Pancreatic and biliary cancers: targeted and precision therapies

Jean-Luc Van Laethem,MD,PhD

BSMO-Bordet symposium 2019

- NO DISCLOSURE

ARE WE READY FOR PRECISION THERAPY ?

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- Therapeutic update in PDAC and perspectives
- Therapeutic update in biliary tract cancer and perspectives
- Relevant targets in practice
- Incremental/maintenance strategies?

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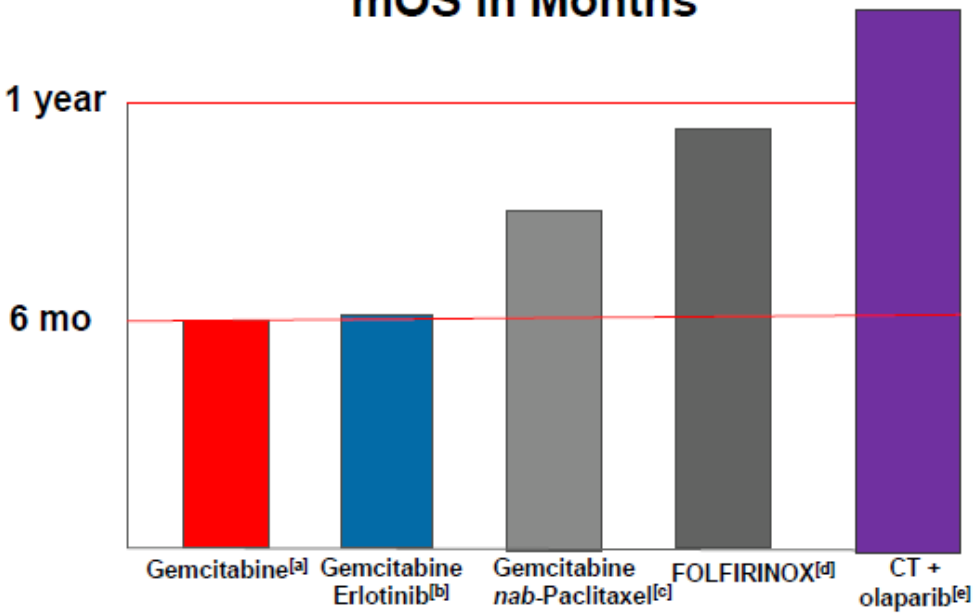
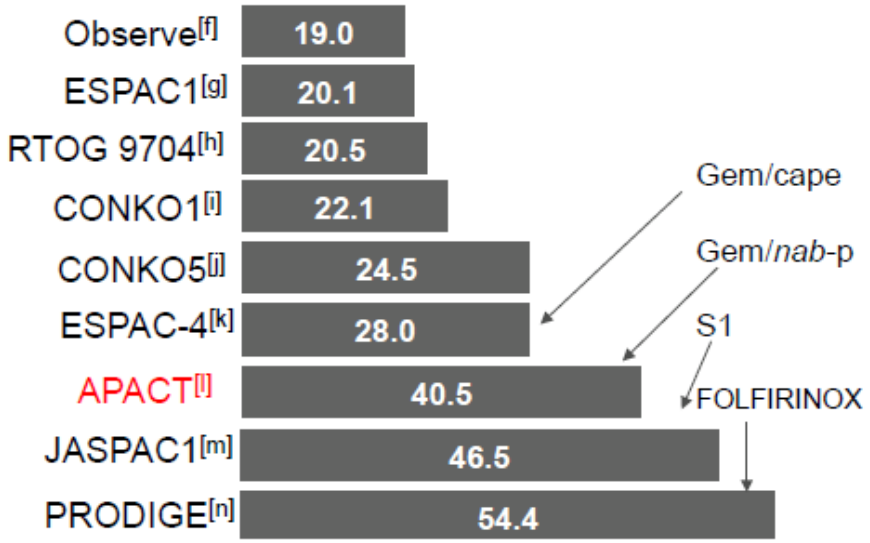
Incremental Improvement in Systemic Therapies That Are Largely Based on Cytotoxic Drugs

Metastatic mOS in Months



Localized/Resectable mOS in Months



FOLFIRINOX = 5FU, leucovorin, irinotecan, oxaliplatin; mOS = median overall survival.

a. Burris HA 3rd, et al. *J Clin Oncol.* 1997;15:2403-2413; b. Moore MJ, et al. *J Clin Oncol.* 2007;25:1960-1966; c. Von Hoff DD, et al. *N Engl J Med.* 2013;369:1691-1703; d. Conroy T, et al. *N Engl J Med.* 2011;364:1817-1825; e. Golan T, et al. *N Engl J Med.* 2019;381:317-327; f. Klinkenbijl JH, et al. *Ann Surg.* 1999;230:776-785; g. Neoptolemos JP, et al. *N Engl J Med.* 2004;350:1200-1210; h. Regine WF, et al. *Ann Surg Oncol.* 2011;18:1319-1326; i. Oettle H, et al. *JAMA.* 2007;297:267-277; j. Sinn M, et al. *J Clin Oncol.* 2017;35:3330-3337; k. Neoptolemos JP, et al. *Lancet Oncol.* 2017:389:1011-1024; l. Tempero MA, et al. ASCO® 2019, Abstract 4000; m. Uesaka K, et al. *Lancet.* 2016;388:249-257; n. Conroy T, et al. *N Engl J Med.* 2018;379:2395-2406.

WHICH TREATMENT IN 2019 IN MPDAC?

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Which treatment in 2019?			
First Line option	FOLFIRINOX..→ Maintenance ?	Gemcitabine + Abraxane	Gemcitabine
Second line options	Gemcitabine Gemcitabine + Abraxane Gemcitabine + Cisplatine	Nal-IRI + 5FU Oxaliplatin + 5FU FOLFIRINOX	Nal-IRI + 5FU Oxaliplatin + 5FU
Third line options	Clinical trials… NGS-driven?		

Ducreux M, Seufferlein T, Van Laethem JL et al. Semin oncol 2018

FAILURE OF TARGETED THERAPIES IN UNSELECTED POPULATIONS IS A REALITY AND A… PITY

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Drugs and Targets That Failed in Clinical Trials Involving Pancreatic Adenocarcinoma: December 2015 - July 2019

Drug	Target/Mechanism	Phase	Number of Patients
Evofosfamide	Alkylator (Hypoxia)	III	694
Ruxolitinib	JAK1/2	III	Early termination
Necuparanib	Heparan mimetic	I/II	128
Masitinib	TKI (Kit, Lyn, Fyn)	III	353
Vandetanib	TKI (VEGFR2, RET, EGFR)	II	142
Algenpantucel-L	Vaccine	III	722
CRS-207 + GVAX	Vaccine	IIb	240
Tarextumab	Notch2/3	II	177
Demcizumab	DLL4	II	204
^{90}Y-Clivatuzumab tetraxetan	MUC1	III	334
Apatorsen	HSP27	II	132
Z-360	CCK2	II	167
Simtuzumab	LOX-2	II	240 (159)
MM-141	IGF-1R/ErbB-3	II	88
Ibrutinib	BTK	III	424
Napabucasin	STAT3	III	> 1100

MOVING TO TARGETED/PRECISION THERAPIES IN PDAC?

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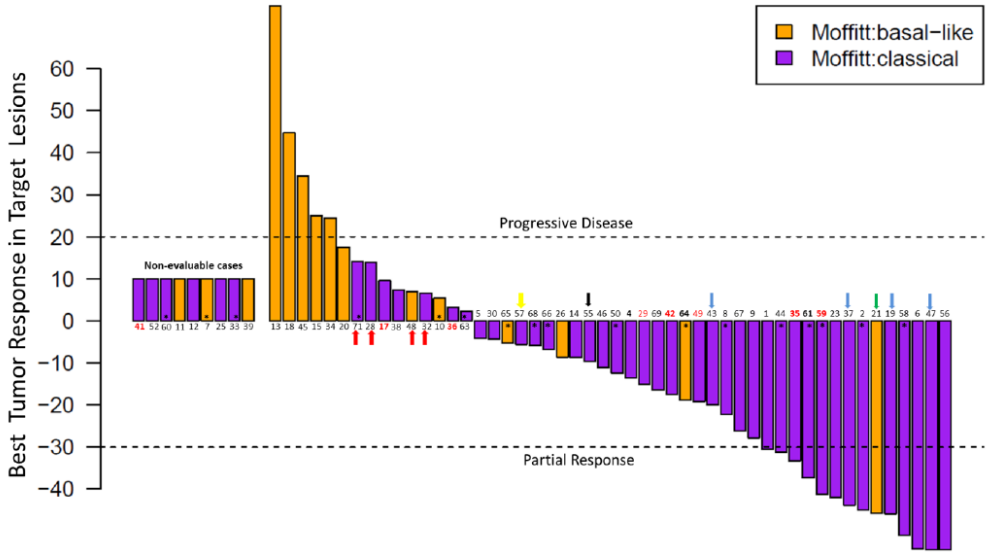
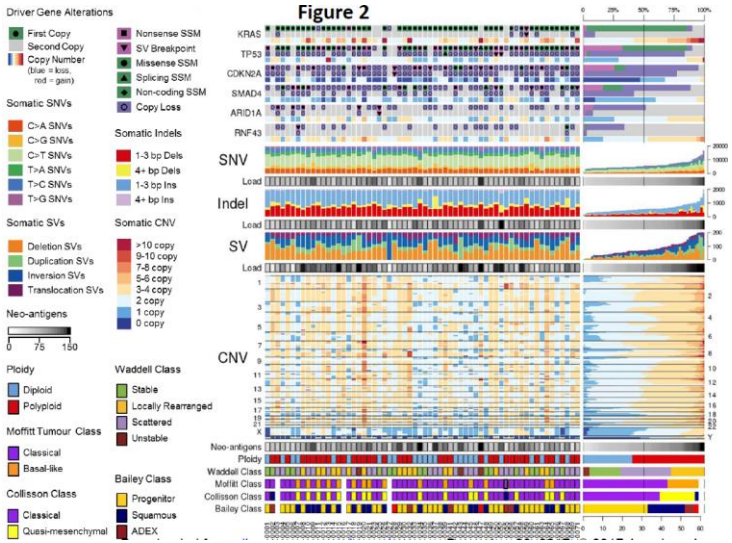
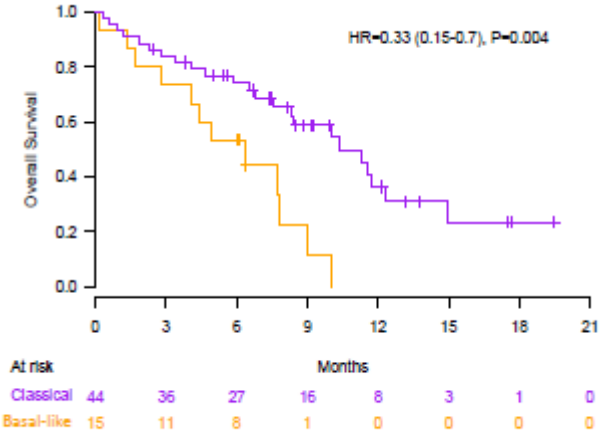
- Mutational profiling
  - Kras :undruggable ! But .. Ki ras codon 12 c is ? (phase I)
  - BRCA → HRR…DDR genes
  - NTRK
  - NRG1 (ligand of ERBB3-4) in RAS WT
- « Targeted » therapy in (enriched) populations
  - stroma :HA ++ (IHC)
  - Metabolic (tumor fuel) pathways : L-asparaginase, mitochondria metabolism
- Genomics/transcriptomics driven therapy
  - Subtyping PDAC :Classical vs basal-like vs …. immunogenic?
- Immuno-oncology…
  - MSI-H :1% !
  - CAF, TAM, microenvironment…priming strategies

CLINICAL APPLICATION OF GENOMICS





Response to chemo
Mainly Folfirinox
for classical subtype



Aung KL, CCR 2017

Real-time Genomic Characterization of Advanced Pancreatic Cancer to Enable Precision Medicine

Andrew J. Aguirre[1,2,3,4], Jonathan A. Nowak[1,4,5], Nicholas D. Camarda[1,2,6,7], Richard A. Moffitt[8],

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Genomic Precision Medicine in Advanced Pancreatic Cancer

RESEARCH ARTICLE

71 pts:
-48% genomic alterations
-18% germline alterations

30% molecular therapies

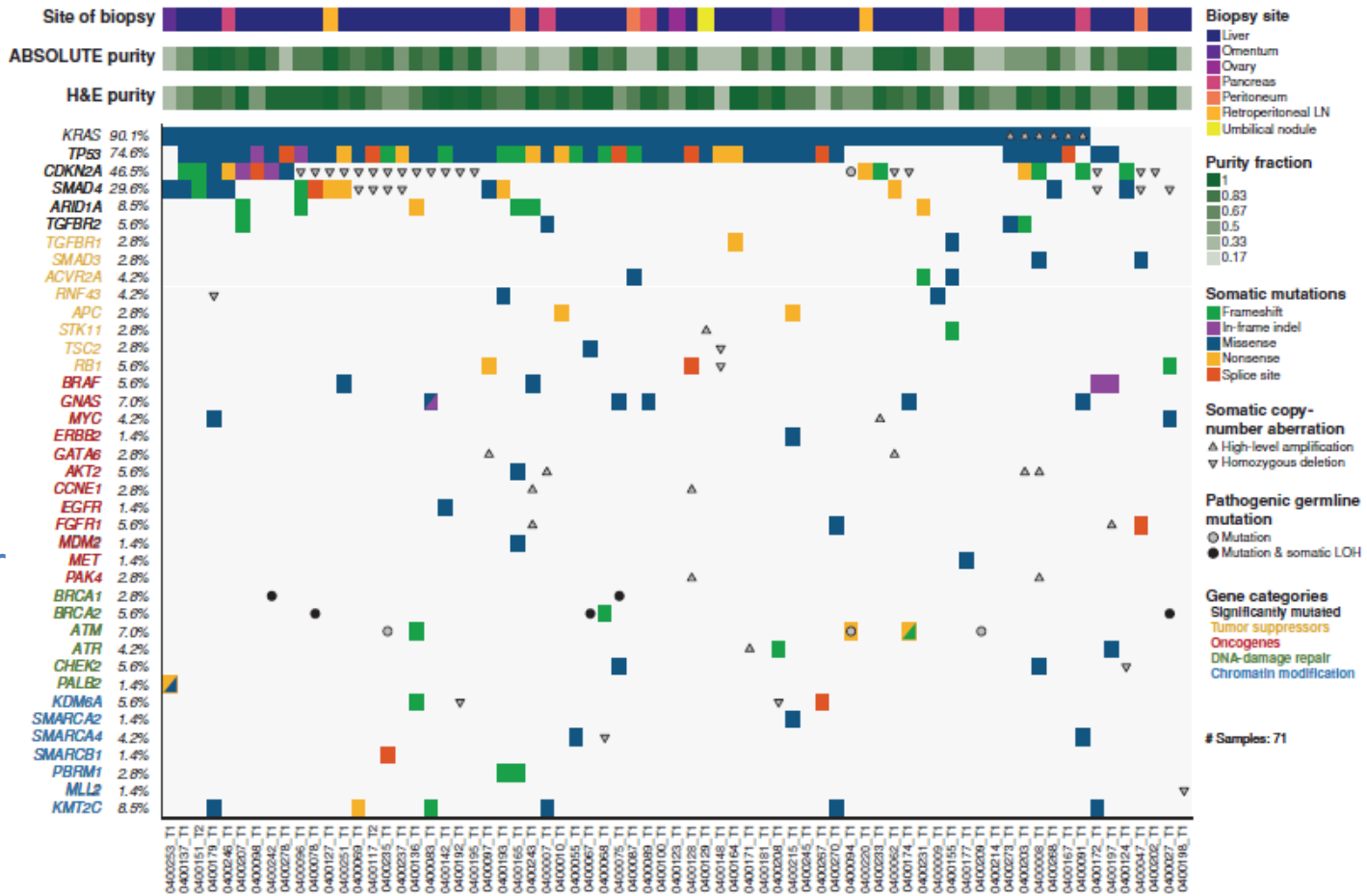
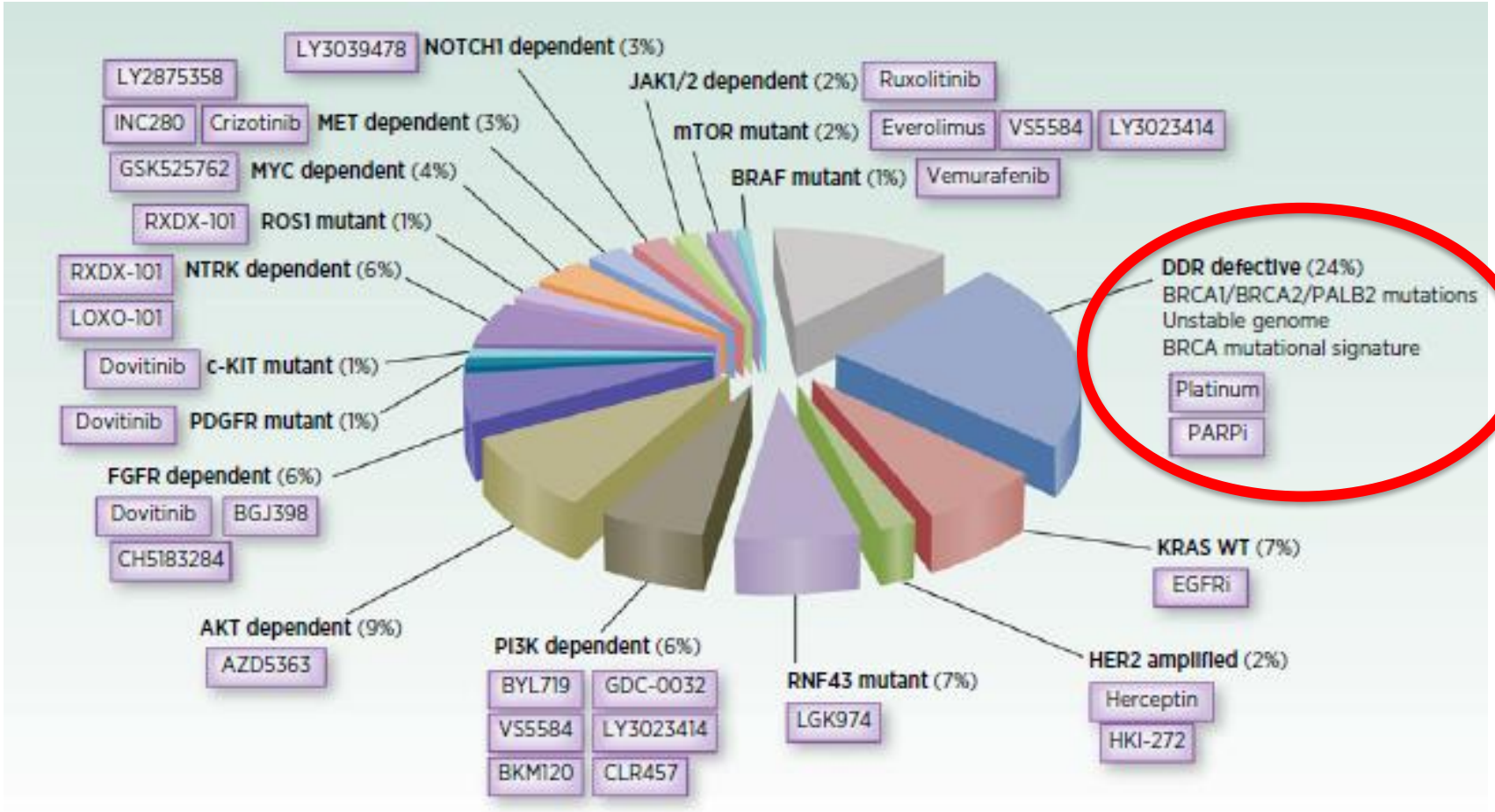


Table 2. Patients on PancSeq protocol who underwent treatment with experimental agents

Identifier	Gender	Age (y)	Stage	Prebiopsy treatments for advanced disease	Genomic features	Post-biopsy treatments
0400068_T1	M	44	Metastatic	No prior chemotherapy	***BRCA2***, *KRAS*	FOLFIRINOX–PARP inhibitor (OL)
0400075_T1	F	58	Metastatic	No prior chemotherapy	*CHEK2*, *KRAS*, ***gBRCA1***	FOLFIRINOX–PARP inhibitor vs. placebo (CT)
0400078_T1	F	39	Metastatic	GA/JAK inhibitor (CT), FOLFIRINOX	*KRAS*, *CDKN2A*, ***gBRCA2***	UBA1 inhibitor (CT)–PARP inhibitor (OL)
0400096_T1	M	57	Metastatic	No prior chemotherapy	*KRAS*, *CDKN2A*	FOLFIRINOX–GA/anti-MUC5AC mAb (CT)
0400097_T1	M	48	Metastatic	No prior chemotherapy	*KRAS*	FOLFIRINOX–GA–CHK1/2 inhibitor (CT)
0400117_T2	F	65	Metastatic	FOLFIRINOX, GA	***KRAS, CDKN2A***	PI3K/mTOR inhibitor/CDK4/6 inhibitor (CT)
0400127_T1	F	60	Metastatic	No prior chemotherapy	***KRAS, CDKN2A***	FOLFIRINOX–GA–CDK4/6 inhibitor/MEK1/2 inhibitor (CT)
0400151_T2	F	61	Metastatic	FOLFIRINOX, GA	*KRAS*, *CDKN2A*	CDK2/5/9 inhibitor (CT)
0400165_T1	F	73	Metastatic	FOLFIRINOX	*ERCC2*, *KRAS*	GA–prostaglandin E2 receptor EP4 antagonist (CT)
0400172_T1	M	58	Metastatic	No prior chemotherapy	***BRAF***, *CDKN2A*	FOLFIRINOX–MEK1/2 inhibitor (OL)–GA–ERK1/2 inhibitor (SP-IND)
0400174_T1	M	77	Metastatic	No prior chemotherapy	***ATM (biallelic)***, *KRAS*, *CDKN2A*	GA–5FU/LV/Nal-Iri–PARP inhibitor (OL)
0400177_T1	F	64	Metastatic	FOLFOX, 5FU/LV/Nal-Iri, GA	*KRAS*, ***NBN, FANCM***	PARP inhibitor/CDK1/2/5/9 inhibitor (CT)
0400197_T1	F	65	Metastatic	FOLFIRINOX, GA	***BRAF***, *FGFR1* (amplification)	MEK1/2 inhibitor (OL)–ERK1/2 inhibitor (SP-IND)
0400202_T1	M	83	Metastatic	ROS1 inhibitor (CT)	*CDKN2A*, ***ROS1 (translocation)***	ROS1 inhibitor (OL)–ROS1 inhibitor (OL)
0400242_T1	F	63	Metastatic	No prior chemotherapy	*KRAS*, *CDKN2A*, ***gBRCA1***	FOLFIRINOX–PARP inhibitor vs. placebo (CT)
0400245_T1	M	57	Metastatic	No prior chemotherapy	*KRAS*	FOLFIRINOX–anti-PD-1 mAb/CXCR4 antagonist (CT)–GA
0400270_T1	F	66	Metastatic	GA, Cape, 5FU/LV/Nal-Iri, FOLFOX	*KRAS*	Anti-PD-1 mAb/anti-GITR mAB agonist (CT)

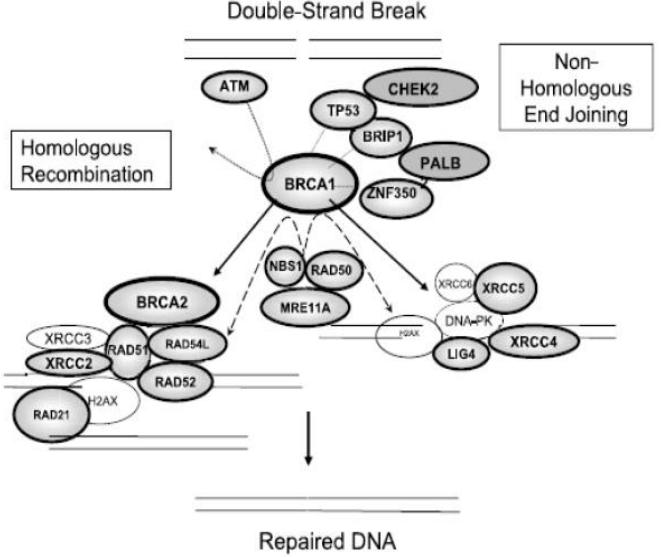
Aguirre, Cancer Discovery 2018

GENES-DRIVEN THERAPIES :FISHING THE RARE TARGET

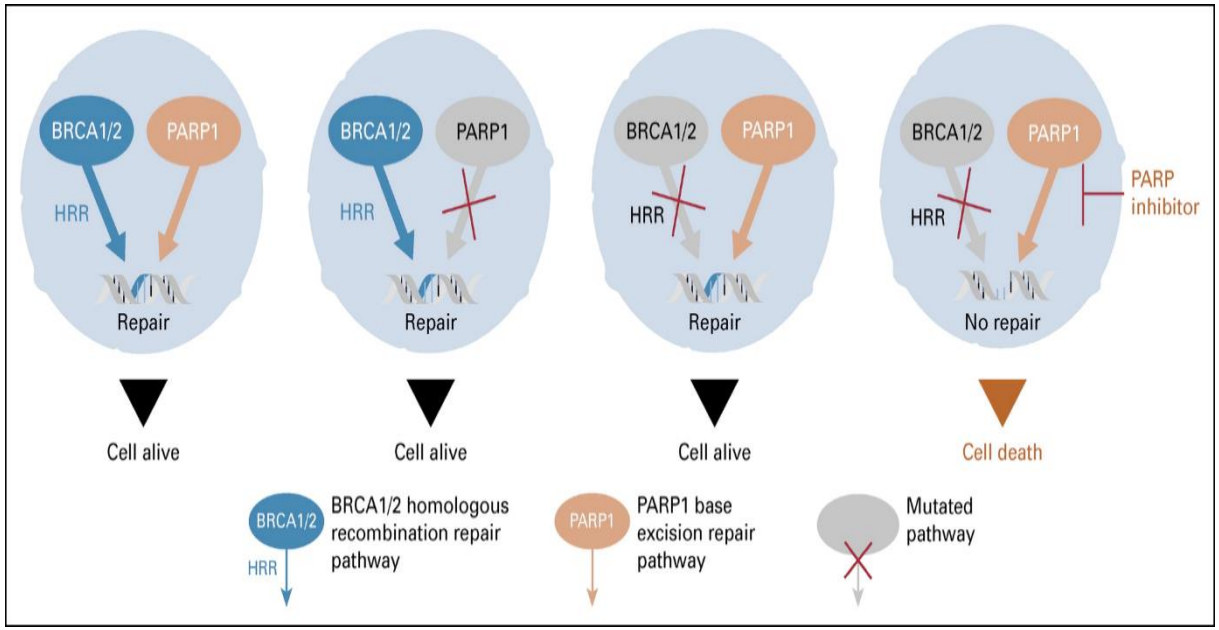


Dreyer, CCR 2017

« BRCANESS »→ DDR GENES IN PDAC



- Germline (5-7%) +/-somatic (10%)
- Better prognosis (slightly)?
- **HRR pathway (BRCA 1/2, ATM,CHEK2,PALB2)**



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Hôpital Erasme ULB

Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma

Koji Shindo, Jun Yu, Masaya Suenaga, Shahriar Fesharakizadeh, Christy Cho, Anne Macgregor-Das, Abdulrehman Siddiqui, P. Dane Witmer, Koji Tamura, Tae Jun Song, Jose Alejandro Navarro Almario, Aaron Brant, Michael Borges, Madeline Ford, Thomas Barkley, Jin He, Matthew J. Weiss, Christopher L. Wolfgang, Nicholas J. Roberts, Ralph H. Hruban, Alison P. Klein, and Michael Goggins

N=854 PDAC
4% mutated

Table 4. Prevalence of Truncating Variants in Pancreatic Cancer Susceptibility Genes: ExAC Controls Versus PDAC Patient Cases

	ExAC Database (frameshift/stop)				PDAC Patient Cases, Present Study		Truncating Only*	
Gene	Truncating Allele, No.	Total Allele, Average	Total Genotypes	Truncating Variant Frequency, %	Truncating Variant, No.	PDAC, No.	Truncating Variant Frequency, %	*P*
BRCA2	251	117,864	58,932	0.43	12	854	1.41	< .0001
ATM	129	115,856	57,928	0.22	8	854	0.94	< .0001
BRCA1	134	111,384	55,692	0.24	3	854	0.35	.7625
CDKN2A	13	96,030	48,015	0.03	1	854	0.12	.1237
MLH1	36	116,544	58,272	0.06	1	854	0.12	.5218
PALB2	81	116,899	58,449.5	0.14	2	854	0.23	.4602

NOTE: Truncating mutations only were considered because the functional significance of many missense mutations is not known. *TP53* is not included in this list because most deleterious mutations in *TP53* are missense.
Abbreviation: PDAC, pancreatic ductal adenocarcinoma.
*All of them are heterozygous.

Table 1. Significantly mutated genes in the DDR pathway in PDAC

Gene symbol	Therapeutic	Rationale	References	Estimated prevalence (%)
ARID1A	ATR inhibitor/PARP inhibitor/platinums	Preclinical models	63, 64	16
ATM	ATR inhibitor/PARP inhibitor/platinums	Clinical trials/case reports/preclinical models	4, 55, 59, 60, 62, 78–8	10
ATR	PARP inhibitor/ATM inhibitor	Preclinical models	60	1
BRCA1; BRCA2	Platinums/PARP inhibitor/ATR inhibitor	Clinical trials/case reports/preclinical models	9, 23, 40, 41, 82, 83	7
PALB2	Platinums/PARP inhibitor	Case reports/preclinical models	9, 41, 84	2
RAD51; RAD51C	PARP inhibitors	Clinical trials/preclinical models	85, 86	1
RPA1	Platinums/PARP inhibitor	Preclinical models	9, 85	3

GERM-LINE >> SOMATIC?

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Table 1. Patients with pathogenic/likely pathogenic germline mutations

Case	Germline mutation	Somatic event	Family history of cancer	Age at Dx (y)
0400094_T2	*ATM* (p.D1013fs) *CDKN2A* (p.G101W)	Nonsense mutation None	Mother: breast cancer Father: melanoma	51
0400209_T1	*ATM* (splice site)	None	No family history	61
0400235_T1	*ATM* (p.E1978*)	None	Mother: breast cancer Maternal uncle: melanoma	65
0400027_T1	*BRCA2* (p.S1982fs)	LOH	Sister: breast cancer	64
0400067_T1	*BRCA2* (p.S1982fs)	LOH	Maternal half-brother: melanoma Maternal half-sister: colon cancer Paternal grandfather: unknown primary cancer	59
0400078_T1	*BRCA2* (p.W1692Mfs*3)	LOH	Father: melanoma and prostate cancer Paternal aunt 1: breast cancer Paternal aunt 2: brain cancer Paternal grandmother: lung cancer	39
0400075_T1	*BRCA1* (p.Q1756fs)	LOH	Mother: ovarian cancer Maternal grandmother: ovarian cancer	58
0400242_T1	*BRCA1* (p.T276Afs*14)	LOH	Mother: breast cancer Brother: pancreatic cancer	63
0400124_T1	*CHEK2* (Ex2_3del)	LOH	Mother: breast cancer Father: prostate cancer Brother: prostate cancer Paternal grandfather: colon cancer Maternal grandmother: intra-abdominal/ pelvic cancer	73
0400211_T1	*BLM* (p.P1320fs)	None	Brother: glioblastoma Father: lung cancer Maternal grandmother: brain cancer	53
0400214_T1	*FANCA* (p.Q343*)	None	Sister: ovarian cancer	59
0400164_T1	*FANCL* (p.T367fs)	None	No family history	70
0400192_T1	*RAD50* (p.S653*)	None	Daughter: lung cancer	67

NOTE: Family history was obtained by review of the patient's medical records. The following samples harbor Ashkenazi Jewish founder mutations: 0400027_T1, 0400067_T1, and 0400075_T1.

Aguirre, Cancer Discovery 2018

POLO TRIAL

Precision therapy is beginning in PDAC…

MUTATIONAL PROFILE PREDICTS RESPONSE TO PLATINUM/PARPi THERAPY

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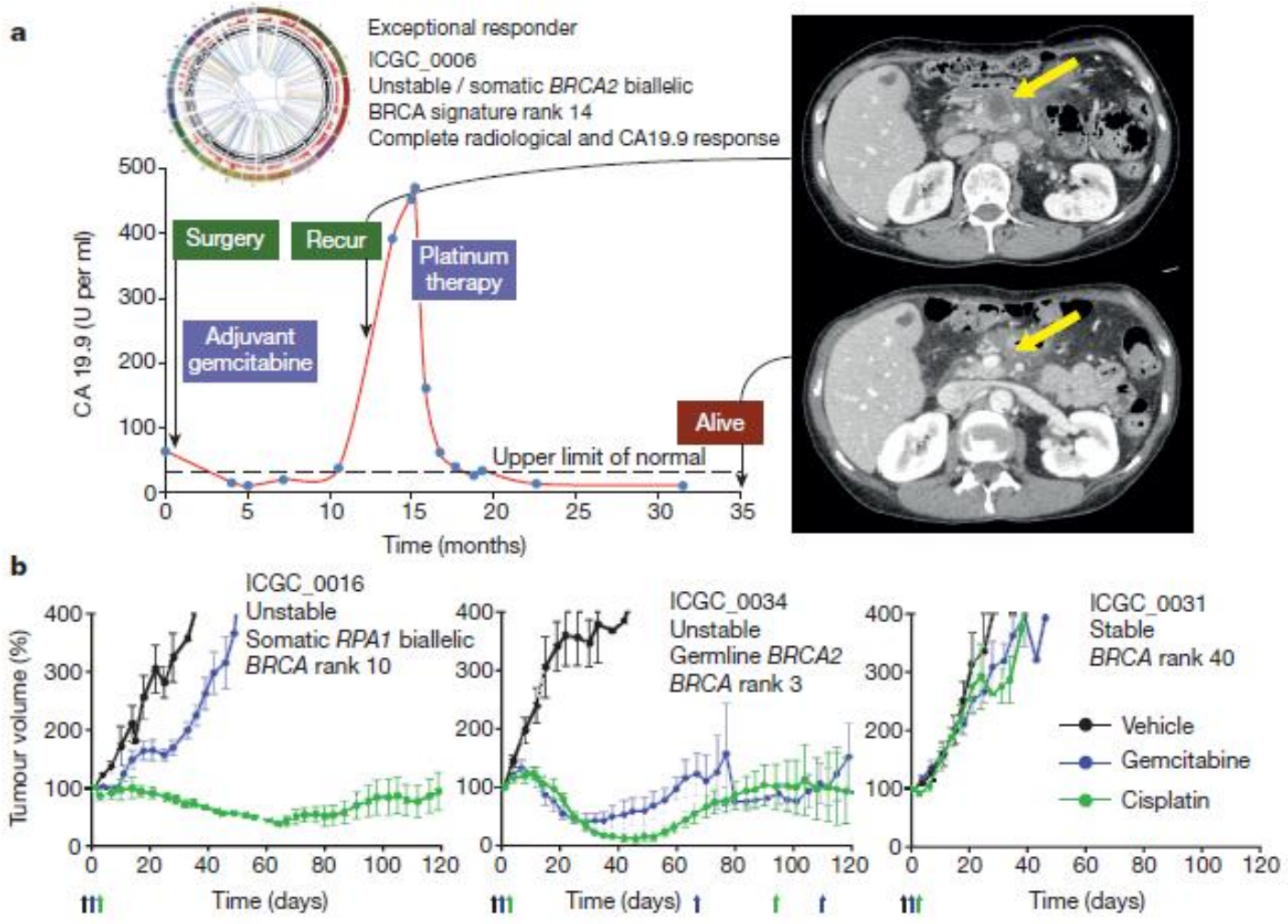

Waddell Nature 2015

OLAPARIB AS MAINTENANCE TREATMENT FOLLOWING FIRST-LINE PLATINUM-BASED CHEMOTHERAPY (PBC) IN PATIENTS WITH A GERMLINE BRCA MUTATION AND METASTATIC PANCREATIC CANCER (MPC): PHASE III POLO TRIAL

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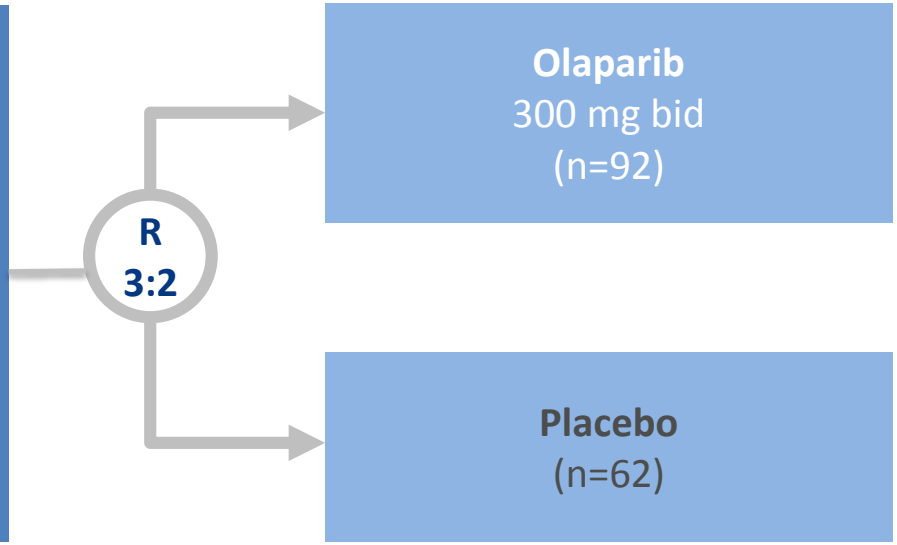
- Study objective
  - Assess the efficacy and safety of olaparib as maintenance therapy in patients with a germline BRCA mutation and metastatic pancreatic cancer
  - Primary Endpoint: PFS
  - Secondary Endpoints: OS, ORR and safety
- Inclusions:
  - n= 154 patients

Key patient inclusion criteria

- Metastatic pancreatic cancer
- Deleterious or suspected deleterious germline BRCA1 and/or BRCA2 mutation
- ≥16 weeks of 1L platinum-based CT with no limit to duration, without progression



Kindler H. et al. ASCO 2019,
Golan T. NEJM 2019

POLO: Select Patient Characteristics

	Olaparib N = 92	Placebo N = 62
Age, years	57	57
BRCA mutation, %		
*BRCA*1	31.5	25.8
*BRCA*2	67.4	74.2
Both	1.1	0
First-line platinum, %		
FOLFIRINOX	85.9	80.6
Gem-cis	2.2	4.8
Other	10.9	12.9
CR/PR response to first-line, %	50	48.8

Cis = cisplatin; CR = complete response; Gem = gemcitabine; PR = partial response

Golan T, et al. *N Engl J Med.* 2019;381:317-327.

OLAPARIB AS MAINTENANCE TREATMENT FOLLOWING FIRST-LINE PLATINUM-BASED CHEMOTHERAPY (PBC) IN PATIENTS WITH A GERMLINE BRCA MUTATION AND METASTATIC PANCREATIC CANCER (MPC): PHASE III POLO TRIAL

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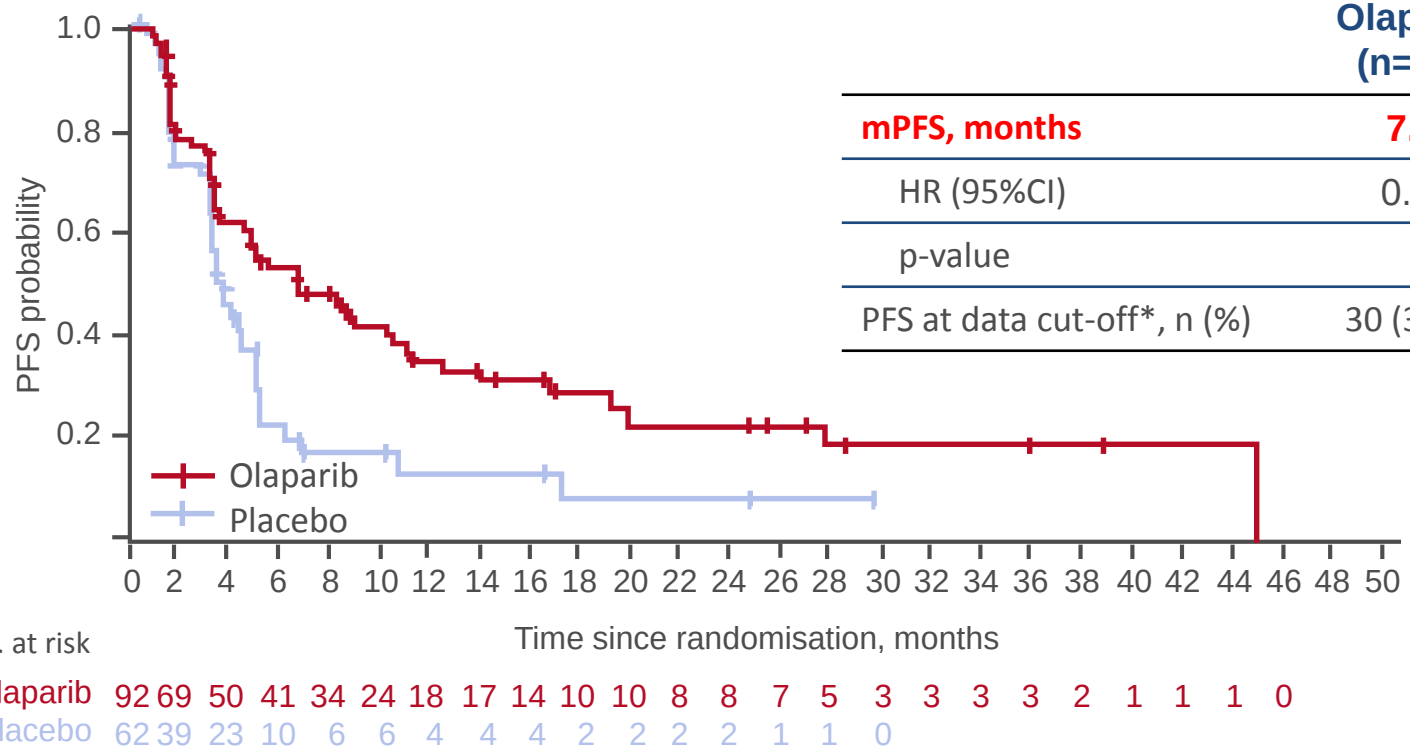
Primary endpoint: PFS by blinded independent central review



	Olaparib (n=92)	Placebo (n=62)
mPFS, months	**7.4**	**3.8**
HR (95%CI)	0.53 (0.35, 0.82)	
p-value	0.0038	
PFS at data cut-off*, n (%)	30 (32.6)	12 (19.4)

Kindler H. et al. ASCO 2019

OLAPARIB AS MAINTENANCE TREATMENT FOLLOWING FIRST-LINE PLATINUM-BASED CHEMOTHERAPY (PBC) IN PATIENTS WITH A GERMLINE BRCA MUTATION AND METASTATIC PANCREATIC CANCER (MPC): PHASE III POLO TRIAL

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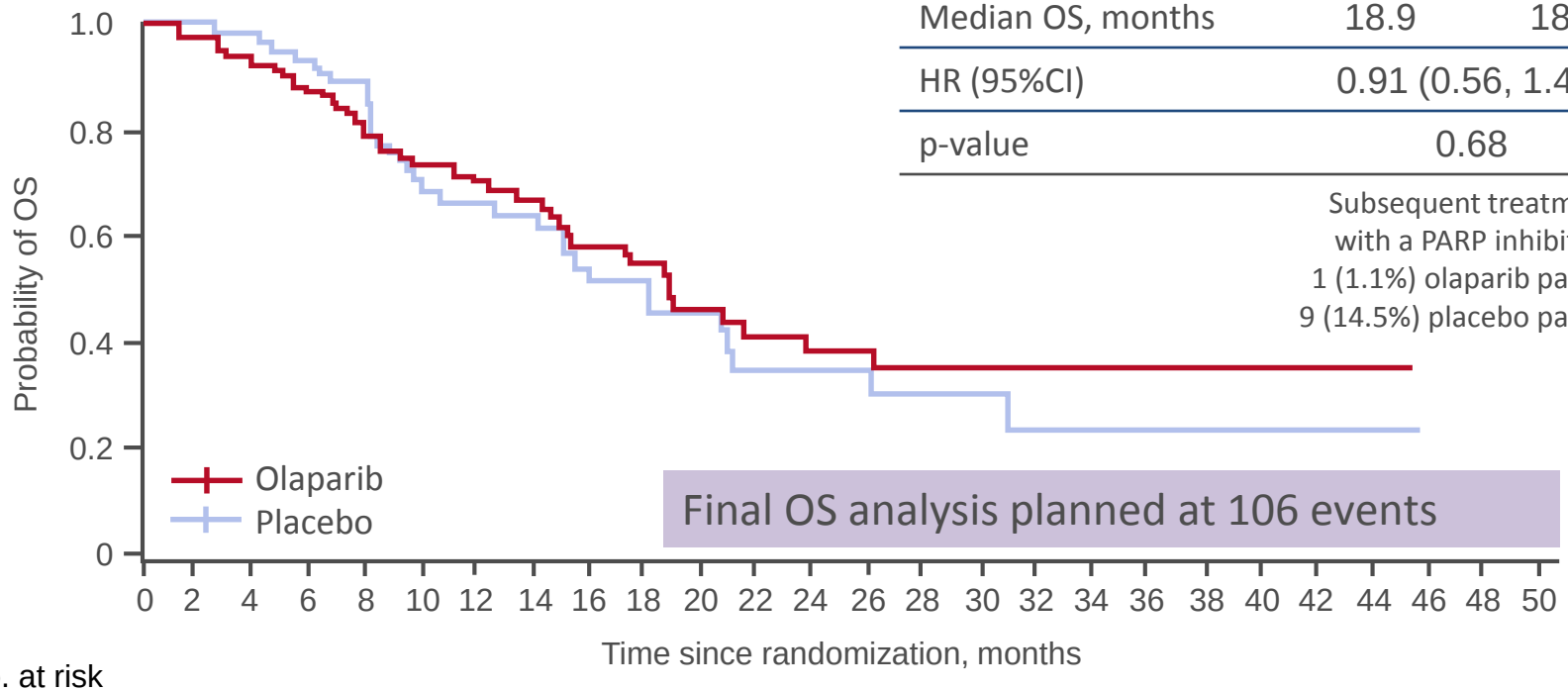
Overall survival (46% maturity)

	Olaparib (n=92)	Placebo (n=62)
Median OS, months	18.9	18.1
HR (95%CI)	0.91 (0.56, 1.46)	
p-value	0.68	

Subsequent treatment with a PARP inhibitor:
1 (1.1%) olaparib patient
9 (14.5%) placebo patients



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

Kindler H. et al. ASCO 2019

OLAPARIB AS MAINTENANCE TREATMENT FOLLOWING FIRST-LINE PLATINUM-BASED CHEMOTHERAPY (PBC) IN PATIENTS WITH A GERMLINE BRCA MUTATION AND METASTATIC PANCREATIC CANCER (MPC): PHASE III POLO TRIAL

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- ORR in patients with measurable disease

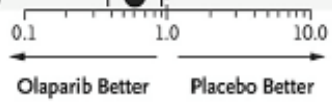
	Olaparib (n=78)	Placebo (n=52)
ORR, n (%)	18 (23.1)	6 (11.5)
Median time to onset of response, months	5.4	3.6
Median DoR, months	24.9	3.7

  - 2 patients who received Olaparib had a CR

Kindler H. et al. ASCO 2019

Subgroup Analyses for PFS

Subgroup	Olaparib	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	60/92 (65.2)	44/62 (71.0)	0.53 (0.35–0.82)
Previous chemotherapy			
FOLFIRINOX variants	50/79 (63.3)	35/50 (70.0)	0.54 (0.35–0.84)
Other	8/10 (80.0)	6/8 (75.0)	0.76 (0.27–2.32)
Absence of biliary stent	59/91 (64.8)	40/58 (69.0)	0.54 (0.36–0.82)
Type of previous chemotherapy			
Doublet chemotherapy	12/15 (80.0)	8/10 (80.0)	0.59 (0.24–1.50)
Triplet chemotherapy	45/73 (61.6)	33/46 (71.7)	0.51 (0.32–0.82)
Duration of first-line treatment before randomization			
16 wk to 6 mo	42/61 (68.9)	29/40 (72.5)	0.69 (0.43–1.12)
>6 mo	18/30 (60.0)	15/21 (71.4)	0.35 (0.17–0.72)
Best response with first-line treatment			
Partial or complete response	30/46 (65.2)	20/30 (66.7)	0.62 (0.35–1.12)
Stable disease	30/45 (66.7)	24/31 (77.4)	0.50 (0.29–0.87)
Disease at baseline			
Measurable	53/78 (67.9)	39/52 (75.0)	0.57 (0.37–0.88)
Not measurable or no evidence of disease	7/13 (53.8)	5/6 (83.3)	0.45 (0.14–1.57)
Germline *BRCA* mutation type (determined by BRACAnalysis CDx test)			
BRCA1	20/29 (69.0)	12/16 (75.0)	0.40 (0.20–0.85)
BRCA2	38/59 (64.4)	32/45 (71.1)	0.63 (0.39–1.02)
Age at randomization			
<65 yr	39/64 (60.9)	37/49 (75.5)	0.45 (0.28–0.72)
≥65 yr	21/28 (75.0)	7/13 (53.8)	1.02 (0.45–2.60)
Sex			
Male	33/53 (62.3)	23/31 (74.2)	0.46 (0.27–0.80)
Female	27/39 (69.2)	21/31 (67.7)	0.66 (0.37–1.19)
White race	55/82 (67.1)	41/59 (69.5)	0.59 (0.39–0.90)

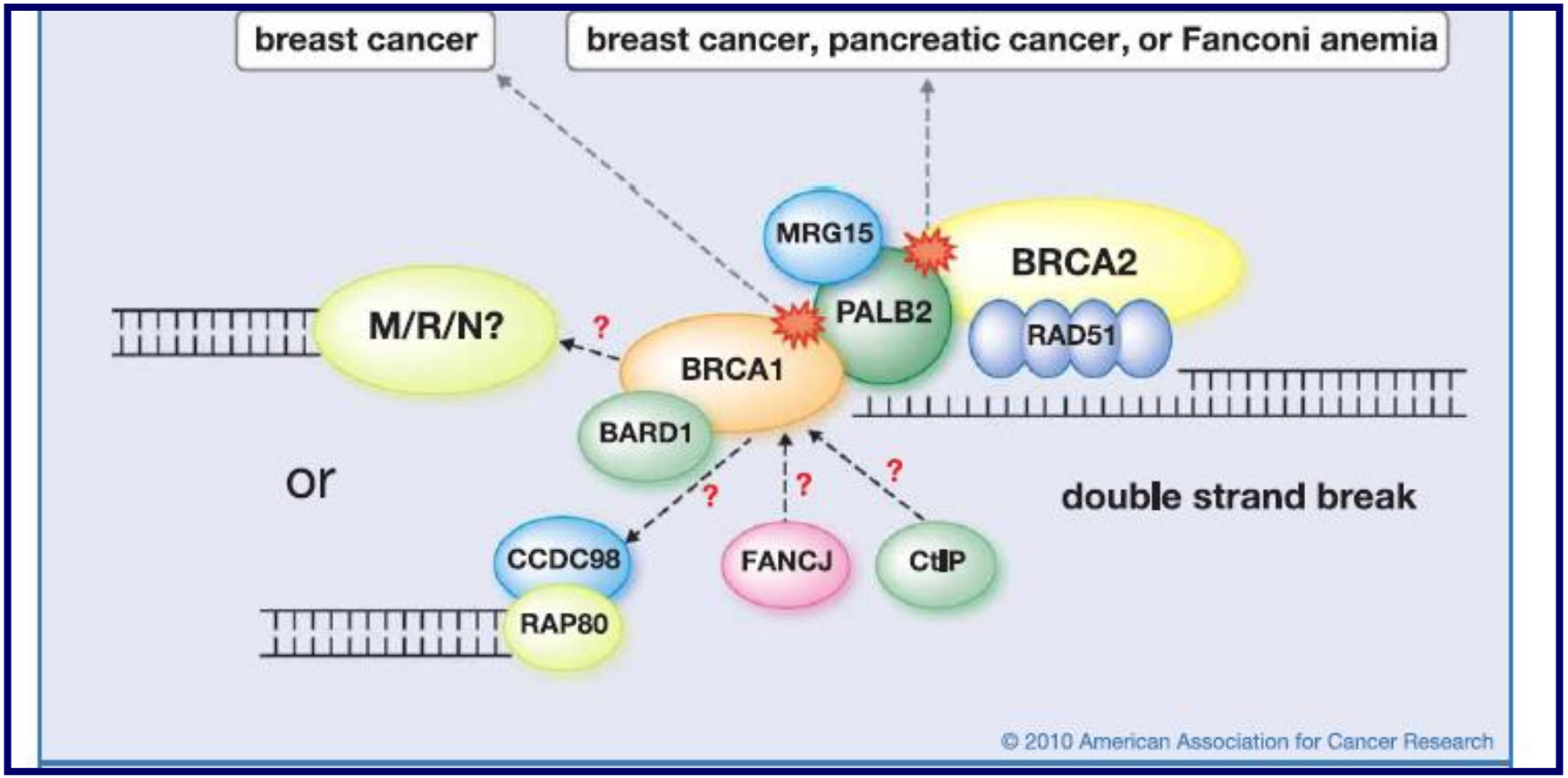


Golan T, et al. *N Engl J Med.* 2019;381:317-327.

NCCN Now Recommends Germline Testing in Newly Diagnosed Pancreatic Cancer Irrespective of Family History

- NCCN Pancreatic Cancer (V2.2019 – released 4/9/2019)
  - Germline testing ~~should be considered~~ 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 pathogenic mutation or for patients with a positive family history of cancer
  - Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anticancer therapy, to identify uncommon but actionable mutations
- NCCN Genetic/Familial High-Risk Assessment BC/OC (V3.2019 – 1/18/2019)
  - Genetic risk evaluation recommended for any individual diagnosed with pancreatic cancer

PANELS OF GERMLINE ALTERATIONS ARE NOW AVAILABLE

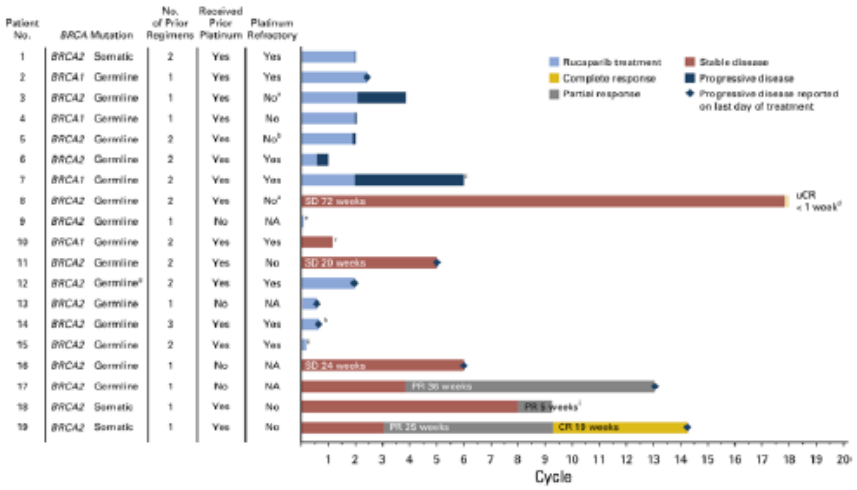


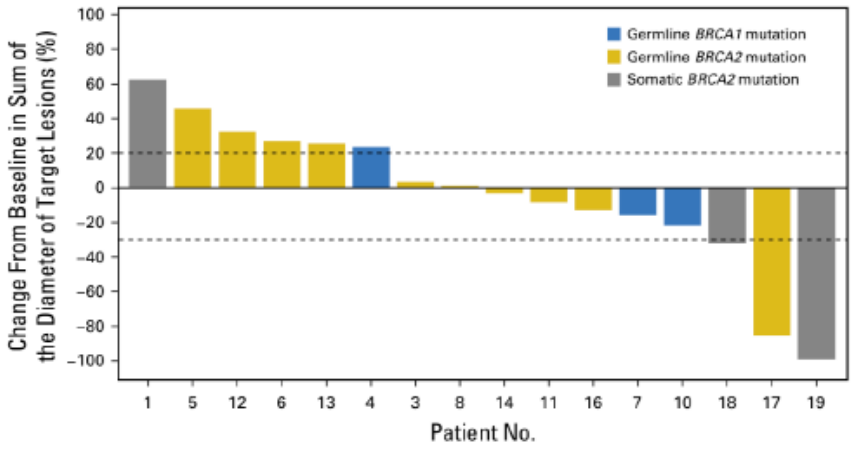
DDR BASKET TRIAL

Hôpital Erasme

ULB

RUCAPANC: Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious *BRCA* Mutation

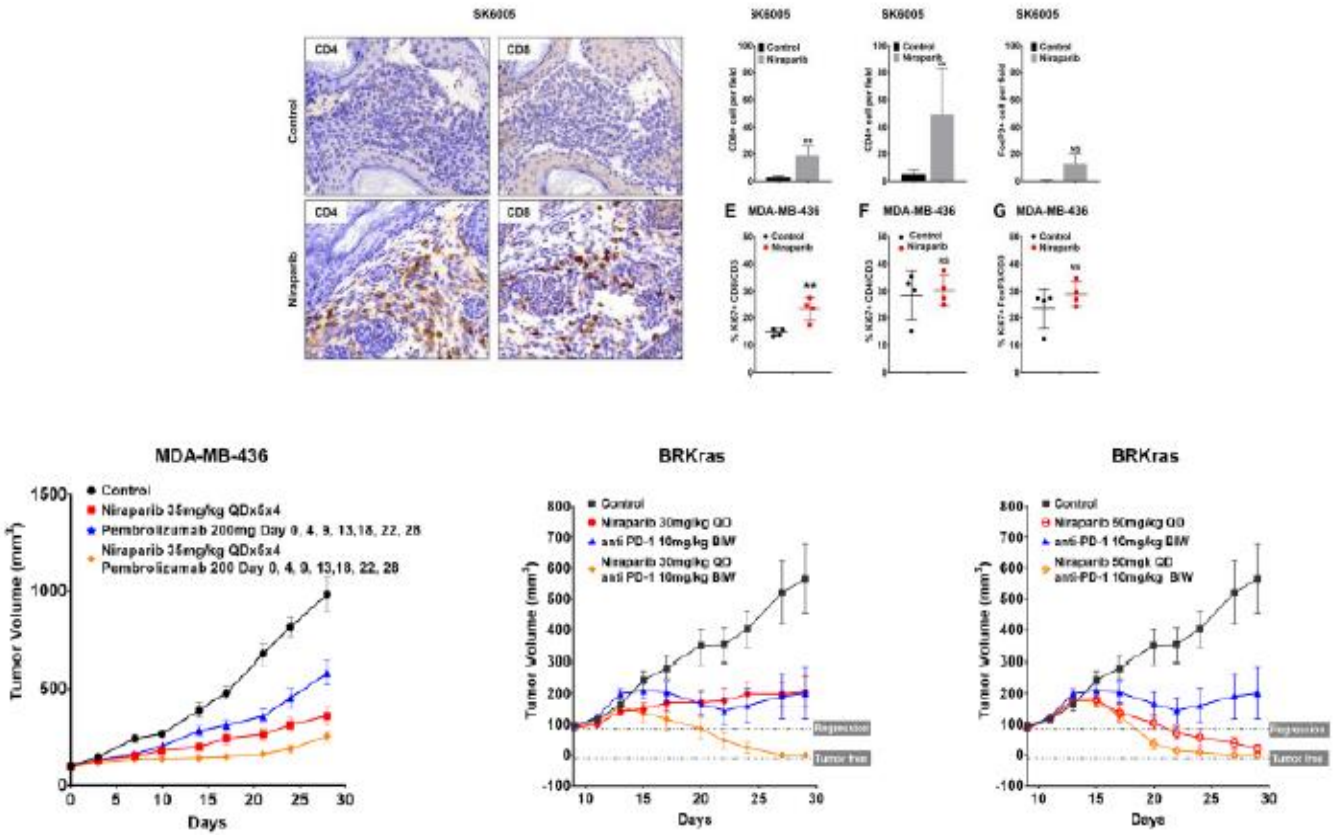




Shroff RT, et al. *JCO Precis Oncol.* 2018;2018.

Hôpital Erasme | ULB

Strategies to Augment PARPi Response

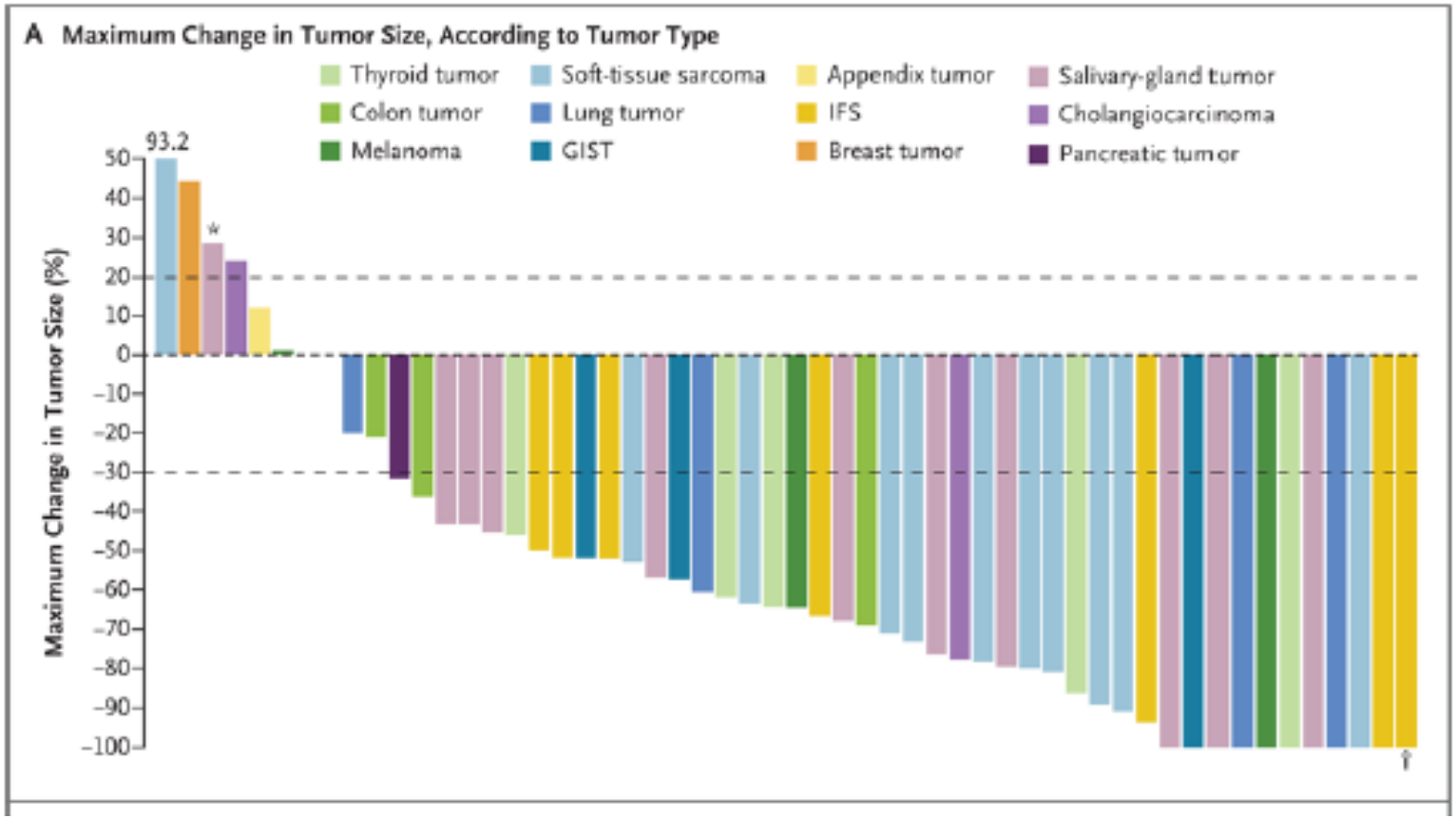


Wang Z, et al. *Sci Rep.* 2019;9:1853.

N Engl J Med. 2018 February 22; 378(8): 731–739. doi:10.1056/NEJMoa1714448.

Hôpital Erasme ULB

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

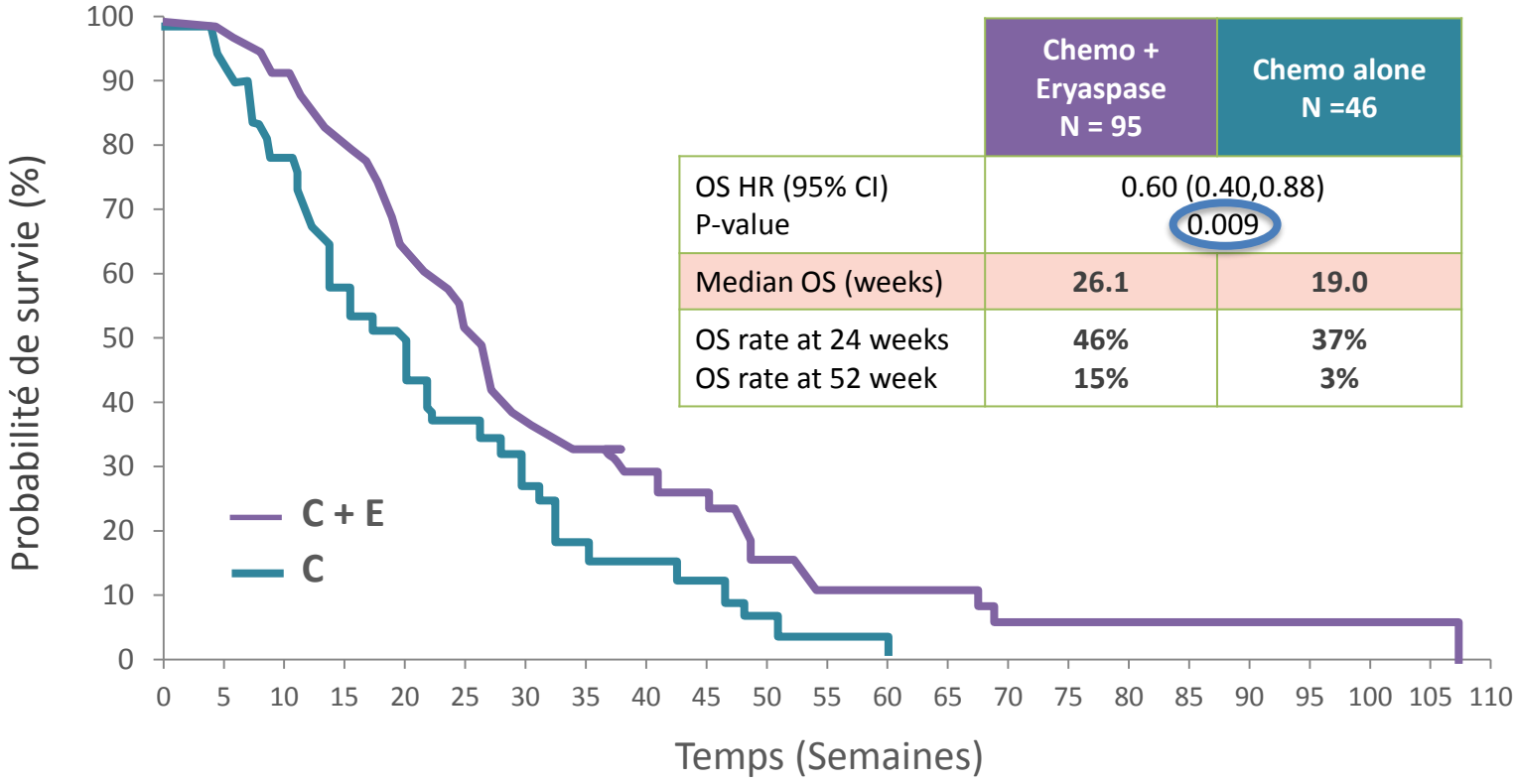


NTRK 3 > NTRK1

Exact prevalence in PDAC? 5-6%

A PHASE 2B OF ERYASPASE (E-ASPARGINASE) IN COMBINATION WITH GEMCITABINE OR FOLFOX AS SECOND-LINE THERAPY IN PATIENTS WITH METASTATIC PANCREATIC ADENOCARCINOMA. → PHASE III IN PROGRESS IN L2 (CHEMO +/- E) =GRASPANC

Hôpital Erasme — ULB

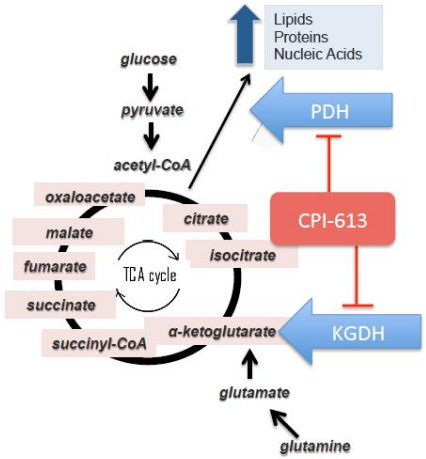


	Chemo + Eryaspase N = 95	Chemo alone N =46
OS HR (95% CI) P-value	0.60 (0.40,0.88) 0.009	
Median OS (weeks)	**26.1**	**19.0**
OS rate at 24 weeks OS rate at 52 week	**46%** **15%**	**37%** **3%**

Bras 1	95	89	82	71	58	46	32	25	22	19	12	8	6	4	2	2	2	1	1	1	1	1	0
Bras 2	46	40	34	25	19	15	10	6	5	4	2	1	1										

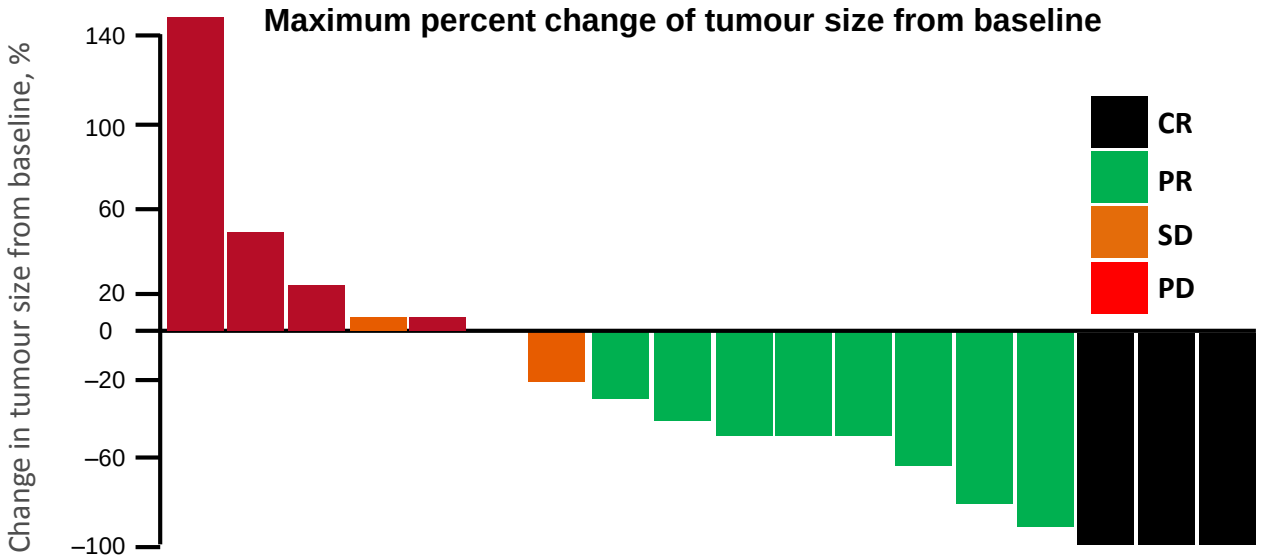
Hammel P. et al. ASCO 2017

NEW PROMISING COMBINATION THERAPY OF A MITOCHONDRIAL METABOLISM INHIBITOR WITH FOLFIRINOX IN PANCREATIC CANCER – ALISTAR AT, ET AL



Key results : n=18 pts

- Maximum tolerated dose was 500 mg/m^2



	CPI-613 + mFOLFIRINOX
mOS, months	20.1
mPFS, months	10.4
ORR, %	61

Alistar AT, et al. Ann Oncol 2017;28(Suppl 5):Abstr 1733PD

Phase III ongoing (RAFAEL)

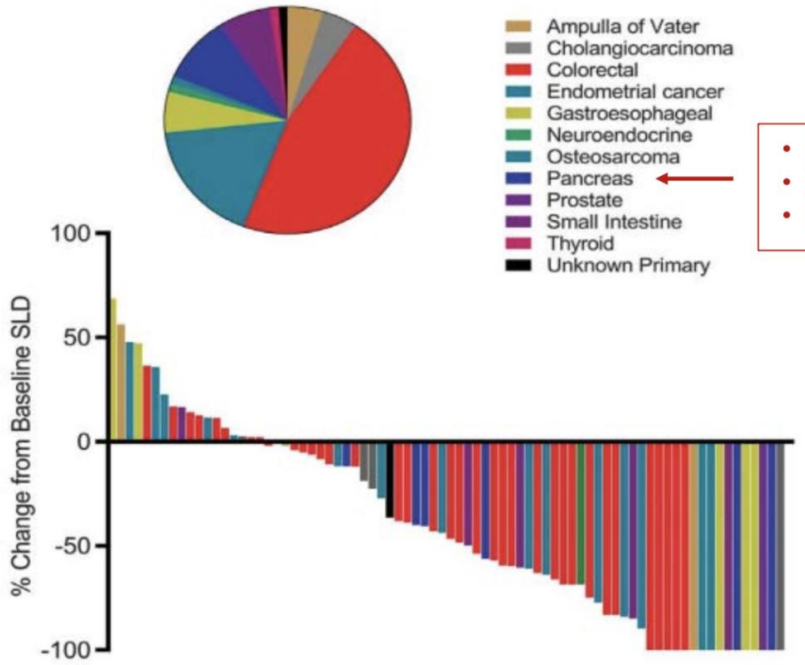
WHAT ABOUT I/O IN PDAC?

Hôpital Erasme

ULB

MSI-high/dMMR across 12 tumor types
N = 86

- **Aprox. 1% mPCA MSI-H/dMMR (IHC, PCR, NGS)**



- **8 mPCA patients**
- **ORR 62% (2/8 CR)**
- **DCR 75%**

ORR for all patients were 53% (21% CR), responses were durable, mPFS and mOS not reached.

DCR, disease control rate IHC, immunohistochemistry; NGS, next generation sequencing; PCR, polymerase chain reaction.
Le DT, et al. *Science.* 2017;357:409-413.

ANTI-PDL1 IN PANCREATIC CANCER :KEYNOTE-164 AND 158 IN MSI-H CANCERS

Hôpital Erasme

ULB

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)	–

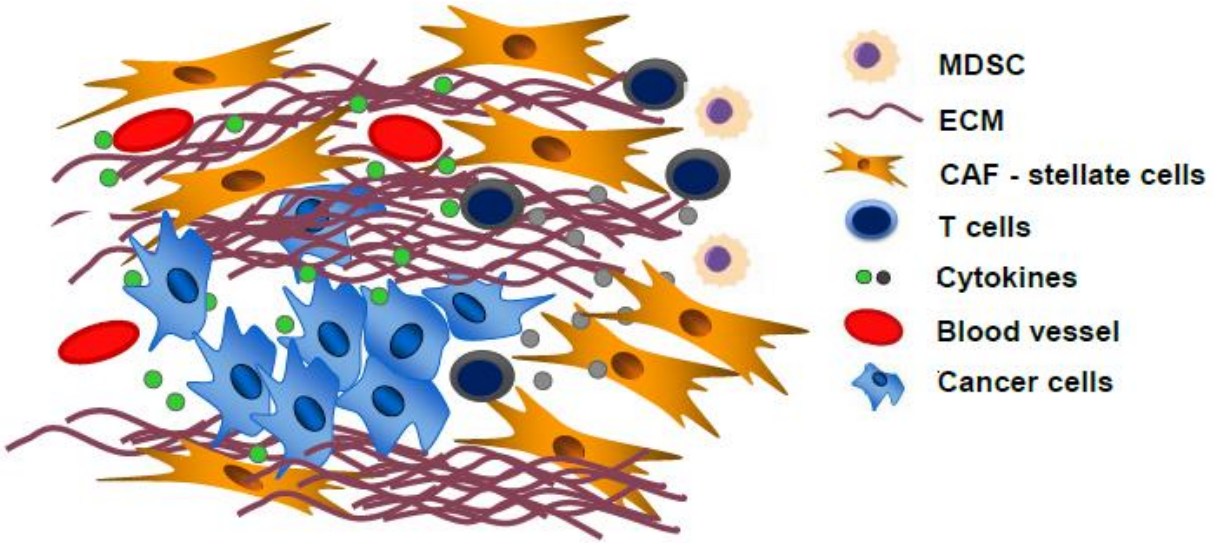
Diaz, ESMO 2019

THE TME OF PDAC IS HIGHLY COMPLEX AND IMMUNOSUPPRESSIVE

Hôpital Erasme

ULB

The Microenvironment Is Composed of Multiple Cell Types and ECM Components

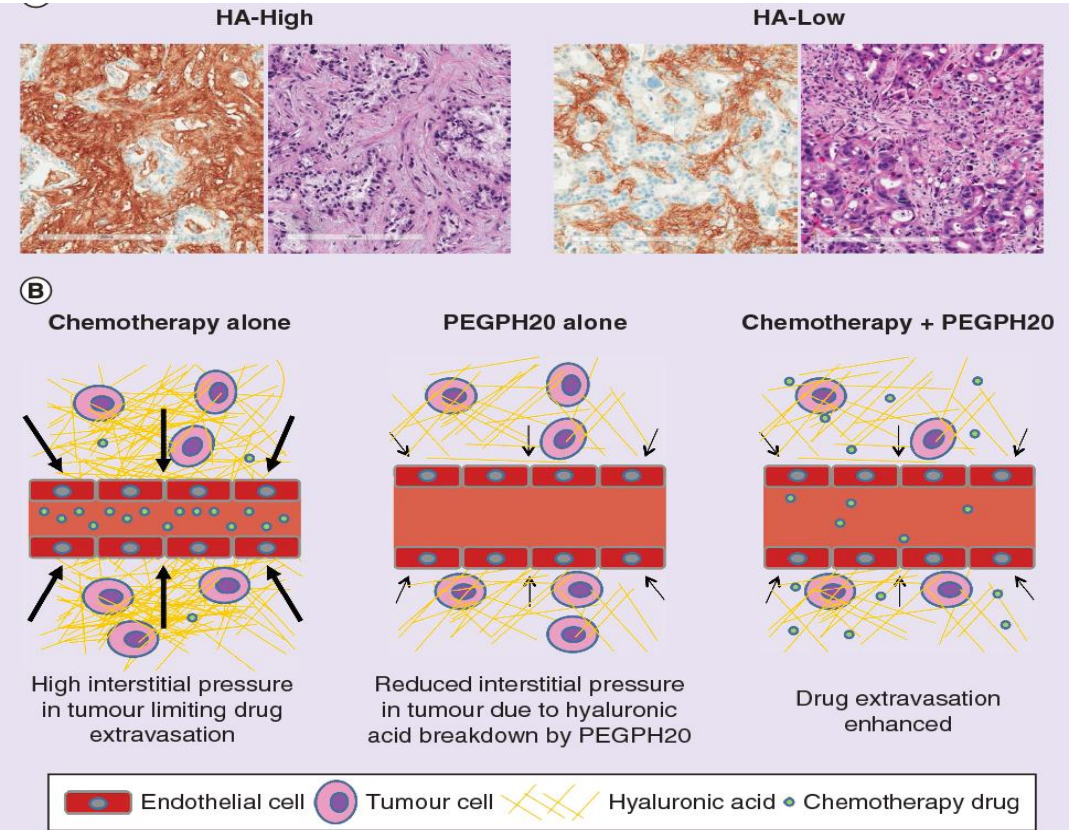


CAF = cancer-associated fibroblast; ECM = extracellular matrix; MDSC = myeloid-derived suppressor cells

Neesse A, Ellenrieder V. *Gut.* 2017;66:211-212.

TARGETING THE STROMA

- PEGPH20 :
  - Leads to degradation of stromal hyaluronan (HA) and ↑ drug delivery in preclinical studies



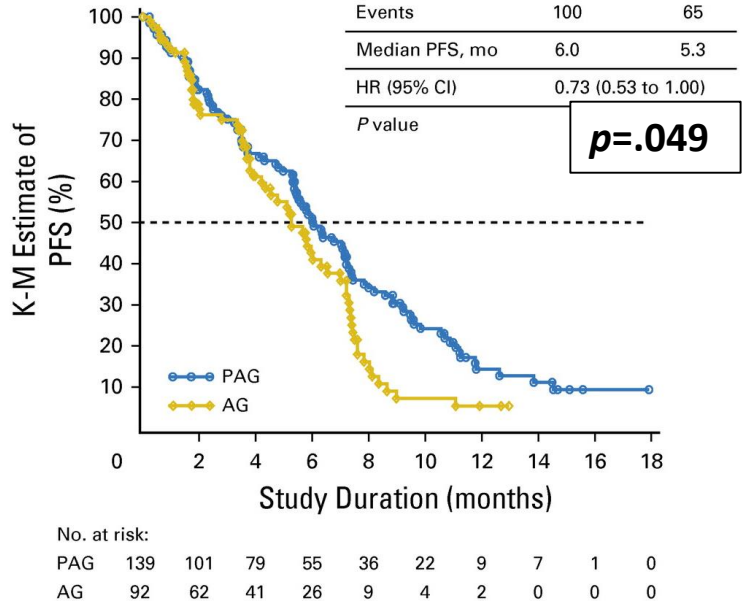
Doherty et al. Future Oncology 2018

TARGETING THE STROMA

- PEGPH20 in phase II:
  - 279 patients randomized in Phase II study HALO202 for untreated metastatic PDAC: **Gem/Nab-P +/- PEGPH20**
  - Primary end-point : PFS
  - Secondary end-points: OS, PFS by HA levels, objective RR

All

Stages 1 + 2	PAG (n = 139)	AG (n = 92)
Events	100	65
Median PFS, mo	6.0	5.3
HR (95% CI)	0.73 (0.53 to 1.00)	
P value	***p*=.049**	

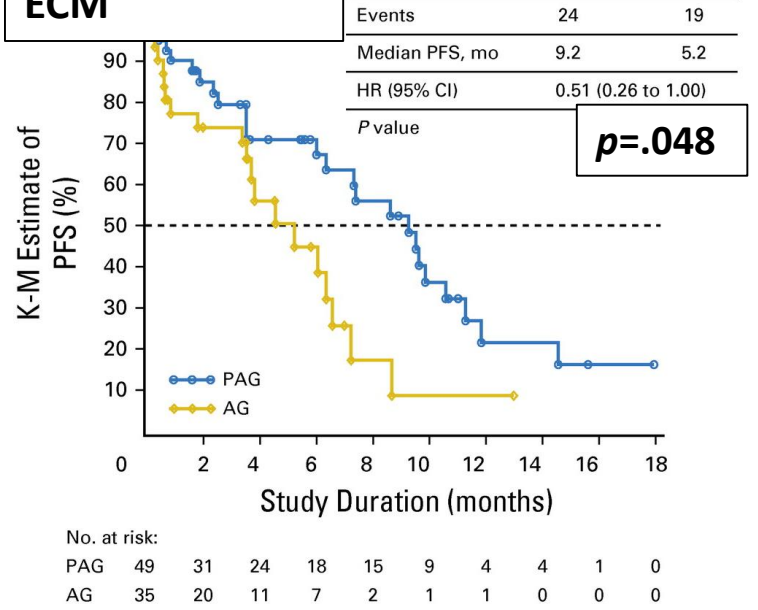


No. at risk:

PAG	139	101	79	55	36	22	9	7	1	0
AG	92	62	41	26	9	4	2	0	0	0

HA-High >50% ECM

Stages 1 + 2 (HA-High)	PAG (n = 49)	AG (n = 35)
Events	24	19
Median PFS, mo	9.2	5.2
HR (95% CI)	0.51 (0.26 to 1.00)	
P value	***p*=.048**	



No. at risk:

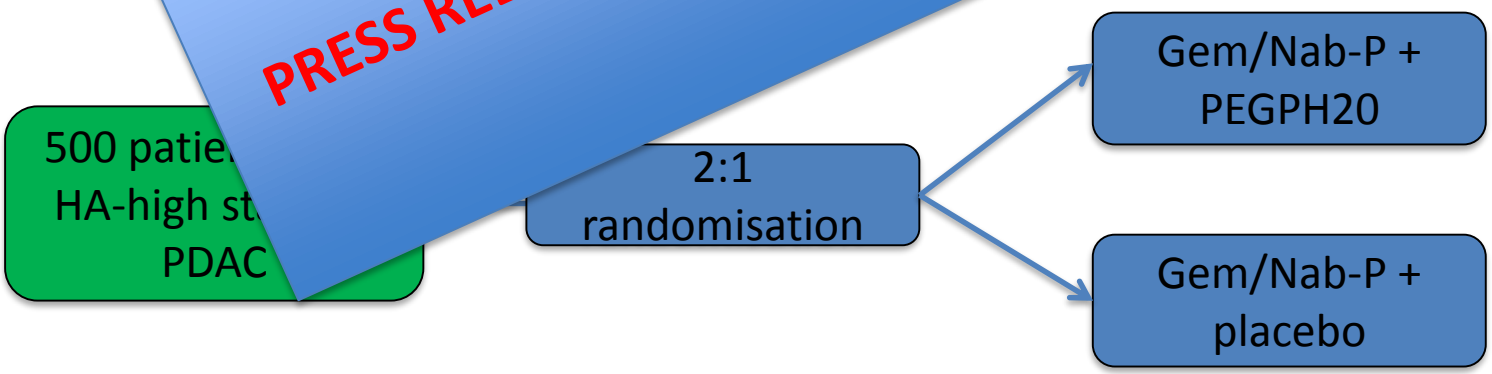
PAG	49	31	24	18	15	9	4	4	1	0
AG	35	20	11	7	2	1	1	0	0	0

Hingorani et al. J Clin Oncol 2018

TARGETING THE STROMA

- PEGPH20 :
  - Toxicity: thromboembolic events (requires anti- -ulant prophylaxis), myalgia/muscles spasms, r- -dema, neutropenia…
  - Phase III trial HALO- -e IV PDAC [NCT02-

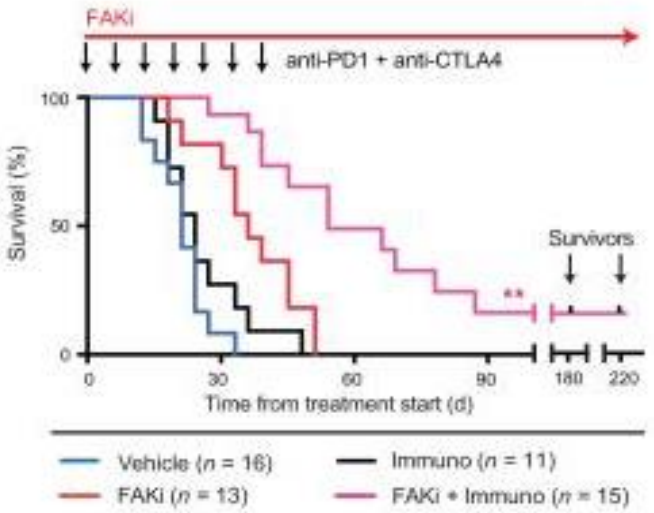
PRESS RELEASE : NEGATIVE TRIAL ;HR=1.1 !



Hingorani et al. J Clin Oncol 2018; Ramanathan et al. J Clin Oncol 2018; Doherty et al. Future Oncology 2018

TARGETING THE STROMA (CYTOSKELET)

- FAK inhibitors: defactinib…
  - Focal Adhesion Kinase: promotes tumor progression and M+ < CSC maintenance, EMT, angiogenesis…
  - Pre-clinical studies : ↓ fibrosis, angiogenesis, TAMs/Treg/MDSCs infiltrates. Render a previously unrespsonsive mouse-model responsive t anti-PD-1. Maximum synergic effect with Gem.

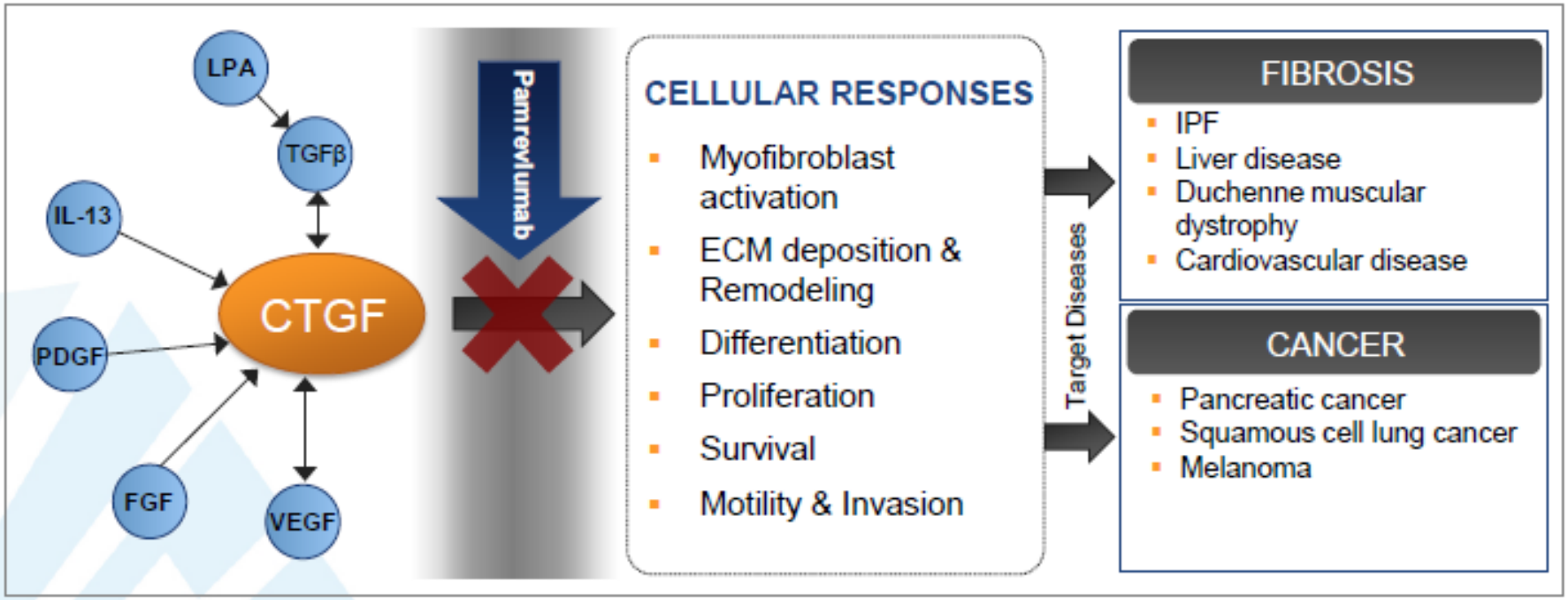


  - Phase I trial expansion cohort for 50 advanced PDAC is ongoing [NCT02546531] :

    Gem + Pembrolizumab + Defactinib

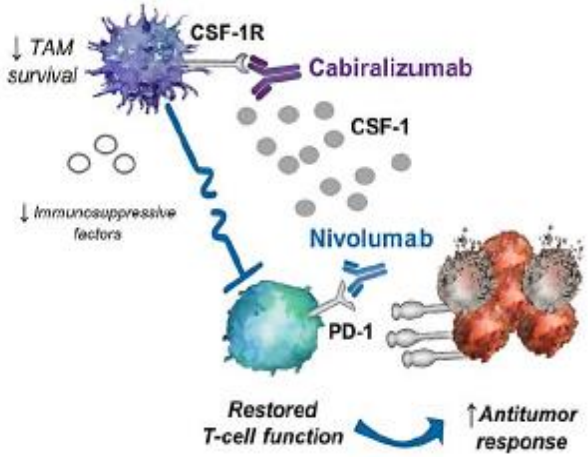
Jiang et al. Nat Med 2016; Wang-Gillam et al. J Clin Oncol 2018

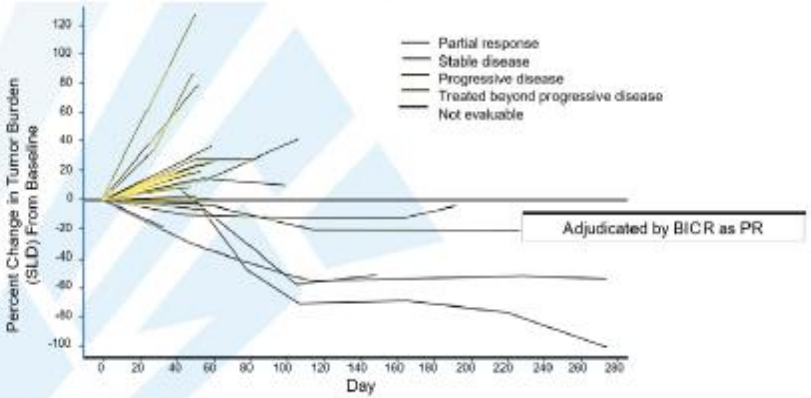
TARGETING STROMA AND CYTOSKELET

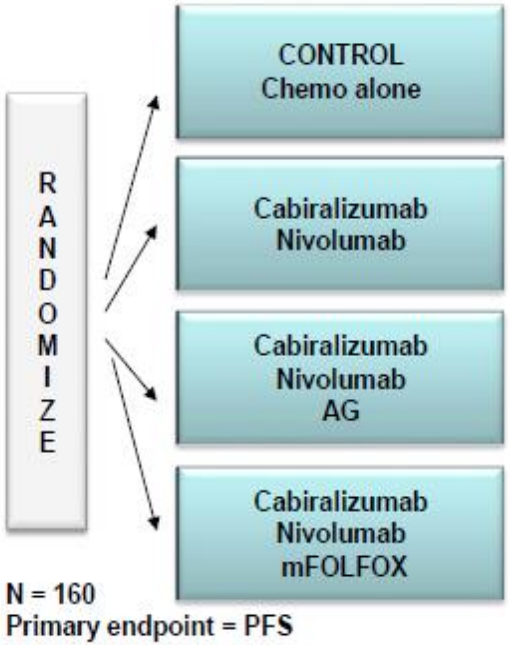


- ✓ **CTGF overexpression is associated with tissue adhesion**
- ✓ **CTGF expression is elevated in pancreatic cancer**
- ✓ **Pamrevlumab (FG-3019) is an antibody to CTGF**
- ✓ **In mouse models, tissue adhesion was inhibited by pamrevlumab**

ANTI-TAM AND ANTI-TGF BETA STRATEGIES





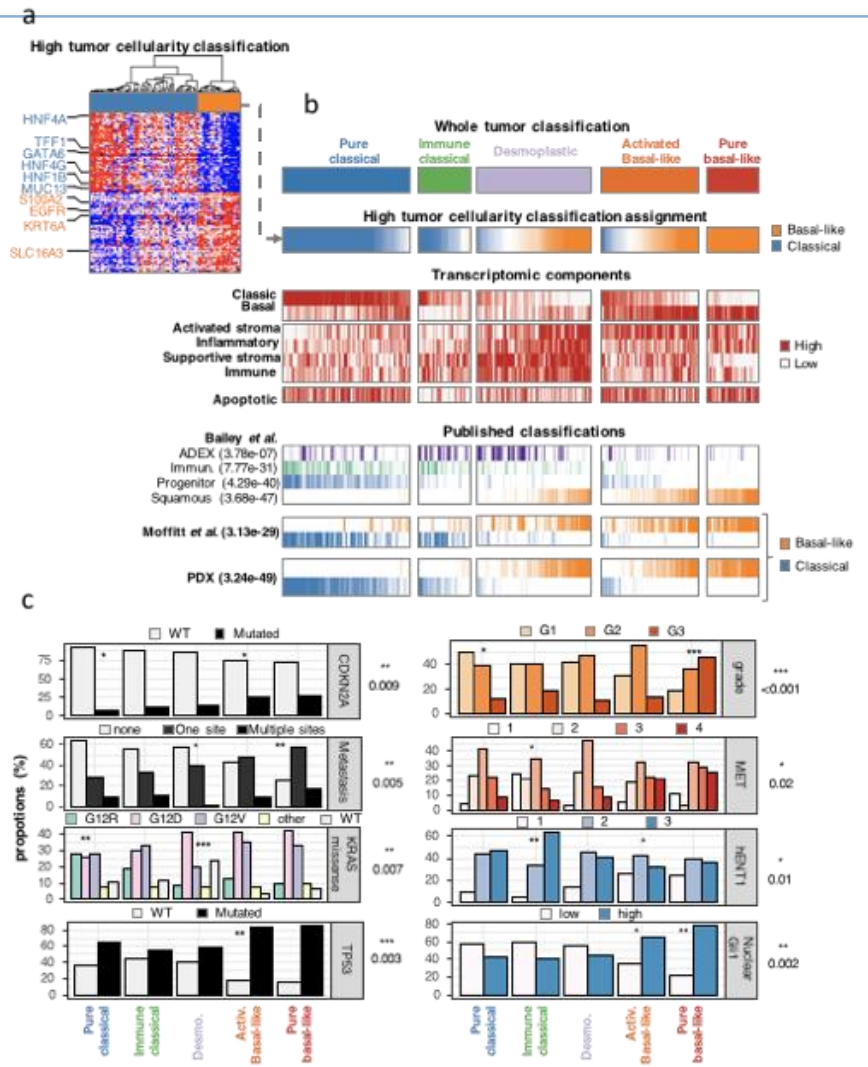


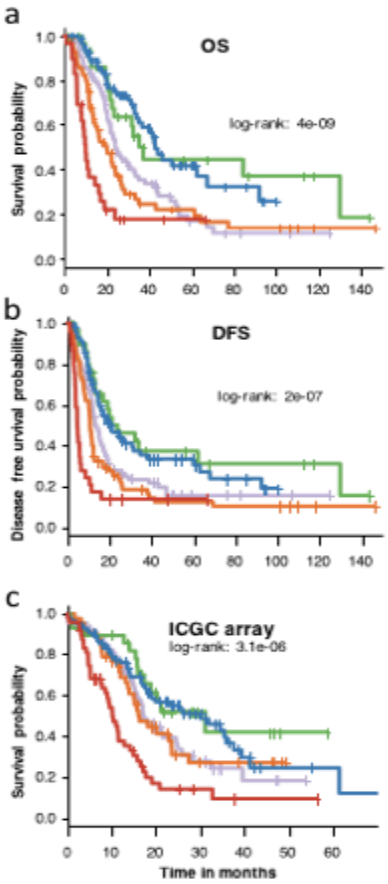
Colony stimulating factor 1 receptor (CSF1R), also known as macrophage colony-stimulating factor receptor (M-CSFR), and CD115 (Cluster of Differentiation 115)

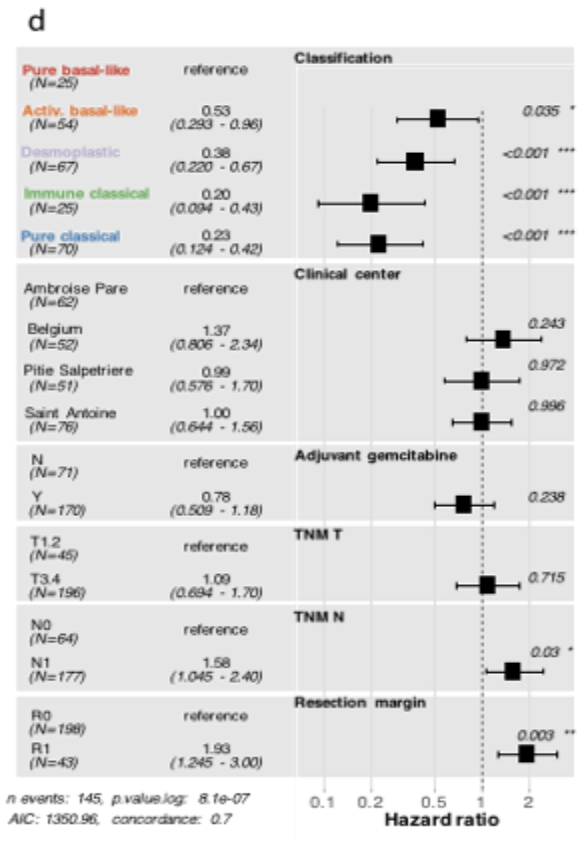
Wainberg ZA, et al. SITC 2017. Abstract O42; Ries CH, et al *Cancer Cell*. 2014;25:846-859; Goswami KK, et al. *Cell Immunol*. 2017;316:1-10; Bellovin DI et al. AACR 2917. Abstract 1599; ClinicalTrials.gov. NCT03336216.

TUMOR AND MCE-BASED STRATIFICATION; N=309 PDAC

Hôpital Erasme | ULB







e

Median survival (in months) [95% CI]	OS	DFS	ICGC OS
Pure basal-like	**10.3** [8.36, 17.3]	**4.57** [3.75, 6.32]	**10.1** [8.55, 14.8]
Activated basal-like	**20.2** [15.03, 26.8]	**10.69** [9.97, 12.24]	**16.3** [13.91, 27.5]
Desmoplastic	**24.3** [21.81, 35.1]	**12.93** [11.78, 17.5]	**17.2** [15.25, 25.9]
Immune classical	**37.4** [23.75, inf]	**21.09** [13.09, inf]	**31** [17.19, inf]
Pure classical	**43.1** [35.33, 92.3]	**20.13** [14.7, 34.51]	**30** [18.51, 39.5]

Puleo, Gastroenterology 2018

MPDAC: TAKE HOME IN PRACTICE

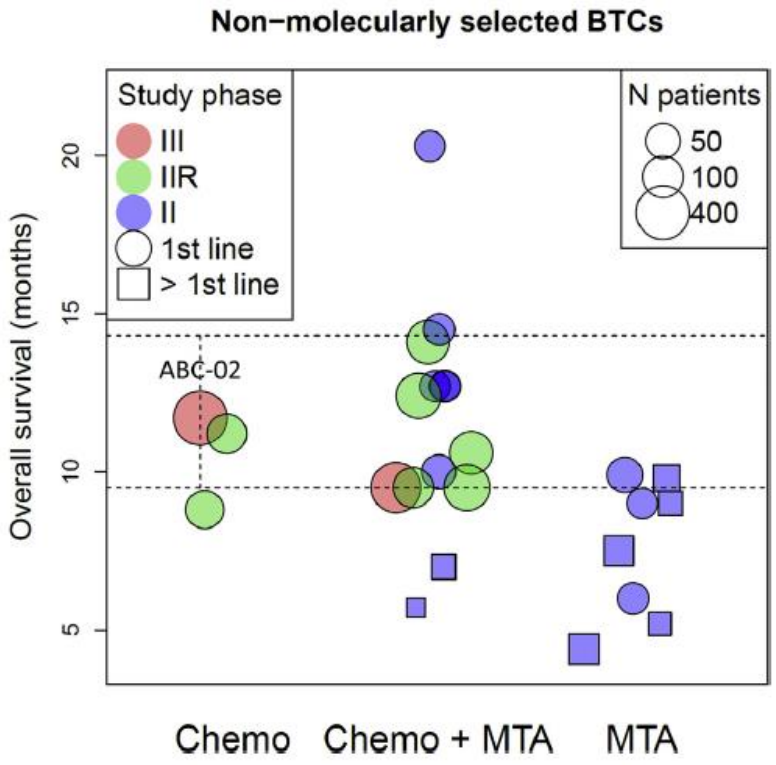
Hôpital Erasme | ULB

- Chemotherapy remains the backbone in mPDAC (FFX,G+/-Nab-P, NAL-IRI)
- Maintenance therapy is emerging in selected cases (gBRCA, Phase III PAN-OPTIMOX awaited)
- Targeting stroma, metabolic pathways and immune cells are ongoing (+chemo) …but complex (reverse immunosupressive environment by specific combo)

- What to test nowadays → tomorrow ; « all » patients
  - gBRCA → BRCAness, HRR/DDR → olaparib, trials (rucaparib)
  - MSI → ?
  - NTRK promising

BILIARY TRACT CANCER

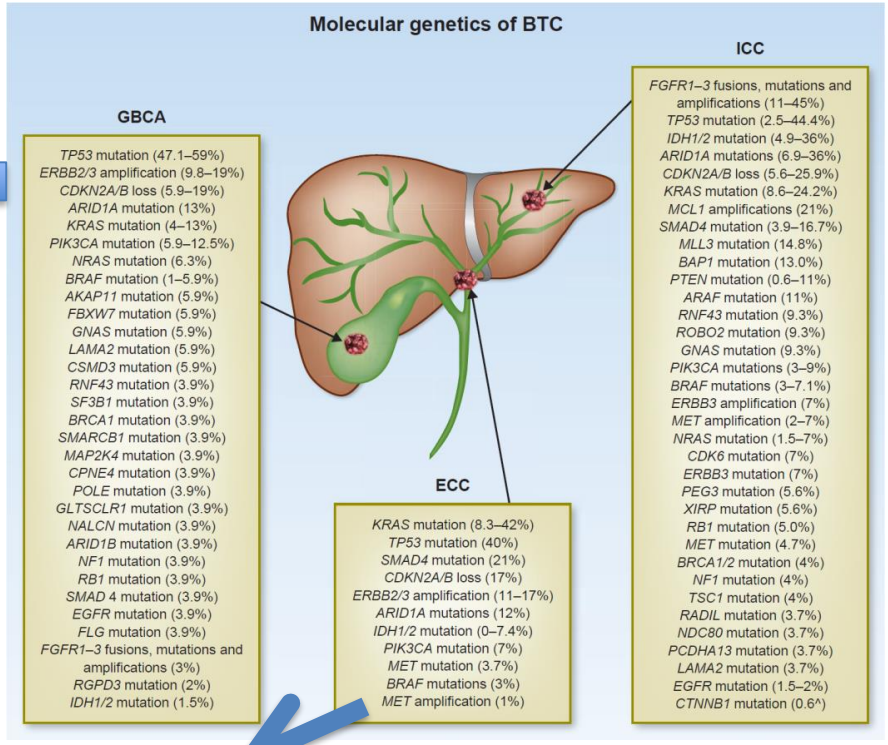
- First line therapy is chemotherapy (CDDP-GEM)-GEMOX/5FU-based is alternative
- 2d line « standard » =FOLFOX (ABC-06 modest increase in OS)
- Unselected targeted therapies do not work
- OS=12-15 months



Valle, NEJM, 2010,Lamarca, ASCO 2019,Verlingue, EJC 2017

MAIN MOLECULAR ABNORMALITES IN BTC

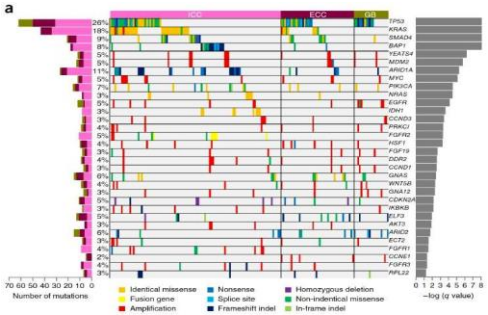
HER 2(16%)
PIK3CA
KRAS



FGFR2 fusion (10-12%)
IDH 1 IDH 2 (15-23%)
KRAS

HER2
PIK3CA
KRAS (40%)

Nakamura et al., *Nat Genet* 2015



CANCERS BILIAIRES ET CIBLES THÉRAPEUTIQUES POTENTIELLES

Analyse échantillons tumoraux

- recherche de mutations BRCA

	Cohorte totale N=1295	Extra-hépatique N=185	Intra-hépatique N=752	Vésicule biliaire N=354
BRCA 1	0,6%	2,1%	0,4%	0,3%
BRCA 2	3,0%	2,6%	2,7%	4,0%
BRCA 1 ou 2	3,6%	4,8%	3,1%	4,0%

➢ Fréquence des mutations BRCA selon la localisation

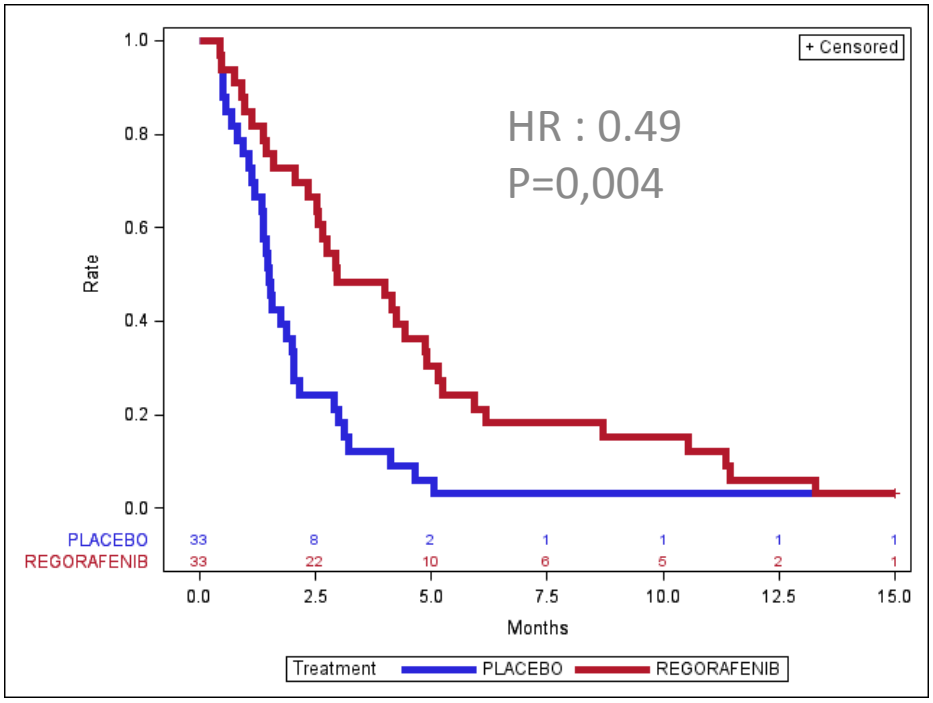
Autres altérations : IDH1 15%, FGFR2 11% (fusions 85%), BRAF 5%, ERBB2 5%, BRCA2 2.2%, MET 2%, EGFR 2%, MSI-H 1%, BRCA 1 1% FGFR3, RET, FGFR1, ALK et fusions ROS1 <0,5%
Au total, une cible potentielle thérapeutique a pu être identifiée dans 35% des cas

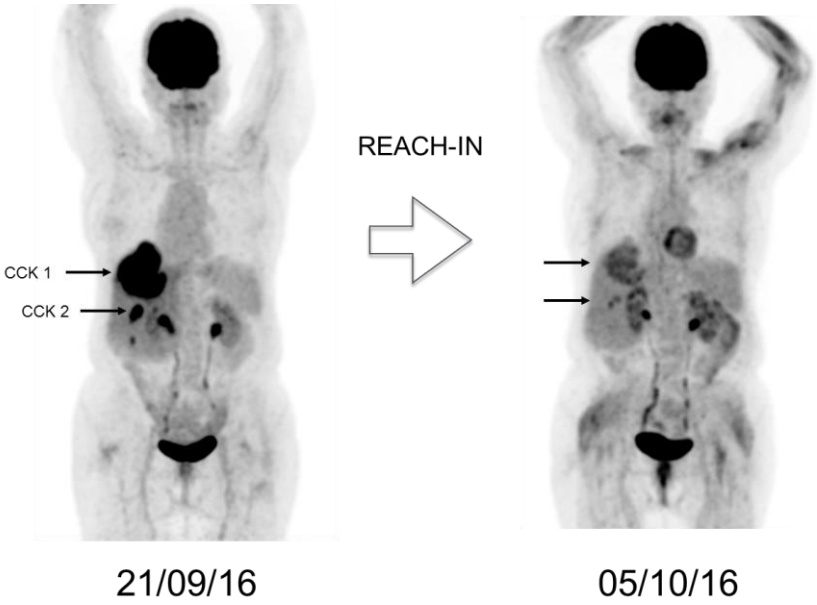
Seeber–A # 4085, ASCO 2019

TARGETED THERAPY IN BTC

- Multi targeted
  - regorafenib R Phase II > L1
- FGFR inhibitors: pan-FGFR TKI
  - Infigratinib (BGJ398) phase II
  - Pemigatinib R Phase II →phase III L1 vs chemo (FIGHT study)
  - ARQ 089 phase II > L1
- IDH1/2
  - AG 120 R phase III > L1
- Immune therapy
  - Pembrolizumab R Phase II L2. , R phase III L1 (chemo+/-pembro)
  - Nivolumab
- NTRK 1-2-3
  - Larotrectinib

REACH IN /BGDO RANDOMISED PHASE II (66 PTS) : MEDIAN PFS 3.0 VS 1.5 MONTHS FOR REGORAFENIB





Demols , ASCO 2019

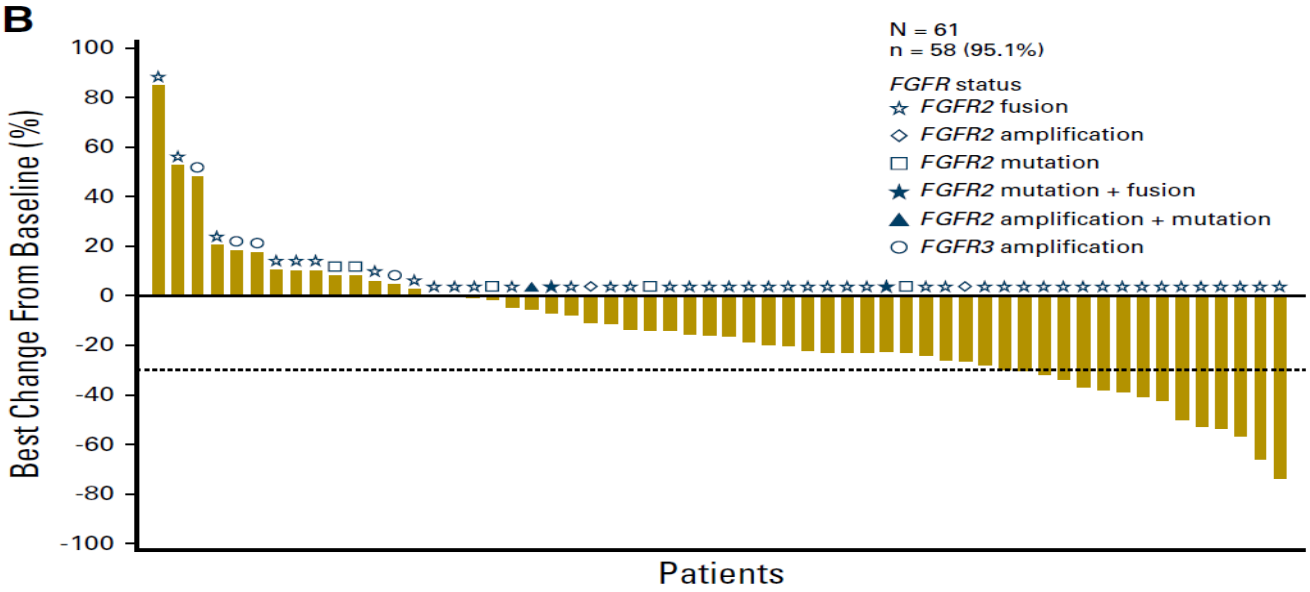
Phase II: Infigratinib

VOLUME 36 · NUMBER 3 · JANUARY 20, 2018
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Response rate 21%
Disease control 78%

Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma

Milind Javle, Maeve Lowery, Rachna T. Shroff, Karl Heinz Weiss, Christoph Springfeld, Mitesh J. Borad, Ramesh K. Ramanathan, Lipika Goyal, Saeed Sadeghi, Teresa Macarulla, Anthony El-Khoueiry, Robin Kate Kelley, Ivan Borbath, Su Pin Choo, Do-Youn Oh, Philip A. Philip, Li-Tzong Chen, Thanyanan Reungwetwattana, Eric Van Cutsem, Kun-Huei Yeh, Kristen Ciombor, Richard S. Finn, Anuradha Patel, Suman Sen, Dale Porter, Randi Isaacs, Andrew X. Zhu, Ghassan K. Abou-Alfa, and Tanios Bekaii-Saab

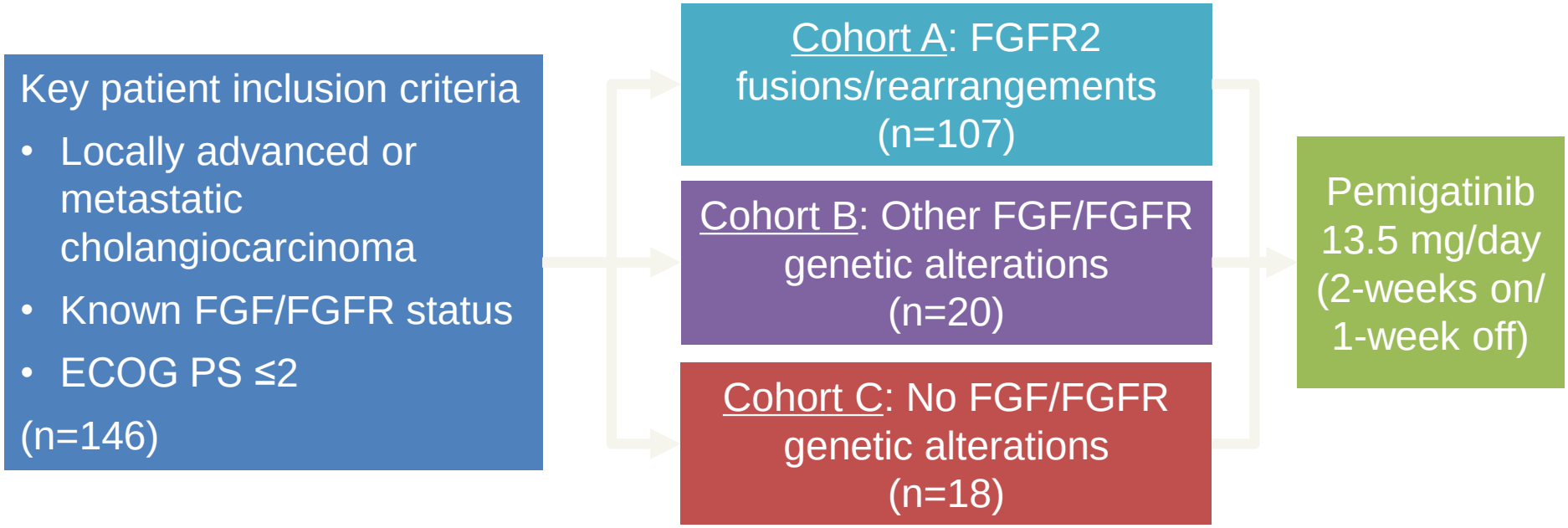


Javle et al. J Clin Oncol 2018

LBA40: FIGHT-202: A PHASE II STUDY OF PEMIGATINIB IN PATIENTS (PTS) WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC CHOLANGIOCARCINOMA (CCA) – VOGEL A, ET AL

Study objective

- To investigate the efficacy and safety of pemigatinib in patients with locally advanced or metastatic cholangiocarcinoma



PRIMARY ENDPOINT

- ORR

SECONDARY ENDPOINTS

- DoR, DCR, PFS, OS, safety

Vogel A, et al. Ann Oncol 2019;30(suppl):abstr LBA40

LBA40: FIGHT-202: A PHASE II STUDY OF PEMIGATINIB IN PATIENTS (PTS) WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC CHOLANGIOCARCINOMA (CCA) – VOGEL A, ET AL

Key results

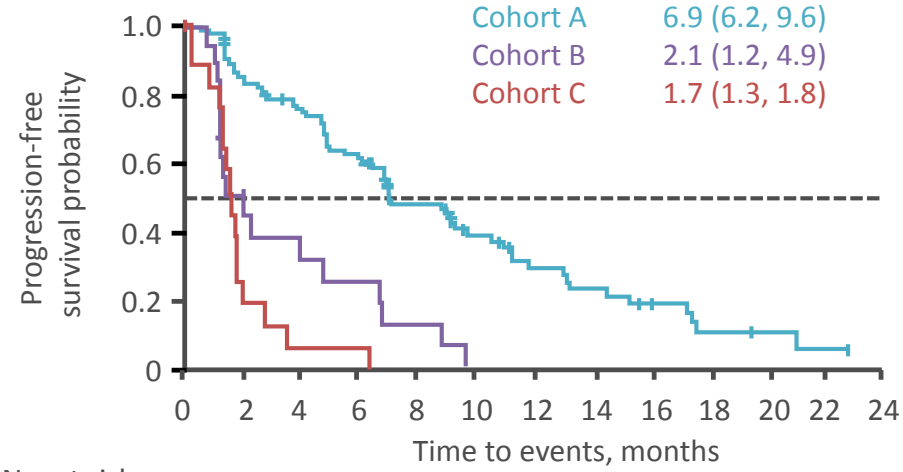
	Cohort A (n=107)	Cohort B (n=20)	Cohort C (n=18)
ORR, % (95%CI)	35.5 (26.50, 45.35)	0	0
Response, n (%)			
CR	3 (2.8)	0	0
PR	35 (32.7)	0	0
SD	50 (46.7)	8 (40.0)	4 (22.2)
PD	16 (15.0)	7 (35.0)	11 (61.1)
NE	3 (2.8)	5 (25.0)	3 (16.7)
Median DoR, months (95%CI)	7.5 (5.7, 14.5)	-	-
DCR, % (95%CI)	82 (74, 89)	40 (19, 64)	22 (6, 48)

Vogel A, et al. Ann Oncol 2019;30(suppl):abstr LBA40

LBA40: FIGHT-202: A PHASE II STUDY OF PEMIGATINIB IN PATIENTS (PTS) WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC CHOLANGIOCARCINOMA (CCA) – VOGEL A, ET AL

Key results (cont.)

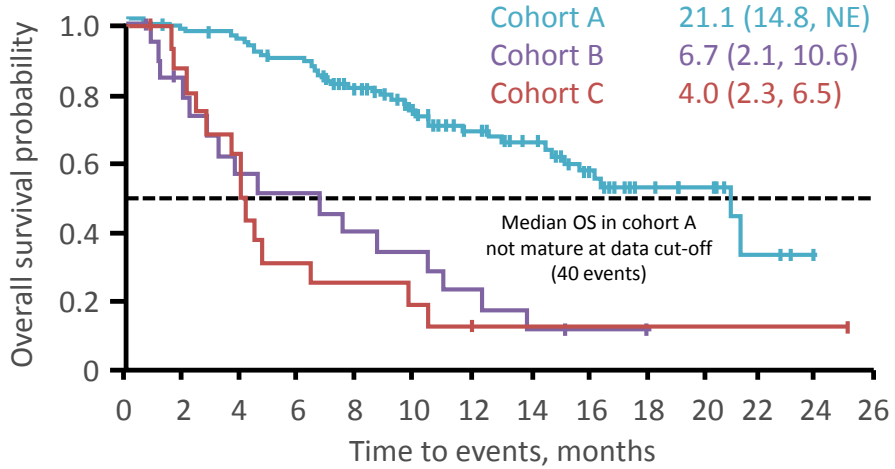
PFS



No. at risk

A	107	88	76	61	37	22	14	11	7	4	2	1	0
B	20	9	6	4	2	0	0	0	0	0	0	0	0
C	18	3	1	1	0	0	0	0	0	0	0	0	0

OS



A	107	102	99	92	73	52	41	34	24	12	9	3	0	0
B	20	14	10	9	7	6	4	2	1	1	0	0	0	0
C	18	13	8	5	4	3	1	1	1	1	1	1	1	0

	Cohort A	Cohort B	Cohort C
Median duration of follow-up, months (range)	15.4 (7.0–24.7)	19.9 (16.2–23.5)	24.2 (22.0–26.1)
Median duration of treatment, months (range)	7.2 (0.2–24.0)	1.4 (0.2–12.9)	1.3 (0.2–4.7)

Vogel A, et al. Ann Oncol 2019;30(suppl):abstr LBA40

LBA10: CLARIDHY: A GLOBAL, PHASE III, RANDOMIZED, DOUBLE-BLIND STUDY OF IVOSIDENIB (IVO) VS PLACEBO IN PATIENTS WITH ADVANCED CHOLANGIOCARCINOMA (CC) WITH AN ISOCITRATE DEHYDROGENASE 1 (IDH1) MUTATION

Study objective

- To investigate the efficacy and safety of ivosidenib in patients with advanced cholangiocarcinoma and IDH1 mutation

Key patient inclusion criteria

- Advanced cholangiocarcinoma
- IDH1 mutation status by NGS
- 1–2 prior therapies (at least 1 gemcitabine or 5FU-containing regimen)
- ECOG PS 0–1

(n=185)

R 2:1

Ivosidenib 500 mg/day (n=124)

Placebo (n=61)

Stratification

- Number of prior therapies

Crossover permitted at radiographic PD

PRIMARY ENDPOINT

- **PFS**

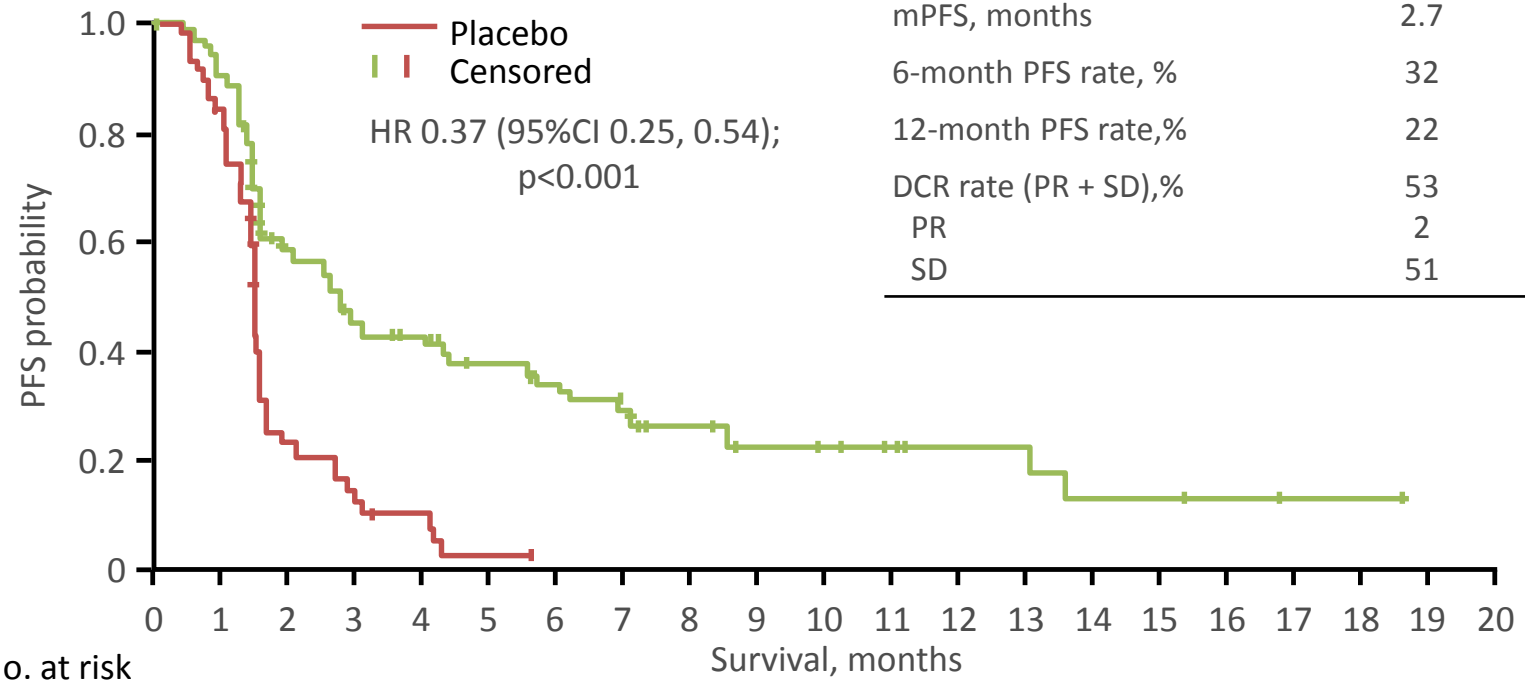
SECONDARY ENDPOINTS

- OS, ORR, QoL, safety

Abou-Alfa GK, et al. Ann Oncol 2019;30(suppl):abstr LBA10_PR

LBA10_PR: CLARIDHY: A GLOBAL, PHASE III, RANDOMIZED, DOUBLE-BLIND STUDY OF IVOSIDENIB (IVO) VS PLACEBO IN PATIENTS WITH ADVANCED CHOLANGIOCARCINOMA (CC) WITH AN ISOCITRATE DEHYDROGENASE 1 (IDH1) MUTATION

Key results



PFS

	Ivosidenib	Placebo
mPFS, months	2.7	1.4
6-month PFS rate, %	32	NE
12-month PFS rate,%	22	NE
DCR rate (PR + SD),%	53	28
PR	2	0
SD	51	28

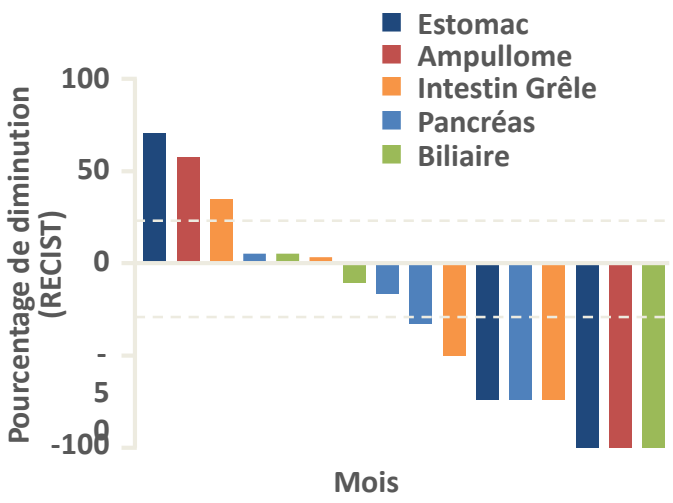
Abou-Alfa GK, et al. Ann Oncol 2019;30(suppl):abstr LBA10_PR

PEMBROLIZUMAB AND MSI CANCERS

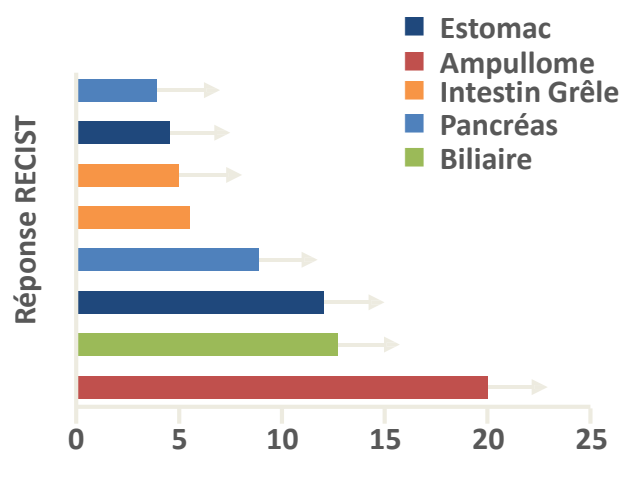
- Response rate : 47 % (n = 8)
- Tumoral control rate : 76 % (n = 13)
- Follow up : 5,3 months

!!! MSI high
- GBC: 5%
- ICC: 5-13%
- ECC: 5-10%

Objective response



Response duration



D.T. Le *et al.*,NEJM,2018

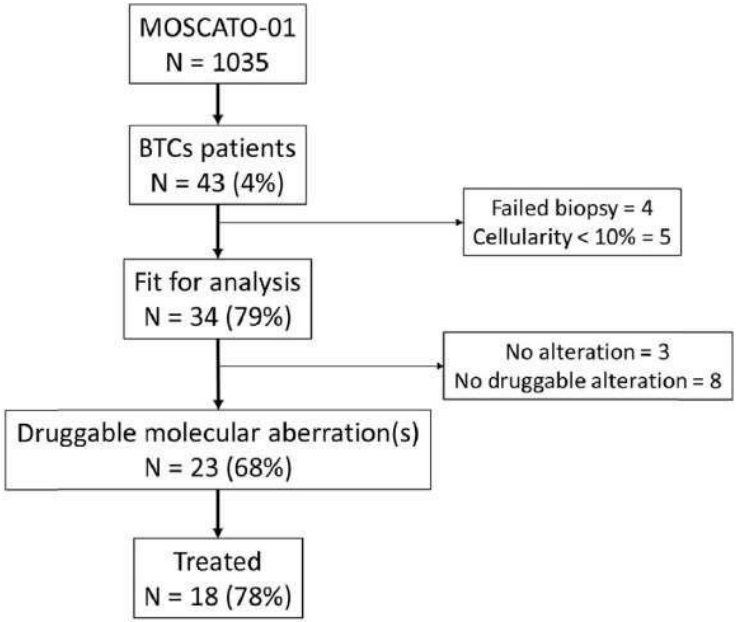
PEMBROLIZUMAB AND BTC AFTER L1

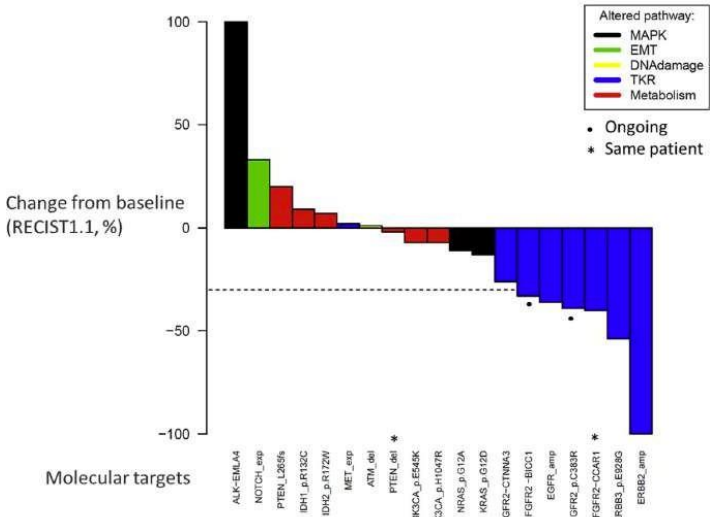
	Global Population N=104	PLD1+ N = 61	PLD1- N = 34
Objective response	5.8%	6.6%	2.9%
Partial response	6 (5,8%)	4 (7%)	1 (3%)
Stable disease	17 (16%)	6 (10%)	11 (32%)
Progression	65 (63%)	44 (72%1)	17 (50%)
PFS	2	1,9	2.1
OS	9,1	7,2	9,6

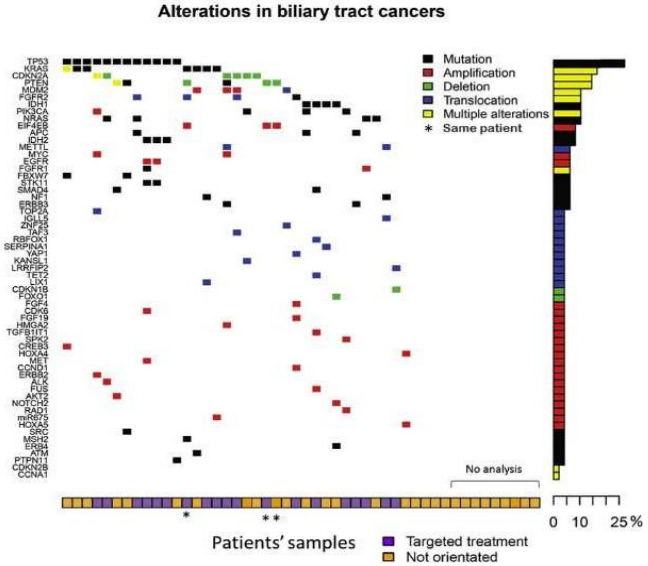
ORR modest but DOR interesting

Pruitt SK et al. - ESMO® 2018 - Abs. 625 PD

MOLECULAR-DRIVEN THERAPY IN BTC: THE MOSCATO-01 TRIAL (IGR)





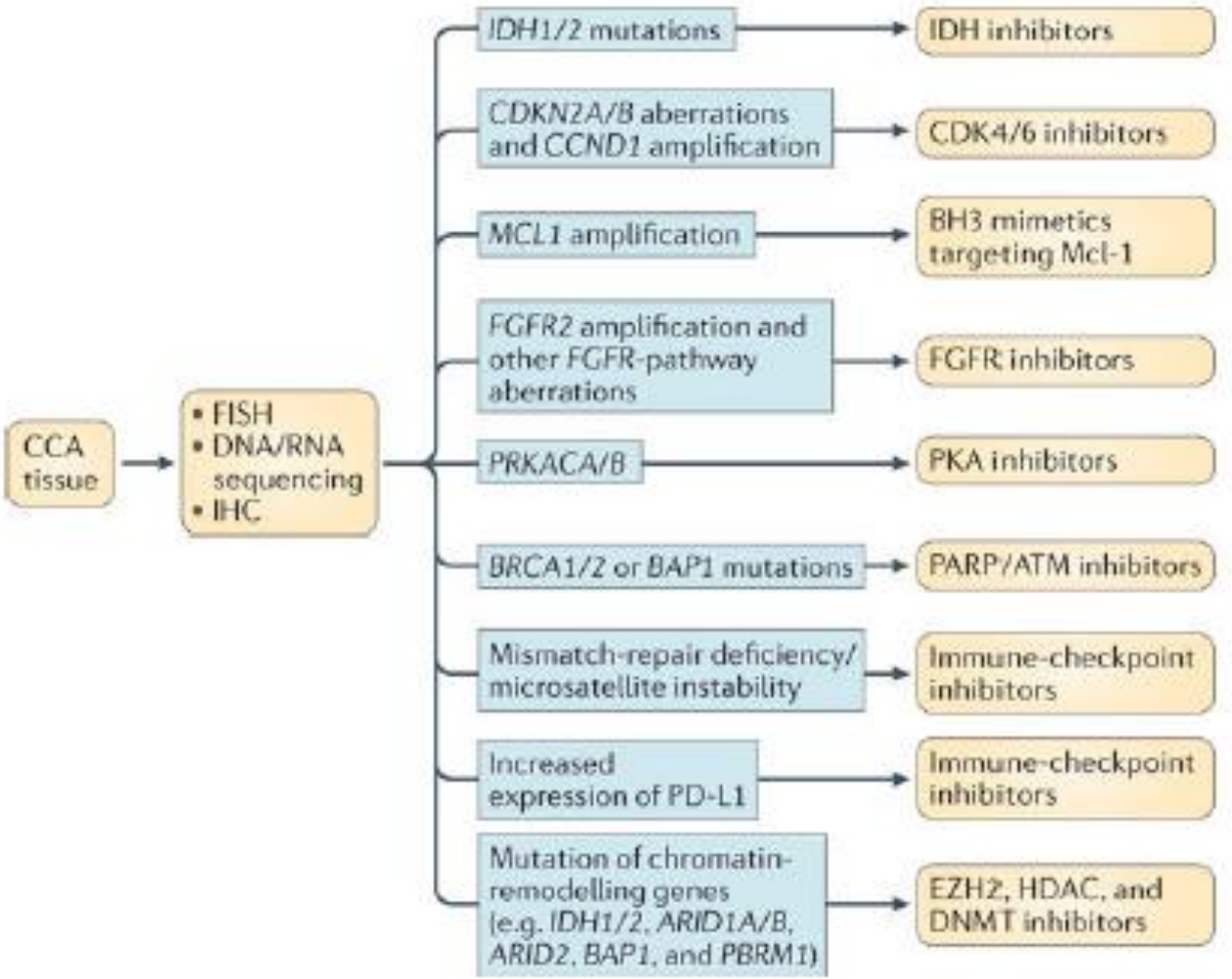


- ORR :33%, DCR :88%
- PFS 2/PFS 1 :1,3
- very good responders :FGFR2,ERBB2,ERBB3
- mOS=17 months vs 5 (non molecular – driven)

Verlingue et al., *Eur J Cancer* 2017

Molecular alteration			Incidence	Patients treated
No targetable alteration			40%	217
Targets and drugs	'Established' targets and drugs	FGFR fusion	10%	40
		IDH1 mutation	10%	40
		HER2 amplification	10%	40
		HER2/HER3 mutation	5%	20
		MSI	3%	12
		BRAF V600E mutation	3%	10 + 5
		BRCA mutation	3%	12
		N-TRK fusion	<1%	2
	'Experimental' targets and drugs	KRAS mutation	15%	84
		BRAF non V600E mutation	1.5%	7
		cMET amplification	3%	17
		BAP1/BRCAness	3%	17
		ATM (non-MSI)	<5%	17

TOWARDS GENE-DRIVEN TRIALS IN BTC



BTC : TAKE HOME IN PRACTICE

- Chemotherapy active but limited efficacy (L1-L2)
- Molecular-driven therapies desirable in BTC: a lot of targetable genes (+/- 50% of tumors)with potential survival benefit →trials
- (M)TKI are of benefit (regorafenib?), rather in selected populations (FGFR,IDH..)
- I/O needs more consistent data