Update in Upper Gastrointestinal Cancers

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Disclosure

- Employer- Massachusetts General Hospital
- Consulting
  - Synthetic Biologics
  - Novocure
  - Merck
  - Syndax
- Research Funding (Clinical Trials)
  - Taiho
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  - BMS
  - Tesaro
  - IntraOp
  - Ipsen
  - Puma
  - SU2C/Lustgarten Pancreatic Cancer Collective

Learning Objectives

- To understand emerging data regarding dose escalation and adjuvant immunotherapy in esophageal cancer
- To critically evaluate neoadjuvant treatment paradigms for borderline resectable pancreatic cancer
- To understand the role of dose escalation in locally advanced pancreatic cancer

Outline

- Esophageal Cancer
- Borderline Resectable Pancreas Cancer
- Locally Advanced Pancreatic Cancer

Outline

- Esophageal Cancer
  - Role of adjuvant immunotherapy- Checkmate 577
  - Dose escalation Re-visited- ART DECO
  - Role of Trastuzumab in neoadjuvant therapy for esophageal cancer- RTOG 1010
- Borderline Resectable Pancreas Cancer
- Locally Advanced Pancreatic Cancer

Esophageal Cancer

- Preoperative chemoradiation is standard of care per CROSS trial
- Chemoradiation can be given as definitive therapy in non-operative patients

Adjuvant Immunotherapy after preoperative chemoradiation

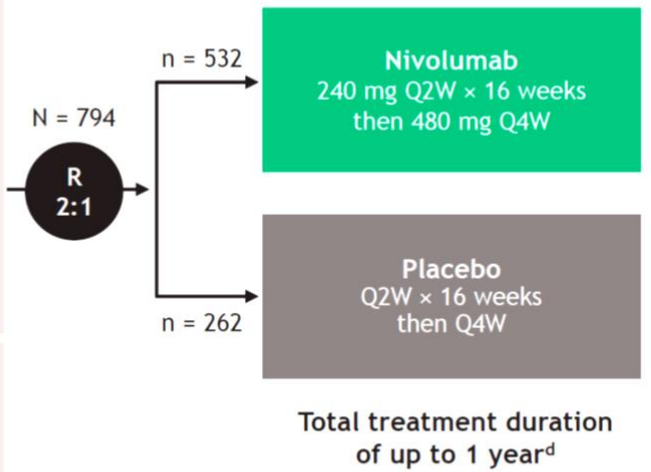
- Checkmate 577 (Kelly RJ, et al, ESMO 2020)

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2-44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

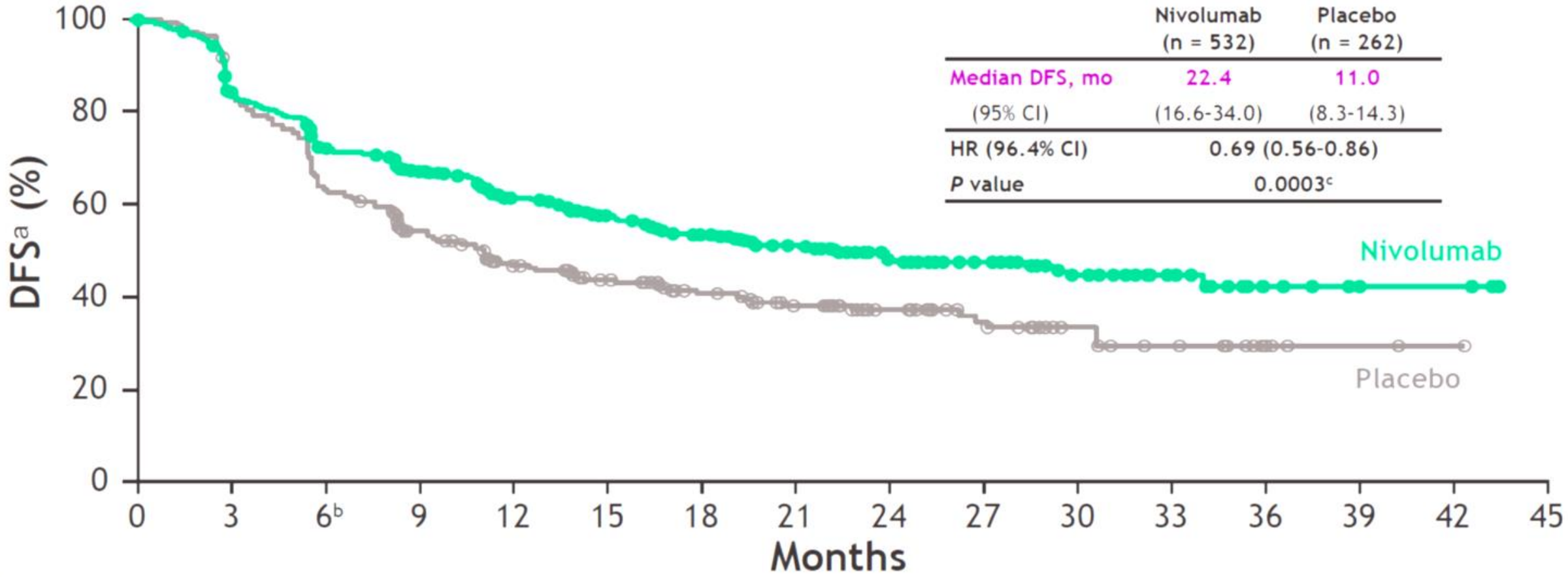
[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Baseline characteristics

	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62.0 (26-82)	61.0 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis, %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology, %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor cell PD-L1 expression,[b] %		
≥ 1%	17	15
< 1%	70	75
Indeterminate/nonevaluable	13	10

[a]Other races not shown; [b]Tumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

Disease-free survival



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

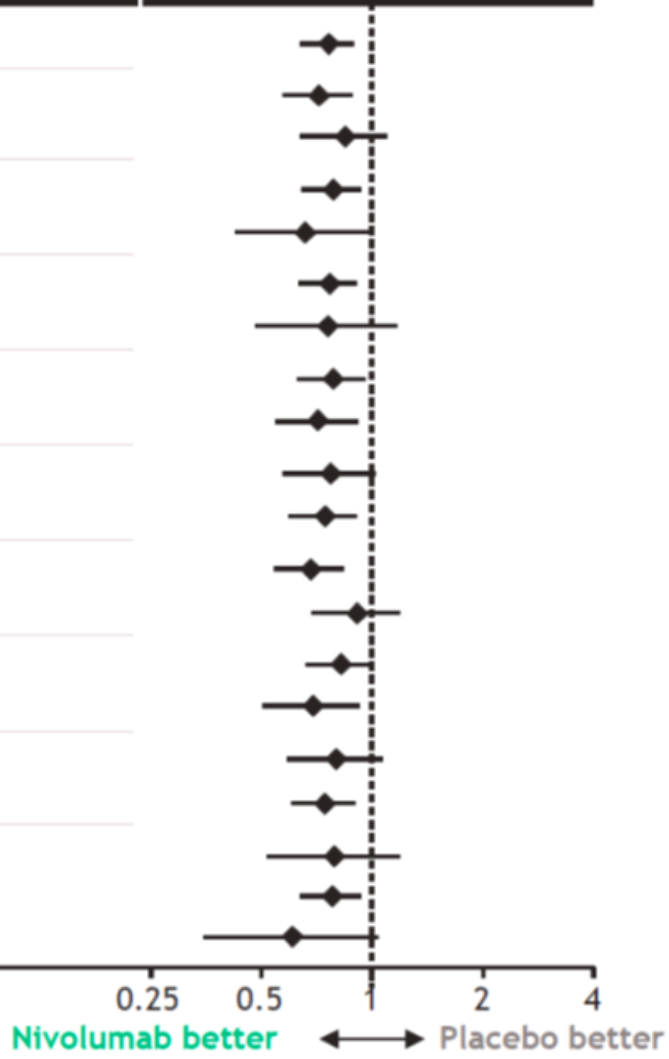
No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the pre-specified interim analysis required the *P* value to be less than 0.036.

Disease-free survival by subgroups

Subgroup		Median DFS, months		Unstratified HR
		Nivolumab	Placebo	
Overall (N = 794)		22.4	11.0	0.70
Age, years	< 65 (n = 507)	24.4	10.8	0.65
	≥ 65 (n = 287)	17.0	13.9	0.80
Sex	Male (n = 671)	21.4	11.1	0.73
	Female (n = 123)	Not reached	11.0	0.59
Race	White (n = 648)	21.3	10.9	0.71
	Asian (n = 117)	24.0	10.2	0.70
ECOG PS	0 (n = 464)	29.4	11.1	0.73
	1 (n = 330)	17.0	10.9	0.66
Disease stage at initial diagnosis	II (n = 278)	34.0	13.9	0.72
	III (n = 514)	19.4	8.5	0.68
Tumor location	EC (n = 462)	24.0	8.3	0.61
	GEJC (n = 332)	22.4	20.6	0.87
Histology	Adenocarcinoma (n = 563)	19.4	11.1	0.75
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74
	≥ ypN1 (n = 457)	14.8	7.6	0.67
Tumor cell PD-L1 expression	≥ 1% (n = 129)	19.7	14.1	0.75
	< 1% (n = 570)	21.3	11.1	0.73
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54



- DFS favored nivolumab versus placebo across these pre-specified subgroups

Checkmate 577 Conclusions

- Adjuvant nivolumab improves DFS in esophageal cancer after preoperative chemoradiation
- All subgroups trend towards benefit

Dose Escalation for inoperable esophageal cancer

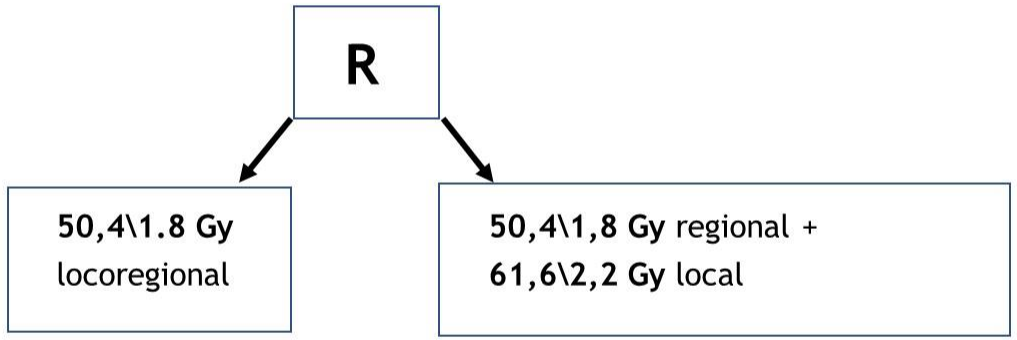
- LF rate after definitive chemoRT is ~50%
- INT0123 failed to show a benefit to dose escalation

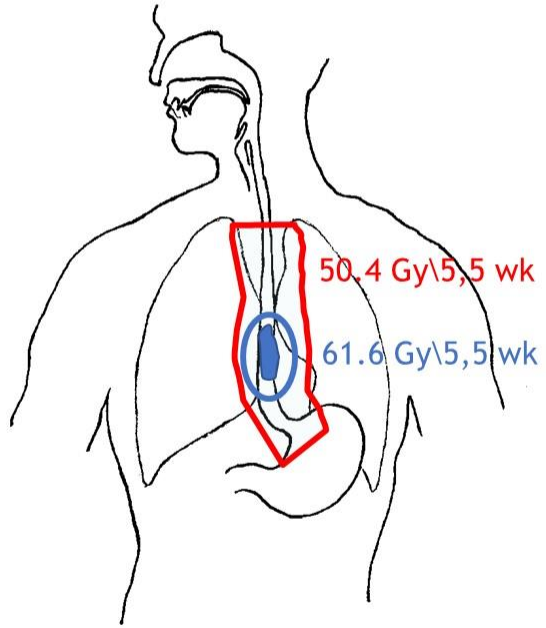
ART DECO SCHEMA

Amsterdam UMC
Universitair Medische Centra

Trial design

Inclusion T2-4a,N0-3,M0





Weekly (6 times) concurrent Carboplatin (2x AUC) and Paclitaxel (50 mg\m^2)

Stratification for histological subtype

Presented By Maarten Hulshof at 2020 Gastrointestinal Cancer Symposium

ART DECO Objectives

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Objectives and statistics

Primary objective:
To improve local tumor control with 15%: from 50% → 65%

Secondary objectives:
Overall survival, toxicity and locoregional control

Statistics:
For 80% power at a 2-sided log-rank test, with a 0.05 significance: 260 patient needed

Trial completed in 5,5 years (june 2018)

Median FU at analysis: 48 months

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Tumor and patient characteristics

	Standard arm (n=130)	Boost arm (n=130)
Mean age	70	71
WHO	0: 44% 1: 45% 2: 10%	0: 32% 1: 59% 2: 9%
Squamous cell carc Adenocarc	61% 39%	63% 37%
Localization	Cervical: 6% Upper thoracic: 25% Mid thoracic: 21% Lower thoracic: 40% GEJ: 7%	3% 21% 31% 39% 6%
T stage	T2-3: 86% T4: 6%	88% 8%
N stage	N0: 25% N1: 45% N2: 22% N3: 7%	28% 43% 25% 4%
Medically unfit	28%	31%

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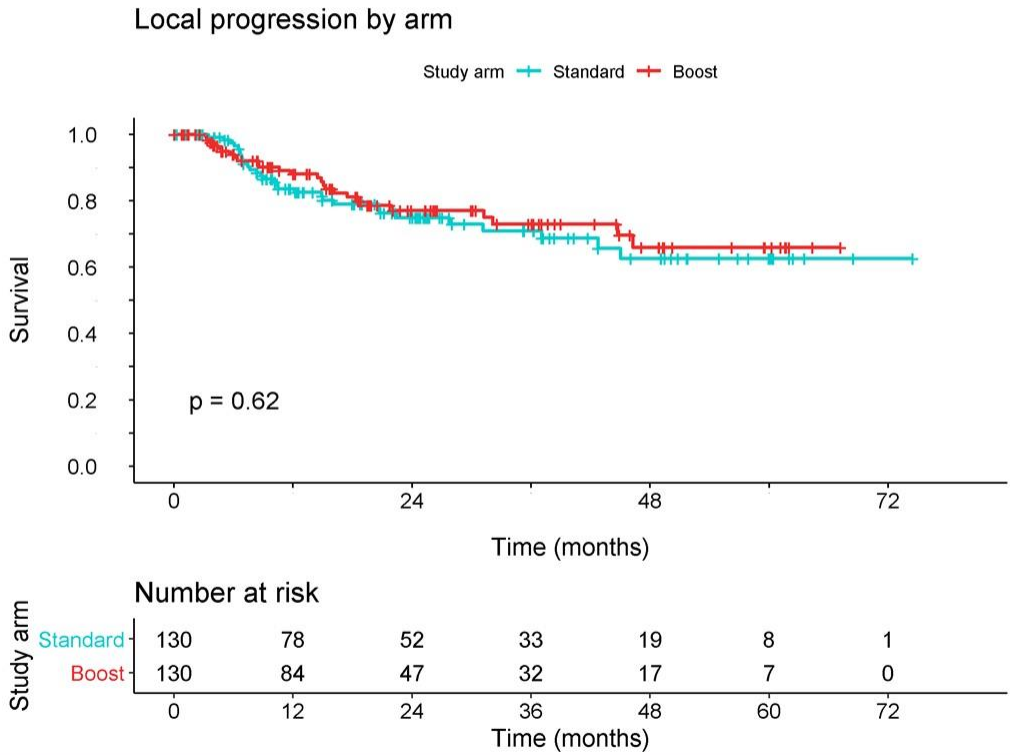
Results



3-year Local progression free survival:
Standard: 71%
Boost : 73%

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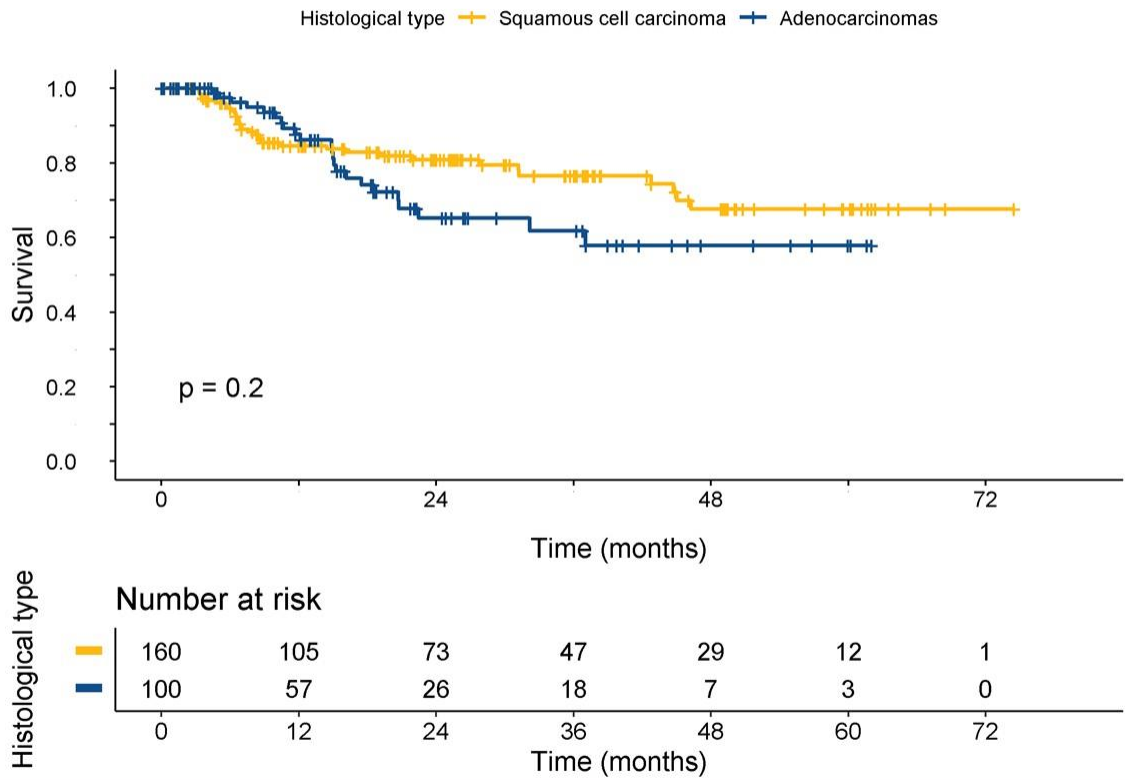
Local progression by histological type



3-year local progression free survival:
SCC: 77%
AC : 62%

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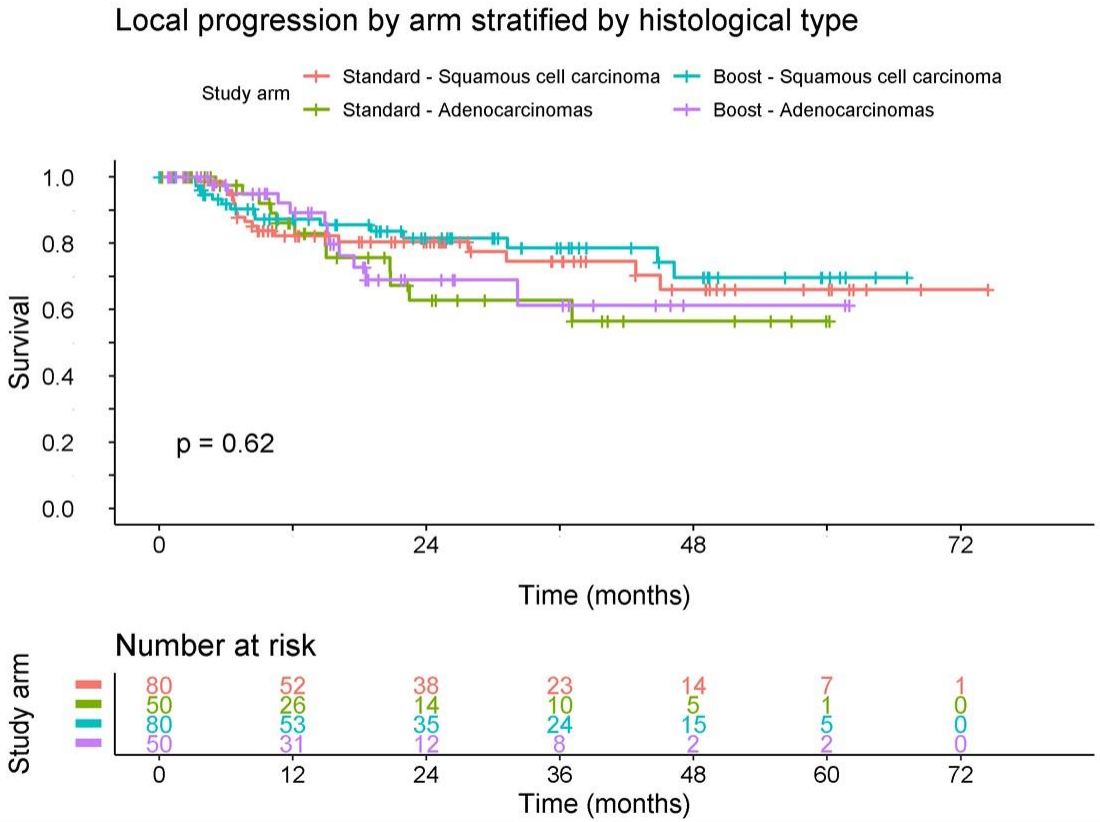

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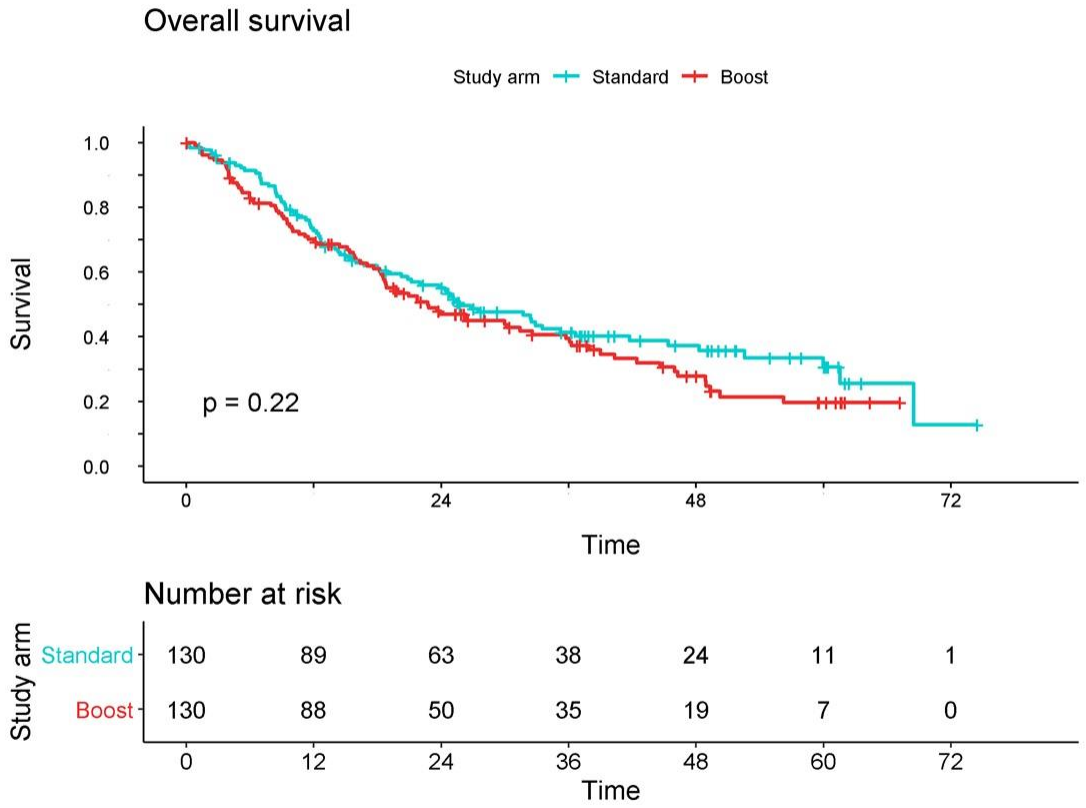

3-year overall survival:
Standard: 41%
Boost : 40%

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ART DECO CONCLUSIONS

- No benefit to dose escalation
- Confirms the results of INT0123 in the modern era
  - Modern staging
  - Modern treatment techniques

HER2 Expression In Esophageal Adenocarcinoma
RTOG 1010

- The human epidermal growth factor receptor 2 (HER2) is a member of a family of receptors associated with tumor cell proliferation.
- HER2 gene overexpression occurs in 19-32% of esophageal adenocarcinoma.
- The HER2 gene encodes a transmembrane glycoprotein receptor, $p185^{HER2}$, that is targeted by the humanized anti-$p185^{HER2}$ monoclonal antibody trastuzumab.
- Does adding trastuzumab help in the neoadjuvant setting?

Safran H, et al, ASCO 2020.

Schema

STEP 1 REGISTRATION

↓

HER2 Testing
Mandatory submission of tissue for HER2 testing

↓

STEP 2 REGISTRATION

STRATIFY

Presence of adenopathy: No vs. Yes—celiac absent vs. Yes—celiac present ≤ 2 cm

RANDOMIZE

↓	↓
Arm 1 Radiation (50.4 Gy), paclitaxel, carboplatin, and trastuzumab Followed by surgery 5-8 weeks after completion of radiation Then maintenance trastuzumab, every 3 weeks for 13 treatments	**Arm 2** Radiation (50.4 Gy), paclitaxel, and carboplatin Followed by surgery 5-8 weeks after completion of radiation

Treatment

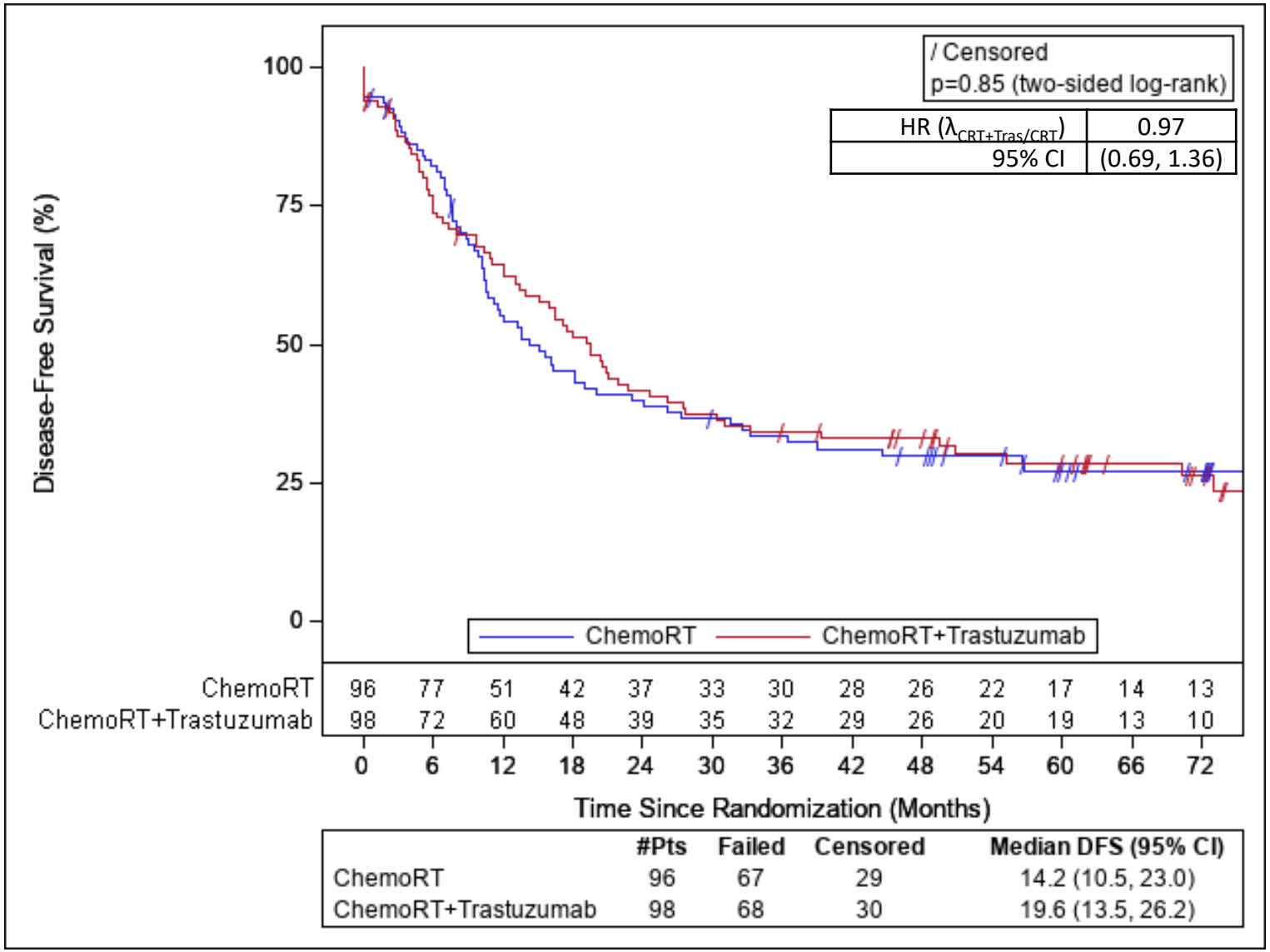
- RT: 5040 cGy in 180 cGy daily fractions (28 fx over 5 ½ weeks)
- Chemotherapy: Paclitaxel, 50 mg/m^2, and carboplatin AUC = 2, weekly for 6 weeks.
- Trastuzumab
  - 4 mg/kg week 1
  - 2 mg/kg/weekly x 5 during ChemoRT
  - 6 mg/kg for 1 dose prior to surgery
  - 6 mg/kg every 3 weeks for 13 treatments after surgery

Selected Adverse Events Related to Treatment

	ChemoRT + Trastuzumab (n=95†)	ChemoRT (n=96)
Adverse Event	**Grades ≥ 3**	**Grades ≥ 3**
Hematologic (including febrile neutropenia)	53 (56%)	55 (57%)
Cardiac disorders	5 (5%)	3 (3%)
Gastrointestinal disorders	28 (29%)	20 (21%)
Infections and infestations	11 (12%)	7 (7%)
Metabolism and nutrition disorders	12 (13%)	19 (20%)
Overall highest grade	66 (69%)	76 (79%)

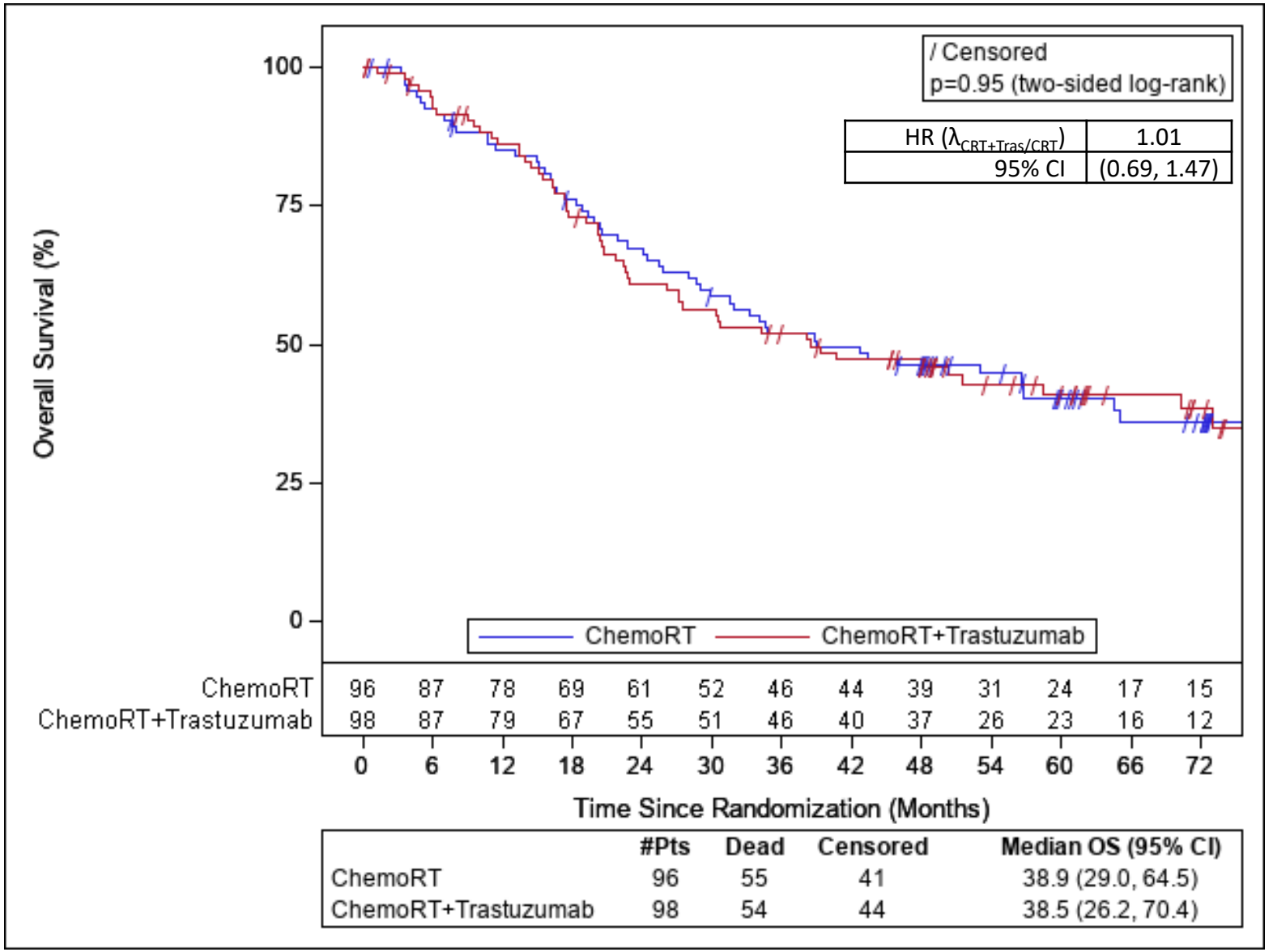
†Excludes no protocol treatment patients

Disease-Free Survival



	#Pts	Failed	Censored	Median DFS (95% CI)
ChemoRT	96	67	29	14.2 (10.5, 23.0)
ChemoRT+Trastuzumab	98	68	30	19.6 (13.5, 26.2)

Overall Survival



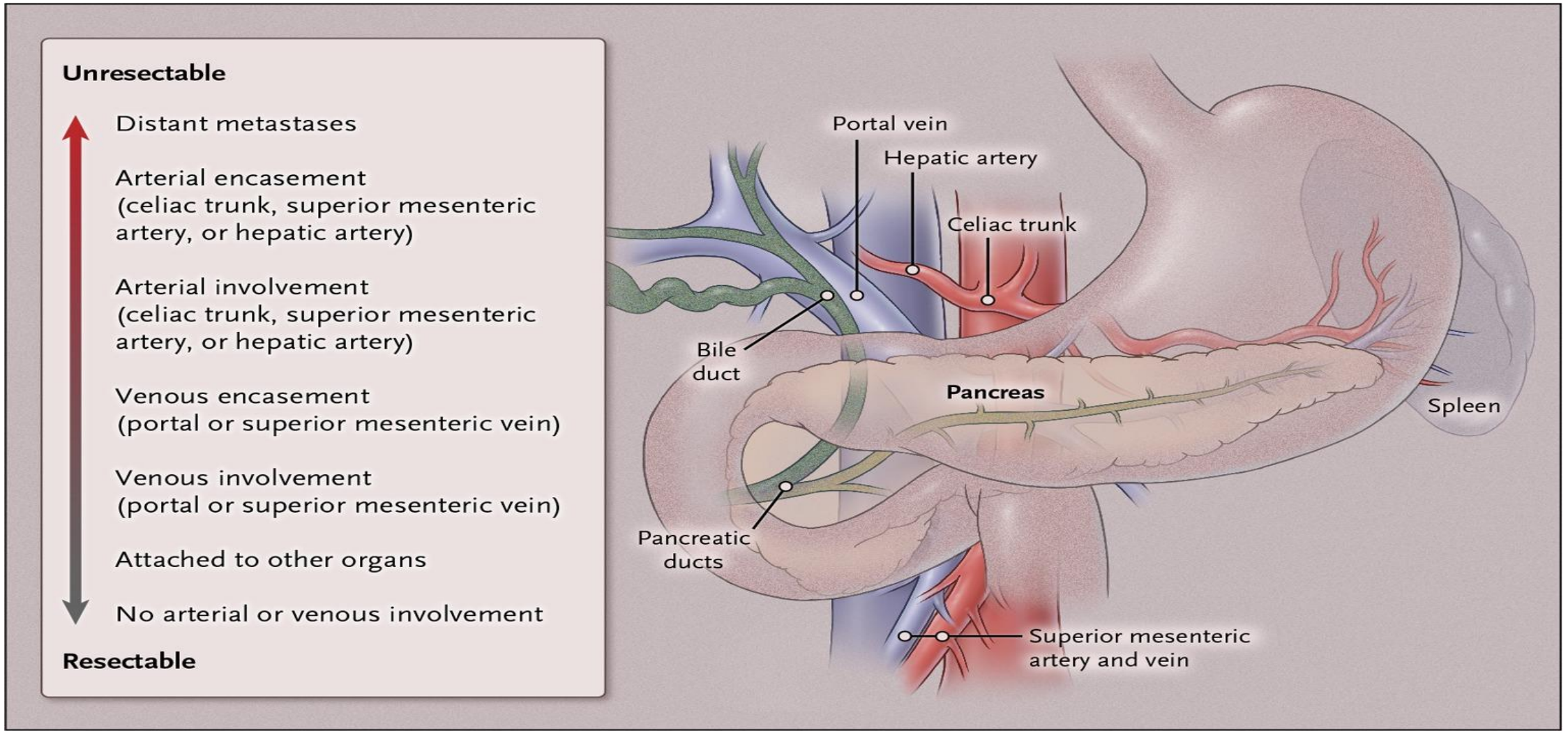
	#Pts	Dead	Censored	Median OS (95% CI)
ChemoRT	96	55	41	38.9 (29.0, 64.5)
ChemoRT+Trastuzumab	98	54	44	38.5 (26.2, 70.4)

Conclusions

- The addition of trastuzumab did not increase DFS when added to trimodality treatment of esophageal cancer.
- The addition of trastuzumab did not increase pathologic complete response or OS.
- There was no increase in cardiac toxicity or other adverse events with the addition of trastuzumab.

Outline

- Esophageal Cancer
- Borderline Resectable Pancreas Cancer
  - Radiation for borderline resectable pancreatic cancer
- Locally Advanced Pancreatic Cancer



Ryan DP et al. N Engl J Med 2014;371:1039-1049

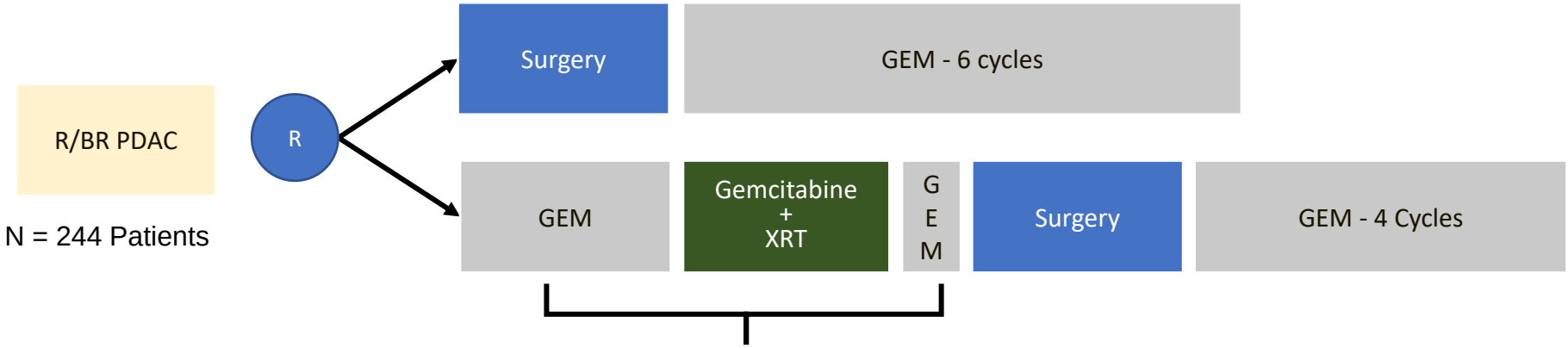
Pancreatic Cancer

- Borderline Resectable (Alliance Definition)
  - (1) a tumor-vessel interface (TVI) with the superior mesenteric vein (SMV) or portal vein (PV) measuring 180° or more of the circumference of either vein's wall, or short-segment occlusion of either vein with a normal vein above and below the obstruction amenable to reconstruction;
  - (2) any TVI with the common hepatic artery (CHA) with a normal artery proximal and distal to the TVI amenable to reconstruction; and
  - (3) a TVI with the superior mesenteric artery (SMA) measuring less than 180° of the circumference of the vessel wall

Neoadjuvant Therapy

- Potential benefits
  - Better tolerated
  - May facilitate R0 resection
  - Earlier incorporation of the most active systemic regimen
  - May allow for better selection of patients for surgery

Preoperative Radiochemotherapy Versus Immediate Surgery For (Borderline) Resectable Pancreatic Cancer: (PREOPANC)



Primary Endpoint: ITT Overall Survival

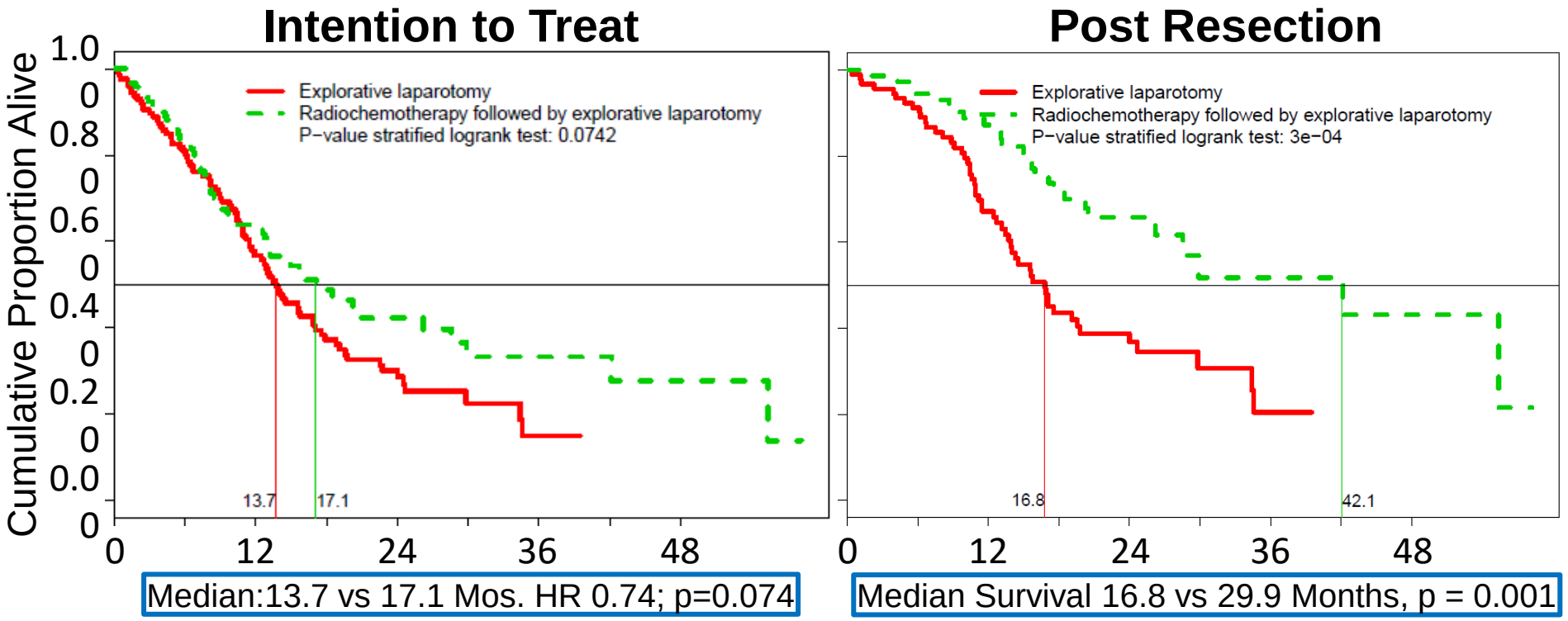
RT- 2.4 Gy x 15=36 Gy

Versteijne E, et al. JCO 2020;38:1763-1773

Resection Rate

	Immediate Surgery N=127	Neoadjuvant CRT N=119	P-value
Resection Rate (%)	72	62	.065
R0 Resection Rate PP (%)	31	63	<.001
Serious Adverse Events(%)	39	46	<.28

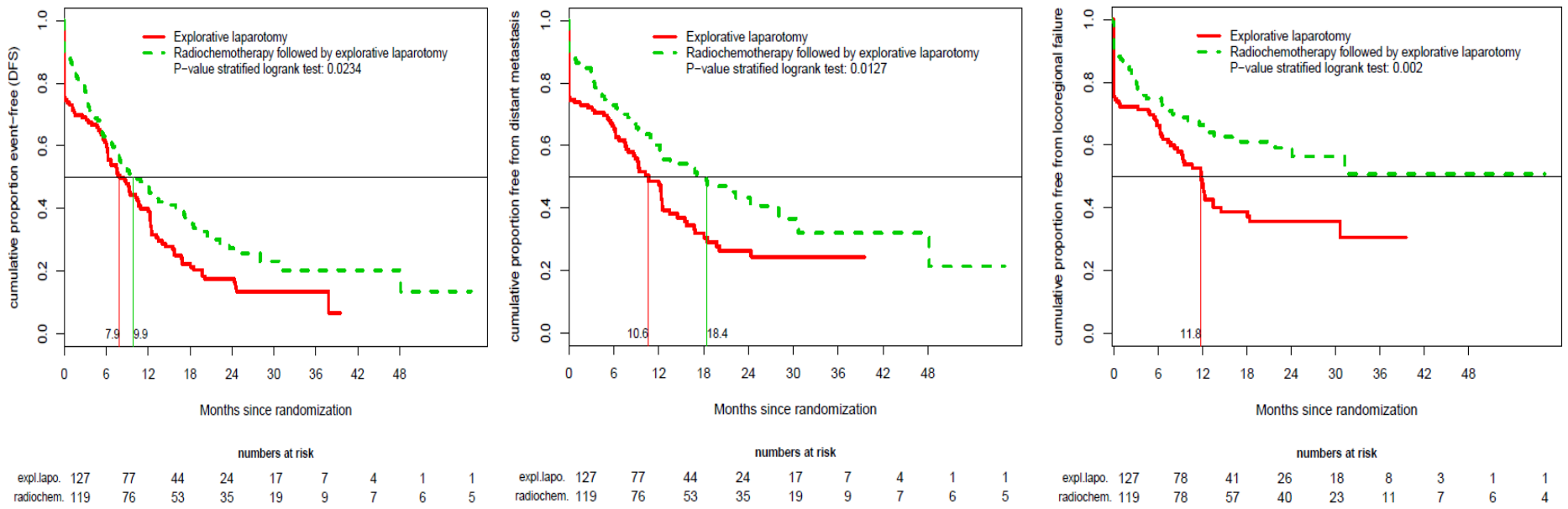
Overall Survival Analyses



Median:13.7 vs 17.1 Mos. HR 0.74; p=0.074

Median Survival 16.8 vs 29.9 Months, p = 0.001

Disease-Free Survival



DFS

DFS: 7.9 vs 9.9 Months, HR 0.71; p=0.023

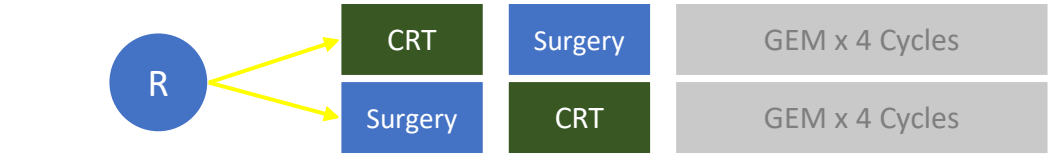
DMFS

HR 0.71; p = 0.013

Locoregional failure-free survival

HR 0.55; p = 0.002

Neoadjuvant Versus Adjuvant – Chemoradiation (CRT): Korean Borderline Study



N = 110 BRPC Planned
N = 57 BRPC Enrolled

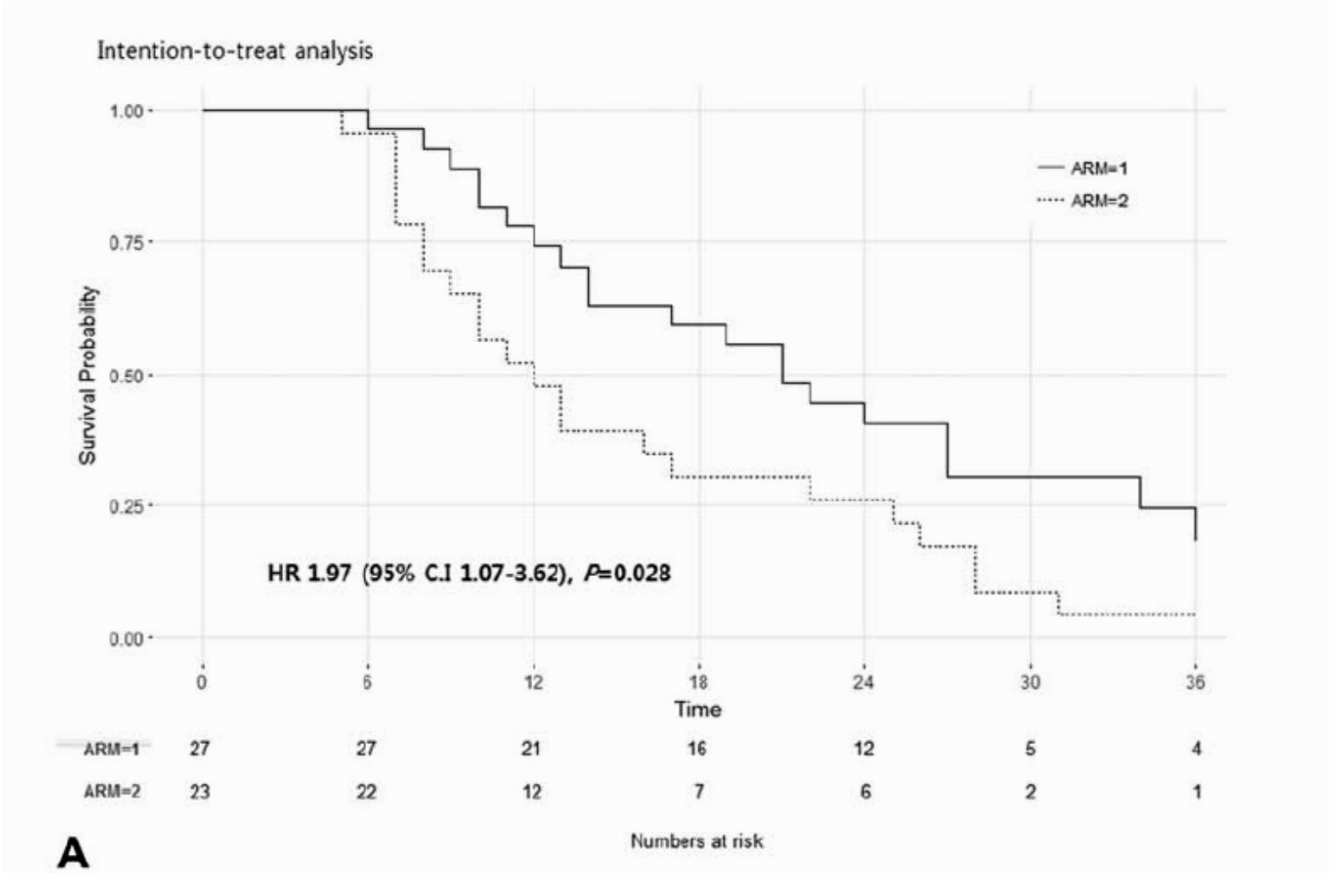
Primary Endpoint = 2-Yr Survival

	Neoadjuvant CRT	Adjuvant CRT	
2 year survival - ITT	**40%**	26%	p = 0.004
Median OS (months) – ITT	**21**	12	HR 1.97; p = 0.028
R0 Resection Rate - ITT	**51%**	26%	p = 0.004
R0 Resection Rate - Resected	**82%**	33%	p = 0.010
Positive Lymph Nodes	**0.5 ± 0.9**	1.9 ± 1.6	p = 0.004

CRT- 1.8 Gy x 30 =54 Gy with gemcitabine

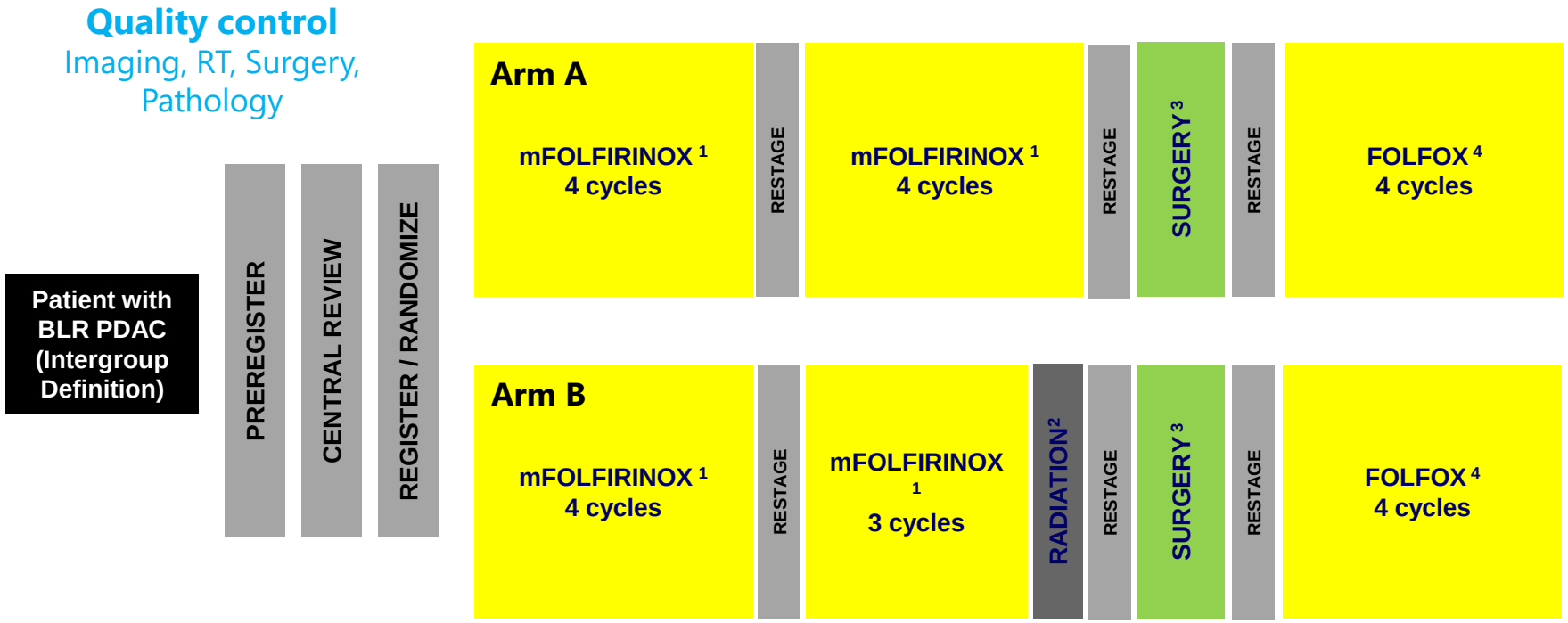
Jang, J-Y et al, Annals of Surgery 2018

Neoadjuvant Versus Adjuvant – Chemoradiation (CRT): Korean Study



Jang, J-Y et al, Annals of Surgery 2018

Alliance A021501



[1] Oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 h
[2] Stereotactic Body RT, 33-40 Gy in 5 fx or hypofractionated image guided RT, 25 Gy in 5 fx
[3] Segmental pancreatectomy with regional lymphadenectomy +/- vascular resection
[4] Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 h

Katz M, et al. GI ASCO 2021

Trial logistics

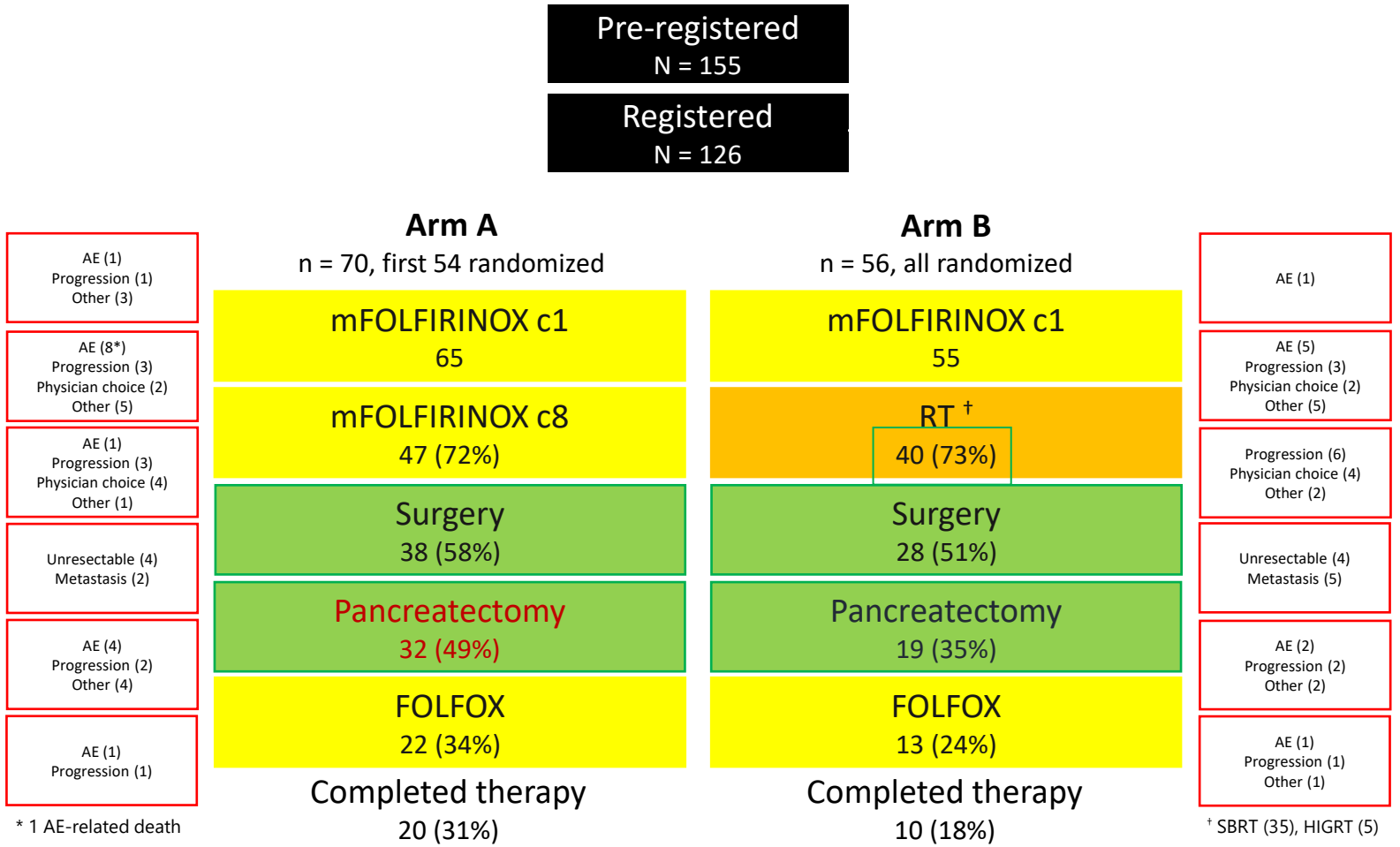
Enrollment targets, sites, and activation/closure dates

Characteristic	Trial	Arm A mFOLFIRINOX	Arm B mFOLFIRINOX → RT
Enrollment target, N	134	67	67
Activation date	12/01/2016		
Interim analysis (R0 in first 30 pts)	8/1/2018 †	17 (57%)	10 (33%)
Closure date	5/31/2019	5/31/2019	8/13/2018
Actual enrollment, N *	126	70	56

* 50 sites accrued ≧ 1 patient

† Alliance DSMB released the interim analysis data

CONSORT


Pre-registered
N = 155
Registered
N = 126
Arm A
n = 70, first 54 randomized
mFOLFIRINOX c1
65
mFOLFIRINOX c8
47 (72%)
Surgery
38 (58%)
Pancreatectomy
32 (49%)
FOLFOX
22 (34%)
Completed therapy
20 (31%)
AE (1)
Progression (1)
Other (3)
AE (8*)
Progression (3)
Physician choice (2)
Other (5)
AE (1)
Progression (3)
Physician choice (4)
Other (1)
Unresectable (4)
Metastasis (2)
AE (4)
Progression (2)
Other (4)
AE (1)
Progression (1)
* 1 AE-related death
Arm B
n = 56, all randomized
mFOLFIRINOX c1
55
RT †
40 (73%)
Surgery
28 (51%)
Pancreatectomy
19 (35%)
FOLFOX
13 (24%)
Completed therapy
10 (18%)
AE (1)
AE (5)
Progression (3)
Physician choice (2)
Other (5)
Progression (6)
Physician choice (4)
Other (2)
Unresectable (4)
Metastasis (5)
AE (2)
Progression (2)
Other (2)
AE (1)
Progression (1)
Other (1)
† SBRT (35), HIGRT (5)

Baseline profile

Baseline clinicodemographic profile of all treated patients

Characteristic	Arm A mFOLFIRINOX (n = 65)	Arm B mFOLFIRINOX → RT (n = 55)
Age, yr, median (range)	62 (37 – 83)	64 (40 – 80)
Female gender, n (%)	32 (49)	28 (51)
White race, n (%)	54 (83)	50 (91)
ECOG 0, n (%)	33 (51)	32 (58)
CA 19-9, U/ml, median (range)	167 (1 – 13,220)	260 (0 – 14,010)

Preoperative treatment-related toxicity

AE during treatment, n (%)	Arm A mFOLFIRINOX (n = 65)	Arm B mFOLFIRINOX → RT (n = 55)
Experienced ≧ 1 grade 3+ AE	37 (57)	35 (64)
During mFOLFIRINOX	37 (57)	35 (64)
During RT*	--	5 (13)
Experienced ≧ 1 grade 4+ AE	11 (17) †	5 (9)
During mFOLFIRINOX	11 (17)	5 (9)
During RT*	--	0 (0)

* 40 patients received RT

† 1 patient experienced a grade 5 AE (sepsis)

Surgery and pathology

Characteristic, n (%)	Arm A mFOLFIRINOX (n = 32)	Arm B mFOLFIRINOX → RT (n = 19)
Pancreatoduodenectomy	30 (94)	18 (95)
SMV/PV resection	12 (38)	6 (32)
Hepatic artery resection	1 (3)	2 (11)
R0, n (%)	28 (88)	14 (74)
N0, n (%)	15 (47)	9 (47)
pCR	0	2 (11) *

* < 5% viable cancer cells: Arm A 4 (13%); Arm B 5 (26%)

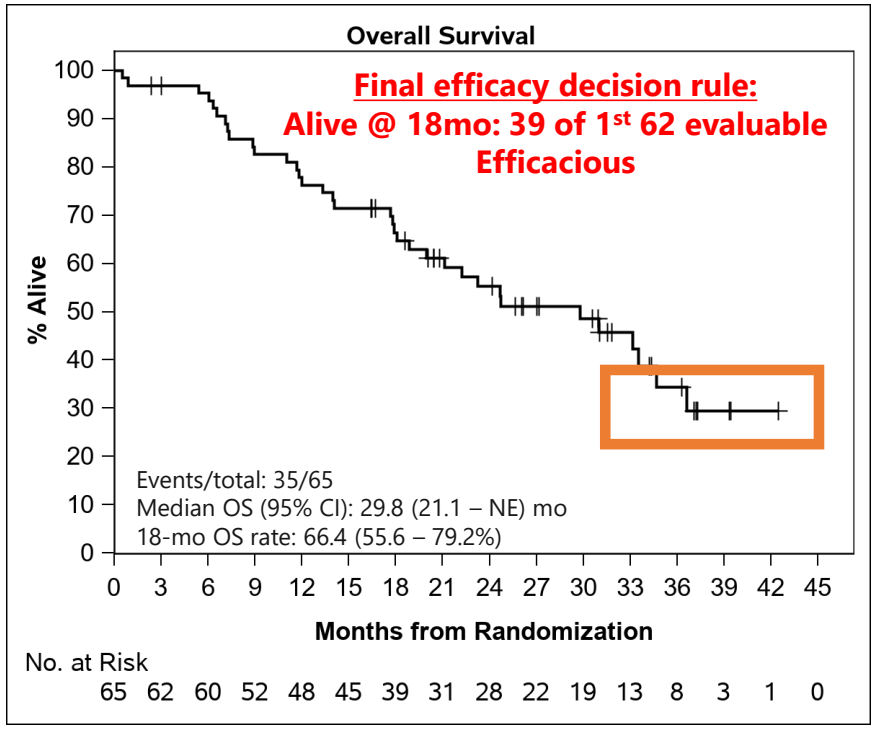
Surgical Adverse Events

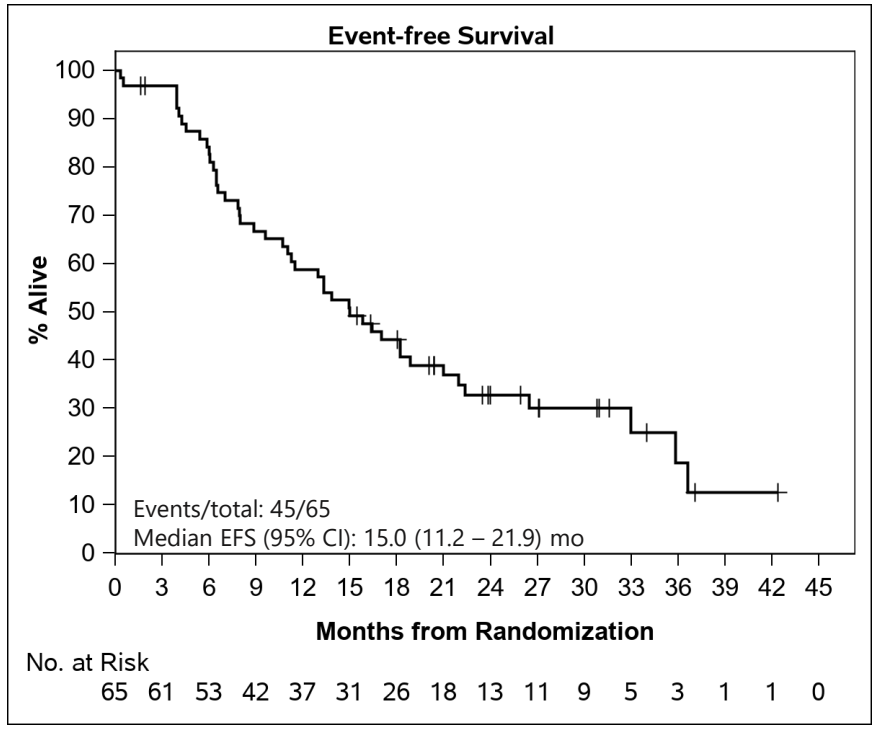
Perioperative adverse events

AE, n (%)	Arm A mFOLFIRINOX (n = 32)	Arm B mFOLFIRINOX → RT (n = 19)
Weight Loss (Grade 3+) *	3 (11)	1 (8)
Anemia (Grade 3+) *	1 (4)	2 (17)
Pancreatic fistula or intra-abdominal abscess	3 (9)	3 (16)
Wound infection	2 (6)	3 (16)
Readmission	5 (16)	8 (42)
Reoperation	4 (13)	1 (5)
Death	1 (3)	2 (11)

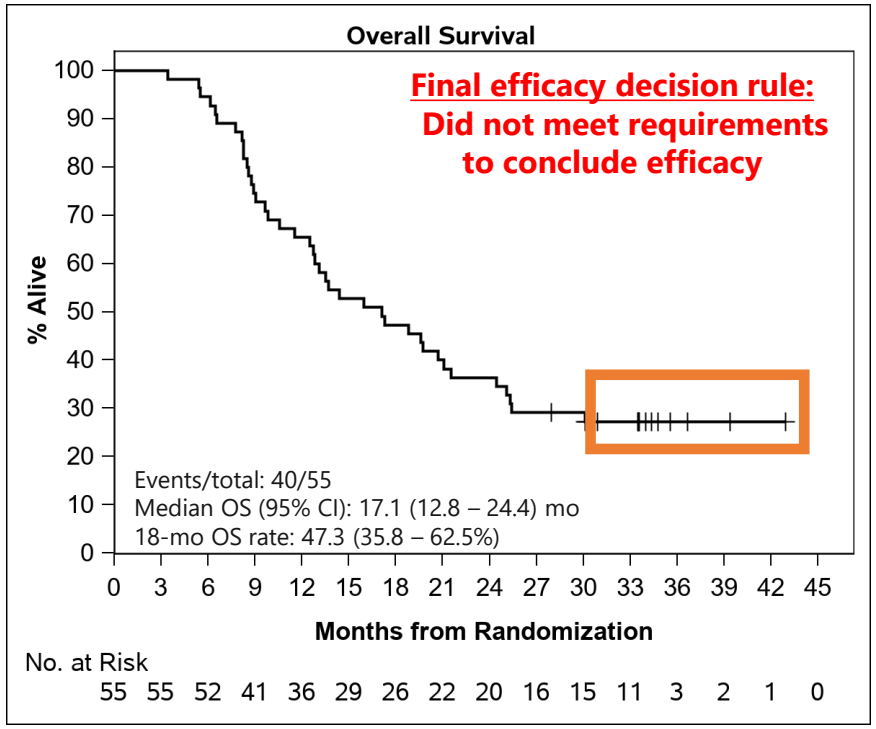
* Most common perioperative AEs (related to treatment)

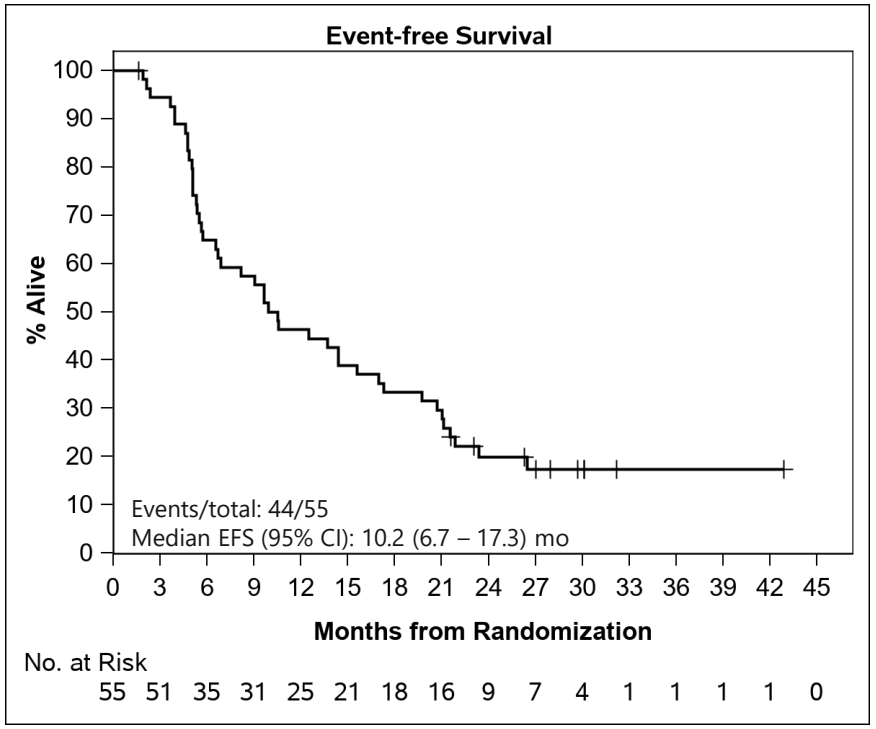
Arm A: mFOLFIRINOX





Arm B: mFOLFIRINOX → RT





Summary

Arm A: mFOLFIRINOX
Efficacious

- **18-month OS rate (KM) 66.4%**
- EFS: 15.0 months
- Resection rate: 49%
- pCR rate: 0%
- Preoperative 3+ AE rate: 57%

Arm B: mFOLFIRINOX → RT
Did not meet requirements to conclude efficacy

18-month OS rate (KM) 47.3%

EFS: 10.2 months

Resection rate: 35%

pCR rate: 11%

Preoperative 3+ AE rate: 64%

AUTHOR: Conclusion/Takeaway/Questions

- Preoperative mFOLFIRINOX was associated with favorable OS relative to historical data in patients with BR PDAC
- mFOLFIRINOX → RT met the predefined futility boundary for R0 resection at interim analysis
- mFOLFIRINOX represents a reference preoperative regimen for patients with borderline resectable PDAC
- Study was not powered to compare two arms
- Why did so many SBRT patients (50%) not have surgery? Ca 19-9? Experience of surgeon and/or rad onc?

Was the radiation group a higher risk group?

- Median CA19-9 167 vs. 260
- Metastases Prior to Resection
  - Arm A- 8/65 (12.3%)
  - Arm B- 14/55 (25.5%)
  - 2 pCRs in radiation
  - Is it plausible that a single cycle of FOLFIRINOX contributed to such a discrepancy in metastatic rate? Numbers are small

MGH Prospective Studies
Borderline Resectable and Locally Advanced

Stage	Intervention	R0 Resection Rate	mDFS (mo)	mOS (mo)	DFS-2	OS-2
06248-RESECTABLE	*Short course RT/Adjuvant Gem*	***62%***				
All Patients			10.4	**17.3**	20%	**40%**
Resected Patients			14.5	**27**	25%	**53%**
11073-RESECTABLE	*Short Course RT/Adjuvant Gem+ HCQ*	***72%***				
All Patients			11.7	**23.3**	32%	**43%**
11328-BORDERLINE RESECTABLE	*FOLFIRINOX x 8 Individualized CRT*	***56%***				
All Patients			14.7	**37.7**	43%	**59%**
Resected Patients			48.6	**NR**	55%	**81%**
13051-LOCALLY ADVANCED	*FOLFIRINOX x 8+losartan Individualized CRT*	***50%***				
All Patients			21	**33**	32%	**67%**
Resected Patients			28	**33**	52%	**89%**

MGH Borderline Trial
Phase II- TNT with FOLFIRINOX

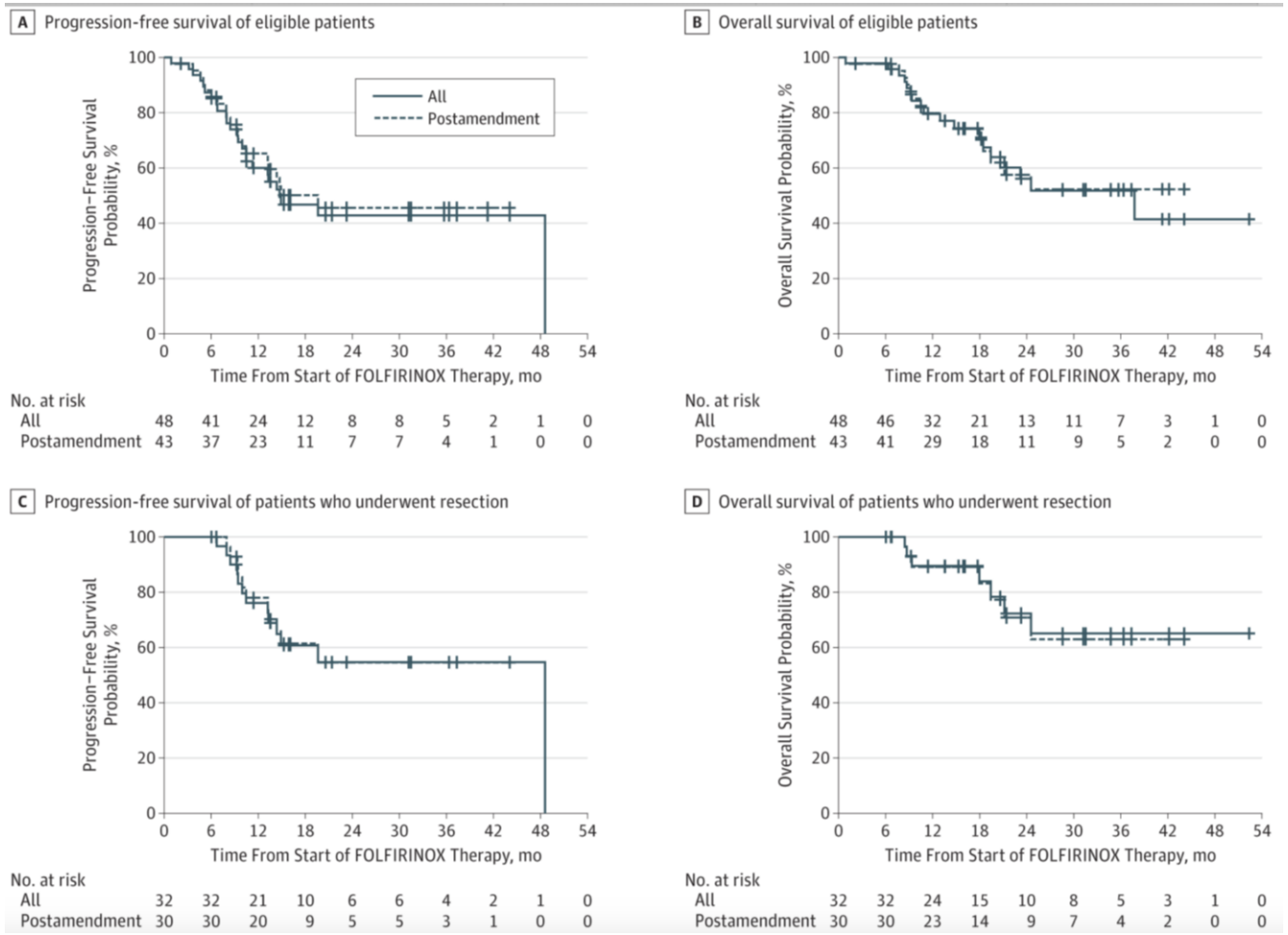
- 50 pts with borderline resectable pancreatic cancer
- FOLFIRINOX x 8
- Individualized chemoradiation
  - If no vascular involvement short course per prior studies
  - If vascular involvement- standard chemoradiation
- Surgery +/- IORT (10 Gy if resected, 15 Gy if not)
- Primary Endpoint- R0 resection rate

Murphy JE, et al, JAMA Oncol 2018

MGH Borderline Phase II Results

- Gr 3 tox in 48% of pts (diarrhea most common)
- 48 patients evaluable
- 40/48 completed all therapy (83%)
- 29/48 underwent resection
  - R0-28 (56% in ITT population (28/50)
  - R1- 1

TNT Borderline Resectable



JAMA Onc 2018

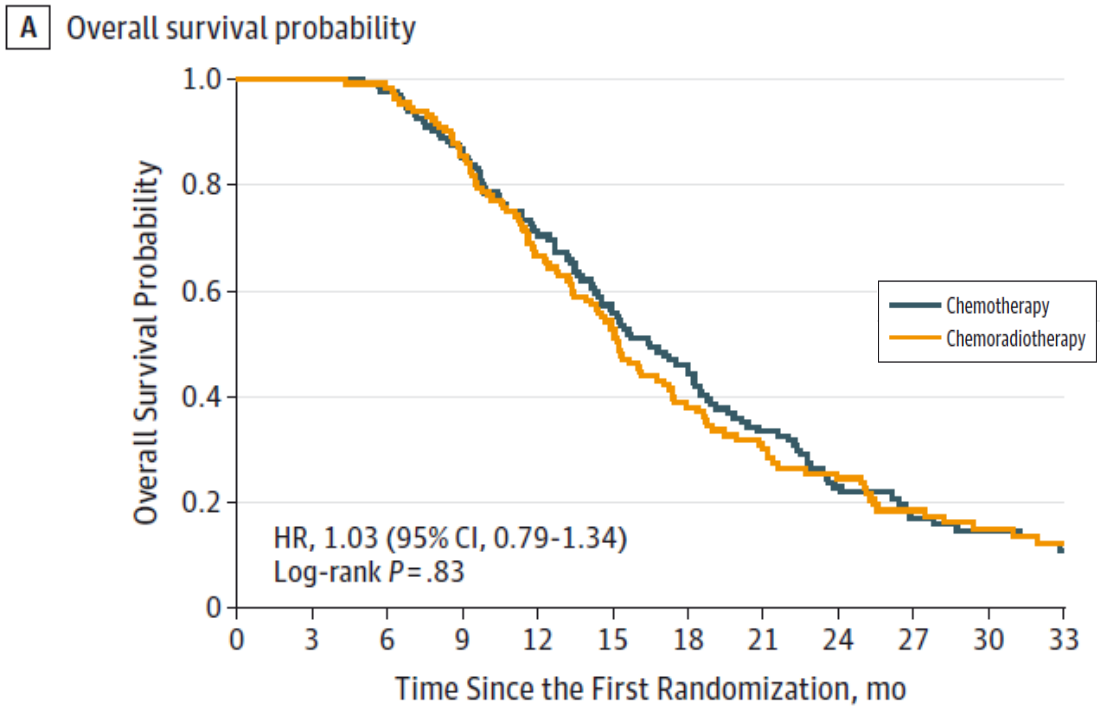
Comparison of Arms with the MGH TNT Borderline Phase II

Arm	Arm A	Arm B	MGH TNT Phase II
Number of Patients	70	56	43
Resection N(%)	32 (49%)	19 (35%)	30 (70%)
R0 Resection	28 (40%)	14 (25%)	29 (67.4%)
mPFS	15 mo	10.2 mo	19.6 mo
OS 18 mo	66.4%	47.3%	70%

Outline

- Esophageal Cancer
- Borderline Resectable Pancreas Cancer
- Locally Advanced Pancreatic Cancer
  - Does dose matter?

LAP-07

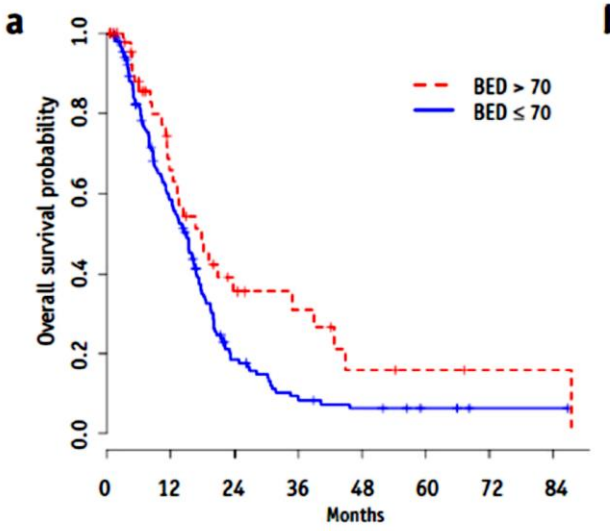


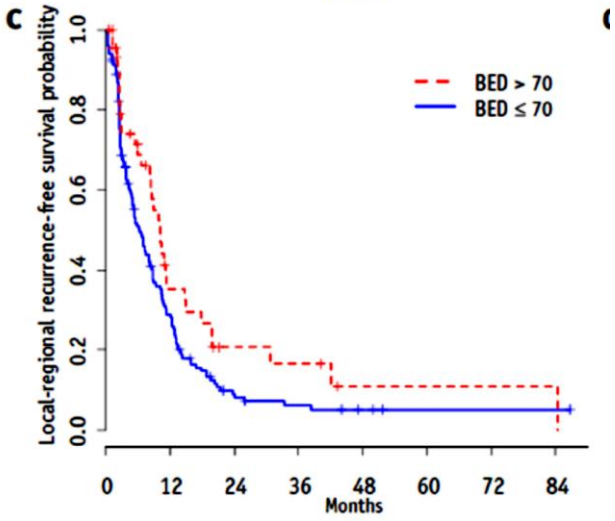
LAP-07

- 4% converted to resectable
- MS- 16 mo
- Initial standard dose chemoradiation is inadequate

Hammel P, et al. JAMA 2016

Role of Radiation: Does Dose Matter?





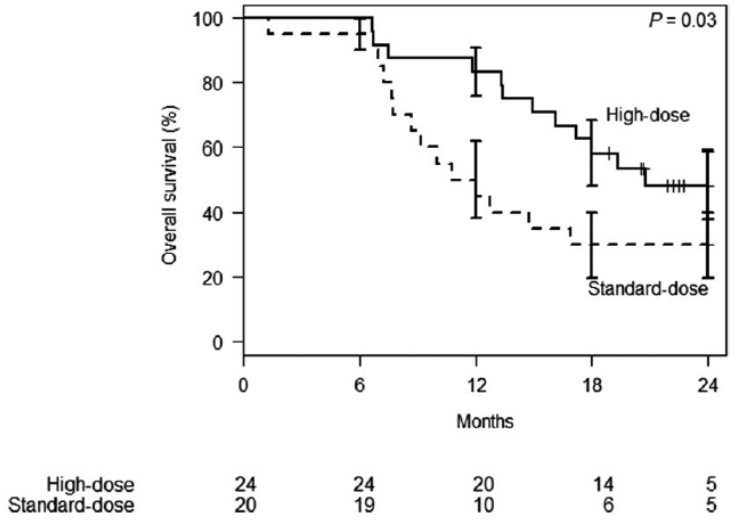
MS 17.8 mo vs 15 mo, p=0.03

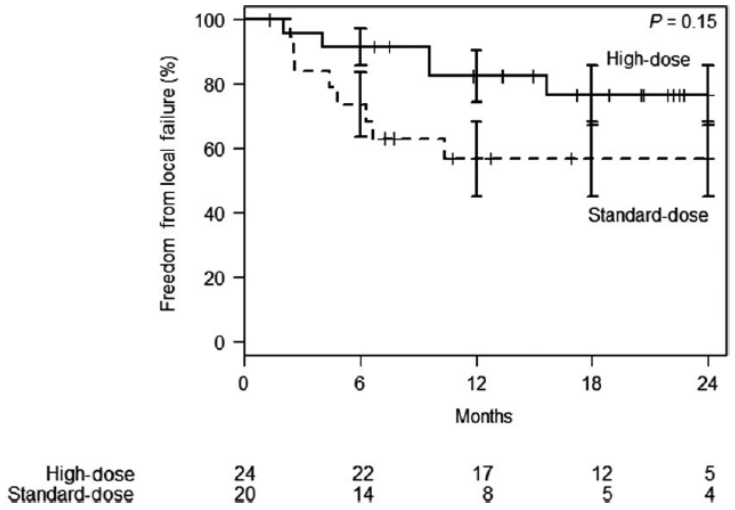
$$BED = nd\left[1+\frac{d}{\alpha/\beta}\right]$$

where n is the number of fractions, d is the dose per fraction, and α/β for tumors = 10.

Krishnan S, et al. Int J Radiat Oncol Biol Phys 2016;94:755-765

MRI Guided Dose results





-44 patients with unresectable panc ca
-Analyzed by BED10 of > or < 70 Gy
-OS2- 67% vs 30%, p=0.03

Rudra S et al. Cancer Medicine 2019

MSKCC- Ablative Radiation

- Retrospective
- 119 patients
- Prior multiagent chemo (most 3-6 mo)
- Localized, unresectable tumors with < 5cm luminal abutment
- Ablative dosing (98 Gy BED)

Reyngold M, et al. JAMA Oncol 2021

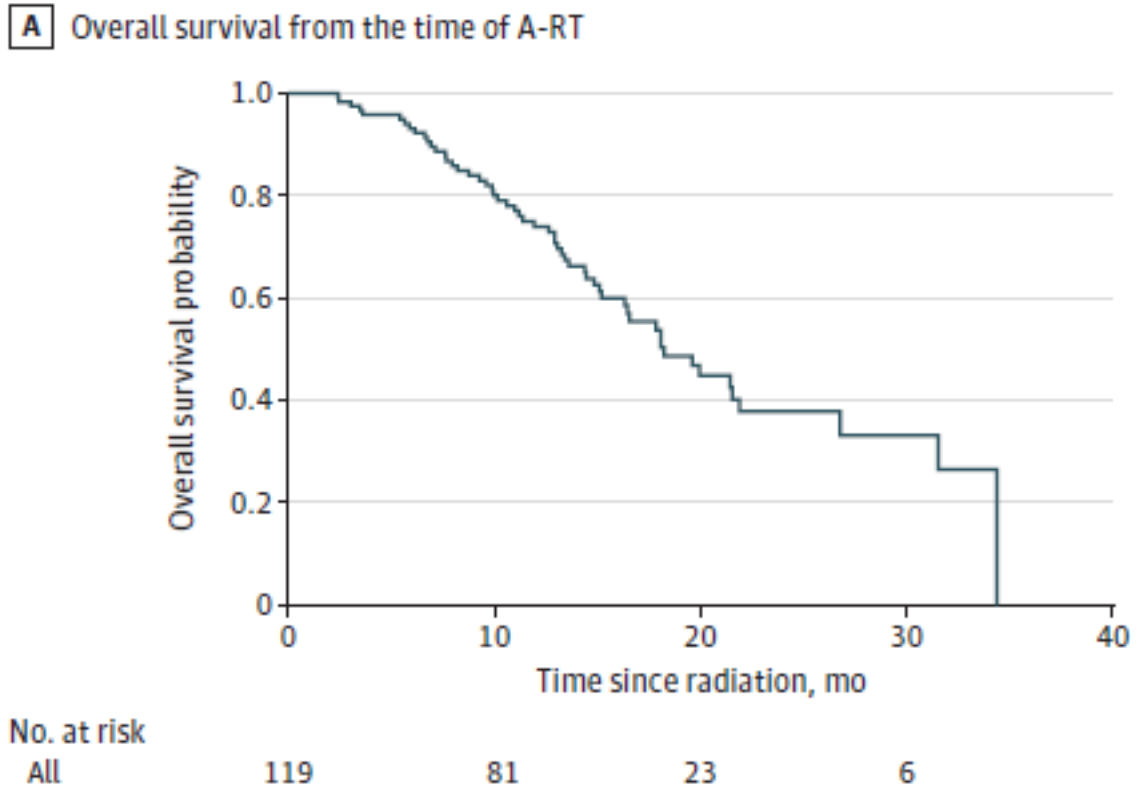
Radiation Details

- 75 Gy in 25 fractions or 67.5 Gy in 15 fractions
- Elective nodal coverage included peripancreatic nodes with 1 cm of tumor, celiac, and SMA
- Incomplete coverage of the GTV allowed, Daily CBCT

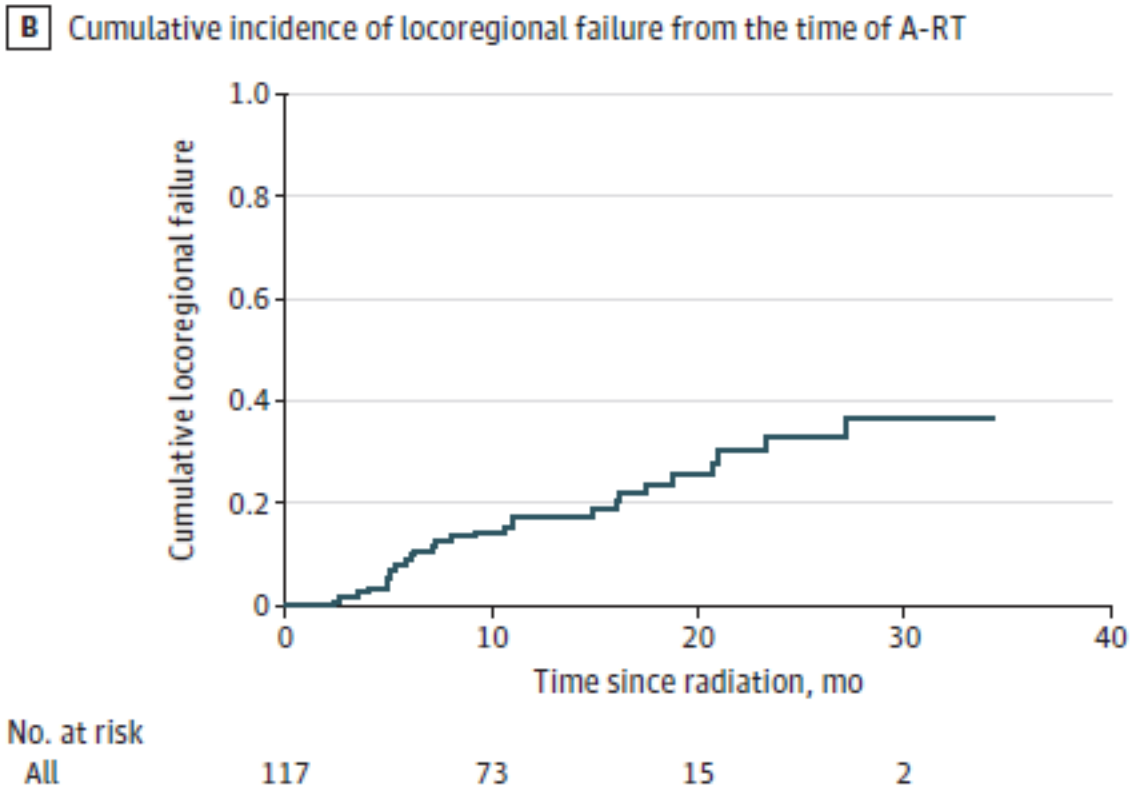
Results

- MS from diagnosis- 24 mo
- mPFS- 13.6 mo
- 12 mo LRP- 17.6%
- 24 mo LRP- 32.6%

Overall Survival



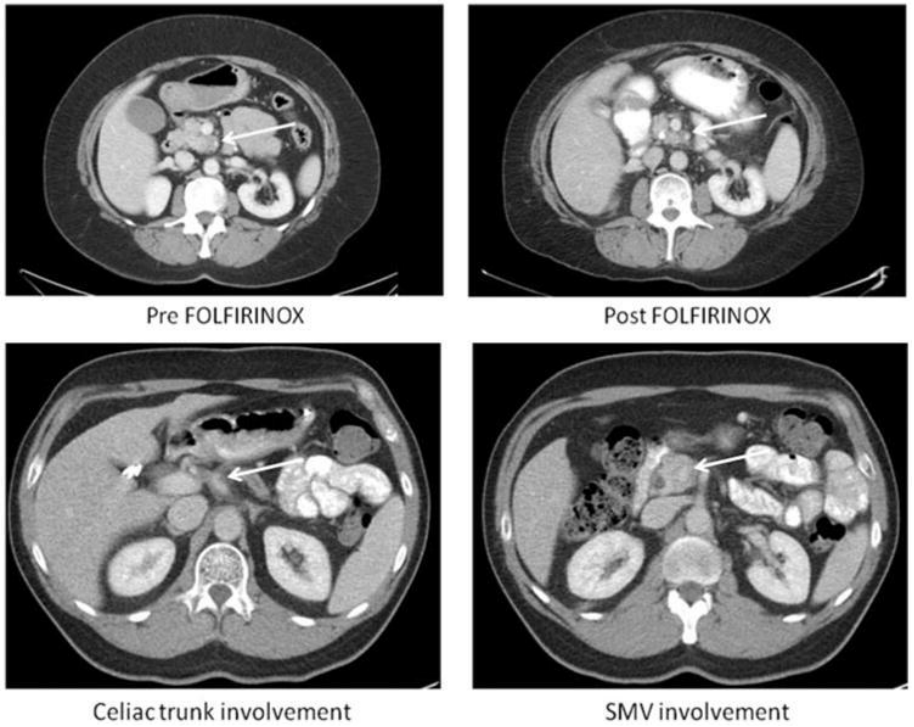
Locoregional Failure



Conclusions

- Long term survival feasible without surgery
- Requires high dose radiation

MGH Perspective on Locally Advanced Pancreas Cancer-Try to Resect



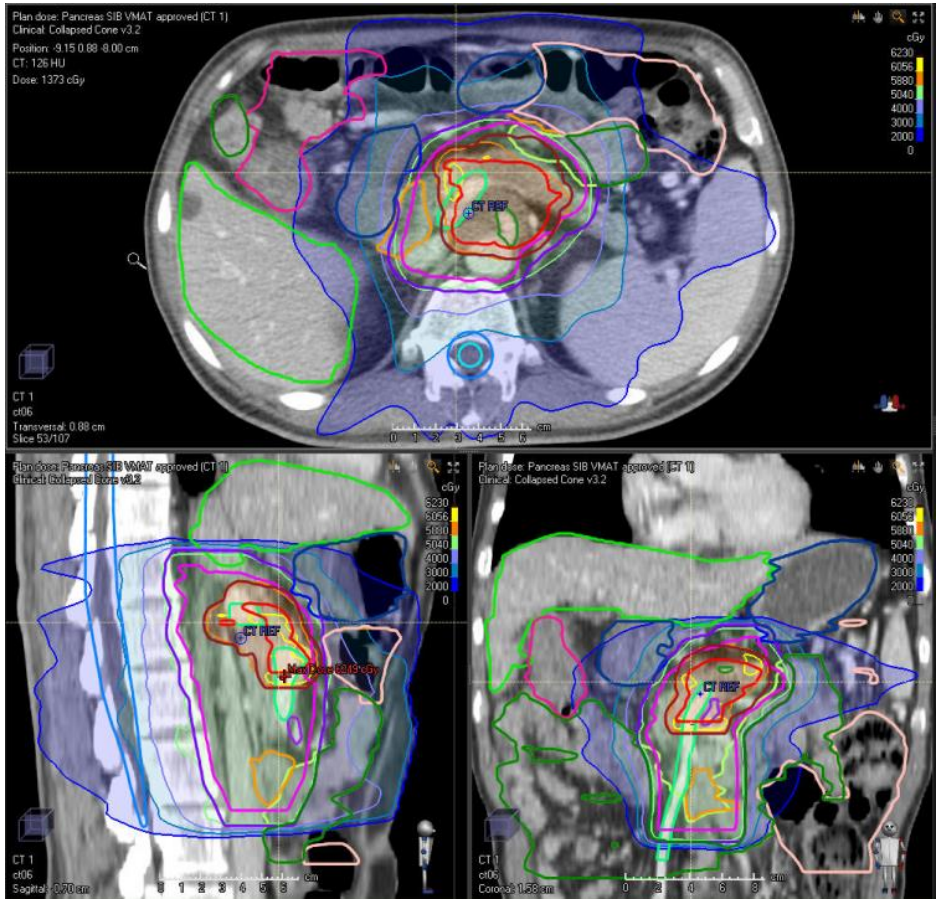
Back to First Principles

- R0 resection is the goal of therapy
- Chemotherapy with multiagent chemotherapy increases ability to resect
- CT scans still look unresectable
- Pathology demonstrates near path CR in many patients

Ferrone et al Ann Surg 2015

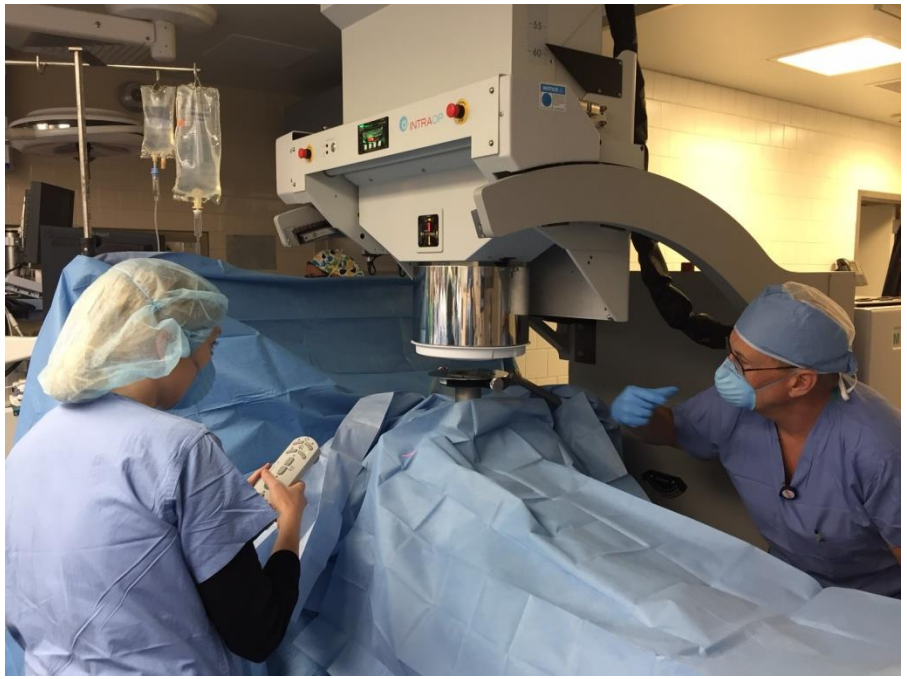
Individualized Radiation: Dose-Painted Chemoradiation

- MGH
  - Standard elective volume 50.4 Gy
  - Higher dose by vacular involvement (58.8 Gy)

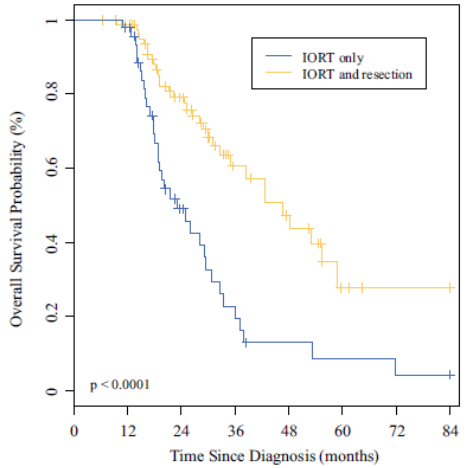


Wo JY, et al. AJCO 2017

Electron IORT



MGH Long Term F/u IORT with FOLFIRINOX (Retrospective)



FOLFIRINOX x 8
CRT- 2.1 Gy x 28=58.8 Gy
IORT- 15 Gy if unresected, 10 Gy if resected

Harrison JM et al. Ann Surg Onc 2019

TABLE 3 Overall 12, 24, 48 and 60-month survival by treatment method after *FOLFIRINOX-based* treatment ($N = 132$)

Months	Whipple/total pancreatectomy with IORT ($N = 55$) (%)	Distal pancreatectomy/appleby with IORT ($N = 31$) (%)	Combined resection with IORT ($N = 86$) (%)	IORT alone ($N = 46$) (%)
12	98.1	100	98.8	97.8
24	79.4	78.6	79.2	49.1
48	43.3	54.7	47.3	13.1
60	31.6	20.5	27.8	8.7

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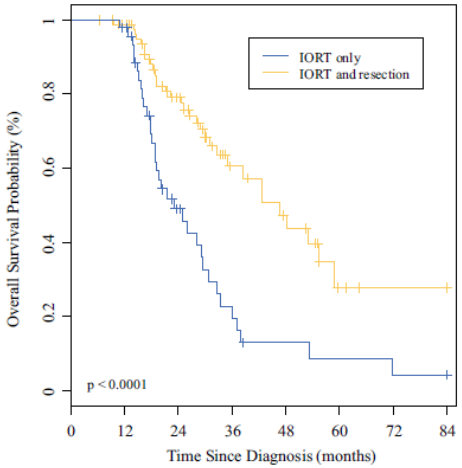

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Harrison JM et al. Ann Surg Onc 2019

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60	31.6	20.5	27.8	8.7

MGH Phase II Study of Losartan/FOLFIRINOX in LAPC

- Locally advanced pancreatic cancer (NCCN criteria)
- FOLFIRINOX/losartan 50 mg for 8 cycles.
- If the tumor was radiographically resectable after chemotherapy, pts received short-course chemoradiation (CRT) in 5 fractions (protons 25 GyE, capecitabine 825 mg/m2 bid). If it was still abutting vasculature, pts received CRT to 50.4 Gy with a vascular boost to 58.8 Gy.
- Exploration with IORT
- **Primary endpoint – R0 resection rate**

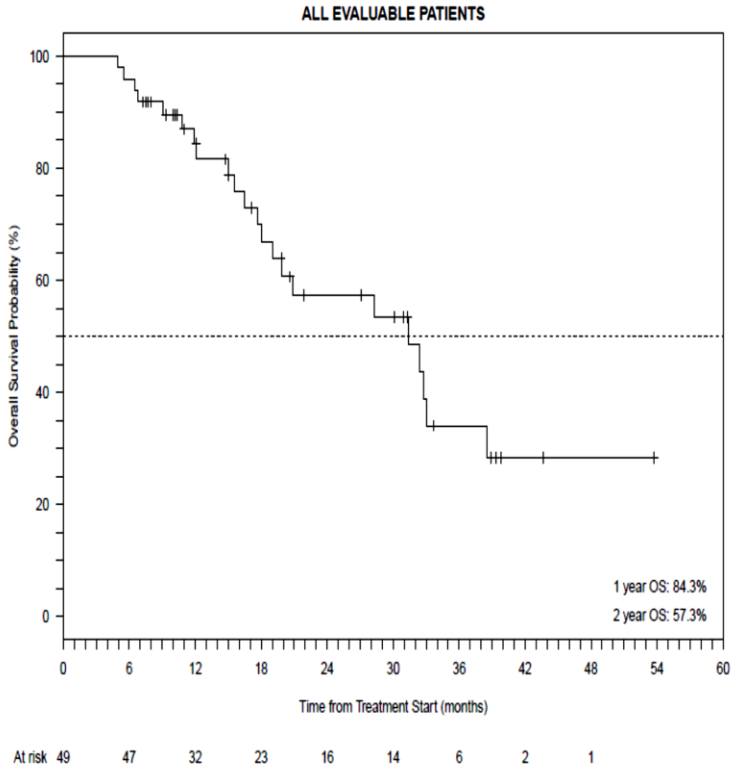
- **Secondary endpoints**:
  - PFS/OS
  - Toxicity
  - Correlatives (circulating TGF-B, TSP-1)

Murphy JE, et al. JAMA Oncol 2019

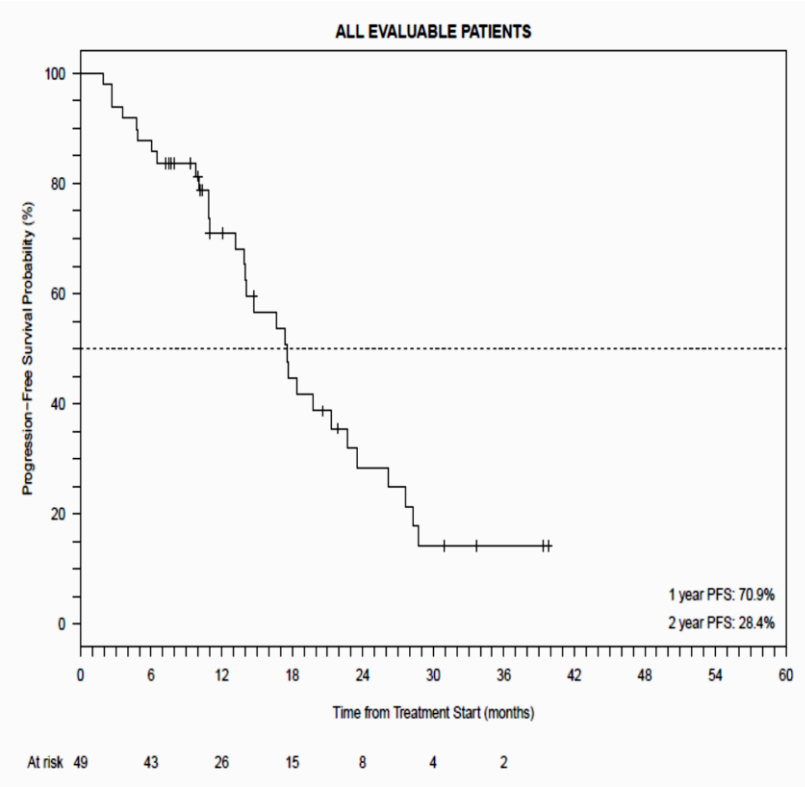
Survival

Stage	Intervention	R0 Resection Rate	mDFS (mo)	mOS (mo)	DFS-2	OS-2
13051-LOCALLY ADVANCED	*FOLFIRINOX x 8+losartan Individualized CRT*	***61%***				
All Patients			17.5	**31.4**	28%	**57%**
Resected Patients			21.3	**33**	44%	**83%**

Survival Data for All Evaluable Pts

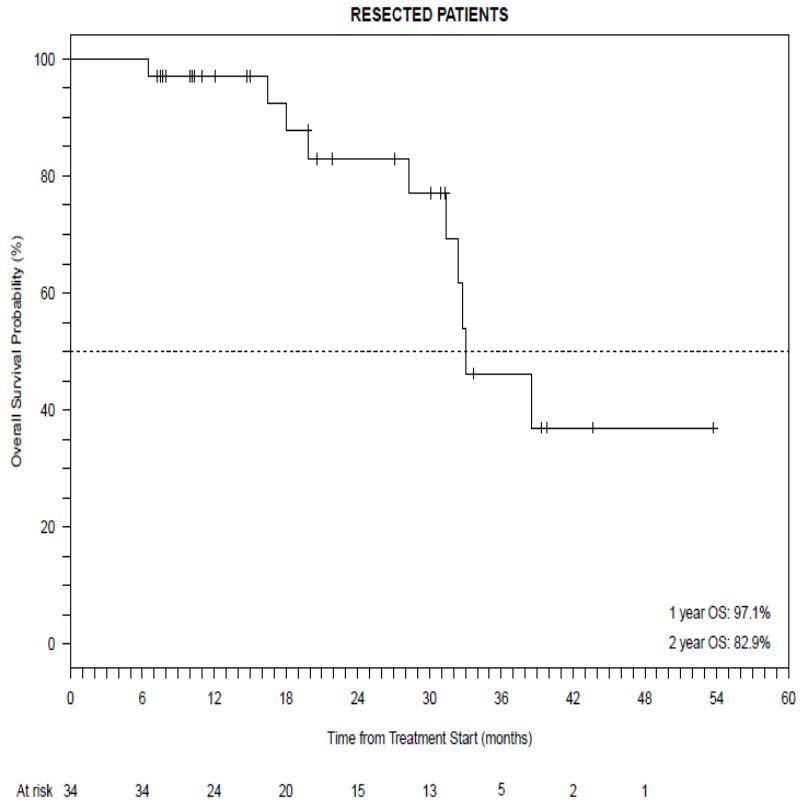


OS

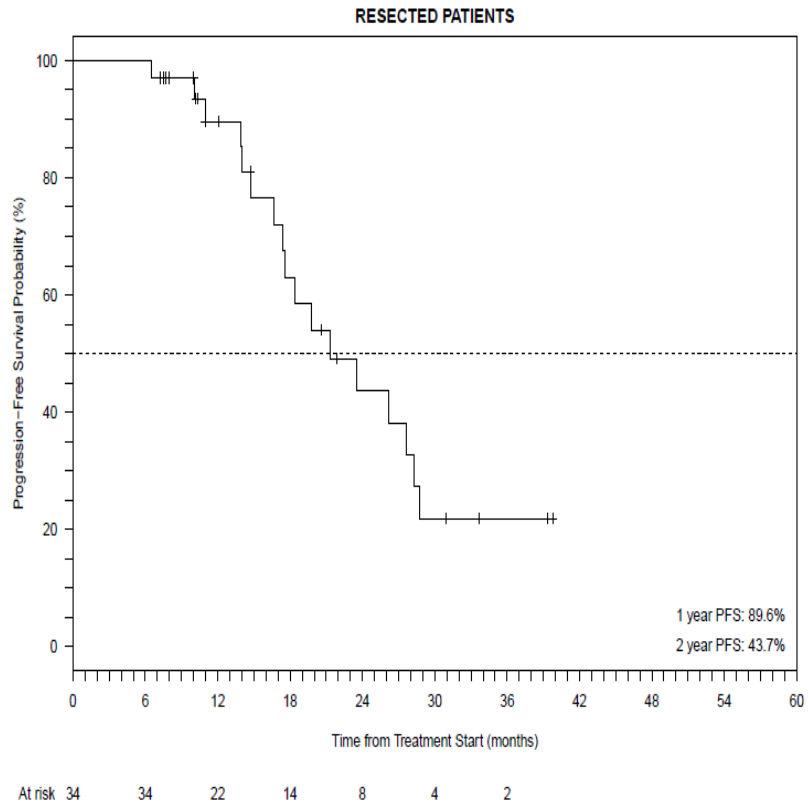


PFS

Survival Data for Resected Pts



OS



PFS

Conclusions

- TNT with losartan in LAPC is associated with a 61% R0 resection
- Compare to historical control of 25.9% reported in FOLFIRINOX meta-analysis
- A randomized, multicenter trial sponsored by SU2C/Lustgarten is underway

Combined Long-term Update 2021 submitted to ASCO 2021 (Ryan G, et al)

- 97 eligible patients
  - 90 patients completed therapy.
    - 80 patients were taken to the operating room.
      - 61 patients had R0 resection and 5 patients had R1 resection.
- median follow-up of 5.2 years

	N	mOS (mos)	LR only	LR+M	M alone	DwD nos	DwoD	NED
All	97	32.3	13	7	35	12	4	26
Unresected *	31	14.5	7	3	13	4	1	3
R0+R1	66	46.0	6	4	22	8	3	23
R0	61	43.8	5	4	20	7	3	22
R1	5	46.0	1	0	2	1	0	1

Comparing Intensity of Radiation Regimens

$$BED = nd\left[1+\frac{d}{\alpha/\beta}\right]$$

where n is the number of fractions, d is the dose per fraction, and α/β for tumors = 10.

Regimen	Chemo (Y/N)	Total Dose (Gy)	Number Fractions	Dose/Fraction (Gy)	B.E.D (10) (Gy)
Standard CRT	Y	50.4	28	1.8	**59.5**
MDACC short course	Y	30	10	3	**39**
SBRT (JHU/Alliance)	N	33	5	6.6	**54.6**
PREOPANC	Y	36	15	2.4	**44.6**
Crane 15 fx	N	67.5	15	4.5	**97.9**
Crane 25 fx	N	75	25	3	**97.5**
MGH CRT	Y	58.8	28	2.1	**71.1**
MGH SBRT	N	40	5	8	**72**
MGH CRT+IORT	Y	SBRT 40 OR CRT 58.8 + IORT 15	28+1	2.1/15	**108.6**

If Goal is R0 Resection for Borderline Patients

$$BED = nd\left[1+\frac{d}{\alpha/\beta}\right]$$

where n is the number of fractions, d is the dose per fraction, and α/β for tumors = 10.

Regimen	Chemo (Y/N)	Total Dose (Gy)	Number Fractions	Dose/Fraction (Gy)	B.E.D (10) (Gy)
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If Goal is Long Term Survival WITHOUT SURGERY

$$BED = nd\left[1+\frac{d}{\alpha/\beta}\right]$$

where n is the number of fractions, d is the dose per fraction, and α/β for tumors = 10.

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If UNCERTAIN of RESECTION, Planned Exploration with IORT

$$BED = nd\left[1+\frac{d}{\alpha/\beta}\right]$$

where n is the number of fractions, d is the dose per fraction, and α/β for tumors = 10.

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My (MGH) current approach

- For good performance status patients
  - Start with FOLFIRINOX
  - Assess after 2 months with CT and then another 2 months with CT
  - If after 4 months, no progression of disease we administer 5FU/XRT
  - Surgical consult after completing chemoradiation- IORT if not resectcable

Conclusion/Summary

- Esophagus
  - No evidence for dose escalation
  - Adjuvant nivolumab may become standard for some patients
  - No evidence for neoadjuvant/adjuvant trastuzumab
- Borderline Resectable Pancreas
  - Chemoradiation has improved R0 resection rate and disease control in borderline resectable pancreatic cancer
  - SBRT does not improve R0 resection rates- some concerns about the study
- Locally Advanced Pancreatic Cancer
  - Dose may matter

Thank You