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PARP Inhibition in Pancreatic Cancer; Other Investigational Strategies

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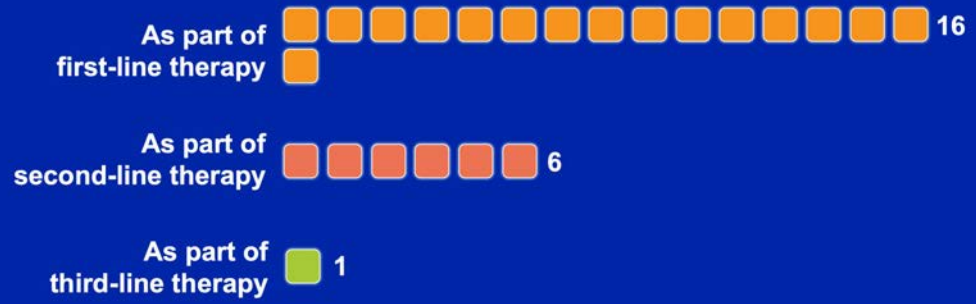
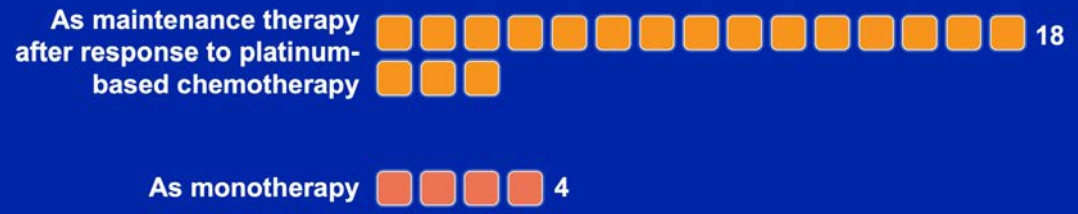
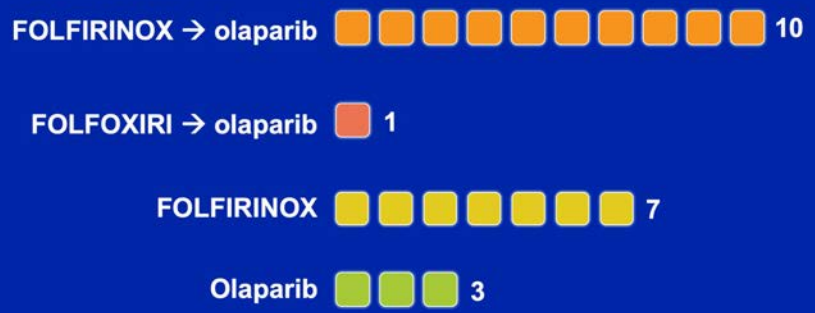
For a patient with metastatic pancreatic cancer and a germline BRCA mutation to whom you would administer a PARP inhibitor, in which line of therapy would you most likely do so?



For a patient with metastatic pancreatic cancer and a germline BRCA mutation to whom you would administer a PARP inhibitor, what treatment strategy would you likely use?



A 65-yo patient is diagnosed with unresectable metastatic pancreatic cancer with a deleterious germline BRCA2 mutation. Regulatory and reimbursement issues aside, which treatment would you recommend?



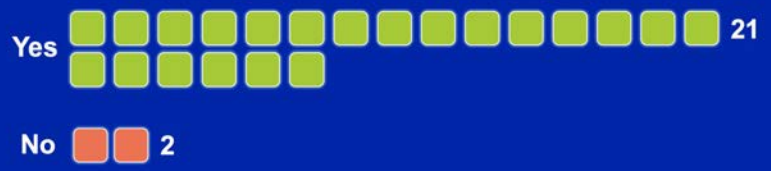
FOLFOX → olaparib (1), mFOLFIRINOX or cis/gem → olaparib (1)

PARP inhibitors and other novel agents

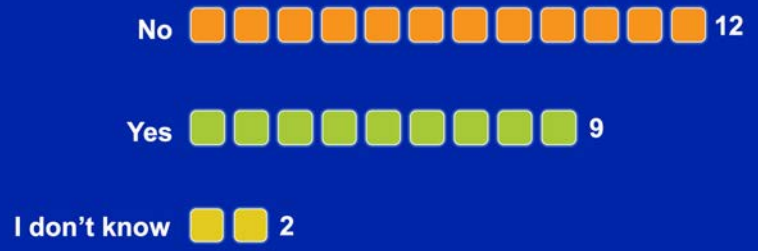
Investigational strategies

- Multiplex somatic and germline testing
- Advantages and disadvantages of liquid biopsy
- PARP inhibitors as maintenance therapy
- Toxicity of PARP inhibitors

Do you routinely order next-generation sequencing for your patients with metastatic pancreatic cancer and good performance status who have received all approved treatment options?



Regulatory and reimbursement issues aside, would you generally administer a PARP inhibitor to a patient with metastatic pancreatic cancer and a germline mutation other than BRCA at some point?



For which germline mutations other than BRCA would you consider administering a PARP inhibitor?

- PALB mutation
- I would consider with somatic BRCA as well as potential other DNA damage (eg. ATM)
- PALB2, ATM, etc.
- All "BRCA-ness" conditions are worth considering
- CHEK2, PALB2 , etc...
- Any non-germ line BRCA
- Pathogenic somatic mutations and potentially other HRD mutations

PARP inhibitors and other novel agents

Investigational strategies

- Multiplex somatic and germline testing
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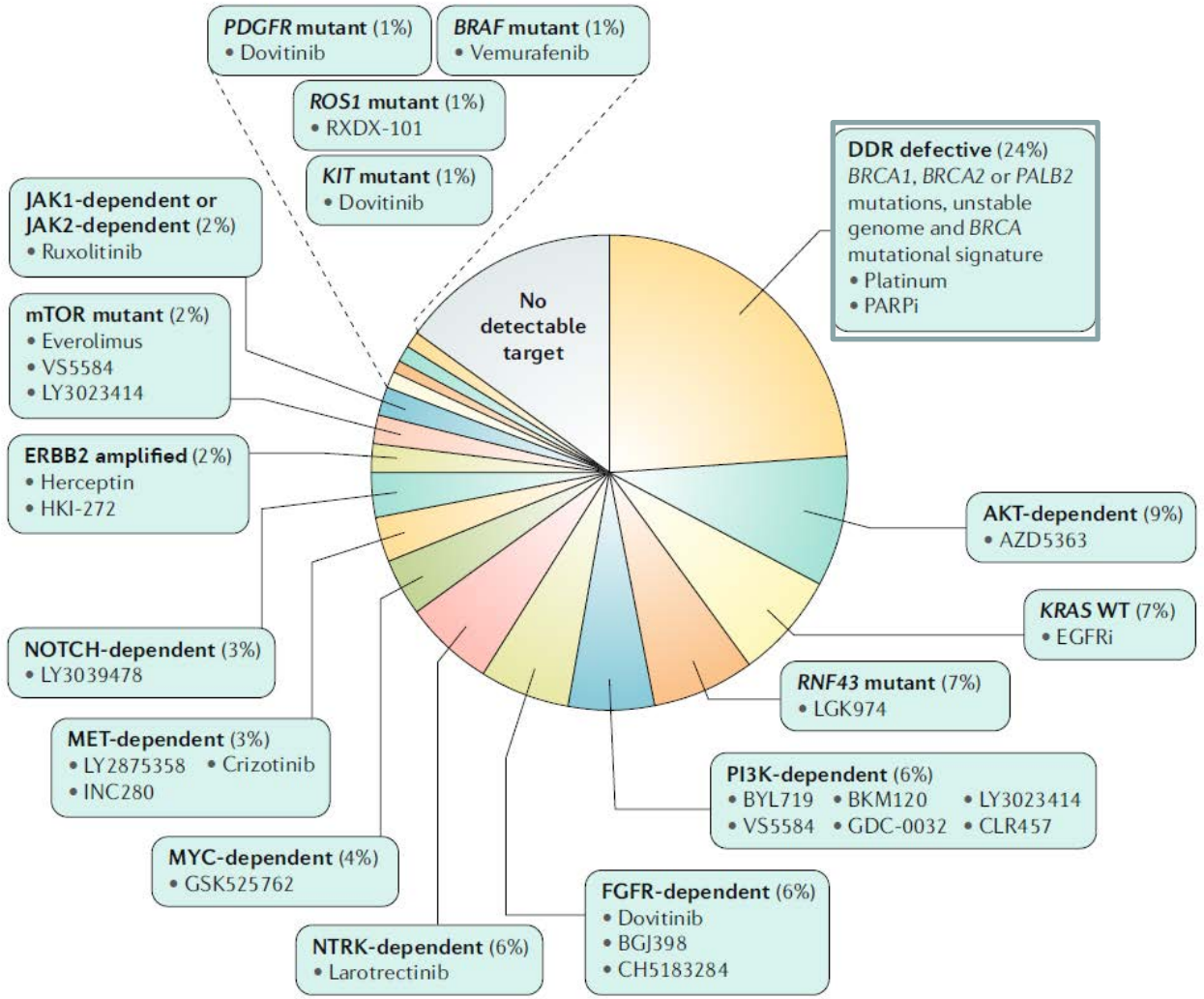
Disclosures

- Participation to advisory boards for Array, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, GSK, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier, Sirtex, Taiho
- Research grants from Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier paid to institution

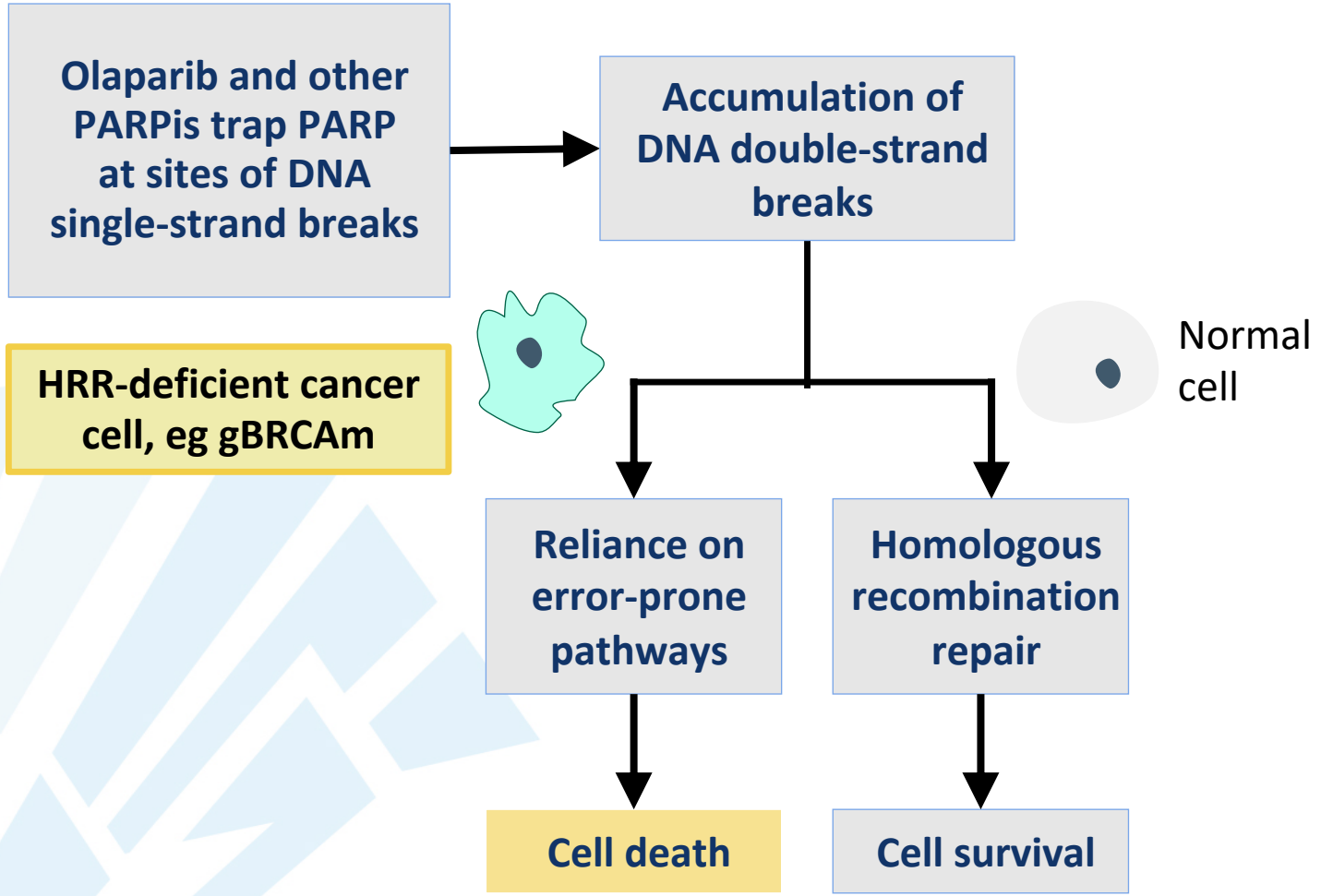
Many druggable alterations



But only very few with proven clinical activity

Collisson et al. Nat Rev Gastroenterol Hepatol 2019

Rationale for PARP inhibition in BRCA-deficient tumours



Demonstrated clinical efficacy in gBRCAm ovarian and breast cancers[2,3]

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;60:547–60; 2. Moore K *et al. New Engl J Med* 2018;379:2495–2505; 3. Robson M *et al. New Engl J Med* 2017;377:523–33

ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D., Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D., Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O'Reilly, M.D., David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D., Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

N Engl J Med. 2019 Jul 25;381(4):317-327.
doi: 10.1056/NEJMoa1903387. Epub 2019 Jun 2.

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

Kindler HL et al. *Proc ASCO* 2019;Abstract LBA4.

Kindler HL et al. *Proc ASCO* 2019;Abstract LBA4.

Patient characteristics

		Olaparib (N=92)	Placebo (N=62)
Age	Median, years (range)	57.0 (37–84)	57.0 (36–75)
Sex, n (%)	Male	53 (57.6)	31 (50.0)
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
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 first-line chemotherapy, n (%)	Measurable Non-measurable or no evidence of disease	78 (84.8) 13 (14.1)	52 (83.9) 6 (9.7)

Patient disposition

	Olaparib (N=92)	Placebo (N=62)
Screened, n	3315	
Found to have a gBRCAm, n (%)	247 (7.5)	
Excluded, n	93	
Disease progression or death	43	
Ineligible	22	
Patient or physician decision	28	
Randomized, n	92	62
Treated, n	90	61
Discontinued treatment, n (%)	60 (65.2)	53 (85.5)
Disease progression by BICR	43 (46.7)	40 (64.5)
Disease progression by investigator assessment	12 (13.0)	9 (14.5)
Adverse event	4 (4.3)	2 (3.2)
Patient decision	1 (1.1)	1 (1.6)
Ineligible	0	1 (1.6)
Continuing assigned treatment at data cut-off*, n (%)	30 (32.6)	8 (12.9)
Median follow-up for progression, months (range)†	9.1 (0–39.6)	3.8 (0–29.8)

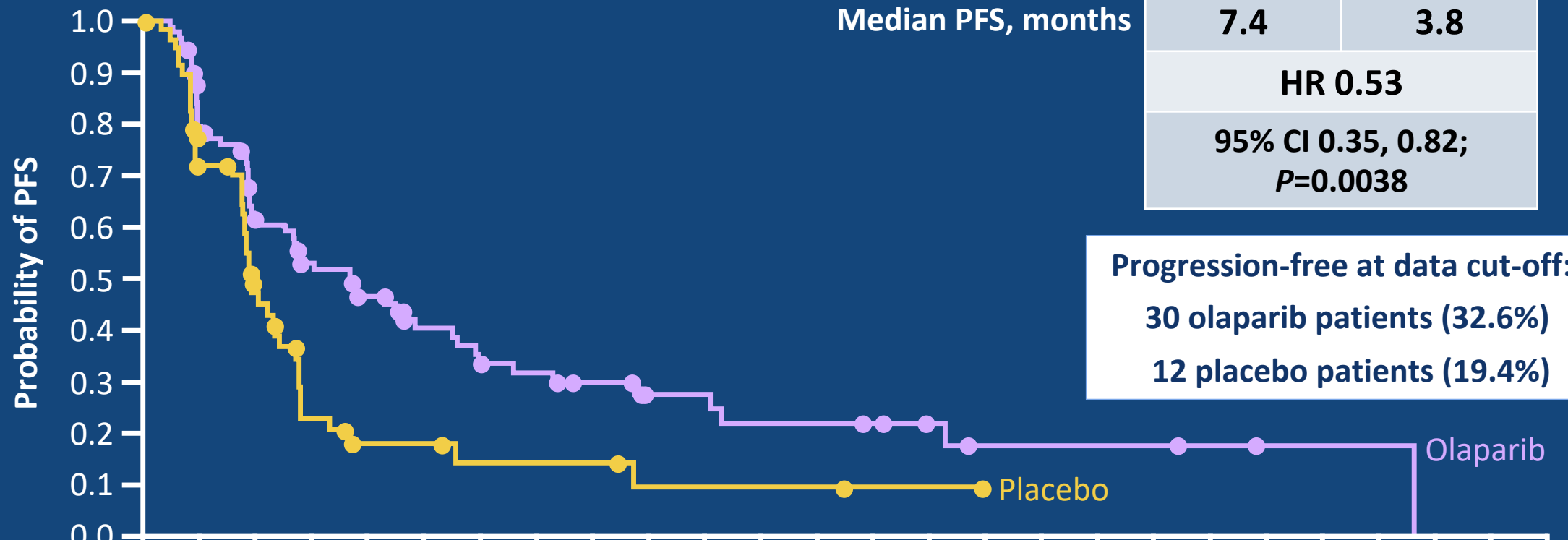
*15 January 2019. †Censored patients. BICR, blinded independent central review

Kindler HL et al. *Proc ASCO* 2019;Abstract LBA4.

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%)



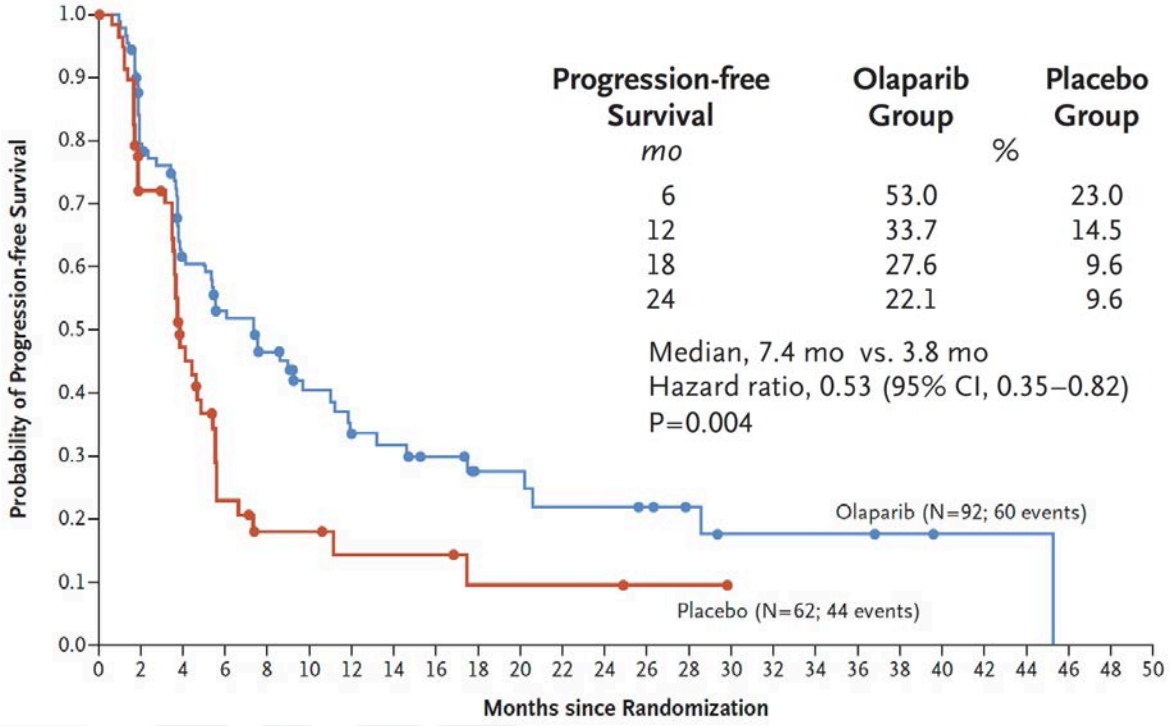
No. at risk																								
Olaparib	92	69	50	41	34	24	18	17	14	10	10	8	8	7	5	3	3	3	3	2	1	1	1	0
Placebo	62	39	23	10	6	6	4	4	4	2	2	2	2	1	1	0								

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

Kindler HL et al. *Proc ASCO* 2019;Abstract LBA4.

POLO Trial: Olaparib vs placebo in gBRCA mutant PDAC -- *Survival Analyses*

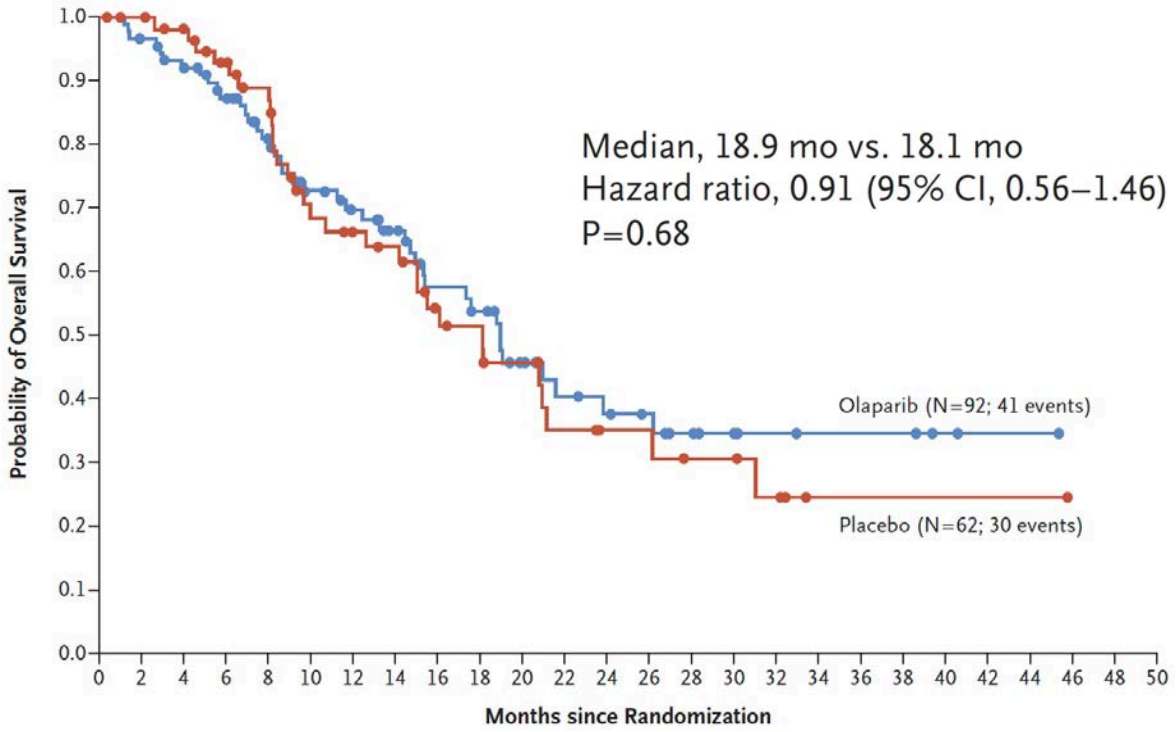
Progression-Free Survival



Progression-free Survival *mo*	Olaparib Group %	Placebo Group %
6	53.0	23.0
12	33.7	14.5
18	27.6	9.6
24	22.1	9.6

Median, 7.4 mo vs. 3.8 mo
Hazard ratio, 0.53 (95% CI, 0.35–0.82)
P=0.004

Overall Survival



Golan T, Van Cutsem E et al. NEJM 2019 July 25;381(4):317-327.

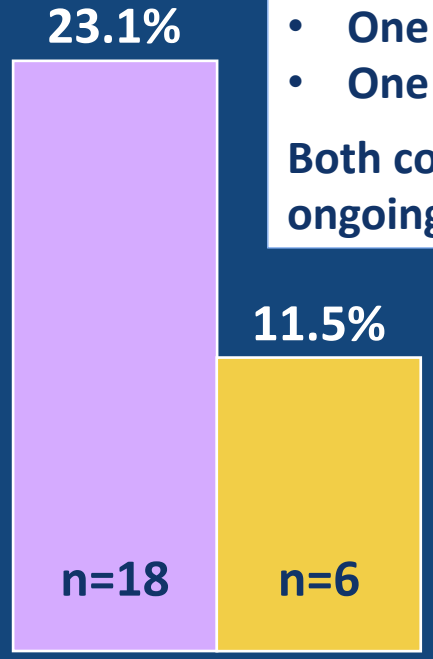
Objective response* in patients with measurable disease by blinded independent central review

Two olaparib arm patients had a complete response to olaparib

Following first-line chemotherapy:

- One had a partial response
- One had stable disease

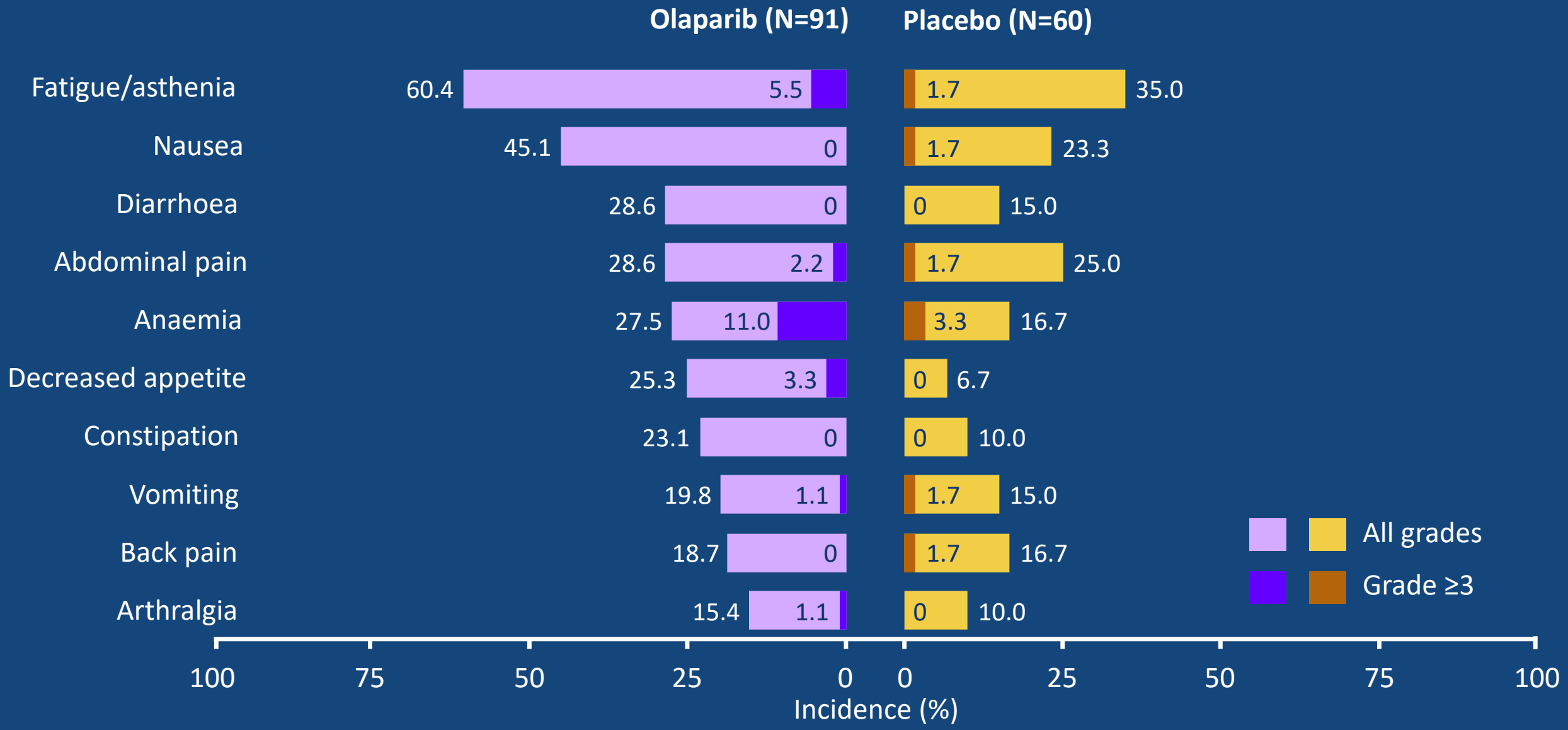
Both complete responses were ongoing at the data cut-off†



Kindler HL et al. *Proc ASCO* 2019;Abstract LBA4.

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

Most common AEs



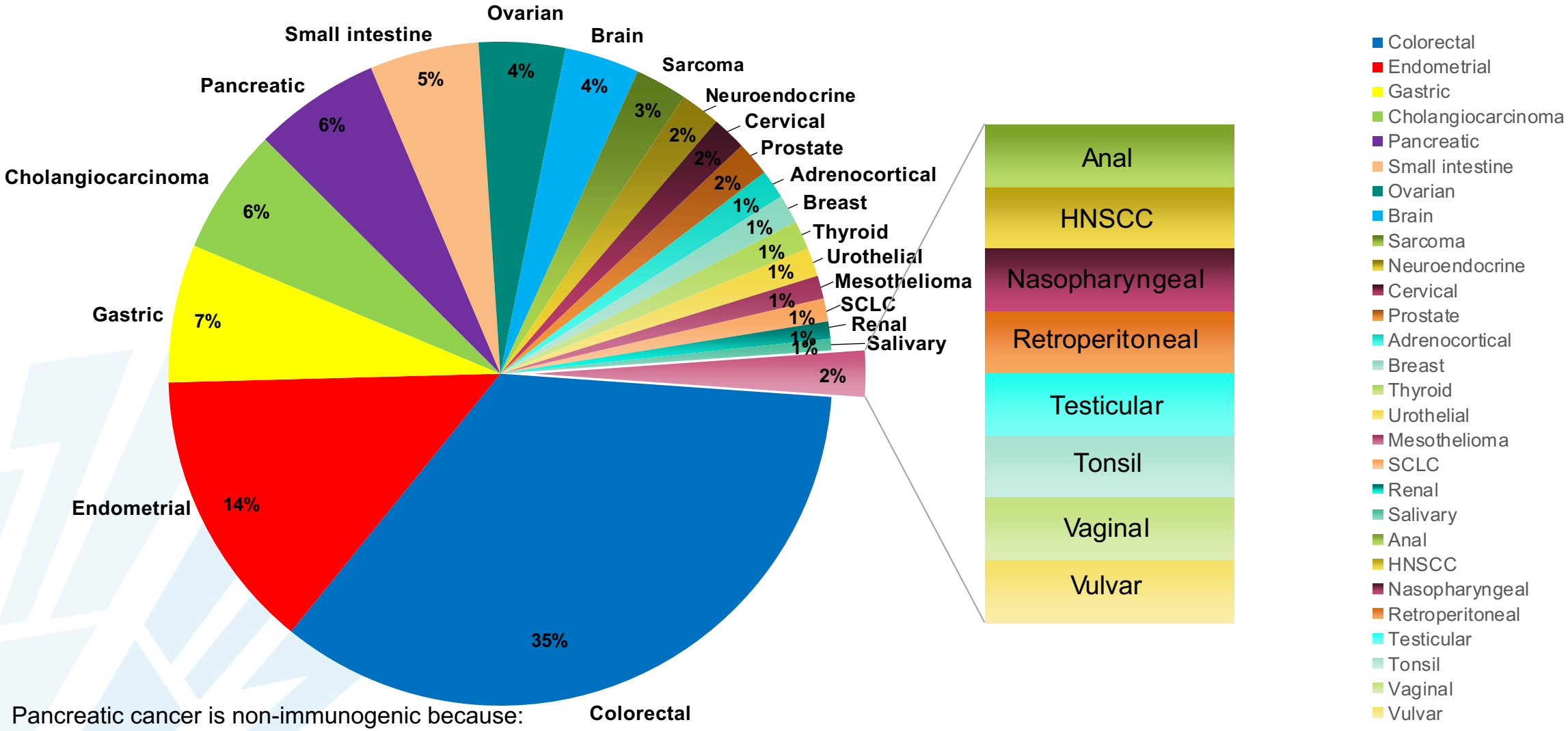
Kindler HL et al. *Proc ASCO* 2019;Abstract LBA4.

Select Ongoing Studies of PARP Inhibitors in Advanced Pancreatic Cancer

Study	Phase	N	Setting	Treatment
NCT03601923	II	32	Germline or somatic HRD DNA repair mutation; ≥ 2nd line	• Niraparib
NIRA-PANC (NCT03553004)	II	18	Germline or somatic DNA repair mutation; Prior chemotherapy as 1st- and/or 2nd-line	• Niraparib
Parpvax (NCT03404960)	I/II	84	Maintenance after platinum-based therapy	• Niraparib + Ipilimumab or Nivolumab
NCT03140670	II	42	Germline or somatic BRCA or PALB2 mutation; Maintenance after platinum-based therapy	• Rucaparib
NCT01585805	II	107	BRCA1 or 2 or PALB2 mutation for patients with no prior therapy; 1st or 2nd line for patients with previous treatment	***No prior therapy*** • Veliparib + Gem/Cis • Gem/Cis ***Previously treated*** • Veliparib

Clinicaltrials.gov, Accessed Jan 23, 2020

KEYNOTE-164 and KEYNOTE-158 Studies
MSI-H Tumor Types



- Pancreatic cancer is non-immunogenic because:
  - immunosuppressive cells and cytokines
  - low tumor mutational burden
  - paucity of T cells in tumor (number and function)
  - ~1% of PDAC are MSI

Diaz L, … Van Cutsem E et al, ESMO 2019: oral presentation

KEYNOTE-164 and KEYNOTE-158 Studies

Antitumor Activity Across Tumor Types

Tumor type	N	CR, n	PR, n	ORR, % (95% CI)	Median (95% CI) PFS, months	Median (95% CI) OS, months	Median (range) DOR, months
Endometrial	49	8	20	57.1 (42.2–71.2)	25.7 (4.9–NR)	NR (27.2–NR)	NR (2.9–27.0+)
Gastric	24	4	7	45.8 (25.6–67.2)	11.0 (2.1–NR)	NR (7.2–NR)	NR (6.3–28.4+)
Cholangio-carcinoma	22	2	7	40.9 (20.7–63.6)	4.2 (2.1–NR)	24.3 (6.5–NR)	NR (4.1+–24.9+)
Pancreatic	22	1	3	18.2 (5.2–40.3)	2.1 (1.9–3.4)	4.0 (2.1–9.8)	13.4 (8.1–16.0+)
Small Intestine	19	3	5	42.1 (20.3–66.5)	9.2 (2.3–NR)	NR (10.6–NR)	NR (4.3+–31.3+)
Ovarian	15	3	2	33.3 (11.8–61.6)	2.3 (1.9–6.2)	NR (3.8–NR)	NR (4.2–20.7+)
Brain	13	0	0	0.0 (0.0–24.7)	1.1 (0.7–2.1)	5.6 (1.5–16.2)	–

Efficacy analyses included all patients who received at least one dose of pembrolizumab. Only confirmed responses are included.
Response was assessed per RECIST version 1.1 by independent central radiological review. Data cutoff: Sept 4, 2018 (KN164); Dec 6, 2018 (KN158).

Diaz L, … Van Cutsem E et al, ESMO 2019: oral presentation

The Tumor Microenvironment Defines the Molecular Properties of PDAC

Transcriptome
of resected PDAC samples

↓

Unraveling the PDAC
transcriptomic landscape

↓

Redefining
PDAC molecular subtypes

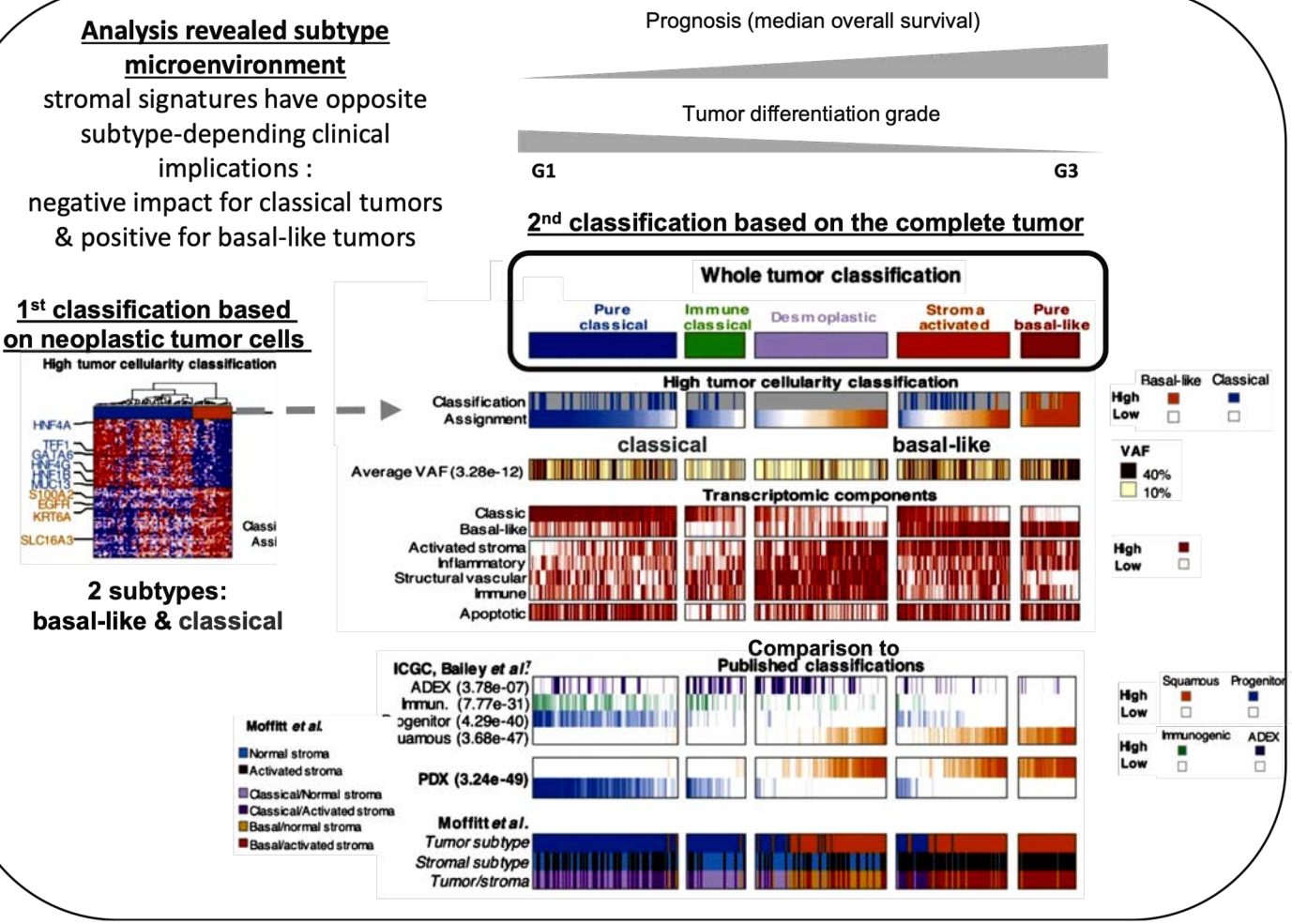
↓

5 PDAC subtypes
defined by specific characteristics
in tumor & tumor microenvironment

New classification
integrating the stromal
and neoplastic compartments of PDAC

RNA-determined subtypes can reflect
patient outcomes → clinical
applicable setting

Analysis revealed subtype microenvironment
stromal signatures have opposite subtype-depending clinical implications :
negative impact for classical tumors
& positive for basal-like tumors



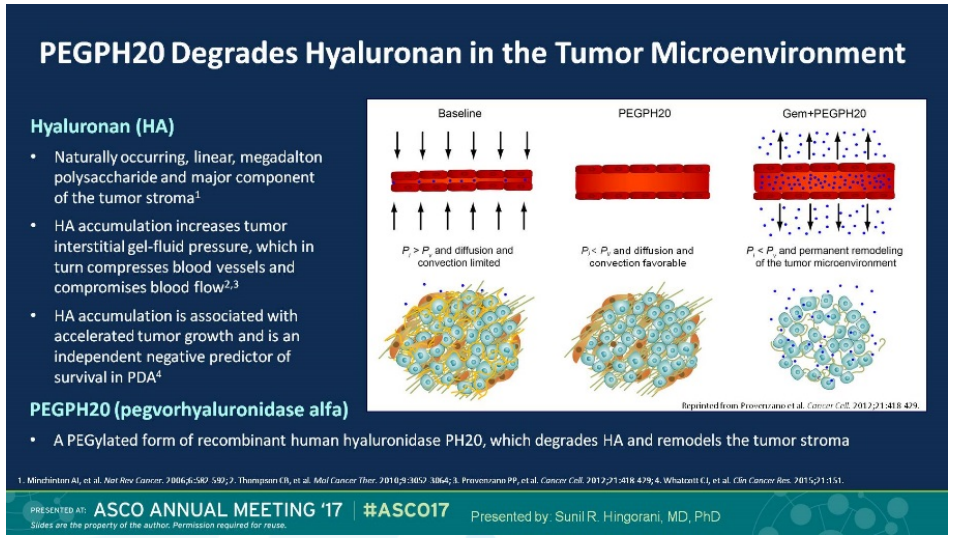
Puleo F, et al. *Gastroenterology.* 2018;155:1999-2013.

Targeting of:

- ✓ **Stroma- and CAF (Cancer-Associated fibroblasts) - derived factors**
- ✓ **Tumor cell–derived factors**
- ✓ **Cytoskeletal regulators**

- ✓ **Structural components of the stroma**
- ✓ **Cellular and other components of the microenvironment**
- ✓ **The stroma-associated immune system**

HALO-301 Study: Gem/*nab*-Paclitaxel +/- PEGPH20 in HA-High Untreated PDAC



Phase 3 trial

- 1L metastatic PDCA
- High-HA

N = 420-570

R 2:1

PAG
PEGPH20 + *nab*-P + Gem

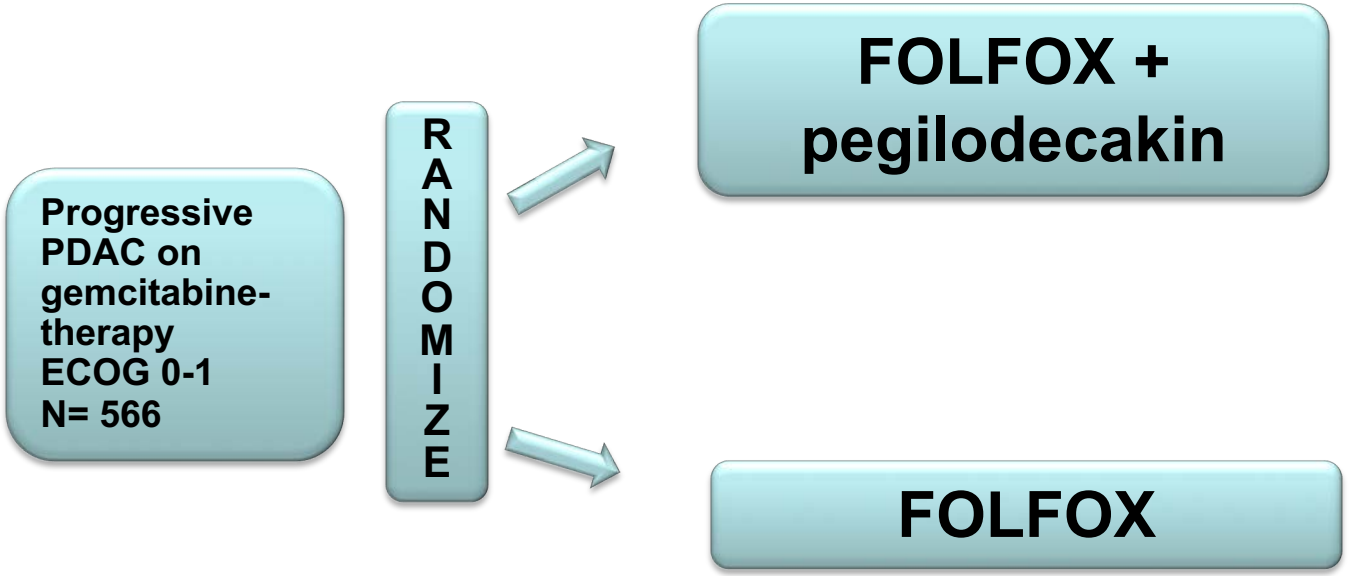
AG
***nab*-P + Gem**

- Primary endpoints: PFS and OS
- Secondary endpoints: ORR, DOR, and safety

ClinicalTrials.gov. NCT02715804.
PI's: Eric Van Cutsem & Margaret Temperov

SEQUOIA: Randomized phase III study of FOLFOX +/- Pegilodecakin (pegylated IL-10) in second line metastatic pancreatic cancer

- IL-10
  - Enhances CD8+ cytotoxicity
  - Suppresses inflammatory cytokines
  - Induces phagocytosis and antigen presentation
  - Induces antigen-specific immunity



Primary endpoint = Overall survival

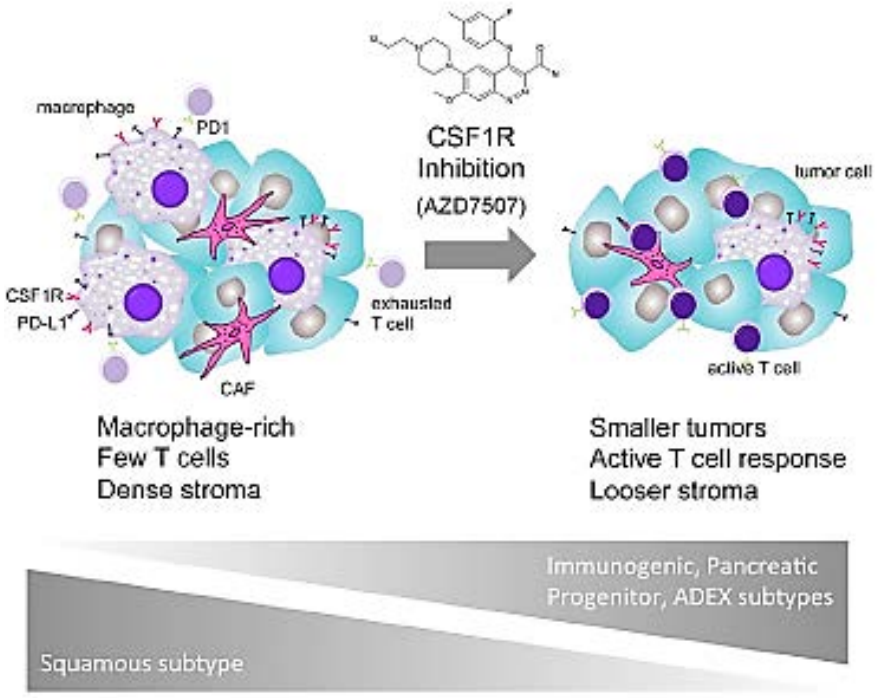
https://clinicaltrials.gov/ct2/show/NCT02923921

Oft M, Cancer Immunology Research, 2:194-199, 2013

Targeting Cellular Components of The Microenvironment:

CSF1R+ Macrophages Sustain Pancreatic Tumor Growth Through T-Cell Suppression and Maintenance of Key Gene Programs that Define the Squamous Subtype

- Macrophages contribute to the squamous subtype of PDAC
- Inhibition of CSFR1 alters the tumor microenvironment and leads to enhanced T cell immune response
- Loss of macrophages leads to change in PDAC gene expression and switches subtype and results in prolonged survival
- Marked differences between targeting macrophages and neutrophils



Colony stimulating factor 1 receptor (CSF1R), also known as macrophage colony-stimulating factor receptor (M-CSFR), and CD115 (Cluster of Differentiation 115)

RANDOMIZE

- **CONTROL**
  Chemo alone
- **Cabiralizumab**
  Nivolumab
- **Cabiralizumab**
  Nivolumab
  AG
- **Cabiralizumab**
  Nivolumab
  mFOLFOX

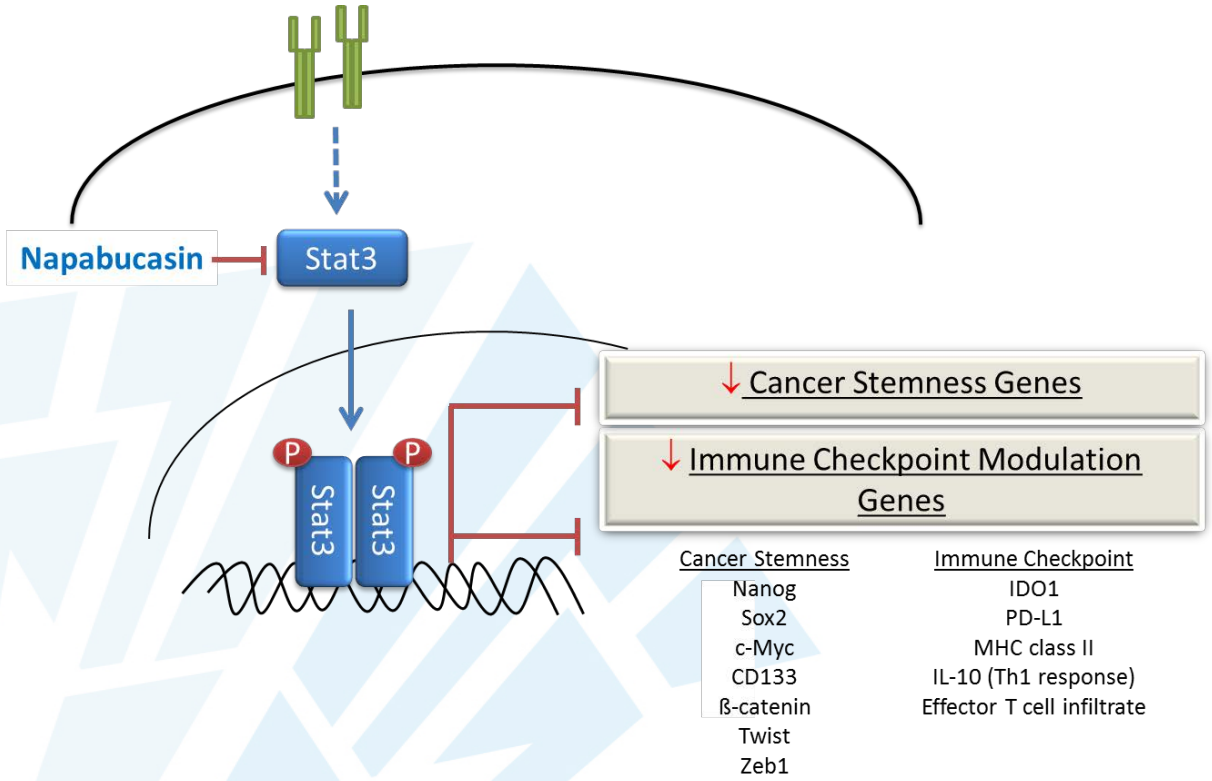
N = 160
Primary endpoint = PFS

Candido JB, et al. *Cell Rep.* 2018;23:1448-1460.

Weinberg ZA, et al. SITC, 2017

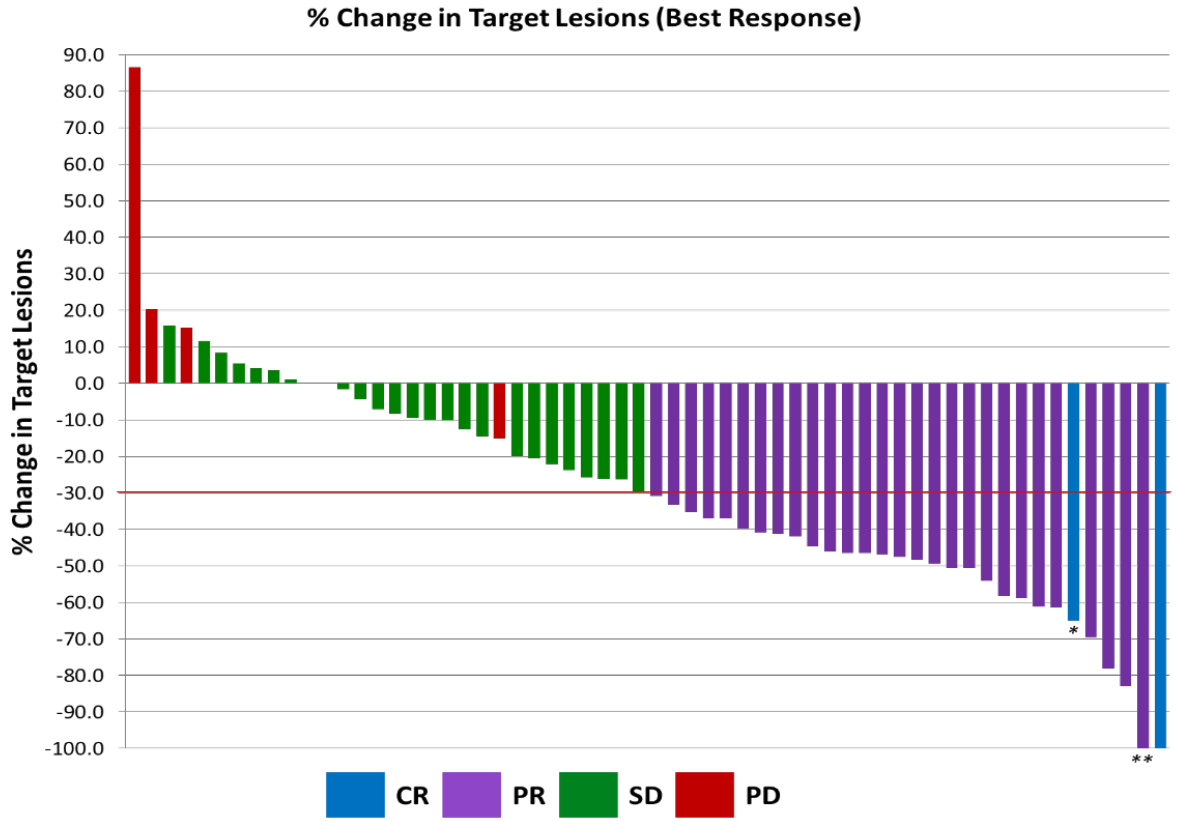
Napabucasin Targets STAT3 Signaling in Cancer Stem-Like Cells

- **Oral**
- **Blocks cancer stem cells self renewal**
- **Kills cancer stem cells, and cancer cells**



Lee C et al. J Clin Oncol. 2008;26(17):2806-2812. Li C, et al. Cancer Res. 2007;67(3):1030-1037. Li Y, et al. Proc Natl Acad Sci U S A. 2015;112(6):1839-1844.

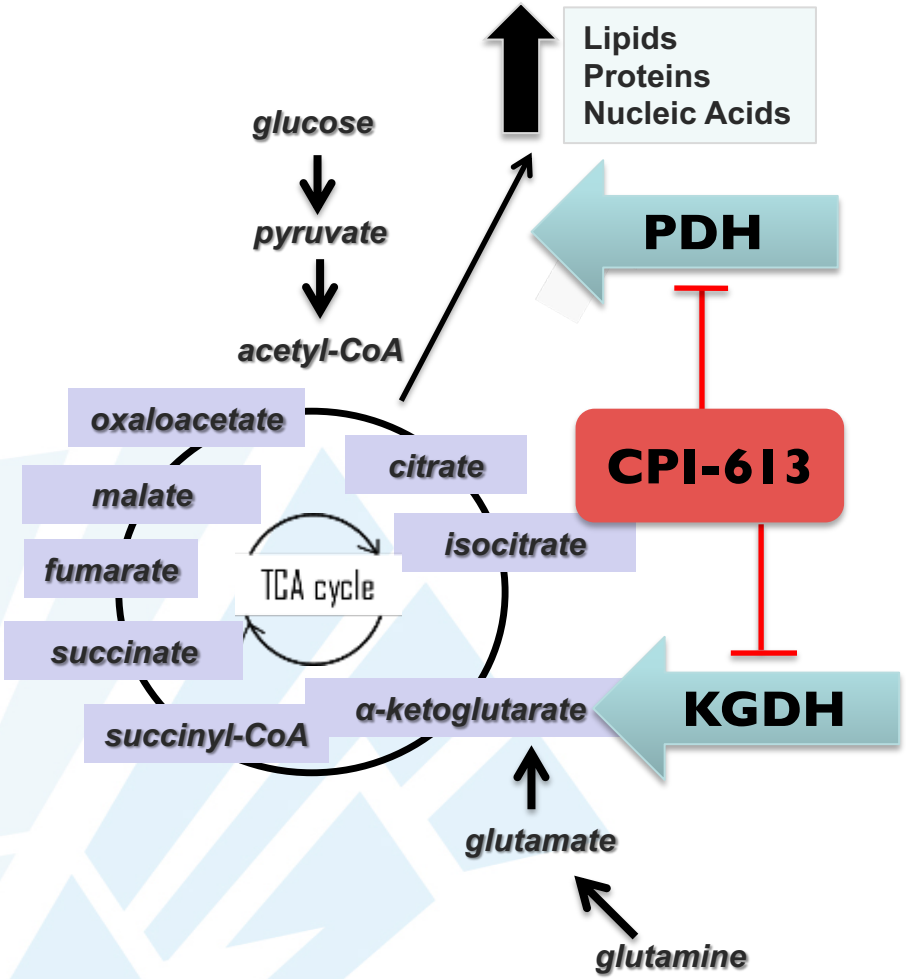
Phase Ib/II study of Gemcitabine/*nab*-Paclitaxel + napabucasin: N = 66



- **Median PFS = 7.1 months**
- **Median OS = 10.7 months**
- **Mainly added GI toxicity**

Bekaii-Saab TS, et al. *J Clin Oncol.* 2017;35(Suppl 4): Abstract 4106.

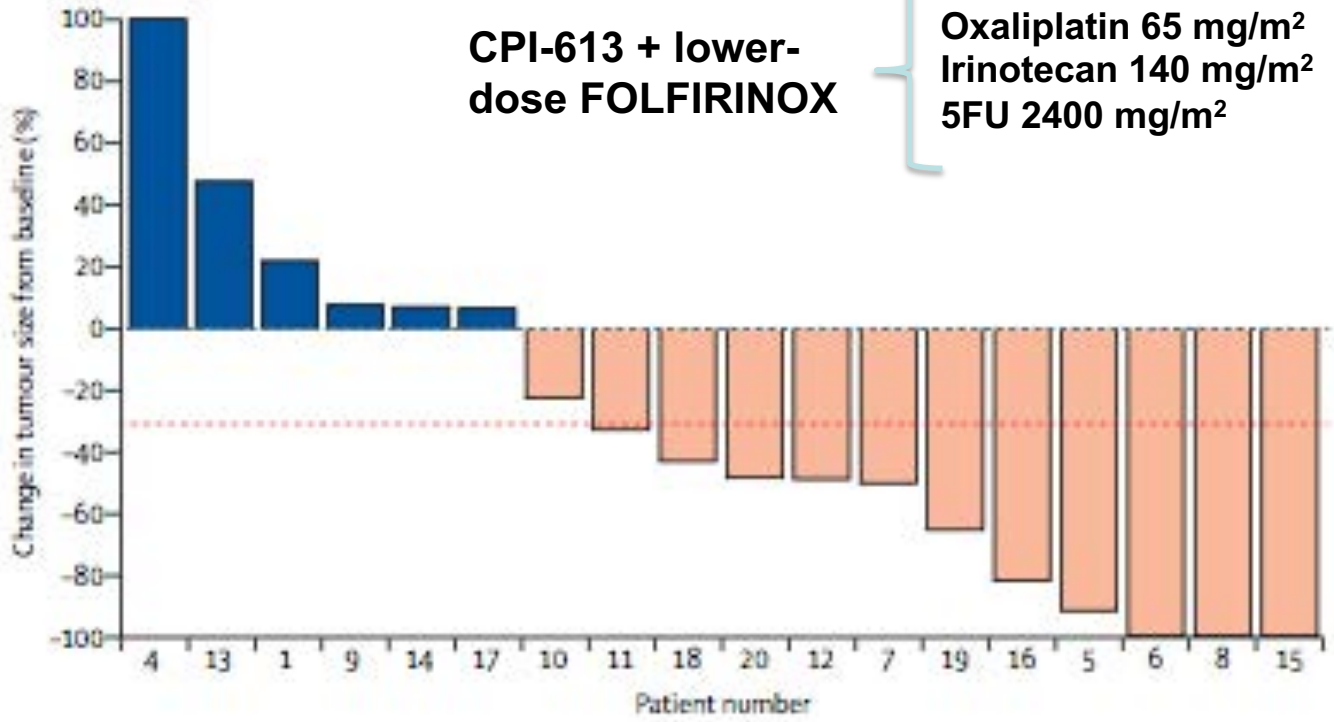
CPI-613: Selectively Blocks PDH and KGDH Triggering Cell Death That Is Highly Selective to Tumor Cells



Pilot clinical trial

CPI-613 + lower-dose FOLFIRINOX

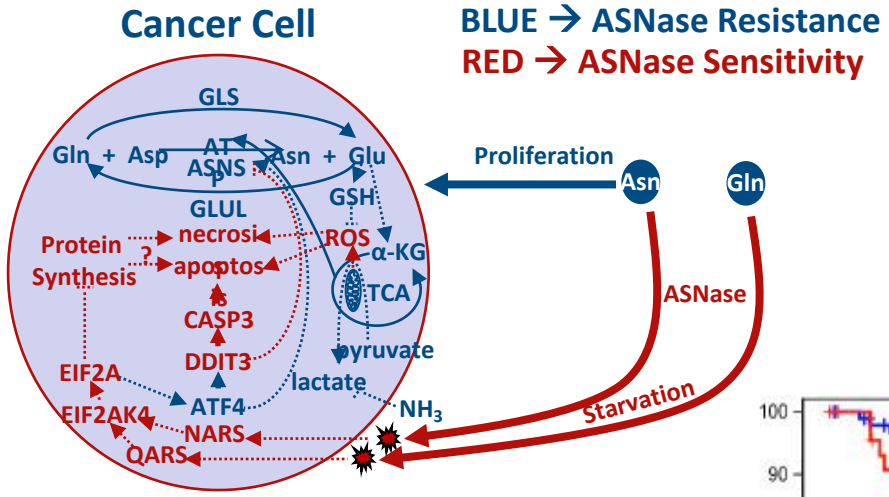
- Oxaliplatin 65 mg/m²
- Irinotecan 140 mg/m²
- 5FU 2400 mg/m²



PDH: pyruvate dehydrogenase
KGDH: alpha-ketoglutarate dehydrogenase

Alistar A, et al. *Lancet Oncol.* 2017;18(6):770-778.

Eryaspase Prolongs Survival in a Pilot Trial in Patients After Failure of Front-Line Therapy



Study design:

- Metastatic pancreatic adenocarcinoma
- Second line, previously treated with gemcitabine based chemotherapy or FOLFIRINOX
- Performance status 0 and 1
- N=141 (70% ASNS 0/1, 30% ASNS 2/3)

RANDOMIZE 2:1

- Gemcitabine or FOLFOX + eryaspase (N = 95)
- Gemcitabine or FOLFOX (N=46)

Follow up

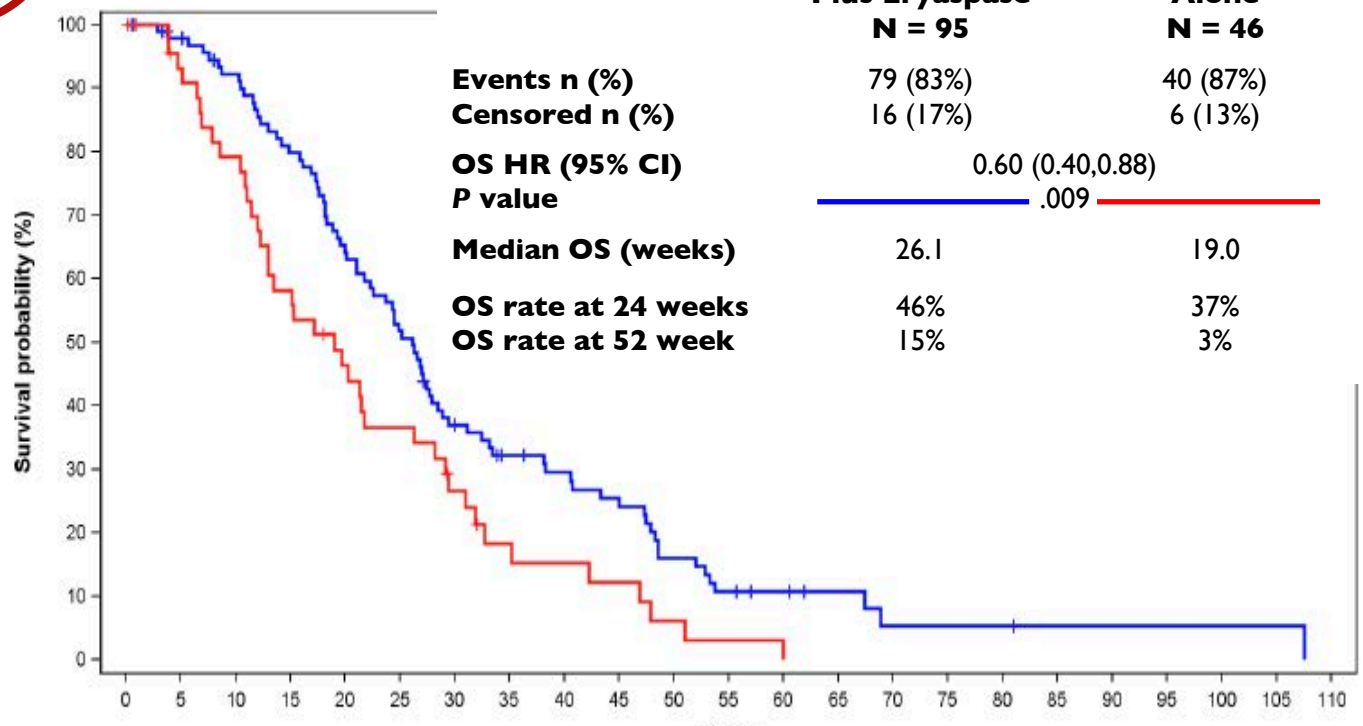
6 cycles of 4 weeks

- **OS advantage regardless of asparaginase synthetase (ASNS) expression level**
- **Similar safety profiles in both groups**

Eryaspase = L-asparaginase encapsulated in erythrocytes

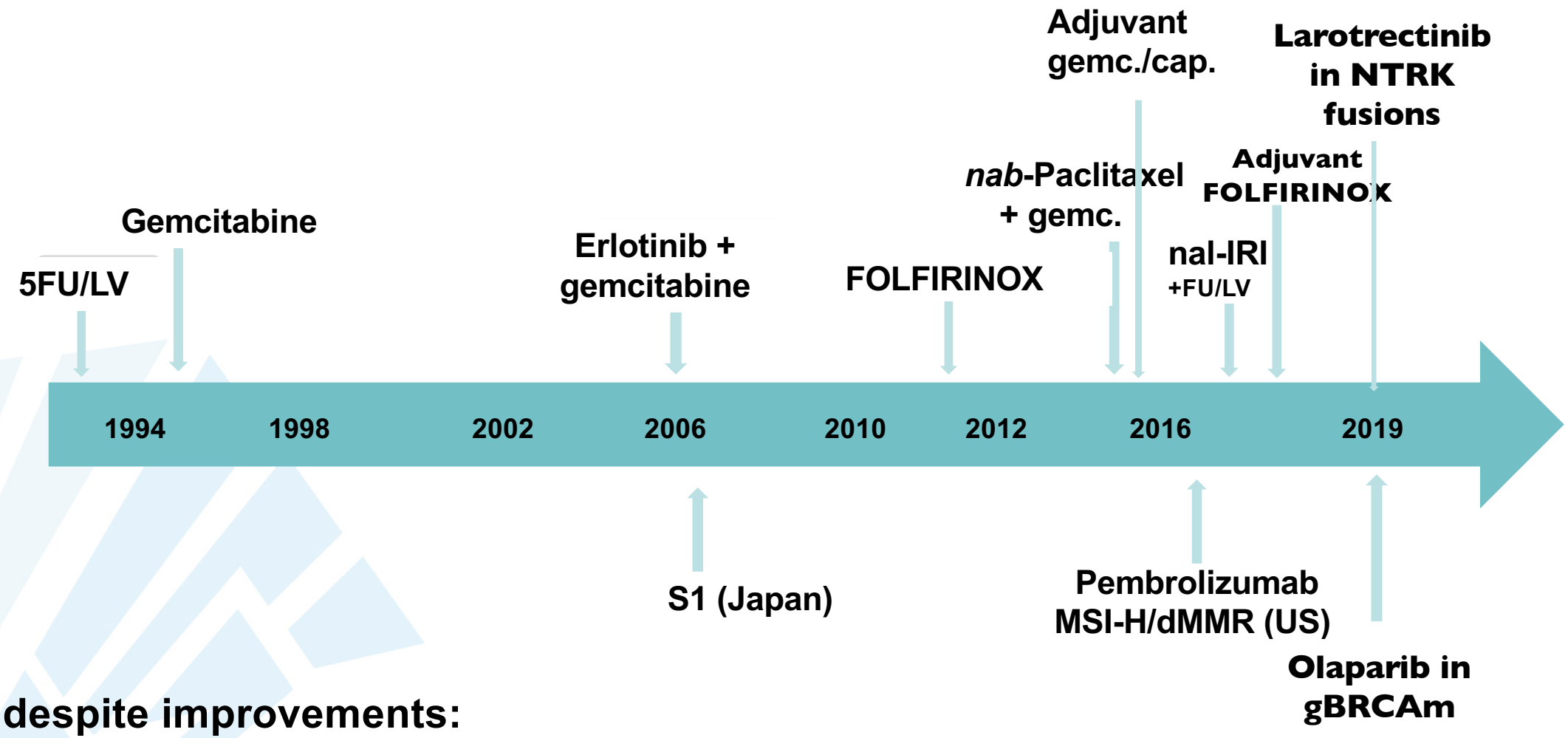
Overall Survival

	Chemotherapy Plus Eryaspase N = 95	Chemotherapy Alone N = 46
Events n (%)	79 (83%)	40 (87%)
Censored n (%)	16 (17%)	6 (13%)
OS HR (95% CI)	0.60 (0.40,0.88)	
P value	.009	
Median OS (weeks)	26.1	19.0
OS rate at 24 weeks	46%	37%
OS rate at 52 week	15%	3%



Hammel P, et al. *Ann Oncol.* 2019

Treatment of Pancreatic Cancer
Key Milestones



But despite improvements:

- Median survival remains under 1 year in advanced stage
- In early stage, 5-year survival rate is only about 20-25%: expertise, high volume, laparoscopic