Pancreatic Cancer: Emerging Strategies

Edward J. Kim, M.D., Ph.D.

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CANCER CENTER

Outline

- Pancreatic Cancer
  - Germline testing
  - PARPi maintenance
  - Adjuvant therapy
  - Immunotherapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Pancreatic Adenocarcinoma
NCCN Evidence Blocks™

NCCN Guidelines Index
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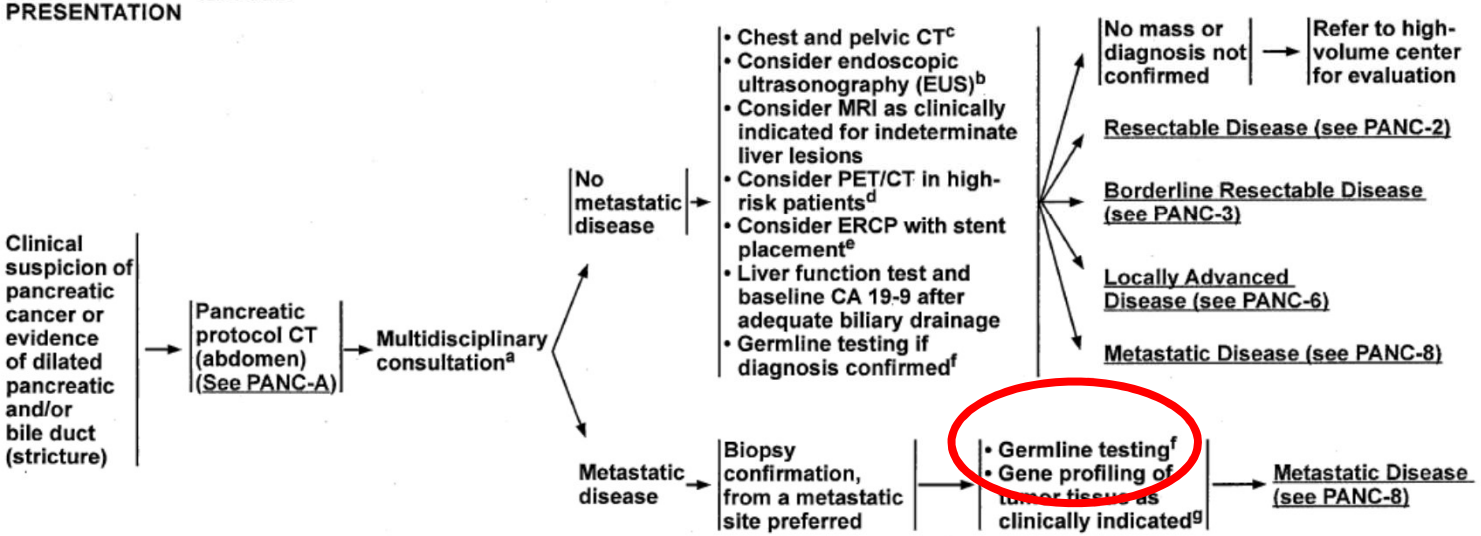
Discussion

CLINICAL PRESENTATION **WORKUP**



[a] Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, pathology, geriatric medicine, and palliative care. Consider consultation with a registered dietitian. See NCCN Guidelines for Older Adult Oncology and NCCN Guidelines for Palliative Care.

[b] EUS to confirm primary site of involvement; EUS-guided biopsy if clinically indicated.

[c] Imaging with contrast unless contraindicated.

[d] PET/CT scan may be considered after formal pancreatic CT protocol in high-risk patients to detect extra pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT. See Principles of Diagnosis, Imaging, and Staging (PANC-A).

[e] See Principles of Stent Management (PANC-B).

[f] Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. Okur V, Chung WK. The impact of hereditary cancer gene panels on clinical care and lessons learned. *Cold Spring Harb Mol Case Stud.* 2017;3(6):a002154. See Discussion and see NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast and Ovarian.

[g] Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon but actionable mutations. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. See Discussion.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Why test everyone?

- Prior recommendation – based on family history
- Multiple studies show that the old strategy based on family history misses half of cases
  - [1]Mayo Clinic case control – freq. of germline mutations
    - 7.9% (27 of 343) with family history
    - 5.2% (140 of 2676) withOUT family history
  - [2]Vancouver CA Hereditary Cancer Program
    - 18.4% (12/65) with family history
    - 17.1% (13/76) withOUT family history

1. Hu et al. JAMA (2018) 319: 2401-9.
2. Cremin et al. ASCO annual mtg 2019. Abstract #1582

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Homologous Recombination Deficiency

- 5-8% of pancreatic cancer patients have a pathogenic mutation in one of the HR genes: *BRCA1, BRCA2* or *PALB2*[1-5], leading to an HRD
- Patients with HRD have an increased sensitivity to platinum therapy and possibly PARP inhibitors due to synthetic lethality[6-10]

[1]Goggins et al, Cancer Res, 1996; [2]Hofstatter et al, Fam Cancer, 2011; [3]Salo-Mullen et al, Cancer, 2015; [4]Pishvaian et al, CCR, 2018; [5]Singhi et al, Gastroenterology, 2019; [6]Golan et al, Br J Cancer, 2014; [7]Kaufman et al, JCO, 2015; [8]Reiss et al, JCO PO, 2018; [9]Shroff et al, JCO PO, 2018; [10]Yu et al, JCO PO, 2019

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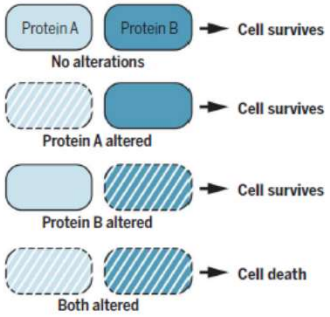
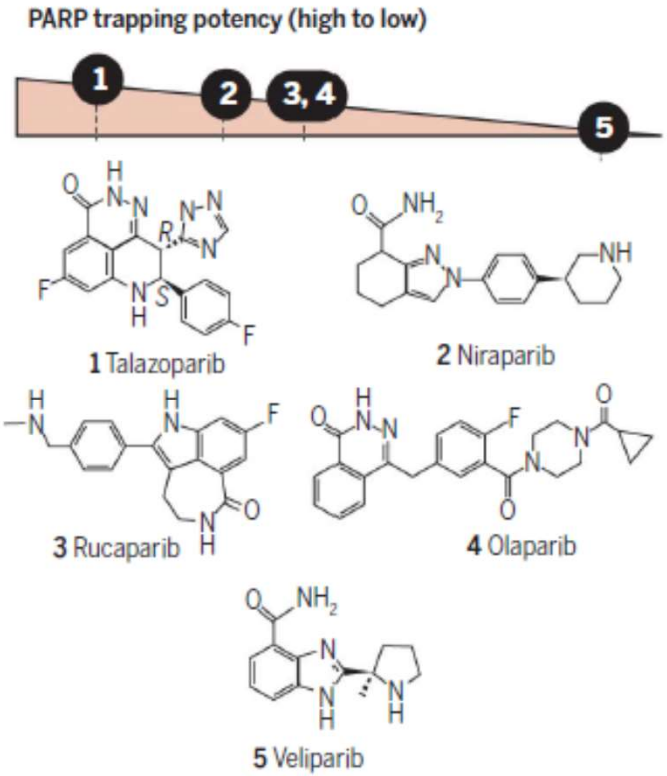
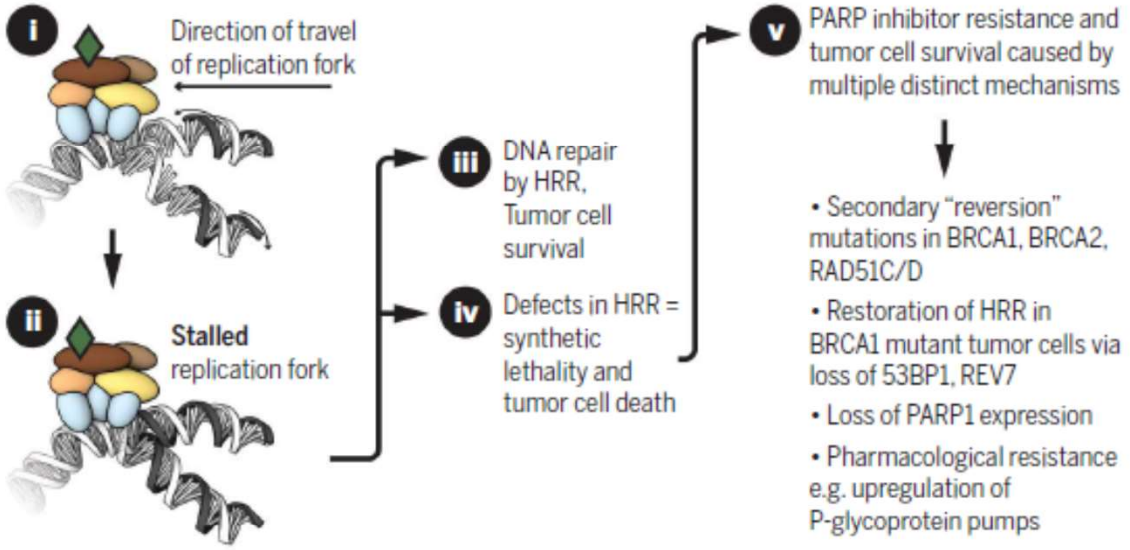
PARP inhibitors







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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

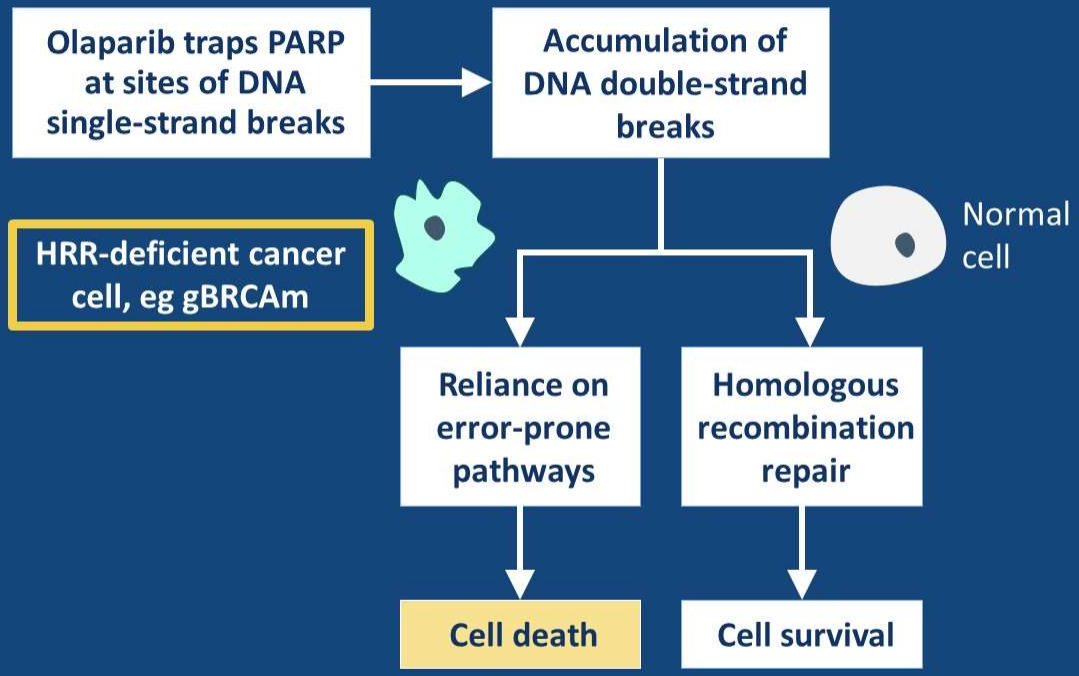
Hedy L Kindler,[1] Pascal Hammel,[2] Michele Reni,[3] Eric Van Cutsem,[4] Teresa Macarulla,[5] Michael J Hall,[6] Joon Oh Park,[7] Daniel Hochhauser,[8] Dirk Arnold,[9] Do-Youn Oh,[10] Anke Reinacher-Schick,[11] Giampaolo Tortora,[12] Hana Algül,[13] Eileen M O'Reilly,[14] David McGuinness,[15] Karen Y Cui,[16] Katia Schlienger,[17] Gershon Y Locker,[16] Talia Golan[18]

[1]The University of Chicago, Chicago, IL, USA; [2]Hôpital Beaujon (AP-HP), Clichy and University Paris VII, Paris, France; [3]IRCCS Ospedale, San Raffaele Scientific Institute, Milan, Italy; [4]University Hospitals Gasthuisberg and KU Leuven, Leuven, Belgium; [5]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Fox Chase Cancer Center, Philadelphia, PA, USA; [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [8]University College London Cancer Institute, London, UK; [9]Asklepios Tumorzentrum Hamburg AK Altona, Hamburg, Germany; [10]Seoul National University Hospital, Seoul, South Korea; [11]St Josef-Hospital, Ruhr University Bochum, Bochum, Germany; [12]Azienda Ospedaliera Universitaria Integrata Verona, Verona and Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy; [13]Klinikum Rechts der Isar, Department of Internal Medicine II, Technische Universität München, Munich, Germany; [14]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [15]AstraZeneca, Cambridge, UK; [16]AstraZeneca, Gaithersburg, MD, USA; [17]Merck & Co, Inc, Kenilworth, NJ, USA; [18]The Oncology Institute, Sheba Medical Center at Tel-Hashomer, Tel Aviv University, Tel Aviv, Israel

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)

Rationale for PARP inhibition in BRCA-deficient tumors

Mode of action[1]



Clinical evidence

	Phase II olaparib trial[2] (N=298; pancreatic cancer, n=23)
Patient population	gBRCAm Prior gemcitabine for advanced pancreatic cancer 1–8 prior lines of therapy
Median PFS	4.6 months
ORR	21.7%

Demonstrated clinical efficacy in gBRCAm ovarian and breast cancers[3,4]

BRCA, *BRCA1* and/or *BRCA2;* HRR, homologous recombination repair; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase

1. O'Connor M *et al. Mol Cell* 2015;60:547–560; 2. Kaufman B *et al. J Clin Oncol* 2015;33:244–250; 3. Moore K *et al. New Engl J Med* 2018;379:2495–2505; 4. Robson M *et al. New Engl J Med* 2017;377:523–533

Presented By Hedy Kindler at 2019 ASCO Annual Meeting

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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

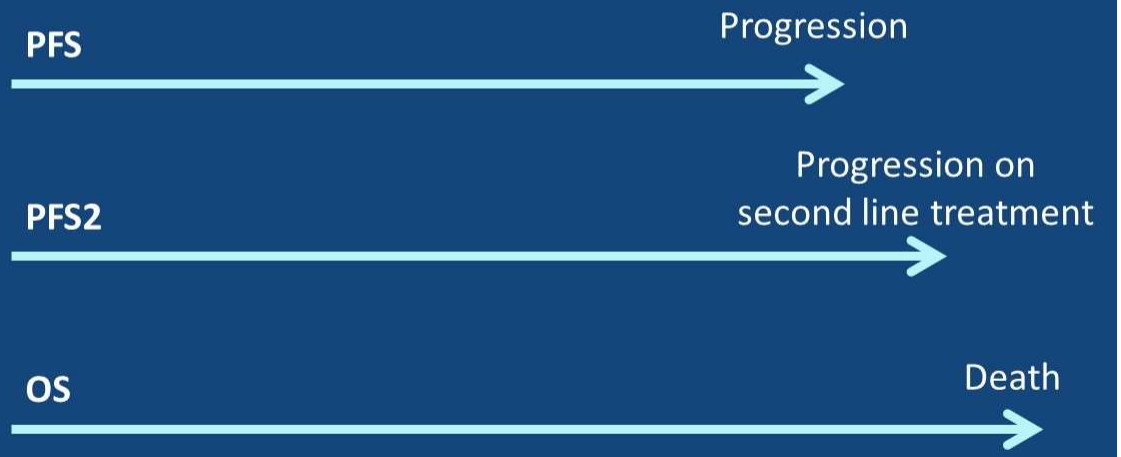
Study endpoints

Primary endpoint:

PFS using modified RECIST v1.1 by blinded independent central review

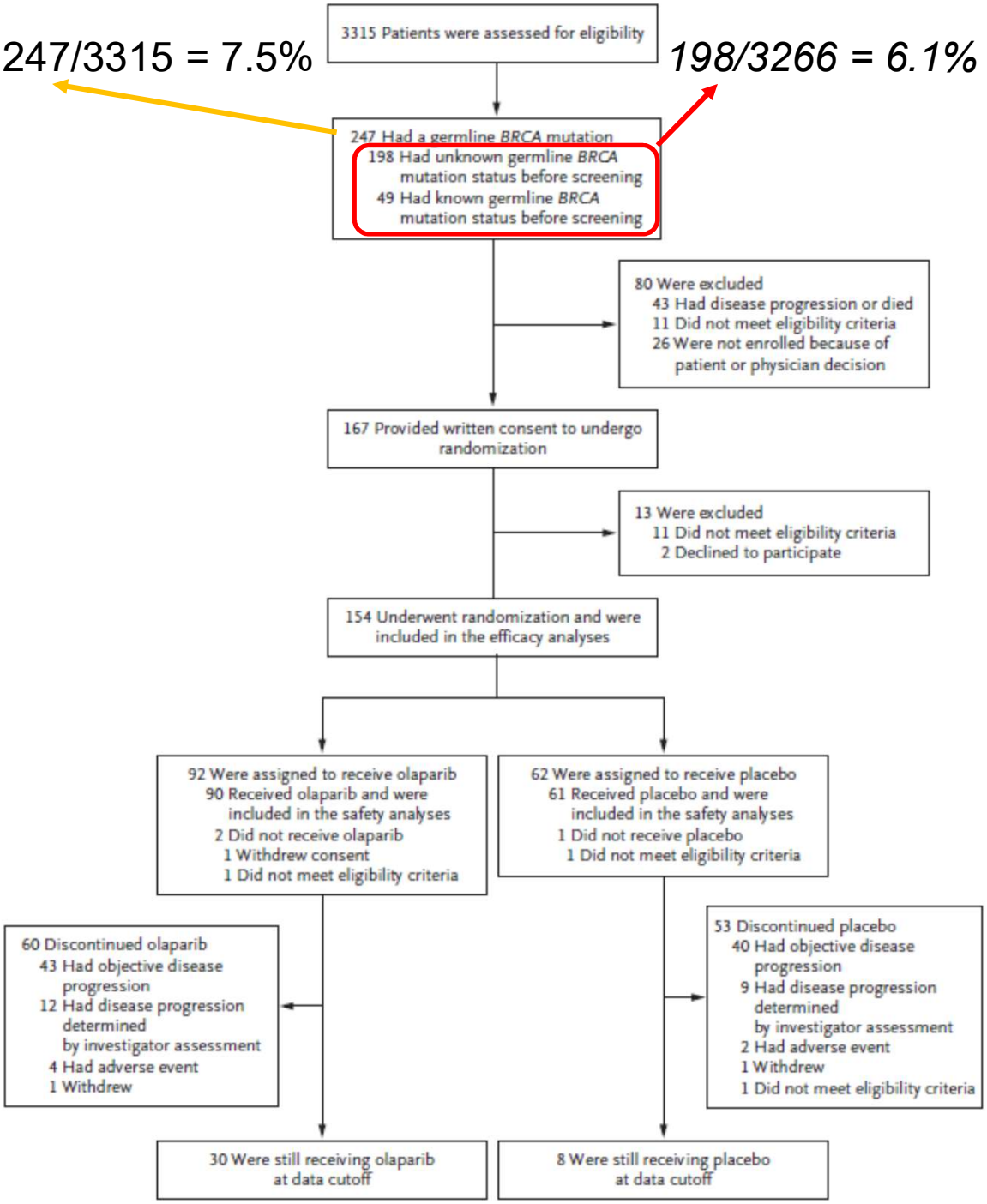
Key secondary endpoints:

- Time to second progression (PFS2)
- Objective response rate
- HRQoL
- Safety and tolerability
- Overall survival



247/3315 = 7.5%

198/3266 = 6.1%



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Patient characteristics

		Olaparib (N=92)	Placebo (N=62)
Age	Median, years (range) ≥65 years, n (%)	57.0 (37–84) 28 (30.4)	57.0 (36–75) 13 (21.0)
Sex, n (%)	Male	53 (57.6)	31 (50.0)
Race, n (%)	Caucasian	82 (89.1)	59 (95.2)
ECOG performance status, n (%)	0 1	65 (70.7) 25 (27.2)	38 (61.3) 23 (37.1)
BRCA mutation status, n (%)	*BRCA1* *BRCA2* Both	29 (31.5) 62 (67.4) 1 (1.1)	16 (25.8) 46 (74.2) 0
Location of primary tumor in pancreas, n (%)*	Head Body Tail	46 (50.0) 41 (44.6) 29 (31.5)	34 (54.8) 17 (27.4) 22 (35.5)
Biliary stent, n (%)	Present	1 (1.1)	4 (6.5)
Albumin concentration	Median, g/dL (range)	4.1 (3.2–4.8)	4.0 (3.4–5.0)

*Patients may be counted in more than one category. ECOG, Eastern Cooperative Oncology Group

Patient characteristics

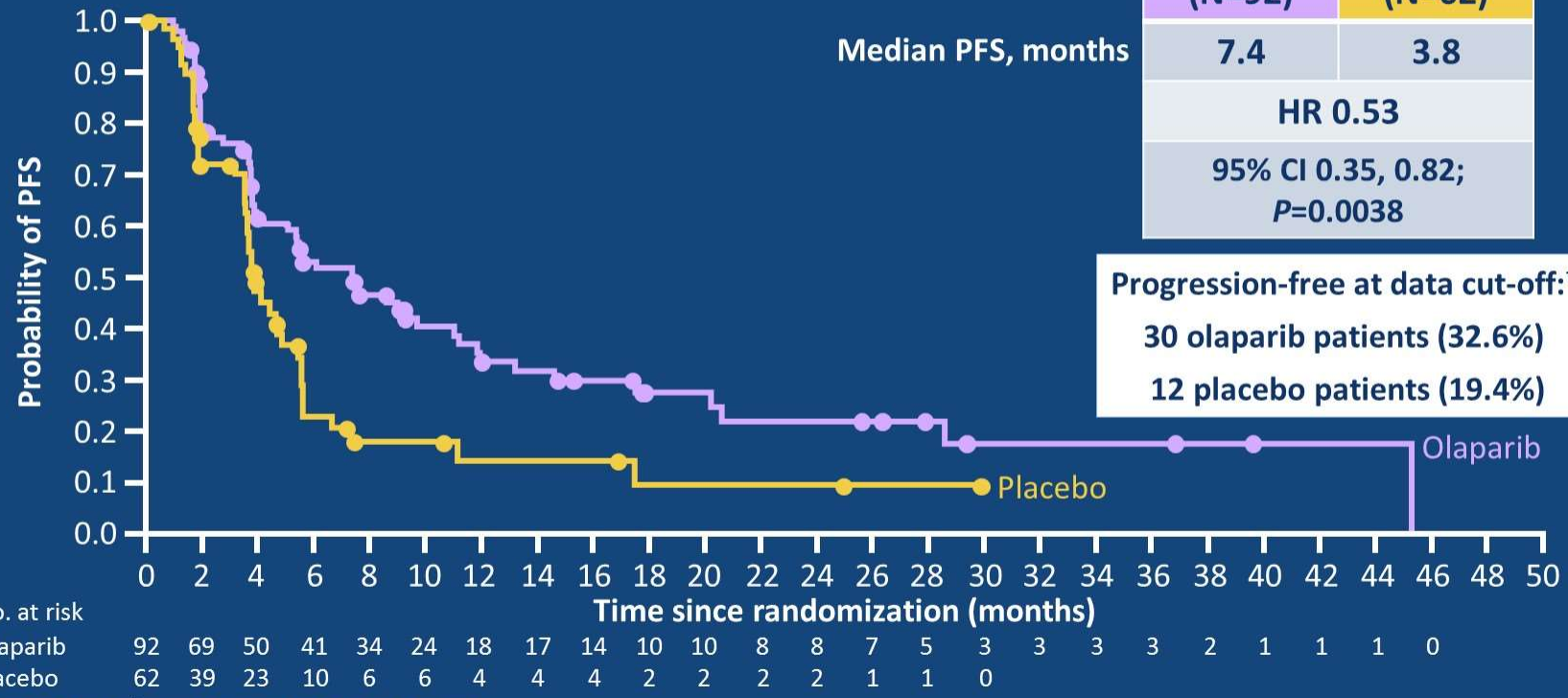
		Olaparib (N=92)	Placebo (N=62)
Time from diagnosis to randomization	Median, months (range)	6.9 (3.6–38.4)	7.0 (4.1–30.2)
Duration of first-line chemotherapy	Median, months (range) 16 weeks to 6 months, n (%) >6 months, n (%)	5.0 (2.5–35.2) 61 (66.3) 30 (32.6)	5.1 (3.4–20.4) 40 (64.5) 21 (33.9)
First-line platinum-based chemotherapy, n (%)	FOLFIRINOX variants Gemcitabine/cisplatin Other	79 (85.9) 2 (2.2) 10 (10.9)	50 (80.6) 3 (4.8) 8 (12.9)
Best response on first-line chemotherapy, n (%)	Complete or partial response Stable disease	46 (50.0) 45 (48.9)	30 (48.4) 31 (50.0)
Disease status following platinum-based chemotherapy, n (%)	Measurable Non-measurable or no evidence of disease	78 (84.8) 13 (14.1)	52 (83.9) 6 (9.7)
Site of metastases prior to chemotherapy, n (%)*	Liver Lung Peritoneum Other	61 (66.3) 10 (10.9) 10 (10.9) 14 (15.2)	48 (77.4) 5 (8.1) 5 (8.1) 8 (12.9)

*Patients may be counted in more than one category

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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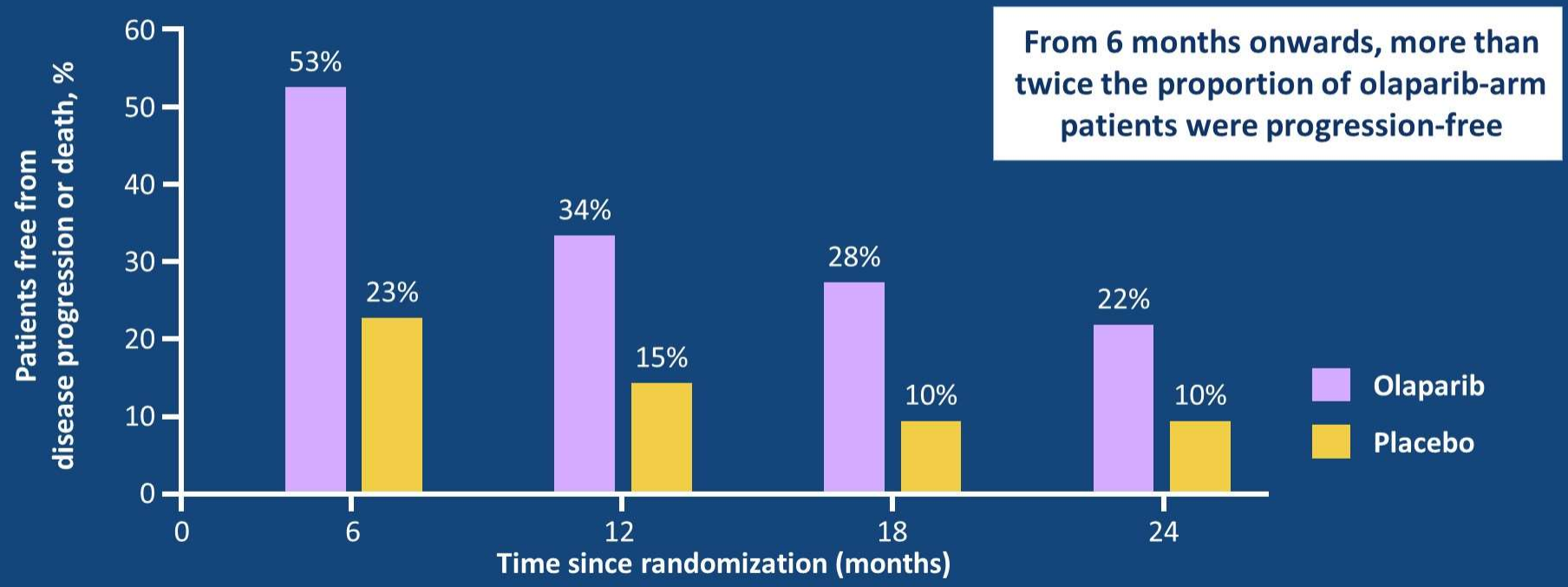
PFS at prespecified timepoints by blinded independent central review*



*Kaplan-Meier method

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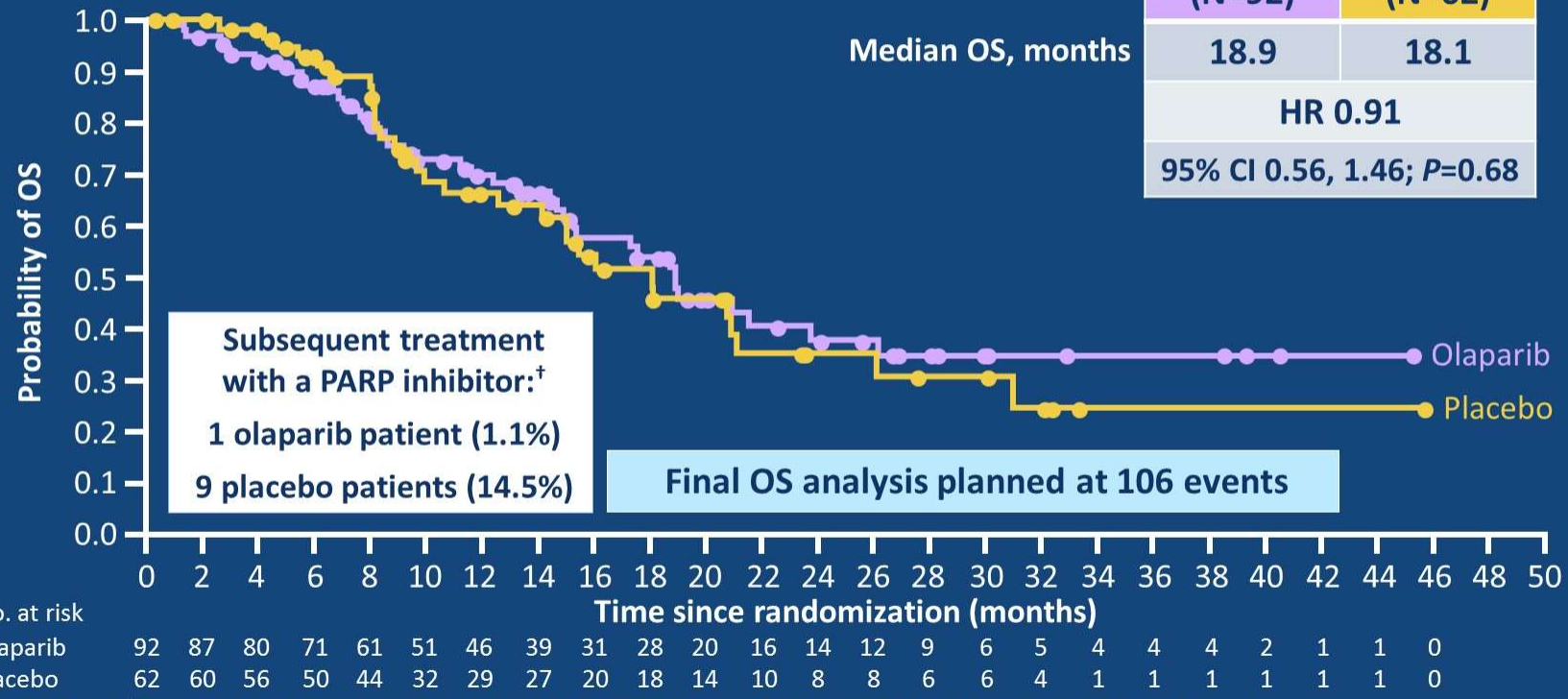
OS: interim analysis, 46% maturity*

	Olaparib (N=92)	Placebo (N=62)
Median OS, months	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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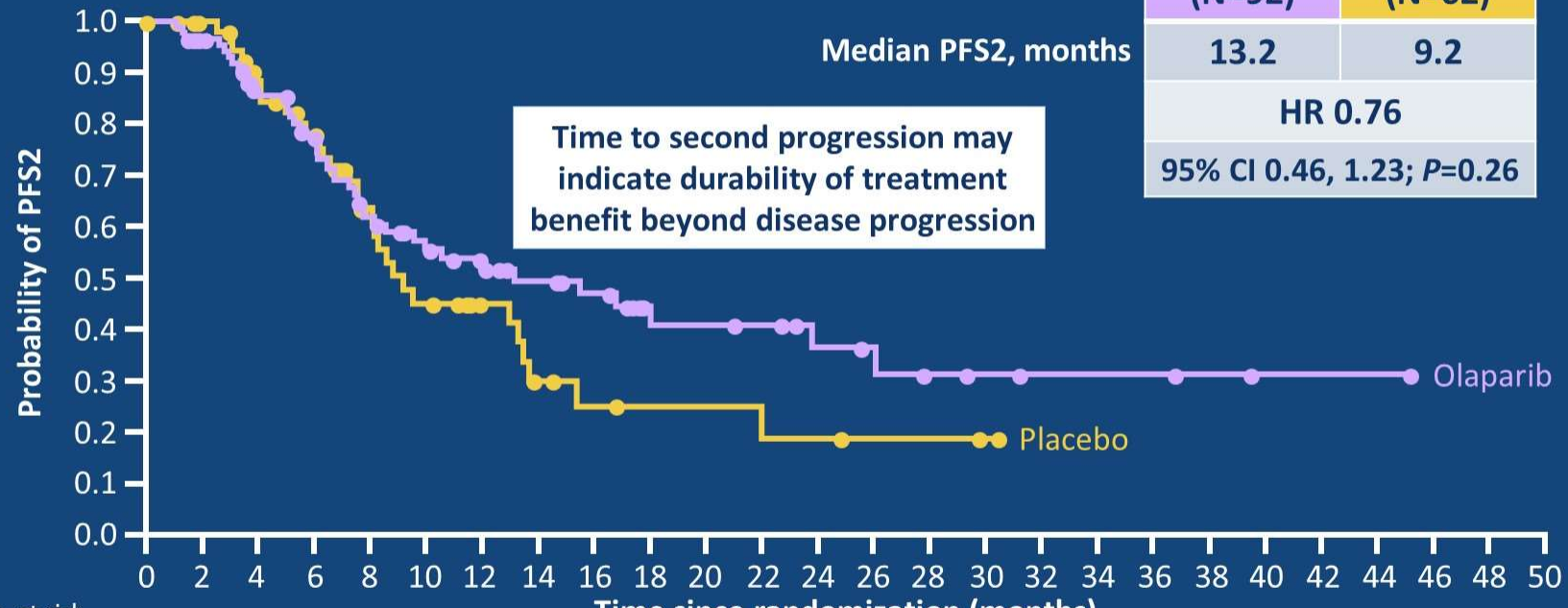
PFS2 by investigator assessment: interim analysis, 46% maturity*

	Olaparib (N=92)	Placebo (N=62)
Median PFS2, months	13.2	9.2
HR 0.76		
95% CI 0.46, 1.23; *P*=0.26		



No. at risk																								
Olaparib	92	82	65	56	43	32	27	22	19	13	12	11	8	7	5	4	3	3	3	2	1	1	1	0
Placebo	62	54	43	36	24	17	12	7	5	4	4	4	3	2	2	1	0							

*Dots indicate censorship. PFS2, time to second progression

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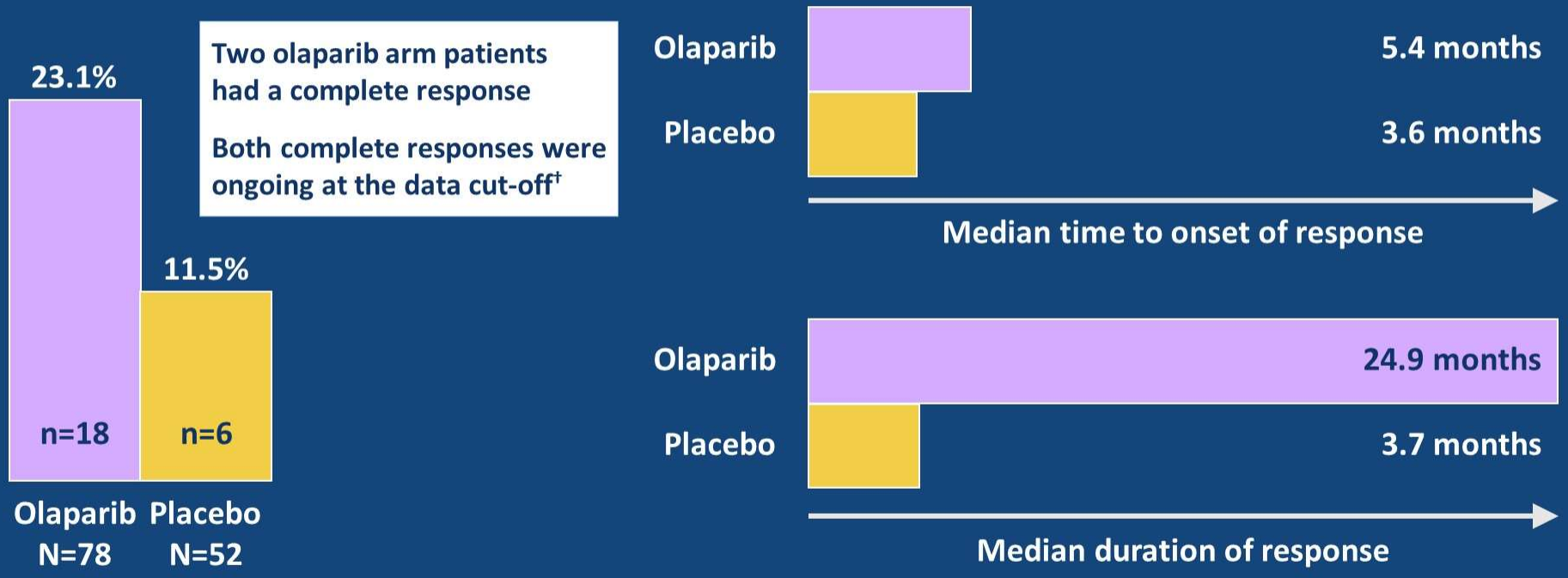
Objective response* in patients with measurable disease by blinded independent central review



*By modified RECIST v1.1. †January 15, 2019

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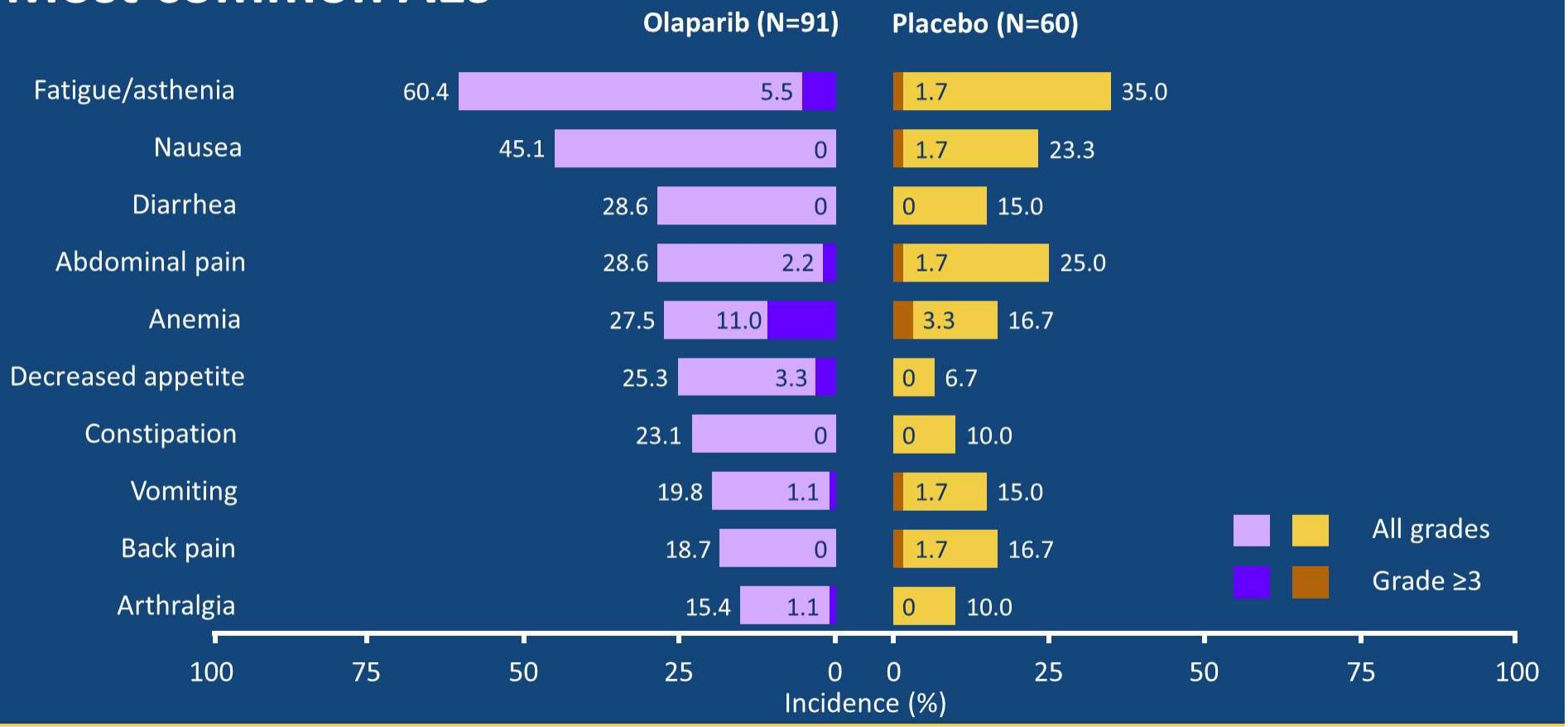
Safety summary: AEs and exposure

	Olaparib (N=91)	Placebo (N=60)
Any grade, n (%)	87 (95.6)	56 (93.3)
Grade ≥3, n (%)	36 (39.6)	14 (23.3)
AEs leading to dose interruption, n (%)	32 (35.2)	3 (5.0)
AEs leading to dose reduction, n (%)	15 (16.5)	2 (3.3)
AEs leading to treatment discontinuation, n (%)	5 (5.5)	1 (1.7)
Median duration of treatment, months (range)	**6.0 (0.8–45.3)**	**3.7 (0.1–30.1)**

AE, adverse event

Most common AEs



Discussion

Strengths

- Well designed and executed prospective randomized phase III study
- Biomarker-selected patients
- First evidence of maintenance strategy

Limitations

- Small percentage of pancreatic cancer patients eligible
- Discontinuation strategy
- No OS benefit but data not mature
- A lot of new questions…

Practice Changing?

- Yes

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Key Unanswered Questions

- Germline vs somatic
- BRCA1/2 vs BRCAness
- platinum vs PARPi
  - Platinum insensitive = PARPin insensitive?
- Not all PARPi's are created equal
- Maintenance setting vs other
- Chemo combination
- Resistance
- Super-responders

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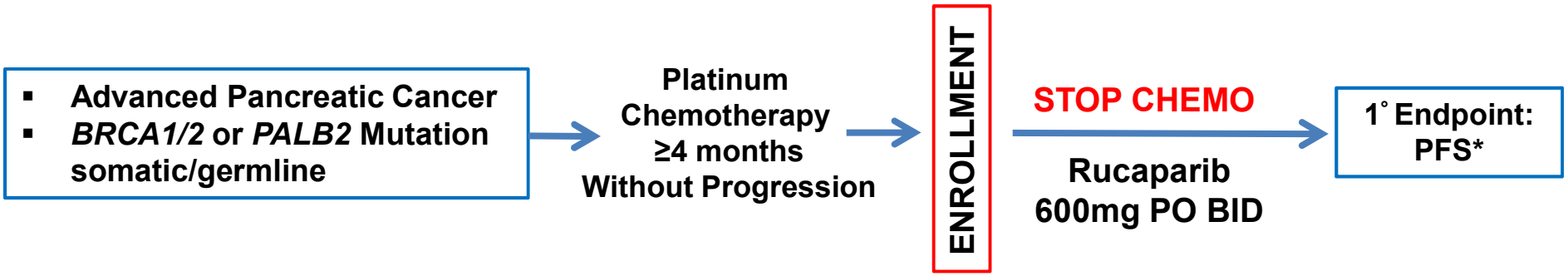
Rucaparib Maintenance for Advanced, Platinum Sensitive *BRCA* or *PALB2* Related Pancreatic Cancer: An Interim Analysis

Kim A. Reiss Binder, Rosemarie Mick, Mark O'Hara, Ursina Teitelbaum, Thomas Karasic, Charles Schneider, Peter J. O'Dwyer, Erica Carpenter, Austin Pantel, Mehran Makvandi, David Mankoff, Katherine Nathanson, Kara Maxwell, Stacy Cowden, Mary Jane Fuhrer, Janae Romeo, Gregory L. Beatty, Susan Domchek.

American Association for Cancer Research
2019 Annual Meeting

Study Schema



*Null hypothesis: PFS6 rate in this population of subjects is 44%. The alternative hypothesis is that the PFS6 rate is 60%. Forty-two patients provide 81% power to detect this increase in PFS6, at a two-sided 5% significance level.

Key Study Entry Criteria and Study patient characteristics

Inclusion Criteria

- ✓ Advanced pancreatic carcinoma
- ✓ Pathogenic somatic or germline mutation in *BRCA1*, *BRCA2* or *PALB2*
- ✓ ≥16 weeks of platinum chemotherapy without cancer progression *unless* a legitimate toxicity prevents the full 16 weeks to be given
- ✓ ECOG 0-1

Exclusion Criteria

- ✓ Prior PARPi
- ✓ Progressive disease on platinum therapy

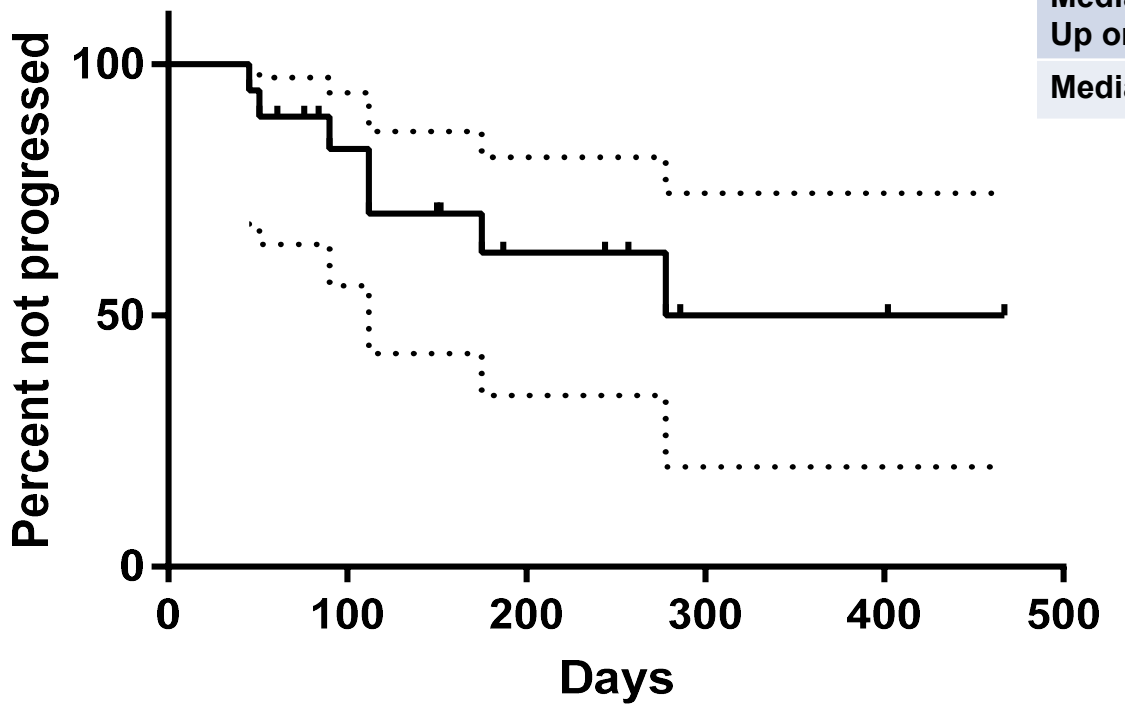
Age, y	
Median (range)	61 (35-81)
Sex, n (%)	
Male	3 (15.8)
Female	16 (84.2)
Ethnicity, n (%)	
Caucasian	18 (94.7)
African American	1 (5.3)
Mutation, n (%)	
Germline *BRCA1*	3 (15.8)
Germline *BRCA2*	13 (68.4)
Germline *PALB2*	2 (10.5)
Somatic *BRCA2*	1 (5.3)
Number of weeks on platinum prior to enrollment, n (%)	
<16	4 (21)
16-52	13 (68.4)
>52	2 (10.5)
Measurable disease at time of enrollment, n (%)	
Yes	17 (89.5)
No	2 (10.5)

Toxicities At Least Possibly Related to Treatment*

Event	Grade 1 or 2; n(%)	Grade 3 or 4; n(%)	All Grades; n(%)
Gastrointestinal			
Nausea	10 (43.4)	0 (0)	10 (43.4)
Vomiting	3 (13.0)	0 (0)	3 (13.0)
Diarrhea	4 (17.4)	0 (0)	4 (17.4)
ALT Increase	5 (21.7)	0 (0)	5 (21.7)
AST Increase	3 (13.0)	0 (0)	3 (13.0)
Dysgeusia	8 (34.8)	0 (0)	8 (34.8)
Hematological			
Anemia	2 (8.6)	0 (0)	2 (8.6)
Constitutional			
Fatigue	6 (26.1)	0 (0)	6 (26.1)

*Toxicities occurring in >1 patient

Progression Free Survival on Monotherapy Rucaparib

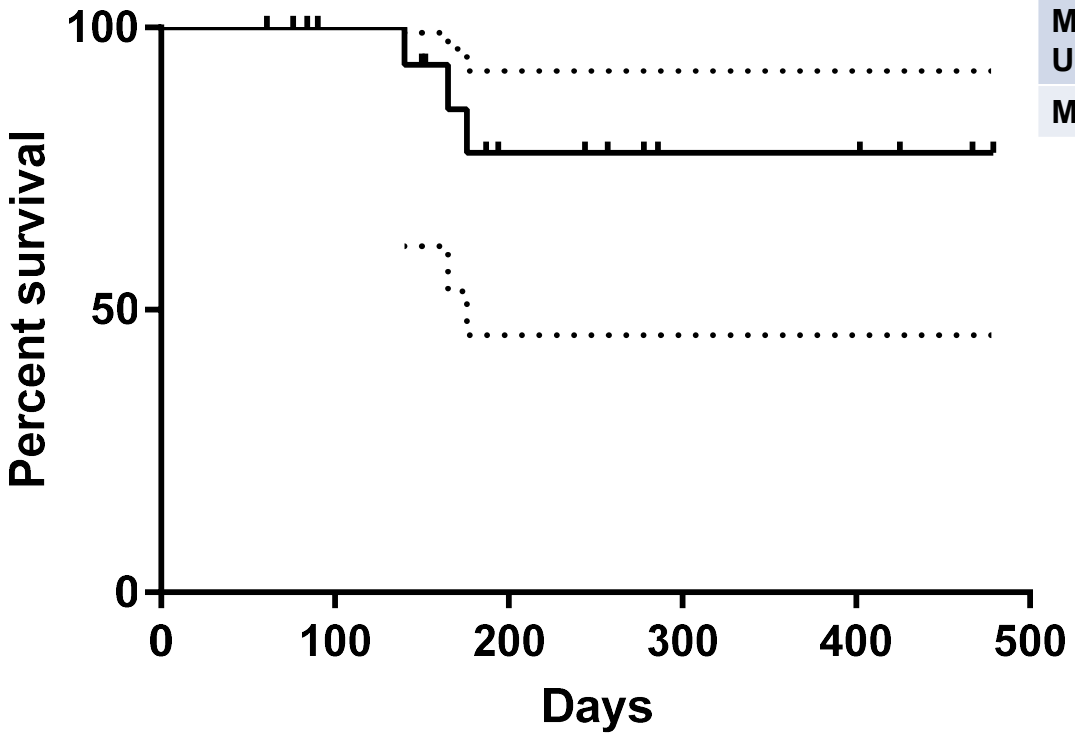


Median Potential Follow-Up on Trial, days	**257**
Median PFS, days	**278**

..... 95% CI

No. at Risk:	**19**	**14**	**8**	**3**	**3**	**1**

Overall Survival on Monotherapy Rucaparib

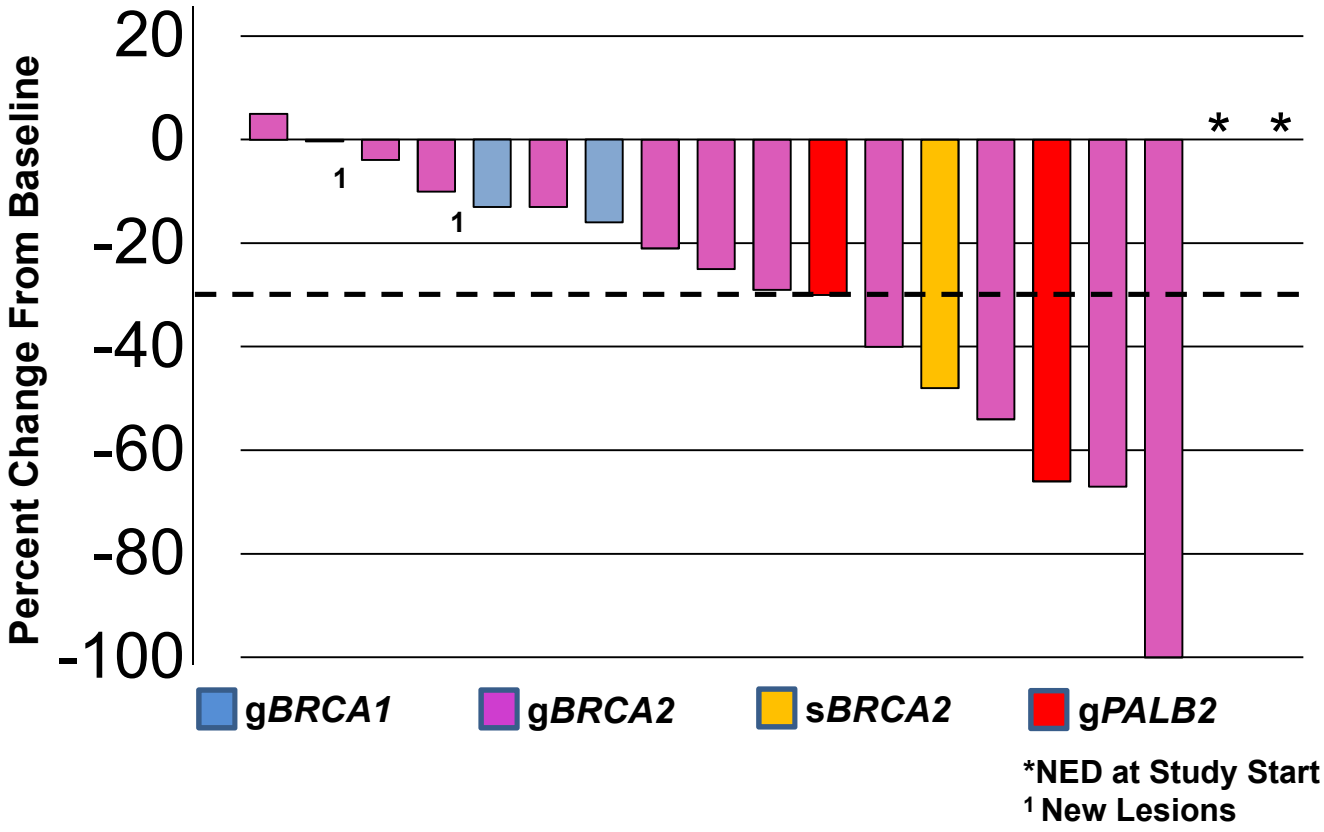


Median Potential Follow-Up, days	**244**
Median OS, days	**-**

95% CI

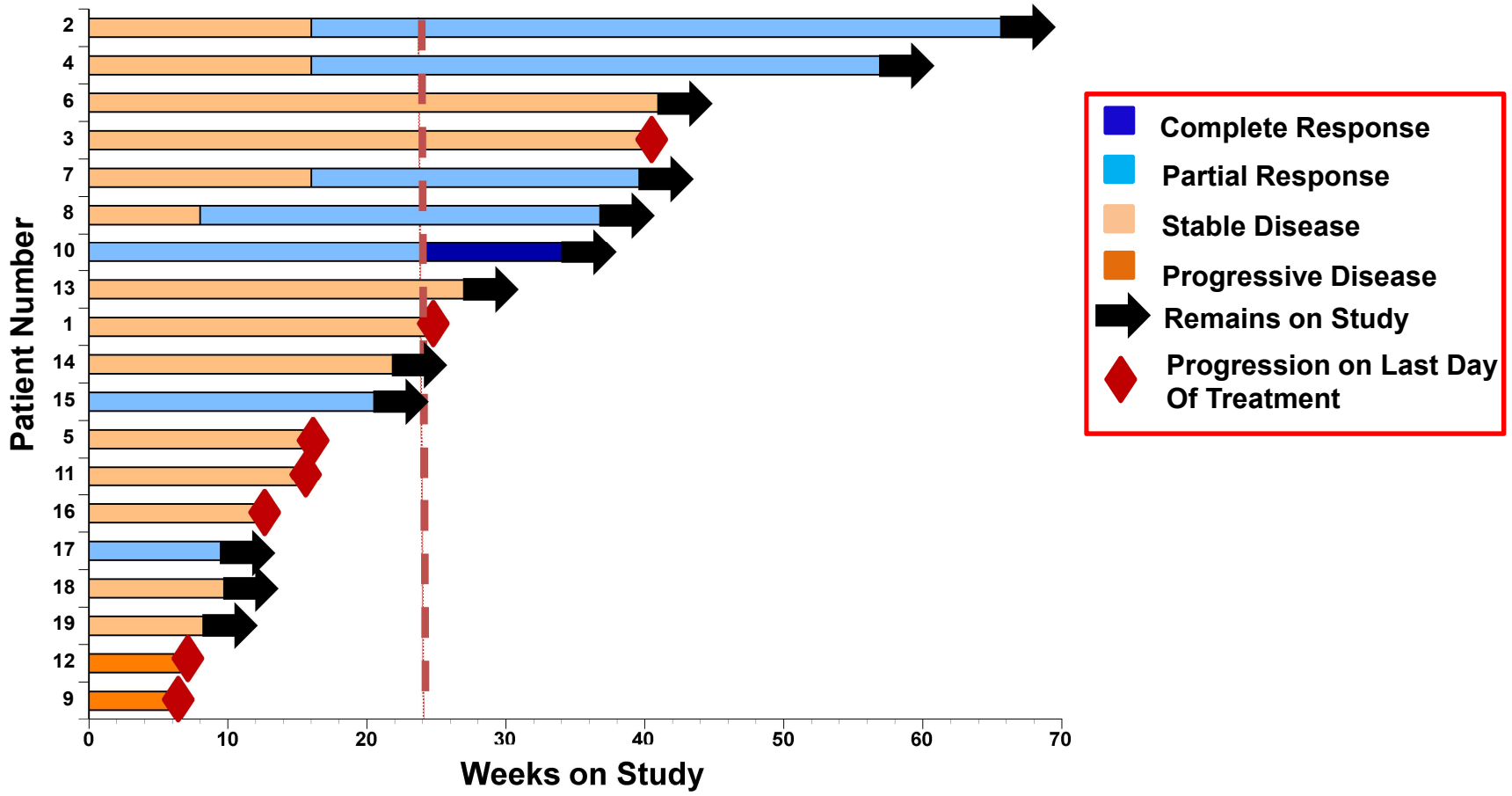
No. at Risk: 19 16 9 5 5 1

Best Percent Change by RECIST v1.1



ORR all patients	37.8%
ORR evaluable patients	41.1%
DCR at 8 weeks	89.5%

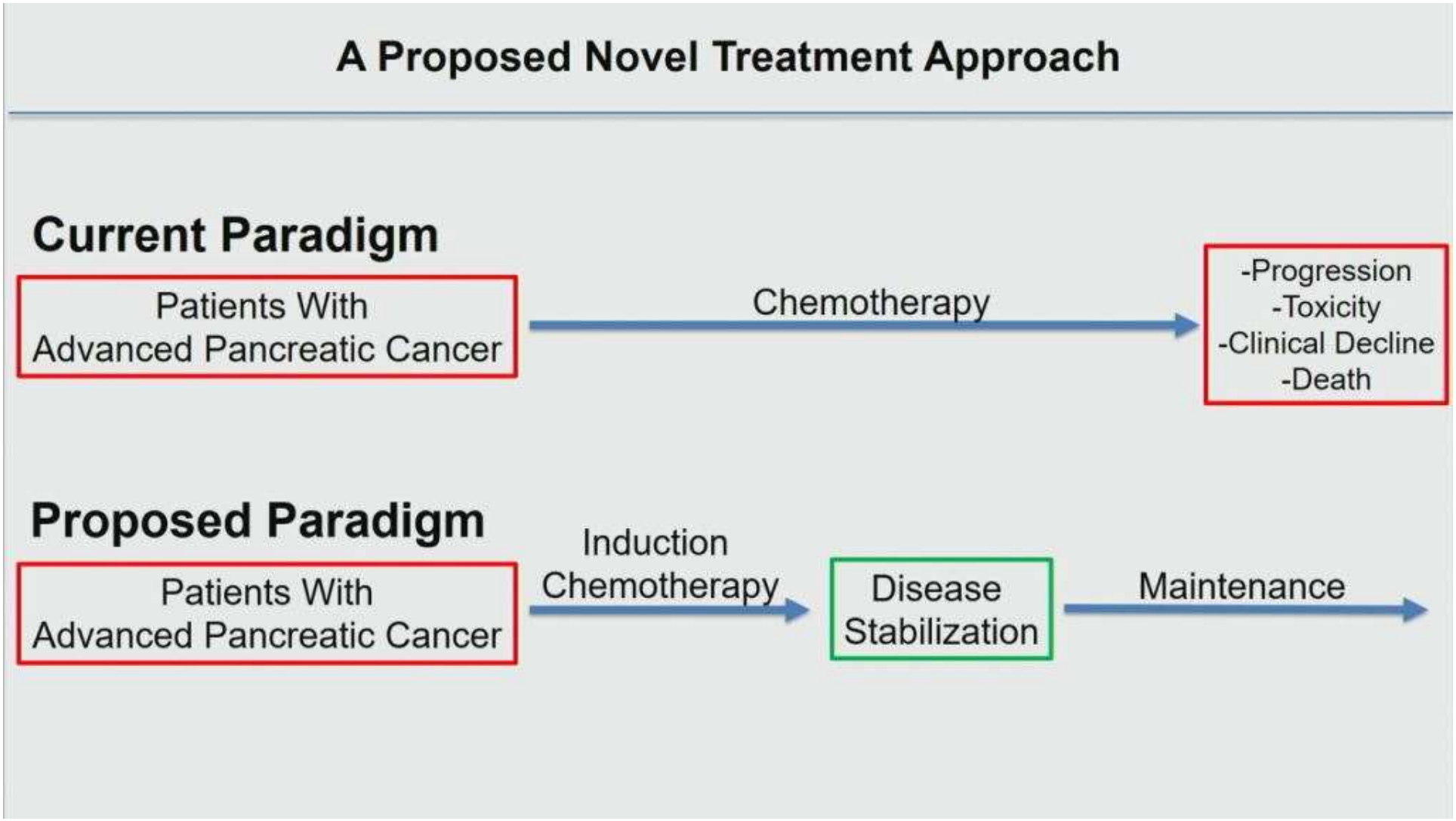
Response Rate Over Time



Advanced Pancreatic Cancer Clinical Trials Summary

	# pts	Year Reported	Where done	Overall Survival	1 year Survival	Progressi on-Free Survival	Response Rate
	126	1997	North America				
	569	2007	International				
	342	2011	France				
	861	2013	International				

A Proposed Novel Treatment Approach



Outline

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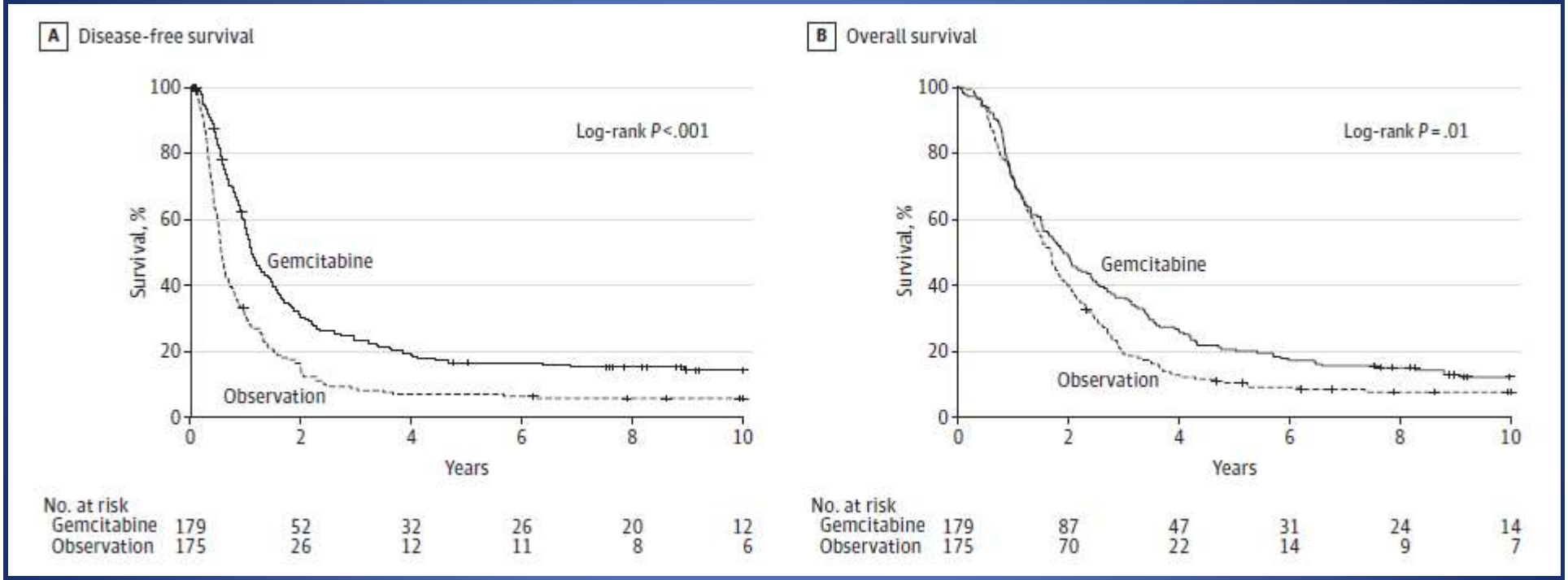
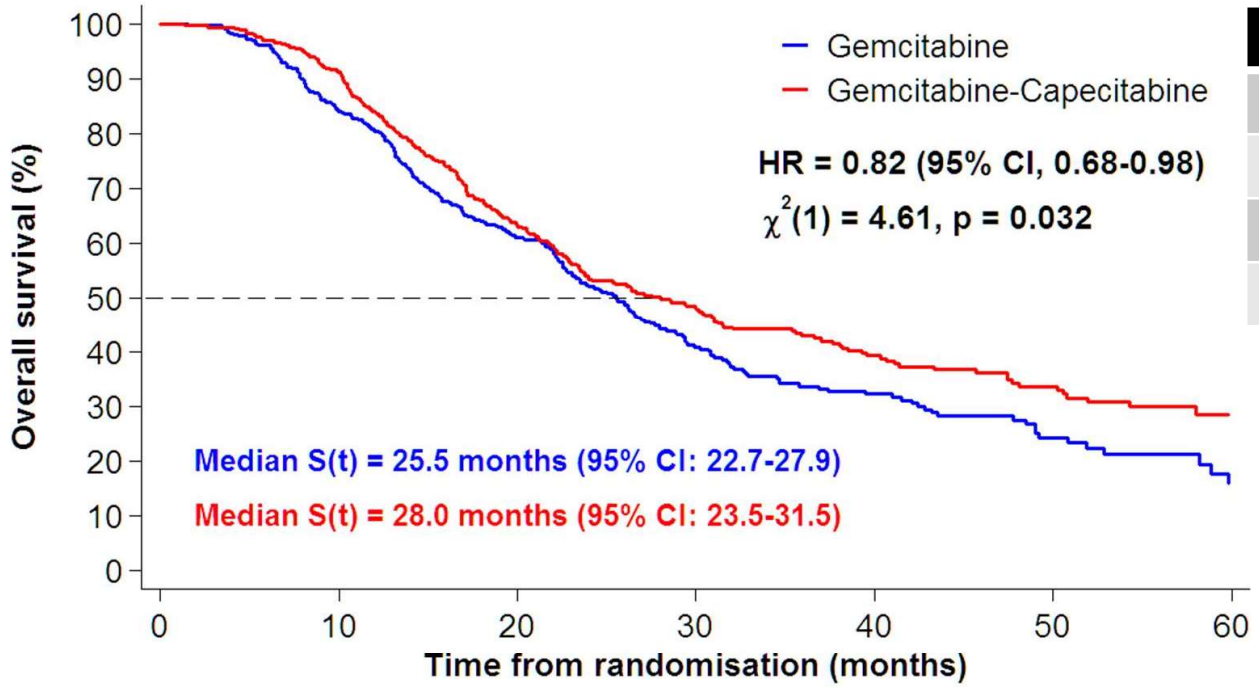
  - Immunotherapy

Conko-001



Oettle et al. JAMA 2013 Oct 9:1473-81

ESPAC-4 – gem vs gem/capecitabine



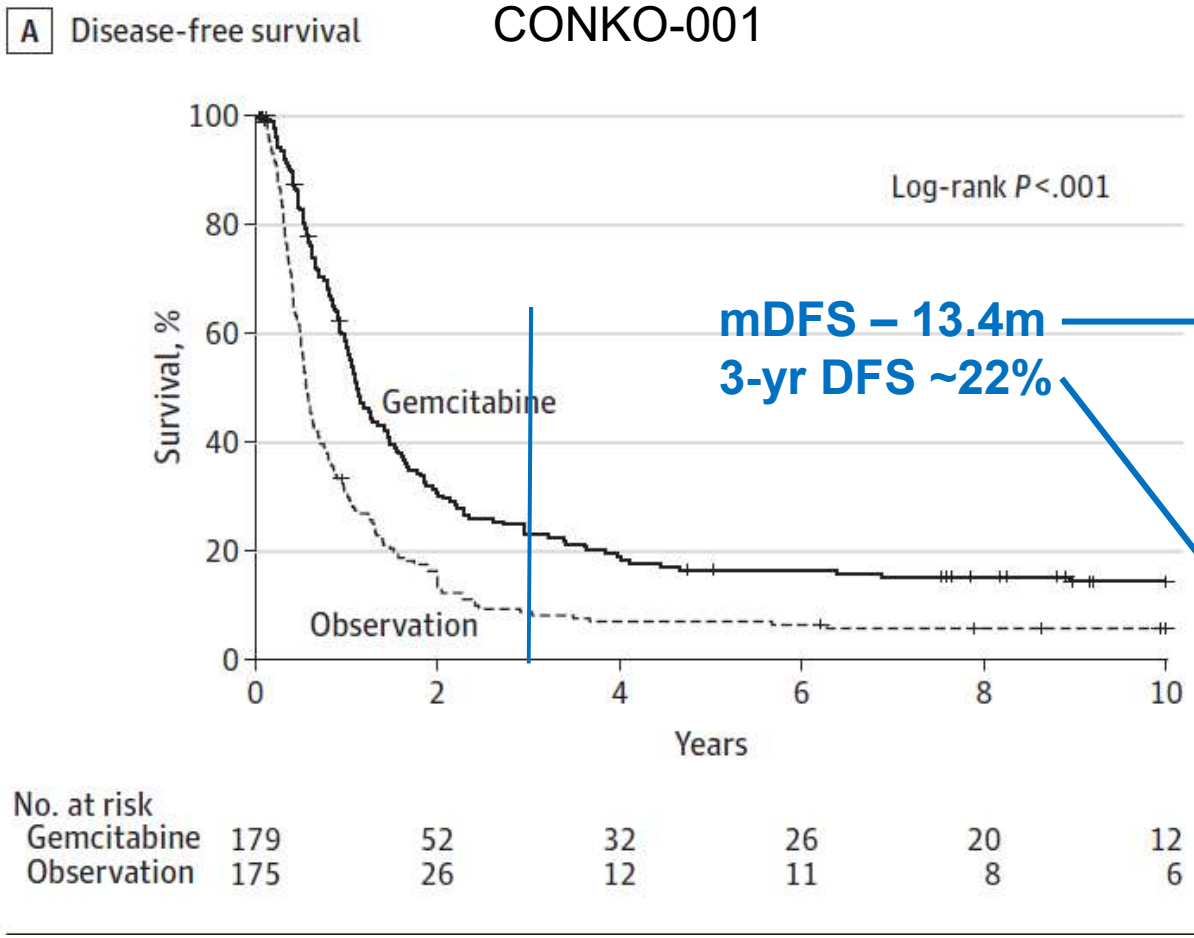
Gr 3/4	Gem	Gem-Cap
SAE's	26%	24%
ANC	24%	38%
Hand Foot	0	7%
Diarrhea	2%	5%

Presented By John Neoptolemos at 2016 ASCO Annual Meeting

Primary Endpoint

Disease-Free Survival

CONKO-001



mDFS – 13.4m
3-yr DFS ~22%

No DFS events: 314

Median DFS:

- 21.6 mths [95%CI: 17.7-27.6] with mFolfirinox
- 12.8 mths [95%CI: 11.7-15.2] with Gemcitabine

3-year DFS:

- 39.7% [95%CI: 32.8-46.6] with mFolfirinox
- 21.4% [95%CI: 15.8-27.5] with Gemcitabine

Presented By Thierry Conroy at 2018 ASCO Annual Meeting

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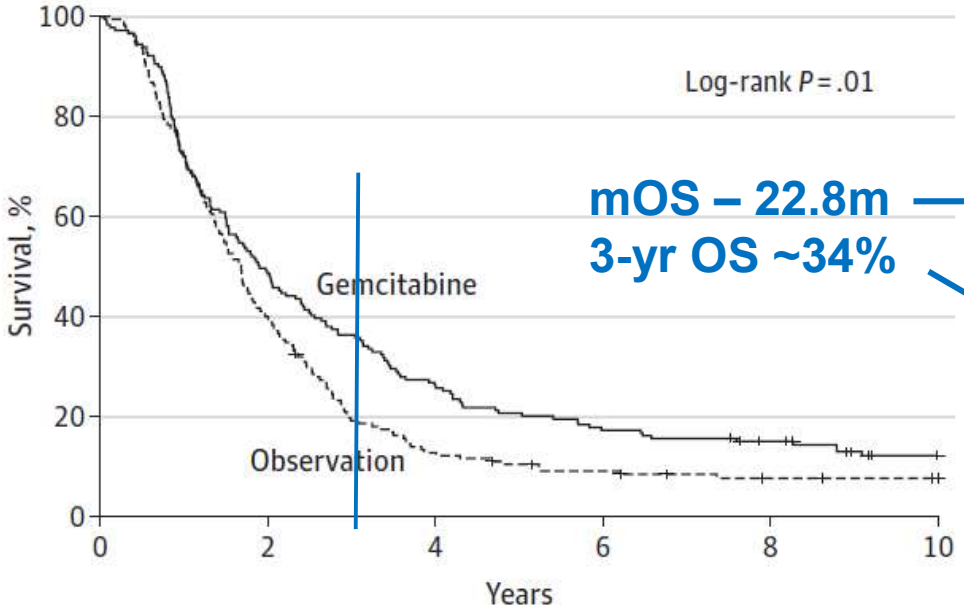
Overall Survival

B Overall survival

CONKO-001



No. at risk

Gemcitabine	179	87	47	31	24	14
Observation	175	70	22	14	9	7

mOS – 22.8m
3-yr OS ~34%

Median overall survival:

- **54.4 months** [95%CI: 41.8-NR] **with mFolfirinox**
- **35.0 months** [95%CI: 28.7-43.9] **with Gemcitabine**

3-year overall survival:

No OS events=192

- **63.4% (mFolfirinox) vs 48.6 % (Gem)**

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

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.

Abstract 4000

APACT: Phase III, Multicenter, International, Open-Label, Randomized Trial of Adjuvant *nab*®-Paclitaxel Plus Gemcitabine vs Gemcitabine for Surgically Resected Pancreatic Adenocarcinoma

Margaret A. Tempero,[1] Michele Reni,[2] Hanno Riess,[3] Uwe Pelzer,[3] Eileen M. O'Reilly,[4] Jordan Winter,[5] Do-Youn Oh,[6] Chung-Pin Li,[7] Giampaolo Tortora,[8,9] Heung-Moon Chang,[10] Charles D. Lopez,[11] Josep Tabernero,[12] Eric Van Cutsem,[13] Philip Philip,[14] David Goldstein,[15] Jordan D. Berlin,[16] Stefano Ferrara,[17] Mingyu Li,[17] Brian Lu,[17] Andrew Biankin[18]

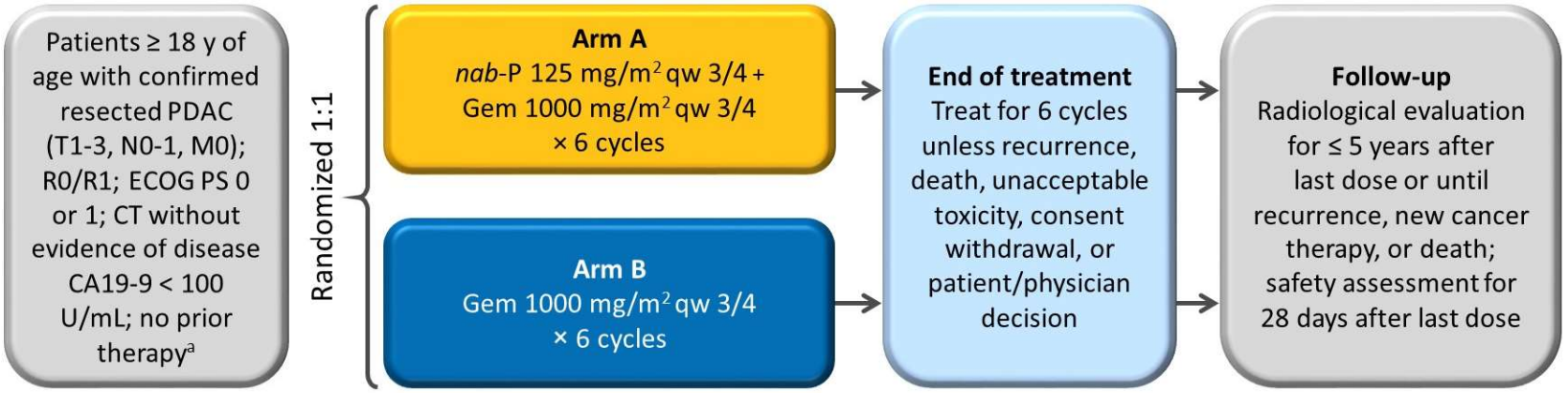
[1]University of California, San Francisco, Helen Diller Comprehensive Cancer Center, San Francisco, CA; [2]IRCCS Ospedale San Raffaele, Milan, Italy; [3]Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany; [4]Memorial Sloan Kettering Cancer Center, New York City, NY; [5]Thomas Jefferson University Hospital, Philadelphia, PA; [6]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; [7]Taipei Veterans General Hospital, Taipei, Taiwan; [8]Azienda Ospedaliera Universitaria, Verona, Italy; [9]Fondazione Policlinico Universitario Gemelli, IRCCS, Rome, Italy; [10]Asan Medical Center, Seoul, South Korea; [11]Oregon Health and Science University, Portland, OR; [12]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [13]University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; [14]Karmanos Cancer Institute, Detroit, MI; [15]Nelune Cancer Centre, Prince of Wales Hospital, University of New South Wales, Randwick, NSW, Australia; [16]Vanderbilt-Ingram Cancer Center, Nashville, TN; [17]Celgene Corporation, Summit, NJ; [18]University of Glasgow, Glasgow, Scotland

Presented By Margaret Tempero at 2019 ASCO Annual Meeting

STUDY DESIGN

apact
Adjuvant Pancreatic Adenocarcinoma Clinical Trial
albumin-bound paclitaxel (ABI-007-PANC-003) + gemcitabine

APACT: phase III, multicenter, international, open-label, randomized trial



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

Sample Size and Power Considerations

Endpoint	*nab*-P + Gem	Gem
Primary (independently assessed DFS)		
Median, months	18.5	13.5
HR for disease recurrence or death	0.73	
Events required for 90% power at 2-sided α of 0.05, n	438	
Secondary (OS)		
Events to be analyzed as supportive analysis, n	≈ 630	
Type 1 error control for OS	None	

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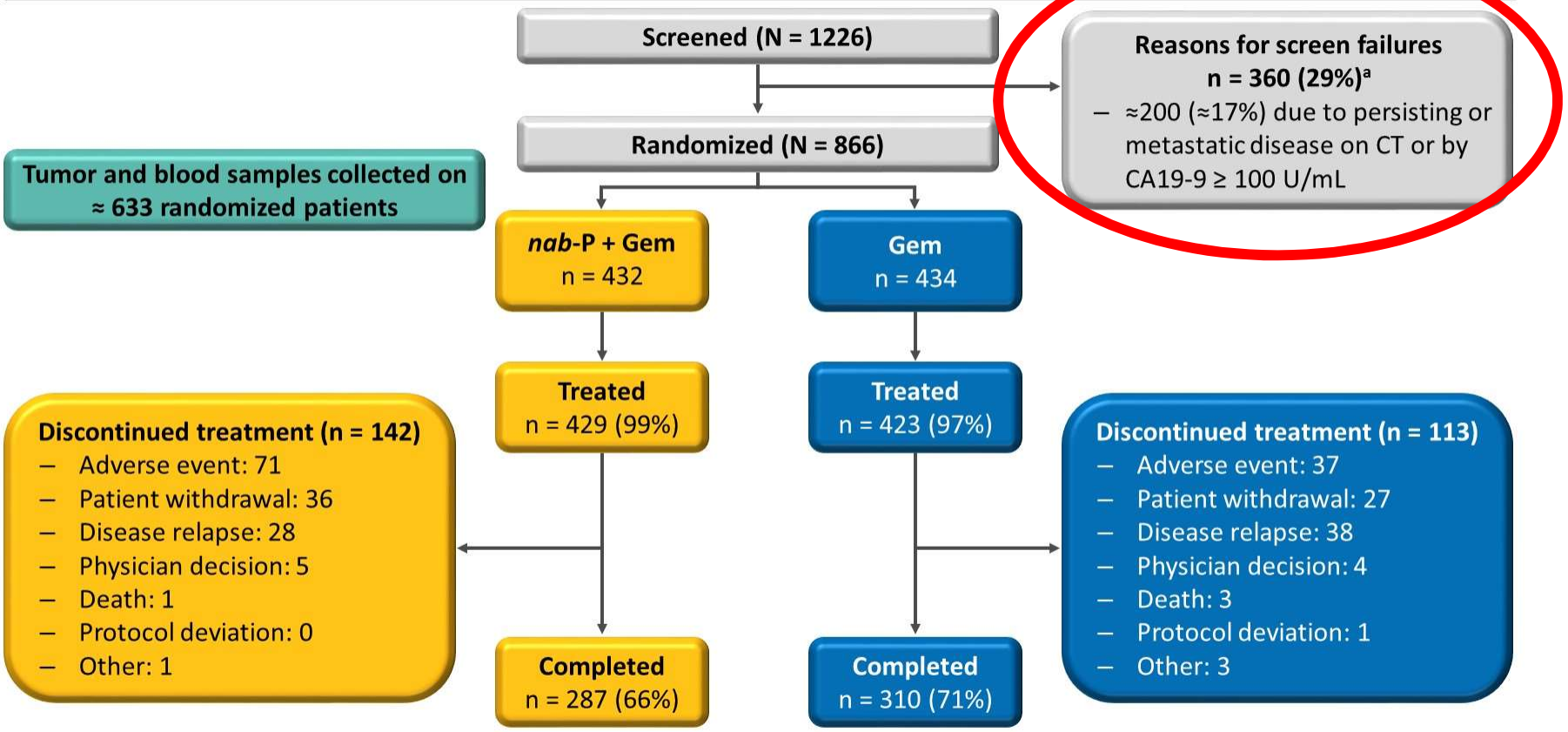
PATIENT DISPOSITION



[a] Patients could have > 1 reasons for screen failures.

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SELECTED BASELINE CHARACTERISTICS (ITT POPULATION)

apact
Adjuvant Pancreatic Adenocarcinoma Clinical Trial
albumin-bound paclitaxel (ABI-007-PAN(-003) + gemcitabine

Characteristic	*nab*-P + Gem (n = 432)	Gem (n = 434)	Total (N = 866)
Age, median (range), years	64.0 (34 - 83)	64.0 (38 - 86)	64.0 (34 - 86)
Sex, male, n (%)	228 (53)	253 (58)	481 (56)
ECOG PS, n (%)			
0	252 (58)	268 (62)	520 (60)
1	180 (42)	166 (38)	346 (40)
Resection status, n (%)			
R0 (tumor-free margin)	327 (76)	334 (77)	661 (76)
R1 (microscopically positive margin)	105 (24)	100 (23)	205 (24)
Nodal status, n (%)			
Lymph node negative	121 (28)	122 (28)	243 (28)
Lymph node positive	311 (72)	312 (72)	623 (72)
Baseline CA19-9			
n	423	429	852
Median, U/mL	14.31	12.90	13.65
Tumor grade, n (%)			
Well differentiated	49 (11)	55 (13)	104 (12)
Moderately differentiated	264 (61)	241 (56)	505 (58)
Poorly differentiated	101 (23)	115 (26)	216 (25)
Undifferentiated	1 (< 1)	2 (< 1)	3 (< 1)
Other/unknown	17 (4)	21 (5)	38 (4)

Gem, gemcitabine; ITT, intention-to-treat; *nab*-P, *nab*-paclitaxel.

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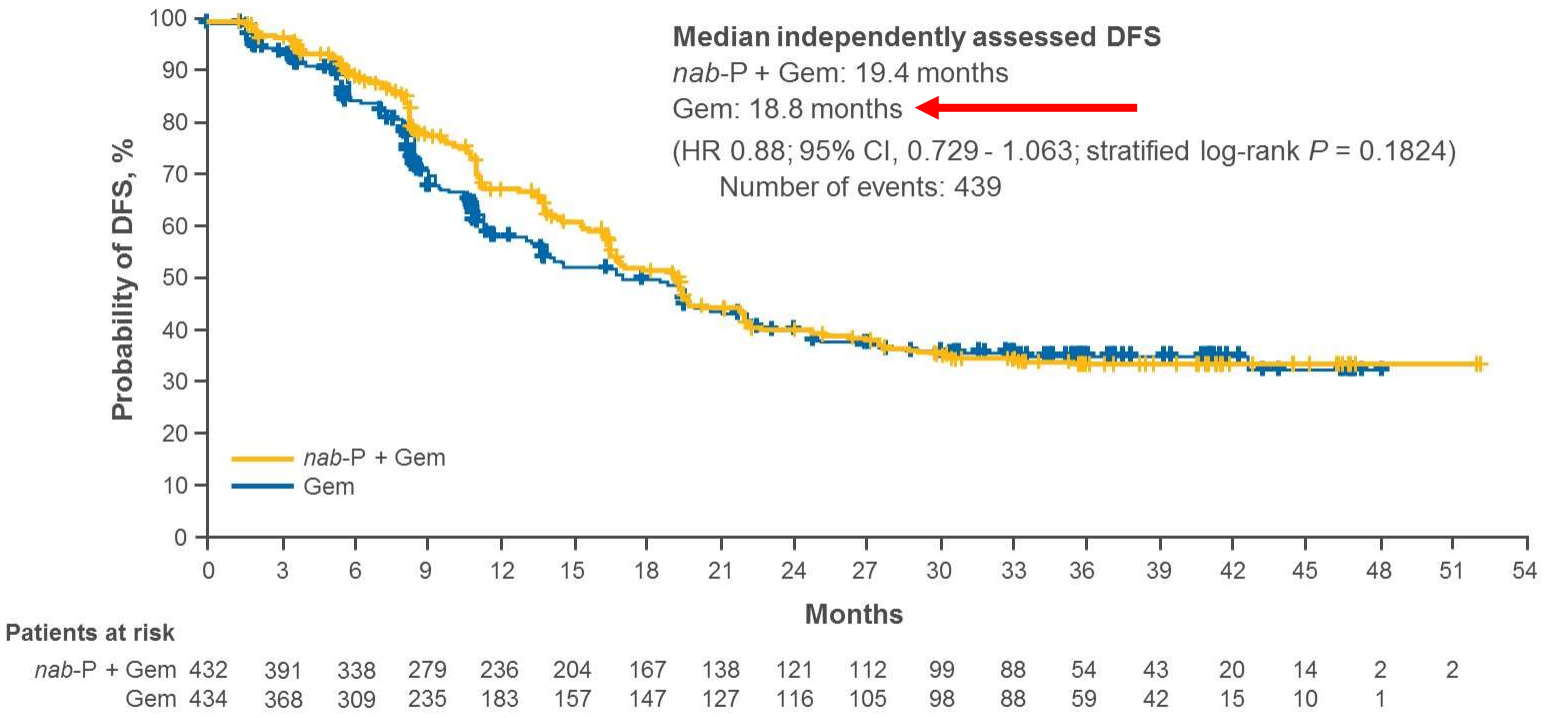
TREATMENT EXPOSURE AND DOSE MODIFICATIONS (TREATED POPULATION)

Parameters	*nab*-P + Gem		Gem
Treatment exposure	**(n = 429)**		**(n = 423)**
Treatment duration, median (range), weeks	24.0 (0.7 - 33.0)		24.0 (1.3 - 31.9)
Treatment cycles, median (range), n	6.0 (1 - 6)		6.0 (1 - 6)
	***nab*-P**	**Gem**	
Relative dose intensity, median, %	75.1	80.0	91.2
Cumulative dose, median, mg/m^2	1500	13,200	15,000
Dose modifications			
Patients with ≥ 1 dose reduction, n (%)	273 (64)	266 (62)	213 (50)

- Overall, 69% of patients completed 6 treatment cycles (*nab*-P + Gem, 66%; Gem, 71%)
- 59% of patients on *nab-P* + Gem received dosing of *nab-P* in cycle 6

Presented by Margaret Tempero, MD, at ASCO 2019; abstract 4000: Adjuvant *nab*-Paclitaxel Plus Gemcitabine vs Gemcitabine

PRIMARY ENDPOINT: INDEPENDENTLY ASSESSED DFS (ITT POPULATION)



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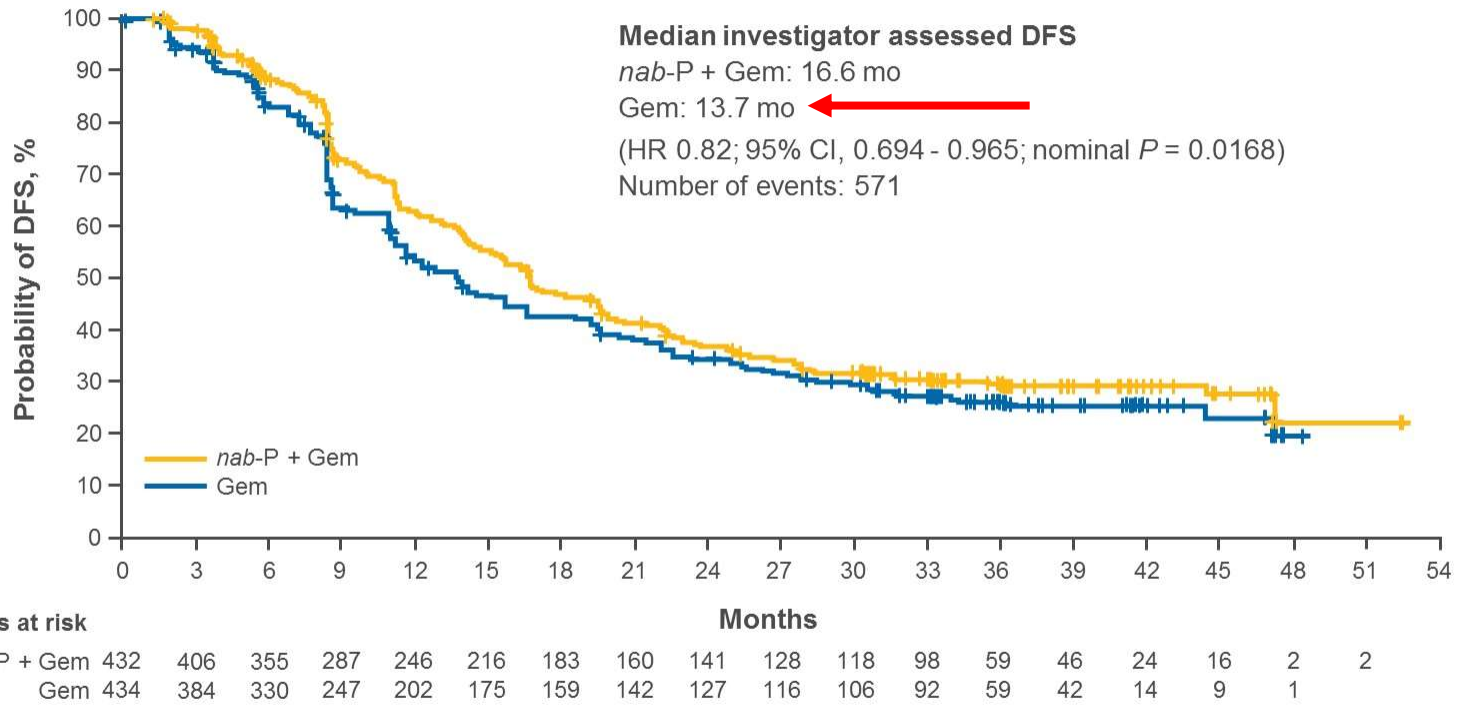
PRESPECIFIED SENSITIVITY ANALYSIS: INVESTIGATOR ASSESSED DFS (ITT POPULATION)



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

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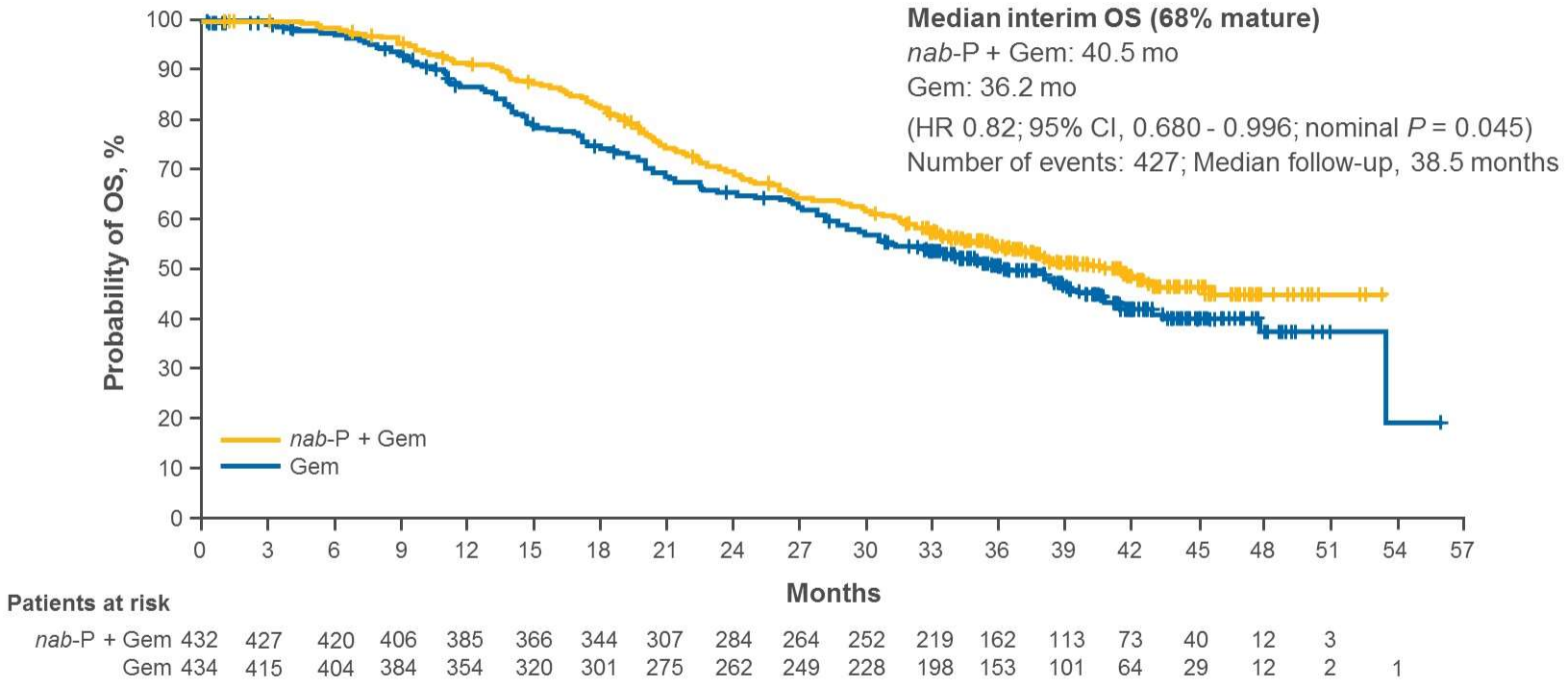
SECONDARY ENDPOINT: INTERIM OS (ITT POPULATION)



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SAFETY (TREATED POPULATION)

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

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

MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

[a] Reported as a group term.

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CONCLUSIONS

apact
Adjuvant Pancreatic Adenocarcinoma Clinical Trial
albumin-bound paclitaxel (ABI-007-PAN(-003) + gemcitabine

- The primary endpoint of independently assessed DFS was not met
  - APACT is the first trial of adjuvant therapy in PC to use independently assessed DFS
  - Investigator-assessed DFS aligned more closely with OS results than independently assessed DFS
- Consistent with other trials, the survival with Gem monotherapy was markedly improved, suggesting better patient selection and benefit from treatment with contemporary therapies upon recurrence of disease
- The *nab*-P + Gem safety profile was consistent with what was observed in the MPACT trial[1]
- Results of ongoing biomarker and QoL analyses will be presented at future meetings
- Final OS data will clarify the role for adjuvant *nab*-P + Gem in resected PC
  - Continued investigation of the regimen (eg, in patients with positive lymph nodes or R1 resection as well as those who are not candidates for FOLFIRINOX) is warranted

1. Von Hoff DD, et al. *N Engl J Med.* 2013; 369:1691-1703.

Presented by Margaret Tempero, MD, at ASCO 2019; abstract 4000: Adjuvant *nab*-Paclitaxel Plus Gemcitabine vs Gemcitabine

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Discussion

Strengths

- ~~Well designed~~ ? and executed prospective randomized phase III study
- International multi-center

Limitations

- Negative study
- Final OS pending
- Missed opportunity?

Practice Changing?

- No

UCDAVIS COMPREHENSIVE CANCER CENTER

Adjuvant Pancreatic Cancer Clinical Trials Summary

Trial	Study Arms	# pts	Dates	Where done	DFS (m)	mOS (m)
CONKO-001		354	2007[1] (*1998-04*)	Germany Austria		
ESPAC-4		569	2017[2] (*2008-14*)	GB,Germany, France, Sweden		
PRODIGE 24		493	2018[3] (*2012-16*)	France, Canada		
APACT		866	2019[4] (*2014-18*)	International		

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.

Key Unanswered Questions

- OS benefit
- Role for radiation
  - RTOG 0848
- Neoadjuvant vs adjuvant

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Outline

- Pancreatic Cancer
  - Germline testing
  - PARPi maintenance
  - Adjuvant therapy
  - Immunotherapy

Future = Immunotherapy?

Trial and Strategy	Mechanism of Action	Design of Clinical Trial Table courtesy of and adapted from Eileen O'Reilly, MD
Phase 2 study of GVAX vaccine +/- cyclophosphamide in resectable PDAC NCT00727441	Induction of effector immune cells and inhibition of T regulatory cells via whole cell cancer vaccine	Arm A: GVAX day 1 and 6-10 weeks after surgery on day 15. Arm B: CTX day 0 and GVAX day1 and 6-10 weeks after surgery (day15). Arm C: GVAX day1 and 6-10 weeks after Sx, CTX day1-7 and day 1-7 after surgery PE: Safety, feasibility, and immune response SE: OS and PFS
Phase 1/2 study of neoadjuvant/adjuvant GVAX vaccine +/- nivolumab (anti PD-1). NCT02451982	Induction of effector immune cells with whole cell cancer vaccine +/- removal of negative regulatory signals	Arm A: CTX day 0, GVAX day 1 and 6-10 days after Sx (4 course), Sx day 15 and Adjuvant Arm B: CTX day 0, GVAX day 1 and 6-10 weeks after Sx (4 course), Sx day 15 and nivolumab day 0 and 6-10 weeks after Sx PE: Median IL17A expression in vaccine-induced lymphoid aggregates SE: OS and DFS
Phase 2 study of Ipilimumab (anti-CTLA4) and GVAX vaccine in metastatic PDAC NCT01896869	Induction of effector immune cells with whole cell cancer vaccine +/- removal of negative regulatory signals	Arm A: FOLFIRNOX followed by Ipilimumab+GVAX; Ipilimumab and GVAX will be administered every 3 weeks for 4 doses, then every 8 weeks. Arm B: FOLFIRINOX continuous PE: OS; SE: Adverse effects, PFS, objective response, immune-related PFS, CA19-9
Phase 1 study of antigen-loaded Dendritic cell in combination with chemotherapy NCT02548169	Induction of effector immune cells	Arm A: DC Vaccine + Standard of care chemotherapy in resectable or locally advance disease Arm B: DC Vaccine + Standard of care chemotherapy in metastatic PDAC patients PE: Safety and feasibility; SE: OS, PFS
Phase 2 study of GVAX vaccine and CRS-207 +/- nivolumab in metastatic PDAC patients NCT02243371	Induction of effector immune cells with whole cell cancer vaccine +/- removal of negative regulatory signals	Arm A: CRS day 2 of cycles 3-6, GVAX day 1 of cycles 1 and 2, nivolumab day1 of cycles 1-6. Arm B: CRS day 2 (1×10^9 CFU) of cycles 3-6, GVAX day 1 cycles of 1 and 2 PE: OS; SE: Systemic toxicities, TTP, immune-related PFS, response rate (RECIST), CA19-9
Phase 1 study of ipilimumab with gemcitabine in advanced stage PDAC NCT01473940	Induction of effector immune cells by removing negative regulatory signals	Single Arm Induction: Ipilimumab weeks 1,4,7 and 10; gemcitabine weeks 1-7 and 9-11. Maintenance: Ipilimumab every 12 weeks and gemcitabine once weekly for 3 weeks PE: Safety and adverse effects; SE: OS, PFS, RR and T cell response
Phase 2 study of durvalumab (anti-PD-L1) +/- tremelimumab (anti-CTLA4) in metastatic PDAC NCT02558894	Induction of effector immune cells by removing negative regulatory signals with immune check point inhibitors	Arm A: Durvalumab single agent IV infusion. Arm B: Durvalumab in combination with Tremelimumab IV infusion PE: Objective RR; SE: Duration of response, disease control rate, progression free survival, pharmacokinetics
Phase 1/2A study of pembrolizumab with mFOLFOX in advanced GI cancers NCT02268825	Induction of effector immune cells by removing negative regulatory signals with immune check point inhibitor	Single Arm: Pembrolizumab day 1 of each cycle of FOLFOX (total 14 days) PE: Safety and tolerability in combination with mFOLFOX
Phase 1 study of Nivolumab with Nab-paclitaxel ± gemcitabine in advanced PDAC NCT02309177	Induction of effector immune cells by removing negative regulatory signals with immune check point inhibitor	Arm A: Nivolumab with Nab-paclitaxel Arm B: Nivolumab with Nab-paclitaxel and gemcitabine PE: dose limiting toxicities, safety; SE: OS, PFS, disease control rate, duration of response
Phase I study of Pembrolizumab in combination with hypofractionated RT NCT02303990	Induction of effector immune cells by immune check point inhibitor and sensitization of T cells by RT	Single Arm: Pembrolizumab along with radiation treatment PE: Safety and dose limiting toxicities

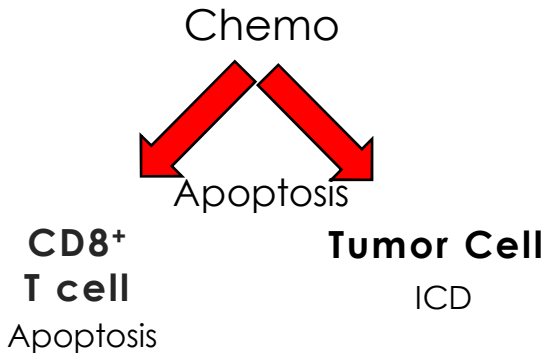
Outline

- Pancreatic Cancer
  - Germline testing
  - PARPi maintenance
  - Adjuvant therapy
  - Immunotherapy
    - IL10
    - CSF1R
    - CD40
    - CpG

Rationale for AM0010 / Chemotherapy Combination to Induce Tumor Immunity

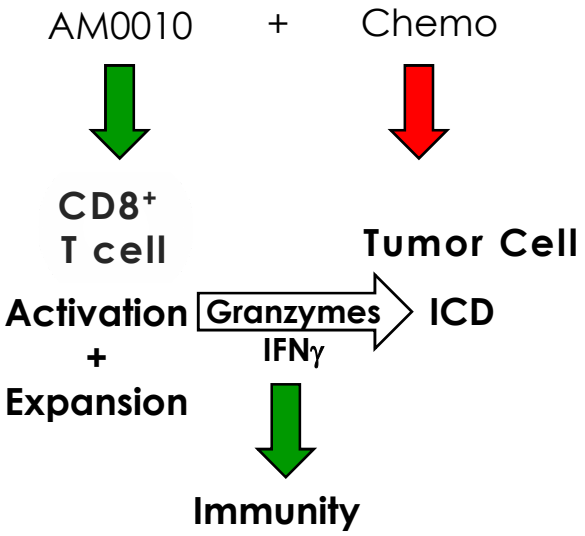
Chemotherapy

- Oxaliplatin induces immunogenic tumor cell death - ICD (Tesniere, Oncogene 2010)
- In the absence of AM0010, chemotherapies also induce apoptosis of CD8+ T cells
- The release of tumor antigens will not trigger an immune response due to a lack of antigen presentation and T cell activation



Chemotherapy + AM0010

- Chemotherapy induces ICD in tumor cell - AM0010 protects CD8+ T cells from apoptosis
  - through STAT3 activation
- IL-10 activates CD8+ T cells to express granzymes and FasL – increase apoptosis of tumor cells
- IL-10 activates CD8+ T cells to induce antigen presentation on tumor cells and macrophages
  - IFNγ expression in CD8+ T cells
- This leads to the expansion of antigen activated, PD1+ CD8+ T cells and tumor immunity

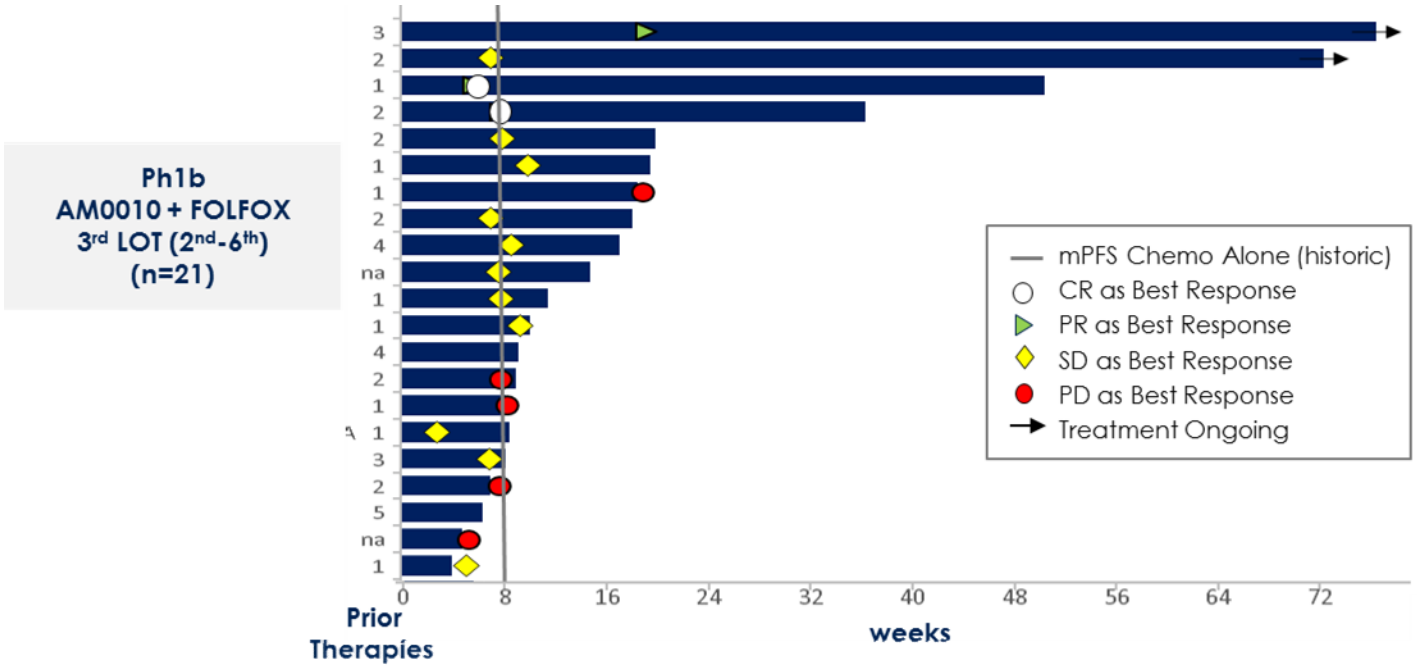


Efficacy of AM0010/ AM0010+FOLFOX in PDAC

Treatment Combo (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	DCR n (%)	ORR (%)	CR (%)	mPFS (Months)	mOS (Months)
AM0010[@] (n=15/22)[+]	3 (2-6)	8 (53%)[*]	0	0	1.7[&]	3.8[&]
AM0010 + FOLFOX (n=19/21)	2 (1-5) (no prior platinum)	15 (79%)	3 (16%)	2[#] (11%)	3.5[&]	10.2[$]
FOLFOX (Zaanan et al BMC 2014)	1	36%	0	0	1.7	4.3

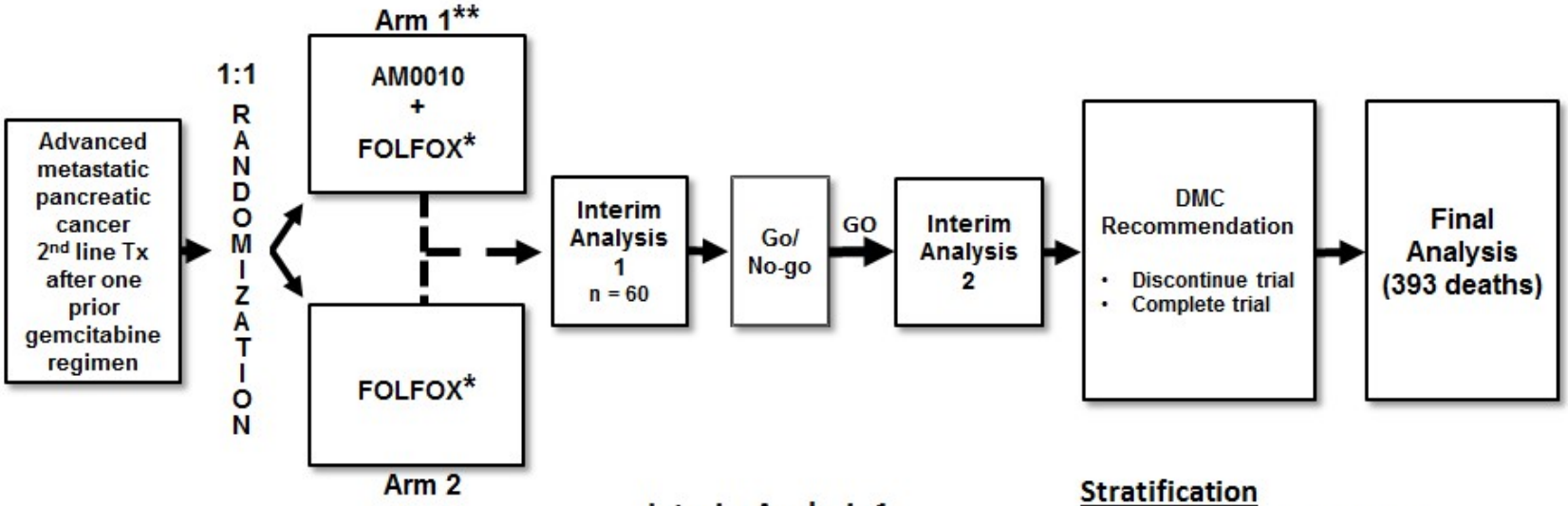
AM0010/FOLFOX Combination: PFS

AM0010/FOLFOX Combo Therapy Induces Durable Clinical Responses in Late Stage Patients (Median 3rd LOT) Compared to FOLFOX in 2nd LOT



- 3.5 mo mPFS of median 3rd LOT (range 2nd – 6th) PDAC patients on AM0010 + FOLFOX (n=21), median follow-up 14.2 months (range 6.8-18.9)
- Compared to FOLFOX alone in 2nd LOT PDAC patients: 1.7 mo mPFS (Zaanan et al. BMC 2014) or 2.8 mo TTP (Pelzer et al Onkologie 2009 (OFF similar to FOLFOX))
- Compared to 3.1 mo mPFS of 2nd LOT PDAC patients on nano-liposomal irinotecan and 5-FU (Wang-Gillam Lancet Onc. 2015)

Phase 3 Pancreatic Study Schema



* Up to 12 cycles of FOLFOX

** Arm 1 in the absence of tumor progression may continue maintenance with AM0010 alone after completion of FOLFOX or FOLFOX intolerance

Interim Analysis 1
Aggregate PK exposure, safety, efficacy analysis

Interim Analysis 2
After 276 deaths (70% of 393 deaths)

Stratification
- Prior Gemcitabine or Prior Gemcitabine/nab-Paclitaxel
- North America vs. Europe vs. APAC

Endpoints
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, Safety

Outline

- Pancreatic Cancer
  - Germline testing
  - PARPi maintenance
  - Adjuvant therapy
  - Immunotherapy
    - IL10
    - CSF1R
    - CD40
    - CpG

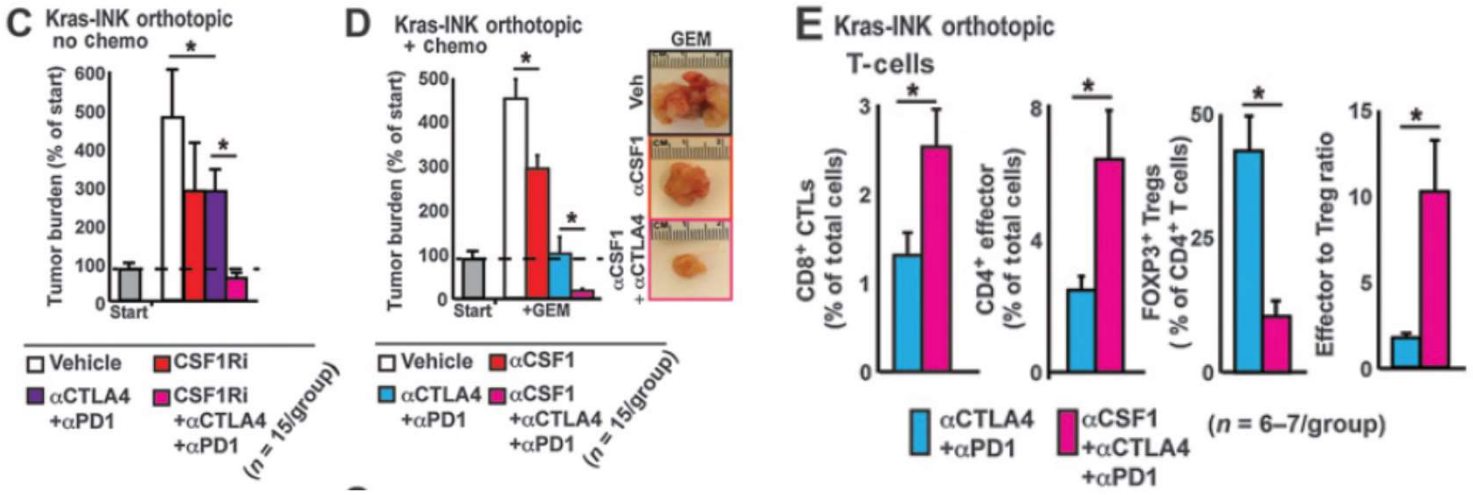
CSF-1R

Microenvironment and Immunology

Cancer Research

CSF1/CSF1R Blockade Reprograms Tumor-Infiltrating Macrophages and Improves Response to T-cell Checkpoint Immunotherapy in Pancreatic Cancer Models

Yu Zhu[1,2], Brett L. Knolhoff[1,2], Melissa A. Meyer[1,2], Timothy M. Nywening[3,4], Brian L. West[5], Jingqin Luo[4,6], Andrea Wang-Gillam[1], S. Peter Goedegebuure[3,4], David C. Linehan[3,4], and David G. DeNardo[1,2,4,7]



Zhu et al. Cancer Res. (2014) 74:5057-69.

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CSF-1R

First-in-human phase I dose escalation and expansion of a novel combination, anti-CSF-1 receptor (cabiralizumab) plus anti-PD-1 (nivolumab) in patients with solid tumors

- 31 evaluable pancreatic cancer patients
- ORR 10%, 6m DCR 13%
- 3 confirmed PR in MSS patients (168+, 27%+, 293 days on)
- 1 prolonged SD (182 days)

Wainberg et al. 2017 SITC annual mtg. Abstract LBA#O42

UCDAVIS COMPREHENSIVE CANCER CENTER

CSF-1R

Followup phase II study ongoing (planned 160 pts):

Arm A: gem/nab-paclitaxel or 5FU+liposomal irinotecan

Arm B: cabiralizumab + nivolumab

Arm C: cabiralizumab + nivolumab + gem/nab-paclitaxel

Arm D: cabiralizumab + FOLFOX

Wainberg et al. 2017 SITC annual mtg. Abstract LBA#O42

UCDAVIS COMPREHENSIVE CANCER CENTER

Outline

- Pancreatic Cancer
  - Germline testing
  - PARPi maintenance
  - Adjuvant therapy
  - Immunotherapy
    - IL10
    - CSF1R
    - CD40
    - CpG

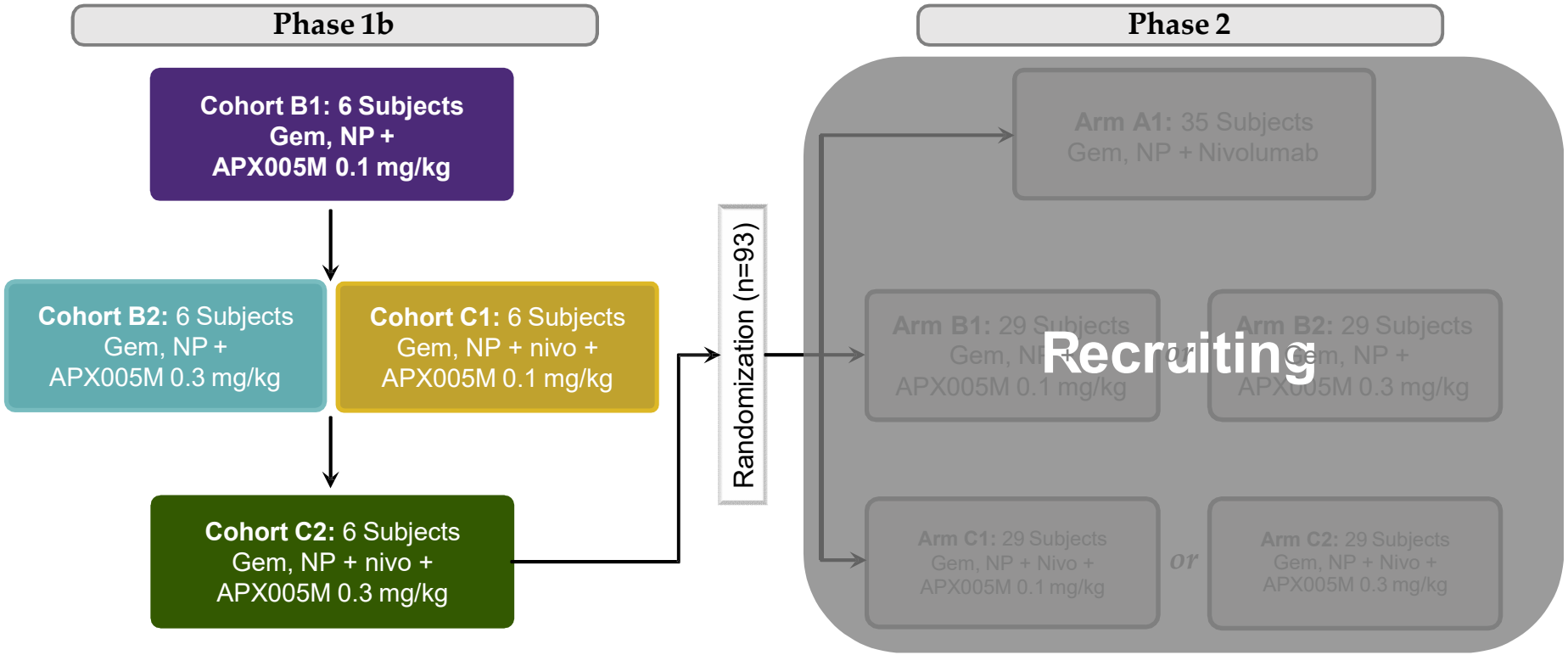
UCDAVIS COMPREHENSIVE CANCER CENTER

Rationale for Combining Chemo/CD40/PD-1

- Chemotherapy releases tumor antigens, which are then presented on antigen presenting cells, including dendritic cells
- Engagement of CD40 primes and activates antigen presenting cells
- In preclinical pancreatic cancer models
  - Gemcitabine, nab-paclitaxel (NP) and agonist CD40 mAb synergize to drive tumor destruction in a T-cell dependent manner[1]
  - Addition of PD-1 mAb to chemo/CD40 further improves survival[2]
- Here, we present the preliminary results of a clinical trial in metastatic PDAC of CD40 agonist, APX005M, with Gem/NP ± nivolumab
  - APX005M is a humanized agonistic IgG1k monoclonal antibody against CD40 with a demonstrated safety profile as a single agent[3]

[1] Byrne and Vonderheide, 2016; [2] Winograd R et al, 2015; [3] Vonderheide RH et al, 2017

Study Design



ClinicalTrials.gov Identifier: NCT03214250

Grade 3/4 Treatment-Related AEs

Occurring in ≥ 20% of N=30 Subjects

MedDRA Preferred Term	Cohort B1 Gem/ NP/ APX005M 0.1 mg/kg (N=7)	Cohort B2 Gem/ NP/ APX005M 0.3 mg/kg (N=7)	Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=8)	Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=8)	Total (N=30)
Lymphocyte count decreased	5 (71.4%)	6 (85.7%)	5 (62.5%)	4 (50.0%)	20 (66.7%)
Neutropenia	3 (42.9%)	5 (71.4%)	1 (12.5%)	3 (37.5%)	12 (40.0%)
Anemia	2 (28.6%)	3 (42.9%)	4 (50.0%)	1 (12.5%)	10 (33.3%)
Fatigue	3 (42.9%)	2 (28.6%)	3 (37.5%)	0	8 (26.7%)
Aspartate aminotransferase increased	0	4 (57.1%)	0	3 (37.5%)	7 (23.3%)
Leukopenia	0	4 (57.1%)	1 (12.5%)	1 (12.5%)	6 (20.0%)

- No grade 3/4 cytokine release syndrome was noted

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Best Overall Response

Determined by RECIST 1.1 in DLT-Evaluable Population

	Cohort B1 Gem/NP/ APX005M 0.1 mg/kg (N=6)	Cohort B2 Gem/NP/ APX005M 0.3 mg/kg (N=6)	Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=6)	Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=6)	Totals (N=24)
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	3 (50%)	2 (33%)	4 (67%)	4 (67%)	13 (54%)
Confirmed PR	2	2	3	4	11
Unconfirmed PR	1	0	1	0	2
Stable Disease (SD)	3 (50%)	3 (50%)	1 (17%)	2 (33%)	9 (38%)
Progressive Disease (PD)	0	1 (17%)	0	0	1 (4%)
Not Evaluable / No Scan	0	0	1 (17%)*	0	1 (4%)*

*Death prior to on-study tumor assessment.

DLT-evaluable Population (N=24)

ORR = 54.2% (95% exact CI: 32.8 – 74.4)

- *Phase 1b Secondary Objective*
- *DCR = 92%*

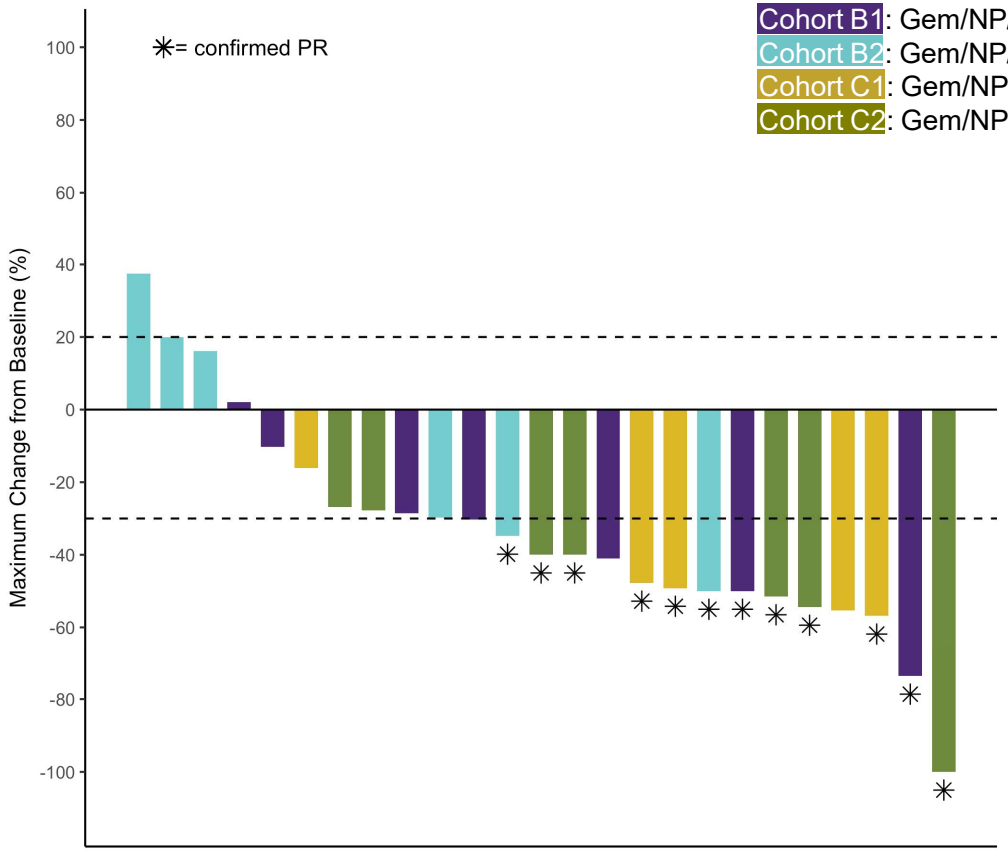
Safety-evaluable Population (N=30)

ORR = 46.7% (14/30) (95% exact CI: 28.3 – 65.7)

- *DCR = 80%*

Clinical Snapshot date: 05MAR19

Percent Change in Sum of Target Lesions (Best Response)



Cohort B1: Gem/NP/APX005M 0.1 mg/kg
Cohort B2: Gem/NP/APX005M 0.3 mg/kg
Cohort C1: Gem/NP/APX005M 0.1 mg/kg + nivo
Cohort C2: Gem/NP/APX005M 0.3 mg/kg + nivo

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Outline

- Pancreatic Cancer
  - Germline testing
  - PARPi maintenance
  - Adjuvant therapy
  - Immunotherapy
    - IL10
    - CSF1R
    - CD40
    - CpG

nature immunology

ARTICLES

https://doi.org/10.1038/s41590-018-0292-y

Metabolic rewiring of macrophages by CpG potentiates clearance of cancer cells and overcomes tumor-expressed CD47–mediated 'don't-eat-me' signal

Mingen Liu[1], Roddy S. O'Connor[2], Sophie Trefely[3,4], Kathleen Graham[1], Nathaniel W. Snyder[3] and Gregory L. Beatty[1,5*]

CANCER DISCOVERY

SD-101 in Combination with Pembrolizumab in Advanced Melanoma: Results of a Phase Ib, Multicenter Study

Antoni Ribas, Theresa Medina, Shivaani Kummar, et al.

Cancer Discov 2018;8:1250-1257. Published OnlineFirst August 28, 2018.

PNAS

Intratumoral injection of a CpG oligonucleotide reverts resistance to PD-1 blockade by expanding multifunctional $CD8^+$ T cells

Shu Wang[a,1], Jose Campos[a,1], Marilena Gallotta[a], Mei Gong[a], Chad Crain[a], Edwina Naik[a], Robert L. Coffman[a,2], and Cristiana Guiducci[a,2]

[a]Discovery, Dynavax Technologies Corporation, Berkeley, CA 94710

Contributed by Robert L. Coffman, September 30, 2016 (sent for review May 31, 2016; reviewed by Wolf Fridman and Miriam Merad)

UCDAVIS COMPREHENSIVE CANCER CENTER

A PILOT STUDY OF INTRATUMORAL SD-101 (TOLL-LIKE RECEPTOR 9 AGONIST), NIVOLUMAB, AND RADIOTHERAPY FOR TREATMENT OF CHEMOTHERAPY-REFRACTORY METASTATIC PANCREATIC ADENOCARCINOMA

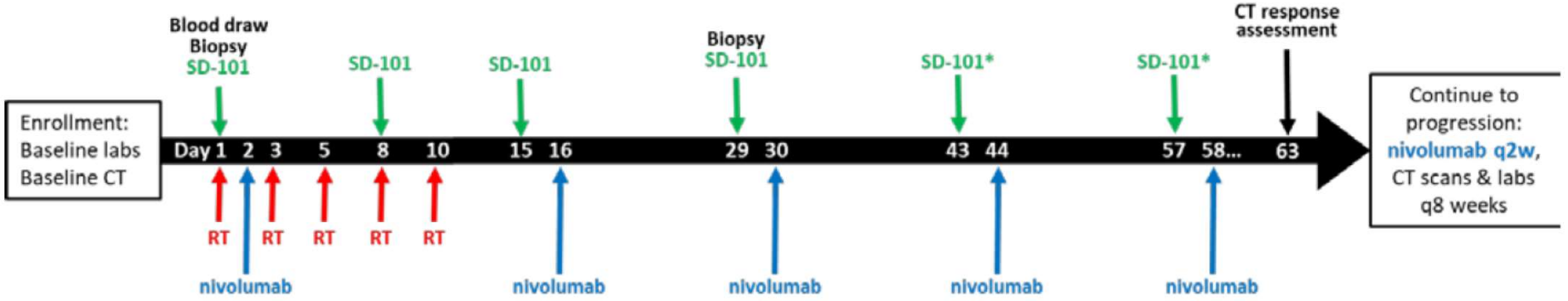
Study Number:	UCDCC#281 (BMS# CA209-8YM; DVX# DISR-018)

General Enrollment Criteria

Metastatic pancreatic cancer with liver metastases
Age ≥18
14 day prior treatment washout period
At least one candidate treatment lesion (liver)
- Accessible for radiotherapy (RT)
- Accessible and safe for repeat intralesional injections

At least one candidate target lesion, outside of the RT field evaluable for response per RECIST v1.1
Adequate hematologic and end organ function
No active autoimmune disease
Patients with previous checkpoint blockade therapy are eligible

UCDAVIS COMPREHENSIVE CANCER CENTER



RT

(Cycle 1, Day 1, 3, 5, 8, 10)

6-10 Gy x 5 fractions

+

Intratumoral SD-101

(Day 1 and 8 of cycle 1, then day 1 of cycles 2, 3, 4*, 5*)

2 mg injection into RT treatment lesion

+

Nivolumab

(Day 2 of each cycle)

240 mg

*optional

1 cycle = 2 weeks (14 days)

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Thank You

Questions?

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