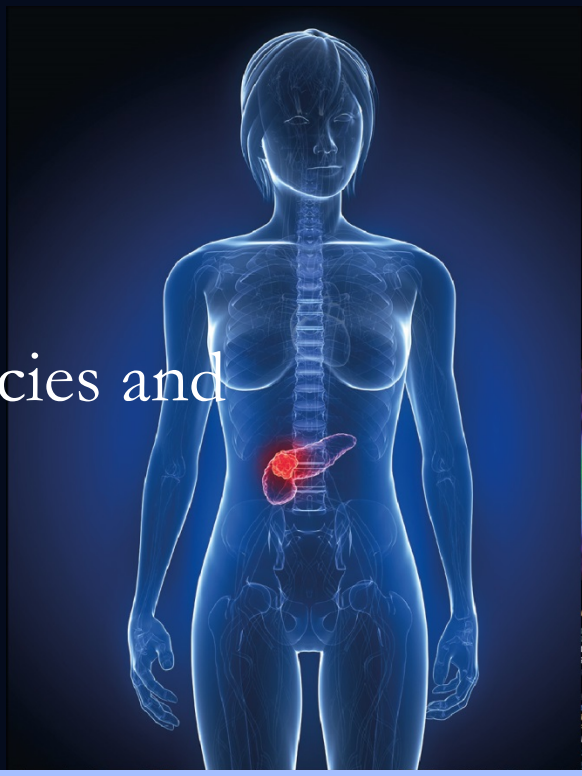
Emerging biomarkers of pancreatic malignancies and neuroendocrine tumour



ANGELA CHOU
Staff specialist SYDPATH, St Vincent's Hospital
Research Fellow, Garvan Institute of Medical Research

SYDPATH
ST VINCENT'S PATHOLOGY

GARVAN INSTITUTE OF MEDICAL RESEARCH

APGI
Australian Pancreatic Cancer Genome Initiative

THE UNIVERSITY OF SYDNEY
cancer diagnosis & pathology

My talk

- Molecular biology of pancreatic cancer

- Emerging biomarkers for clinical practice:

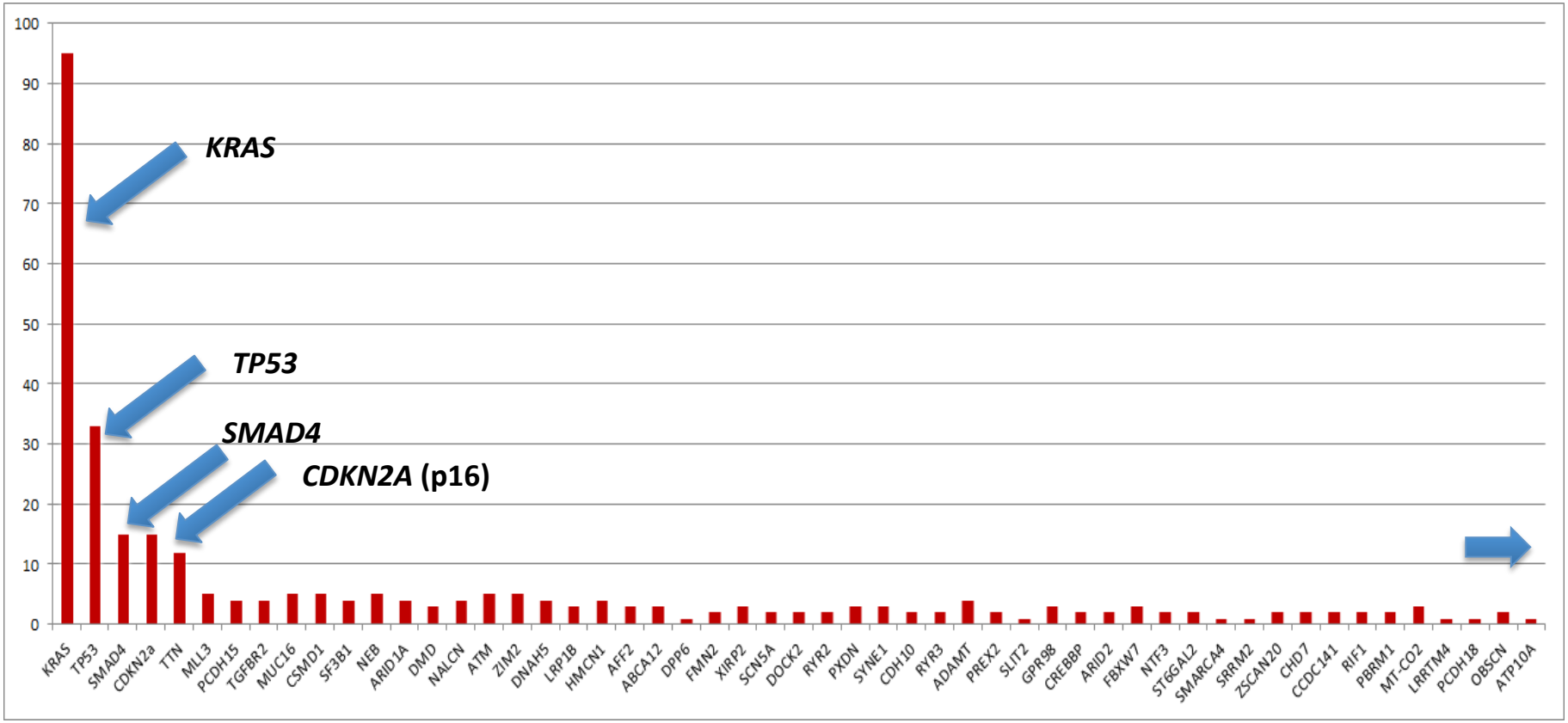
    1. Pancreatic ductal adenocarcinom (PDAC)

    Briefly on:

    2. Pancreatic acinar cell carcinoma (PACC)
    3. Pancreatic neuroendocrine tumour (PNET)

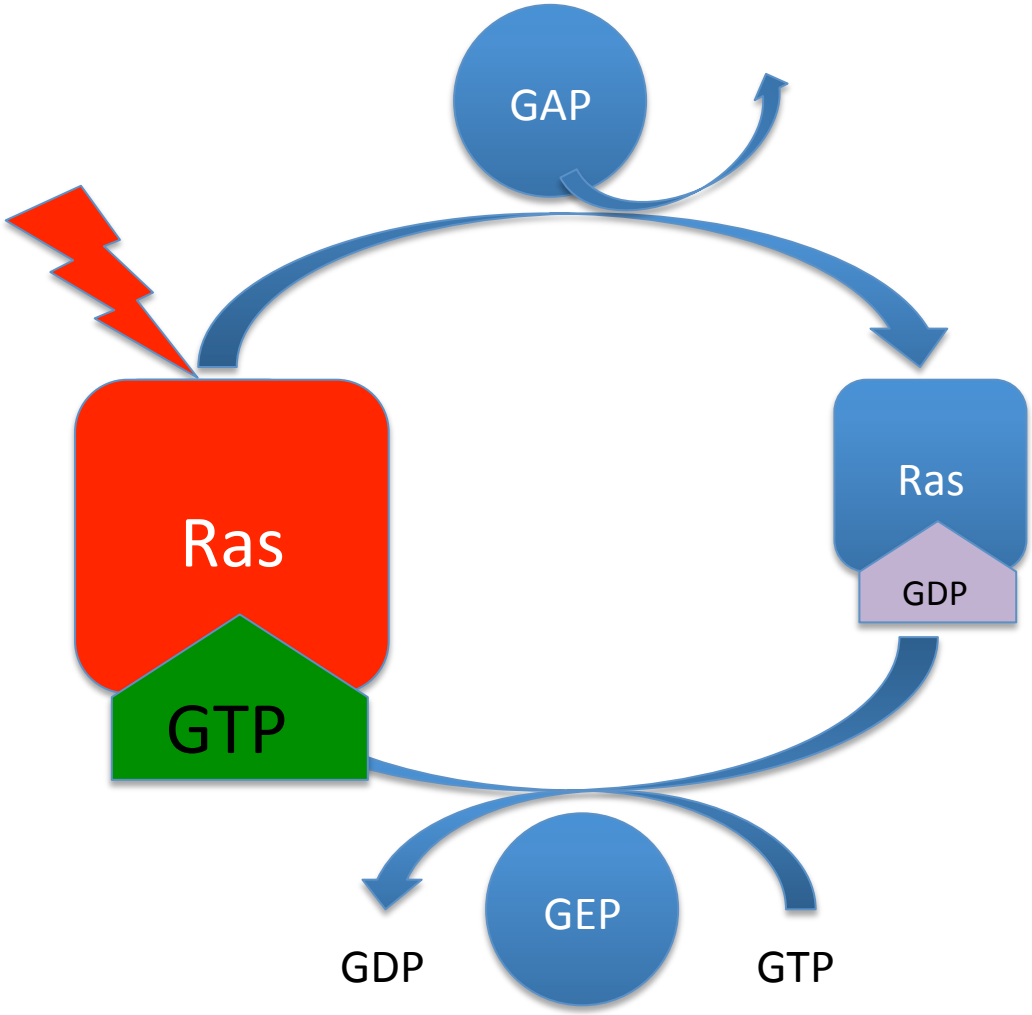
PDAC
Mutational landscape is heterogeneous

- Approx 1500 mutated genes detected
- average 60 gene alterations/tumour



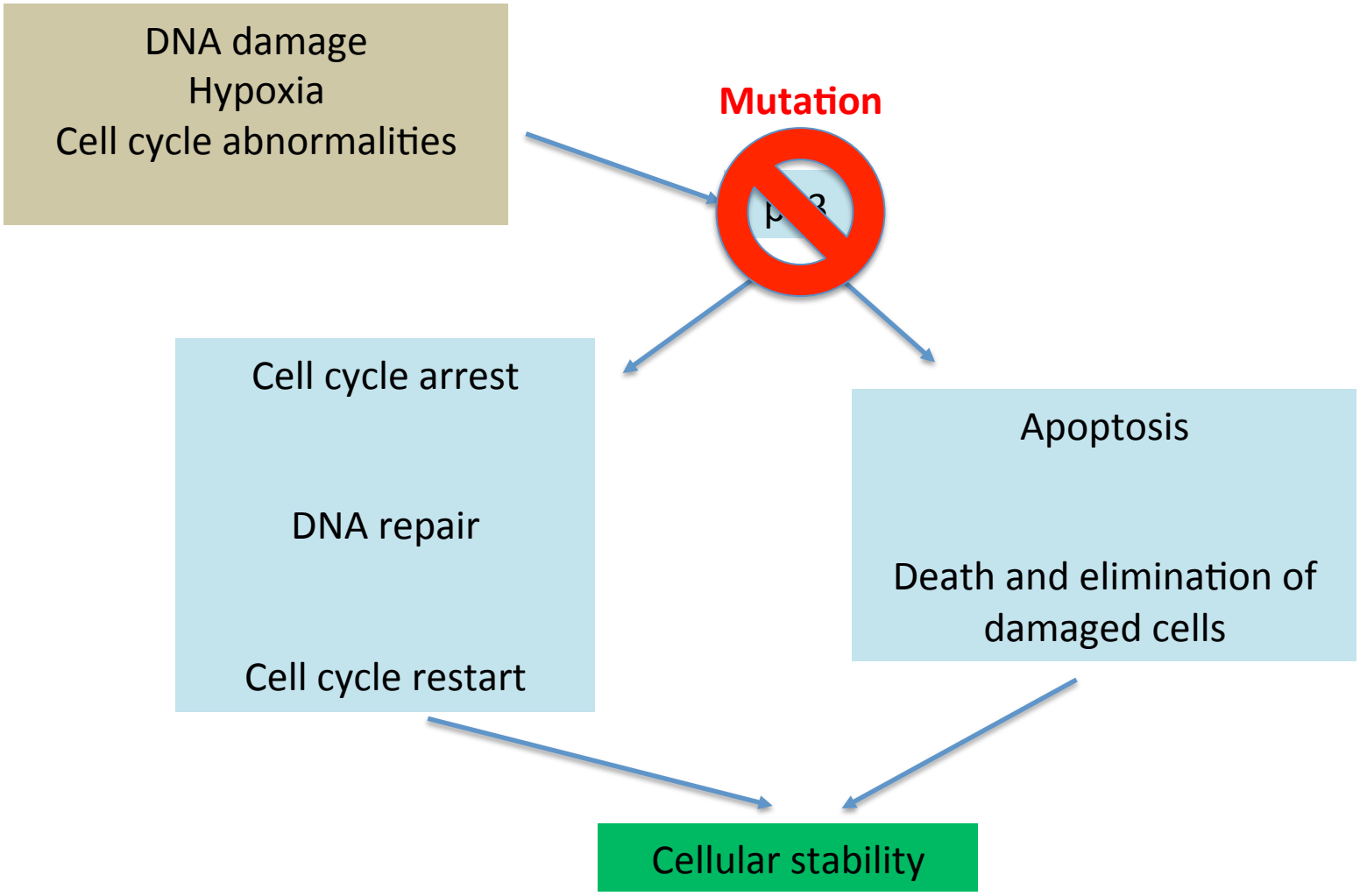
Biankin et al. Nature 2012

PDAC
KRAS is an oncogene that regulate cell division

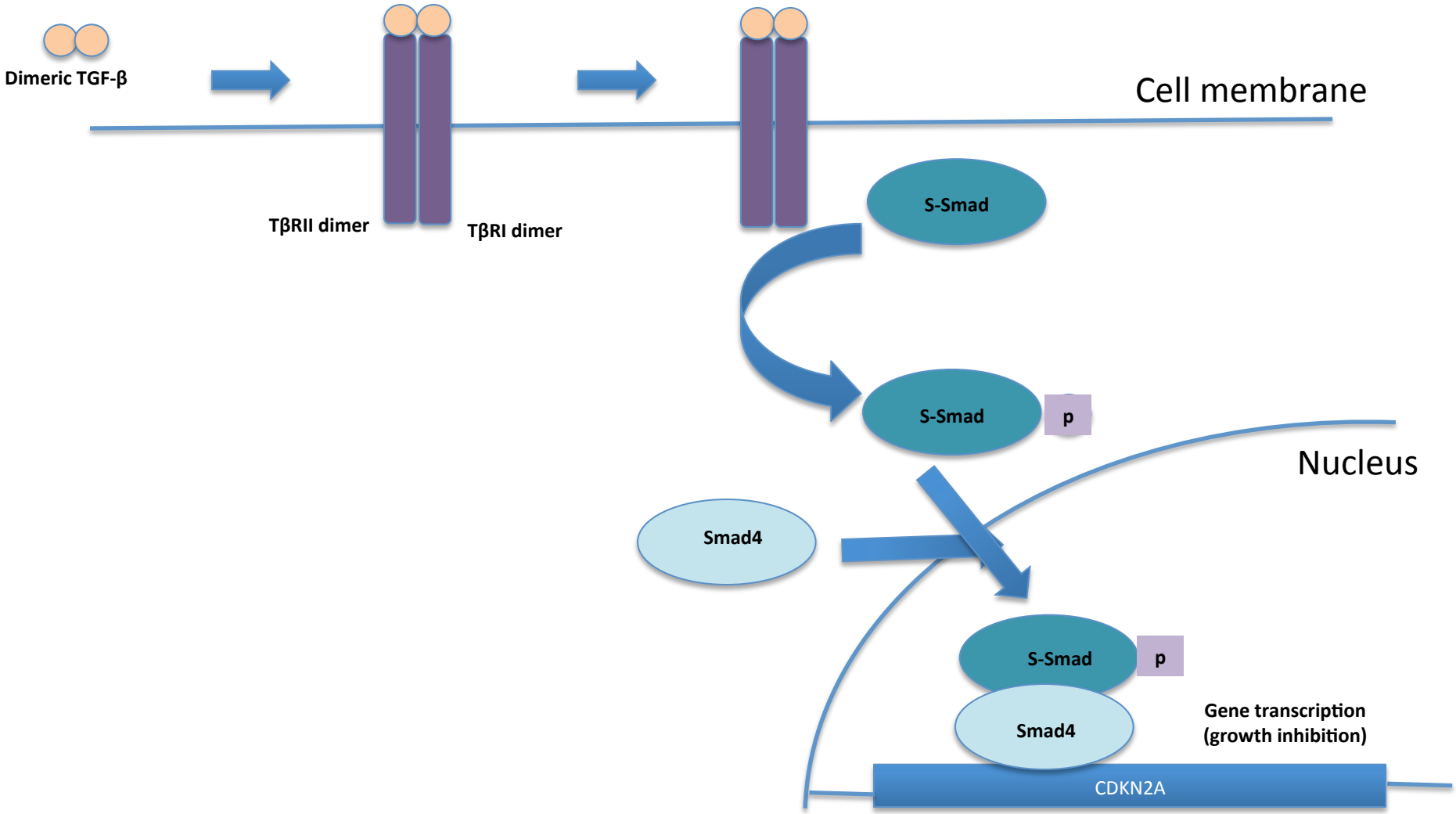


- most common (95%)
- Cell division
- Mutant *KRAS* in GTP-bound active state
- Cause continuous growth stimulation
- No inhibitor

PDAC
TP53 is a tumour suppressor



PDAC
SMAD 4 activates growth inhibitor genes

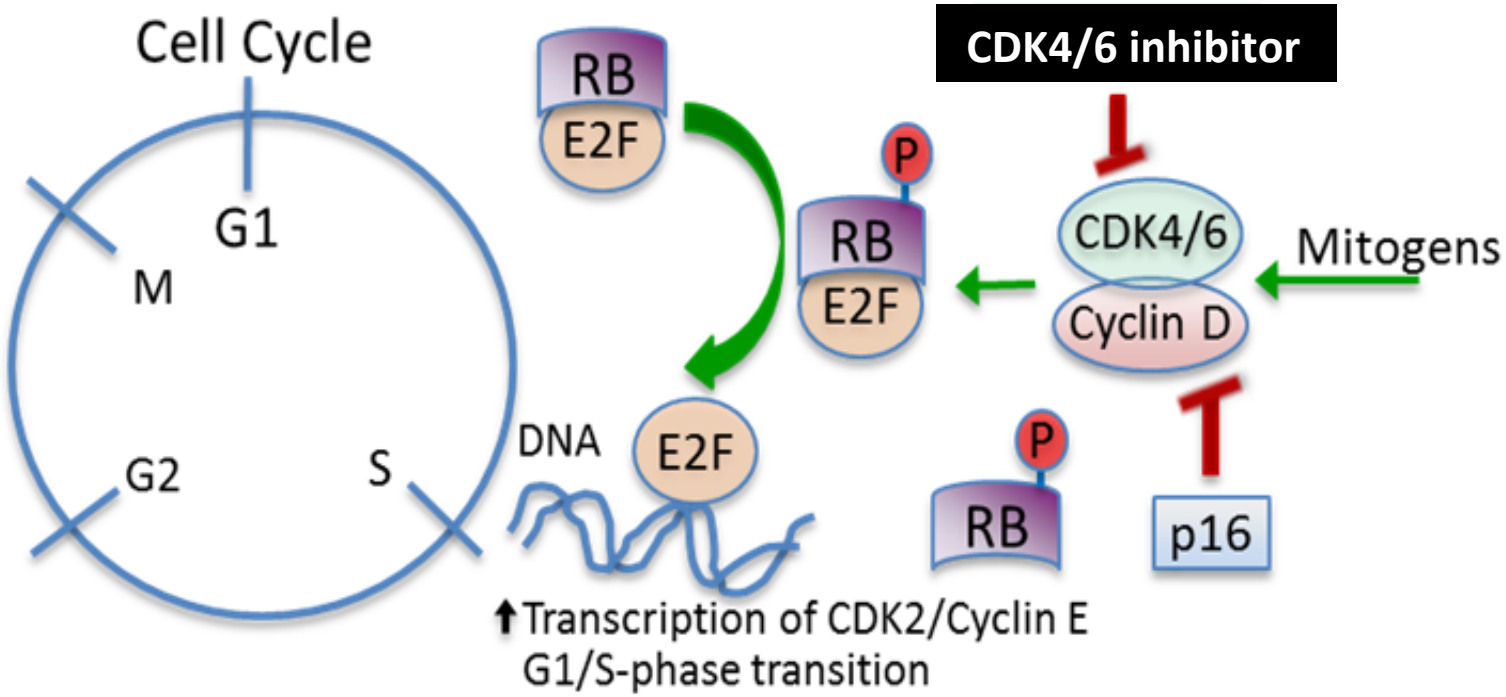


PDAC
CDKNA2 (p16) regulates G1/S

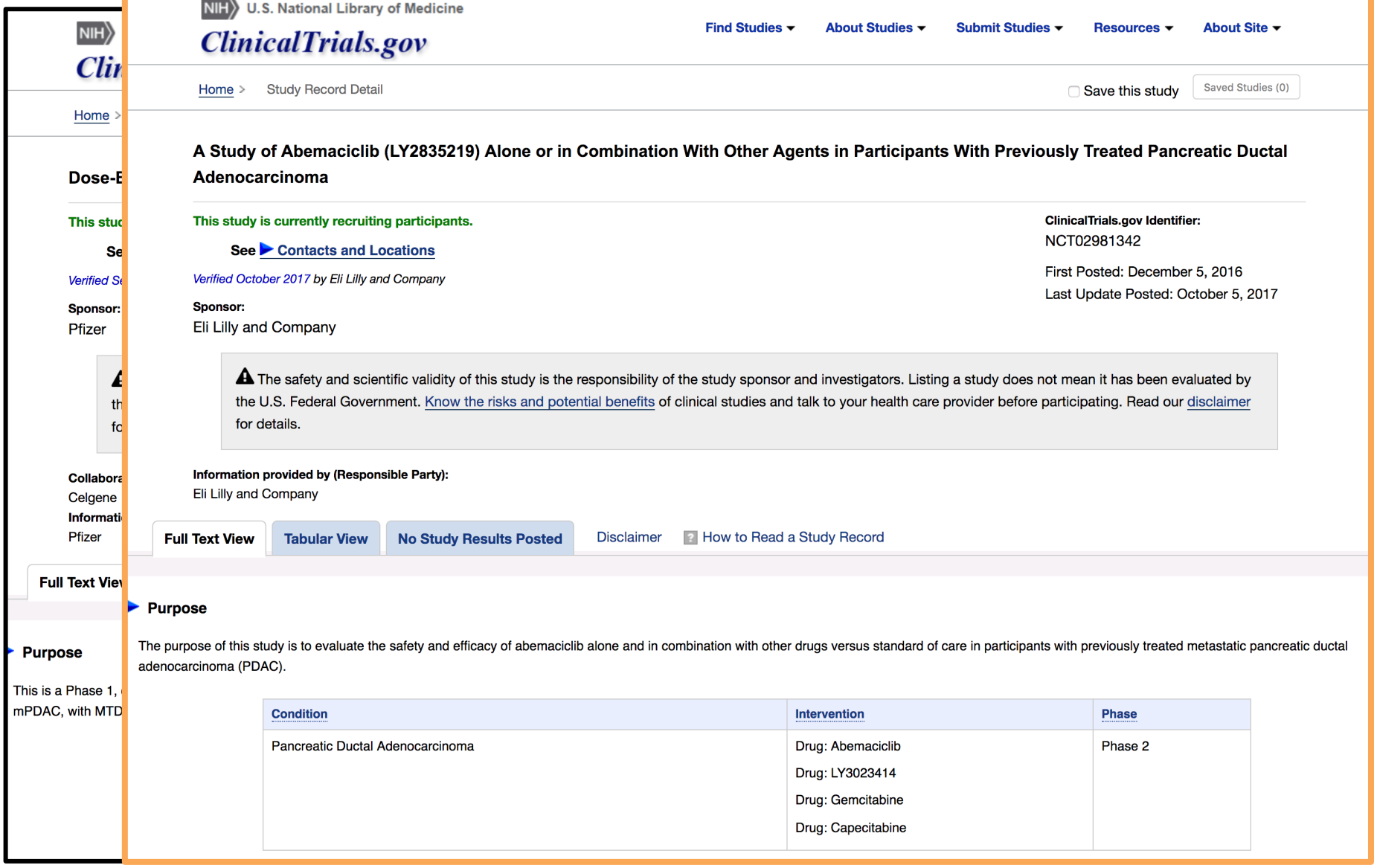
CDK4/6 inhibitor:
1. Palbociclib (Pfizer) – FDA approved
2. Ribociclib (Novartis) – FDA approved
3. Abemaciclib (Eli Lilly)

→ ER+/HER2- breast cancer

CDK4/6 pathway



CDK4i trials



NIH U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site

Home > Study Record Detail

Save this study | Saved Studies (0)

A Study of Abemaciclib (LY2835219) Alone or in Combination With Other Agents in Participants With Previously Treated Pancreatic Ductal Adenocarcinoma

This study is currently recruiting participants.

See Contacts and Locations

Verified October 2017 by Eli Lilly and Company

Sponsor:
Eli Lilly and Company

ClinicalTrials.gov Identifier:
NCT02981342

First Posted: December 5, 2016
Last Update Posted: October 5, 2017

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Information provided by (Responsible Party):
Eli Lilly and Company

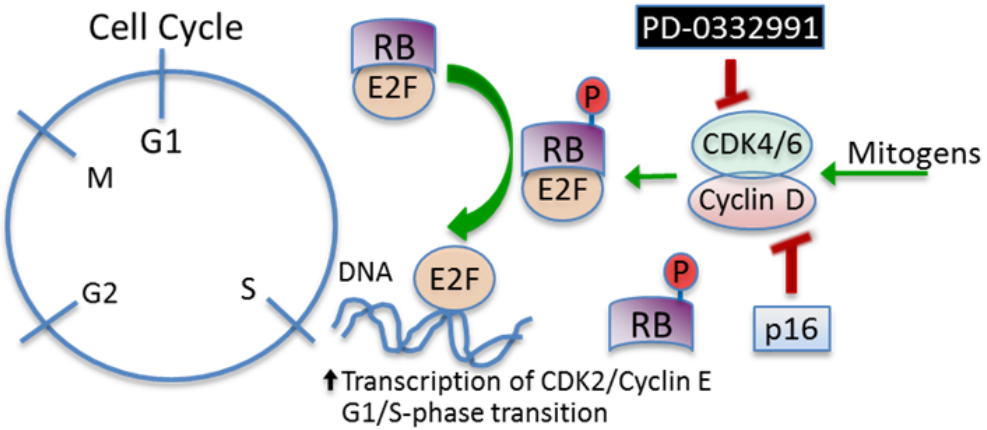
Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

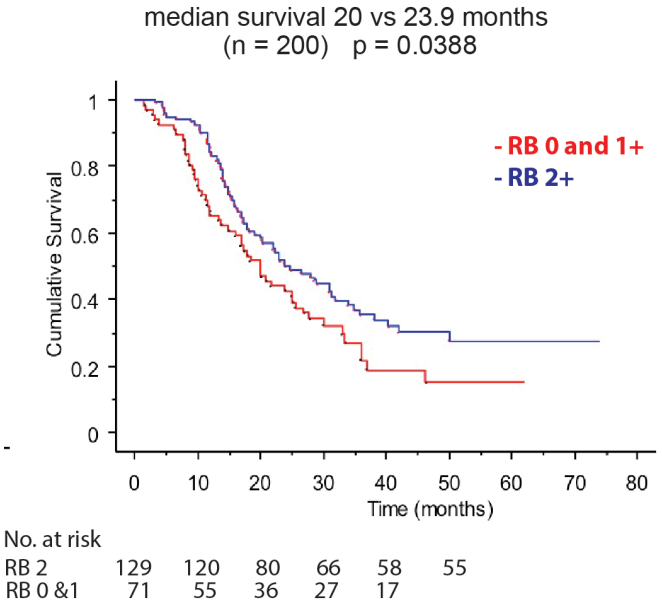
Purpose

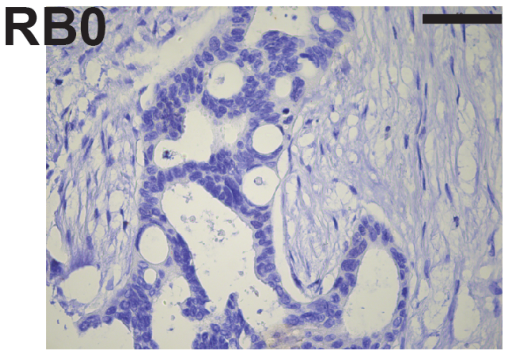
The purpose of this study is to evaluate the safety and efficacy of abemaciclib alone and in combination with other drugs versus standard of care in participants with previously treated metastatic pancreatic ductal adenocarcinoma (PDAC).

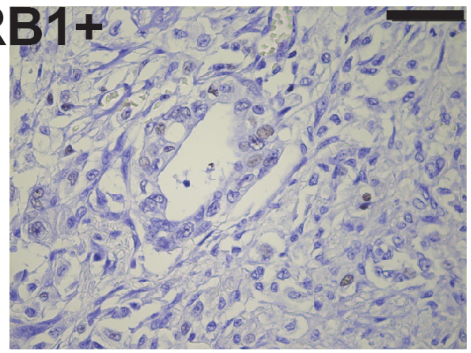
Condition	Intervention	Phase
Pancreatic Ductal Adenocarcinoma	Drug: Abemaciclib Drug: LY3023414 Drug: Gemcitabine Drug: Capecitabine	Phase 2

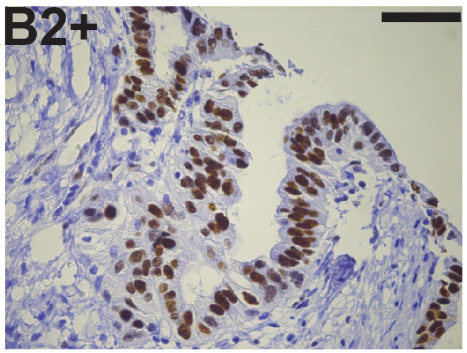
In-vivo Model – Sensitivity to CDK4i correlates with high RB expression





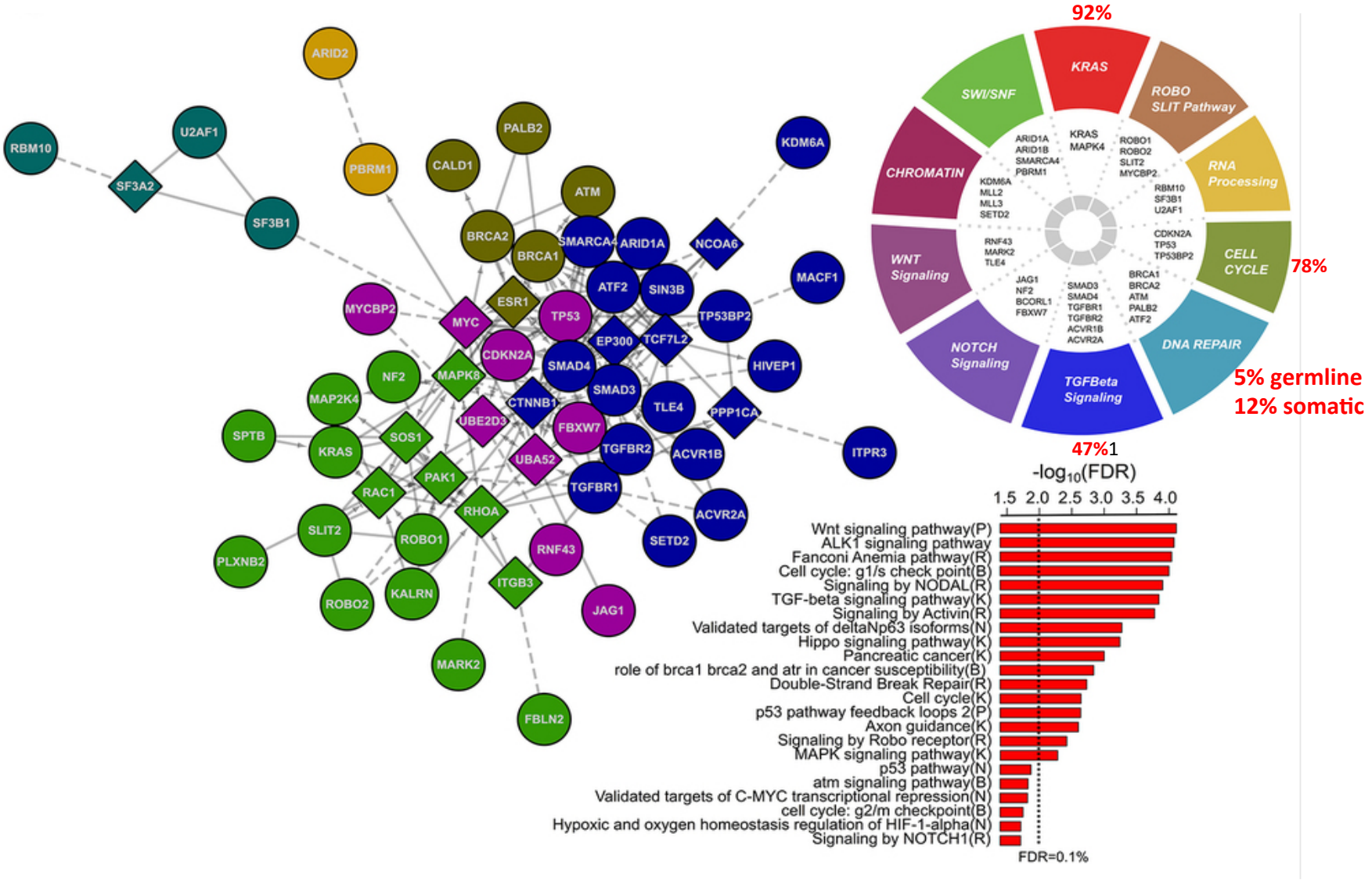






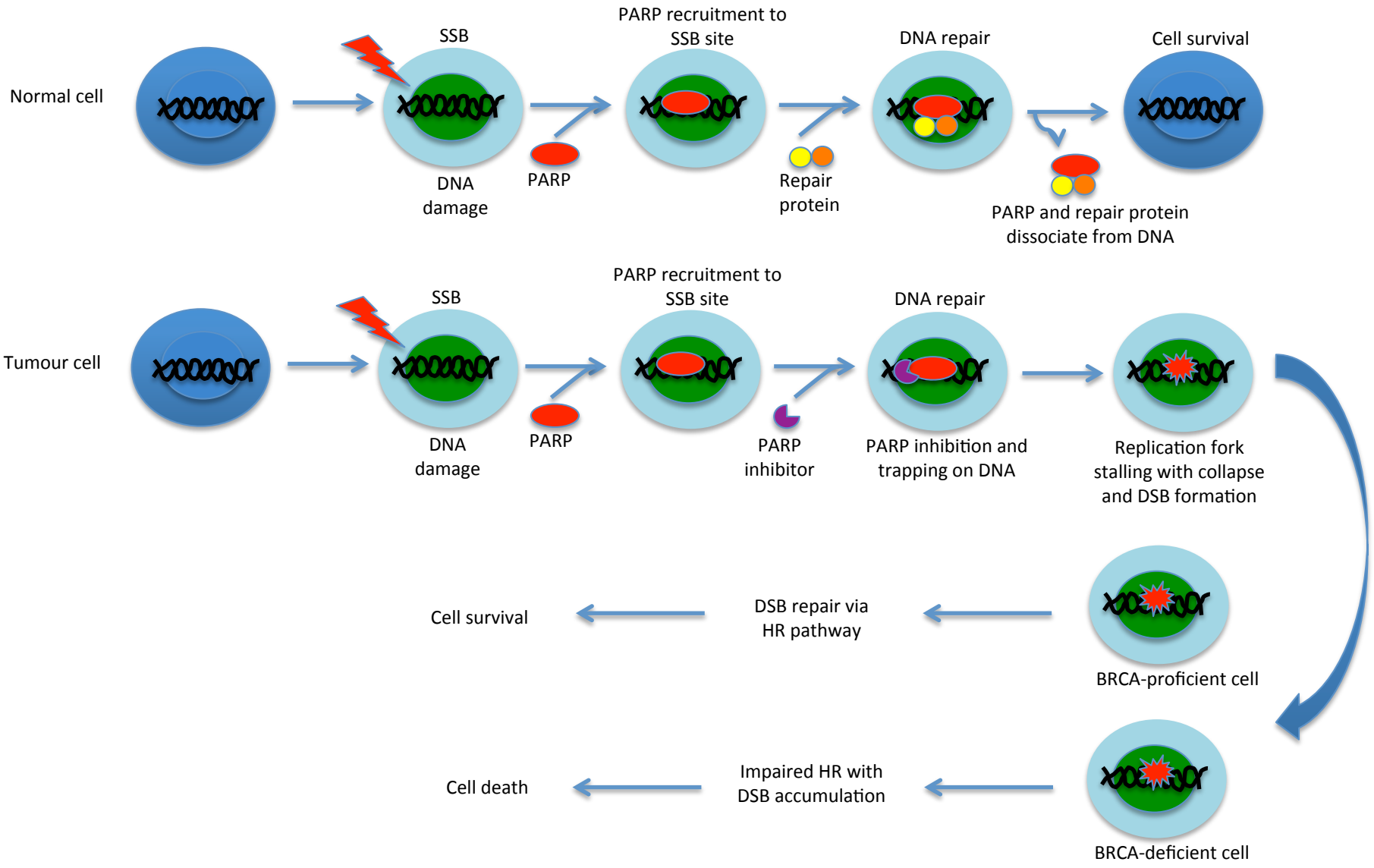
Chou et al. Gut accepted Sep 2017

PDAC –Mutated genes cluster into 10 molecular



Bailey et al *Nature* 2016

PARPi causes cell death in BRCA deficient cells



Olaparib in gBRCA Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy (POLO)

This study is currently recruiting participants.

See Contacts and Locations

Verified September 2017 by AstraZeneca

Sponsor:
AstraZeneca

ClinicalTrials.gov Identifier:
NCT02184195

First Posted: July 9, 2014
Last Update Posted: September 22, 2017

Collaborator:
Myriad Genetic Laboratories, Inc.
Information provided by (Responsible Party):
AstraZeneca

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

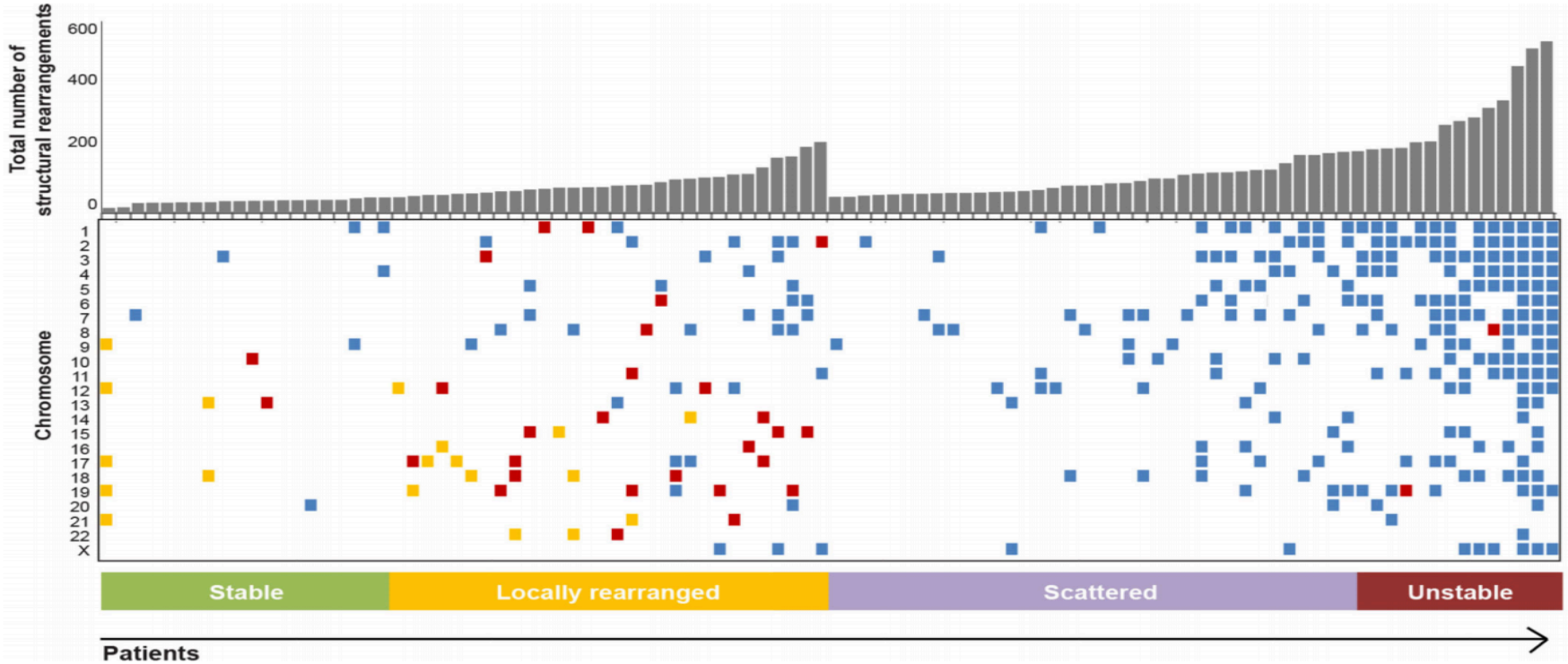
Purpose

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Condition	Intervention	Phase
Germline BRCA1/2 Mutations and Metastatic Adenocarcinoma of the Pancreas	Drug: Olaparib Drug: Placebo	Phase 3

PDAC – structural variation

- 4 subtypes of PDAC based by structural variation profile **UNSTABLE subtype potentially targetable**



≤50 structural variation, 20%

Significant event on 1 or 2 chromosomes, 30%

<200 structural variation, 36%

≥200 structural variation, 14%

good correlation of DNA repair genes *BRCA1, BRCA2, PALB2, ATM, FANCM, XRCC4, XRCC6*

Platinum and PARP response?

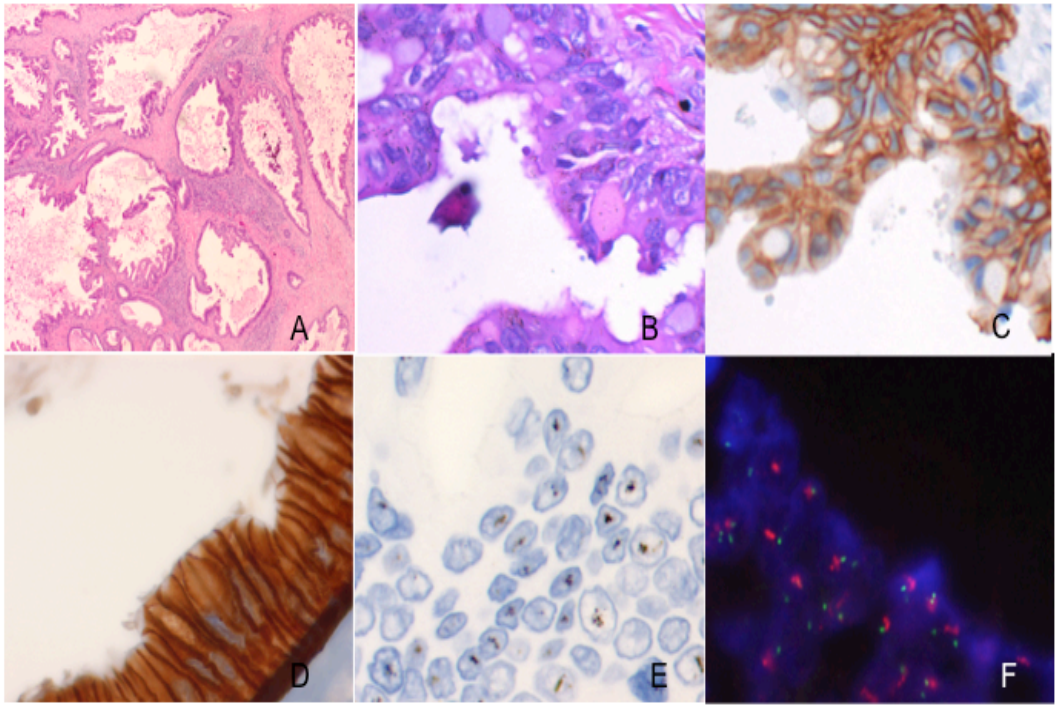
Waddell N. Nature 2015

HER2 amplification is present in 2% of PDAC

Her2 Immuno-histochemical score	IHC scores (n=469)	*HER2* FISH positive (n=10)	*HER2* FISH negative (n=459)
3+	7 (1.5%)	7	0
2+	27 (5.8%)	3	24
1+	59 (12.6%)	0	59
0	376 (80.2%)	0	376

Criteria for scoring Her2 by immunohistochemistry and in situ hybridization in PDAC.

Her2 IHC score	Criteria (modified from Hofmann et al.[21])
0	No staining of any pattern or intensity
1+	Weak discernable membrane staining
2+	Mild to moderate complete or baso/lateral membrane staining
3+	Strong, complete or baso/lateral membrane staining
***HER2* ISH**	**Criteria**
Non amplified	Her2 count <4 and Her2:cep17 ratio <2
Amplified	Her2 count ≥4 and Her2:cep17 ratio ≥2



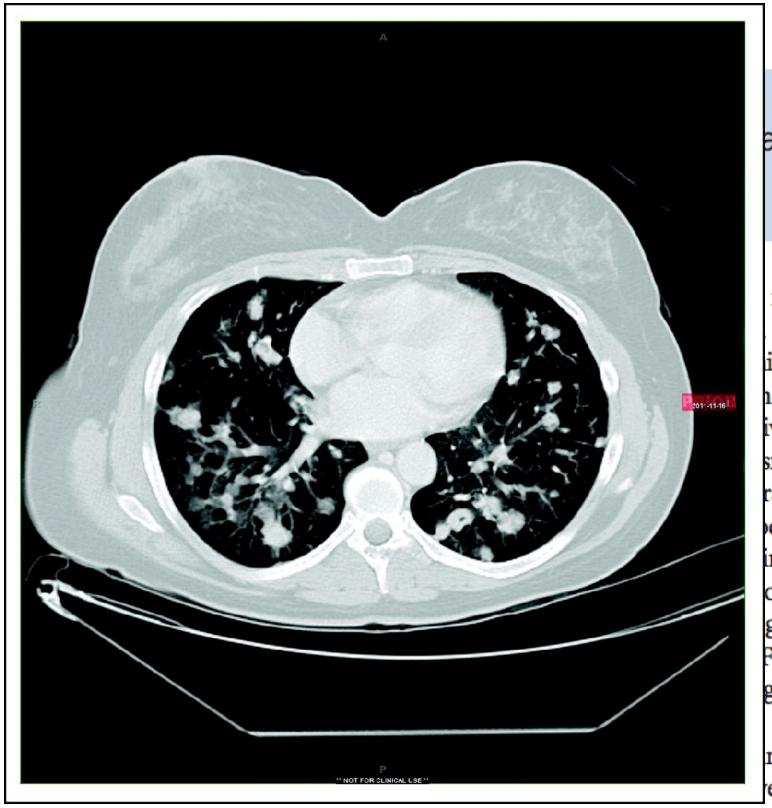
variables	no.	HER2 amp	Non-HER2 amp	
Outcome				
Follow-up (months)	0.03-240	5.0-43.6	0.03-240	
Median FU (months)	16	23	16	
Death PDAC	369	8	361	
Death Other	32	2	30	
Death Unknown	16	0	16	1.0000*
Alive	49	0	49	
Lost to follow-up	3	0	3	
Cancer specific survival				
Mean (months)	20	28	20	0. 2502 #
Standard deviation	19.43	19.65	19.55	
Recurrence				
Present	258	5	253	
Absent	79	2	77	
Unknown	132	3	130	
Pattern of recurrence				
Lung without liver metastasis	22 (8.5% n=258)	4 (50% n=8)	18 (7.2% n=250)	0.0022*
Any recurrence without liver metastasis	124 (48% n=258)	8 (100% n=8)	119 (48% n=250)	0.0031*
Adjuvant therapy				
Yes	175	3	172	
No	289	7	282	
unknown	5	0	5	

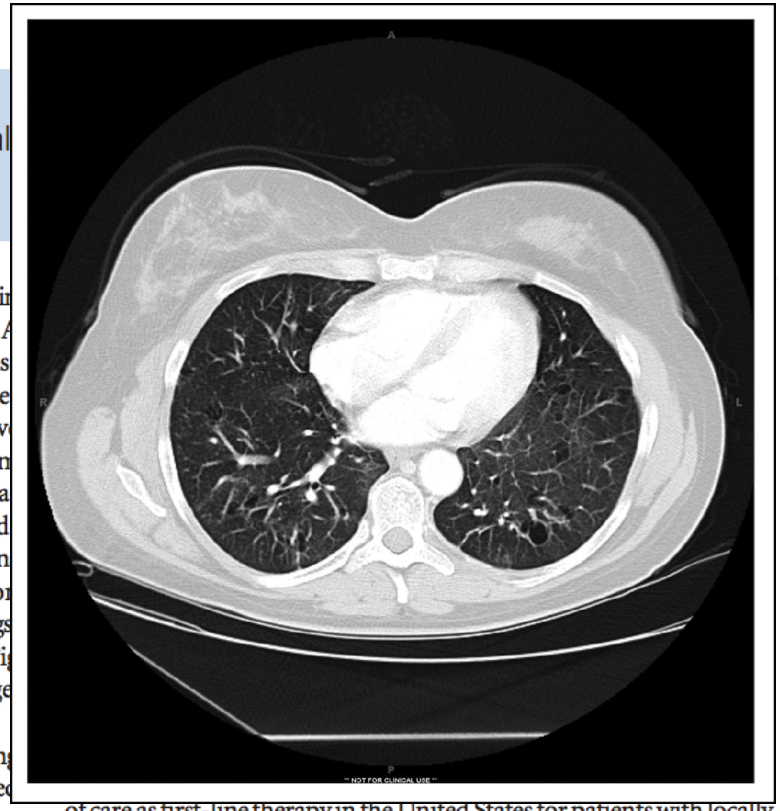
Chou et al *Genome Medicine* 2013

VOLUME 30 · NUMBER 27 · SEPTEMBER 20 2012

JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY





this treatment from September 2010 through January 2011. Because of disease progression and after consulting an academic tertiary care center, the patient's therapy was changed to gemcitabine with capecitabine, which she was given from February 2011 through August 2011.

The patient's disease continued to progress, and in September 2011, she was started on third-line treatment with gemcitabine and

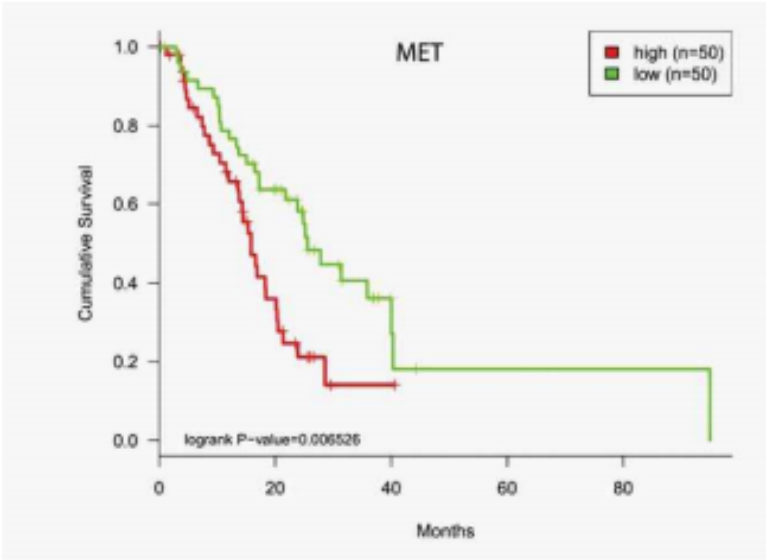
of care as first-line therapy in the United States for patients with locally advanced or metastatic biliary tract cancer.

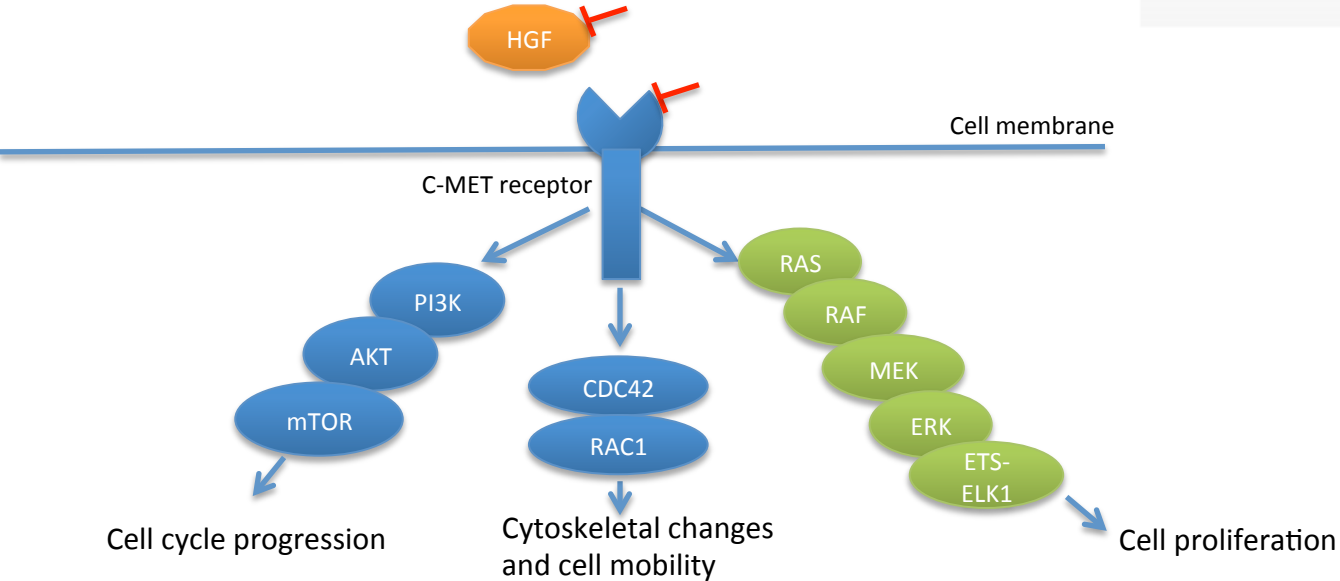
PDAC
Differential Methylation Analysis

- DNA methylation is widespread involving 3522 genes

- Enchriched in 6 core cancer signalling pathways:
  1. Invasion
  2. proliferation
  3. Stellate cell activation
  4. Axon guidance
  5. Cell adhesion
  6. Apoptosis

Deregulation of MET signaling





Nones et al. Int J of Cancer 2014

PDAC – transcription network profile

Classified into 4 subgroups - associated histological characteristics

1. Squamous

- Adenosquamous morphology (p=0.0011)
- inflammation, MYC pathway, autophagy

2. Pancreatic progenitor

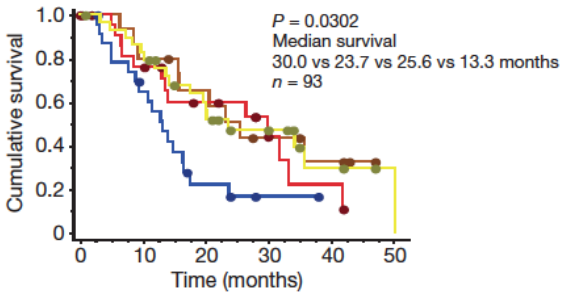
- Pancreatic development
- Invasive IPMN, colloid carcinoma morphology (p=0.0005)

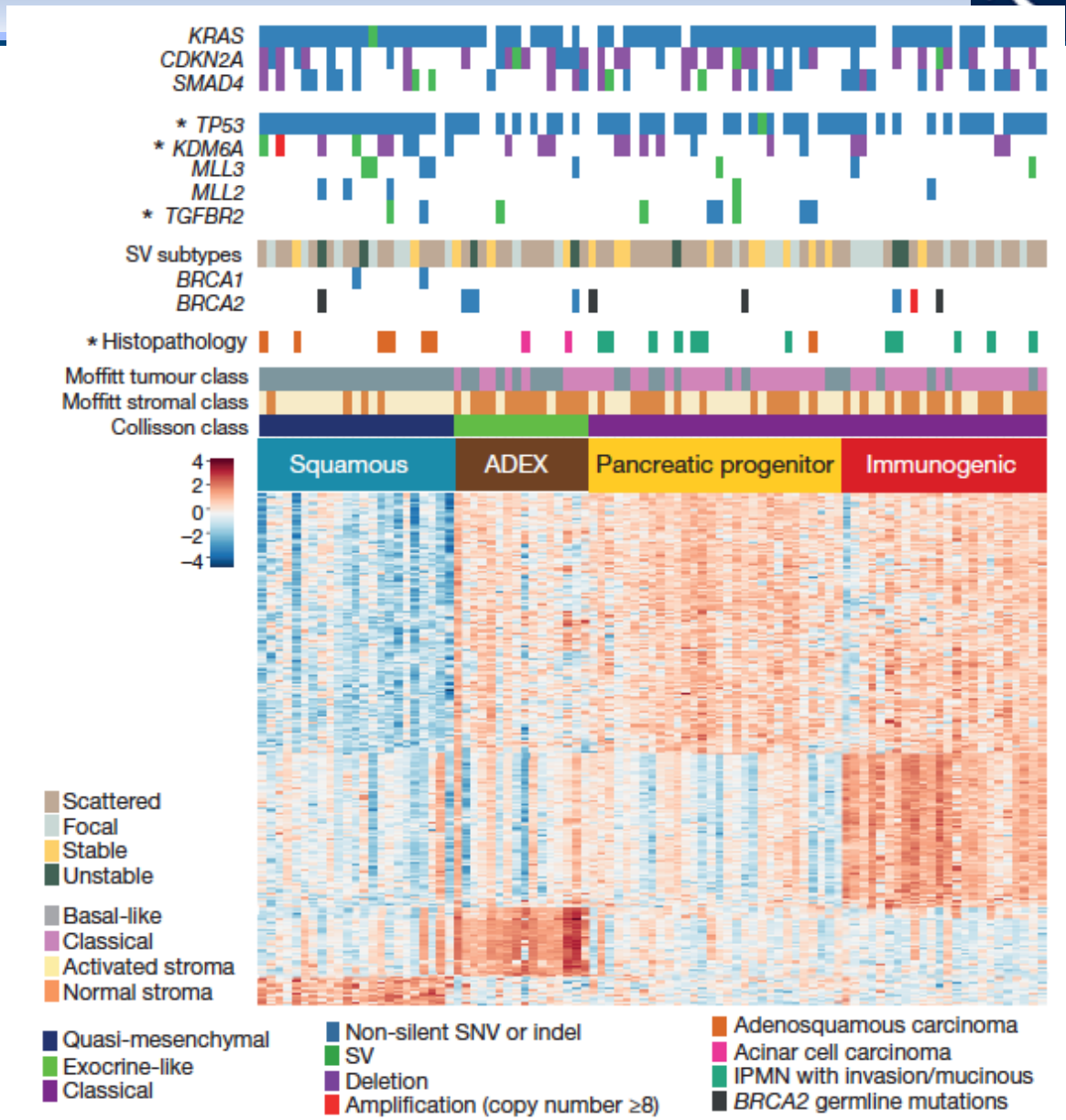
3. Immunogenic

- Immune gene programmes – B cell and T cell signaling pathways

4. ADEX (aberrantly differentiated endocrine exocrine)

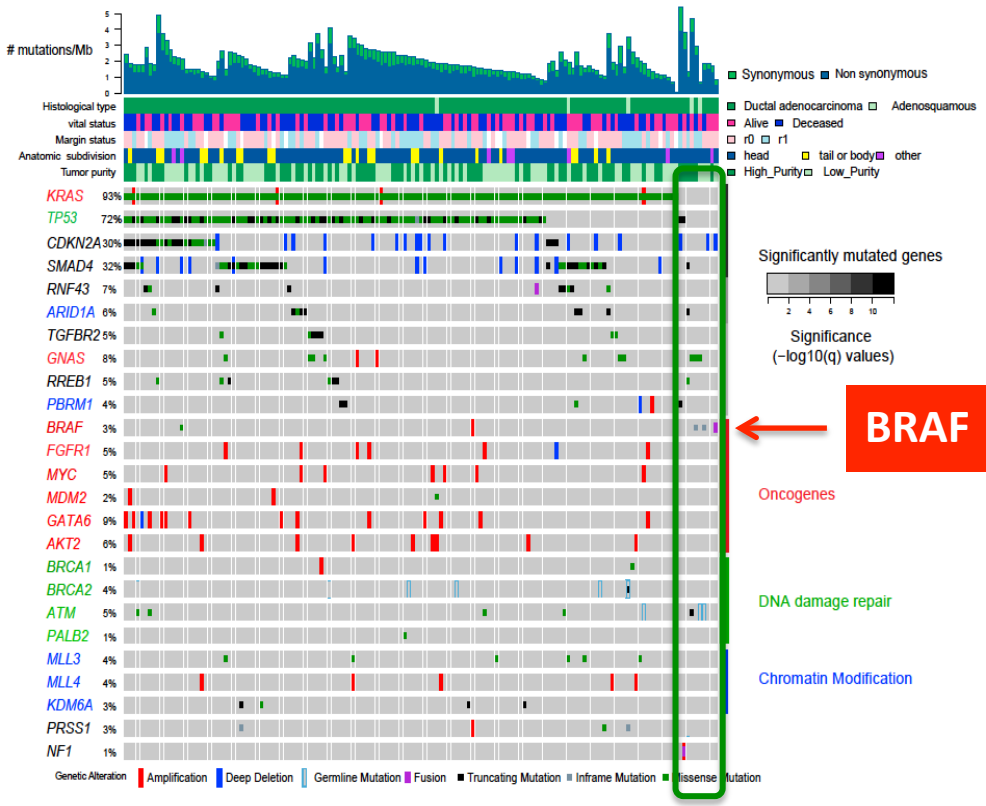
- Late pancreatic development and differentation





Bailey et al *Nature* 2016

PDAC - KRAS wild-type



Significantly mutated genes

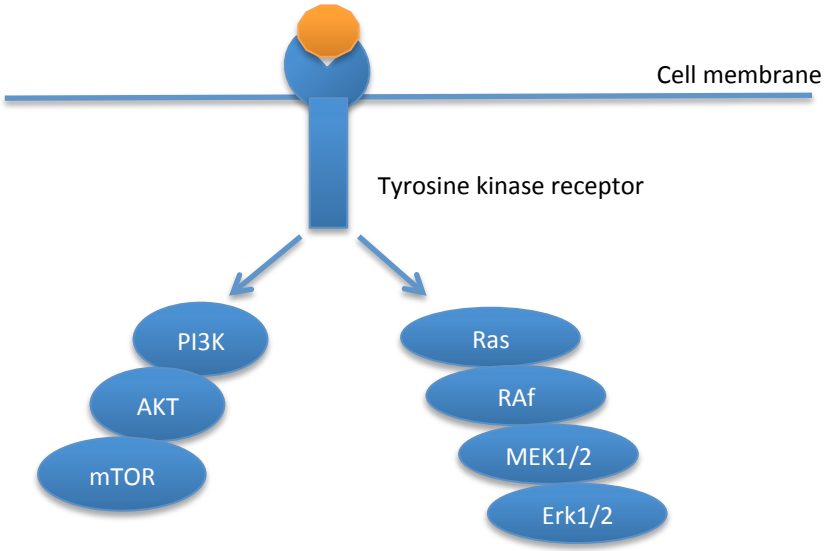
Significance (−log10(q) values)

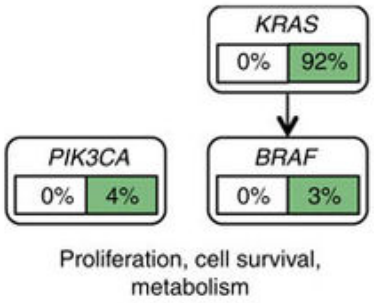
BRAF

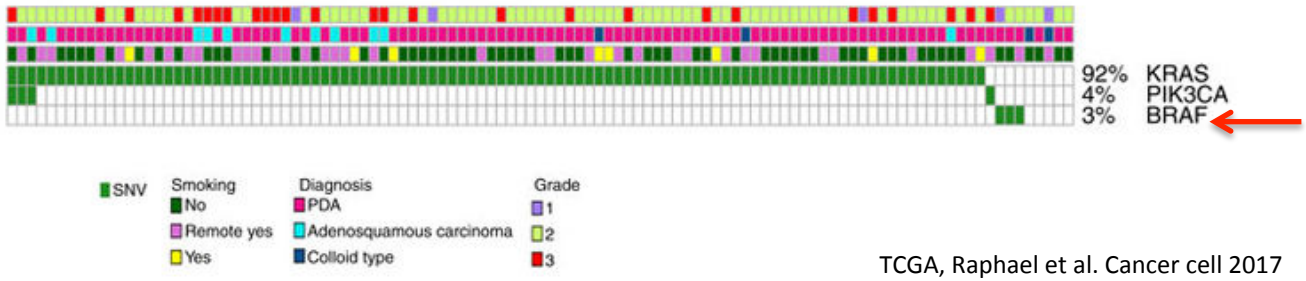
Oncogenes

DNA damage repair

Chromatin Modification







TCGA, Raphael et al. Cancer cell 2017

Witkiewicz et al. Nature communications 2015

Cancer Chemother Pharmacol
Published online 2015 Mar 31

Phase II study (in patients with

S. Kordes,[✉#] H. J. Klümp
Author information ▶ Article

This article has been cited

Abstract

Purpose

The combination of an of preclinical evidence capecitabine and everc

Methods

Patients with advanced performance status 0–1 capecitabine 1000 mg/ schedule. Tumor asses resp surv

Res

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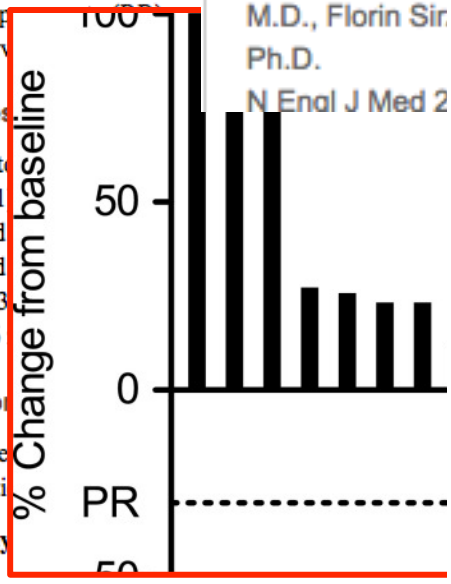


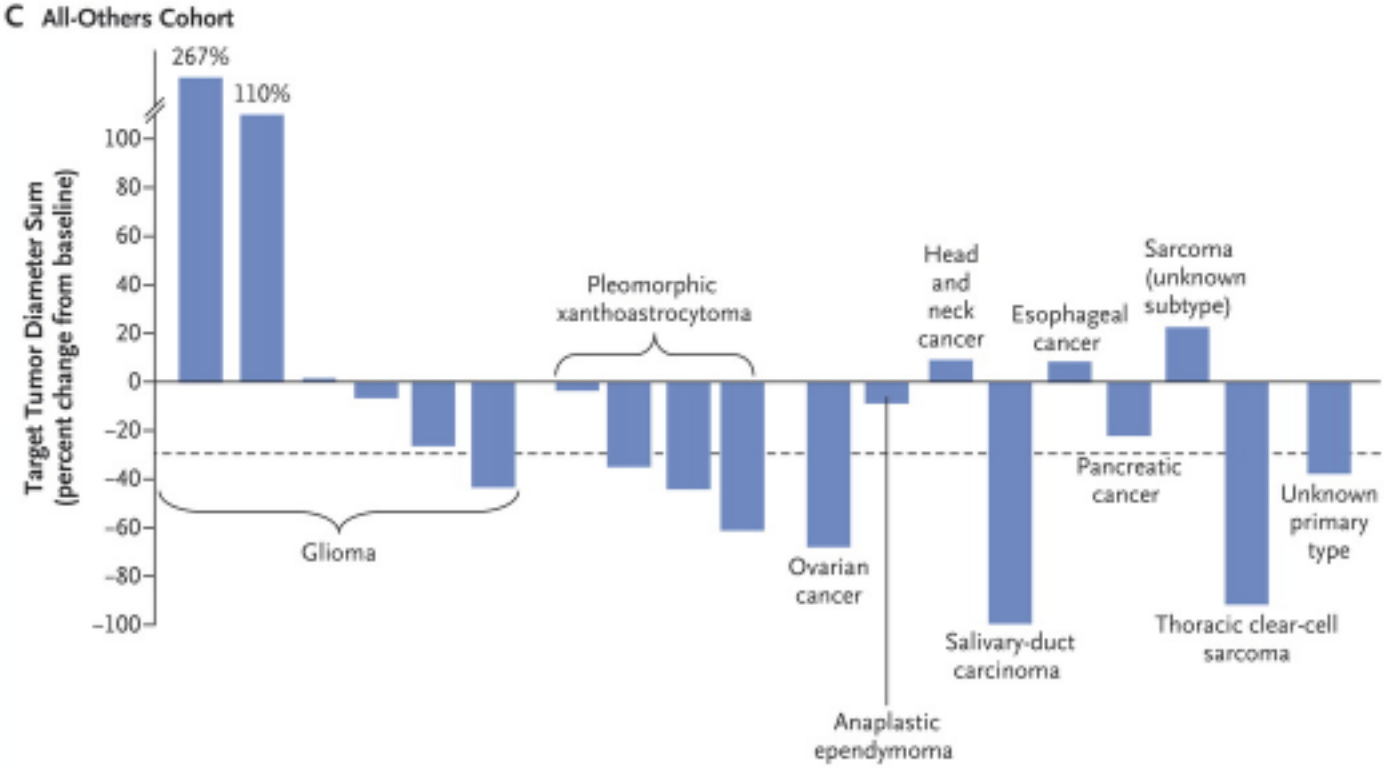
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

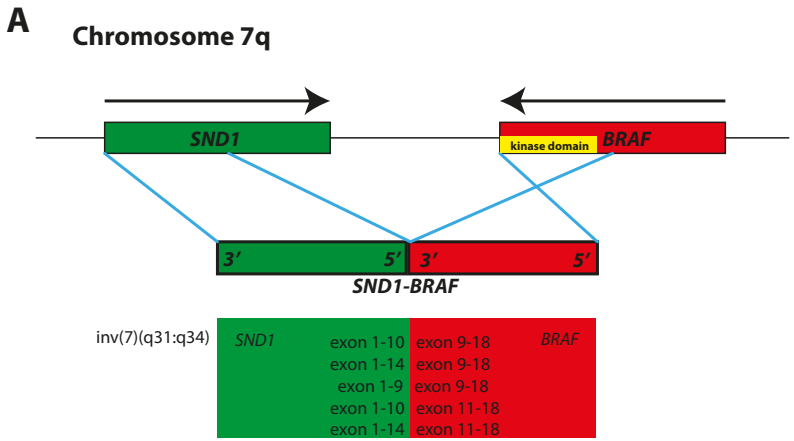
David M. Hyma
M.D., Ph.D., Jü
Gervais, M.D.,
Hidalgo, M.D.,
M.D., Florin Sir
Ph.D.

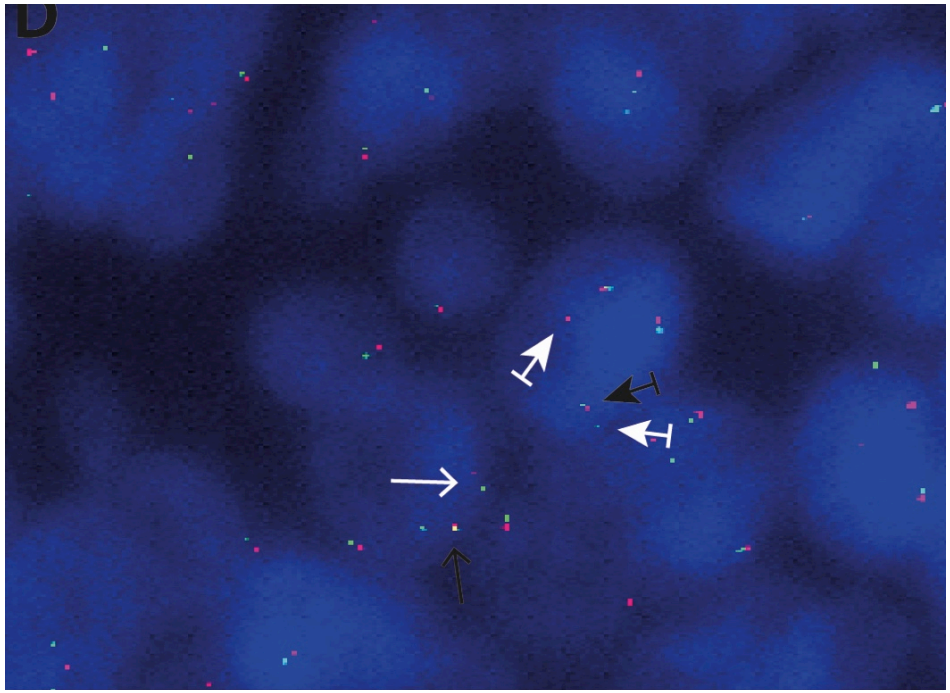
N Engl J Med 2

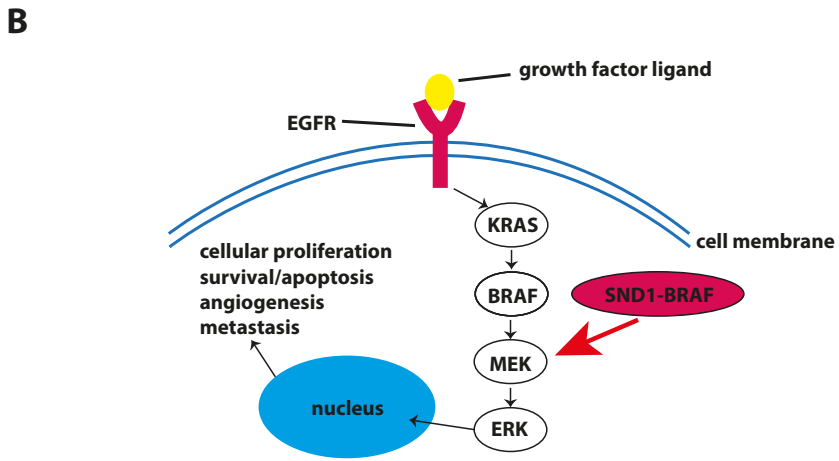


Pancreatic acinar cell carcinoma

- Approximately 20% have a BRAF rearrangement by FISH
- Confirmed by 2 independent studies







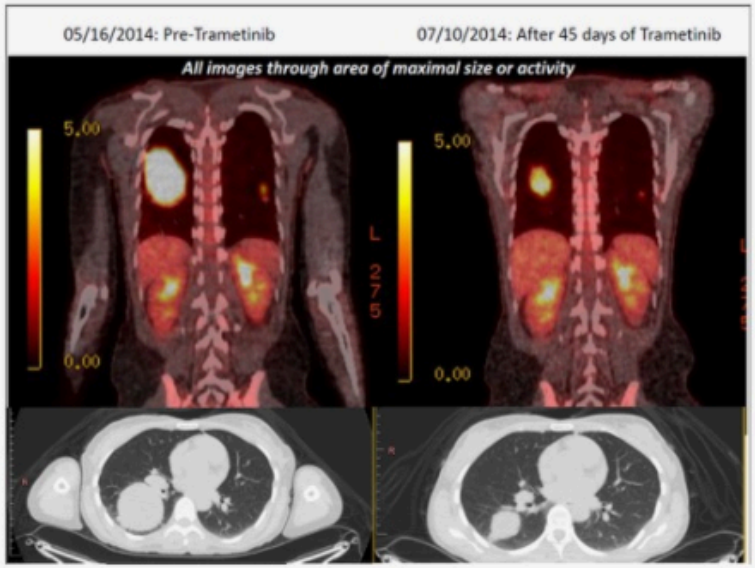
Chou et al. Pathology accepted Sep 2017
Want et al. Modern Pathology Sep 2017

Targeting BRAF rearrangement with MEK inhibitor

Int J Cancer. 2016 Feb 15; 138(4): 881–890.
Published online 2015 Sep 8. doi: 10.1002/ijc.29825
PMCID: PMC5049644

The distribution of *BRAF* gene fusions in solid tumors and response to targeted therapy

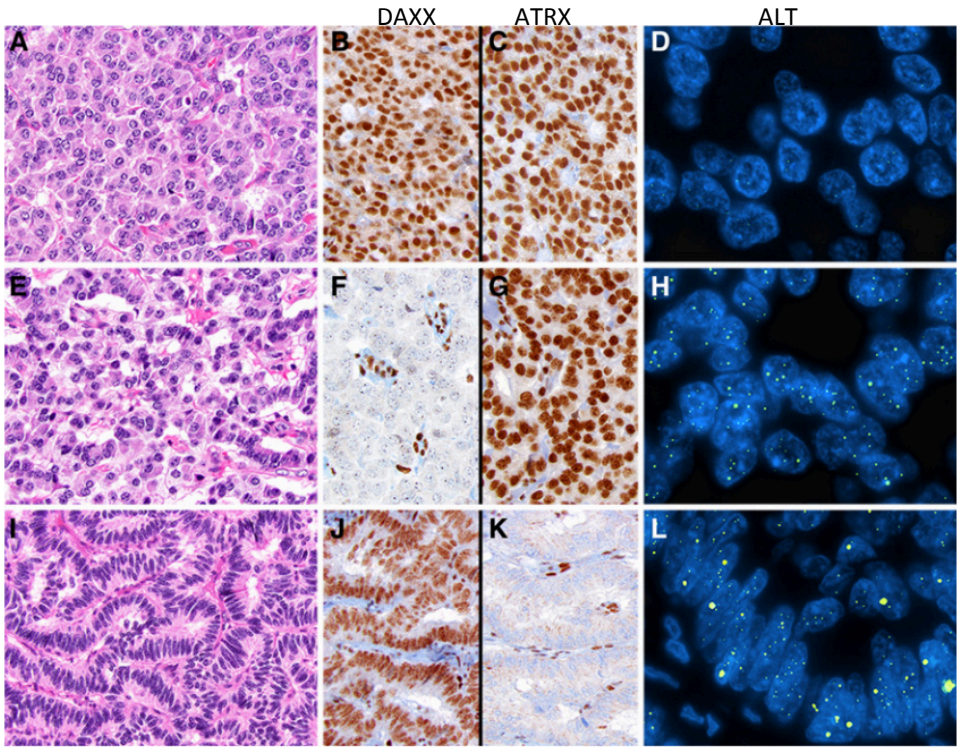
Jeffrey S. Ross,[1,2,†] Kai Wang,[1,†] Juliann Chmielecki,[1] Laurie Gay,[1] Adrienne Johnson,[1] Jacob Chudnovsky,[1] Roman Yelensky,[1] Doron Lipson,[1] Siraj M Ali,[1] Julia A. Elvin,[1] Jo-Anne Vergilio,[1] Steven Roels,[1] Vincent A Miller,[1] Brooke N. Nakamura,[3] Adam Gray,[3] Michael K Wong,[3] and Philip J Stephens[1]

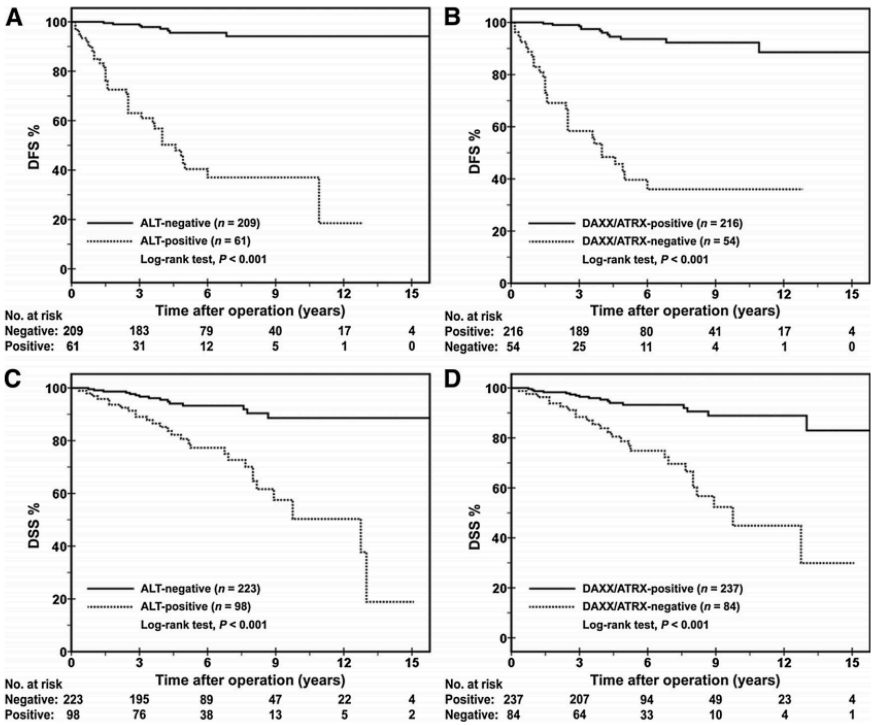


Fused PET/CT imaging results of trametinib therapy in a metastatic Spitzoid melanoma (Case 38) from a 46-year-old Caucasian woman that featured a *ZKSCAN1-BRAF* fusion (*ZKSCAN1* exons 1–5–*BRAF* exons 10–18) and responded to the MEK inhibitor trametinib. Subcutaneous tumor nodules exhibited overt clinical responses within 14 days of therapy, and her dominant bulky right lung metastases showed significant response by Day 45 such that she subsequently underwent robotic-assisted lobectomy. The patient is currently alive with stable disease at 6 months post-thoracic surgery.

ATRX/DAXX in Pancreatic neuroendocrine tumours

- 40% inactivation of apoptotic regulator pathway involving Death domain-associated protein gene (**DAXX**) or ATR-X gene (**ATRX**) - mutually exclusive
- proteins involved in chromatin remodeling (causing alternative lengthening of telomeres and chromosomal instability)
- Independent markers of prognosis.





Singhi et al. Clin Cancer Res 2016

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- Garvan Institute
  - Personalised Cancer Therapeutic Group - Marina Pajic
- Cancer diagnostic and pathology group and APGI leader – Anthony Gill
- Cancer Institute NSW ECF

cancer diagnosis & pathology

NSW GOVERNMENT

cancer institute NSW

GARVAN INSTITUTE OF MEDICAL RESEARCH

APGI Australian Pancreatic Cancer Genome Initiative