CMF
Canadian Mesothelioma Foundation

Toronto 26th November 2020

Stratified Therapy for Mesothelioma

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Mesothelioma Research Programme LEICESTER

Disclosures

Advisor

Astra Zeneca/Medimmune, Atara, Aldeyra,
Bayer, Bristol Myers Squibb, Bergen Bio, Boehringer Ingelheim, Clovis,
Eli lilly, Inventiva, Lab21, MSD, Roche/Genentech, Paredox

Research funding/support

Astex, Bayer, Boehringer Ingelheim, BMS, Clovis, Eli Lilly, Bergen Bio,
FuijiBio, Pierre Fabre, Roche Genentech

Speaker Bureau

BMS, Roche, Eli Lilly

Inter-patient heterogeneity: a barrier to effective therapy

Synthetic lethal strategies

Master protocols to deliver stratified therapy

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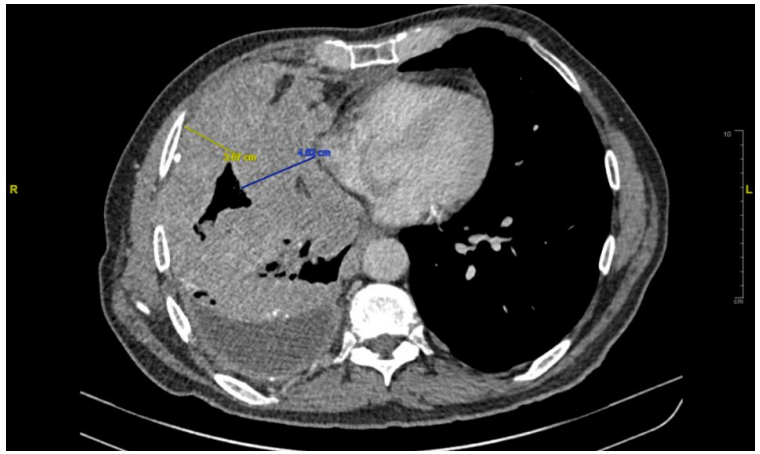
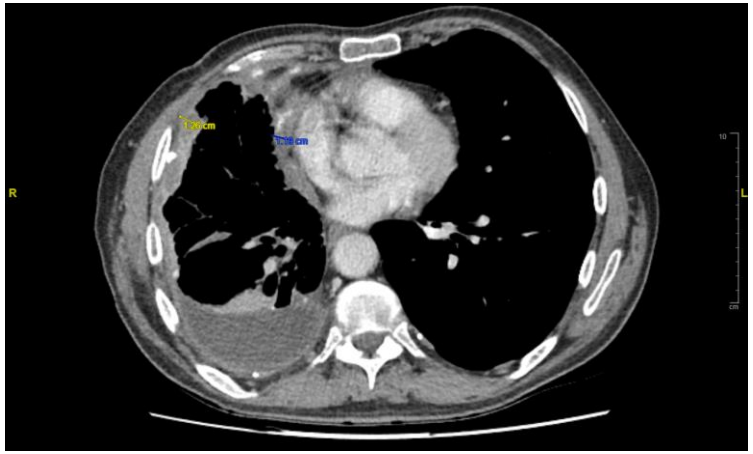
Synthetic lethal strategies

Master protocols to deliver stratified therapy

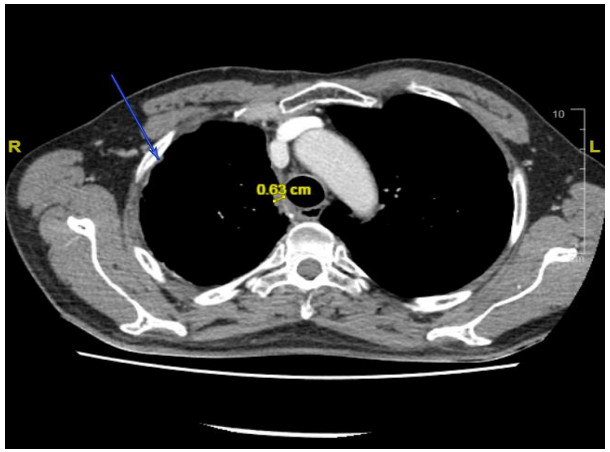
14 November 2017



22 February 2018

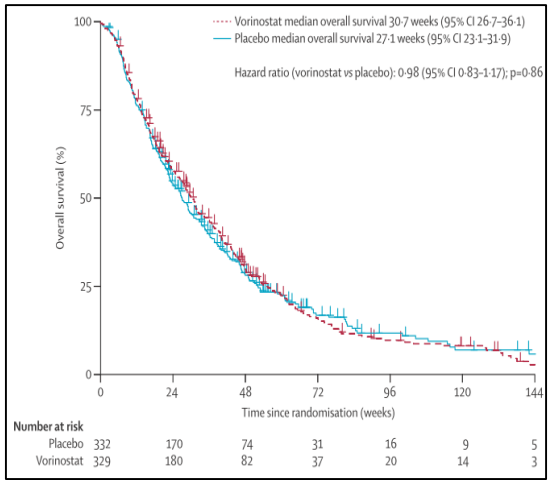


30 May 2018



Inter-patient Heterogeneity: a barrier to effective therapy ?

VANTAGE



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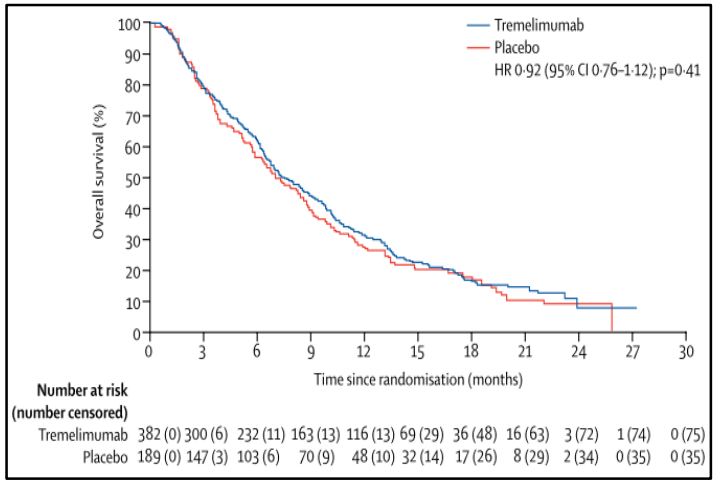

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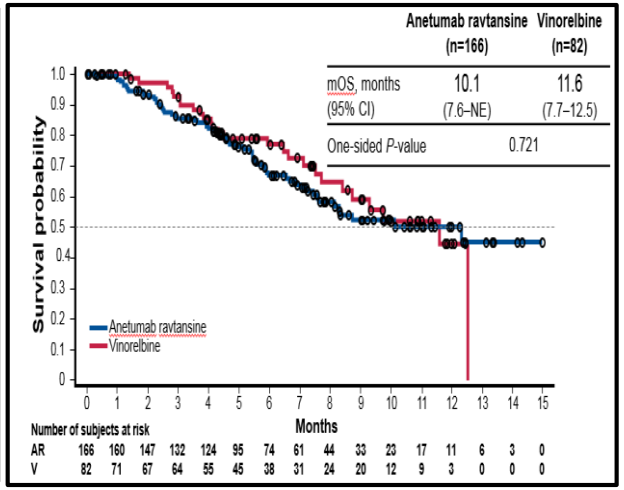

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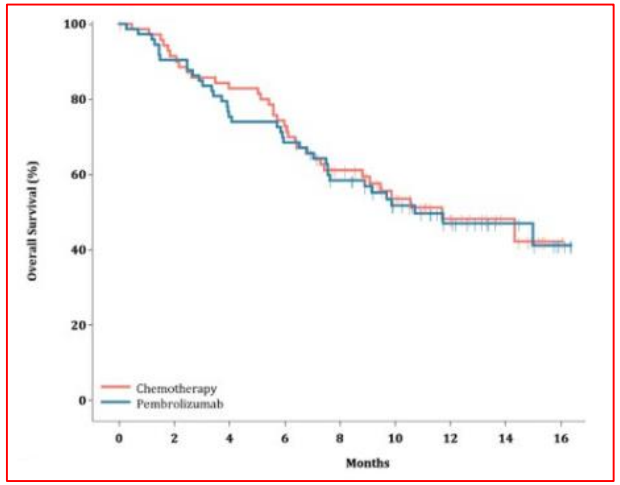

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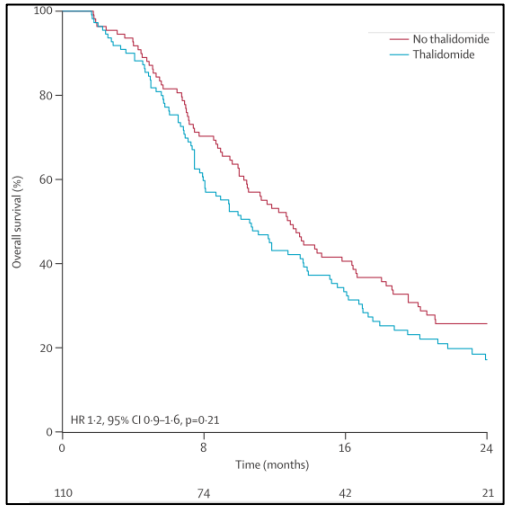

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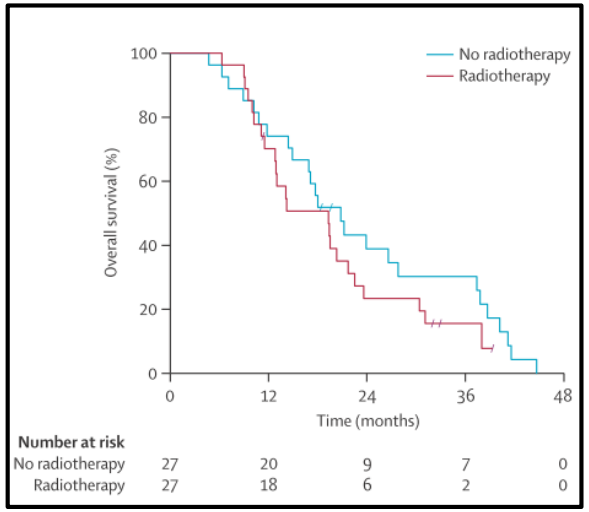
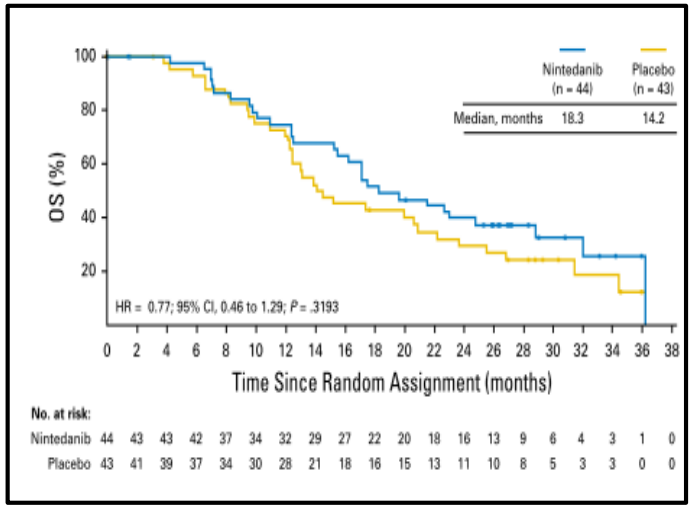


LUME MESO



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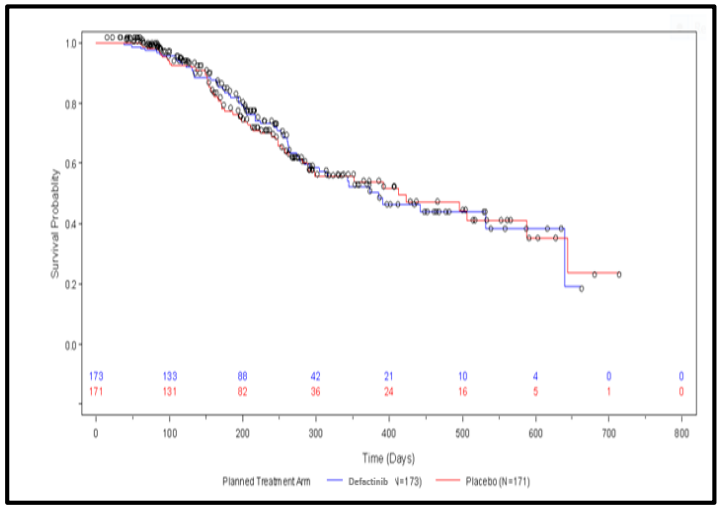
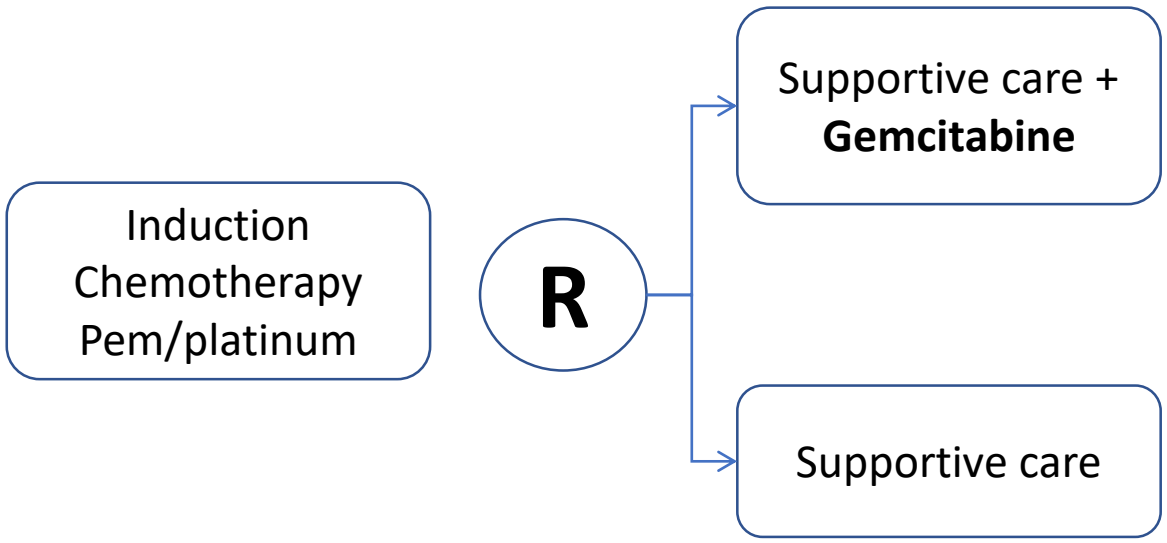
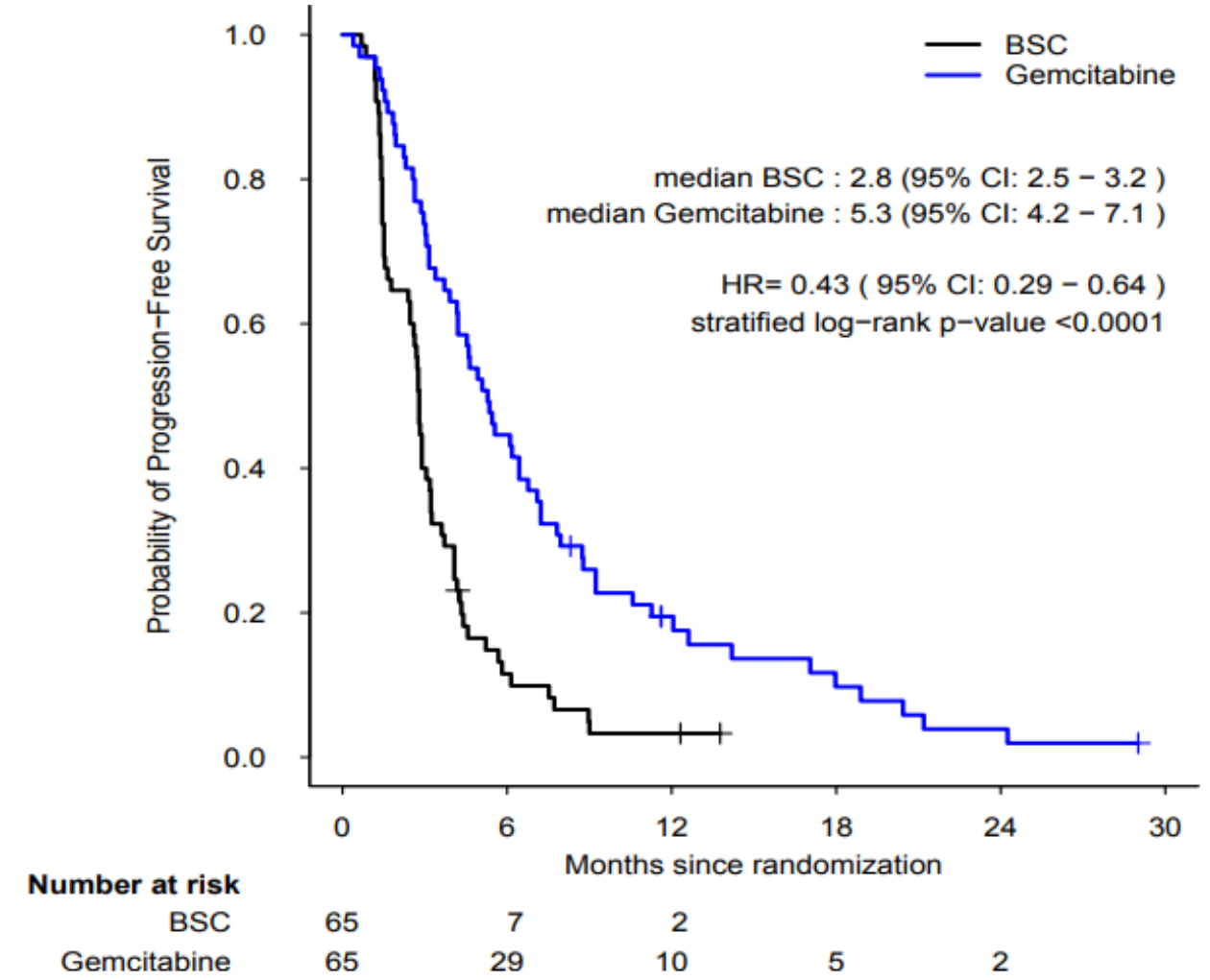


Patient Stratification based on *response* to chemotherapy



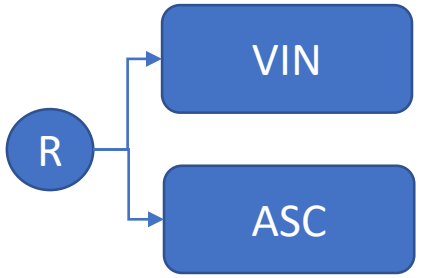


Burgers et al, ESMO 2019

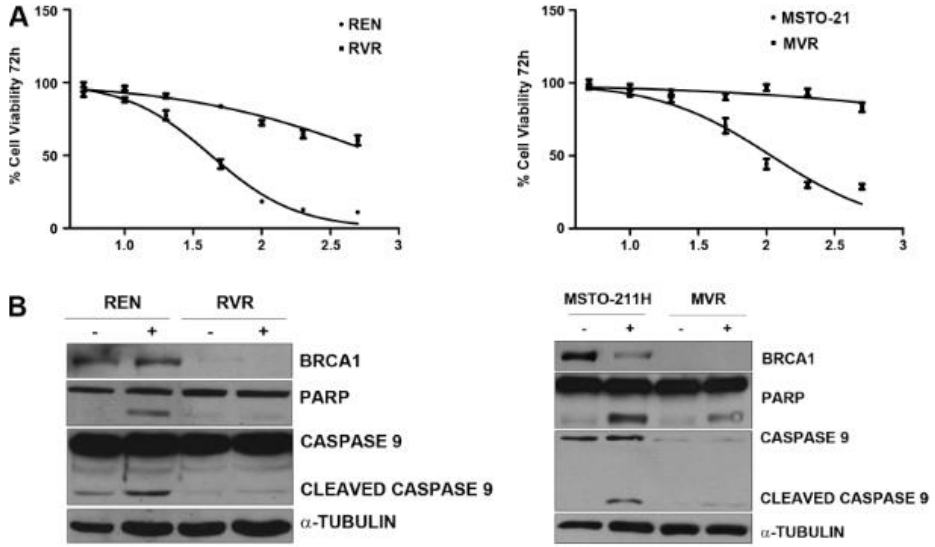
Molecular stratification of vinorelbine via spindle assembly checkpoint status

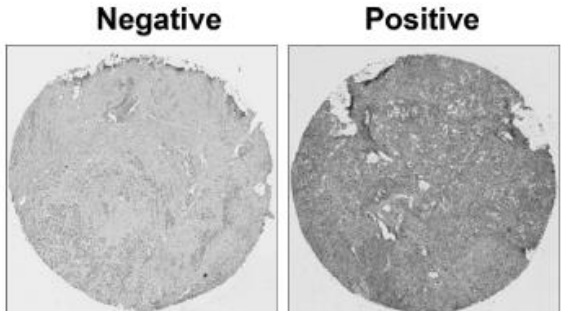
VIM (NCT02139904)

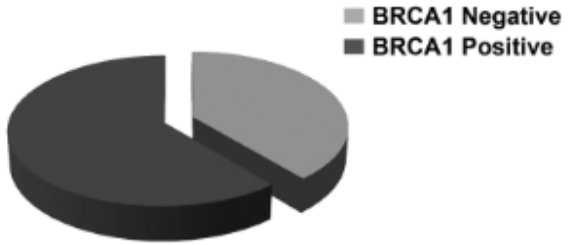
2nd Line MPM



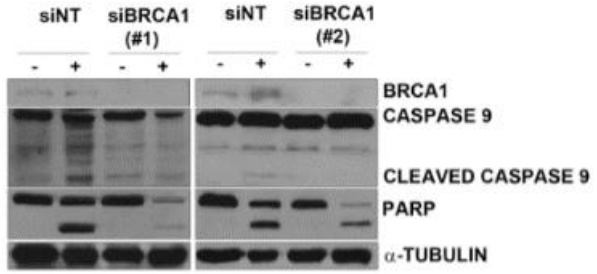
Loss of BRCA1 in acquired resistance



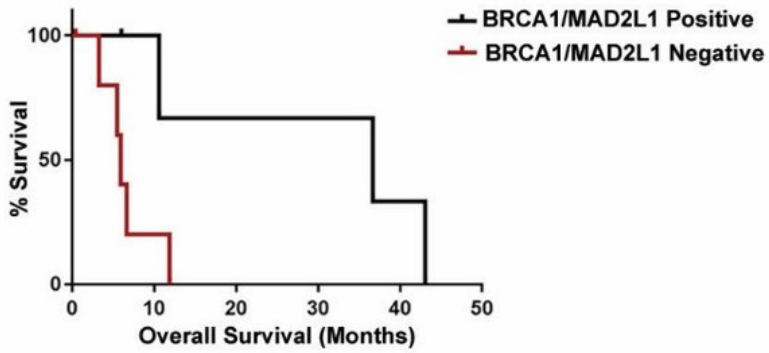




BRCA1 siRNA induces resistance



E58



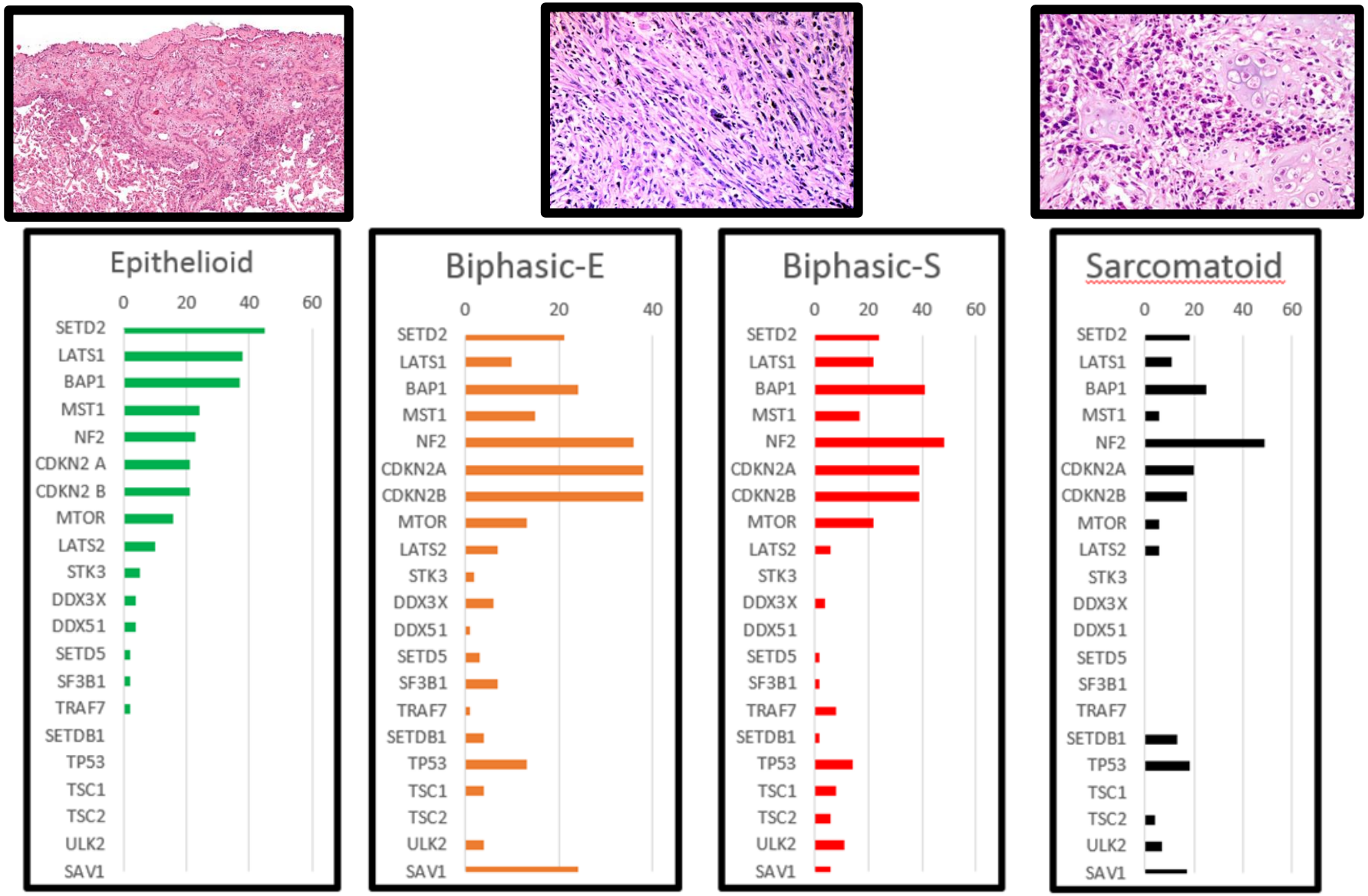
Busacca et al, J Pathol 2012; Kindler et al, IASLC 2017; Stebbing et al, Lung Cancer 2009; Busacca et al, unpublished

Inter-patient heterogeneity: a barrier to effective therapy

Synthetic lethal strategies

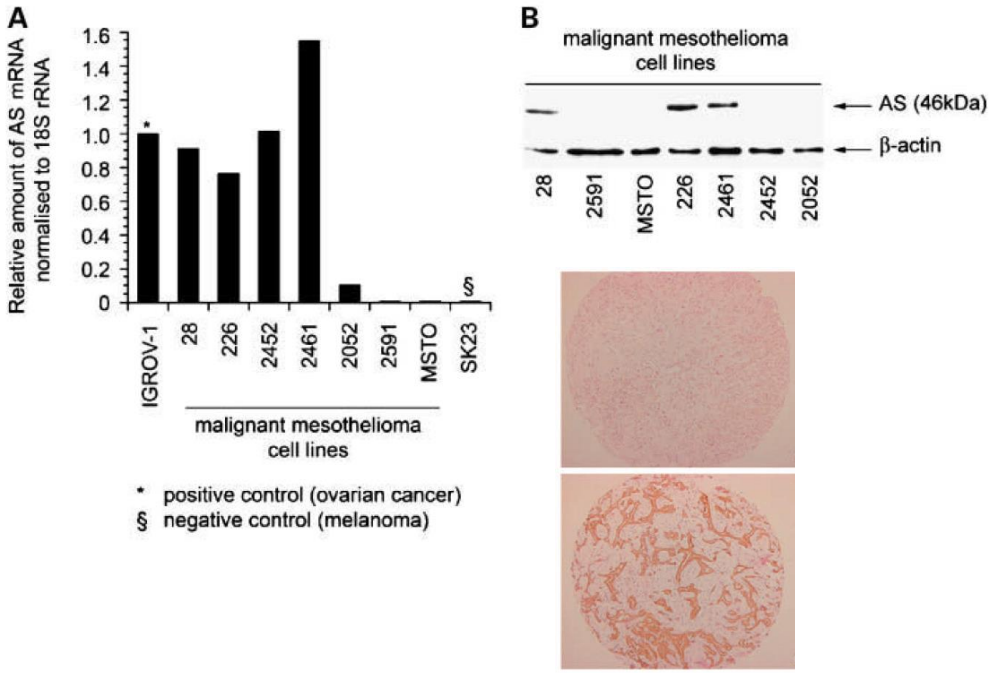
Master protocols to deliver stratified therapy

Mesothelioma subtypes exhibit distinct histologies, genomic landscapes and Prognoses

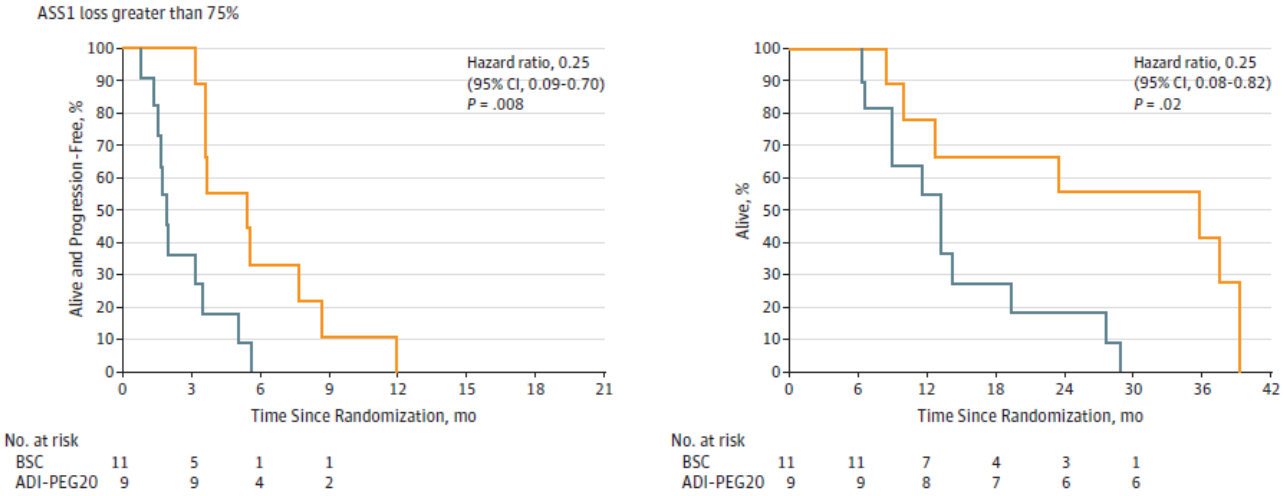


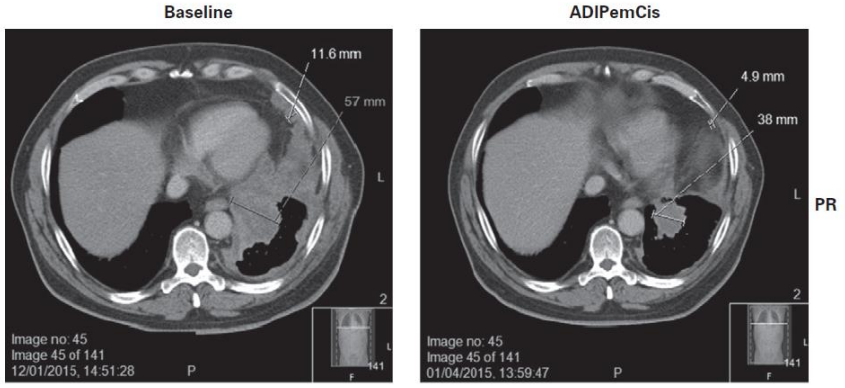
Bueno et al, Nature Genetics 2016, Yap et al, Nature reviews Cancer 2017; courtiol et al, Nat Med 2019

Stratifying by histology: Arginine Deprivation



ADI monotherapy

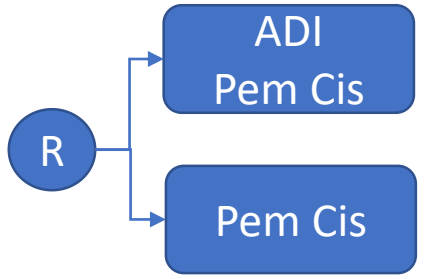




Sarcomatoid MPM

ATOMIC (phase II/ III)

Biphasic / Sarcomatoid MPM



Szlosarek et al, CCR 2006
Szlosarek et al, JAMA Oncol 2017

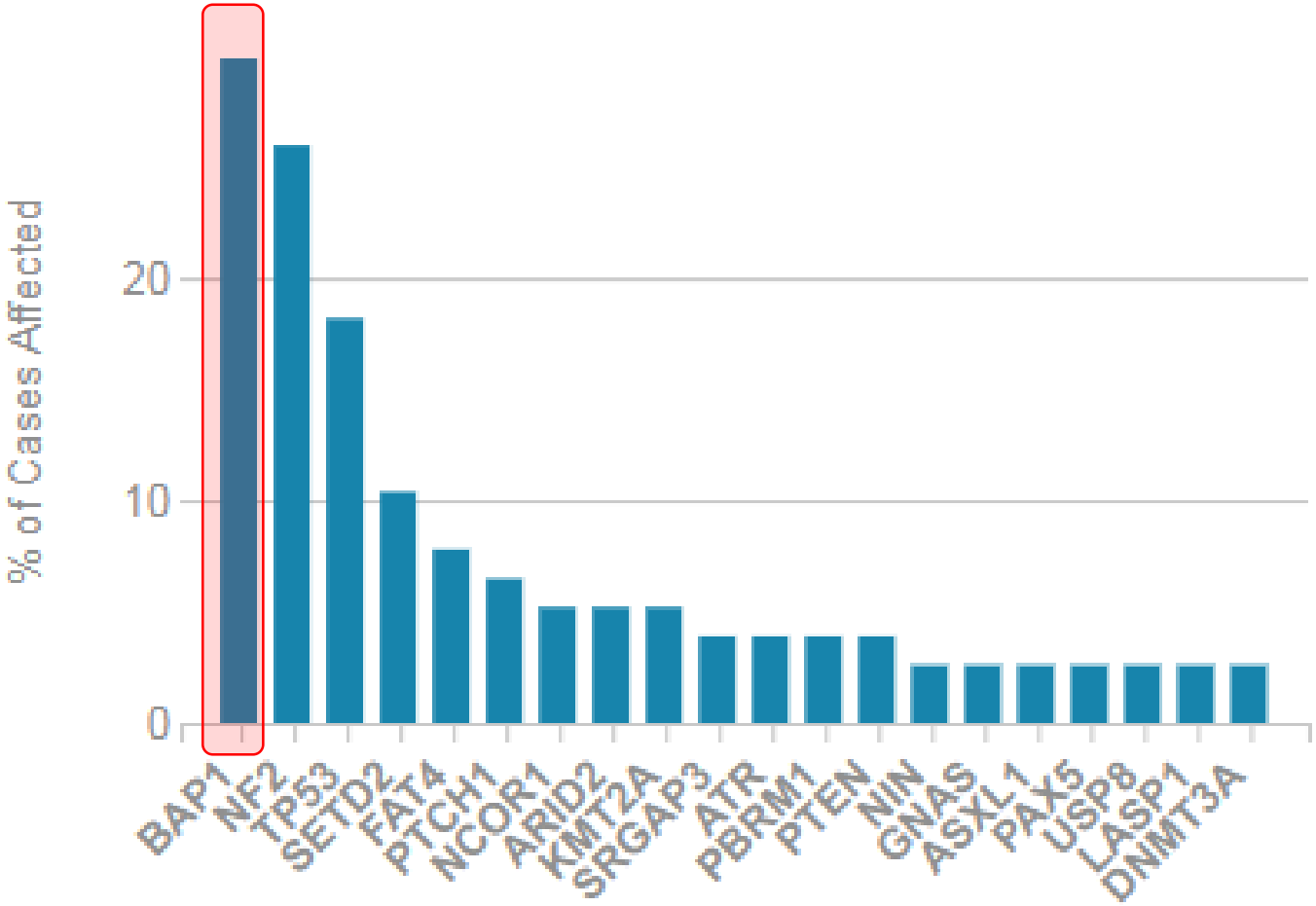
BAP1

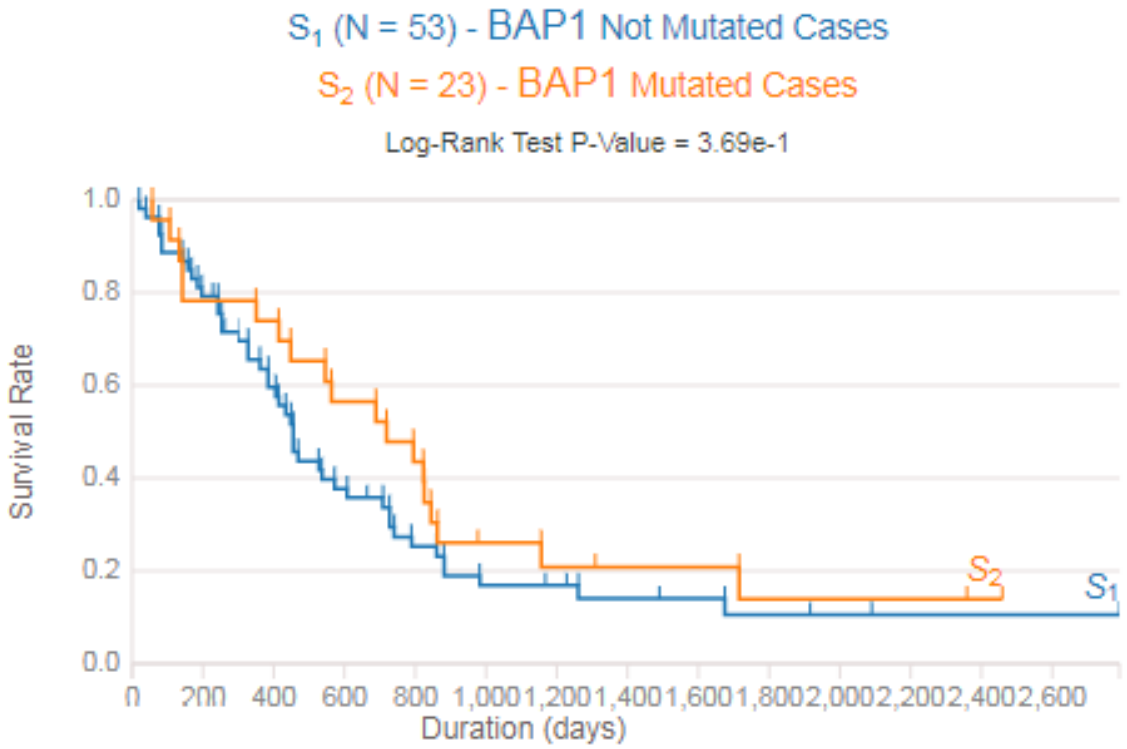
SETD2

NF2

CDKN2A

BAP1 is the most frequently mutated gene in mesothelioma

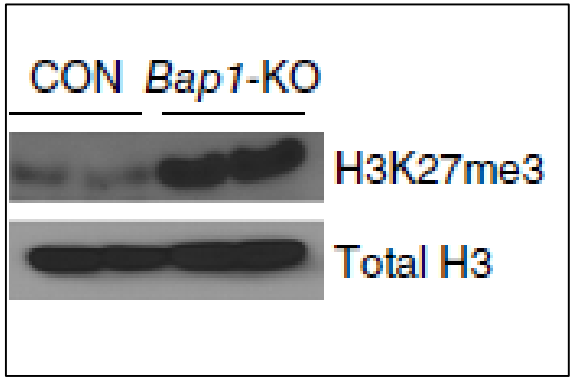


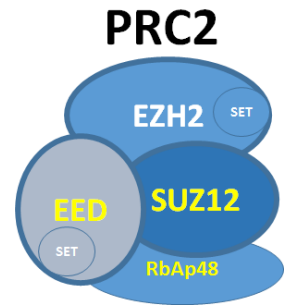


TCGA

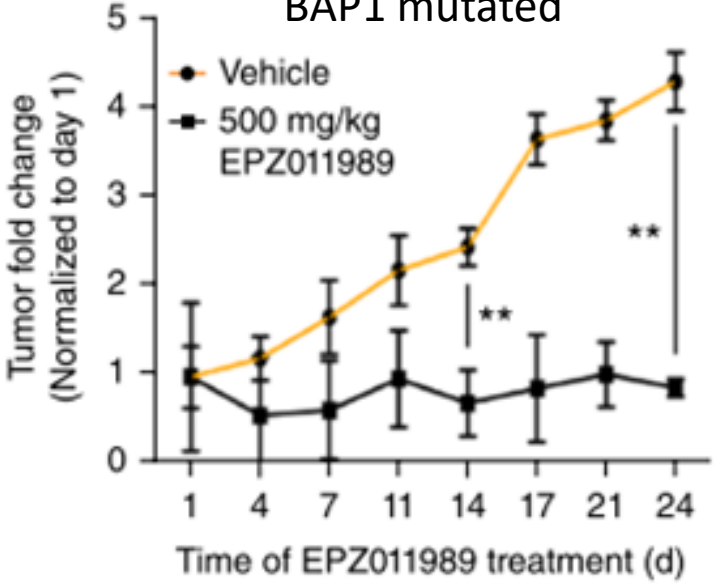
NIH NATIONAL CANCER INSTITUTE GDC Data Portal

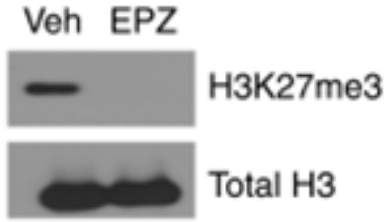
The Gene BAP1 when mutated, sensitizes to inhibitors of EZH2



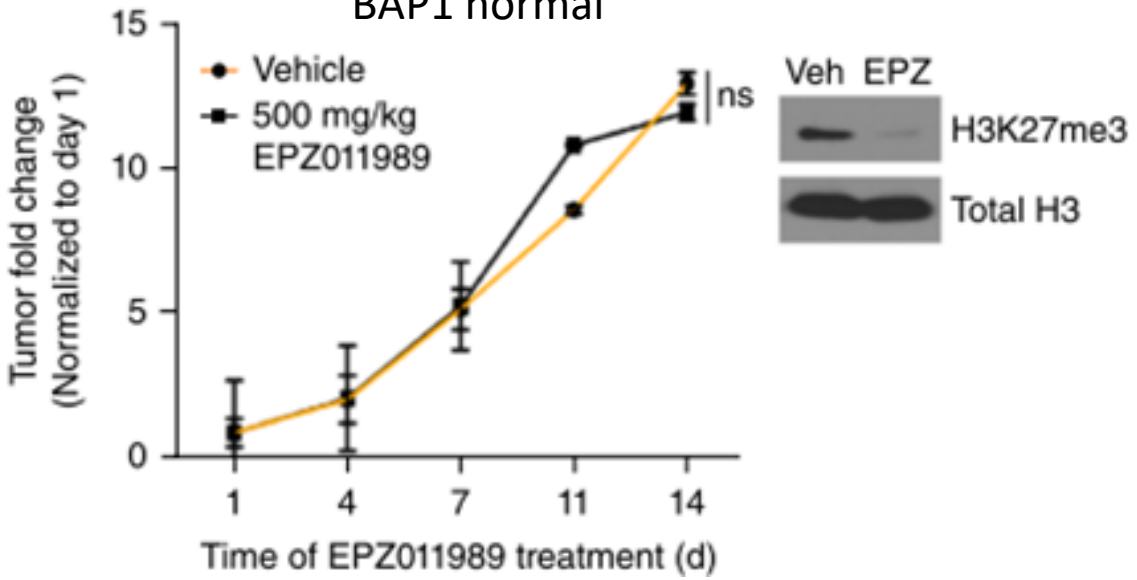


BAP1 mutated





BAP1 normal

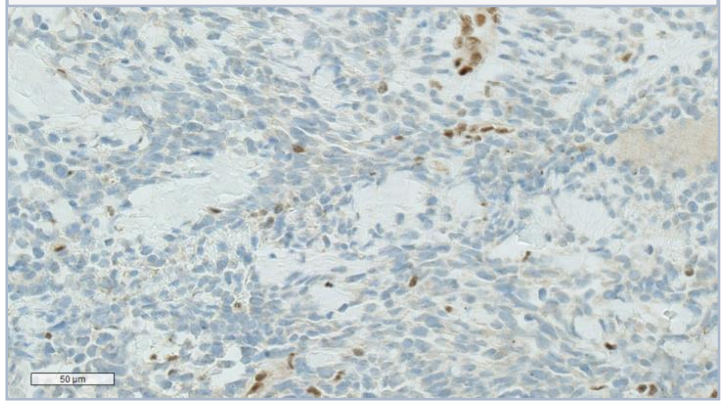


Phase II trial of tazemetostat in BAP1 negative mesothelioma NCT02860286

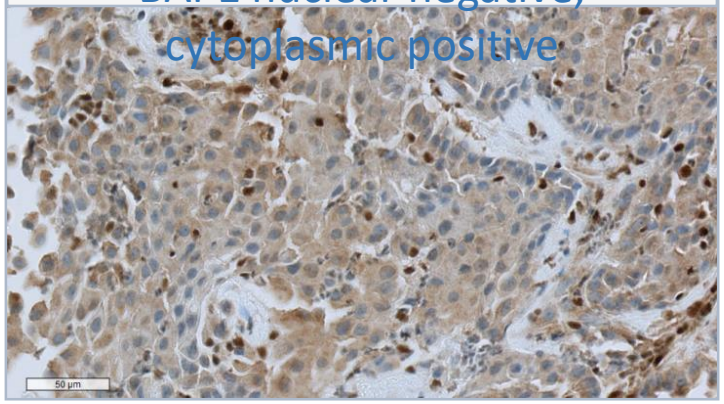
Le Fave et al, Nat Med 2015

Molecular stratification based on BAP1 immunohistochemistry

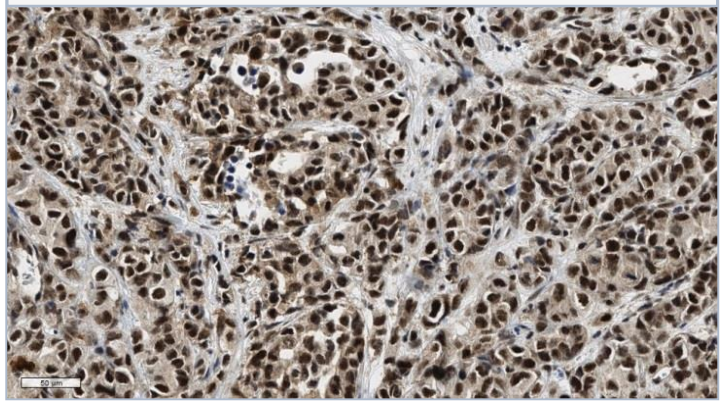
BAP1 nuclear & cytoplasmic negative



BAP1 nuclear negative, cytoplasmic positive



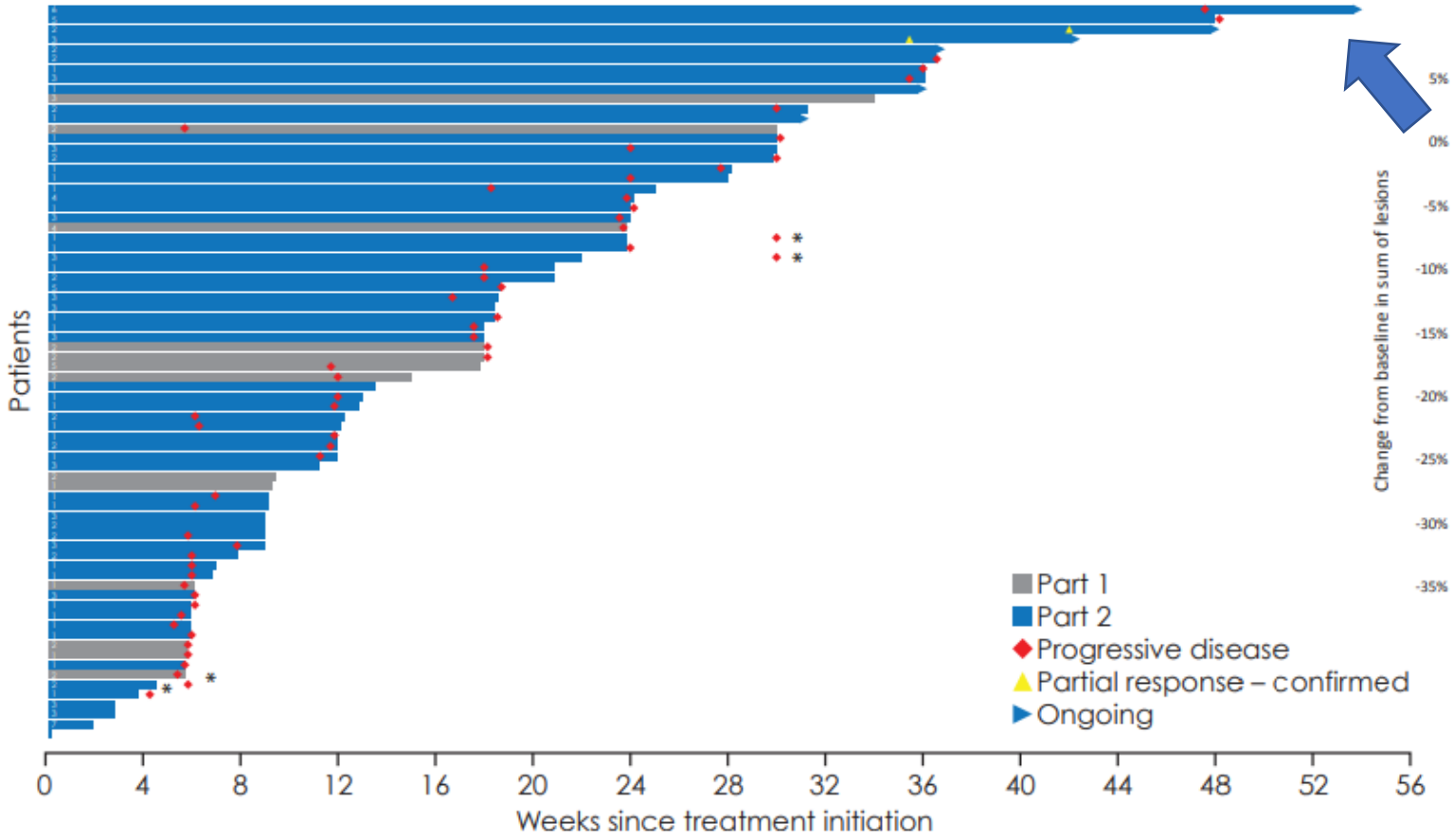
BAP1 nuclear positive, cytoplasmic positive

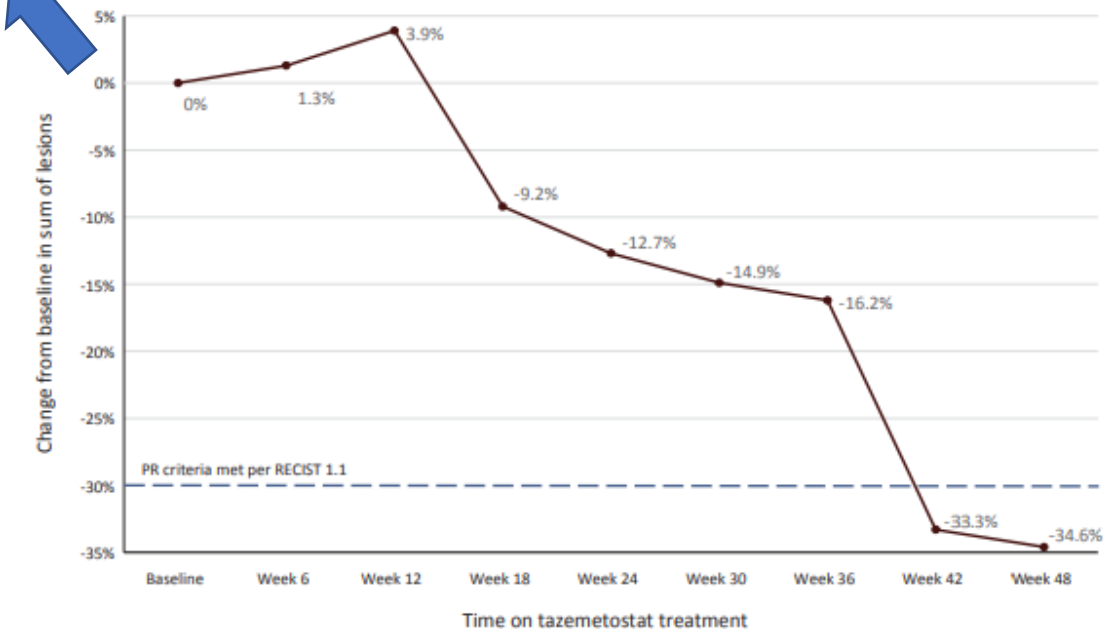


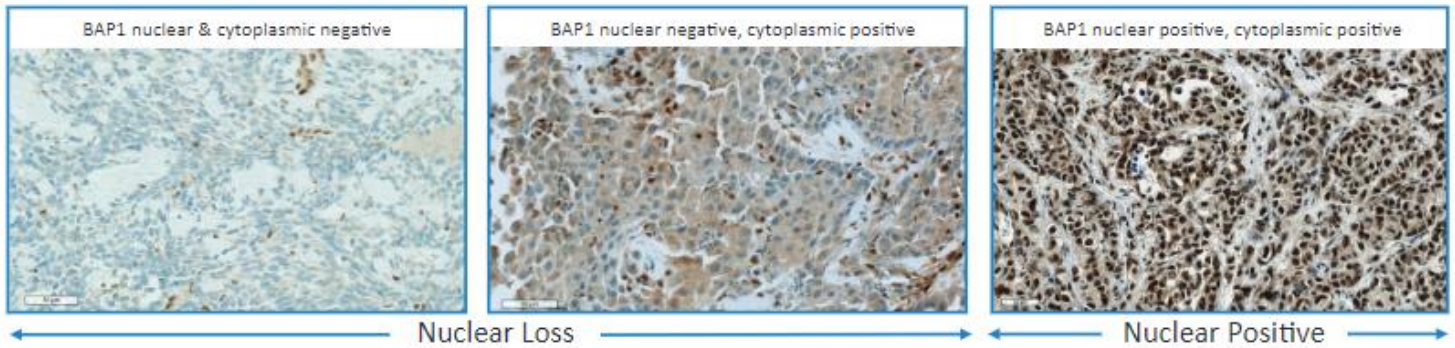
- Tumor material from 69/74 cases was submitted for central testing
- Concordance was not evaluable in 9/74 cases
  - Local BAP1 testing was not required in Part 1 (n=6)
  - Sample failed central IHC testing (n=3)
- Local vs. central concordance of BAP1 testing observed in 64/65 cases

Fennell et al, IMIG 2018

Clinical targeting of BAP1: Tazemetostat phase IIA (NCT02860286)

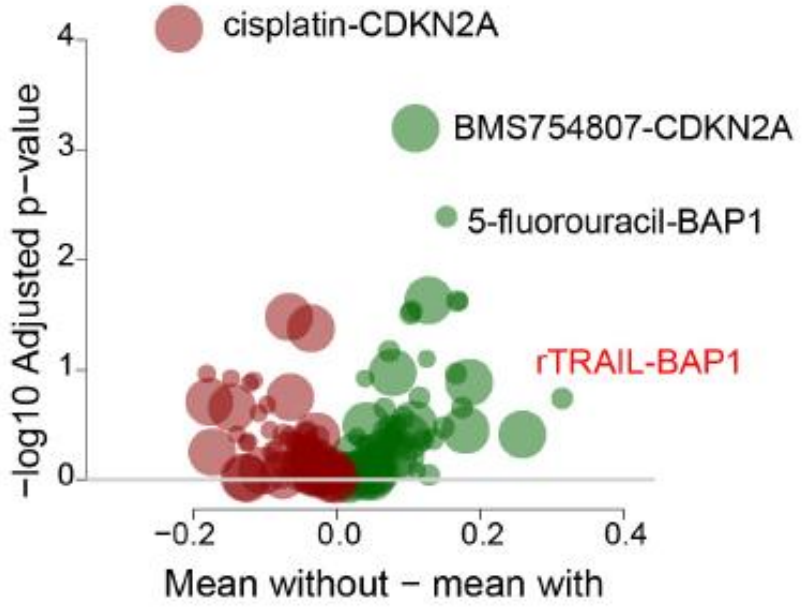


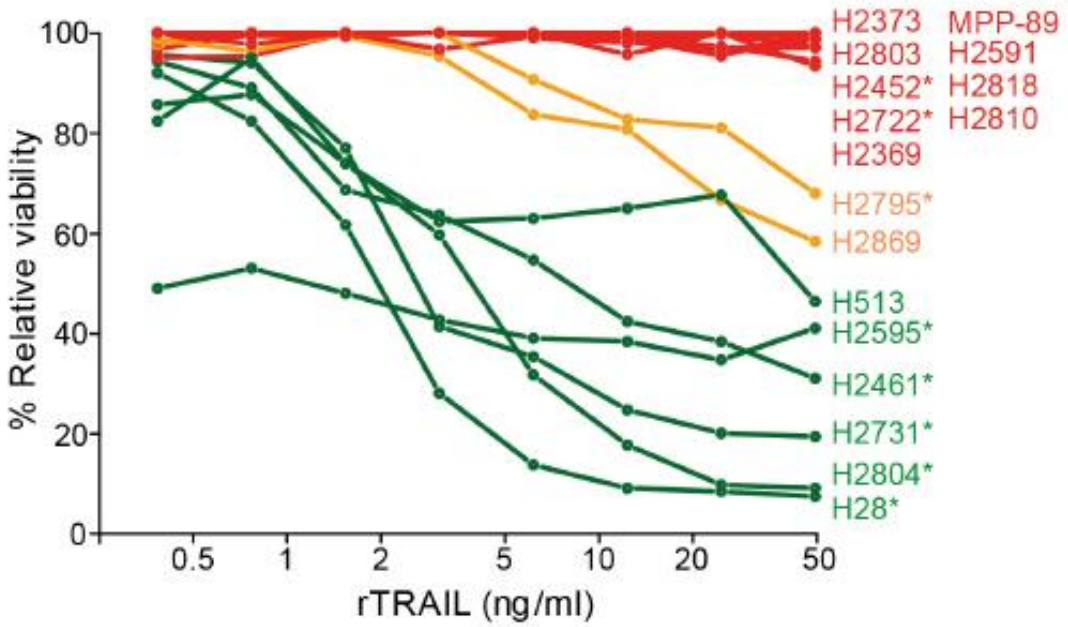


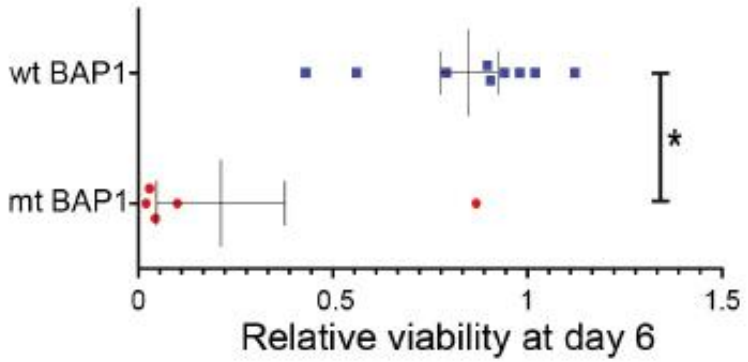


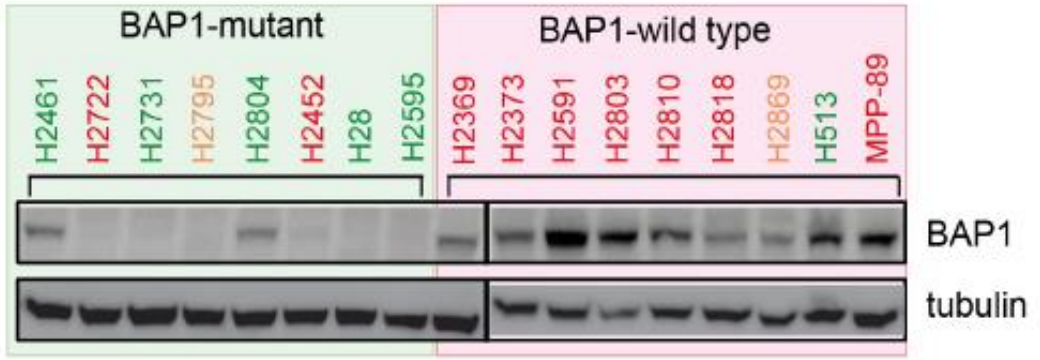
Zauderer et al, ASCO 2018

BAP1 inactivation sensitizes to TRAIL



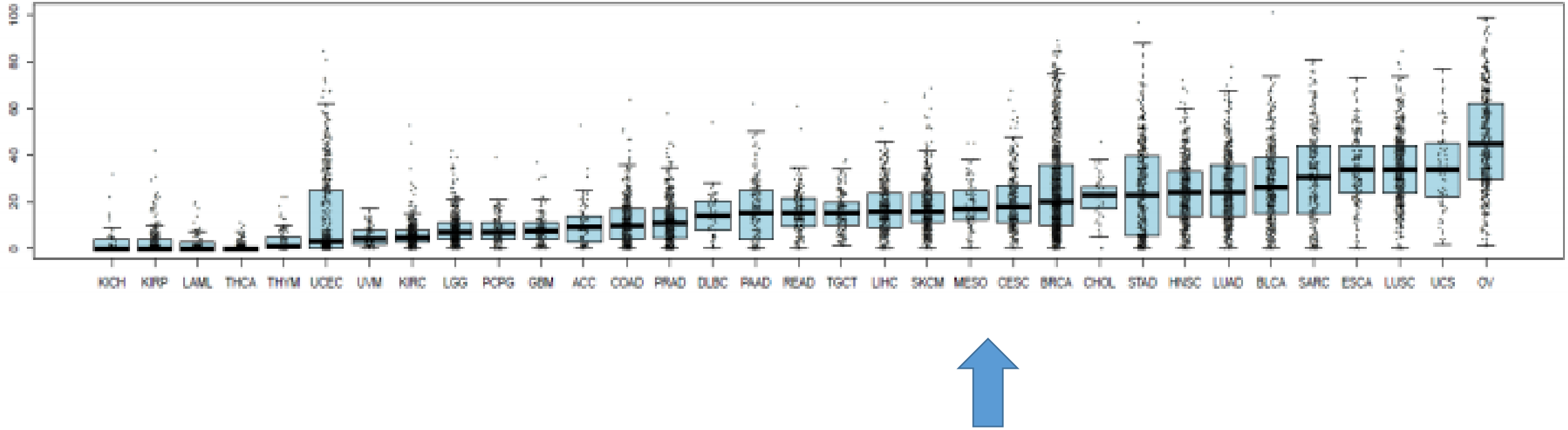






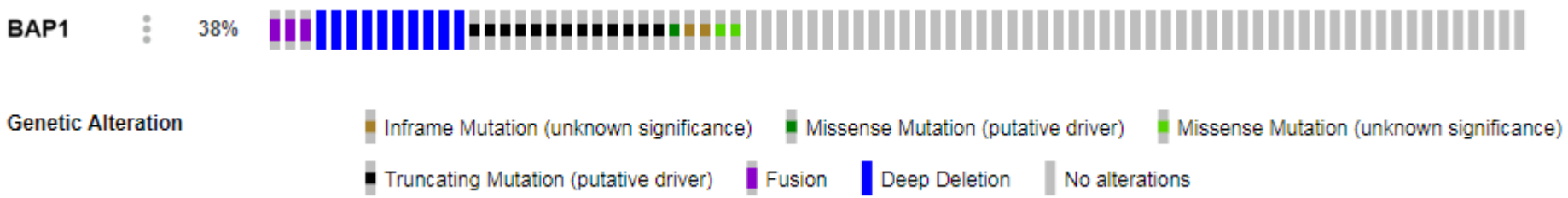
Kolluri et al, eLIFE 2017

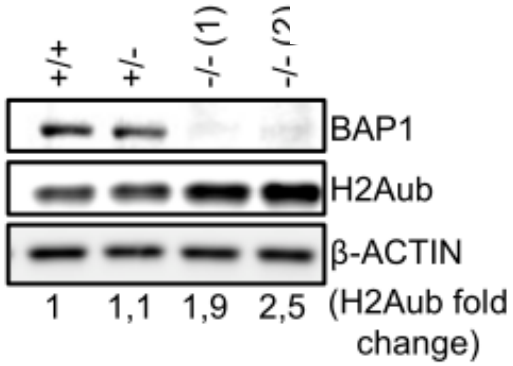
Homologous deficiency scores :pan-cancer analysis

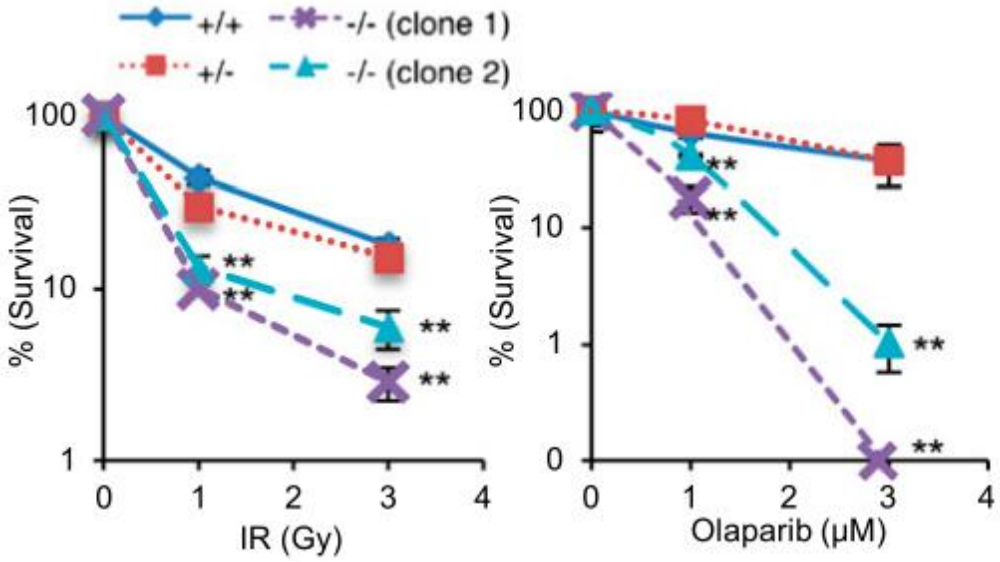


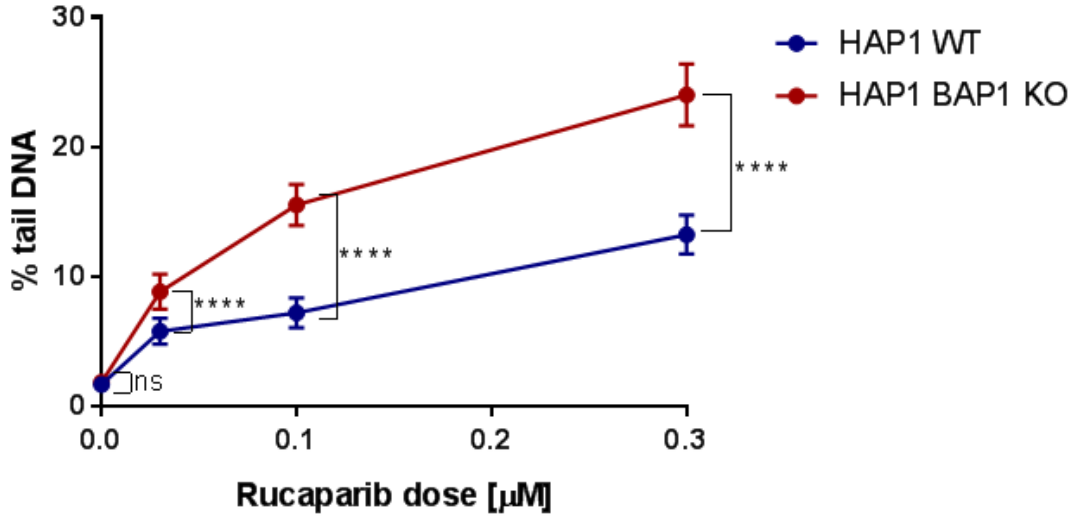
Knijnenburg et al, Cell Rep 2018

BAP1 regulates DNA repair and sensitivity to PARP inhibition



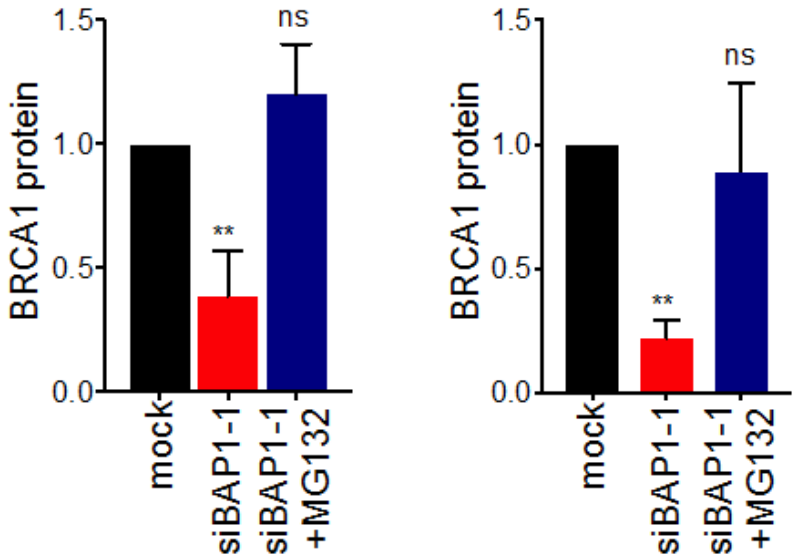


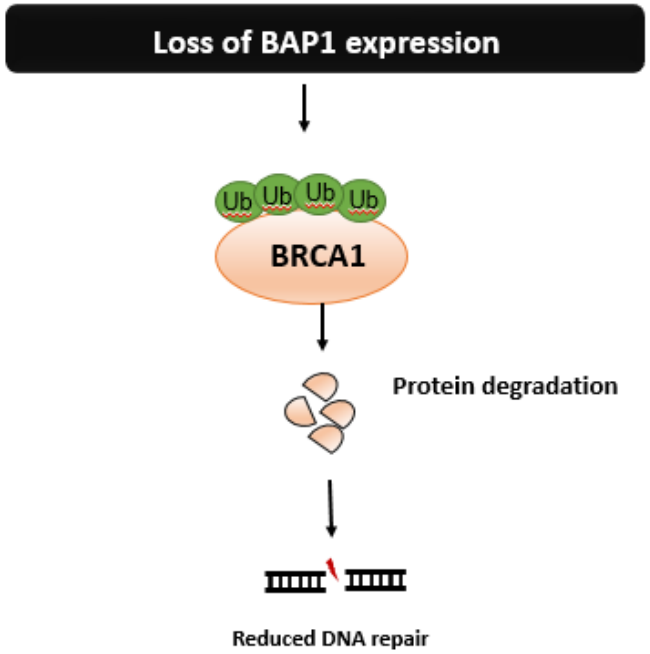


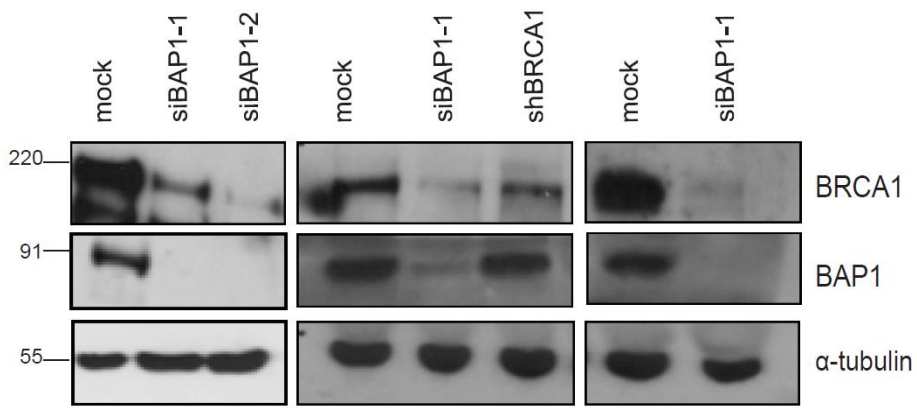


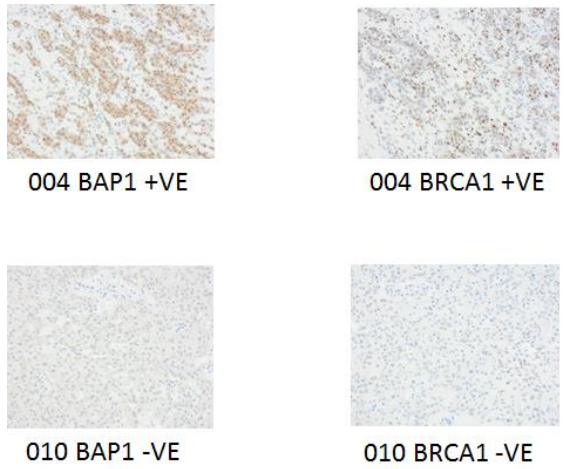
Yu et al, PNAS 2014, Hmeljak et al, Cancer Discovery 2018, Bononi et al, Nature 2018, Bzura et al, unpublished

BAP1 regulates BRCA1 protein stability



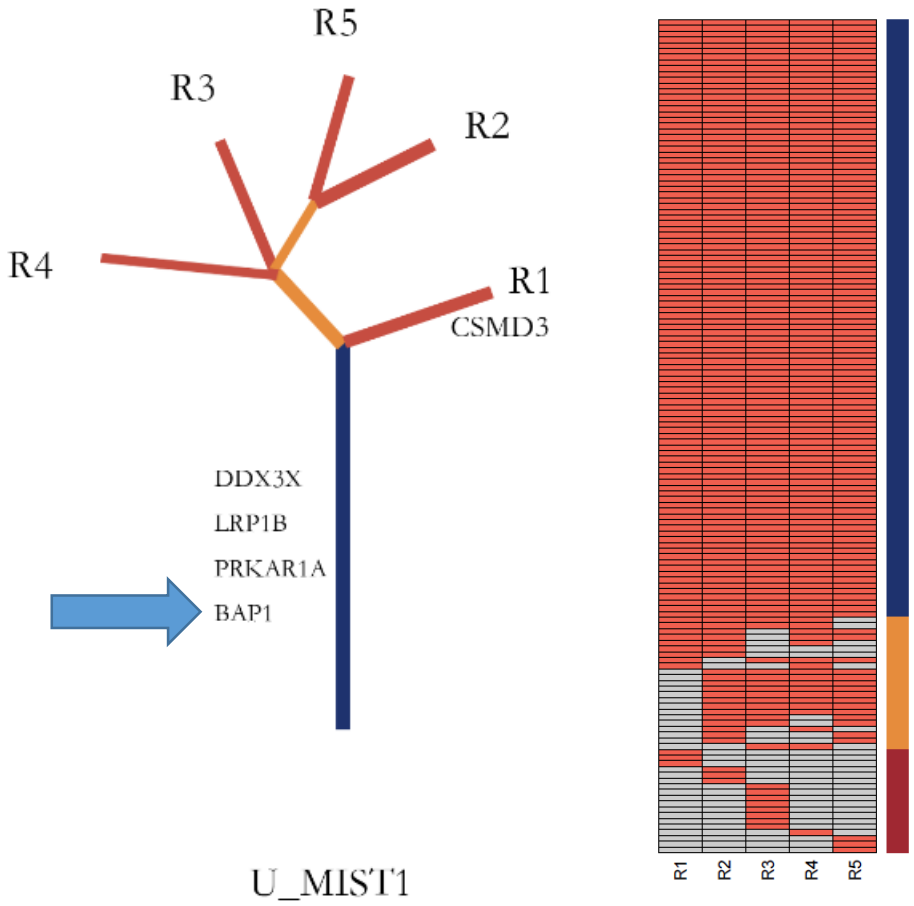


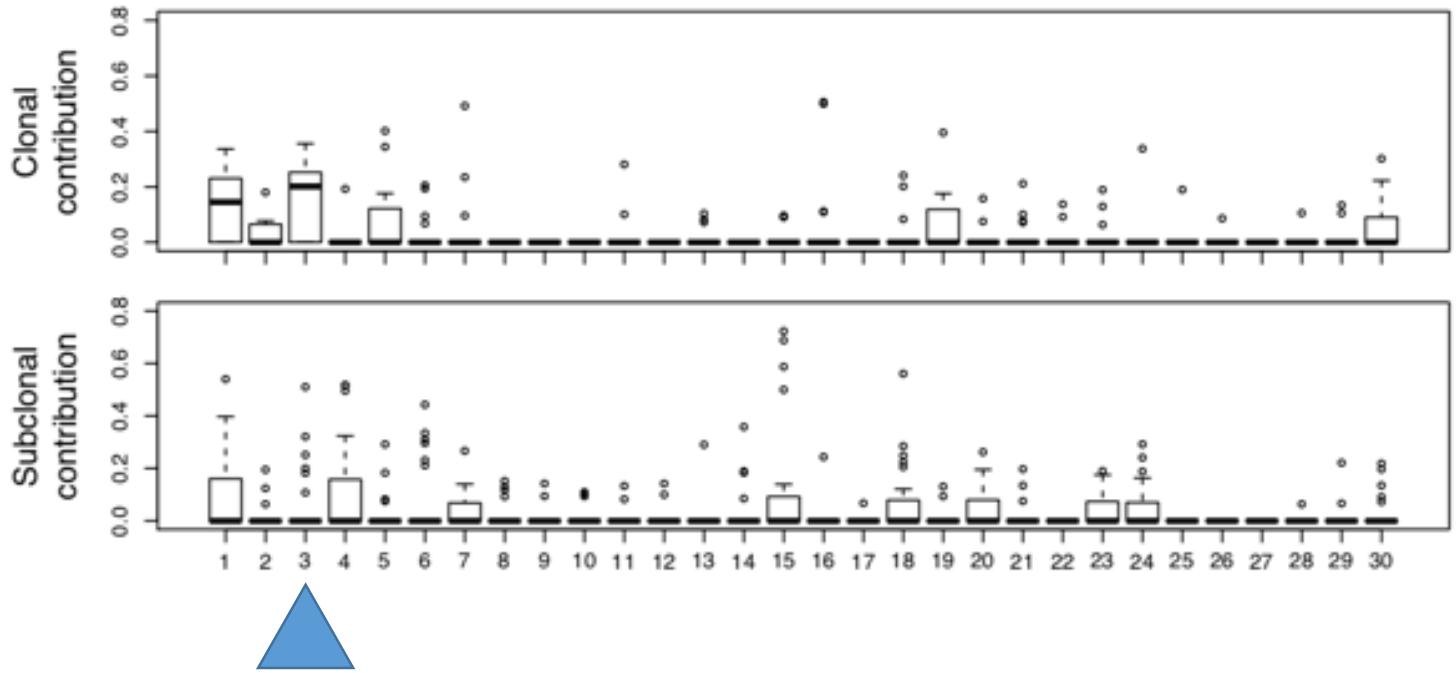




Anita Singh, Andrew Fry

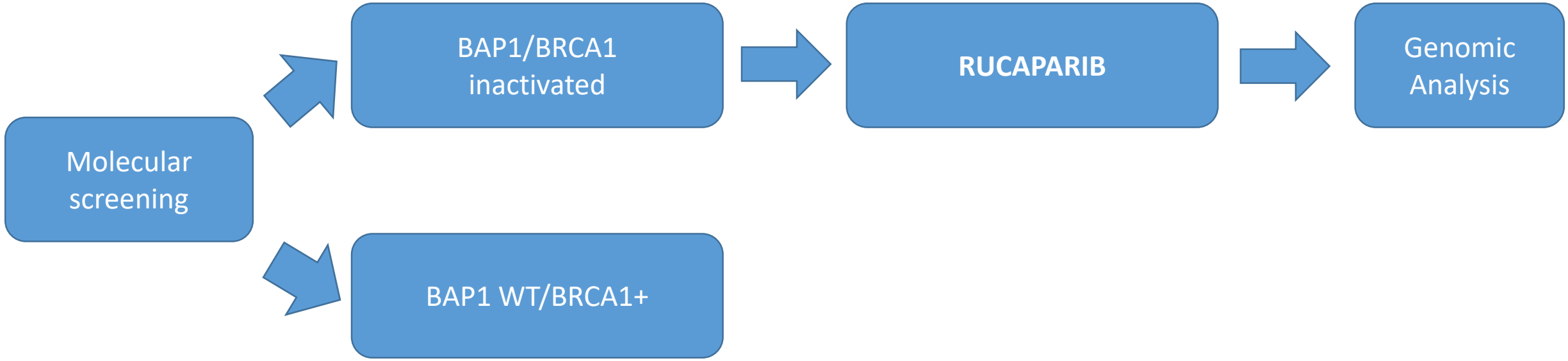
BAP1 alterations are frequently *truncal* implicating potentially ubiquitious HRD



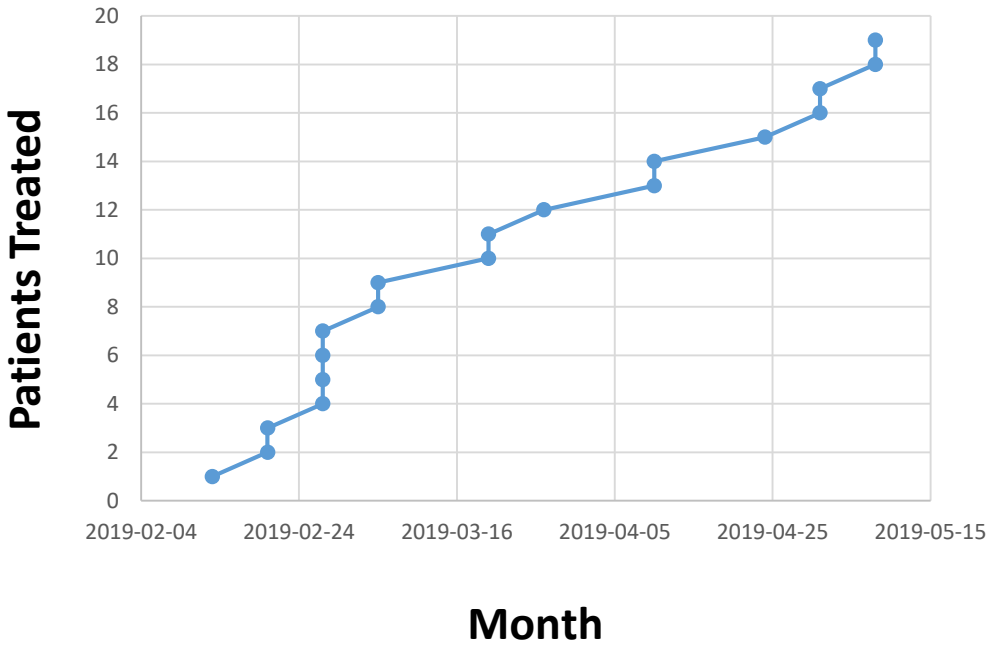


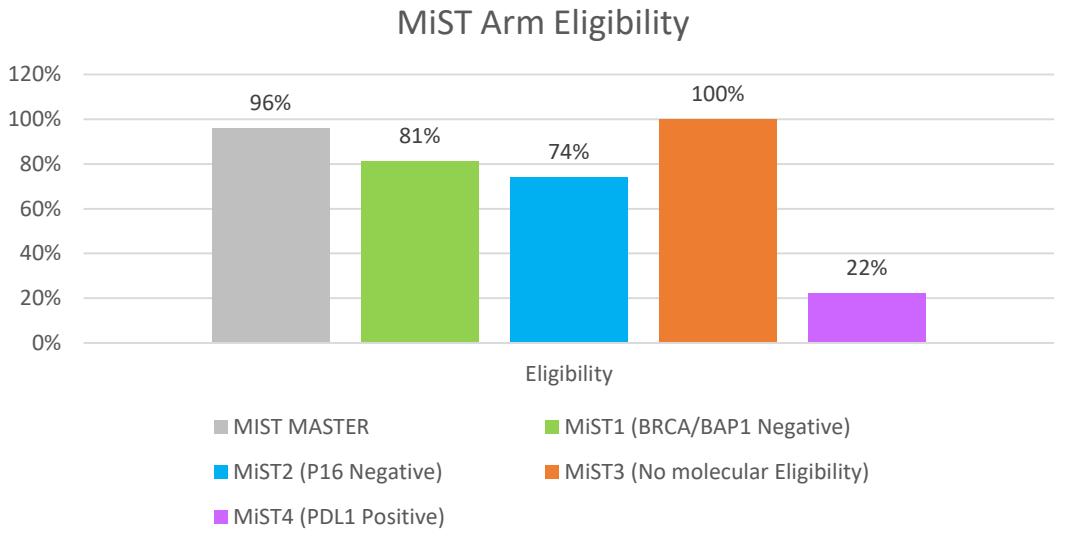
Jinli Luo, Min Zhang, Qianqian Sun

MiST1: Rucaparib in BAP1/BRCA1 inactivated mesothelioma



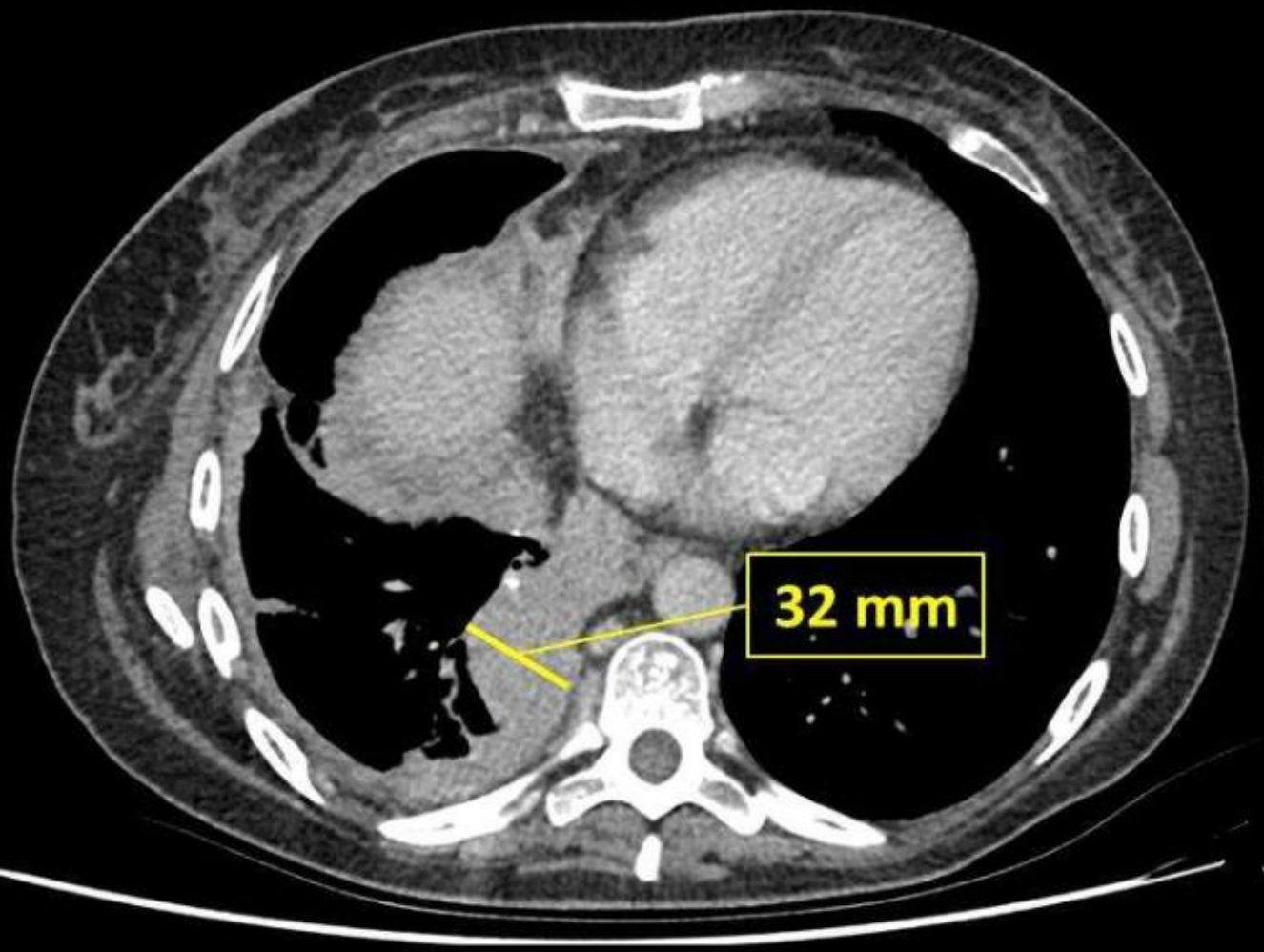
MiST arm 1 (Rucaparib) - completed



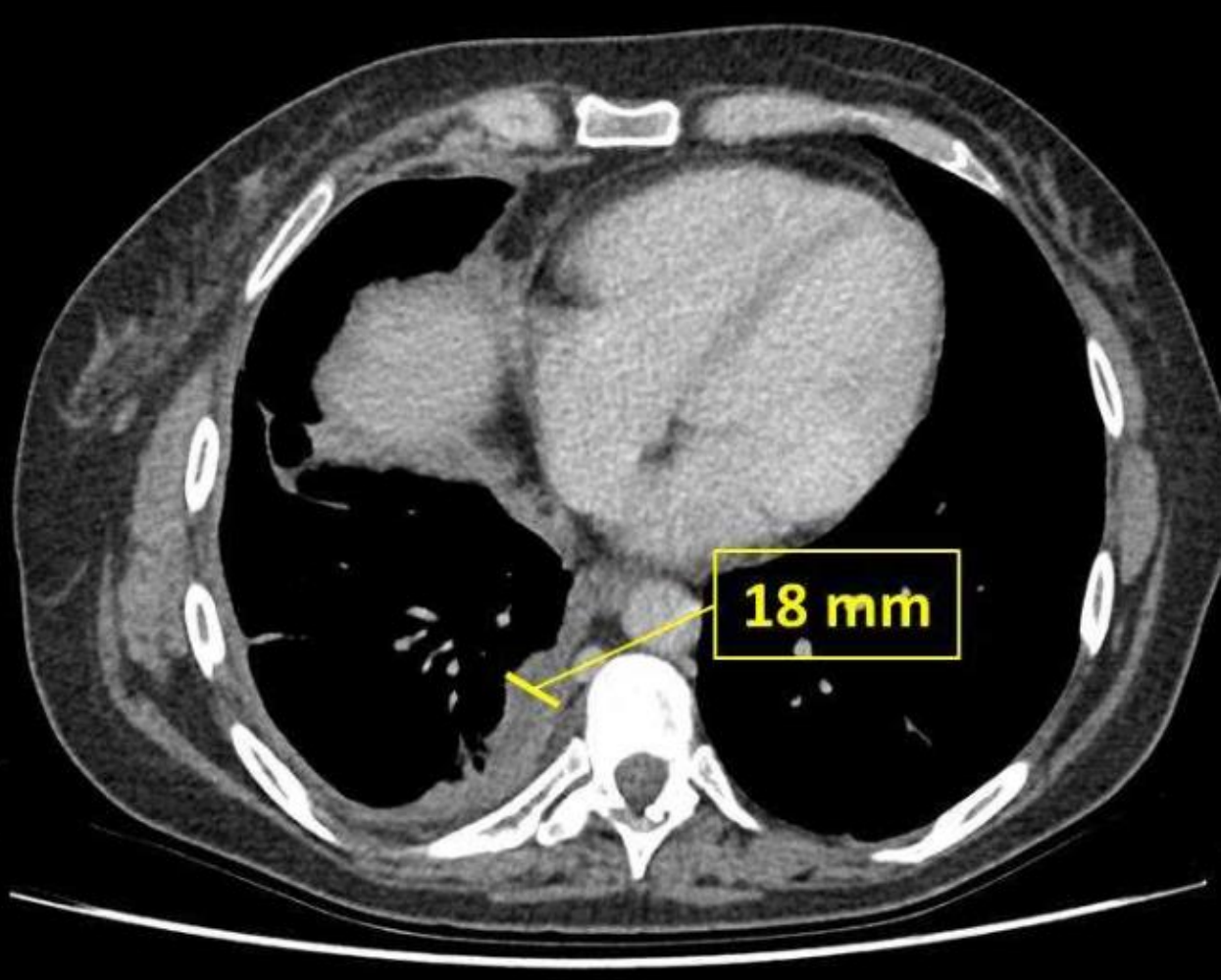


Results to be presented ASCO 2020

MiST1 (Rucaparib) Partial Response (mRECIST)



Baseline: Day -7



1st follow up: Day 43 Post treatment

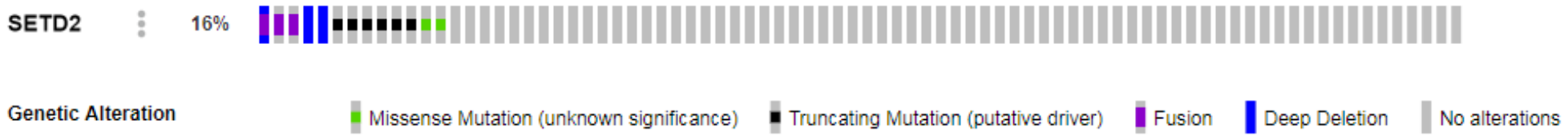
BAP1

SETD2

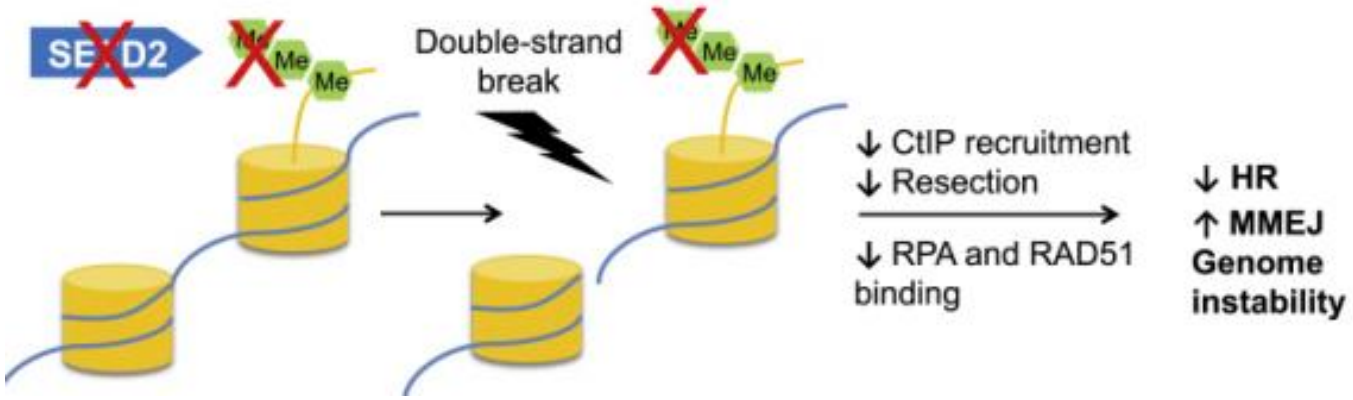
NF2

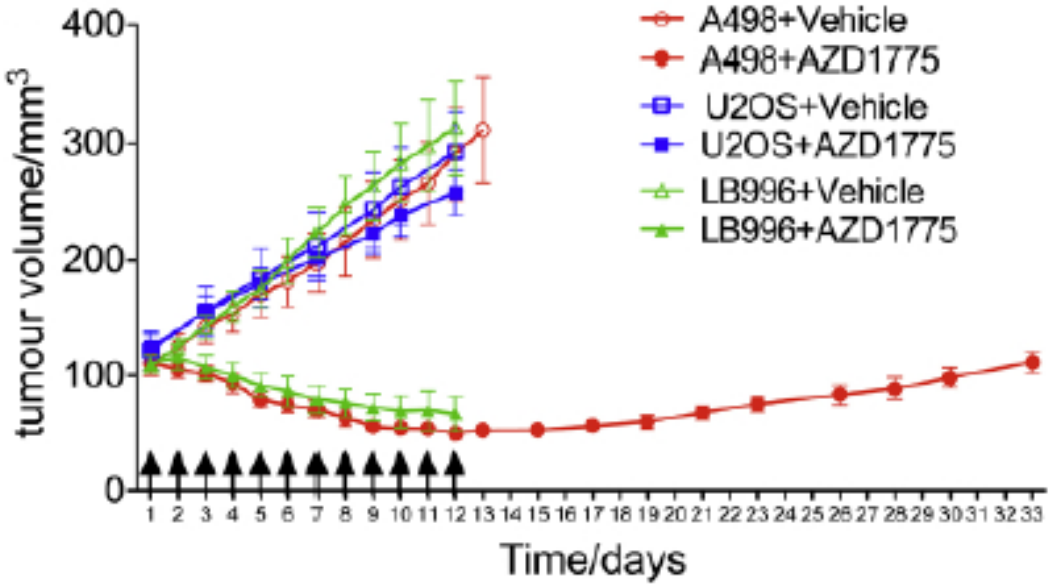
CDKN2A

SETD2 regulates Homologous recombination via H3 trimethylation



H3K36me3





Pfister et al Cell Rep 2014; Pfister et al, Cancer Cell 2015

SETD2-Wee1 synthetic lethality

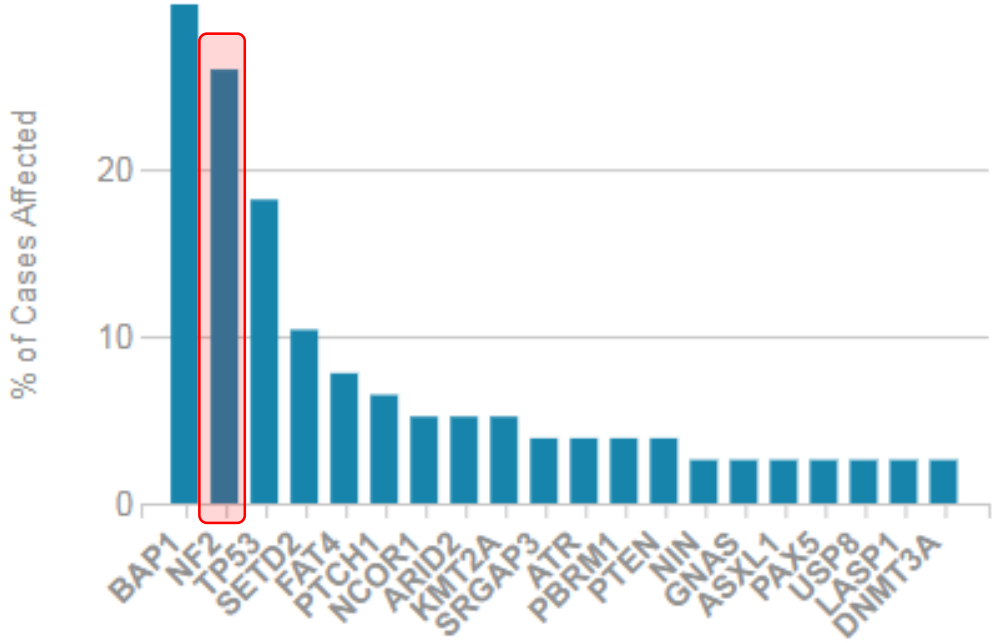
BAP1

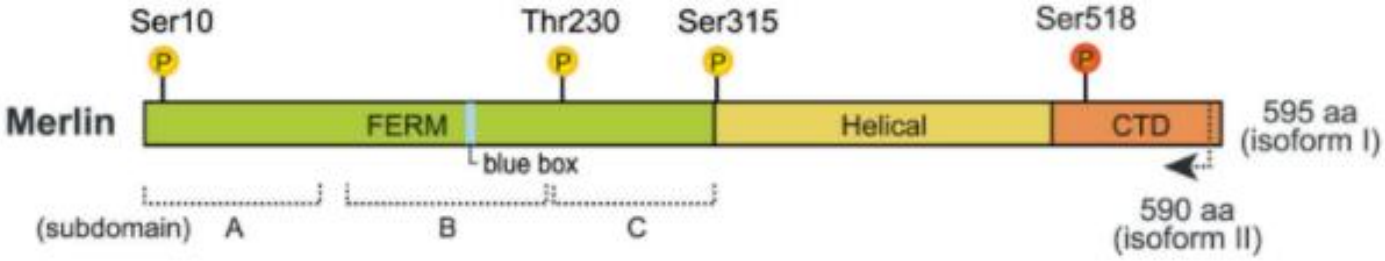
SETD2

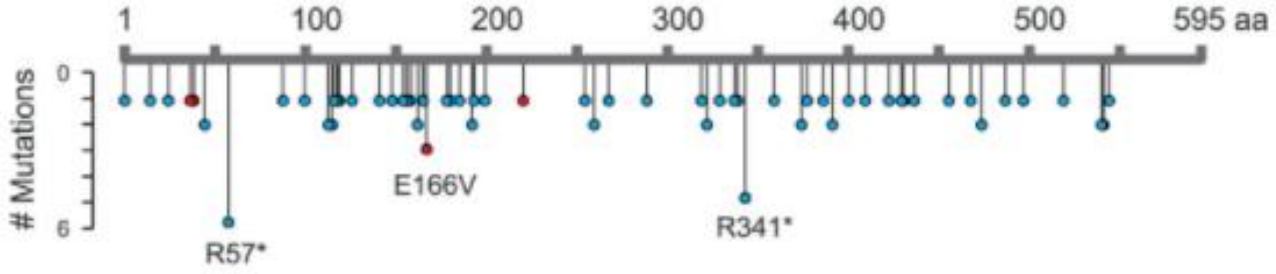
NF2

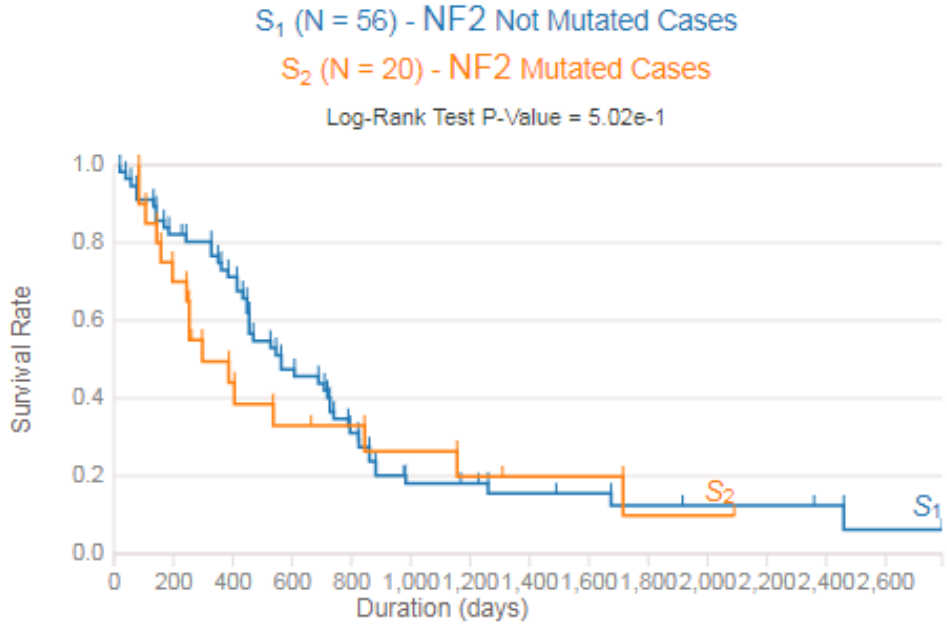
CDKN2A

NF2 is the second most commonly mutated gene in mesothelioma

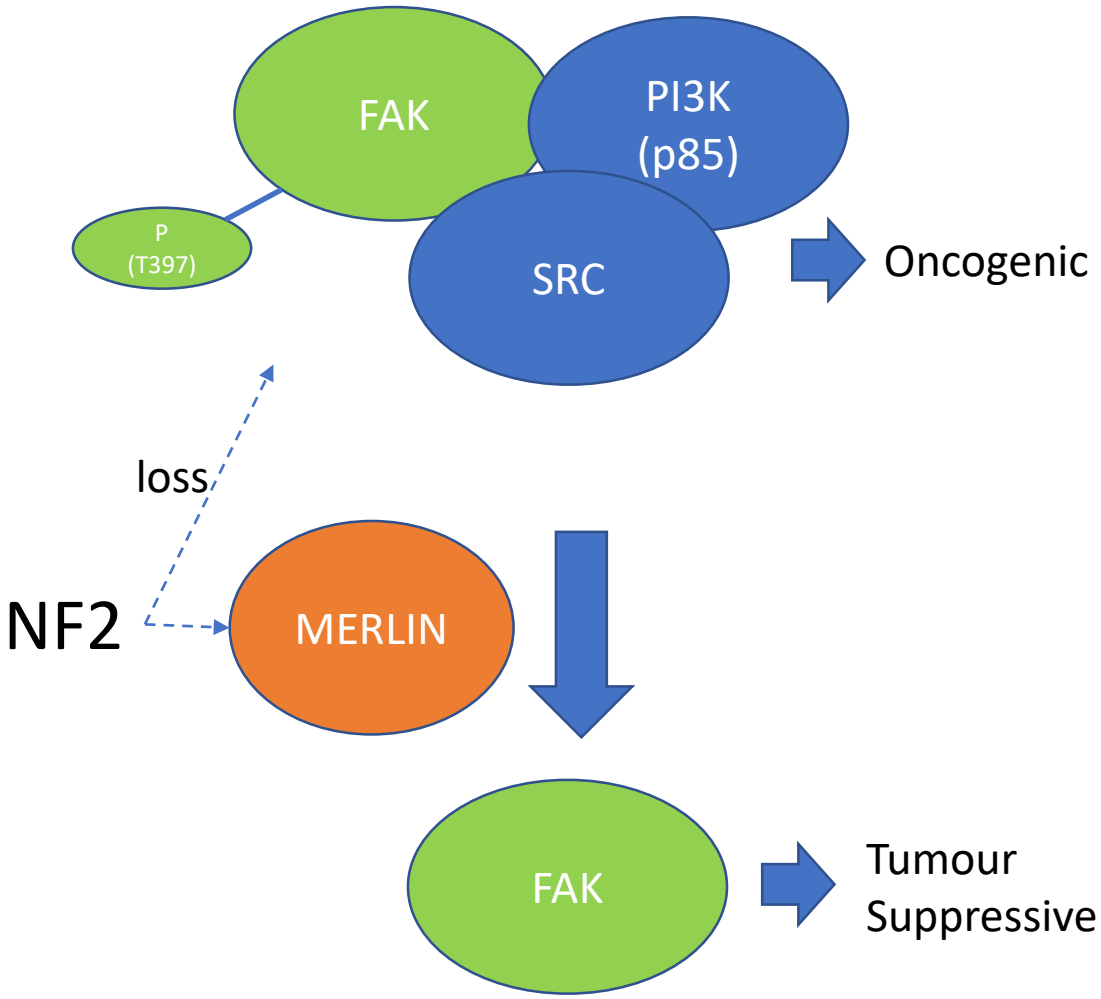


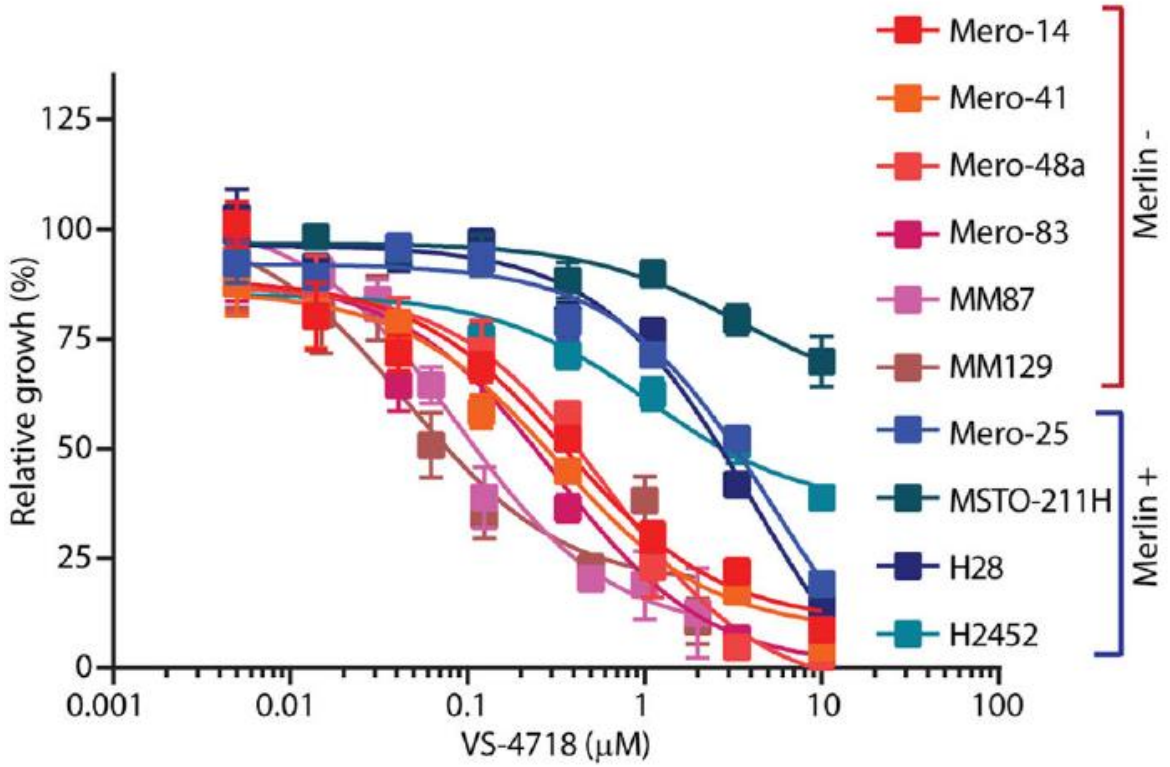






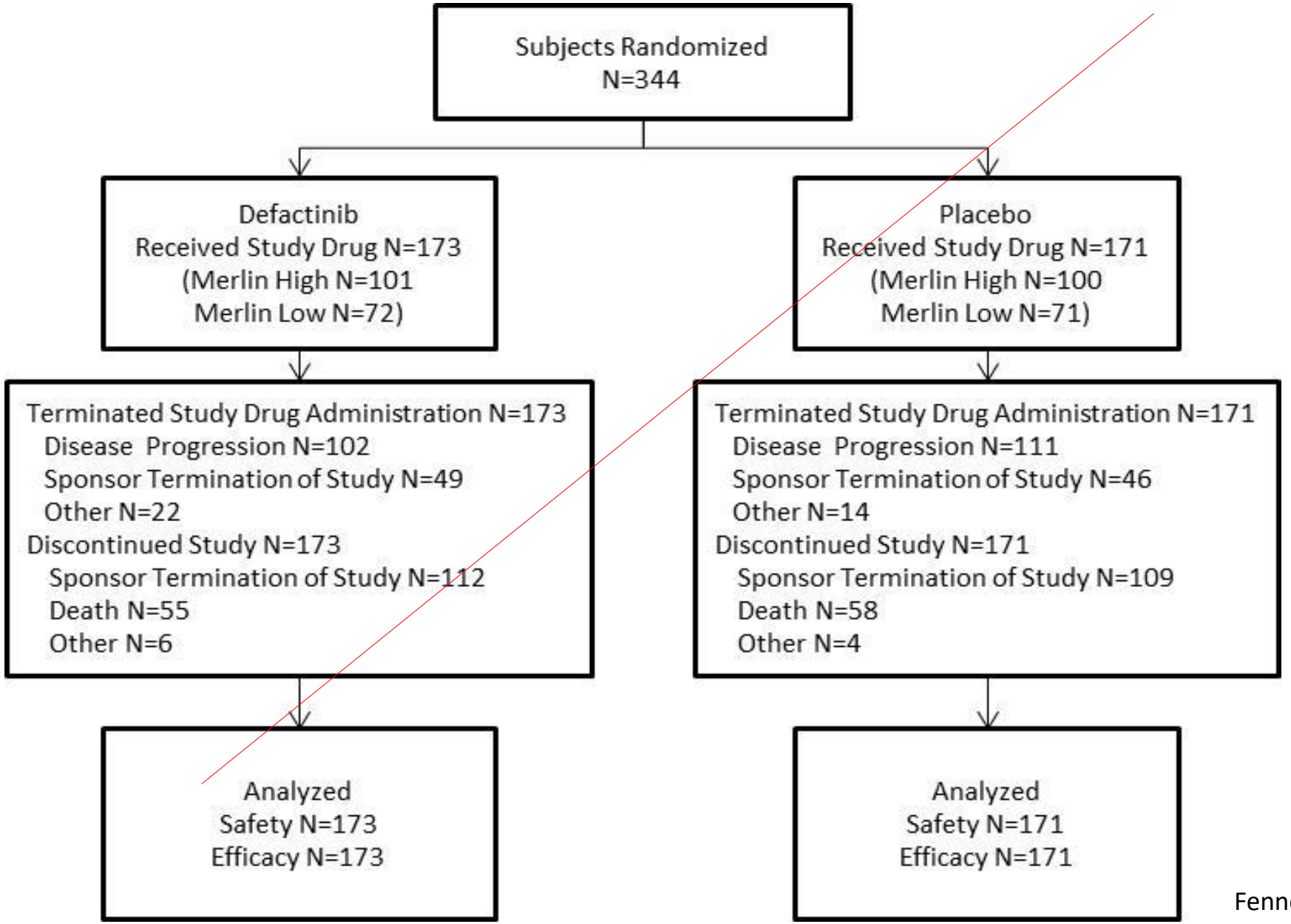
Merlin loss confers FAK inhibitor induced synthetic lethality





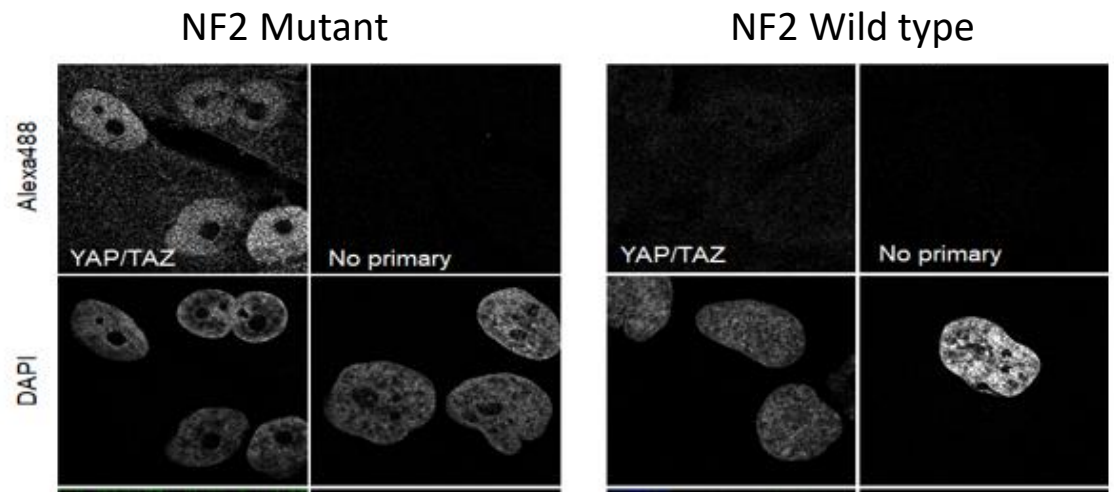
Shapiro et al, 2014 Sci Transl Med
Testa et al Oncogene 2006

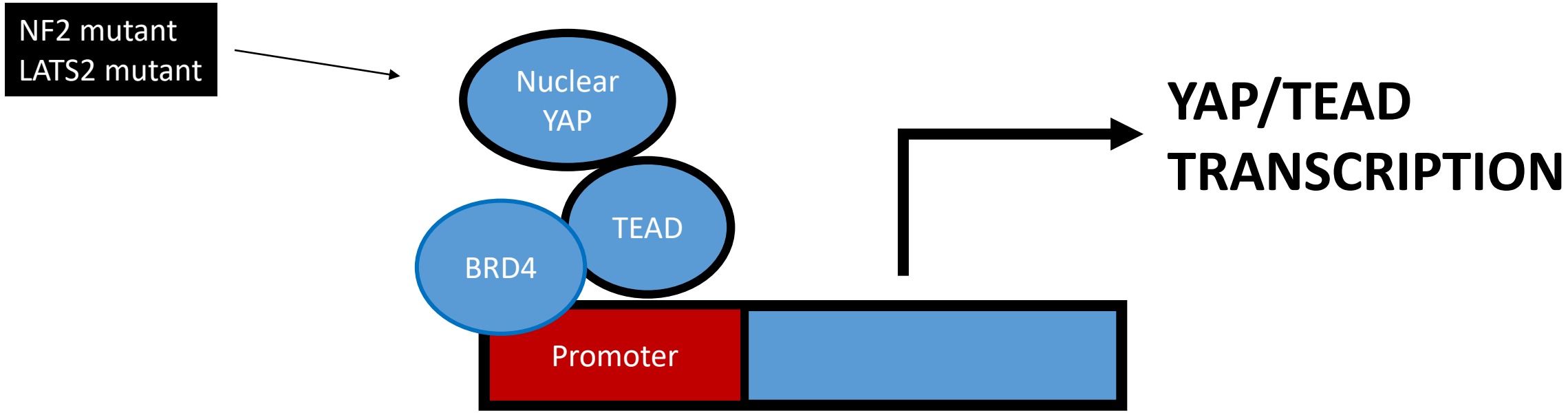
COMMAND TRIAL



Fennell et al, J Clin Oncol 2019

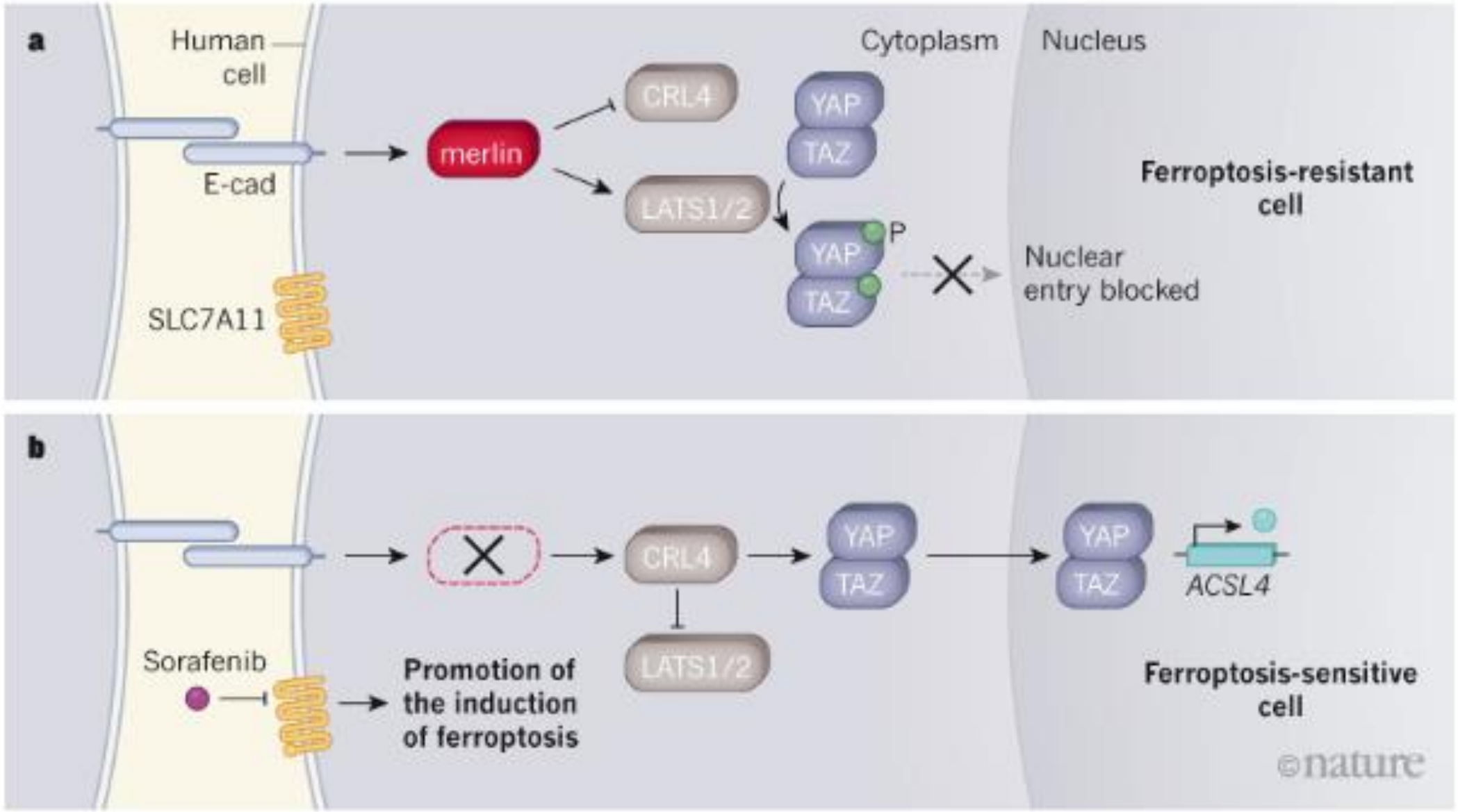
TEAD transcription driven by NF2 may be blocked pharmacologically





Essa Battei

Induction of Ferroptosis may target NF2 mutant mesothelioma



Fennell Nature 2019, Wu et al Nature 2019

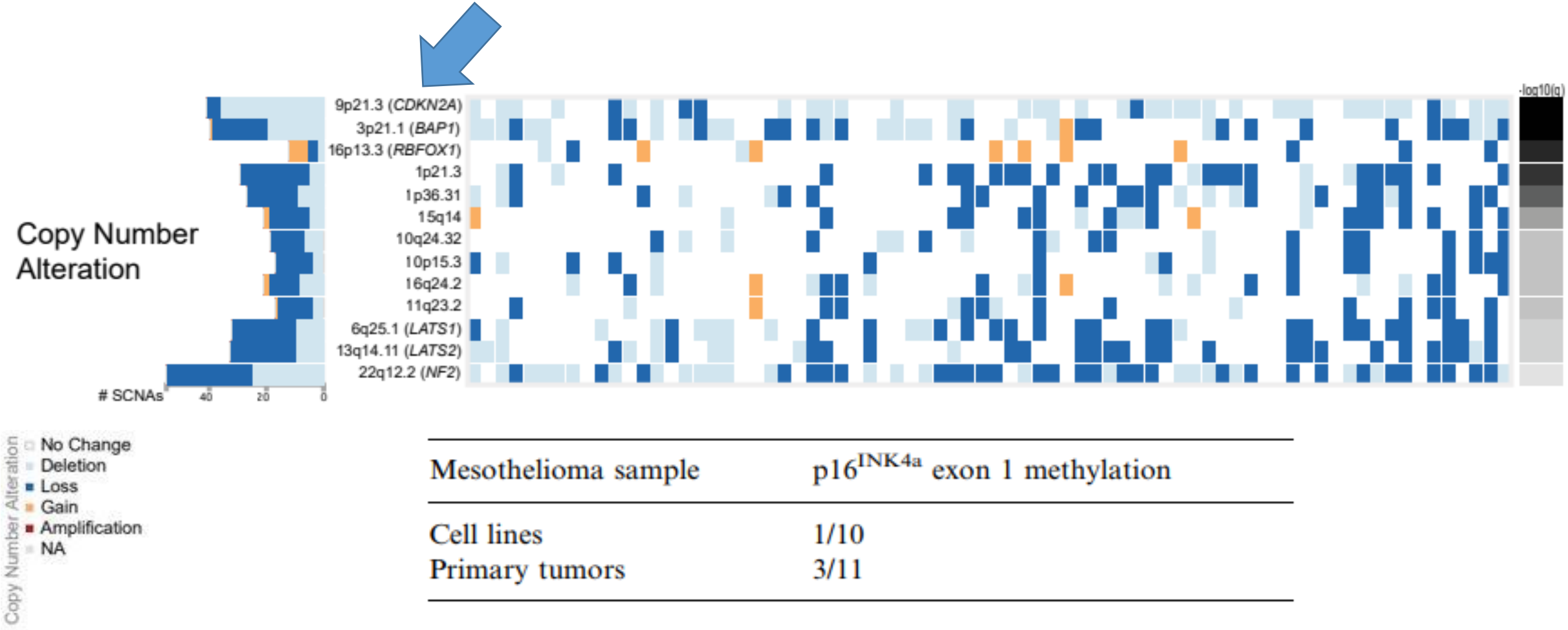
BAP1

SETD2

NF2

CDKN2A

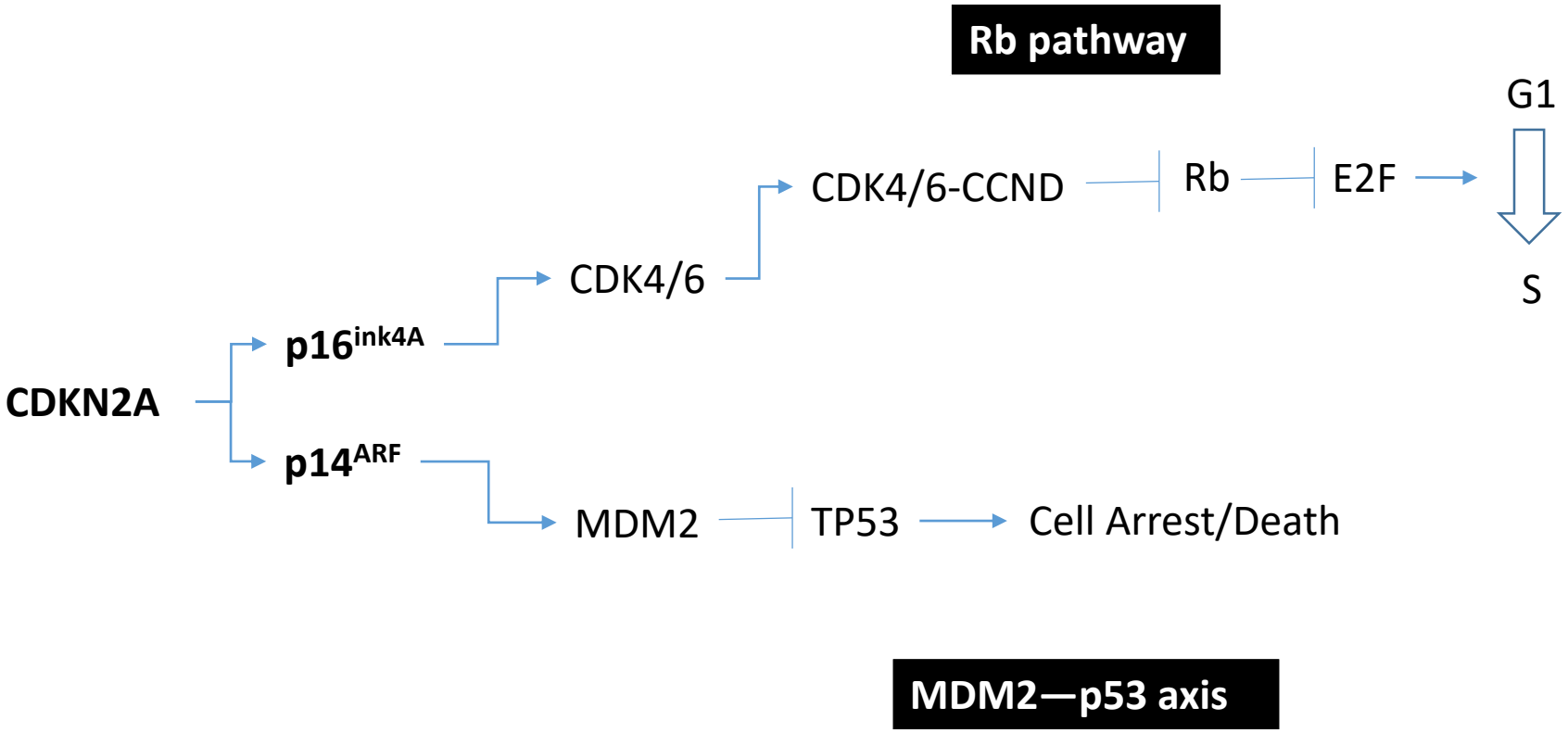
9p21.3 loss (CDKN2A/MTAP) is the most common copy number deletion



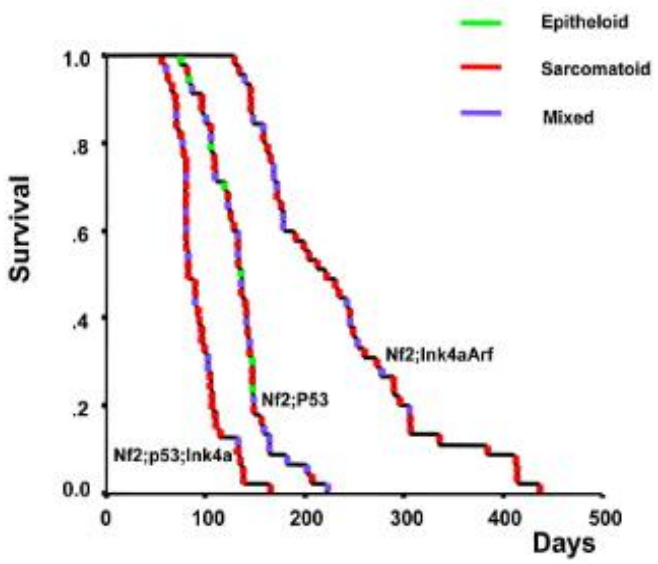
Mesothelioma sample	$p16^{INK4a}$ exon 1 methylation
Cell lines	1/10
Primary tumors	3/11

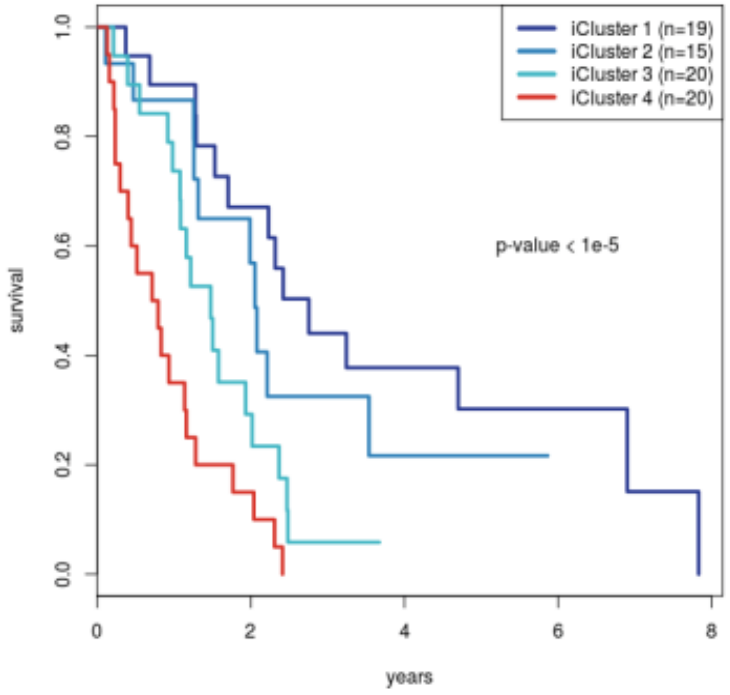
Hmeljak et al,Cancer Discov 2018 Oct 15. pii: CD-18-0804
Wong et al, Lung Cancer 2002

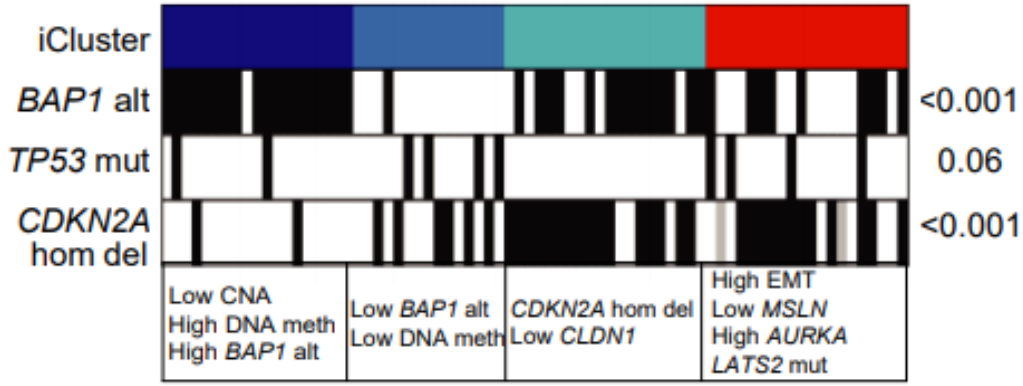
CDKN2A regulates *two* tumour suppressor pathways



CDKN2A is associated with a poor prognosis

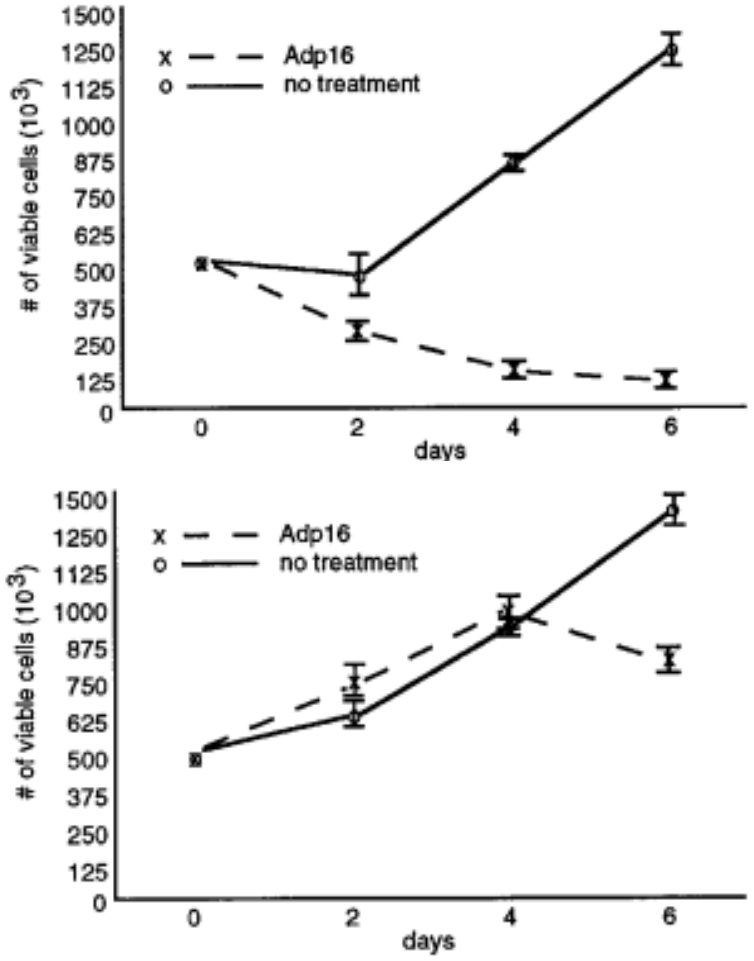






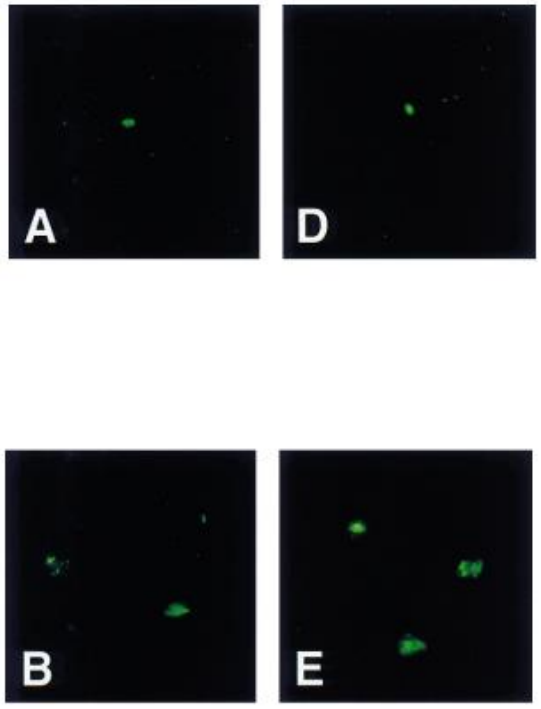
Hmeljak et al,Cancer Discov 2018
Jongsma et al, Cancer Cell 2008

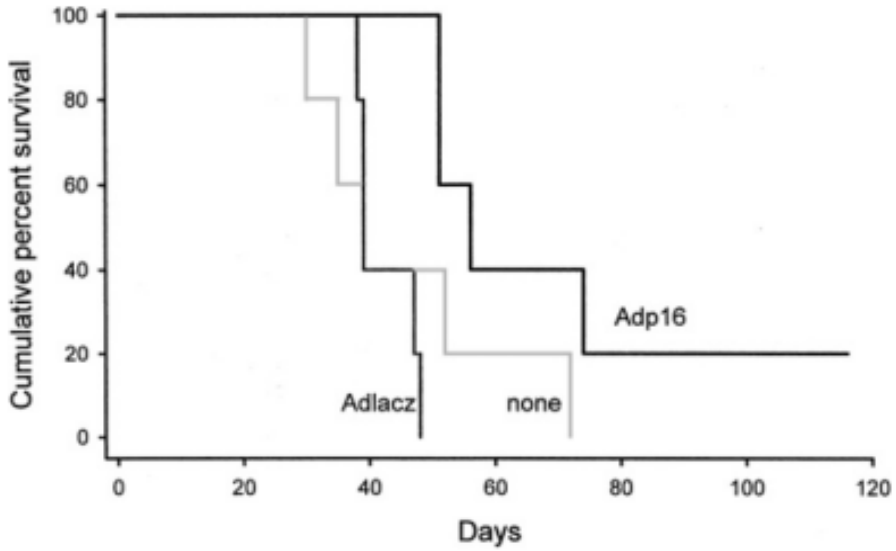
Restoring p16ink4a in CDKN2A deleted mesothelioma induces apoptosis



TUNEL (apoptosis)

Untreated

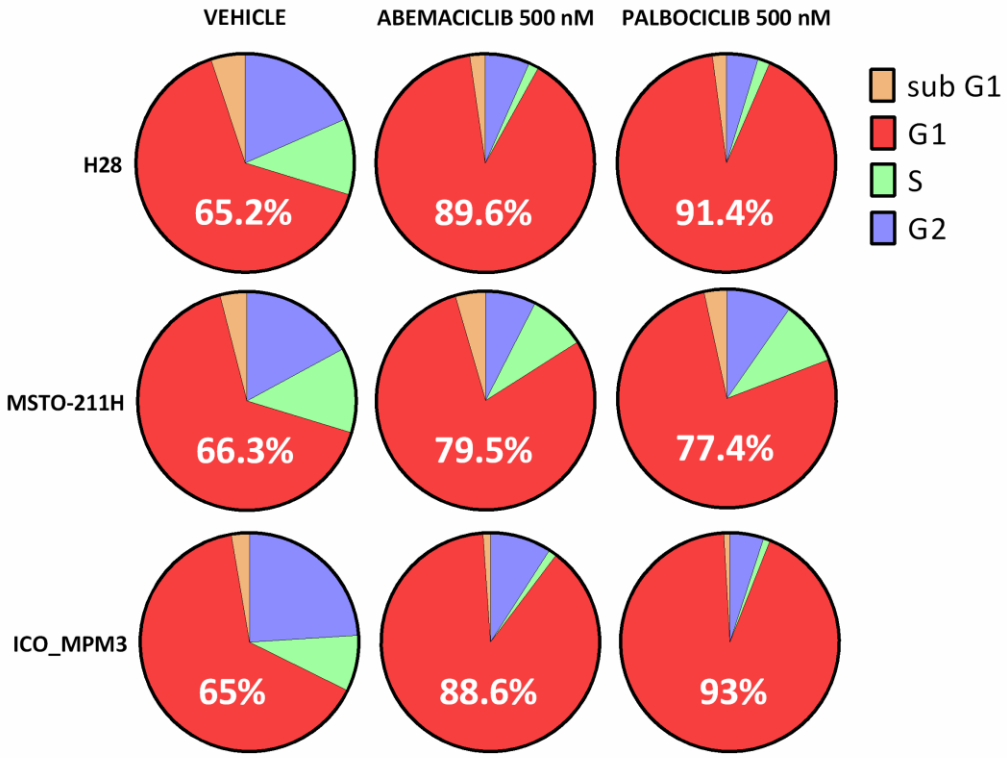




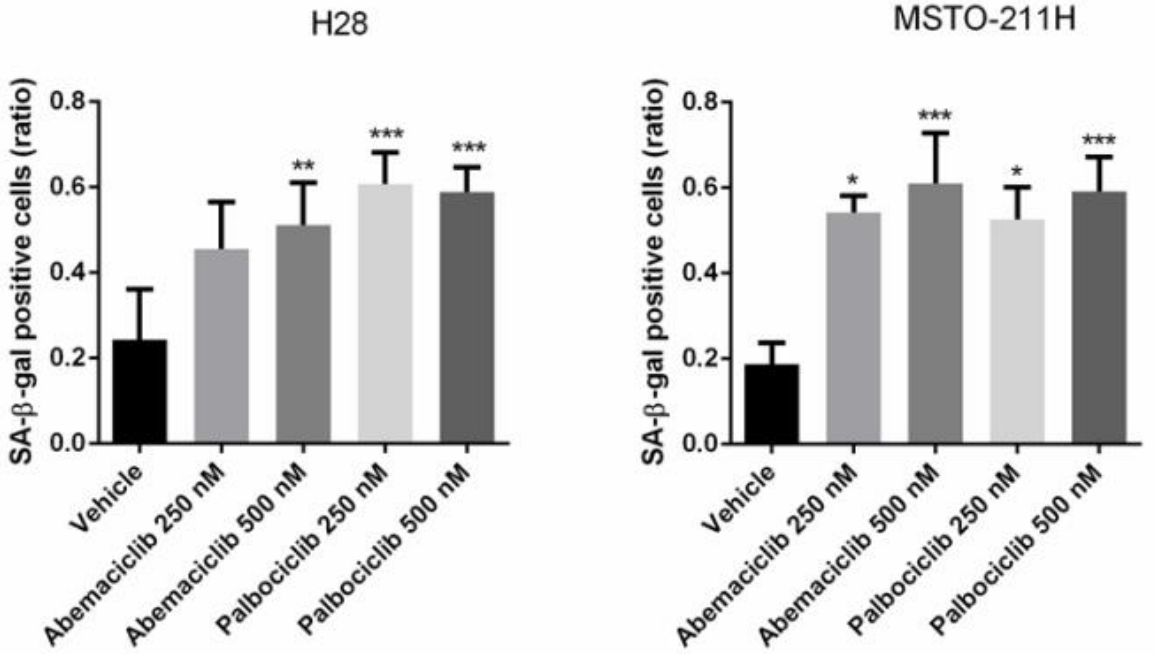
Frizelle et al, Oncogene 1998
Frizelle et al, Cancer Gene Therapy 2000

CDK4/6 inhibitors promoted cell cycle arrest in G1 phase and significantly increased the senescence in human MPM models

Cell cycle assessed by flow cytometry



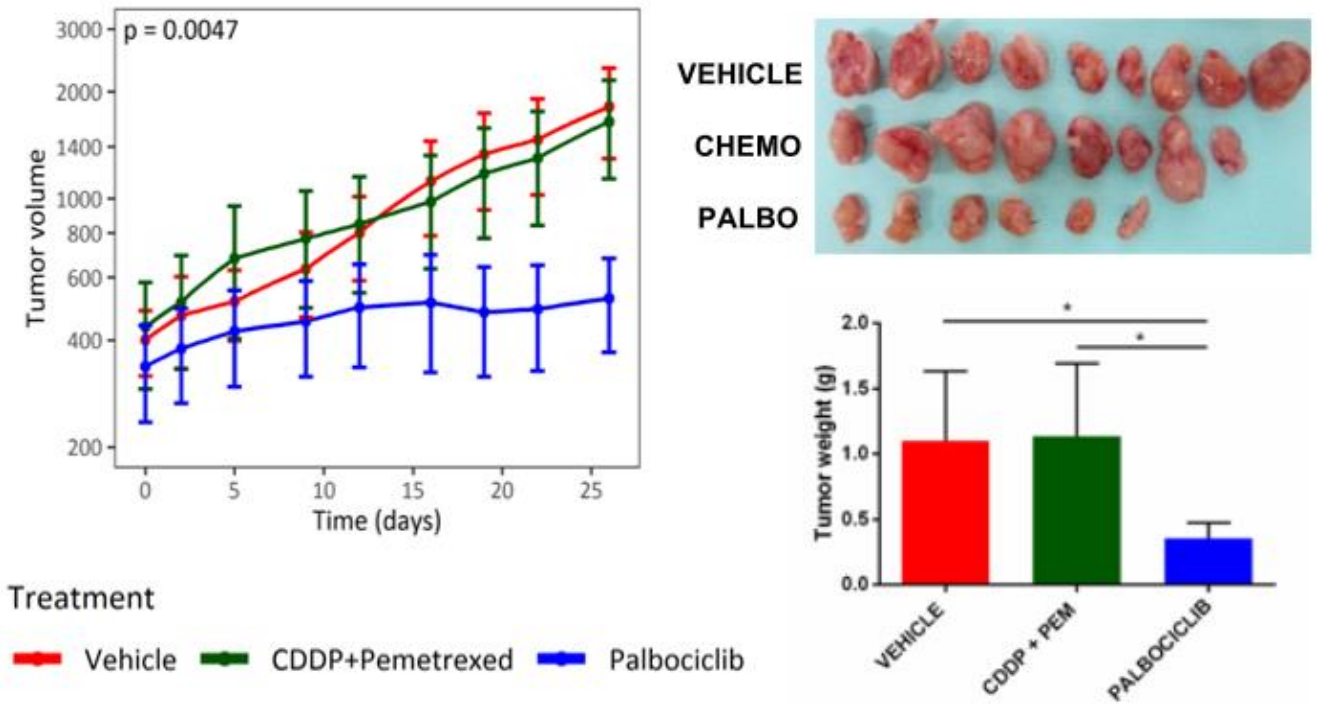
Senescence measured by SA-β-galactosidase



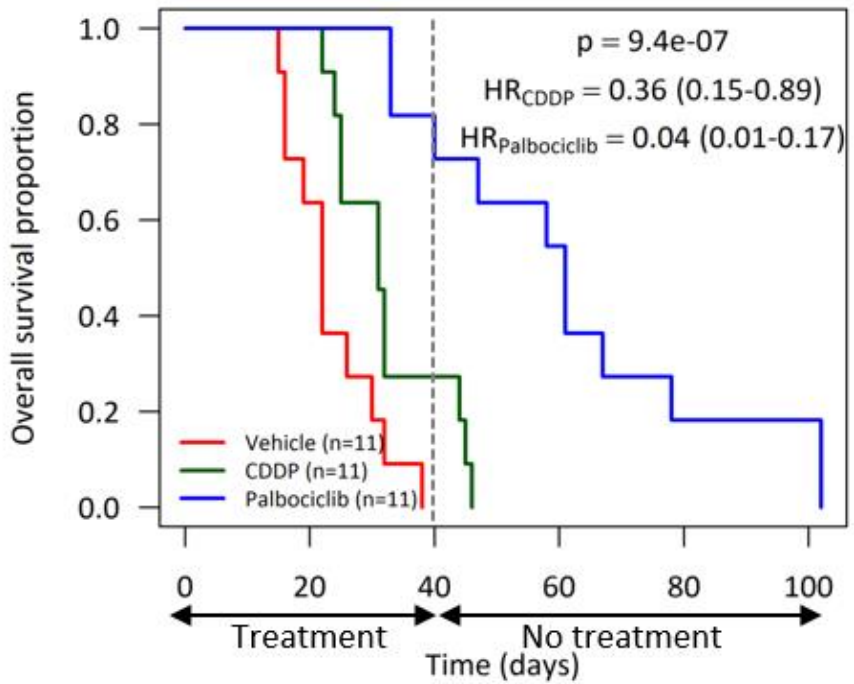
Aliagas et al, IASLC 2019.

Palbociclib reduced tumor growth in subcutaneous and orthotopic xenograft models of MPM

MSTO-211H subcutaneously implanted in athymic mice

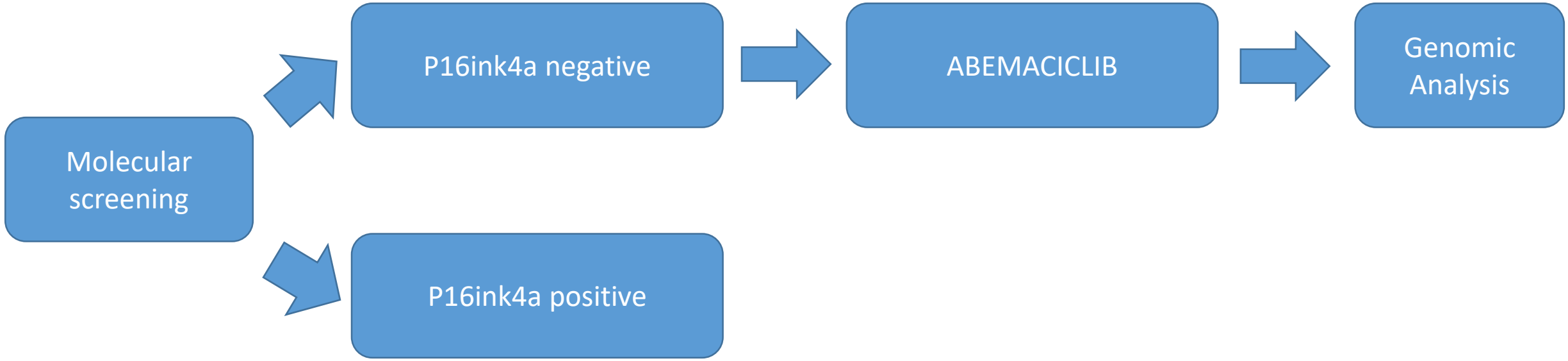


MSTO-211H orthotopically implanted in athymic mice

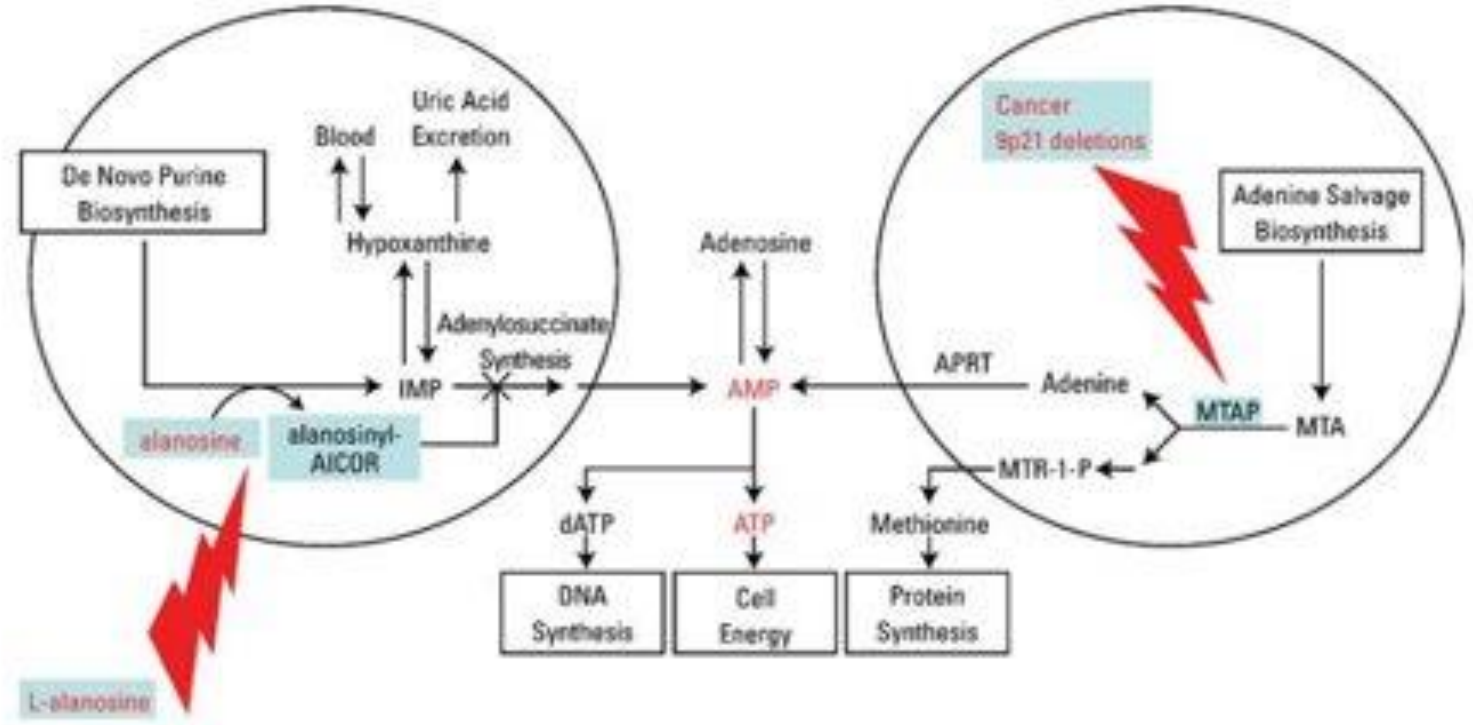


Aliagas et al, IASLC 2019.

MiST2: Abemaciclib in p16ink4a negative mesothelioma



Targeting L-alanosine in MTAP negative mesothelioma is ineffective

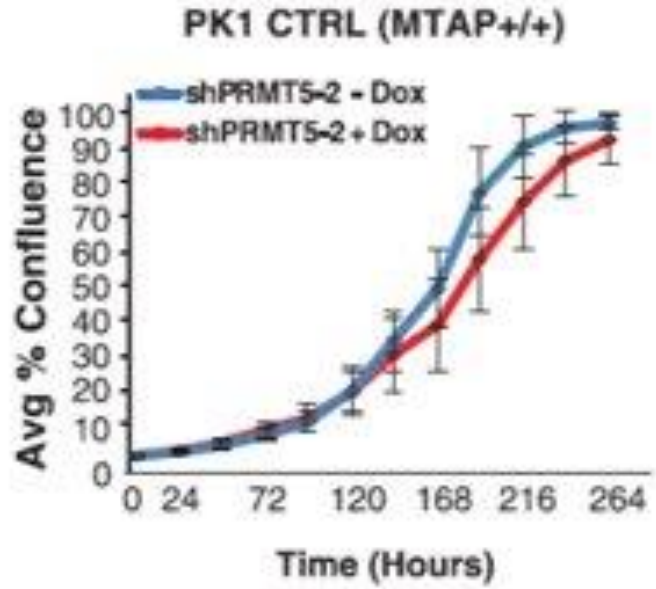


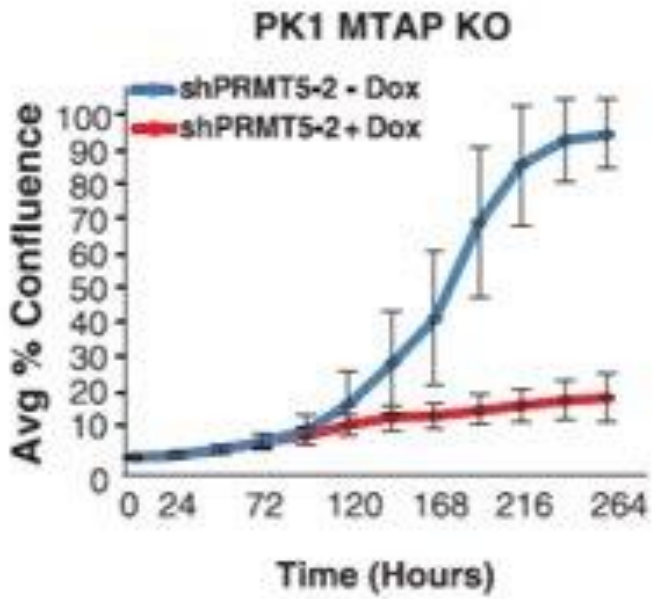
	Mesothelioma $n=16$
Best overall response	
Complete response, *n* (%)	0 (0)
Partial response, *n* (%)	0 (0)
Stable disease, *n* (%)	5 (31.3)
Progressive disease, *n* (%)	8 (50.0)
Not evaluable[a], *n* (%)	3 (18.8)
Progression-free survival	
Median, mo	2.1
95% CI	(1.7, 3.9)
Survival time	
Median, mo	5.5
95% CI	(3.2, 12.0)

Kindler et al, Investgational new Drugs 2008

Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5

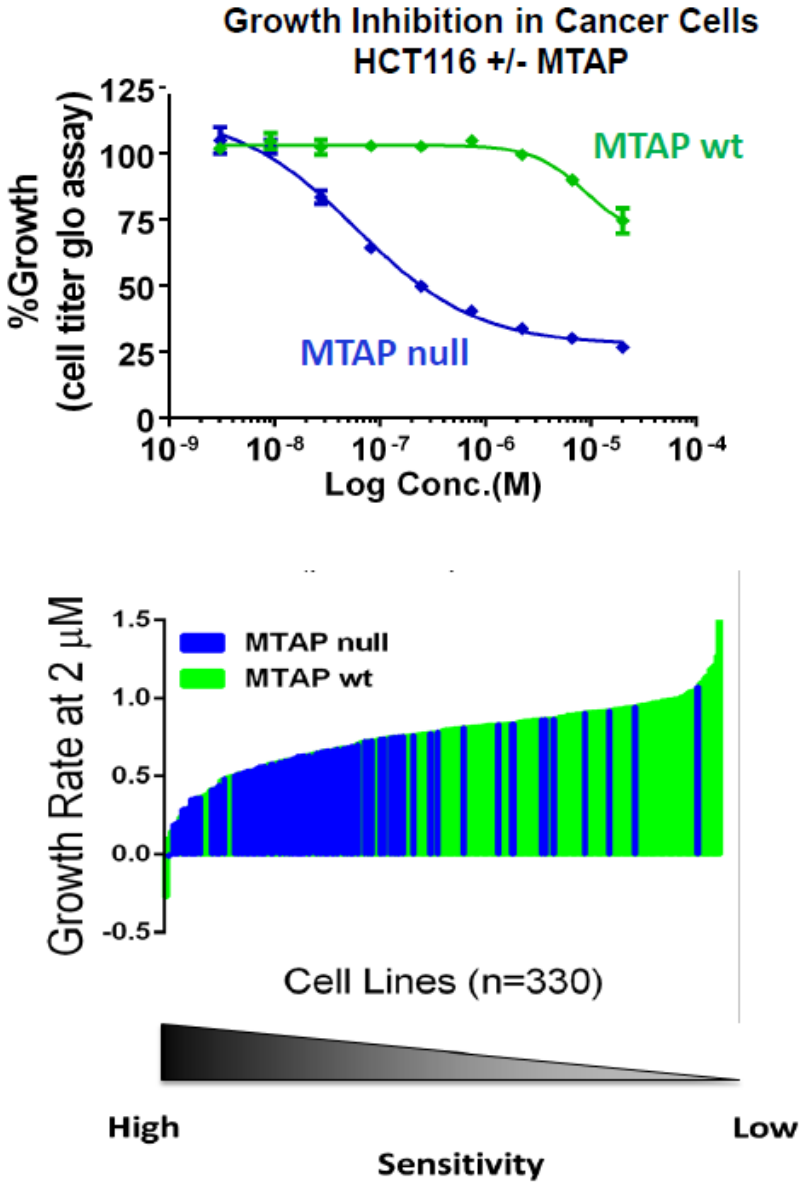
Konstantinos J. Mavrakis,[1*] E. Robert McDonald III,[1*] Michael R. Schlabach,[1*] Eric Billy,[2*] Gregory R. Hoffman,[1*] Antoine deWeck,[2] David A. Ruddy,[1] Kavitha Venkatesan,[1] Jianjun Yu,[3] Gregg McAllister,[1] Mark Stump,[1] Rosalie deBeaumont,[1] Samuel Ho,[1] Yingzi Yue,[1] Yue Liu,[1] Yan Yan-Neale,[1] Guizhi Yang,[1] Fallon Lin,[1] Hong Yin,[1] Hui Gao,[1] D. Randal Kipp,[1] Songping Zhao,[1] Joshua T. McNamara,[1] Elizabeth R. Sprague,[1] Bing Zheng,[3] Ying Lin,[4] Young Shin Cho,[1] Justin Gu,[4] Kenneth Crawford,[3] David Ciccone,[1] Alberto C. Vitari,[3] Albert Lai,[3] Vladimir Capka,[1] Kristen Hurov,[1] Jeffery A. Porter,[1] John Tallarico,[1] Craig Mickanin,[1] Emma Lees,[1] Raymond Pagliarini,[1] Nicholas Keen,[1] Tobias Schmelzle,[2*] Francesco Hofmann,[2*] Frank Stegmeier,[1*†] William R. Sellers[1*†]





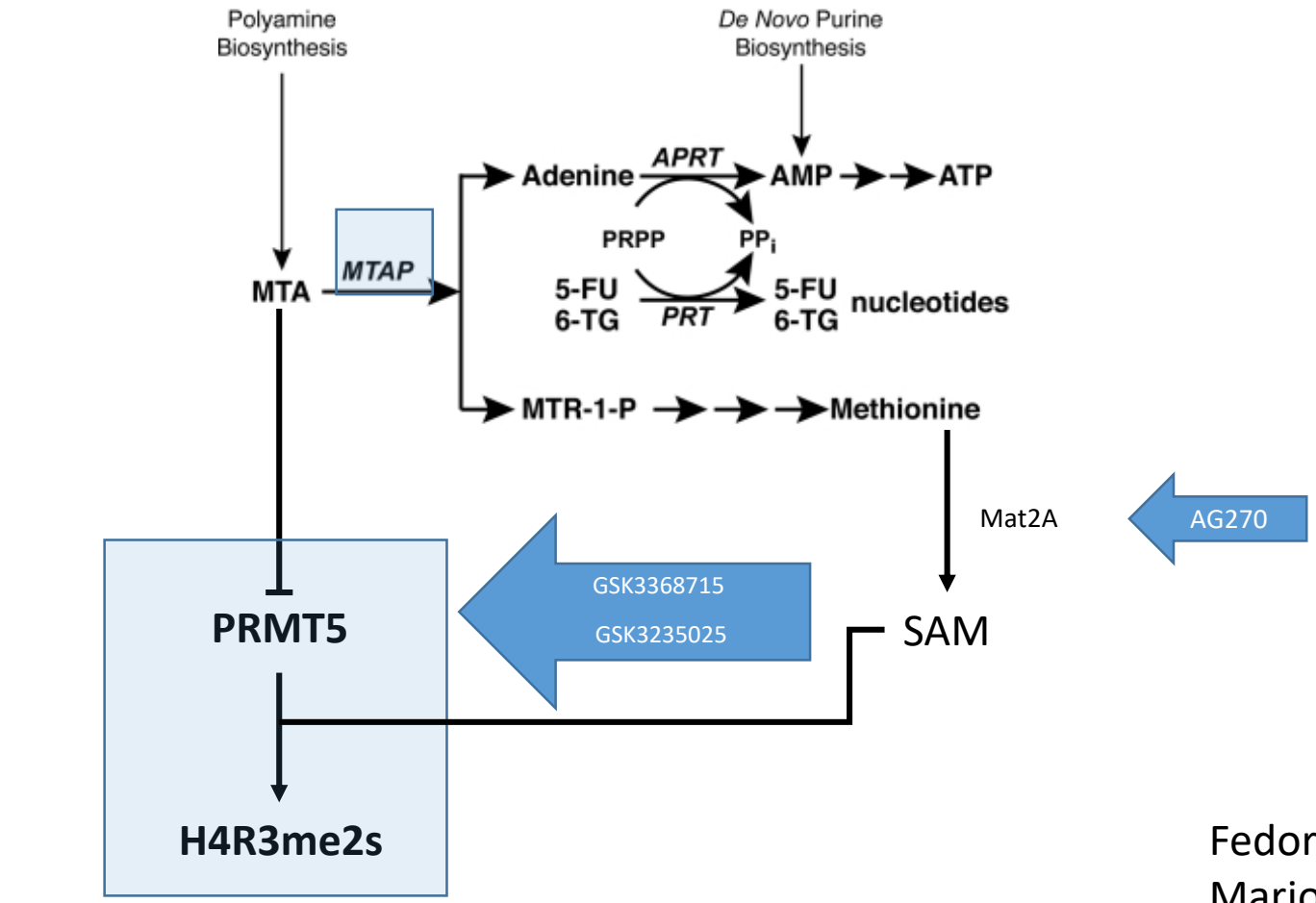
Mavarakis et al, Science 2016

MTAP deletion confers sensitivity to MAT2A inhibition



Marks AACR 2019

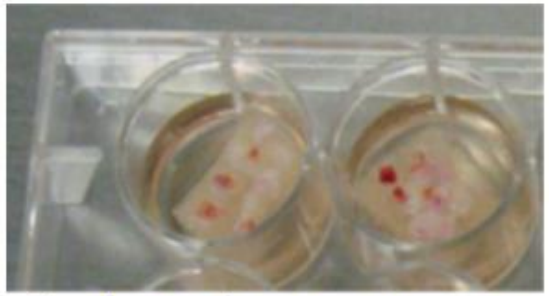
Targeting MTAP mesothelioma – potentially 3 different ways to do it



Fedoriw et al, Cancer Cell 2019,
Marjon et al, Cell Rep,
Kryukov et al, Science 2016,
Mavrakis et al, Science 2016

Exploring ARF dependent MDM2 inhibition in MPM explants

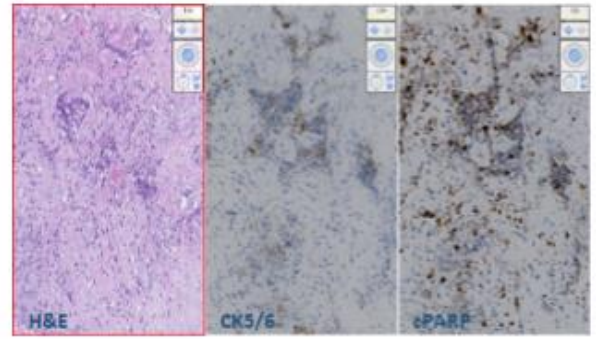
Surgery



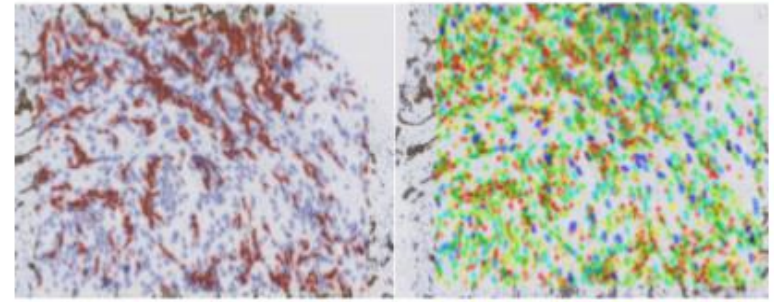
Explants drug treatment

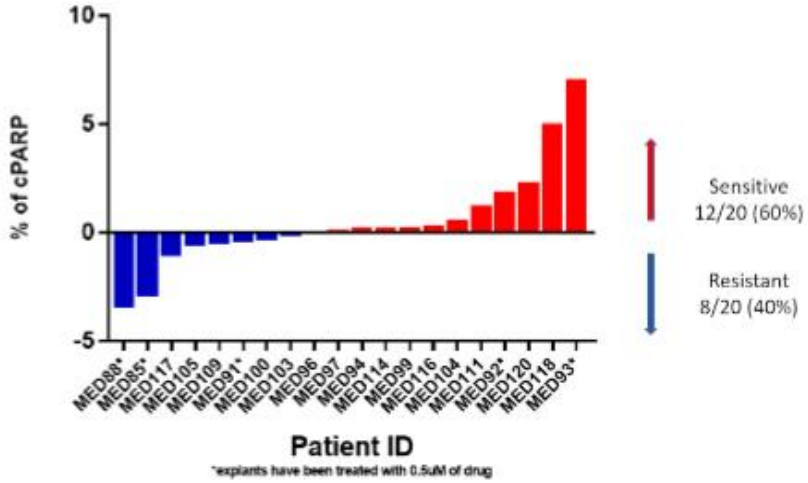
histoprocessing
sectioning

IHC staining



Quantification using
digital pathology tools





Joanna Diazalo; Busacca et al, Oncogene 2017: Kolluri et al, eLIFE 2018

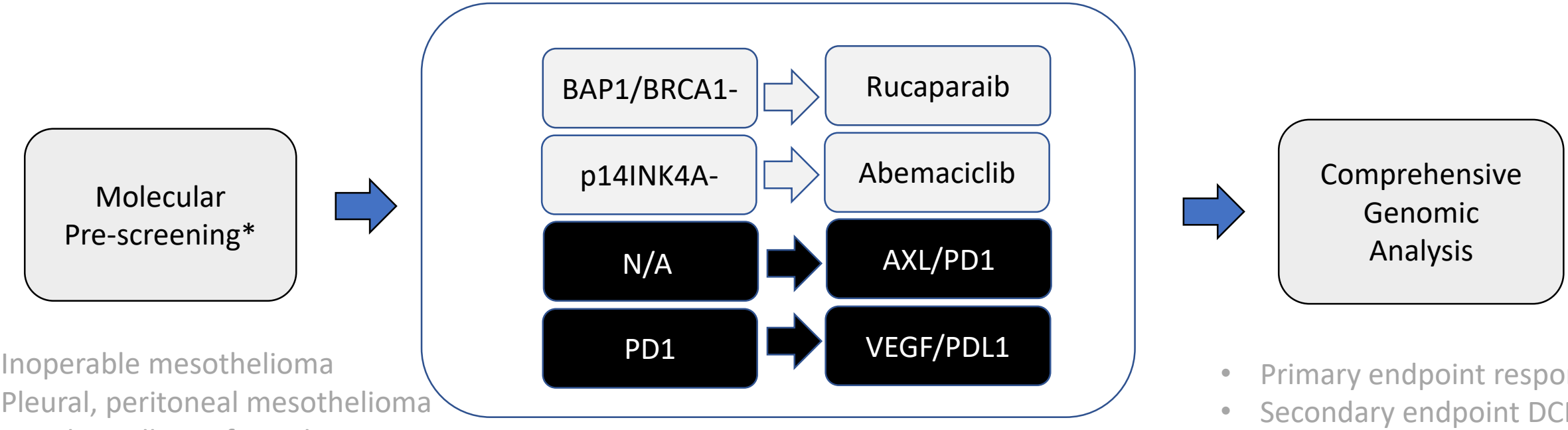
Inter-patient heterogeneity: a barrier to effective therapy

Synthetic lethal strategies

Master protocols to deliver stratified therapy

Mesothelioma Stratified Therapy (MIST, NCT03654833)

Stage 1 Molecular Pre-Screening | **Stage 2** Treatment Stratification | **Stage 3** Genomic interrogation



- Inoperable mesothelioma
- Pleural, peritoneal mesothelioma
- Histologically confirmed
- ECOG 0-1
- Post 1st line therapy
- Consent for tissue

- Primary endpoint response
- Secondary endpoint DCR
- Rebiopsy, responders

British Lung Foundation

Mesothelioma Research Programme
LEICESTER

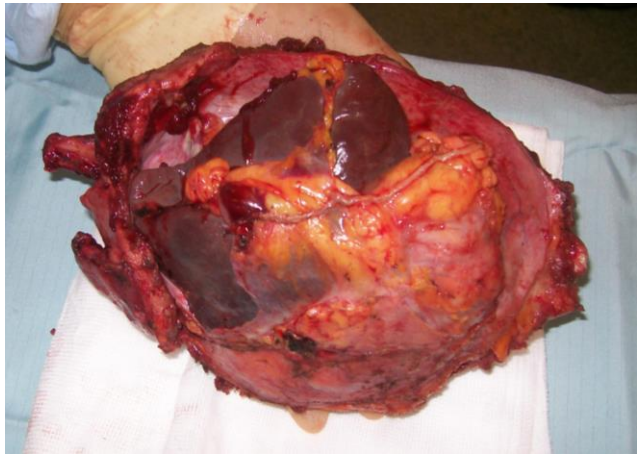
Expanding
- the MiST Umbrella
- Industrial Collaboration

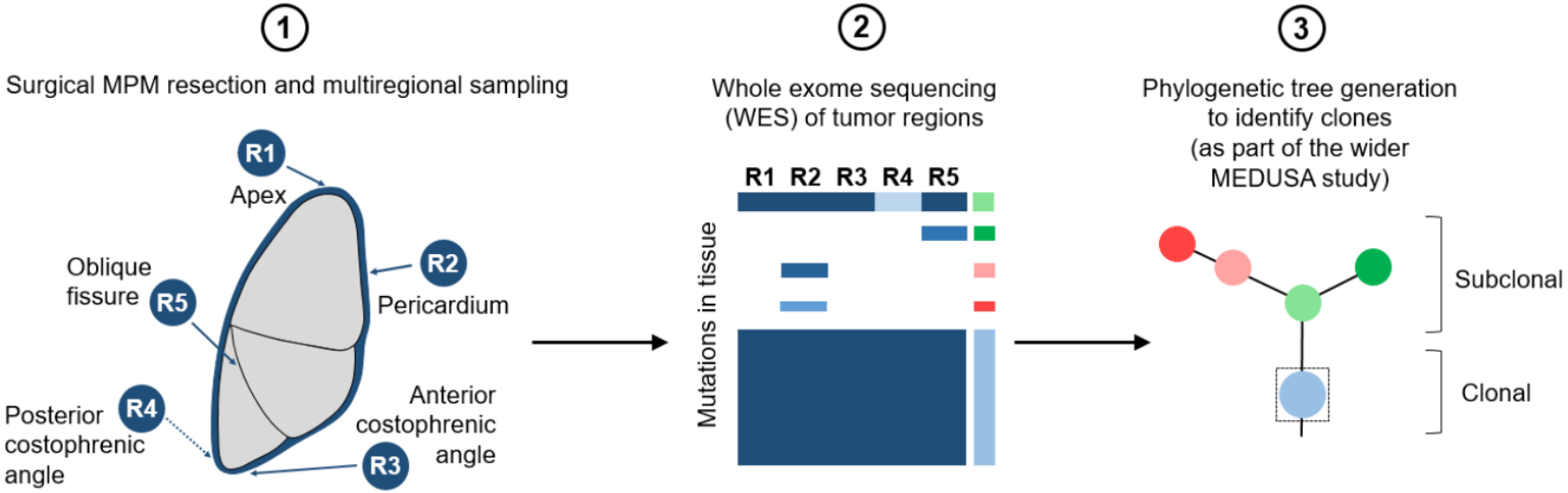
Expanding
- the molecular targets
- Bench-to-bedside translation

Laboratory Bench-to-Bedside Research
(*PhD, project grant)

astex pharmaceuticals
CLOVIS ONCOLOGY
Paradox Pharmaceuticals, Inc.
inventiva
BAYER
erytech

Revealing Clonal Architecture in mesothelioma



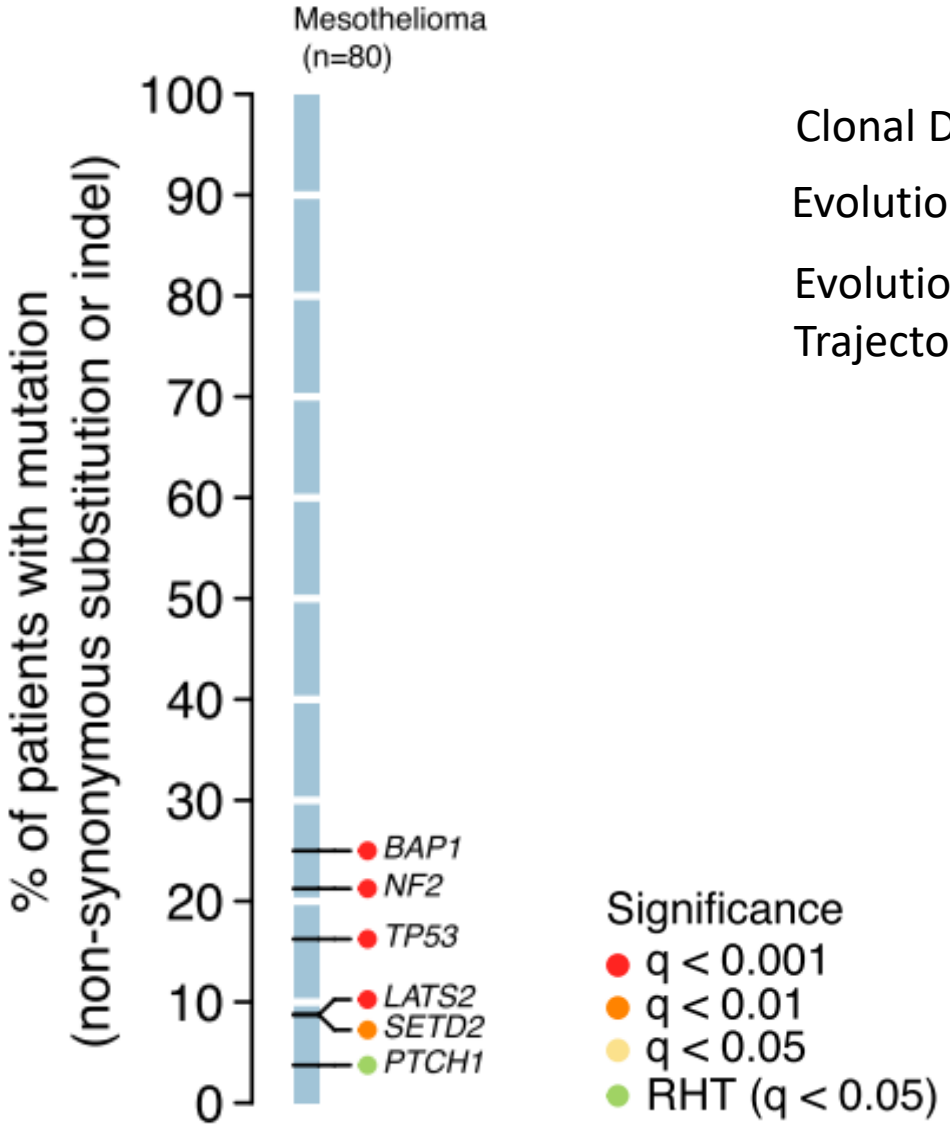


M-E:DUSA

Mesothelioma Evolution: Drugging Somatic Alterations

Seeking patient *homogeneity*: repeated evolutionary trajectories

Positive Selection

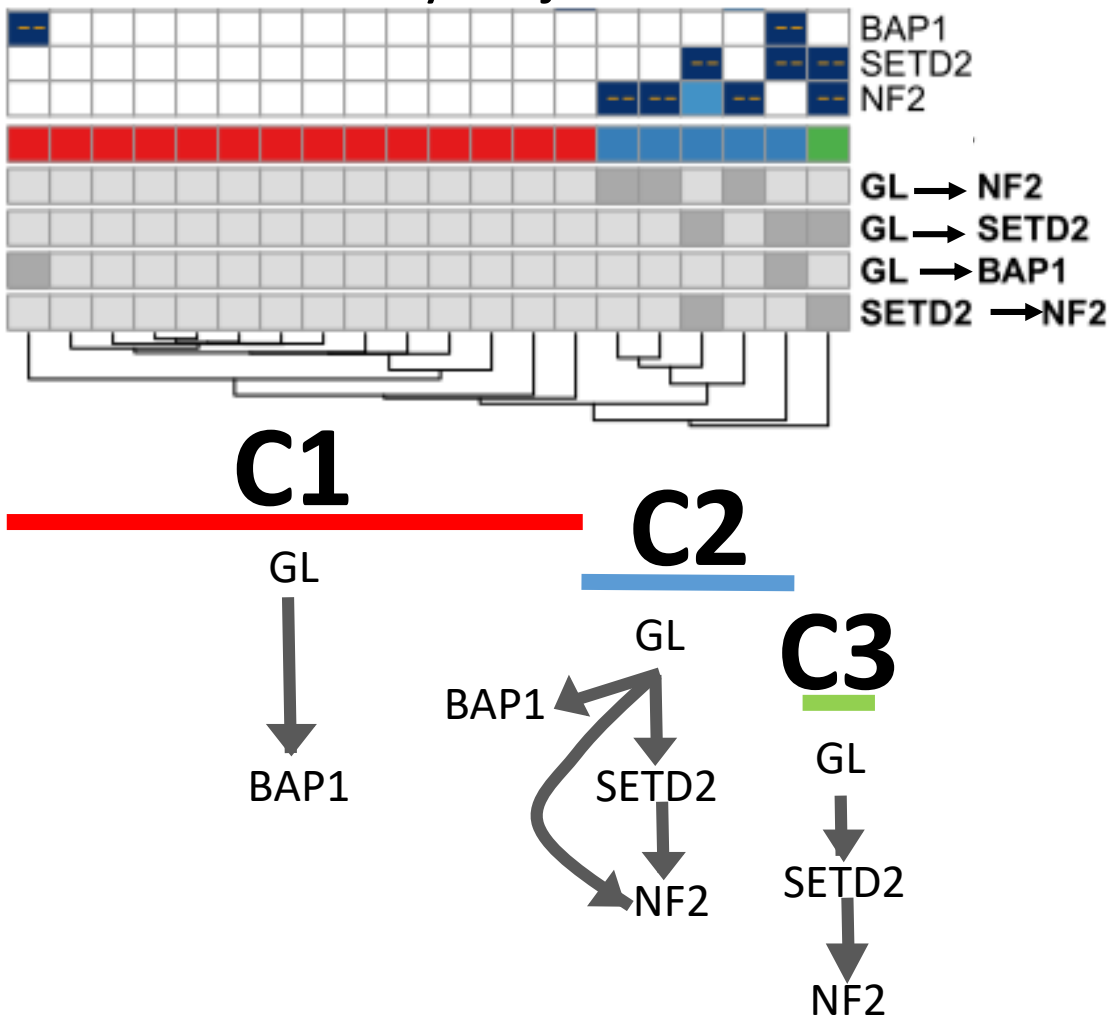


Clonal Driver SNV

Evolutionary Cluster

Evolutionary Trajectory

Evolutionary Trajectories



Martincorena et al, Cell 2017, Caravagna et al, Nat methods 2019

Jinli Luo, Min Zhang, Qianqian Sun

Summary

Heterogeneity in mesothelioma presents a massive challenge for the development of effective therapy

Advances in biology have uncovered promising approaches to exploit vulnerabilies

New study designs are needed to rapidly generate proof of concept data and to underpin pragmatic randomised trials

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