Memorial Sloan Kettering
Cancer Center

Genetics and Molecular Alterations in Pancreatic Cancer

ESMO World GI Congress July 3rd, 2019

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Disclosures

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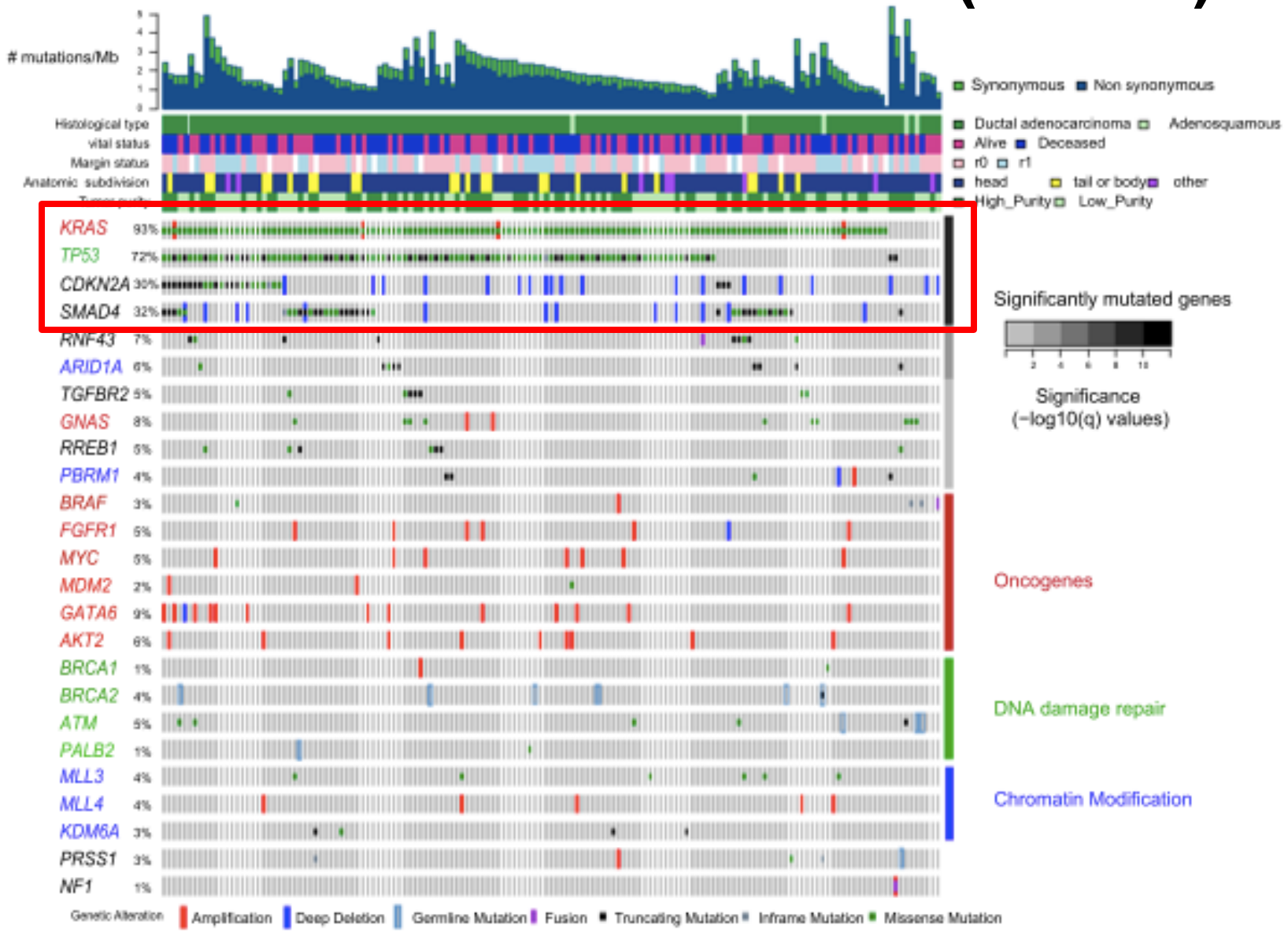
Olaparib, rucaparib, veliparib, niraparib, ipilimumab, nivolumab

Agenda

- Molecular landscape of PDAC
- Somatic and germline testing in PDAC
- DNA damage repair directed strategies
  - Platinum agents
  - PARP inhibitors

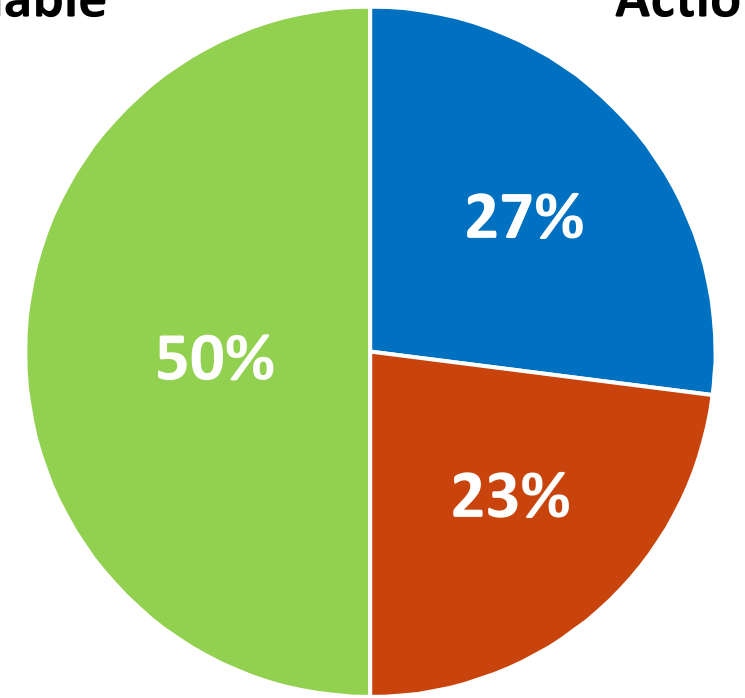
The Pancreatic Cancer Genome (TCGA)

KRAS WT 7-8%



Aguirre, A. Cancer Cell, 2017 Pancreas TCGA

Know Your Tumor: Actionable Somatic Alternations



Modifies Options
(Pathway implication: WNT, AKT, MET, etc)

Highly Actionable

- *BRCA1/2*
- *PALB2*
- *ATM*
- *CHEK1/2*
- *FANCA/C*

Platinum/PARP inhibitor

- *NTRK1/3* — TRK inhibitor
- *ALK* — ALK inhibitor
- *ROS1* — ROS inhibitor
- *BRAF* — BRAF inhibitor
- *FGFR1/4* — FGFR inhibitor
- *ERBB2* — HER2 inhibitor
- *TOP2A* — Anthracycline
- *CDK4/6* — CDK inhibitor
- *STK11*
- *AKT1/2/3*
- *TSC12*
- *RET*

mTOR/AKT inhibitor

Pishvaian, M. Clin Cancer Res. 2018.

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Dana Farber PDAC Profiling

- Real-time genomic profiling in CLIA-environment
  - Whole genome sequencing in clinically actionable timeframe
  - RNA sequencing for integrated analysis

- Clinically relevant alterations in PDAC
  - 42% theoretically actionable
  - 25% two or more alterations
  - 8% germline findings

Aguirre, A. Cancer Cell, 2017 Pancreas TCGA
Aguirre, A. Cancer Disc, 2018

MSK: *KRAS* Wild-Type (N= 19)

	Samples	Alteration
1	Intraductal tubulopapillary neoplasm	FGFR2-MYOF fusion
2	EBV poorly differentiated carcinoma	FAT1 nonsense
3	Adenocarcinoma with mucinous features	NTRK3-ETV fusion
4	Colloid carcinoma arising from IPMN	GNAS R201C
5	Colloid carcinoma	GNAS R201H
6	Pancreas adenocarcinoma	MGA nonsense
7	Pancreas adenocarcinoma	BRCA2 loss (also germline)
8	Pancreas adenocarcinoma	TP53 mutant, RB1 loss
9	Pancreas adenocarcinoma	TP53 mutant, CDKN2A, MYC AMP
10	Pancreas adenocarcinoma	TP53 mutant, CDKN2A, SMAD4 loss, MYC AMP
11	Pancreas adenocarcinoma	ERBB2 AMP, CDKN2A loss
12	Pancreas adenocarcinoma	APC Missense
13	Pancreas adenocarcinoma	TP53 mutant, APC missense, NCOR1 amp
14	Pancreas adenocarcinoma	CCNE1 AMP
15	Pancreas adenocarcinoma	BRAF V600E, SMAD4 Loss
16	Pancreas adenocarcinoma	SMARCB1 loss
17	Pancreas adenocarcinoma	BCOR loss
18	Pancreas adenocarcinoma	ROS1-SLC4A4 Fusion, ATM loss, ERBB2 AMP
19	Pancreas adenocarcinoma	TP53 mutant, SMAD4 loss, BRAF-JHDM1Dfusion

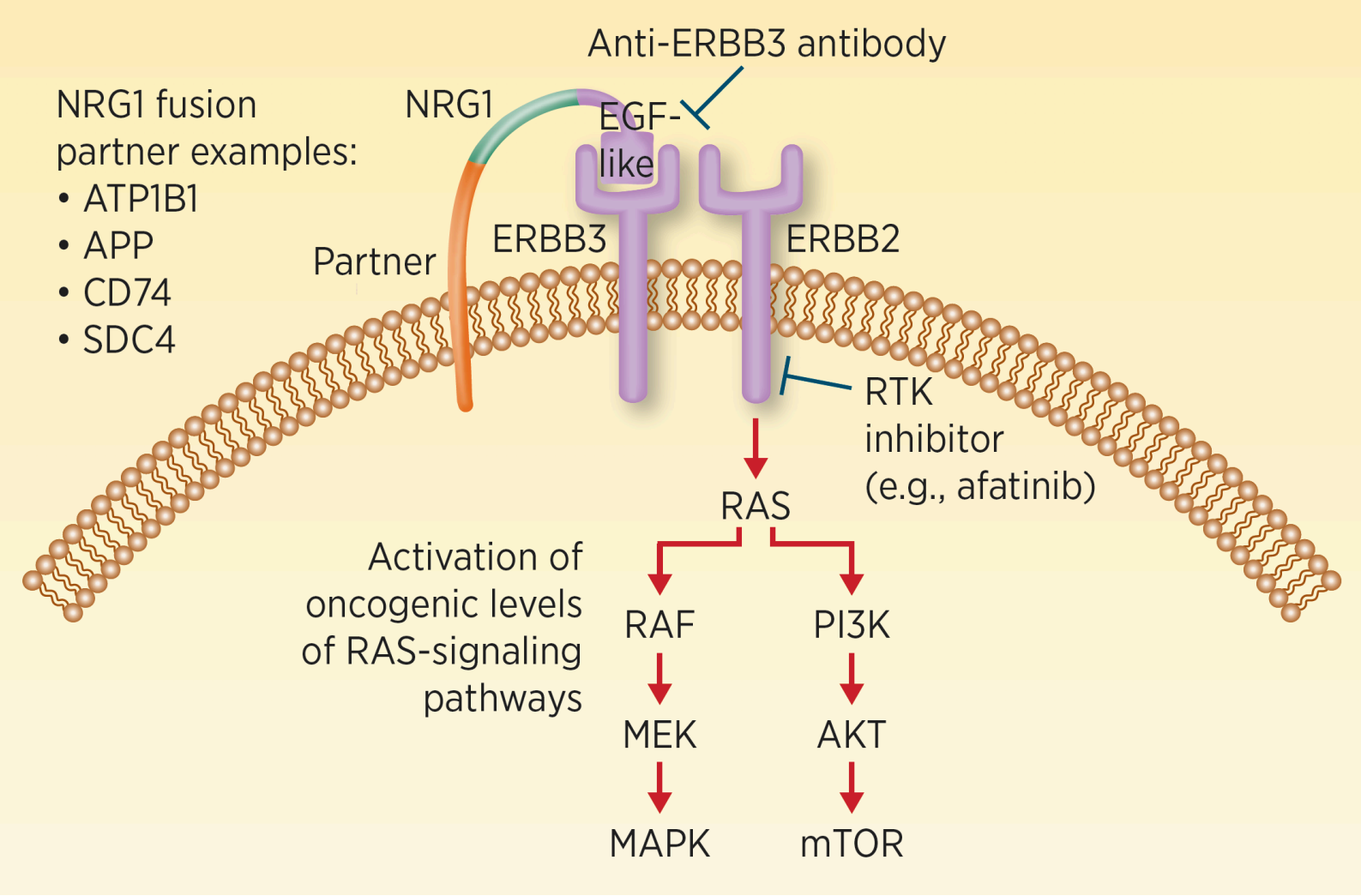
NRG-1 fusion
Cancer Discovery, 2018
CCR, 2018

MSK data 2019
N= 24 NRG-1 fusions
N= 7, PDAC, *KRAS*-WT
(after NSCL)

G12C *KRAS*-mut PDAC*
1-2%

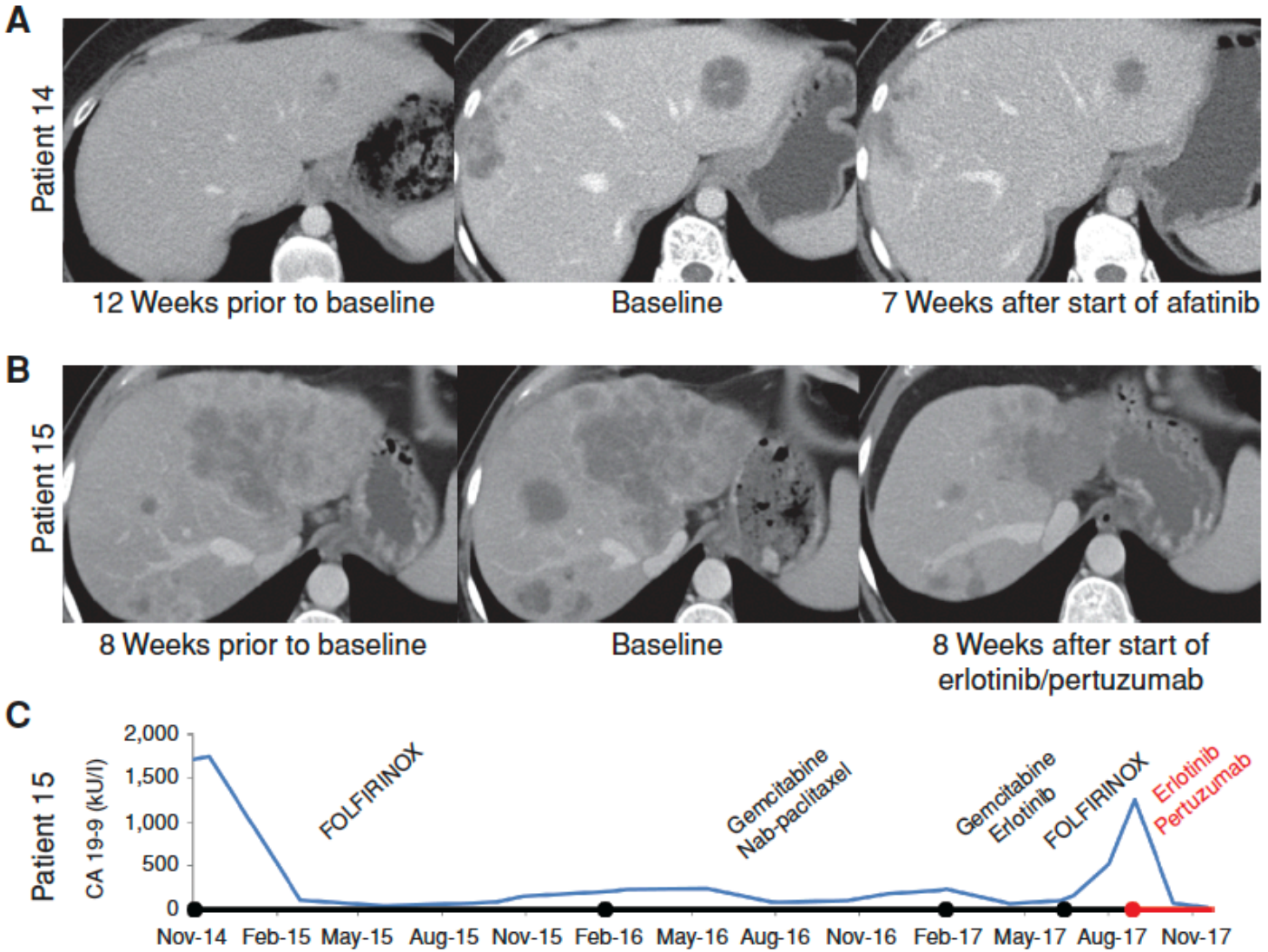
Lowery, M..O'Reilly, EM. Clin Cancer Res, 2017. Schram, et al. J Clin Oncol, 2019, Abst #3129

Targeting NRG-1 Fusions in PDAC



Clin Cancer Research, 2019

Treatment Response in NRG-1 Fusion PDAC



Heining. Cancer Discovery, 2018

PDAC and Mismatch Repair Deficiency

- Literature sparse
- Varied on germline vs sporadic gene associated

Author	N	MMR-D	Germline vs Sporadic	Reference
Humphris	385	4 (1%)	Somatic inactivation MSH1, MSH2	Gastro, 2016
Connor	160	4 (2%)	3 germline; 1 somatic	JAMA Oncol, 2016
Yamamoto	103	16 (15.5%)	6 MLH1 promotor hypermethylation	Can Res, 2001

More recent NGS studies ~1-2% frequency

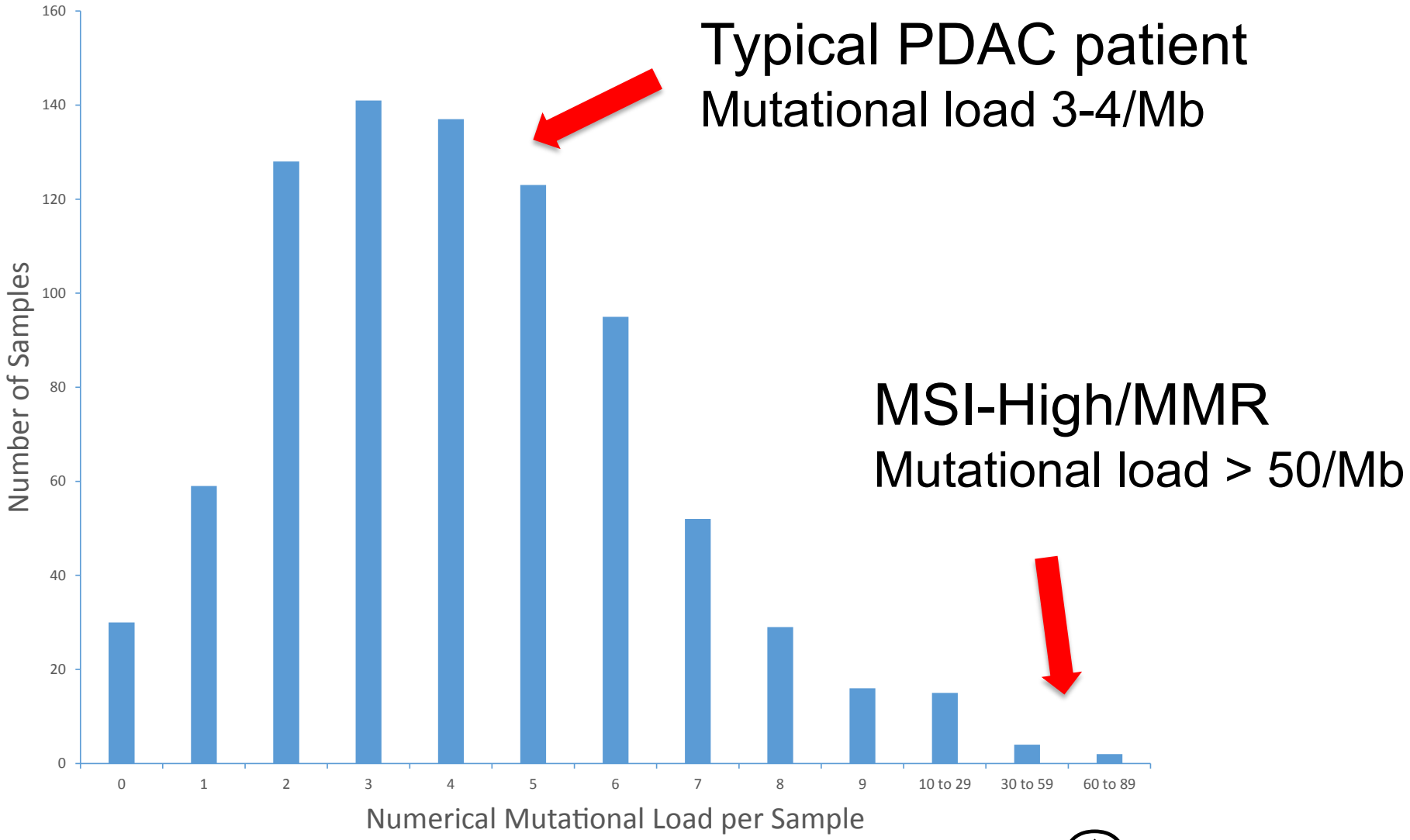
MSK: PDAC and Microsatellite Instability

- N= 833 NGS
- 7/833 (0.8%) MMR-D; all Lynch syndrome (germline)
  - 4 anti-PD1 therapy; 4 response (1 CR, 2 PR, 1 SD)

- MMR-D PDAC associated with:
  - Loss of MMR protein expression
  - High mutational tumor load
  - Elevated MSI sensor score (> 10) by NGS

Hu, Z, O'Reilly, EM. Clinical Cancer Research, 2018

Mutational Load in PDAC (N= 831)



Hu, Z, O'Reilly, EM. Clinical Cancer Research, 2018

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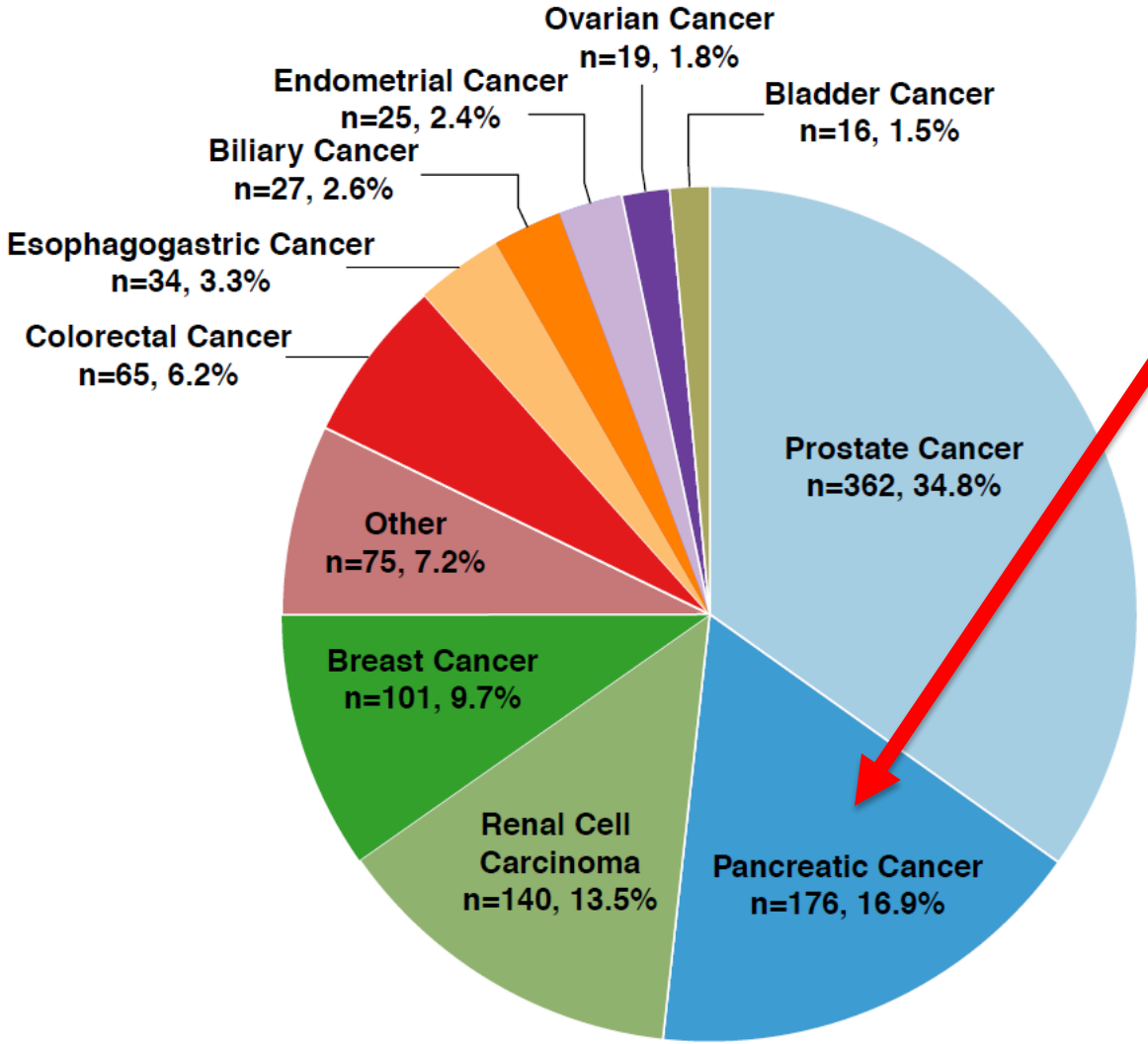
MSK IMPACT: Germline Testing N= 1,040



PDAC N= 176 (16.9%)

BRCA 1
BRCA 2
CDKN2A
PALB2
ATM
CHEK2
APC
MUYTH

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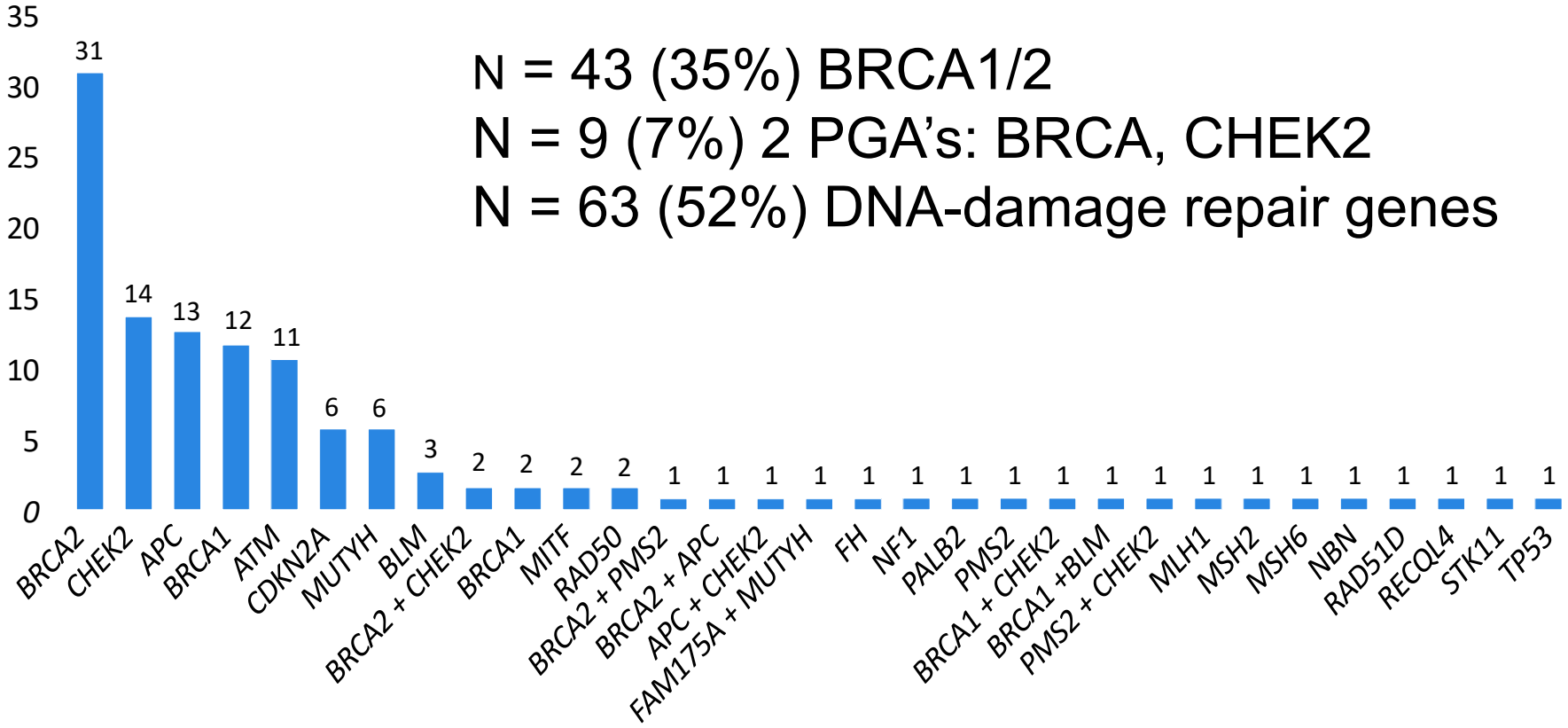
Spectrum of Pathogenic Germline Alterations (PGA)
N= 122/615 (19%) in 24 genes



N = 43 (35%) BRCA1/2

N = 9 (7%) 2 PGA's: BRCA, CHEK2

N = 63 (52%) DNA-damage repair genes

Lowery. M…. O'Reilly, EM. J Nat Cancer Inst. 2018

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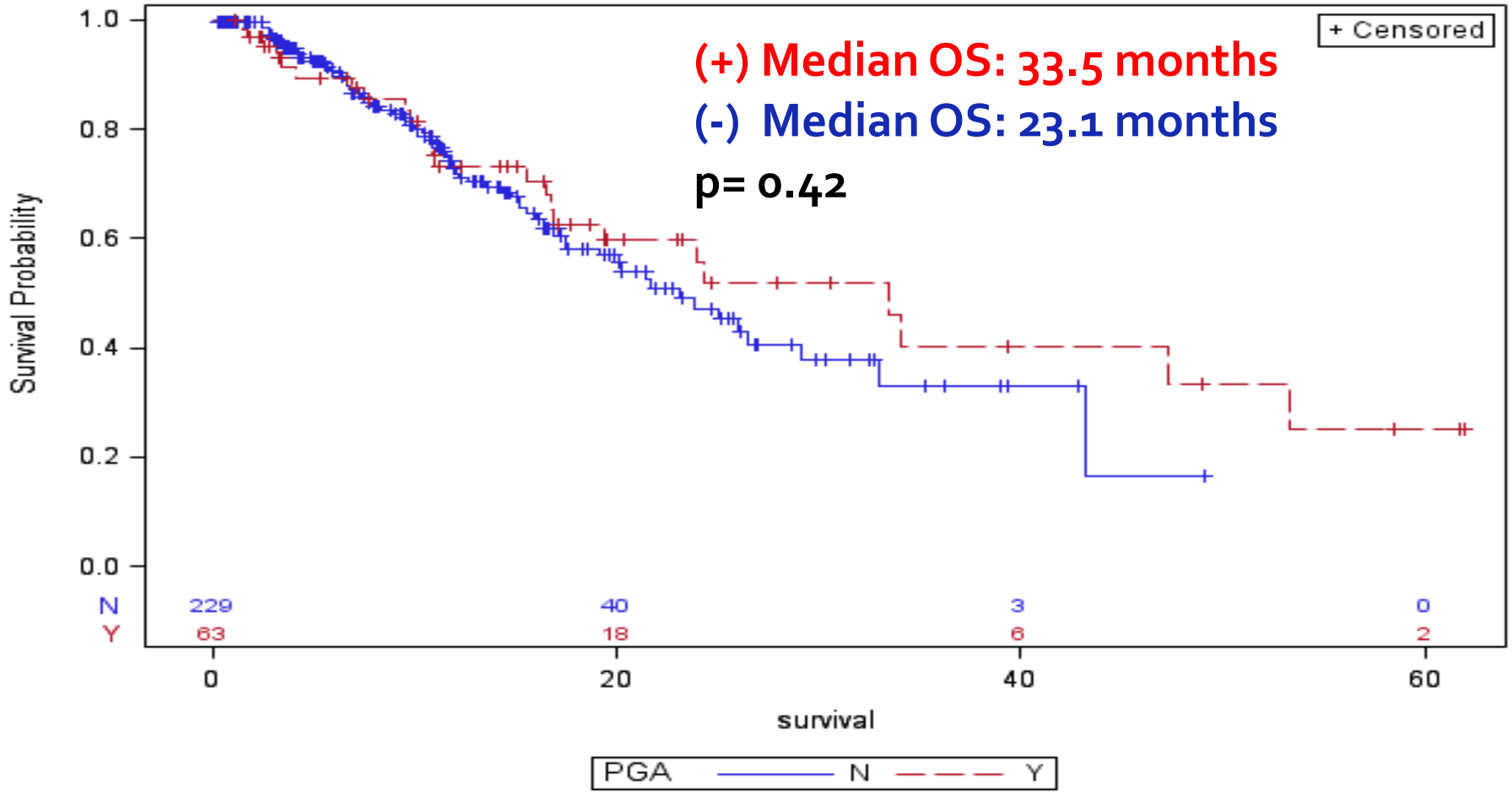
Survival in PDAC With/Without Germline Mutation (N= 292) Advanced Disease Cohort



Lowery. M…. O'Reilly, EM. J Nat Cancer Inst. 2018

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Multi-Gene Panel Testing in PDAC

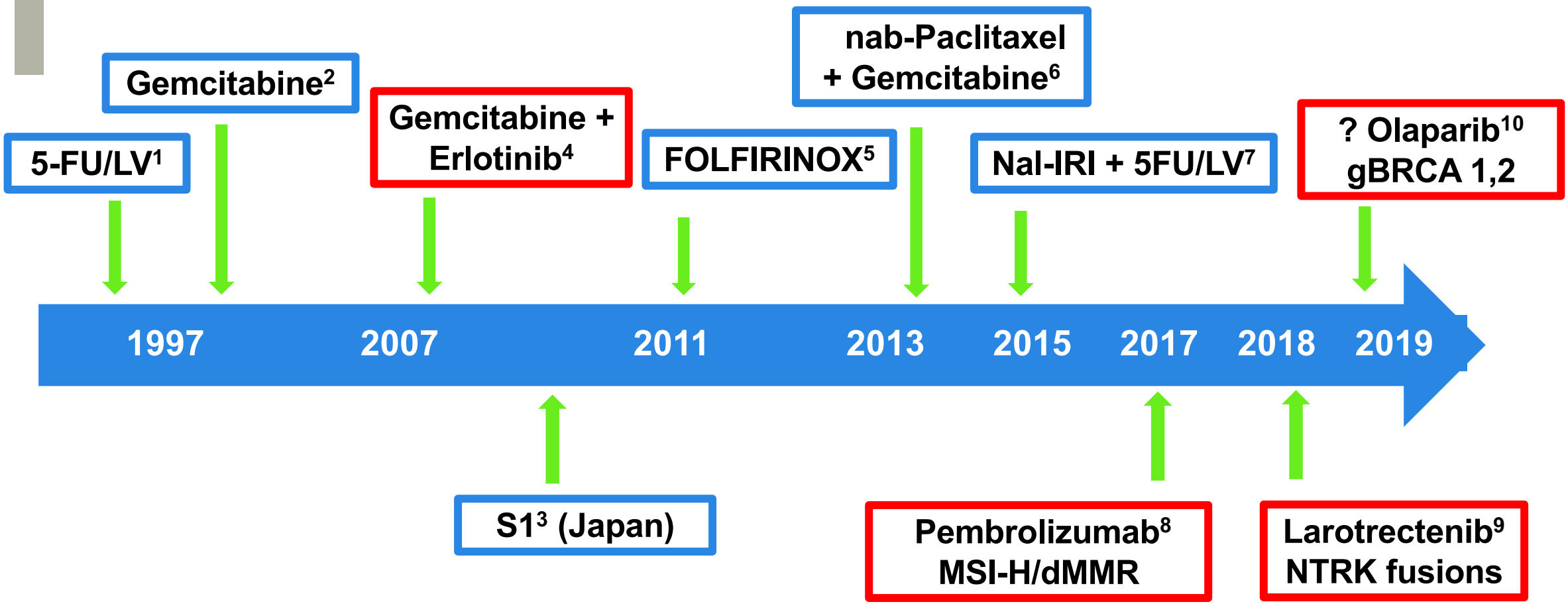
Study	N	# Genes	Germline Mutations	Comments
Shindo et al. JCO 2017	854	32	3.9% 3.5% PDAC genes	15% Familial syndrome 9% Family hx PDAC
Hu et al. CEBP 2016	96	22	13.5% 9.4% PDAC genes	
Lowery et al. JNCI 2018	615	76-88	19.8% 12.2% PDAC genes	**42% Did not meet testing guidelines**
Yurgelun et al. GIM 2018	289	24	9.7%	
Hu et al. JAMA 2018	3,030	21	5.9% 5.5% PDAC genes	7.9% Family hx PDAC

Courtesy: Zsofia Stadler, MD (with thanks)

NCCN Updated Guidelines v2.2019

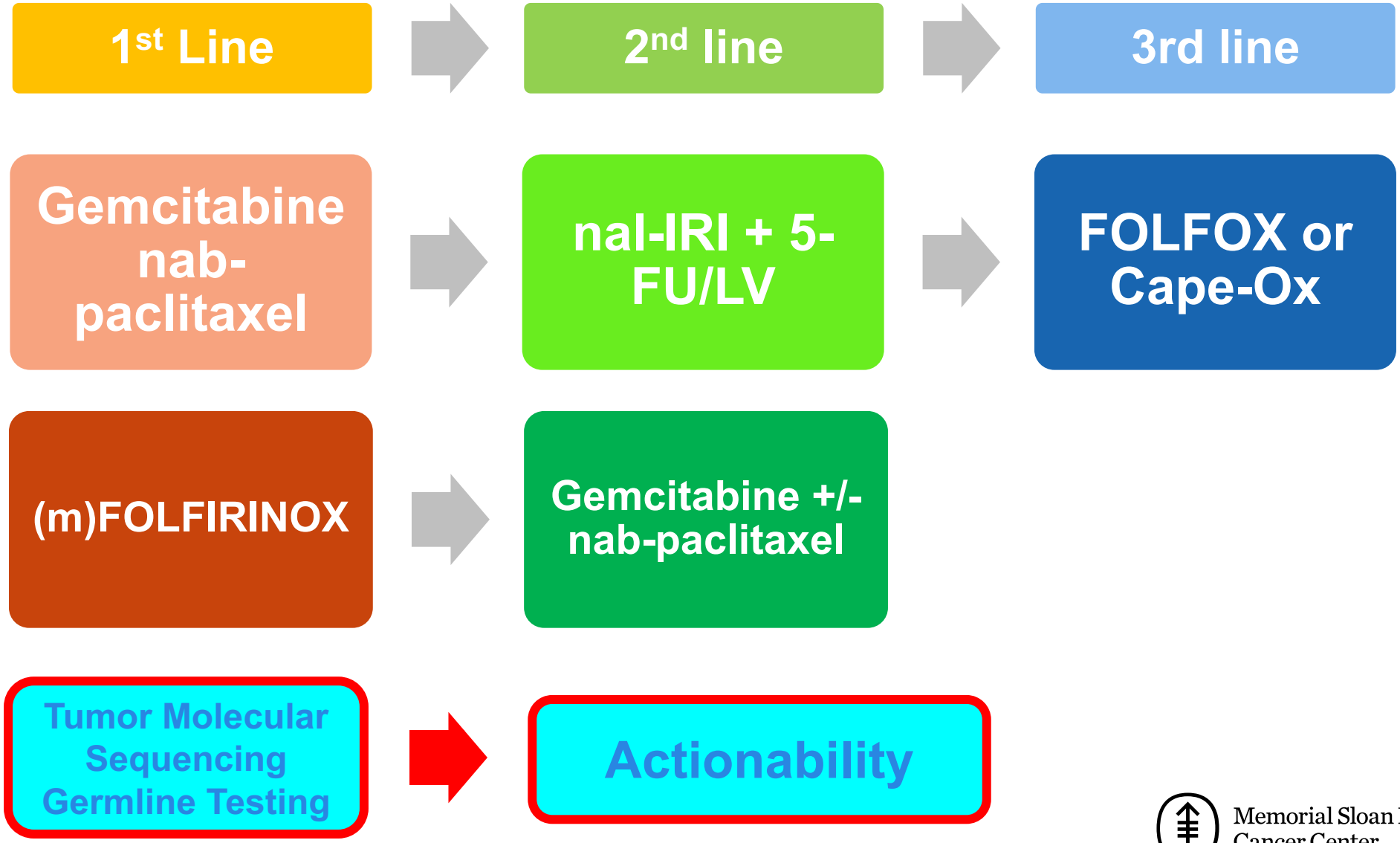
- NCCN Pancreatic cancer (Version I.2019 – 11/8/2018)
  - **Tumor/somatic profiling recommended** for all locally advanced/metastatic patients who are candidates for anti-cancer therapy to identify uncommon actionable mutations
    - Tissue testing preferred
    - cfDNA back up if insufficient tumor
  - **Germline testing recommended** for any patient with PDAC
    - Multigene panel

Therapeutic Landscape for PDAC 2019



1. Glimelius B. Ann Oncol. 1996. 2. Burris HA 3rd. J Clin Oncol. 1997. 3. Ueno H. J Clin Oncol. 2013. 4. Moore MJ. J Clin Oncol. 2007. 5. Conroy T. N Engl J Med. 2011. 6. Von Hoff DD. N Engl J Med. 2013. 7. Wang-Gillam A. Lancet. 2916. 8. Le DT. N Engl J Med. 2015. 9. Drilon A. N Engl J Med, 2018. 10. Golan, T. N Engl J Med. 2019

Therapeutic Approach in PDAC 2019



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Targeting Genetic Subgroups in Pancreas Adenocarcinoma

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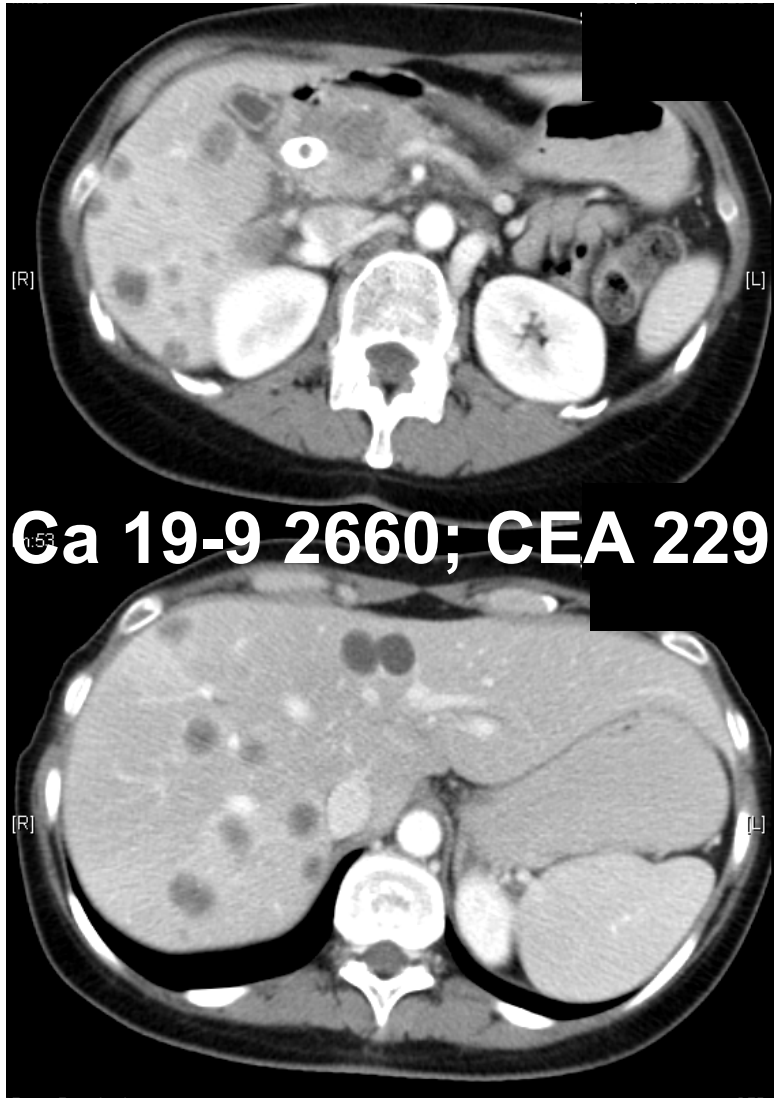
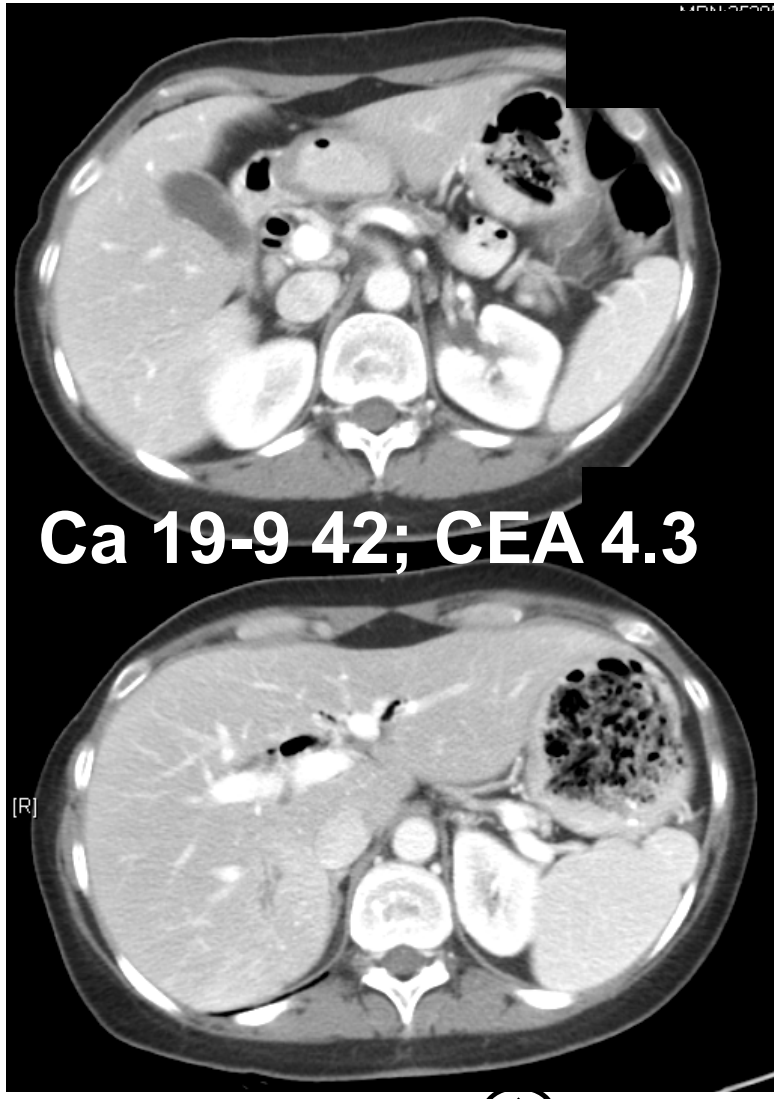
PDAC *BRCA1* Mutation: Profound and Durable Response to Platinum, PARP Inhibitor Therapy





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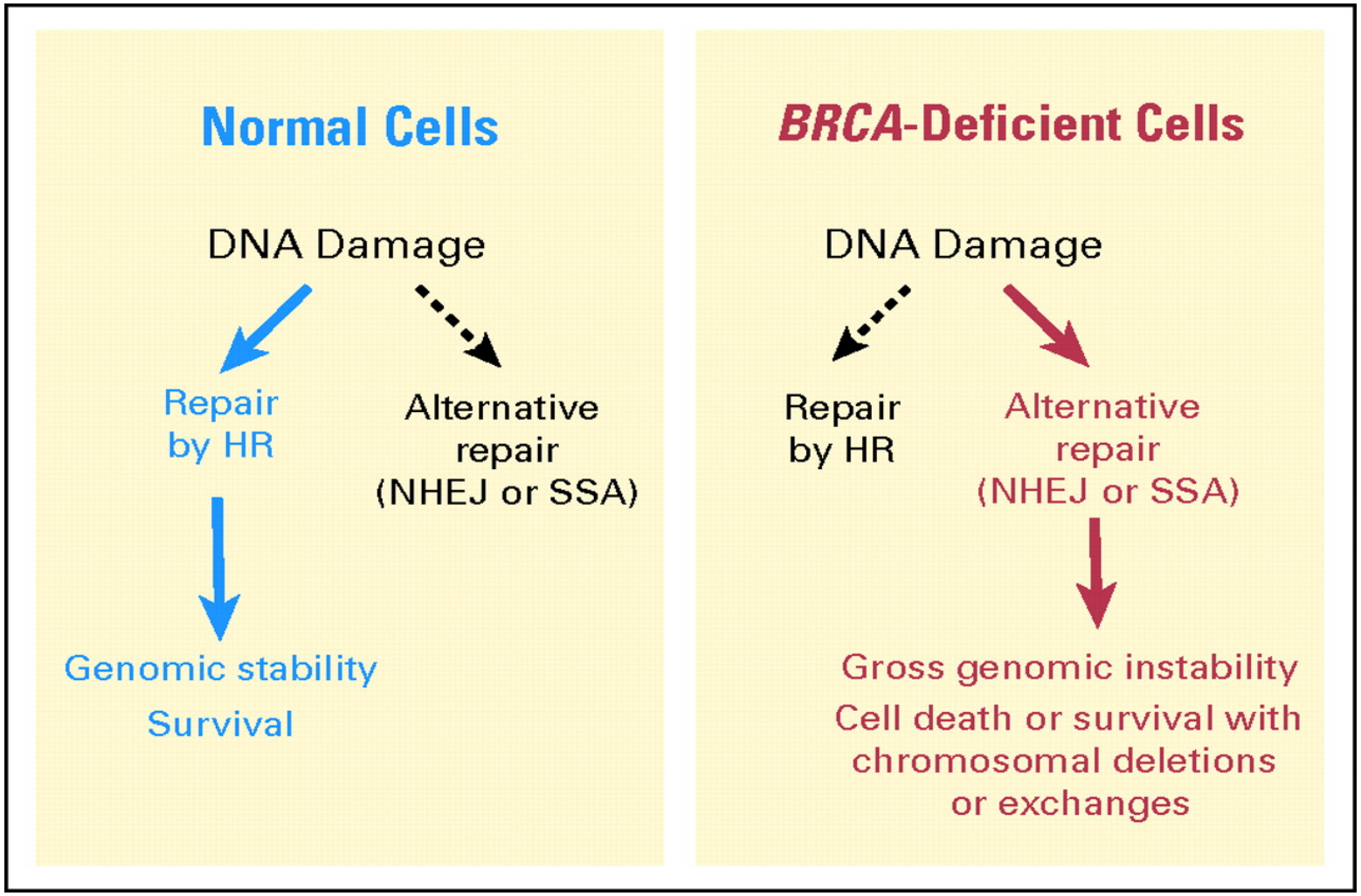
Loss of Functional BRCA 1/2 Affects DNA-Double-Strand Repair Pathway



Ashworth, et al. J Clin Oncol, 2008

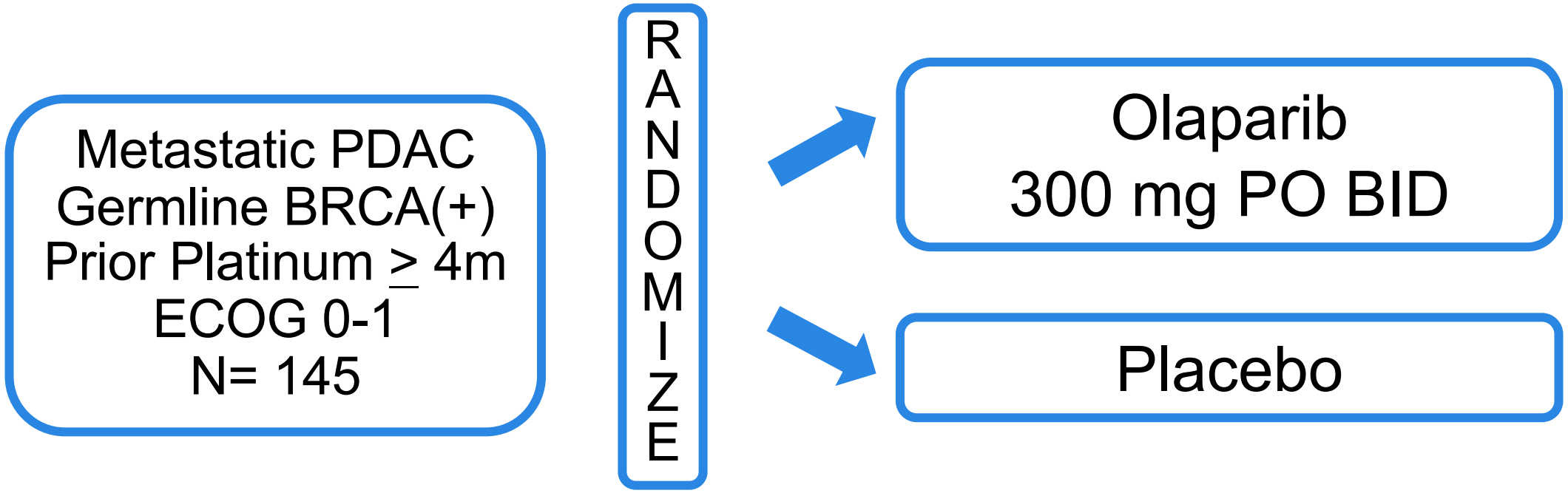
Know Your Tumor
Pancreas Cancer Action Network

- N= 822
  - Resected vs advanced
  - HR-DDR mutated (gene profile) vs proficient
  - Platinum treated vs platinum naiive
- Results
  - 17% HR DNA-damage response mutations
  - No prognostic impact for HR-DDR platinum naiive
  - Platinum therapy conferred survival benefit
    - Resected: 4.35 vs 3 years (p= 0.1)
    - Advanced 2.37 vs 1.45 years (p< 0.0001)

Pishvaian, M. Gastrointestinal Cancers Symposium, 2019. In press, 2019

Maintenance Therapy in Germline BRCA Pancreas Adenocarcinoma

Phase III Maintenance (POLO): ASCO 2019
Platinum Therapy → Olaparib/Placebo



Randomization 3: 2

Primary Endpoint: PFS (blinded independent central review mRECIST 1.1)

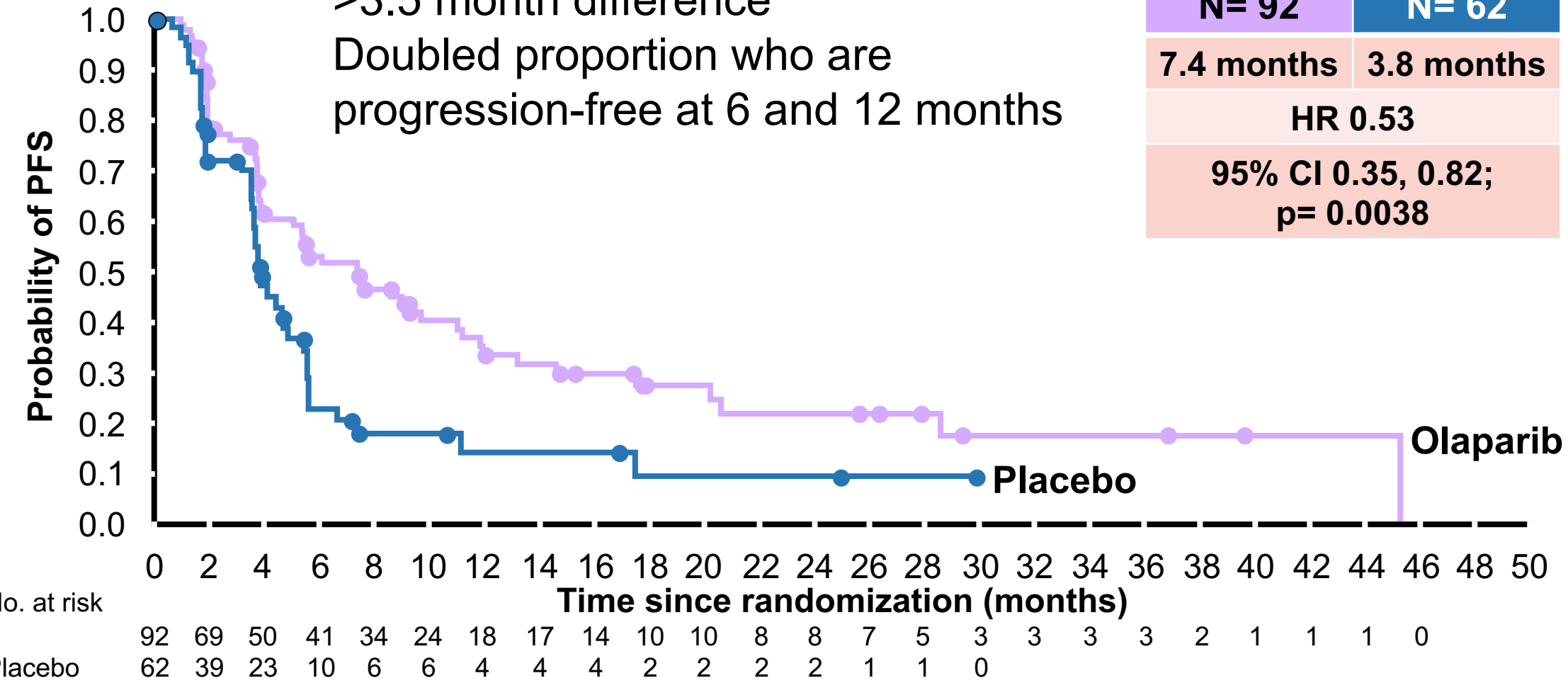
N ~ 3,500 screened

Golan, T. New Engl J Med, 2019

Primary Endpoint: Blinded Central Review

>3.5 month difference
Doubled proportion who are progression-free at 6 and 12 months

Olaparib N= 92	Placebo N= 62
7.4 months	3.8 months
HR 0.53	
95% CI 0.35, 0.82; p= 0.0038	



No. at risk

	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								

Golan, T. New Engl J Med, 2019

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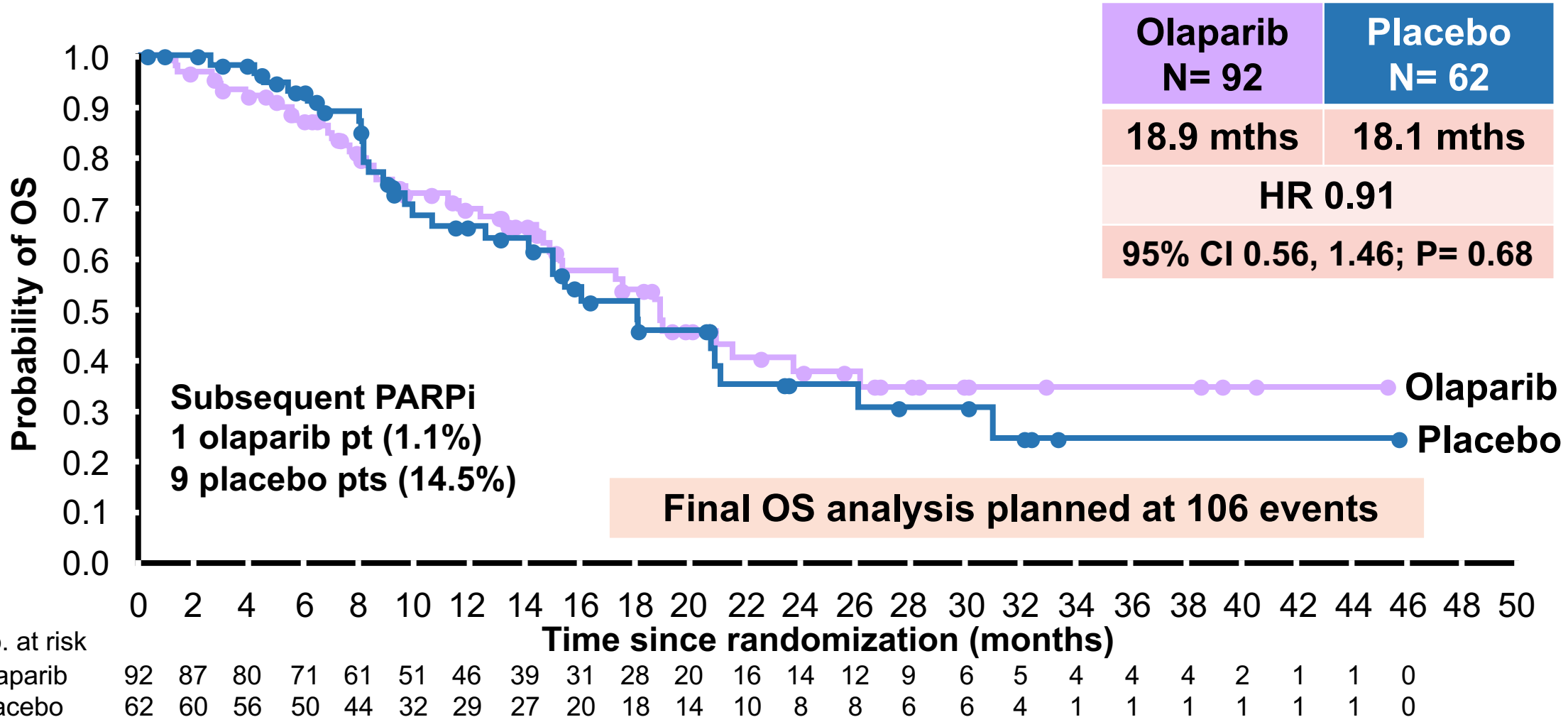
Overall Survival (46% Maturity)



	Olaparib N= 92	Placebo N= 62
	18.9 mths	18.1 mths
	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

Golan, T. New Engl J Med, 2019

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PARP Inhibitors in Previously Treated Pancreas Adenocarcinoma

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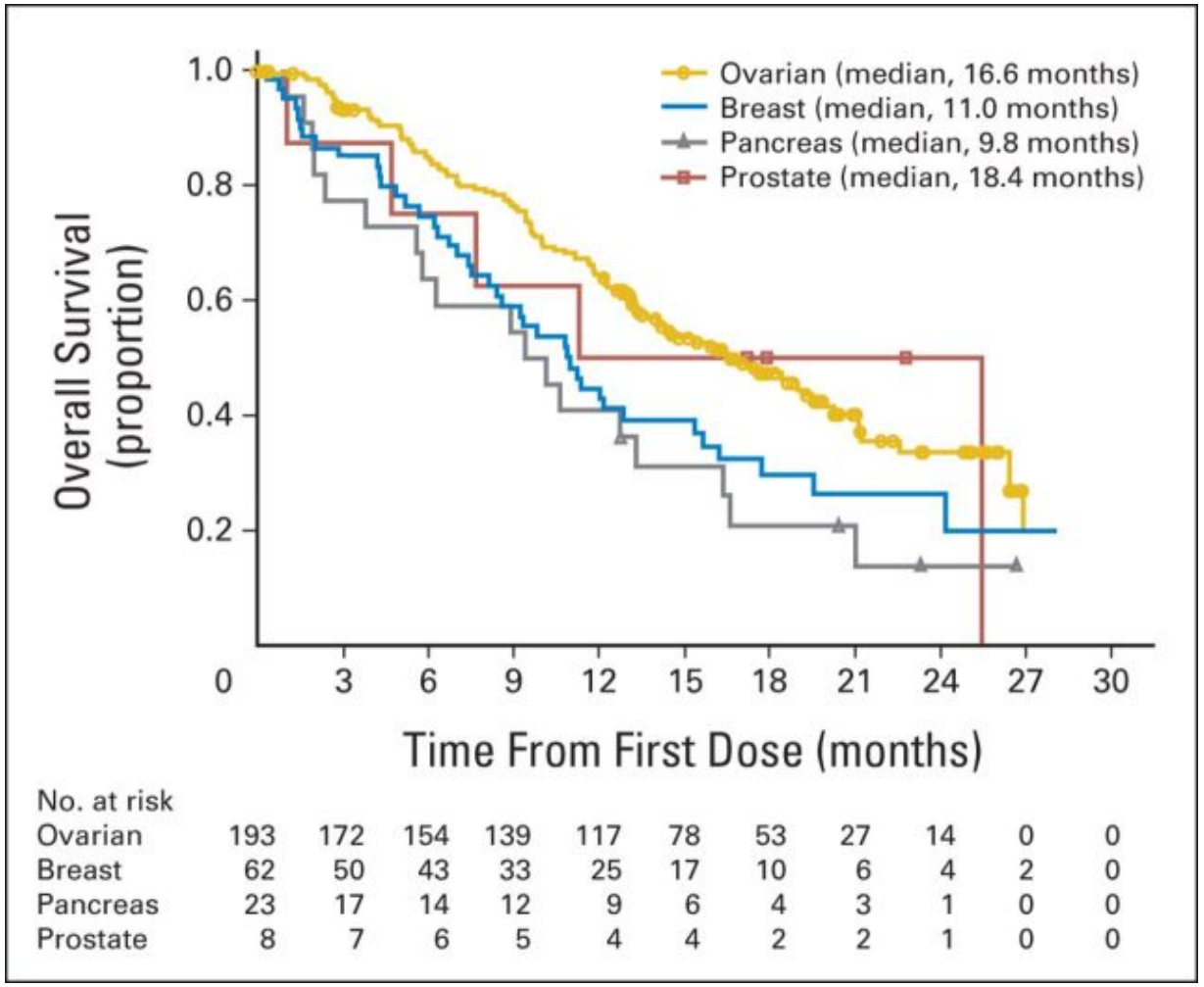
Olaparib Monotherapy in Germline *BRCA*(+) Previously Treated PDAC: Overall Survival



PDAC cohort (N= 23)

Median 1-8 prior lines
Median PFS 4.6 months
Response Rate 22%
I CR, 4 PR's

No responses in platinum resistant

Kaufman et al, J Clin Oncol. 2015

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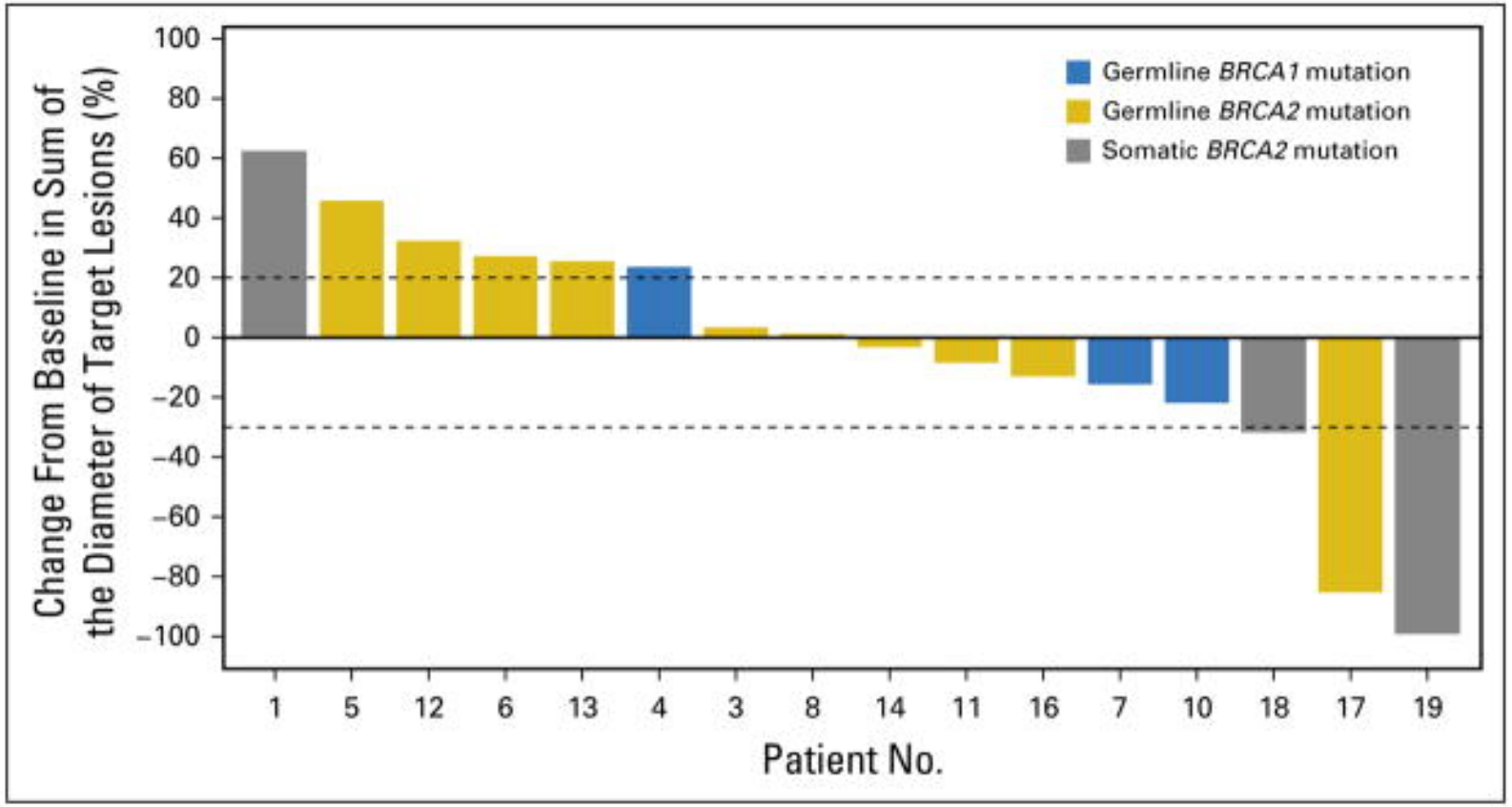
Phase II: Rucaparib Monotherapy in Previously Treated BRCA(+) PDAC



N= 19

16% RR: 2 CR, 2 PR

30% Disease control

Shroff R. JCO Precis Oncol. 2018

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Phase II Rucaparib Maintenance in *BRCA*, *PALB2* Mutated PDAC

- Somatic or germline mutation in *BRCA, PALB2*
- Platinum therapy stable/responding
- Rucaparib 600 mg BID maintenance
- N= 24 (19 included in analysis)

- Results
  - Median PFS 9.1 months
  - Overall RR 37% (1 CR)
  - DCR 90% at 8 weeks

Reiss Binder, K. AACR, 2019 Abstr CT234

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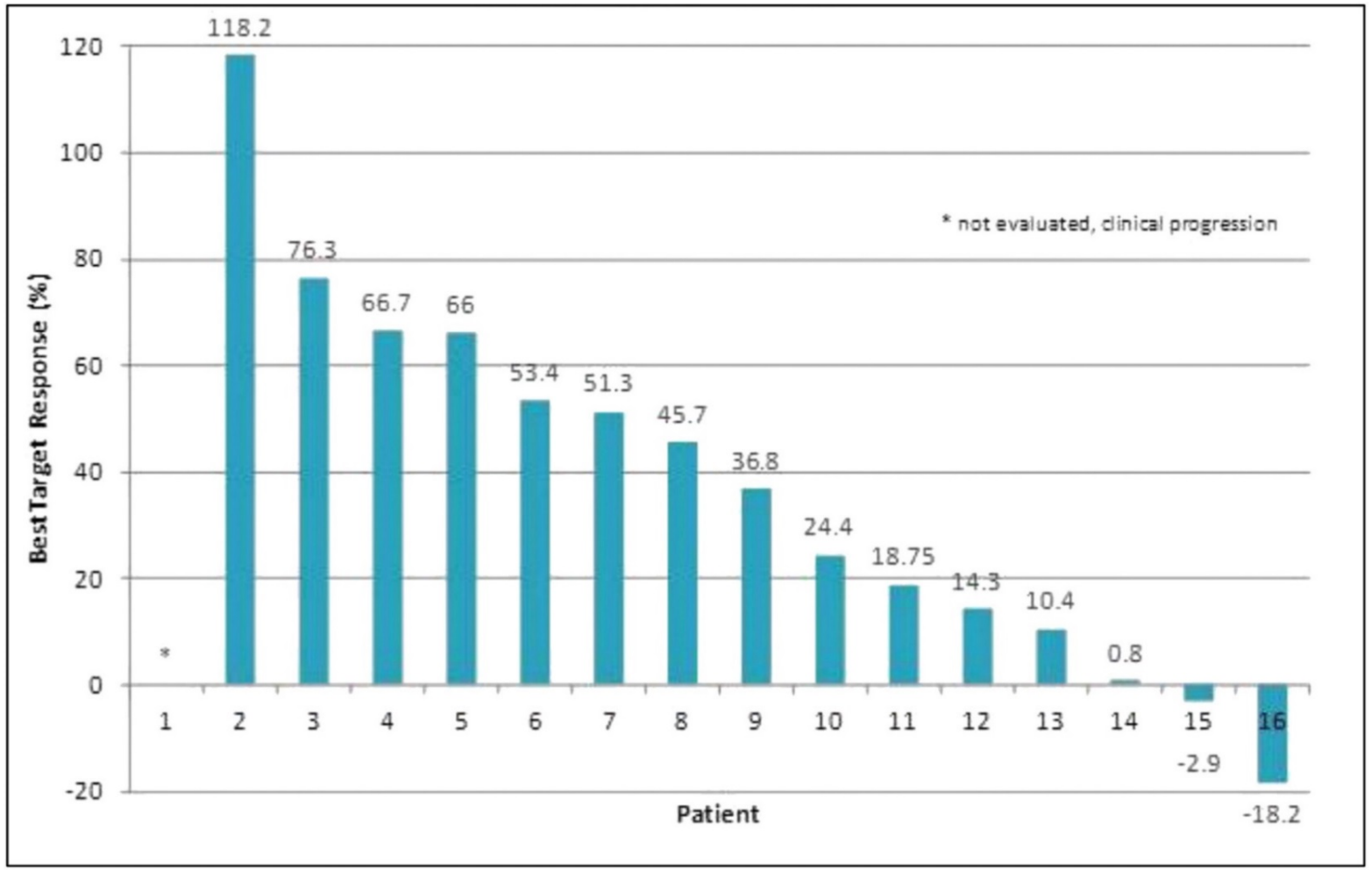
Veliparib Monotherapy in Previously Treated (Platinum Resistant) Germline *BRCA*(+) PDAC



N= 1 unconf. PR (no platinum)
N= 4 (25%) SD ≥ 4 months
N= 11 (69%) POD

Lowery MA, O'Reilly, EM. Eur J Cancer, 2018

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DDR (DNA-Damage Response) /HRD (Homologous Repair Deficiency): PDAC Active Areas Exploration

- Value of PARP inhibitor maintenance for those who have not had prior platinum agent; unselected population

- Evaluation of HRD approaches beyond germline BRCA, e.g., somatic mutations, other HRD genes
  - Zygosity, LOH

- Evaluation of PARP inhibitor + other agents (IO, anti-VEGF, cytotoxics) in germline/somatic BRCA(+)

Conclusions: Genomic Analysis in PDAC

- Germline, somatic testing recommended in PDAC
  - Significant frequency of actionable findings
  - Testing recommended early
    - Increasingly may define therapy
  - Liquid biopsies: more data needed
    - Subsets: no tissue, stage III
- Established
  - DNA repair targeting
  - *KRAS* wild-type population: actionable fusions

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