Cancéropôle Ile de France
13 mars 2025

Mesotheliome Pleural & mutations BAP1

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G. Zalcman liens d'intérêt

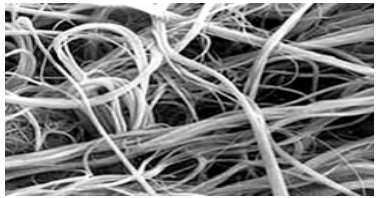
Investigateur d'essais de phases I, II & III à promotion industrielle par Lilly, GSK, Roche, MSD, Merck-Serrono, Pfizer, Astra-Zeneca, Sanofi-Aventis, Pierre Fabre, Boerhinger, BMS, Novartis, Ariad, Takeda, Roche sans paiement personnel, **tous les honoraires investigateur étant perçus par mes Institutions** (AP-HP.Nord, Hôpital Bichat, CIC 1425 INSERM, Fondation Recherche de l'AP-HP), ou par l'Intergroupe Francophone de Cancérologie thoracique (IFCT) en accord avec leurs statuts et objectifs de recherche...

SUBVENTIONS ou AVANTAGES COLLECTIFS	PAIEMENTS Personnels ou AVANTAGES
Lilly, Roche, Pfizer, Astra-Zeneca, Sanofi-Aventis, GSK, BMS, Amgen, Chugaï, Pierre Fabre, Borhinger-Ingelheim, Merck-Serono, Chugai, Novartis, Janssen-Cilag, MSD **(Subventions For Intergroupe Francophone de Cancérologie Thoracique, IFCT, dont GZ est Président honoraire** **Roche a fourni le bevacizumab et accordé une subvention de recherche à l'IFCT pour les études de biomarqueurs de l'essai MAPS (PI: GZ).** **BMS a fourni le Nivolumab et l'Ipilumumab et accordé une subvention de recherche à l'IFCT pour l'essai MAPS2 (PI: GZ).** **Regeneron fournit le Fianlimab et le Cemiplimab plus unbe subvention de recherche à l'IFCT pour l'essai LAG-MAPS (co-PI: GZ)** Roche, Astra-Zeneca, Pfizer, MSD, Borhinger-Ingelheim, Inventiva, BMS, Da Volterra, Sanofi: Honoraire pour reunion de conseil ou presentations didactiques payés à la **Fondation Recherche de l'AP-HP**	**Invitations, voyage et hébergement pour des congrès internationaux (ASCO, ESMO, ERS, ELCC AACR, WCLC)** : Roche, MSD, BMS, Astra-Zeneca, Lilly, Pfizer, Abbvie **Honoraires pour participation à des reunions de conseil scientifique ou de conseil, organisés par** Lilly, Astra-Zeneca, BMS, Pfizer, Roche, MSD, Boerhinger, Inventiva, Paredox Therapeutics, Elsevier-Masson **Le montant total de ces paiements perçus n'excède pas 15 000 Euros dans les 10 dernières années.**

PM epidemiology

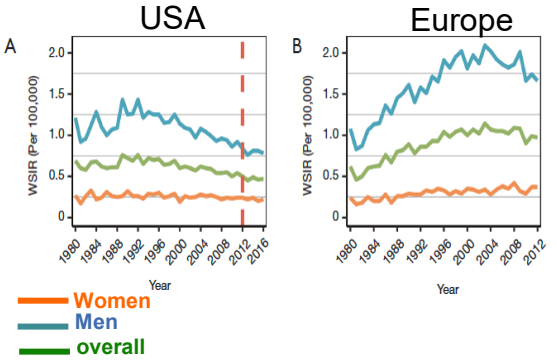
A causal agent: Inhaled **asbestos** mineral fibers (95% Chrysotile)

Chrysotile – White, fine, silky, flexible = **serpentine**



friction and thermic isolation

Rare cancer, orphan disease



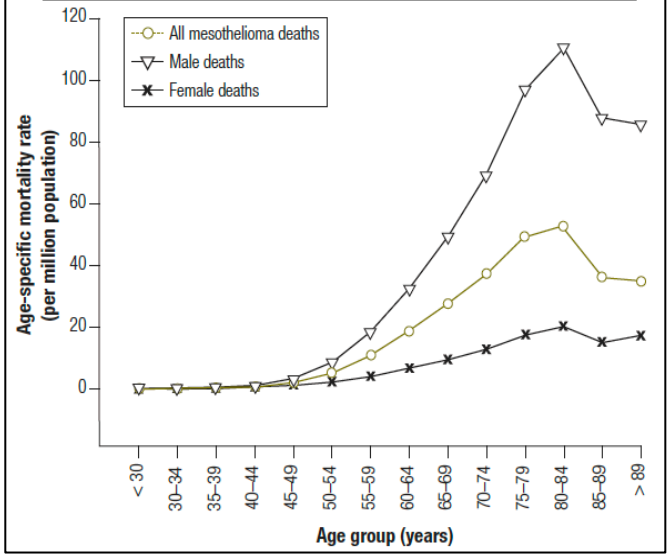
2.14 / 1000 000/ year

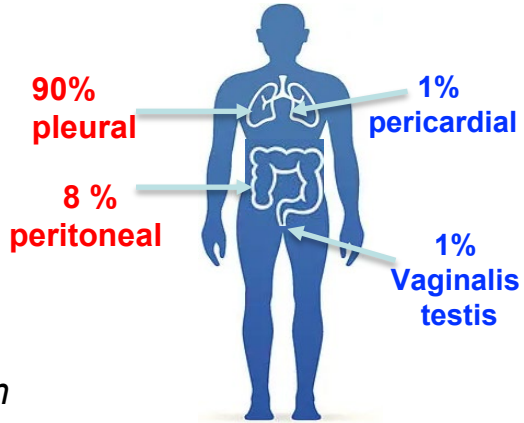
900-1100 /year in France

3000/ year in UK

- < 1 case / million inhabitants / year, in non-exposed population
- 100 cases/million inhabitants /year in occupational-exposed population

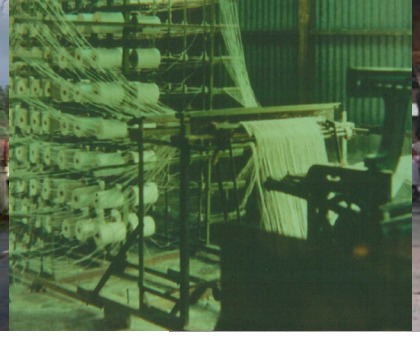
Long latency, elderly patients



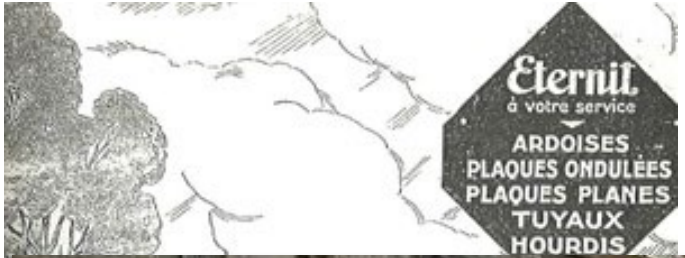


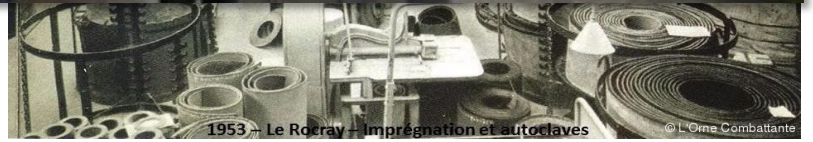
w/o asbestosis exposure: post thoracic RT for Hodgkin

Roche d’amiante



Condé sur Noirau (61)





1953 – Le Rocray – Imprégnation et autoclaves

© L'Orne Combattante

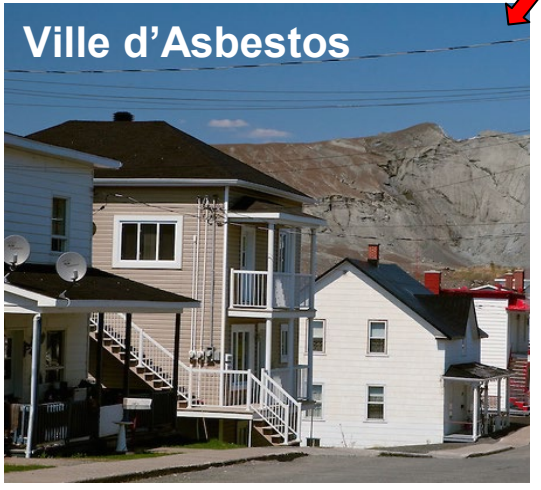

MMMTM


1955


1939


1918

Canada (Quebec)



Epidemiologie du MP

Nombreuses professions exposées

Ouvrier de la fabrication de produits en amiante-ciment
Maçon-fumiste industriel
Calorifugeur à la machine (bâtiment)
Ajusteur-monteur de moteurs marins
Calorifugeur à la main (bâtiment)
Docker
Charpentier en fer, construction navale
…teurs de fours de 2eme fusion et fours à
…navire
… four de verrerie
…rs-monteurs, installateur de machines et mécaniciens de précision
Tuyauteur, en général
Tôlier-chaudronnier, en général
Mécanicien d'entretien d'établissements
Soudeur au chalumeau et à l'arc électrique, en général
Manœuvre
Manutentionnaire
Ajusteur-électricien, en général
Ajusteur en construction mécanique, en général

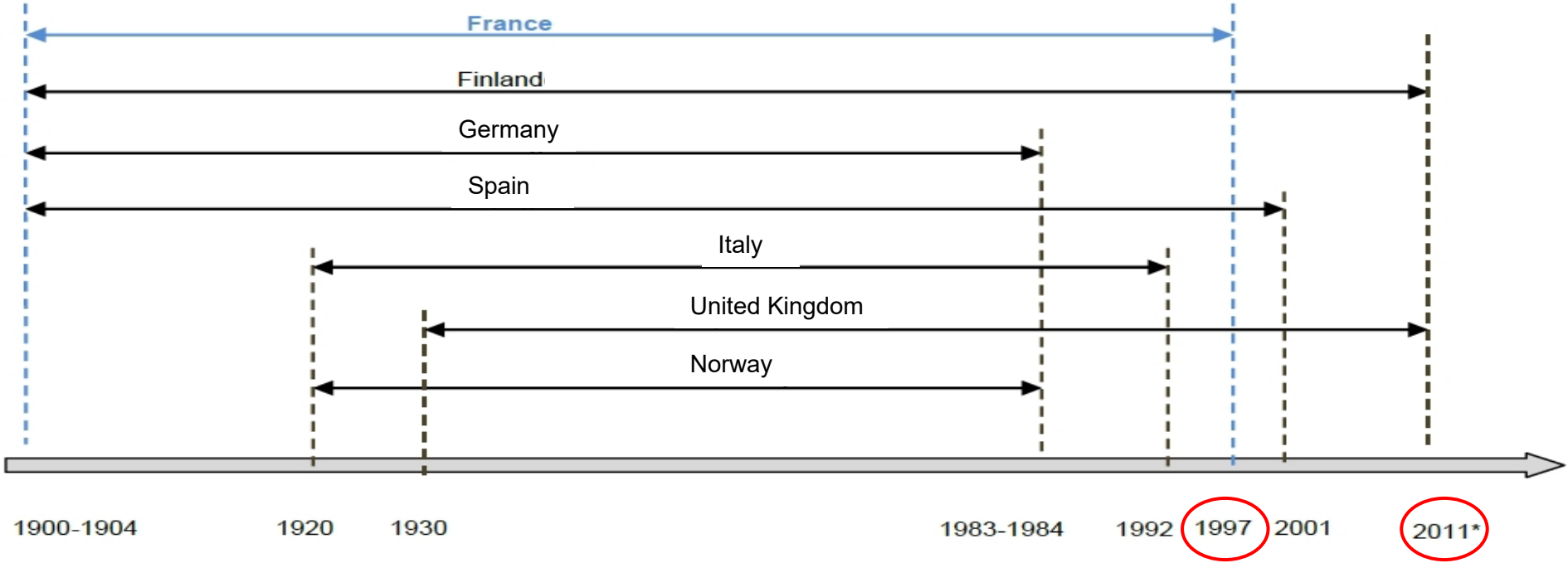
Femmes résidant dans les régions des mines de chrysotile, Québec :

Standardized Mortality Ratio$_{\text{cancer pleural}}$ = 7,6 [3,0-15,7]

(Camus et al, 1998)

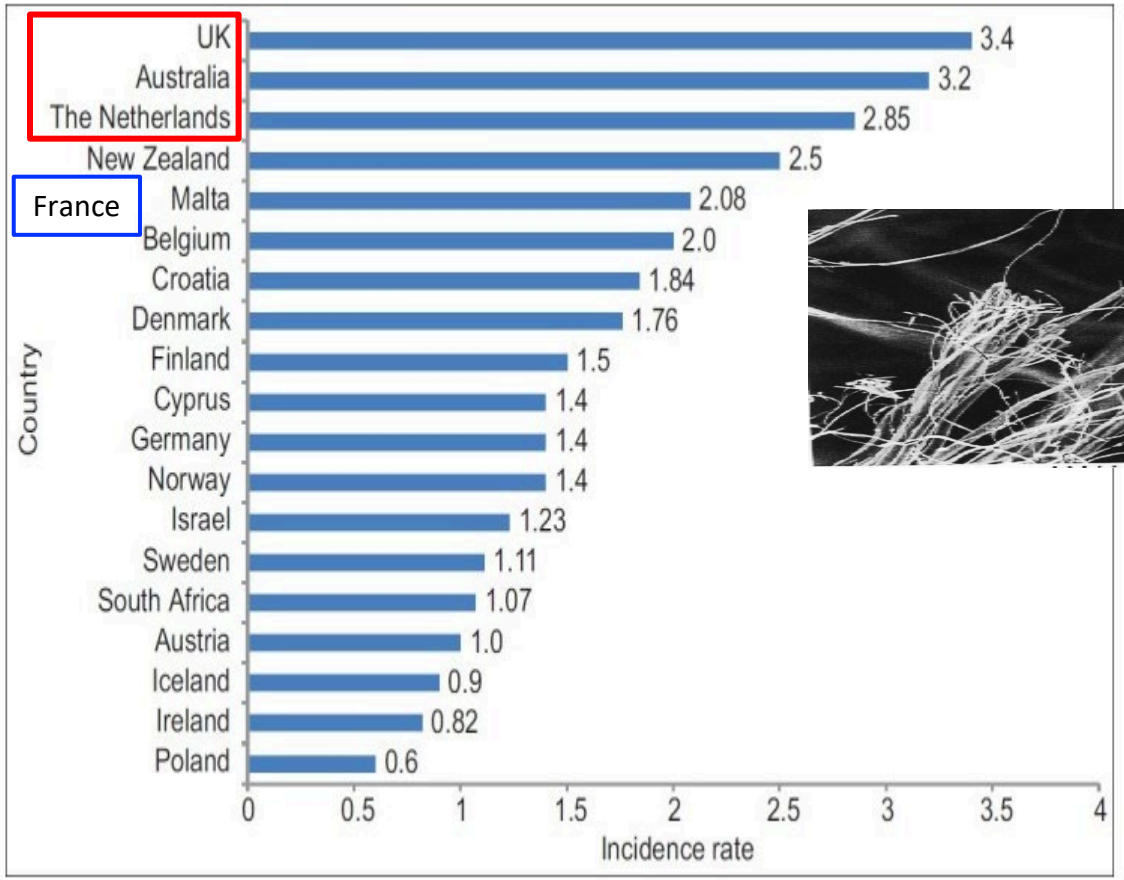
PM epidemiology

28 years ago France banned asbestos use in Industry



Epidemiology

France= 2,14/100 000 hab

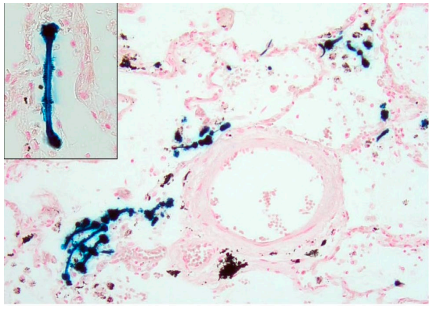


Global mesothelioma epidemic: Trend and features

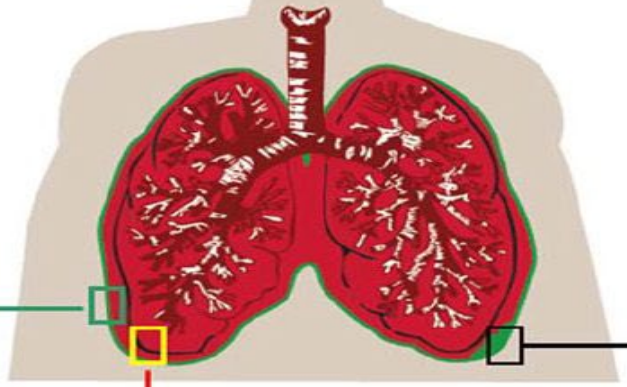
Indian J Occup Environ Med. 2014 May-Aug; 18(2): 82–88.

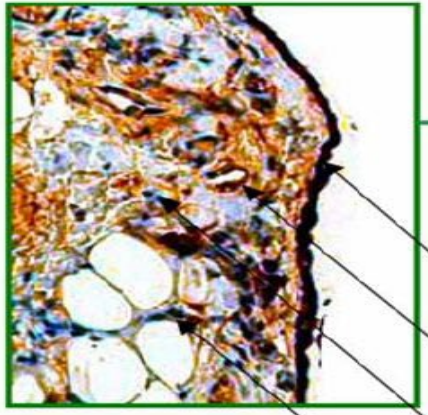
Worker in an asbestos processing unit (India, *18/06/2004)*

Chinese Asbestos Textile Workers



Pleura mesothelioma begins in PARIETAL pleura





Parietal pleura

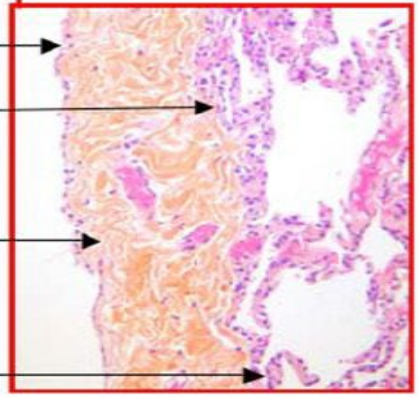
Mesothelium

Vascular endothelium

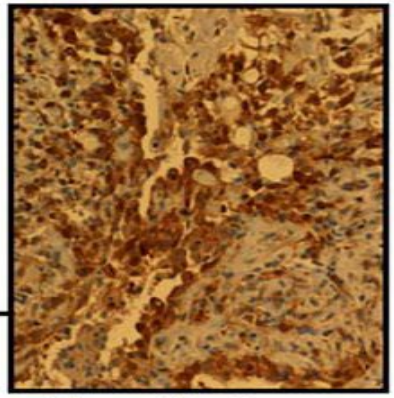
Stroma with Fibrocytes, fibroblasts and collagen

Fat cells

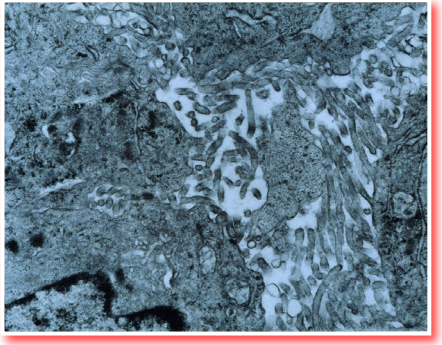
Alveolar cells



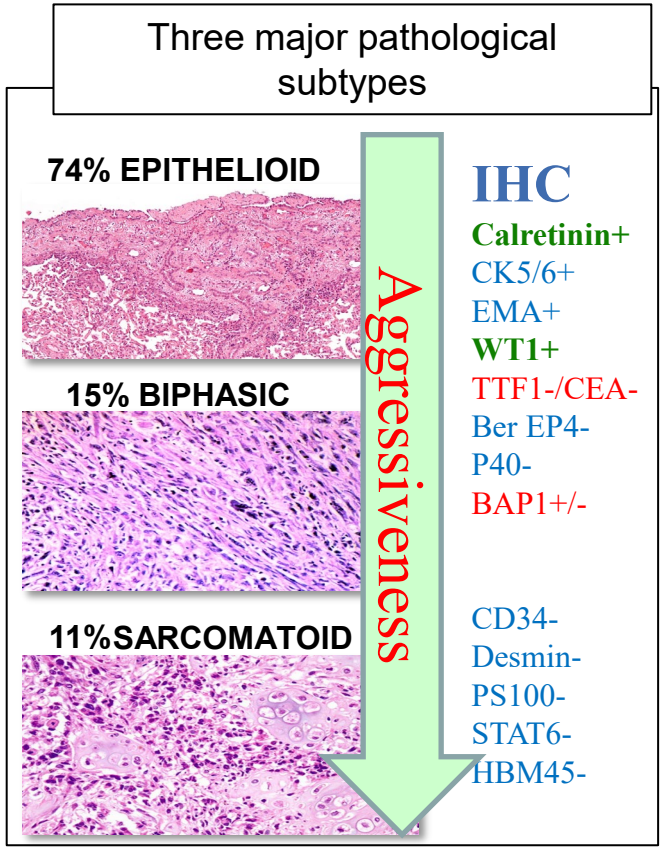
Visceral pleura



Mesothelioma
(>80% tumour cells)



Diffuse Mesothelioma =malignant



Chan JKC et al.
Pleural and pericardial tumours. In: WHO Classification of tumours. 5e éd. Lyon: International Agency for Research on Cancer, 2021

- **Mesothelioma *in situ concept***

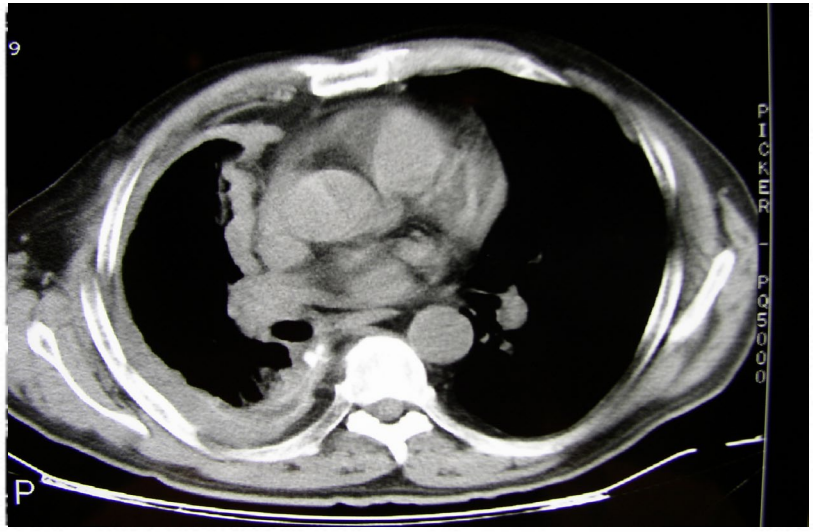
  = BAP1 loss, CDKN2A (p16) loss w/o visible stromal invasion
  (beware superficial samplings)

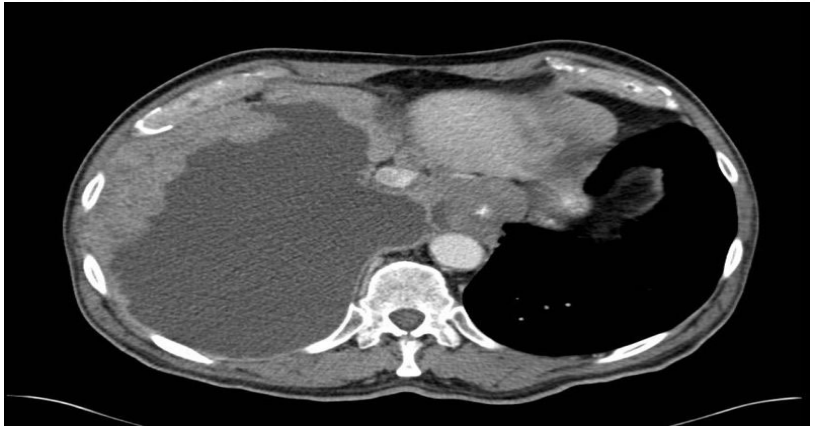
Table 1. 2021 WHO Classification of Tumors of the Pleura and Pericardium: ICD-O Coding and Terminology

Tumors	ICD-O Code[a]
Mesothelial tumors	
Benign and preinvasive mesothelial tumors	
Adenomatoid tumor	9054/0
Well-differentiated papillary mesothelial tumor	9052/1[b]
Mesothelioma in situ	9050/2[c]
Mesothelioma	
Localized mesothelioma	9050/3[b]
Diffuse mesothelioma, NOS	9050/3[b]
Sarcomatoid mesothelioma	9051/3
Epithelioid mesothelioma	9052/3
Mesothelioma, biphasic	9053/3

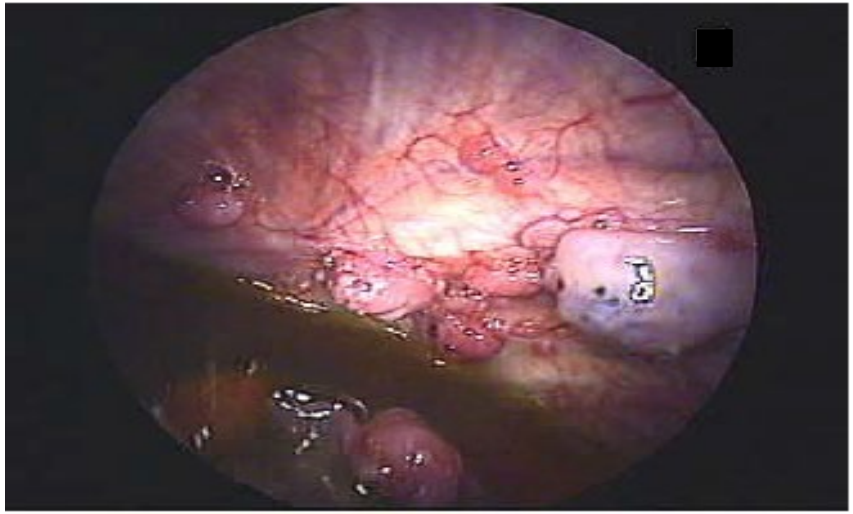
The 2021 WHO Classification of Tumors of the Pleura: Advances Since the 2015 Classification. Journal of Thoracic Oncology. Sauter JL et al.

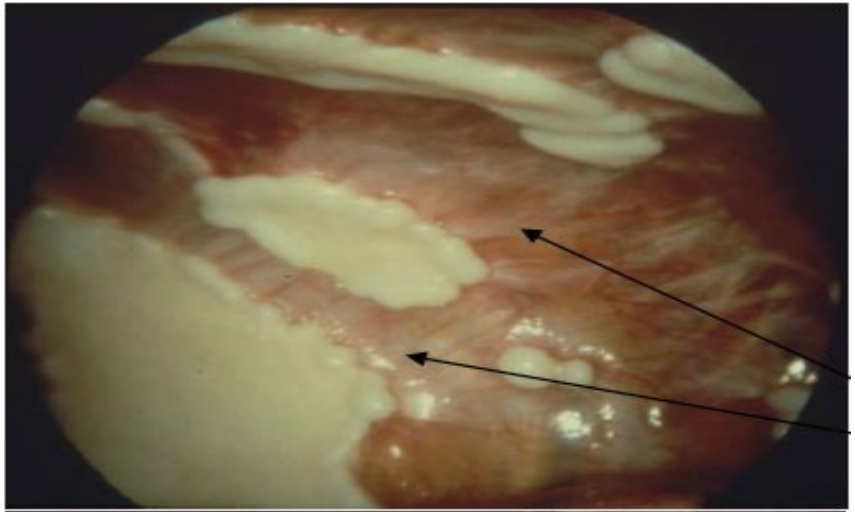
Key radiological examination: injected CT-scan with arterial & portal time





Pleuroscopic features

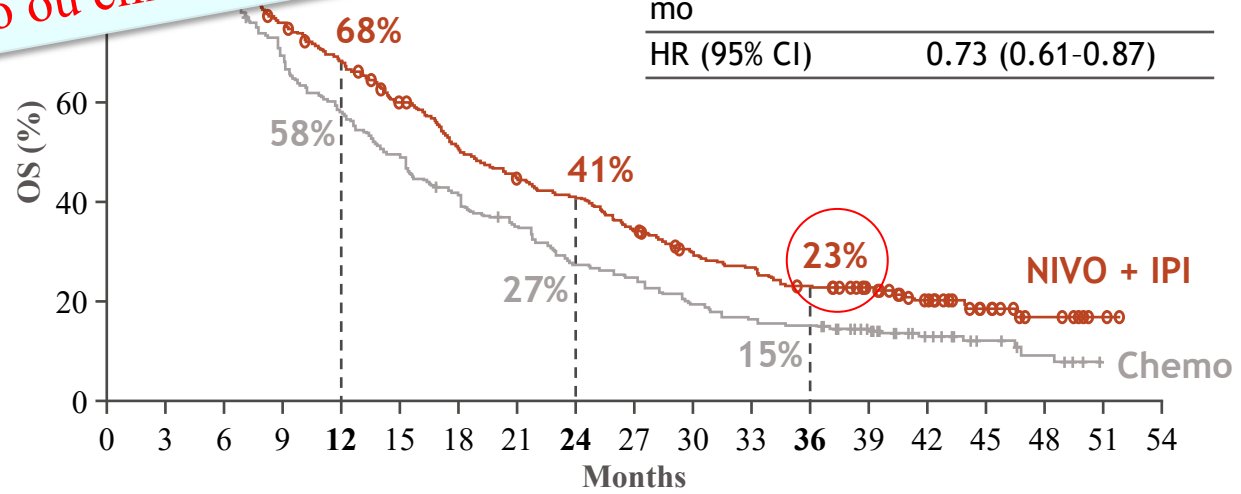




3-year update CheckMate-743

Un plateau de survie autour de 18-19 mois de médiane: double immuno ou chimio-bevacizumab

	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS,[a] mo	18.1	14.1
HR (95% CI)	0.73 (0.61-0.87)	



No. at risk

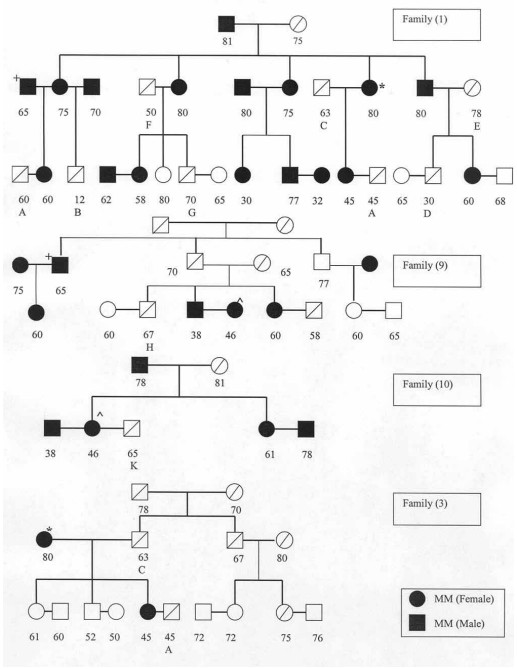
NIVO + IPI	303	273	251	226	200	173	145	126	116	97	80	73	62	49	35	18	7	2	0
Chemo	302	269	234	192	164	138	114	97	76	69	54	46	43	33	20	11	6	0	0

Minimum follow-up: 35.5 months.

Subsequent systemic therapy was received by 45% of patients in the NIVO + IPI arm and 42% in the chemo arm; subsequent immunotherapy was received by 4% and 22%, and subsequent chemotherapy by 43% and 33%, respectively.

[a]95% CIs were 16.8–21.0 (NIVO + IPI) and 12.4–16.3 (chemo).

BAP1 history in Mesothelioma : Gene x Environment Interaction (Michele Carbone)



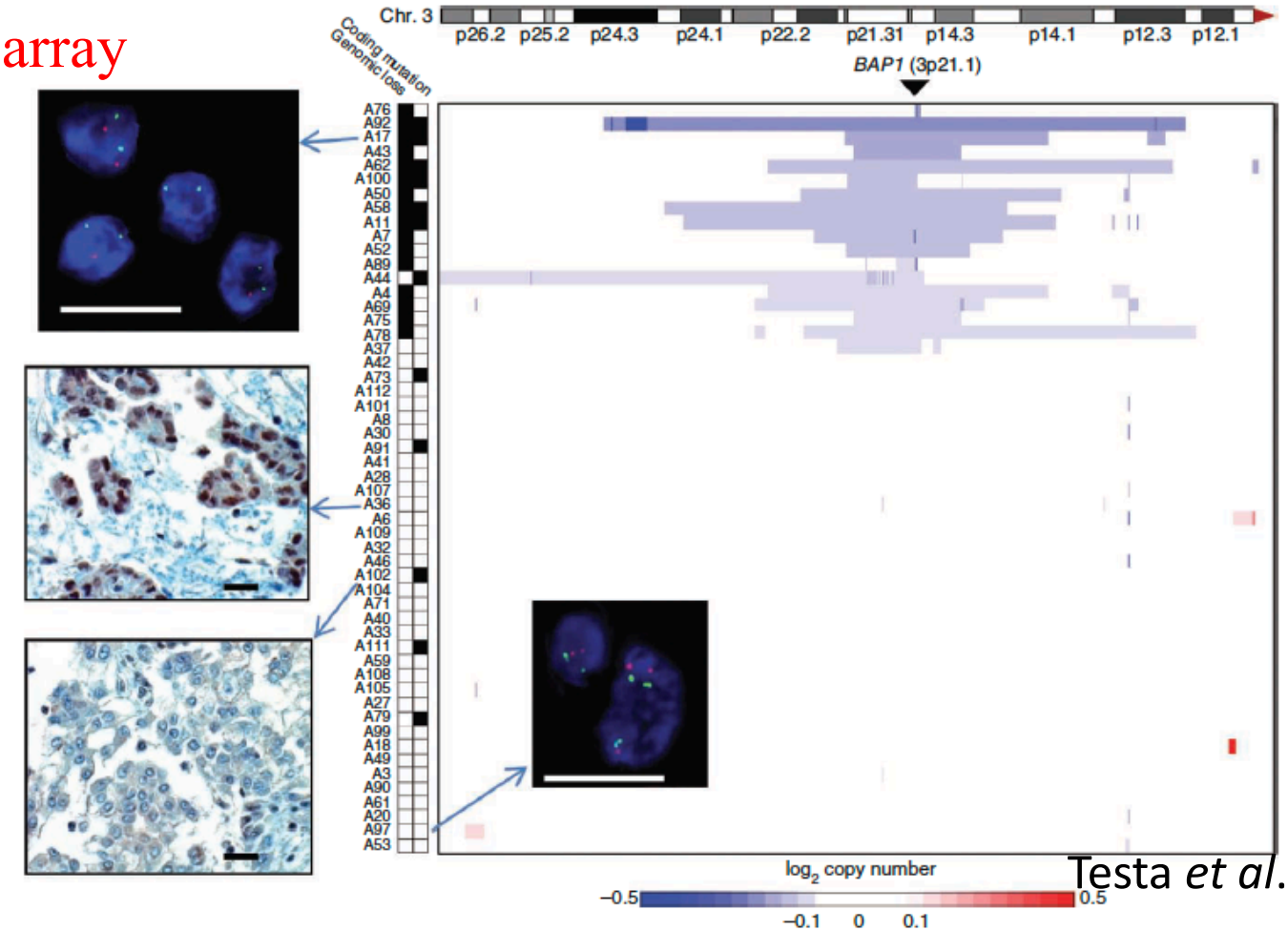
Transmission **mendélienne** de la susceptibilité au MP
(50% des exposés)

Roushdy-Hammady and Carbone M., The Lancet 2001; Carbone M et al. Nat. Rev Cancer 2007

Old Sarihidir

Marche sur le chromosome 3p

cgh array



Familial Linkage analysis=>3p21

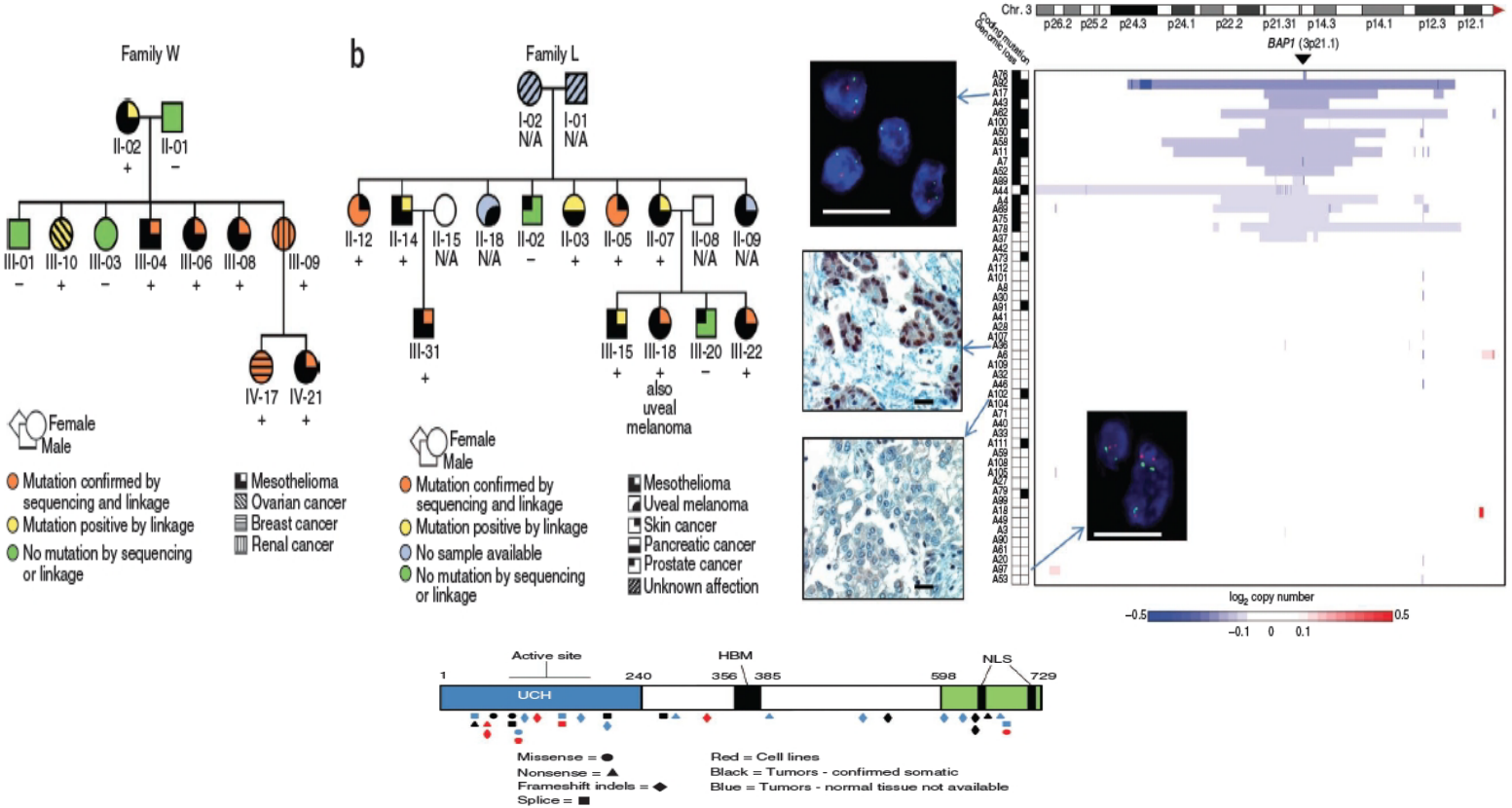
2 individus avec mélanome uvéal

BAP1 identifié dans mélanome uvéal sur 3p21

Candidate gene Approach: sequencing

Testa *et al*. Nature Gen. 2011

BAP-1, un nouveau gène suppresseur de tumeur en 3p21.1



Testa JR et al. Nat Gen. 2011,

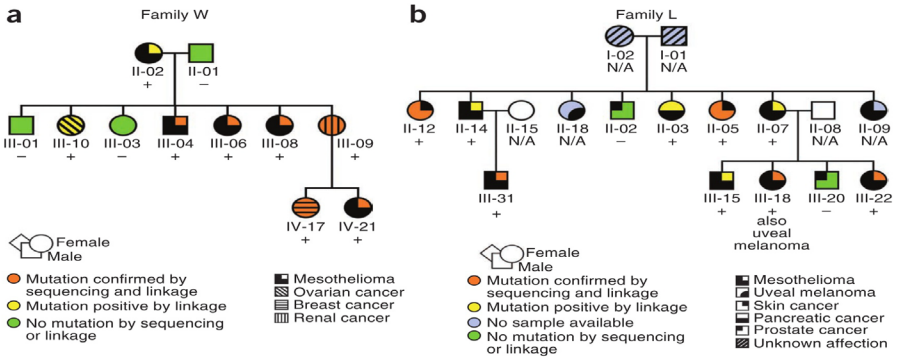
Bott. M et al. Nat Gen 2011

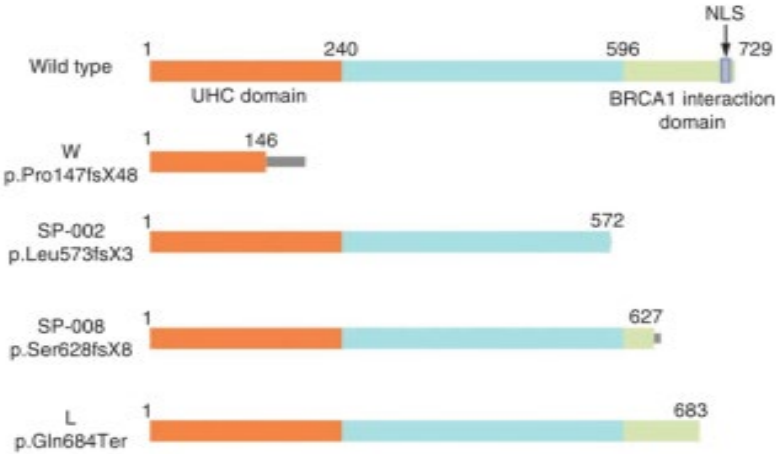
“BAP1 cancer syndrome” with 100% penetrance

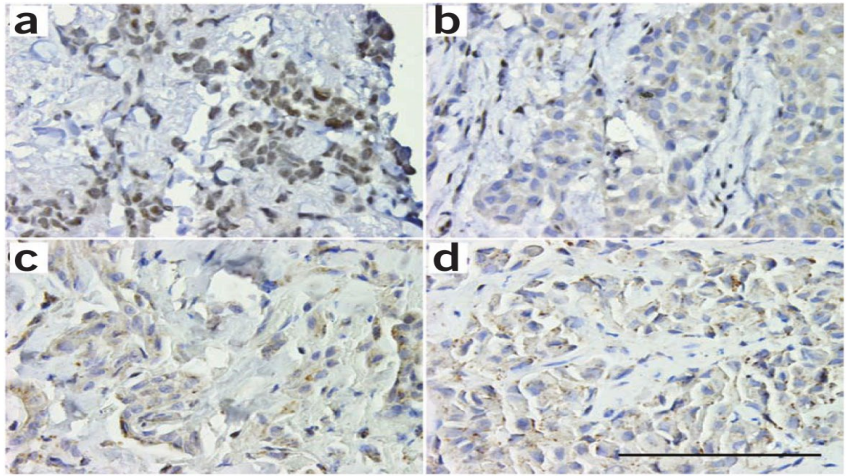
Germline *BAP1* mutations predispose to malignant mesothelioma

Joseph R Testa[1], Mitchell Cheung[1], Jianming Pei[1], Jennifer E Below[2], Yinfei Tan[1], Eleonora Sementino[1], Nancy J Cox[2,3], A Umran Dogan[4,5], Harvey I Pass[6], Sandra Trusa[6], Mary Hesdorffer[7], Masaki Nasu[8,9], Amy Powers[8], Zeyana Rivera[8,9], Sabahattin Comertpay[8,9], Mika Tanji[8,9], Giovanni Gaudino[8], Haining Yang[8,10] & Michele Carbone[8]

Nature Genetics, 43, 2011; 561







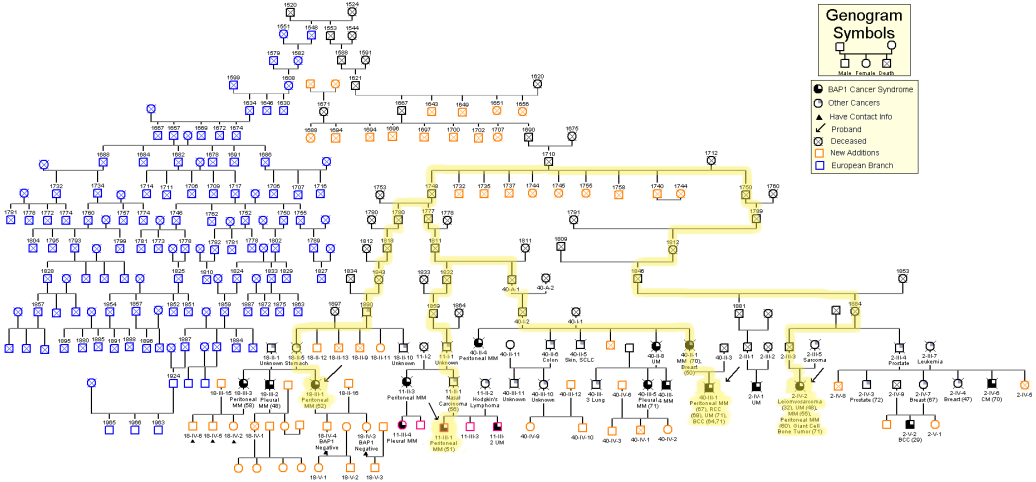
PLOS | GENETICS

4 familles US
non apparentées

RESEARCH ARTICLE

Combined Genetic and Genealogic Studies Uncover a Large BAP1 Cancer Syndrome Kindred Tracing Back Nine Generations to a Common Ancestor from the 1700s

Michele Carbone[1☯*], Erin G. Flores[1☯], Mitsuru Emi[1☯], Todd A. Johnson[2], Tatsuhiko Tsunoda[2], Dusty Behner[1], Harriet Hoffman[3], Mary Hesdorffer[4], Masaki Nasu[1], Andrea Napolitano[1], Amy Powers[1], Michael Minaai[1], Francine Baumann[1], Peter Bryant-Greenwood[1], Olivia Lauk[5], Michaela B. Kirschner[5], Walter Weder[5], Isabelle Opitz[5], Harvey I. Pass[6], Giovanni Gaudino[1], Sandra Pastorino[1], Haining Yang[1*]



181 familles recensées dans le Monde

Suisse alémanique & Allemagne

K4 original home built in 1488

Les mutations germinales de BAP1 définissent un nouveau syndrome de susceptibilité aux tumeurs associant mélanome uvéal et mésothéliome

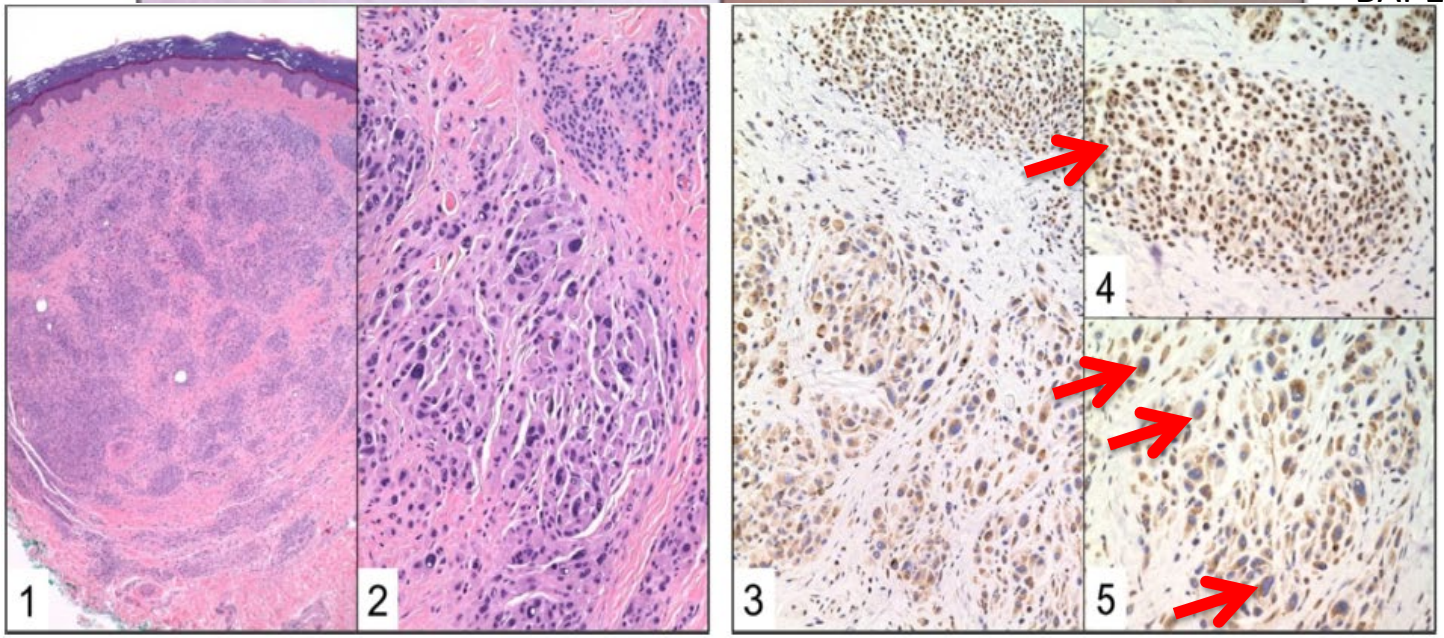
Tumors with somatic BAP1 mutations

Tumor type	Total tumors analyzed	Tumors with somatic *BAP1* mutations *n*	%	Ref(s).
Melanocytic				
Common nevi	29	0	0.0	
Spitz nevi	17	0	0.0	
Atypical Spitz nevi	18	2[a]	11.1	
Cutaneous melanoma	60	3	5.0	
Uveal melanoma, total	93	41	44.1	
Wiesner *et al.* study	33	13	39.4	
Harbour *et al.* study	60	28	46.7	
Low metastatic risk	26	1	3.8	
High metastatic risk	31	25	80.6	1
Metastatic	3	2	66.7	1
Mesothelioma, total	139	28	20.1	4,2
Testa *et al.* study	18	4	22.2	4
Bott *et al.* study	121	24	19.8	2
Breast	251	1	0.6	5,6
Lung	322	2	0.4	5,6
Ovary	59	2	3.4	5,6
Pancreas	30	0	0.0	5,6

[a]These tumors had morphologic features similar to the melanocytic tumors observed in families 1 and 2 of ref. 3.

75% of BAP1 carriers

BAP1 IHC



JAMA Dermatology | Original Investigation

Genotypic and Phenotypic Features of BAP1 Cancer Syndrome

A Report of 8 New Families and Review of Cases in the Literature

215 cas

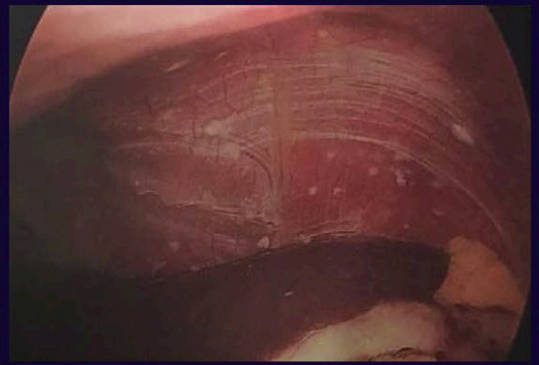
ne

Tumor	Cases, No.	Estimated Penetrance, %[a]	Median Age of Diagnosis in the Literature, y	Median Age of Diagnosis in Our Series, y	Median Age of Diagnosis in General Population, y
Uveal melanoma	60	28.0	53	59	61[15]
Mesothelioma	48	22.0	56	46	74[15]
Cutaneous melanoma	38	18.0	41	43	61[15]
MBAITs	36	17.0	32	31	24[16]
Renal cell carcinoma	20	9.0	47	51	64[15]
Basal cell carcinoma	14	6.5	52	41	75[17]

MBAIT = melanocytic BAP1–mutated atypical intradermal tumors

Haugh AM *et al.* JAMA dermatol., 2017; 153: 999-1006

BAP1 in the clinic, P family



- Patient 1 (I-01)

Patient 2 (I-02)

Patient 3 (II-09)

Early mesothelioma nodules in carriers of germline BAP1 mutations from the P-family. These nodules were identified during laparoscopy (patients 1 and 2)
and VATS (patient 3). These nodules are common in carriers of germline BAP1 mutations, and they often have ***an indolent biological behavior for several years****.*

Taioli E. *et al*. JTO 2022

BAP1 Is Altered by Copy Number Loss, Mutation, and/or Loss of Protein Expression in More Than 70% of Malignant Peritoneal Mesotheliomas

Noémie Leblay, MSc,[a] Frédéric Leprêtre, PhD,[b] Nolwenn Le Stang, MSc,[c,d] Amandine Gautier-Stein, PhD,[e] Laurent Villeneuve, MSc,[f,g,h] Sylvie Isaac, MD,[f,g,i] Denis Maillet, MD,[j] Françoise Galateau-Sallé, MD, PhD,[c,d] Céline Villenet, BS,[b] Shéhérazade Sebda, BS,[b] Alexandra Goracci, MD,[k] Graham Byrnes, PhD,[a] James D McKay, PhD,[a] Martin Figeac, PhD,[b,l] Olivier Glehen, MD, PhD,[f,g,m] François-Noël Gilly, MD, PhD,[f,g,m] Matthieu Foll, PhD,[a] Lynnette Fernandez-Cuesta, PhD,[a,*] Marie Brevet, MD, PhD[f,g,i]

Journal of Thoracic Oncology Vol. 12 No. 4: 724-733

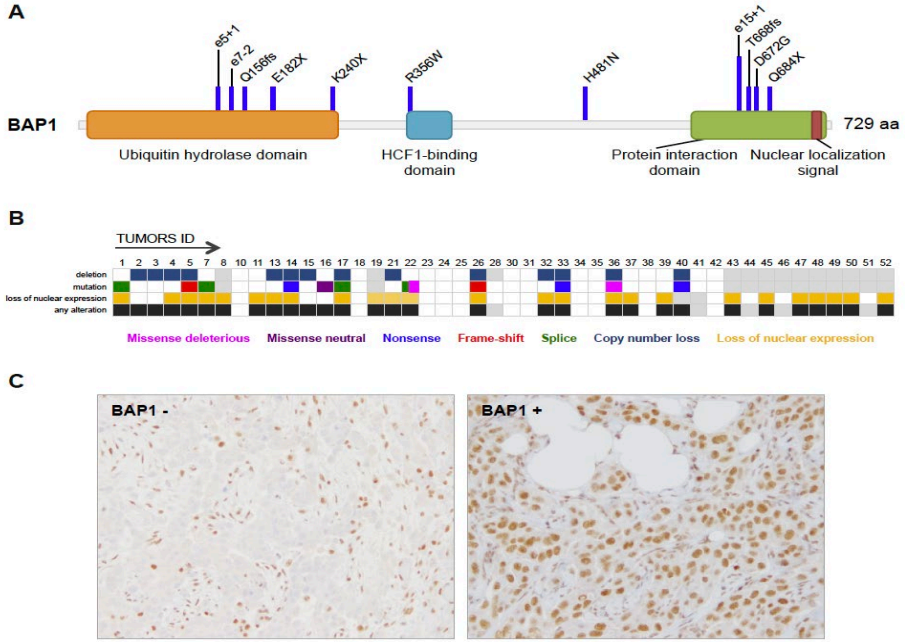
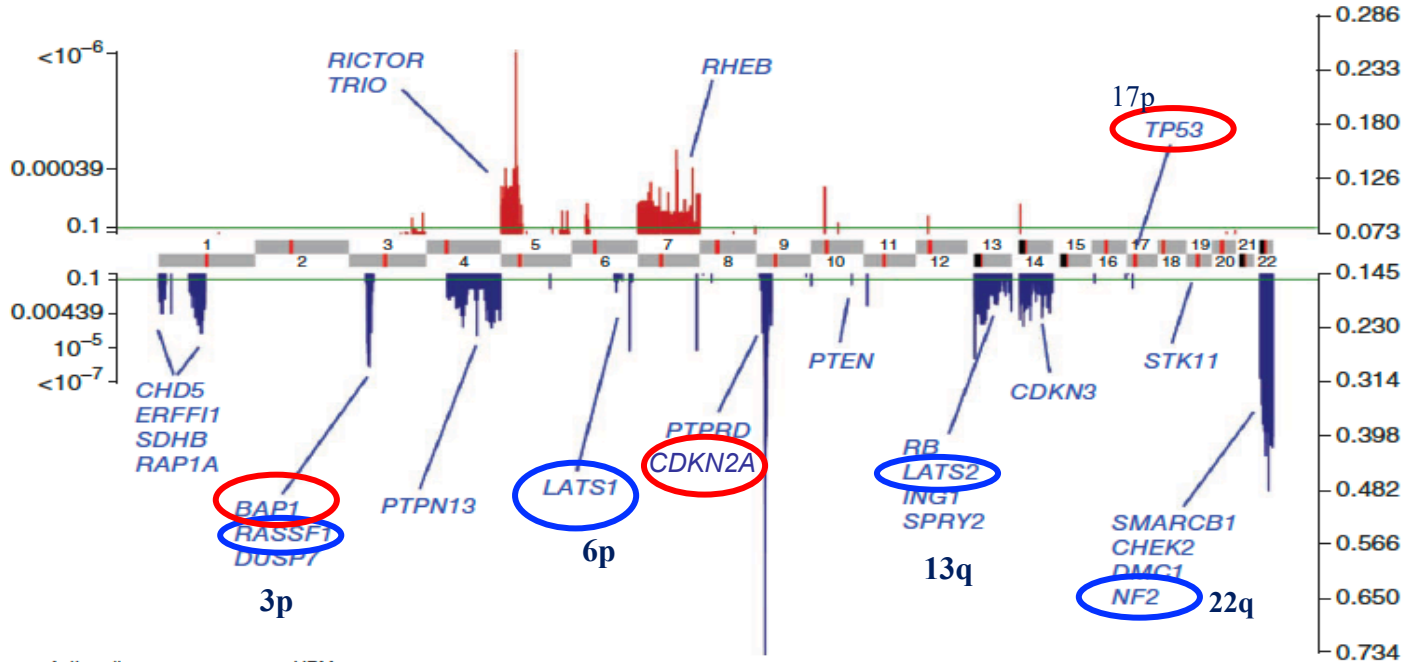


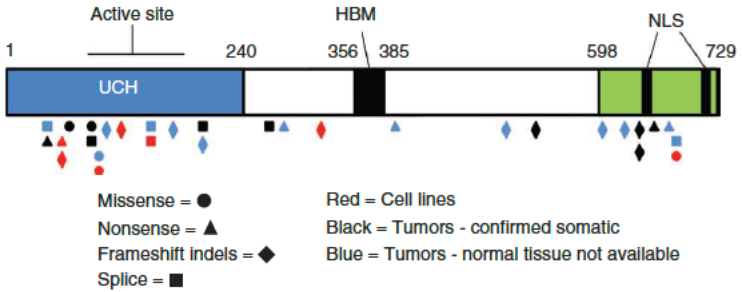
Table 1. Clinicopathological and Epidemiological Data on the 46 Patients with Peritoneal Mesothelioma

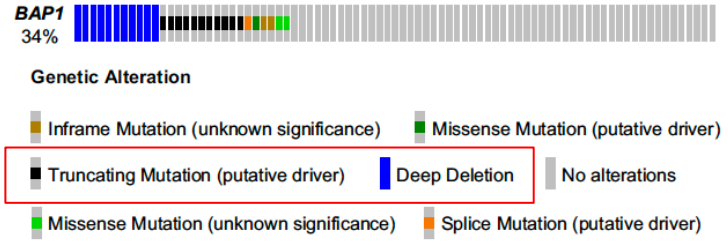
Characteristic	Sex		*p* Value Based on Comparison Test
	Male (n = 26)	Female (n = 20)	
Age, y			0.96[a]
Median	62.5	60	
Range	26-75	17-76	
Histological type			0.78[b]
Epithelioid	24 (92%)	17 (85%)	
Biphasic	1 (4%)	2 (10%)	
Sarcomatoid	1 (4%)	1 (5%)	
Family history of cancer			0.68[b]
No	23 (88%)	16 (80%)	
Yes	3 (12%)	4 (20%)	
Asbestos exposure	n = 25	n = 19	0.007[b]
No	17 (68%)	19 (100%)	
Yes	8 (32%)	0	
Smoking exposure	n = 21	n = 13	0.14[b]
No	12 (57%)	11 (85%)	
Yes	9 (43%)	2 (15%)	

LOH dans le mésothéliome pleural (altérations somatiques)

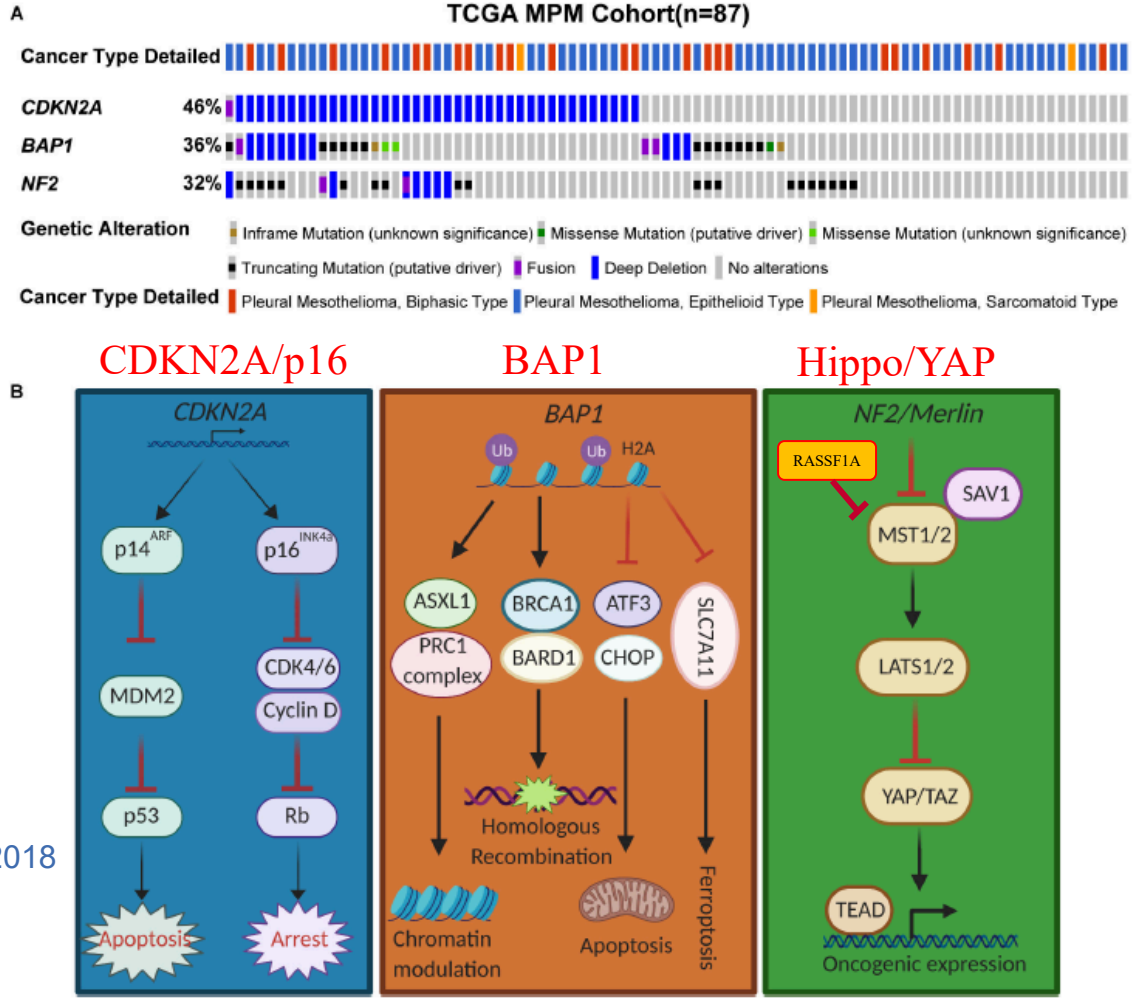


BAP1



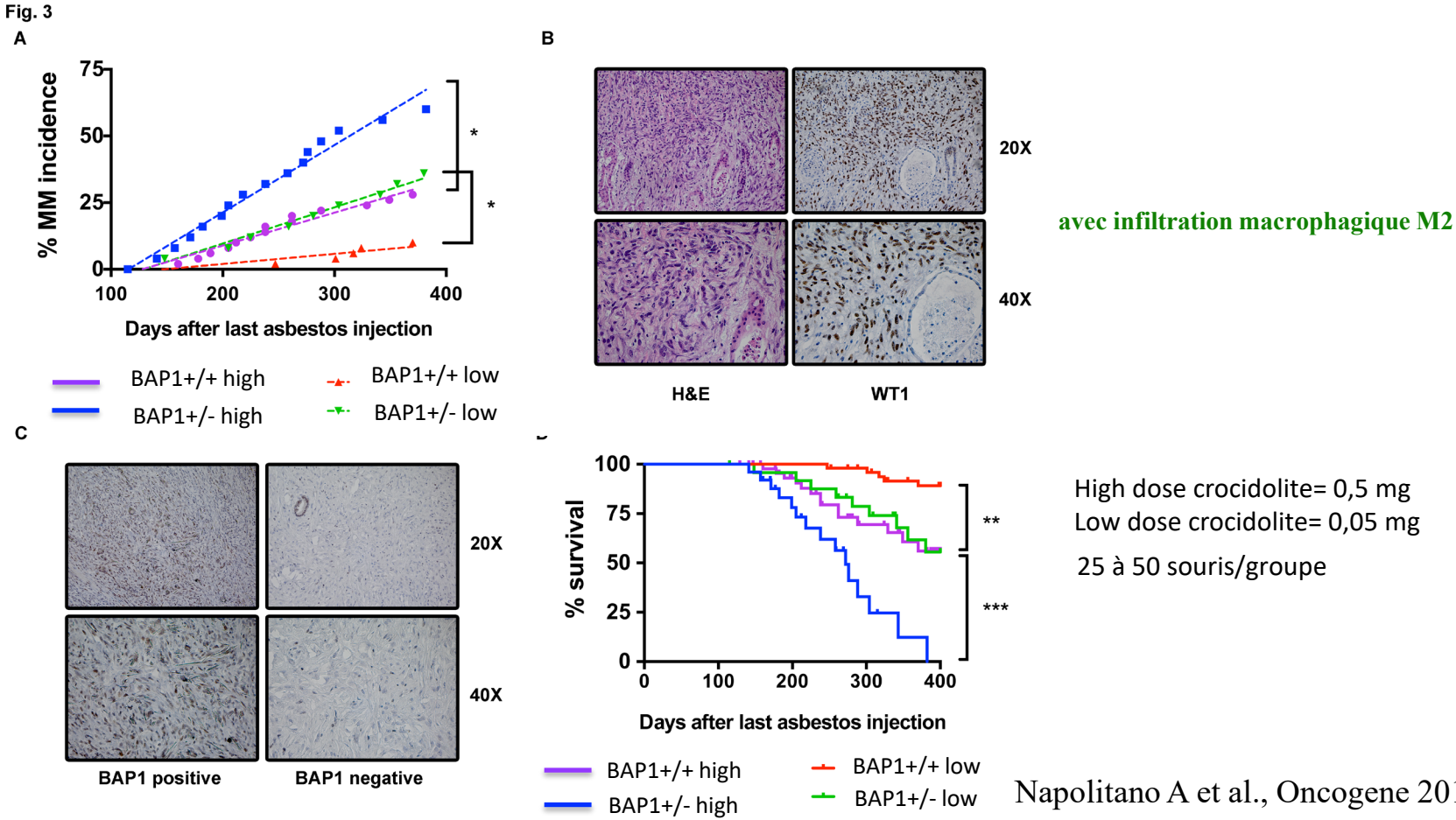


3 grandes signalisations oncogéniques



Bott *et al.* Nat Gen 2011
Testa *et al.* Nat Gen 2012
Bueno *et al.* Nat Gen 2016
Maille E. *et al.* Br. J Cancer 2018

Des souris KO conditionnel BAP1 (cre-lox) sont plus susceptibles à la carcinogénèse induite par injection intra-péritonéale d'amiante crocidolite (1 injection/ semaine x 10)



avec infiltration macrophagique M2

High dose crocidolite= 0,5 mg
Low dose crocidolite= 0,05 mg

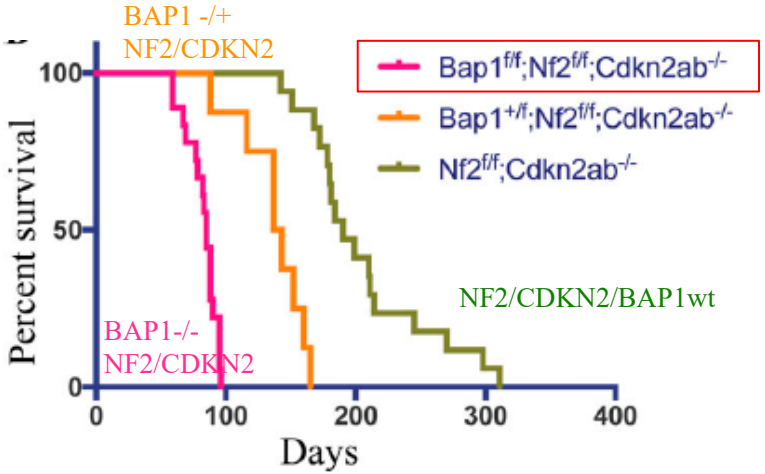
25 à 50 souris/groupe

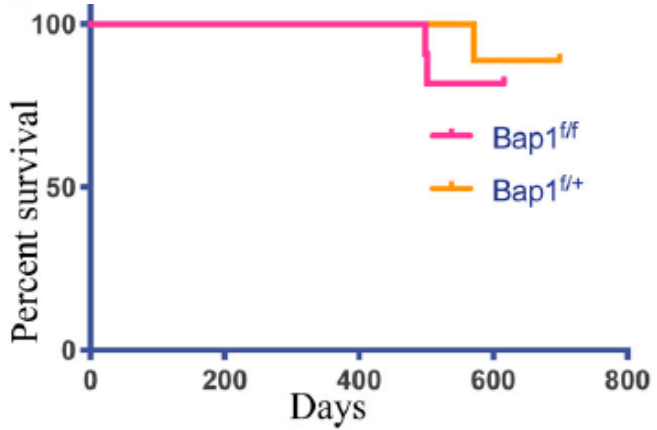
Napolitano A et al., Oncogene 2016

Combined deletion of *Bap1*, *Nf2*, and *Cdkn2ab* causes rapid onset of malignant mesothelioma in mice

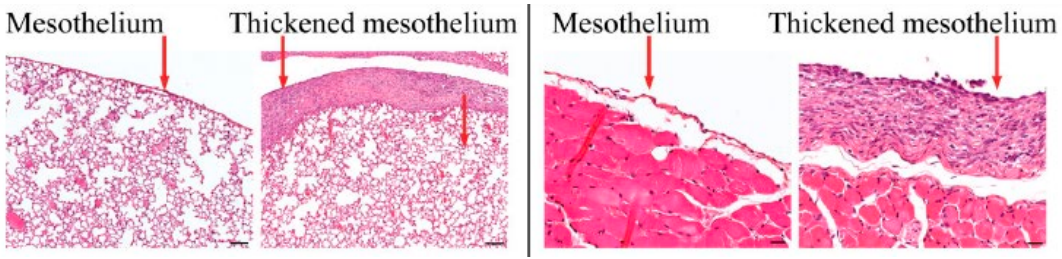
Tumeurs spontanées (sans amiante)

Le « dosage » allélique compte





(Système Cre/Lox)

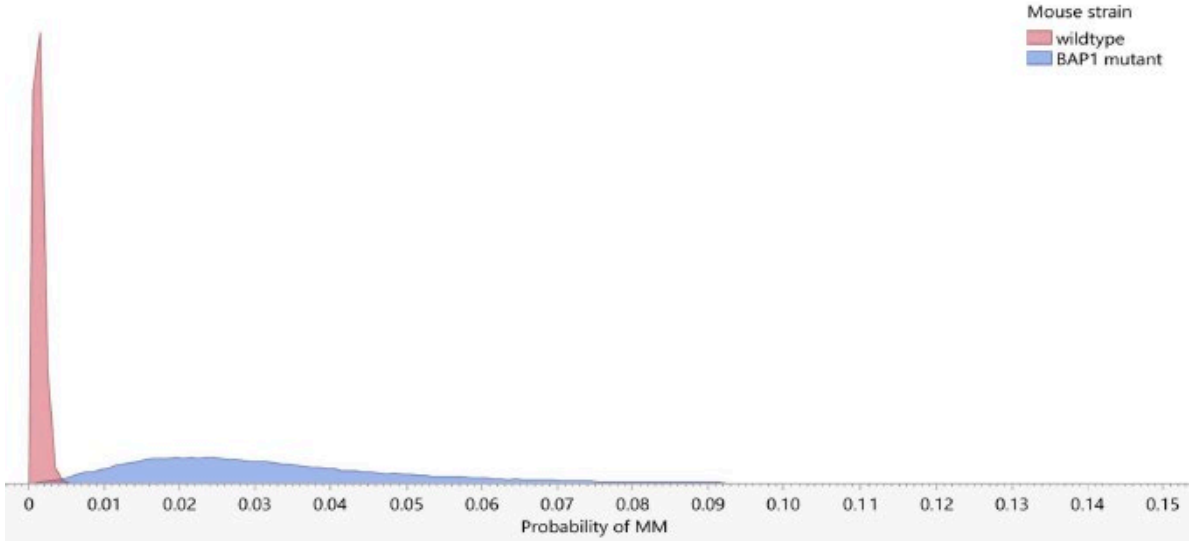


Badhai J. *et al*. J. Exp. Med. 2020, 2017: e20191257

Bayesian analysis of the rate of spontaneous malignant mesothelioma among *BAP1* mutant mice in the absence of asbestos exposure

Nielsen DM *et al*. Sci Rep. 2025, 15:169

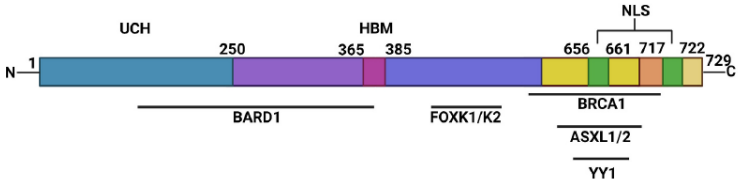
Our Bayesian analyses indicate that the odds of spontaneous MM among germline *BAP1* mutant mice is substantially larger than that of wildtype mice. These results support the existing biological study findings that mesotheliomas can arise in the presence of pathogenic germline mutations, independently of asbestos exposure.

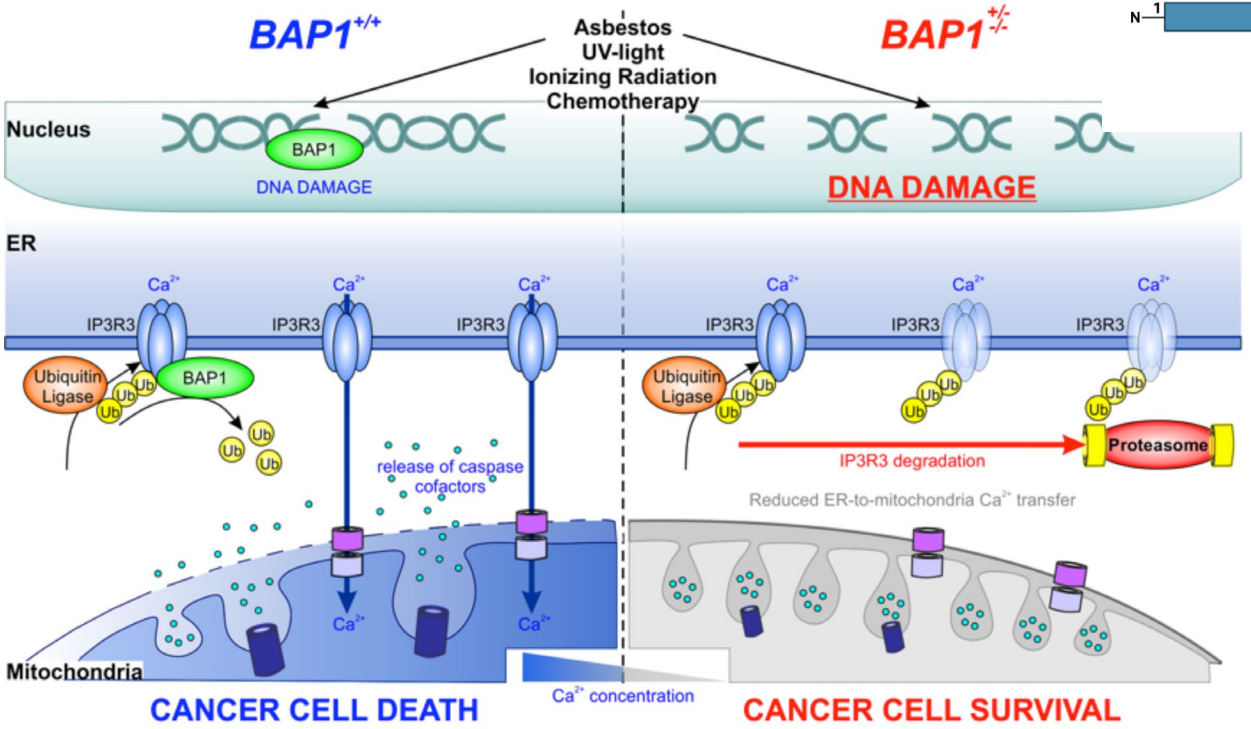


Hypothèses/ données expérimentales sur la carcinogénèse BAP1:

réparation ADN (BRCA1)/ flux calcique mitochondrial (IP3R3)/ régulation transcription (ASXL2,H2A) ?

BAP1 interagit avec BRCA1, BARD1 & Histone H2A
BAP1 est une déubiquitinase qui régule la stabilité de IP3R3 et de ASLX2
BAP1 forme un trimère avec HDAC1 et HMBG1 dans le noyau (séquestre HMBG1: ↘ inflammation)
BAP1 interagit avec HIF1a: déubiquitination et stabilisation





BAP1:
gatekeeper proliferation/apoptosis)
caretaker (genomic stability)
landscaper (chromatin regulation)

Bononi A. Nature 2017
Bononi A. Cell Death Diff. 2017
Daou S. Nature Comms 2018
Novelli F. PNAS 2021
Bononi A. PNAS 2022
Elsayed AM BBA Rev Cancer 2025

Inclusion Criteria for BAP1 genetic testing

1) First or second degree relatives with MM;

2) **Proband or at least one first- or second-degree relative** diagnosed with malignancies such as Uveal Melanoma (UVM), Cutaneous Melanoma (CM) or MBAITs (Melanocytic BAP1-mutated Atypical Intradermal Tumors = Atypical Spitz tumors: both BAP1 & B-RAF mutations), clear-cell Renal Cancer (ccRC), & multiple cutaneous basal cell carcinoma (BCC) (the cancer types we saw frequently in carriers of *BAP1*$^{+/-}$)

3) **History of multiple cancers** in the majority of first and second-degree relatives,–any cancer;

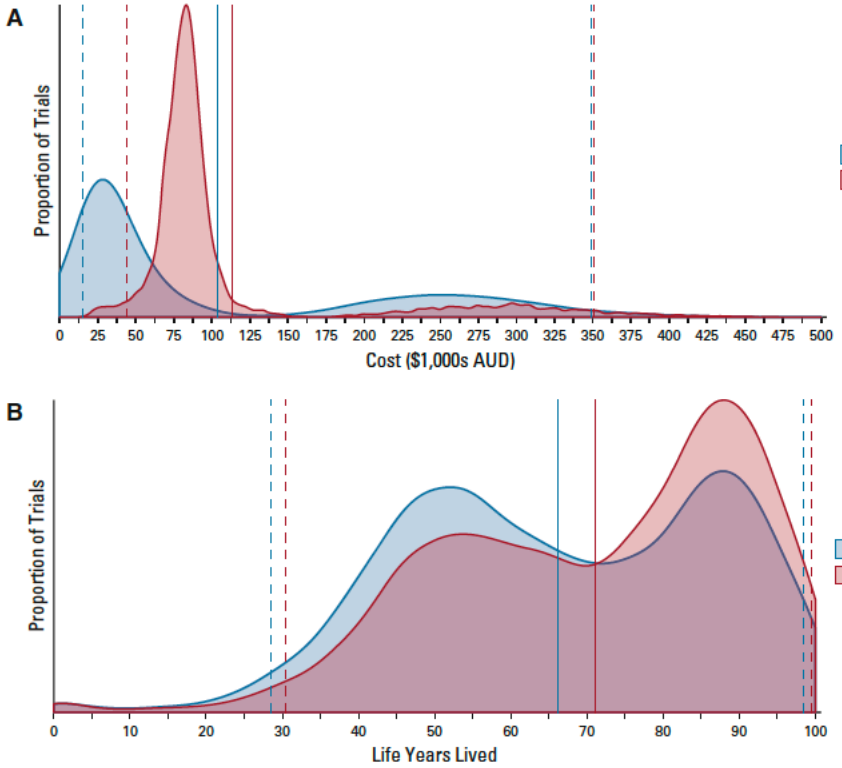
4) **Early MM onset** (age <50*)

*This age was chosen because the incidence of MM before age 50 is rare and suggestive of genetic predisposition or environmental exposure since childhood

GENETICS AND GENOMICS

Microsimulation Model for Evaluating the Cost-Effectiveness of Surveillance in *BAP1* Pathogenic Variant Carriers

Sebastian Walpole, JCO Clin Cancer Inform 5:143-154.



181 familles identifiées dans le monde
374 sujets porteurs mut BAP1 germinale

Une surveillance augmenterait la survie moyenne de 4,9 ans au coût de 6 197 dollars => ICER: 1265 dollars par année de vie gagnée

Walpole S, Pritchard AL, Cebulla CM, et al: Comprehensive study of the clinical phenotype of germline BAP1 variant-carrying families worldwide. J Natl Cancer Inst 110:1328-1341, 2018.

Recommandations NCI 2022

Table 1. NCI Screening Protocol for Individuals With Pathogenic Germline Mutations in the *BAP1* Gene (NCT03830229)

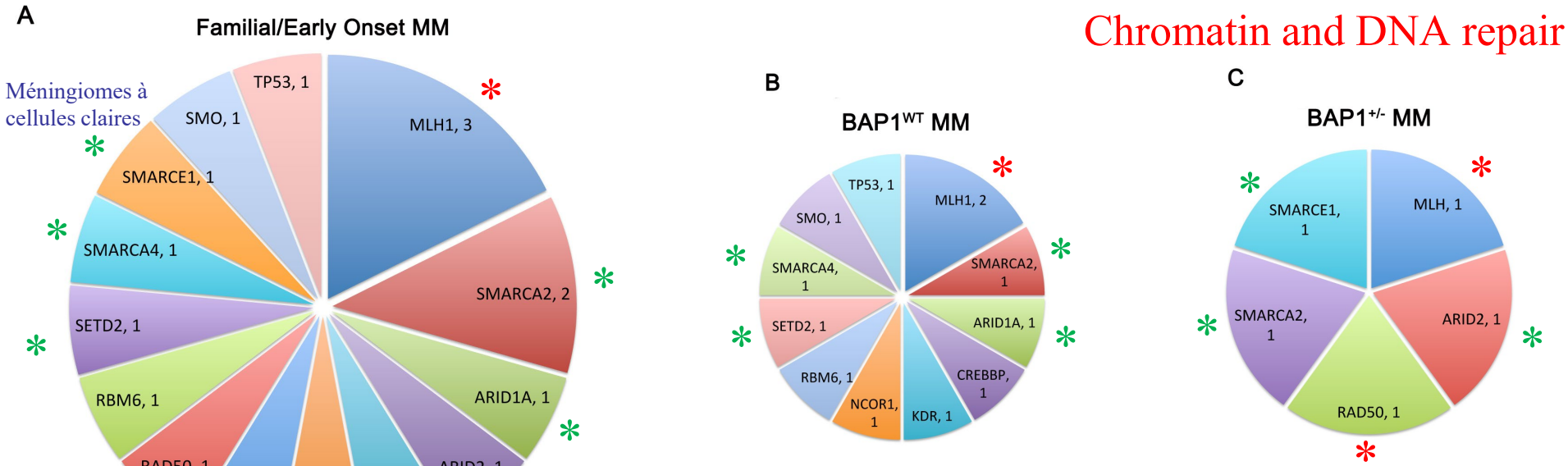
Eligible Participants (Age ≥ 2 yr)	Evaluation of Germline Mutations	Baseline Screening of Individuals With Germline *BAP1* Mutations (Age at Screening)	Surveillance Screening of Individuals With Germline BAP1 Mutations (Frequency)
Cohort 1: Individuals with mesothelioma carrying pathogenic germline mutations in *BAP1* or other DNA repair/cancer predisposition genes Cohort 2: First- and second-degree relatives of cohort 1 and individuals without mesothelioma carrying germline mutations in *BAP1* or other DNA repair/cancer predisposition	Genetic counseling Saliva, cheek swab, or blood for germline genetic testing	Ophthalmology evaluation (≥2 yr) Dermatology evaluation (≥2 yr) MRI: Chest, abdomen, and pelvis (≥30 yr) MRI: Brain (≥18 yr) MRI: Breast (≥30 yr) Mammogram for women (≥40 yr)	Ophthalmology evaluation (annual) Dermatology evaluation (annual) MRI: Chest, abdomen, pelvis, (every other year) MRI: Brain (every other year) MRI: Breast (every other year) Mammogram for women (annual)

MRI, magnetic resonance imaging; NCI, National Cancer Institute.

Carbone M. *et al*. J. Thorac. Oncol. 2022, 17 (7): 873-89

Other Germline mutation in 'familial' MM

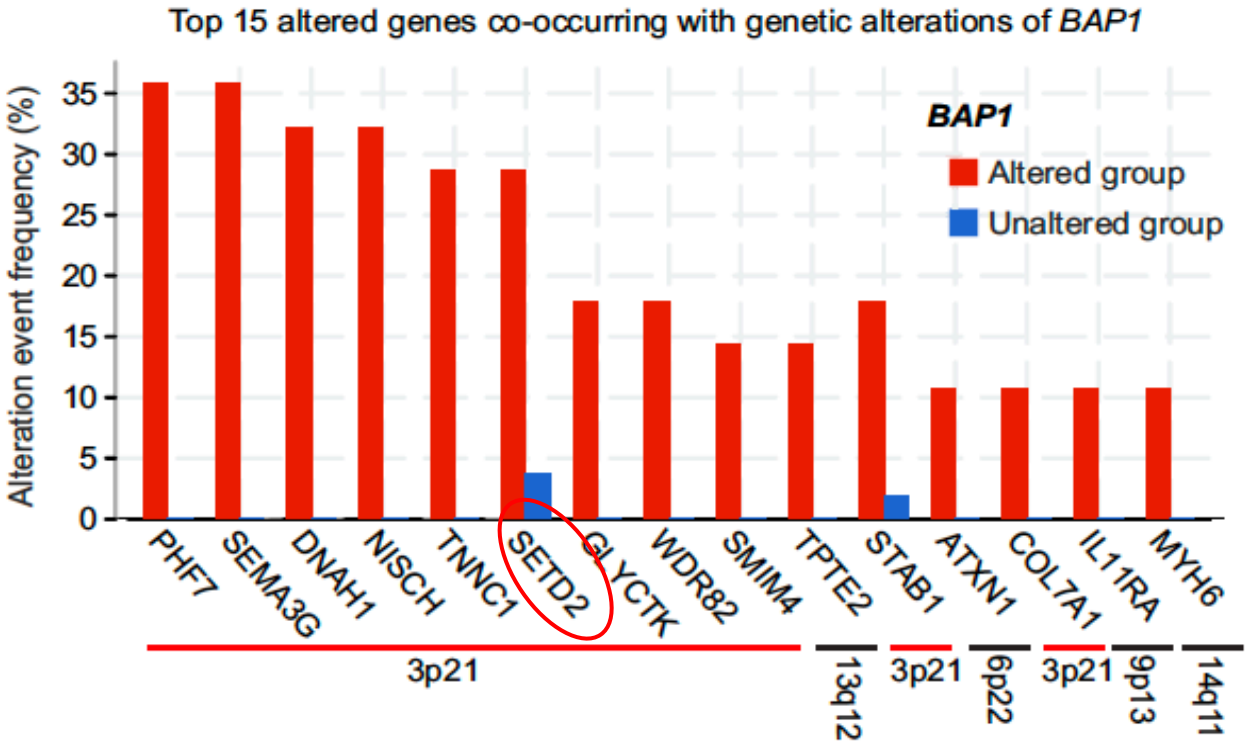
Chromatin and DNA repair



- 12/34 (35%) MMs with *BAP1*^{WT} contained **one germline mutation of 11 different tumor suppressor genes** (2 patients had 2 different deleterious variants of MLH1).
- 5/11 MM with *BAP1*$^{+/-}$ contained one additional germline mutation, each, in 5 different genes

Pastorino S. *et al.* JCO 2018; 36 (35):3485-94

Les phénotypes cellulaires (DNA repair) dans les MP avec perte BAP1 germinale sont d'interprétation difficile car co-mutations



TCGA Mesothelioma cohort

Hang H. *et al*. JTO 2022; 17(8) e67-e70

Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma

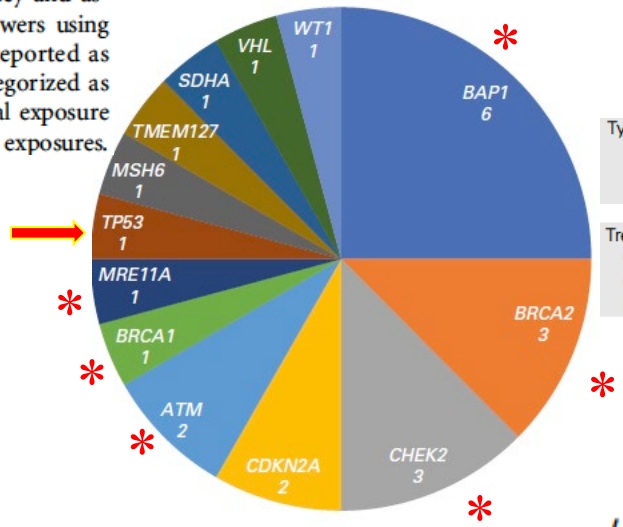
Vasiliki Panou, Meghana Gadiraju, Arthur Wolin, Caroline M. Weipert, Emily Skarda, Aliya N. Husain, Jyoti D. Patel, Buerkley Rose, Shannon R. Zhang, Madison Weatherly, Viswateja Nelakuditi, Amy Knight Johnson, Maria Helgeson, David Fischer, Arpita Desai, Nanna Sulai, Lauren Ritterhouse, Oluf D. Røe, Kiran K. Turaga, Dezheng Huo, Jeremy Segal, Sabah Kadri, Zejuan Li, Hedy L. Kindler, and Jane E. Churpek

Study Population

Unrelated patients with MM who attended The University of Chicago Medicine (UCM) MM clinic from April 2016 to August 2017 were prospectively consented. Saliva, peripheral blood, and tumor specimens were collected. A detailed personal and family history of malignancy and asbestos exposure were obtained in person by trained interviewers using a standardized questionnaire. Asbestos exposure was self-reported as definite, probable, possible, or no known exposure and categorized as primary for those with known occupational or environmental exposure and as secondary for those exposed through family members' exposures.

Table 1. Patient Characteristics

Characteristic	No. (%)
Total	198 (100)
Sex	
Male	136 (69)
Age at diagnosis, median (IQR)	67 (59-73)
Site of origin	
Pleura	148 (75)
Peritoneum	44 (22)
Pleura and peritoneum	3 (2)
Tunica vaginalis	3 (2)
Histology	
Epithelioid	157 (79)
Sarcomatoid	13 (7)
Biphasic	23 (12)
Unknown	5 (3)
Asbestos exposure	
Definite	104 (53)
Probable	22 (11)
Possible	35 (18)
None	35 (18)
Unknown	2 (1)
Type of asbestos exposure‡	
Primary	98 (49)
Secondary	32 (16)
Primary and secondary	31 (16)
Treatments received for MM	
Curative intent surgery	100 (51)
Chemotherapy	165 (83)
Platinum-based chemotherapy	159 (80)

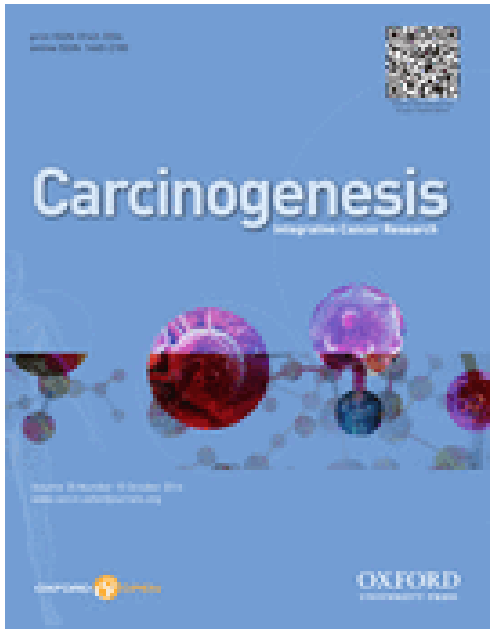


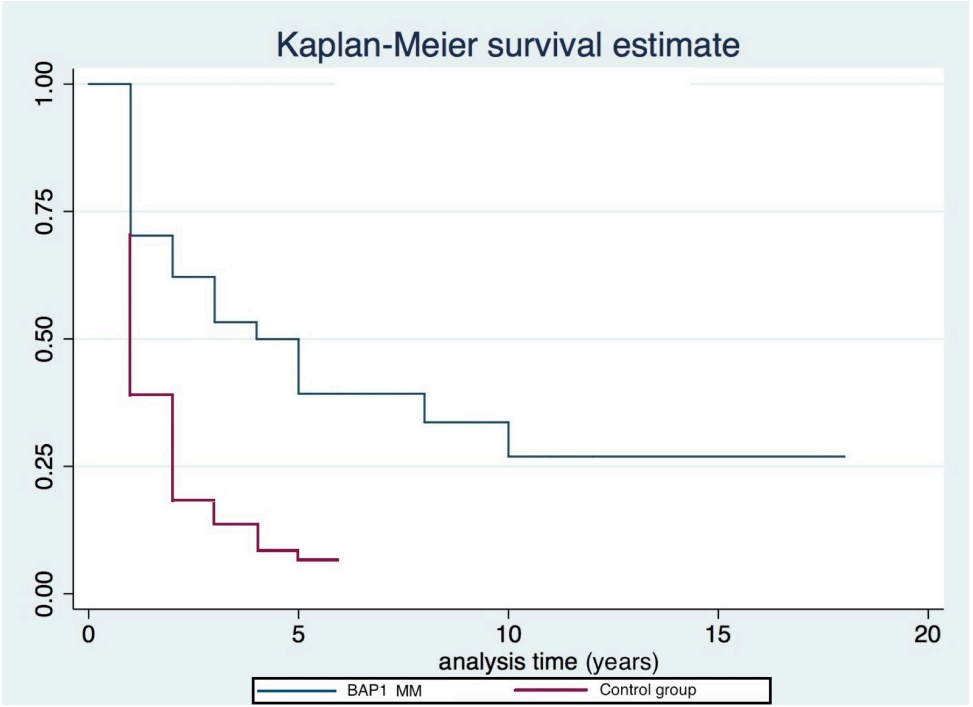
6 BAP1 germ/198= 3%

* HR pathway !

J Clin Oncol 36:2863-2871. © 2018

BAP1 cancer syndrome: Mesothelioma Patients with Germline BAP1 Mutations Have 7-Fold Improved Long-term Survival

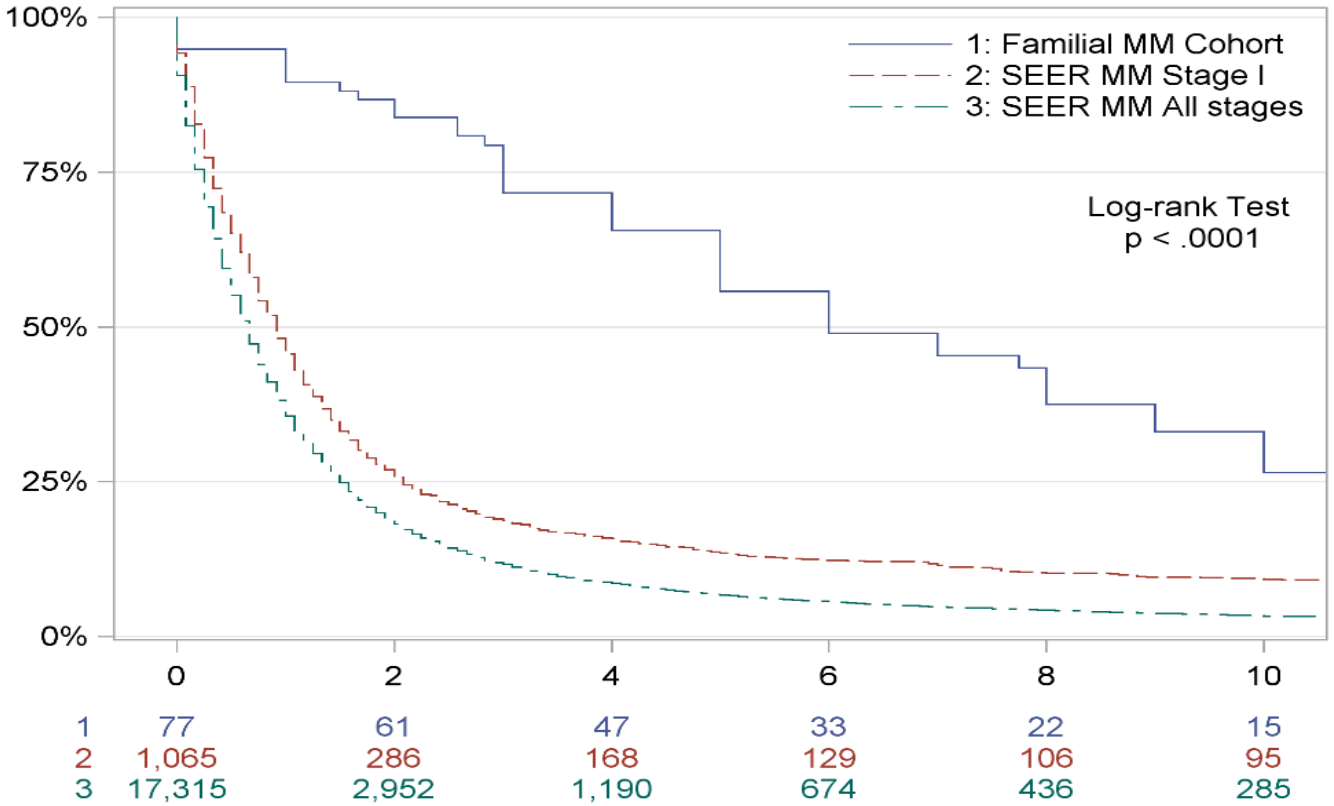




Baumann F. et al Carcinogenesis 2015

Improved survival in familial *vs.* sporadic MM

Indépendamment du statut BAP1

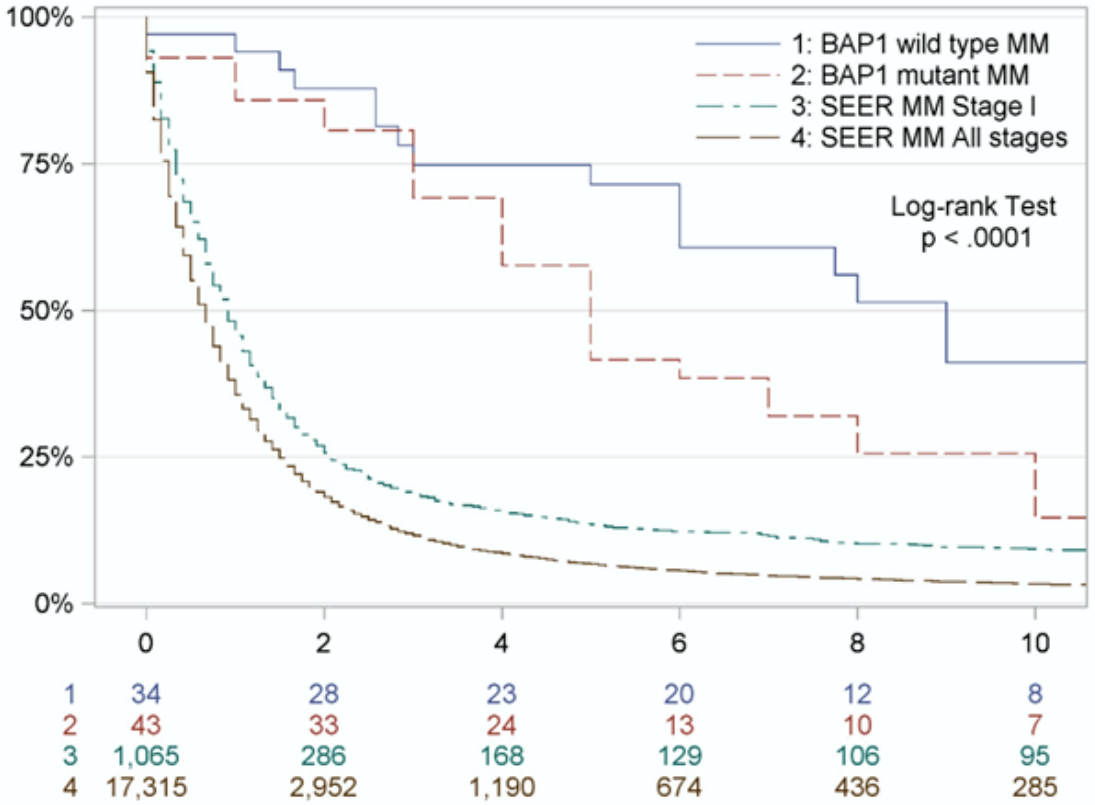


(A) Familial MM cohort (median = 6 years, 10-year = 26%),
SEER Stage I (median = 11 months, 10-year = 9.2%), and SEER all stages (median = 8 months, 10-year = 3.3%).

Pastorino S. *et al.* JCO 2018; 36 (35):3485-94

Improved survival in familial *vs.* sporadic MM

Selon statut BAP1



BAP1 wt familial/jeune

BAP1 mutant familial/jeune

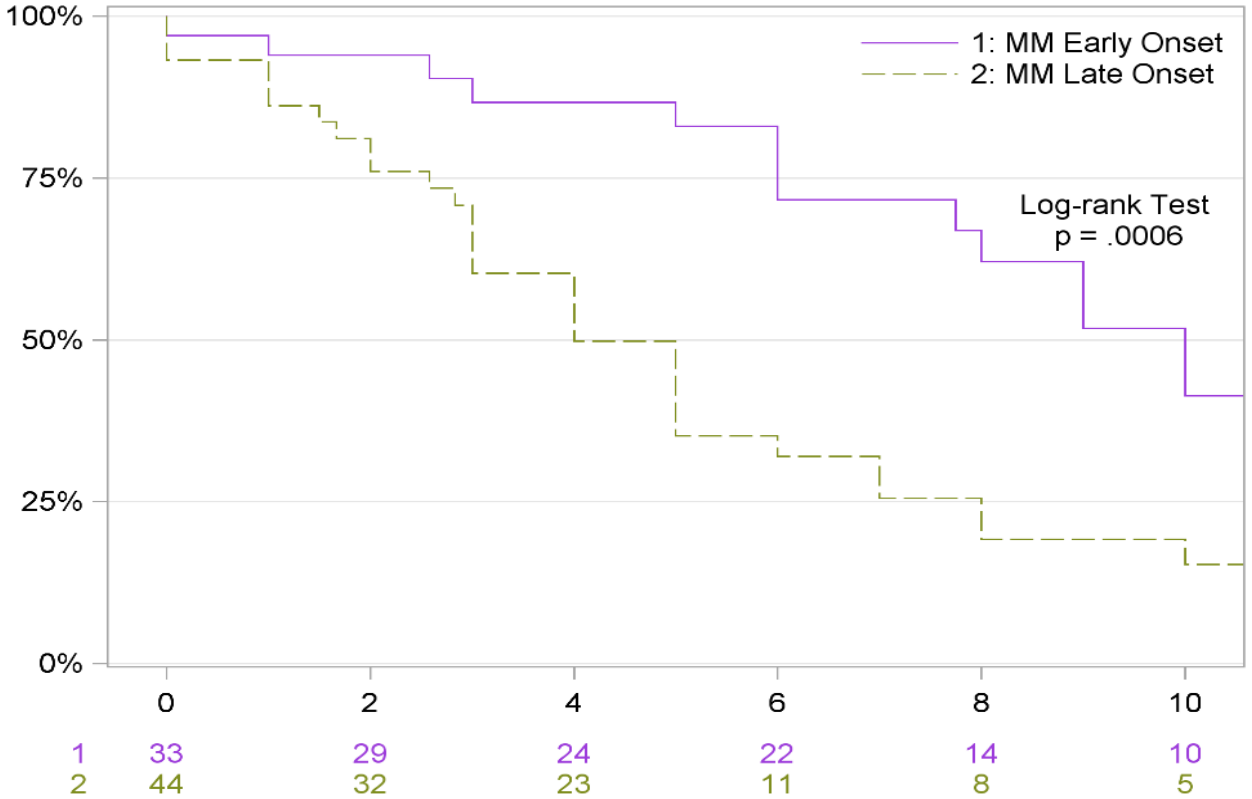
SEER Stade I

SEER tous stades

(A) 1) Familial/Early onset BAP^{WT} MM (median = 9 yrs, 10-yr = 41%); 2) familial/Early onset $BAP^{+/-}$ MM (median = 5 yrs, 10-yr = 15%); 3) SEER Stage I (median = 11 months, 10-yr = 9.2%); 4) SEER all stages (median = 8 months, 10-yr = 3.3%).

Pastorino S. *et al.* JCO 2018; 36 (35):3485-94

Survival in familial MM cohort by age at onset



âge Diag.+ < 50 ans

âge Diag.+ > 50 ans

Familial MM cohort by onset: under 50 (median = 10 years, 10-year = 41%) and 50 or older (median = 4 years, 10-year = 15%).

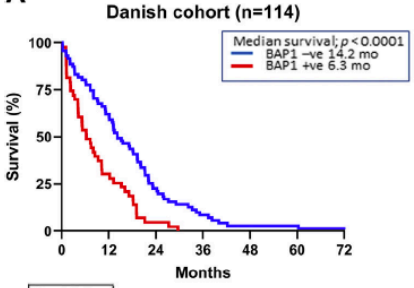
Pastorino S. *et al.* JCO 2018; 36 (35):3485-94

BAP1 Loss by Immunohistochemistry Predicts Improved Survival to First-Line Platinum and Pemetrexed Chemotherapy for Patients With Pleural Mesothelioma: A Validation Study

2022 *Journal of Thoracic Oncology* Vol. 17 No. 7: 921-930

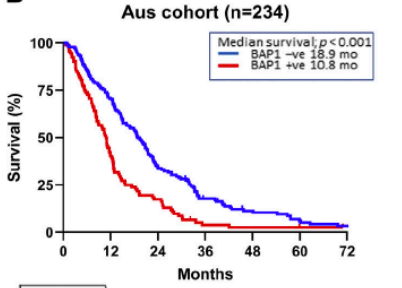
n=348 MP

A



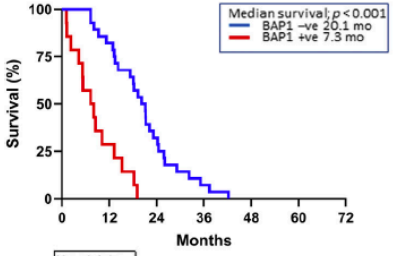
No. at risk							
BAP1 –ve	71	44	16	6	2	2	1
BAP1 +ve	43	13	2	0	0	0	0

B



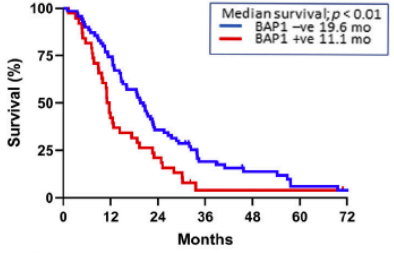
No. at risk							
BAP1 –ve	142	100	49	23	13	7	4
BAP1 +ve	92	37	16	3	2	1	0

C



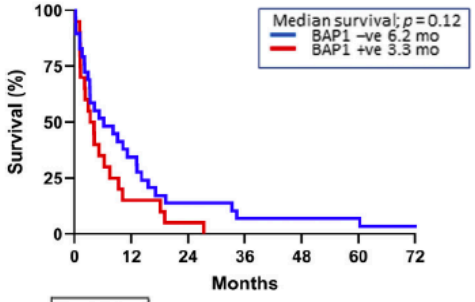
No. at risk					
BAP1 –ve	28	23	9	2	0
BAP1 +ve	14	4	0	0	0

D



No. at risk							
BAP1 –ve	70	52	25	12	7	3	2
BAP1 +ve	38	16	8	1	1	1	0

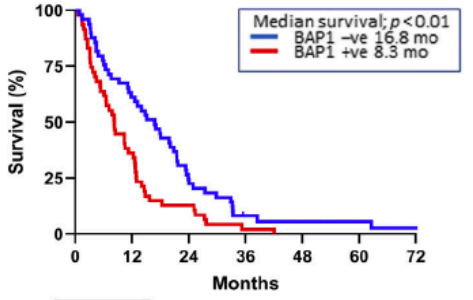
Danish BSC (n=49)



No. at risk							
BAP1 –ve	29	10	4	2	2	2	1
BAP1 +ve	20	3	1	0	0	0	0

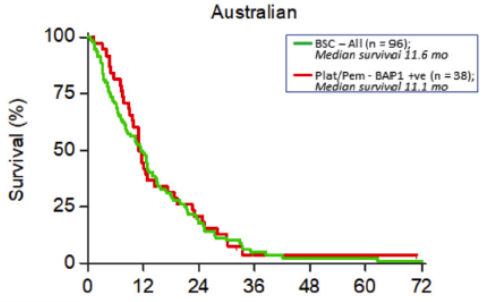
F

Aus BSC (n=96)



No. at risk							
BAP1 –ve	29	10	4	2	2	2	1
BAP1 +ve	20	3	1	0	0	0	0

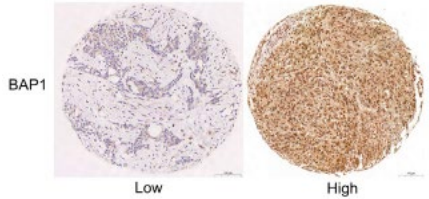
Australian

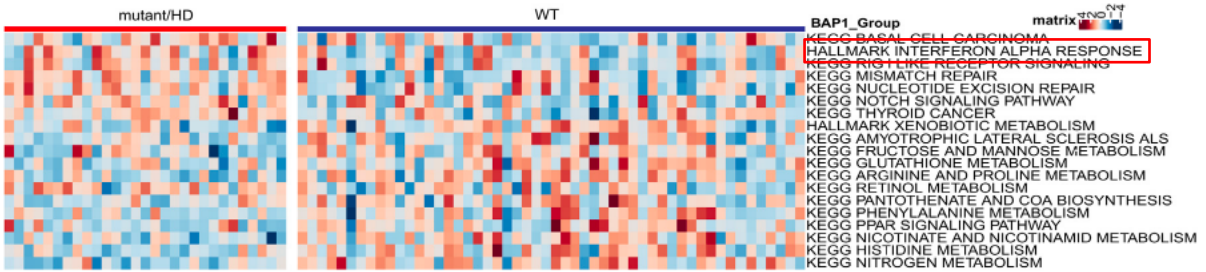


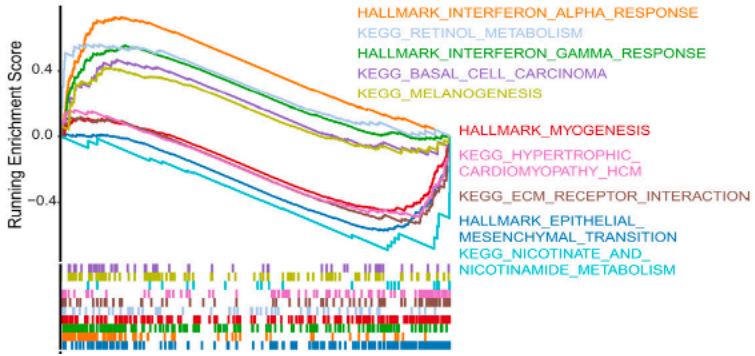
No. at risk							
BSC (all)	96	47	18	4	2	2	1
Plat/Pem BAP1 +ve	38	16	8	1	1	1	0

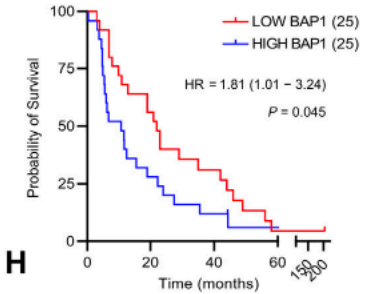
BAP1 Deficiency Inflames the Tumor Immune Microenvironment and Is a Candidate Biomarker for Immunotherapy Response in Malignant Pleural Mesothelioma

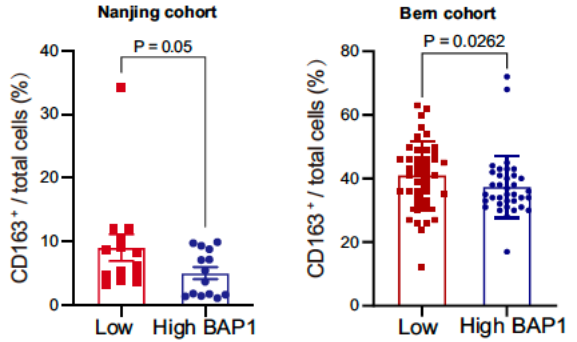
n=116
PPE



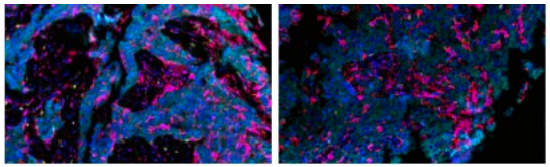








CD163
Macrophages M2



Xu D. et al. *JTO Clinical and Research Reports* 2023; 5: 100672-87

Messages à rapporter à la maison

- Les mutation BAP1 germinales constituent une part infime des MP (≤3%)… alors que les mutations somatiques sont observées dans 30 à 50% des cas
- L'âge de diagnostic est 15 à 20 ans plus jeune que le MP classique et doit faire penser à la possibilité d'une mutation germinale de BAP1
- L'interrogatoire familial est crucial si l'analyse histologique confirme la perte du marquage IHC BAP1 avec un âge de diagnostic ≤ 50 ans
- La présentation pleuroscopique est possiblement différente de celle des MP sans BAP1 germinal. Formes péritonéales non rares… exposition à l'amiante ?
- D'autres anomalies germinales sont associées à des MP survenant jeune et des syndromes familiaux de cancers (gènes DNA repair) ou des formes familiales de MP
- Avec les limites méthodologiques du rétrospectif, la mutation germinale de BAP1 est associée à un meilleur pronostic à l'ère de la seule chimiothérapie… mais pas de données avec l'immunothérapie (micro-environnement inflammatoire)
- Des propositions de surveillance des apparentés avec mutation germinale BAP1 ont été faites par le NCI (oeuil, peau, IRM corps entier)

RCP Netmeso IdF: F. Barthes-Le Pimpec
I. Monnet
G. Zalcman (+DOM-TOM)

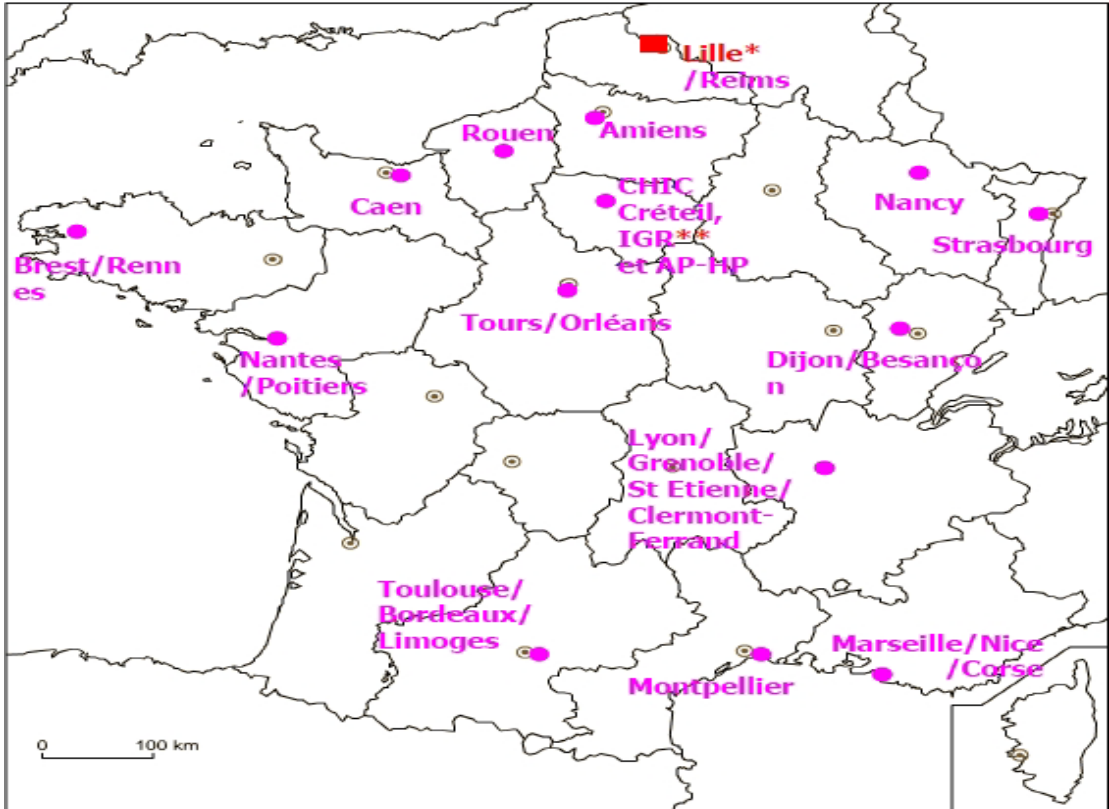
INSTITUT NATIONAL DU CANCER Rare tumor Network

National Expert Centre

Regional Expert Centre

RCP (inter)-régionale

Mesopath-DO ALD31



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Merci de votre attention

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