Tumori dell'apparato gastroenterico

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Gastric Cancer

- Adjuvant Chemotherapy
- Perioperative Chemotherapy/ Preoperative CT-RT
- MSI Gastric Cancer
- Surgery in stage IV disease

Pancreatic Cancer (PDAC)

- Adjuvant chemotherapy
- Borderline Resectable/Locally Advanced
- Maintenance treatment (POLO Trial)
- SBRT

Rectal Cancer

- Preop intensification
- Total Neoadjuvant Therapy

Gastric Cancer Guidelines

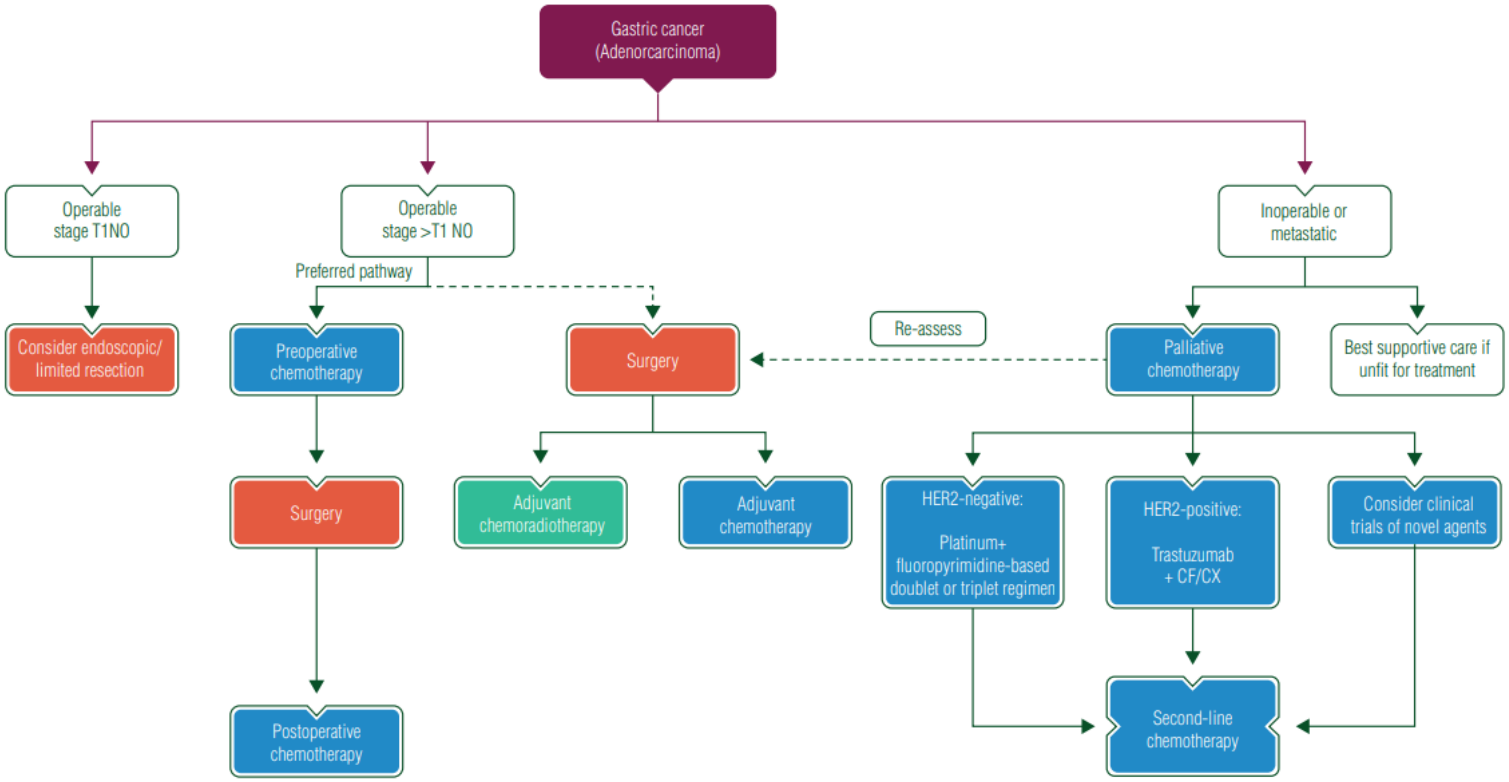

Figure 1. Gastric cancer treatment algorithm.
HER2, human epidermal growth factor receptor 2; CF, cisplatin and 5-fluorouracil; CX, cisplatin and capecitabine

Smith et al, ESMO guidelines Acta Oncol 2016

Gastric Cancer

Resectable:

- Adjuvant Chemotherapy

- Perioperative Chemotherapy

GEJ:

preoperative RTCT vs preop CT

Stratification

- MSI Gastric Cancer

Gastric Cancer

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preoperative RTCT vs preop CT

Stratification

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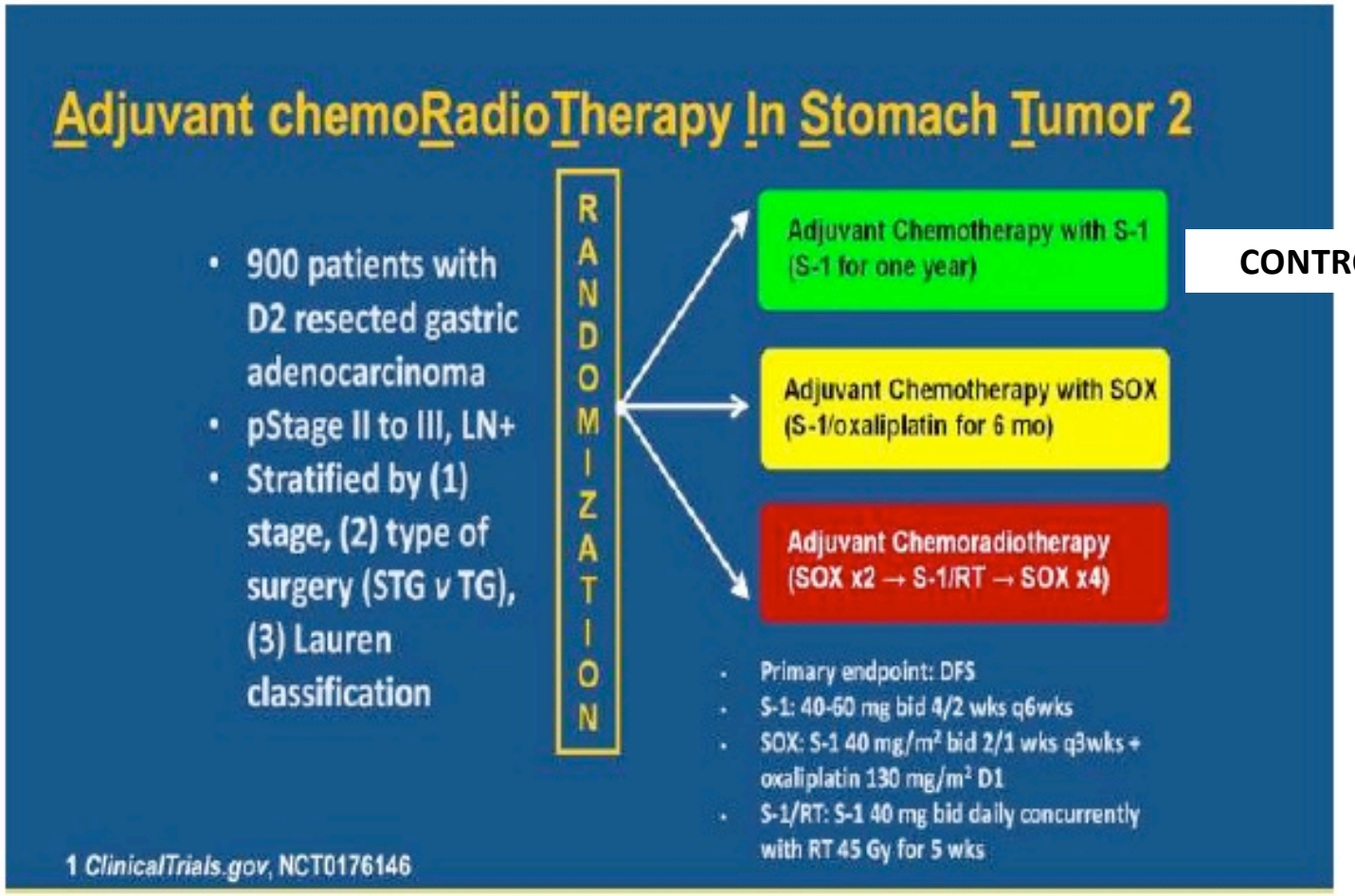
Adjuvant CT

- **GASTRIC** meta-analysis show 6% benefit for 5-FU based adjuvant CT
- Evidences for adjuvant CT mainly from Asian population
  - CLASSIC (XELOX)
  - ACTS-GC (S-1)

- Intensification of adjuvant CT was not proven to be effective in Western trials (es. ITACA-S)
- Adjuvant CT recommended for pts treated with surgery alone
- Role of CT-RT in high-risk, **N positive** resected tumor and in **< D2** or **R1** resection

ARTIST-2 Trial

Interim analysis **534 pts**

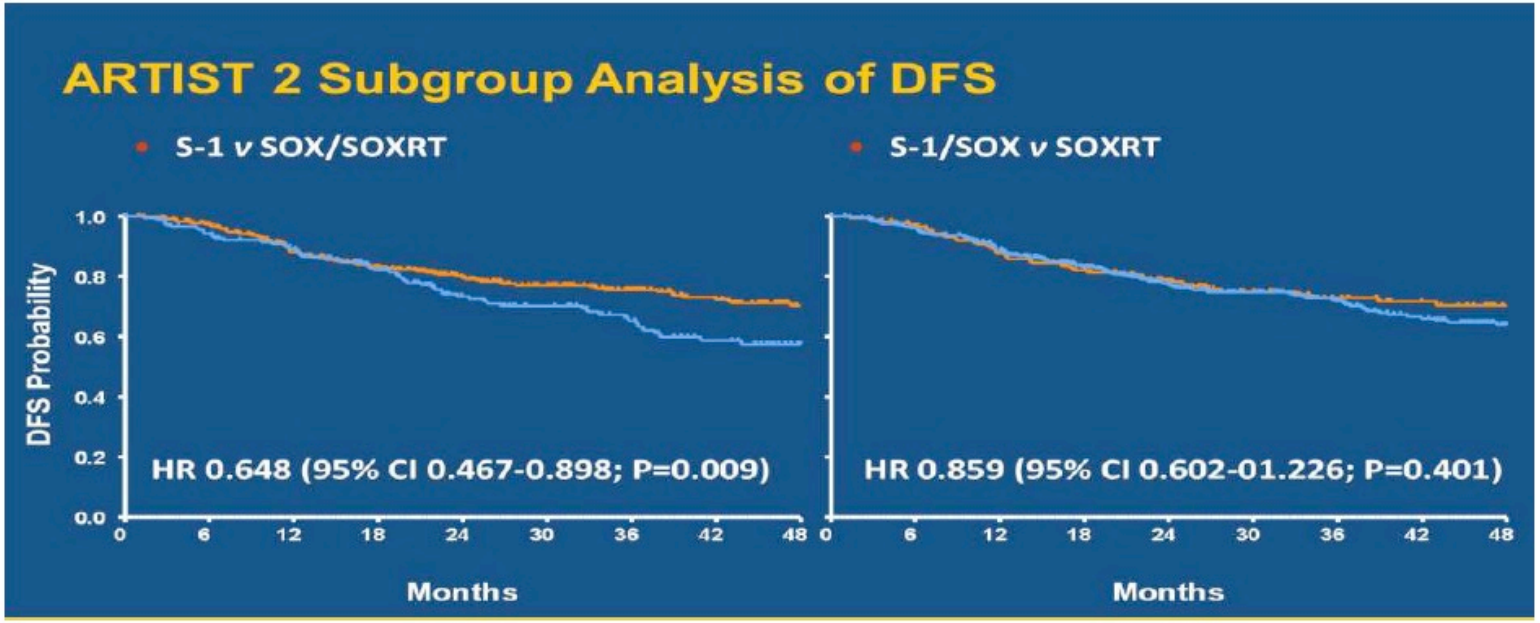


CONTROL ARM

Park SH et al, ASCO 2019

ARTIST-2 Trial: Results

- **Adjuvant SOX or SOX + RT** were superior in terms of **DFS** compared to S-1 monotherapy
- **RTCT→ No additional benefit**



3years DFS: S-1→ 65% SOX →78%; SOX-RT → 73%

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Park SH et al, ASCO 2019

Gastric Cancer

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GEJ:

preoperative RTCT vs preop CT

Stratification

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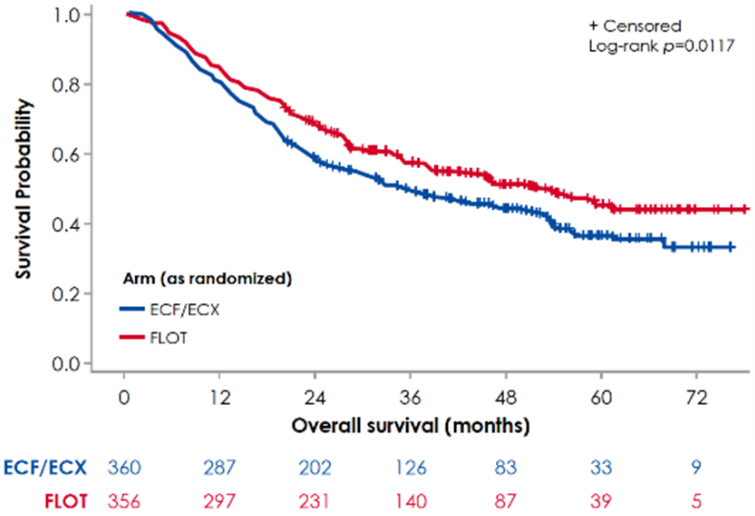
Perioperative CT

Perioperative chemotherapy with fluorouracil plus [redacted], oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial

Salah-Eddin Al-Batran, Nils Homann, Claudia Pauligk, Thorsten O Goetze, Johannes Meiler, Stefan Kasper, Hans-Georg Kopp, Frank Mayer, Georg Martin Haag, Kim Luley, Udo Lindig, Wolff Schmiegel, Michael Pohl, Jan Stoehlmacher, Gunnar Folprecht, Stephan Probst, Nicole Prasnikar, Wolfgang Fischbach, Rolf Mahlberg, Jörg Trojan, Michael Koenigsmann, Uwe M Martens, Peter Thuss-Patience, Matthias Egger, Andreas Block, Volker Heinemann, Gerald Illerhaus, Markus Moehler, Michael Schenk, Frank Kullmann, Dirk M Behringer, Michael Heike, Daniel Pink, Christian Teschendorf, Carmen Löhr, Helga Bernhard, Gunter Schuch, Volker Rethwisch, Ludwig Fischer von Weikersthal, Jörg T Hartmann, Michael Kneba, Severin Daum, Karsten Schulmann, Jörg Weniger, Sebastian Belle, Timo Gaiser, Fuat S Oduncu, Martina Güntner, Wael Hozaeel, Alexander Reichart, Elke Jäger, Thomas Kraus, Stefan Mönig, Wolf O Bechstein, Martin Schuler, Harald Schmalenberg, Ralf D Hofheinz*, on behalf of the FLOT4-AIO Investigators†*

cT2 or higher
nodal positive (cN+)
716 pts

pCR FLOT: 16% vs ECF 6%; p=0,02)
Lancet Oncol 2015



	ECF/ECX	FLOT
mOS	35 months [27-46]	50 months [38-na]
HR	0.77 [0.63-0.94] p=0.012 (log rank)	

OS rate*	ECF/ECX	FLOT
2y	59%	68%
3y	48%	57%
5y	36%	45%

**projected OS rate*

Serious adverse events similar in the 2 groups 27%

Al Batran SE et Al, Lancet 2019

Gastric Cancer

Resectable:

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GEJ:

preoperative RTCT vs preop CT

Stratification

- MSI Gastric Cancer

Neoadj CTRT in adenoca GEJ

Gastric Cancer (2019) 22:245–254
https://doi.org/10.1007/s10120-018-0901-3

REVIEW ARTICLE

Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis

Fausto Petrelli[1] · Michele Ghidini[2] · Sandro Barni[1] · Giovanni Sgroi[3] · Rodolfo Passalacqua[2] · Gianluca Tomasello[2]

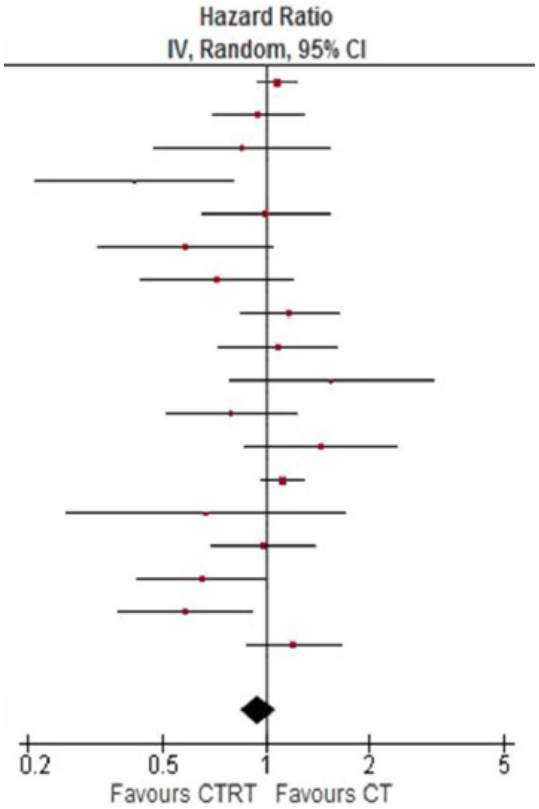
22 studies

18,260 patients included

14,709 neoadjuvant CTRT **3551** patients CT alone

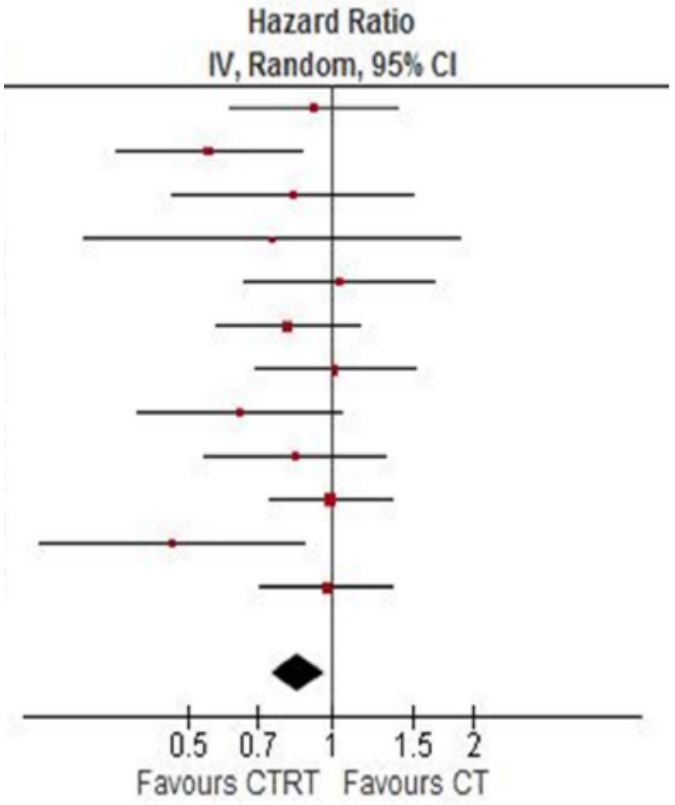
Neoadj CTRT in adenoca GEJ

Overall Survival (18 studies)



HR 0.95 (95% CI 0.84–1.07; *P* = 0.41)

DFS (12 studies)



HR 0.85 (95% CI 0.75–0.97; *P* = 0.01)

Neoadj CTRT in adenoca GEJ

Odds ratio of **pCR** was **2.8** in favor of **CTRT** (95% CI 2.27–3.47;*P* < 0.001).

CTRT improved **locoregional recurrences rate** (OR 0.6, 95% CI 0.39–0.91; *P* = 0.01)

CTRT DID NOT improved **distant metastases** rate (OR 0.81, 95% CI 0.59–1.11; *P* = 0.19)

After **CTRT** a significant proportion of pts **did non receive adj CT** (post surg rec, complications, deaths)

Gastric Cancer

Resectable:

- Adjuvant Chemotherapy

Perioperative Chemotherapy

GEJ:

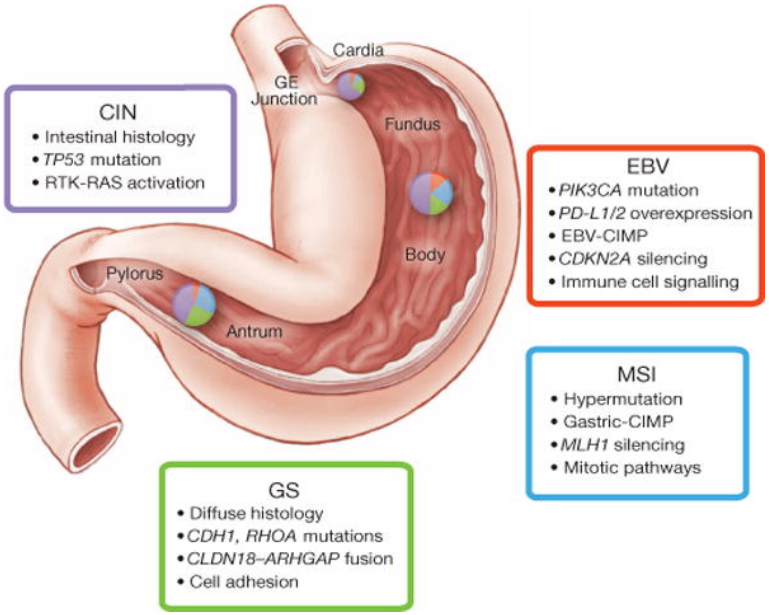
preoperative RTCT vs preop CT

Stratification

- MSI Gastric Cancer

MSI-H in Gastric Cancer

1. MSI-H is found in about **8-10%** of GC
2. *Elderly patients, Female, Stomach site, Intestinal subtype*
3. **Better prognosis** and possible detrimental effect from peri-operative CT and no benefit from adjuvant CT (exploratory analysis from MAGIC and CLASSIC trials)



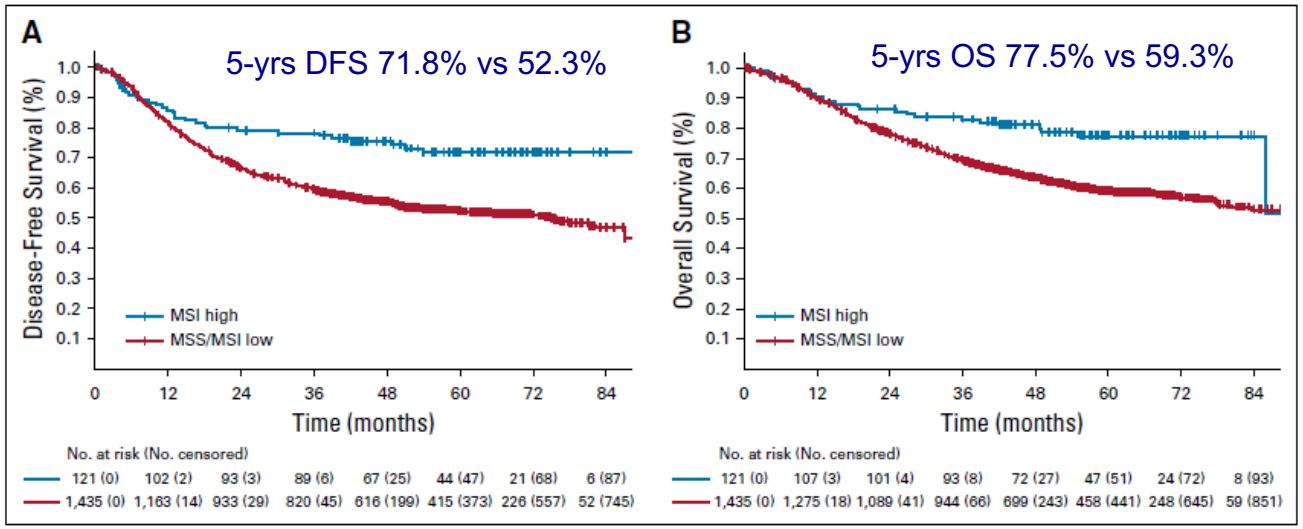
Bass AJ et al, Nature 2014

original report

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

Filippo Pietrantonio, MD[1,2]; Rosalba Miceli, PhD[1]; Alessandra Raimondi, MD[1]; Young Woo Kim, MD, PhD[3]; Won Ki Kang, MD[4]; Ruth E. Langley, MD, PhD[5]; Yoon Young Choi, MD[6]; Kyoung-Mee Kim, MD, PhD[4]; Matthew Guy Nankivell, MSc[5]; Federica Morano, MD[1]; Andrew Wotherspoon, MBBCh[8]; Nicola Valeri, MD, PhD[8,9]; Myeong-Cherl Kook, MD, PhD[3]; Ji Yeong An, MD, PhD[4]; Heike I. Grabsch, MD, PhD, MBA[10,11]; Giovanni Fucà, MD[1]; Sung Hoon Noh, MD, PhD[6]; Tae Sung Sohn, PhD[4]; Sung Kim, MD[4]; Maria Di Bartolomeo, MD[1]; David Cunningham, MD[8]; Jeeyun Lee, MD[4]; Jae-Ho Cheong, MD, PhD[6]; and Elizabeth Catherine Smyth, MD[11]

- IPD meta-analysis of prognostic/predictive role of MSI in resected GC pts from MAGIC, CLASSIC, ARTIST and ITACA-S
- 121/1156 **(7.8%)** had MSI-H and had **longer DFS** and **OS**



Pietrantonio et al, J Clin Oncol 2019

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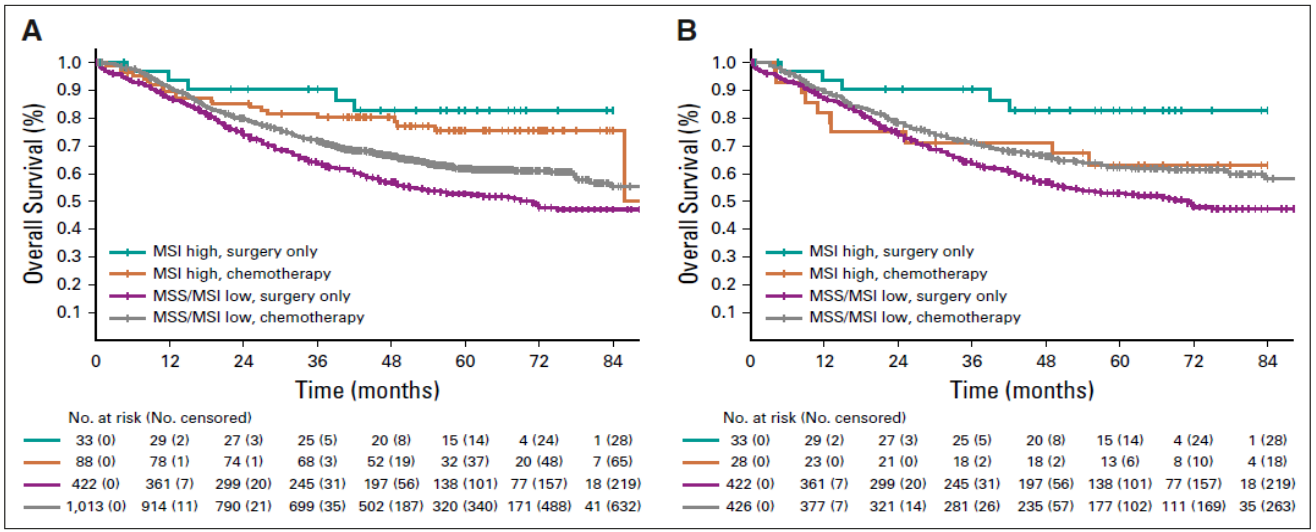
- **MSS/MSI-L** pts had benefit from **adj chemotherapy**
  - **5-year OS** was **62% versus 53%** (HR, 0.75; 95% CI, 0.60 to 0.94) for surgery plus chemotherapy vs surgery alone

- **MSI-H** pts **did not benefit from chemotherapy**
  - **5-yrs-OS** was **83% vs 75%** for surgery alone vs surgery plus chemotherapy



Pietrantonio et al, J Clin Oncol 2019

Gastric Cancer

Resectable:

- Adjuvant Chemotherapy → doublet CT is better DFS than mono therapy, RT no additional benefit
- Perioperative Chemotherapy→ FLOT better that ECF

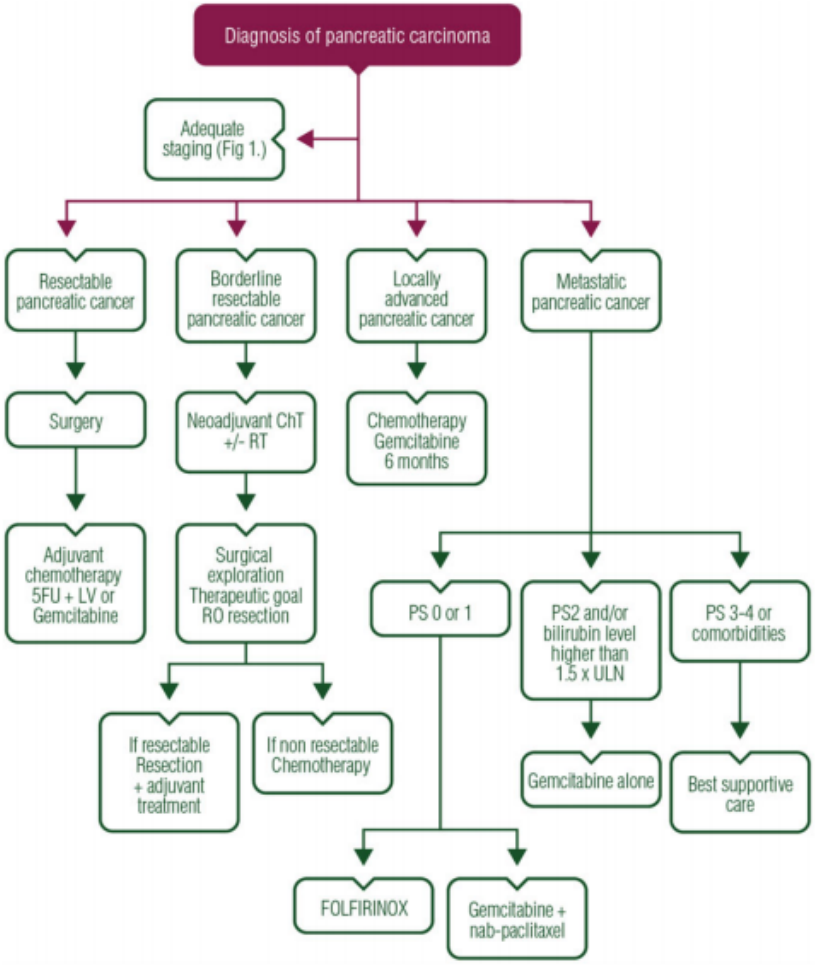
GEJ:

preoperative RTCT better DFS than preop CT, same OS

Stratification

- MSI Gastric Cancer→ MSI-H better prognosis, less response to CT

Pancreatic Cancer Guidelines



Ducreux et al, ESMO guidelines Acta Oncol 2015

Pancreatic Cancer (PDAC)

- Resectable pancreatic cancer
- Borderline Resectable
- Locally Advanced
- Metastatic cancer

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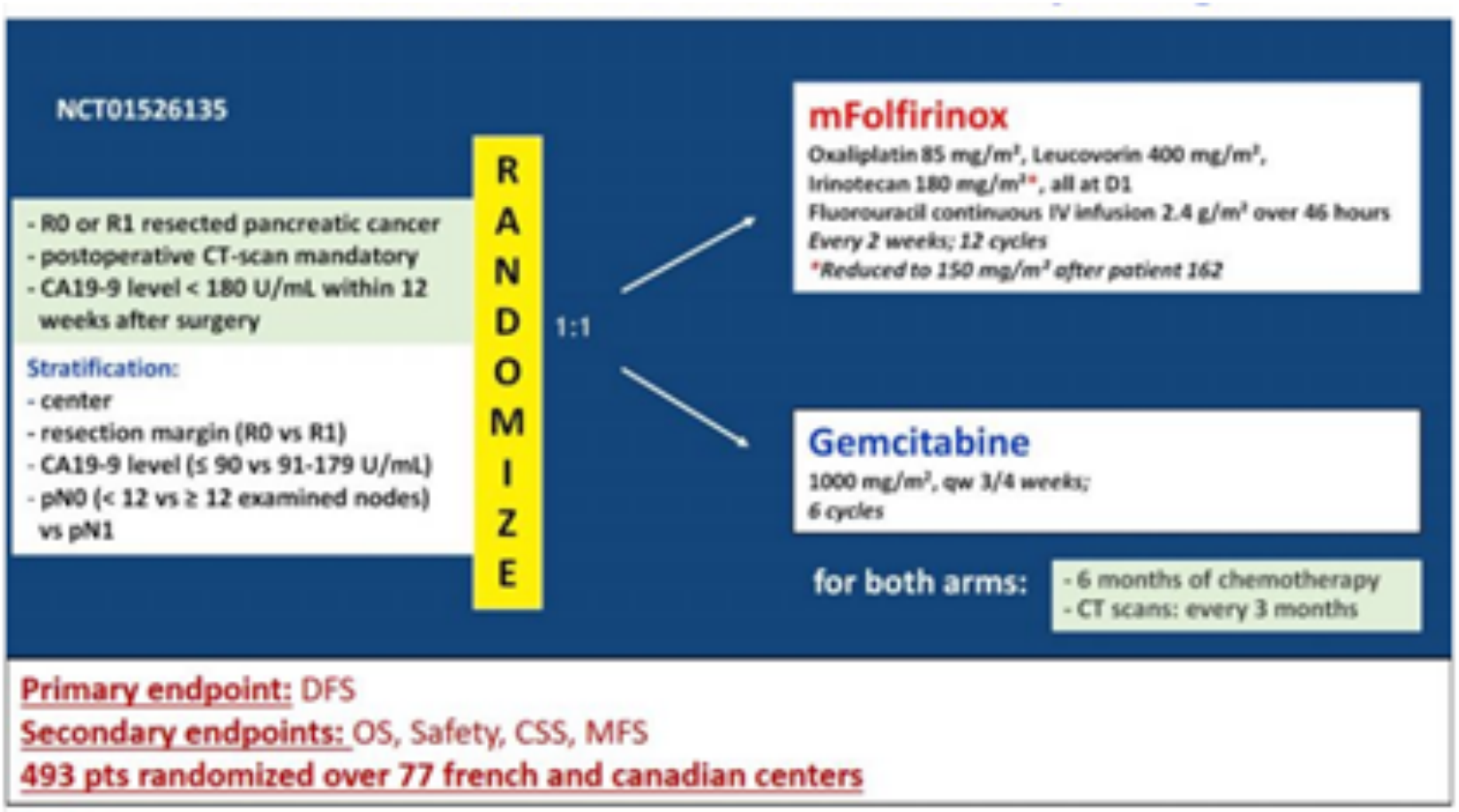
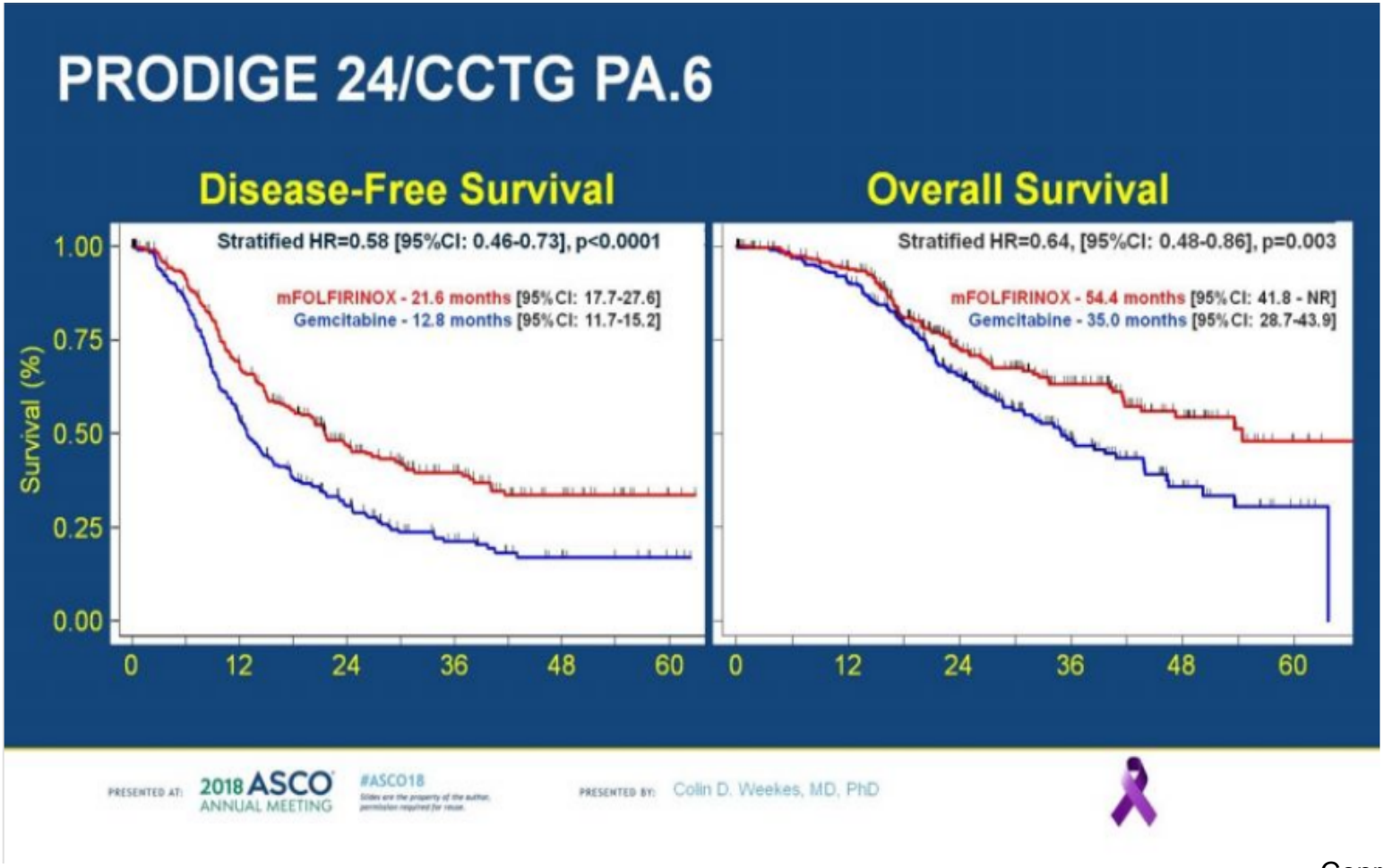
Adjuvant Chemotherapy: PRODIGE 24



Conroy et al. NEJM 2018

PRODIGE 24: Efficacy



Conroy et al. NEJM 2018

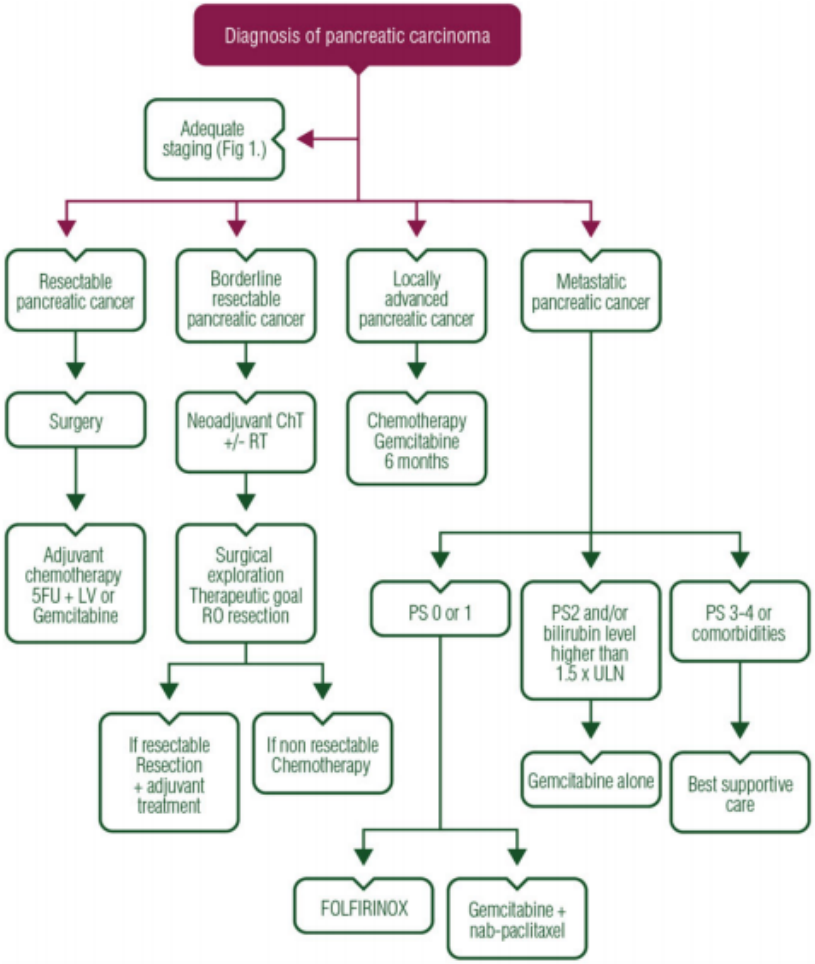
Pancreatic Cancer Guidelines

eUpdate – Cancer of the pancreas treatment recommendations

Published: 15 March 2019. Authors: ESMO Guidelines Committee

ADJUVANT CT IN RESECTABLE CANCER

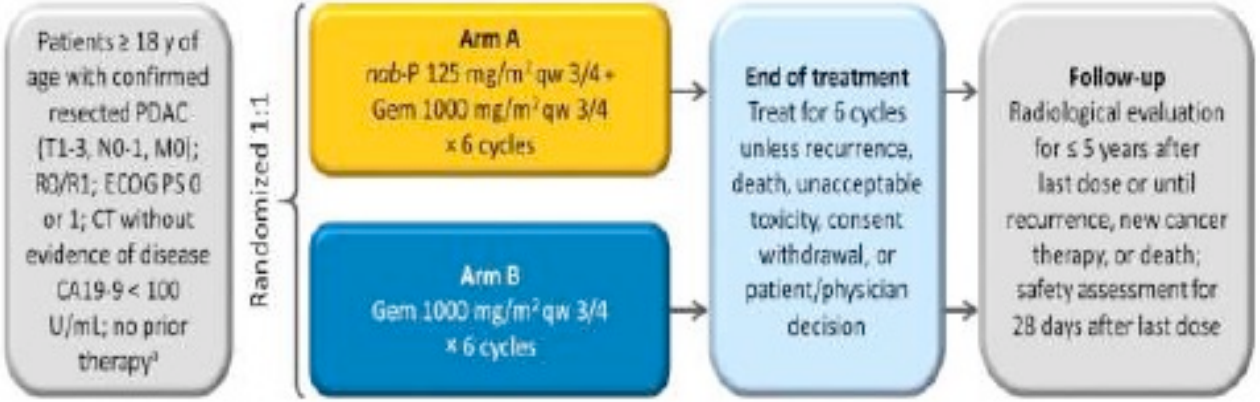
- **mFOLFIRINOX** PRODIGE 24/CCTG PA.6 trial
- **Gemcitabine/capecitabine** in more frail patients (age > 70, Eastern Cooperative Oncology Group performance status 2, or patients who have any contraindication to the drugs used in FOLFIRINOX) ESPAC-4
- **Gemcitabine** alone should be used only in frail patients



Ducreux et al, ESMO guidelines Acta Oncol 2015

Adjuvant CT: APACT Trial

- Phase III, international multicenter, randomized trial
- Primary Endpoint: *Indipendently assessed* ***DFS***
- Secondary Endpoints: ***OS, Safety***



- Patients were randomized as early as possible after adequate recovery from surgery but no later than 12 weeks after surgery
- Stratification factors: resection status (R0 vs R1); lymph node status (LN+ vs LN−); geographic region (North America, Europe and Australia vs Asia Pacific)

Tempero MA et al, ASCO 2019

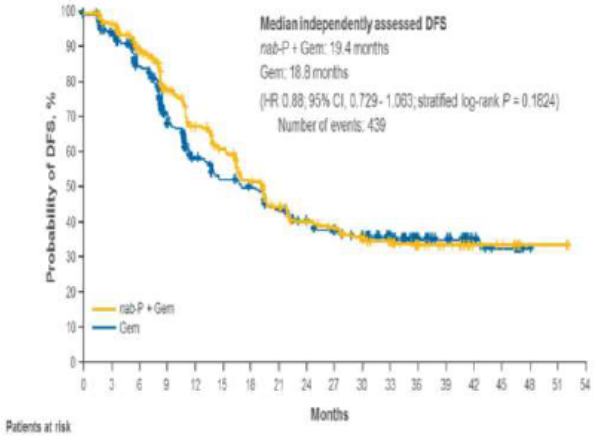
APACT Trial: DFS

IR-assessed DFS	NabP+Gem	Gem	HR (95% CI)
Median, mo	19.4	18.8	0.88 (0.73, 1.06)

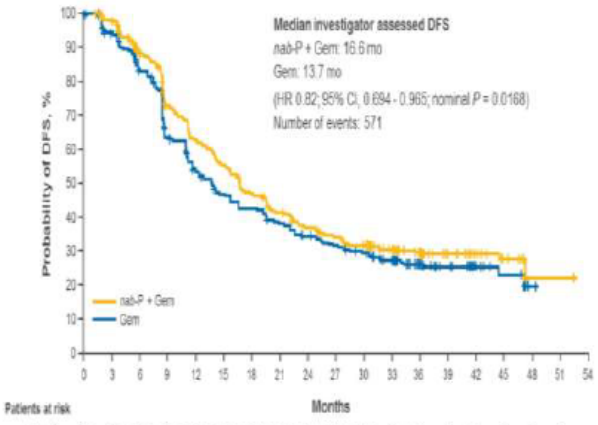
INV-assessed DFS	NabP+Gem	Gem	HR (95% CI)
Median, mo	16.6	13.7	0.82 (0.68, 0.99)

866 pts enrolled

PRIMARY ENDPOINT:
INDEPENDENTLY ASSESSED DFS (ITT POPULATION)



PRESPECIFIED SENSITIVITY ANALYSIS:
INVESTIGATOR ASSESSED DFS



- The concordance rate between disease recurrence by independent radiological review and by investigator review was 77%

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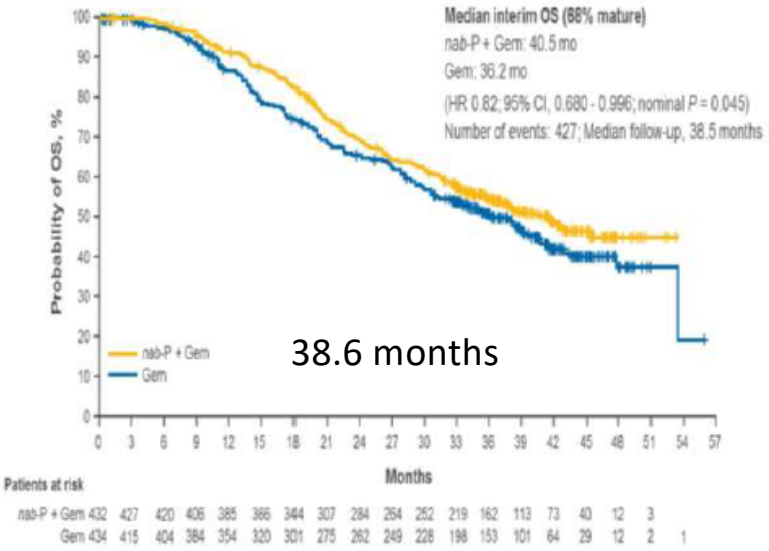
Tempero MA et al, ASCO 2019

APACT Trial: Interim OS, Safety

- Primary endpoint (*independently assessed* **DFS**) not met
- Final OS data may clarify the role of adjuvant *nab*-P and gemcitabine in adjuvant treatment of resected PC

FUP med 38.6 months
Overall survival:
40.5 months vs 36.2 months,
(HR = 0.82; P = .045).



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TOXICITY

86% experimental arm vs 68% single-agent arm

Event, n (%)	*nab*-P + Gem	Gem
Safety summary	(n = 429)	(n = 423)
Patients with ≥ 1 grade ≥ 3 TEAE	371 (86)	286 (68)
Patients with ≥ 1 serious TEAE	176 (41)	96 (23)
Grade ≥ 3 hematologic TEAEs (occurring in ≥ 5% of patients in either treatment arm)		
Any hematologic TEAEs	250 (58)	204 (48)
Neutropenia	212 (49)	184 (43)
Anemia	63 (15)	33 (8)
Leukopenia	36 (8)	20 (5)
Febrile neutropenia	21 (5)	4 (1)
Grade ≥ 3 nonhematologic TEAEs (occurring in ≥ 5% of patients in either treatment arm)		
Peripheral neuropathy (SMQ)[a]	64 (15)	0
Fatigue	43 (10)	13 (3)
Diarrhea	22 (5)	4 (1)
Asthenia	21 (5)	8 (2)
Hypertension	17 (4)	27 (6)

- TEAEs led to death in 2 patients in each arm
- Ten patients (16%) with grade ≥ 3 peripheral neuropathy improved to grade ≤ 1
- The incidence of TEAEs of special interest—gastrointestinal events, hepatic toxicity, and sepsis—was generally low in both arms

Tempero MA et al, ASCO 2019

Pancreatic Cancer (PDAC)

- Resectable pancreatic cancer
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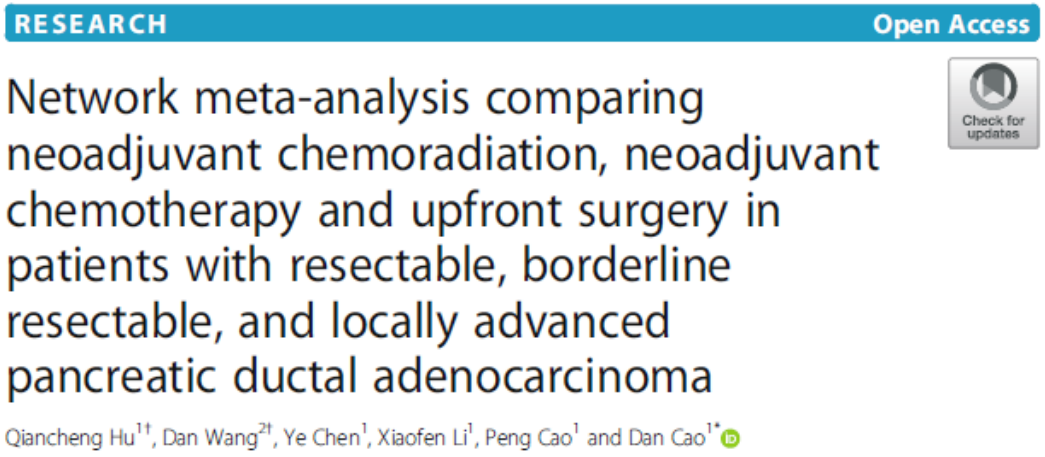
- Locally Advanced
- Metastatic cancer

Preoperative CTRT vs CT vs upfront S



RESEARCH Open Access

Network meta-analysis comparing neoadjuvant chemoradiation, neoadjuvant chemotherapy and upfront surgery in patients with resectable, borderline resectable, and locally advanced pancreatic ductal adenocarcinoma

Qiancheng Hu[1†], Dan Wang[2†], Ye Chen[1], Xiaofen Li[1], Peng Cao[1] and Dan Cao[1*]

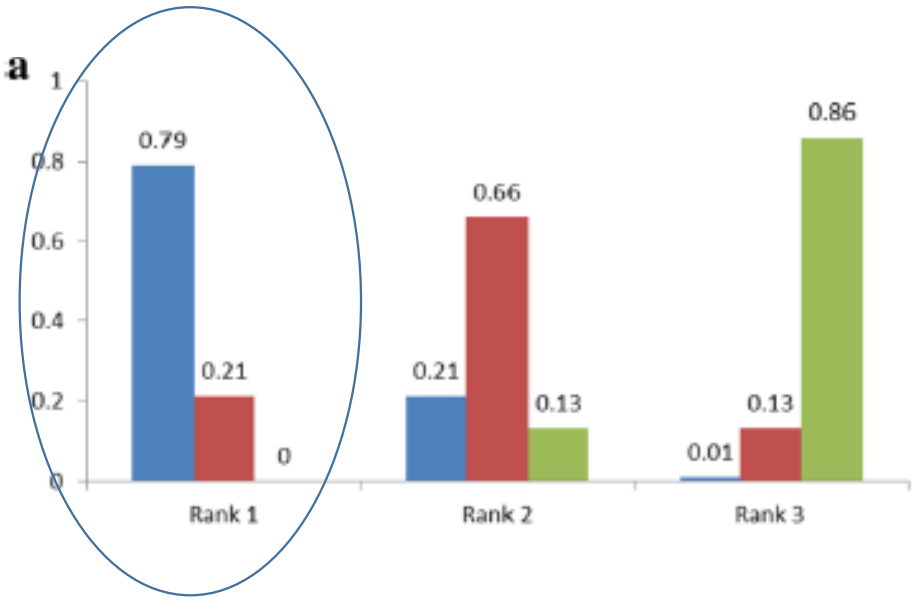
14 publications (3 randomized controlled trials) were included

1056 patients received at least one of the three treatment strategies (RTCT, CT, Upfront S)

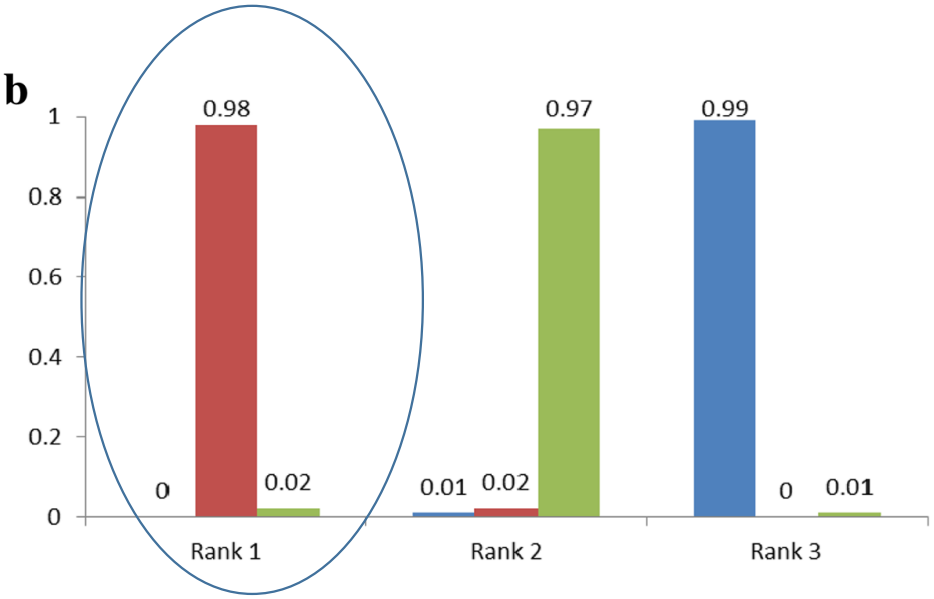
Hu et al. Radiation Oncology (2019) 14:120

Preoperative CTRT vs CT vs upfront S

R0 resection



Overall Survival



chemoradiotherapy Chemotherapy Upfront surgery

Hu et al. Radiation Oncology (2019) 14:120

Pancreatic Cancer (PDAC)

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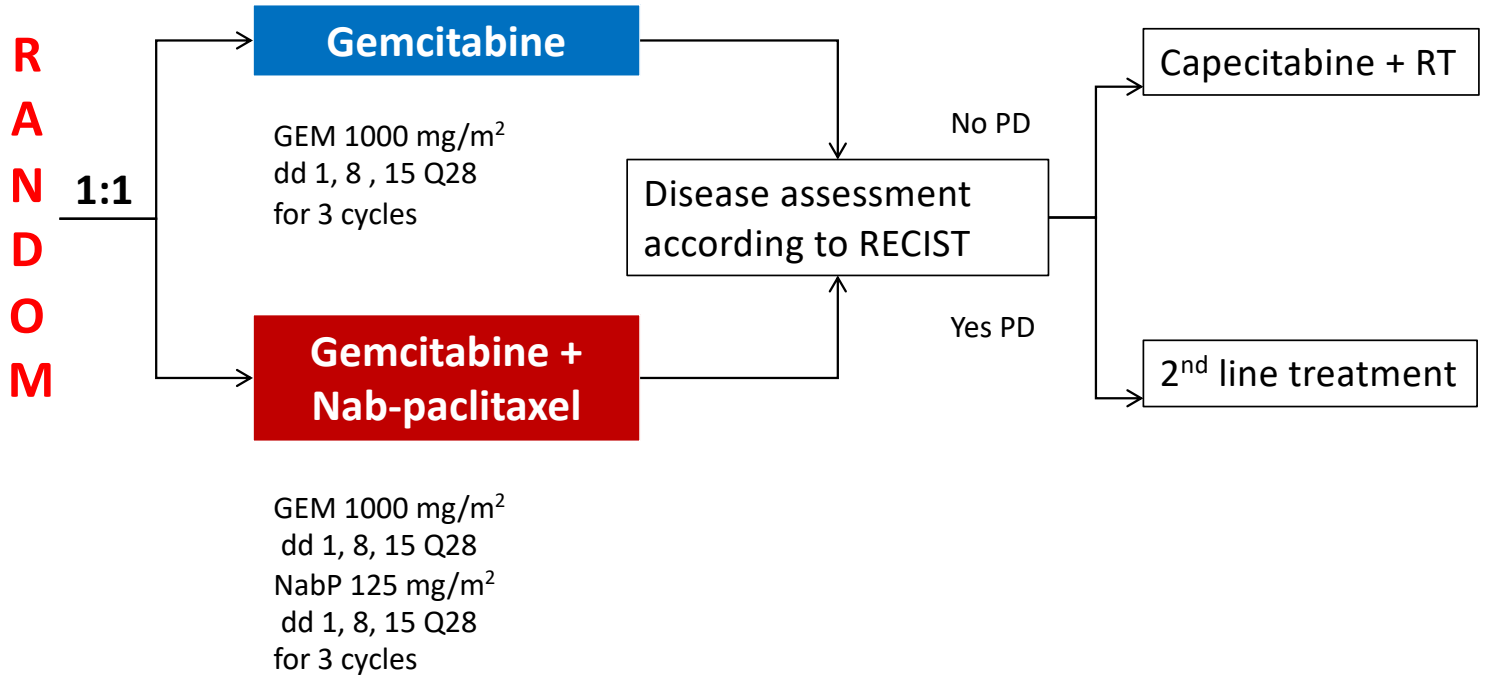
LAPC: GAP Trial

- Phase II trial, randomized trial of gemcitabine + *nab*-P in LAPC patients
- Primary Endpoint: Disease Progression Rate after 3 cycles of CT

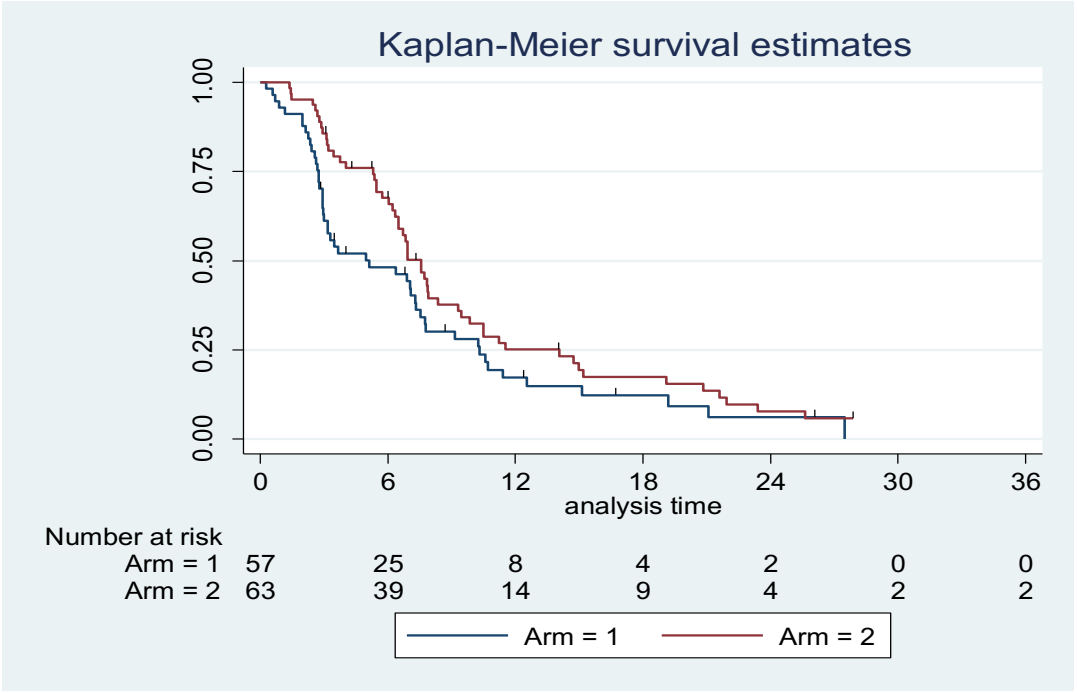


Cascinu et al, ESMO 2019

GAP Trial: Results

Gemcitabine plus Nab-paclitaxel

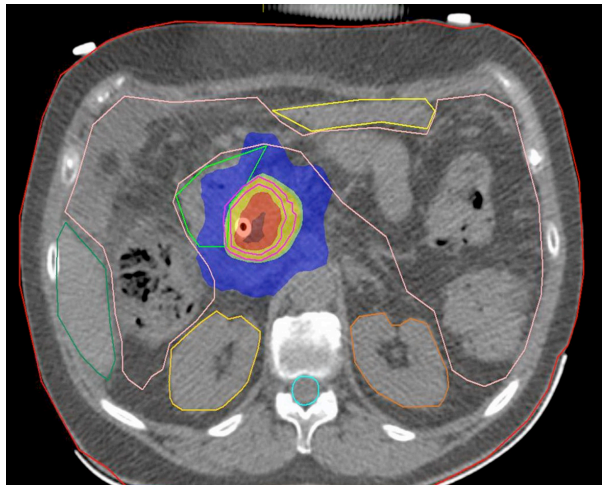
- ***decreased*** *disease progression rate at 3 months* (**25.4% vs 45.6%, p= 0.01**) mainly in terms of **distant metastases**
- **improved** *response rate* (27% vs 5.3%),
- **PFS: 7.6 vs 5.1 m** (HR 0.71; 90% CI 0.51-0.99) and **OS**: **13.1 vs 10.7 m** (HR 0.65; 90% CI 0.44-0.94)



Cascinu et al, ESMO 2019

Stereotactic Body Radiotherapy

- High dose to the TARGET
- **5 fractions:** pts compliance, association with CT
- **Increases LC**
- **NO RCT**
- Restrospective, small studies

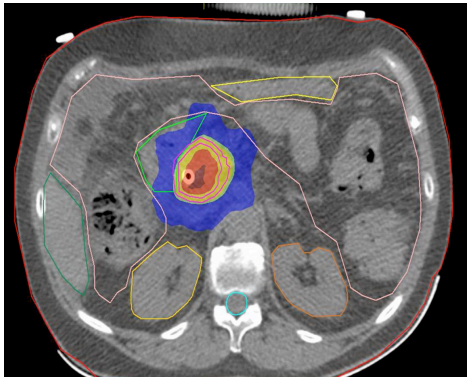


Stereotactic Body Radiotherapy

Higher Biologically Effective Dose Predicts Survival in SBRT of Pancreatic Cancer: A Multicentric Analysis (PAULA-1)

ALESSANDRA ARCELLI[1], ALESSANDRA GUIDO[1], MILLY BUWENGE[1], NICOLA SIMONI[2], RENZO MAZZAROTTO[2], GABRIELLA MACCHIA[3], FRANCESCO DEODATO[3], SAVINO CILLA[4], PIERLUIGI BONOMO[5], VALERIO SCOTTI[6], LILIANA BELGIOIA[7], GIORGIO TOLENTO[1], FRANCESCO CELLINI[8], ELISA GRASSI[9], MARIACRISTINA DI MARCO[9], RICCARDO CASADEI[10], ALESSIO G. MORGANTI[1] and SILVIA CAMMELLI[1]

- **AIRO**-Gastrointestinal Study Group
- Large database on LAPC **434** patients from Italian centers
- **56** pts **SBRT** with or without **CHT** January 2013 - March 2018
- Endpoints: **OS, LC, DMFS, toxicity**



Arcelli et al Antican Res 2020

Stereotactic Body Radiotherapy

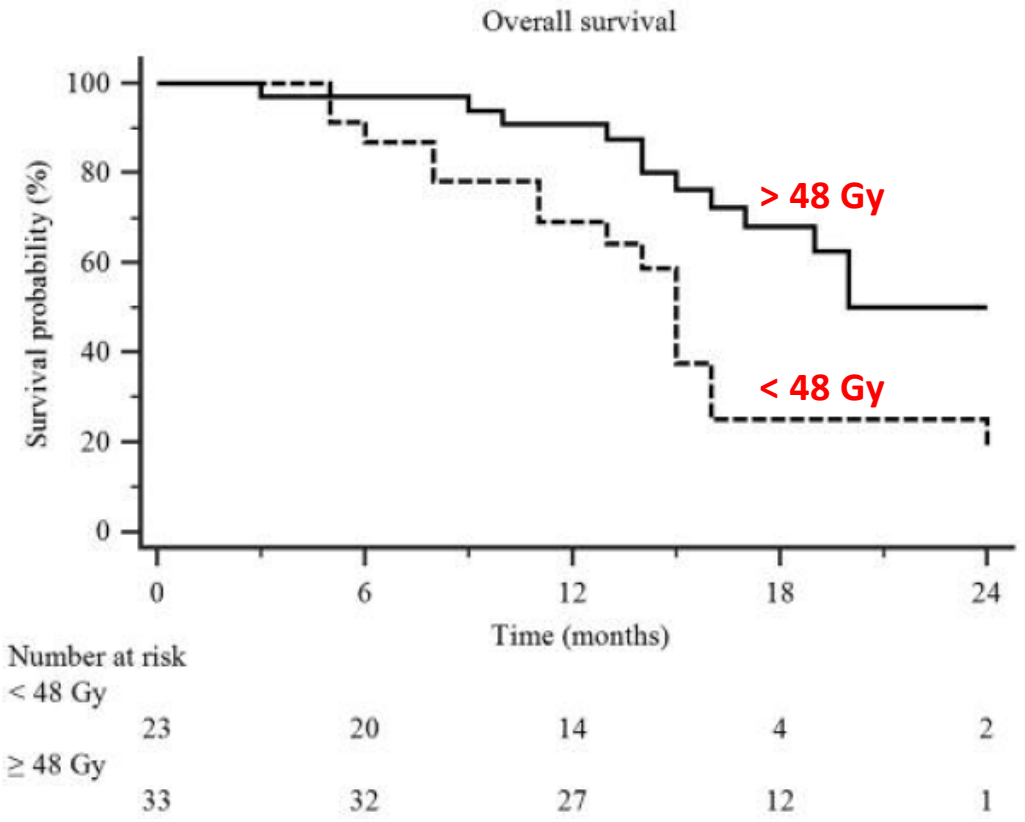
SBRT Median $BED_{\alpha/\beta 10Gy}$ → ***48 Gy*** *(28-78.7 Gy)*

2-year ***OS*** *33.8%*
BEDα/β10Gy≥48 Gy
(HR=0.44, 95% CI=0.20-0.97, *p*=0.042)

2-year ***LC*** *55.4%*
BEDα/β10Gy≥48 Gy
(HR=0.34, 95% CI=0.12-0.97, *p*=0.045)

2-year ***DMFS*** *22.9%*
post-SBRT CHT
(HR=0.22, 95% CI=0.08-0.59, *p*=0.003)

GI Toxicity
acute **G0: 78.5%,** G1: 19.6%, G2: 1.9%, Late G3 2.5%
(upper gastrointestinal bleeding)



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Stereotactic Body Radiotherapy

Univariate analysis

Variable	Patients N (%)	6-month OS	1-year OS	2-year OS	Median OS	*p*-Value	6-month LC	1-year LC	2-year LC	Median LC	*p*-Value	6-month DMFS	1-year DMFS	2-year DMFS	Median DMFS	*p*-Valu
Chemotherapy																
No	15 (26.8)	80.0	58.7	NE	14	**<0.001**	92.3	59.3	NE	14	0.376	93.3	47.5	NE	12	**0.010**
Pre-SBRT	18 (32.1)	100.0	94.4	0.0	24		88.9	88.9	NE	NR		83.3	77.8	NE	NR	
Post-SBRT	10 (17.9)	90.0	80.0	60.0	NR		90.0	68.6	68.6	NR		90.0	57.1	42.9	13	
Pre- and post- SBRT	13 (23.2)	100.0	92.3	54.9	29		100.0	75.0	37.5	22		76.9	30.8	NE	10	
SBRT dose (Gy)																
<30	22 (39.3)	90.9	72.2	19.6	15.0	**0.030**	90.2	57.5	43.1	16.0	**0.024**	81.8	49.5	21.2	12.0	0.415
≥30	34 (60.7)	94.1	88.1	48.4	20.0		94.0	87.5	55.3	NR		88.1	59.8	25.7	14.0	
SBRT dose per fraction (Gy)																
≤6	41 (73.2)	92.7	77.6	46.8	20.0	0.198	97.3	85.9	64.4	NR	**<0.001**	90.0	59.3	25.5	14.0	0.098
>6	15 (26.8)	93.3	93.3	14.4	16.0		80.0	53.3	28.4	14.0		73.3	46.7	NE	10.0	
$BED_{\alpha/\beta Gy10}$																
<48	23 (41.0)	87.0	69.1	18.7	15.0	**0.020**	90.2	57.5	43.1	16.0	**0.024**	82.4	49.8	NE	12.0	0.447
≥48	33 (59.0)	97.0	90.8	49.9	20.0		93.9	87.4	55.2	NR		87.8	59.6	25.6	14.0	

OS: Overall survival; LC: local control; DMFS: distant metastasis-free survival; ECOG: Eastern Cooperative Oncology Group; cT stage: clinical tumor stage, cN stage: clinical nodal stage; NE: not evaluable; NR: not reached; SBRT: stereotactic body radiotherapy; BED: biologically effective dose. Statistically significant *p*-values are shown in bold.

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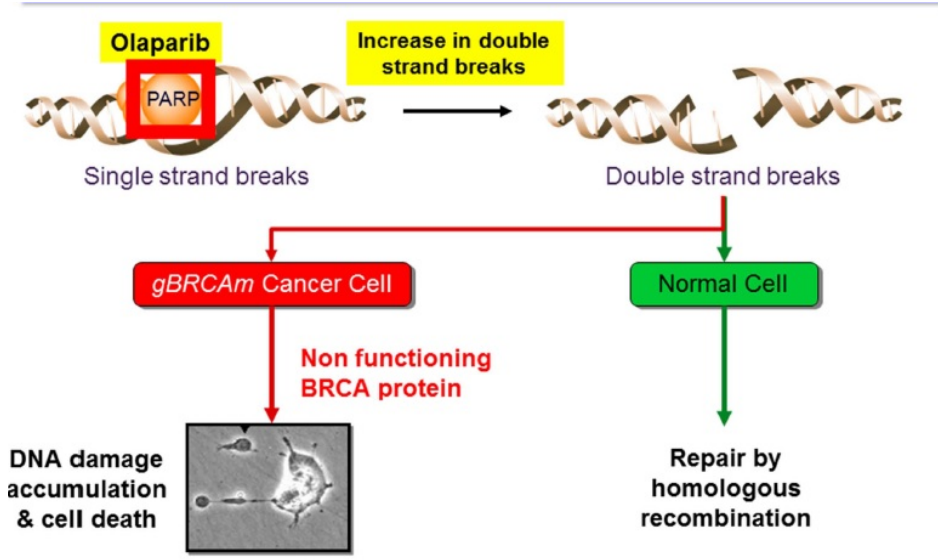
Pancreatic Cancer (PDAC)

- Resectable pancreatic cancer
- Borderline Resectable
- Locally Advanced
- Metastatic cancer

PARP inhibitors in metastatic cancer

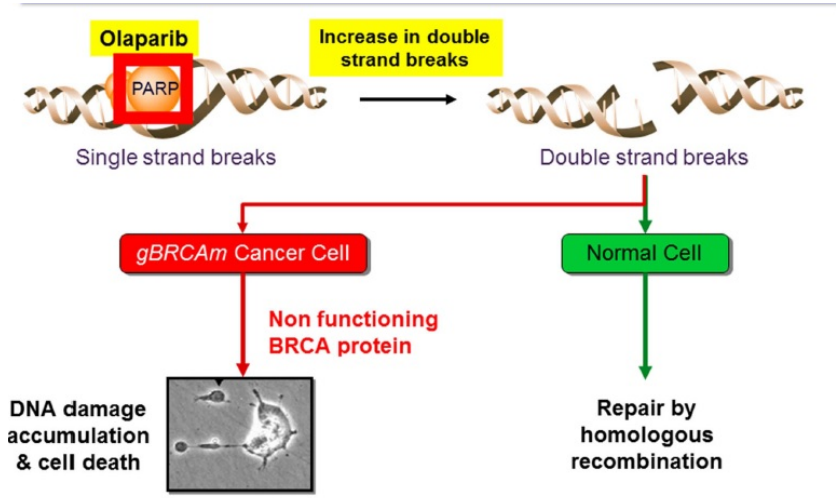


BRACA1 and BRACA 2 mutated:
cells with a deficiency
in homologous recombination repair

→ good response to CDDP

→ sensitive to PARP- Inhibitors

Olaparib Mantenance treatment: Polo Trial



ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Randomized phase III trial (3:2), double-blind

METASTATIC

BRACA-1 or BRACA-2 mutated

No PD after cis-platin based CT

PRIMARY END-POINT: PFS

154 enrolled patients (92 olaparib vs 62 placebo)

Golan T et al, ASCO & NEJM 2019

Olaparib Mantenance treatment: Polo Trial

ORIGINAL ARTICLE

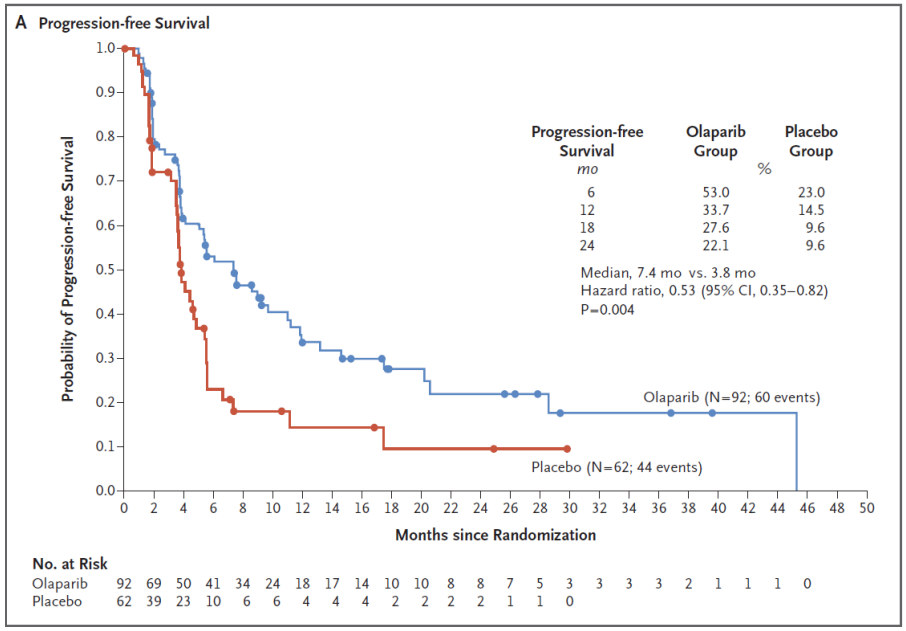
Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

	OLAPARIB	PLACEBO
RESPONSE RATE	23%	12%
MEDIAN DURATION OF RESPONSE	24,9 m	3,7 m
SERIOUS ADVERESE EVENTS	24%	15%

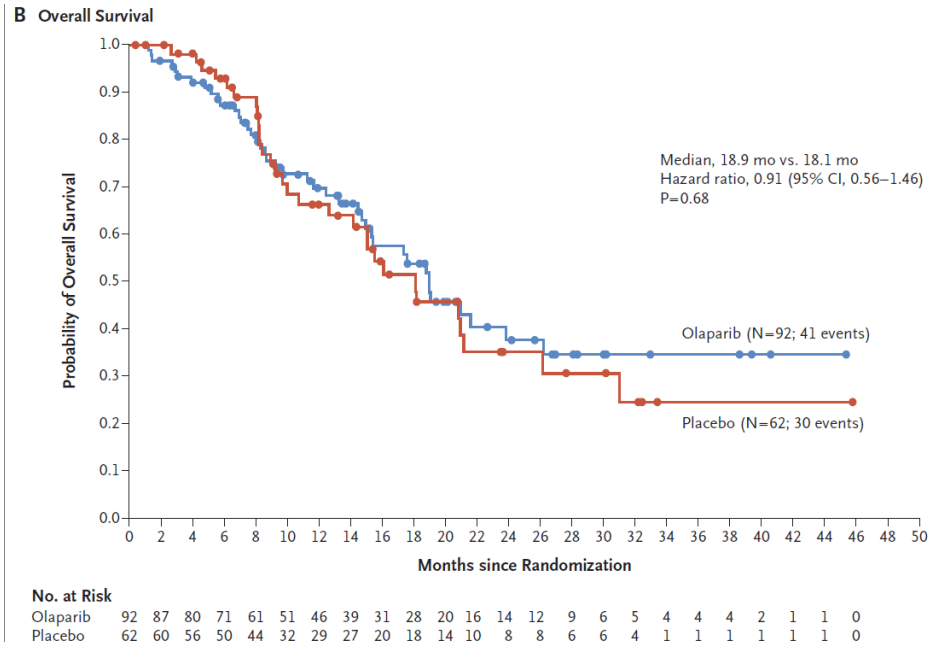
Golan T et al, ASCO & NEJM 2019

Olaparib Mantenance treatment: Polo Trial

PFS: 7.4 vs 3.8 months, HR= 0.53 (95% CI, 0.35-0.82) p= 0.004



OS: 18.9 vs 18.1 months, HR= 0.91



Golan T et al, ASCO & NEJM 2019

Pancreatic Cancer (PDAC)

- **Resectable pancreatic cancer**→ adj CT: according to PS
  - FOLFIRINOX→ doublet GEM/CAPE→ GEM monotherapy
  - GEM + nab paclitaxel option for pts ineligible to FOLFIRINOX
- **Borderline Resectable**→ preop CTRT increases R0 resection, DFS, NO OS
- **Locally Advanced**→ gem + nab paclitaxel better results than monotherapy; consider SBRT is
- **Metastatic cancer**→ PARP inhibitors in *BRACA mutated*

Locally adcvanced rectal cancer (LARC)

- Preop treatment intensification
- Total Neoadjuvant Therapy **(TNT)**

Locally adcvanced rectal cancer (LARC)

- Preop treatment intensification
- Total Neoadjuvant Therapy **(TNT)**

Preoperative intensification

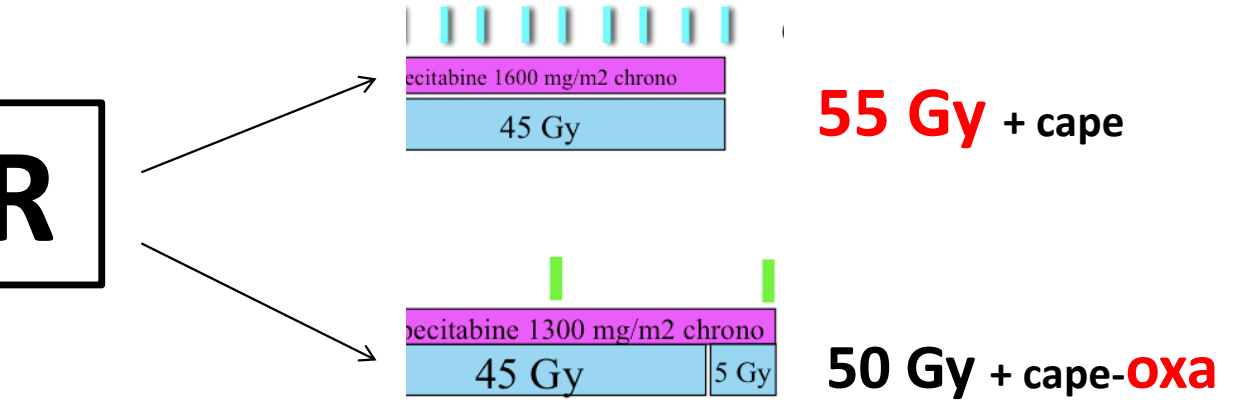
Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)–cT3 rectal cancer

534 resectable
T3 N0-1
Low T2 N1



Valentini V et al. Radiother Oncol 2019

Preoperative intensification

INTERACT ITALIAN TRIAL

Tumor Response

	XELAC	XELOX	p
TRG1	32.3%	32.9%	ns
TRG1-2	61%	52.3%	0.039
pCR	26%	26%	ns

Acute toxicity

ACUTE	XELAC	XELOX	p
hemat	8.7%	18%	0.011
GI	16.9%	10.2%	0.054
Neuro	1.7%	21%	0.001

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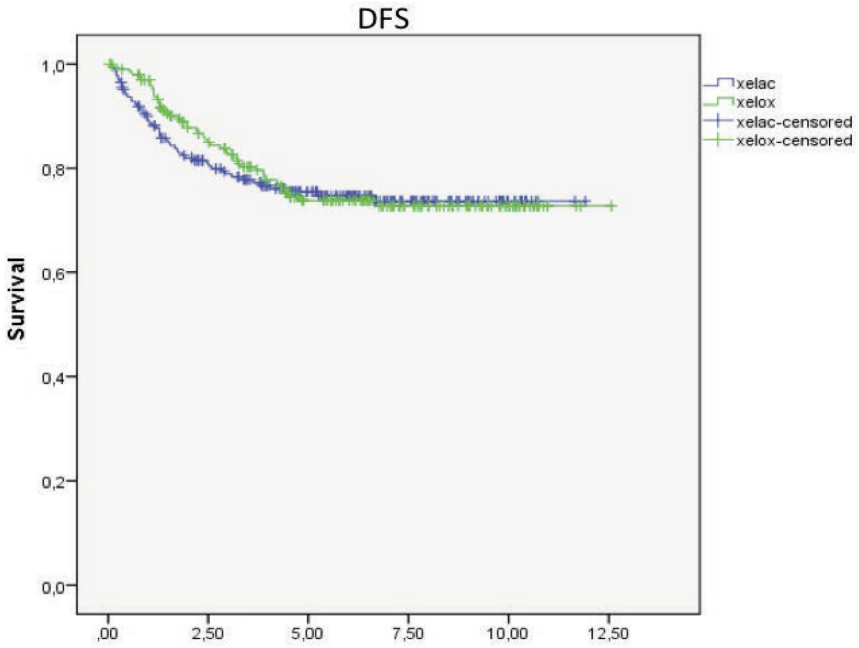
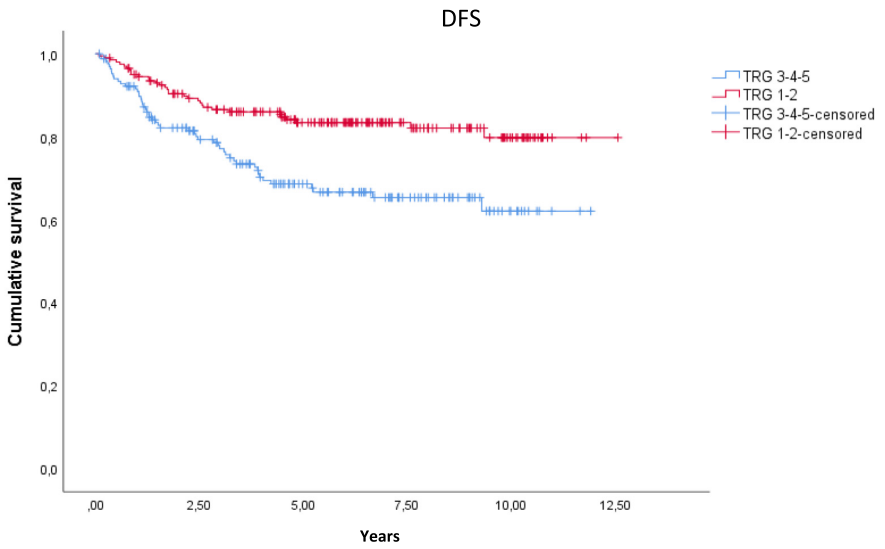
Preoperative intensification

INTERACT ITALIAN TRIAL

All patients



According to TRG



Valentini V et al. Radiother Oncol 2019

Locally adcvanced rectal cancer (LARC)

- Preop treatment intensification
- Total Neoadjuvant Therapy **(TNT)**

Total Neoadjuvant Therapy

Preoperative RTCT in LARC

- < 10% local recurrence
- 25% Distant metastases
- 65% overall survival
- 50% Compliance to post-op CT
- 15% pCR rate Induction

- Post CT do not decrease DM
- Induction CT may decrease DM and increase pCR

Total Neoadjuvant Therapy

original report

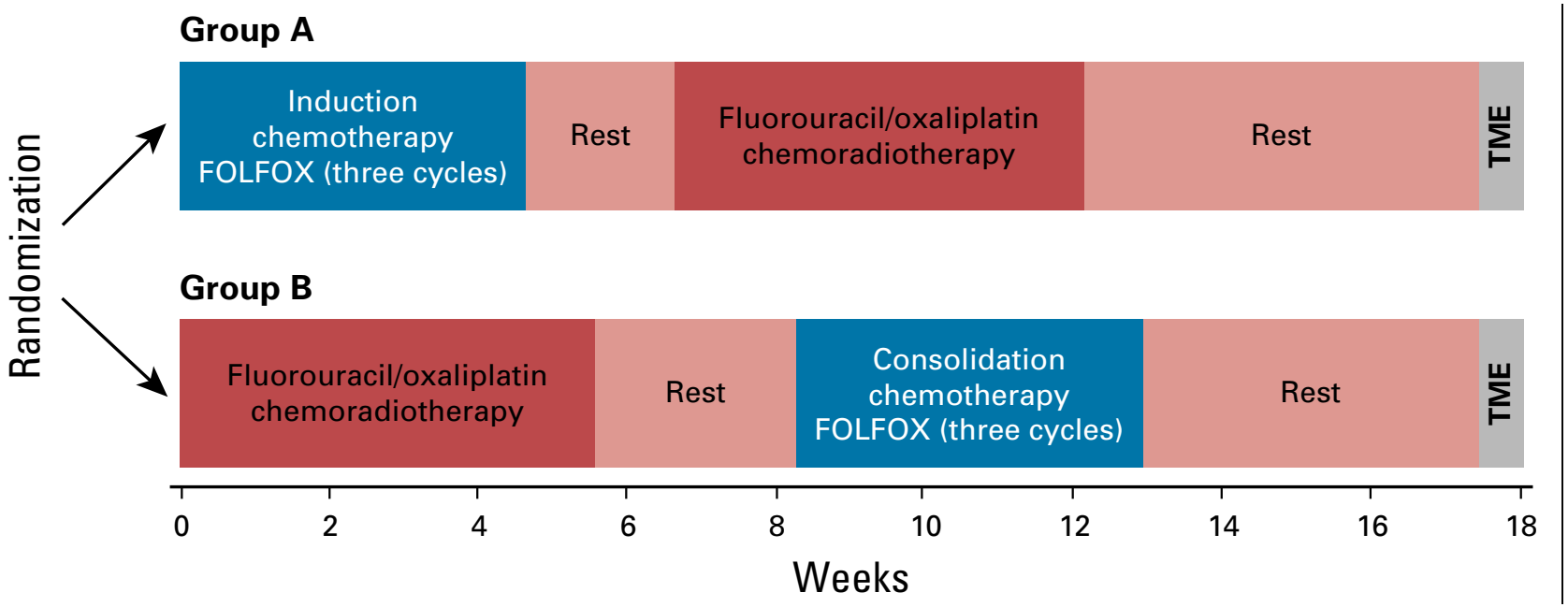
Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12

Emmanouil Fokas, MD, DPhil[1,2,3,4]; Michael Allgäuer, MD[5]; Bülent Polat, MD[6]; Gunther Klautke, MD[7]; Gerhard G. Grabenbauer, MD[8]; Rainer Fietkau, MD[9]; Thomas Kuhnt, MD[10]; Ludger Staib, MD[11]; Thomas Brunner, MD[12,13]; Anca-Ligia Grosu, MD[12]; Wolff Schmiegel, PhD, MD[14]; Lutz Jacobasch, MD[15]; Jürgen Weitz, MD[2,16,17]; Gunnar Folprecht, MD[2,16,17]; Anke Schlenska-Lange, MD[2]; Michael Flentje, MD[6]; Christoph-Thomas Germer, PhD[6]; Robert Grützmann, MD[9]; Matthias Schwarzbach, MD[18]; Vittorio Paolucci, MD[19]; Wolf O. Bechstein, MD[1]; Tim Friede, PhD[20]; Michael Ghadimi, MD[20]; Ralf-Dieter Hofheinz, MD[21]; and Claus Rödel, MD[1,2,3,4]; on behalf of the German Rectal Cancer Study Group

- Patients with **stage II or III** rectal cancer
- Multicenter, **randomized**, phase II trial pick the winner
- Endpoint: increase of **pCR** from **15%** after standard CRT to **25%** after TNT

Total Neoadjuvant Therapy

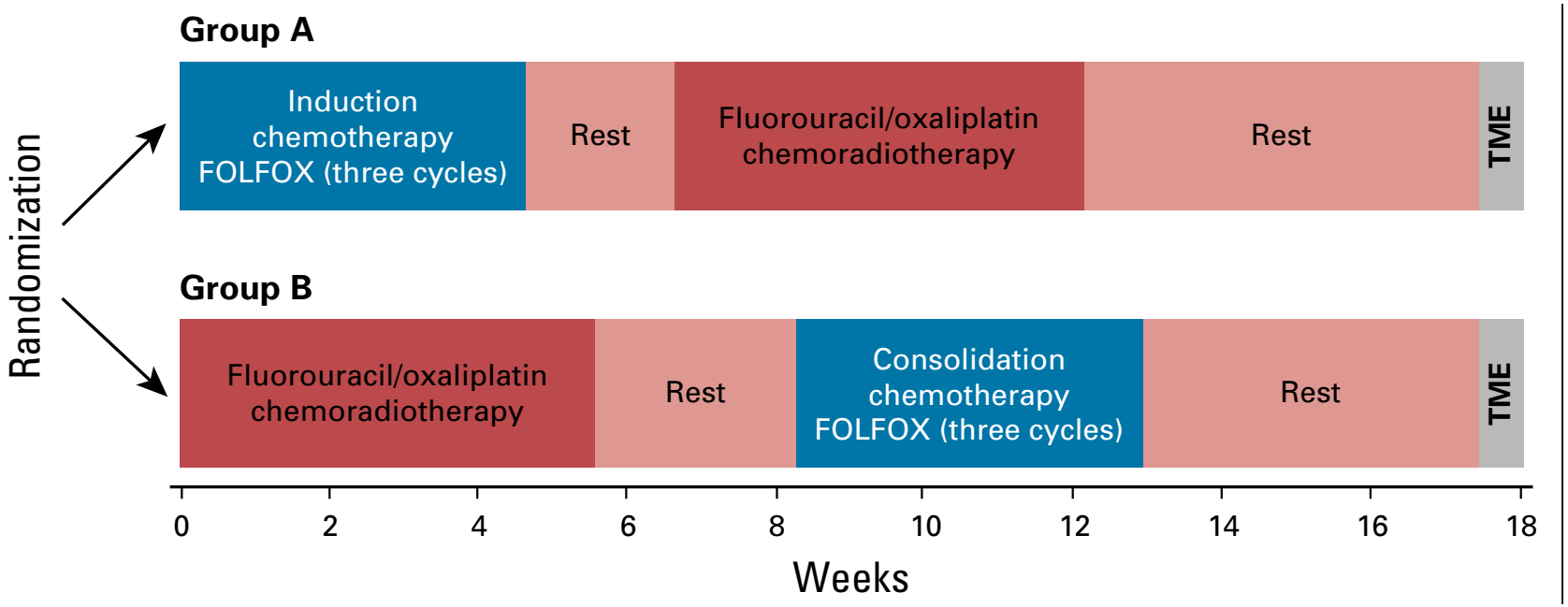
LARC
Stage II-III
306 pts



Primary end point is pCR

Total Neoadjuvant Therapy

LARC
Stage II-III
306 pts



306 pts enrolled

156 in group A

150 in group B

Total Neoadjuvant Therapy

End point	GROUP A	GROUP B
Full RT dose	91%	**97%**
Full conc 5 FU dose	78%	**87%**
Full conc oxa dose	76%	**93%**
Full 5FU dose	**93%**	90%
Full oxa dose	**92%**	85%
Median int to Surg	127 days	127 days
G3 acute tox	**37%** (diarrhea 14%)	**27%** (diarrhea 8%)
NO surgical complication	**54%**	**65%**

Fokas E et al JCO 2019

Total Neoadjuvant Therapy

End point	GROUP A	GROUP B
pCR (pT0N0)	**17%** (p < 0.001)*	**25%** (p= 0.21)*
pCR + cCR (10 pts rejected surgery)	21%	**28%**
R0 resection	92%	90%
Sphincter saving	68%	72%
TRG 4-3	41%	**50%**
Low NAR score	26%	**35%**
Good quality TME	85%	82%
CRM ≤ 1 mm	10%	7%

* Compared to expected 15% after CRT

Fokas E et al JCO 2019

Total Neoadjuvant Therapy

- Consolidation CT achieved better pCR
- Compliance to CRT was better in consolidation CT
- Different waiting time between the end of RTCT and surgery (45d Group A vs 90d group B) may have contributed on tumor response
- pCR surrogate for long term outcomes (?)
- Long term outcomes are awaited
- CAO-ARO-AIO-18 phase III trial: standard CRT vs CRT-CT

Locally adcvanced rectal cancer (LARC)

- **Preop treatment intensification**→ Dose intensification same results than oxaliplatin with less toxicity
- **Total Neoadjuvant Therapy (TNT)**→ increases pCR, long term outcomes awaited