Recent Updates in Management for Locally Advanced Pancreatic Cancer (LAPC)

-Medical Oncology Perspective-

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No conflicts of interest or financial ties to disclose

Contents

1. The role of systemic chemotherapy in the management of LAPC
2. Biomarker development to identify patients with rapidly progressive disease
    - SMAD4 or other candidates
3. Optimal chemotherapy regimen for LAPC

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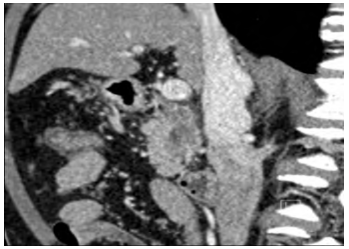
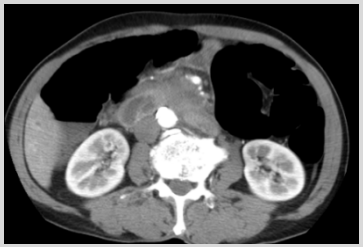
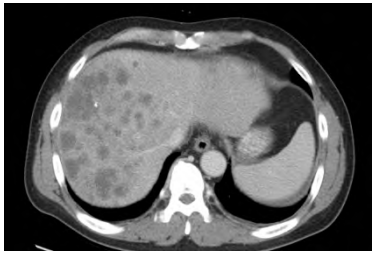
Pancreatic Cancer by Stage

- SEER summary stage (2009-2013) -

Stage Classification		% at Diagnosis	5-Yr Survival, %
Localized		10.6	29.7
Locally advanced/ unresectable		31.6	13.6
Metastatic		45.6	1.7
Unknown		12.2	10.4

Ministry of Health & Welfare, Korea Central Cancer Registry, 2015

Metastasis
- Major Prognostic Factor of LAPC-

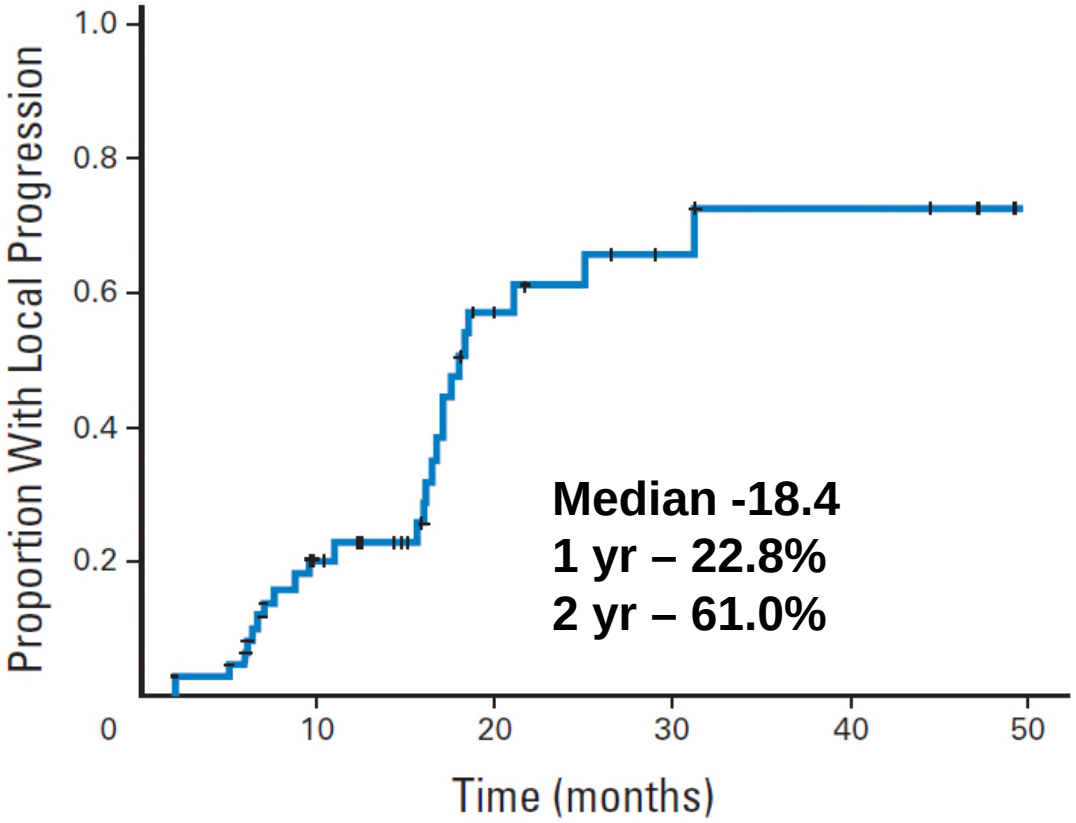
Variables included in final model	P-value	Hazard ratio	Lower 95% CI	Upper 95% CI
Distant mets: yes (n = 144, 59%) versus no (n = 100)	<0.0001	3.56	2.57	4.93
Peritoneal (n = 61) versus no mets (n = 100)	<0.0001	4.30	2.97	6.24
Mixed mets (n = 28) versus no mets (n = 100)	<0.0001	3.64	2.00	6.63
ECOG: 2/3 (n = 98) versus 0/1 (n = 146)	0.0002	1.69	1.28	2.23
CA19-9: >1000 (n = 73) versus ≤1000 (n = 150)	0.0018	1.59	1.19	2.14
Sex: female (n = 108) versus male (n = 136)	0.0015	1.57	1.19	2.08

- **244 unresectable LAPC who initiated first-line palliative chemotherapy between 2001 and 2011**
- **5 provincial British Columbia Cancer Agency clinics**
- **The provincial pharmacy database was used to identify patients who had a pathological confirmation of PDAC and received at least once cycle of palliative-intent chemotherapy**
- **OS for the entire cohort was 11.7 months (95% CI, 10.6–12.8).**

Peixoto RD. Cancer Med. 2015

Local Tumor Progression : Uncommon Before 1 Year

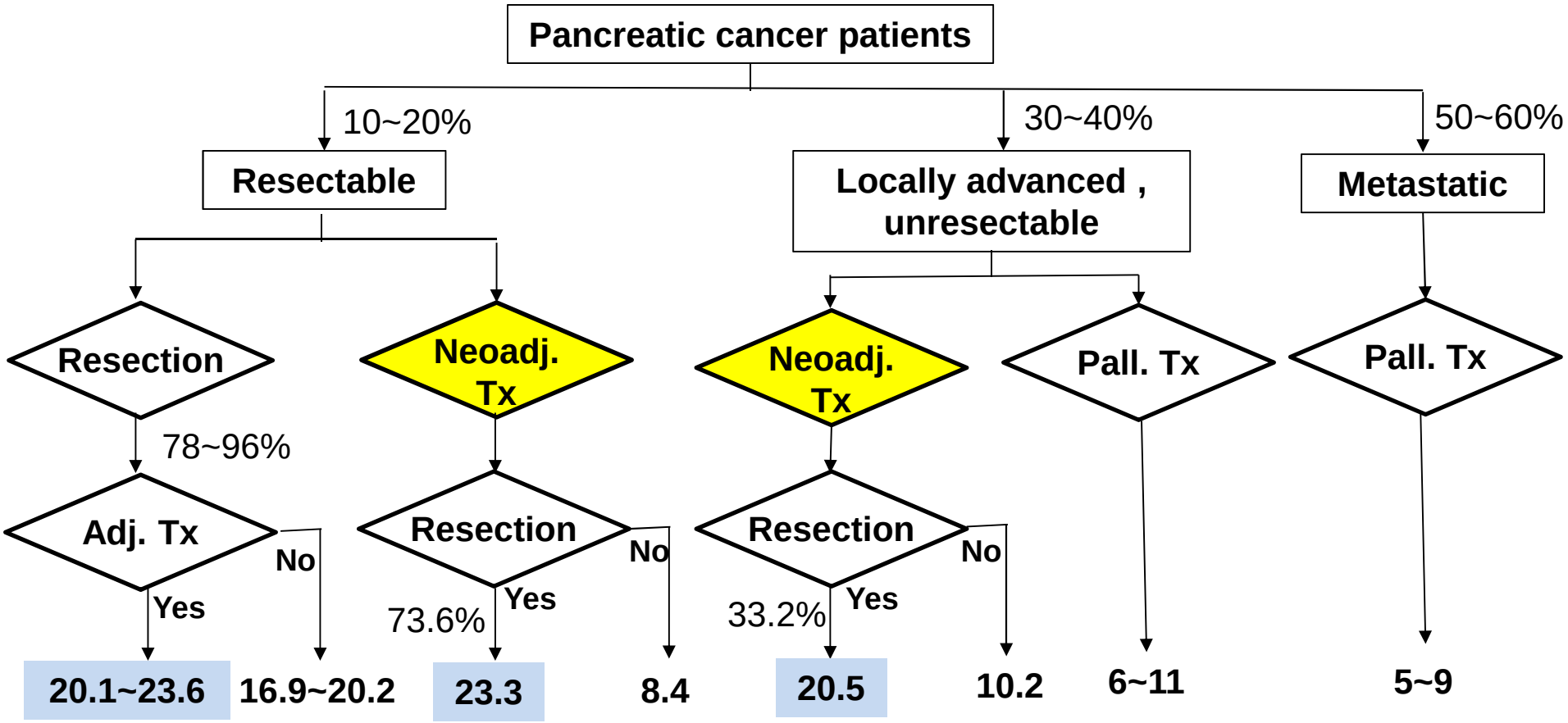
- Phase II Trial of Cetuximab, Gemcitabine, and Oxaliplatin Followed by Chemoradiation With Cetuximab for LAPC (n=69)-



*** Isolated local tumor progression leading to death occurred in 7 patients (10%) between 16.1 and 31.2 months.**

Crane CH. J Clin Oncol. 2011

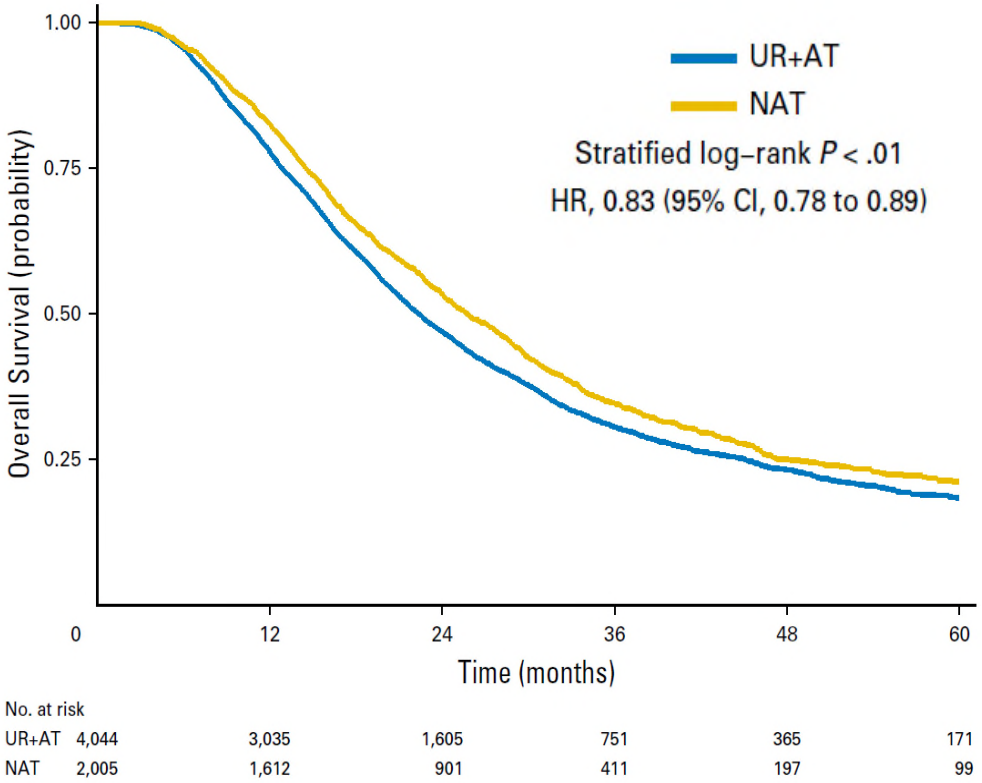
Neoadjuvant Therapy: No Advantage over Resection Followed by Adjuvant Therapy?



Gillen S. PLoS Med 2010

Neoadjuvant Therapy Followed by Resection Versus Upfront Resection for Resectable Pancreatic Cancer: A Propensity Score Matched Analysis

- Adult patients with resected, clinical stage I or II adenocarcinoma of the head of the pancreas were identified in the National Cancer Database from 2006 to 2012. (n=15,237)

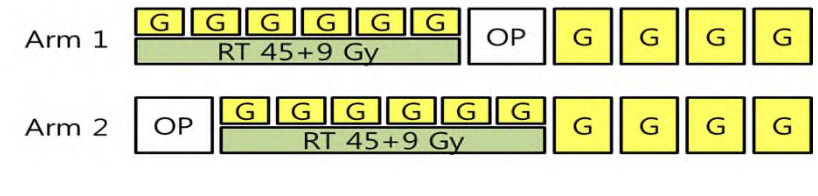


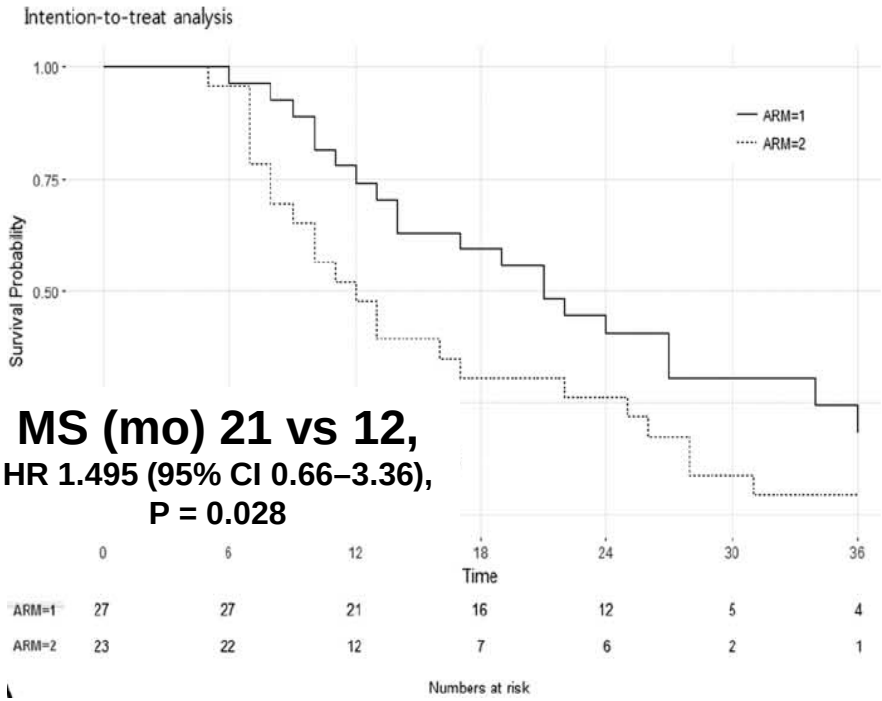
- **Kaplan-Meier curve for overall survival between patients of the upfront resection (UR) group who received adjuvant therapy (UR+AT) and patients of the neoadjuvant therapy (NAT) group.**

Mokdad AA. J Clin Oncol 2016

Oncological Benefits of Neoadjuvant Chemoradiation (CRT) With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial

Arm A	Arm B
Allocated to neoadjuvant CRT (n=30)	Allocated to surgery (n=28)
Received CRT (n=27) Completed CCRT (n=26)	Received surgery (n=23) Resection (n=18, 64%) - R0 n=6 (33.3%)
Received surgery (n=24) Resection (n=17, 56%) - R0 n=14 (82.4%)	Received CRT (n=13)
RECIST criteria, n (%) Partial response, 6 (35.3) Stable disease, 10 (58.8) Progressive disease, 1 (5.9)	
Tumor regression, n (%) Complete response, 2 (11.8) Moderate response, 3 (17.6) Minimal response, 12 (70.6)	





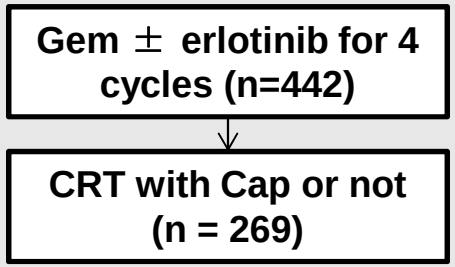
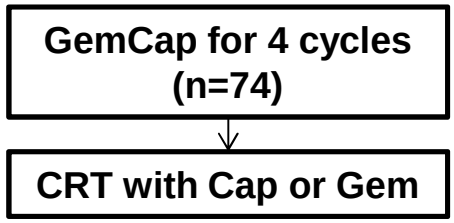
MS (mo) 21 vs 12,
HR 1.495 (95% CI 0.66–3.36),
P = 0.028

Jang JY. Ann Surg 2018

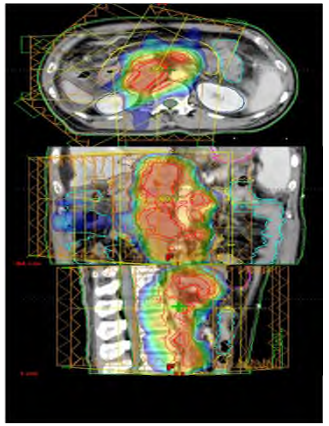
Chemotherapy *vs.* chemoradiotherapy?

Treatment	Study type	No	Median survival (mo)	*P*	Reference
Chemoradiotherapy vs chemotherapy alone					
5-FU and cisplatin + 60 Gy →Gem Gem	RCT	59 60	8.6 13.0	0.03	Chauffert et al. (2008)
Gem + 50.4 Gy Gem	RCT	34 37	11.1 9.2	0.044	Loehrer et al. (2011)
Chemoradiotherapy					
5-FU + 50.4–61.2 Gy Gem + 50.4–61.2 Gy	RCT	18 16	6.7 14.5	0.027	Li et al. (2003)
5-FU + 50.4 Gy Capecitabine + 50.4 Gy	Phase II	53 31	11.9 12.5	0.526	Kim et al. (2012) NCC, Korea

Induction Chemotherapy then CRT

Study	Study design and treatment	Results	Comment on the role of CRT
LAP07 (Hammel P. JAMA 2016)	Phase III 	Overall survival Chemotherapy vs CRT :16.5 vs 15.2 months (HR, 1.03; 95% CI, 0.79-1.34; P = .83)	• Decreased local progression (32%vs 46%, *P* = .03) • no increase in grade 3 to 4 toxicity, except for nausea.
SCALOP (Mukherjee Lancet Oncol 2013)	Phase II 	Progression-free survival. Cap vs Gem : 12.0 vs 10.4 months (adjusted HR 0.60, 95% CI 0.32–1.12; p=0.11)	Gem vs Cap : G 3-4 haematological toxicity (18% vs none, p=0.008) non-haematological toxicity (26% vs 12%, P=0.12)

A Phase II Study of Induction Chemotherapy with Gemcitabine and Cisplatin followed by Simultaneous Integrated Boost-Intensity Modulated Radiotherapy with Concurrent Gemcitabine for Locally Advanced Unresectable Pancreatic Cancer



Inclusion criteria (n=44)

- histologically or cytologically proven, ECOG PS 0-1, no evidence of metastatic disease,
- Criteria for local unresectability included at least one of the following:

long segment occlusion of SMV/PV, more than 180-degree involvement of SMA or involvement of the hepatic artery or celiac trunk.

Scheme

Before Chemotherapy

Test
CBC, Liver function teast, renal function test, EUS guieded fine needle biopsy, CT, MRI
CA19-9 (PET, CEA, if necessary)

- **Blood sample (Blood sampling and storage)**
- **GEM (10000mg/m²)**
- **Cisplatin (25mg/m²)**

D1 D8 D15 D22

3 weeks

After SIB-IMRT

Test
CBC, LFT, CA 19-9, CT
(CEA, if necessary)

- **Blood sample (Blood sampling and storage)**
- **SIB-IMRT [PTV1: 55Gy/22Fx / PTV2: 44Gy/22Fx]**
- **GEM (300mg/m²)**

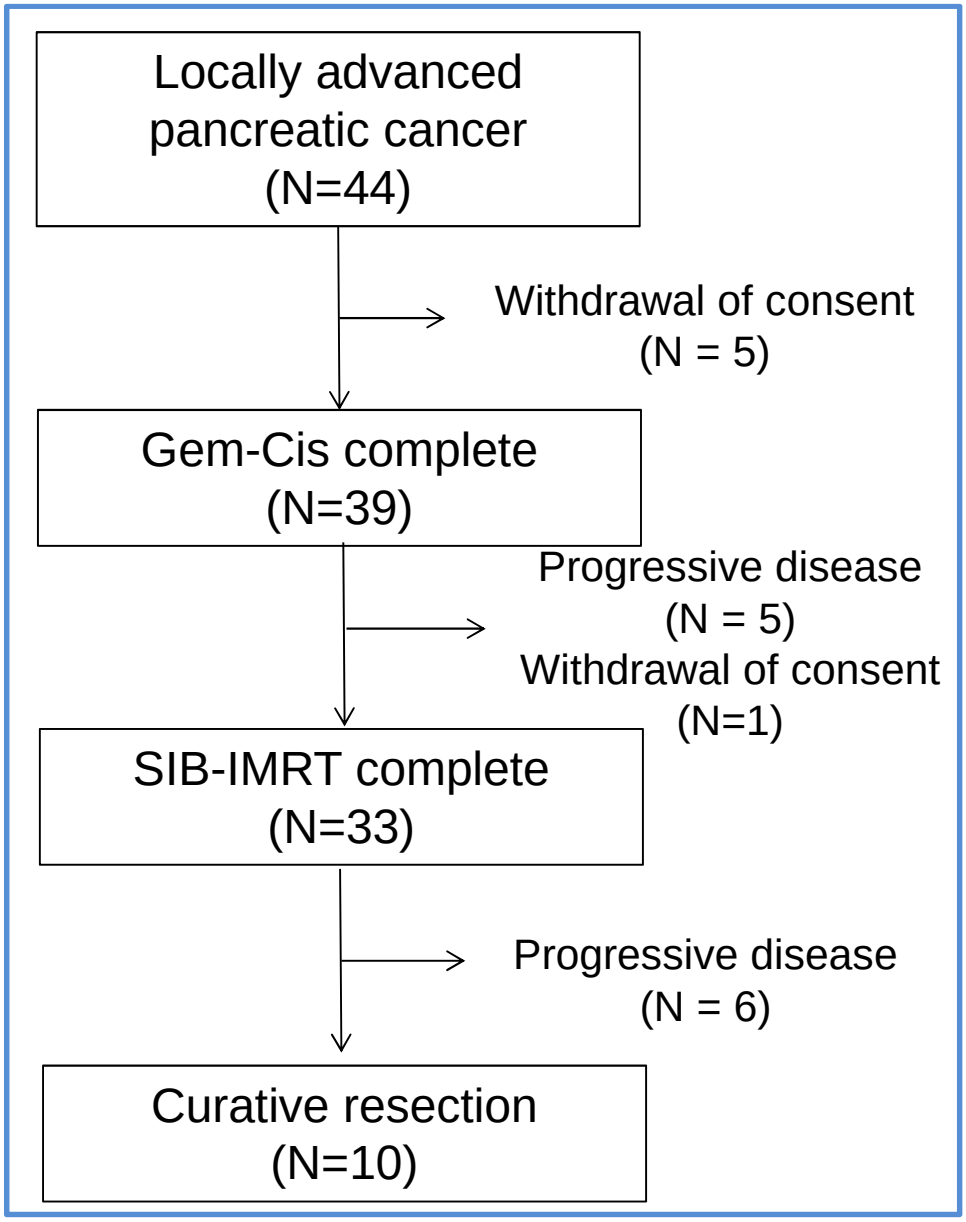
D1 D8 D15 D22 D29

Woo SM. Cancer Res Treat. 2017

Results: Characteristics & Flow

Baseline Characteristics	
Characteristic	N (%) or median (IQR*)
Age, yr	67 (57.5-71)
Gender	
Male	19 (43%)
Female	25 (57%)
Tumor size (longest diameter), cm	3.6 (3.1-4.5)
Tumor location	
Head	25 (57%)
Body and tail	19 (43%)
Pretreatment CA 19-9 (U/ml)	267.5 (64-773)
Pretreatment CEA (U/ml)	4.25 (2.15-7.4)
ECOG Performance status	
0	9 (21%)
1	35 (79%)
Resection	
0: No	34 (77%)
1: Yes	10 (23%)

*IQR, interquartile ranges (Q1-Q3)



Characteristics of Patients who Underwent Curative Resection

Patient No.	Age (y)	Sex	Surgical procedure	Blood vessel excision	Pathology stage	Diff	Blood vessel invasion	Lymphatic invasion	Perineural invasion	Nodal status	FU period (mon)
8	57	M	Total pancreatectomy	PV	(y)pT1N1	MD	-	-	-	1/6	16.2
10	54	F	Distal pancreatectomy (Posterior RAMPS)	-	(y)pT3N0	NS	-	-	Present	0/8	18.8
11	60	F	Total pancreatectomy	Right HA, PV	(y)pT3N1	NS	-	Present	Present	1/13	17.6
12	76	F	PPPD	SMA	(y)pT3N0	NS	-	-	Present	0/17	39.5
13	45	M	Total pancreatectomy	PV, CHA	(y)pT3N0	MD	Present	Present	Present	0/27	15.1
19	68	F	Distal pancreatectomy	celiac axis	No residual tumor	-	-	-	-	0/10	41.9
20	71	M	Distal pancreatectomy (anterior RAMPS)	celiac axis	(y)pT3N0	MD	Present	Present	Present	0/20	23.6
30	56	M	Standard PD	SMA	(y)pT3N1	MD	-	Present	Present	2/21	12.9
32	69	M	Distal pancreatectomy	portal vein	(y)pT3N1	WD	Present	-	Present	7/14	33.4
44	70	M	Distal pancreatectomy (Anterior RAMPS)	celiac axis	(y)pT3N1	MD	Present	Present	Present	1/3	14.6

Ongoing Clinical Trials in Neoadjuvant Setting in Pancreatic Cancer (PC)

Treatment	Setting	Trial identification nu mber	Ph	Duration (weeks)
RT with gemcitabine	BRPC	NCT01458717	II/III	4-6
Gemcitabine	BRPC	NCT01458717	II/III	6
Gemcitabine/Oxaliplatin	Resectable PC	NCT01314027	III	8
Gemcitabine + erlotinib	Resectable PC	NCT00733746	II	5-8
Nab-paclitaxel + gemcitabine	Resectable PC	NCT02047513	III	8
Gemcitabine + capecitabine	Resectable PC	NCT01360593	II	8-10
FOLFIRINOX and gemcitabine during & foll owing RT	BRPC	NCT01661088	II	21
FOLFIRINOX	Resectable PC	NCT01677988	II	10
FOLFIRINOX and RT with capecitabine	BRPC	NCT01821612	II	10
Capecitabine, cisplatin, epirubicin, and gem citabine	Resectable PC	NCT01150630	II/III	12
Gemcitabine, capecitabine, and docetaxel (GTX) and with RT	BRPC	NCT01065870	II/III	12-20
Gem, 5-FU Oregovomab, Nelfinavir + RT	LAPC	NCT01959672	II	13-14

BRPC, borderline resectable PC; LAPC, locally advanced PC

Modified from “Bittoni A. Gastroenterol Res Pract. 2014”

Duration of Initial Chemotherapy?

- No RCT data
- Variable and dependent on patient tolerability and tumor response in practice
- Number of neoadjuvant cycles
  - Only independent predictor of survival (HR 0.49, 95% CI 0.34-0.71, $p < 0.001$) Dhir M. J Clin Oncol. 2018 (abstr 402)

American Society of Clinical Oncology Clinical Practice Guideline

- Initial systemic therapy with combination regimens is recommended for most patients with ECOG PS 0 or 1.
- There is no clear evidence to support one regimen over another.
- For some patients, chemoradiotherapy (CRT) or SBRT may be offered up front, or response or stable disease after 6 months of induction chemotherapy.

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Modified from “J Clin Oncol 2016 May”

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DPC4 Gene Status of the Primary Carcinoma Correlates With Patterns of Failure

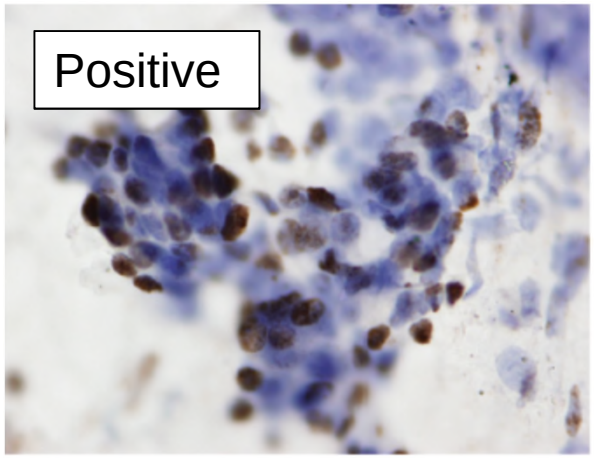
Metastatic Burden by Gene for Primary Carcinoma	Locally Destructive				Locally Confined				P
	0		1-10		11-99		100s-1,000s		
	No.	%	No.	%	No.	%	No.	%	
KRAS2 (n = 59)	6/7	86	11/11	100	19/21	90	20/20	100	.283
	17/18; 94%				39/41; 95%				.672
TP53 (n = 58)	6/6	100	6/11	54	16/21	76	18/20	90	.083
	12/17; 71%				34/41; 83%			.037	
SMAD4 (DPC4) (n = 65)	2/9	22	5/11	45	17/24	71	16/22	73	.032
	7/20; 35%				33/46; 72%			.007	

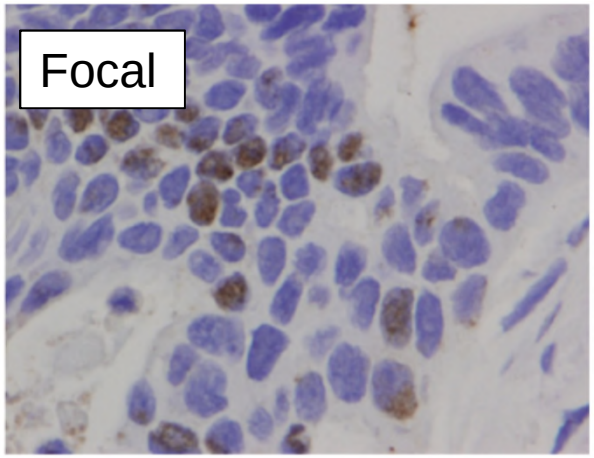
- Rapid autopsies were performed on 76 patients

Iacobuzio-Donahue CA. J Clin Oncol. 2011

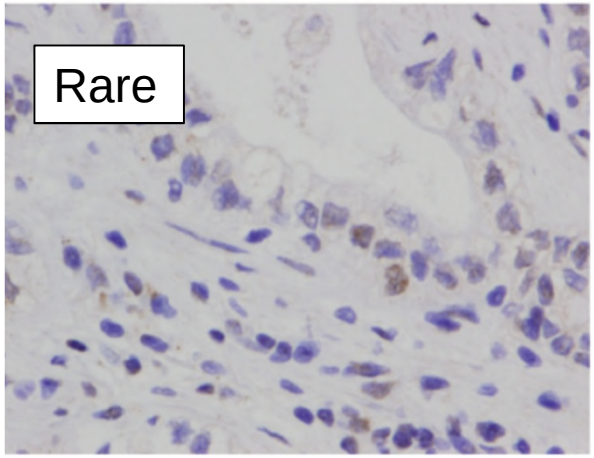
Correlation of Pattern of Progression With SMAD4 (DPC4) Expression

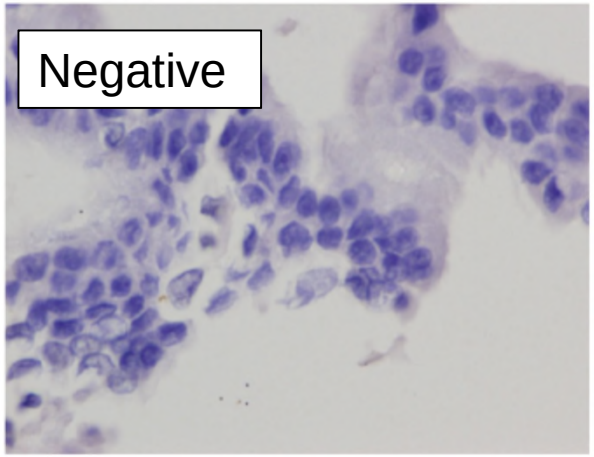
Intact*
7/15 (73.3%): local dominant pattern of progression





Loss*
10/14 (71.4%) : distant dominant pattern of spread



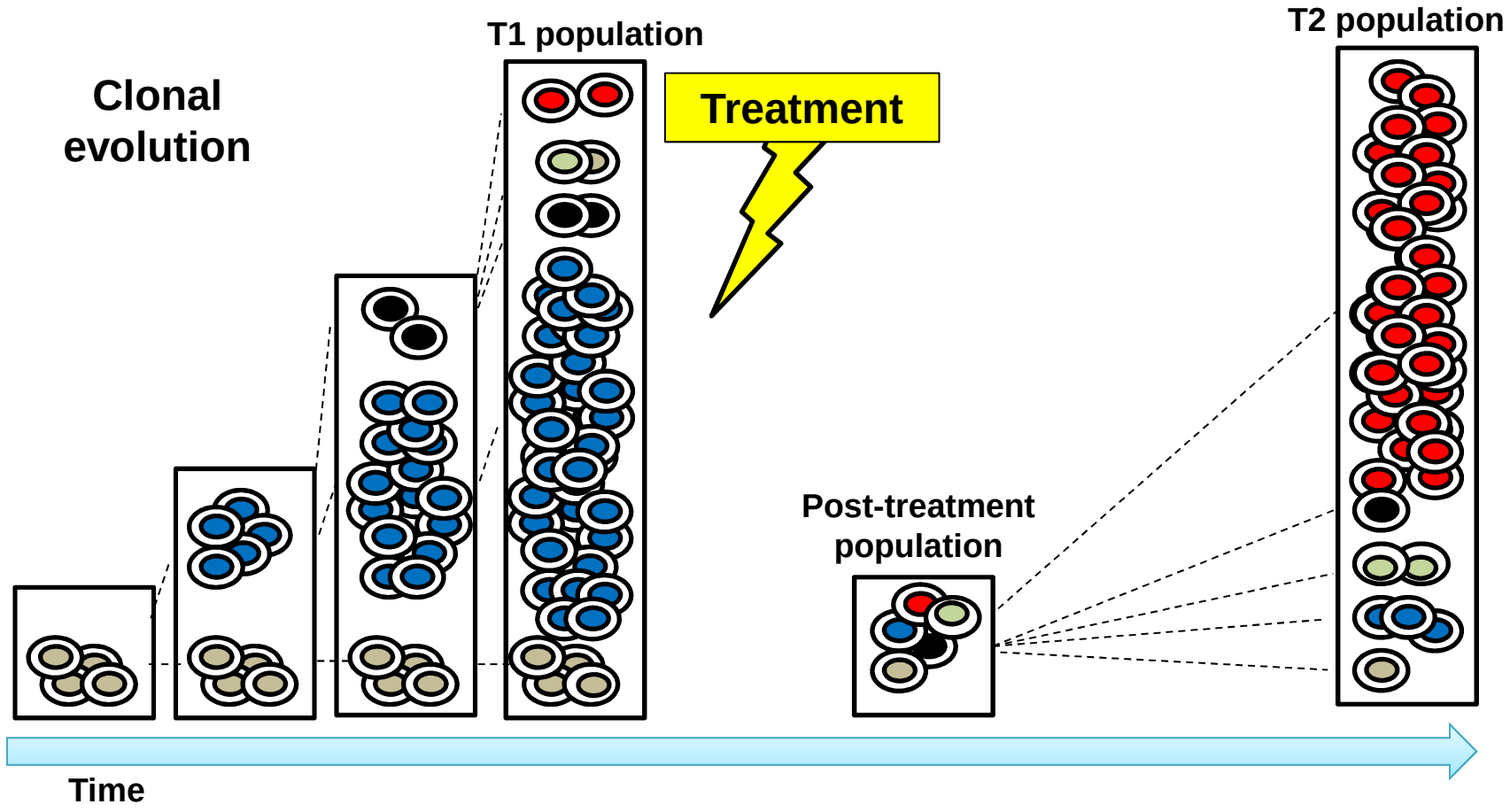


***P=0.016**

Crane CH. J Clin Oncol. 2011

Clonal Mutation Prevalence

- Sensitive genotype vs. resistant genotype
- allelic ratio: pre-treatment vs. post-treatment



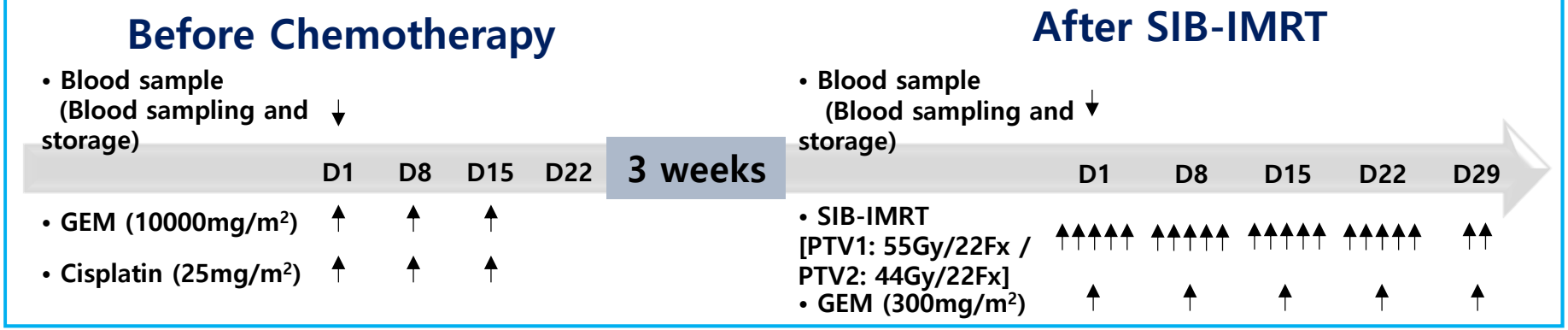
A Phase II Study of Preoperative Chemoradiotherapy with Gemcitabine for Resectable Pancreatic Carcinoma

(**ClinicalTrials.gov Identifier:** NCT01333124)

Day	D1	D8	D15	D22	D29
Radiotherapy (RT) [PGTV: 48.4Gy/22Fx / PCTV: 44Gy/22Fx]	X X X X X	X X X X X	X X X X X	X X X X X	X X
GEM (800mg/m^2)	↑	↑	↑	↑	↑

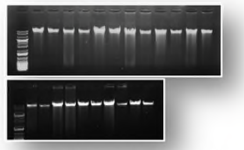
A Phase II Study of Induction Chemotherapy with Gemcitabine and Cisplatin followed by Simultaneous Integrated Boost-Intensity Modulated Radiotherapy with Concurrent Gemcitabine for Locally Advanced Unresectable Pancreatic Cancer

Woo SM. Cancer Res Treat. 2017



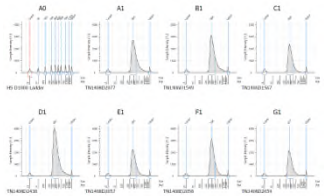
Comprehensive Cancer Panel (CCP)

Pilot study → **Sample prep & QC** → **Library QC** → **Data analysis**

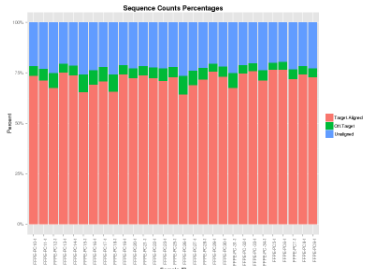


FFPE (formalin-fixed paraffin-embedded tissue) sample

CCP



FFPE CCP



Variant calling

Blood sample CCP

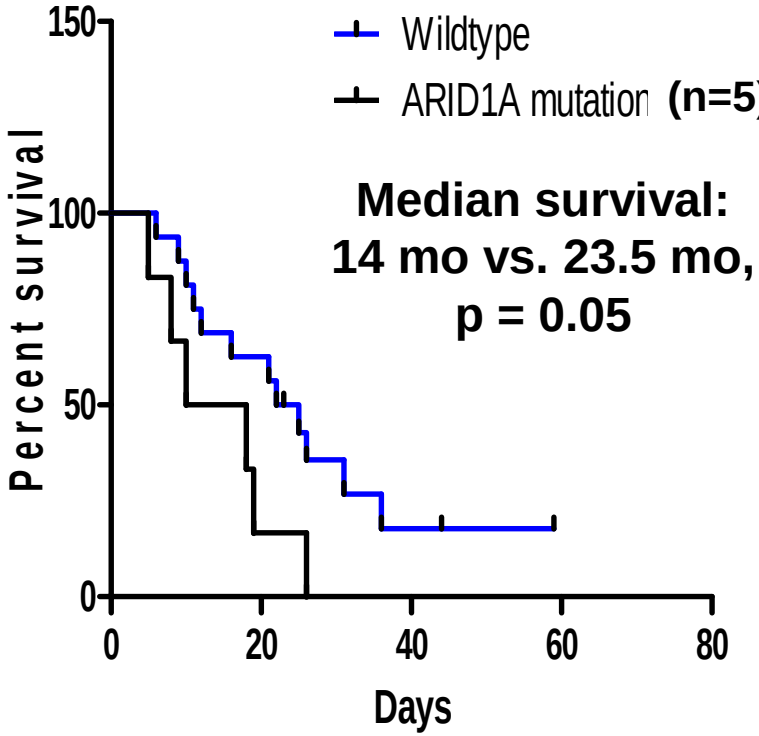
Selection of candidate patients
Sequencing platform

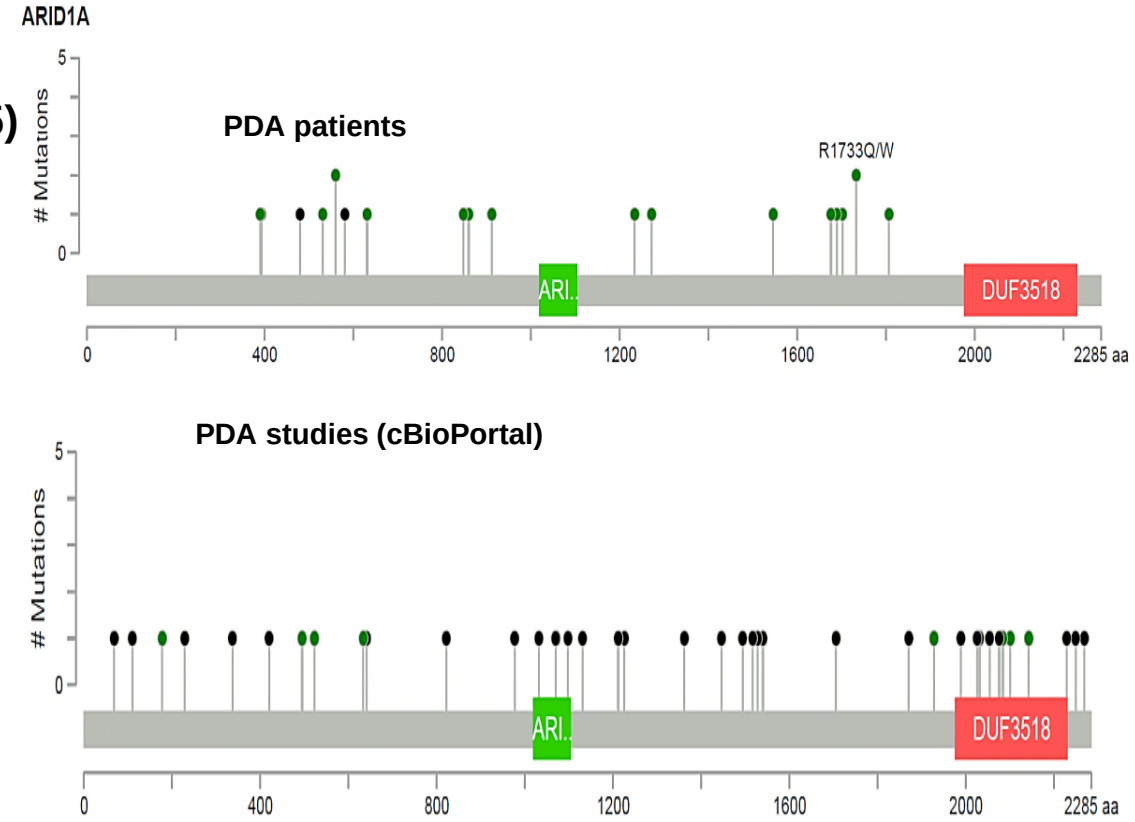
Somatic mutation profile

- **Ion AmpliSeq CCP covering 409 genes (Ion Torrent, Life Technologies, Carlsbad, CA).**
- **Quality of the libraries - 2100 Bioanalyzer (Agilent Technologies, Santa Clara, USA)**
- **Sequencing - Nextseq 500 System platform, with 2 × 151 bp paired end sequencing runs (Illumina Inc., San Diego, CA).**

In submission

ARID1A Gene Mutations and the Association with Disease Outcome.





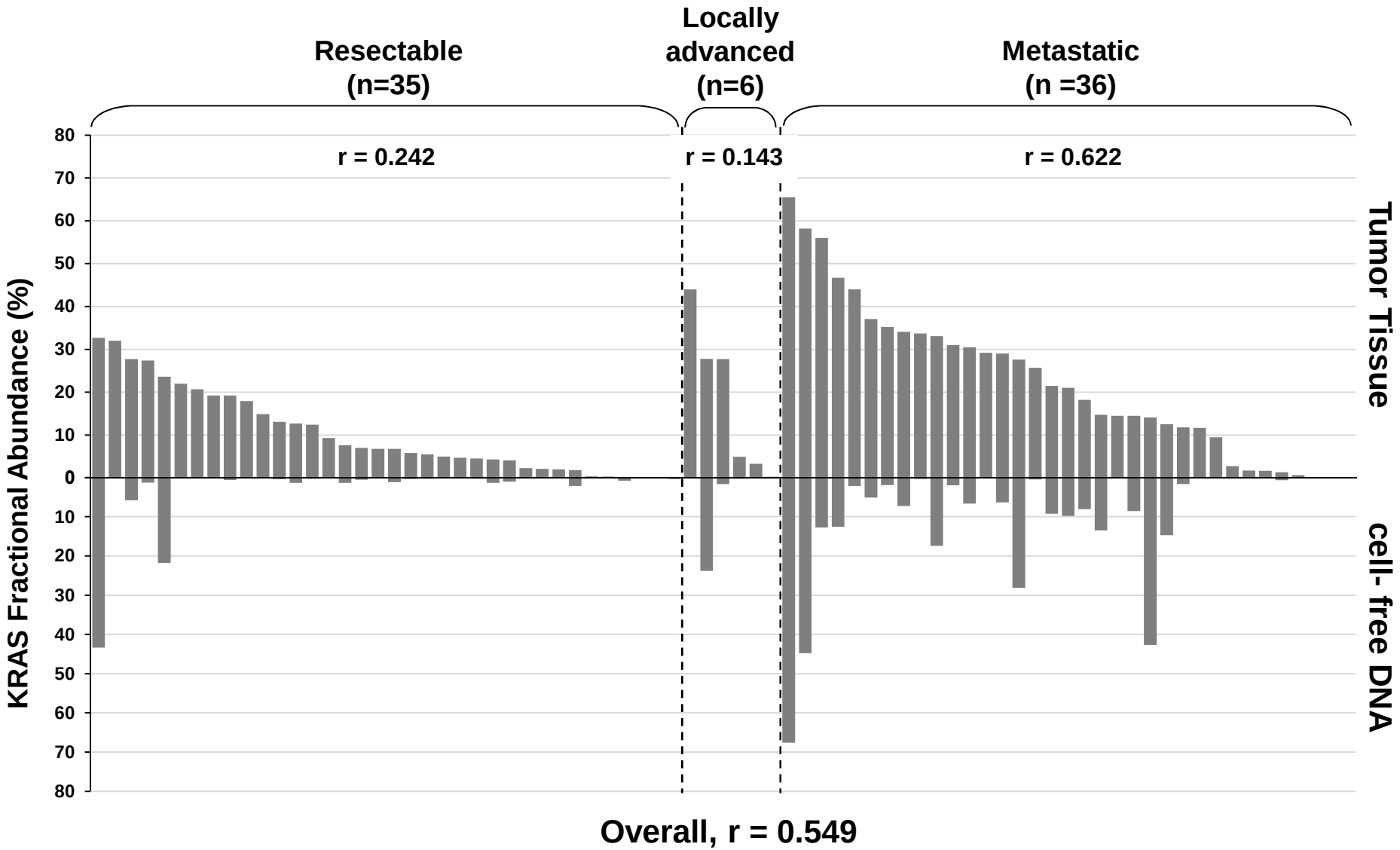
In submission

Somatic Mutations with Decreased Allelic Fraction after Treatment in at least 3 Patients

Gene	Description	Protein change	Patients
KRAS	Kirsten rat sarcoma viral oncogene homolog	G12*	6
WHSC1	Wolf-Hirschhorn syndrome candidate 1	P1020A	4
CDK6	cyclin-dependent kinase 6	p.N284H	3
DDB2	damage-specific DNA binding protein 2, 48kDa	p.W54L	3
EP300	E1A binding protein p300	p.G98A	3
ERCC3	excision repair cross-complementation group 3	p.V193L	3
FBXW7	F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase	p.A105S	3
FLT3	fms-related tyrosine kinase 3	p.R655G	3
KAT6A	K(lysine) acetyltransferase 6A	p.M1389L	3
KAT6B	K(lysine) acetyltransferase 6B	p.Q1513E	3
KDR	kinase insert domain receptor (a type III receptor tyrosine kinase)	p.C246S	3
MMP2	matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	p.E258Q	3
PSIP1	PC4 and SFRS1 interacting protein 1	p.A168G	3
TET2	tet methylcytosine dioxygenase 2	p.M1789I	3
XPA	xeroderma pigmentosum, complementation group A	p.L226W	3
ZNF521	zinc finger protein 521	p.D25E	3

In submission

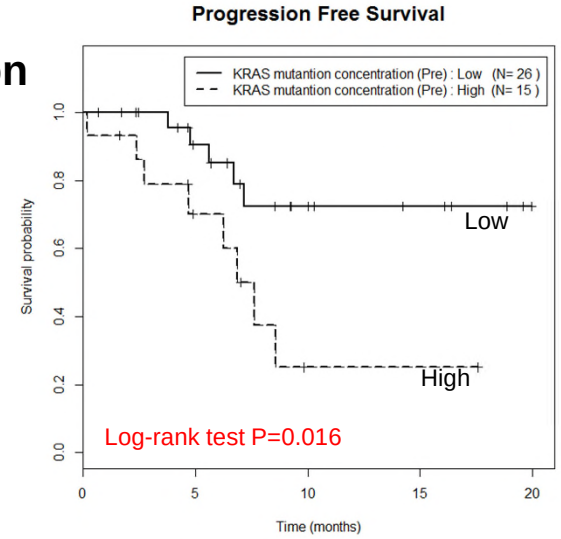
Comparison of KRAS mutation fraction between blood-cfDNA and tissue-DNA according to stage

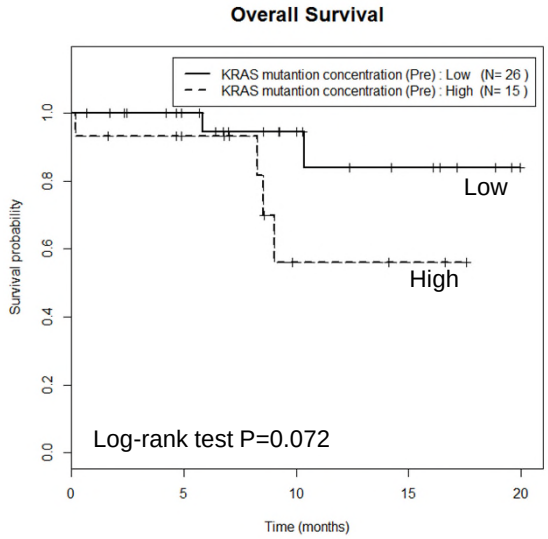


Kim MK and Woo SM. Clin Chem. 2018

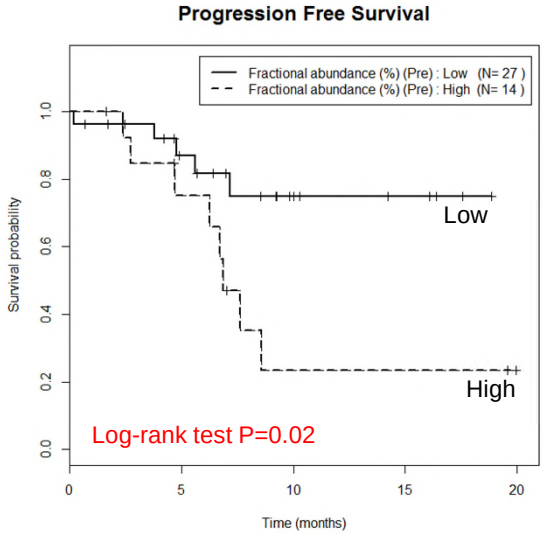
KM Curve according to KRAS Mutation in Resectable Pancreatic Cancer

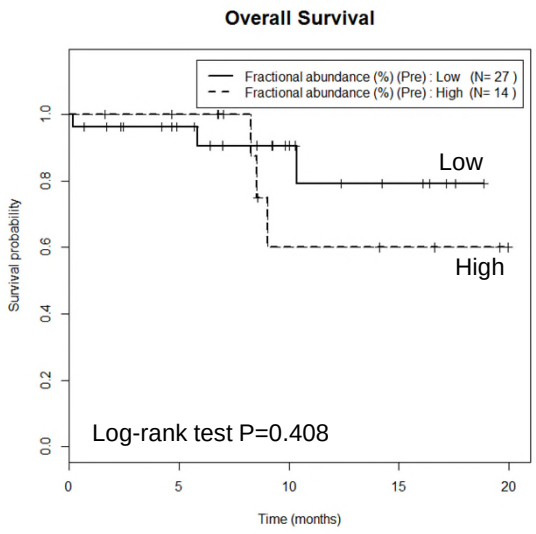
A. KRAS mutant concentration
(cut-point = 165 copies/uL)





B. Fractional abundance
(cut-point=0.415 %)



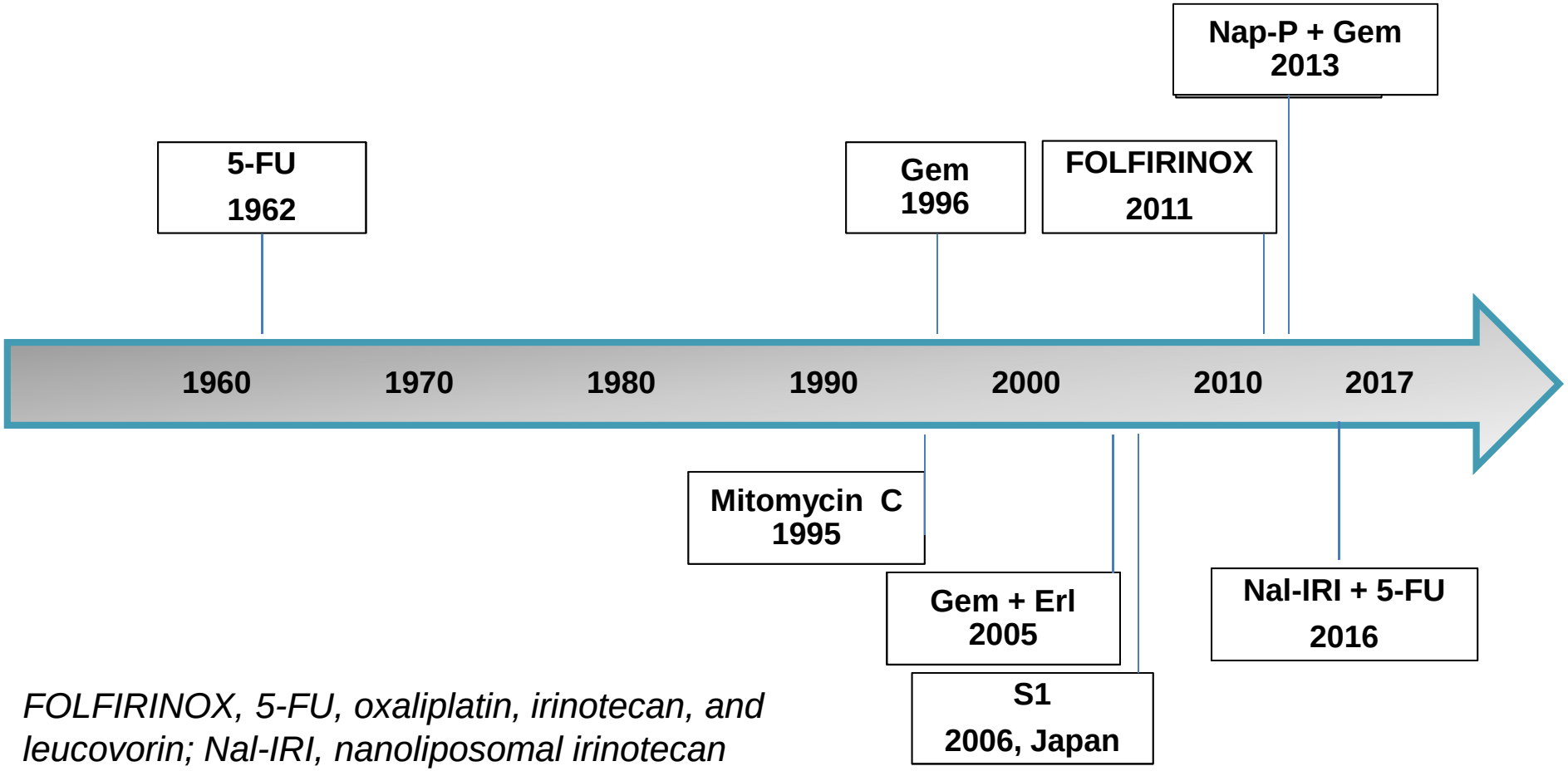


Kim MK and Woo SM. Clin Chem. 2018

Contents

1. The role of systemic chemotherapy in the management of LAPC
2. Biomarker development to identify patients with rapidly progressive disease
    - SMAD4 or other candidates
3. Optimal chemotherapy regimen for LAPC

Key Milestones
-Approvals for Metastatic Pancreatic Cancer (PC)-

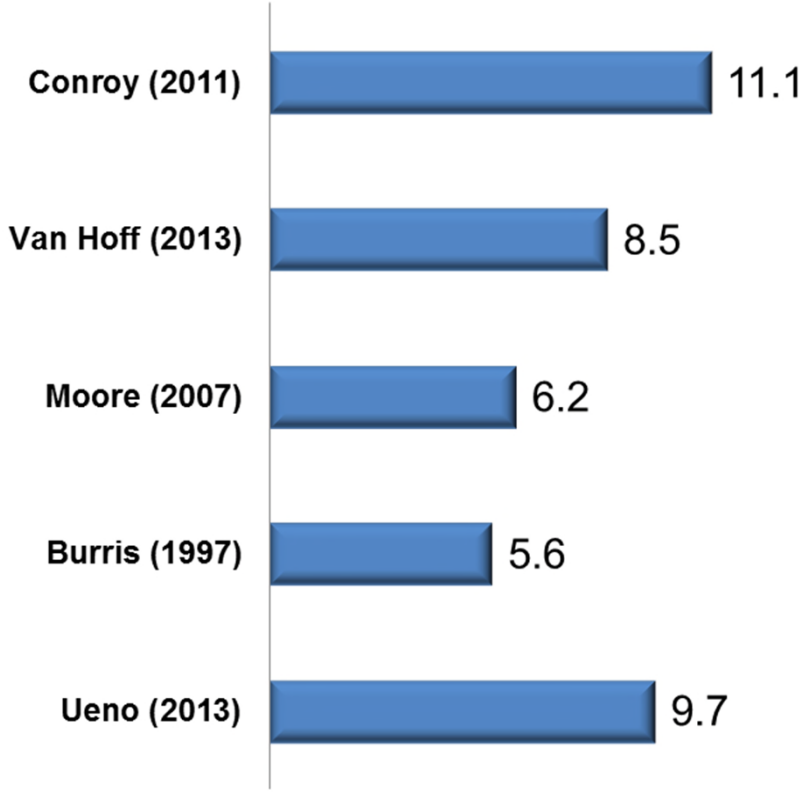


FOLFIRINOX, 5-FU, oxaliplatin, irinotecan, and leucovorin; Nal-IRI, nanoliposomal irinotecan ; Nap-P, nab-paclitaxel

European Medicines Agency, http://www.ema.europa.eu/ema/

First-line Treatment Options in Metastatic PC

	First-line Treatment	Median survival (mo)
Good performance status	▪ FOLFIRINOX (preferred) ▪ Gem + nab-P (preferred) ▪ Gem + erlotinib	
Poor performance status	▪ Gem monotherapy ▪ S1	

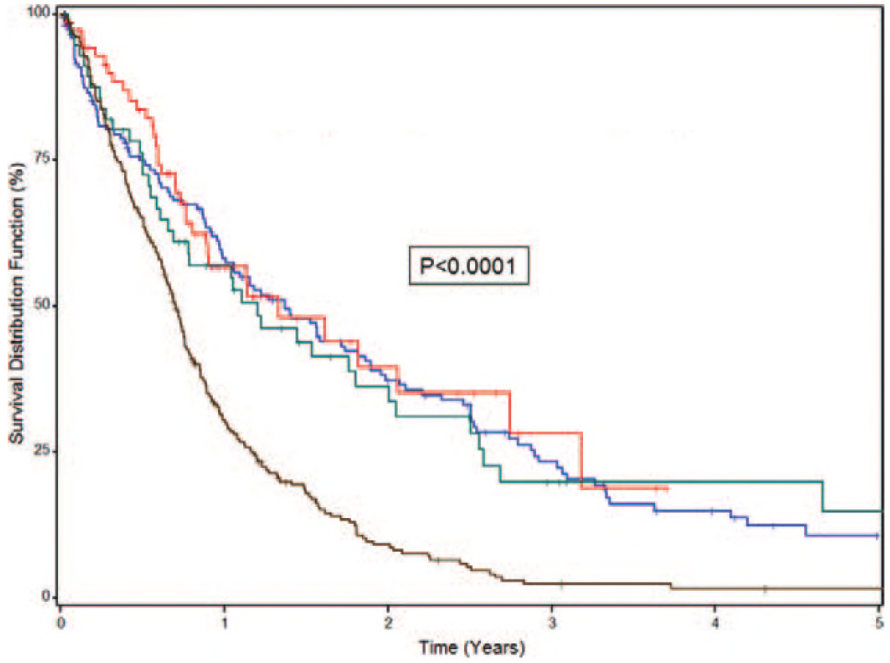


NCCN. Pancreatic adenocarcinoma. v2.2015. www.nccn.org.; Goldman-cCecil Medicine 25e

Neoadjuvant Therapy with FOLFIRINOX Results in Resectability in 60% of the LAPC Patients

- December 2001 and June 2015, University of Heidelberg

Resection rates	FOLFIRINOX	gemcitabine and radiation	others	P
50.8% (292/575)	61% (76/125)	46% (150/322)	52% (66/128)	0.026



Overall survival after resection

- **Fofirinox (N=74): MS 16 mo**
- **Gem plus RTX (N=145): MS: 16.5 mo**
- **TP (N=57): MS 14.5 mo**
- **Expl./Bypass (N=248): MS 6.5 mo**

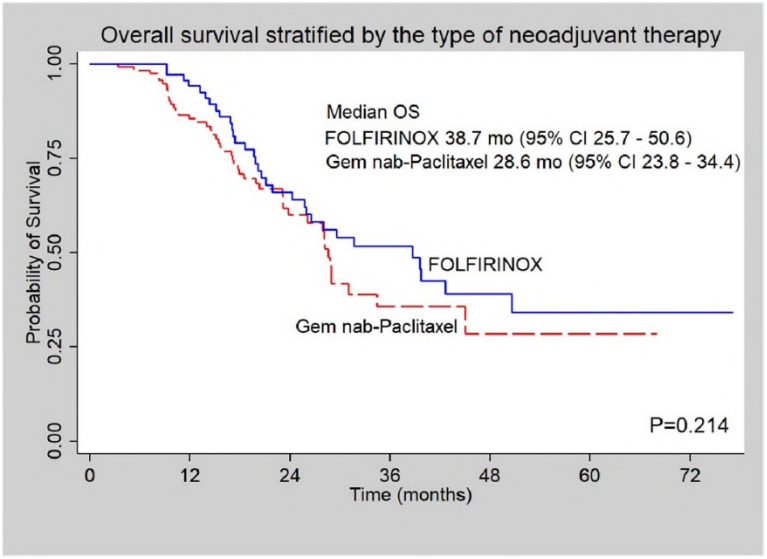
Hackert T. Ann Surg. 2016

FOLFIRINOX versus Gemcitabine/nab-paclitaxel for Neoadjuvant Treatment of Resectable and Borderline Resectable PC : A Propensity Matched Analysis

- A single institution retrospective review (01/11-03/17)

Table 3 Cox regression analysis for OS adjusting for baseline differences and treatment related variables

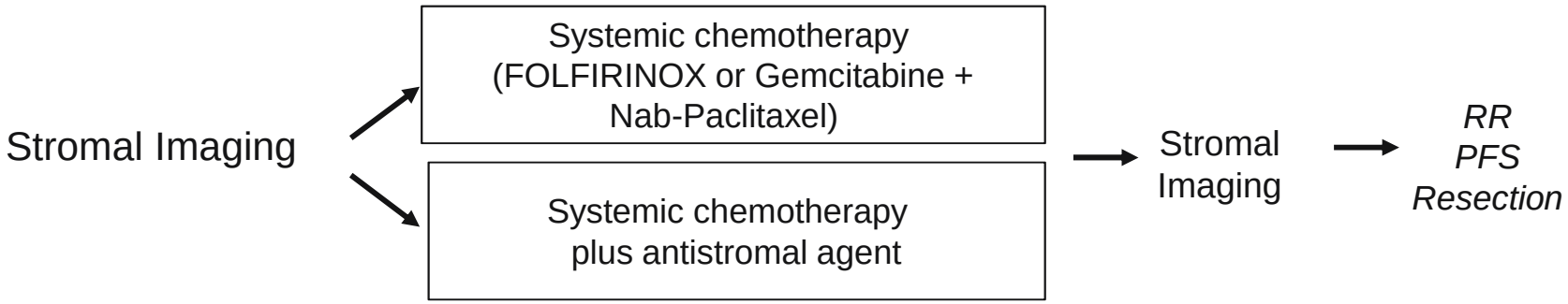
	Hazard Ratio (95% CI)	P value
FOLFIRINOX	0.674 (0.378 - 1.204)	0.183
Age	1.008 (0.981 - 1.038)	0.553
Sex	0.999 (0.602 - 1.661)	0.999
Initial CT size	1.032 (0.795 - 1.339)	0.813
Borderline resectable	1.017 (0.552 - 1.873)	0.958
Initial CA 19-9	1.000 (0.999 - 1.000)	0.701
Number of chemotherapy cycles	0.490 (0.341 - 0.705)	<0.001



- In a propensity matched analysis of 166 patients using the same preoperative variables, the average treatment effect of FOLFIRINOX was to increase OS by 4.9 months above gemcitabine/nab-paclitaxel (p=0.012).

Dhir M. J Clin Oncol. 2018 (abstr 402)

Potential Clinical Trial Designs Targeting the Cancer Stroma in LAPC



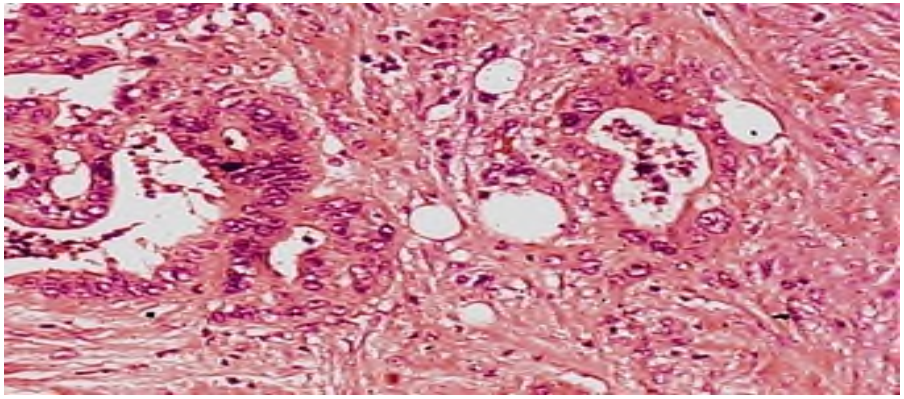
Agents	Combination	Comments	ClinicalTrials.gov Identifier
PEGPH20 (recombinant hyaluronidase)	**Nab-P + Gem (ph3)**	▪ **Hyaluronan-high patients** ▪ **previously untreated metastatic pancreatic cancer**	**NCT02715804**
Vitamin D analogues	**Gem in mouse model**	▪ **vitamin D receptor regulate pancreatic stellate cells*** ▪ **Reprogramming the stroma**	**-**
Necuparanib	**Nab-P + Gem (ph2)**	▪ **Terminated after a pre-planned futility analyses showed an insufficient level of efficacy**	**NCT01621243**

Slide credit: clinicaloptions.com

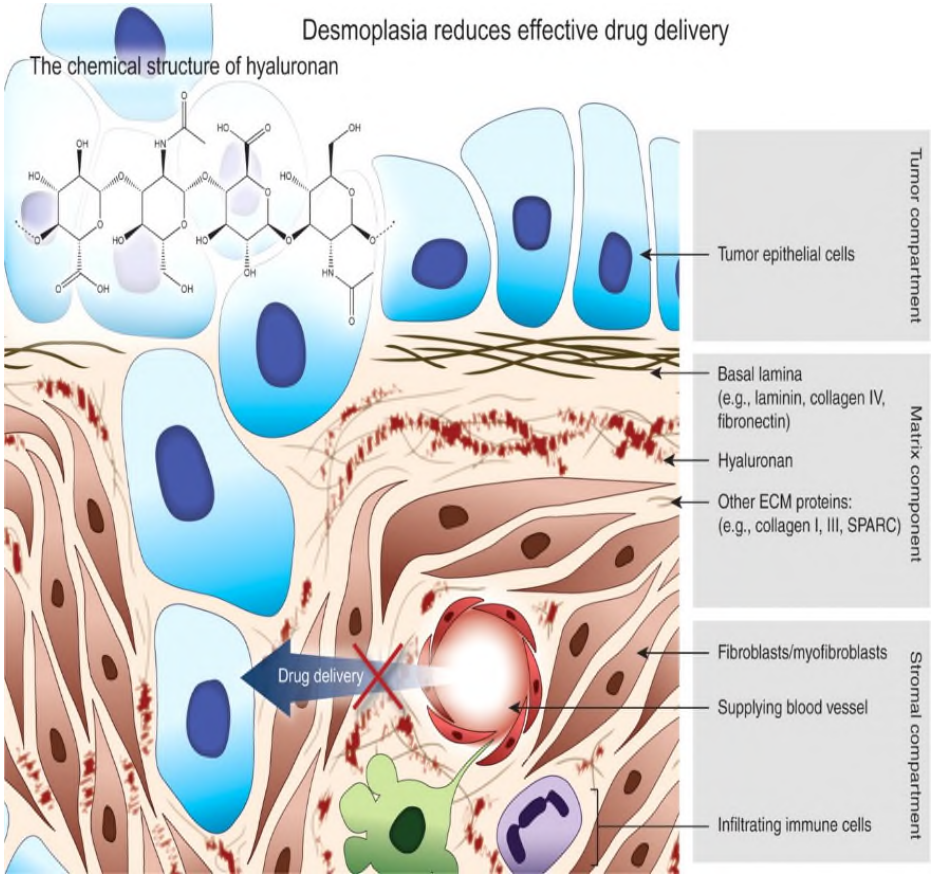
Hidalgo M. Clin Cancer Res 2012

Hyaluronan: Major Component of the Extracellular Matrix

- PEGPH20: recombinant human hyaluronidase
- Hyaluronan degradation can
  - Normalize tumor interstitial pressure
  - Improve drug delivery

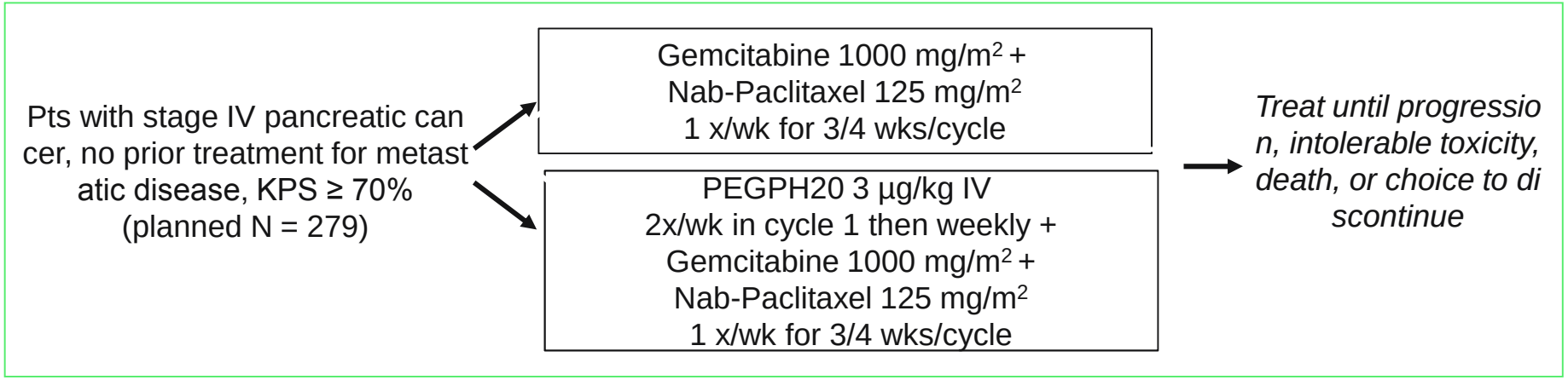


Slide credit: clinicaloptions.com



Reprinted from Cancer Discovery, 2011, Volume 1/Issue 4, pp 291-296, CJ Whatcott, et al., Targeting the tumor microenvironment in cancer: w hy hyaluronidase deserves a second look, with permission from AACR.

Phase II HALO-109-202: Preliminary Results



Outcome by Population	Gem + Nab-P + PEGPH20	Gem + Nab-P	P Value	HR
Total				
▪ Median PFS, mos	5.7	5.2	.11	0.69
▪ ORR, % (n/N)	41 (30/74)	34 (21/61)	.48	
HA-high				
▪ Median PFS, mos	9.2	4.3	.05	0.39
▪ ORR, % (n/N)	52 (12/23)	24 (5/21)	.04	
HA-low				
▪ Median PFS, mos	5.3	5.6	.74	0.89
▪ ORR, % (n/N)	37 (14/38)	38 (9/24)	.96	

- Higher rate of thromboembolic events on PEGPH20-containing arm during first stage of enrollment (42% vs 25%); mitigated during second stage with addition of prophylactic enoxaparin[1]
- Phase III HALO-109-301 study of gem/nab-P ± PEGPH20 limited to HA-high pts currently enrolling[2]

1. Hingorani SR, et al. ASCO 2015. Abstract 4006.
2. ClinicalTrials.gov. NCT02715804.

Summary and Conclusion

- **Initial systemic therapy with combination regimens (FOLFIRINOX or Gemcitabine + Nab-Paclitaxel) is recommended for most LAPC patients with good PS.**
- **Molecular markers are needed better predict responses to specific treatments, including CRT, and to allow for more focused approaches to treatment selection.**
- **Systemic chemotherapy plus anti-stromal agent**