ROLE OF MEDICAL ONCOLOGY IN GI MALIGNANCIES- RECENT ADVANCES IN SYSTEMIC THERAPY IN GI MALIGNANCIES

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SCHEMA

- Gastric/GE junction adenocarcinomas
- Hepatocellular carcinoma
- Gallbladder cancer
- Pancreatic ductal adenocarcinoma (PDAC)
- Colorectal cancers

GASTRIC/GE JUNCTION ADENOCARCINOMAS

- *Perioperative therapy (chemotherapy)*
- *Therapy for advanced cancers*
- *Current status of immunotherapy*
- *TMH data*

Gastric/GE junction adenocarcinomas – perioperative

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Chemoradiotherapy after Surgery Compared with Surgery Alone for Adenocarcinoma of the Stomach or Gastroesophageal Junction

John S. Macdonald, M.D., Stephen R. Smalley, M.D., Jacqueline Benedetti, Ph.D., Scott A. Hundahl, M.D., Norman C. Estes, M.D., Grant N. Stemmermann, M.D., Daniel G. Haller, M.D., Jaffer A. Ajani, M.D., Leonard L. Gunderson, M.D., J. Milburn Jessup, M.D., and James A. Martenson, M.D.

N Engl J Med 2001; 345:725-730 September 6, 2001 DOI: 10.1056/NEJMoa010187

Why post operative /perioperative therapy ?

- Survival of operated GC beyond Stage IA : 3% to 42%
- Local or regional recurrence (anastomotic/nodal/tumor bed) after gastric resection: 40% to 65%
- Prior attempts at adjuvant chemotherapy alone – not very successful

Gastric/GE junction adenocarcinomas – perioperative

ORIGINAL ARTICLE

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., et al., for the MAGIC Trial Participants*

3#ECF+S + 3# ECF >>S

Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial

Prof Yung-Jue Bang, MD • Young-Woo Kim, MD • Prof Han-Kwang Yang, MD • Prof Hyun Cheol Chung, MD • Prof Young-Kyu Park, MD • Prof Kyung Hee Lee, MD • et al. Show all authors • Show footnotes

Published: January 07, 2012 • DOI: https://doi.org/10.1016/S0140-6736(11)61873-4

S+ CAPOX >> S

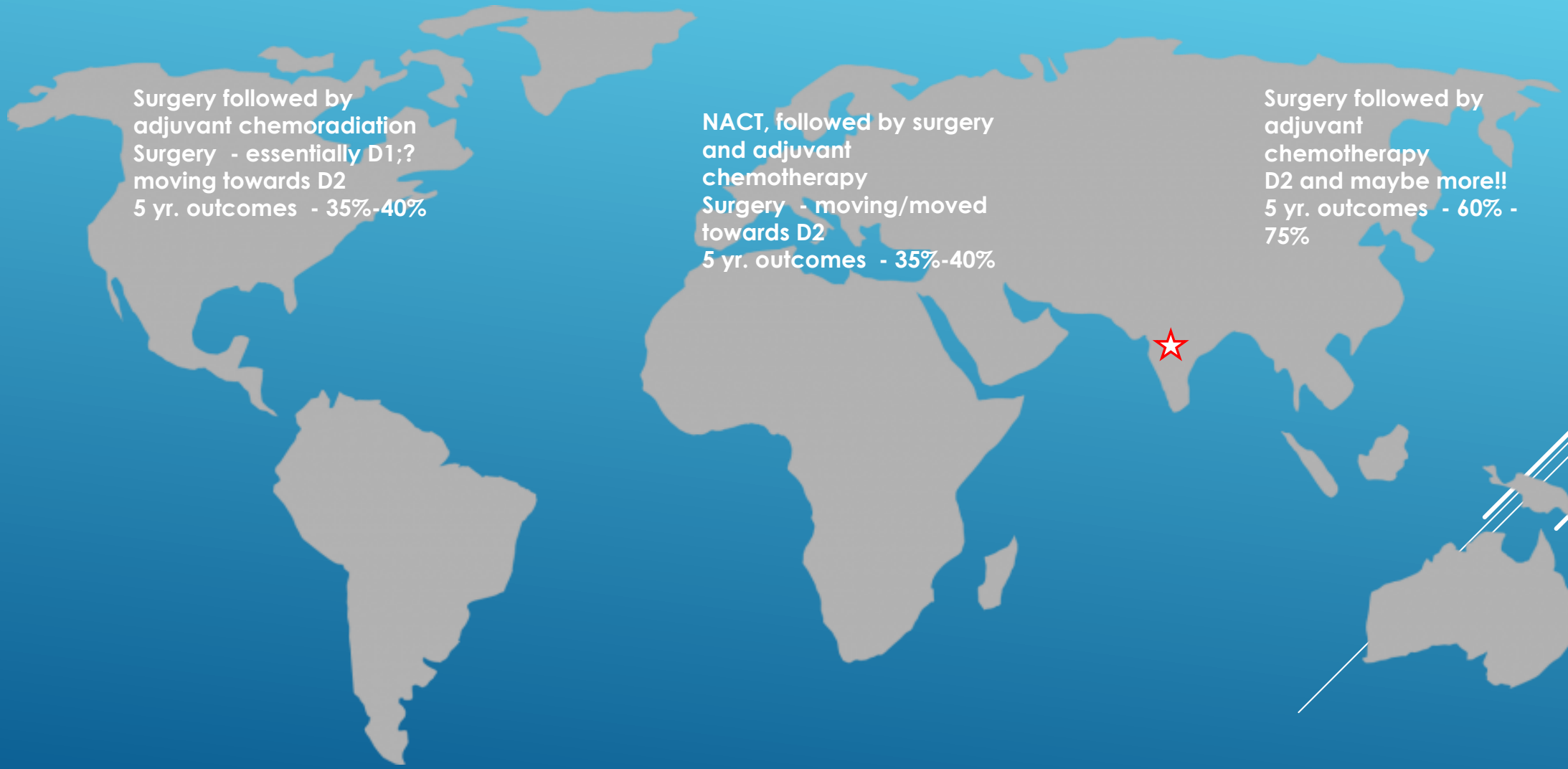
ORIGINAL REPORTS | Gastrointestinal Cancer

Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses

Se Hoon Park , Tae Sung Sohn , Jeeyun Lee , Do Hoon Lim , Min Eui Hong , Kyoung-Mee Kim...
Show More

S + CAPE-CIS
=
S + CAPE – CIS + CAPE-RT

Gastric/GE junction adenocarcinomas – perioperative



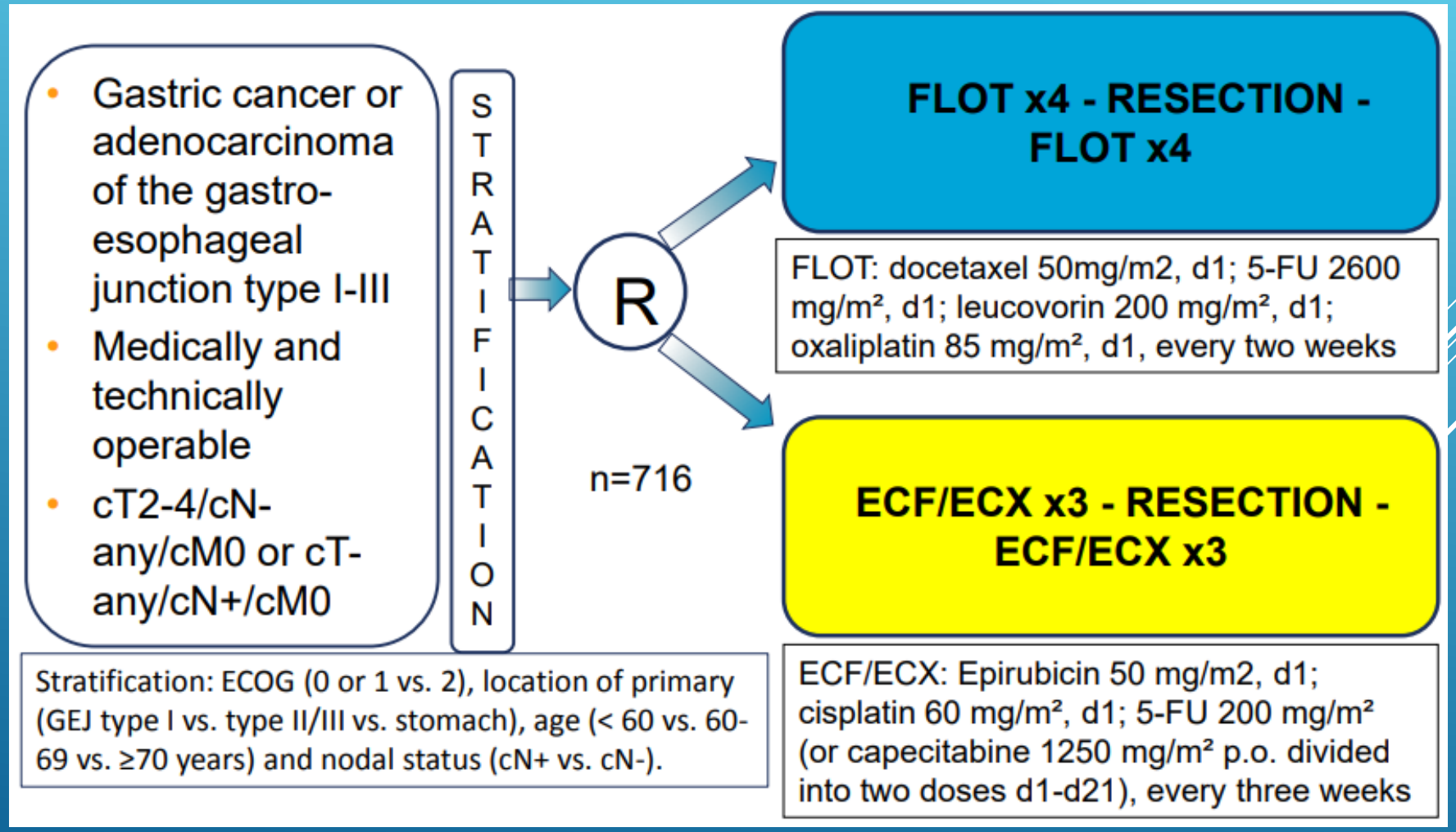
Surgery followed by adjuvant chemoradiation
Surgery - essentially D1;? moving towards D2
5 yr. outcomes - 35%-40%

NACT, followed by surgery and adjuvant chemotherapy
Surgery - moving/moved towards D2
5 yr. outcomes - 35%-40%

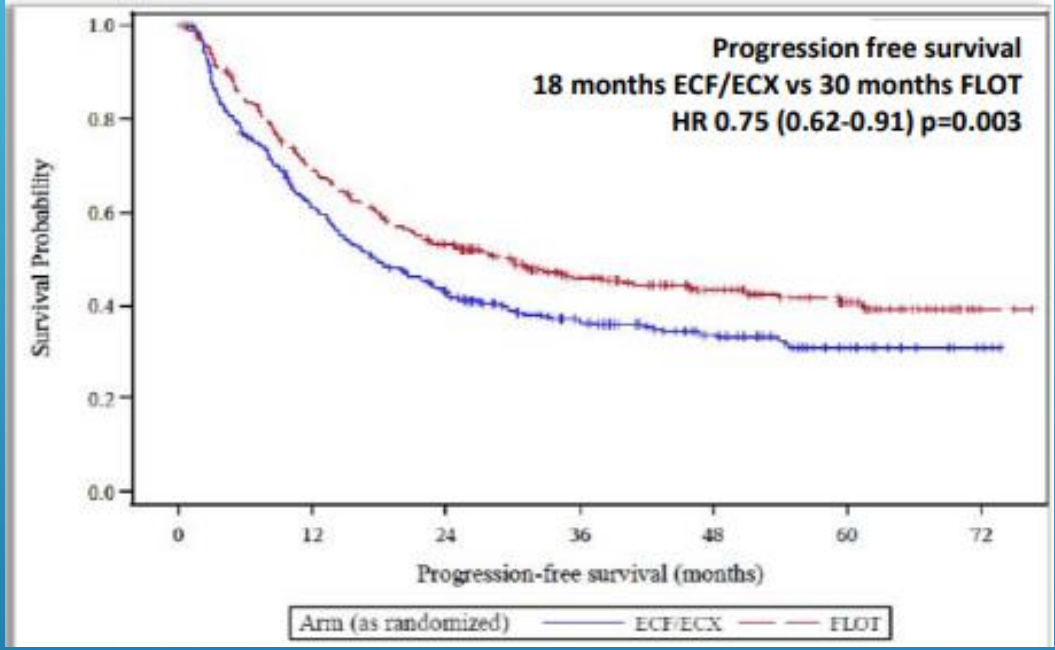
Surgery followed by adjuvant chemotherapy
D2 and maybe more!!
5 yr. outcomes - 60% - 75%

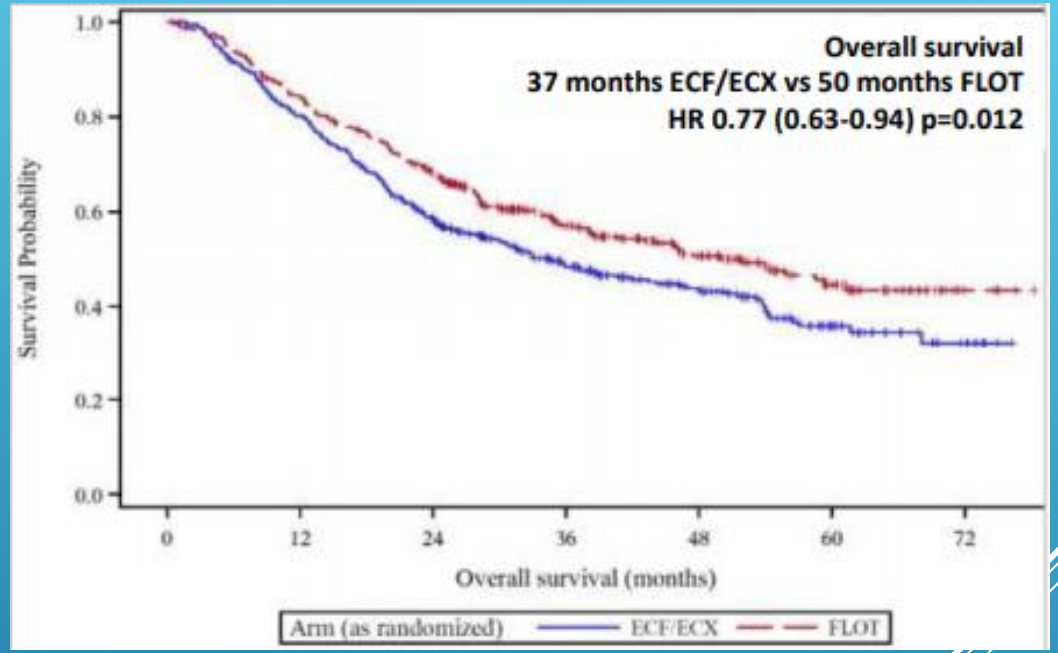
Gastric/GE junction adenocarcinomas – perioperative

FLOT4 - AIO Trial
Primary endpoint - OS



Gastric/GE junction adenocarcinomas – perioperative

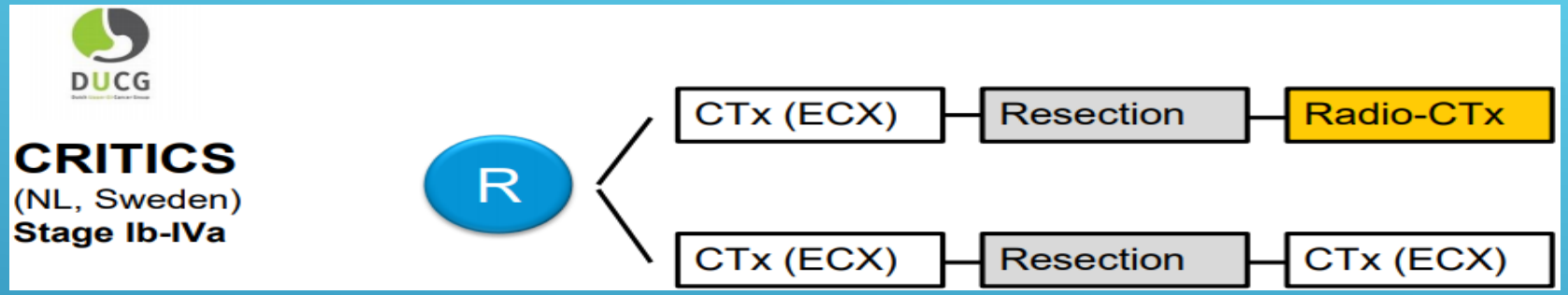


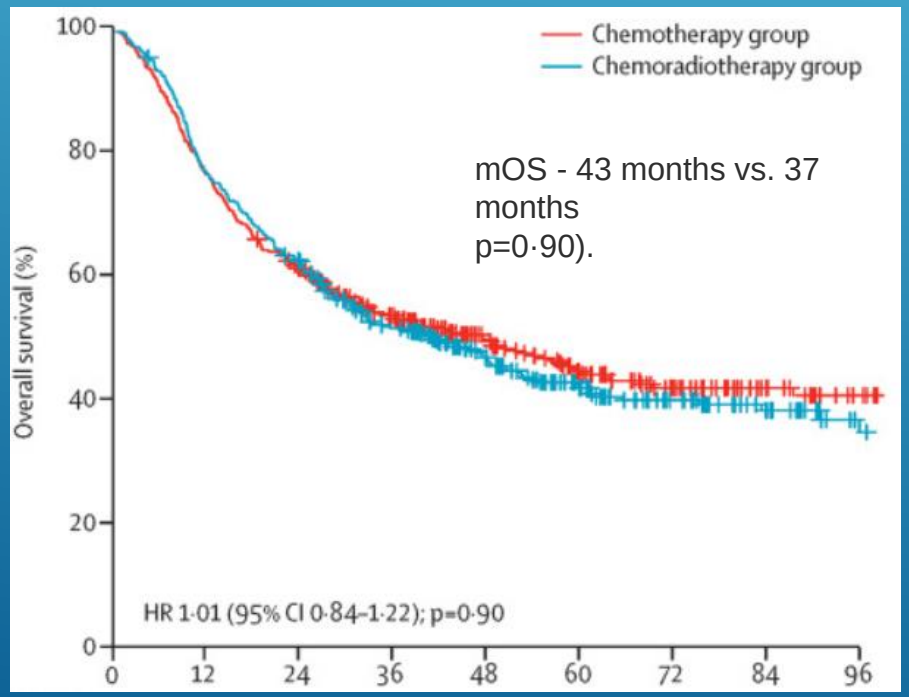


Projected PFS rates		
	ECF/X	FLOT
2 year	43%	53%
3 year	37%	46%
5 year	31%	41%

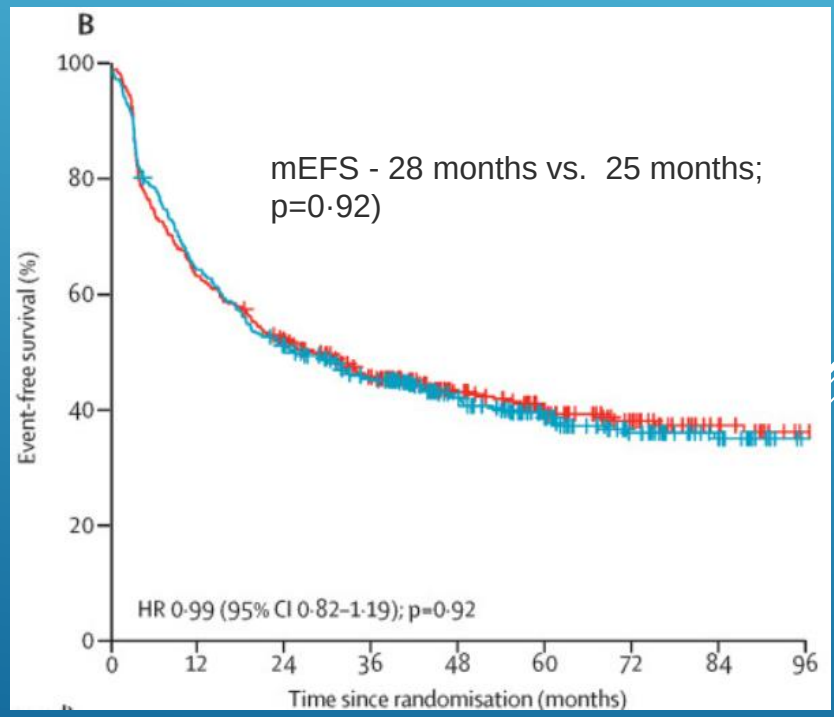
Projected OS rates		
	ECF/X	FLOT
2 year	59%	68%
3 year	48%	57%
5 year	36%	45%

Gastric/GE junction adenocarcinomas – perioperative





mOS - 43 months vs. 37 months
p=0·90).



mEFS - 28 months vs. 25 months;
p=0·92)

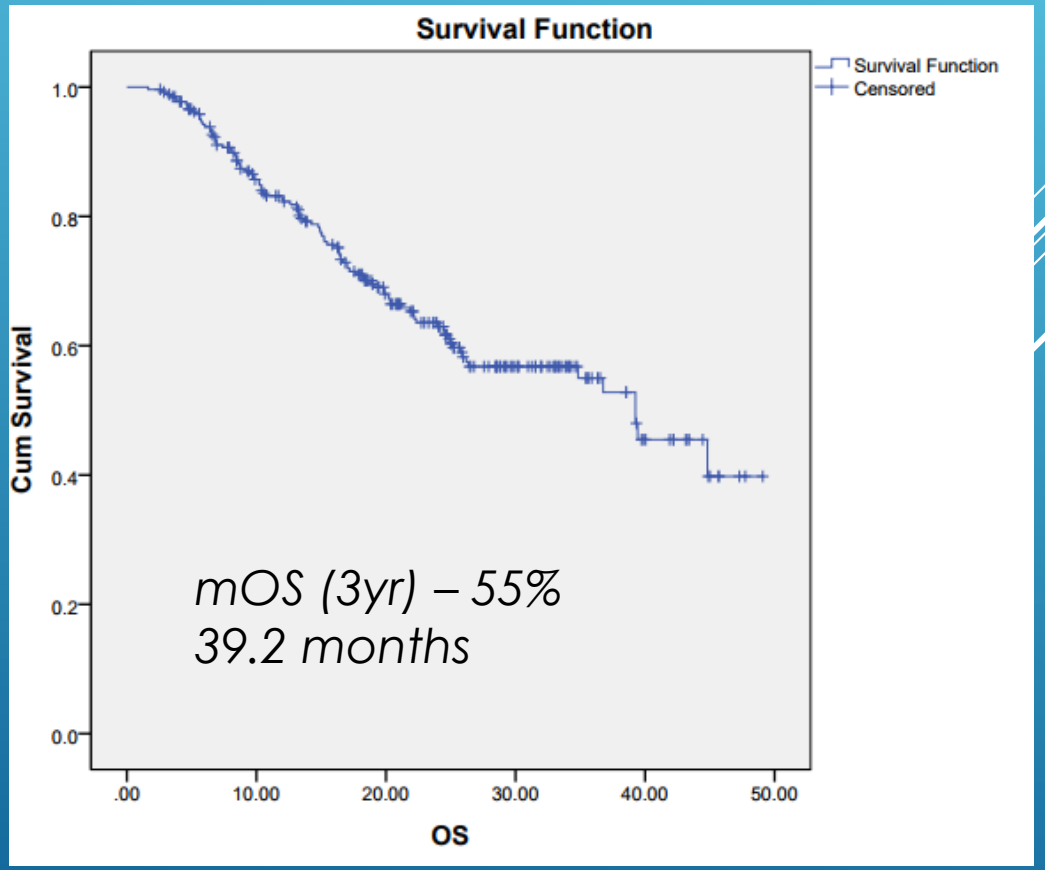
The LANCET Oncology VOLUME 19, ISSUE 5, P616-628, MAY 01, 2018

Gastric/GE junction adenocarcinomas – perioperative

J Gastric Cancer. 2017 Mar; 17(1): 21–32.
Published online 2017 Mar 16. doi: 10.5230/jgc.2017.17.e3
PMCID: PMC5362831

Perioperative Epirubicin, Oxaliplatin, and Capecitabine Chemotherapy in Locally Advanced Gastric Cancer: Safety and Feasibility in an Interim Survival Analysis

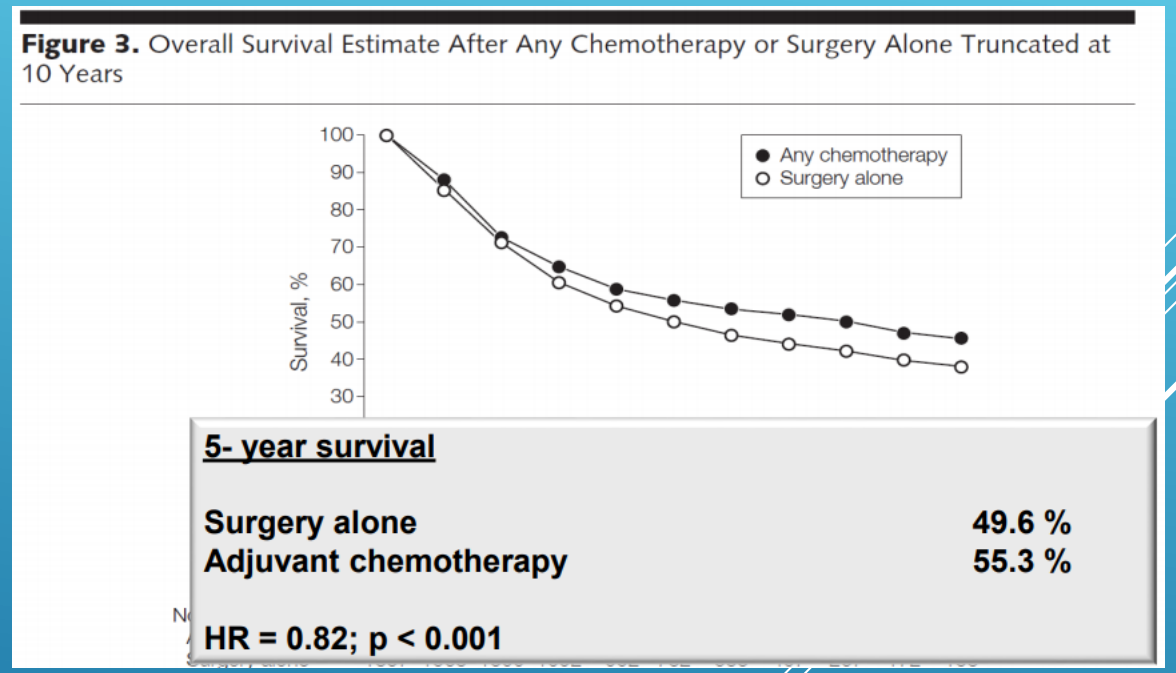
CHARACTERISTIC	NUMBER (%)
Median age (yrs.)	54 (21-80)
Gender • Female • Male	 71 (26.5) 197 (73.5)
ECOG PS • 0,1 • 2	 260 (97) 08 (3)
Disease site • Proximal (GEJ, Cardia, Fundus) • Body • Distal (antral, antropyloric)	 79 (29.5) 65 (24.3) 124 (46.3)
Gastric outlet obstruction • Yes • No	 73 (27.2) 195 (72.8)



Gastric/GE junction adenocarcinomas – perioperative

Current status

- Perioperative chemotherapy – FLOT4 AIO regimen for Gastric/GE junction locoregionally advanced cancers
- Upfront surgery – adjuvant CAPOX/Cape-Cis



Gastric/GE junction adenocarcinomas – advanced/metastatic

What is the appropriate regimen ?

mOS: 10 – 18 mo.

Epirubicin based triplet

- ECF
- ECX
- EOX
- EOF

- Cisplatin-5 FU
- Paclitaxel plus carboplatin/cisplatin
- CAPOX/FOLFOX
- FOLFIRI
- Docteaxel – cisplatin/carboplatin

Docetaxel based triplet

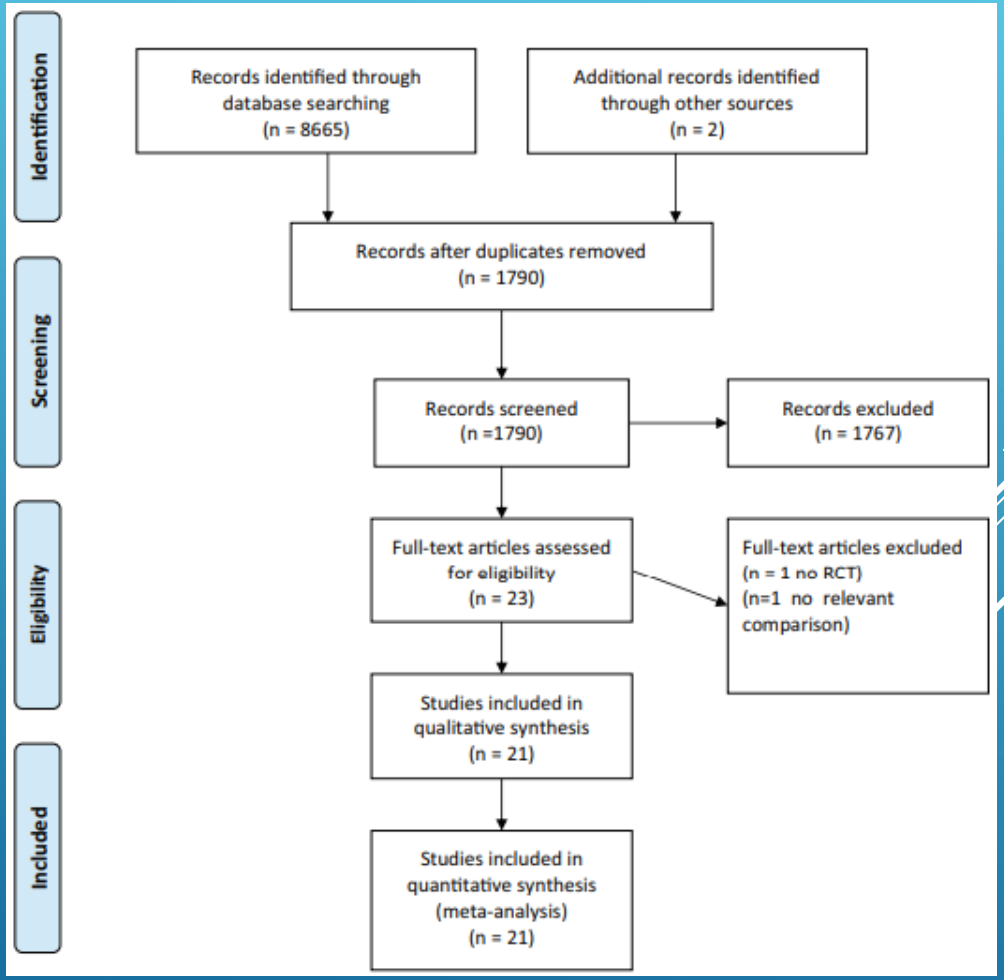
- Modified DCF
- DCF (Carboplatin/Cisplatin)
- DOF
- DOX

Gastric/GE junction adenocarcinomas – advanced/metastatic

Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet *versus* doublet chemotherapy: a systematic literature review and meta-analysis

N. Haj Mohammad[1] · E. ter Veer[1] · L. Ngai[1] · R. Mali[1] · M. G. H. van Oijen[1] · H. W. M. van Laarhoven[1]

- Meta-analysis
- 1980 and March 2015
- Phase II and Phase III studies
- 3475 patients



Cancer Metastasis Rev. 2015 Sep;34(3):429-41.

Gastric/GE junction adenocarcinomas – advanced/metastatic

- Improvement in OS; HR= 0.90, 95 % CI 0.83–0.97
- Improvement in PFS and ORR, statistically significant
- Toxicity was higher with triplets
- **The benefits in OS are modest/limited in view of the hazard ratios (0.9)**

Fluoropyrimidine base

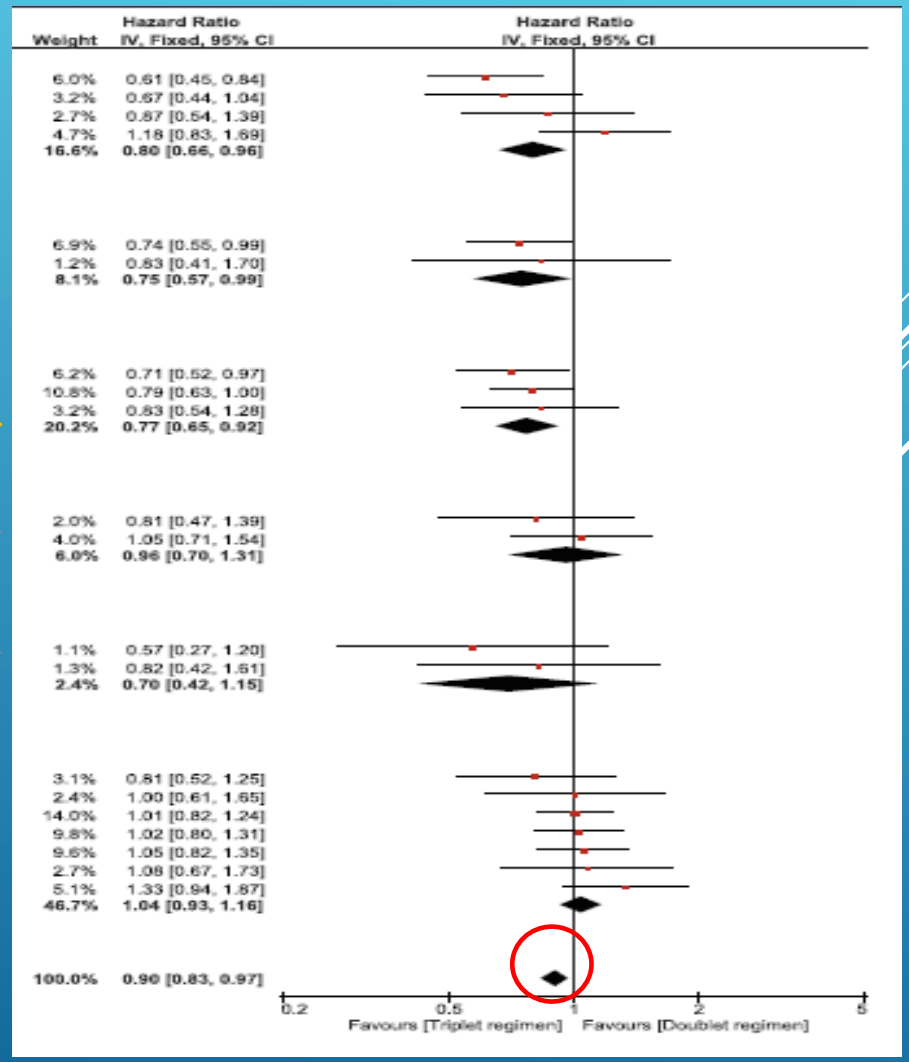
Cisplatin based

Taxane based

MMC based

Anthracycline based

Others

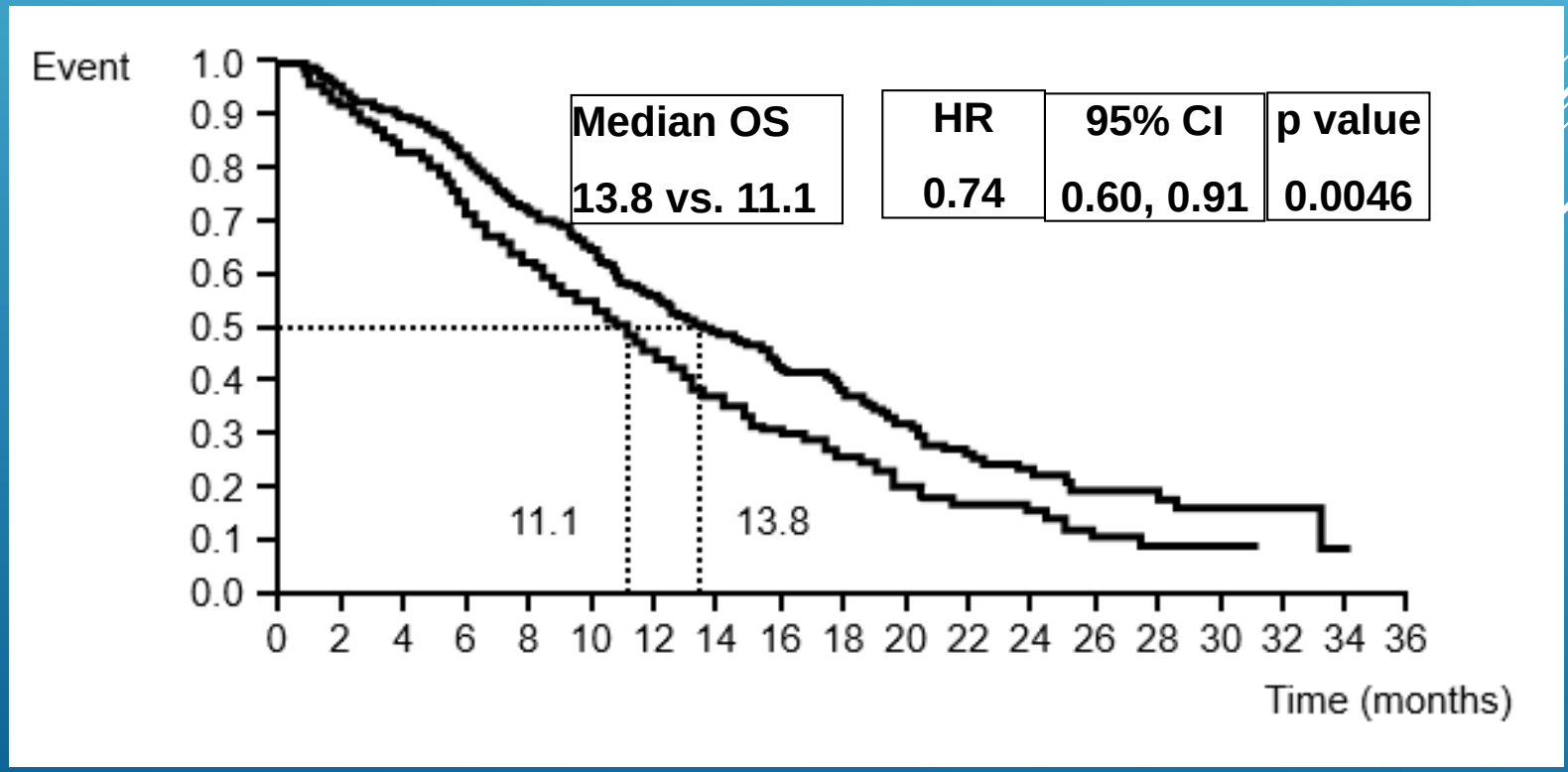


Cancer Metastasis Rev. 2015 Sep;34(3):429-41.

Gastric/GE junction adenocarcinomas – advanced/metastatic

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

- **Anti-HER2 therapy works**
- **Should be considered as first – line in HER2 positive cancers**



Lancet. 2010 Aug 28;376(9742):687-97. doi: 10.1016/S0140-6736(10)61121-X

Gastric/GE junction adenocarcinomas – advanced/metastatic

IJC_353_17R1

Original Article

Docetaxel/Oxaliplatin/Capecitabine (TEX) triplet followed by continuation monotherapy in advanced gastric cancer

Ostwal V, Bose S, Sirohi B[1], Poladia B, Sahu A[2], Bhargava P, Doshi V, Dusane R[3], Nashikkar C[3], Shrikhande SV[4], Ramaswamy A

Table 1: Baseline characteristics

Baseline characteristics	Number (%where required)
Total number of patients	208
Median age (years)	52 (Range: 23-75)
Gender	
Female	52 (25)
Male	156 (75)
ECOG PS*	
0,1	190 (91.3)
≥2	18 (8.7)
Location of primary	
GE** junction/proximal	37 (17.8)
Body	88 (42.3)
Distal	64 (30.8)
Epicentre not identified	19 (9.1)
Sites of metastases	
Peritoneal/Omentum	118 (56.7)
Liver	63 (30.3)
Lung	18 (8.6)
Adnexal/ovarian	17 (8.2)
Bone	16 (7.7)
Soft tissue	06 (2.9)
Degree of differentiation	
Well differentiated/moderately differentiated/Adenocarcinoma NOS*	62 (29.8)
Poorly differentiated	146 (70.2)
Signet ring histology	
Yes	79 (38)
No	129 (62)

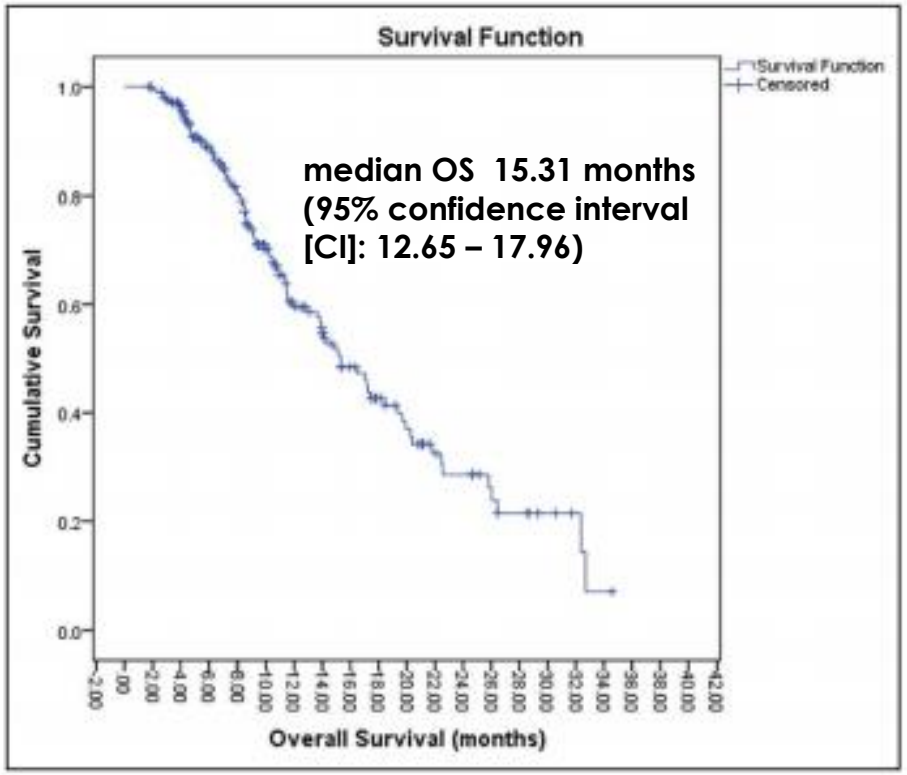
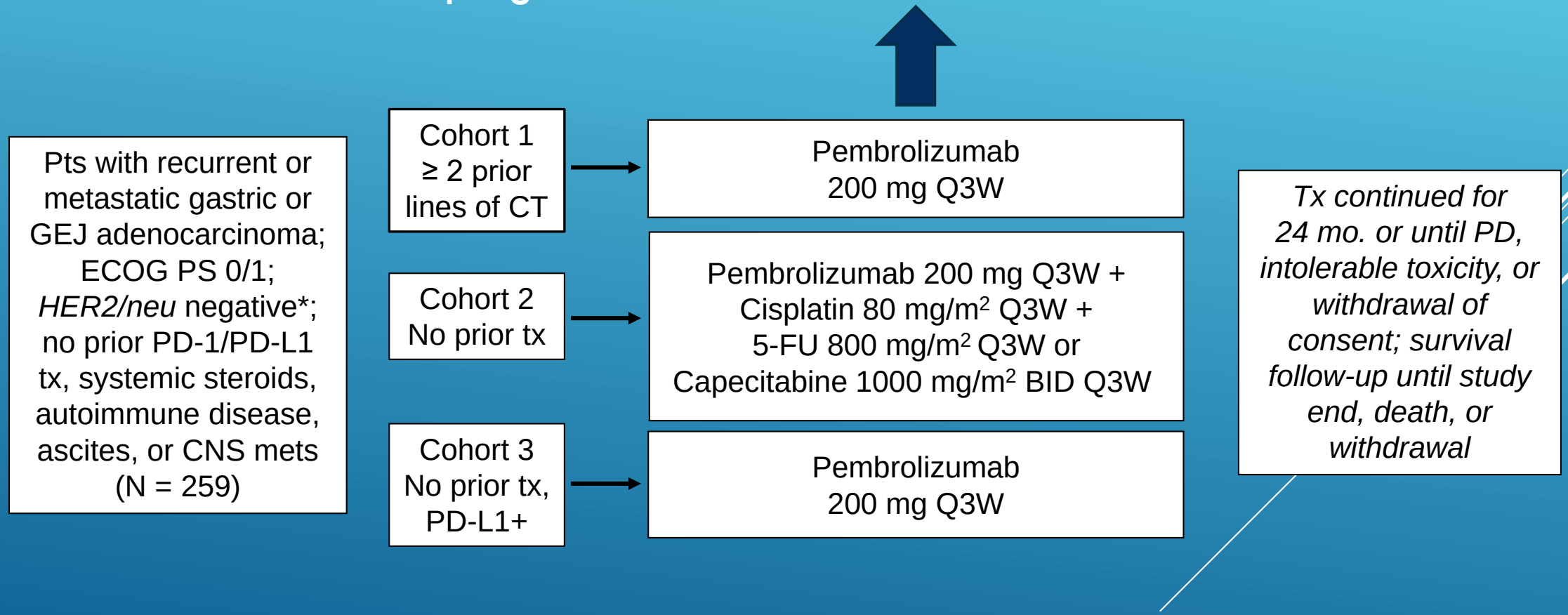


Figure 2: Kaplan–Meier curve for overall survival

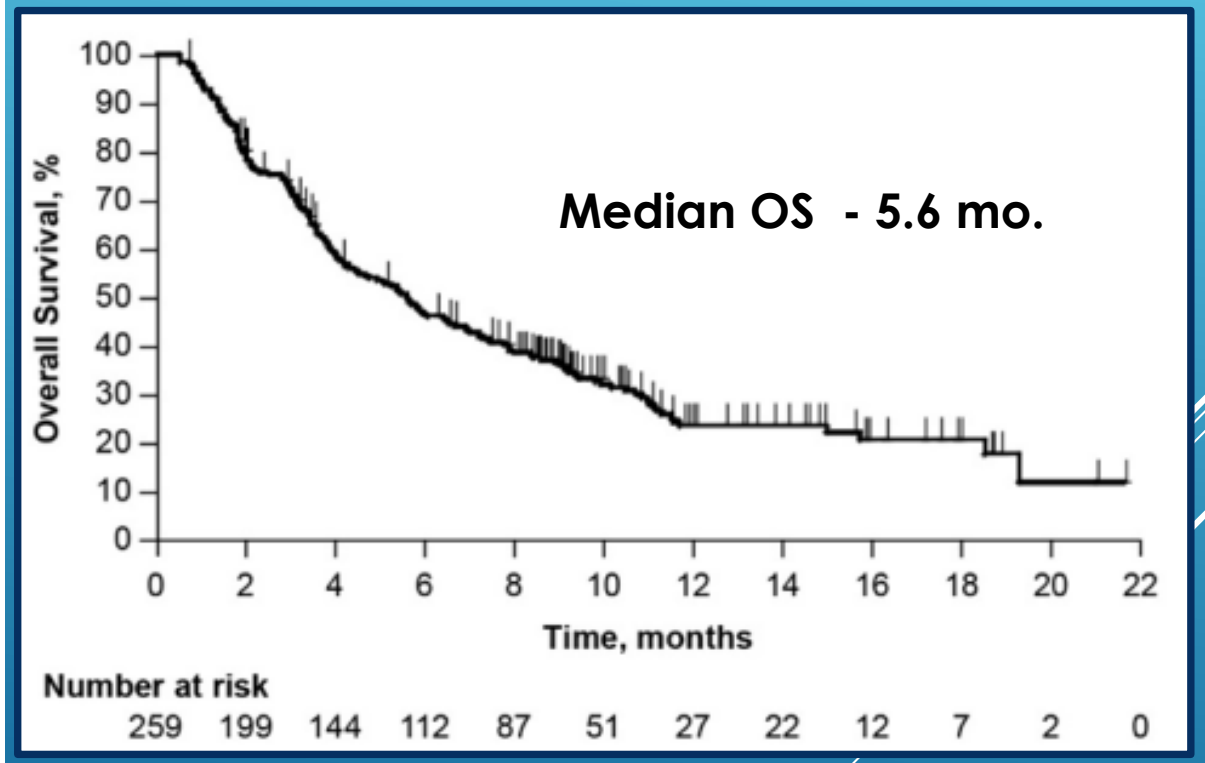
Gastric/GE junction adenocarcinomas – advanced/metastatic

Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer - Phase 2 Clinical KEYNOTE-059 Trial



Gastric/GE junction adenocarcinomas – advanced/metastatic

TRAE Occurring in > 5% of Pts, %	All Pts (N = 259)	
	Any Grade	Grade 3/4
Fatigue	18.9	2.3
Pruritus	8.9	0
Rash	8.5	0.8
Hypothyroidism	7.7	0.4
Decreased appetite	7.3	0
Anemia	6.9	2.7
Nausea	6.9	0.8
Diarrhea	6.6	1.2
Arthralgia	5.8	0.4

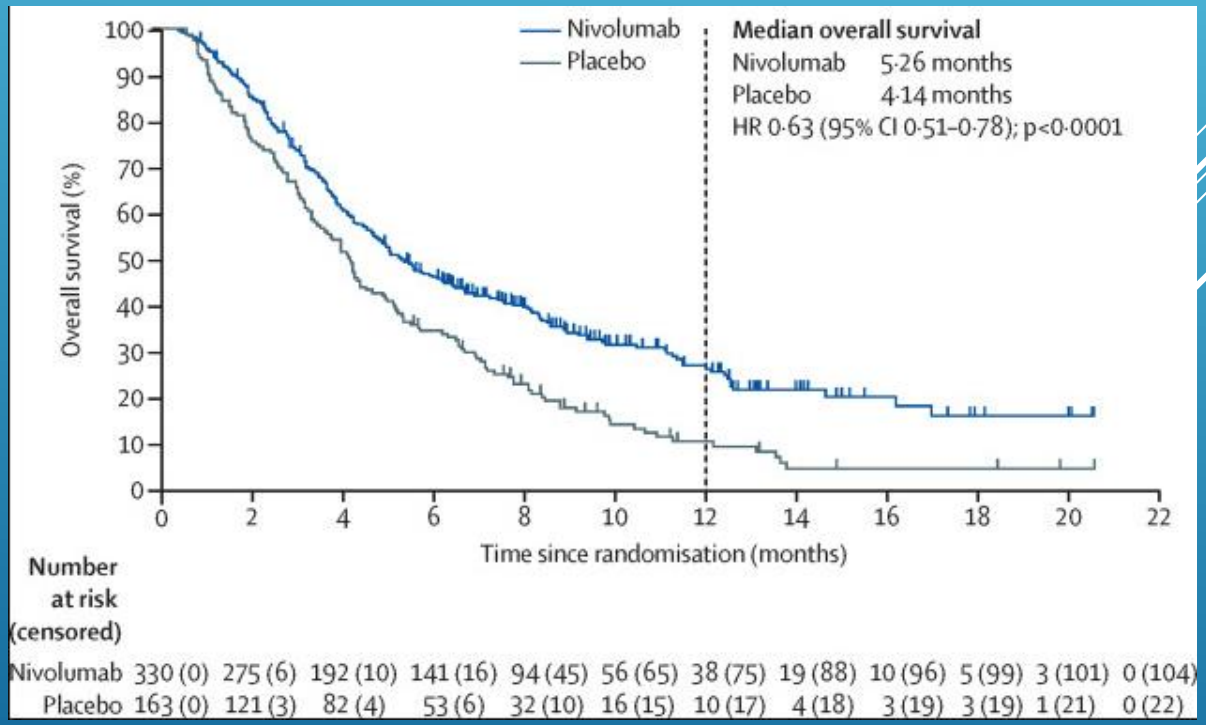


Gastric/GE junction adenocarcinomas – advanced/metastatic

Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial

Characteristics

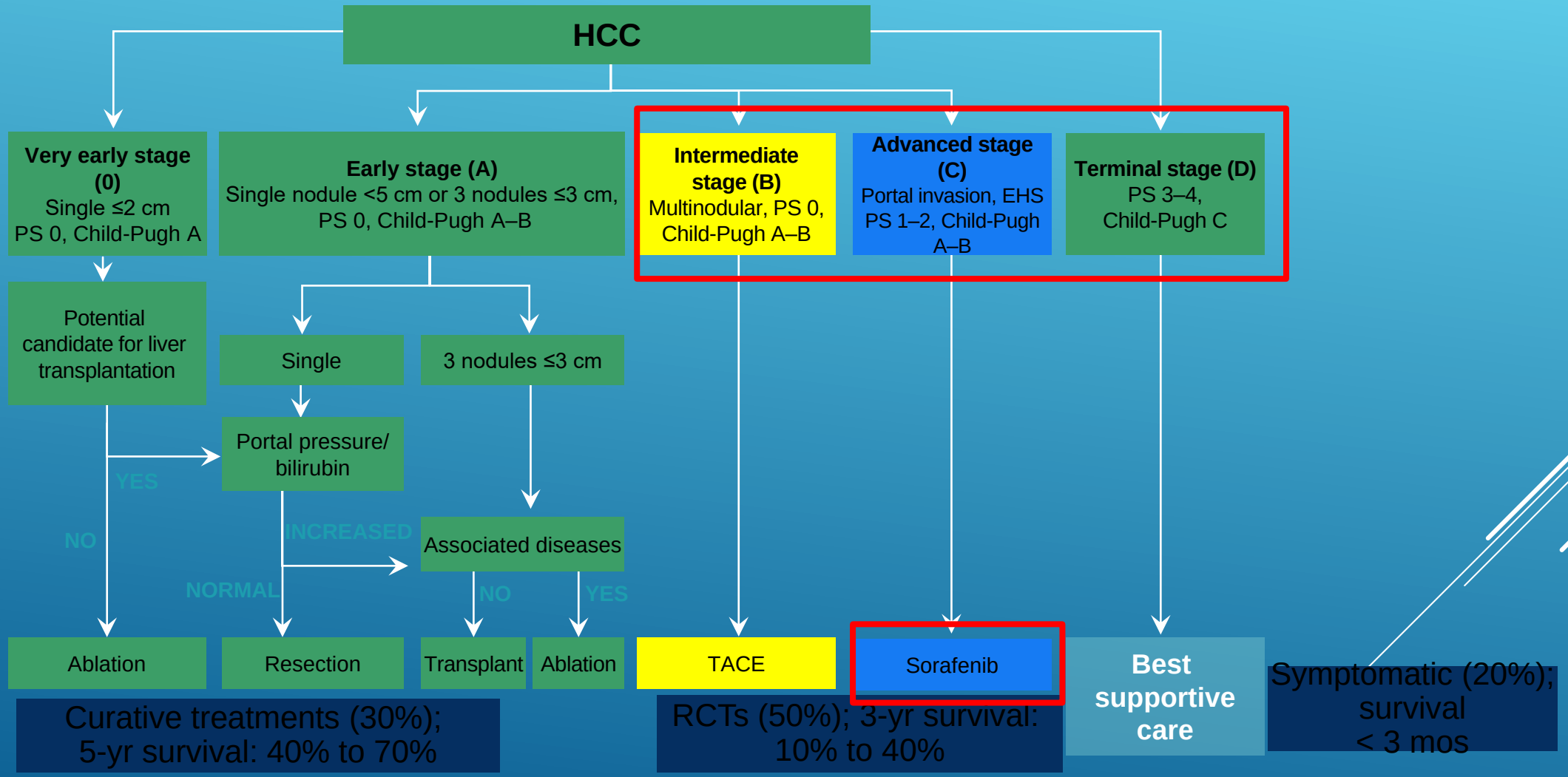
- N=493
- Median follow up – 8.87 mo
- Predominantly nodal metastases- 85%
- 38%-42% had received 3 lines of therapy
- 100% received 5 Fu analogues, 94%-96% platinums, 86% Taxanes
- 60% - 64% prior gastrectomies



HEPATOCELLULAR CARCINOMA

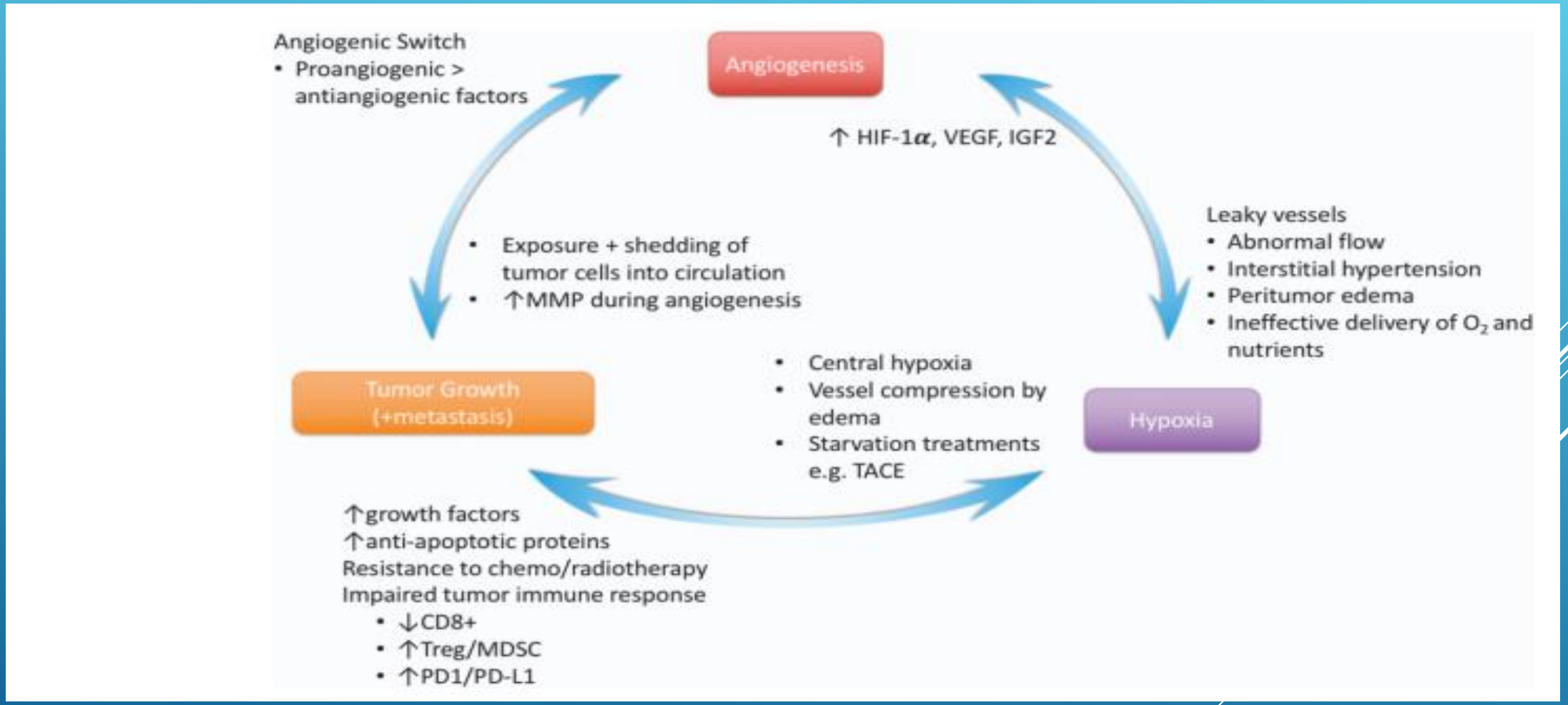
- *Use of Sorafenib with Liver Directed Therapy*
- *Systemic treatment options & Immunotherapy*

Hepatocellular Carcinoma



BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
Bruiix J, et al. *Gastroenterology*.2016;150:835-853.

Hepatocellular Carcinoma – Sorafenib with LDT



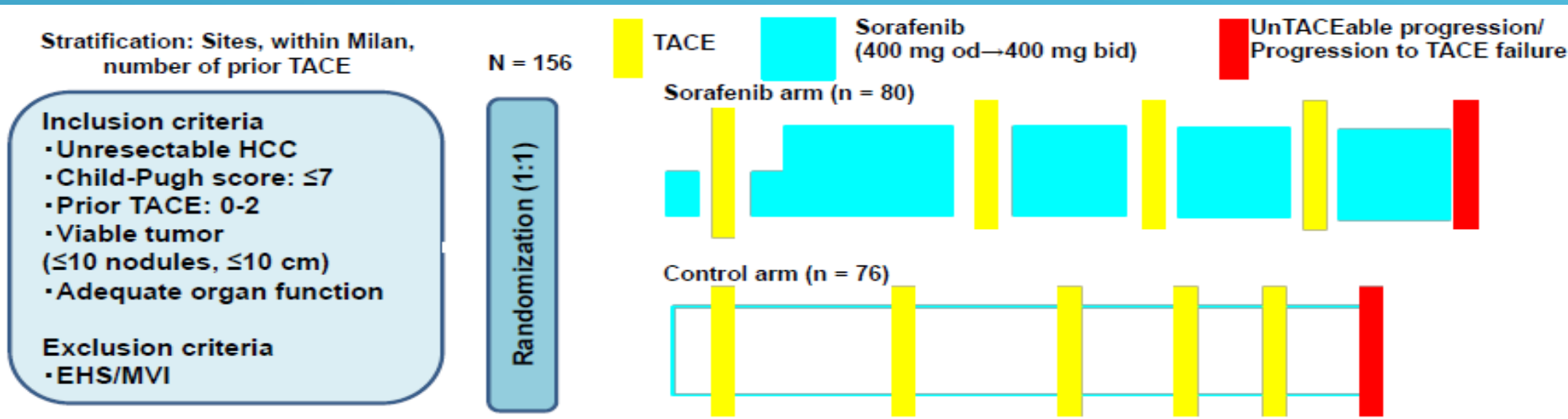
Hepatocellular Carcinoma – Sorafenib with LDT

	Trial name/PI	Results
PHASE III	SPACE Trial	mTTP: (S) 169 d vs. (P) 166 d p<0.072
	Kudo	mTTP: (S) 5.4 m vs. (P) 3.7 m p<0.252
	Sansonno	mTTP: (S) 9.2 m vs. (P) 4.9 m p<0.001
	Hofmann	mTTP: (S) 125 day vs. (P) 171 day m p=0.005
PHASE II	START Trial	mTTP: 9 m ORR: 53.8%
	SOCRATES Trial	mTTP: 16.4 m
	COTSUN Trial	mTTP: 7.1 m

mTTP: median time to progression; d: days; m: months; (S): sorafenib; (P): placebo; ORR: overall response rate.

Hepatocellular Carcinoma – Sorafenib with LDT

TACTICS



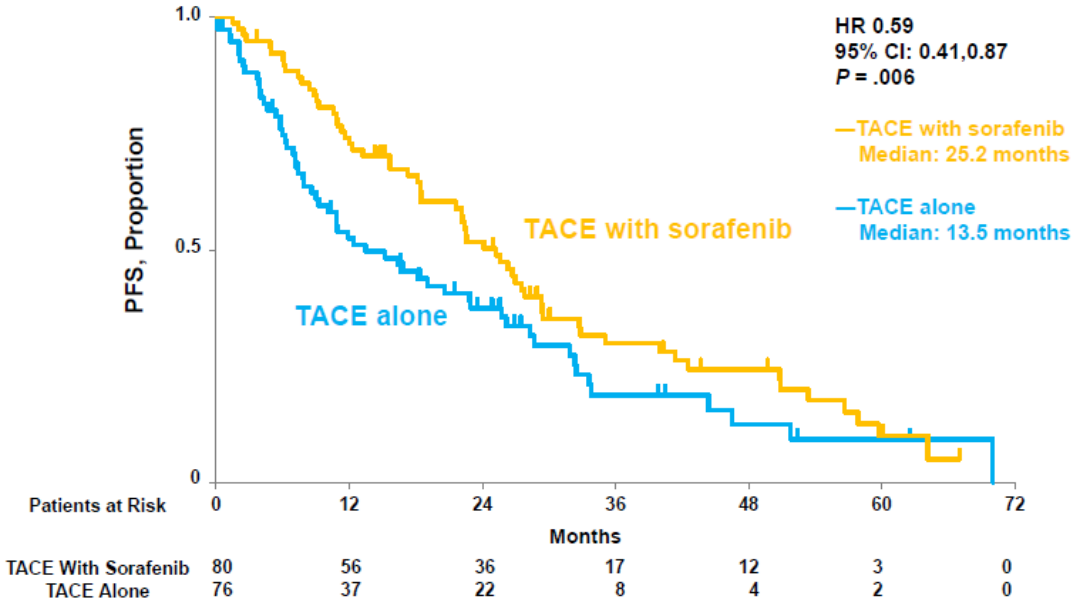
- Sorafenib 400 mg daily was started 2 to 3 weeks before 1st TACE to check the tolerability and to block the VEGF receptors after TACE followed by 800 mg daily
- Sorafenib was interrupted 2 days before and 3 days after each TACE session as long as organ function is maintained within TACE restarting criteria
- Repeated TACE is recommended on demand when viable lesion is more than 50% compared with baseline tumor volume or in the investigator's discretion
- Radiological assessment was done every 8 weeks by investigators

Co-Primary Endpoint
PFS/OS (Gatekeeping strategy)

Secondary Endpoints
TTUP, TTP, ORR, Safety

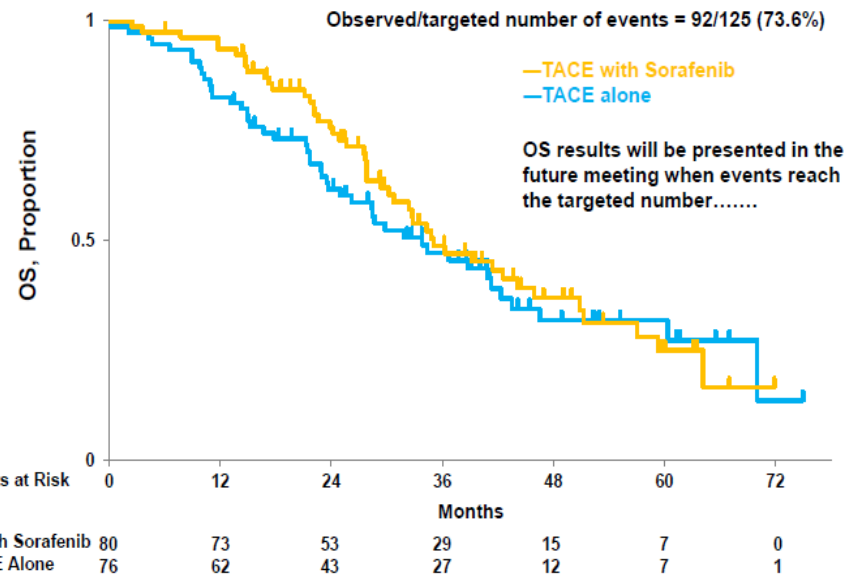
Hepatocellular Carcinoma – Sorafenib with LDT

Primary Endpoint: PFS



Kudo M, et al. *J Clin Oncol.* 2018;36(suppl): Abstract 4017.

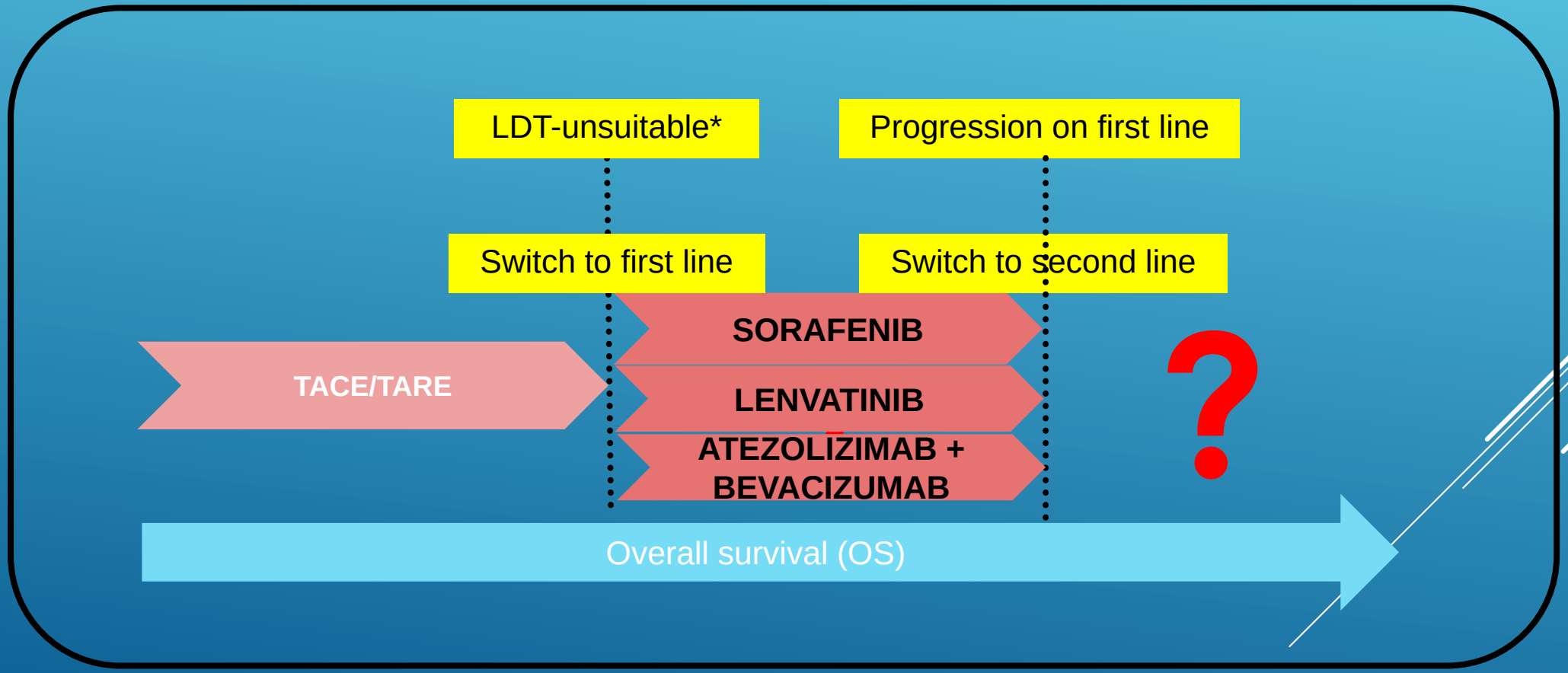
Co-Primary Endpoint: OS (Preliminary)



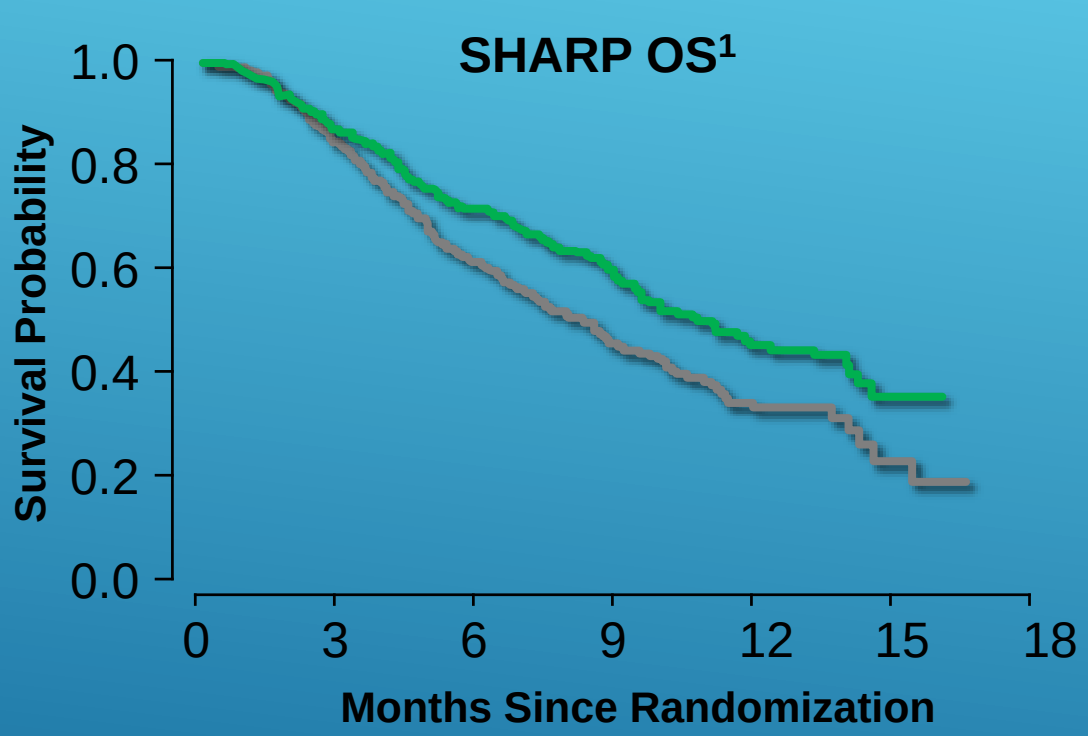
Maturity 73.6%

Kudo M, et al. *J Clin Oncol.* 2018;36(suppl): Abstract 4017.

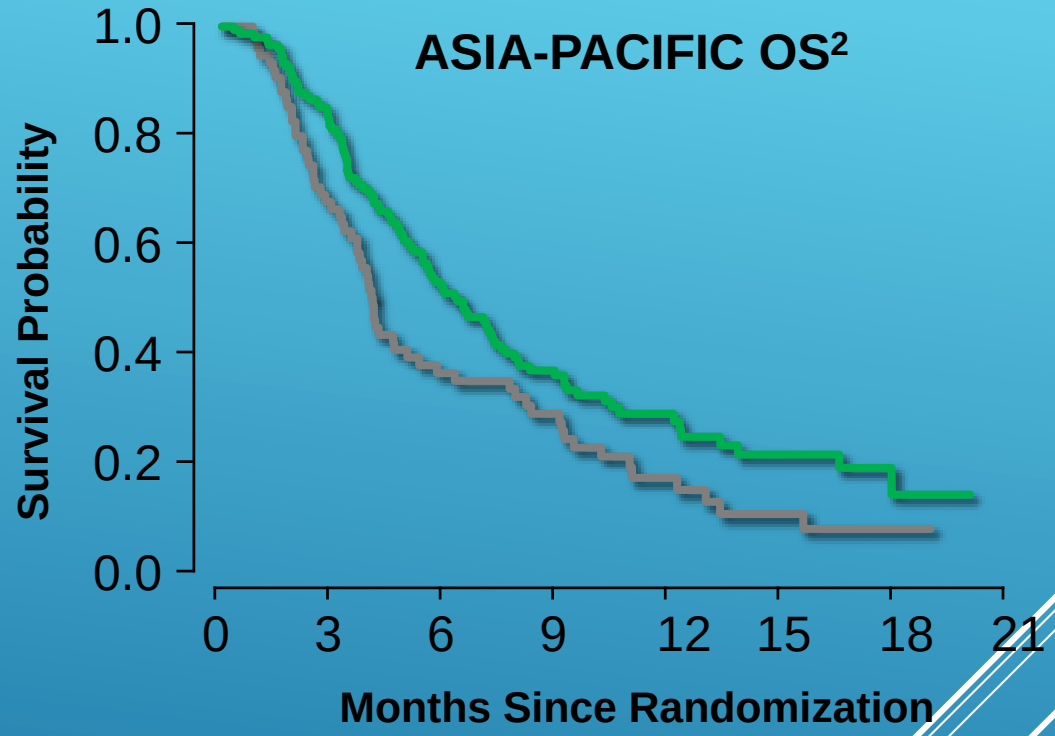
Hepatocellular Carcinoma – Systemic therapy



Hepatocellular Carcinoma – Systemic therapy



	Sorafenib (n=299)	Placebo (n=303)
Median OS	10.7 months	7.9 months
HR: 0.69; 95% CI, 0.55-0.87 *P*<0.001		



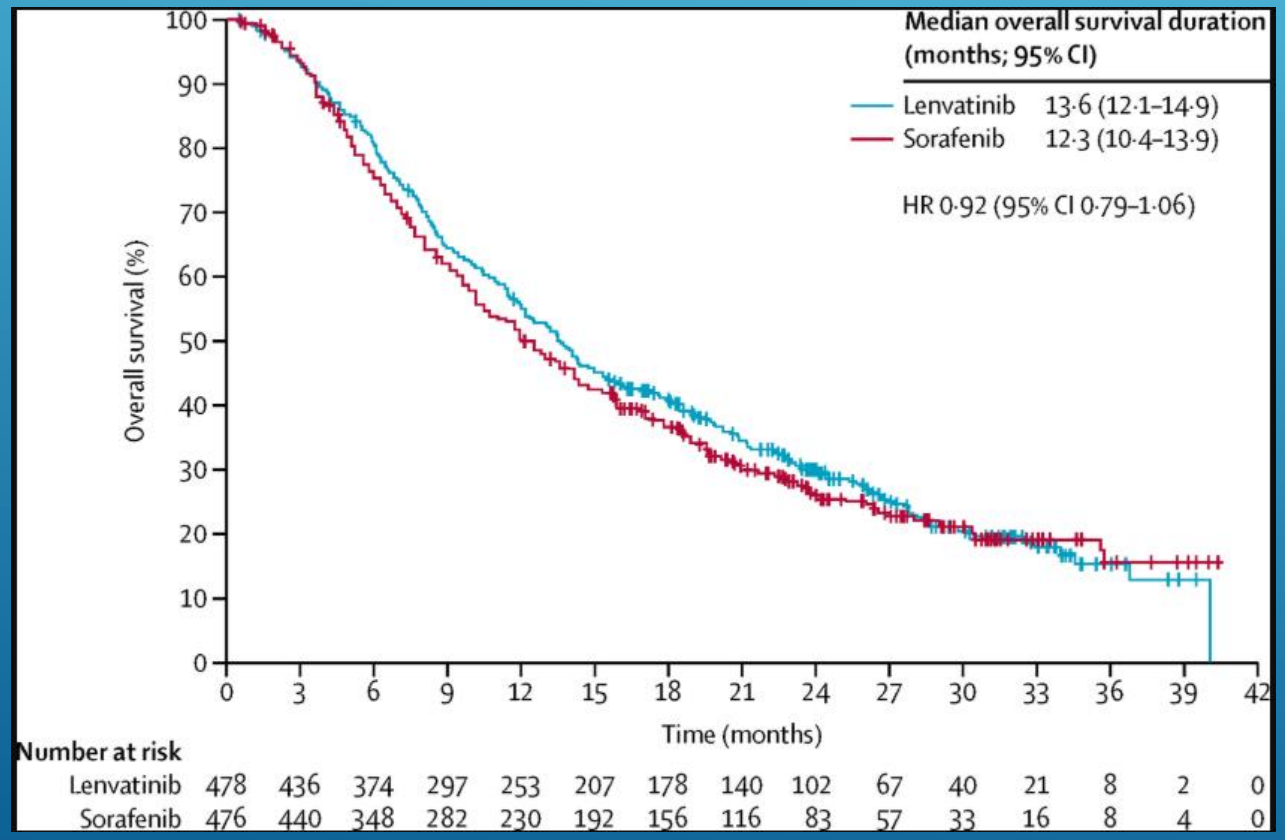
	Sorafenib (n=150)	Placebo (n=76)
Median OS	6.5 months	4.2 months
HR: 0.68; 95% CI, 0.50-0.93 *P*=0.014		

HR, hazard ratio.

1. Llovet J, et al. N Engl J Med. 2008;359:378-390. 2. Cheng A-L, et al. Lancet Oncol. 2009;10:25-34.

Hepatocellular Carcinoma – Systemic therapy

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

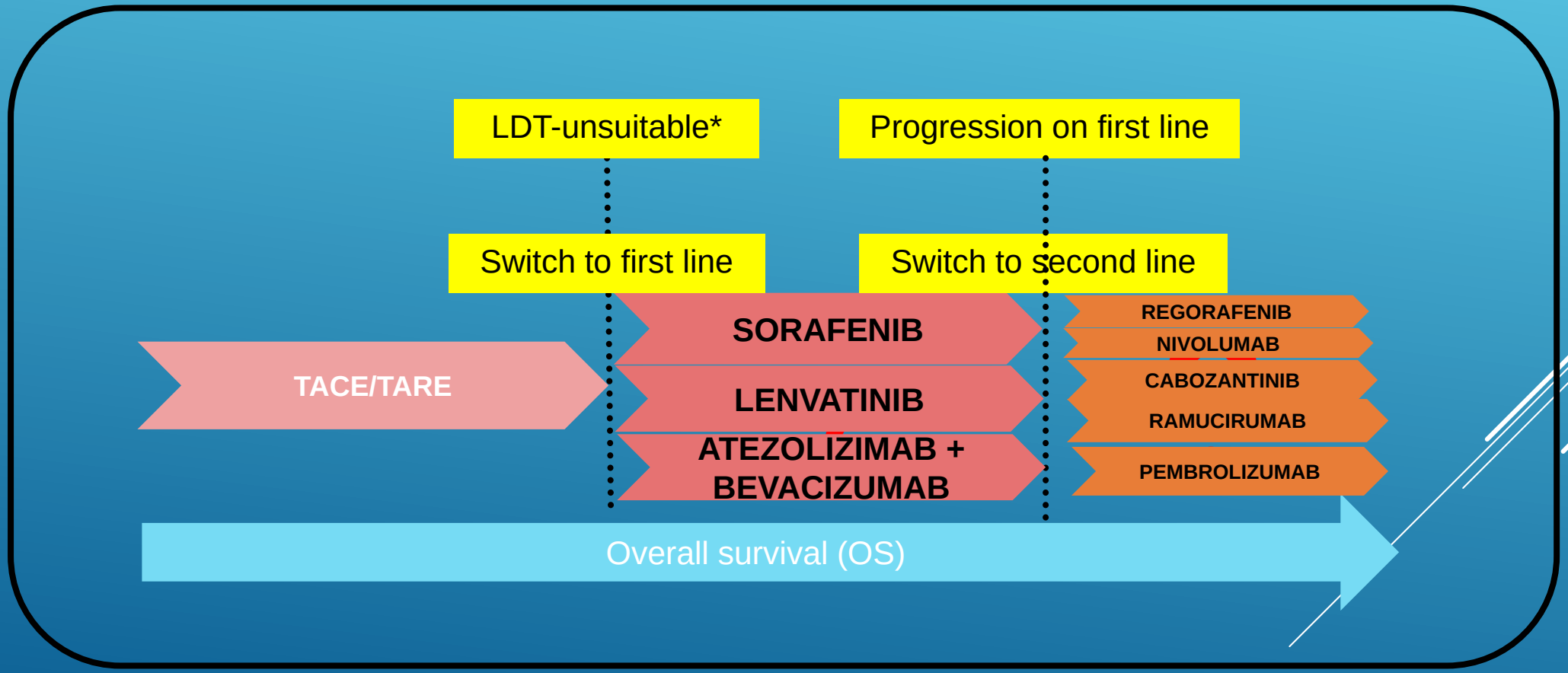


Adverse events

Lenvatinib – HTN, diarrhoea, fatigue, decreased appetite and decreased weight.

Sorafenib – HFS, diarrhoea, hypertension, and decreased appetite

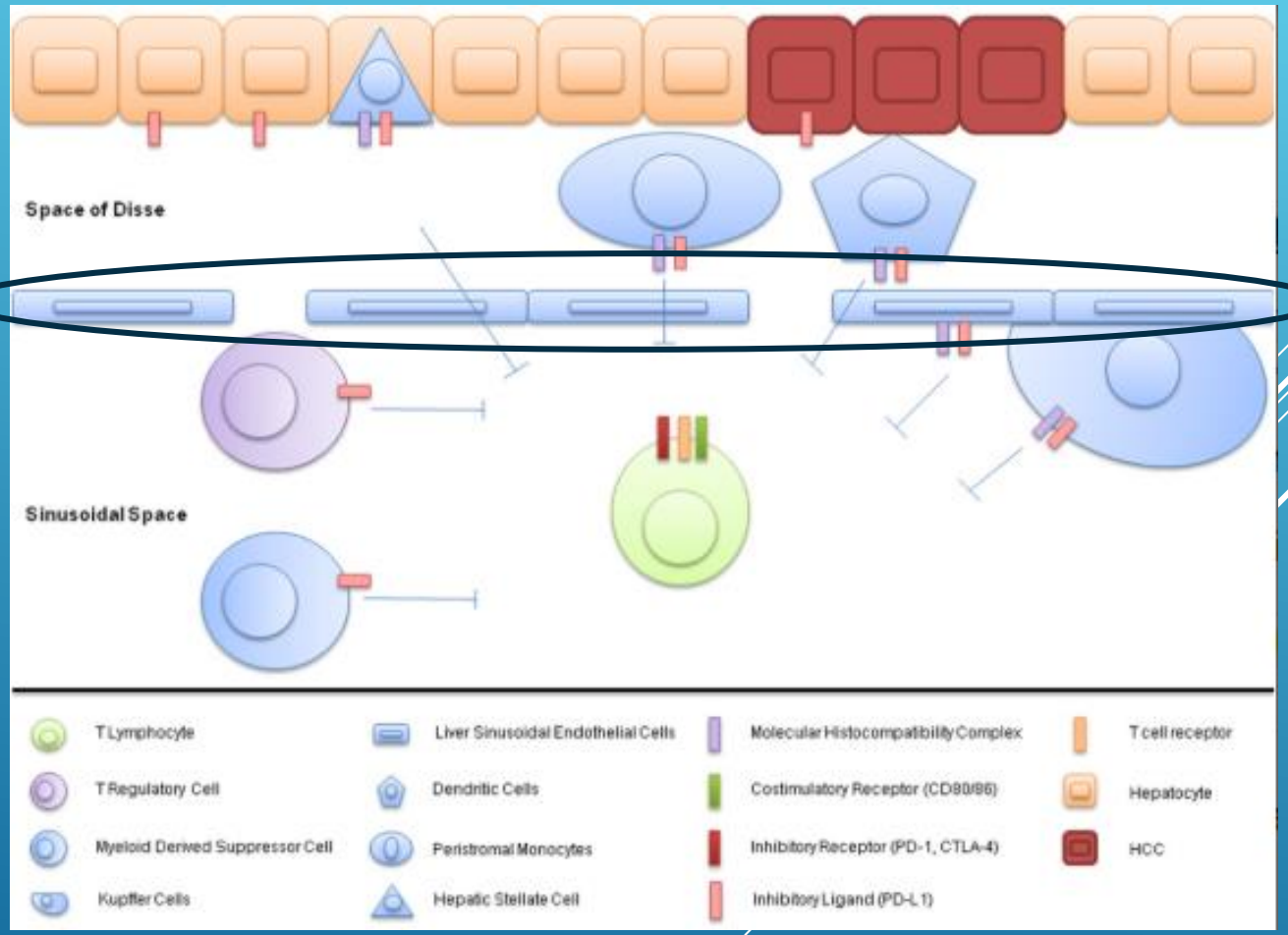
Hepatocellular Carcinoma – Systemic therapy



Hepatocellular Carcinoma – Systemic therapy

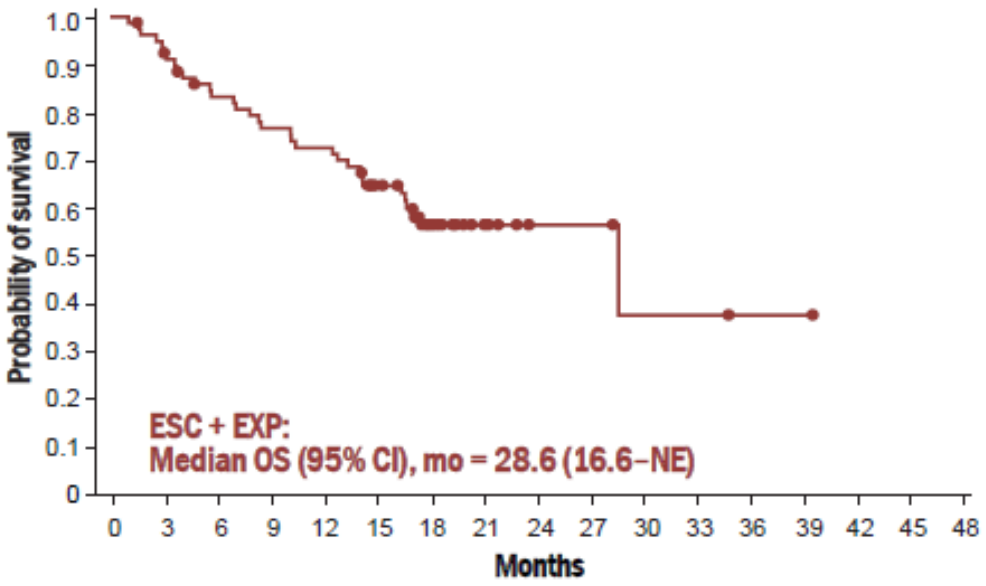
Conceptual points

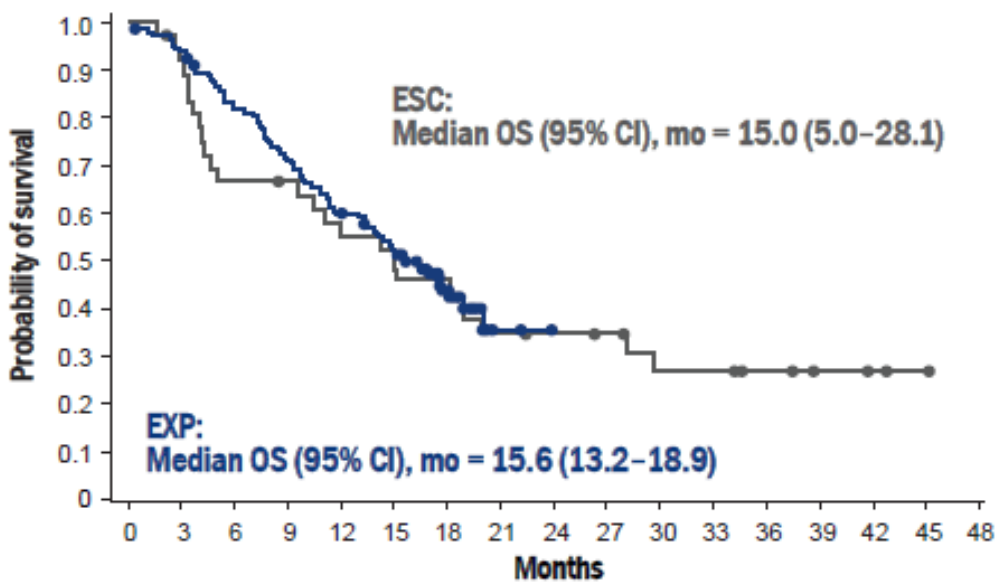
- Immunologic composition of the liver plays a central role in host defense and the maintenance of self-tolerance
- LSECs express high levels of PD-L1 and low levels of the costimulatory molecules CD80 and CD86.
- MHC downregulation by LSEC
- Chronically inflamed livers, create a microenvironment that favors T-cell exhaustion and immunosuppressive environment.



Hepatocellular Carcinoma – Systemic therapy

NIVOLUMAB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (CHECKMATE 040): AN OPEN-LABEL, NON-COMPARATIVE, PHASE 1/2 DOSE ESCALATION AND EXPANSION TRIAL





OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

Kaplan-Meier method; closed circles denote censored patients.

GALLBLADDER CANCERS

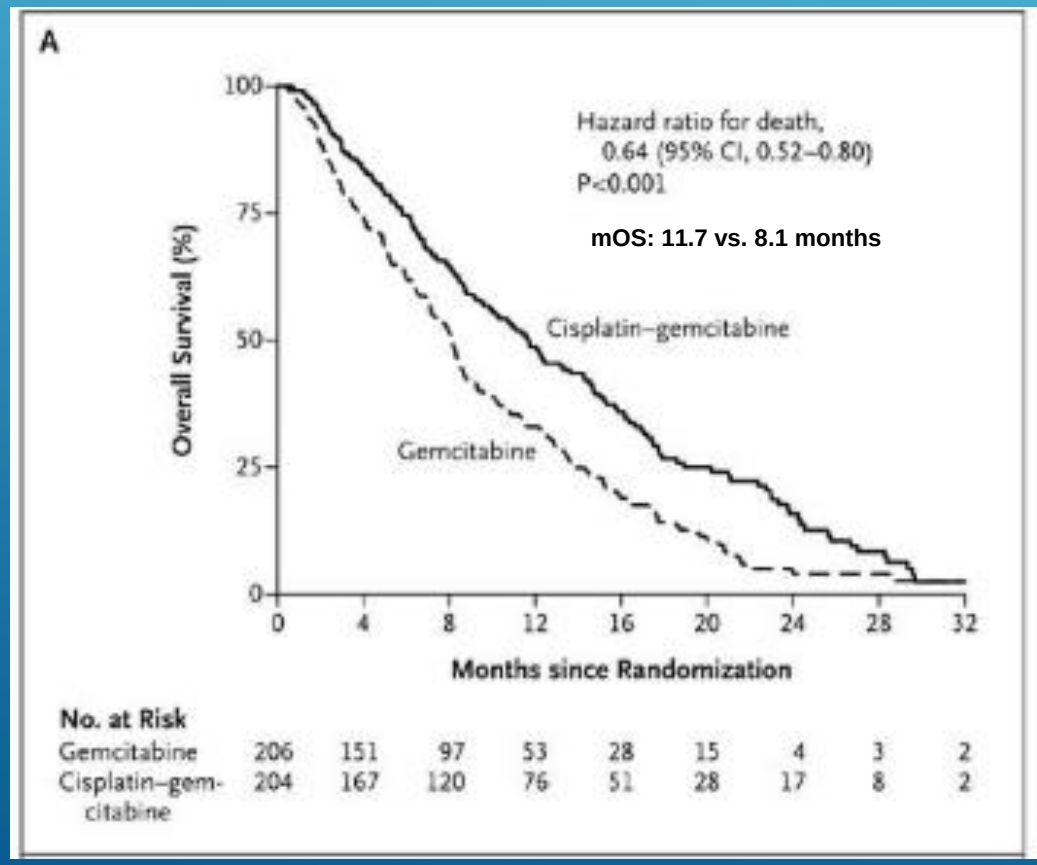
- *Therapy in advanced/metastatic disease*
- *Adjuvant chemotherapy in operated cancers*
- *Emerging concept of neoadjuvant therapy*

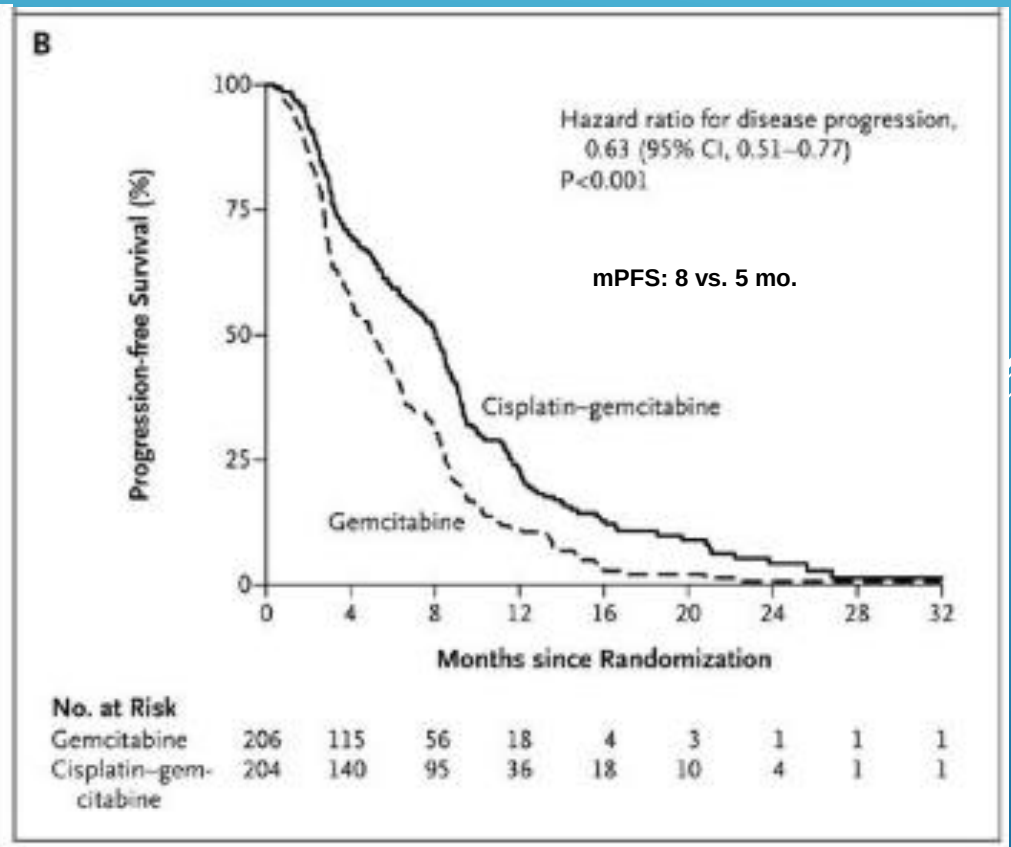
Gallbladder cancers – advanced/metastatic disease

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoney, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D. for the ABC-02 Trial Investigators*





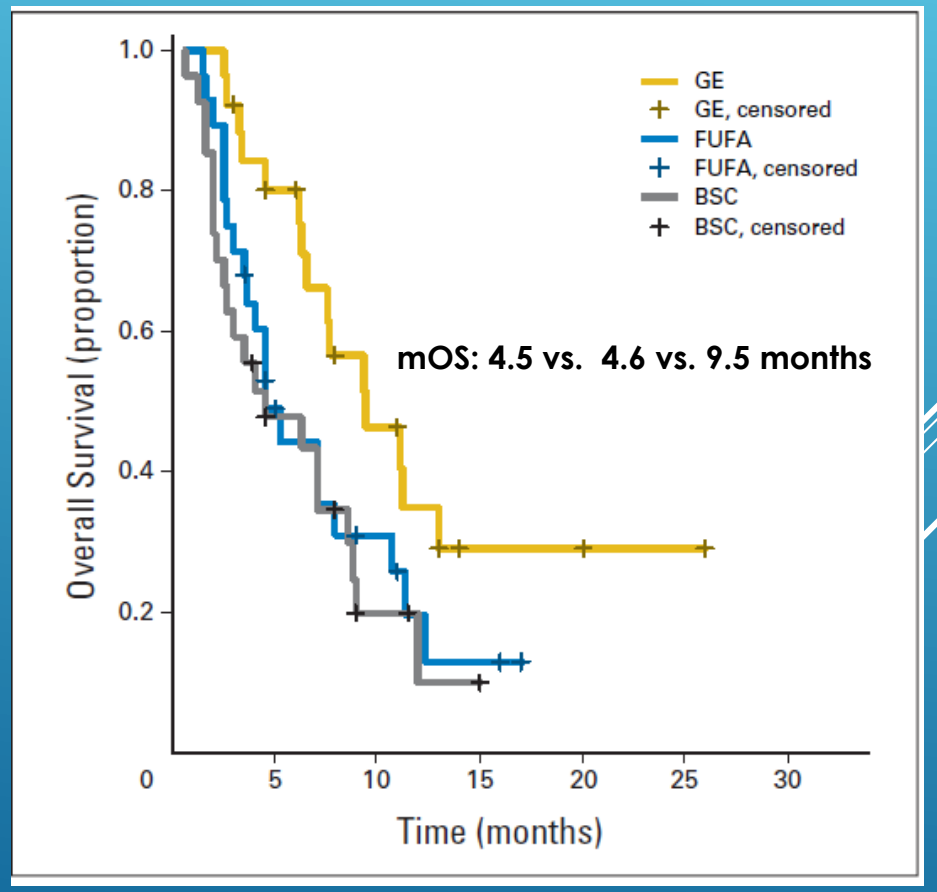
Gallbladder cancers – advanced/metastatic disease

Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study.

RCT

81 patients

3 arm study

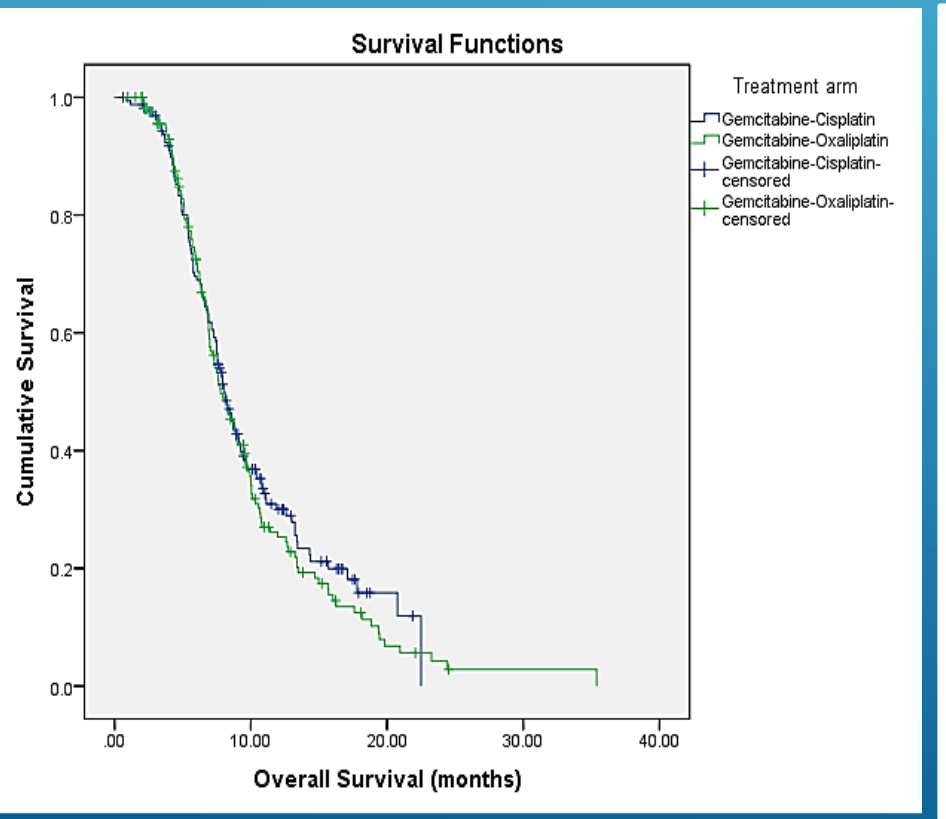


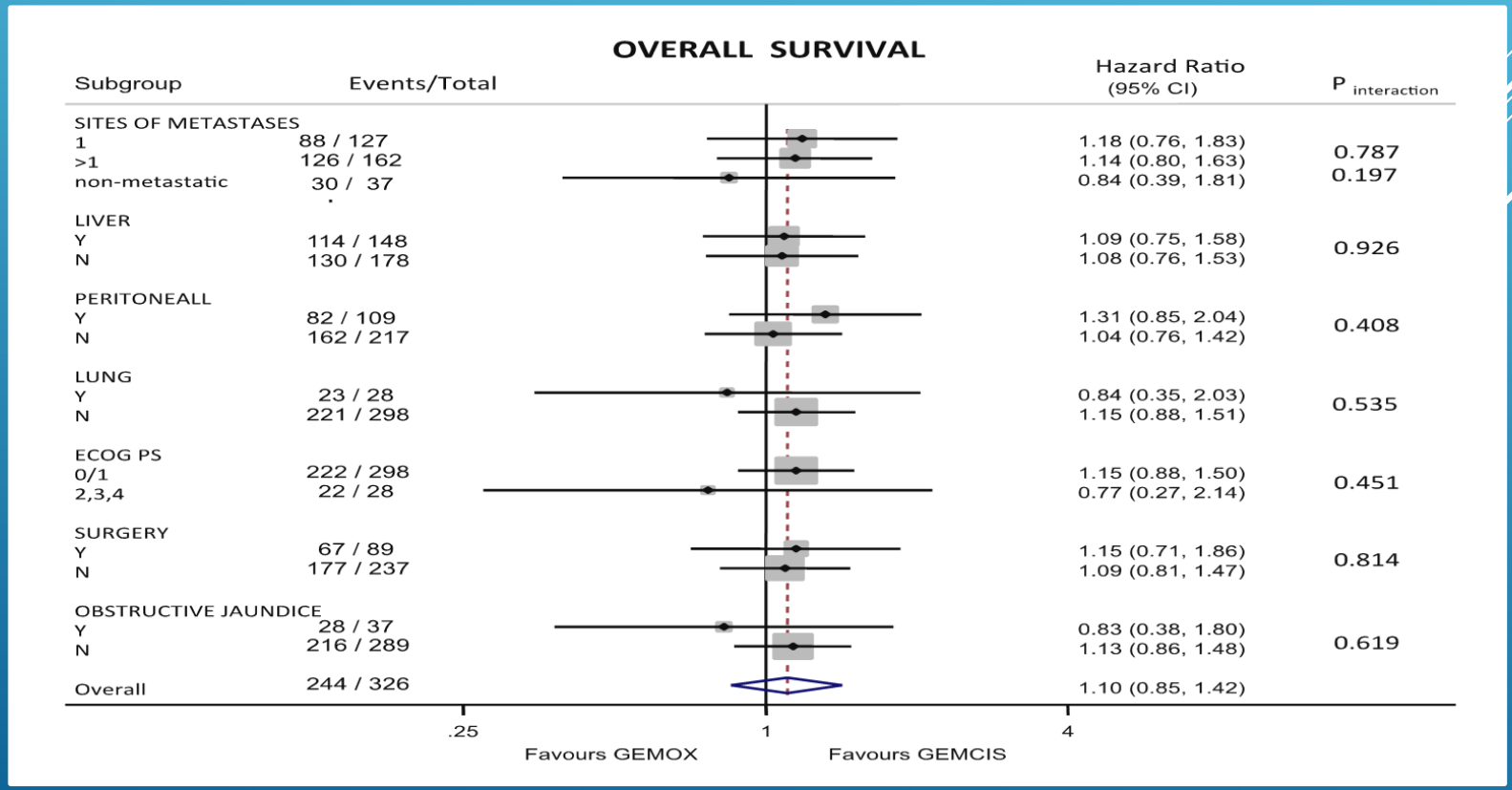
Gallbladder cancers – advanced/metastatic disease

Original Article

Gemcitabine-cisplatin versus gemcitabine-oxaliplatin doublet chemotherapy in advanced gallbladder cancers: a match pair analysis

Anant Ramaswamy, Vikas Ostwal ✉, Rakesh Pinniti, Sadhana Kannan, Prabhat Bhargava, Chaitali Nashikkar, Jimmy Mirani, Shripad Banavali





Gallbladder cancers – adjuvant therapy

NEED FOR ADJUVANT

- For T1a disease, simple cholecystectomy with negative cystic duct margin followed by ***observation***
- T1b tumors– radical cholecystectomy <-> ***equipoise (observation vs. adjuvant)***
- T2 and beyond; Node Positive tumors – radical resection followed by ***adjuvant therapy***

Gallbladder cancers – adjuvant therapy

VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Therapy in the Treatment of Biliary Tract Cancer: A Systematic Review and Meta-Analysis

Anne M. Horgan, Eitan Amir, Thomas Walter, and Jennifer J. Knox

Methods

Studies published between 1960 and November 2010, which evaluated adjuvant chemotherapy (CT), radiotherapy (RT), or both (CRT) compared with curative-intent surgery alone for resected BTC were included. Only tumors of the gallbladder and bile ducts were assessed. Published data were extracted and computed into odds ratios (ORs) for death at 5 years. Subgroup analyses of benefit based on lymph node (LN) or resection margin positivity (R1) were prespecified. Data were weighted by generic inverse variance and pooled using random-effect modeling.

Results

Twenty studies involving 6,712 patients were analyzed. There was a nonsignificant improvement in overall survival with any AT compared with surgery alone (pooled OR, 0.74; $P = .06$). There was no difference between gallbladder and bile duct tumors ($P = .68$). The association was significant when the two registry analyses were excluded. Those receiving CT or CRT derived statistically greater benefit than RT alone (OR, 0.39, 0.61, and 0.98, respectively; $P = .02$). The greatest benefit for AT was in those with LN-positive disease (OR, 0.49; $P = .004$) and R1 disease (OR, 0.36; $P = .002$).

Conclusion

This analysis supports AT for BTC. Prospective randomized trials are needed to provide better rationale for this commonly used strategy. On the basis of our data, such trials could involve two active comparators rather than a no-treatment arm among patients with LN-positive or R1 disease.

Gallbladder cancers – adjuvant therapy

Ma et al. BMC Cancer (2015) 15:615
DOI 10.1186/s12885-015-1617-y

BMC Cancer

RESEARCH ARTICLE Open Access

Adjuvant therapy in the treatment of gallbladder cancer: a meta-analysis

Ning Ma[1,2], Hui Cheng[3], Baodong Qin[1], Renqian Zhong[1*] and Bin Wang[4*]

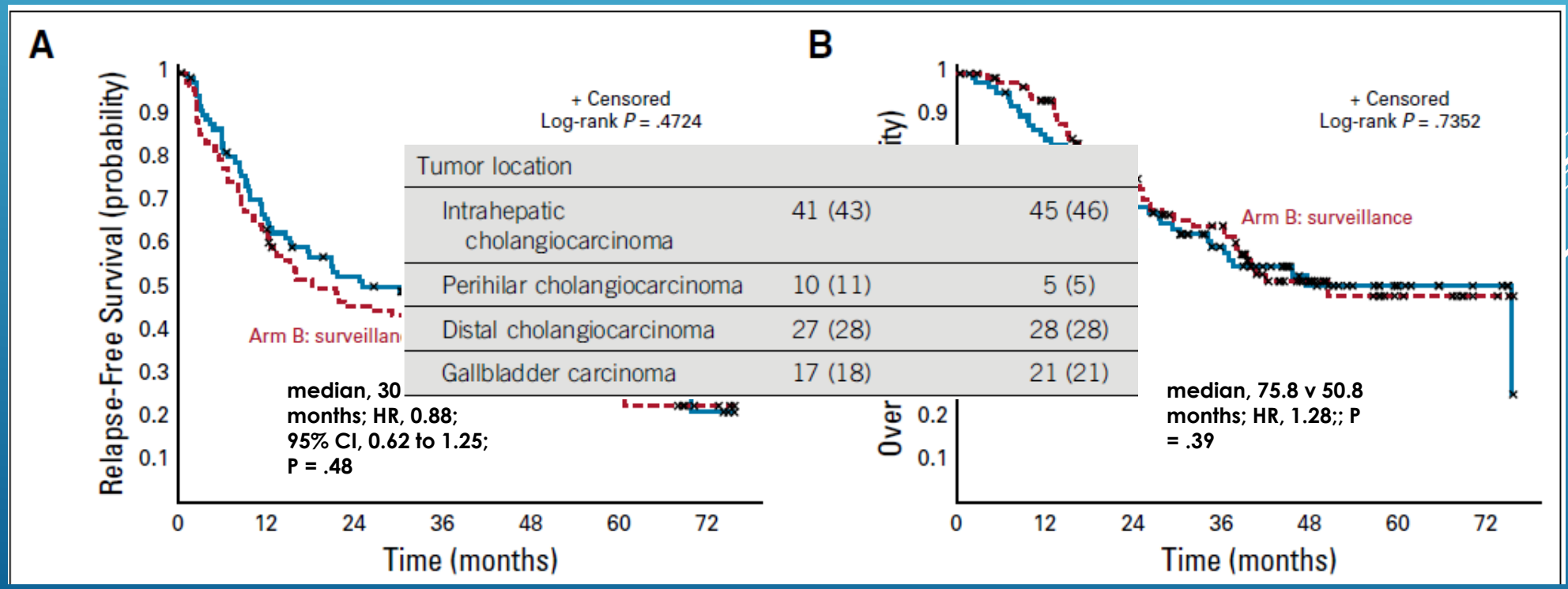
Methods: We used data from MEDLINE, EMBASE and the Cochrane Collaboration Library and published between October 1967 and October 2014. Studies that evaluated AT compared with curative-intent surgery alone for resected GBC were included. Subgroup analyses of benefit based on node status, margins status, and American Joint Committee on Cancer (AJCC) staging were prespecified. Data were weighted and pooled using random-effect modeling.

Results: Ten retrospective studies involving 3,191 patients were analyzed. There was a nonsignificant improvement in OS with AT compared with surgery alone (hazard ratio [HR], 0.76; 95 % confidence interval [CI], 0.56–1.03). A significant improvement was observed in OS with chemotherapy (CT) compared with surgery alone (HR, 0.42; 95 % CI, 0.22–0.80) by sensitivity analysis. The greatest benefit for AT was also observed in those with R1 disease (HR, 0.33; 95 % CI, 0.19–0.59), LN-positive disease (HR, 0.71; 95 % CI, 0.63–0.81), and AJCC staging meeting or exceeding tumor Stage II (HR, 0.45; 95 % CI, 0.26–0.79), but not in those with LN-negative or R0 disease.

Conclusion: Our results strongly support the use of CT as an AT in GBC. Moreover, patients with node positivity, margin positivity, or non-stage I disease are more likely to benefit from AT.

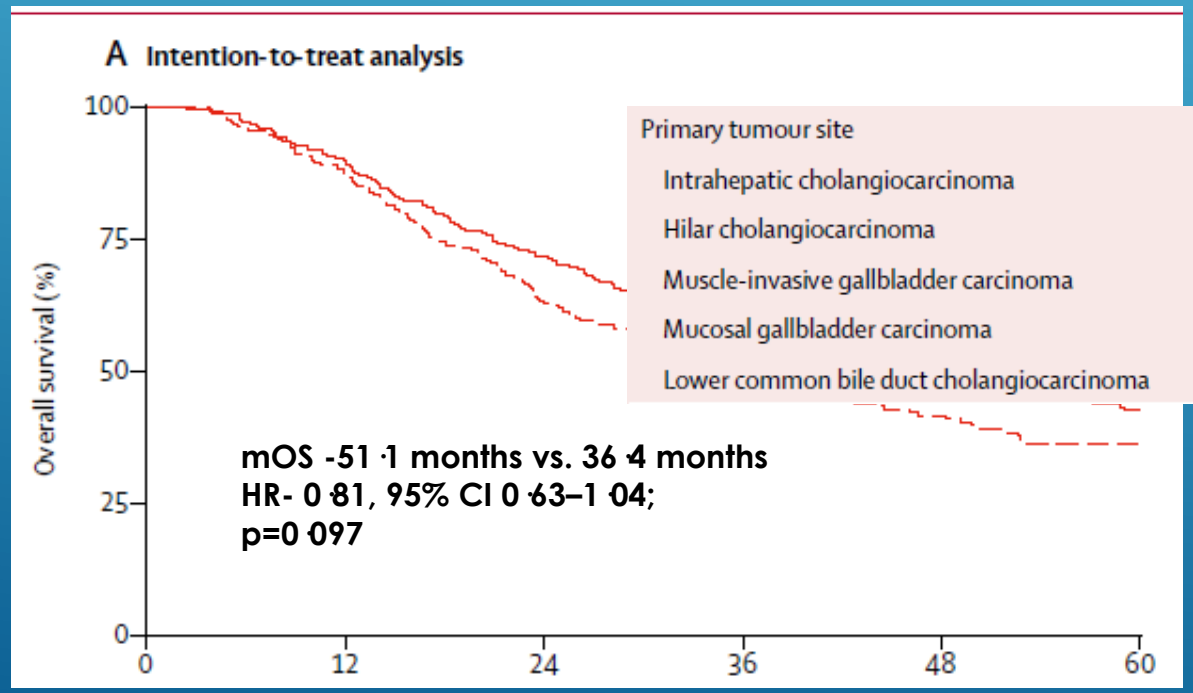
Gallbladder cancers – adjuvant therapy

Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): A Randomized Phase III Study

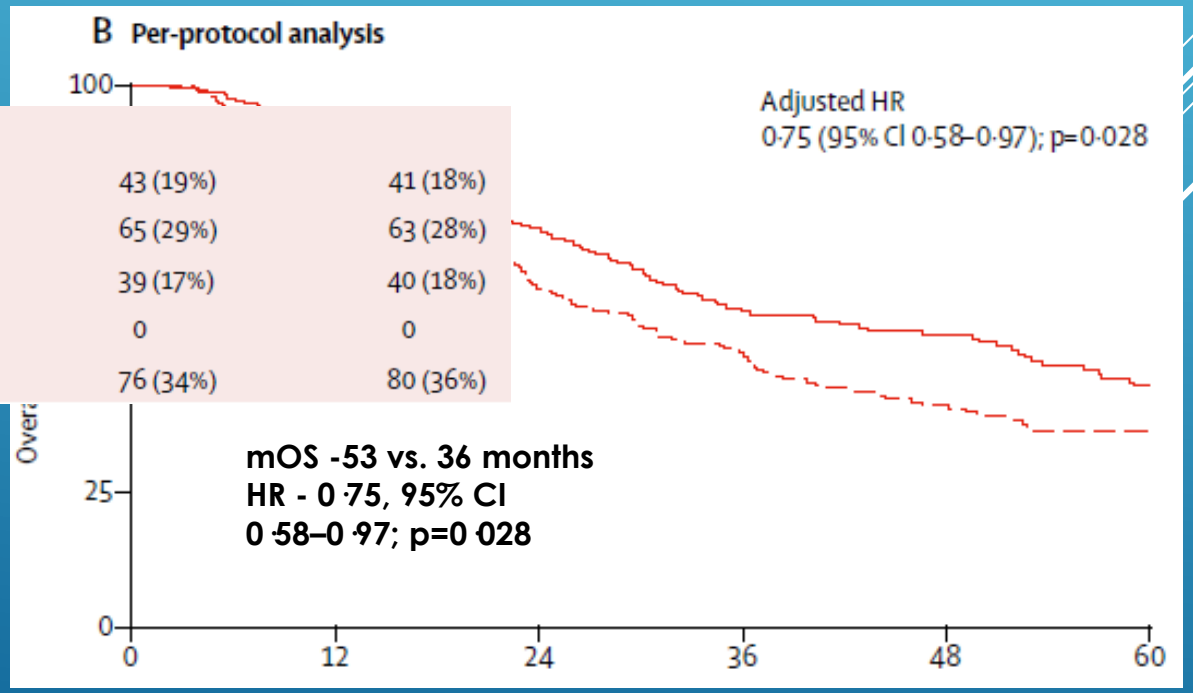


Gallbladder cancers – adjuvant therapy

Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study



Primary tumour site		
Intrahepatic cholangiocarcinoma	43 (19%)	41 (18%)
Hilar cholangiocarcinoma	65 (29%)	63 (28%)
Muscle-invasive gallbladder carcinoma	39 (17%)	40 (18%)
Mucosal gallbladder carcinoma	0	0
Lower common bile duct cholangiocarcinoma	76 (34%)	80 (36%)

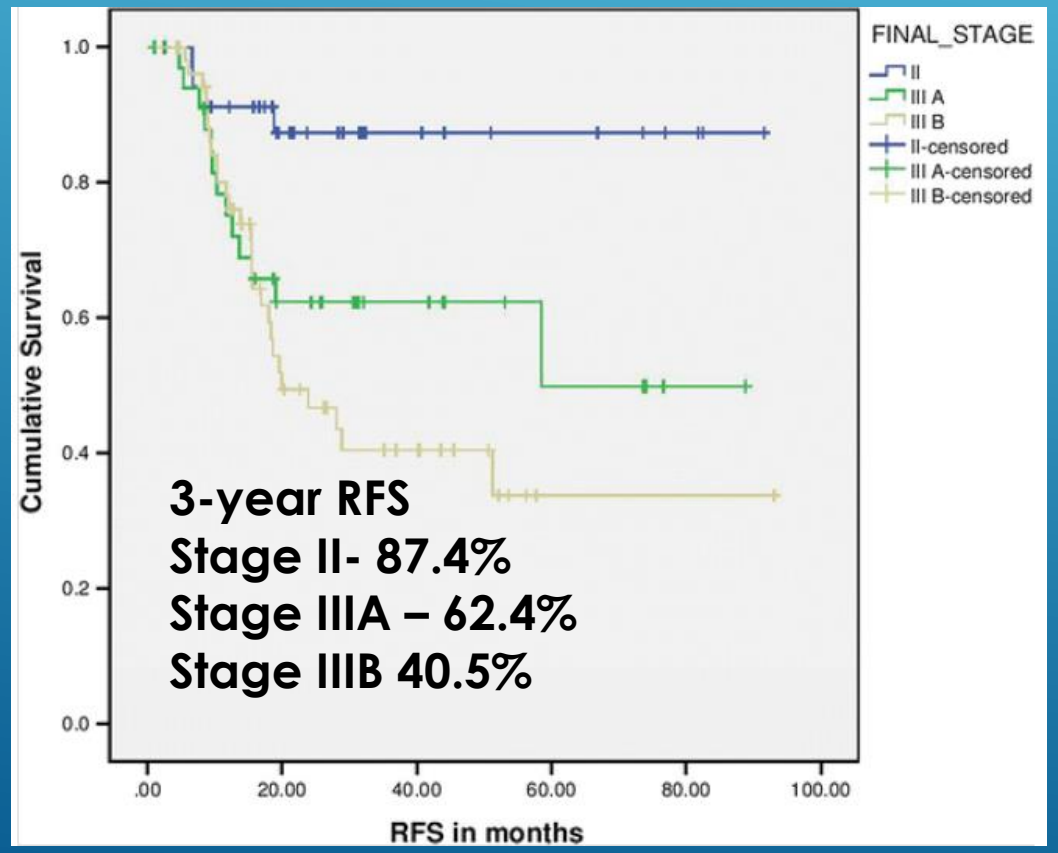


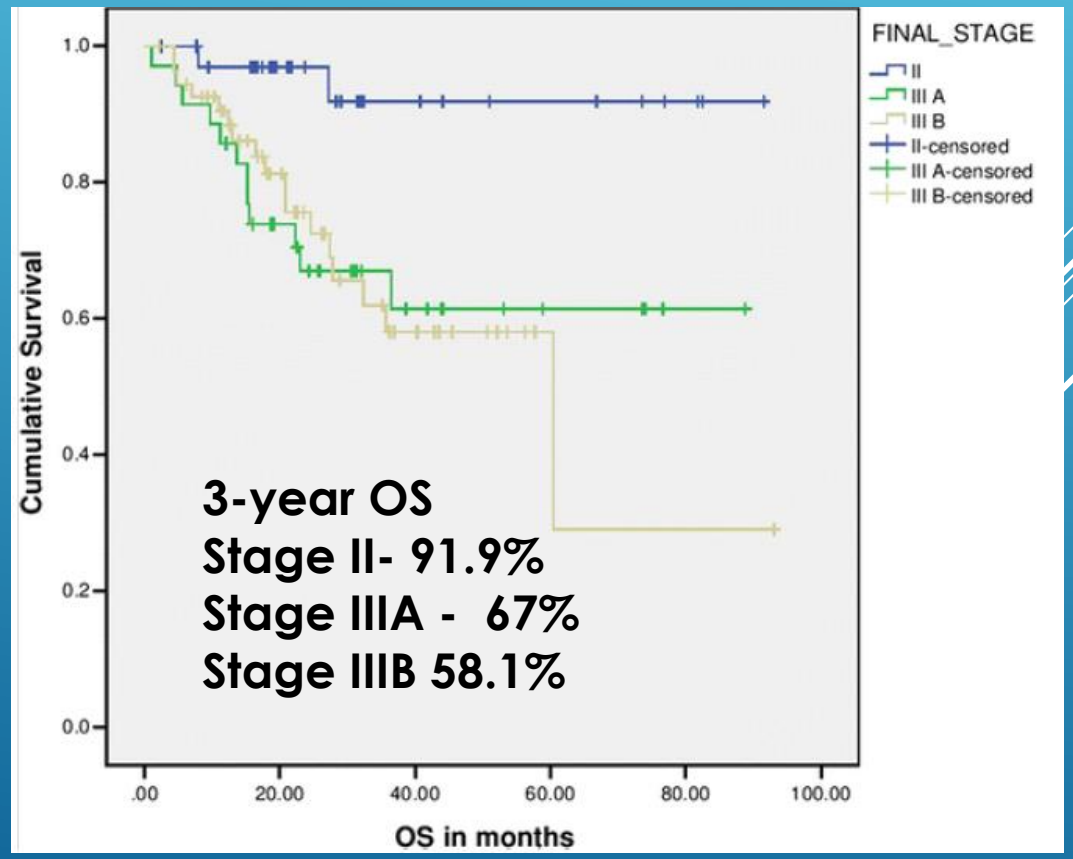
Gallbladder cancers – adjuvant therapy

Med Oncol. 2018 Mar 21;35(4):57. doi: 10.1007/s12032-018-1115-6.

Gemcitabine-cisplatin (GC) as adjuvant chemotherapy in resected stage II and stage III gallbladder cancers (GBC): a potential way forward.

Ostwal V[1], Swami R[1], Patkar S[2], Majumdar S[1], Goel M[2], Mehta S[3], Engineer R[4], Mandavkar S[1], Kumar S[5], Ramaswamy A[6].





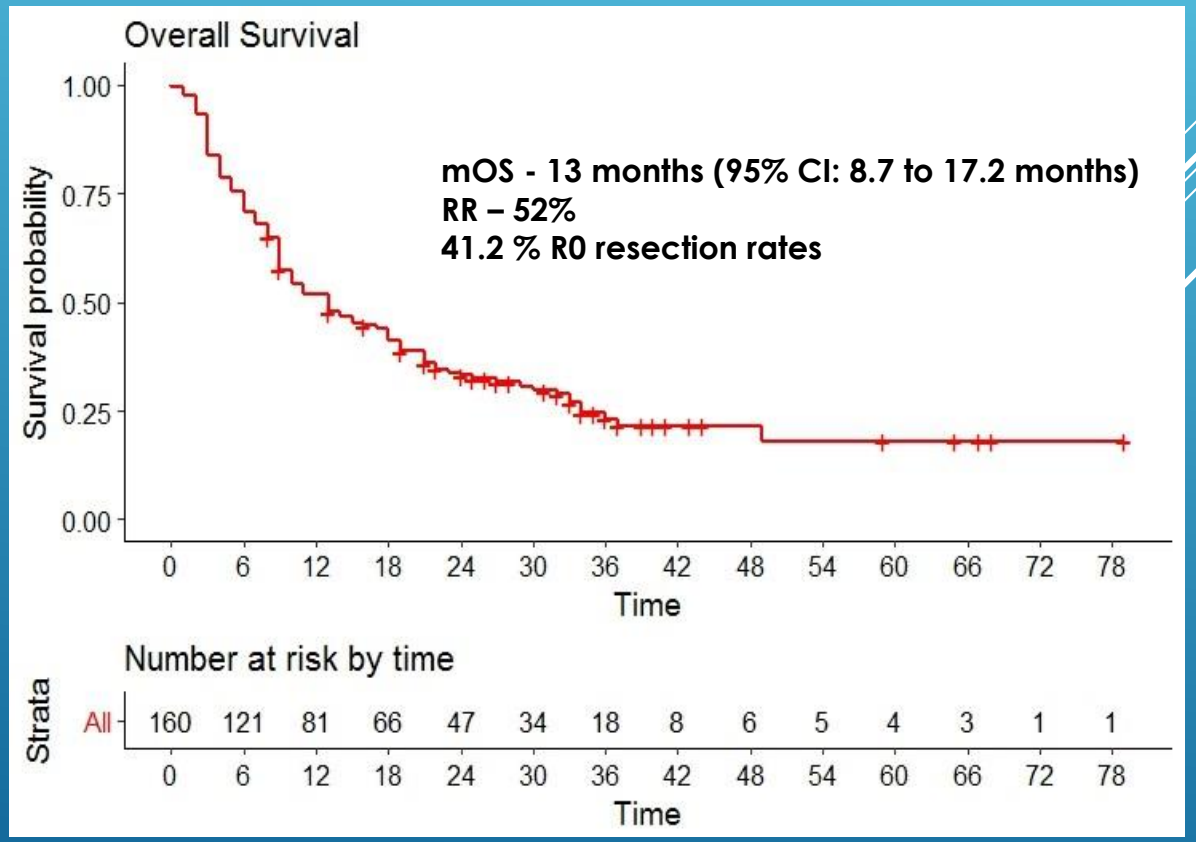
Gallbladder cancers – neoadjuvant therapy

HPB (Oxford). 2018 Sep;20(9):841-847. doi: 10.1016/j.hpb.2018.03.008. Epub 2018 Apr 26.

Outcome of neoadjuvant chemotherapy in "locally advanced/borderline resectable" gallbladder cancer: the need to define indications.

Chaudhari VA[1], Ostwal V[2], Patkar S[1], Sahu A[2], Toshniwal A[2], Ramaswamy A[2], Shetty NS[3], Shrikhande SV[1], Goel M[4].

TUMOR **(T3-T4 tumors)**	▪ **Contiguous Liver involvement > 2cm** ▪ **Involvement of bile duct causing obstructive jaundice (Type I/II block on MRCP/ERCP/PTBD)** ▪ **Radiological / Endoscopic involvement of antropyloric region of stomach, duodenum, hepatic flexure of colon or small intestine**
NODE **(N1 station)**	Radiological suspicion of lymph node involvement N1 ▪ Hepatic artery (Station 8), ▪ Hepatoduodenal ligament (Station12), ▪ Retropancreatic / retroduodenal (Station 13) Size > 1cm in short axis, round in shape, and heterogenous enhancement on CT/PET scan.
VASCULAR **(T4 tumors)**	impingement/ involvement (<180-degree angle) of one or more of the following blood vessels: ▪ Common Hepatic Artery and Right & Left Hepatic artery ▪ Main Portal vein and Right & Left Portal vein
FOR INCIDENTAL GBC	▪ Residual/Recurrent mass in GB fossa /liver bed ▪ N1 nodes as per nodal criteria. ▪ Involvement of bile duct causing OJ (Type I/II Block)



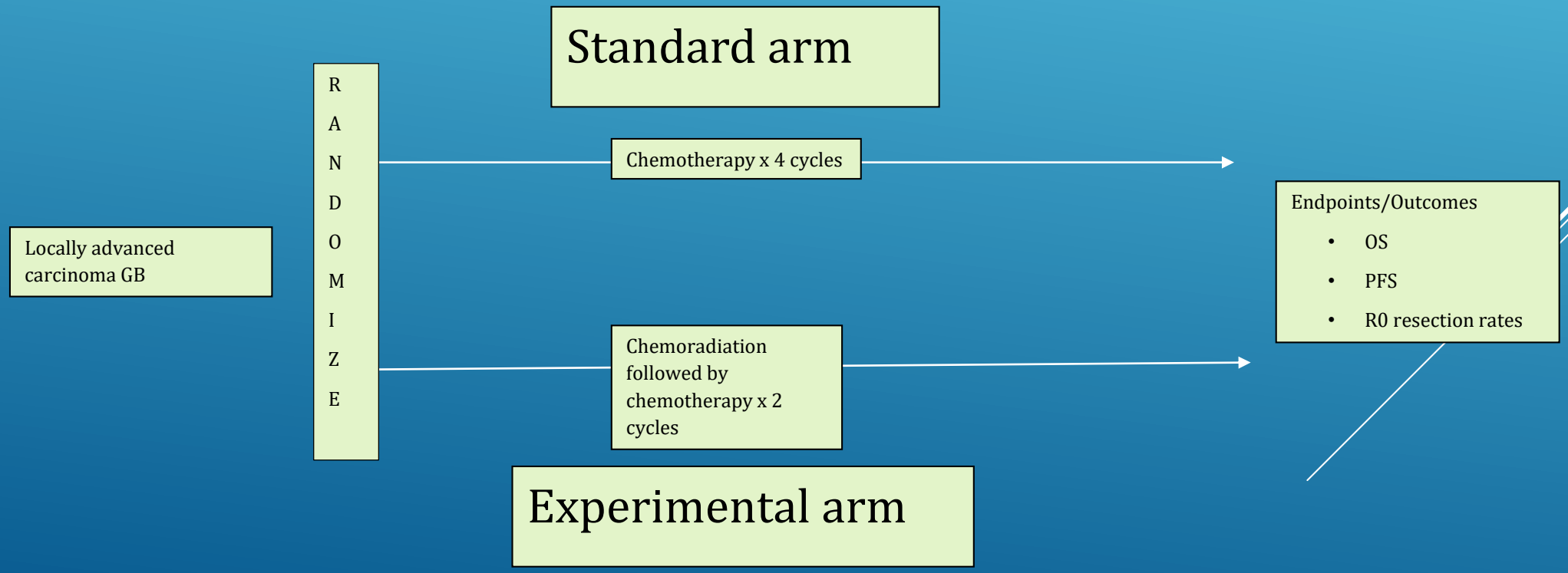
Gallbladder cancers – neoadjuvant therapy

ClinicalTrials.gov

Home > Search Results > Study Record Detail

Save this stu

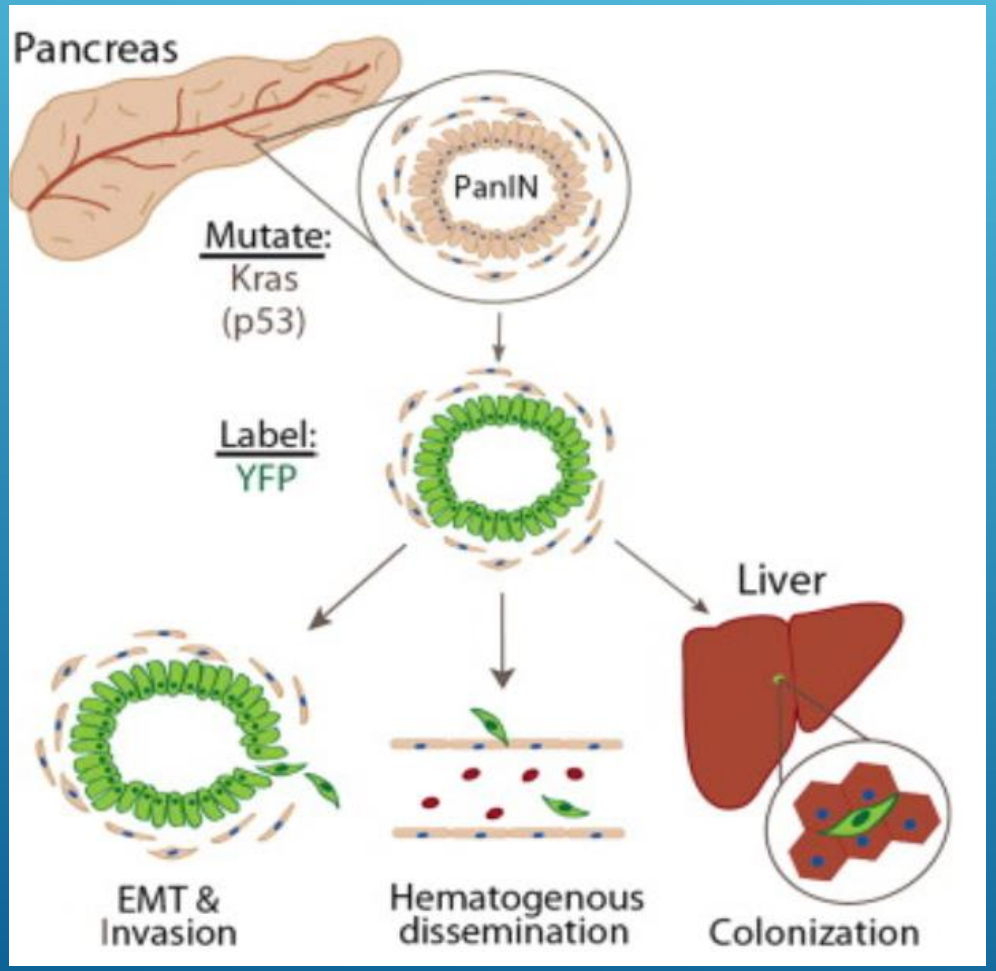
Perioperative Therapy Preoperative Chemotherapy Versus Chemoradiotherapy in Locally Advanced Gall Bladder Cancers (POLCAGB)



PANCREATIC DUCTAL ADENOCARCINOMAS (PDAC)

- *PDAC –a systemic disease*
- *Borderline resectable PDAC (BRPC)*
- *Adjuvant chemotherapy in resected PDAC*

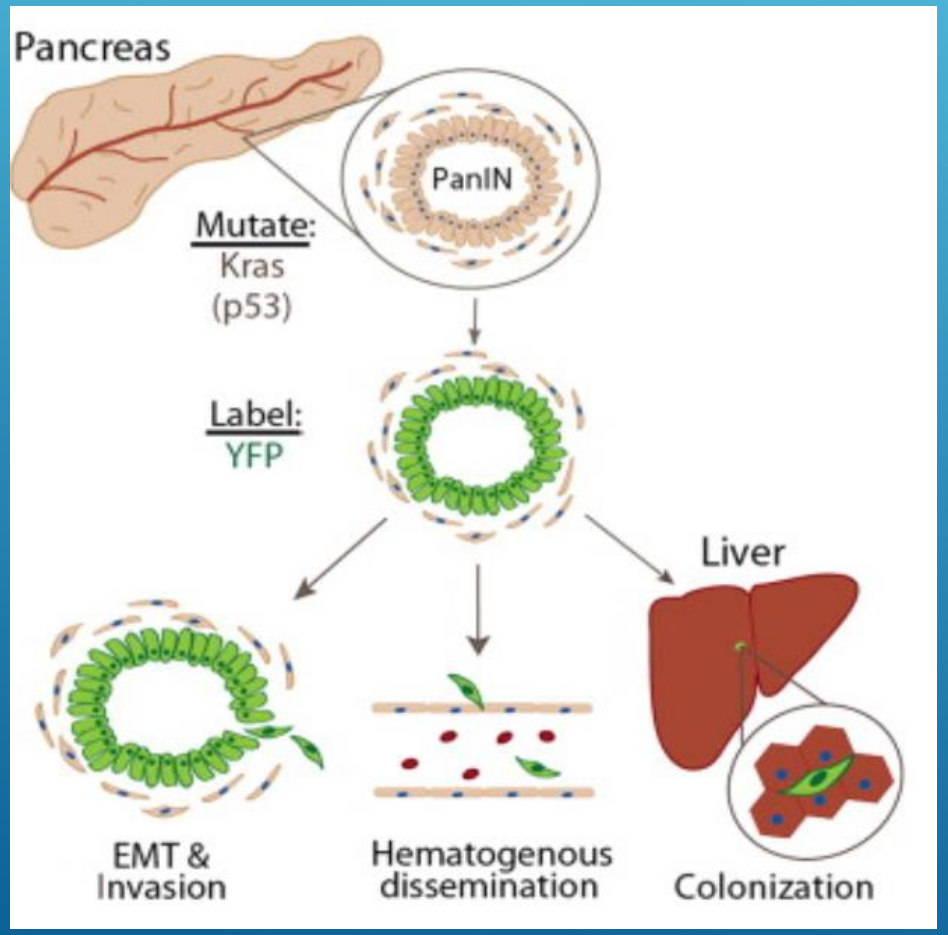
PDAC– A Systemic Disease



EMT, migration of epithelialy derived cells into the stroma, bloodstream entry, and seeding of the liver occur at a stage of pancreatic adenocarcinoma progression previously thought to be pre invasive based on standard histological examination.

EMT and dissemination precede pancreatic tumor formation. Cell. 2012 Jan 20;148(1-2):349-61

PDAC– A Systemic Disease



- Pancreatic cancer progression is a model in which the seeding of distant organs occurs before, and in parallel to, tumor formation at the primary site.
- A vast majority of patients with pancreatic cancer have metastatic disease at the time of diagnosis.
- Treatment with the immunosuppressive agent dexamethasone abolished dissemination.

EMT and dissemination precede pancreatic tumor formation. Cell. 2012 Jan 20;148(1-2):349-61

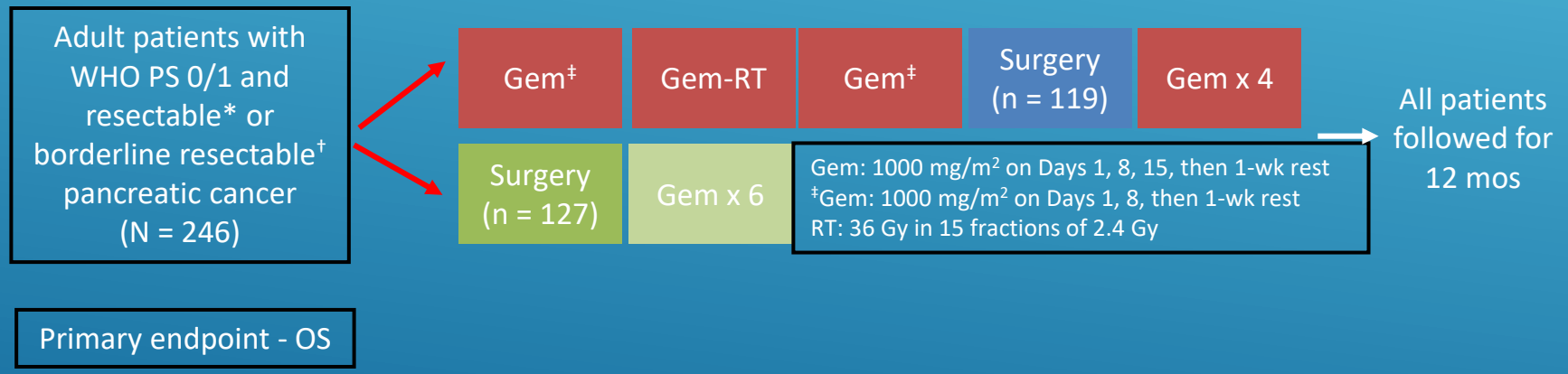
BRPC

Importance of the concept of BRPC

- High risk of a margin positive resection due to tumor-vessel (artery/vein) abutment (poorer outcomes/survival)
- Increased complexity of surgery due to vascular resections and reconstruction (perioperative morbidity and mortality)
- Increased risk for radiologically occult distant metastases (disease biology and avoidance of surgery)

BRPC

Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): A randomized, controlled, multicenter phase III trial



Slide credit: clinicaloptions.com

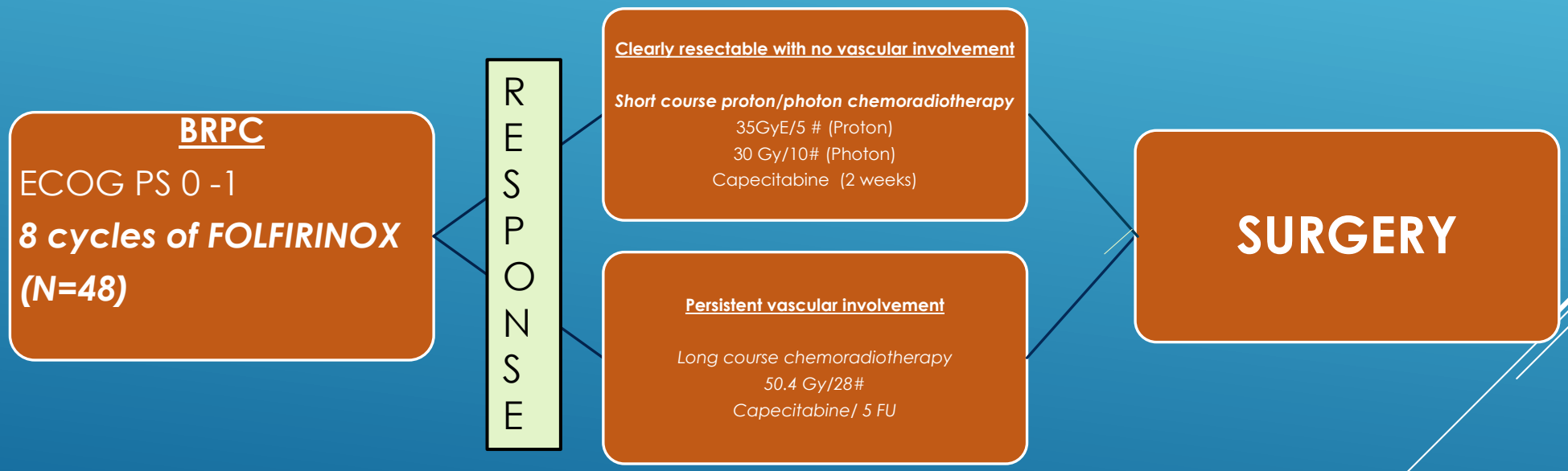
Journal of Clinical Oncology 36, no. 18_suppl, Published online June 07, 2018.

BRPC

Outcome	Preoperative Radiochemotherapy (n = 119)	Immediate Surgery (n = 127)	HR	*P* Value
Resection rate, n (%)	72 (60)	91 (72)	--	.065
R0 resection rate, n/N (%)	45/72 (63)	28/91 (31)	--	< .001
Median DFS, mos	9.9	7.9	0.71	.023
Serious AEs, n (%)	55 (46)	49 (39)	--	.28
ITT*	***17.1***	***13.7***	***0.74***	***.074***
Subset with R0/R1 resection†	***42.1***	***16.8***	***NR***	***< .001***

BRPC

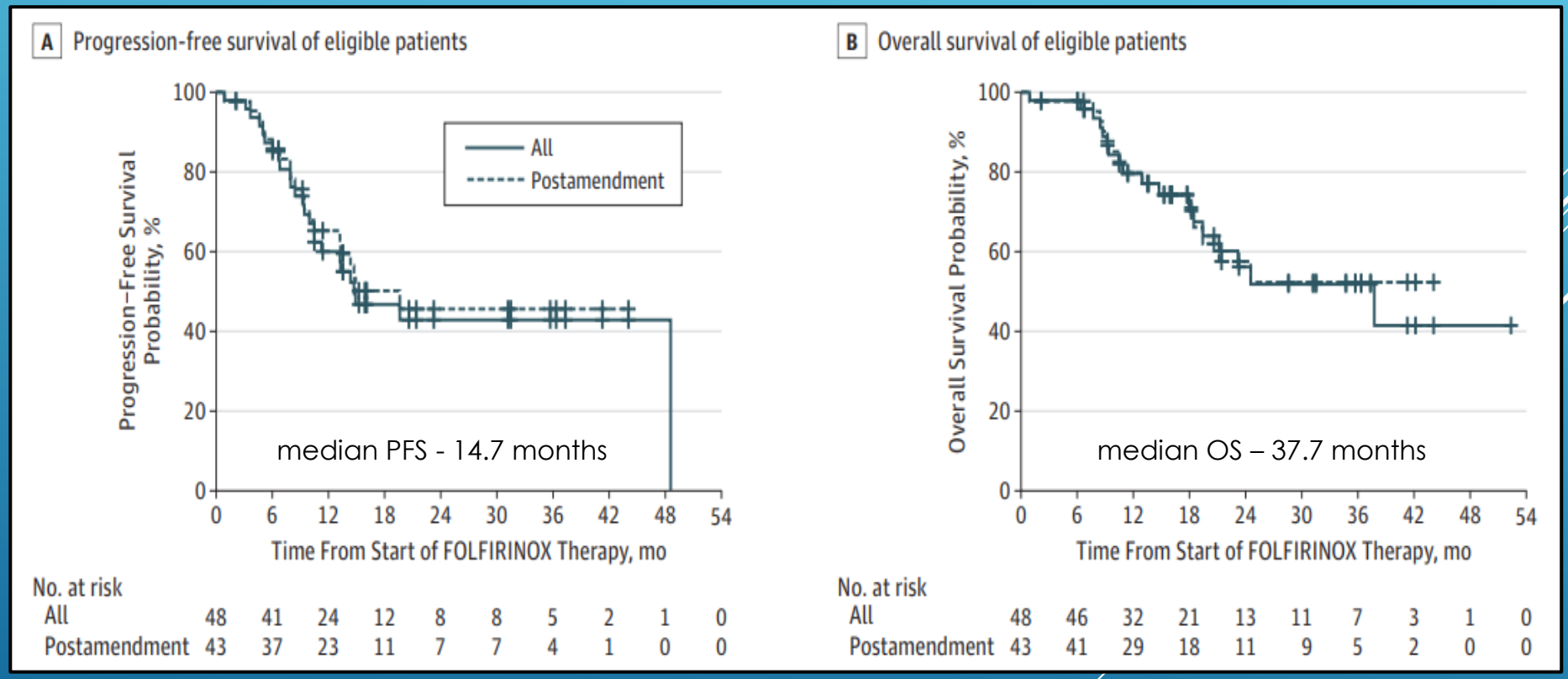
FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma - A Phase 2 Clinical Trial



JAMA Oncol. 2018;4(7):963-969

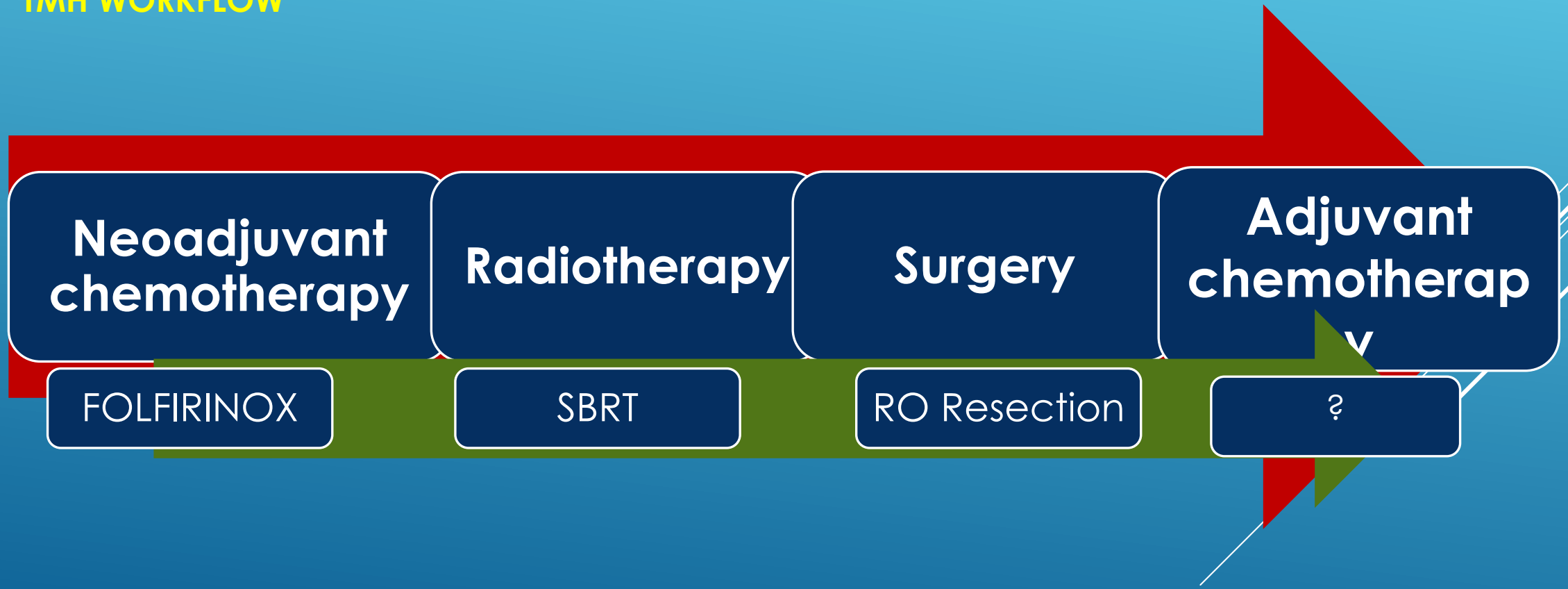
BRPC

- 79% completed 8 # FOLFIRINOX
- 32/48 patients resected
- 31/32 R0 resections
- Median follow up – 18 months



BRPC

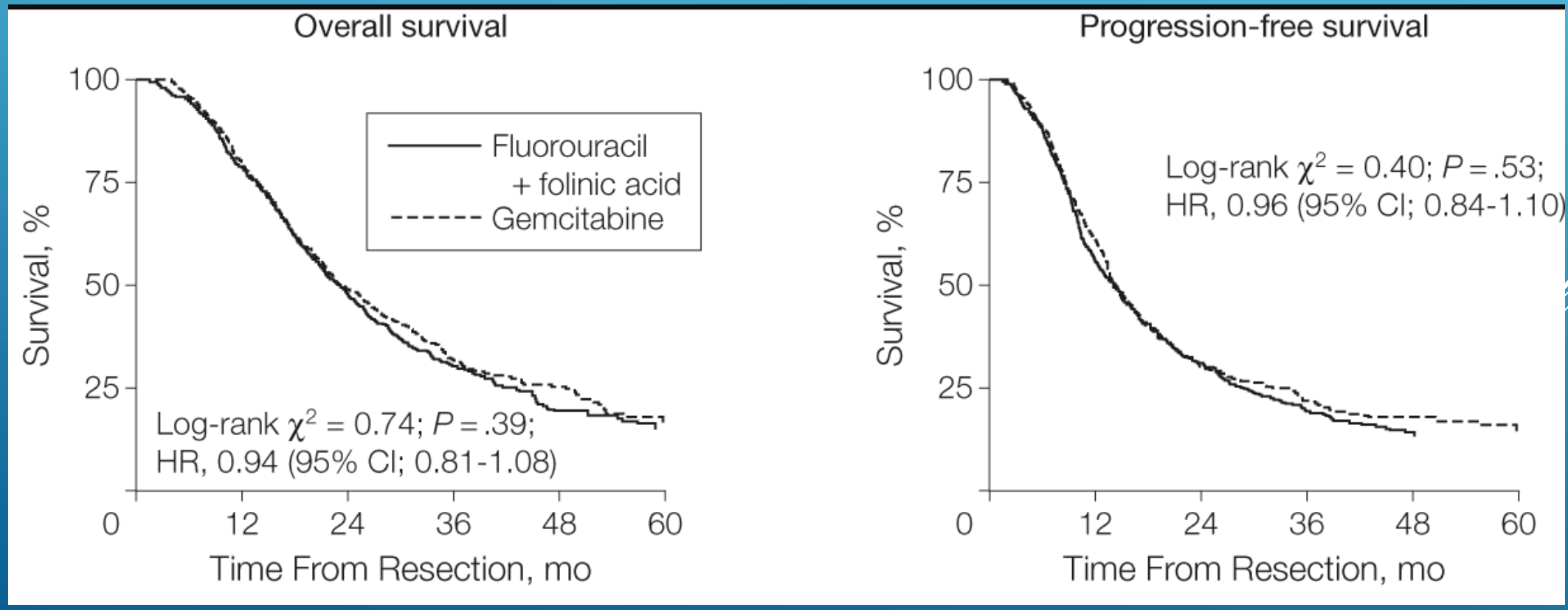
TMH WORKFLOW



Adjuvant chemotherapy in resected PDAC

JAMA. 2010 Sep 8;304(10):1073-81. doi: 10.1001/jama.2010.1275.

Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial.



Adjuvant chemotherapy in resected PDAC

JASPAC-1: 5 year OS (44.1% vs. 24%); S1 vs. gemcitabine

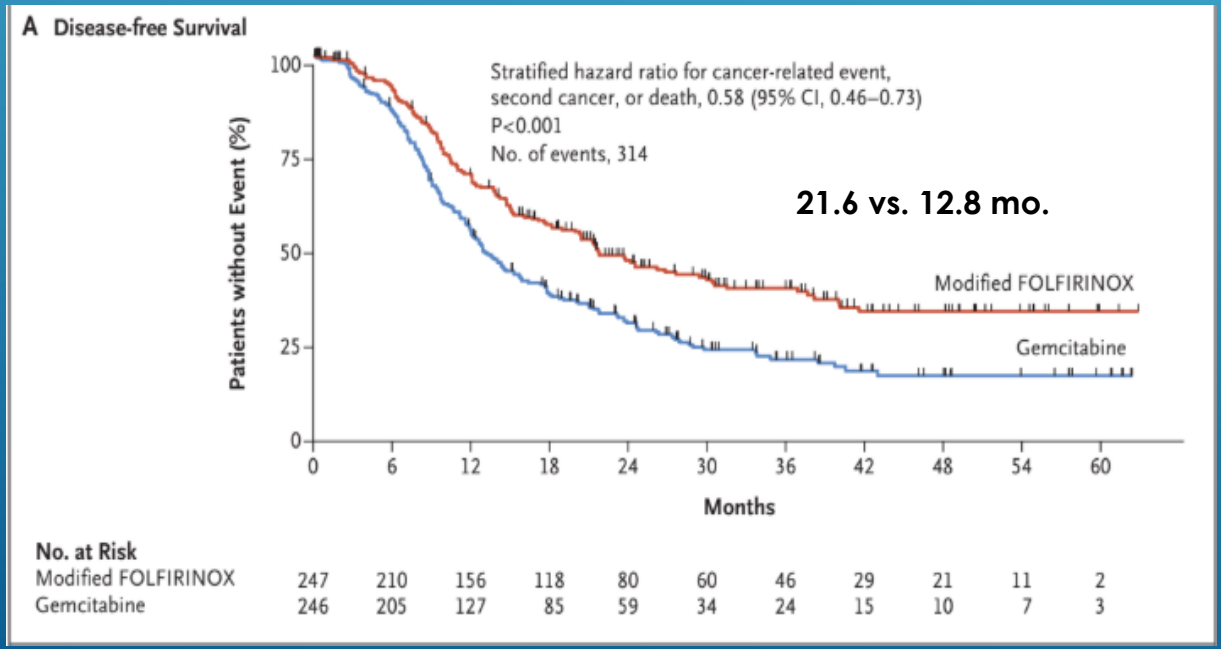
ESPAC-4 : 28 vs 25.5 months ; Gemcitabine-Capecitabine vs. Gemcitabine

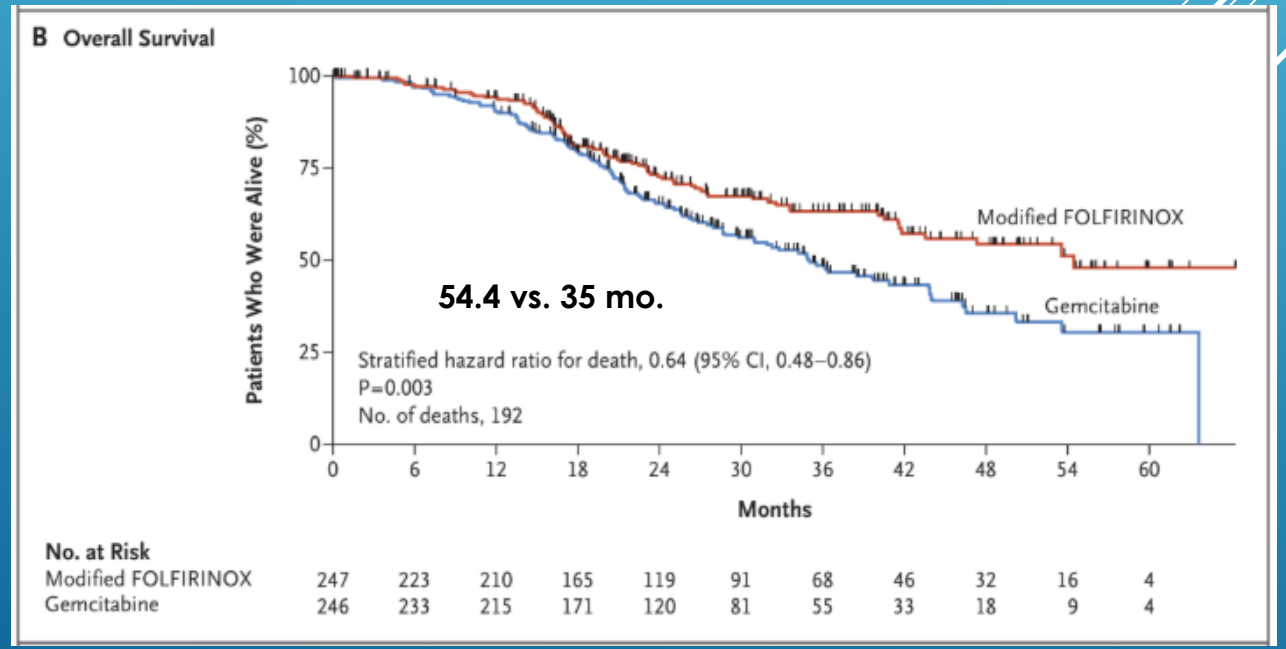
Adjuvant chemotherapy in resected PDAC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 20, 2018 VOL. 379 NO. 25

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer





Adjuvant chemotherapy in resected PDAC

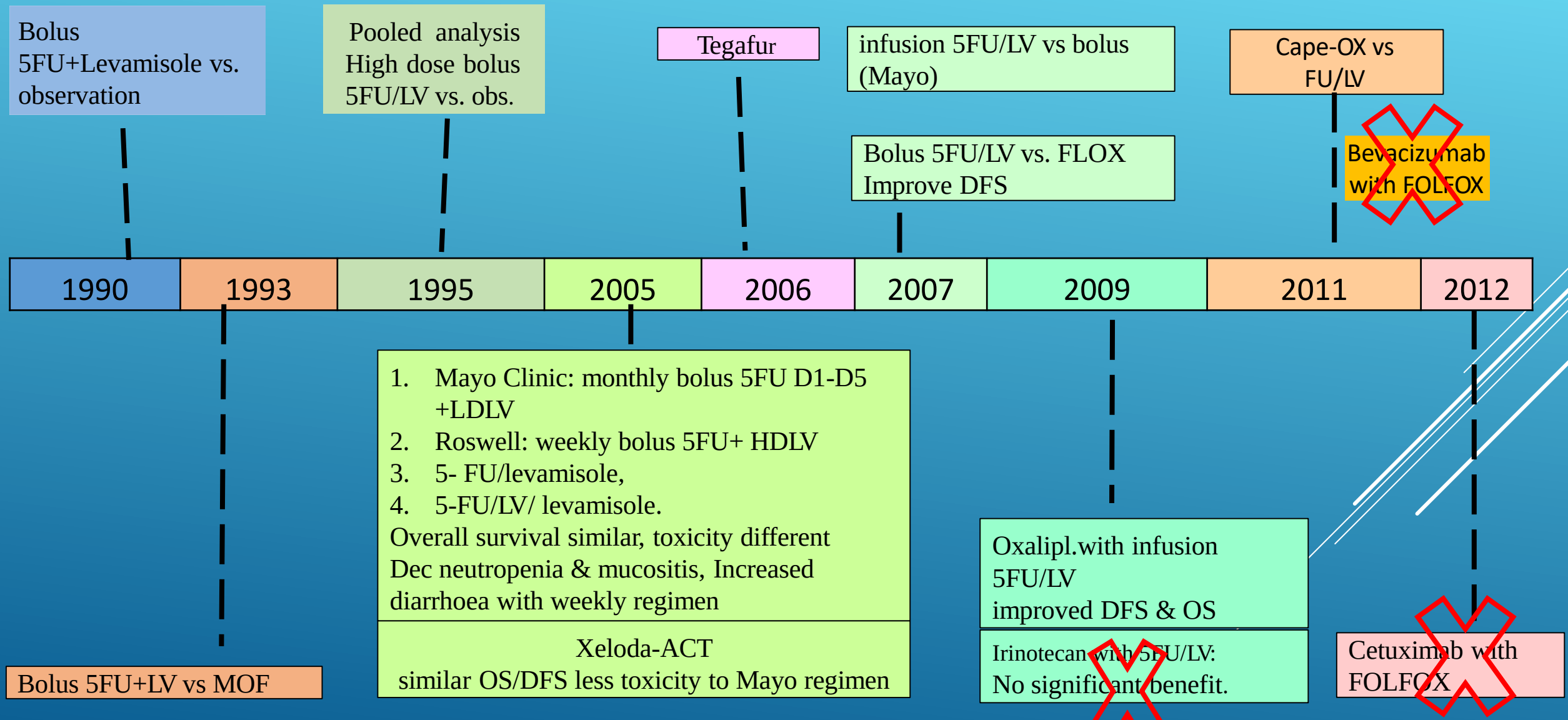
Table 2. Adverse Events during Treatment (Safety Population).*

Event	Modified FOLFIRINOX (N=238)			Gemcitabine (N=243)			P Value
	Any Grade	Grade 3 or 4	Grade 4	Any Grade	Grade 3 or 4	Grade 4	
	number of patients with event (percent)						
Hematologic event†							
Low hemoglobin level	200 (84.7)	8 (3.4)	0	216 (89.3)	6 (2.5)	0	0.56
Neutropenia	157 (66.5)	67 (28.4)	14 (5.9)	154 (63.6)	63 (26.0)	14 (5.8)	0.56
Febrile neutropenia	7 (3.0)	7 (3.0)	2 (0.8)	10 (4.1)	9 (3.7)	1 (0.4)	0.64
Hyperleukocytosis	110 (46.6)	11 (4.7)	2 (0.8)	134 (55.4)	17 (7.0)	1 (0.4)	0.27
Thrombocytopenia	111 (47.0)	3 (1.3)	0	122 (50.4)	11 (4.5)	3 (1.2)	0.03
Lymphopenia	87 (36.9)	3 (1.3)	0	117 (48.3)	7 (2.9)	1 (0.4)	0.34
Nonhematologic event‡							
Fatigue	199 (84.0)	26 (11.0)	0	187 (77.6)	11 (4.6)	0	0.009
Diarrhea	200 (84.4)	44 (18.6)	3 (1.3)	118 (49.0)	9 (3.7)	0	<0.001
Nausea	187 (78.9)	13 (5.5)	0	133 (55.2)	2 (0.8)	0	0.004
Abdominal pain	111 (46.8)	8 (3.4)	0	114 (47.3)	1 (0.4)	0	0.02
Vomiting	108 (45.6)	12 (5.1)	0	70 (29.0)	3 (1.2)	0	0.02
Anorexia	106 (44.7)	6 (2.5)	0	60 (24.9)	3 (1.2)	0	0.34
Sensory peripheral neuropathy	145 (61.2)	22 (9.3)	2 (0.8)	21 (8.7)	0	0	<0.001
Paresthesia	136 (57.4)	30 (12.7)	0	13 (5.4)	0	0	<0.001
Weight loss	90 (38.0)	3 (1.3)	0	49 (20.3)	1 (0.4)	0	0.37
Fever	39 (16.5)	1 (0.4)	0	78 (32.4)	1 (0.4)	0	1.00
Mucositis	80 (33.8)	6 (2.5)	0	36 (14.9)	0	0	0.01
Alopecia§	64 (27.0)	0	—	47 (19.5)	0	—	—
Hand–foot syndrome	12 (5.1)	1 (0.4)	0	2 (0.8)	0	0	0.50
Thrombosis or embolism	14 (5.9)	6 (2.5)	0	19 (7.9)	1 (0.4)	0	0.07
Constipation	49 (20.7)	0	0	52 (21.6)	0	0	—

COLORECTAL CANCERS

- ***Adjuvant chemotherapy in resected cancers***

Colorectal cancers – adjuvant chemotherapy



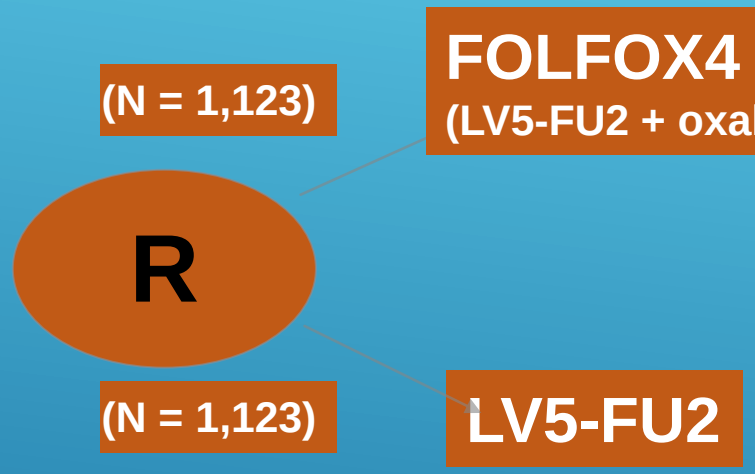
Colorectal cancers – adjuvant chemotherapy

MOSAIC STUDY

N = 2246

Enrollment: Oct 1998=Jan 2001
(146 centers; 20 countries)

- Completely resected colon cancer
- **Stage II, 40%**; Stage III, 60%
- Age 18-75 years
- KPS ≥ 60
- No prior chemotherapy



LV5-FU2: Leucovorin 200 mg/m^2 iv over 2 hours followed by 5-FUl 400 mg/m^2 bolus and 5-FU 600 mg/m^2 iv over 22 hours on Days 1 and 2, every 14 days

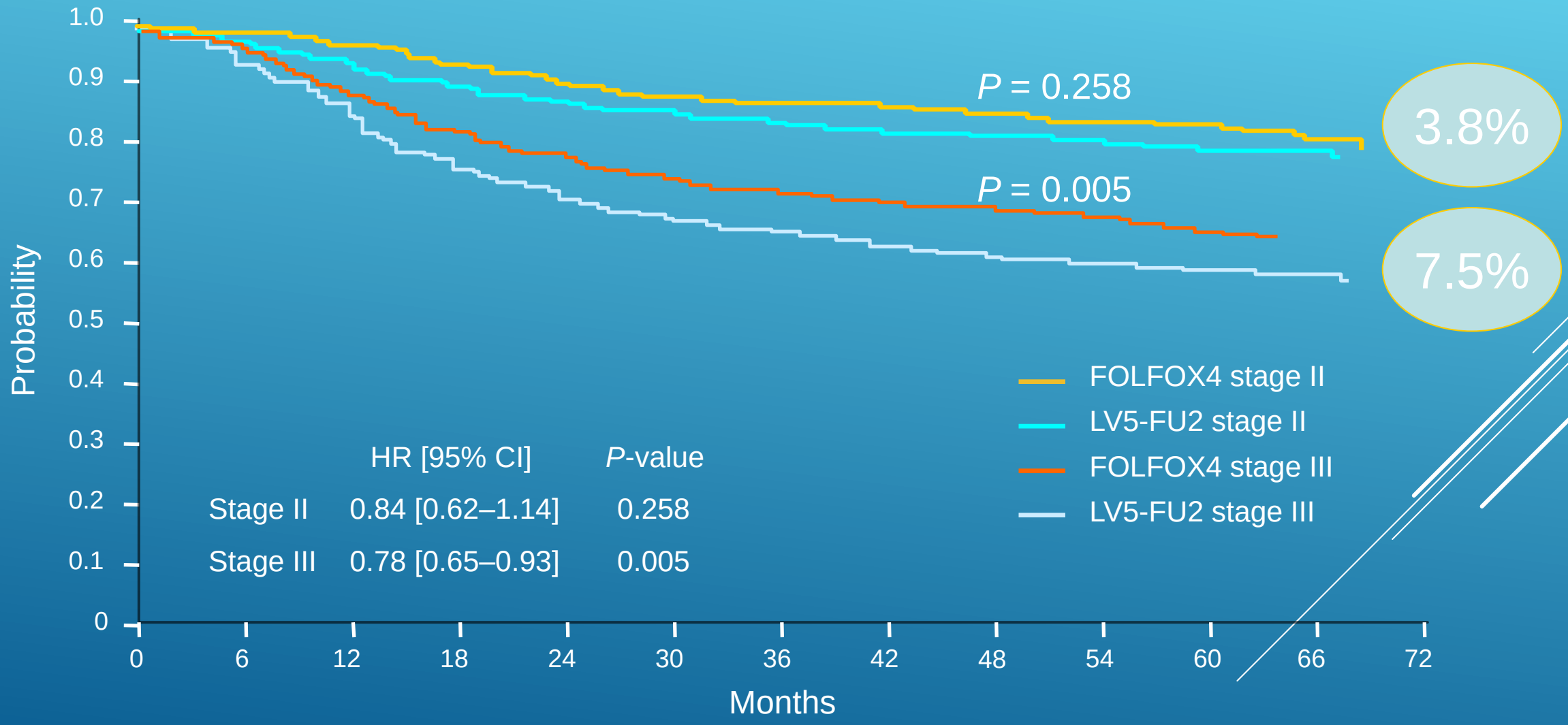
FOLFOX4: LV5-FU2 + oxaliplatin 85 mg/m^2 iv over 2 hours on Day 1

André, et al. N Engl J Med 2004

Colorectal cancers – adjuvant chemotherapy

	FOLFOX4	LV5FU2	*P* Value
Overall DFS (5 y)	**73%**	**67%**	**.003**
Stage III	66%	59%	.005
Stage II	**84%**	**80%**	**.26**
Overall survival (6 y)	**79%**	**76%**	**.06**
Stage III	73%	69%	.03
Stage II	**87%**	**87%**	**.99**

Colorectal cancers – adjuvant chemotherapy



Data cut-off: June 2006

de Gramont A, et al. ASCO 2007. Abstract #4007

Colorectal cancers – adjuvant chemotherapy

STAGE II
LOW RISK

OBSERVATION
OR
SA CAPE/5-FU-LV for 6 MONTHS

STAGE II HIGH RISK

- T4
- POORLY DIFFERENTIATED
- LVSI
- PNI
- BOWEL OBSTRUCTION
- LOCALISED PERFORATION
- CLOSE/POSITIVE MARGINS
- <12 LN SAMPLED

Consider relevance of MSI

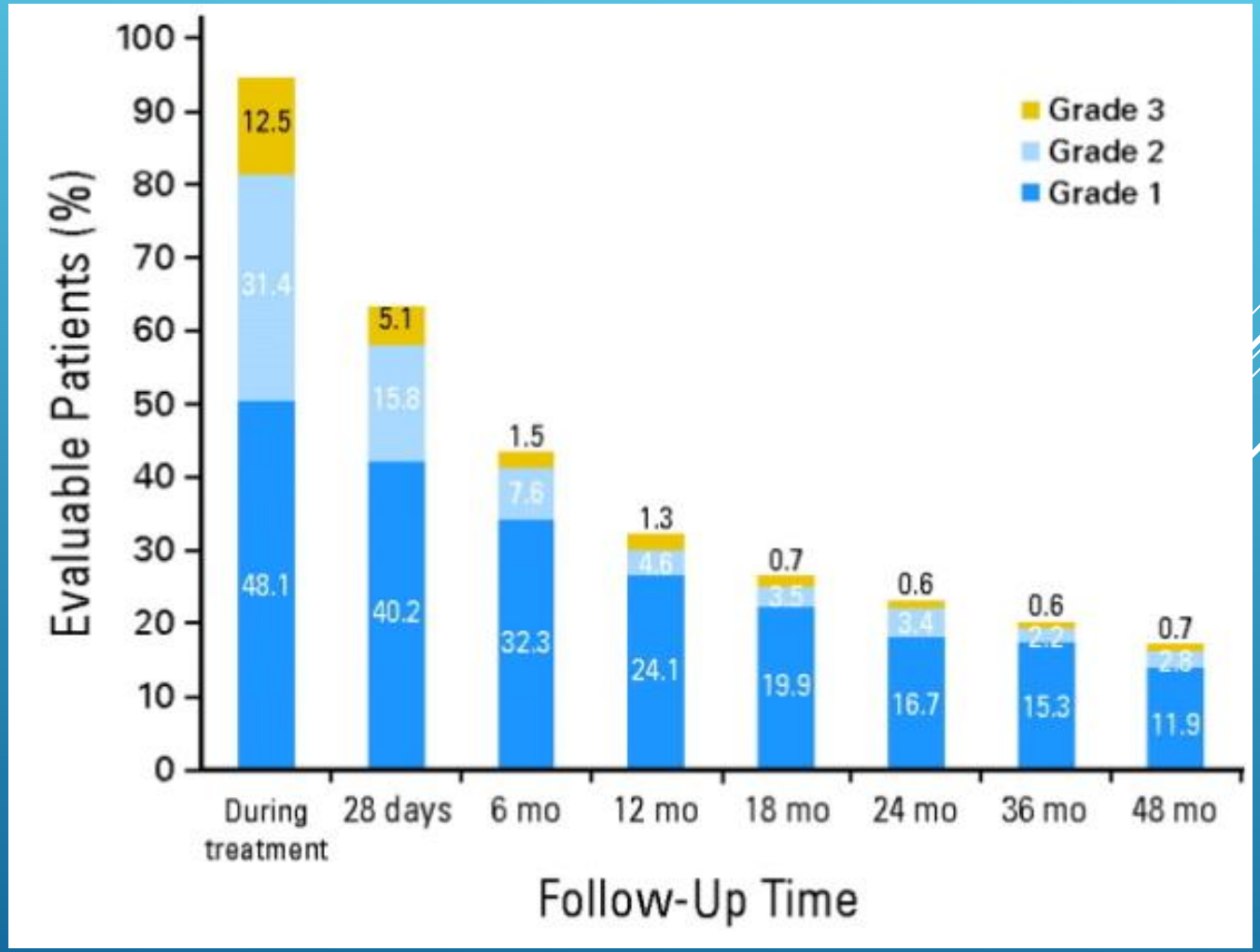
- SA 5-FU/LV
- SA CAPE
- CAPEOX
- FOLFOX

ADJUVANT THERAPY FOR 6 MONTHS
(after discussion with patient)

Colorectal cancers – adjuvant chemotherapy

MOSAIC SAFETY DATA

Regimen	INCIDENCE
FOLFOX4	12.5%
5-FU/LV	0.2%



Colorectal cancers – adjuvant chemotherapy

ORIGINAL ARTICLE

Duration of Adjuvant Chemotherapy for Stage III Colon Cancer

Axel Grothey, M.D., Alberto F. Sobrero, M.D., Anthony F. Shields, M.D., Ph.D., Takayuki Yoshino, M.D., Ph.D., James Paul, Ph.D., Julien Taieb, M.D., John Souglakos, M.D., Qian Shi, Ph.D., Rachel Kerr, Ph.D., Roberto Labianca, M.D., Jeffrey A. Meyerhardt, M.D., M.P.H., Dewi Vernerey, Ph.D., et al.

Prospectively pooled analysis of data from 6 concurrent randomized phase III trials in pts with stage III CC (mITT population: N ≥ 12,834)

Trial	Stage III CC Pts, N	Treatment	Country	Median F/u, Mos	Pts on CAPOX, %
TOSCA	2402	CAPOX or FOLFOX4	Italy	62	35
SCOT	3983	CAPOX or mFOLFOX6	Australia, Denmark, New Zealand, Spain, Sweden, UK	37	67
IDEA France	2010	CAPOX or mFOLFOX6	France	51	10
C80702	2440	mFOLFOX6	Canada, US	35	0
HORG	708	CAPOX or FOLFOX4	Greece	48	58
ACHIEVE	1291	CAPOX or mFOLFOX6	Japan	37	75

Colorectal cancers – adjuvant chemotherapy

- Primary endpoint: DFS in mITT population*
  - DFS: time from randomization to earliest date of relapse, secondary colorectal primary tumor, or death
  - Preplanned subgroup analyses by regimen, **risk groups low risk (T1-3, N1) vs high risk (T4 or N2) subgroups**

- Statistical analyses
  - DFS HR for 3 vs 6 mos (2-sided 95% CI) estimated with Cox model stratified by trial
    - Predefined noninferiority margin for HR < 1.12 (12% increase in relative risk)
    - Requires 3390 DFS events for 90% power with 1-sided $\alpha = 0.025$
  - Predefined noninferiority margin for 3-yr DFS rate difference (3 vs 6 mos): -2.7%
- Additional endpoints: treatment compliance, safety

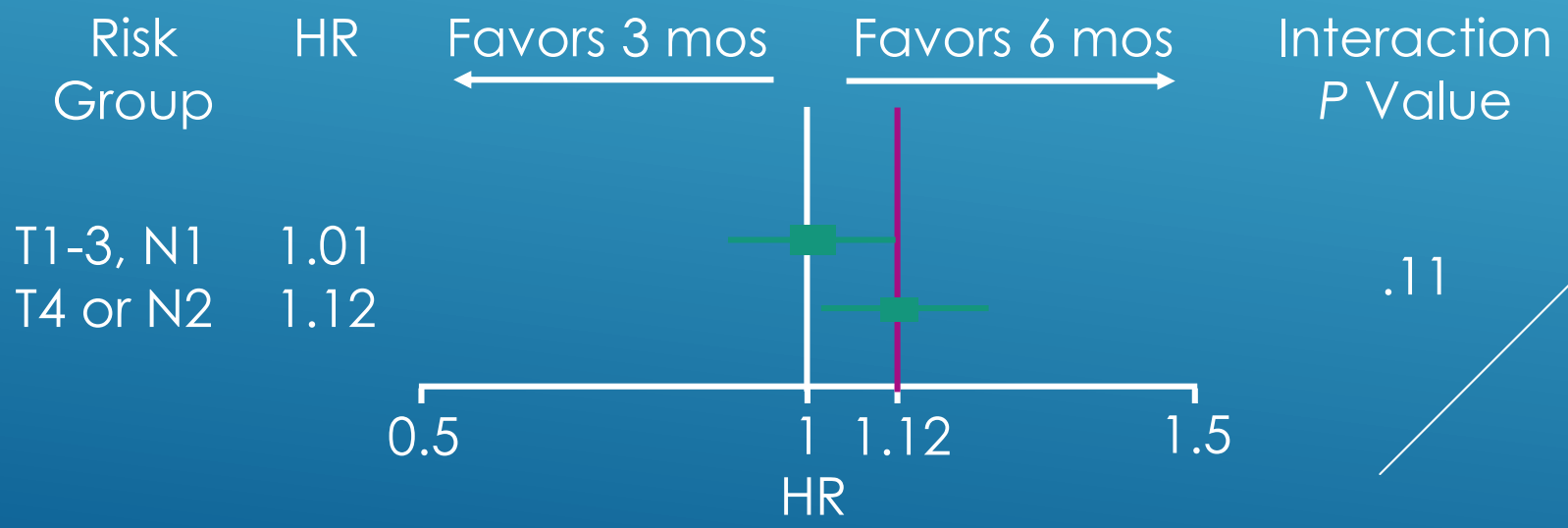
Colorectal cancers – adjuvant chemotherapy

Characteristic	FOLFOX		CAPOX	
	3 Mos (n = 3870)	6 Mos (n = 3893)	3 Mos (n = 2554)	6 Mos (n = 2517)
Median age, yrs	64	64	65	65
ECOG PS 0/1,* %	77/22	77/22	82/18	81/19
T stage, % ▪ T1-2 ▪ T3 ▪ T4	 13 68 19	 14 67 19	 13 63 24	 12 63 25
N stage, % ▪ N1 ▪ N2	 72 28	 73 27	 71 29	 71 29
Reached final planned cycle, %	90	71	86	65

Adverse Events	3m Arm	6m Arm	p-value[1]	3m Arm	6m Arm	p-value[1]
Overall						
G2	32%	32%	<.0001	41%	48%	<.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	14%	32%	<.0001	12%	36%	<.0001
G3-4	3%	16%		3%	9%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

Colorectal cancers – adjuvant chemotherapy

- Noninferiority of oxaliplatin-based tx for 3 vs 6 mos not proven
  - DFS HR: 1.07 (95% CI: 1.00-1.15)
  - Difference in 3-yr DFS rates: -0.9% (95% CI: -2.4% to 0.6%)
- 3-yr DFS rate difference of 20% between low risk (T1-3, N1) vs high risk (T4 or N2) subgroups



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Colorectal cancers – adjuvant chemotherapy

STAGE III
LOW RISK

CAPEOX – 3 OR
6 MONTHS
OR
FOLFOX*- 6
MONTHS

STAGE III
HIGH RISK

CAPEOX
OR
FOLFOX*

For 6 MONTHS

THANK YOU