Is the concept of personalised medicine applicable to:

Pancreatic Cancer?

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Disclosures

- Speaker/Consultant:
  - AstraZeneca/MedImmune, Perthera, Sirtex Medical, Merck, Halozyme, Foundation Medicine, Caris, Pfizer
- Travel, accommodations and expenses support:
  - AstraZeneca/MedImmune, Perthera, Sirtex Medical, Merck
- Stock:
  - Perthera
- Research funding to my institution:
  - Bavarian Nordic, Astra Zeneca/MedImmune, Seattle Genetics, Pfizer/Array, Merck

- I will be discussing “off-label” use of approved and not yet approved therapies
  - Almost by definition
  - Includes: Rucaparib, afatinib, binimetinib, encorafenib, trametinib, dabrafenib, seribantumab, zenocutuzumab, pralsetinib (BLU-667)

What is Our Goal?

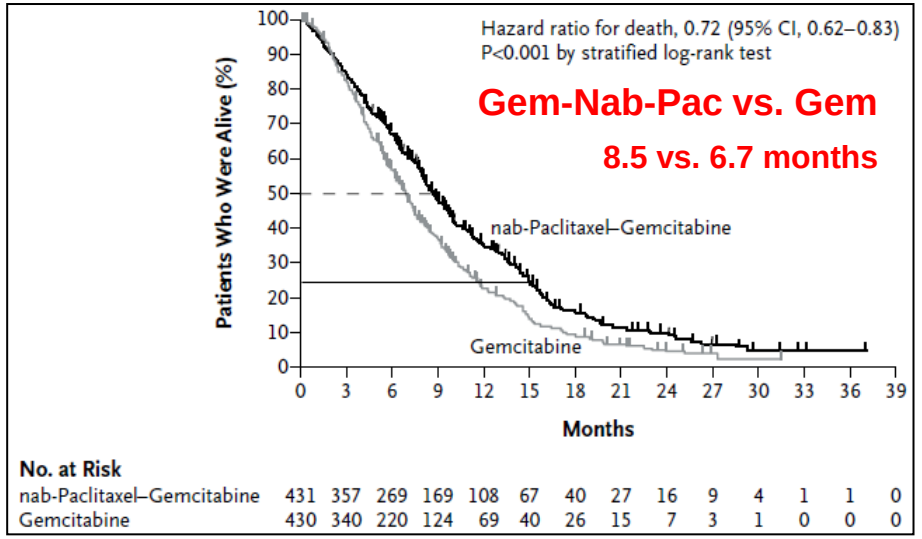
- Pancreatic cancer is the deadliest solid tumor
  - The 5 year overall survival rate is <10%
  - It will soon be the second leading cause of cancer-related death (in the United States)
  - The median overall survival, even in the most recent Phase III trials is 14 – 15 months
- As with any incurable cancer, our goals are to:
  - Extend survival
  - While maintaining as high a quality of life as possible
  - “Disease control” is linked to a better quality of life
    - So even extending progression-free survival is clinically meaningful

Personalised Medicine for Pancreatic Cancer Should be the Standard of Care

- The benefits of standard chemotherapy are limited
  - Standard chemotherapy has *extended* survival by at best 1 year (in 30 years)
  - Standard chemotherapy is EXPENSIVE
- Testing DOES reveal legitimately “actionable” mutations
- Actionable mutations lead to a disproportionate benefit in survival
  - WITH an overall survival benefit

Standard of Care Benefits are Expensive and Benefits Have Been Incremental

- There is no question that SOC chemotherapy improves survival
- But the benefits have been measured in months
  - Improved mOS from 6 to at best ~15 months
  - Control arm of two recent Chemo +/- PEGPH20 trials
    - FOLFIRINOX = 14.5 months
    - Gem-nab pac = 11.5 months
- SOC chemotherapy IS expensive
  - Both Gem-nab-pac AND FOLFIRINOX
- NGS Testing + Fusion testing RETAIL costs
  - At most, $7800
  - Recent panel - $1800 including RNA sequencing



28 days of Gem-Nab-Pac = $12,221

Von Hoff, DD, et al. NEJM 2013; 369 (18):1691-1703; Goldstein DA, et al. Med Oncol. 2016; 33 (5):48

The Promise of “Personalized” or “Precision” Medicine:

That we can use *predictive biomarkers* to identify who will benefit from specific therapies

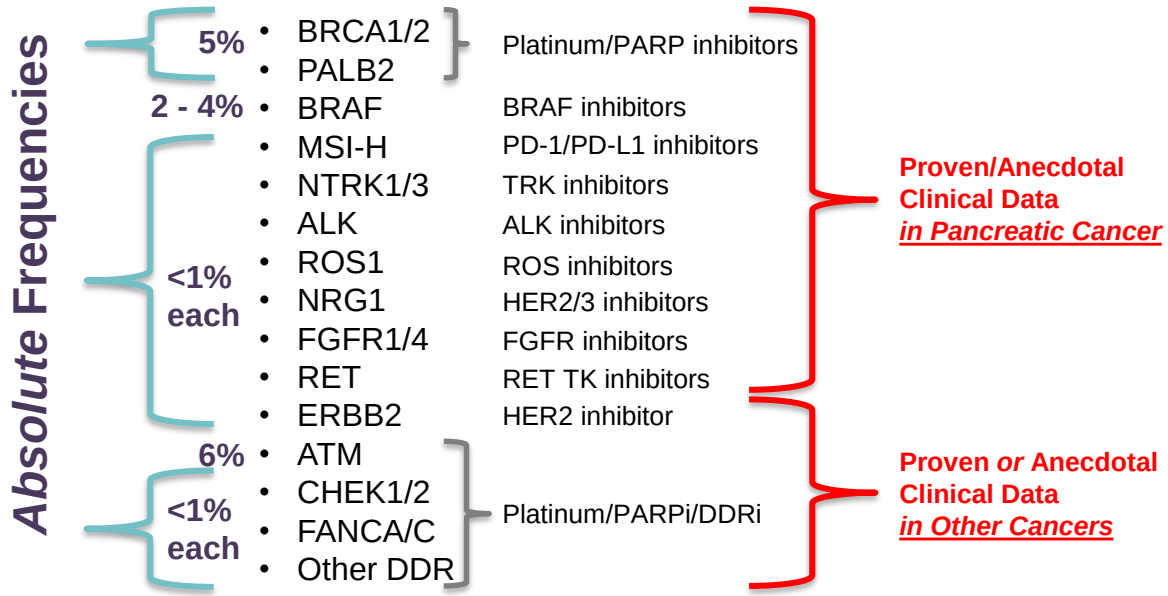
Precision Medicine

- Molecular testing for a therapeutic purpose
  - In any individual patient, there may be distinct, targetable, molecular abnormalities
    - Potent predictive markers of response
    - “Actionable biomarkers”

- Definition of actionability
  - Literature supports “significant activity” in patients with that molecular abnormality – IN ANY CANCER TYPE
    - Appropriate therapy leads to “disproportionate benefit”

Pancreatic Cancers DO Harbor Actionable Mutations

- NGS efforts have consistently revealed that ≥25% of pancreatic cancers have potentially actionable molecular biomarkers

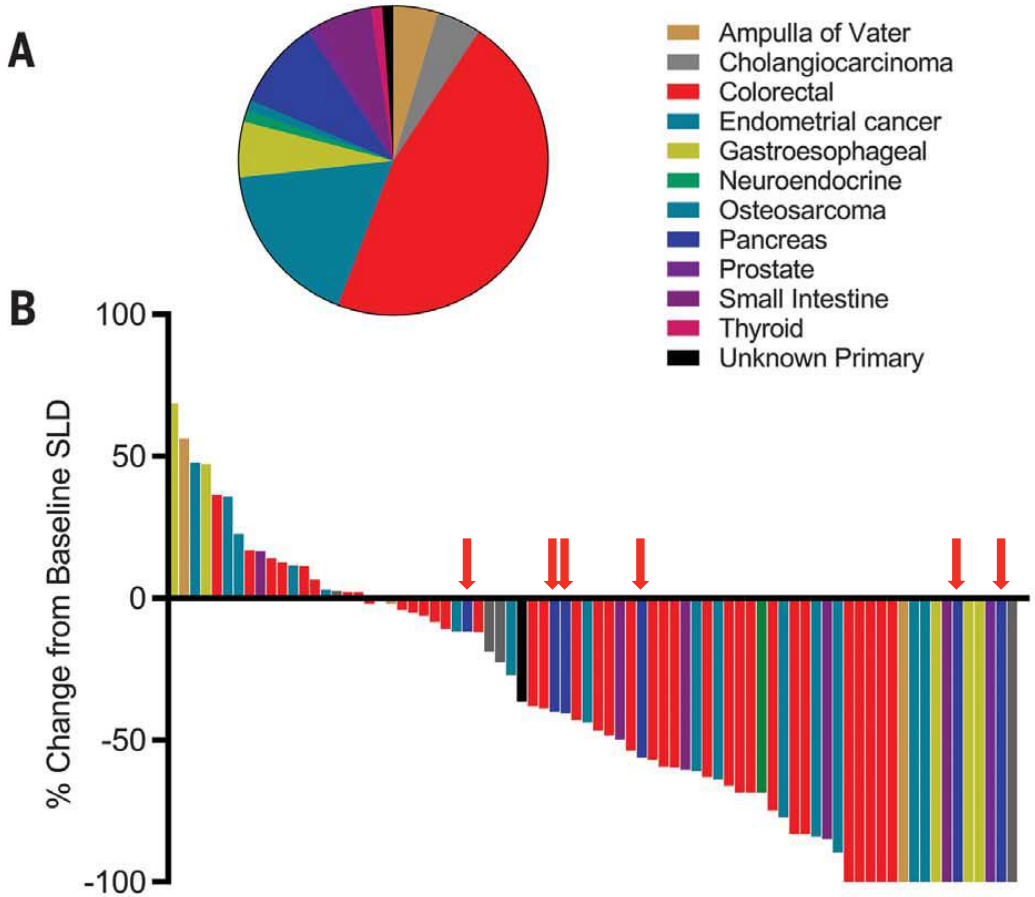


- 17% are DDR mutations
  - **Platinums!**
- All other subgroups are uncommon
  - **2% $BRAF^{V600E}$**
  - **<1% MSI-high**
  - **<<1% NTRK fusion+**
  - **<<1% NRG1 fusion+**
  - **<<<1% ALK/ROS2/FGFR/RET fusion+**

Singhi, et al, Gastroenterology, 2019; Pishvaian, et al, Clinical Cancer Research, 2018; Heeke, et al, JCO Precision Oncology, 2018; Aguirre, et al, Cancer Discovery, 2018; Witkiewicz, et al, Nat Commun, 2015; Lowery, et al, Clinical Cancer Research, 2017; Waddell, et al, Nature, 2015; Bailey, et al, Nature, 2016; Biankin, et al, Nature, 2012; Collisson, et al, Nat Med, 2011; Pishvaian and Brody, Oncology (Williston Park). 2017

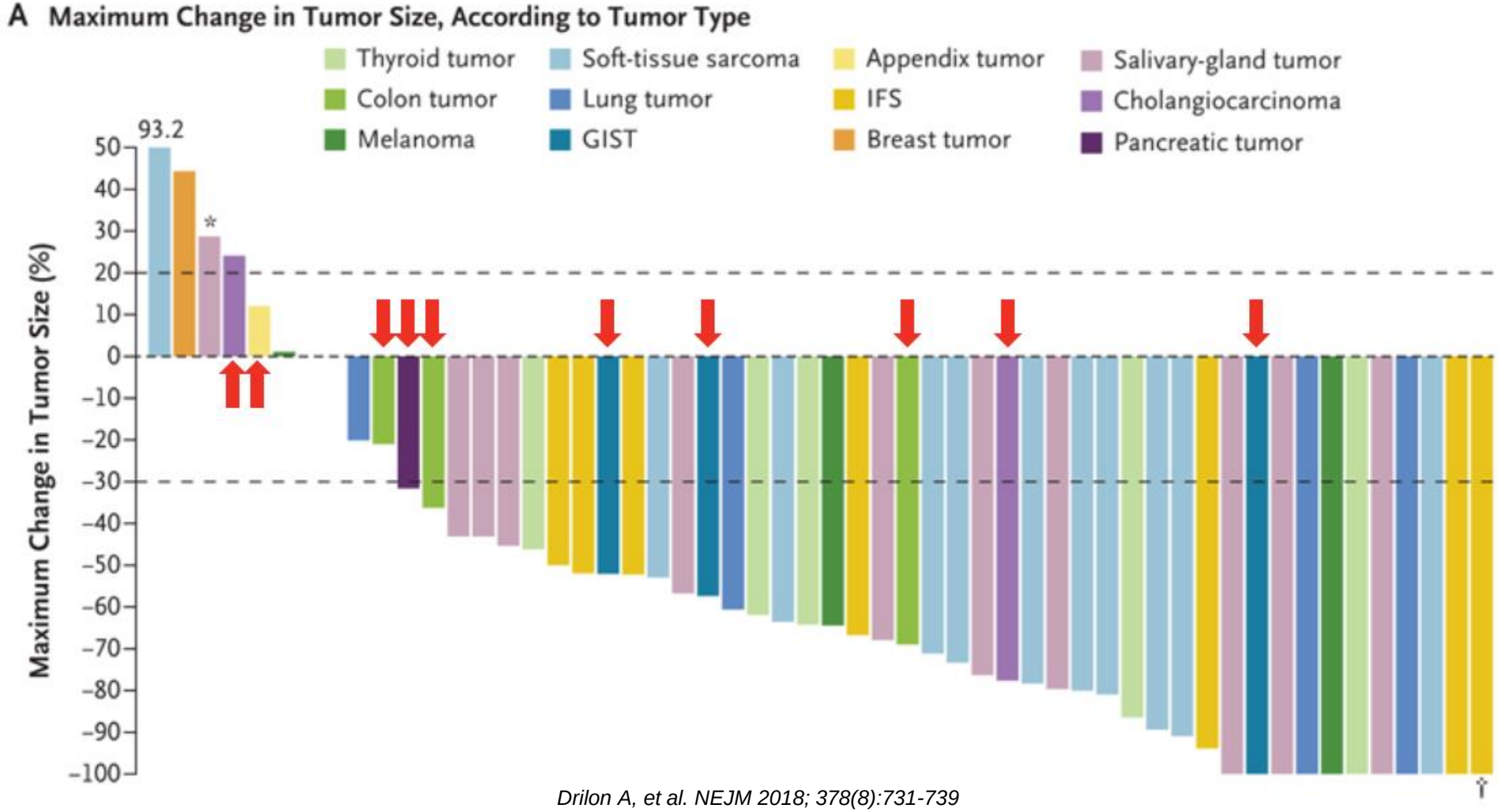
Disproportionate Benefit: MSI-High

- There have been biomarker-based approvals
- E.g. Pembrolizumab/Nivolumab in MSI-high disease
  - 3-5% of CRCs
  - 22% of gastric cancers
  - 1% of pancreatic cancers
    - **4 out of 6 "responded"**
    - **All patients benefited**



Le DT, et al. Science 2017; 357: 409-413

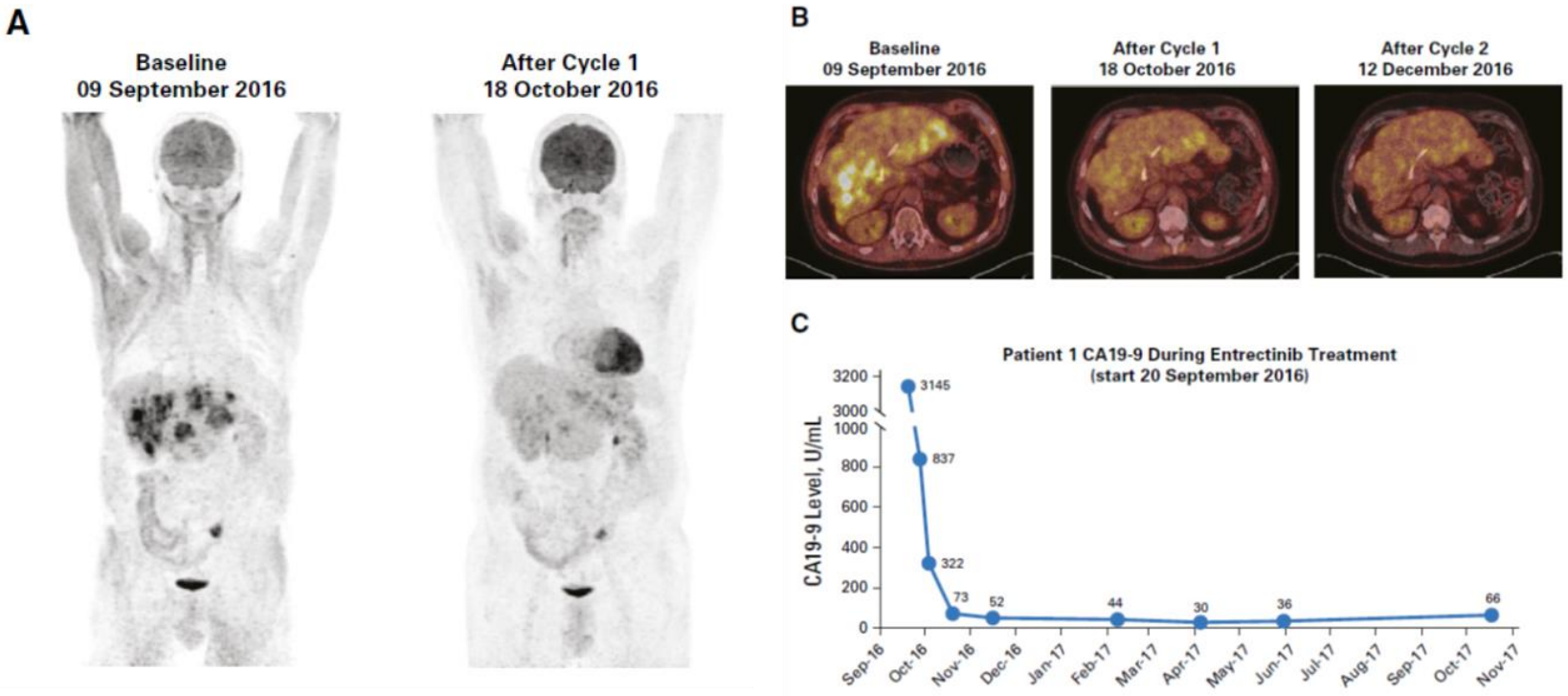
Disproportionate Benefit: TRK inhibitors



Drilon A, et al. NEJM 2018; 378(8):731-739

NTRK Fusions

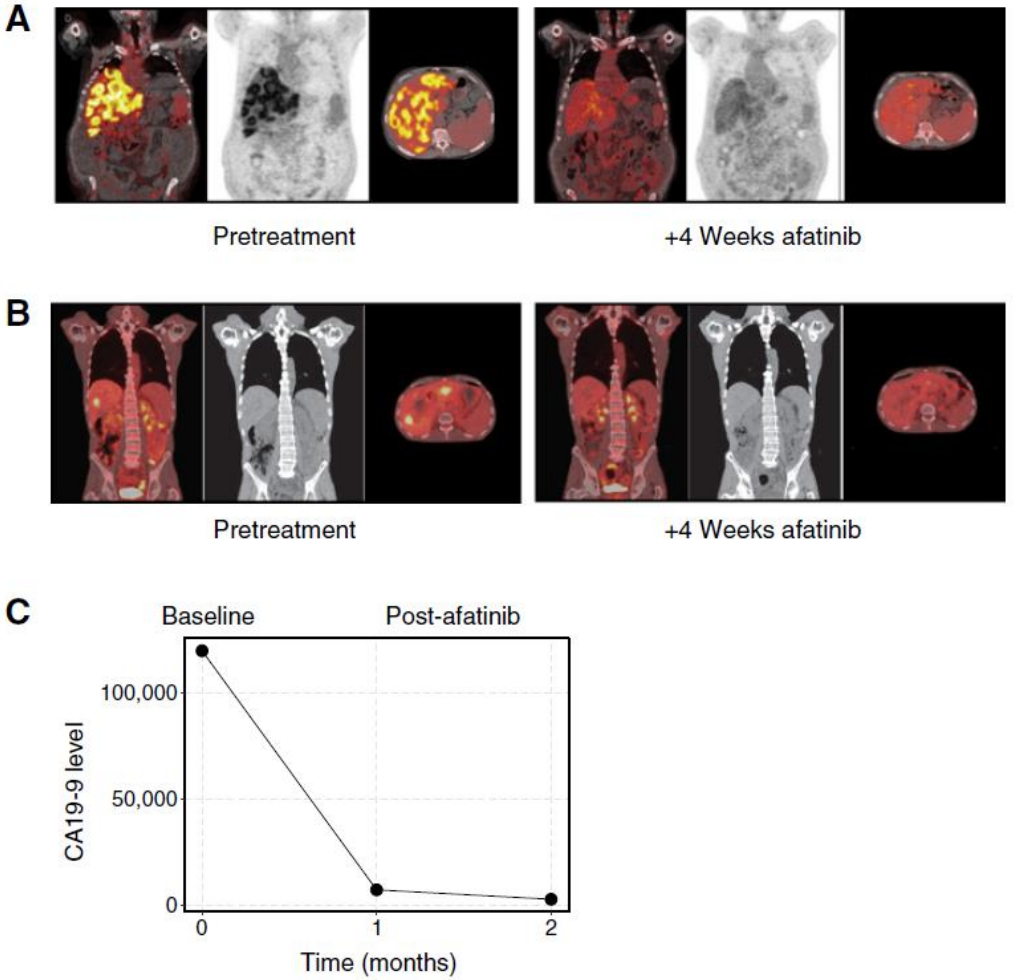
- Entrectanib case reports
  - 2 NTRK fusion and 1 ROS1 fusion cases
  - Prolonged, and occasionally dramatic benefit



Pishvaian, et al, JCO-PO, 2018

NRG1 Fusions

- Neuregulin 1 oncogenic fusions occur across disease types
  - <1% of PDAC
- Can respond to pan-HER inhibitors
  - E.g. afatinib
- And to HER2/3 Inhibitors
  - E.g. seribantumab or zenocutuzumab



Jones MR, et al. Clin Cancer Res 2019;25:4674–81

BRAF Mutated Pancreatic Cancer

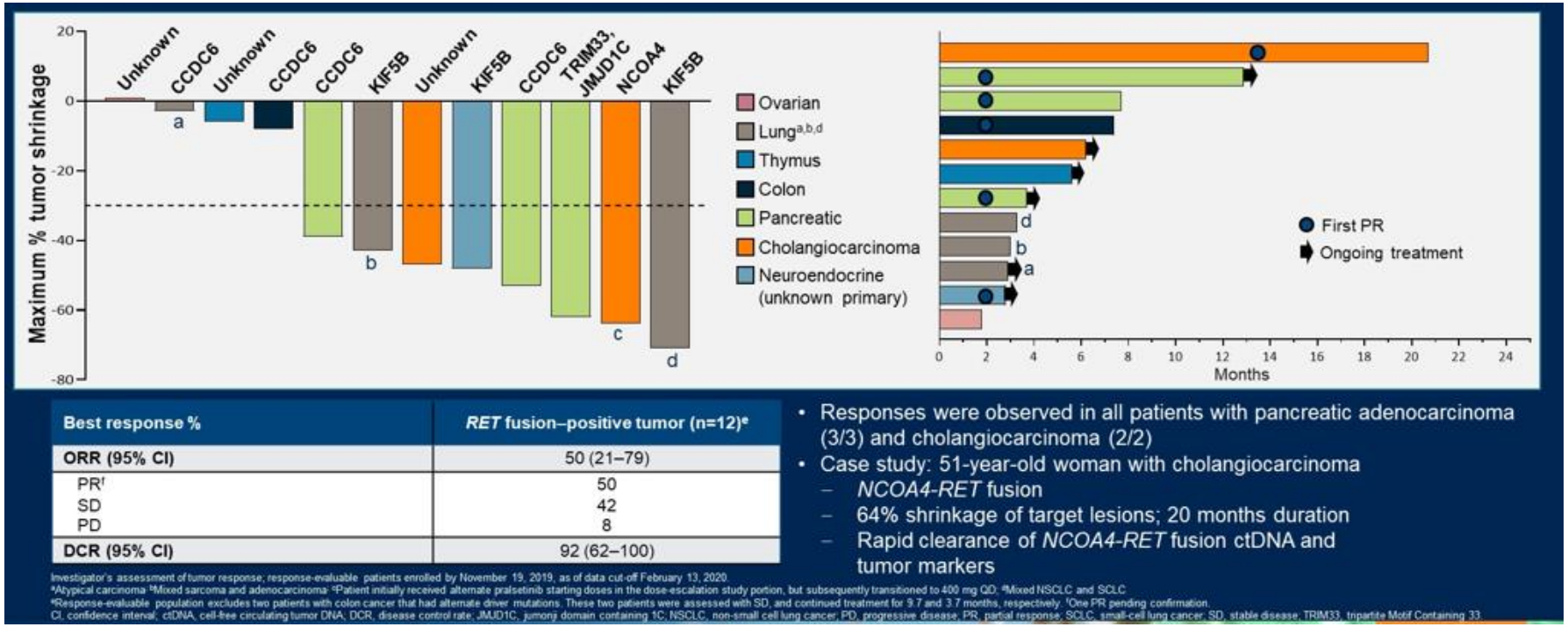
- From the KYT database - of 766 patients
- 18 *BRAF* mutations
  - 5 V600E, 13 other mutations
  - Almost always exclusive of *KRAS* mutations
- Sustained PR in a $BRAF^{V600E}$ mutated patient treated with dabrafenib + trametinib

- Phase II trial of encorafenib and binimetinib for $BRAF^{V600E}$-mutated pancreatic cancer (ACCRU:*NCT04390243*)
  - ROAR: Dabrafenib + trametinib in $BRAF^{V600E}$-mutated cholangiocarcinoma
    - Objective Response Rate – 51%

Hendifar A, JCO Precis Oncol. 2021. 5:1325-1338
Subbiah V, et al, Lancet Oncol. 2020 Sep;21(9):1234-1243

RET Fusions

- Pralsetinib (BLU-667) in RET fusion-positive tumors
  - 3 pancreatic cancer patients



Best response %	*RET* fusion–positive tumor (n=12)[e]
ORR (95% CI)	50 (21–79)
PR[f]	50
SD	42
PD	8
DCR (95% CI)	92 (62–100)

- Responses were observed in all patients with pancreatic adenocarcinoma (3/3) and cholangiocarcinoma (2/2)
- Case study: 51-year-old woman with cholangiocarcinoma
  - *NCOA4-RET* fusion
  - 64% shrinkage of target lesions; 20 months duration
  - Rapid clearance of *NCOA4-RET* fusion ctDNA and tumor markers

Investigator's assessment of tumor response; response-evaluable patients enrolled by November 19, 2019, as of data cut-off February 13, 2020.
[a]Atypical carcinoma [b]Mixed sarcoma and adenocarcinoma [c]Patient initially received alternate pralsetinib starting doses in the dose-escalation study portion, but subsequently transitioned to 400 mg QD; [d]Mixed NSCLC and SCLC
[e]Response-evaluable population excludes two patients with colon cancer that had alternate driver mutations. These two patients were assessed with SD, and continued treatment for 9.7 and 3.7 months, respectively. [f]One PR pending confirmation.
CI, confidence interval; ctDNA, cell-free circulating tumor DNA; DCR, disease control rate; JMJD1C, jumonji domain containing 1C; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SCLC, small-cell lung cancer; SD, stable disease; TRIM33, tripartite Motif Containing 33.

Subbiah V, et al, , et al, J Clin Oncol 39, 2021 (suppl 3; abstr 467)
2021 Gastrointestinal Cancers Symposium

2019 NCCN Guidelines on Pancreatic Cancer

JOHNS HOPKINS MEDICINE

"Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease [80% of patients] who are candidates for anti-cancer therapy to identify uncommon but actionable mutations"

NCCN Guidelines. Pancreatic Adenocarcinoma. Version 2.2019; https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. Accessed April 25, 2019

DDR Mutations in Pancreatic Cancer

- 17 – 25% of pancreatic adenocarcinomas harbor mutations in the DDR genes
  - DNA damage response and repair (DDR) mutations
  - *BRCA1, BRCA2, ATM, PALB2, ATRX, RAD51*, and others

KYT Dataset (16.5% DDR)

Gene	n, % (N = 616)
ATM	28 (4.5)
BRCA2	18 (2.9)
SMARC4	10 (1.6)
BAP1	8 (1.3)
BRCA1	8 (1.3)
BRIP1	6 (1.0)
PALB2	5 (0.8)
CHEK2	4 (0.6)
FANCA	4 (0.6)
FANCC	3 (0.5)
RAD50	3 (0.5)
STAG2	2 (0.3)
BARD1	1 (0.2)
CHEK1	1 (0.2)
FANCG	1 (0.2)

Caris Dataset (17.4% DDR)

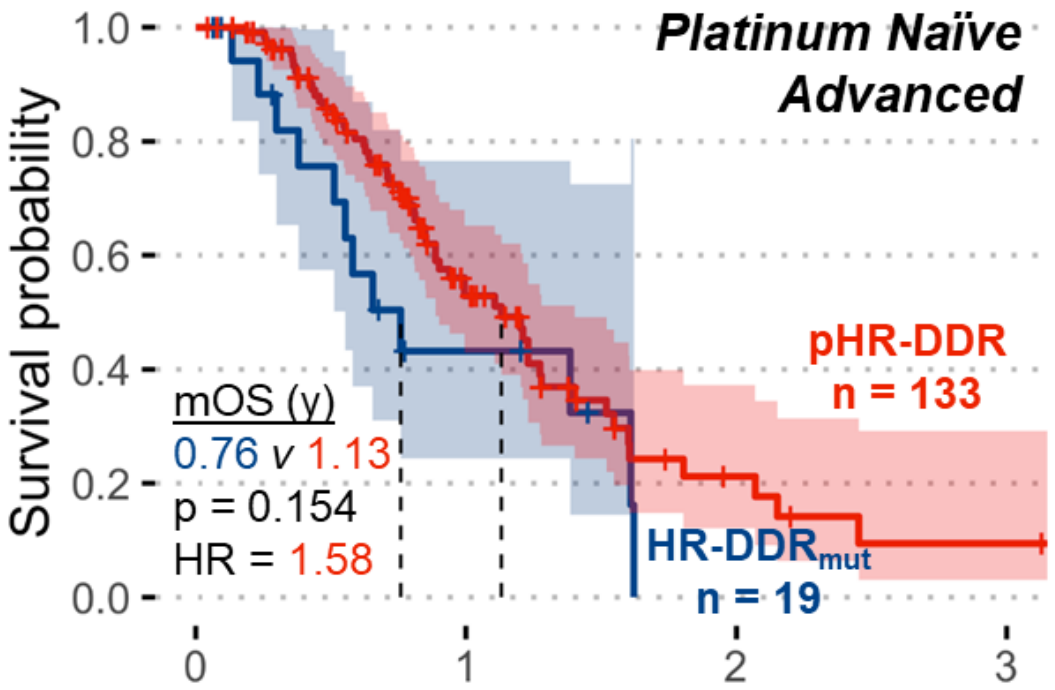
Pancreas Gene	% (N = 833)
ATM	3.60%
BRCA2	3.33%
BRCA1	1.41%
PALB2	1.20%
CHEK2	0.60%
BAP1	0.48%
BRIP1	0.48%
NBN	0.12%
WRN	0.12%
ATRX	0%
BLM	0%
FANCC	0%
MRE11A	0%
RAD50	0%
ARID1A	5.54%

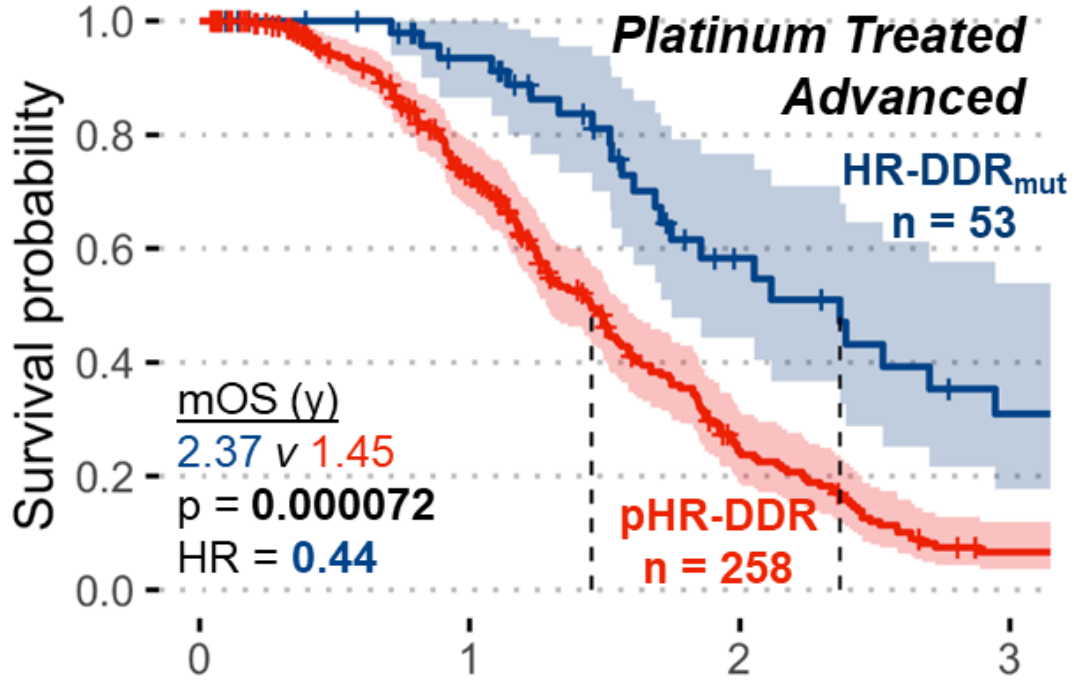
Pishvaian, et al, Clinical Cancer Research, 2018; Heeke, et al, JCO Precision Oncology, 2018; Aguirre, et al, Cancer Discovery, 2018; Witkiewicz, et al, Nat Commun, 2015; Lowery, et al, Clinical Cancer Research, 2017; Waddell, et al, Nature, 2015; Bailey, et al, Nature, 2016; Biankin, et al, Nature, 2012; Collisson, et al, Nat Med, 2011

DDR Mutated Pancreatic Cancers Should be Treated with Platinums

JOHNS HOPKINS MEDICINE

- For patients with DDR mutated tumors, treatment with platinum-based Tx improves OS
  - One YEAR improvement in overall survival compared to DDR proficient patients
  - More than one year improvement compared to NON-platinum-based therapy
- 50% of patients with pancreatic adenocarcinomas are treated with NON-platinum-based chemo
  - It is critical to know who these patients are as treatment decisions are made





Pishvaian, et al, JCO Precision Oncology, October, 2019

BRCA1/2 Mutations in Pancreatic Cancer

JOHNS HOPKINS MEDICINE

- 5%-7% of PDAC patients have germline *BRCA1* or *BRCA2* mutation
  - Ashkenazi Jewish: 5%-16%
  - Familial PDAC: 5%-19%

- **40% of patients who are germline *BRCA1/2* gene mutation carriers do NOT have a family history**

Hahn SA et al. Gastroenterology. 2003;124:544-560; Murphy KM et al. Cancer Res. 2002;62:3789-3793; Ozçelik H et al. Nat Genet. 1997;16:17-18; Lal G et al. Cancer Res. 2000;60:409-416; Lucas AL et al. Clin Cancer Res. 2013;19:3396-3403; Ferrone C et al. J Clin Oncol. 2009;27:433-438; Stadler ZK et al. Cancer. 2012;118:493-499; Brose MS et al. J Natl Cancer Inst. 2002;94:1365-1372; Holter S et al. J Clin Oncol. 2015;33:3124-3129; Chaffee KG et al. Genet Med. 2018;20:119-127; Petersen GM et al. Semin Oncol. 2016;43:548-553

2019 NCCN Guidelines on Pancreatic Cancer

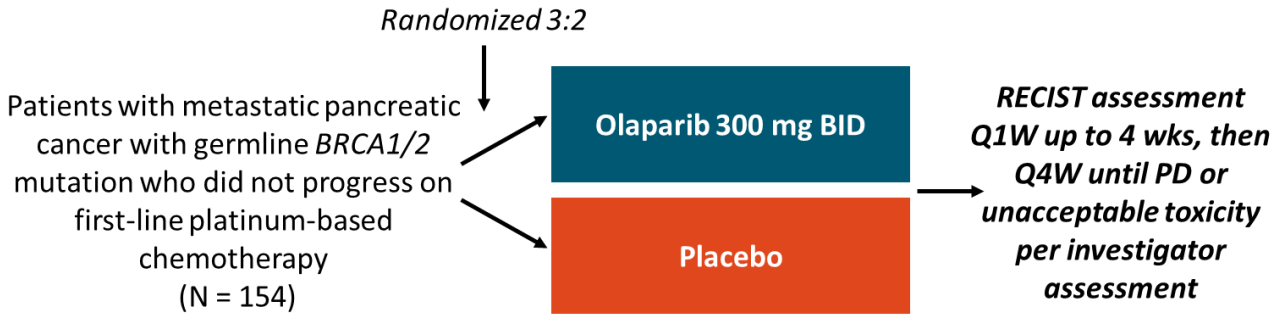
JOHNS HOPKINS MEDICINE

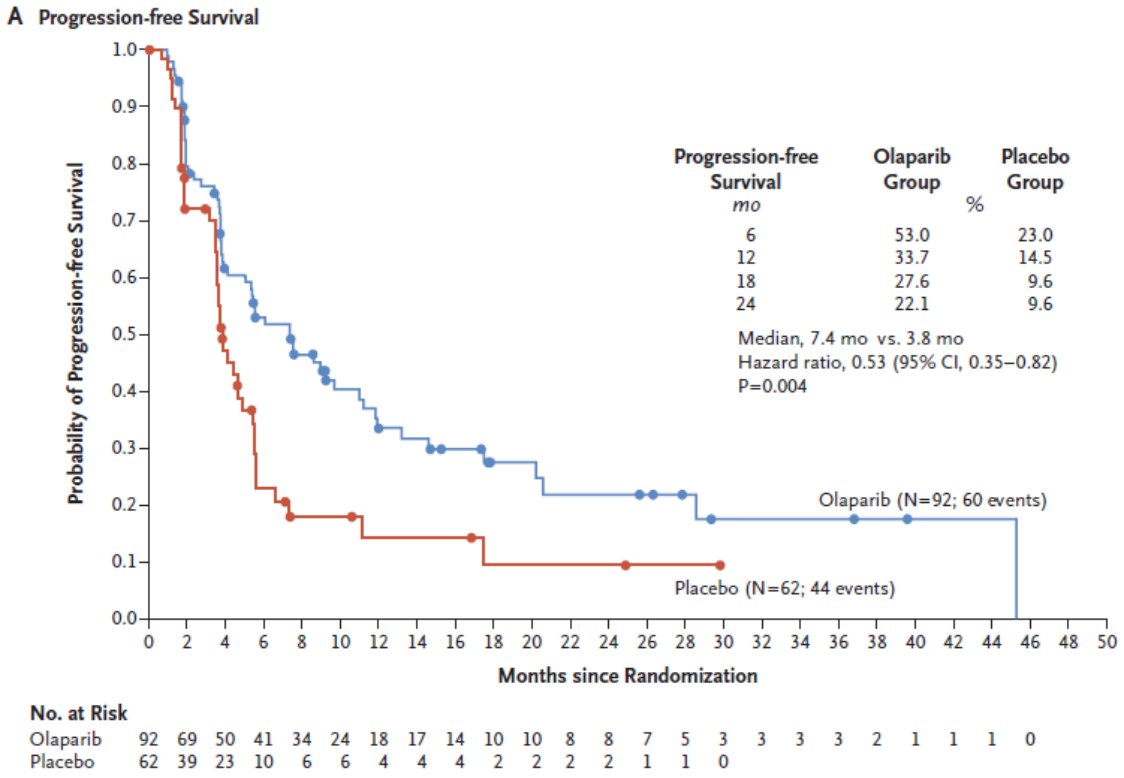
"Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes"

NCCN Guidelines. Pancreatic Adenocarcinoma. Version 2.2019; https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. Accessed April 25, 2019

PARP Inhibitors: Phase III Trial

- POLO: Olaparib as Maintenance Therapy in Germline *BRCA1/2*-Mutated Pancreatic Cancer
- Randomized, double-blind phase III trial
  - Improved PFS with olaparib vs. placebo

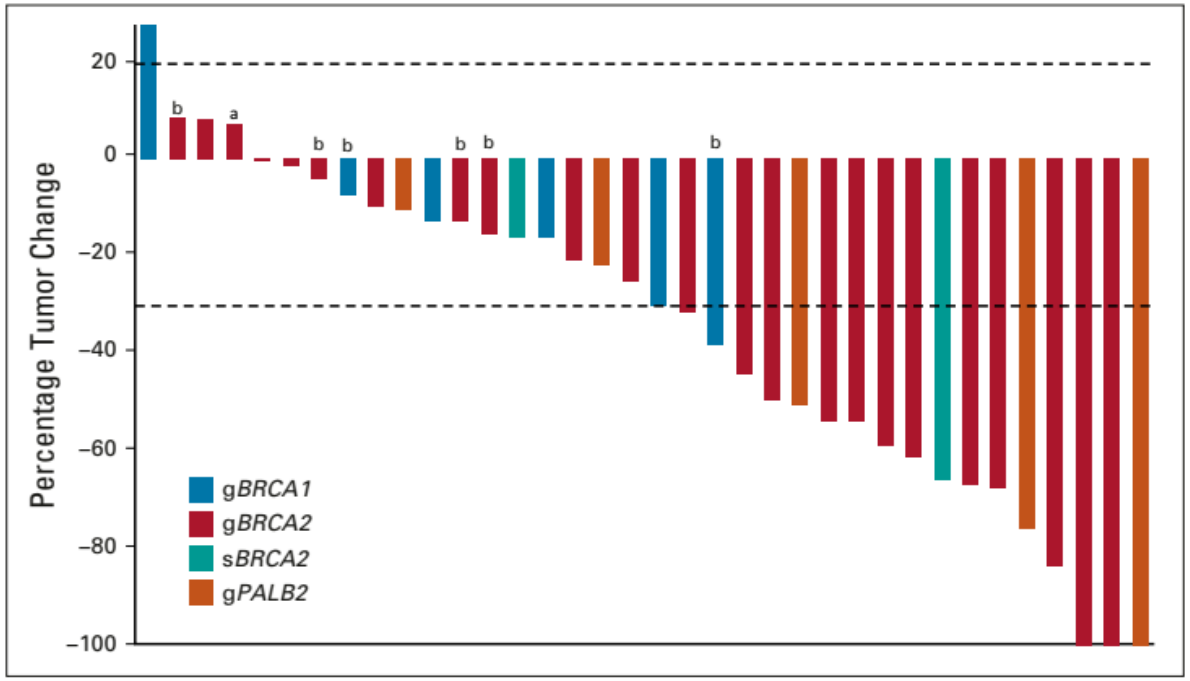




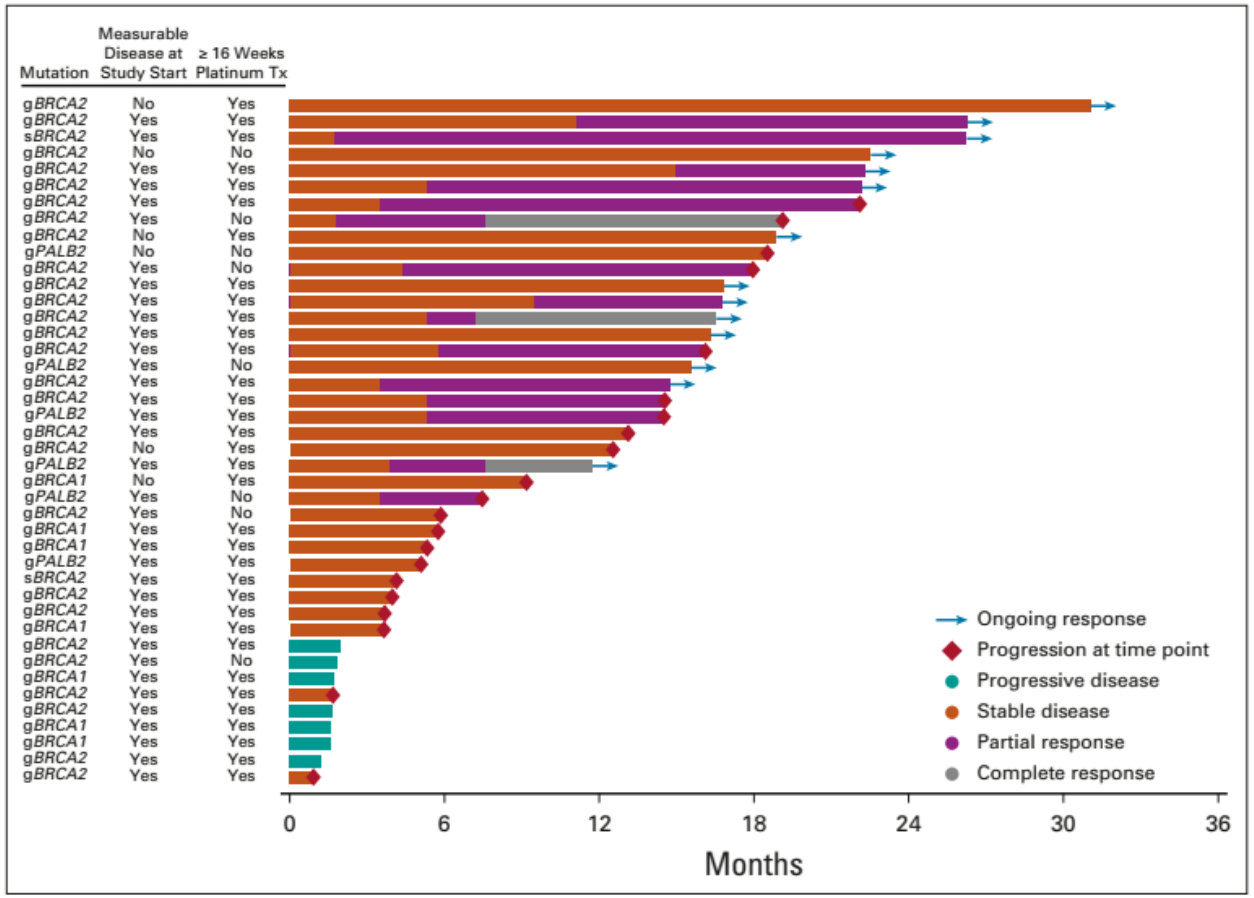
- 1º endpoint: investigator-assessed PFS (RECIST v1.1)
- 2º endpoints: safety, OS, PFS2, TFST, TSST, TDT, OR, DCR, QoL

Golan T, NEJM, 2019

Maintenance Rucaparib



36 Evaluable Patients	
ORR	41.7 %
Median DOR	17.3 months
Disease Control Rate	66.7 %

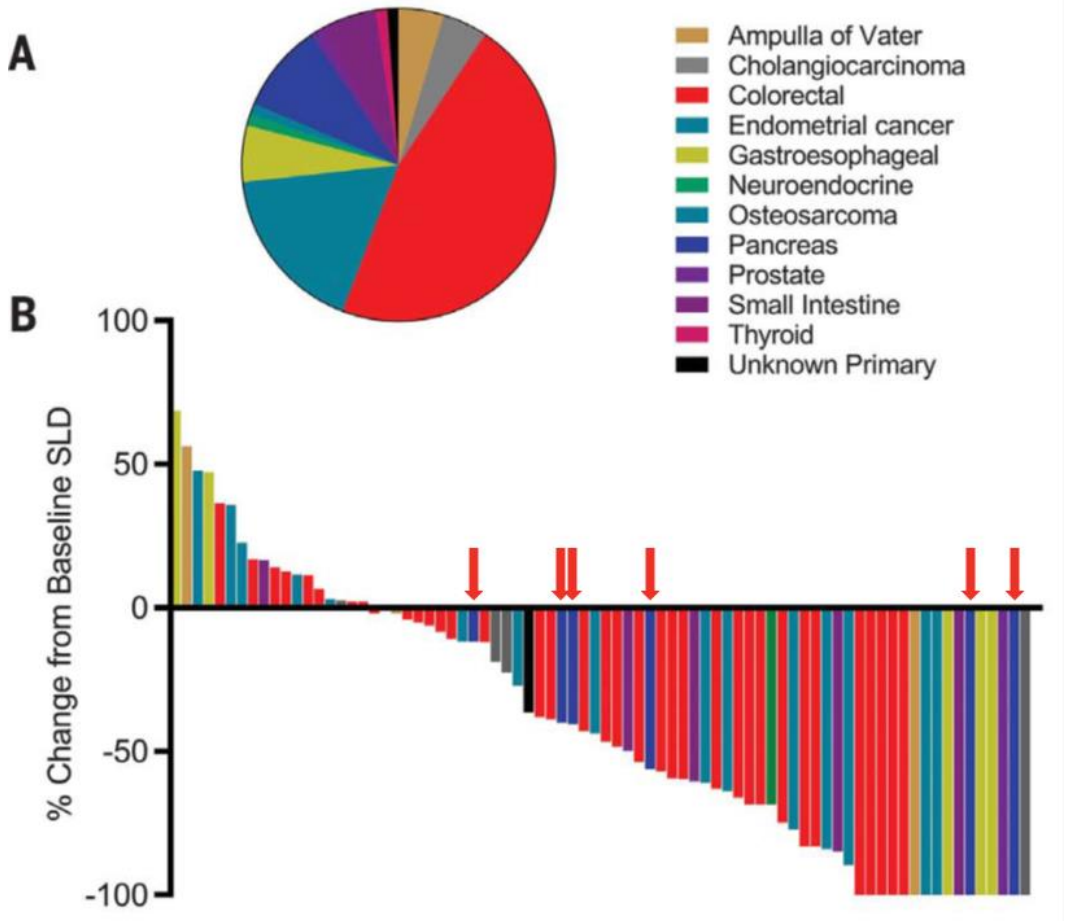


Reiss KA, J Clin Oncol. 2021 Aug 1;39(22):2497-2505

The Next Step is to Understand Resistance

Even MSI-High Pancreatic Cancer is Still PDAC

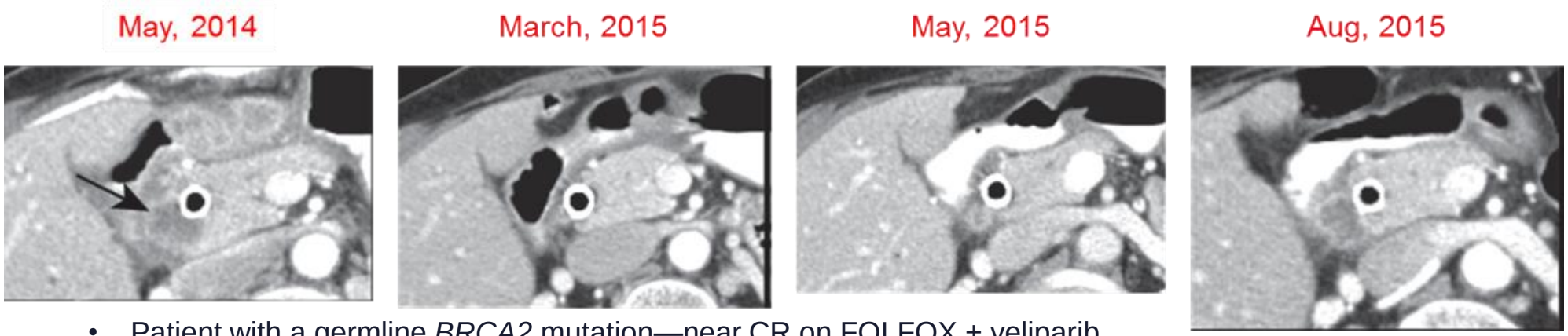
- Pembrolizumab in MSI-high PDAC
  - <1% of pancreatic cancers
    - 4 out of 6 “responded”
    - All patients benefited
- BUT……
  - Marabelle, et al update on 22 pts
    - ORR only 18%
    - mPFS of 2.1 months
    - Duration of response of 13.4 months
    - Lowest compared to all other disease types



Le DT, et al. Science 2017; 357: 409-413; Marabelle A, et al, J Clin Oncol 2020;38(1):1-10

Not all *BRCA1/2*-Mutated Tumors Respond

- Spectrum of responsiveness
  - 1/3 have a robust response
  - 1/3 respond for a while, and then progress
  - 1/3 are innately resistant



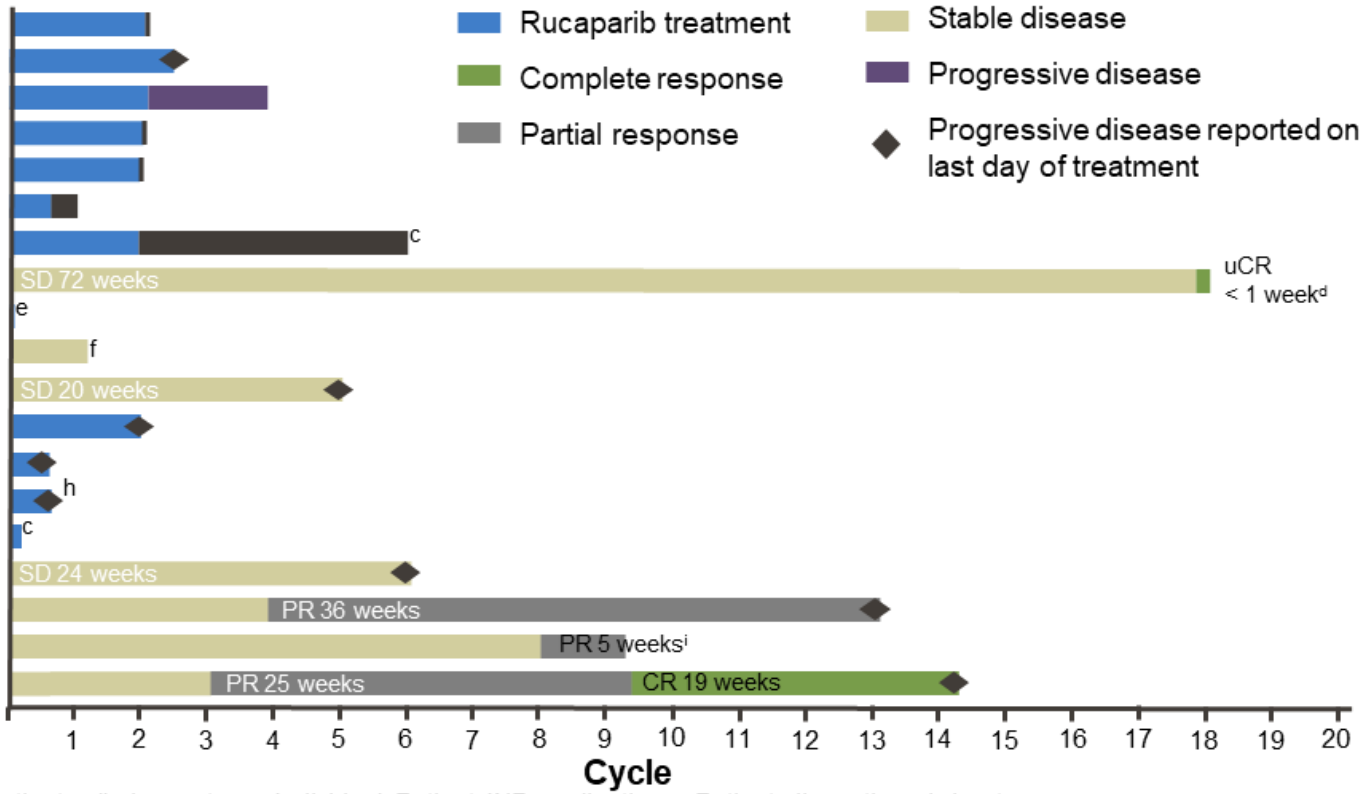
- Patient with a germline *BRCA2* mutation—near CR on FOLFOX + veliparib

- **Sequencing of the new tumor revealed:**
  - Original *BRCA2*, *KRAS,* and *TP53* mutations
  - New somatic (secondary) *BRCA2* mutation
    - ➢ New deletion 13 bp upstream of the germline deletion
    - ➢ Restored the reading frame of the *BRCA2* gene

Bouwman P, Jonkers J. Clin Cancer Res. 2014;20:540-547; Pishvaian MJ et al. Br J Cancer. 2017;116:1021-1026

PARP Inhibitors Are Ineffective in Platinum-Refractory Disease

Patient Number	BRCA Mutation	Prior Regimens, n	Received Prior Platinum	Platinum Refractory
1	*BRCA2* somatic	2	Yes	Yes
2	*BRCA2* germline	1	Yes	Yes
3	*BRCA2* germline	1	Yes	No[a]
4	*BRCA2* germline	1	Yes	No
5	*BRCA2* germline	2	Yes	No[b]
6	*BRCA2* germline	2	Yes	Yes
7	*BRCA2* germline	2	Yes	Yes
8	*BRCA2* germline	2	Yes	No[a]
9	*BRCA2* germline	1	No	N/A
10	*BRCA2* germline	2	Yes	Yes
11	*BRCA2* germline	2	Yes	No
12	*BRCA2* germline[g]	2	Yes	Yes
13	*BRCA2* germline	1	No	N/A
14	*BRCA2* germline	3	Yes	Yes
15	*BRCA2* germline	2	Yes	Yes
16	*BRCA2* germline	1	No	N/A
17	*BRCA2* germline	1	No	N/A
18	*BRCA2* somatic	1	Yes	No
19	*BRCA2* somatic	1	Yes	No



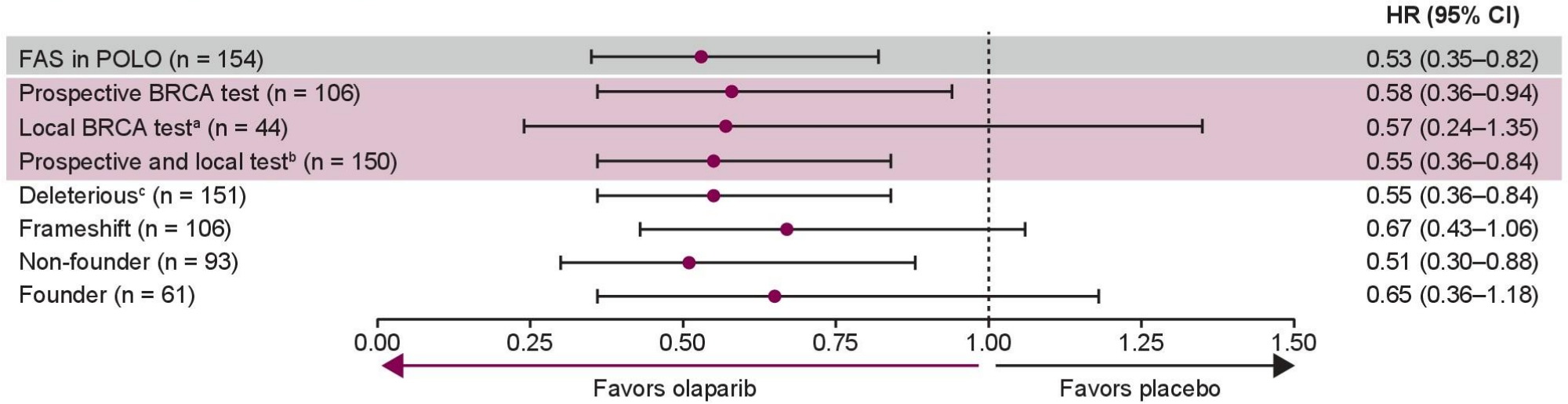
[a] Patients discontinued treatment for other reason. [b] Study terminated; patient rolled over to an Individual Patient IND application. [c] Patient discontinued due to investigator decision. [d] Patient discontinued due to an AE and scan with stable disease performed after last treatment day. [e] Patient discontinued due to AE and progressive disease. [f] Patient withdrew consent; partial response confirmed with a scan after last treatment day.

Shroff RT et al. JCO Precis Oncol. 2018;2018; Domcheck SM et al. ASCO 2016. Abstract 4110.

Is Response a Function of the Specific Mutation?

- Assessed outcomes of POLO 3 trial as a function of the TYPE of BRCA mutation
  - The efficacy of Olaparib vs. placebo was consistent across mutational subtypes

Figure 5. Progression-free survival, grouped by types of BRCA testing and gBRCAm, during treatment with olaparib compared with placebo.

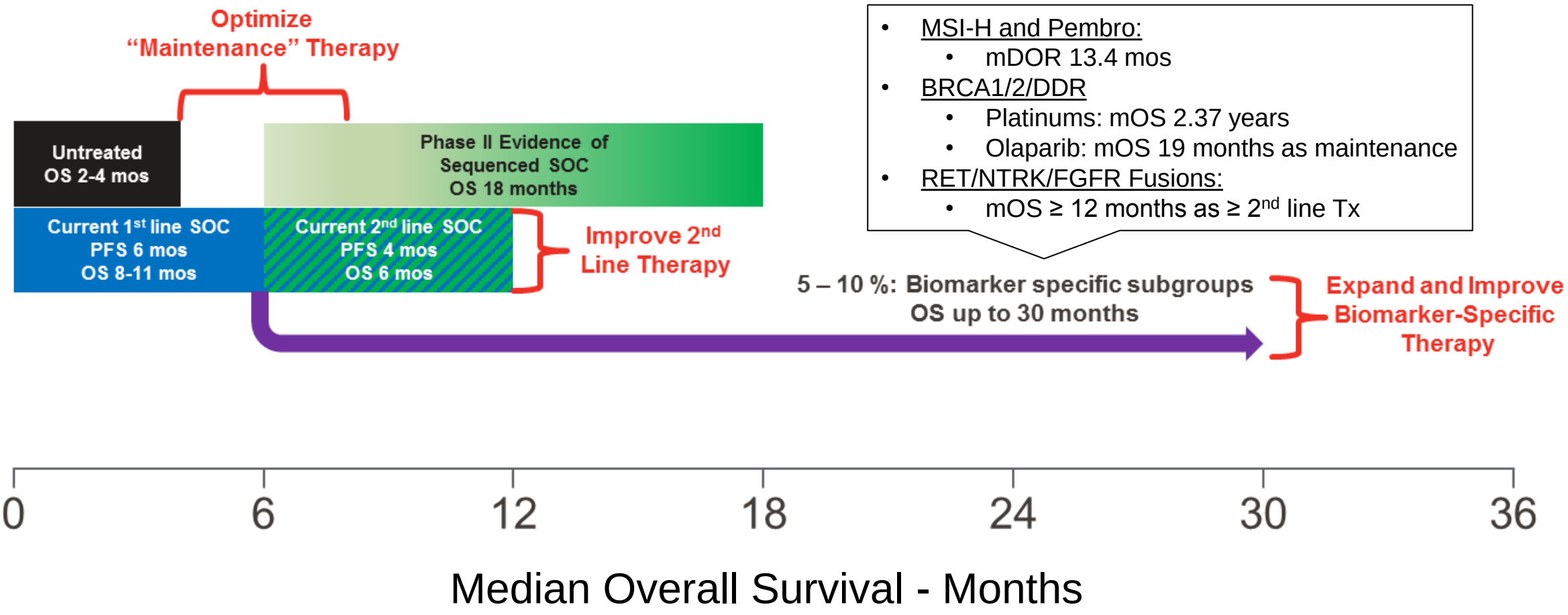


[a]Retrospectively confirmed by centralized testing using the BRACAnalysis CDx test. [b]Prospectively, centrally tested or local test result retrospectively confirmed by centralized testing using the BRACAnalysis CDx test. [c]Not including 3 patients with suspected deleterious mutations, who had PFS of 5.6 and 5.5 months during treatment with olaparib and 1.9 months with placebo, relative to median (95% CI) PFS in the FAS of 7.4 (4.14–11.01) and 3.8 (3.52–4.86) months with olaparib and placebo, respectively.
CI, confidence interval; FAS, full analysis set; HR, hazard ratio

Golan T, et al; ASCO-GI 2021: J Clin Oncol 39, 2021 (suppl 3; abstr 420)

How and When to Incorporate Biomarker Testing

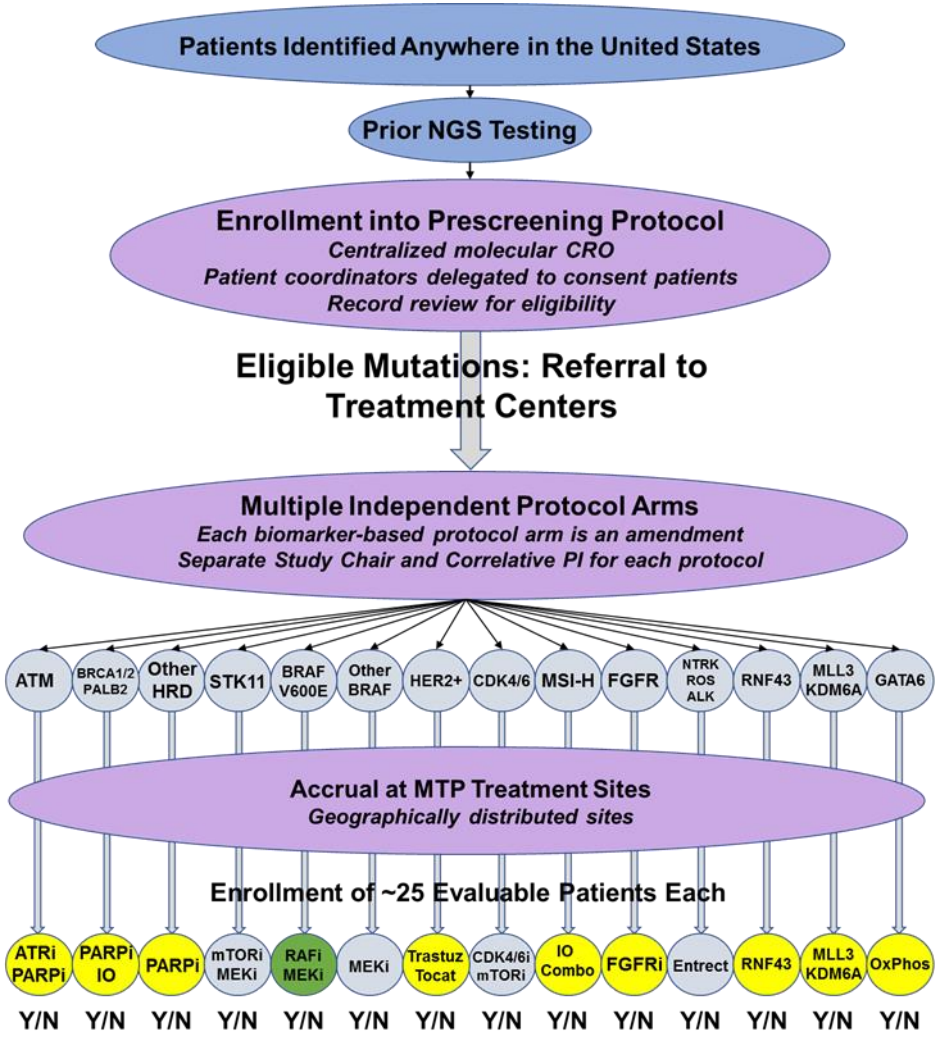
Metastatic Pancreatic Cancer Survival



TARGET Panc

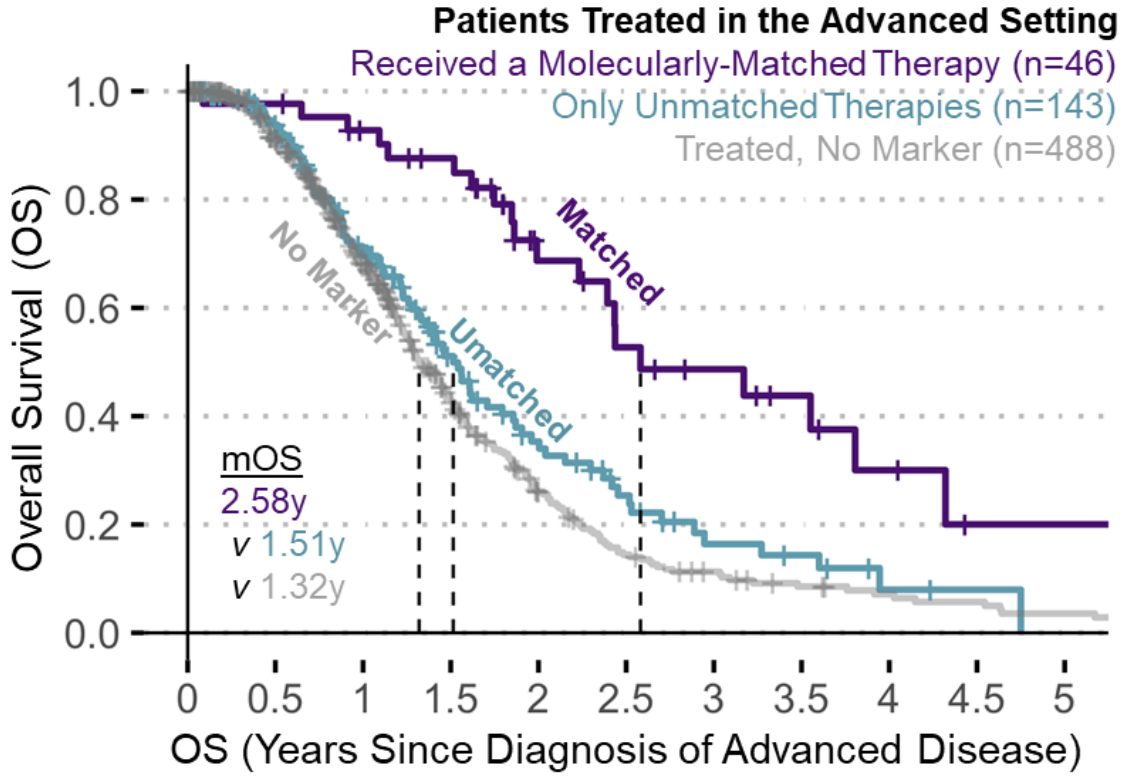
A Clinical Trial of Treatment Targeted Towards Actionable Biomarkers for Patients with Metastatic Pancreatic Cancer

- Centralized screening and referral protocol to biomarker-based clinical trials for patients with pancreatic cancer
- Multiple Independent Protocols
  - Biomarker-based
  - Many, many possibilities
  - ***Incorporate SOC arm(s)***
  - ***Incorporate NON-biomarker-based arms***
- Each protocol designed essentially as a single arm Phase II
  - To make a “go/no-go” determination
- “Successful” trials could be expanded into “definitive” trials



Gold Standard: Overall Survival Benefit

- 1028 pancreatic cancer patients
  - All underwent molecular profiling (w/NGS)
- 677 patients with outcomes information
  - 189 with Actionable Findings
    - 46 received molecularly matched therapy
    - 143 received “unmatched” therapy
  - 488 with no actionable findings
- Overall survival
  - Matched 1y > unmatched
  - Matched 1.3y > no actionable marker



Molecularly-Matched *vs* Only Unmatched History (Highly Actionable)
p-value = 0.000388, HR = **0.42** [0.26-0.68]
Molecularly-Matched *vs* Patients without Highly Actionable Findings
p-value = 0.00000229, HR = **0.34** [0.22-0.53]

Pishvaian, et al, Lancet Oncology, March, 2020

Summary and Recommendations

- Actionable mutations are not “rare” in pancreatic cancers
  - EU definition of rare: <1/2000 people = .05%
  - Testing DOES reveal legitimately actionable mutations in 25% of patients
  - 100% of patients should be germline tested; virtually all should ALSO have somatic/tumor testing
- Testing is MUCH less expensive than standard (and targeted) therapies
- Multiple small subgroups of patients with other actionable mutations
- Actionable mutations overall lead to a disproportionate benefit
  - With survival benefit

Thank you and Questions?