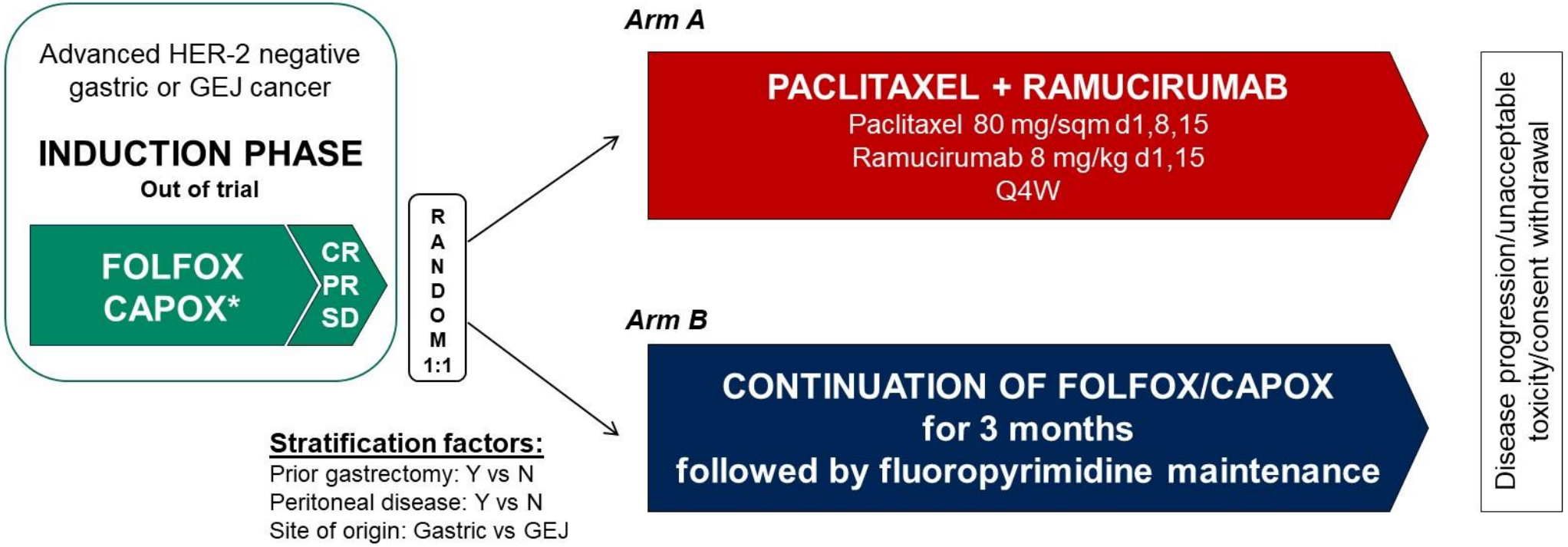
KNOWLEDGE CONQUERS CANCER

Background:

- In HER2 negative, PD-L1 low/absent, advanced Gastric/GEJ adenocarcinoma:
  - 5FU/Platinum doublet is standard 1L
  - Paclitaxel + Ramucirumab is standard 2L
- Only 40% of patients proceed to second line therapy
- ARMANI investigated if ‘switch maintenance’ with Ram/Taxol was superior to continuing FOLFOX/CAPOX after 3 months.

ARMANI study design



**6 bi-weekly cycles or 4 three-weekly cycles (12 weeks)*

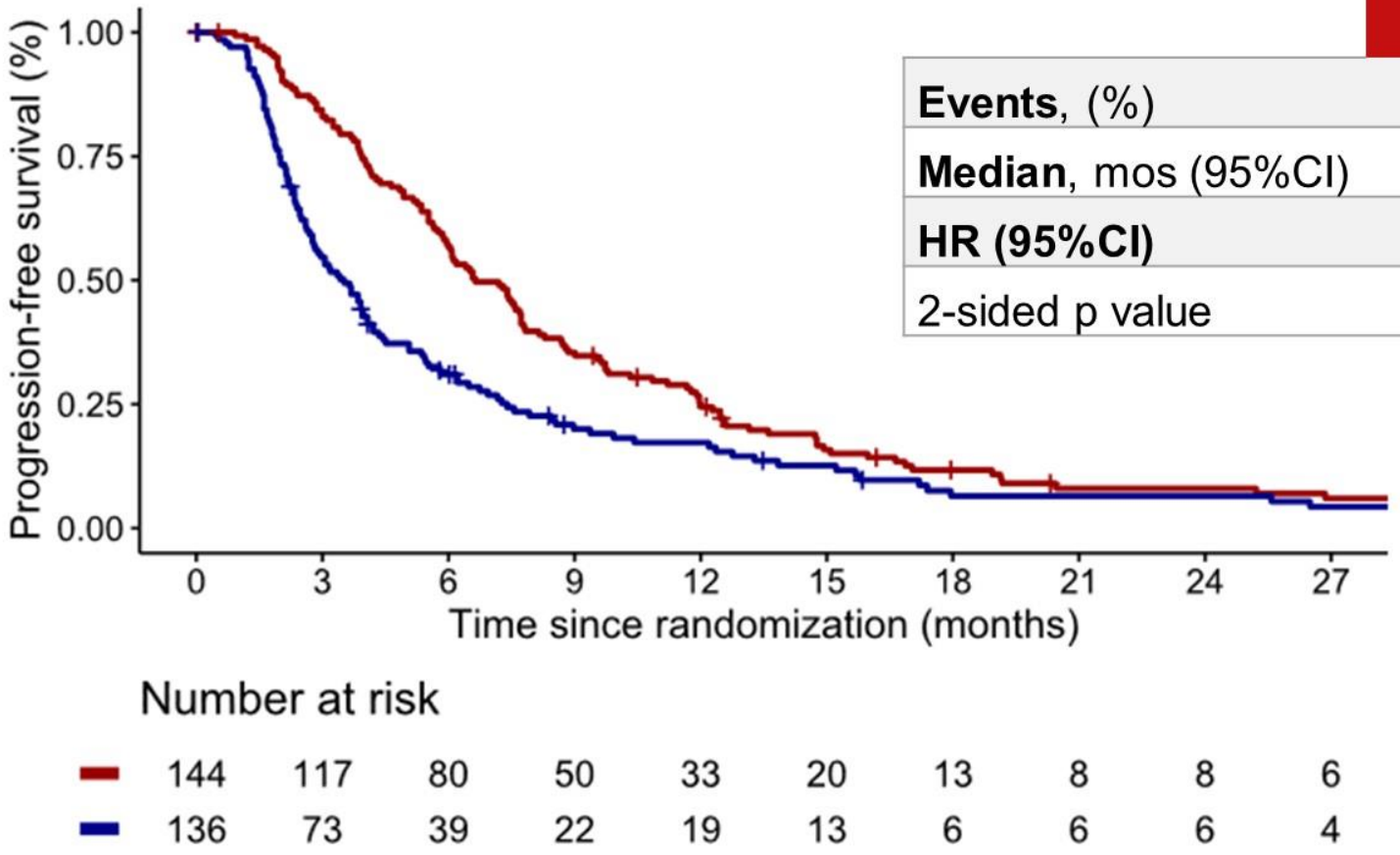
NCT02934464

Baseline Characteristics

	Arm A (PTX-RAM) *N*=144 (%)	Arm B (FOLFOX/CAPOX) *N*=136 (%)
Gender (M/F)	67/33	61/39
Median age (years, IQR)	64 (57-71)	66 (57-72)
ECOG performance status (0/1)	74/26	64/36
★ **Site of origin** (gastric/GEJ)	74/26	74/26
Prior gastrectomy (Y/N)	28/72	23/77
★ **Peritoneal metastases** (Y/N)	53/47	43/57
Liver metastases (Y/N)	24/76	30/70
★ **Number of metastatic sites** (0-1/>1)	48/62	42/68
Synchronous metastases (Y/N)	76/23	81/19
Histotype (intestinal/diffuse/NOS)	41/40/19	34/43/23
★ **First line induction regimen** (FOLFOX/CAPOX)	81.2/18.8	86.8/13.2

The reported numbers are % in the ITT

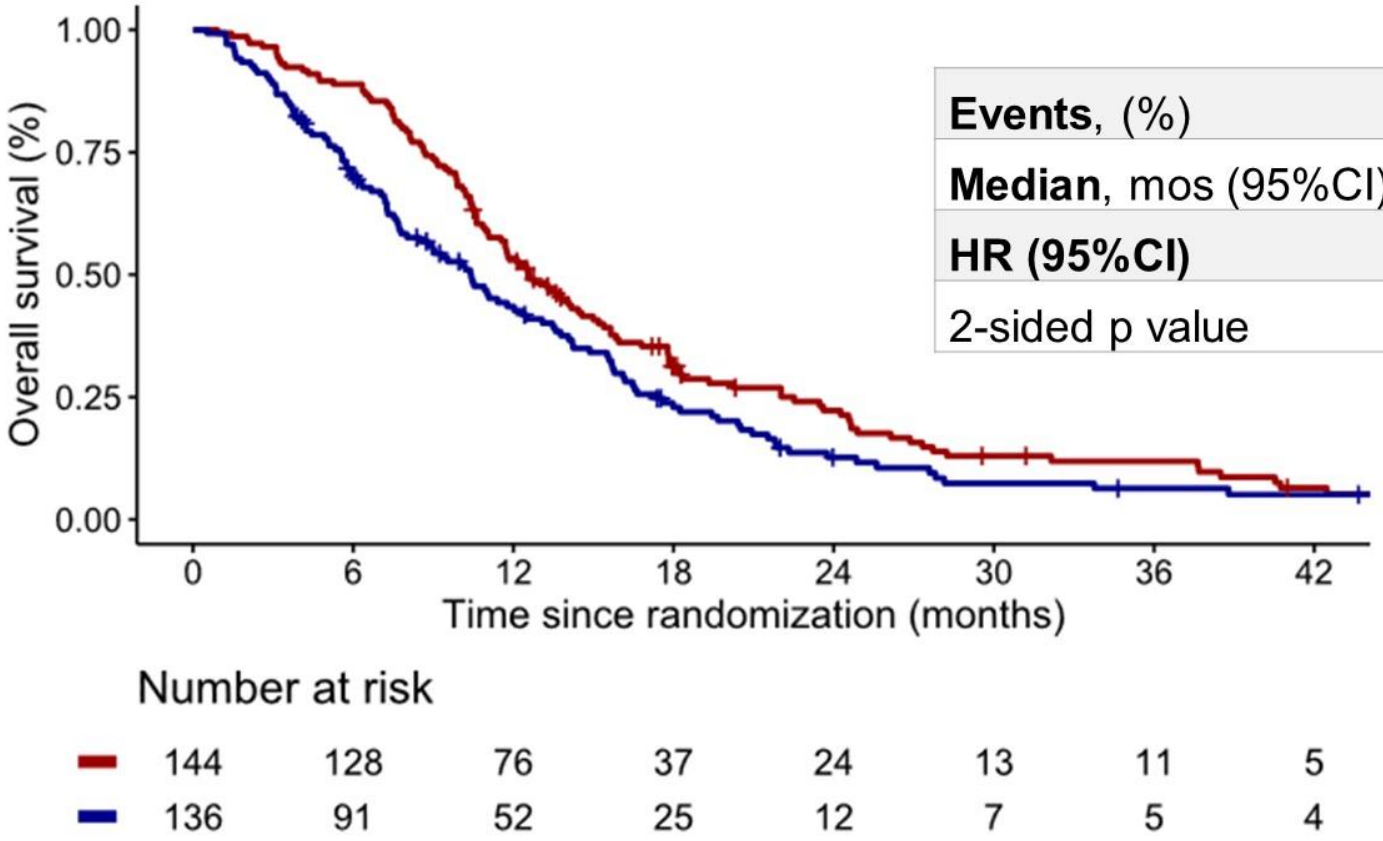
Primary endpoint: PFS



	Arm A (PTX-RAM) n=144	Arm B (FOLFOX/CAPOX) n=136
Events, (%)	91%	90%
Median, mos (95%CI)	**6.6** (6.0-7.8)	**3.5** (2.8-4.2)
HR (95%CI)	**0.64 (0.49-0.81)**	
2-sided p value	**P<0.001**	

24-month RMST analysis showed a 2.4-mos average increment in PFS, which was statistically significant (p=0.002).

Key secondary endpoint: OS



	Arm A (PTX-RAM) n=144	Arm B (FOLFOX/CAPOX) n=136
Events, (%)	86%	85%
Median, mos (95%CI)	**12.6** (11.5-15.0)	**10.4** (8.0-13.1)
HR (95%CI)	**0.75 (0.58-0.97)**	
2-sided p value	**P=0.028**	

Subsequent anti-cancer therapies

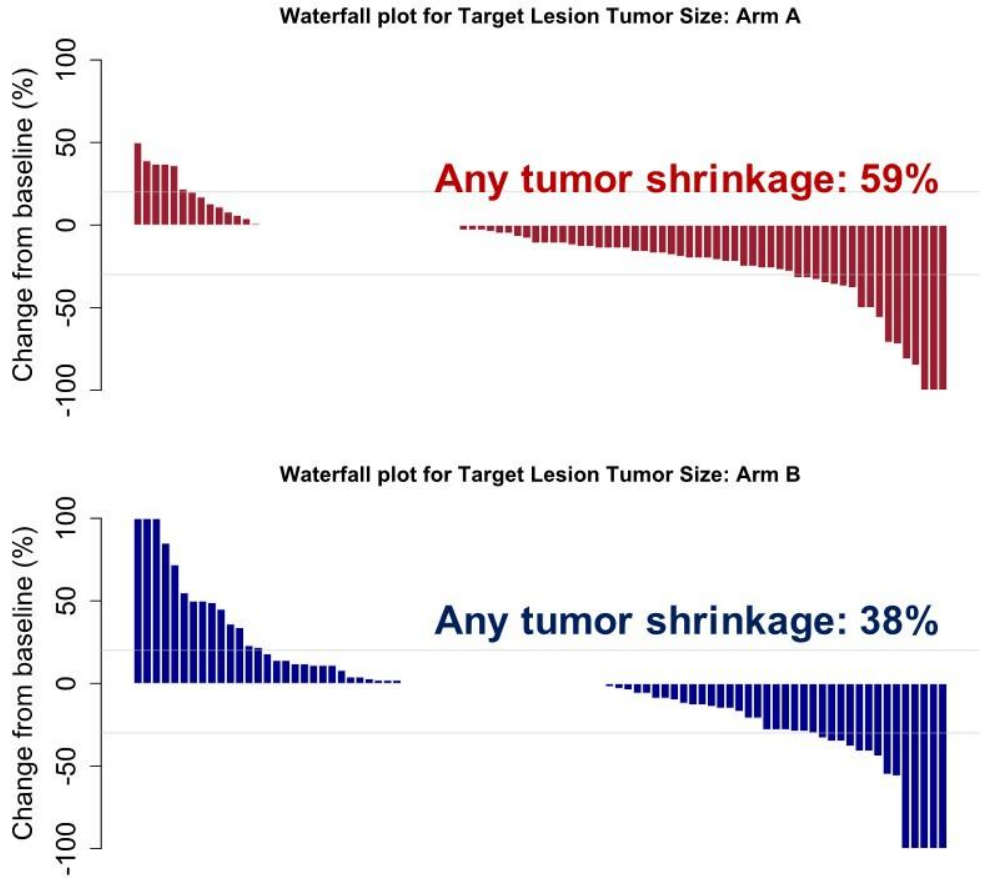
	Arm A (PTX-RAM) *N*=144	Arm B (FOLFOX/CAPOX) *N*=136
Any subsequent therapy, (%)	**58**	**56**
Type of regimen, (%)*		
- Paclitaxel-Ramucirumab	**3**	**45**
- Paclitaxel/docetaxel	1	5
- FOLFOX/CAPOX/CDDP-5FU	18	4
- Irinotecan/FOLFIRI/CAPIRI	37	21
- Trifluridine/Tipiracil	17	4
- 5FU/capecitabine	5	2
- anti-PD-1-based	2	2
- Other investigational drugs	3	4

*The percentages are related to ITT patients exposed to a specific regimen in any treatment line

Key secondary endpoint: ORR

	Arm A n=95[a]	Arm B n=102[a]
ORR, %	**18.9**	**15.7**
DCR, %	**85.3**	**54.0**
CR	1 (1%)	3 (3.0%)
PR	17 (17.9%)	13 (12.8%)
SD	63 (66.3%)	39 (38.2%)
PD	9 (**9.5%**)	33 (**32.3%**)
NE[b]	5 (5.3%)	14 (13.7%)

a. Included patients with RECIST measurable disease.
b. included patients without one post-baseline CT scan.



Graph is cut for values exceeding increase in SLD > 100%

Safety analysis

Adverse Events	Arm A (PTX-RAM) *N*= 141		Arm B (FOLFOX/CAPOX) *N* = 135	
	Any Grade (%)	Grade ≥ 3 (%)	Any Grade (%)	Grade ≥ 3 (%)
Stomatitis/Oral mucositis	14.2	1.4	14.0	1.5
Nausea	12.8	0	18.5	0
Vomiting	6.4	0	6.7	0
Diarrhea	16.3	0	8.9	0
Hand-foot syndrome	1.4	0	11.8	0
Peripheral Neuropathy	61.7	5.7	45.2	6.7
Neutropenia	55.3	26.2	23.0	9.6
Febrile neutropenia	1.4	1.4	0	0
Anemia	27.7	2.1	13.3	3.0
Thrombocytopenia	14.2	0	28.1	0
Hypertension	23.4	6.4	0.7	0
Venous thromboembolism	5.7	2.8	2.2	0

Grade 3 or higher treatment-related adverse events were observed in **40.4%** of patients in the PTX-RAM arm versus **20.7%** of patients in the FOLFOX/CAPOX arm

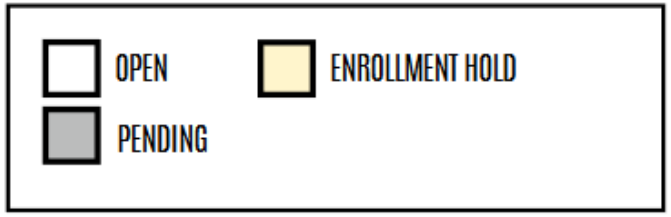
Conclusion:

- In patients with advanced, HER2 negative, gastric/GEJ adenocarcinoma with disease control after FOLFOX/CAPOX x 3 months, switch maintenance with paclitaxel + ramucirumab significantly improved PFS and OS compared to continuation of oxaliplatin based chemotherapy.
- Switch strategy resulted in a higher rate of Grade 3 or more TRAE, however the safety profile was not unexpected.

Discussion:

- Consideration of risk vs. benefit in a switch maintenance approach.
  - OS improved by ~2 months with increased toxicities and increased clinic visits (D1/8/15 schedule)
- Incorporation in an increasingly biomarker driven treatment landscape?

GASTRIC/GASTROESPHAGEAL CANCER



1L

A022102
Criteria: Unresectable or metastatic HER2- adenocarcinoma of esophagus, GEJ, or stomach; no prior treatment for unresectable or metastatic disease

PI: Saima Sharif

NCT05677490

METASTATIC

BGB-A317-A3055-101: A Phase 1a/1b Study Investigating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of BGB-A3055, Alone and in Combination With Tislelizumab in Patients With Selected Advanced or Metastatic Solid Tumors

PI: Muhammad Furqan

NCT05935098

ACCRU GI-1810:
Criteria: LA, unresectable, metastatic disease that has progressed ≤ 180 days from last treatment, patient must have received 5-FU or capecitabine and platinum or trastuzumab in case of HER2+ disease

PI: Saima Sharif

NCT04660760

OBT076-001:
A Phase I, Open-label, Dose Finding Study to Assess the Safety, Tolerability, PK, and Preliminary Efficacy of OBT076, a CD205-directed ADC, in Recurrent and/or Metastatic CD205+ Solid Tumors

PI: Doug Laux

NCT04064359

NRG ONCOLOGY

Advancing Research. Improving Lives.™

NRG Oncology/RTOG 0848 Trial: Adjuvant Chemotherapy +/- Chemoradiation For Patients With Resected Head of Pancreas Adenocarcinoma -

Results of the RT + 5FU/Capecitabine Randomization Step

Ross A Abrams, MD, Kathryn A Winter, MS, Karyn A Goodman, MD, William F Regine, MD, Howard P Safran, MD, Adam C Berger, MD, Chandan S Guha, MD, PhD, Lisa A Kachnic, MD, Michael T Gillin, PhD, Samantha A Seaward, MD, Abraham J Wu, MD, Jennifer J Wu, MD, Raid M Aljumaily, MD, Thomas A Dipetrillo, MD, Ravit Geva, MD, Pramila Rani Anne, MD, Jennifer Yannucci, MD, Darla K Liles, MD, Jennifer Moughan, MS, Christopher H Crane, MD

ASCO 2024

6/4/2024

NCI National Clinical Trials Network — a National Cancer Institute program

NCI Community Oncology Research Program — A program of the National Cancer Institute of the National Institutes of Health

Adjuvant Radiation in Pancreatic Cancer

- The role of adjuvant radiation in pancreatic cancer is unclear.

Year	Trial	Adjuvant Treatment	OS
(1985)	GITSG	5FU + RT vs. none	Better
(2004)	ESPAC-1	5FU +RT vs. 5FU vs. 5FU + RT => 5FU vs. none	Worse
(2007)	EORTC-40891	5FU + RT vs. none	Same
(2010)	EORTC-40013	Gem vs. Gem+ RT	Same

Trial Objective:

- RTOG 0848 was designed to determine if addition of chemoRT to curative surgery and 6m of adjuvant chemotherapy improves OS.
- The trial was designed in 2008 when adjuvant gemcitabine was SOC.

- Eligibility: M0, Zubrod PS 0-1, CA19-9 ≤ 180, R0/R1 resection*

SCHEMA

Patients with resected pancreatic head adenocarcinomas

→ REGISTER

FIRST STEP:
ADJUVANT SYSTEMIC TREATMENT*

Arm 1:
Gemcitabine alone

Arm 2:
Gemcitabine + Erlotinib x 5 cycles (Arm 2 closed to accrual effective 4/02/14)

Abrams et al., *Am J Clin Oncol 2020;* 43:173-179

REASSESS AND IF NO PROGRESSION, THEN:

STRATIFY

Nodal Status:
1: involved
2: uninvolved
CA19-9 result:
1: ≤ 90
2: > 90 – 180
Surgical margins:
1: positive (R1)
2: negative (R0)
Adjuvant Systemic Treatment:
1. Gemcitabine alone
2. FOLFIRINOX or mFOLFIRINOX
3. Non-oxaliplatin gemcitabine combinations

RANDOMIZE

SECOND STEP:
RT RANDOMIZATION
For Non-Progressing Patients

Arm 3:
1 month of gemcitabine or combination chemotherapy

Arm 4:
1 month of gemcitabine or combination chemotherapy followed by XRT with either capecitabine or 5-FU

NRG ONCOLOGY *Note: Up to 3 months may be initiated prior to registration. NRG/RTOG 0848

Abrams, et al. Presented by Karyn Goodman, MD, FASCO, MS. Mount Sinai

Results: Adjuvant Systemic Treatment Received

	Chemo	Chemo+CRT	Total
Enrollment Timing	174	180	354
Before June 28, 2016	148	161	309
After June 28, 2016	26	19	45
Regimen Received			
Gemcitabine	116	120	236 (67%)
Gemcitabine+Erlotinib	50	50	100 (28%)
Non Oxaliplatin Gem Combo	8	10	18 (5%)
FOLFIRINOX / mFOLFIRINOX	0	0	0 (0%)

Results: Patient and Tumor Characteristics

		Chemo (n=174)	Chemo+CRT (n=180)	Total (n=354)
Pathologic T stage	T1/T2	29 (17%)	37 (21%)	66 (19%)
	T3	145 (83%)	143 (79%)	288 (81%)
Pathologic N stage	N0	42 (24%)	49 (27%)	91 (26%)
	N1	132 (76%)	131 (73%)	263 (74%)
	1-3 nodes/> 3 nodes	95 (55%)/ 37 (21%)	79 (44%)/ 52 (29%)	174 (49%)/ 89 (25%)
Surgery	Classic PD	121 (70%)	139 (77%)	260 (73%)
	PPP/Other	53 (30%)	41 (23%)	94 (27%)
Surgical Margins	Negative	144 (83%)	151 (84%)	295 (83%)
	Positive	30 (17%)	29 (16%)	59 (17%)

NRG ONCOLOGY PD: Pancreaticoduodenectomy; PPP: Pylorus preserving PD NRG/RTOG 0848

Abrams, et al. Presented by Karyn Goodman, MD, FASCO, MS. Mount Sinai

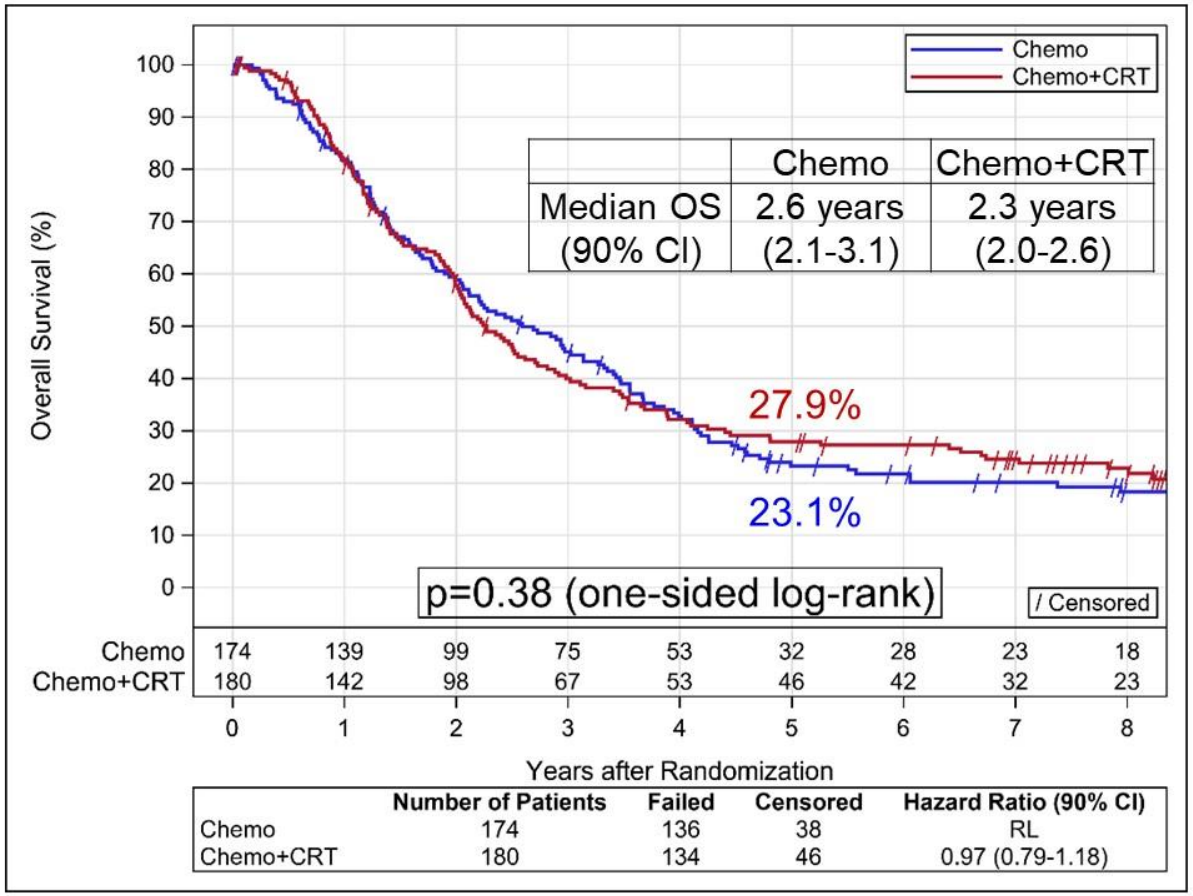
Results: Treatment-Related Adverse Events Reported after 2nd Step Randomization

Grade	Chemo (n=174)	Chemo+CRT (n=180)
1	35 (20%)	25 (14%)
2	72 (41%)	62 (34%)
3	33 (19%)	68 (38%)
4	7 (4%)	9 (5%)
5	1 (1%)	1 (1%)
Grades 2, 3 (p=0.02)	105 (60%)	130 (72%)
Grades 4, 5 (p=0.68)	8 (5%)	10 (6%)

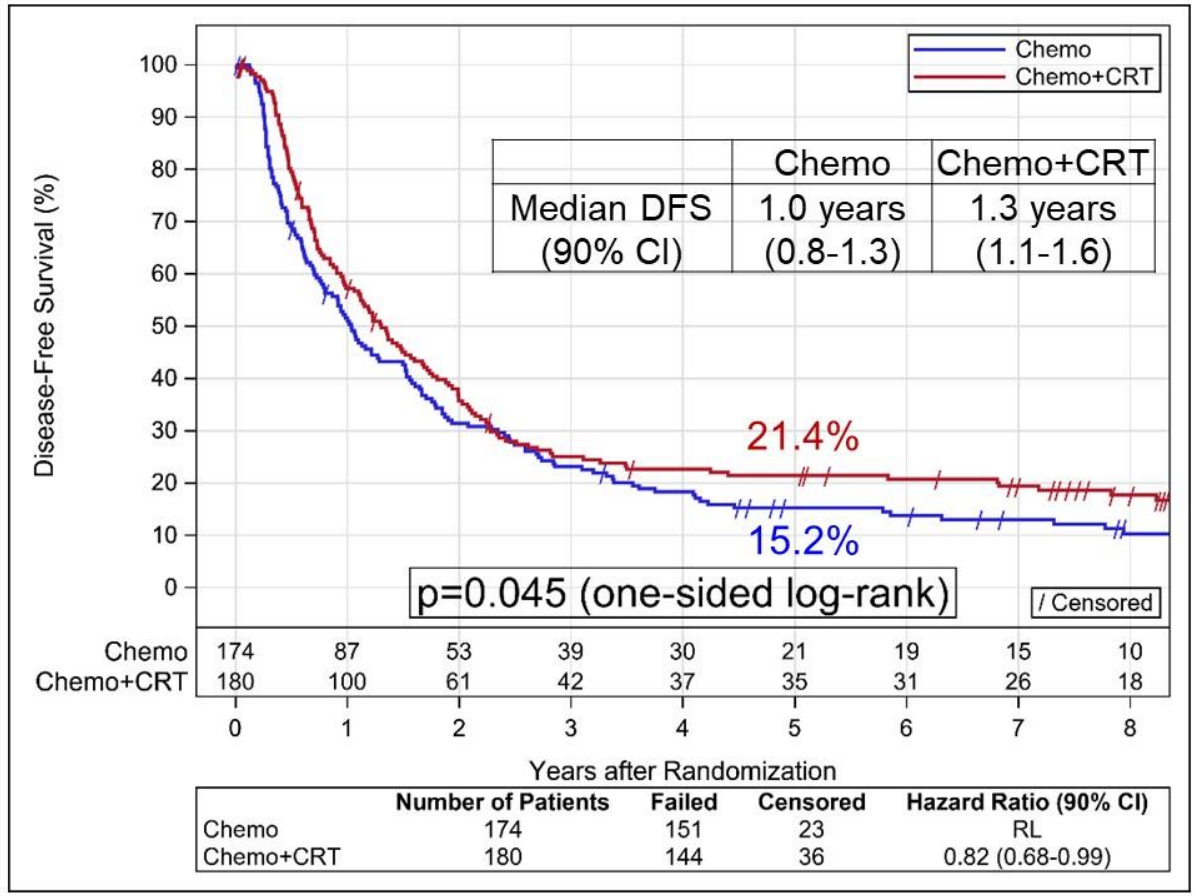
NRG ONCOLOGY CTCAE version 4 NRG/RTOG 0848

Abrams, et al. Presented by Karyn Goodman, MD, FASCO, MS. Mount Sinai

Results: OS and DFS for All Patients



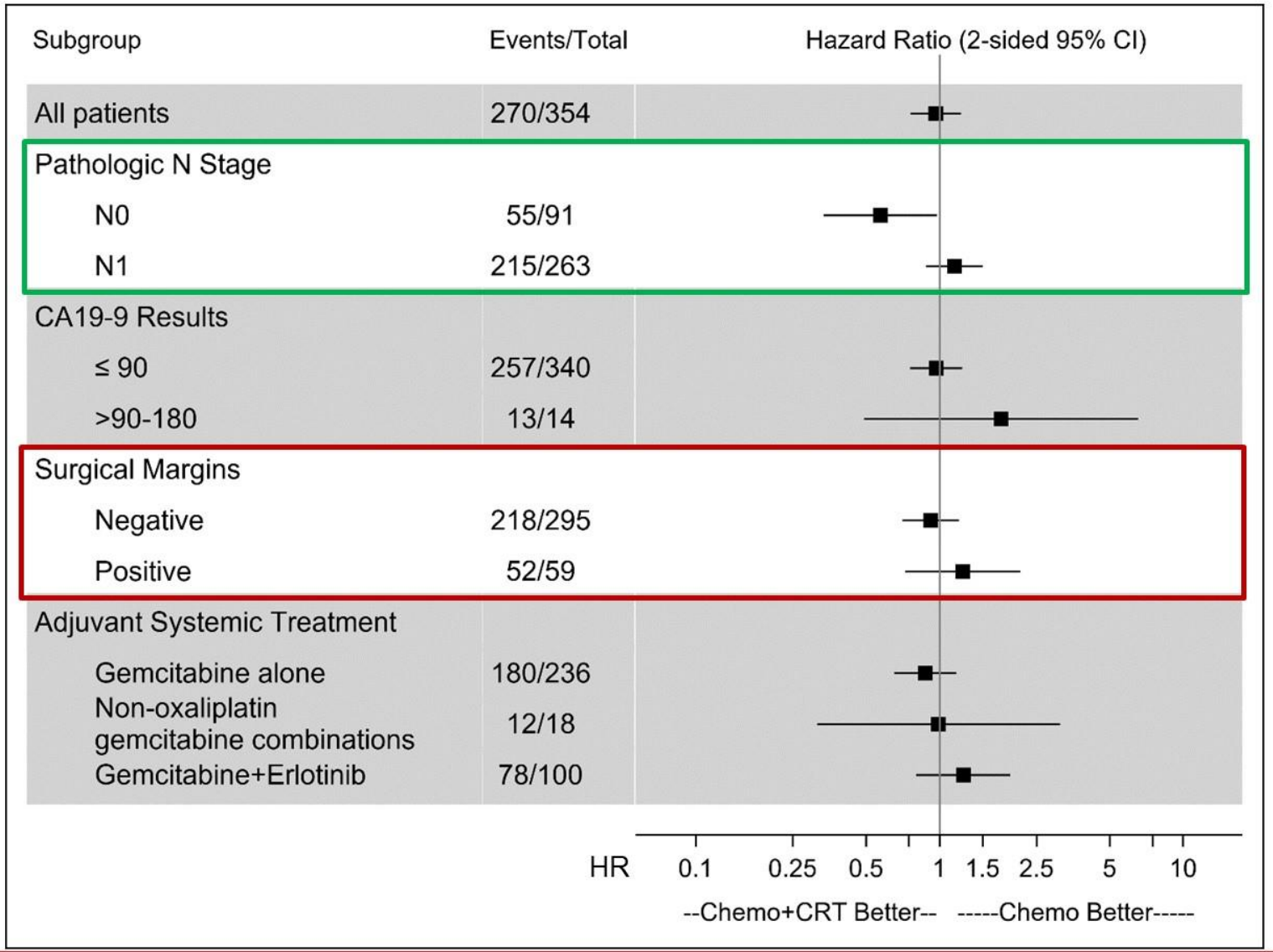
Overall Survival



Disease-Free Survival

Abrams, et al. Presented by Karyn Goodman, MD, FASCO, MS. Mount Sinai

Results: Forest Plot for OS Treatment Effect

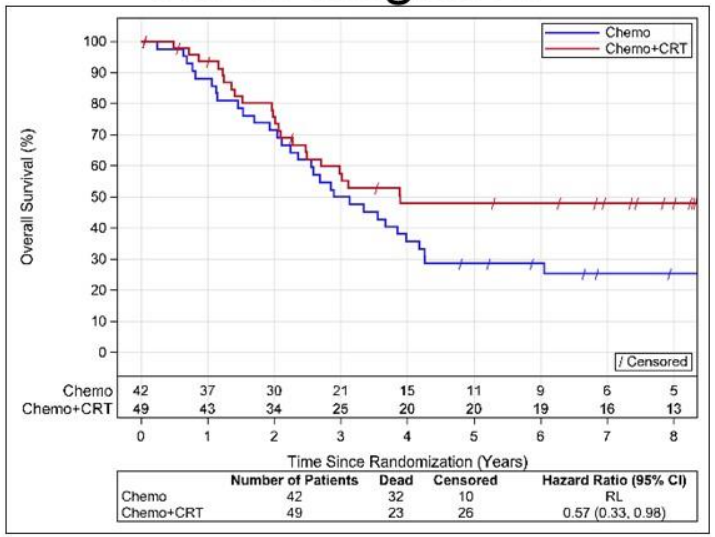


Abrams, et al. Presented by Karyn Goodman, MD, FASCO, MS. Mount Sinai

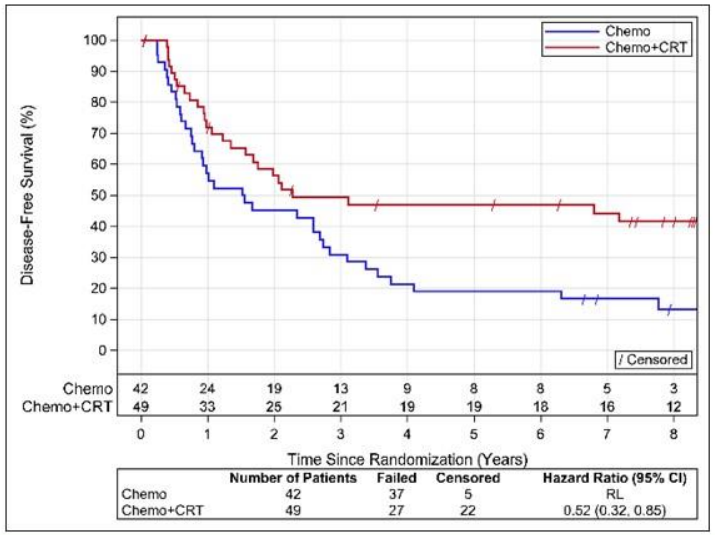
Results: Treatment by Nodal Status Interaction for OS/DFS

Node negative

OS

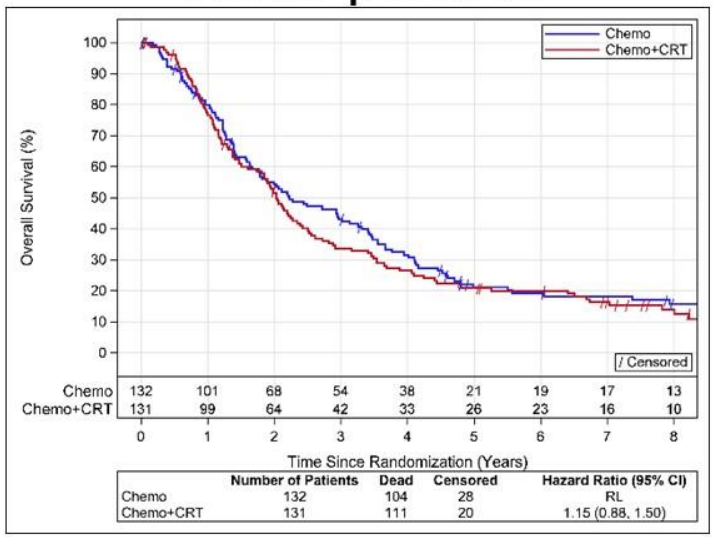


DFS

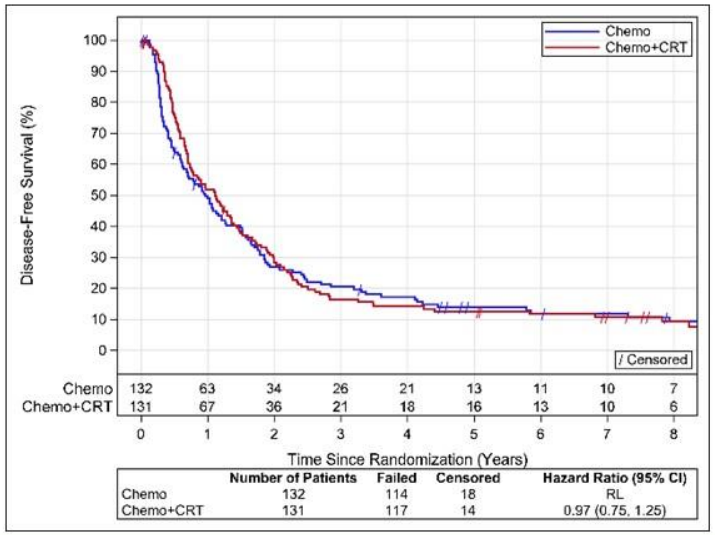


Node positive

OS



DFS



NRG ONCOLOGY

Significant interaction results hold on multivariable analyses

NRG/RTOG 0848

Abrams, et al. Presented by Karyn Goodman, MD, FASCO, MS. Mount Sinai

Conclusions

The addition of radiation + 5FU/capecitabine to adjuvant systemic treatment

- Did not increase grade 4 or 5 Adverse Events
- Did not improve OS for All Patients
- Significantly Improved DFS for All Patients
- Significantly Improved OS and DFS for Node Negative Patients

Abrams, et al. Presented by Karyn Goodman, MD, FASCO, MS. Mount Sinai

Discussion:

- Evolution of clinical therapy:
  - Adjuvant therapy has changed since 2008 incorporating mFOLFIRINOX
  - Neoadjuvant chemotherapy is now often used
- This trial is enriched for patients:
  - 2 step randomization allowed selection of patients who have not progressed
  - Ca 19-9 limits of <180
  - Head of PDAC only
  - No R2 resection
- Future Questions:
  - Does adjuvant CRT have more benefit when combined with more effective systemic therapy?

2024 ASCO ANNUAL MEETING

ECOG-ACRIN cancer research group

A randomized phase II study of gemcitabine and nab-paclitaxel compared with 5-fluorouracil, leucovorin, and liposomal irinotecan in older patients with treatment-naive metastatic pancreatic cancer (**GIANT**) ECOG-ACRIN EA2186

Efrat Dotan[1], Paul J. Catalano[2], Leon Lenchik[3], Robert Boutin[4], Xin Yao[5], James P. Ohr[6], Kian-Huat Lim[7], Namrata Vijayvergia[1], Sreenivasa R. Chandana[8], Aparna Kalyan[9], Richard F. Dunne[10], David B. Zhen[11], Daneng Li[12], Melissa A. Simon[9], Jordan Berlin[13], Lynne I. Wagner[3], Peter J. O'Dwyer[14].

[1]Fox Chase cancer Center, [2]Dana Farber Cancer Institute – ECOG ACRIN Biostatistics Center, [3]Wake Forest University Health Sciences, [4] Stanford University, [5]ThedaCare Regional Cancer Center, [6]UPMC Hillman Cancer Center, [7]Washington University School of Medicine, [8]Trinity Health Muskegon Hospital, [9]Northwestern University, [10]University of Rochester, [11]Fred Hutchinson Cancer Center, [12]City of Hope Comprehensive Cancer Center, [13]Vanderbilt University/Ingram Cancer Center, [14]University of Pennsylvania Abramson Cancer Center.

PRESENTED BY: Efrat Dotan, MD

Background:

- Median age of PDAC diagnosis is 70 making geriatric comorbidities a significant consideration in management
- The median age of most fundamental PDAC trials is 60

Phase III mPDAC Studies	Median Age of enrolled patients (years)
PRODIGE	61
MPACT	62-63
NAPOLI 3	62-64

- The GIANT trial was designed to evaluate palliative chemotherapy in metastatic PDACC for elderly patients.

EA2186 (GIANT) - Study Design

Study Patients

- Untreated metastatic pancreatic cancer
- Age ≥70
- ECOG PS: 0-2

Stratification

- ECOG 0-1 vs 2
- Age 70-74 vs ≥75

Screening Geriatric Assessment (GA)

Fit

No GA abnormalities

Standard of care treatment off study

Vulnerable

Mild-moderate GA abnormalities

Complete Geriatric & Quality of Life (QOL) Assessment

Frail

Severe GA abnormalities

Supportive care off study

Arm A (control): Modified Gemcitabine + Nab-Paclitaxel every 2 weeks

1:1 Randomization

Arm B (experimental) : Dose-reduced 5FU + Liposomal Irinotecan every 2 weeks

Disease evaluation + repeat modified GA + QOL assessment every 8 weeks

Treatment until disease progression or intolerance

Primary Endpoint: Overall Survival (OS)

Key Secondary Endpoints: Progression Free Survival (PFS), Objective Response Rate (ORR)

Additional Secondary Endpoints: QOL, Toxicities of Interest to Older Adults

EA2186 (GIANT) - Screening Geriatric Assessment

Domain	Assessment Tool	Fit - no abnormalities	Vulnerable- any mild-moderate abnormalities	Frail- any severe abnormalities
Function[1]	ADL IADL (Female/Male)	6 8 /5	5 6-7/4	≤4 ≤5/≤3
Co-morbidities[2]	CIRS-G	No score 3-4 AND <5 comorbidities with a score of 2	No score 3-4 AND 5-8 comorbidities with a score of 2	≥1 score 3-4 OR >8 comorbidities with a score of 2
Cognition[3]	Blessed Orientation Memory Concentration Test	0-4	5-10	≥11
Age[2]*			≥80	
Geriatric Syndromes[4]	• Falls (>3 in 6m) • Urinary/Fecal incontinence	None	None	Presence of any of these would exclude patients

[1]Corre et al. JCO 2016 [2]Tucci et al; Leukemia and Lymphoma 2015. [3] Mohile et al; JCO 2018. [4]GrantPax study - Betge et al. BMC 2018

Baseline characteristics

	Gemcitabine+ Nab-Paclitaxel (N=88)	5FU+ Liposomal Irinotecan (N=88)	Total (N=176)	P-value
Age, Median (Range)	77 (70-90)	77 (70-89)	77 (70-90)	
Gender, n (%)				0.228
Female	48 (54.5%)	39 (44.3%)	87 (49.4%)	
Male	40 (45.5%)	49 (55.7%)	89 (50.6%)	
Race/Eth, n (%)				0.033
White	77 (88.5%)	64 (74.4%)	141 (81.5%)	
Black/AA	7 (8.0%)	11 (12.8%)	18 (10.4%)	
Hisp/Lat	1 (1.1%)	7 (8.1%)	8 (4.6%)	
Asian	1 (1.1%)	4 (4.7%)	5 (2.9%)	
Mult	1 (1.1%)	0 (0.0%)	1 (0.6%)	
Missing	1	2	3	
Age Stratification, n (%)				1.000
Age 70-74	33 (37.5%)	34 (38.6%)	67 (38.1%)	
Age 75+	55 (62.5%)	54 (61.4%)	109 (61.9%)	

Baseline characteristics

	Gemcitabine+ Nab-Paclitaxel (N=88)	5FU+ Liposomal Irinotecan (N=88)	Total (N=176)	P-value
Prior Neo/Adj Ch, n (%)				0.307
No	77 (87.5%)	82 (93.2%)	159 (90.3%)	
Yes	11 (12.5%)	6 (6.8%)	17 (9.7%)	
Prior Neo/Adj Rad, n (%)				0.432
No	82 (93.2%)	78 (88.6%)	160 (90.9%)	
Yes	6 (6.8%)	10 (11.4%)	16 (9.1%)	
Prior Surg, n (%)				0.254
No	80 (90.9%)	74 (84.1%)	154 (87.5%)	
Yes	8 (9.1%)	14 (15.9%)	22 (12.5%)	

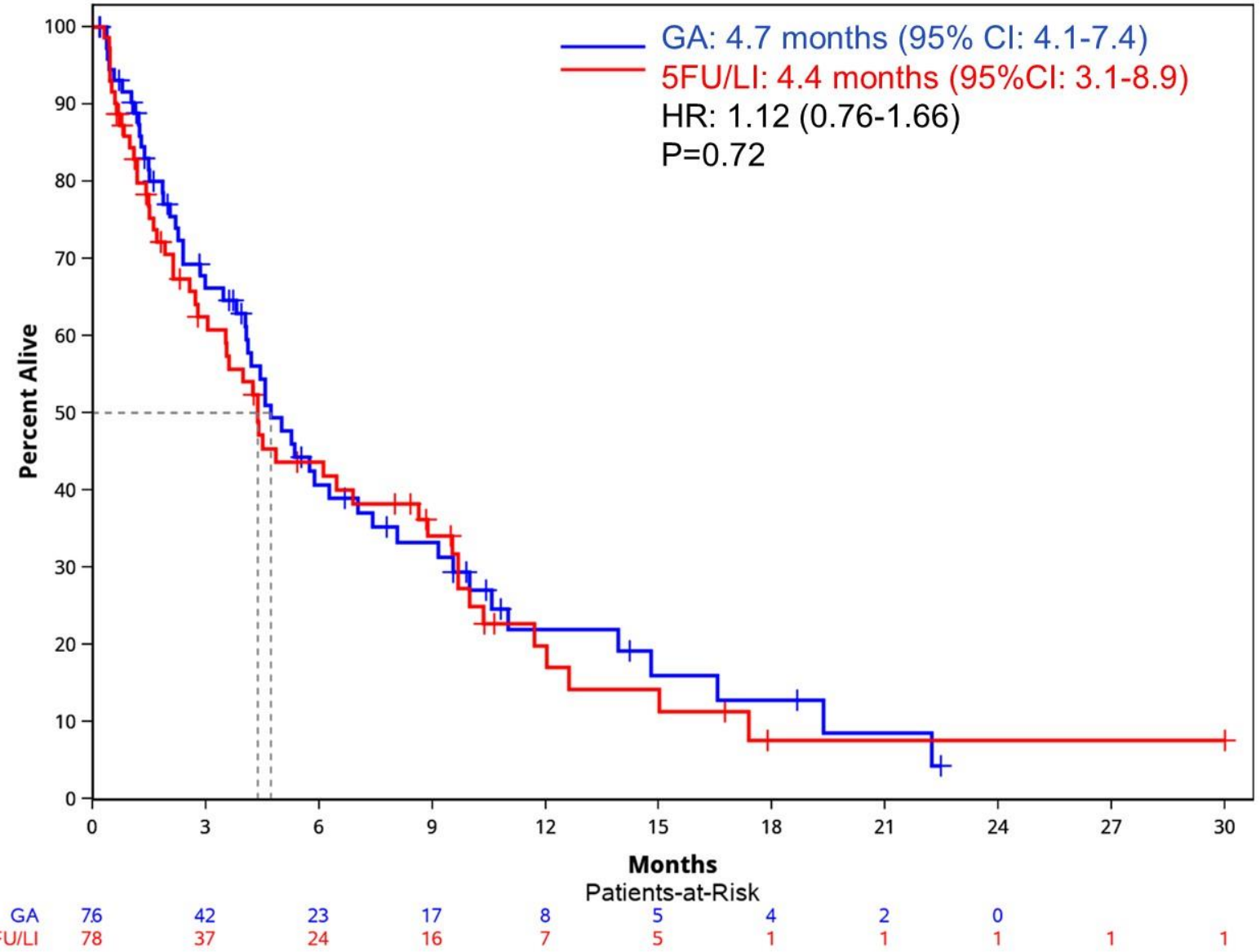
Baseline characteristics – Geriatric screening

	Gemcitabine+ Nab-Paclitaxel (N=88)	5FU+ Liposomal Irinotecan (N=88)	Total (N=176)	P-value
Performance Status, n (%)				0.974
0	20 (22.7%)	22 (25.0%)	42 (23.9%)	
1	57 (64.8%)	55 (62.5%)	112 (63.6%)	
2	11 (12.5%)	11 (12.5%)	22 (12.5%)	
Screening vulnerability, n (%)				
Age	32 (36.4%)	33 (36.4%)	64 (36.4%)	
Co-Morbidity	25 (28.4%)	32 (36.4%)	57 (32.4%)	
Cognition	36 (41.4%)	43 (49.4%)	79 (45.4%)	
Function (ADL)	5 (5.7%)	7 (8.0%)	12 (6.9%)	
Function (IADL)	18 (20.7%)	16 (18.4%)	34 (19.5%)	
# of Vulnerability Domains, n(%)				
1	53 (60.9%)	43 (49.4%)	96 (55.2%)	0.532
2	20 (23.0%)	25 (28.7%)	45 (25.9%)	
≥3	6 (6.9%)	10 (11.5%)	16 (9.2%)	

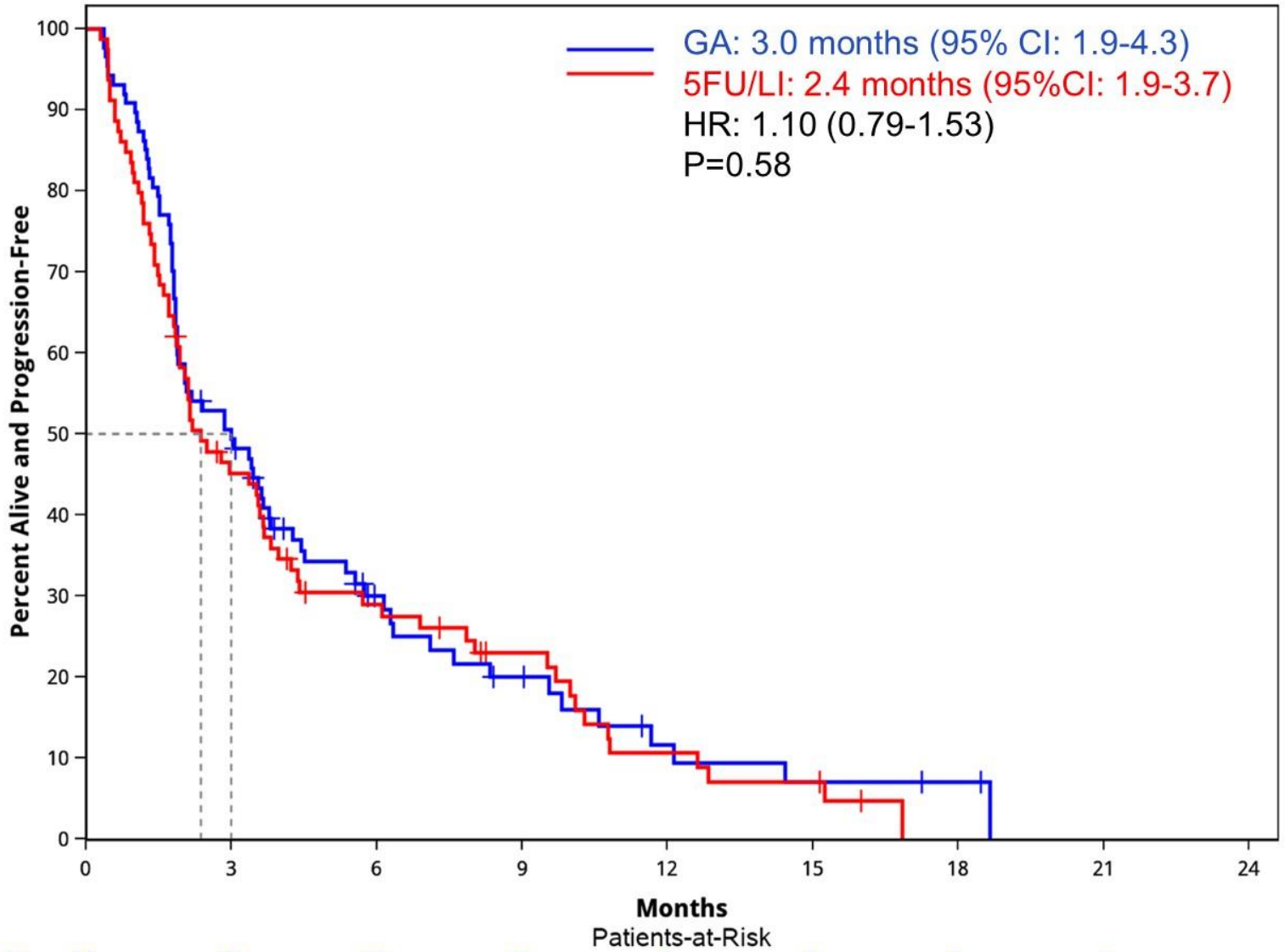
Treatment Pattern

	Gemcitabine+ Nab-Paclitaxel (N=88)	5FU+ Liposomal Irinotecan (N=88)	Total (N=176)	P-value
Started Treatment, n (%)				0.495
No	9 (10.2%)	13 (14.8%)	22 (12.5%)	
Yes	79 (89.8%)	75 (85.2%)	154 (87.5%)	
No Treatment Reason, n (%)				0.098
PD before start	0 (0.0%)	6 (46.2%)	6 (27.3%)	
AE	2 (22.2%)	0 (0.0%)	2 (9.1%)	
Died before start	1 (11.1%)	2 (15.4%)	3 (13.6%)	
W/D before start	1 (11.1%)	1 (7.7%)	2 (9.1%)	
Med decision	3 (33.3%)	3 (23.1%)	6 (27.3%)	
Other	2 (22.2%)	1 (7.7%)	3 (13.6%)	
Eligible, n (%)				0.303
No	17 (19.3%)	11 (12.5%)	28 (15.9%)	
Yes	71 (80.7%)	77 (87.5%)	148 (84.1%)	

Primary end point OS - ITT

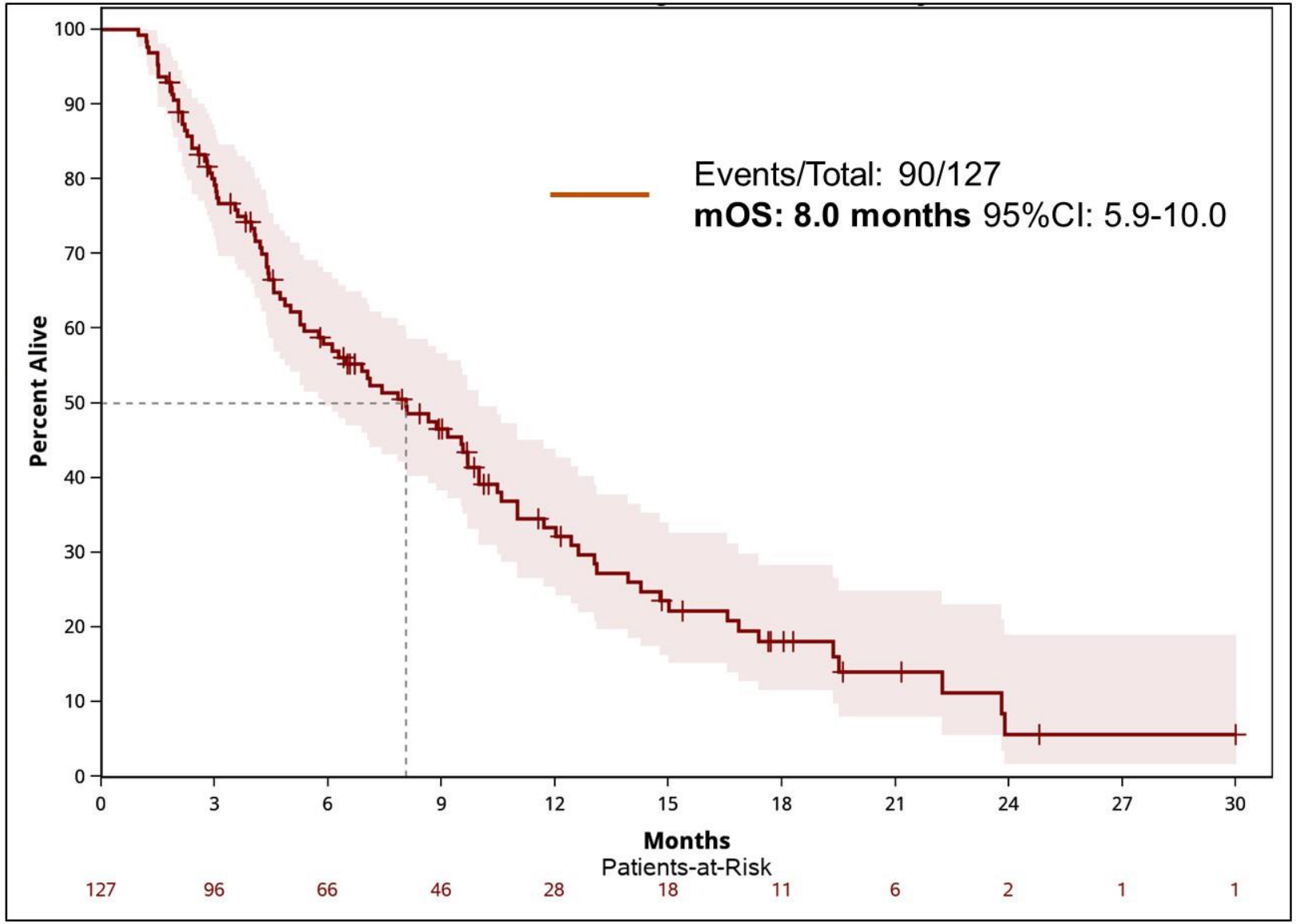


Secondary end point PFS - ITT



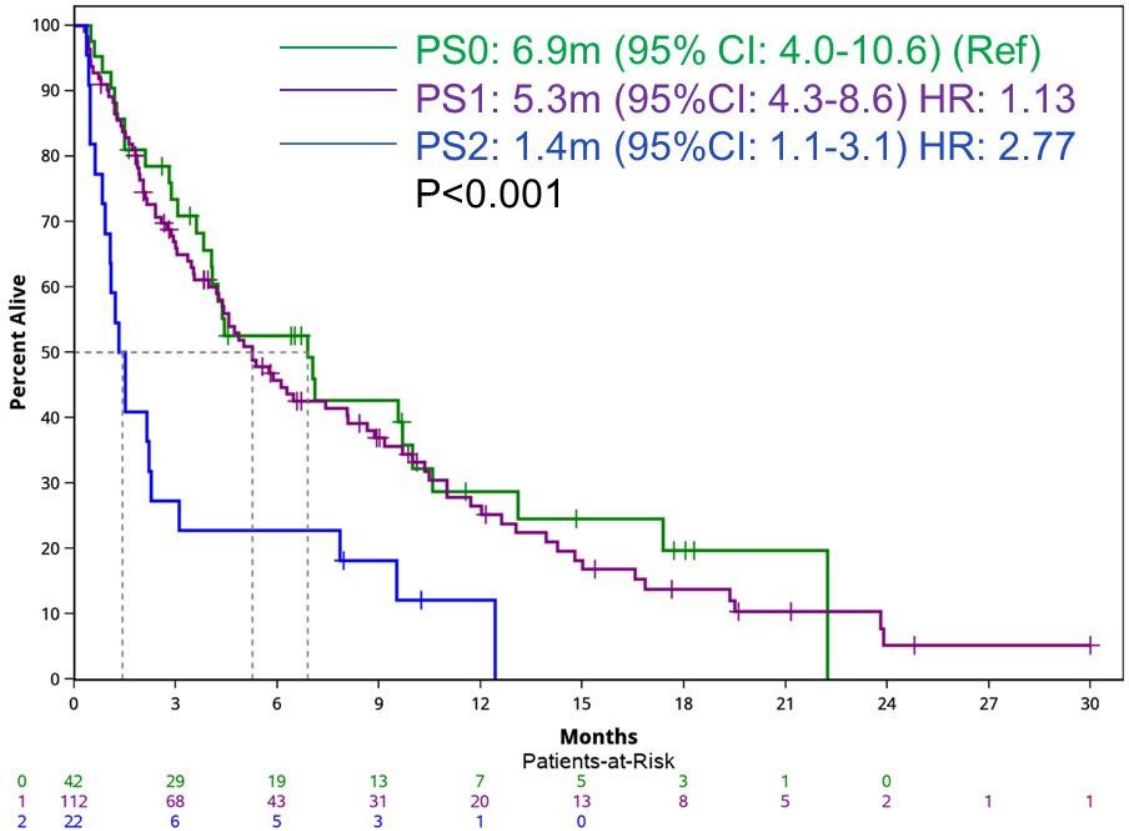
OS analysis of patients who received ≥ 4 weeks of treatment

Number of chemotherapy doses	N (%)
0	22 (12.5%)
1	22 (14.3%)
≥2	127 (72%)

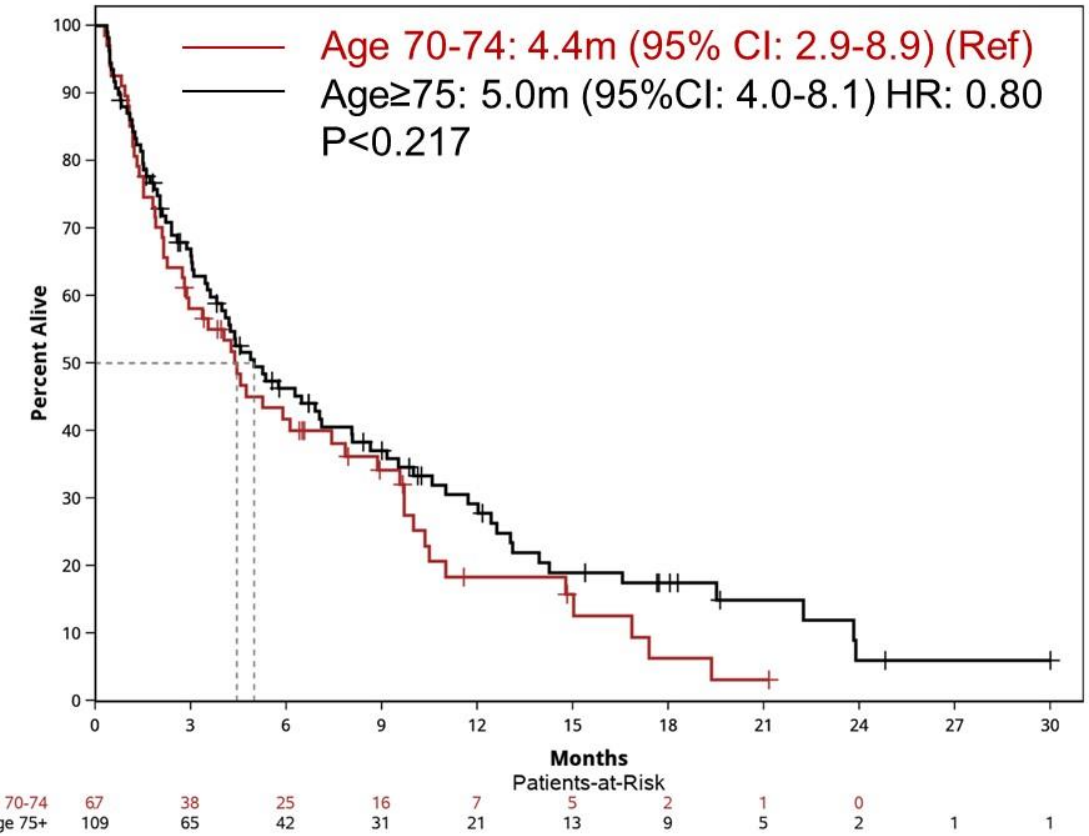


Primary end point OS – by stratification factors:

Performance Status



Age



PRESENTED BY: Efrat Dotan, MD

Reasons for treatment discontinuation

	Gemcitabine+ Nab-Paclitaxel (N=88)	5FU+ Liposomal Irinotecan (N=88)	Total (N=176)	P-value
Total number of cycles (each 14d)				
Median (Range)	4.0 (1.0-42.0)	4.0 (1.0-45.0)	4.0 (1.0-45.0)	0.470
1-3	27 (34.2%)	32 (42.7%)	59 (38.3%)	0.651
4-7	18 (22.8%)	16 (21.3%)	34 (22.1%)	
8-11	13 (16.5%)	8 (10.7%)	21 (13.6%)	
12+	21 (26.6%)	19 (25.3%)	40 (26.0%)	
Reason Off Tx, n (%)				0.575
PD/Symptomatic PD	38 (53.5%)	33 (49.3%)	71 (51.4%)	
AE	13 (18.3%)	10 (14.9%)	23 (16.7%)	
Death	7 (9.9%)	8 (11.9%)	15 (10.9%)	
W/D	6 (8.5%)	8 (11.9%)	14 (10.1%)	
Alt Therapy	2 (2.8%)	0 (0.0%)	2 (1.4%)	
Compl Dx	1 (1.4%)	0 (0.0%)	1 (0.7%)	
Other	4 (5.6%)	8 (11.9%)	12 (8.7%)	
Missing	8	8	16	

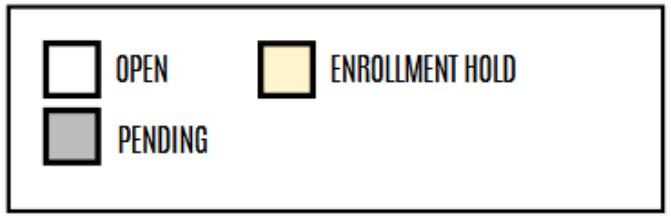
Adverse event profile

	Gemcitabine + Nab-Paclitaxel (N=88)			5FU+ Liposomal Irinotecan (N=88)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Hematologic						
Anemia (%)	58	14	-	47	13	-
Neutropenia (%)	14	9	3	13	12	8
Thrombocytopenia (%)	24	4	1	17	5	-
Non-Hematologic						
Diarrhea (%)	32	5	-	48	12	-
Constipation (%)	11	1	-	12	-	-
Nausea (%)	49	4	-	45	7	-
Vomiting (%)	24	4	-	25	4	-
Fatigue (%)	65	9	-	51	15	-
Peripheral neuropathy						
Sensory(%)	27	4	-	12	-	
Overall ≥grade 3	**51% (8% ≥ Grade 4)**			**58% (15% ≥ Grade 4)**		
Grade 5 toxicity	2 cases: sepsis, pneumonitis			2 cases: sepsis		

Conclusion

- In vulnerable older adults with treatment naïve mPDAC, Gem/Nab-Paclitaxel and 5FU + Liposomal irinotecan produced similar OS and tolerance.
- Survival outcomes were lower than expected with a high percentage of patients not able to start treatment.
- Vulnerabilities that strongly affect outcomes that are not captured by ECOG
- Better tools are needed to identify patients who can benefit from treatment.

PANCREATIC CANCER



ADJUVANT

AMPLIFY7P Criteria: Up front resectable stage I, II, or III disease per current AJCC staging criteria, with radiographic NED (no evidence of disease) status within 6 months following completion of locoregional treatment

PI: Naomi Fei

NCT05726864

NON-RESECTABLE

TIGER-PAC/RENOVO
Criteria: Histo/ctyo confirmed diagnosis within 6 weeks of consent; no prior treatment for pancreatic cancer OR more than 1 cycle of gem delivery and nab-paclitaxel; no evidence of metastatic disease; arterial anatomy suitable of intra-arterial of gemcitabine to intended tumor

PI: Naomi Fei

NCT05249101

METASTATIC

CG-745-2-08
Criteria: Locally advanced or metastatic pancreatic adenocarcinoma without evidence of progression on initial chemo for metastatic disease (CR, PR or SD); FOLFIRINOX at full or modified dose for a minimum of 16 wks with no evidence of progression

PI: Naomi Fei

NCT05249101

P-MUC1C-ALLO1-001:
A Phase 1 Dose Escalation and Expanded Cohort Study of P-MUC1C-ALLO1 in Adult Subjects With Advanced or Metastatic Solid Tumors

PI: Muhammad Furqan

NCT05239143

BGB-A317-A3055-101:
A Phase 1a/1b Study Investigating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of BGB-A3055, Alone and in Combination With Tislelizumab in Patients With Selected Advanced or Metastatic Solid Tumors

PI: Muhammad Furqan

NCT05935098

2024 ASCO ANNUAL MEETING

Addition of stereotactic body radiotherapy to systemic chemotherapy in locally advanced cholangiocarcinoma (ABC-07)

Maria A. Hawkins, Juan W. Valle, Harpreet Wasan, Mark Harrison, Helen Morement, Prakash Manoharan, Ganesh Radhakrishna, David Eaton, Douglas Brand, Temi Adedoyin, Ka Man Mak, Natasha Hava, Shumona Shelly, Memuna Rashid, Andre Lopes, John A Bridgewater on behalf of ABC-07 investigators

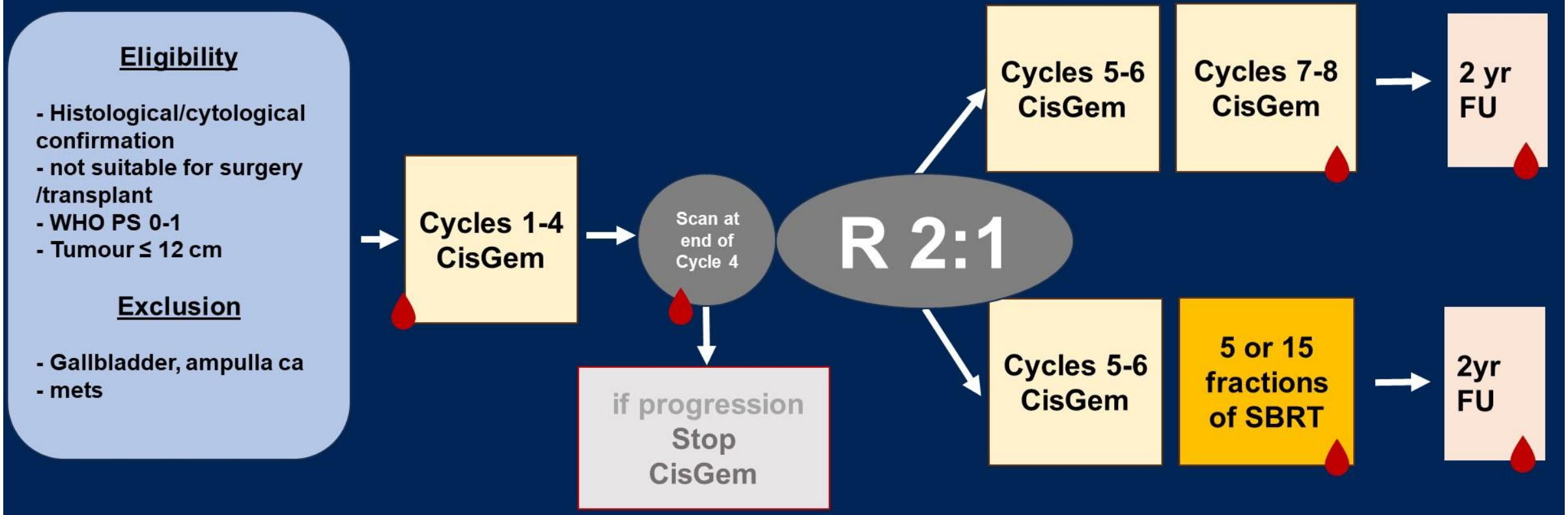
CANCER RESEARCH UK | Cancer Trials Centre | UCL

The CR UK & UCL Cancer Trials Centre acknowledged the funding received from CRUK to support this trial (Grant Reference: C43735/A27885)

Background:

- Locoregional treatments for inoperable, non-metastatic cholangiocarcinoma remains undefined.
- Single arm phase 2 data suggested hypofractionated high dose radiation in localized intrahepatic cholangiocarcinoma may improve clinical outcomes.
  - Hong et al (2015), JCO
- Aim: to investigate the efficacy and safety of the addition of SBRT to CisGem in locally advanced inoperable cholangiocarcinoma

ABC-07 Study Design



CisGem: Cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2 on D1 and 8 of a 21-D cycle
SBRT: Tumours ≤6cm: 50Gy/5 fractions
Tumours >6cm and ≤12cm: 67.5Gy /15 fractions
= ctDNA at 4 timepoints prior to treatment at cycle 4, end of treatment, at progression or 2 yr FU

- **Independent RTQA** - all
- **Independent image review** - all

Baseline Characteristics

	6 CisGem+SBRT N=45 (%)	8 CisGem N=24 (%)
Age (years)		
Median (range)	63 (38-83)	67 (38 to 77)
Sex		
Male	22 (48.9%)	13 (54.2%)
Female	23 (51.1%)	11 (45.8%)
WHO PS		
0	24 (53.3%)	12 (50%)
1	21 (46.7%)	12 (50%)
Median Tumour Size (mm)		
Median (range)	36 (16 to 105)	32 (6 to 76)

Baseline Characteristics

	6 CisGem + SBRT N=45 (%)	8 CisGem N=24 (%)
Current indwelling stent		
Yes	33 (73.3%)	15 (62.5%)
No	12 (26.7%)	9 (37.5%)
Location		
Perihilar CCA	18 (40%)	14 (58.3%)
Distal CCA	20 (44.4%)	7 (29.2%
Intrahepatic CCA	7(15.6%)	3 (12.5%)
RECIST measurable		
Yes	33 (73.3%)	21 (87.5%)
No	12(26.7%)	12(12.5%)

PRESENTED BY: Professor Maria A. Hawkins, Professor of Radiation Oncology

Treatment Compliance

	6 Cycles CisGem+SBRT Arm	8 Cycles CisGem Arm
No. of pts completed 6 cycles of CisGem	45/45 (100%)	24/24 (100%)
No. pts completed 7 cycles of CisGem	N/A	20/24 (83%)
No. pts completed 8 cycles of CisGem	N/A	18/24 (75%)
No. of pts received SBRT	41/45 (91%)	N/A

PRESENTED BY: Professor Maria A. Hawkins, Professor of Radiation Oncology

Adverse Events

Max Grade	6 CisGem+SBRT N (%)	8 CisGem N (%)
Grade 1	2 (4%)	0 (0%)
Grade 2	9 (20%)	3 (13%)
Grade 3	24 (53%)	15 (63)
Grade 4	9 (20%)	6 (25%)
Grade 5	1 (2%)	0 (0%)
Any grade 3 or higher event (Each patient counted once)	**34 (76%)**	**21 (88%)**

Treatment Related Adverse Events – Infections

Any AE/SAE reported	6 CisGem+SBRT N (%)	8 CisGem N (%)
Sepsis		
Prior cycle 6	*3 (7%)*	*1(4%)*
Post cycle 6	*5 (11%)*	*2 (8%)*
Other infections (respiratory, urinary, viral)		
Prior cycle 6 all grades	19 (42%)	7(29%)
Post cycle 6 all grades	17(38%)	6 (25%)
Biliary tract infections – treatment related		
Prior cycle 6 grade 3-4	4 (9%)	-
Post cycle 6 grade 3-4	1(4%)	-

PRESENTED BY: Professor Maria A. Hawkins, Professor of Radiation Oncology

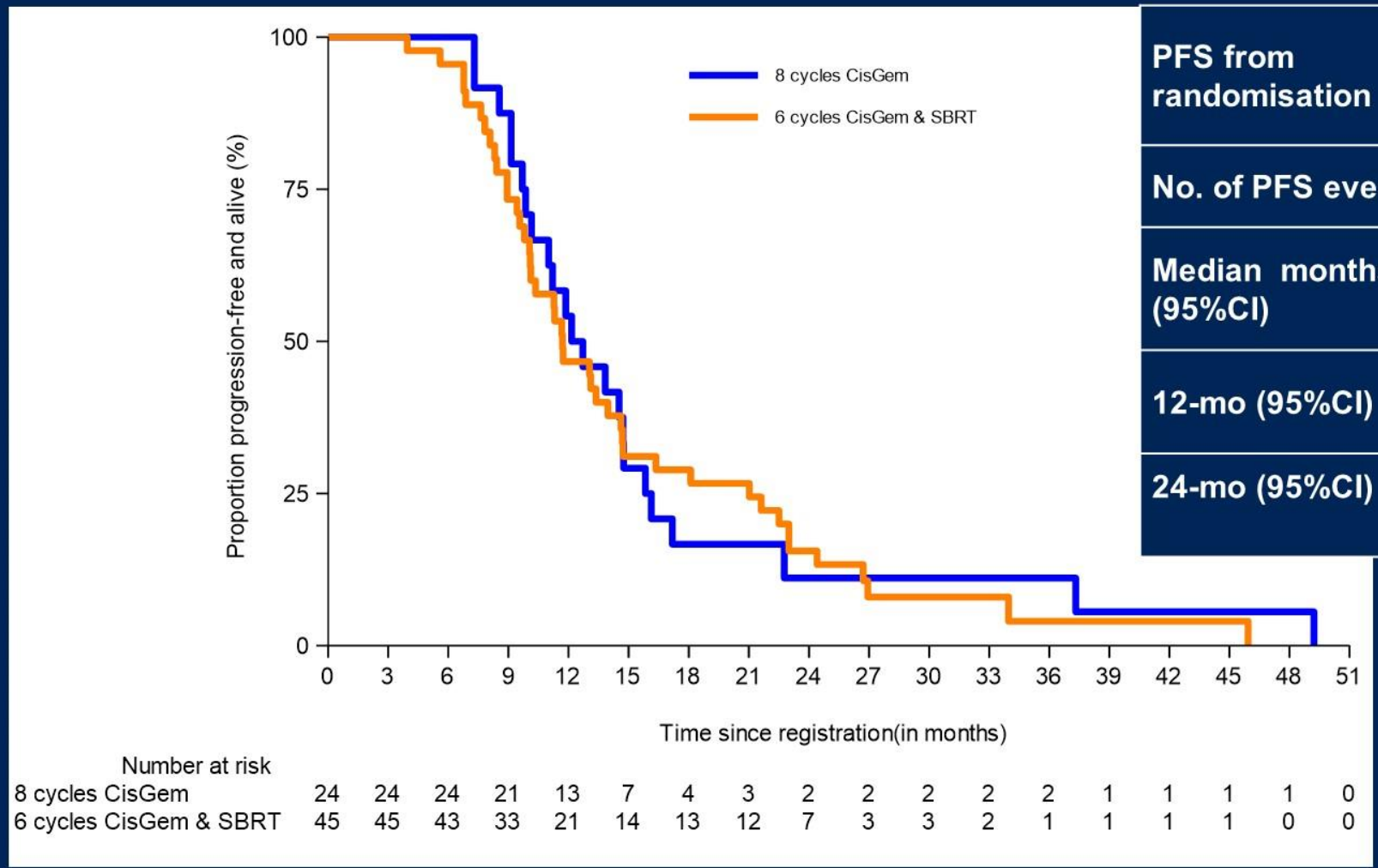
SBRT Related Adverse Events

Max Grade	6 CisGem+SBRT N (%)
Grade 1	28 (62%)
Grade 2	8(17%)
Grade 3	5 (11.1%)
Grade 4	2 (4.4%)
Grade 5	1 (2.2%)

1 patient had grade 5 event: duodenal perforation

1 patient had 2x grade 4 events: sepsis & duodenal perforation

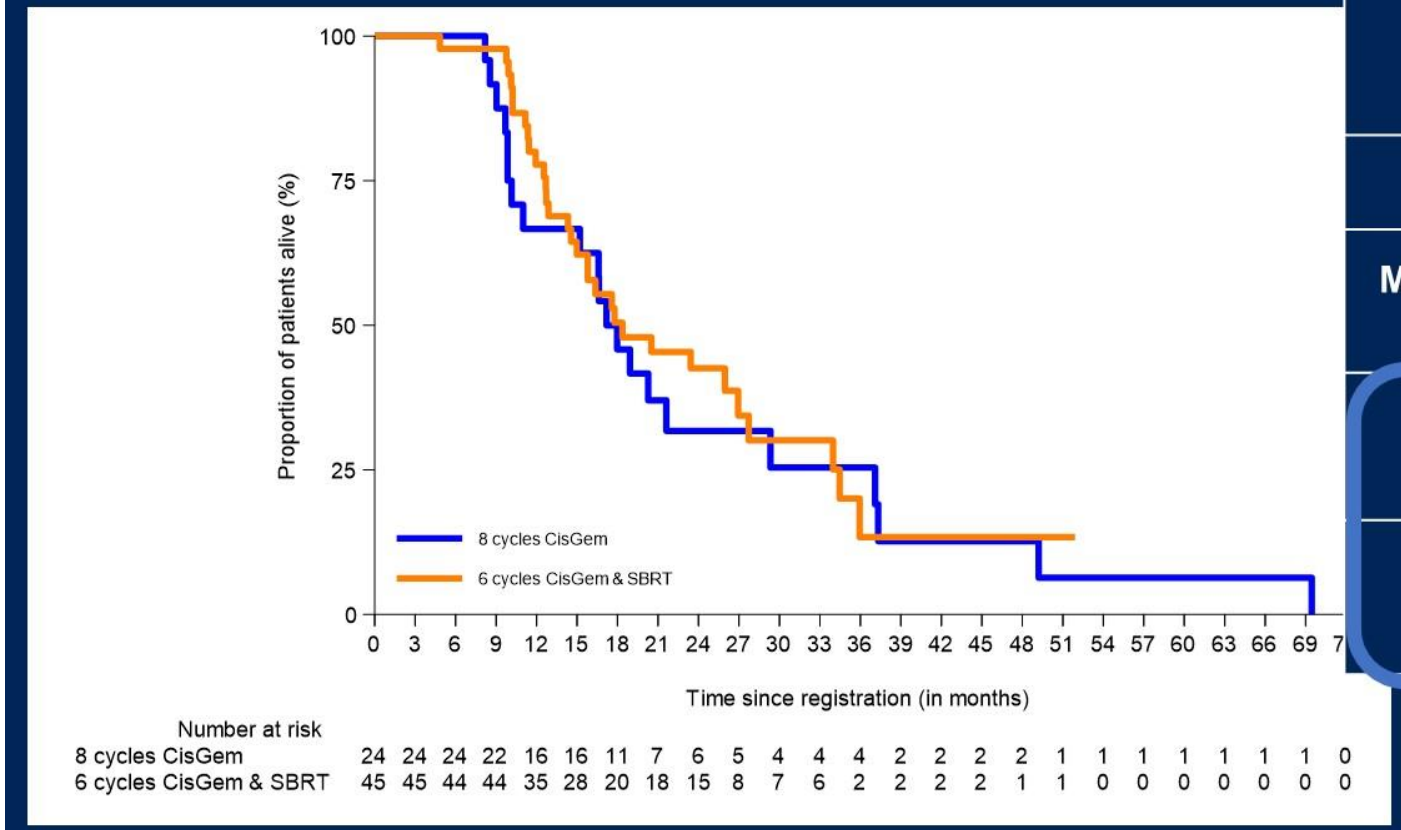
Progression Free Survival (PFS) from registration



PFS from randomisation	6 CisGem + SBRT N=45	8 CisGem N=24
No. of PFS events	43 (96%)	23 (96%)
Median months (95%CI)	11.7 (10.1 to 14.6)	12.2 (9.9 to 14.8)
12-mo (95%CI)	46.7% (31.7% to 60.3%)	54.2% (32.7% to 74.1%)
24-mo (95%CI)	15.6% (6.8% to 27.5%)	11.1% (2.3% to 28.0%)

HR: 1.1 95% (CI 0.6 to 1.8)
p = 0.810

Overall Survival (OS) from Registration



OS from registration	6 CisGem + SBRT N=45	8 CisGem N = 24
No. of deaths (%)	31(69%)	21(88%)
Median months (95%CI)	18.4 (14.6 to 26.9)	17.2 (10.2 to 29.3)
12-mo (95%CI)	77.8% (62.6% to 87.4%)	66.7% (44.3% to 81.7%)
24-mo (95%CI)	42.6% (27.6% to 56.8%)	31.8% (14.3% to 50.9%)

Hazard ratio: 1 (95% CI 0.5 to 1.5), p=0.633
Median follow-up 26.7 months

Site of 1st Progression (RECIST v1.1)

Progression \ group	6 Cycles CisGem+SBRT N=45	8 Cycles CisGem N=24
	N (%)	N(%)
Local	6 (14%)	**5 (21%)**
Local + metastatic	**2 (4.6%)**	3 (13%)
Metastatic	**26 (57%)**	6 (25%)
Died	3 (7%)	**8 (34%)**
Symptomatic deterioration/other	6 (14%)	1 (4.0%)

PRESENTED BY: Professor Maria A. Hawkins, Professor of Radiation Oncology

Causes of Death from Registration

Type of event \ group	6 x CisGem+SBRT N=45	8 x CisGem N=24
	N deaths=31	N deaths=21
Progression of disease (PD)	21 (67%)	11(52%)
Sepsis + PD	5 (16%)	3 (15%)
Sepsis	3 (9%)	3 (15%)
Hepatic failure	0	5* (23%)
Failure to thrive	1 (3%)	-
Unknown/other	1(3%)	1 (4.0%)

* 2=liver failure, 1 ascites, 1cirrhosis of liver, 1 biliary obstruction

Conclusions:

- No evidence of benefit in terms of PFS and OS with addition of SBRT to Gemcitabine + Cisplatin in locally advanced cholangiocarcinoma.
- SBRT was well tolerated and did not increase biliary infection rates
- Fewer patients in the radiotherapy cohort died to liver failure.
  - Slightly better local control with SBRT after induction chemotherapy, but does not translate to PFS or OS benefit.
- The use of SBRT in the context of Immunotherapy needs to be further investigated.

Thank you

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Questions?

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