ADENOCARCINOMA del PANCREAS

highlights from ASCO GI 2016

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adjuvant

center volume

Resected pancreatic cancer: Impact of adjuvant therapy (Rx) at a high-volume center (HVC) on overall survival (OS)

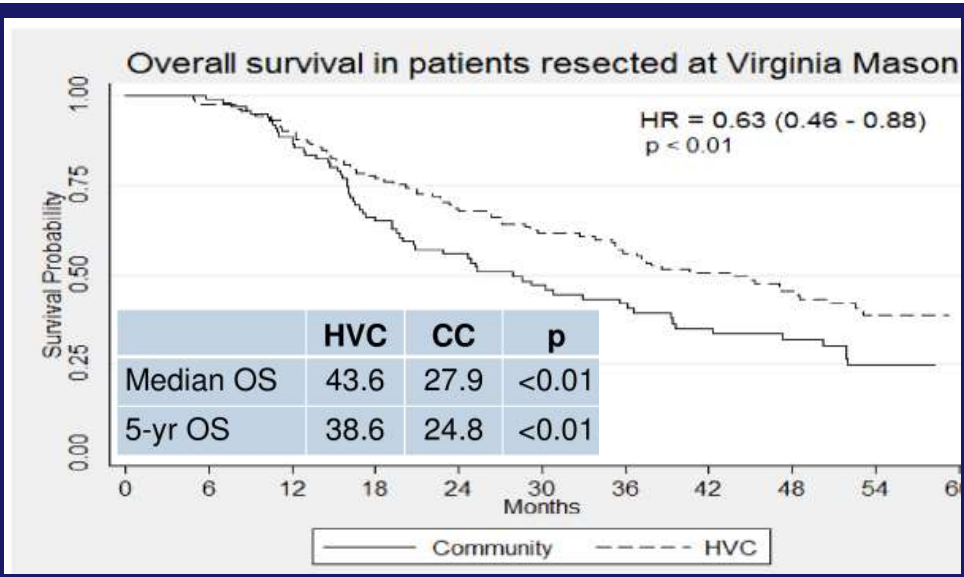
Margaret Mandelson, PhD MPH and Vincent Picozzi, MD, MMM
Floyd and Delores Jones Cancer Institute, Digestive Disease Institute Virginia Mason Seattle, WA

METHODS

Patient were identified through VM cancer registry (reports to western WA SEER) and program-specific database

Eligible:	Diagnosis 2003-2014
	Primary resection at VM
	Intention to give adjuvant Rx at VM or referral to medical oncologist
Exclusions:	Neoadjuvant Rx
	Synchronous cancer
	Death, lost to follow-up or disease progression within 3 mos following surgery
	Refusal to receive adjuvant Rx
	Medical oncologist and/or receipt of Rx absent in medical record and SEER registry

	HVC* (n=139)	CC n=(106)	p
T stage (%1 or 2)	15	13	ns
Node status (% pos)	69	72	ns
Margin status (% positive)	22	20	ns
ECOG %0/1	73/27	70/30	ns



	HVC	CC	p
Median OS	43.6	27.9	<0.01
5-yr OS	38.6	24.8	<0.01

I LINE

Metastatic

Locally advanced

Evofosfamide (TH-302) in combination with gemcitabine in previously untreated patients with metastatic or locally advanced unresectable pancreatic ductal adenocarcinoma: primary analysis of the randomized, double-blind phase III MAESTRO study

Eric Van Cutsem

Lenz H-J, Furuse J, Tabernero J, Heinemann V, Ioka T, Bazin I, Ueno M, Csoszi T, Wasan H, Melichar B, Karasek P, Macarulla T, Guillen-Ponce C, Kalinka-Warzocha E, Horvath Z, Prenen H, Schlichting M, Ibrahim A, Bendell J

University Hospitals Leuven, Leuven, Belgium

PRESENTED AT: 2016 Gastrointestinal Cancers Symposium

Pancreatic cancer, hypoxia, and novel therapy

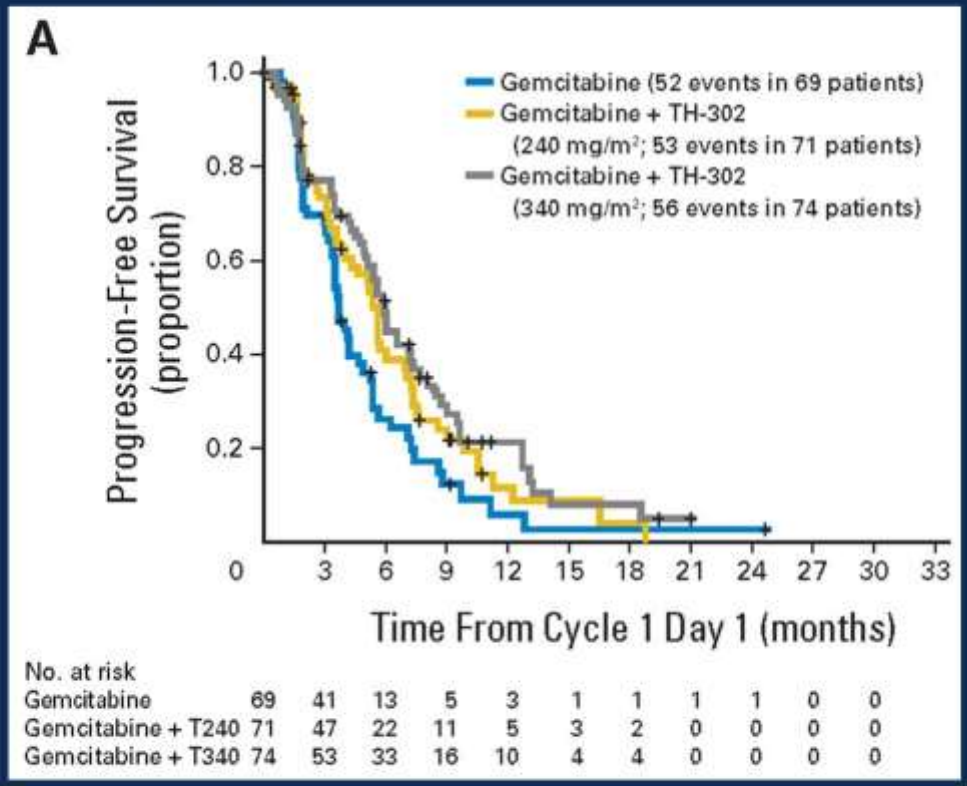
- Median OS for advanced pancreatic cancer is 6–11 months[1,2]
- The tumor microenvironment in pancreatic cancer is characterized by hypoxia, which modulates many of the key features of cancer[2–4]
- Hypoxia-activated prodrugs (HAPs) are designed to preferentially release chemotherapeutic agents within hypoxic tumor regions[5]
- Evofosfamide is a HAP that preferentially releases the cytotoxic bromo-isophosphoramide mustard (Br-IPM) in areas of severe hypoxia[5,6]
- Combining evofosfamide with conventional chemotherapy has the potential to induce cell death in hypoxic and normoxic tumor cells, and demonstrated activity in a randomized phase II trial[7]

1. Cid-Arregui, et al. 2015; 2. Neuzillet, et al. 2015; 3. Stewart, et al. 2010; 4. Kim, et al. 2009; 5. Liang, et al. 2015; 6. Meng, et al. 2012; 7. Borad, et al. 2015

Phase II primary endpoint: PFS

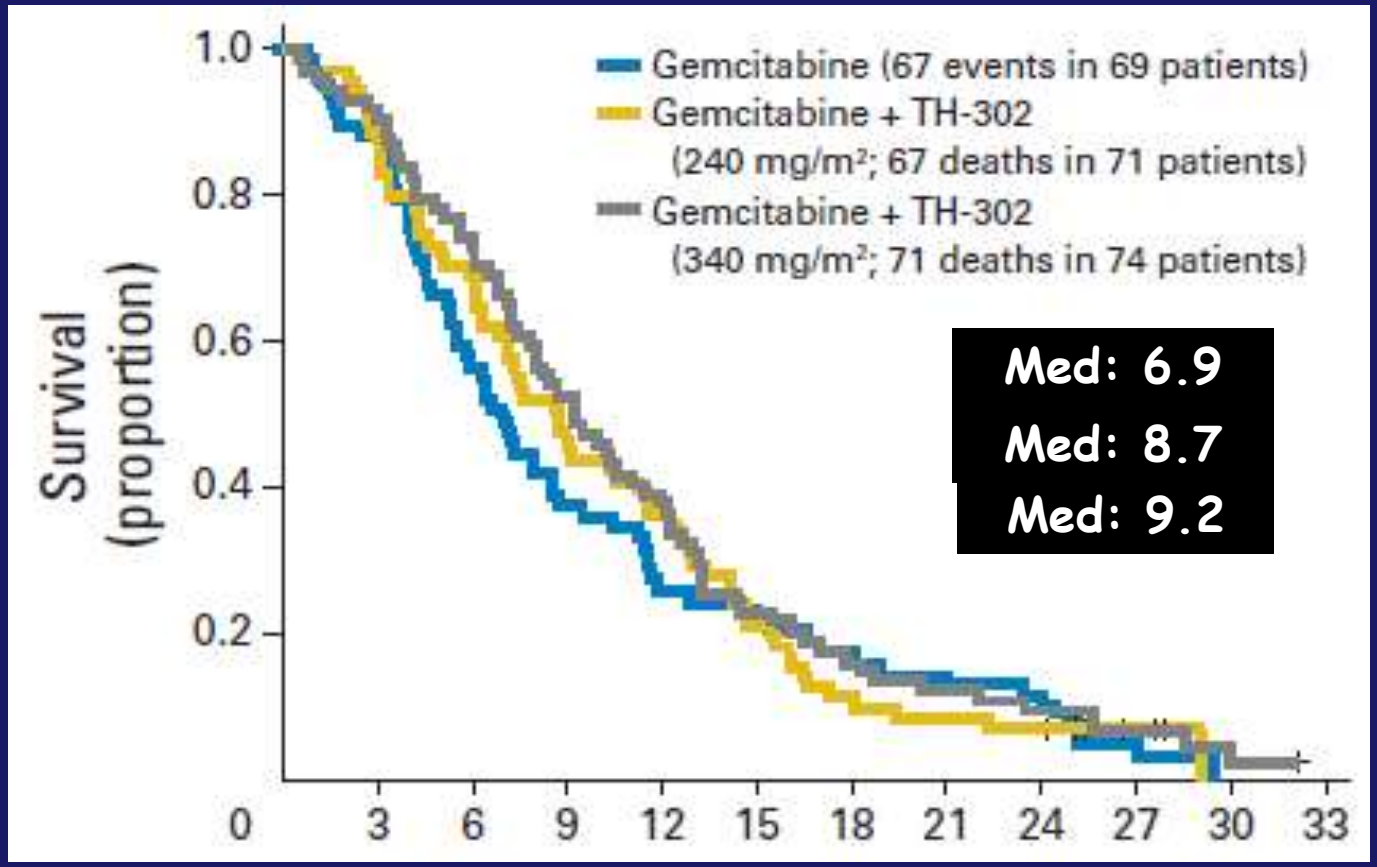
Median PFS

- 3.6 months for gemcitabine
- 5.6 months for G+T240 (P=0.040; HR, 0.66)
- 6.0 months for G+T340 (P=0.008; HR, 0.59)



Borad et al., JCO 2014

GEM + TH-302



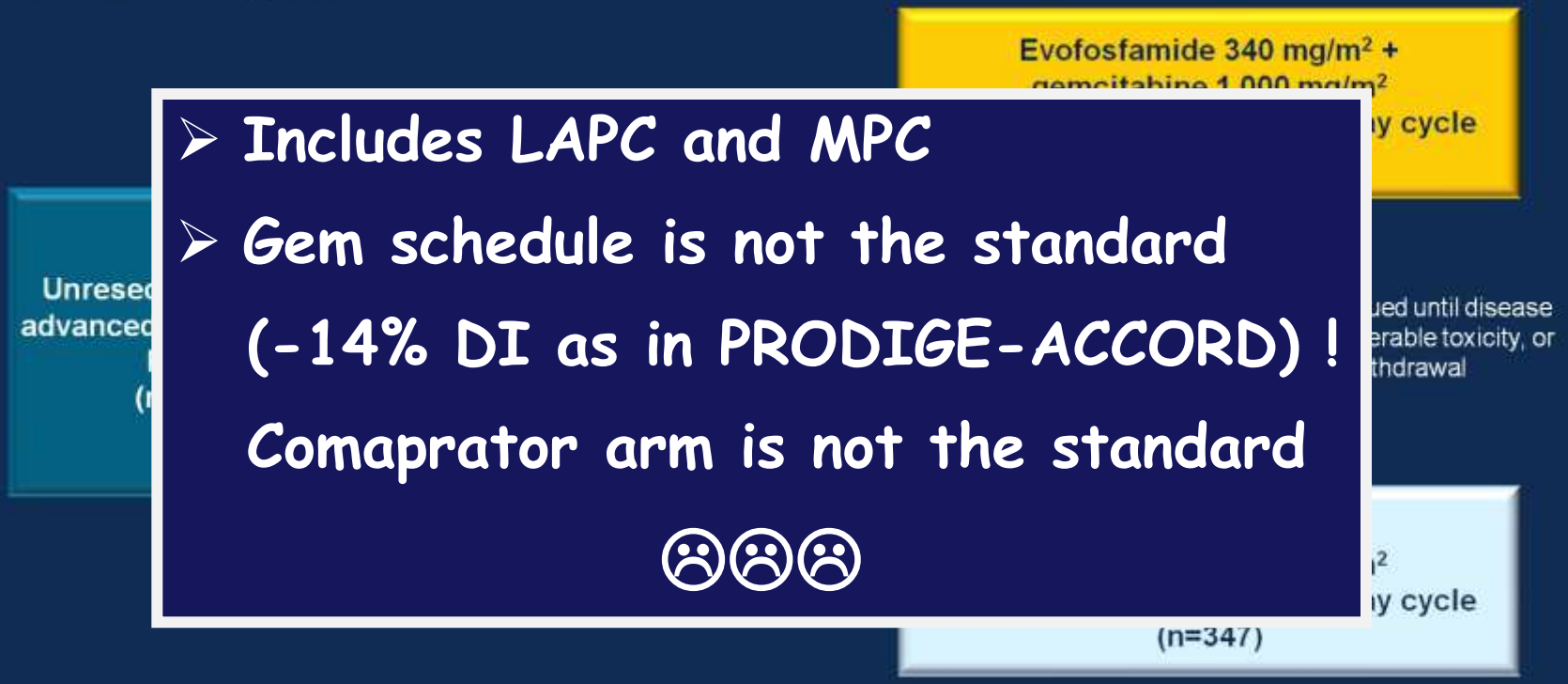
Gem vs gem + TH-302 (340 mg)
HR: 0.86; p=0.39

Gem vs gem + TH-302 (240 mg)
HR: 0.95; p=0.77

Includes LAPC and MPC ☹

Borad et al., JCO 2014

Randomized, double-blind phase III MAESTRO trial: design



- Includes LAPC and MPC
- Gem schedule is not the standard (-14% DI as in PRODIGE-ACCORD) !

Comaprator arm is not the standard

☹☹☹

Phase III MAESTRO trial: patient eligibility

- ≥18 years with histologically or cytologically confirmed, measurable or unmeasurable locally advanced unresectable or metastatic pancreatic ductal adenocarcinoma
- ECOG PS 0 or 1
- Acceptable liv function
- No prior chem py other than radiosensitizing doses of 5-FU occurred ≥6 months after completion of ant or adjuvant chemotherapy <6 months pri
- Patients suitable for FOLFIRINOX were ineligible; unless the patient refused FOLFIRINOX

Phase III MAESTRO trial: statistical considerations

- A sample size of 660 patients randomized 1:1
- 508 events (deaths) required to ensure 90% power to detect a HR of 0.75 for OS (median OS 8.67 vs 6.5 months) at a two-sided significance level of α=0.05
- PFS and
- Further

edure with a 2-side

Wrong hypothesis: this is inferior to expected outcome for a mixed population

Patient demographics and baseline characteristics

Characteristic	Gemcitabine + placebo (n=347)	Evofosfamide + gemcitabine (n=346)
Median age, years (range)	65 (35–84)	66 (27–87)
Male/female, n (%)	179/168 (51.6/48.4)	191/155 (55.2/44.8)
Region, n (%)		
Europe	212 (61.1)	213 (61.6)
Asia (Japan and South Korea)	58 (16.7)	65 (18.8)
USA/Canada	49 (14.1)	47 (13.6)
Rest of the world	28 (8.1)	21 (6.1)
Race		
White	245 (70.6)	243 (70.2)
Asian	61 (17.6)	65 (18.8)
Black	7 (2.0)	9 (2.6)
Other	34 (9.8)	29 (8.4)

Patient demographics and baseline characteristics (cont'd)

Characteristic	Gemcitabine + placebo (n=347)	Evofosfamide + gemcitabine (n=346)
ECOG PS, n (%)		
0	116 (33.4)	115 (33.2)
≥3.5 g/dL	241 (69.5)	237 (68.5)
Hemoglobin, n (%)*		
<12 g/dL	116 (33.4)	129 (37.3)
≥12 g/dL	223 (64.3)	210 (60.7)
Concomitant diabetes, n (%)	125 (36.0)	146 (42.2)

Unsuitable for FOLFIRINOX ?

*Do not total 100% because data are missing for some patients

Disease characteristics

Characteristic	Gemcitabine + placebo (n=347)	Evofosfamide + gemcitabine (n=346)
Site of primary tumor involves, n (%)		
Head	189 (54.5)	187 (54.0)
Body	115 (33.1)	123 (35.5)
Tail	83 (23.9)	89 (25.7)
Extent of disease, n (%)		
Locally advanced	74 (21.3)	75 (21.7)
Metastatic	273 (78.7)	271 (78.3)
No. of metastatic sites, n (%)		
0	78 (22.5)	81 (23.4)
1/2	202 (58.2)	215 (62.1)
>2	67 (19.3)	50 (14.5)
Site of metastases (>10% occurrence), n (%)		
Liver	201 (73.6)	193 (71.2)
Lung	66 (24.2)	82 (30.3)
Peritoneal	52 (19.0)	45 (16.6)
Para-aortic lymph node	38 (13.9)	31 (11.4)

Overview of adverse events

	Gemcitabine + placebo (n=341)	Evofosfamide + gemcitabine (n=338)
Any adverse event, n (%)	337 (98.8)	335 (99.1)
Any grade 3/4 adverse event, n (%)	273 (80.1)	308 (91.1)
Serious adverse events, n (%)	177 (51.9)	183 (54.1)
Adverse events leading to death, n (%)	37 (10.9)	31 (9.2)
Adverse events resulting in dosing interruption ≥1 study drug, n (%)	187 (54.8)	251 (74.3)
Adverse events resulting in dose reduction ≥1 study drug, n (%)	128 (37.5)	211 (62.4)

Most commonly reported clinical adverse events*

	Gemcitabine + placebo (n=341)			Evofosfamide + gemcitabine (n=338)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Nausea, n (%)	152 (44.6)	13 (3.8)	0	169 (50.0)	9 (2.7)	0
Decreased appetite, n (%)	118 (34.6)	10 (2.9)	0	118 (34.9)	6 (1.8)	1 (0.3)
Diarrhea, n (%)	89 (26.1)	6 (1.8)	0	114 (33.7)	15 (4.4)	1 (0.3)
Vomiting, n (%)	117 (34.3)	14 (4.1)	0	110 (32.5)	10 (3.0)	1 (0.3)
Constipation, n (%)	107 (31.4)	1 (0.3)	0	104 (30.8)	1 (0.3)	0
Fatigue, n (%)	109 (32.0)	13 (3.8)	0	99 (29.3)	15 (4.4)	1 (0.3)

*According to MedDRA PTs; events occurring in ≥30% of patients in either treatment arm (apart from blood and lymphatic disorders)

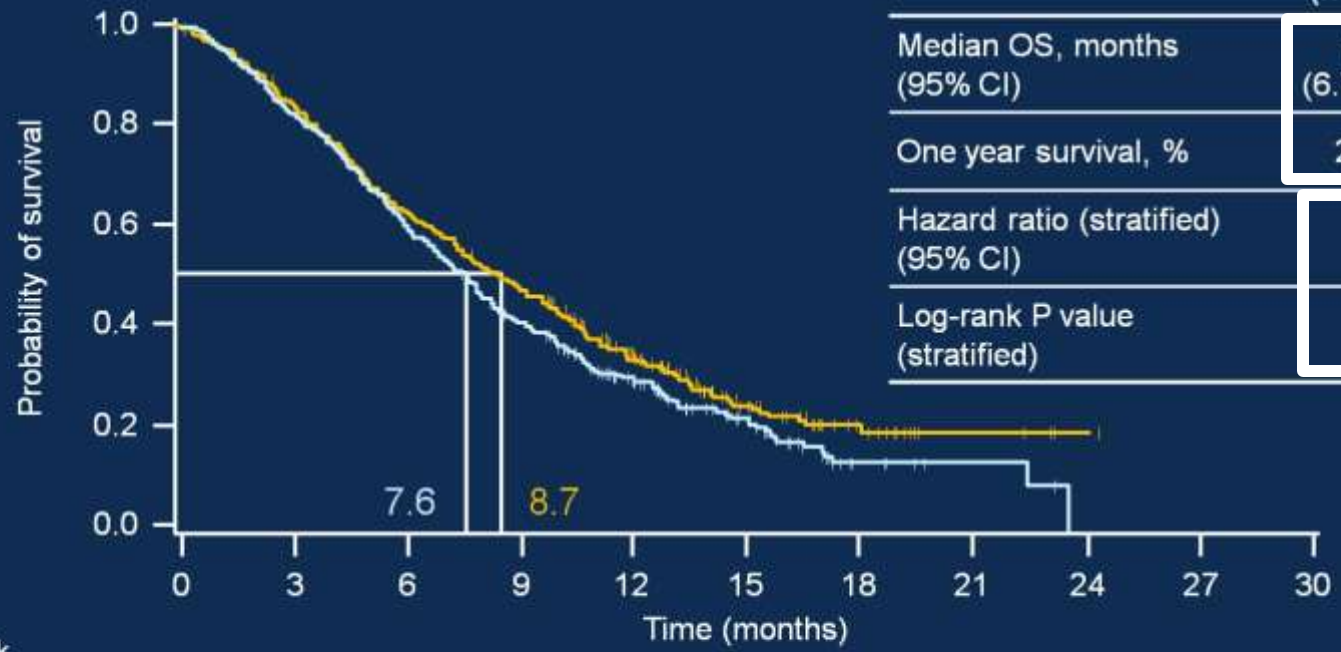
Hematologic events and biochemical toxicities

	Gemcitabine + placebo (n=341)			Evofosfamide + gemcitabine (n=338)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Neutropenia*, n (%)	119 (34.9)	66 (19.4)	22 (6.5)	188 (55.6)	103 (30.5)	49 (14.5)
Febrile neutropenia, n (%)	2 (0.6)	1 (0.3)	1 (0.3)	7 (2.1)	7 (2.1)	0
Thrombocytopenia*, n (%)	103 (30.2)	20 (5.9)	6 (1.8)	241 (71.3)	88 (26.0)	72 (21.3)
Anemia*, n (%)	115 (33.7)	39 (11.4)	2 (0.6)	172 (50.9)	73 (21.6)	3 (0.9)
ALT increased, n (%)	30 (8.8)	19 (5.6)	0	35 (10.4)	15 (4.4)	1 (0.3)
ALP increased, n (%)	29 (8.5)	17 (5.0)	0	21 (6.2)	10 (3.0)	0

*According to pooled MedDRA PTs including blood and lymphatic disorders and laboratory investigations

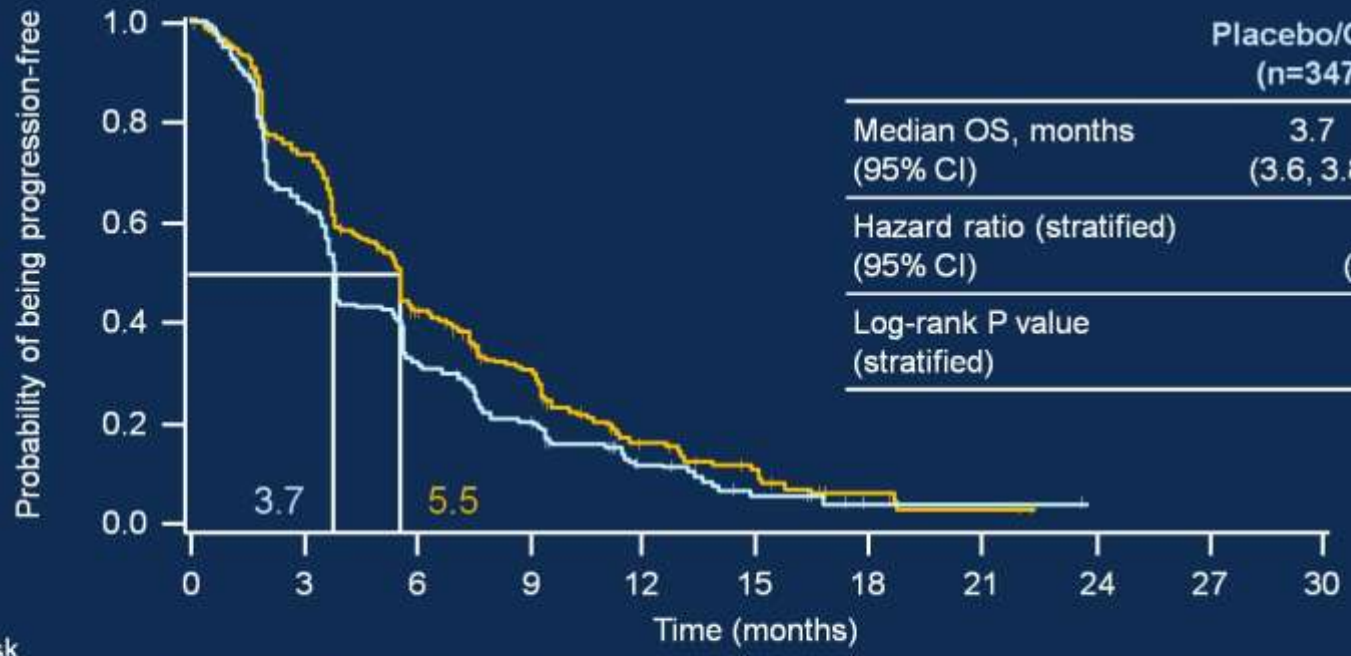
Overall survival

	Placebo/Gem (n=347)	Evo/Gem (n=346)
Median OS, months (95% CI)	7.6 (6.7, 8.3)	8.7 (7.6, 9.9)
One year survival, %	29.8	34.2
Hazard ratio (stratified) (95% CI)	0.84 (0.71, 1.01)	
Log-rank P value (stratified)	0.059	



At risk											
Placebo/Gem	347	284	205	141	75	35	7	3	0	0	0
Evo/Gem	346	293	219	168	87	38	14	4	1	0	0

Progression-free survival



	Placebo/Gem (n=347)	Evo/Gem (n=346)
Median OS, months (95% CI)	3.7 (3.6, 3.8)	5.5 (4.8, 5.6)
Hazard ratio (stratified) (95% CI)	0.77 (0.65, 0.92)	
Log-rank P value (stratified)	0.004	

At risk											
Placebo/Gem	347	197	92	56	20	6	1	1	0	0	0
Evo/Gem	346	223	118	76	29	10	4	2	0	0	0

Objective response rate in patients with measurable disease

	Gemcitabine + placebo (n=325)	Evofosfamide + gemcitabine (n=323)
Objective response rate unconfirmed (%)	16.3	20.4
	Odds ratio 1.32 (0.88, 1.97) P=0.17	
Objective response rate confirmed (%)	8.6	15.2
	Odds ratio 1.90 (1.16, 3.12) P=0.0086	

Subsequent therapy

	Gemcitabine + placebo (n=347)	Evofosfamide + gemcitabine (n=346)
Patients receiving any anticancer drug therapy after study drug discontinuation, n (%)	170 (49.0)	158 (45.7)
Chemotherapy, n (%)	167 (48.1)	154 (44.5)
FOLFIRINOX	29 (8.4)	16 (4.6)
FOLFOX	27 (7.8)	24 (6.9)
Gemcitabine/nab-paclitaxel	24 (6.9)	17 (4.9)
Single-agent gemcitabine	23 (6.6)	32 (9.2)
TS-1	23 (6.6)	25 (7.2)
Other chemotherapy*	56 (16.1)	57 (16.5)

*Includes GEMOX, CAPOX, FOLFIRI, carboplatin/cisplatin + paclitaxel, single-agent paclitaxel, and single-agent capecitabine

Conclusions

- The phase III MAESTRO trial did not meet its primary endpoint of overall survival (P=0.059)
- A signal for overall antitumor activity was observed with evofosfamide + gemcitabine in PDAC (OS, PFS and ORR)
- No new safety findings were identified and the safety profile was consistent with that in other studies
- Discontinuations, dose interruptions and dose reductions were more frequently observed with evofosfamide + gemcitabine

concurrent medications

Impact of concurrent medications use on outcome of pancreatic cancer SEER Medicare analysis.

Muhammad Shaalan Beg MD MS, Tyler Stewart MD, Ang Gao PhD, Chul Ahn PhD, Jarett Berry MD, Eric Mortensen MD.
Division of Hematology/Medical Oncology, Department of Internal Medicine; University of Texas Southwestern Medical Center, Dallas, TX

Results

- There were 13,702 cases which met inclusion criteria and had available Part D data.
- Median age was 76 years, There were 42.5% males, 77.1% were white and 34.0% had diabetes.
- The results of the Cox proportional hazard models are summarized in table 2.
- Beta blockers, heparin, insulin, warfarin were associated were significantly with improved survival ($p<0.05$).

Variable	Total (%)	Diabetes (%)	No diabetes (%)
Age (years)	76	77	75
White	10,545 (77)	7118 (78)	3427 (74)
Male	5820 (43)	3739 (41)	2081 (45)
Stage 4	5906 (50)	3966 (51)	1940 (47)
Grade 3/4	1813 (44)	1143 (44)	670 (44)
Head of pancreas	6842 (50)	4491 (50)	2351 (50)
Medication			
Beta blockers	5209 (38)	3208 (35)	2001 (43)
Statin	4680 (34)	2722 (30)	1958 (42)
Insulin	2319 (17)	885 (10)	1434 (31)
Metformin	2276 (17)	565 (6)	1711 (37)
Thiazolidinediones	1037 (8)	351 (4)	686 (15)
Warfarin	1857 (14)	1185 (13)	672 (14)
Heparin	764 (6)	477 (5)	287 (6)

Table 2: Cox Proportional hazards

	HR (CI)
Medication	
Beta blocker	0.92 (0.88, 0.96)
Insulin	0.89 (0.84, 0.93)
Warfarin	0.90 (0.84, 0.95)
Heparin	0.76 (0.70, 0.82)
Age	1.03 (1.03, 1.03)
Race	1.07 (1.03, 1.14)
Stage	2.48 (2.37, 2.59)
Charlson score	1.42 (1.24, 1.62)
Site	1.09 (1.04, 1.13)

Conclusions

- Concurrent medication use, particularly heparin, insulin warfarin and beta-blockers are associated with improved survival in patients with pancreatic cancer.
- Diabetes medications (metformin, TZD) did not have an impact in the multivariable model.
- Additional studies are needed to examine whether these medications may improve outcomes for patients with pancreatic cancer.

(Ir)relevance of metformin treatment in patients with metastatic pancreatic cancer: an open-label, randomized phase 2 trial

Reni M, Dugnani E, Cereda S, Belli C, Balzano G, Nicoletti R, Liberati D, Pasquale V, Scavini M, Maggiora P, Sordi V, Lampasona V, Ceraulo D, Di Terlizzi G, Doglioni C, Falconi M, Piemonti L.

Clin Cancer Res. 2015 Oct 12

	PEXG	PEXG+metformin	p
N	29	31	
PFS-6	52%	42%	0.61
mPFS	6.1	4.9	0.036*
mOS	10.4	6.8	0.13°
PR	34.5%	35.5%	
DCR	79.5%	64.5%	0.26

* adjusted p-value; HR 2.00 (1.05-3.8)
° adjusted p-value; HR 1.56 (0.87-2.8)

real life

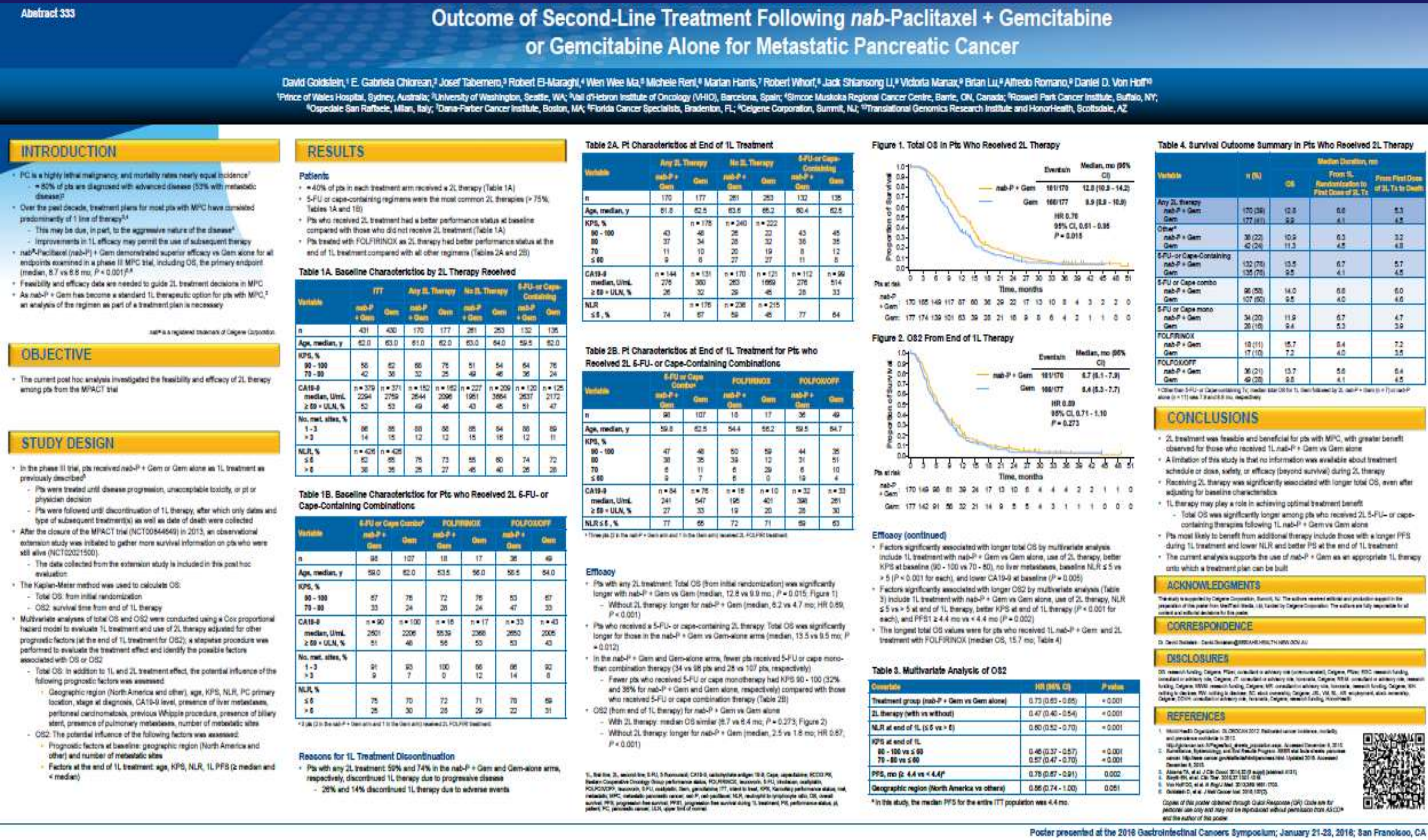
MODIFIED FOLFIRINOX

	Stein[1] (# 395)	Uesugi[2] (#422)	Conroy (NEJM)
N	37	19	171
ECOG 0	46%	nr	37%
M+ liver	54%	nr	88%
CA19.9 <59 ULN	49%	nr	44%
mOS	10.2	10.3[2]	11.1
PR	35%	nr	31.6%
(stage III)	17%	na	na

1. OXA 85; FU 300+2400; IRI 135
2. OXA 85; FU 0+2400; IRI 150 includes locally advanced

II LINE

Outcome of Second-Line Treatment Following *nab-Paclitaxel + Gemcitabine* or Gem Alone for M+ Pancreatic Cancer



Goldstein D and Chiorean EG et al, Abstract 333; 2016, Gastrointestinal Cancers Symposium; January 21-23, 2016; San Francisco, CA

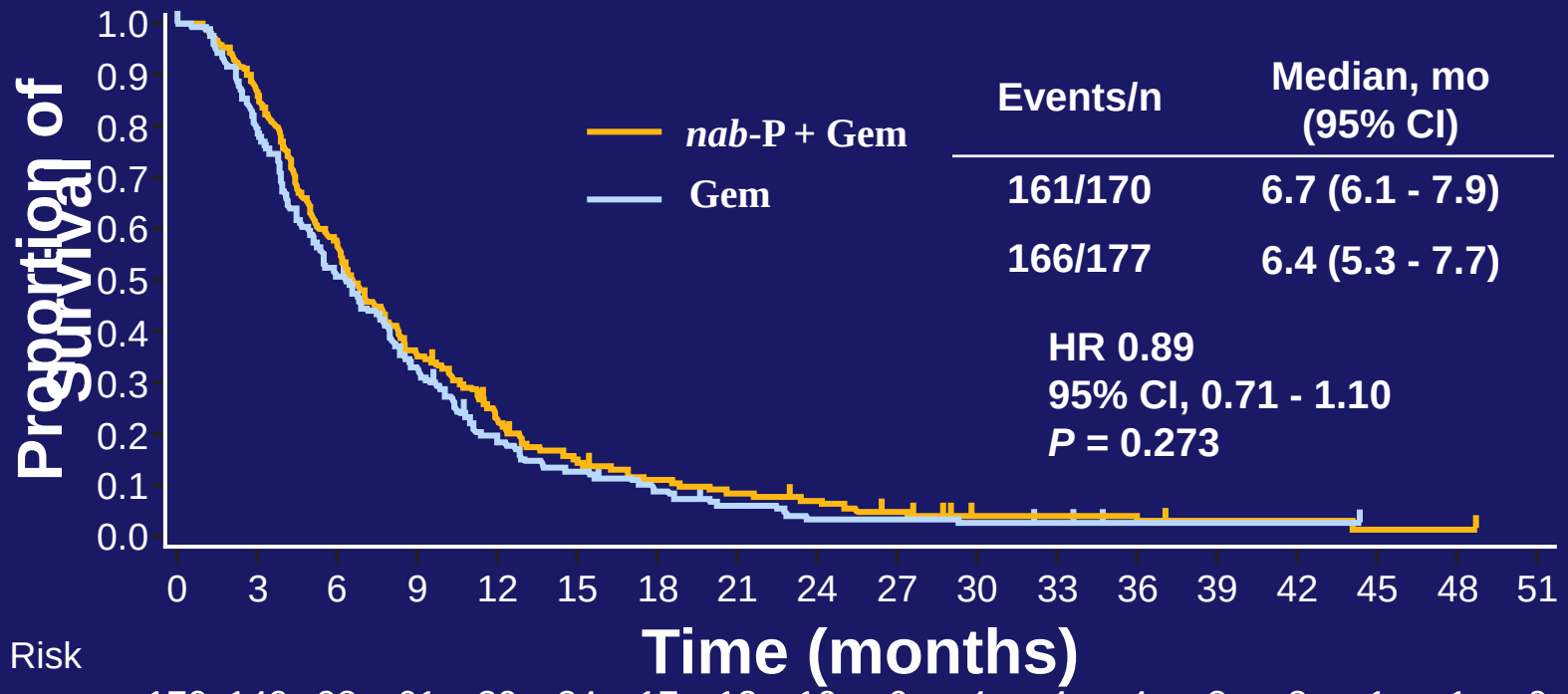
Overview of Survival Times with Duration of 1L

Variable	n, %	OS median, mo	Time from randomization to 1st dose of 2L tx, median, mo	Time from 1st dose of 2L tx to death, median, months
Any 2L Therapy				
nab-P + Gem	**170 (39)**	**12.8**	**6.6**	**5.3**
Gem	**177 (41)**	**9.9**	**4.1**	**4.5**
5FU/cape containing				
nab-P + Gem	**132 (39)**	**13.5**	**6.7**	**5.7**
Gem	**135 (41)**	**9.5**	**4.1**	**4.5**
Other than 5/Fu/cape)				
nab-P + Gem	38 (22)	10.9	6.3	3.2
Gem	42 (24)	11.3	4.5	4.8
5-FU or Cape Combo				
nab-P + Gem	**98 (74)**	**14.0**	**6.6**	**6.0**
Gem	**107 (79)**	**9.5**	**4.0**	**4.6**
5-FU or Cape Mono				
nab-P + Gem	34 (26)	11.9	6.7	4.7
Gem	28 (21)	9.4	5.3	3.9
FOLFIRINOX				
nab-P + Gem	18 (14)	15.7	8.4	7.2
Gem	17 (13)	7.2	4.0	3.5
FOLFOX/OFF				
nab-P + Gem	36 (27)	13.7	5.6	6.4
Gem	49 (36)	9.8	4.1	4.5

Goldstein D and Chiorean EG et al, Abstract 333; 2016, Gastrointestinal Cancers Symposium; January 21-23, 2016; San Francisco, CA

MPACT - Pts With Second-line Therapies After AG

Survival From End of 1L Therapy (OS2)



Pts at Risk

nab-P + Gem:	170	149	98	61	39	24	17	13	10	6	4	4	4	2	2	1	1	0
Gem:	177	142	91	56	32	21	14	9	5	5	4	3	1	1	1	0	0	0

Variable	Statistic	*nab*-P + Gem n = 431	Gem n = 430	P-value BETWEEN treatment
With Any 2nd-lineTherapies	n (%) Survival time, median mo (95% CI)	170/431 (39) 6.7	177/430 (41) 6.4	 0.273
Without Any 2nd-lineTherapies	n (%) Survival time, median mo (95% CI)	250/431 (58) 2.5	226/430 (53) 1.6	 < 0.001
	P-value WITHIN treatment	< 0.001	< 0.001	--

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MPACT - Pts With Second-line Therapies After AG

Multivariate Analysis (MVA) of OS2

Covariate	HR (95% CI)	*P* value
Treatment group (*nab*-P + Gem vs Gem alone)	0.73 (0.63 - 0.85)	< 0.001
2L therapy (with vs without)	0.47 (0.40 - 0.54)	< 0.001
NLR at end of 1L (≤ 5 vs > 5)	0.60 (0.52 - 0.70)	< 0.001
KPS at end of 1L **90 - 100 vs ≤ 60** **70 - 80 vs ≤ 60**	 0.46 (0.37 - 0.57) 0.57 (0.47 - 0.70)	 < 0.001 < 0.001
PFS, months (≥ 4.4 vs < 4.4)[a]	**0.78 (0.67 - 0.91)**	**0.002**
Geographic region (North America vs others)	0.86 (0.74 - 1.00)	0.051

[a] In this study, the median PFS for the entire ITT population was 4.4 months.

Goldstein D and Chiorean EG et al, Abstract 333; 2016, Gastrointestinal Cancers Symposium; January 21-23, 2016; San Francisco, CA

GEM vs nab-GEM

348 retrospective series MGH II line

	GEM	nab-GEM	p-value
N	36	33	
mOS (days)	145	183	0.18

beyond II line

PD-1 Blockade in Mismatch Repair-Deficient Non-Colorectal Gastrointestinal Cancers

Dung Le, Jennifer Uram, Hao Wang, Holly Kemberling, Aleksandra Eyring, Bjarne Bartlett, Justin Poling, Richard Goldberg, Todd Crocenzi, George Fisher, James Lee, Tim Greten, Daniel Laheru, Nilo Azad, Ross Donehower, Brandon Luber, Minori Koshiji, James Eshleman, Robert Anders, Bert Vogelstein and Luis Diaz Jr.

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Ohio State University Comprehensive Cancer Center, Columbus, OH; Providence Cancer Center, Portland, OR; Stanford University School of Medicine, Stanford, CA; University of Pittsburgh, Pittsburgh, PA; National Cancer Institute, Bethesda, MD; Merck & Co., Inc., Kenilworth, NJ

Figure 1 . Average Mutations in Different Tumors

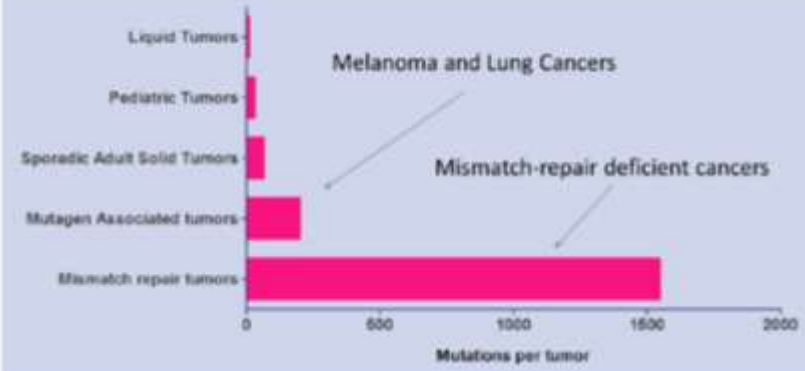


Figure 2 . Study Design

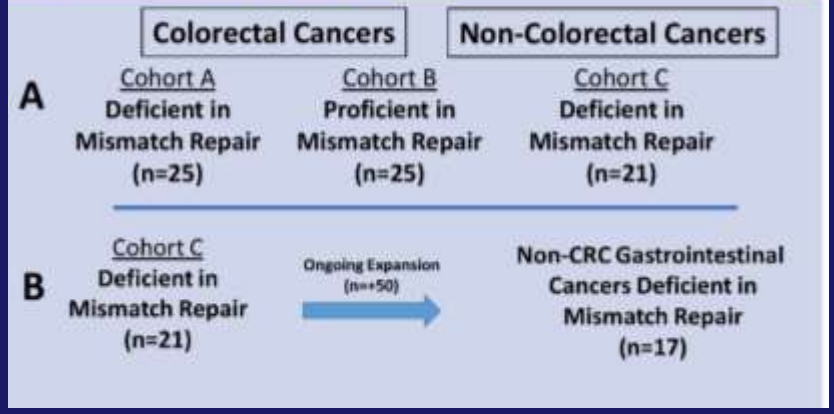
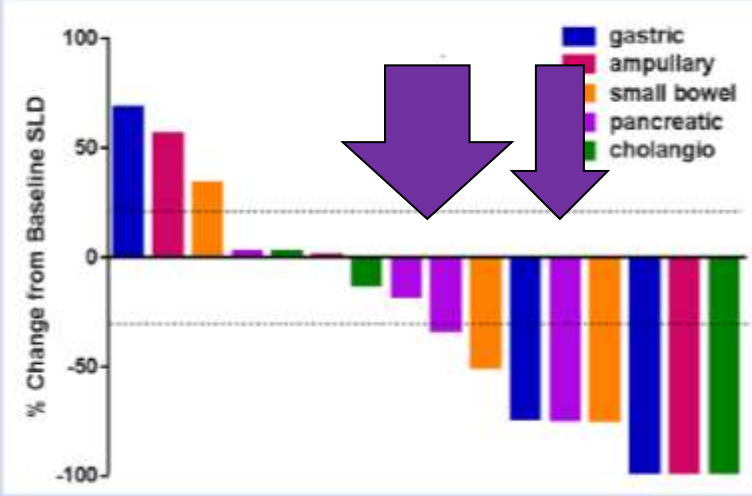


Figure 3. Percent Change in Target Lesions



Durability of Disease Control

Figure 5. Duration of Response