



Latest Advances in Gastrointestinal Cancers

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11/16/2024
25th Advances in Oncology Conference

Outline



PDAC

Pancreatic Adenocarcinoma

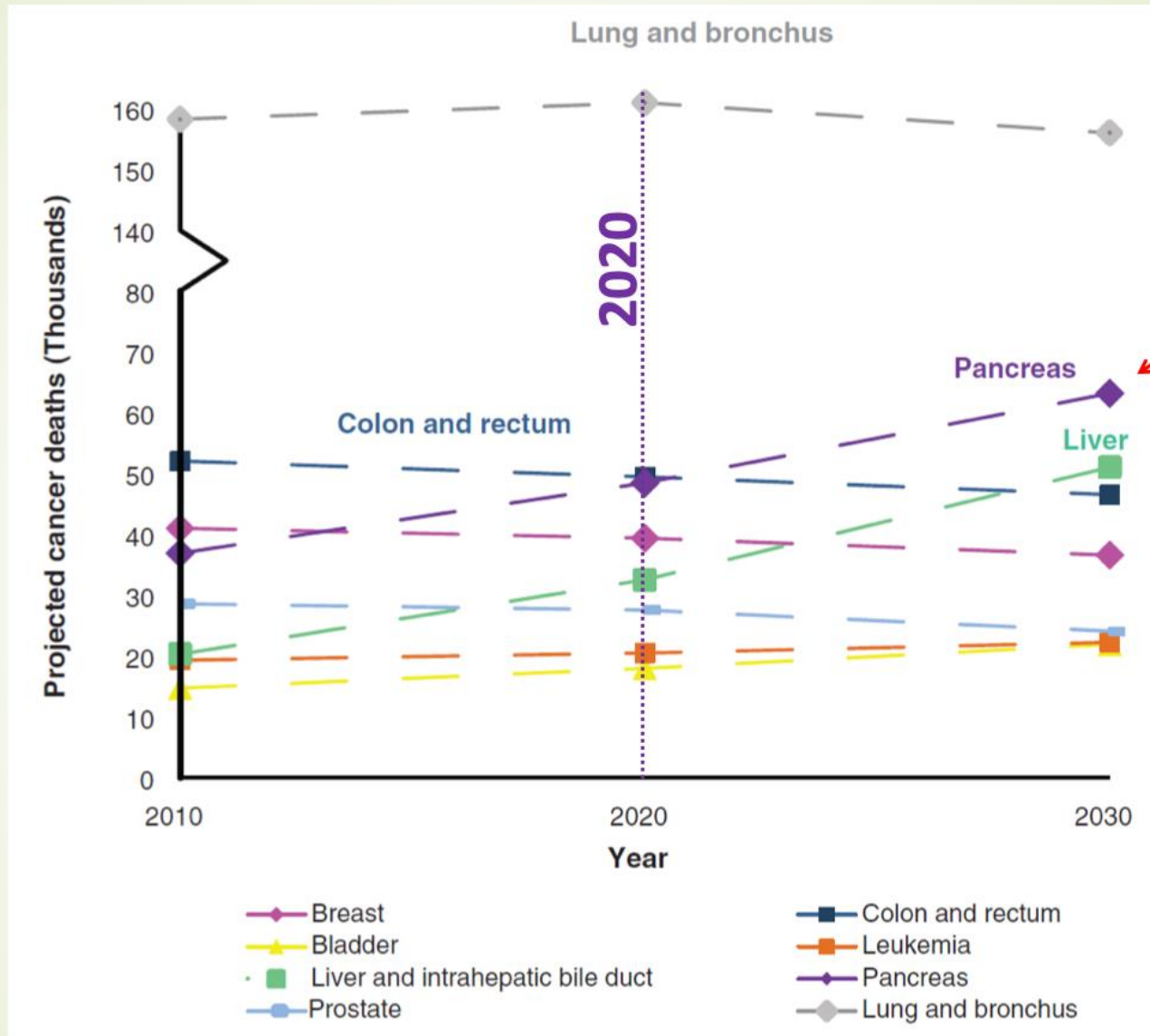
HCC

Hepatocellular Carcinoma

GEC

Gastro-Esophageal Cancer

PDAC



Have we made any progress?

Resectable

Borderline Resectable

Locally Advanced UNResectable

Metastatic

Resectable Pancreatic Adenocarcinoma

Surgery -> Adjuvant Chemotherapy

	+ CONKO-001	+ ESPAC-4	+ PRODIGE 24-ACCORD	- AFACT
Treatment	gemcitabine	gemcitabine capecitabine	mFOLFIRINOX	gemcitabine nab-paclitaxel
mOS (m)	22.8	28.0	54.4	41.8
mPFS (m)	13.4	13.9	21.6	19.4
	JAMA 2007 297:267-277	Lancet 2017 389:1011-1024	NEJM 2018 379:2395-2406	JCO 2023 41:2007-2019

Resectable Pancreatic Adenocarcinoma

Surgery -> Adjuvant Chemotherapy

	+ CONKO-001	+ ESPAC-4	+ PRODIGE 24-ACCORD	- AFACT
Control arm	gemcitabine			
mOS (m)	22.8*	25.5	35.0	37.7
mPFS (m)	13.4*	13.1	12.8	18.8* (13.7)

JAMA 2007
297:267-277

Lancet 2017
389:1011-1024

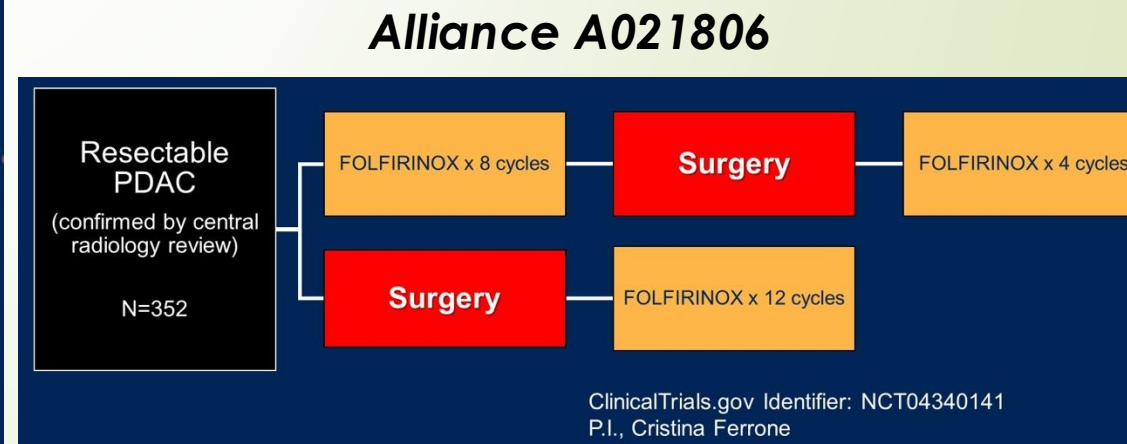
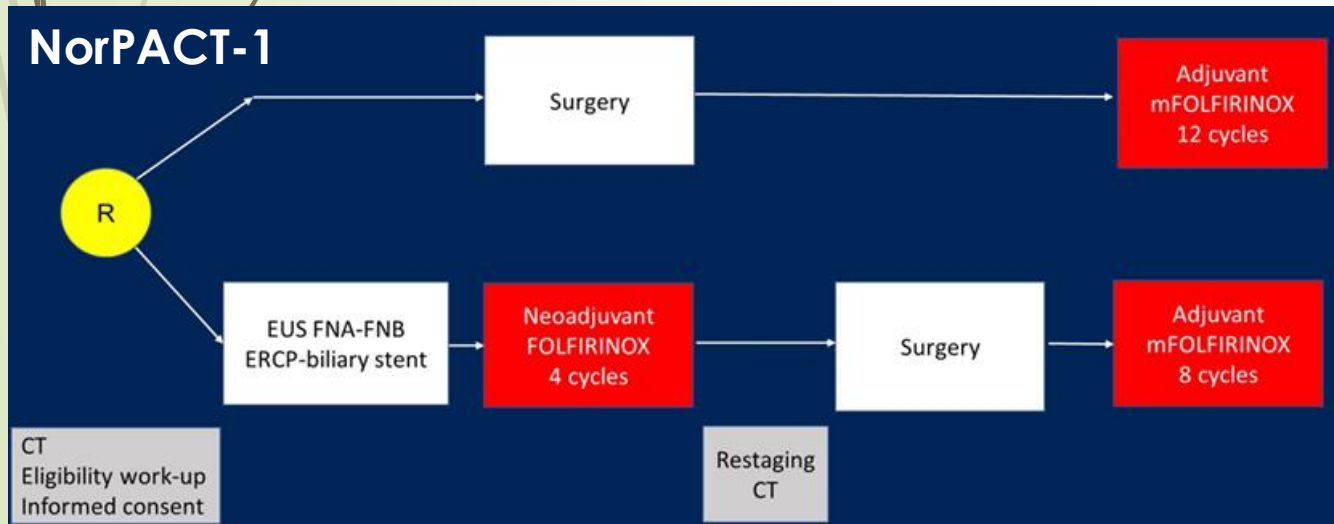
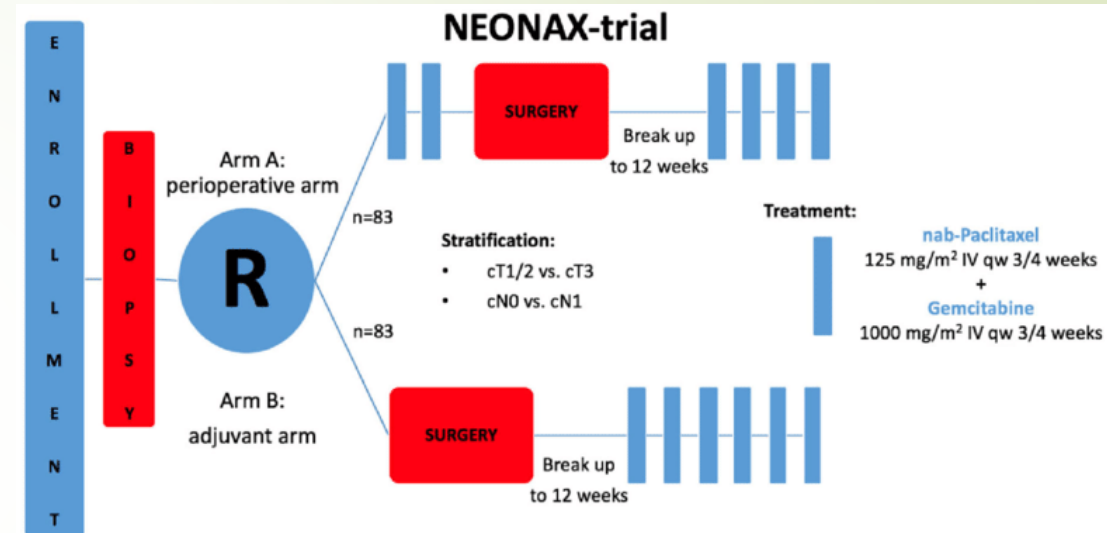
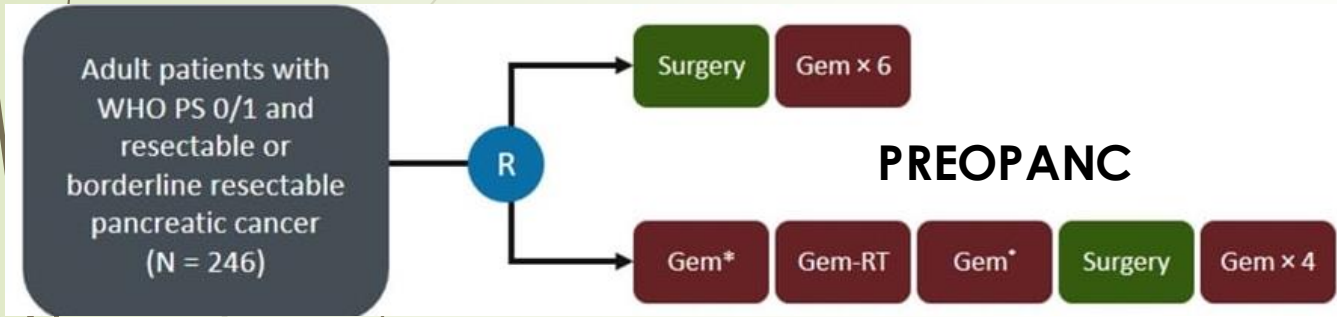
NEJM 2018
379:2395-2406

JCO 2023
41:2007-2019

Resectable Pancreatic Adenocarcinoma

PDAC

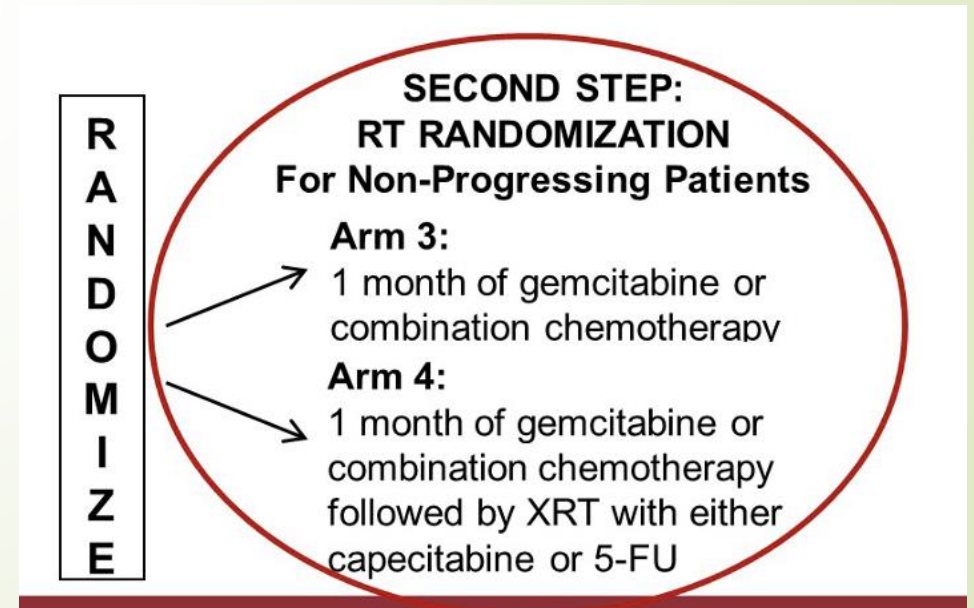
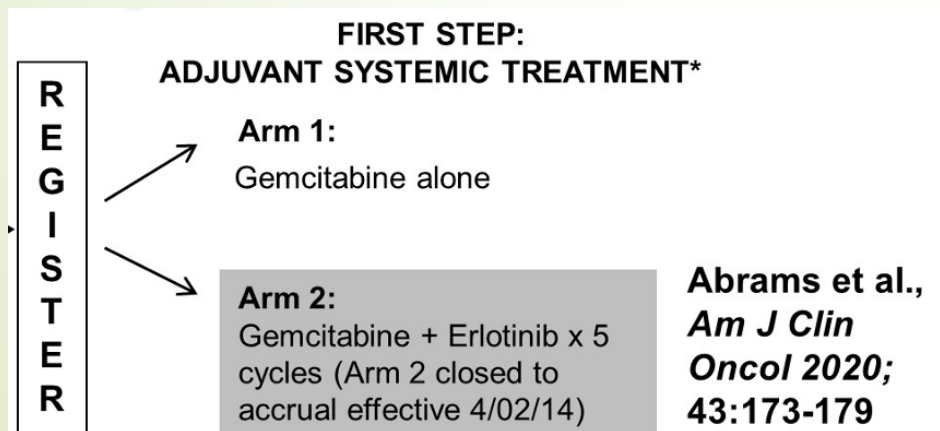
Neoadjuvant Chemotherapy -> Surgery -> Adjuvant Chemotherapy



Resectable Pancreatic Adenocarcinoma

Surgery -> Adjuvant Chemotherapy -> ChemoRT

NRG Oncology/RTOG 0848 Trial: Adjuvant Chemotherapy +/- Chemoradiation For Patients With Resected Head of Pancreas Adenocarcinoma - Results of the RT + 5FU/Capecitabine Randomization Step



Resectable Pancreatic Adenocarcinoma

Surgery -> Adjuvant Chemotherapy -> ChemoRT

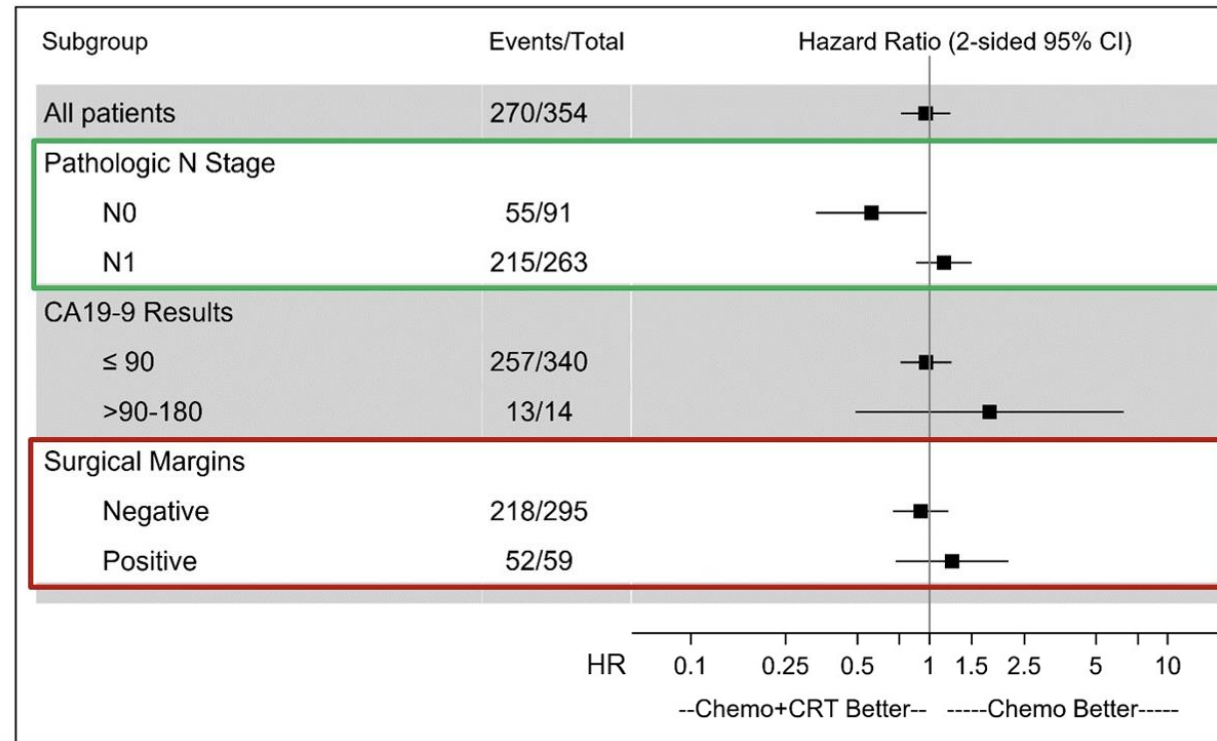
- Protocol Opened to Accrual November 17, 2009
 - Randomization gemcitabine vs gemcitabine + erlotinib
 - Gemcitabine + Erlotinib arm closed April 2, 2014 (response to LAP 07 data)
- After June 28, 2016 amendment
 - FOLFIRINOX or mFOLFIRINOX, or non-oxaliplatin gemcitabine combinations were permitted
 - Up to 3 months of chemotherapy could be initiated prior to registration

	Chemo	Chemo+CRT	Total
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%)

Resectable Pancreatic Adenocarcinoma

Surgery -> Adjuvant Chemotherapy -> **ChemoRT**

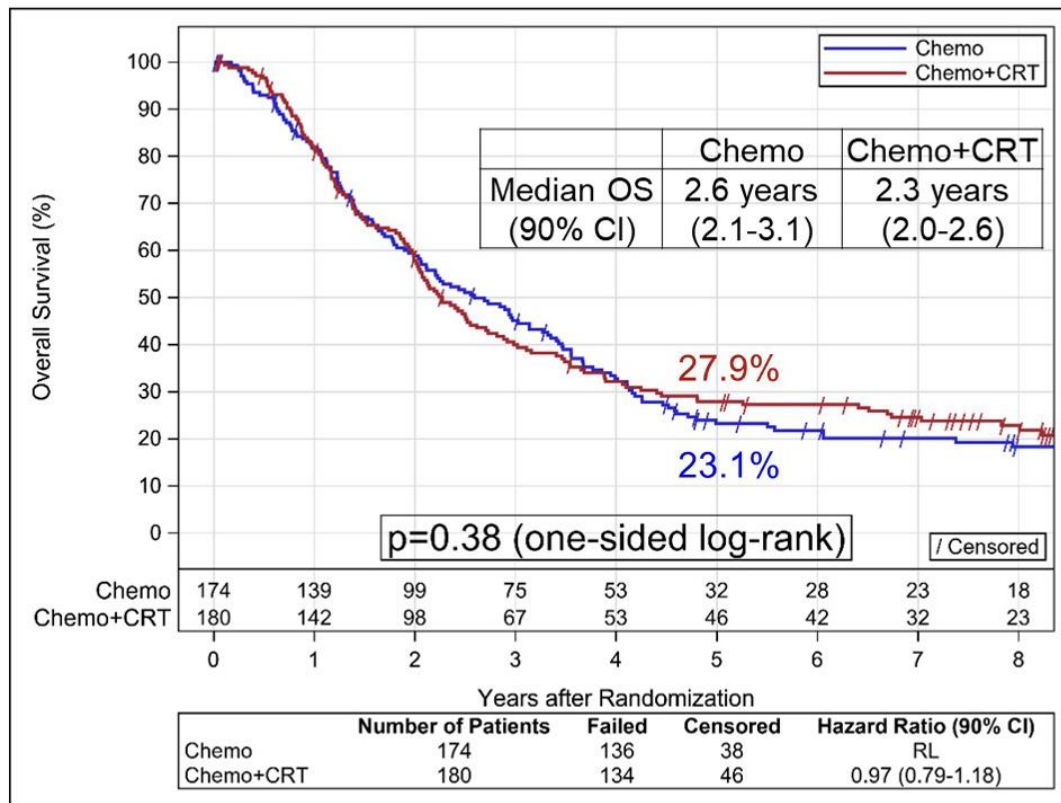
		Chemo (n=174)	Chemo+CRT (n=180)	Total (n=354)
Pathologic N stage	N0	42 (24%)	49 (27%)	91 (26%)
	N1	132 (76%)	131 (73%)	263 (74%)
	1-3 nodes/> 3 nodes	95 (55%)/ 37 (21%)	79 (44%)/ 52 (29%)	174 (49%)/ 89 (25%)
Surgical Margins	Negative	144 (83%)	151 (84%)	295 (83%)
	Positive	30 (17%)	29 (16%)	59 (17%)



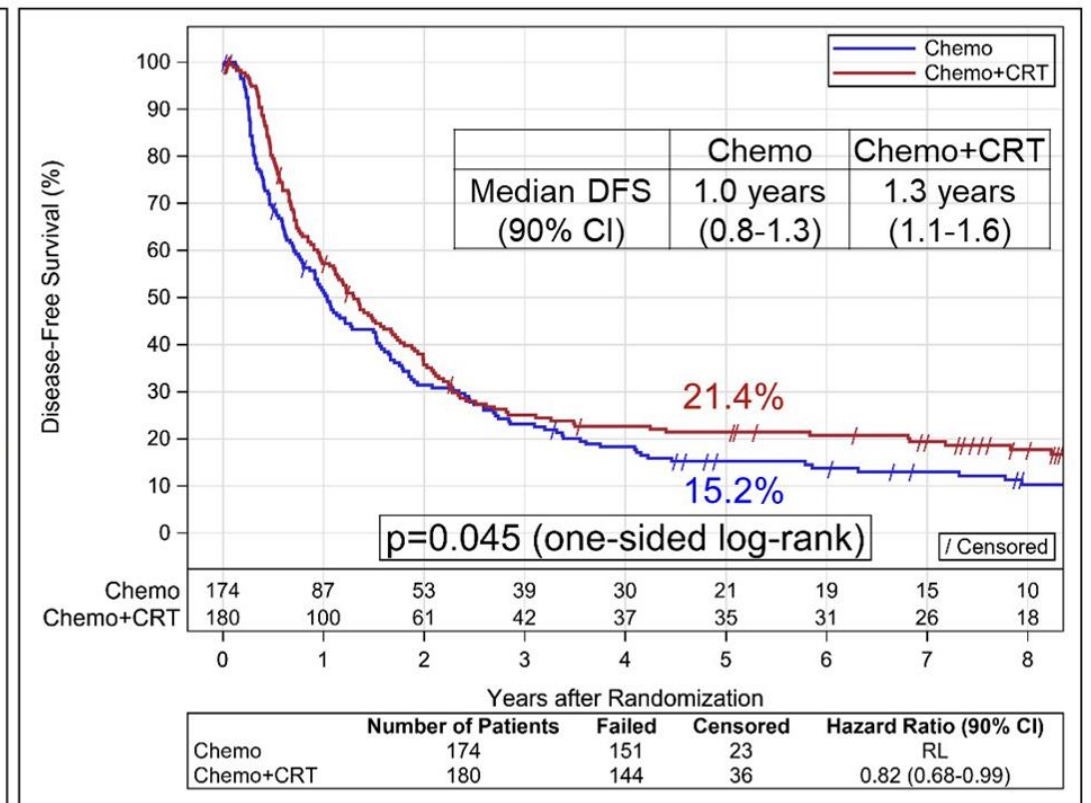
PDAC

Resectable Pancreatic Adenocarcinoma

Surgery -> Adjuvant Chemotherapy -> **ChemoRT**



Overall Survival



Disease-Free Survival

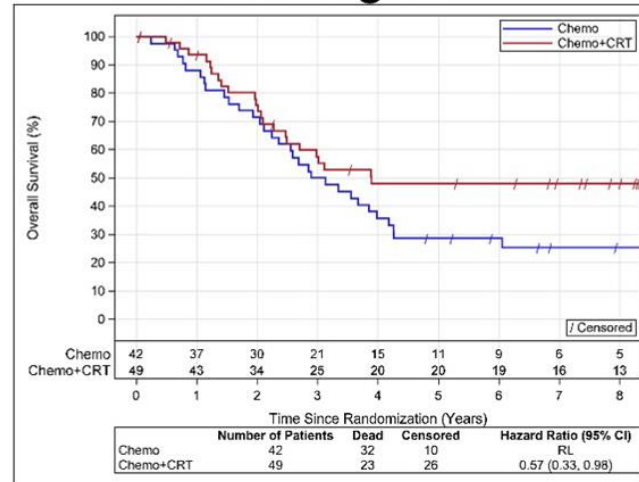
PDAC

Resectable Pancreatic Adenocarcinoma

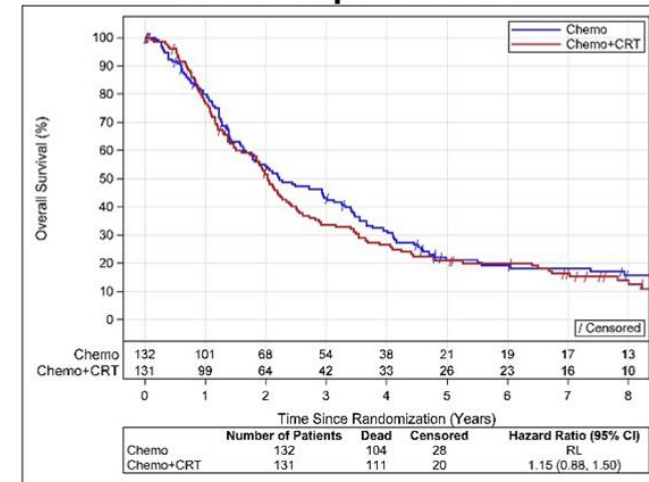
Surgery -> Adjuvant Chemotherapy -> **ChemoRT**

OS

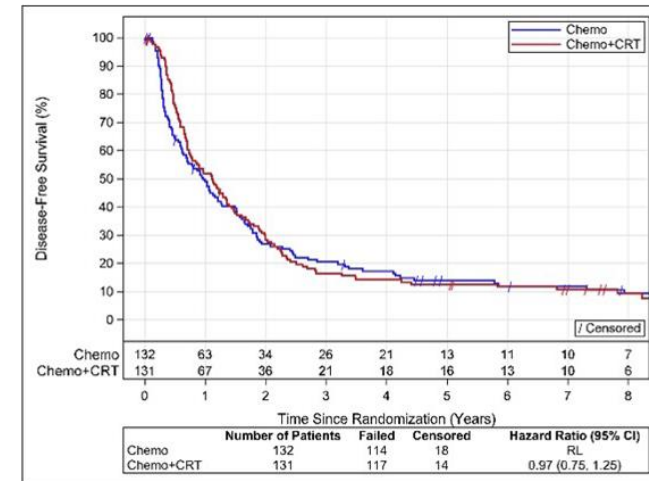
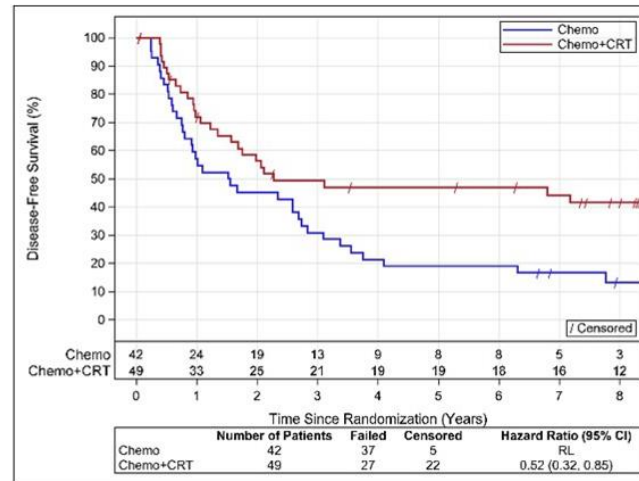
Node negative



Node positive



DFS



Outline



PDAC

Pancreatic Adenocarcinoma

HCC

Hepatocellular Carcinoma

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Gastro-Esophageal Cancer

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sorafenib

sorafenib

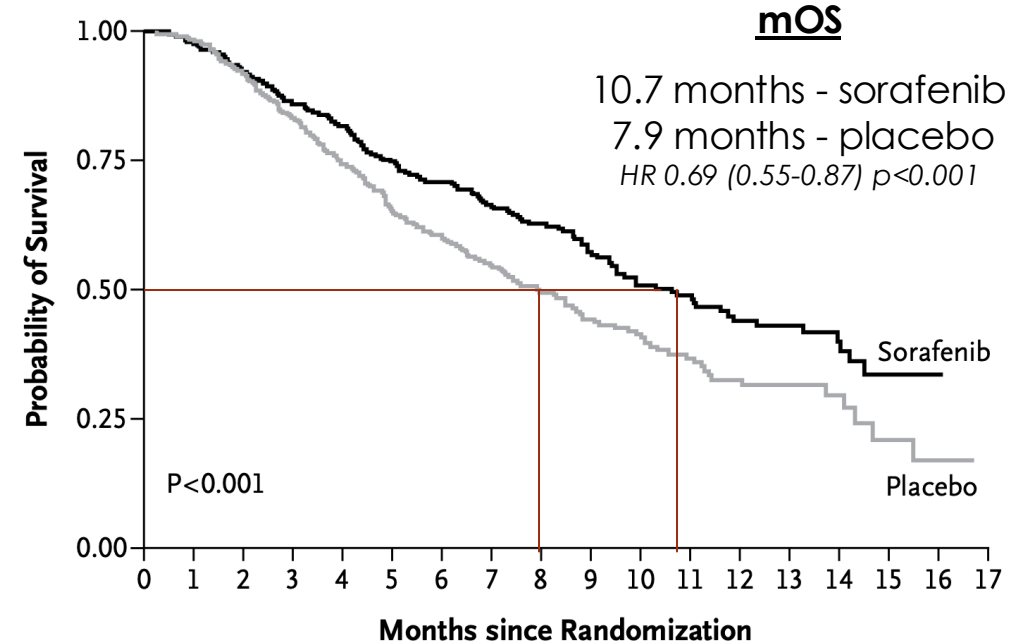


2007

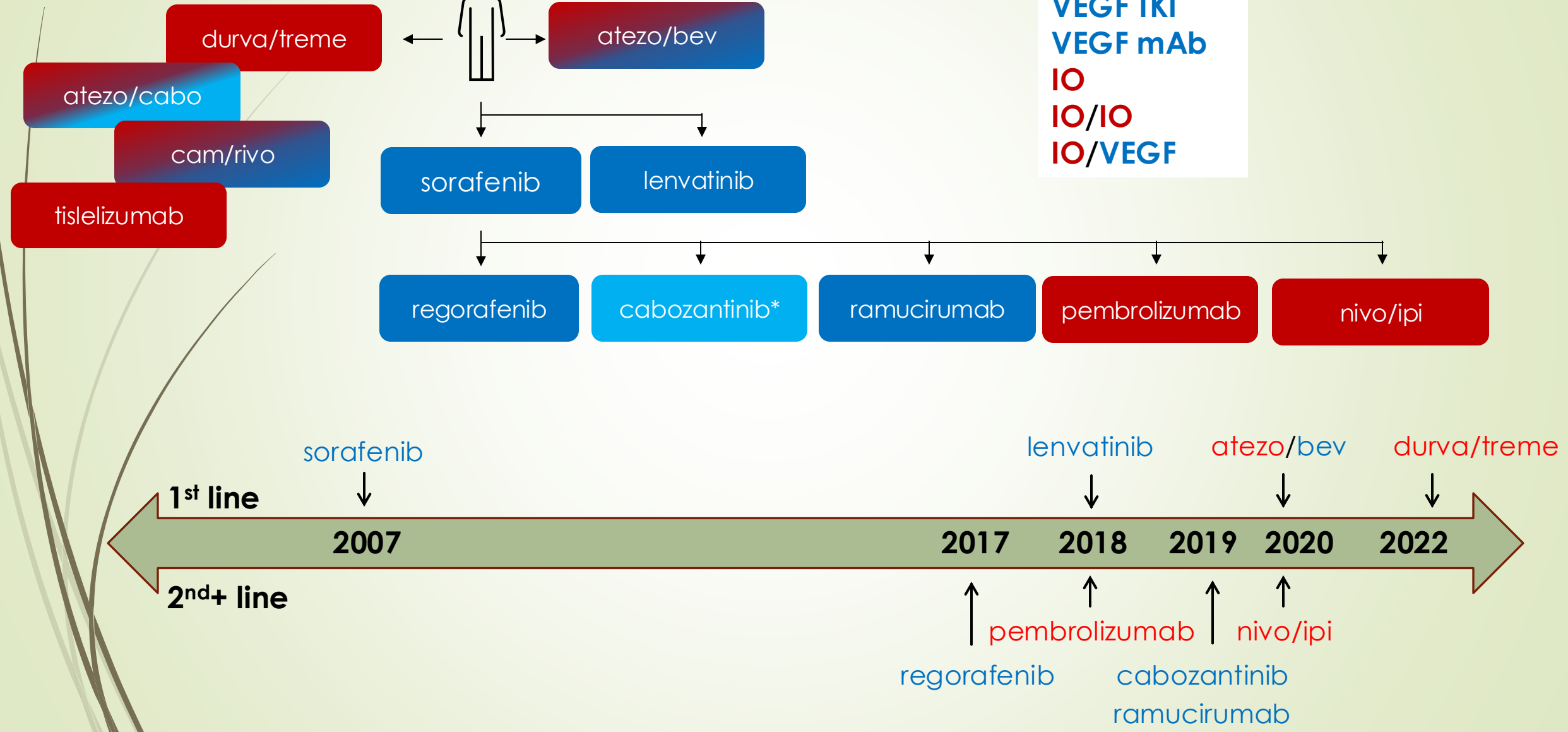
ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

A Overall Survival



HCC



DRUG CLASS
VEGF TKI
VEGF mAb
IO
IO/IO
IO/VEGF

1st line

2nd+ line

sorafenib

2007

lenvatinib

2018

atezo/bev

2019

durva/treme

2022

2017

pembrolizumab

regorafenib

nivo/ipi

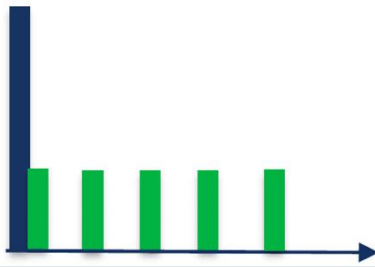
cabozantinib
ramucirumab

IO/IO update

HCC

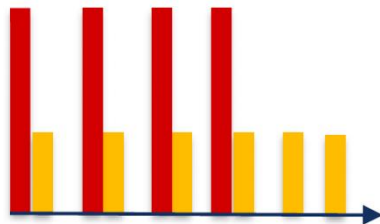
BARCELONA 2024 **ESMO** congress

Tremelimumab 300 mg x 1 (■)
Durvalumab q 4 week (■)

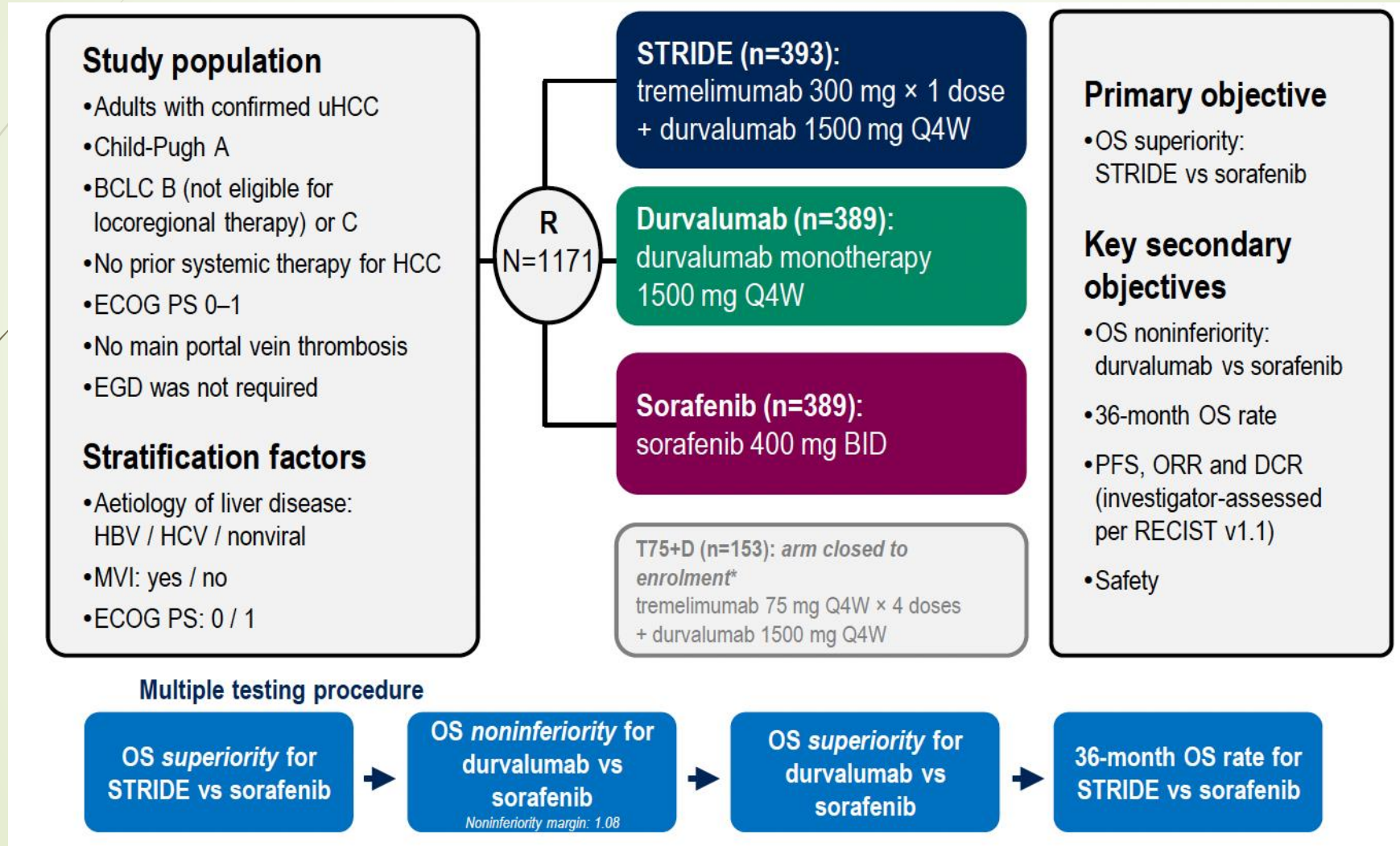


Five-year overall survival (OS) and OS by tumour response measures from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma (uHCC)

Ipilimumab 3mg/kg q3 weeks x 4 (■)
Nivolumab 1mg/kg q3 weeks x 4 (■)
Nivolumab maintenance

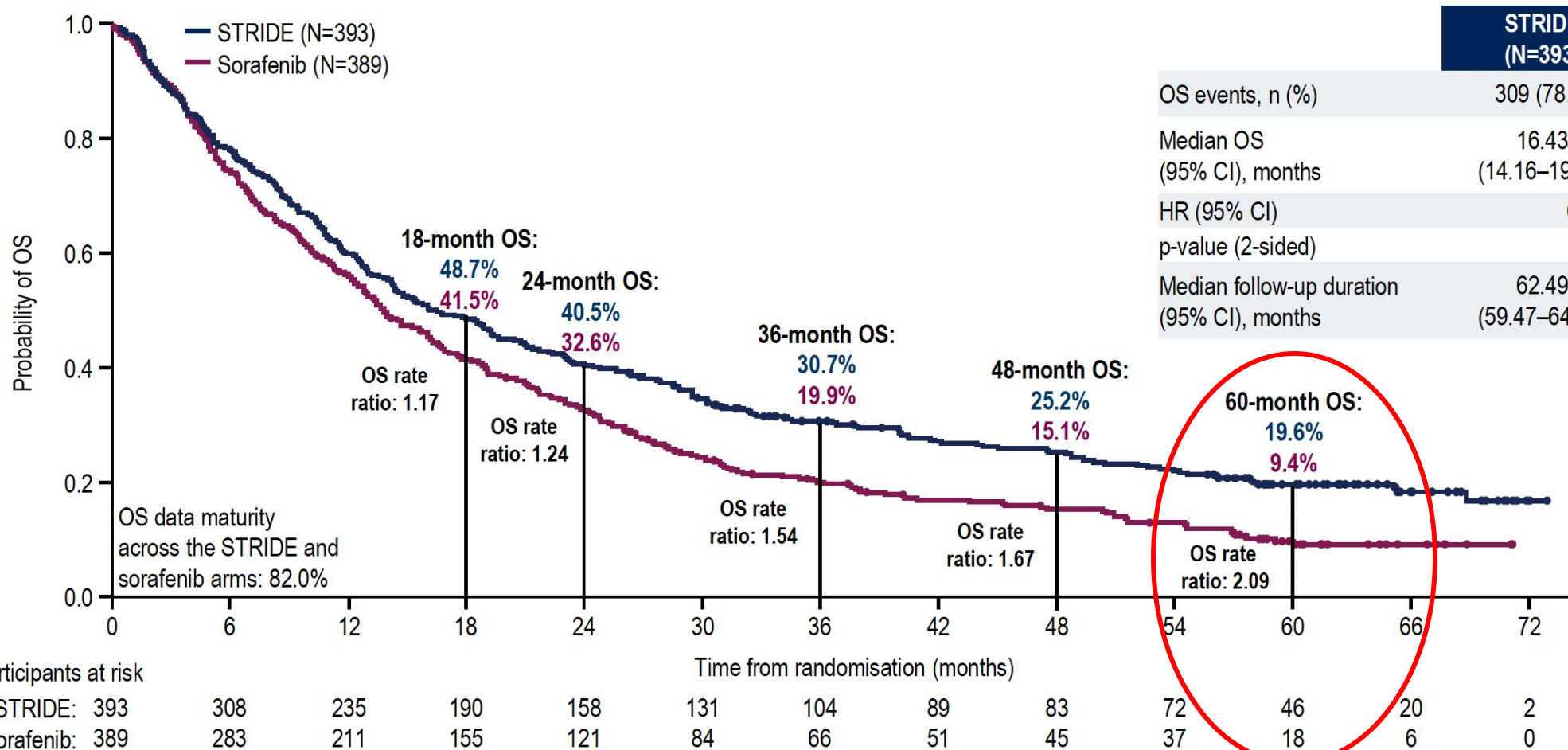


Nivolumab plus ipilimumab vs lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma: expanded analyses from CheckMate 9DW



HIMALAYA

HCC



	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS (95% CI), months	16.43 (14.16–19.58)	13.77 (12.25–16.13)
HR (95% CI)	0.76 (0.65–0.89)	
p-value (2-sided)	0.0008	
Median follow-up duration (95% CI), months	62.49 (59.47–64.79)	59.86 (58.32–61.54)

CHECKMATE 9DW

HCC

Key eligibility criteria

- Unresectable HCC^b
- At least 1 measurable lesion (RECIST v1.1)
- Systemic therapy naive
- Child-Pugh score 5 or 6
- ECOG PS 0 or 1
- No main portal vein invasion (Vp4)

Stratification factors

- Etiology (HBV vs HCV vs uninfected)^c
- MVI/EHS (present vs absent)
- AFP (< 400 vs ≥ 400 ng/mL)

N = 668

R
1:1

n = 335

**NIVO 1 mg/kg IV + IPI 3 mg/kg IV Q3W
(up to 4 cycles)
then NIVO 480 mg Q4W^d**

n = 333

Investigator's choice of
LEN 8 mg^e or 12 mg^f PO QD
or SOR 400 mg PO BID

Treatment until disease progression,
unacceptable toxicity, withdrawal of consent
(all arms), or a maximum treatment duration
of 2 years (NIVO + IPI arm only)

Among 325 patients treated with LEN/SOR:
275 (85%) received LEN and 50 (15%) received SOR

Primary endpoint

- OS

Secondary endpoints

- ORR and DOR by BICR per RECIST v1.1

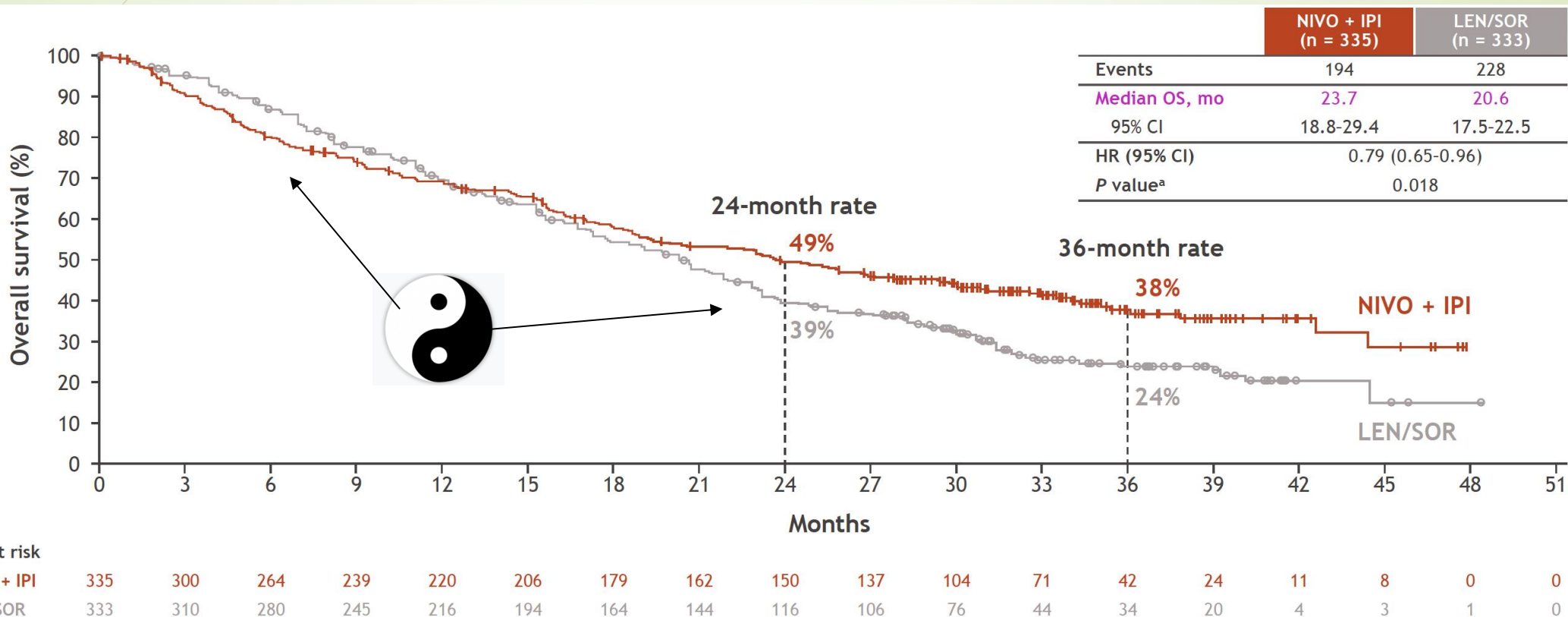
Key exploratory endpoints

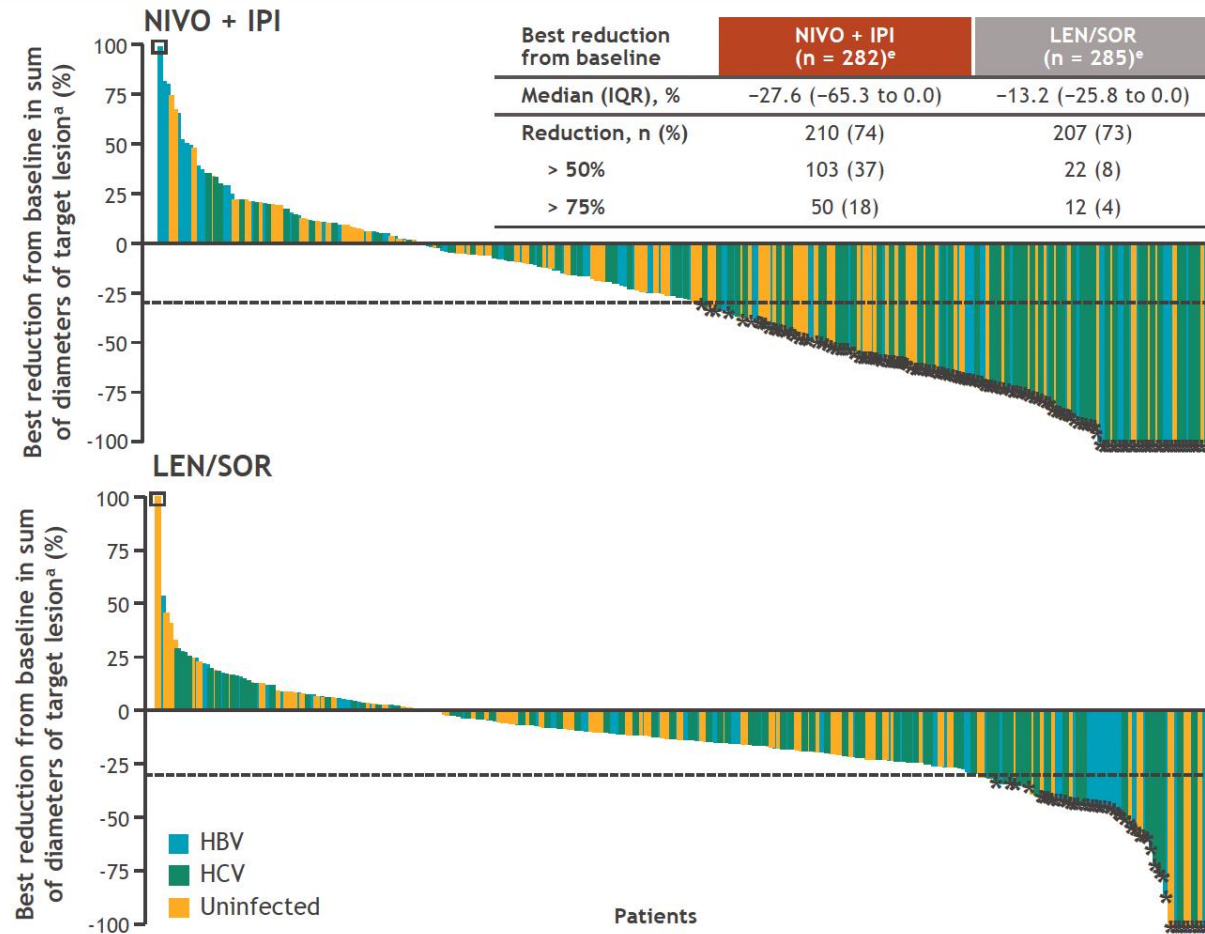
- PFS by investigator per RECIST v1.1
- PFS2 by investigator
- Safety

- At data cutoff (January 31, 2024), the median follow-up^g was 35.2 months (range, 26.8-48.9)

CHECKMATE 9DW

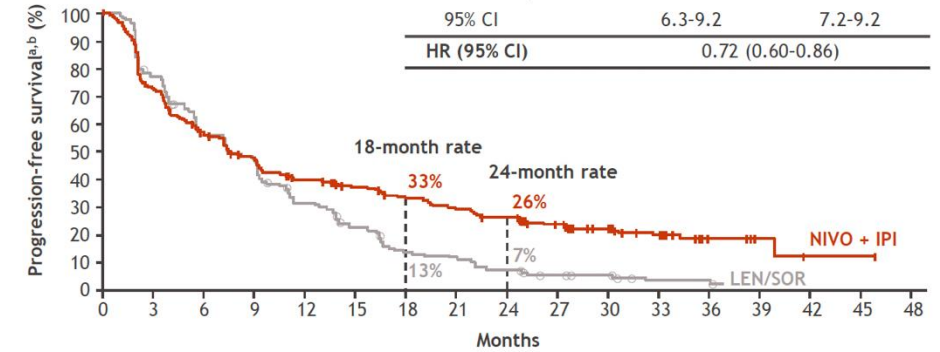
HCC





Progression-free survival

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	242	281
Median PFS, ^{a,b} mo	7.5	7.5
95% CI	6.3-9.2	7.2-9.2
HR (95% CI)	0.72 (0.60-0.86)	

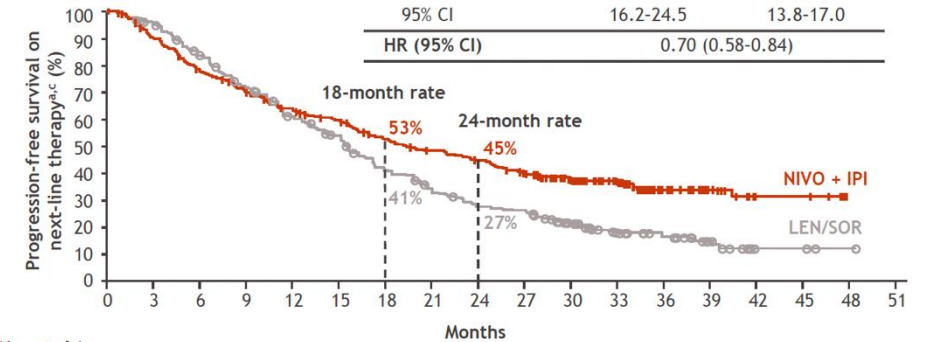


No. at risk

NIVO + IPI	335	236	173	143	114	101	89	78	69	53	35	23	9	3	1	1	0
LEN/SOR	333	243	170	140	88	62	34	28	18	11	8	3	2	0	0	0	0

Progression-free survival on next-line therapy (PFS2)

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	206	257
Median PFS2, ^{a,c} mo	19.3	15.4
95% CI	16.2-24.5	13.8-17.0
HR (95% CI)	0.70 (0.58-0.84)	



No. at risk

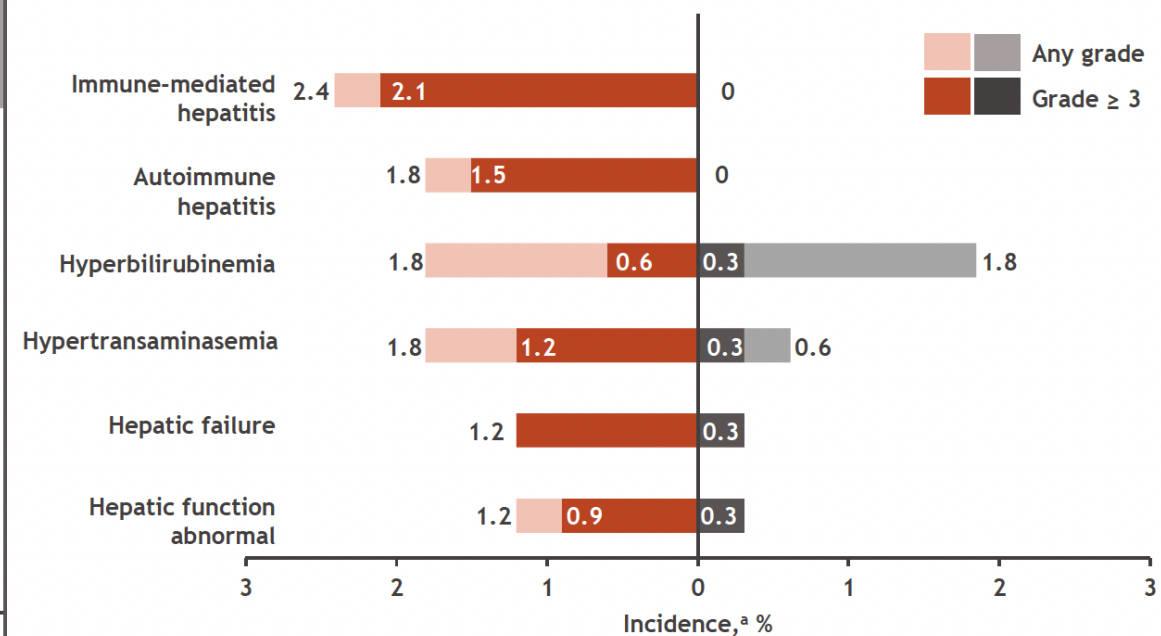
NIVO + IPI	335	298	256	228	205	189	163	148	136	120	90	61	33	18	6	6	0	0
LEN/SOR	333	310	269	229	190	162	124	101	80	76	50	32	25	13	3	3	1	0

CHECKMATE 9DW

HCC

All treated patients, n (%)	NIVO + IPI (n = 332)			LEN/SOR (n = 325)		
	Any grade	Grade 3/4	Any grade leading to D/C	Any grade	Grade 3/4	Any grade leading to D/C
Any TRAEs ^a	278 (84)	137 (41)	59 (18)	297 (91)	138 (42)	34 (10)
Treatment-related hepatic events						
Hepatobiliary disorders	44 (13)	35 (11)	15 (5)	15 (5)	10 (3)	4 (1)
Hepatobiliary investigations ^b						
AST increased	65 (20)	20 (6)	4 (1)	27 (8)	2 (< 1)	1 (< 1)
ALT increased	63 (19)	16 (5)	3 (< 1)	19 (6)	3 (< 1)	0
Bilirubin increased	14 (4)	1 (< 1)	1 (< 1)	23 (7)	5 (2)	1 (< 1)
Treatment-related deaths ^c	12 (4) ^d			3 (< 1) ^e		

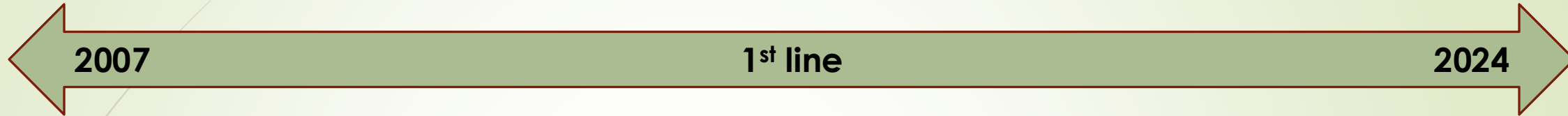
Hepatobiliary disorders occurring in ≥ 1% of patients



- Most treatment-related hepatic events with NIVO + IPI were grade 1/2 laboratory abnormalities and generally resolved with dose modifications or established management algorithms

HCC

Phase III trials – 1st line



Trial	SHARP	REFLECT	ImBrave 150	HIMALAYA	RATIONALE 301	LEAP 002	CARES 310	CM 9DW
Treatment	sorafenib	lenvatinib	atezo bev	durva treme	tislelizumab	len pem	camrelizumab rivoceranib	nivo ipi
mOS (m)	10.7	13.6	19.2	16.4	15.9	21	21.1	23.7
Sorafenib mOS	10.7	12.3	13.2	13.8	14.1		15.2	
Lenvatinib mOS		13.6				19		20.6 (85% len)

Ongoing challenges in HCC

- **Optimal sequencing of treatment options**
- **Applicability to general population – CP-A only**
- **Application in earlier stage disease**
- **Clinical trial design/execution in this environment**

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Gastro-Esophageal Cancer

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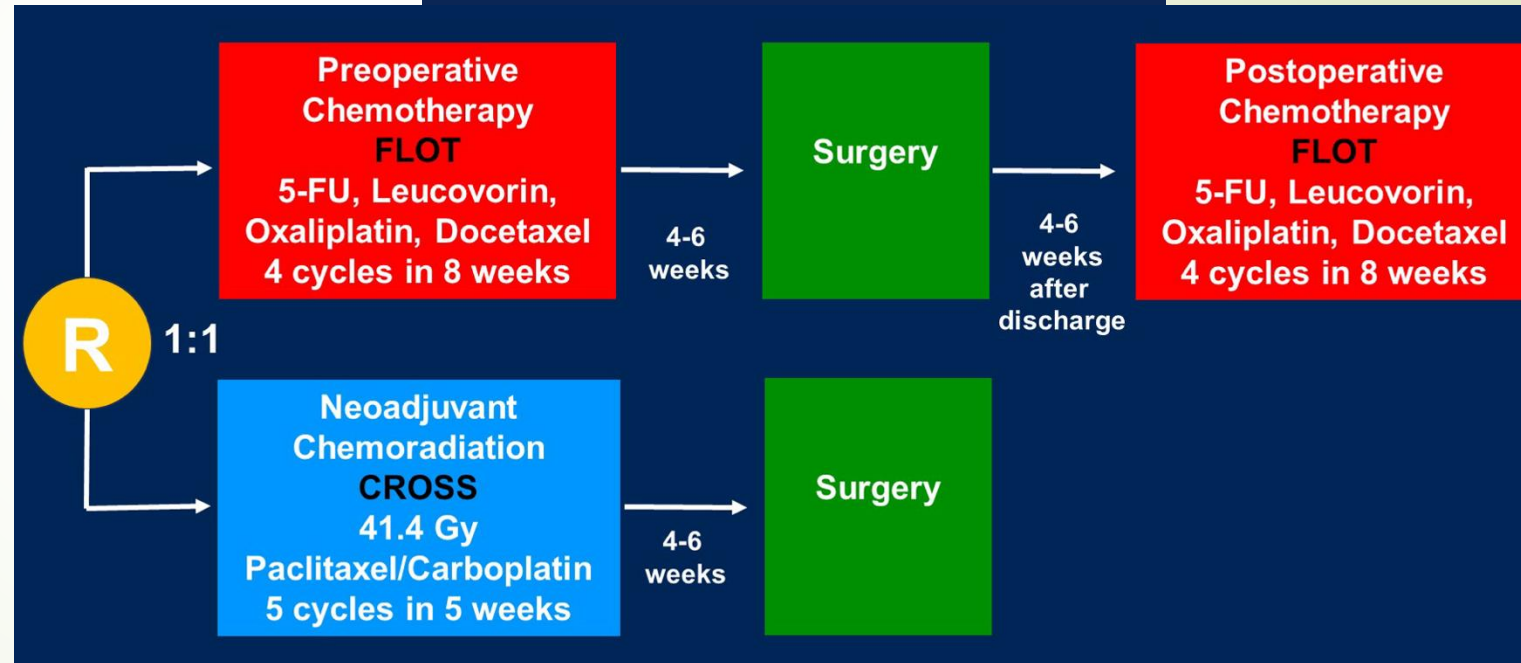
Resectable Esophageal Adenocarcinoma Current SOC

Chemo -> Surgery -> Chemo

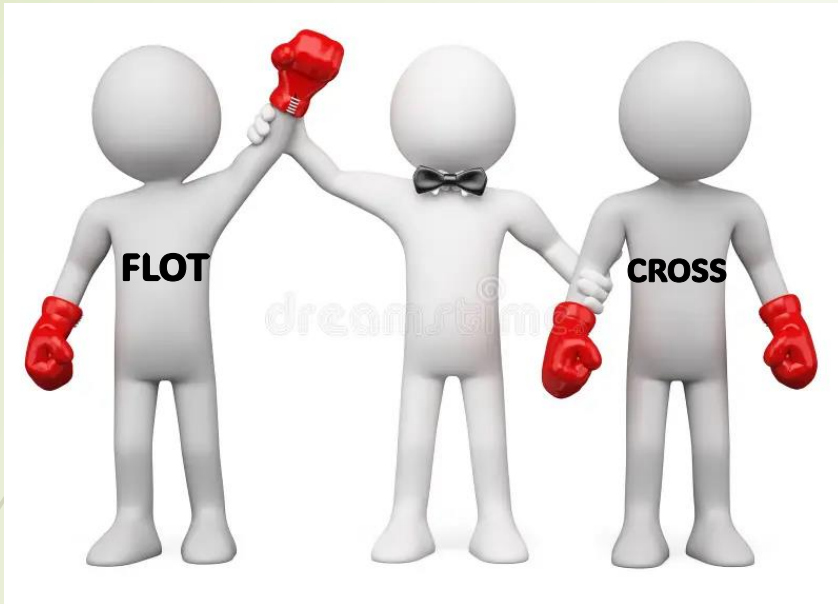
VS

ChemoRT -> Surgery

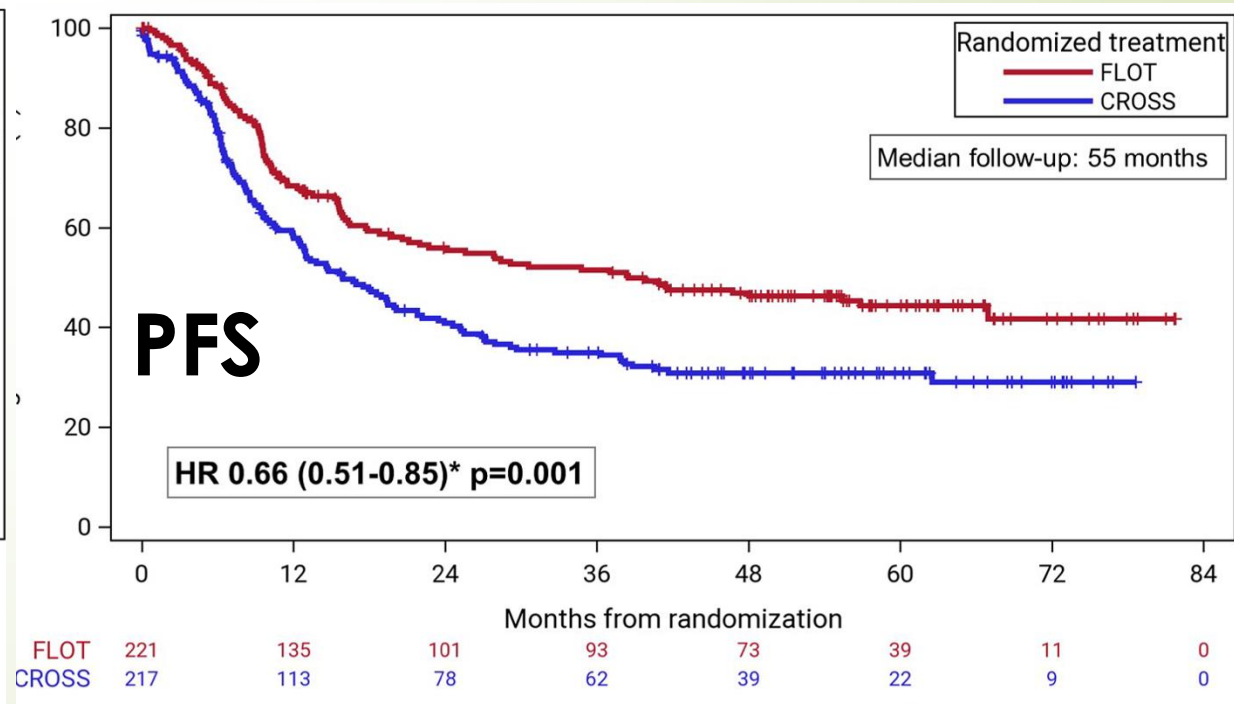
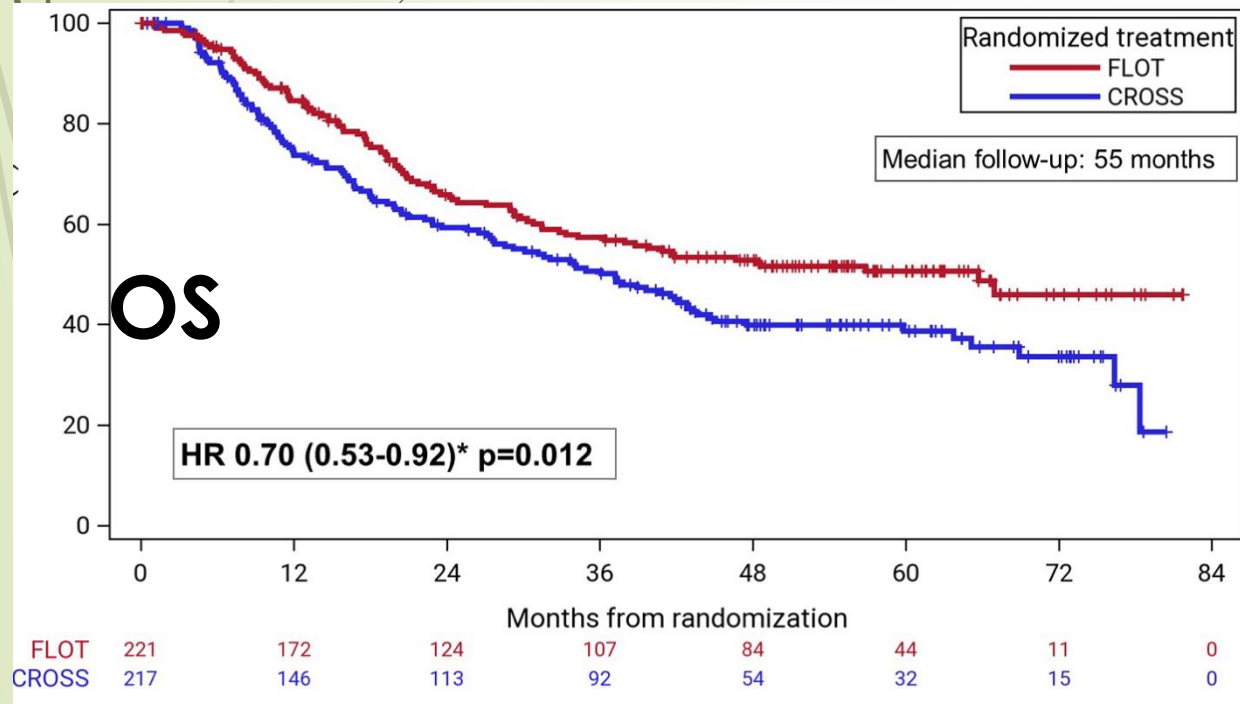
The ESOPEC Trial



GEC



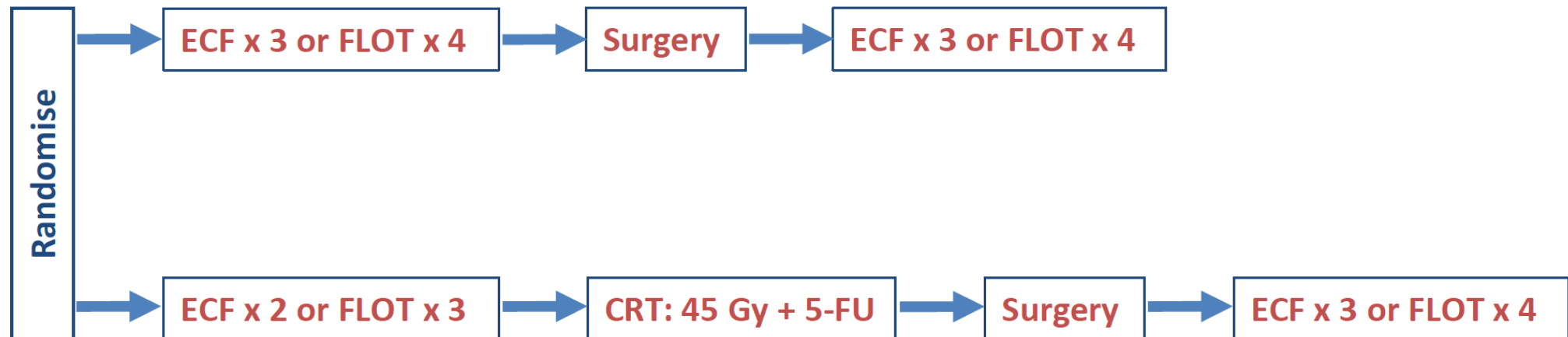
	FLOT Group	CROSS Group
N	191	180
Resection status		
No resection	0.5%	1.1%
R0	94.2%	95.0%
R1	5.2%	3.9%
Postoperative N-Stage		
ypN-	50.8%	54.4%
ypN+	48.7%	44.4%
Pathological complete remission		
ypT0 ypN0	16.8%	10.0%
Tumor regression grade (Becker ¹)		
Complete regression	18.3%	13.3%
Near complete regression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



Resectable Gastric Adenocarcinoma

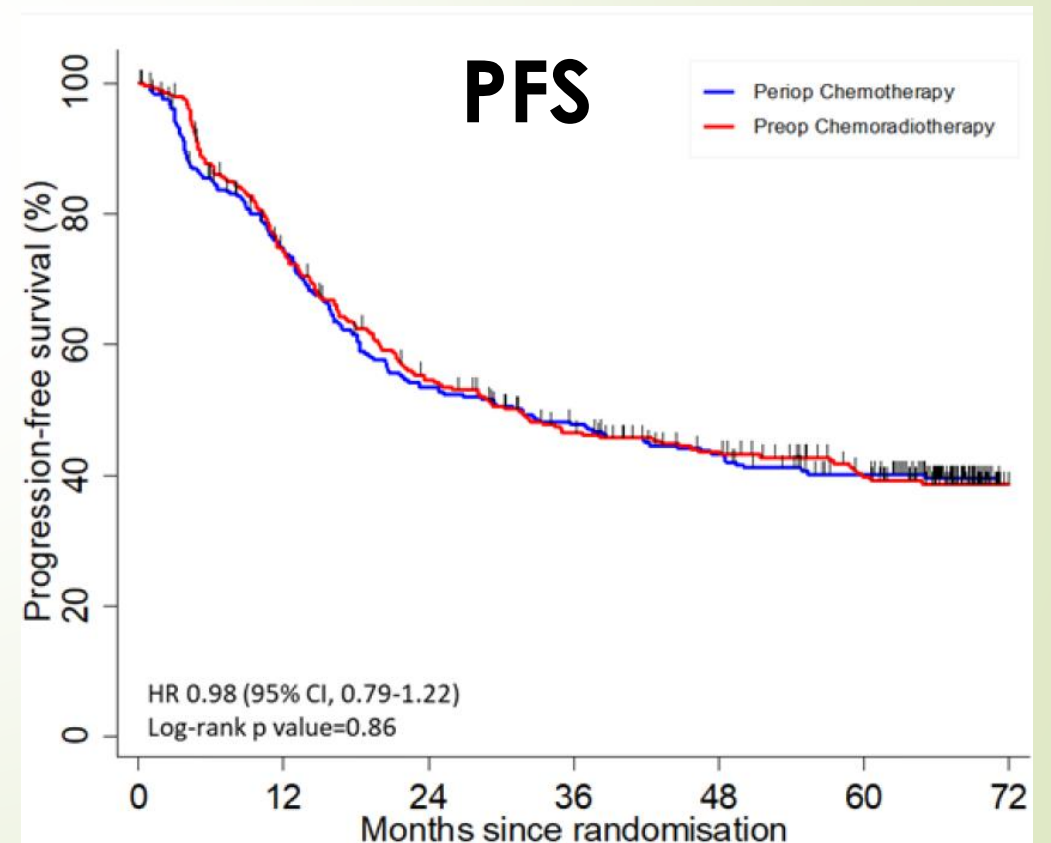
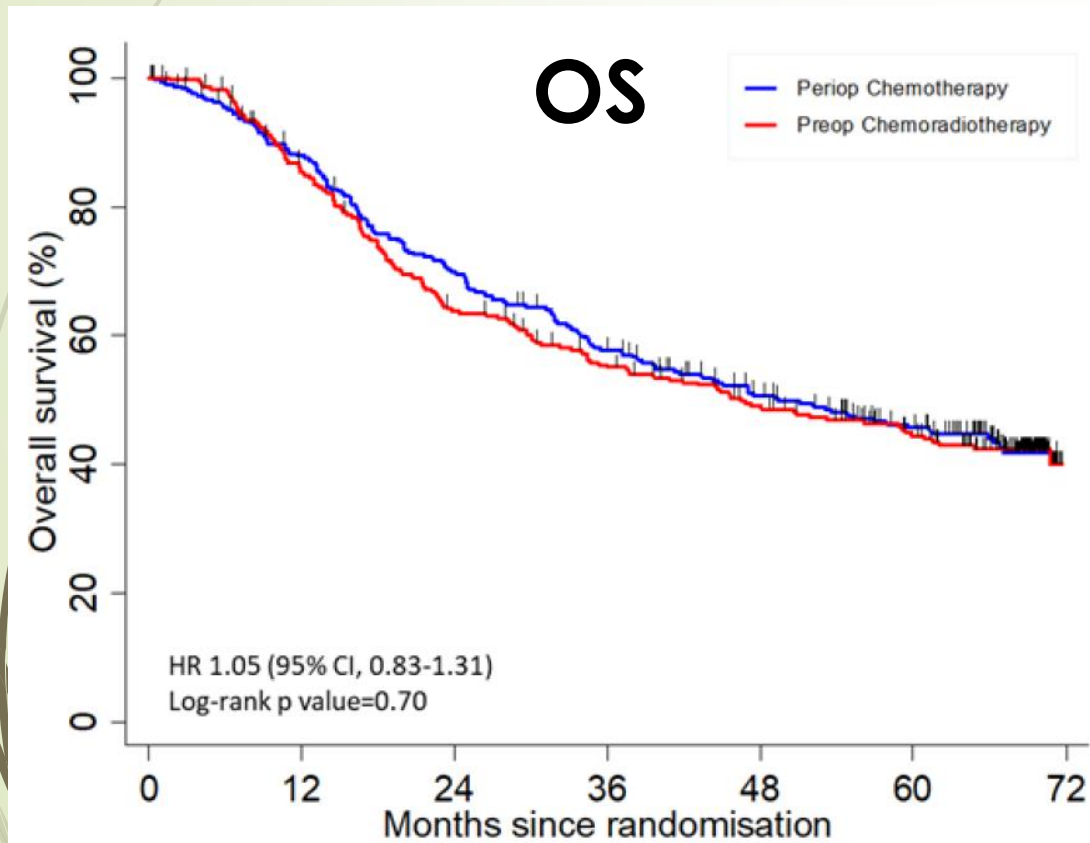
Chemo -> ChemoRT -> Surgery -> Chemo

A randomized phase 3 trial of perioperative chemotherapy with or without preoperative chemoradiotherapy for resectable gastric cancer (TOPGEAR)



GEC

Characteristic	Category	Preop CRT N = 286	Periop CT N = 288
Tumour Location	Gastro-esophageal junction	98 (34%)	101 (35%)
	Upper/Middle third	80 (28%)	89 (31%)
	Multiple sites	36 (13%)	28 (10%)
	Lower third	72 (25%)	70 (24%)
Planned Chemotherapy	ECF/ECX	192 (67%)	194 (67%)
	FLOT	94 (33%)	94 (33%)



GEC

FLOT TFLO OLFT LFTO
FLTO TFOL OLTF LFOT
FTLO TLOF OTLF LTOF
FTOL TLFO OTFL LTFO
FOLT TOLF OFLT LOTF
FOTL TOFL OFTL **LOFT**

**Evaluating pathological response to guide
adjuvant FLOT chemotherapy in
gastroesophageal cancer (SPACE- **LOFT**)**

An international cohort study of real-world data



Questions?

Thank you!