Pancreatic Cancer: Emerging Strategies

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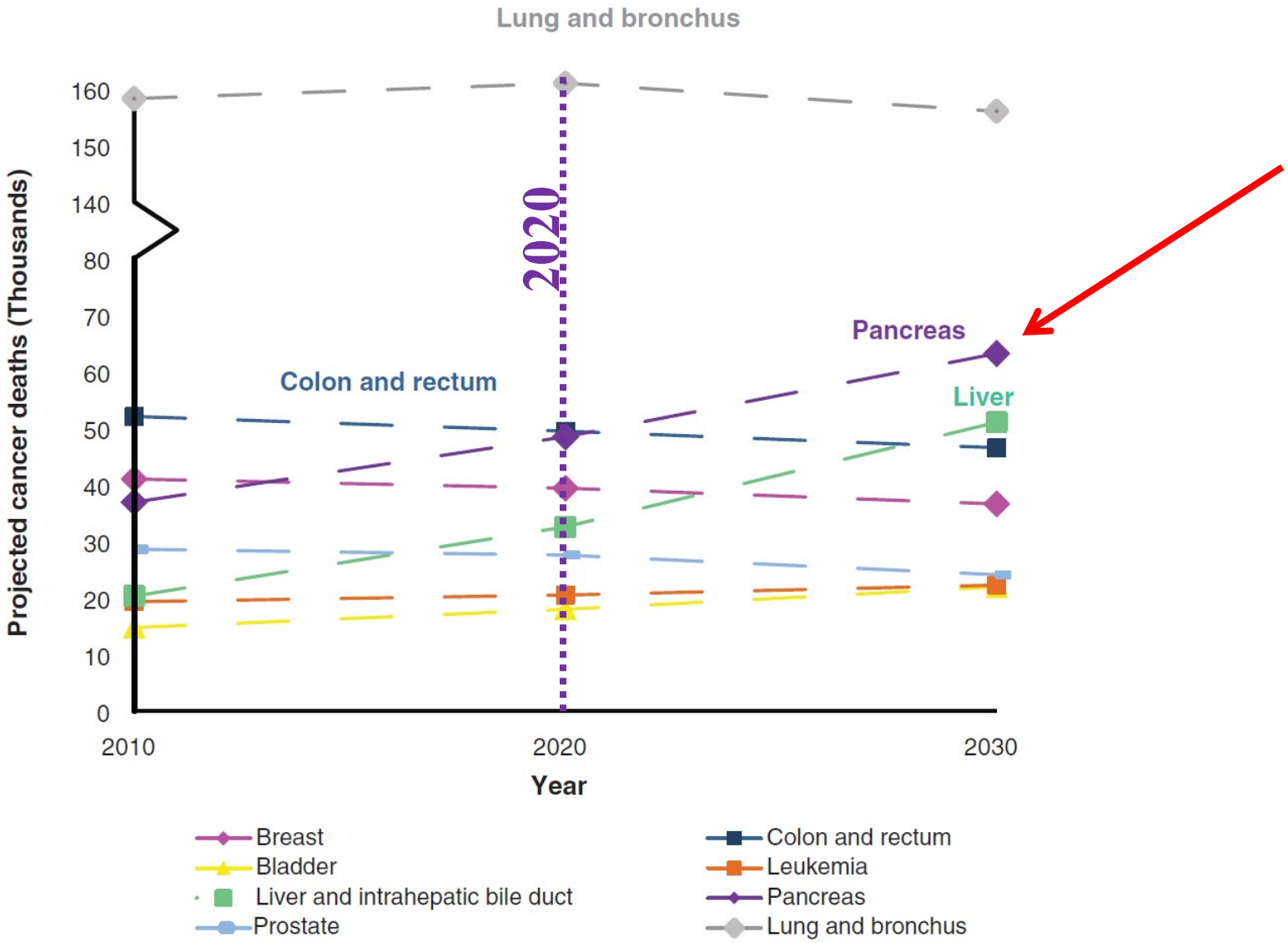
Disclosures

- Clinical trial support: Celgene, BMS, Astellas, Samumed, Boston Biomedical, Halozyme, EpicentRx, Merck, Oncomed
- Consultant: Lilly, Celgene, Eisai
- Speaker Bureau: Celgene, Eisai



Rahib et al. Cancer Res. 2014 Jun 1;74(11):2913-21.

Outline

- Pancreatic Cancer
  - PARPi update
  - Stroma update
  - (Neo)adjuvant update

PARPi in pancreatic cancer

Olaparib as maintenance treatment following first-line platinum-based chemotherapy in patients with a germline BRCA mutation and metastatic pancreatic cancer: Phase III POLO trial

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ClinicalTrials.gov identifier: NCT02184195. This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA (MSD)

Presented By Hedy Kindler at 2019 ASCO Annual Meeting

Study design

Key eligibility criteria

Metastatic pancreatic cancer

Deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutation

≥16 weeks first-line platinum-based chemotherapy with no limit to duration, without progression (CR, PR or SD)*

Randomized 3:2

No stratification factors

Olaparib tablets 300 mg bid

or

Placebo

Until investigator-assessed disease progression or unacceptable toxicity

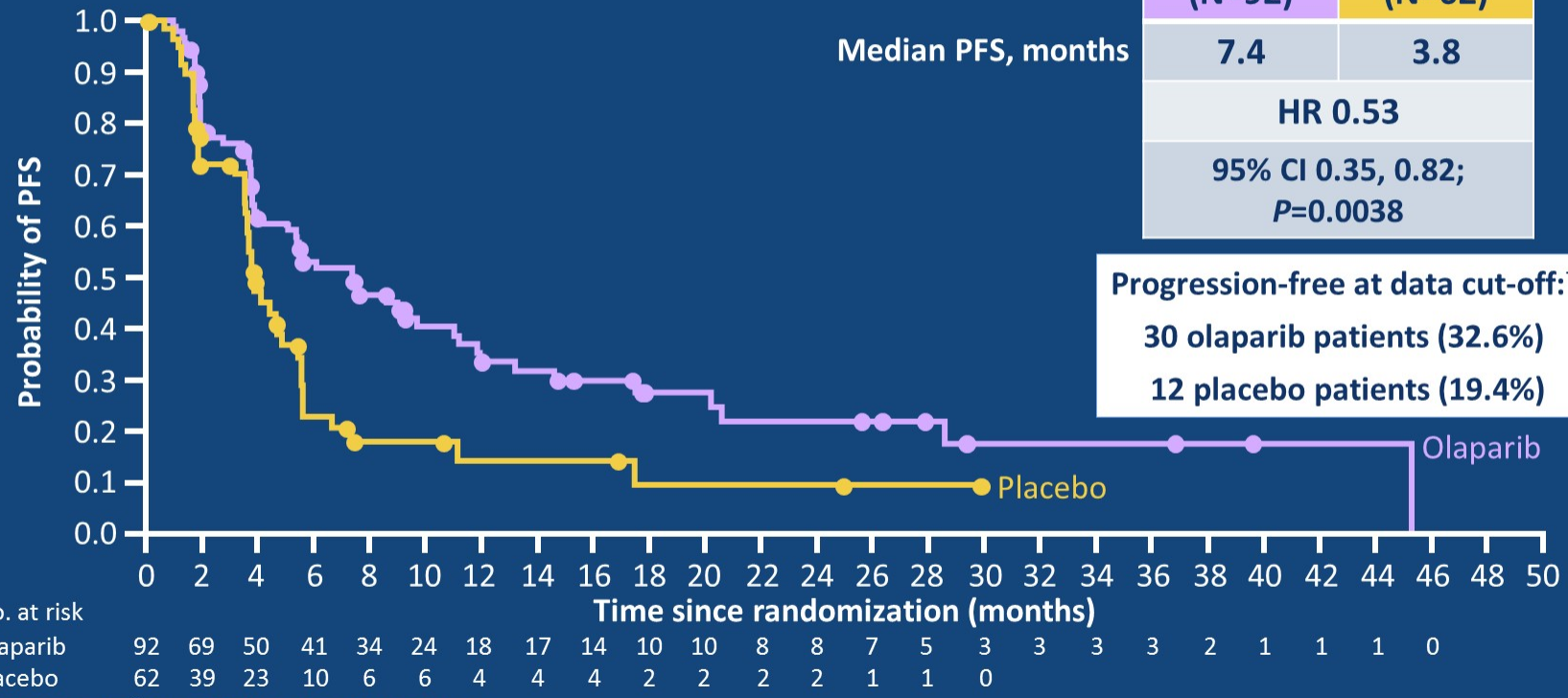
38% of gBRCAm patients had disease progression, were ineligible, or declined randomization

*There was no maximum limit to the duration of first-line chemotherapy. bid, twice daily; CR, complete response; PR, partial response; SD, stable disease

Primary endpoint: PFS by blinded independent central review*

	Olaparib (N=92)	Placebo (N=62)
Median PFS, months	7.4	3.8
HR 0.53		
95% CI 0.35, 0.82; *P*=0.0038		

Progression-free at data cut-off:†
30 olaparib patients (32.6%)
12 placebo patients (19.4%)



No. at risk																								
Olaparib	92	69	50	41	34	24	18	17	14	10	10	8	8	7	5	3	3	3	3	2	1	1	1	0
Placebo	62	39	23	10	6	6	4	4	4	2	2	2	2	1	1	0								

*Dots indicate censorship. †January 15, 2019. CI, confidence interval

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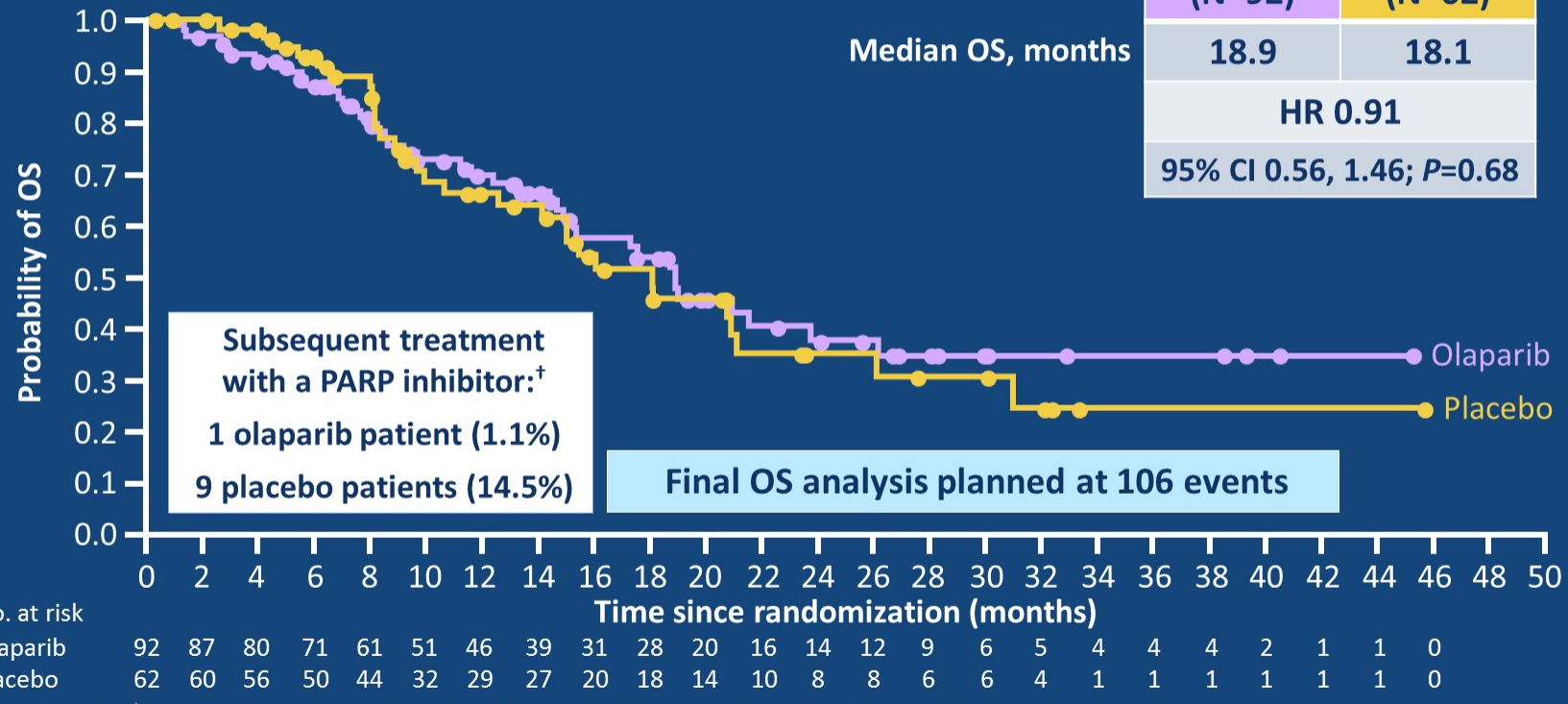
OS: interim analysis, 46% maturity*



Median OS, months	Olaparib (N=92)	Placebo (N=62)
	18.9	18.1
HR 0.91		
95% CI 0.56, 1.46; *P*=0.68		

No. at risk																								
Olaparib	92	87	80	71	61	51	46	39	31	28	20	16	14	12	9	6	5	4	4	4	2	1	1	0
Placebo	62	60	56	50	44	32	29	27	20	18	14	10	8	8	6	6	4	1	1	1	1	1	1	0

*Dots indicate censorship. †Crossover to olaparib was not permitted during this study; subsequent therapies were given at the investigators' discretion

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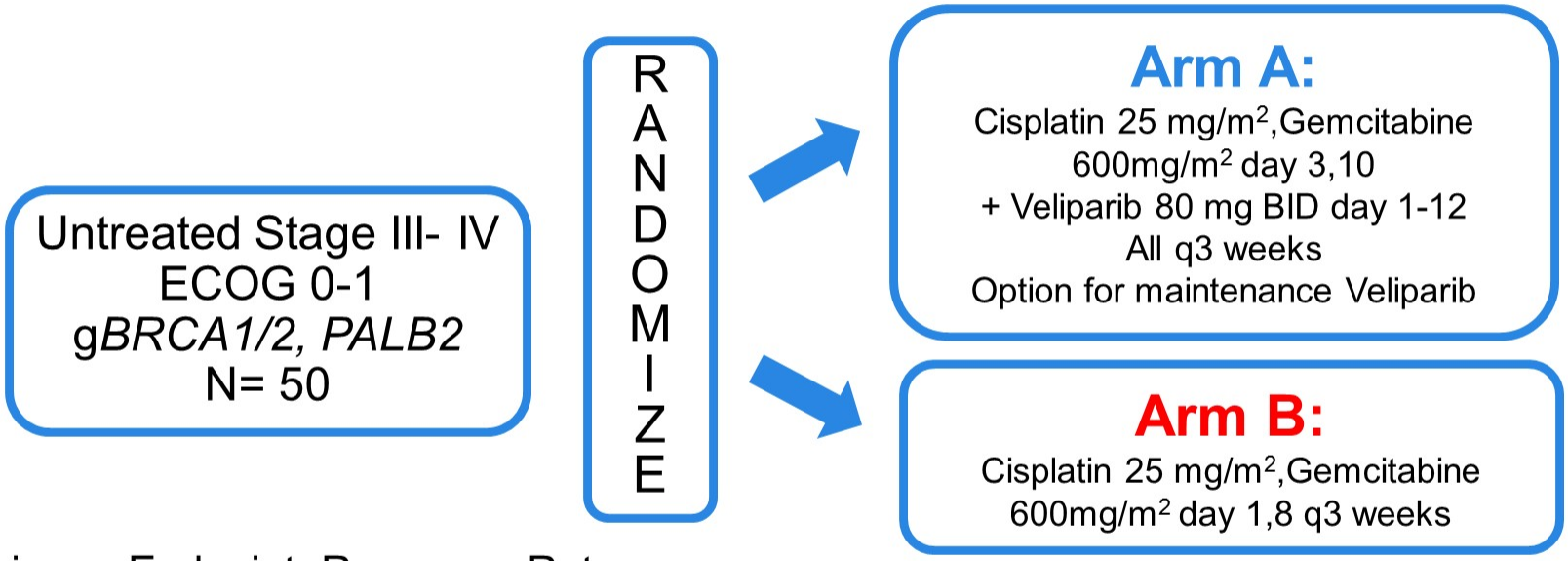
Randomized Phase II Cisplatin, Gemcitabine +/- Veliparib; Germline *BRCA/PALB2*



Primary Endpoint: Response Rate
Secondary: PFS, DCR, OS, exploratory
Simon 2-stage design: 16-25/arm
Unacceptable RR 10%; Promising 20%; Type 1, II errors 10%

NCT01585805; O'Reilly, et al. Cancer, 2018

Memorial Sloan Kettering Cancer Center

Patient Demographics (N= 50)*

Characteristic	Arm A N= 27	Arm B N= 23	A+B N= 50
Total Patients	27 (54%)	23 (46%)	50 (100%)
Age (years)	64 (48-82)	63 (37-81)	63.5 (37-82)
Sex			
Male	12 (44)	10 (43)	22 (44%)
Female	15 (56)	13 (57)	28 (56%)
AJCC Stage			
III (Locally advanced)	5 (19)	3 (13)	**8 (16%)**
IV (Metastatic)	22 (81)	20 (87)	**42 (84%)**
ECOG			
0	15 (56)	8 (35)	23 (46%)
1	12 (44)	15 (65)	27 (54%)

Characteristic	Arm A N= 27	Arm B N= 23	A+B N= 50
Genomic Descriptors			
BRCA1	7 (26%)	5 (22%)	**12 (24%)**
BRCA2	19 (70)	16 (70)	**35 (70%)**
PALB2	1 (4)	2 (9)	**3 (6%)**
***BRCA* AJ Founder**		N = 28 (56)	
BRCA1 187delAG	2 (7)	1 (4)	3 (6%)
BRCA1 5385insC	2 (7)	2 (9)	4 (8%)
BRCA2 6174delT	13 (48)	8 (35)	21 (42%)
Sites of Metastases			
Liver	20 (74)	17 (74)	**37 (74%)**
Lung	7 (26)	7 (30)	14 (28%)
Lymph nodes	10 (37)	8 (35)	18 (36%)
Peritoneum	3 (11)	4 (17)	7 (14%)

*2 withdrew consent from Arm B – arm assigment

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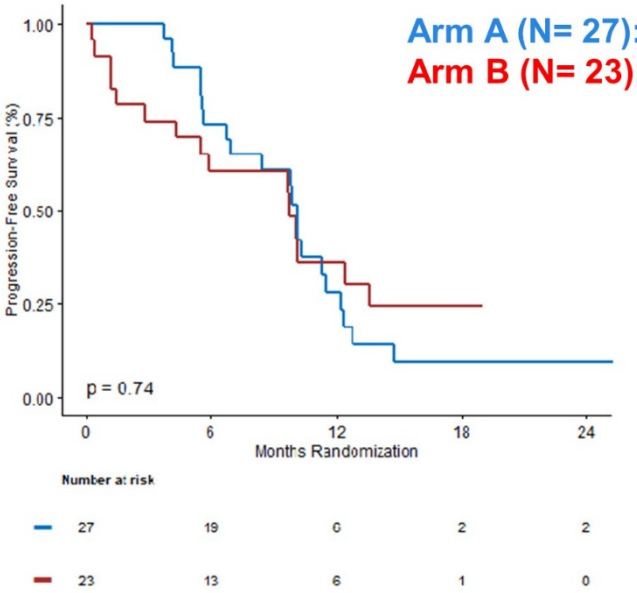
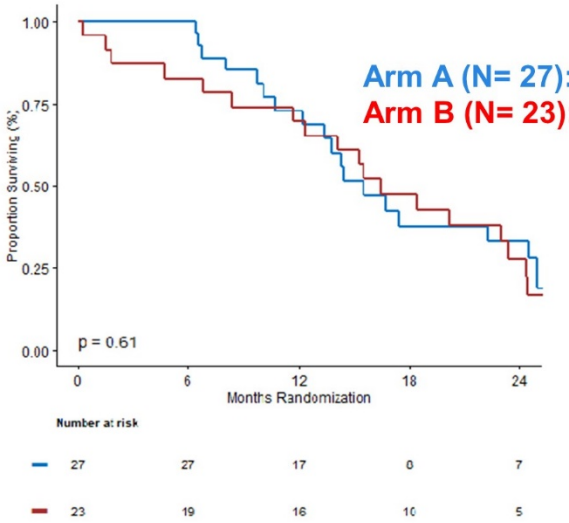
Progression-Free Survival & Toxicity



Arm A (N= 27): 10.1 months (95% CI 6.7- 11.5)
Arm B (N= 23): 9.7 months (95% CI 4.2-13.6)

Gd 3-4 Toxicity	Arm A	Arm B
Anemia	14 (52%)	8 (35%)
Thrombocytopenia	15 (55%)	2 (9%)
Neutropenia	13 (41%)	7 30%)
Dose Reductions		
Heme toxicity	18 (90%)	4 (17%)

Overall Survival



Arm A (N= 27): 15.5 months (95% CI 12.2- 24.3)
Arm B (N= 23): 16.4 months (95% CI 11.7- 23.4)

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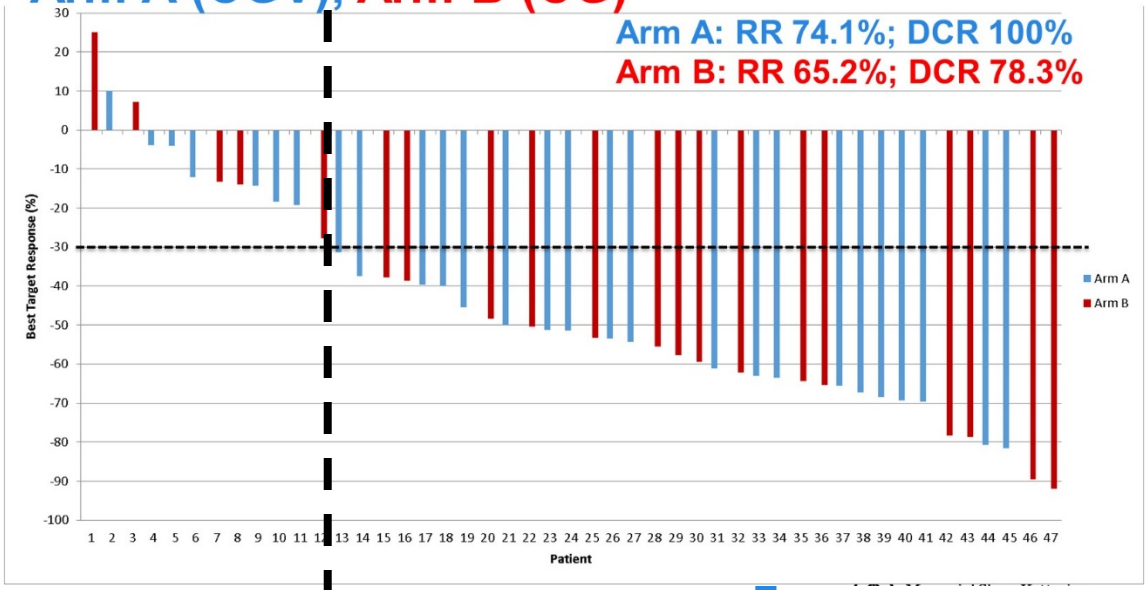
Primary Endpoint: RECIST Response

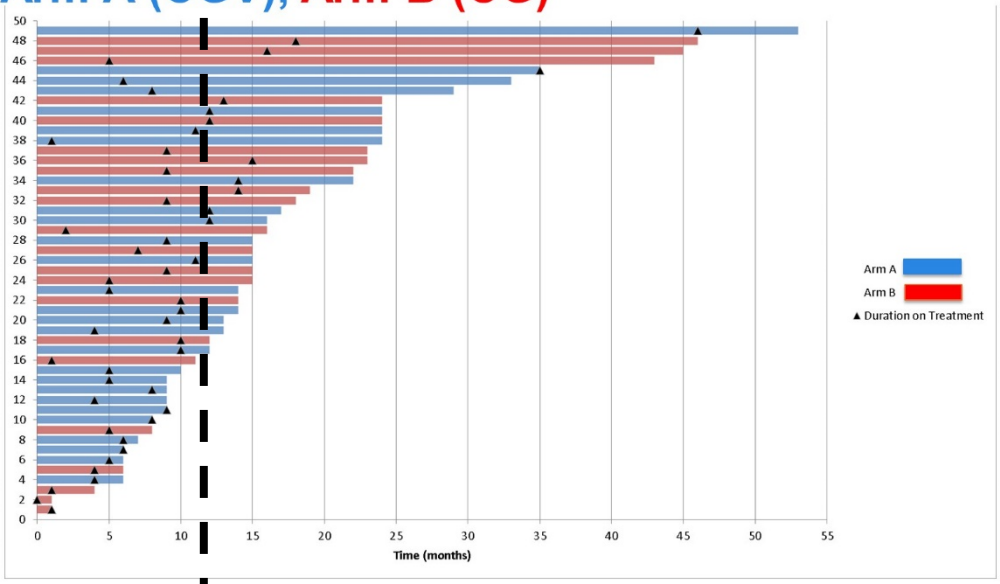
Arm A (CGV), Arm B (CG)



RR: Response Rate; DCR: Disease Control Rate

Treatment Duration and Survival

Arm A (CGV), Arm B (CG)



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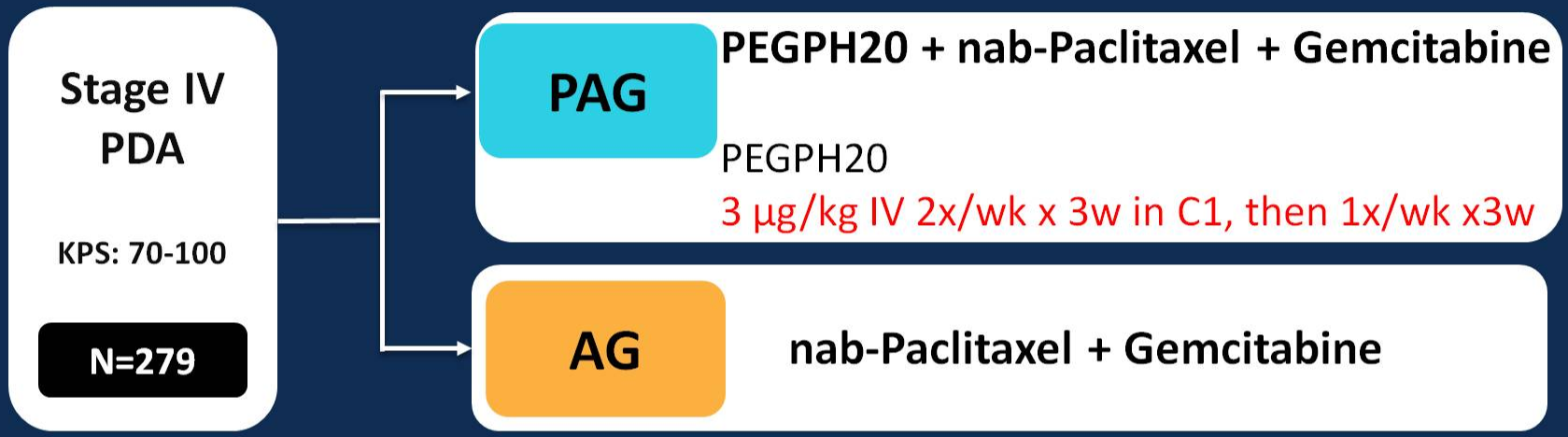
Targeting stroma in pancreatic cancer

PEGPH20

Pamrevlumab

HALO-202: Phase 2 Randomized Study



Primary Endpoints:

- PFS
- Thromboembolic Event Rate

Secondary Endpoints:

- PFS by HA Level
- ORR
- OS

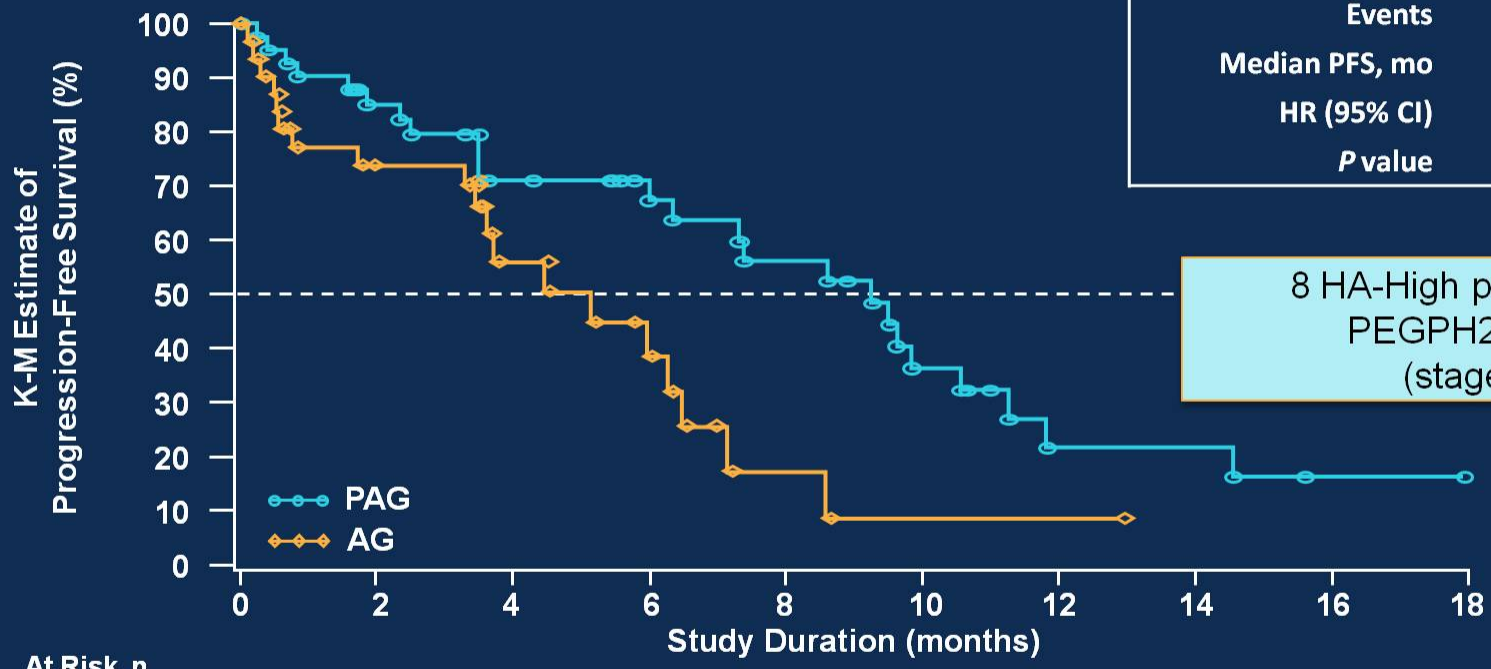
Exploratory Endpoints:

- OS by HA Level
- DoR
- DCR (CR+PR+SD)

Primary & Secondary PFS Endpoint: 80% power at 2-sided alpha level of 0.1

PFS HA-High (Stage 1 & 2)

	PAG (n = 49)	AG (n = 35)
Events	24	19
Median PFS, mo	9.2	5.2
HR (95% CI)	0.51 (0.26-1.00)	
P value	0.0480	



8 HA-High pts stopped PEGPH20 early (stage 1)

At Risk, n										
PAG	49	31	24	18	15	9	4	4	1	0
AG	35	20	11	7	2	1	1	0	0	0

Other Phase II and III Clinical Trials with PEGPH20

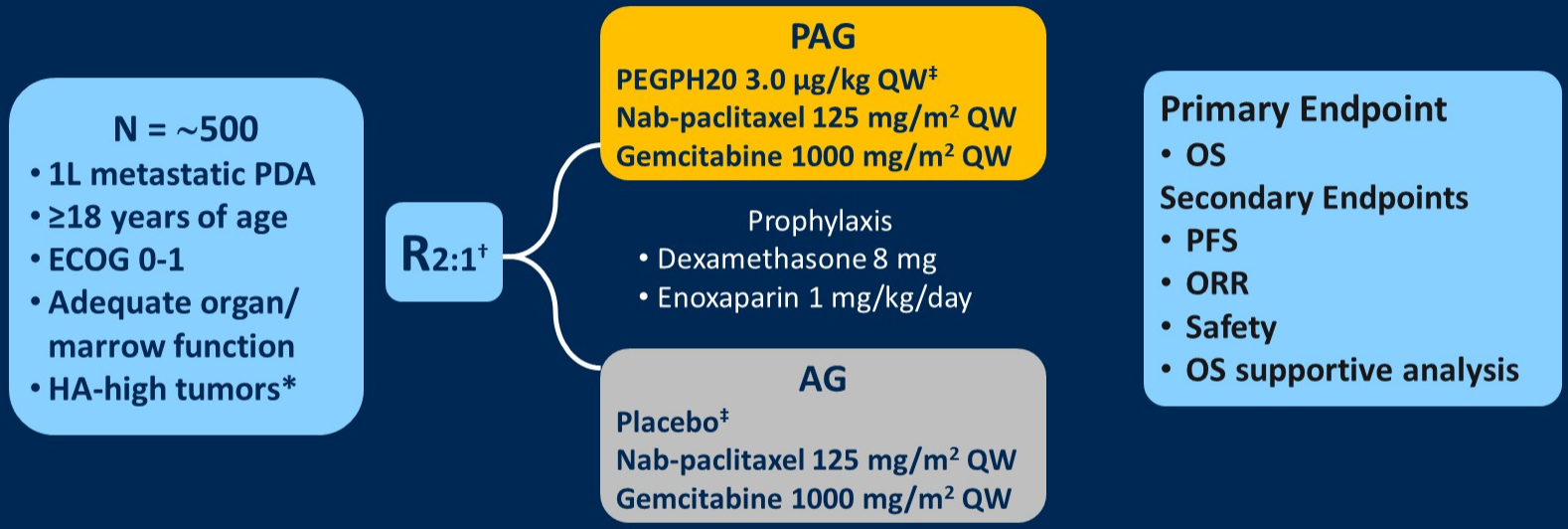
Phase II
FOLFIRINOX
±
PEGPH20
3 µg/kg Q2W

SWOG S1313
- Unselected population
- DSMB stopped study for futility 04/2017

- Why?
  - PEGPH20 dose less frequent?
  - drug interaction?
  - more toxicity and less chemo exposure?

HALO-301 Phase III
Gemcitabine/*Nab*-Paclitaxel
+
PEGPH20 vs placebo
HA-high PDAC

HALO 109-301 Study Design

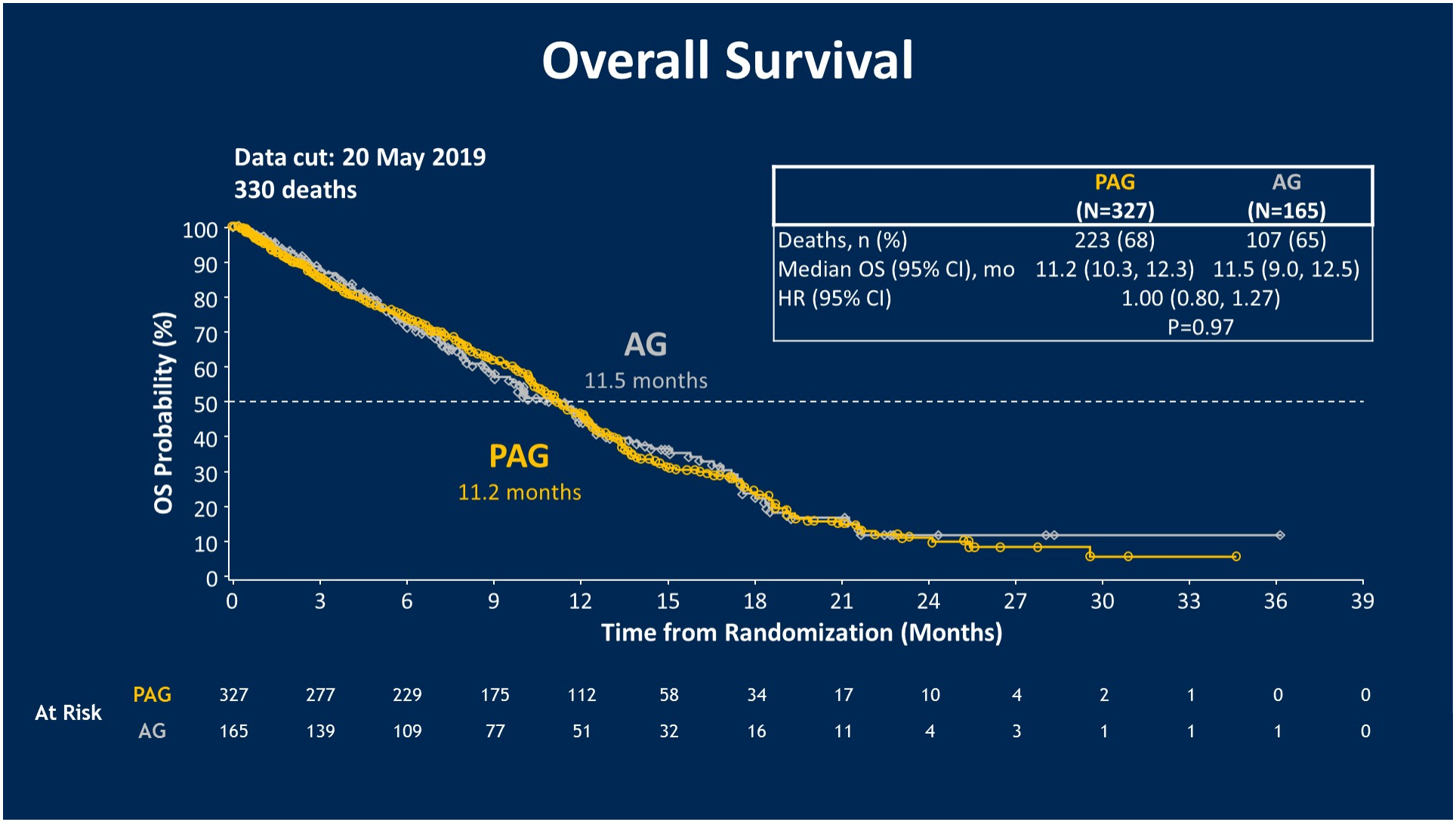


Statistical assumptions

- Median OS of ~8.5 months for AG arm
- 330 deaths will have 93% power to detect HR 0.67 with 2-sided alpha of 0.05
- 50% increase in median OS to 12.7 months

*≥50% hyaluronan staining in tumor samples (fresh or archival after metastatic diagnosis) by HA affinity histochemistry assay (Ventana HA RxDx Assay); †stratified by geographic region (North America, Europe, other territories); ‡twice weekly for Cycle 1 (4-week cycles: 3 weeks on/1 week off)
1L=first line; ECOG=Eastern Cooperative Oncology Group; ORR=objective response rate; OS=overall survival; QW=once weekly; R=randomization

Overall Survival



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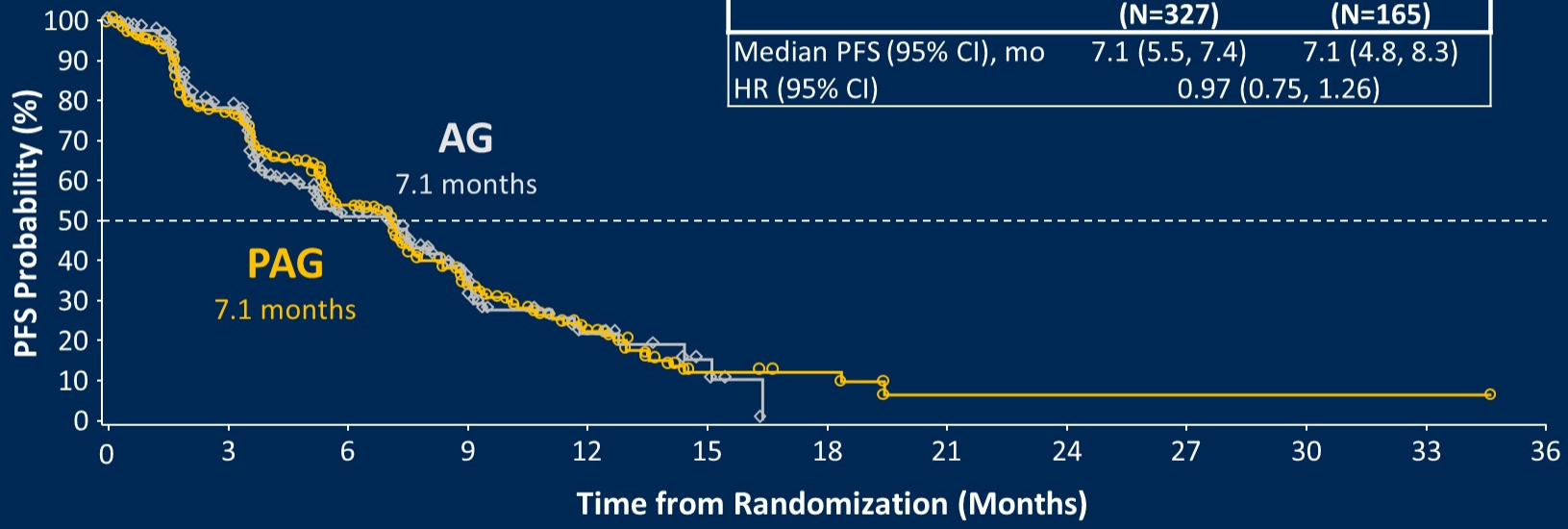
Progression-Free Survival

	PAG (N=327)	AG (N=165)
Median PFS (95% CI), mo	7.1 (5.5, 7.4)	7.1 (4.8, 8.3)
HR (95% CI)	0.97 (0.75, 1.26)	



At Risk													
PAG	327	200	103	46	21	7	5	1	1	1	1	1	0
AG	165	99	52	23	11	3	0	0	0	0	0	0	0

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Response Outcomes

	PAG (N=327)	AG (N=165)
ORR, %*	47%	36%
ORR ratio (95% CI)	1.29 (1.03, 1.63)	
Best response, n (%)		
Complete response	2 (0.6)	1 (0.6)
Partial response	152 (46.5)	59 (35.8)
Stable disease	71 (21.7)	54 (32.7)
Non-CR/Non-PD	9 (2.8)	2 (1.2)
Progressive disease	47 (14.4)	22 (13.3)
Not evaluable/unknown	46 (14.1)	27 (16.4)
DOR, median, months†	6.1	7.4
Confirmed ORR, %	34%	27%
Confirmed ORR ratio (95% CI)	1.22 (0.91, 1.62)	

*Complete and partial responses assessed by blinded independent centralized review based on RECIST version 1.1
†Estimated by the Kaplan-Meier method
CR=complete response; DOR=duration of response; PD=progressive disease

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Drugs that failed in clinical trials involving pancreatic adenocarcinoma: 2004-2014

Summary of main negative studies (i.e. studies that do not have statistically significant results) evaluating targeted agents in advanced pancreatic ductal adenocarcinoma.

Class	Molecule [Ref]	Type	Phase	Endpoint	Result	Hypothesis for failure
Antiangiogenesis inhibitors	Bevacizumab (Kindler et al., 2010; Van Cutsem et al., 2009)	mAb	III	OS	Negative	PDAC avascular hypoxic microenvironment selecting anaerobic cancer cells that are intrinsically resistant to hypoxia-induced apoptosis and, consequently, to antiangiogenics
		SMI	III	OS	Negative	
	Axitinib (Kindler et al., 2011)	SMI	III	PFS	Negative	
	Sorafenib (Goncalves et al., 2012)					
MMP inhibitors	Marimastat (Bramhall et al., 2002)	SMI	III	OS	Negative	Poor selectivity of MMP inhibitors, poor target validation, and complexity of MMP biological effects
EGF and HER2 receptor inhibitors	Cetuximab (Philip et al., 2010)	mAb	III	OS	Negative	Frequent (>90%) activating *KRAS* mutations downstream of the receptor driving resistance, as described in colorectal cancer
	Erlotinib (Moore et al., 2007)	SMI	III	OS	Positive[a]	
	Trastuzumab (Harder et al., 2012)	mAb	II	PFS	Negative	
	Lapatinib (Safran et al., 2011)	SMI	II	OS	Negative	
IGF receptor inhibitors	Cixutumumab (Philip et al., 2014)	mAb	II	PFS	Negative	Crosstalk with other signaling pathways, benefit maybe restricted to a subset of patients with high levels of circulating factors of the IGF axis (McCaffery et al., 2013)
	Ganitumab (NP: NCT01231347)	mAb	III	OS	Negative (stopped)	
Farnesyl-transferase inhibitors (K-Ras-directed agents)	Tipifarnib (Van Cutsem et al., 2004)	SMI	III	OS	Negative	Existence of other Ras isoforms (e.g. N-Ras) that do not rely on farnesylation, and geranylgeranylation working as an alternative pathway for K-Ras membrane attachment when farnesylation is inhibited
MEK inhibitors	CI-1040 (Rinehart et al., 2004)	SMI	II	Response	Negative	Crosstalk with other signaling pathways, particularly with the mTOR pathway, potential activity of dual MEK/mTOR pathway inhibition (Tolcher et al., 2015)
	Selumetinib (Bodoky et al., 2012)	SMI	II	OS	Negative	
	Trametinib (Infante et al., 2014)	SMI	II	OS	Negative	
mTOR inhibitors	Everolimus (Wolpin et al., 2009)	SMI	II	PFS	Negative	Crosstalk with other signaling pathways, particularly with the MAPK pathway
	Temsirolimus (Javle et al., 2010)	SMI	II	OS	Negative	
Hedgehog inhibitors	Vismodegib (NP: NCT01064622)	SMI	II	PFS	Negative	Stroma depletion may enhance cancer cell invasion and accelerate PDAC progression (Ozdemir et al., 2014; Rhim et al., 2014)
	Saridegib (NP: NCT01130142)	SMI	II	OS	Negative (stopped)	

EGF: epidermal growth factor; IGF: insulin-like growth factor; mAb: monoclonal antibody; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; NP: not published; OS: overall survival; PFS: progression-free survival; SMI: small molecule inhibitor.

[a] Marginal overall survival benefit (14 days).

Drugs that failed in clinical trials involving pancreatic adenocarcinoma: 2015-2018

Drug	Target/Mechanism	Phase	Number of patients
Evofosfamide	Alkylator (Hypoxia)	3	694
Ruxolotinib	JAK1/2	3	Early termination
Necuparanib	Heparan mimetic	1/2	128
Masatinib	TKI (Kit, Lyn, Fyn)	3	353
Vandetanib	TKI (VEGFR2, RET, EGFR)	2	142
Algenpantucel-L	Vaccine	3	722
CRS-207 + GVAX	Vaccine	2b	240
Tarextumab	Notch2/3	2	177
Demcizumab	DLL4	2	204
^{90}Y-Clivatuzumab Tetraxetan	MUC1	3	334
Apatorsen	HSP27	2	132
Simutuzumab	LOX-2	2	240 (159)

Slide courtesy of Philip Philip, MD

Current clinical trial model

Phase I – treatment refractory *advanced* multi-histology

Phase II – histology-specific *advanced* tx refractory / tx naive

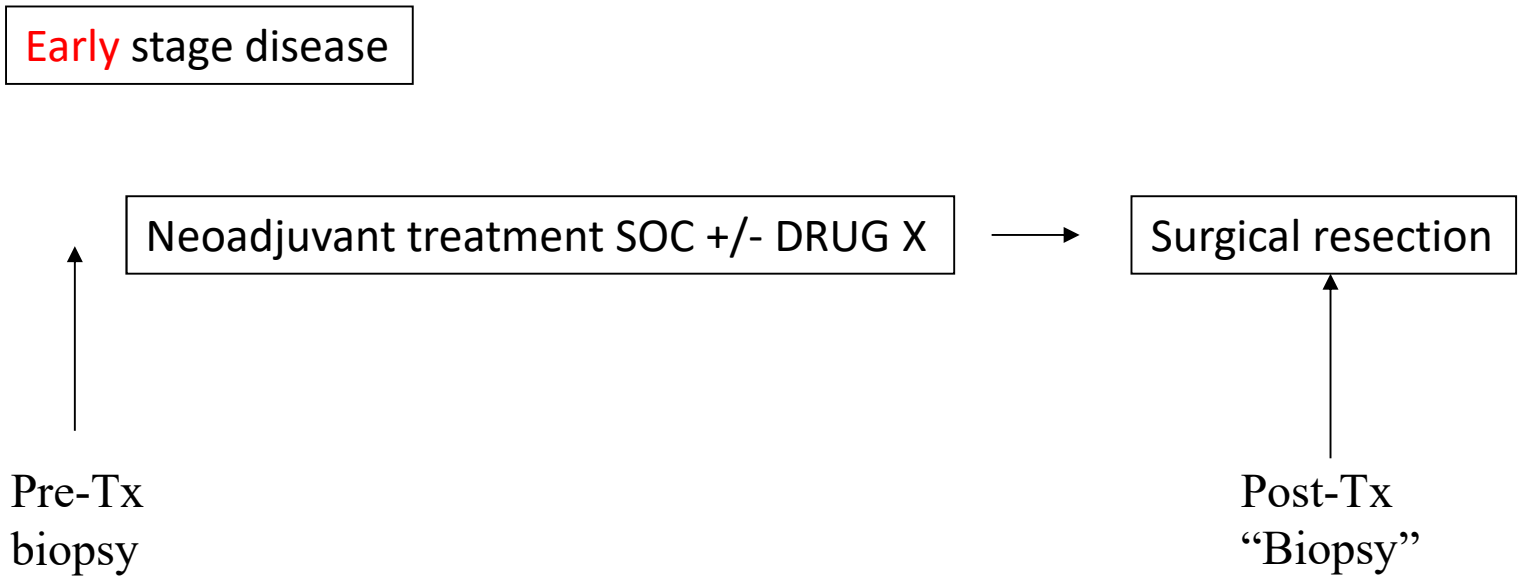
Phase III – randomized histology-specific *advanced* tx refractory / tx naive

Correlatives – paired biopsy specimens

Issues:

- sufficient material?
- successful paired specimens?
- heterogeneity, representative?
- prior treatment effect?

"Window of opportunity" study



Correlatives – paired biopsy specimens

Issues:

- sufficient material?
- successful paired specimens?
- heterogeneity, representative?
- prior treatment effect?

Targeting stroma in pancreatic cancer

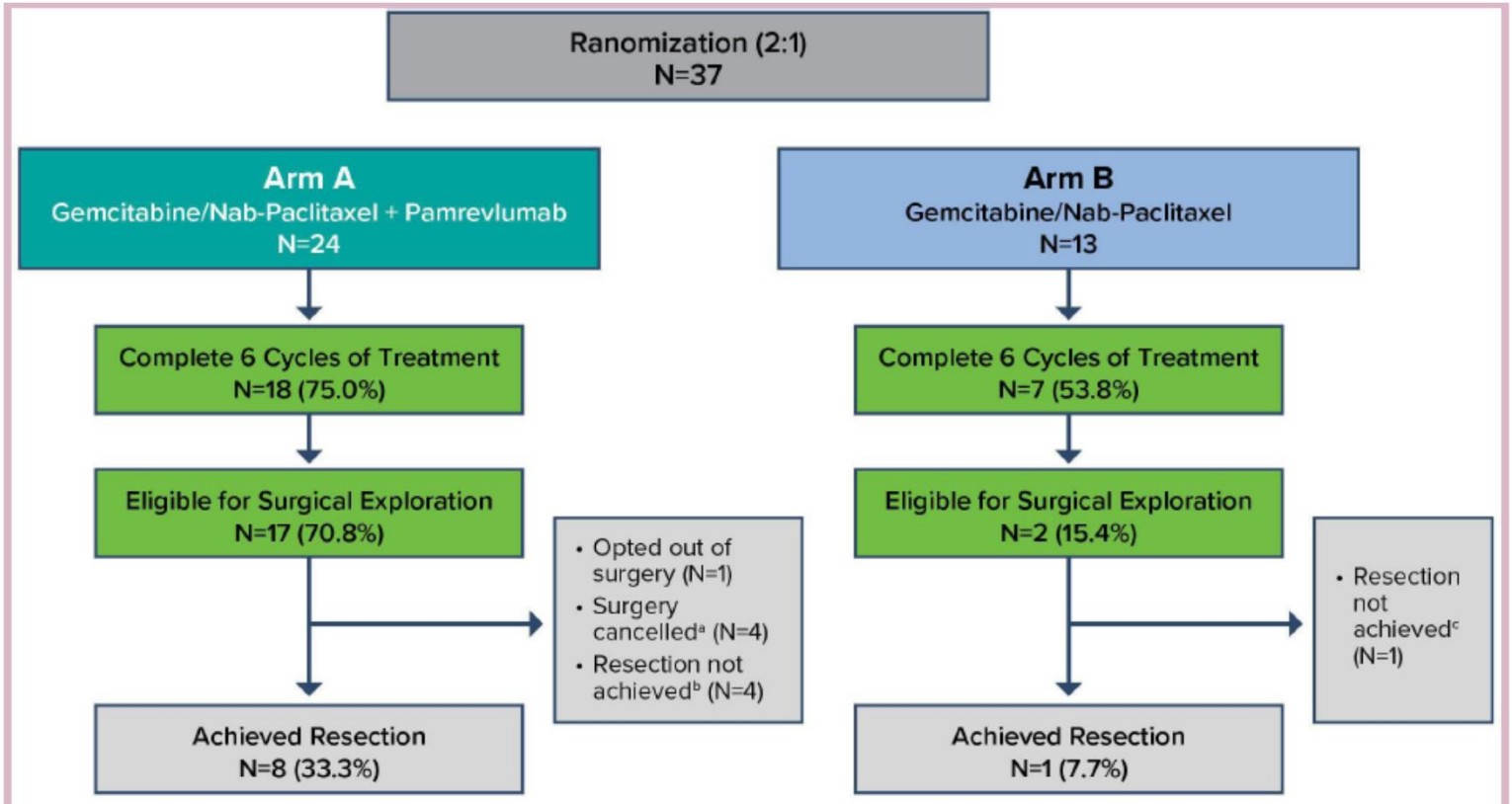
PEGPH20

Pamrevlumab

Neoadjuvant setting

- Pamrevlumab
  - Fully recombinant human monoclonal antibody against connective tissue growth factor -1 (CTGF-1)
    - Studies in Idiopathic pulmonary fibrosis

- Phase I/II trial of Locally advanced Unresectable Pancreatic adenocarcinoma
  - 37 pts 2:1 randomization gemcitabine/nab-paclitaxel +/- pamrevlumab



a. In Arm A, four of the eligible subjects had their surgeries canceled (1 = portal vein thrombosis, 3 = medical issues precluding surgery)

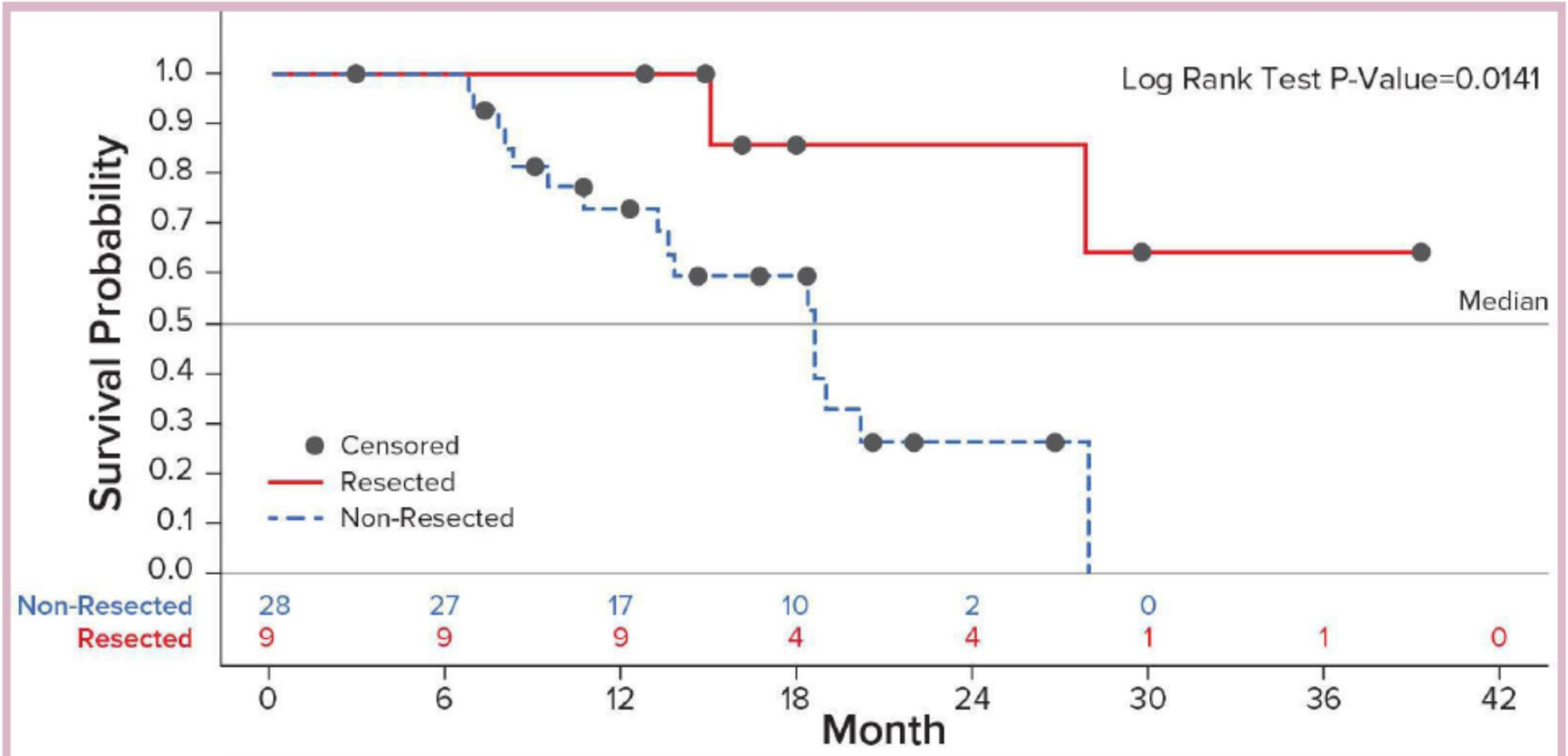
b. In Arm A, four eligible subjects underwent surgery, but resection was not achieved (3 = metastatic disease discovered, 1 = extensive SMA encasement)

c. In Arm B, one eligible subject underwent surgery, but resection was not achieved (1 = extensive vascular encasement)

Figure 1 Patient flow and surgery outcomes. In Arm A, four of the eligible subjects had their surgeries cancelled (1=portal vein thrombosis, 3=medical issues precluding surgery). In Arm A, four eligible subjects underwent surgery, but resection was not achieved (3=metastatic disease discovered, 1=extensive SMA encasement). In Arm B, one eligible subject underwent surgery, but resection was not achieved (1=extensive vascular encasement). SMA, superior mesenteric artery.

Table 3 Summary of resected patients

Site-subject ID	Treatment arm	Response to treatment*	NCCN baseline	NCCN end of treatment	Resection status
1001–1001	A	1, 2, 3	Unresectable (coeliac)	Unresectable (coeliac)	R0
1001–1004	A	1, 2	Unresectable (SMA, SMV)	Unresectable (SMA, SMV)	R1
1001–1005	A	1, 2	Unresectable (coeliac)	Unresectable (coeliac)	R0
1001–1009	A	2, 4	Unresectable (coeliac)	Borderline resectable	R0
1001–1015	A	1, 3	Unresectable (SMV)	Unresectable (SMV)	R1
1001–1017	A	1, 2	Unresectable (SMA)	Unresectable (SMA)	R1
1008–8001	A	1, 2	Unresectable (SMA, SMV, coeliac)	Unresectable (coeliac)	R1
1008–8005	A	2	Unresectable (SMA)	Unresectable (SMA)	R0
1001–1008	B	1, 2	Unresectable (coeliac)	Unresectable (coeliac)	R0



	N	Event	Censored	Median (95% CI)
Non-Resected	28	16 (57.1%)	12 (42.9%)	18.56 (13.27, 20.21)
Resected	9	2 (22.2%)	7 (77.8%)	NE (15.01, NE)

Figure 2 Overall survival Resected vs. Non-resected patients.

Phase III trial ongoing

Locally Advanced
Pancreatic cancer

Stratification:

- SMA> or $\leq 180^0$
- Unreconstructible or reconstructible
- Geographic region

Neoadjuvant treatment
6 cycles

Arm A
G/NP + Pamrevlumab

1:1

Arm B
G/NP + placebo

→ Surgical resection

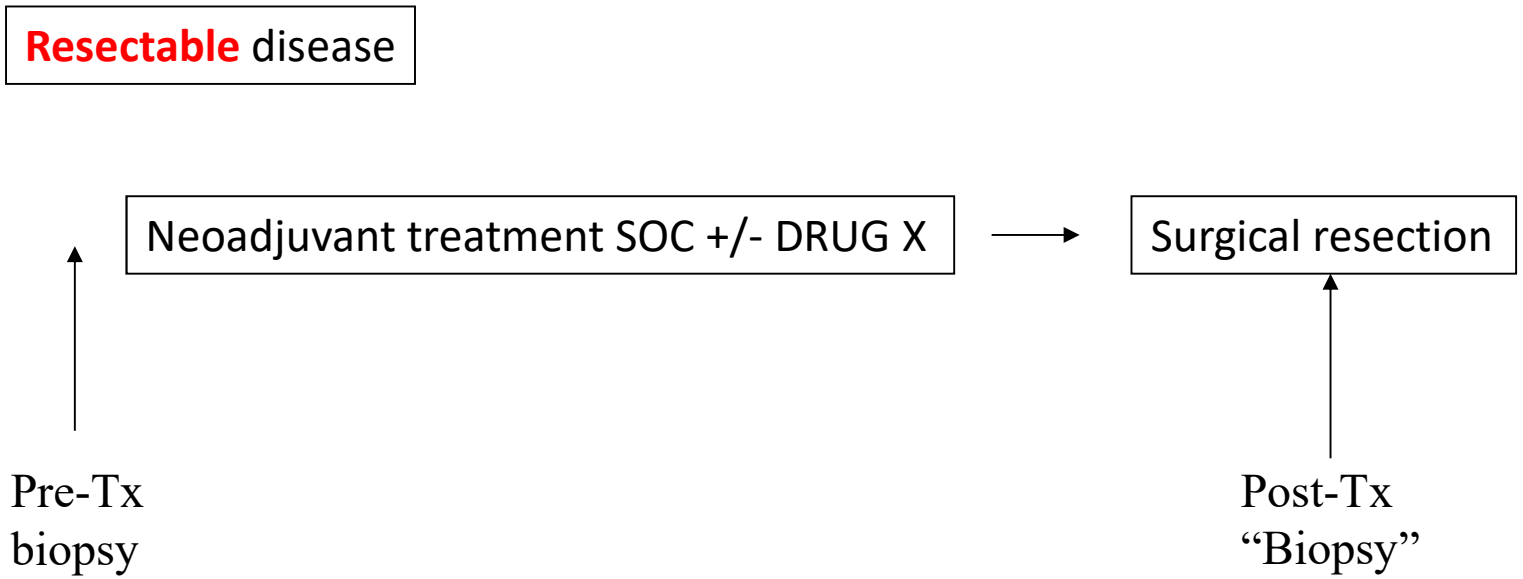
↓

Resected tissue collected for exploratory analysis

Primary Endpoint = OS

Surrogate endpoint for accelerated approval =
proportion of randomized pts achieving R0/R1 resection

"Window of opportunity" study



Correlatives – paired biopsy specimens

Issues:

- sufficient material?
- successful paired specimens?
- heterogeneity, representative?
- prior treatment effect?

Adjuvant Pancreatic Cancer Clinical Trials Summary

Trial	Study Arms	# pts	Dates	Where done	DFS (m)	mOS (m)
CONKO-001	Gemcitabine	354	2007[1] (*1998-04*)	Germany Austria	13.4	22.1
	observation				6.9	20.2
ESPAC-4	Gemcitabine	569	2017[2] (*2008-14*)	GB,Germany, France, Sweden	13.1	25.5
	Gem + Capecitabine				13.9	28.0
PRODIGE 24	Gemcitabine	493	2018[3] (*2012-16*)	France, Canada	12.8	35
	FOLFIRINOX				21.6	54.4
APACT	Gemcitabine	866	2019[4] (*2014-18*)	International	*13.7*	36.2*
	Gem + nab-paclitaxel				*16.6*	40.5*

1. Oettle et al. JAMA (2007) 297: 267-77.
2. Neoptolemos et al. Lancet (2017) 389: 1011-24.
3. Conroy et al. NEJM (2018) 379: 2395-2406.
4. Tempero et al. ASCO 2019. Abstract #4000.

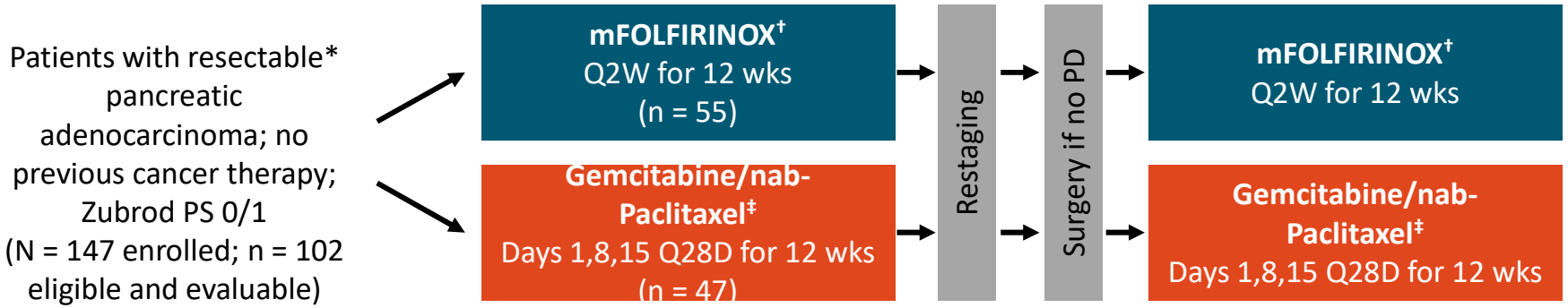
Neoadjuvant Therapy for Resectable Pancreatic Cancer?

Advantages	Disadvantages
▪ Greater ability to administer systemic therapy without delay or concern regarding postoperative complications ▪ Can assess drug sensitivity of tumor in vivo ▪ Can select patients most likely to benefit from surgical intervention	▪ Could lose window of opportunity for curative operation? ▪ Requires preoperative biopsy/biliary decompression and stent management

Slide credit: clinicaloptions.com

SWOG S1505: Perioperative mFOLFIRINOX vs Gem/nab-Paclitaxel for Resectable Pancreatic Cancer

- Randomized, open-label phase II trial



- Baseline scans underwent retrospective central radiology review for eligibility; determined that 44/147 enrolled patients ineligible for trial
- Primary endpoint: 2-yr OS ("pick the winner" design: 2-yr OS for each arm first compared with historical rate of 40%; arms compared if 2-yr OS rate ≥ 58% (power: 88%; 1-sided $\alpha = 0.05$); 90% probability of selecting OS with HR ≥ 1.4 if 50 patients/arm

*Resectability determined by CT or MRI of C/A/P within 28 days of registration: no interface with celiac, common hepatic, or superior mesenteric arteries; < 180° interface with portal and superior mesenteric veins; patent portal vein/splenic vein confluence; no lesions suspicious for metastases (nodes beyond surgical basin, visceral lesions). †5-FU 2400 mg/m^2 over 46 hrs + irinotecan 180 mg/m^2 + oxaliplatin 85 mg/m^2. ‡Gemcitabine 1000 mg/m^2 + nab-paclitaxel 125 mg/m^2.

Sohal. ASCO 2020. Abstr 4504. NCT02562716.

Slide credit: clinicaloptions.com

SWOG S1505: Survival and Resection Outcomes

Outcome	mFOLFIRINOX	Gemcitabine/nab-Paclitaxel
OS	n = 55	n = 47
▪ 2-yr OS rate (primary endpoint), %	43.1	46.9
▪ Median OS, mos	22.4	23.6
Surgery outcomes, n (%)	n = 40	n = 33
▪ R0 resection	34 (85)	28 (85)
▪ Complete/major pathologic response	10 (25)	14 (42)
▪ Median no. total nodes resected (range)	19 (1-56)	18 (3-45)
▪ Node-negative resection	16 (40)	15 (45)
▪ DFS after resection, mos	10.9	14.2

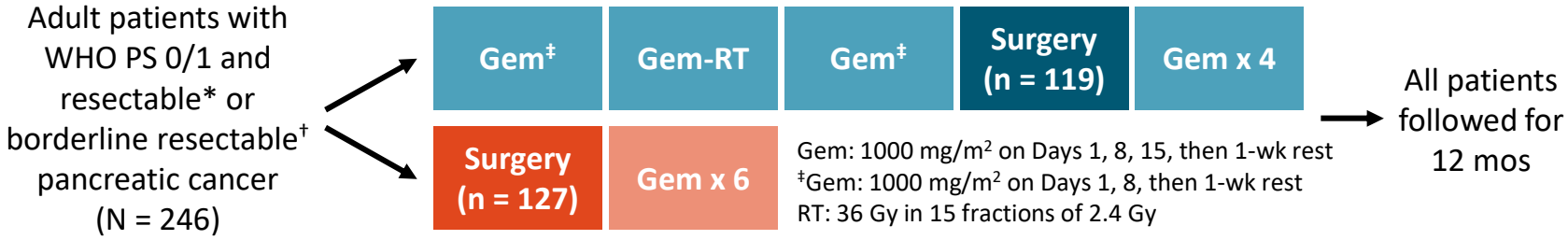
- Study failed to meet primary endpoint (2-yr OS rate ≥ 58%)

Sohal. ASCO 2020. Abstr 4504.

Slide credit: clinicaloptions.com

PREOPANC-1: Neoadjuvant Chemoradiotherapy vs Immediate Surgery for Resectable Pancreatic Cancer

- International, randomized, controlled phase III trial



*No contact with superior mesenteric, celiac trunk, or common hepatic arteries and ≤ 90° contact with superior mesenteric portal vein.
†≥ 1 of the following required: ≤ 90° contact with superior mesenteric, celiac trunk, or common hepatic arteries or 90° to 270° contact with superior mesenteric portal vein and no occlusion.

- Primary endpoint: OS (ITT)
- Secondary endpoints: R0 resection rate, DFS, distant metastases–free interval, locoregional recurrence-free interval, perioperative complications

van Tienhoven. ASCO 2018. Abstr LBA4002.

Slide credit: clinicaloptions.com

PREOPANC-1: Efficacy

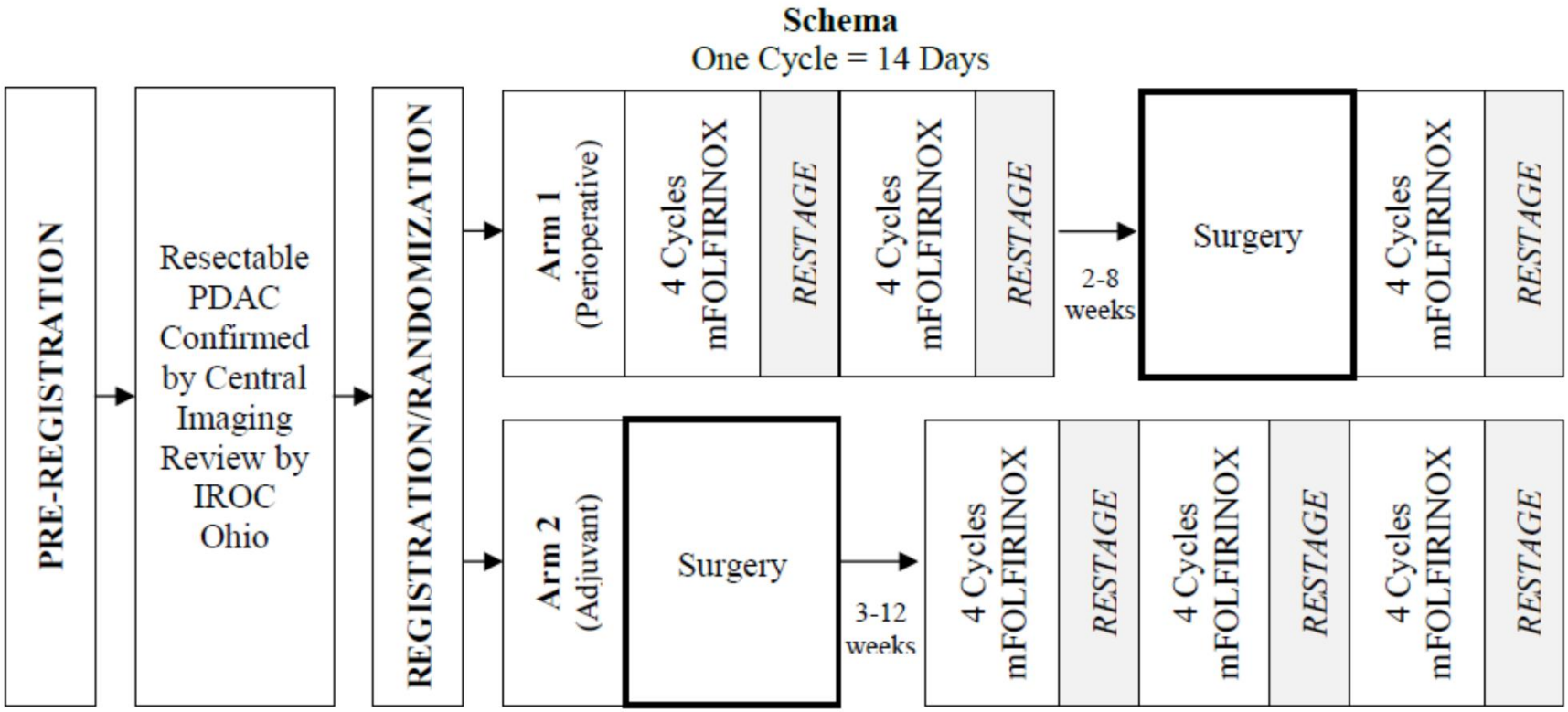
Outcome	Preoperative Radiochemotherapy (n = 119)	Immediate Surgery (n = 127)	HR	*P* Value
Median OS, mos (ITT population)*	**17.1**	**13.7**	**0.74**	**.074**
▪ **Subset with R0/R1 resection†**	**42.1**	**16.8**	**NR**	**< .001**
Resection rate, n (%)	72 (60)	91 (72)	--	.065
R0 resection rate, n/N (%)	45/72 (63)	28/91 (31)	--	< .001
Median DFS, mos	9.9	7.9	0.71	.023
Median distant metastases–free interval, mos	18.4	10.6	0.71	.013
Median locoregional recurrence-free interval, mos	Not reached	11.8	0.55	.002
Serious AEs, n (%)	55 (46)	49 (39)	--	.28

*Preliminary analysis; only 149/176 events. †Preoperative radiochemotherapy, n = 72; immediate surgery, n = 91.

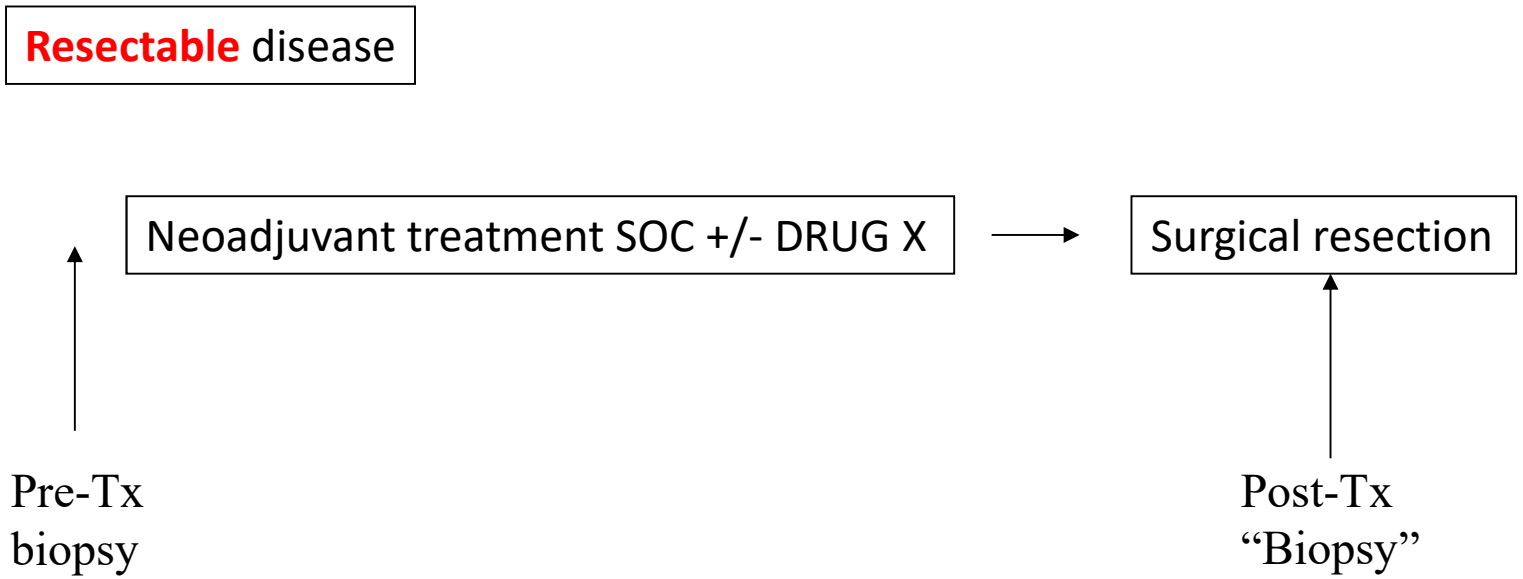
van Tienhoven. ASCO 2018. Abstr LBA4002.

Slide credit: clinicaloptions.com

A021806 – A Phase III trial of perioperative vs adjuvant chemotherapy for resectable pancreatic cancer



“Window of opportunity” study



Are we ready to study new drugs in this setting?

Thank You

Questions?