La caratterizzazione molecolare in funzione terapeutica

Marcello Tiseo

Dipartimento di Medicina e Chirurgia

Università degli Studi di Parma

U.O.C Oncologia Medica

Azienda Ospedaliero-Universitaria di Parma

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Disclosures

- **Advisory boards and speakers' fee**
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- **Research Grant:**
  - Astrazeneca
  - Boehringer Ingelheim
  - AIRC
  - Cariparma

Agenda

- Introduction and comprehensive molecular studies in MPM
- BRCA1-associated protein 1 (BAP1)
- Neurofibromatosis type 2 (NF2)
- Cyclin-dependent kinase inhibitor 2A (CDKN2A)
- Other potential targets
- Parma pre-clinical experience
- Conclusions

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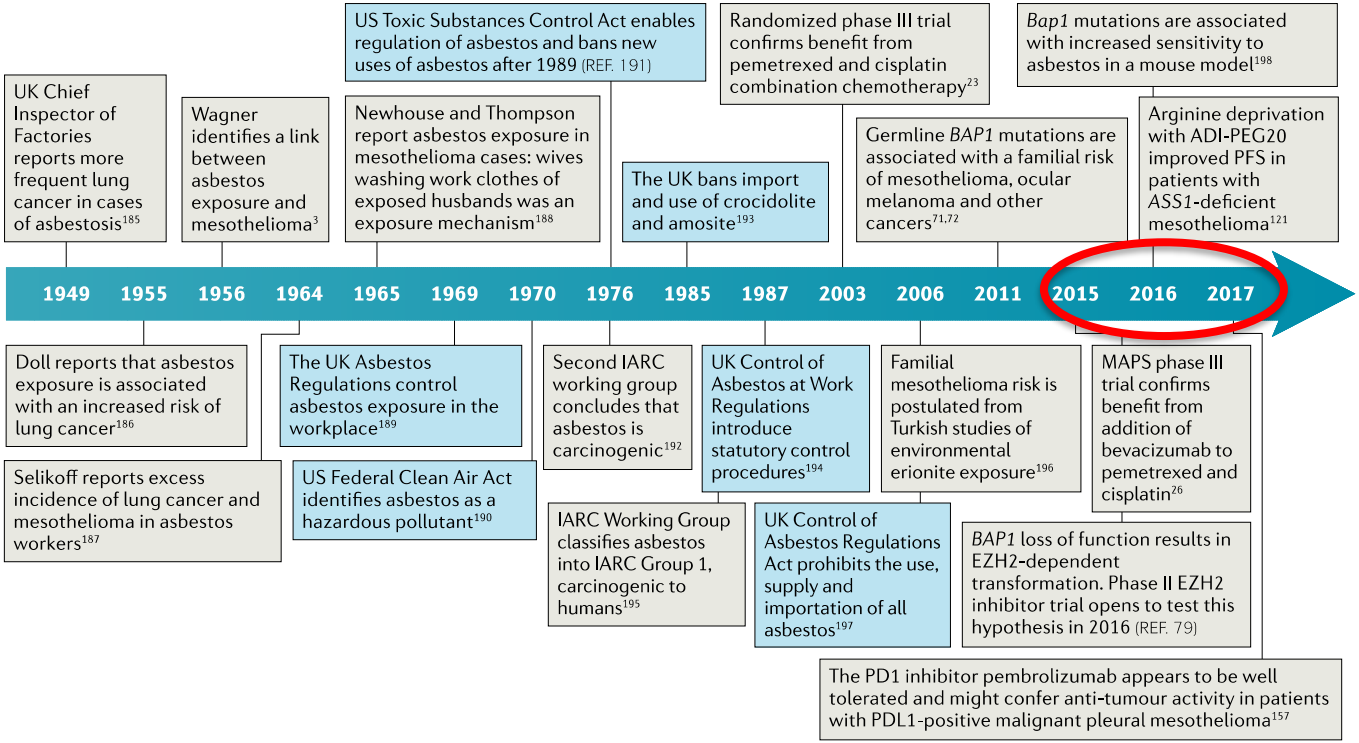
Timeline of research and legal milestones in mesothelioma



Yap TA et al, Nat Rev 2017

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Comprehensive Molecular Studies in MPM

- **Sequencing studies**
  - **Genome/Exome**
    - Bueno R et al. PLoS ONE 5 (2010) **(1 MPM case)**
    - Guo et al. Cancer Res (2015) **(22 MPM cases)**
    - De Rienzo et al. Cancer Res. (2015) **(10 MPM cases)**
  - **Target regions/candidate genes**
    - Bott et al. Nature Genetics, 2011 **(53 MPM cases)**
    - Lo Iacono M. et al., J Thorac Oncol 2015 **(123 MPM cases)**
    - Kato et al, Molecular Cancer Therapeutics 2016 **(42 MPM cases)**
- **Integrative analysis – genetic/transcriptional**
    - de Reyniès et al. Clin Cancer Res (2014) **(38 MPM cases)**
    - Bueno et al. Nature Genetics (2016) **(216 MPM cases)**
    - Hmeljak et al, Cancer Discovery 2018 **(74 MPM cases)**

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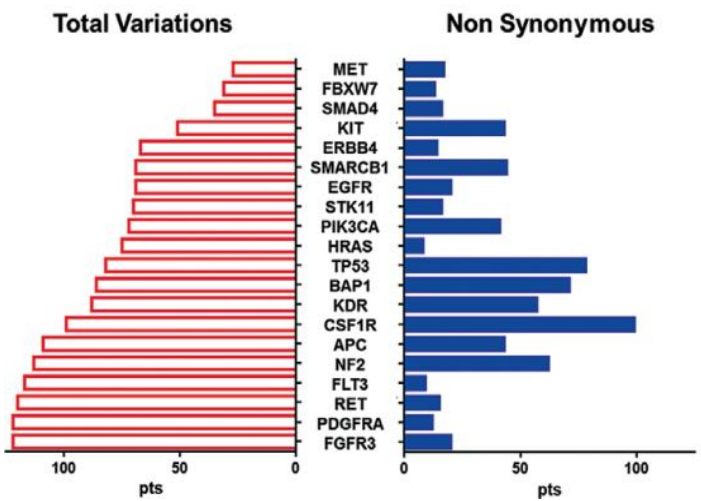
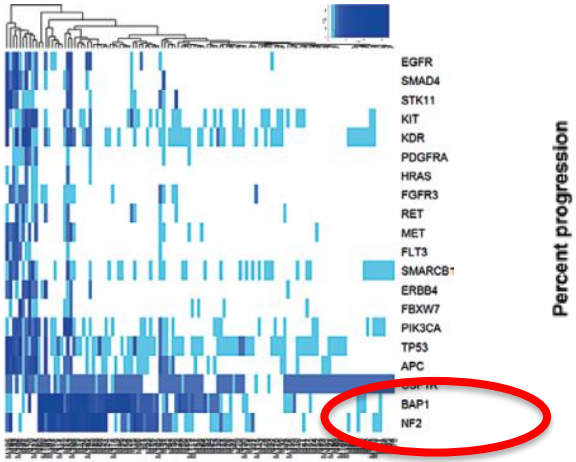
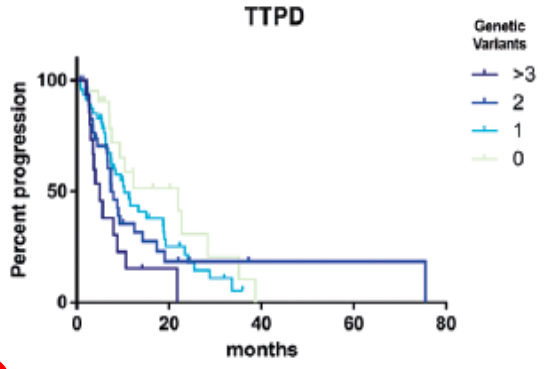
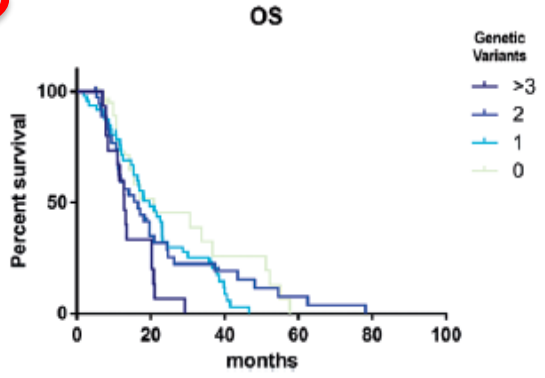
Targeted NGS in 123 MPM samples





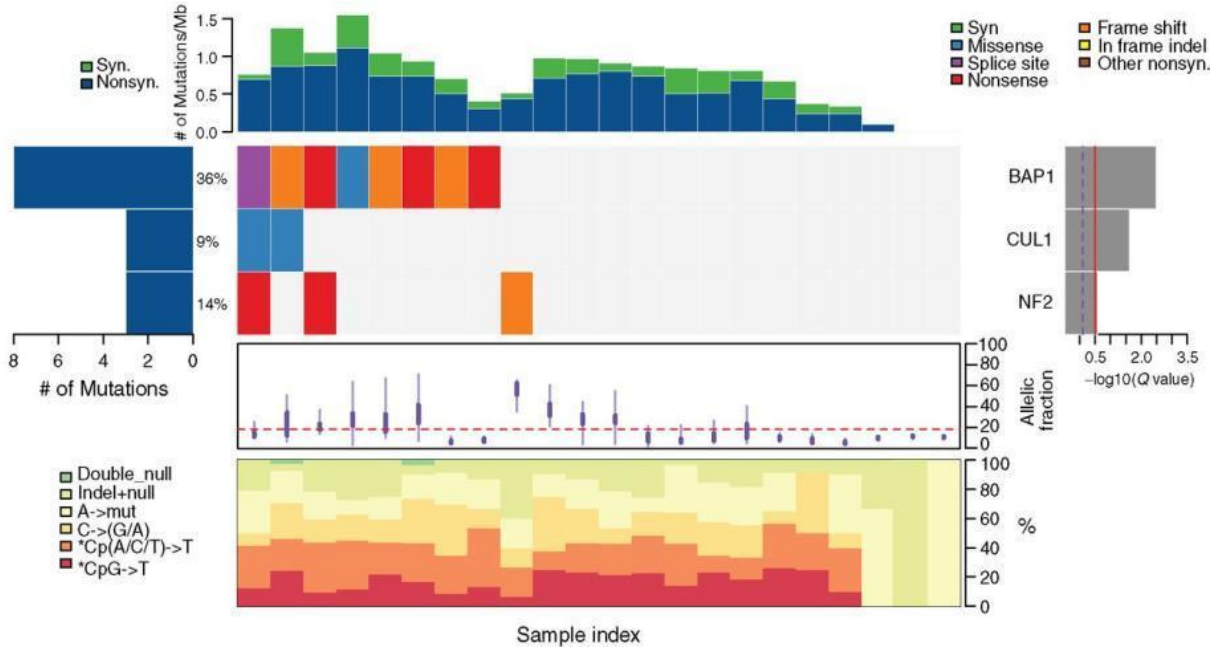




- The commonest genetic variations were clustered in two main pathways: the **p53/DNA repair** (TP53, SMACB1, and BAP1) and **phosphatidylinositol 3-kinase-AKT pathways** (PDGFRA, KIT, KDR, HRAS, PIK3CA, STK11 and NF2)
- Accumulation of genetic alterations correlated with shorter TTPD and reduced OS

Lo Iacono et al, J Thor Onc 2015

MPM genome results



- 22 MPM samples;
- Whole-exome sequencing: 517 somatic mutations across 490 mutated genes;
- No specific mutation in a single driver gene; accumulation of several non-driver mutations;
- Frequent alterations in BAP1, NF2, CUL1, CDKN2A

Guo G et al. Cancer Res 2015

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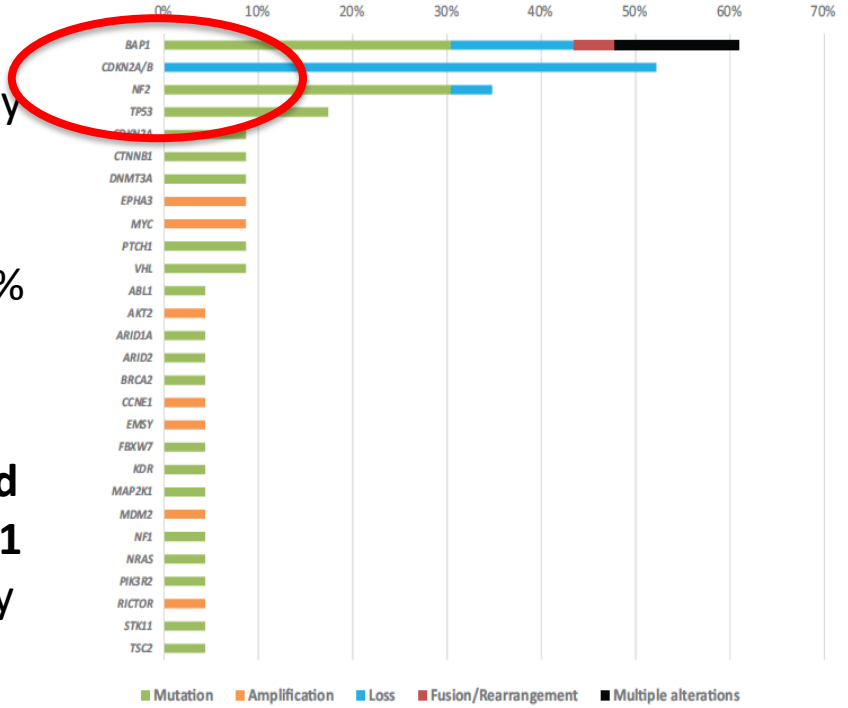
Insights Emerging from Malignant Mesothelioma Genome Sequencing

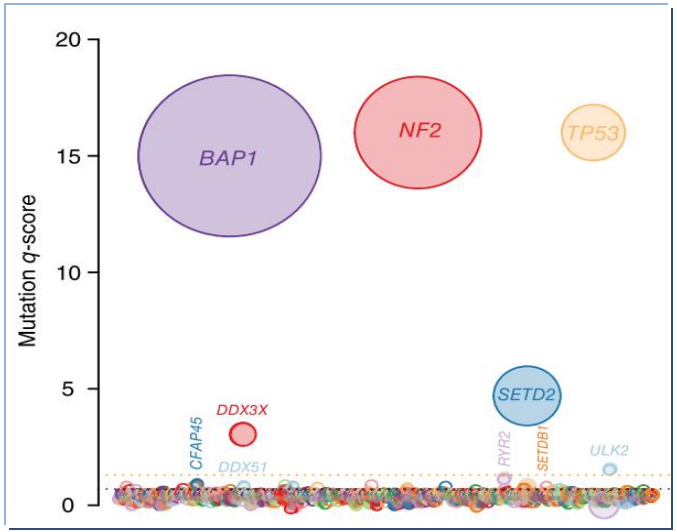
- In both studies, the biopsies from patients previously treated with CT; therefore, the CT may have contributed to some of the mutations
- Both studies detected frequent somatic nonsynonymous BAP1 mutations in 41% and 58%
- Both studies report frequent mutations of NF2
- These two NGS analyses reveal that **inactivating mutations occur randomly and are rarely shared among MM biopsies**, with the exception of **BAP1** and to a lesser extent **NF2, CDKN2A** and possibly CUL1

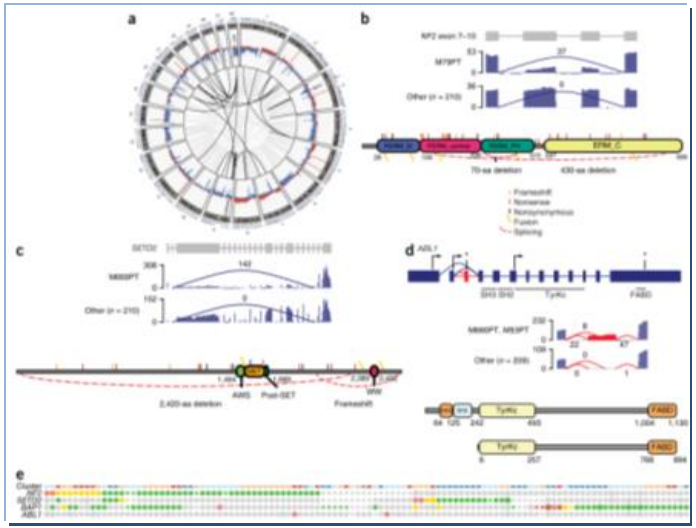


Carbone et al, JTO 2017

Kato et al, Molecular Cancer Therapeutics 2016

Integrated molecular analyses in 216 MPM



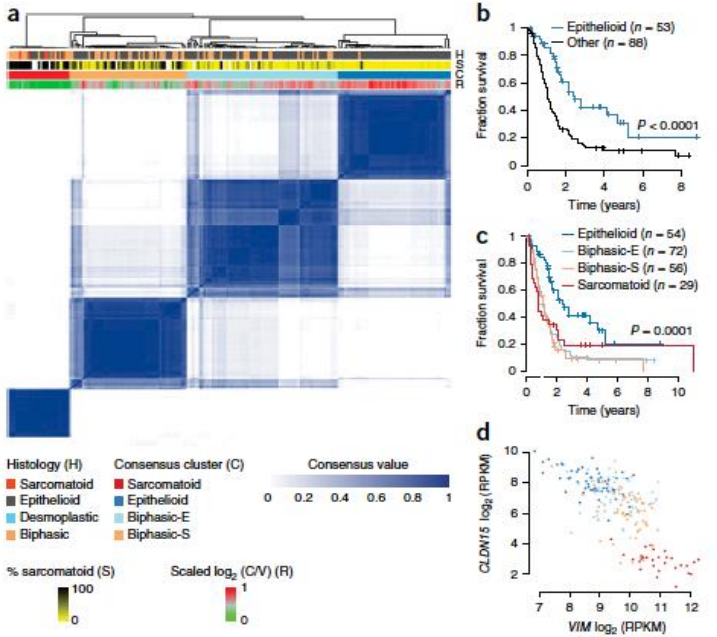


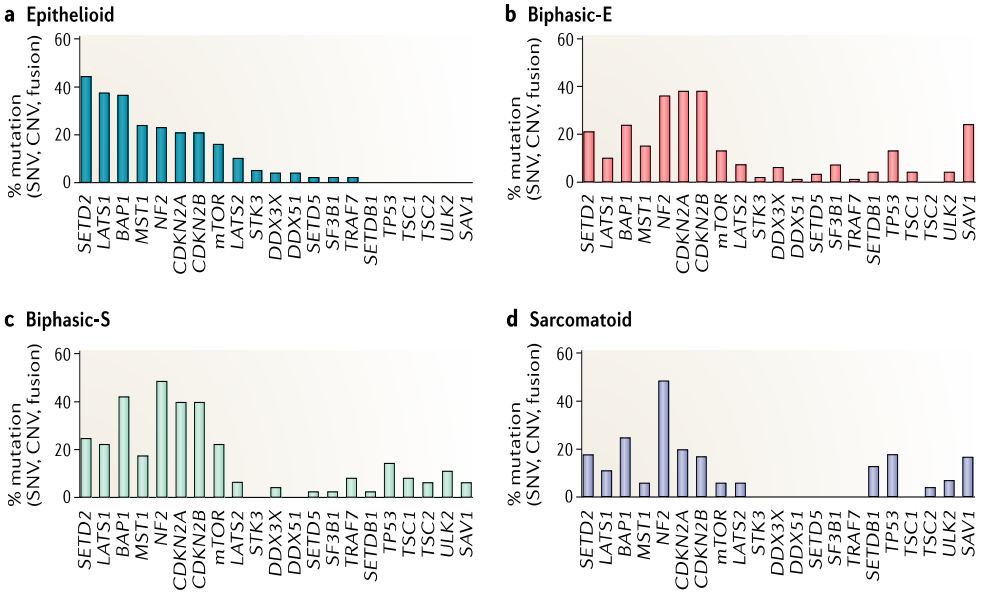
Analyzed transcriptomes (*n* = 211), whole exomes (*n* = 99) and targeted exomes (*n* = 103) from 216 MPM

- BAP1, NF2, TP53, SETD2, DDX3X, ULK2, RYR2, CFAP45, SETDB1 and DDX51 were the most mutated genes
- Multiple molecular mechanisms lead to activation or inactivation of genes (SNV, CNV, fusion)

Bueno et al. Nat Genetics 2016

Integrated molecular analyses in 216 MPM



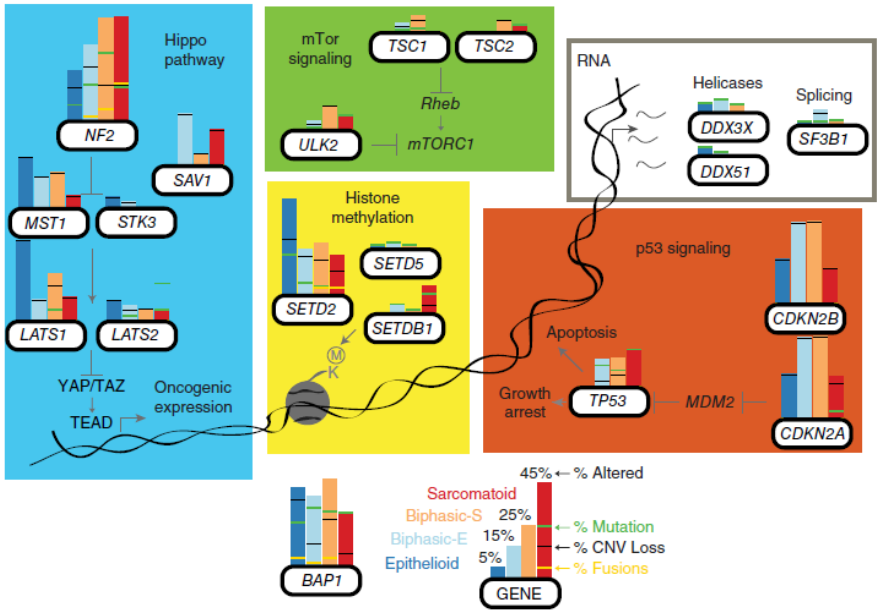


Using RNA-seq data identified **four distinct molecular subtypes**: sarcomatoid, epithelioid, biphasic-epithelioid (biphasic-E) and biphasic-sarcomatoid (biphasic-S)

TP53 mutations were absent in the epithelioid subtype; mutually exclusive genetic alterations between epithelioid and sarcomatoid subtypes

Bueno et al. Nat Genetics 2016

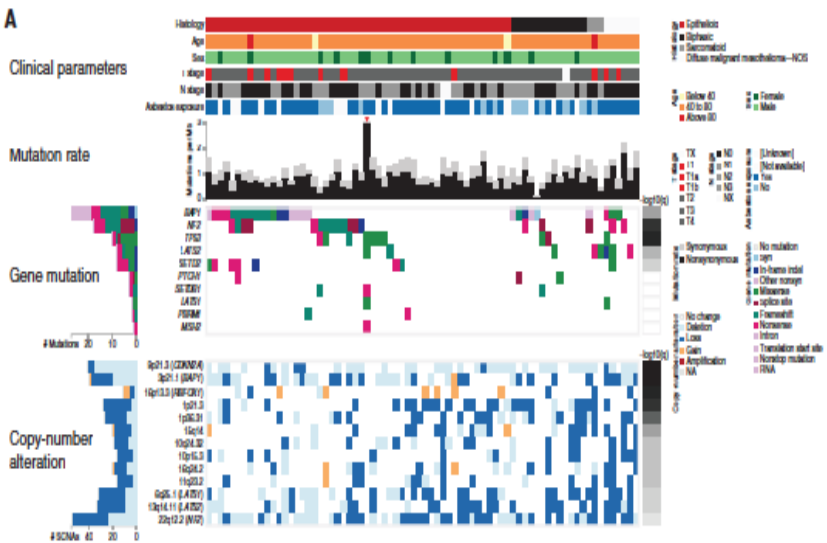
Integrated molecular analyses in MPM



Bueno et al. Nat Genetics 2016

Integrative Molecular Characterization of Malignant Pleural Mesothelioma

SIGNIFICANCE: Through a comprehensive integrated genomic study of 74 MPMs, we provide a deeper understanding of histology-independent determinants of aggressive behavior, define a novel genomic subtype with *TP53* and *SETDB1* mutations and extensive loss of heterozygosity, and discovered strong expression of the immune-checkpoint gene *VISTA* in epithelioid MPM. *Cancer Discov; 8(12); 1548–65. ©2018 AACR.*



Hmeljak et al, Cancer Discovery 2018

Genetic alterations in MPM and TMB

Table 1. Landscape of somatic mutations in the exomes of 22 MPMs

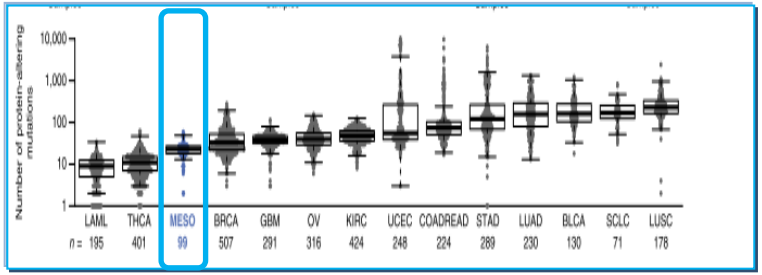
Case ID	Tumor bases sequenced	Normal bases sequenced	Tumor exome coverage	Normal exome coverage	Callable positions	Callable (%)	Point mutations	Coding indels	Mutation rate (per Mb)
NYU269	3.55×10^9	3.14×10^9	107.3	95	2.94×10^7	88.9	2	1	0.1
NYU274	2.94×10^9	3.32×10^9	88.8	100.3	2.92×10^7	88.3	31	1	1.08
NYU321	3.58×10^9	3.05×10^9	108.2	92.2	2.94×10^7	89	30	2	1.07
NYU460	3.69×10^9	4.23×10^9	111.5	127.8	2.95×10^7	89.3	22	1	0.77
NYU517	3.12×10^9	4.10×10^9	94.2	124	2.93×10^7	88.6	29	3	1.08
NYU587	3.82×10^9	3.78×10^9	115.7	114.3	2.97×10^7	89.9	23	1	0.79
NYU589	3.76×10^9	3.97×10^9	113.7	120	2.97×10^7	89.7	0	2	0.07
NYU647	3.10×10^9	3.30×10^9	93.8	99.8	2.94×10^7	88.9	30	0	1
NYU658	3.03×10^9	3.33×10^9	91.8	100.6	2.94×10^7	89	28	2	1
NYU695	3.60×10^9	3.9×10^9	108.9	93.5	2.92×10^7	88.3	12	3	0.51
NYU754	3.64×10^9	4.20×10^9	110	127.1	2.94×10^7	89	26	2	0.94
NYU872	3.76×10^9	3.64×10^9	113.7	109.9	2.94×10^7	89	46	5	1.71
NYU929	3.39×10^9	3.67×10^9	102.6	111	2.96×10^9	89.4	22	1	0.77
NYU937	3.41×10^9	3.28×10^9	103.1	99	2.94×10^7	89	39	2	1.37
NYU939	3.01×10^9	3.99×10^9	91.1	120.5	2.92×10^9	88.3	24	3	0.91
NYU1162	3.11×10^9	3.42×10^9	94.1	103.4	2.92×10^7	88.4	24	2	0.88
NYU1189	3.46×10^9	3.34×10^9	104.7	101	2.93×10^7	88.4	9	1	0.34
NYU1245	3.05×10^9	4.35×10^9	92.2	131.6	2.92×10^7	88.2	15	0	0.51
NYU1283	3.97×10^9	3.30×10^9	119.9	99.7	2.96×10^7	89.6	27	4	1.03
NYU1353	3.08×10^9	3.68×10^9	93.2	111.2	2.91×10^7	88	11	1	0.41
NYU1363	3.37×10^9	3.00×10^9	101.8	90.8	2.93×10^7	88.5	27	1	0.95
NYU1396	4.15×10^9	4.11×10^9	125.4	124.2	2.97×10^7	89.7	2	0	0.07

NOTE: The mutation rate was calculated by dividing the total number of somatic mutations by the total number of callable nucleotide positions (≥1× in tumor and ≥8× in matched normal samples).

Low mutation rate (range 0.07 -1.08 mutations per Mb)

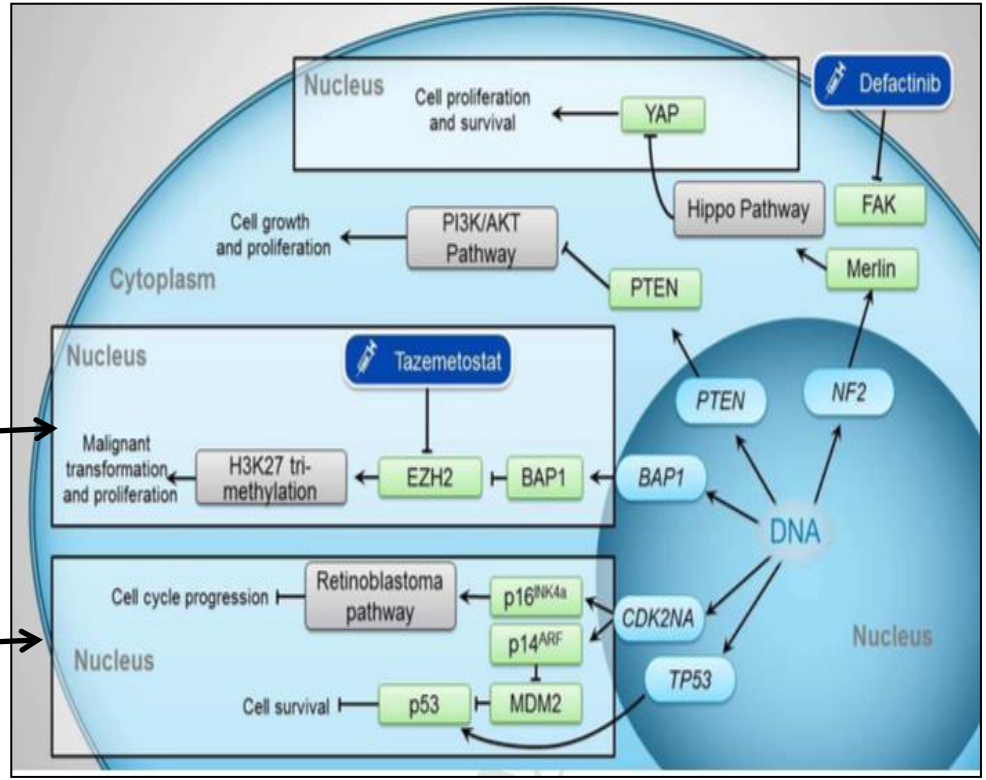
Guo G et al. Cancer Res 2015

Mesothelioma mutation rate seems in the low range



Bueno et al. Nat Genetics 2016

Genetic alterations in MPM and potential therapeutic targets



PARP inhibitors

CDK4/6 inhibitors

- **No specific mutation in a single driver gene; accumulation of several non-driver mutations** (long latency phase);
- Frequent alterations in **BAP1, NF2, CDKN2A**
- Most genetic alterations are **loss of function of tumor suppressor genes**, rather than activation of proto-oncogenes (like lung cancer)
- Therefore **we must identify surrogate targets whose activity is increased** and necessary to cell survival as a consequence of these mutations

McCambridge et al, JTO 2018

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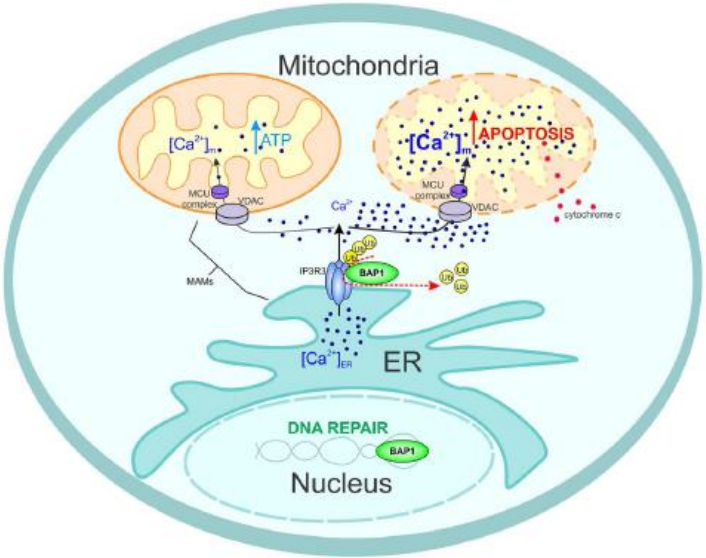
- Cyclin-dependent kinase inhibitor 2A (CDKN2A)
- Other potential targets
- Parma pre-clinical experience
- Conclusions

BRCA1-associated protein 1 (BAP1)

BAP1 encode for a deubiquitylase that modulates the activity of multiple genes and proteins controlling DNA replication, DNA repair and cell death

After DNA damage, BAP1 regulates both DNA repair by interacting with DNA-repair mechanisms, and apoptosis by modulating the stability of the IP3R3 Ca^{2+}-channel.

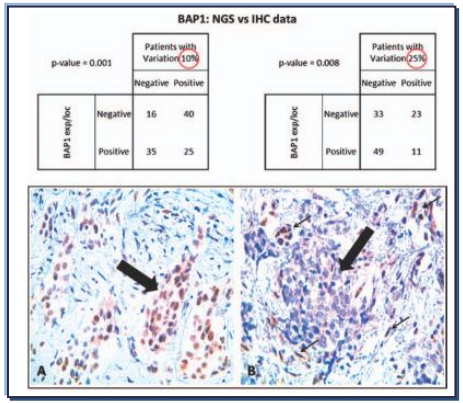


Carbone M et al, Cancer J Clin, 2019

BRCA1-associated protein 1 (BAP1)

- Approximately 65% of mesotheliomas harbour inactivation of the tumour suppressor *BAP1*
- Although rare (< 5%), germline mutation of *BAP1* confers a higher risk of mesothelioma
- BAP1 functions as a deubiquitinase (DUB), is encoded at the 3p21.1 locus and exhibits both somatic mutations and copy number losses in mesothelioma
- BAP1 mutations correlate with a better prognosis

- *BAP1* gene alterations and protein loss
- 100% concurrence between molecular alterations and absence of BAP1 nuclear staining
- BAP1 nuclear loss (with or without cytoplasmic stain) indicates mutated gene

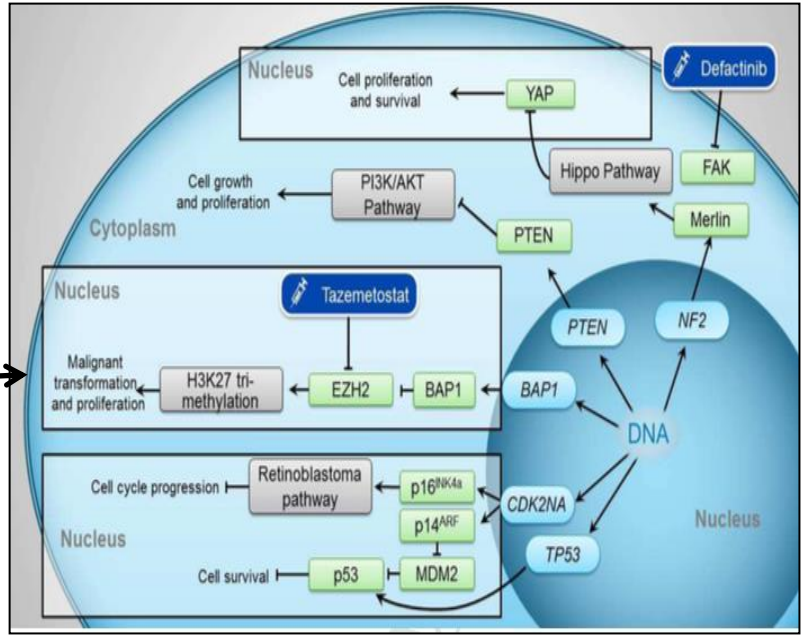


Lo Iacono M. et al, JTO 2015

BRCA1-associated protein 1 (BAP1)

BAP1 downregulation in MPM cell lines increases the sensitivity for HDAC inhibitors
VANTAGE 014 study (Vorinostat in Patients With Advanced Malignant Pleural Mesothelioma who have progressed on Previous Chemotherapy phase 3 trial including 661 patients: vorinostat did not improve OS in an unselected group of patients compared with placebo.

PARP inhibitors

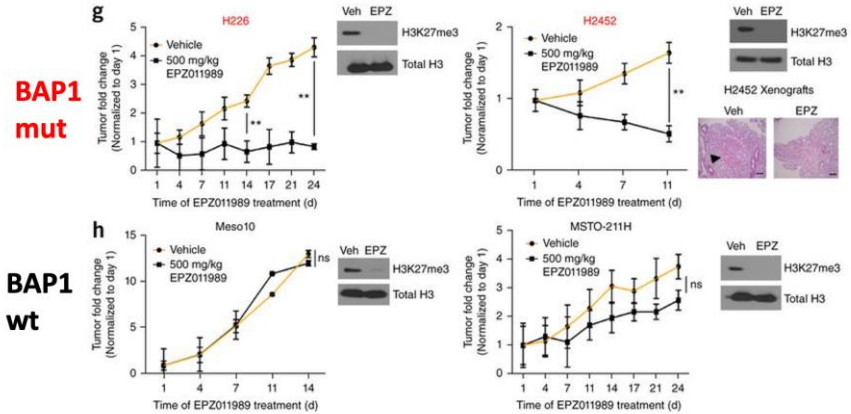


EZH2 (enhancer of zeste-homolog 2) is an histone methyltransferase. In BAP-1 mutant MPM cell lines, **EZH2 inhibition reduced tumor cell growth**

BAP1 modulates double-strand DNA damage repair and cells with **BAP1 mutations are more sensitive to the PARP inhibitor olaparib**

Loss of BAP1 function leads to EZH2-dependent transformation

Mesothelioma cells that lack BAP1 (H226 and H2452, that have BAP1 mutations) are sensitive to EZH2 inhibition



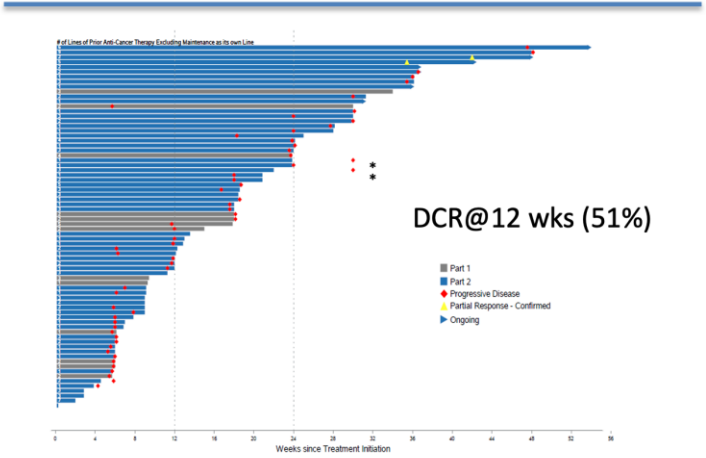
EZH2 inhibition may present a novel strategy for the treatment of patients with BAP1-loss mesotheliomas.

La Fave LM et al, Nat Med. 2015

Recurrent/progressive meso

- 12 patients irrespective of BAP1 status
- 55 with BAP1 deficient tumors

→ **Tazemetostat** 800 mg po BID (Epizyme EZH2 inhibitor)



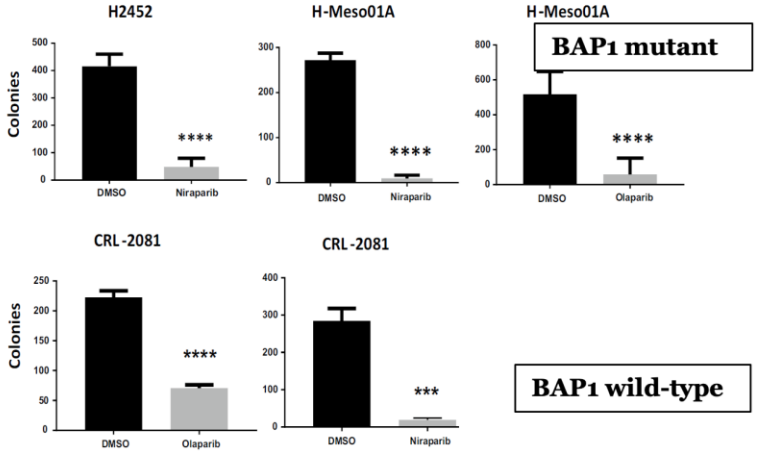
DCR@12 wks (51%)

Zauderer ASCO Annual Meeting 2018; NCT02860286

Synthetic lethality with PARP inhibition

- BAP1, a member of the BRCA complex, plays a role in homologous recombination DNA double-strand break repair
- Similar to BRCA1/2 deficient cancers, BAP1 mutation leads to a deficient HR pathway, increasing the reliance on other DNA repair pathways for survival during replication
- All MPM cell lines examined, regardless of BAP1 status, were addicted to PARP1-mediated DNA repair for survival
- The requirement of MPM cells for PARP1 suggests that they may generally arise from defects in HR DNA repair

PARP inhibition is lethal in both BAP1 mutant and wild-type mesothelioma



Studies with Niraparinb and Olaparib currently ongoing

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Synthetic lethality with PARP inhibition

Rucaparib in patients with BAP1-deficient or *BRCA1*-deficient mesothelioma (MiST1): an open-label, single-arm, phase 2a clinical trial

Lancet Oncology 2021

Dean A Fennell, Amy King, Seid Mohammed*, Amy Branson, Cassandra Brookes, Liz Darlison, Alan G Dawson, Aarti Gaba, Margaret Hutka, Bruno Morgan, Adrian Nicholson, Cathy Richards, Peter Wells-Jordan, Gavin James Murphy, Anne Thomas, on behalf of the MiST1 study group†*

Disease control rate at 12 weeks was 58% (95% CI 37–77; 15 of 26 patients), and at 24 weeks was 23% (9–44; six of 26 patients)

Rucaparib in patients with BAP1-negative or *BRCA1*-negative mesothelioma met the prespecified criteria for success, showing promising activity with manageable toxicity

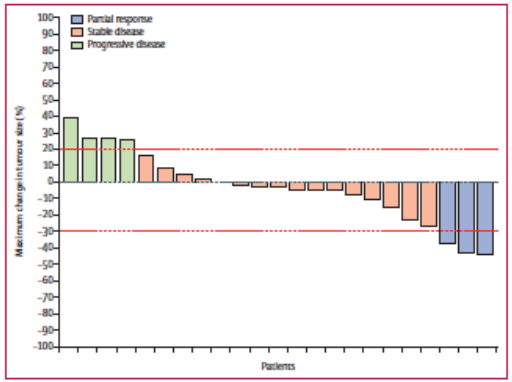

Figure 3: Waterfall plot for the radiologically evaluable population showing best overall response within 24 weeks

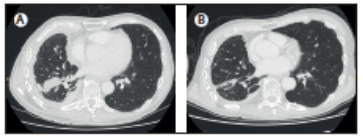

Figure 4: Cross-sectional CT scans of the chest in a patient receiving rucaparib at baseline (A) and at 18 weeks showing a partial response (B)

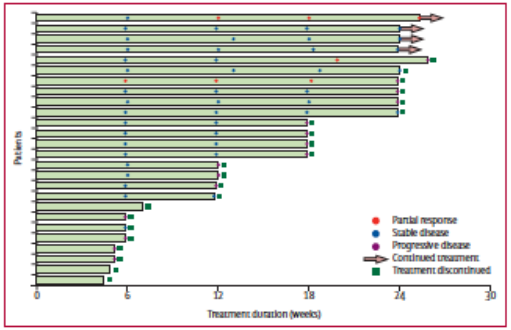

Figure 2: Swimmer's plot for tumour response up to week 24

	Participants (N=26)
Tumour response at 12 weeks	
Complete response	0
Partial response	2 (8%)
Stable disease	13 (50%)
Progressive disease	10 (38%)
Not evaluable	1 (4%)
Disease control rate	15 (58%)
Tumour response at 24 weeks	
Complete response	0
Partial response	1 (4%)
Stable disease	5 (19%)
Progressive disease	15 (58%)
Not evaluable	3 (12%)
Disease control rate	6 (23%)
Best response within 24 weeks	
Complete response	0
Partial response	3 (12%)
Stable disease	16 (62%)
Progressive disease	4 (15%)
Not evaluable	3 (12%)
Objective response rate	3 (12%)

Data are n (%). Disease control rate includes the patients with complete response, partial response, or stable disease. Objective response rate includes the patients whose best response was complete response or partial response.

Table 2: Rucaparib activity

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Synthetic lethality with PARP inhibition

Titolo dello studio	Studio prospettico, multicentrico, di fase II, a braccio singolo, sulla combinazione Niraparib + Dostarlimab in pazienti con carcinoma polmonare non a piccole cellule avanzato e/o mesotelioma pleurico maligno, positivo per espressione di PD-L1 e mutazioni germinali o somatiche nei geni homologous recombination repair (HRR).
Fase dello studio	Fase II non randomizzato
Indicazioni cliniche	Terapia di seconda linea o successive in pazienti in progressione di malattia dopo almeno una precedente linea di terapia sistemica
Tipo di studio	Terapeutico, farmacologico
Sponsor	Università degli Studi di Torino
Coordinatore	Prof. Giorgio Vittorio Scagliotti – Dipartimento di Oncologia, Università di Torino
Farmaci	Niraparib + Dostarlimab
Via di somministrazione del farmaco	Orale (Niraparib); endovenosa (Dostarlimab)
Studio in cieco	No
Gruppi di trattamento	Cohorte A: NSCLC avanzato con mutazioni germinali e/o somatiche nei geni HRR ed espressione del PD-L1 ≥ 1% Cohorte B: Mesotelioma avanzato con mutazioni germinali e/o somatiche nei geni HRR ed espressione del PD-L1 ≥ 1%
Obiettivi	Primario: Sopravvivenza libera da progressione Secondari: Tasso di risposte obiettive; durata delle risposte obiettive; tasso di controllo di malattia; sopravvivenza globale; tollerabilità.
Numero di soggetti inclusi	Cohorte A: 35 pazienti Cohorte B: 35 pazienti

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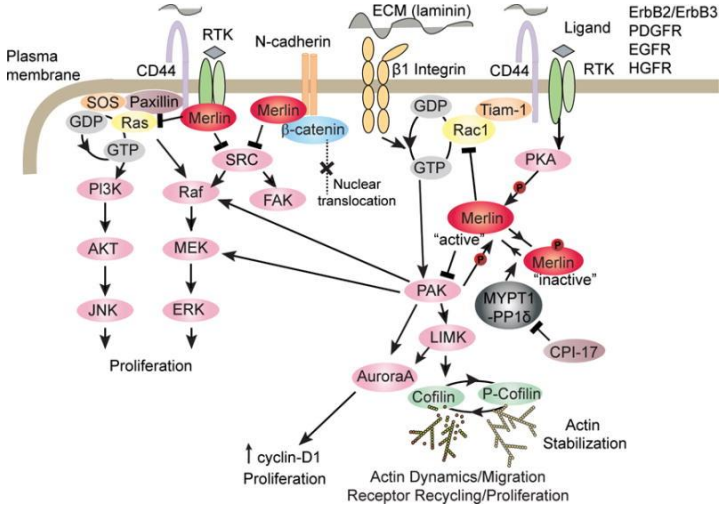
Neurofibromatosis type 2 (NF2)

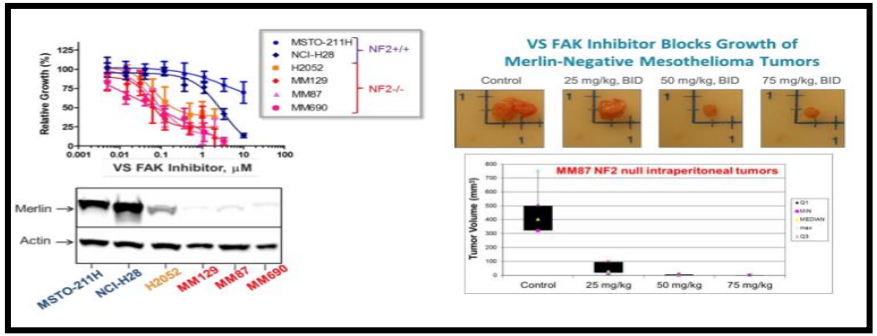
- Located on chromosome 22q12; encoding for the Merlin tumor suppressor protein
- Loss of function occurs in 40% to 50% of pts with mesothelioma
- Acts as a TSG in the NF2 associated tumors and merlin mutants promote tumorigenesis
- Interacts with several transmembrane and intracellular proteins
- Regulates cell motility, invasion and several RTKs
- Functions upstream of the Hippo signaling pathway that controls cell proliferation and survival and exerts merlin‘s inibitory effect on cancer growth & progression



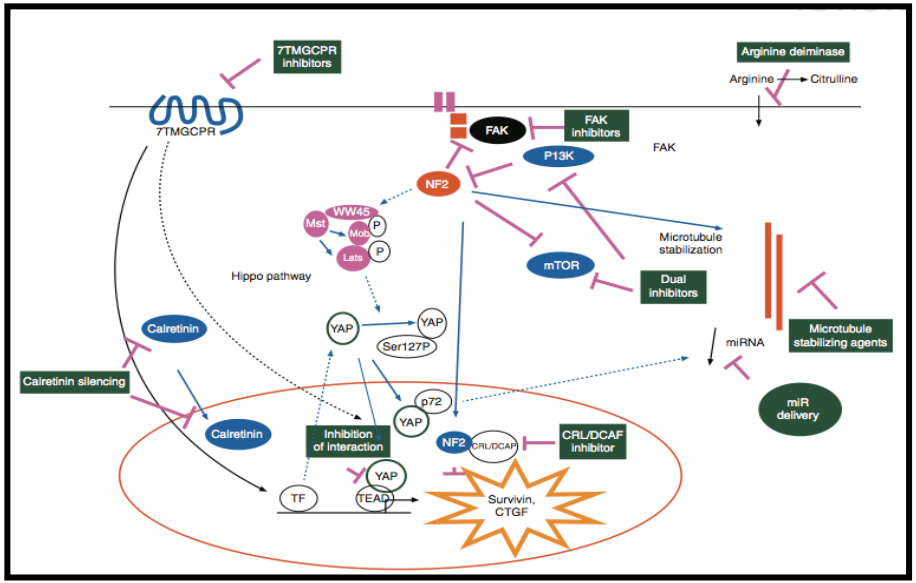
Neurofibromatosis type 2 (NF2)

Preclinical data indicate *NF2*-loss results in increased invasion and increased Focal adhesion kinase (FAK) expression

FAK is a non-receptor tyrosine kinase that mediates growth-factor and adhesion-dependent signaling.

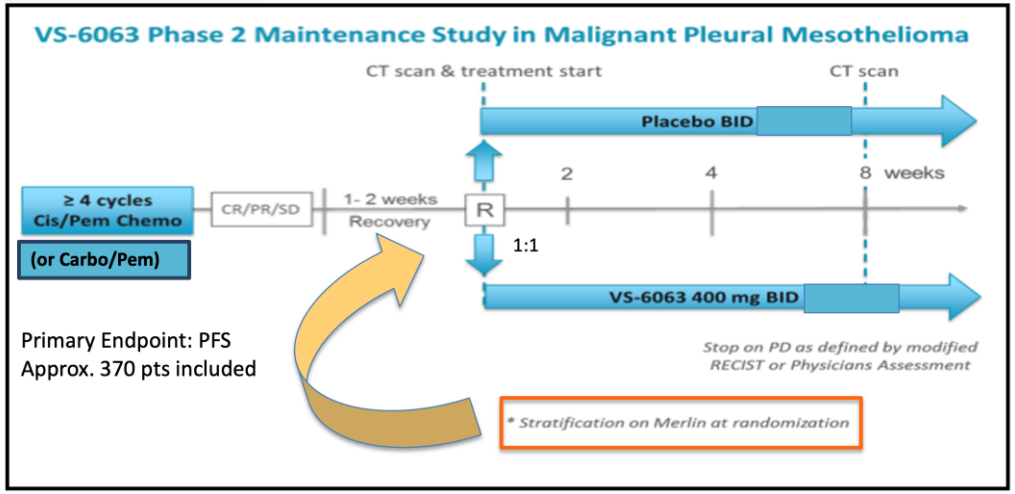


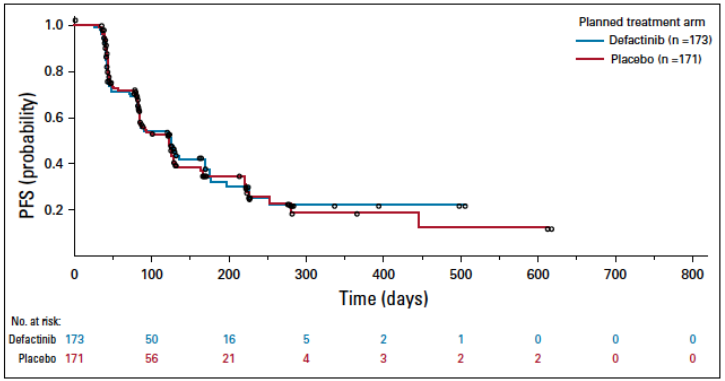
Shapiro et al., Science Transl Med 2014

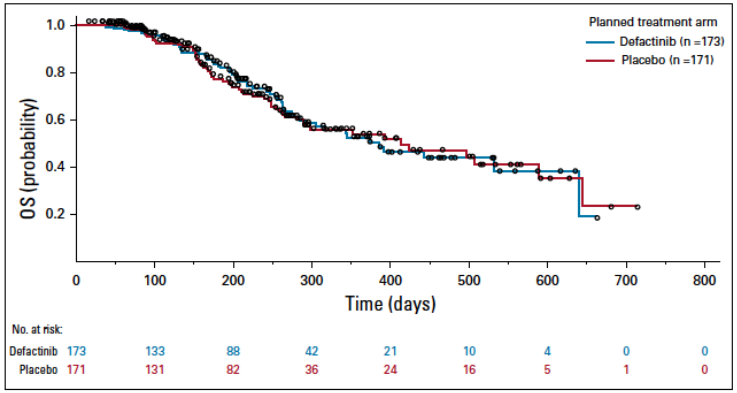


Thurneysen C, et al. Lung Cancer. 2009
Bianchi AB, et al. Proc Natl Acad Sci U S A. 1995
Sekido Y, et al. Cancer Res. 1995
Fleury-Feith J, et al. Oncogene. 2003
Poulikakos PI, et al. Oncogene. 2006.

Defactinib: COMMAND trial





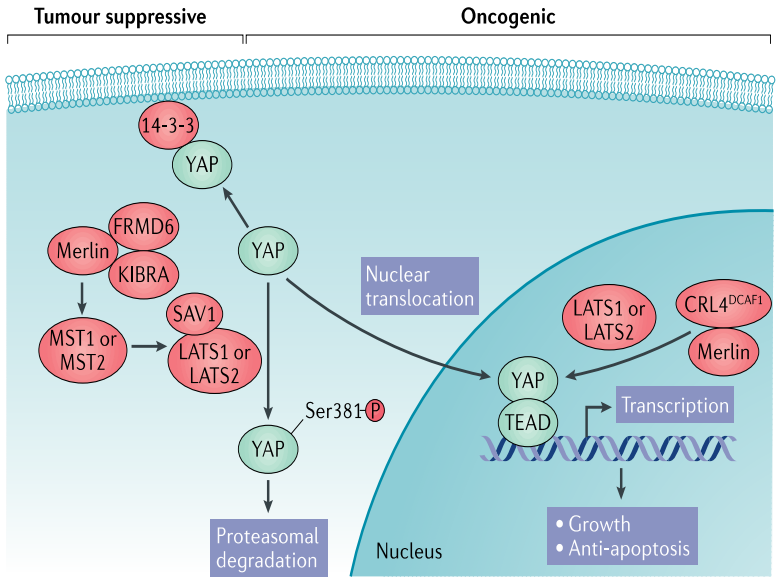


- NCT02004028: **Neoadjuvant study with Defactinib** in subjects with MPM eligible for surgery. Pre- and post-treatment biopsies and blood samples were collected with the purpose to assess biomarker responses from tumor tissue. Termined in June 2019.
- NCT02758587: A Phase I/IIA Study to Assess Safety, Tolerability and Preliminary Activity of the **Combination of FAK (Defactinib) and PD-1 (Pembrolizumab) Inhibition** in Patients With Advanced Solid Malignancies (FAK-PD1). Recruiting, end in 2021.

Fennel et al., J Clin Oncol 2019

NF2 and Hippo Pathway

- Merlin loss drives tumorigenesis by inhibiting the Hippo pathway component Lats resulting in constitutive activation of the YAP1/TAZ transcriptional coactivators
- YAP1/TAZ interact with several distinct transcription factors including TEA domain (TEAD) transcription factors
- **K-975 is a small molecule that inhibits TEAD and showed a potent inhibitory effect on the proliferation of MPM cell lines, with a greater activity on NF2-non-expressing cells.**



Yap TA et al, Nat Rev 2017

Kaneda et al, Am J Cancer Res 2020

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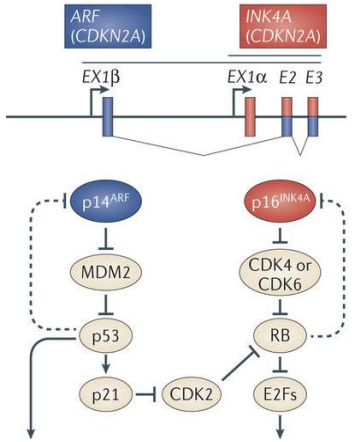
CDKN2A

- The most frequently activated tumor suppressor gene in MPM
  - Homozygous deletion in 50%
  - CDKN2A loss is associated with shorter survival and non-epithelioid histology
- CDKN2A encodes INK4A (p16) and ARF (p14)
- INK4A inhibits formation of the complex cyclin D1-CDK4/6 by binding to CDK4/6, maintaining Rb in its hypo-phosphorylated active form, with subsequent G1 cell cycle arrest
- **Deletion of the CDKN2A/ARF locus facilitates cell cycle progression, escape from apoptosis and immortalization**

Mechanisms of *CDKN2A/ARF* loss	
homozygous deletion	50-100%
epigenetic inactivation	19%
mutation	7 %



Cell cycle blockade DNA repair

Phase S genes induction

Modified from Sharpless NE, Nature Reviews Cancer 2015

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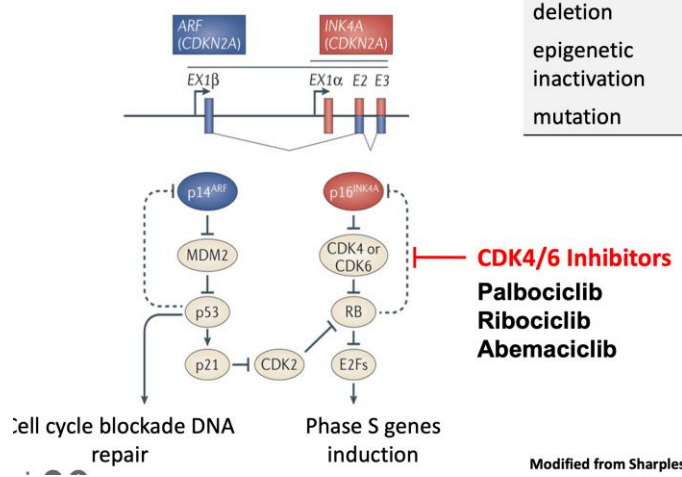
CDKN2A



CDK4/6 Inhibitors
Palbociclib
Ribociclib
Abemaciclib

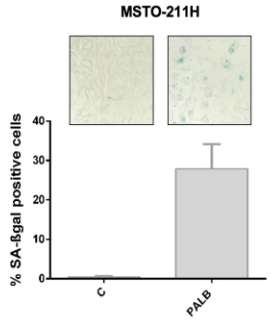
Mechanisms of *CDKN2A/ARF* loss	
homozygous deletion	50-100%
epigenetic inactivation	19%
mutation	7 %

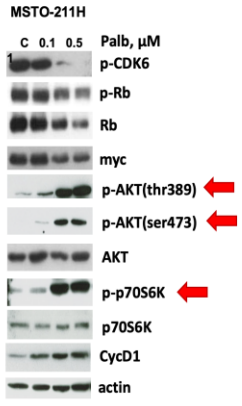
Modified from Sharpless NE, *Nature Reviews Cancer* 2015

MPM cell lines harbouring *CDKN2A/ARF* loss were sensitive to CDK4/6 inhibitors palbociclib and abemaciclib

	Histological subtypes	*cdkn2a /arf*	*bap1*	*nf2*	IC_{50} (μM) *Palb*	*Abe*
MSTO-211H	biphasic	del	wt	nd	0.3	0.13
H2452	epithelioid	del	mut	wt	0.7	1
H28	epithelioid	del	mut	wt	0.3	1
H2052	sarcomatoid	del	wt	mut	1.2	0.5
ZS-LP	biphasic	del	nd	nd	0.1	0.5

CDK4/6 inhibitors induced cell cycle blockade and cellular senescence in MPM cell lines





CDK4/6 inhibitors affected the activation of PI3K/AKT/mTOR pathway

Zhang J et al., Molecular Cell, 2016

Bonelli MA et al, *Neoplasia*, 2017

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Abemaciclib

Abemaciclib in patients with p16ink4A-deficient mesothelioma (MiST2): a single-arm, open-label, phase 2 trial

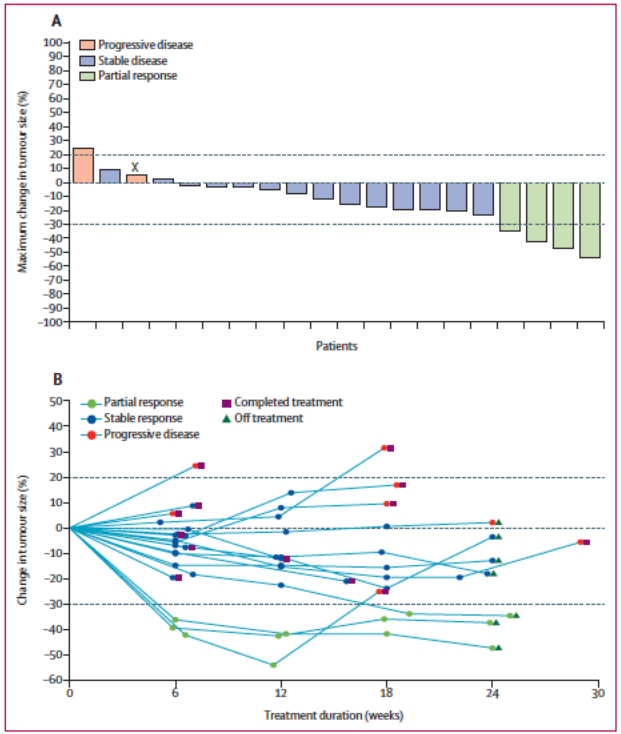
Dean A Fennell, Amy King, Seid Mohammed, Alastair Greystoke, Sarah Anthony, Charlotte Poile, Nada Nusrat, Molly Scotland, Vina Bhundia, Amy Branson, Cassandra Brookes, Liz Darlison, Alan G Dawson, Aarti Gaba, Margaret Hutka, Bruno Morgan, Amrita Bajaj, Cathy Richards, Peter Wells-Jordan, Anne Thomas, on behalf of the MiST2 study group

Disease control at 12 weeks was reported in 14 (54%) of 26 patients (95% CI 36–71).

	All patients (n=26)
Partial response	3 (12%; 3–27)
Stable disease	11 (42%; 26–60)
Progressive disease	2 (8%; 1–22)
Not evaluable	6 (23%; 9–44)
Disease control rate at 12 weeks	14 (54%; 36–71)

Data are n (%; 95% CI).

Table 2: **Best responses within 12 weeks**



This study met its primary endpoint, showing promising clinical activity of abemaciclib in patients with p16ink4A-negative mesothelioma who were previously treated with chemotherapy, and warrants its further investigation in a randomised study as a targeted stratified therapy.

Lancet Oncology 2022

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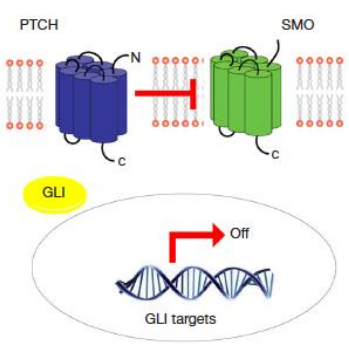
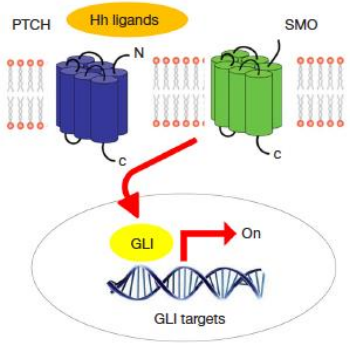
Hedgehog signaling

- **Hh is involved in cell proliferation, survival, epithelial-to-mesenchymal transition, stemness and differentiation during embryonic development.**
- Hh ligands bind to PTCH1 and PTCH2 receptors. If the ligand is absent, PTCH1 or PTCH2 binds to the SMO co-receptor, repressing its activity. Consequently, the transcription factors (GLI family) are not activated and transcription is stopped. In contrast, when the ligand binds to the receptor, the SMO repression is released, leading to transcriptional activation

Normally the Hh pathway is inactive in adult tissues





Signorelli et al, TLCR 2020

Hedgehog signaling

Table 4 Association between mutated genes in at least five patients and OS

Gene	HR (95% CI)	P
Any mutation-wild type	1.09 (0.71–1.67)	0.70
BAP1	1.14 (0.57–2.30)	0.73
NF2	1.16 (0.66–2.07)	0.60
TP53	0.91 (0.54–1.54)	0.36
SMO	4.36 (2.32–8.18)	<0.0001
PTCH1	1.16 (0.66–2.07)	0.71

OS is expressed as hazard ratio (HR) with 95% confidence interval (CI). Wild-type patients for the specific gene were used as reference to calculate P values.

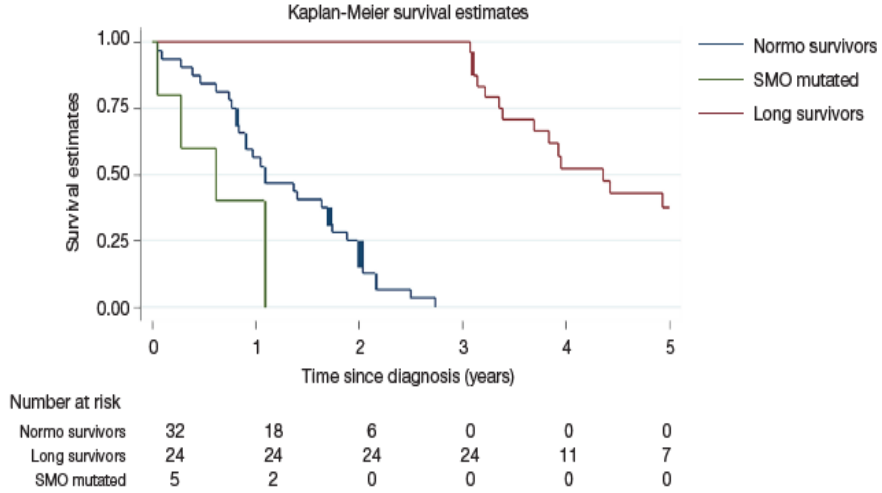
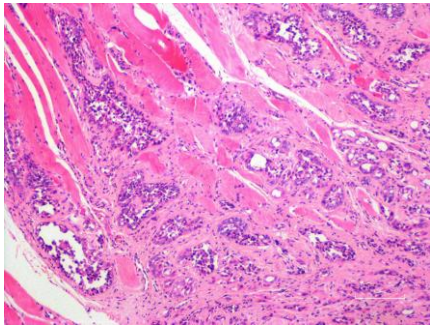


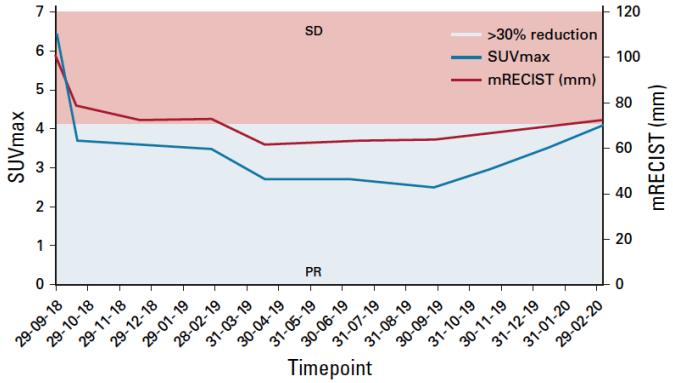
Figure 2 Kaplan-Meier survival estimates. Normo-survivors patients, OS ≤3 years, in blue; long survivors patients, OS >3 years, in red; SMO mutated patients in green.

Signorelli et al, TLCR 2020

Hedgehog signaling

- An aberrant hedgehog signaling is present in MPM, and inhibition of hedgehog signaling decreases tumor growth indicating potential new therapeutic approach



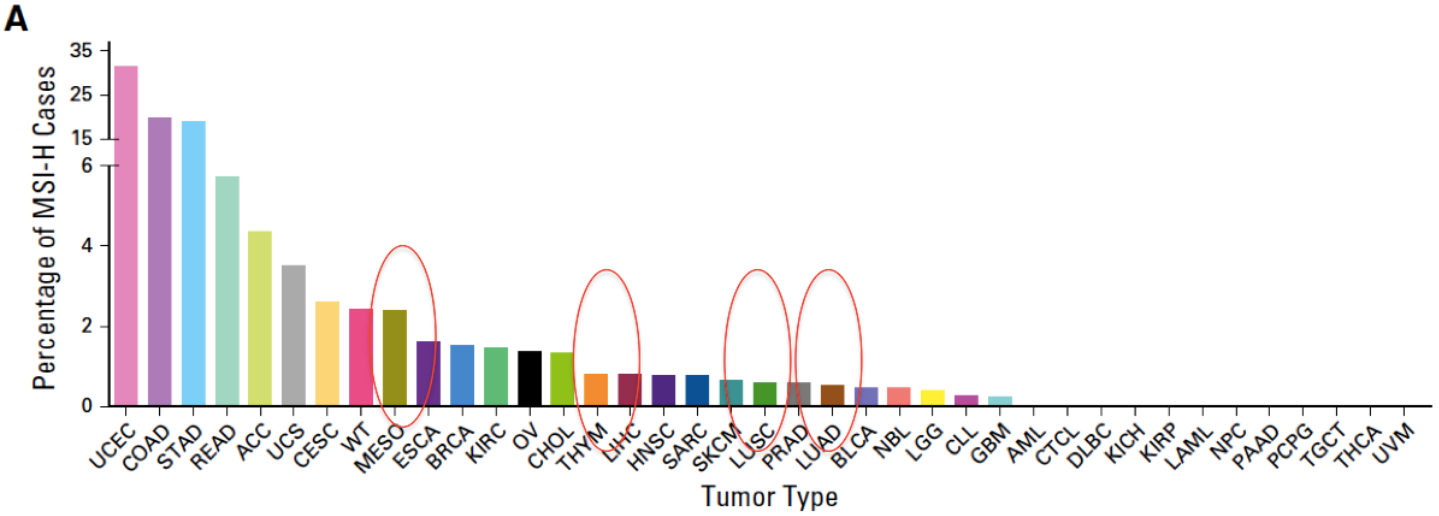


PTCH1 pathogenic mutation

- This gene is involved in the Hedgehog pathway and is druggable by vismodegib, already approved for the treatment of basal cell carcinoma (BCC)
- Despite the patient underwent several lines of treatment, vismodegib lead to a very good partial response which lasted for over two years

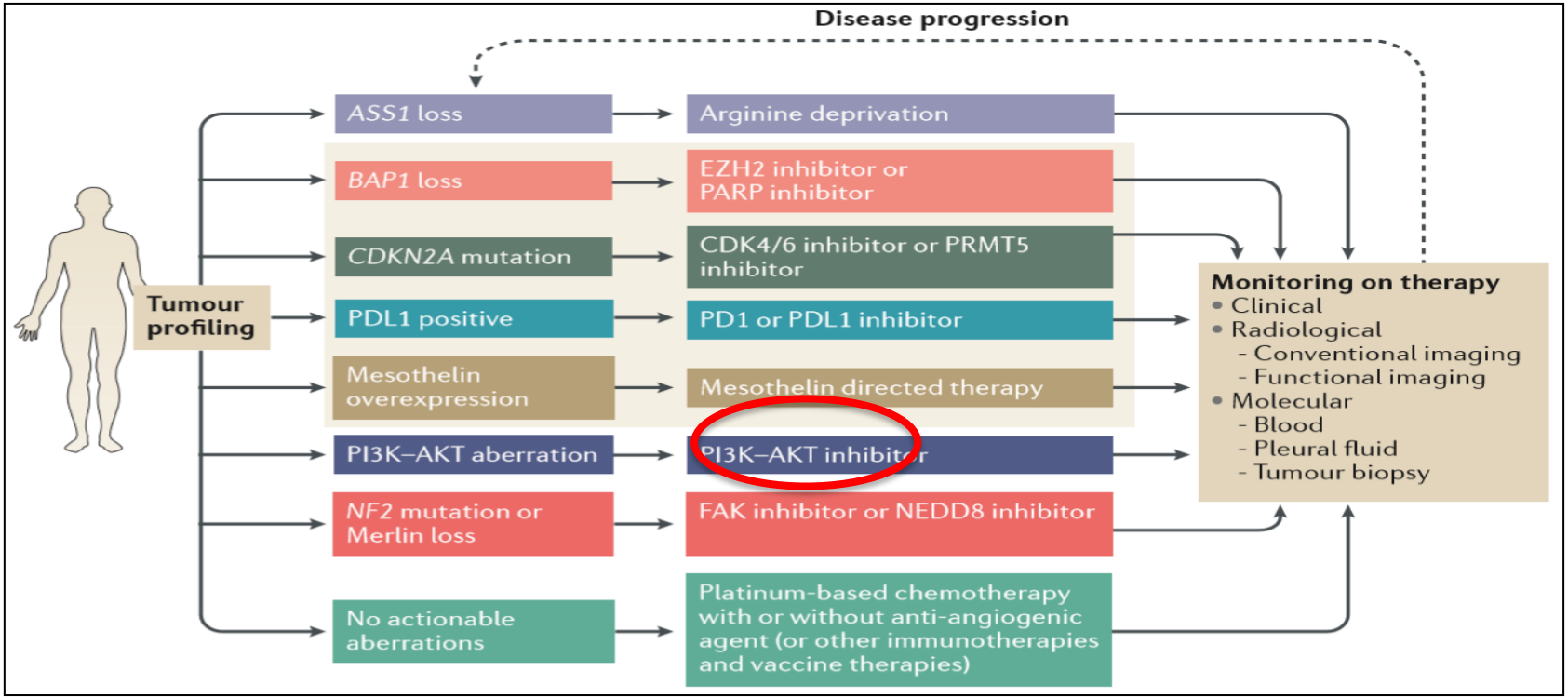
Popat, ASCO 2021

Landscape of Microsatellite Instability Across 39 Cancer Types



Bonneville et al, JCO Precision Oncology 2017

Other targets



Yap TA et al, Nat Rev 2017

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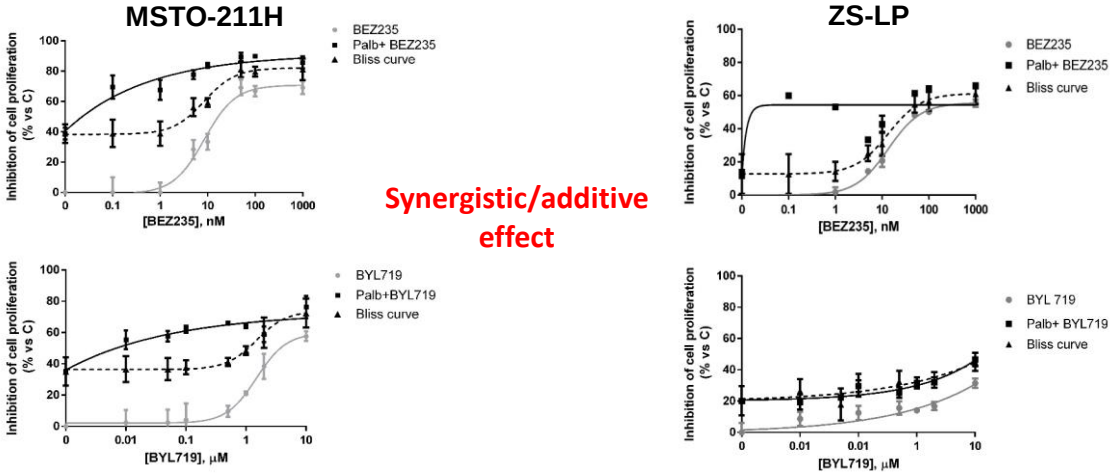
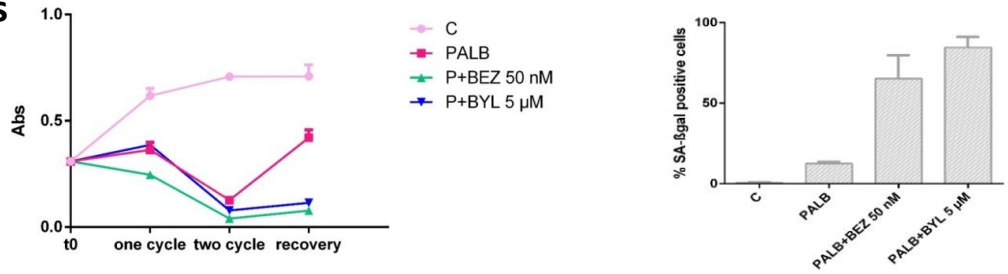
Anti-proliferative effect of the combined treatment with CDK4/6 and PI3K/mTOR inhibitors NVP-BEZ235 and NVP-BYL719



Anti-proliferative effect and senescence induction were mantained after drug withdrawal only with the combined tretament with CDK4/6 and PI3K/mTOR inhibitors



Bonelli MA et al, Neoplasia 19(8):637-648, 2017

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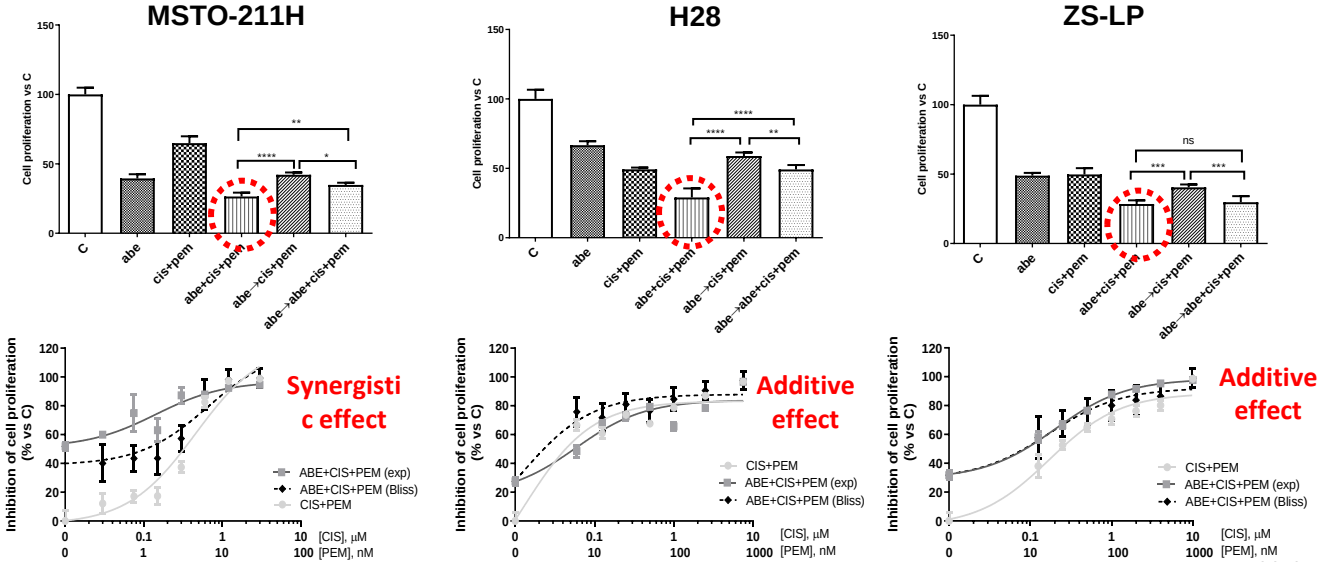
CDK4/6 inhibitors in association with standard chemoterapy used as first line treatment for MPM patients

simultaneous treatment

sequential treatment

sequential combined treatment



Unpublished data

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- **Loss of *CDKN2A/ARF* is a common alteration in MPM**
- The CDK4/6 inhibitors induced cell growth arrest in sensitive MPM cells
- **The sequential combined association of palbociclib with PI3K/mTOR** inhibitors showed a synergistic interaction on the inhibition of cell growth and had an irreversible effect on the inhibition of cell proliferation and the induction of senescence.
- The combination of palbociclib and PI3K/mTOR inhibitors affected cell metabolism, by reducing GLUT-1 expression and glucose uptake
- **The combined treatment of abemaciclib with cisplatin and pemetrexed shows an additive/synergistic inhibiton of cell proliferation in MPM cell lines**
- In addition, the association of abemaciclib and chemotherapy induces senescence or autophagy, depending on MPM cells.

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Conclusions

- Genetic alterations were identified in several tumor suppressor genes (TSG), but not in oncogene drivers.
- **Mutations in BAP1, CDKN2A, and NF2** have been reported in a high percentage of MPM and TP53 has been found mutated at a lower rate in comparison with other human cancers
- The **biological diversity of MPM** is also suggested by the difficulty to define single specific biomarkers
- Interesting results with PARP-inhibitors and CDK4/6 inhibitors
- Potential future with molecular screening also in MPM

Mesothelioma Stratified Therapy (MiST) study design

Trials.gov ID NCT03654833

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

Molecular/ Phenotypical Pre-screening*

Arm		
1	BAP1/BRCA1 -	Rucaparib*
2	p16INK4A-	Abemaciclib**
3	N/A	Bemcentinib Pembrolizumab
4	PDL1	Atezolizumab Bevacizumab
5	DNA damage sensitiive	Niraparib Dostarlimab

DNA and RNA sequencing (arms 1-5)

Gut microbiome (arms 3-5)

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

* Fennell et al, Lancet Resp Med 2021

** Fennell et al, *Journal of Clinical Oncology* 39, no. 15_suppl (May 20, 2021) 8558-8558 (ASCO)

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

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Grazie per l'attenzione

marcello.tiseo@unipr.it