Traitements du Mésothéliome Malin Pleural (MPM):

G. Zalcman

Service d'Oncologie thoracique
& Unité de Phase I CIC1425/CLIP$_2$ Paris-Nord
GH Bichat-Claude Bernard,

Inserm
Institut national de la santé et de la recherche médicale
U830 « Génétique et biologie des cancers »

Liens d'intérêt

Investigateur d'essais cliniques de phases I, II & III promus par Lilly, GSK, Roche, MSD, Merck-Serrono, Pfizer, Astra-Zeneca, Sanofi-Aventis, Pierre Fabre, Borhinger, BMS, Novartis, Ariad… sans rétribution personnelle, **tous les honoraires étant perçus par mon Institution (Hôpital Bichat-APHP, Centre d'Instigation Clinique, CIC1425/CLIP$_2$ Paris-Nord France**)

SUBVENTIONS OU AVANTAGES COLLECTIFS	RETRIBUTIONS OU AVANTAGES PERSONNELS
Lilly, Roche, Pfizer, Astra-Zeneca, Sanofi-Aventis, GSK, BMS, Amgen, Chugaï, Pierre Fabre, Borhinger-Ingelheim, Merck-Serono, Chugai, Novartis, Janssen-Cilag, MSD **(Subventions pour l'Intergroupe Francophone de Cancérologie Thoracique – IFCT dont GZ a été président)** Honoraires pour **participation a des conseils scientifiques ou "advisory boards"**: Roche, Astra-Zeneca, Pfizer, MSD, Borhinger-Ingelheim, Inventiva, BMS, Inventiva, versés à la **Fondation Recherche de l'Assistance-Publique-Hôpitaux de Paris (AP-HP)** **Roche a fourni le bevacizumab et versé une subvention de recherche à l'IFCT pour les études de biomarqueurs de l'essai MAPS** **BMS a fourni le Nivolumab et l'Ipilimumab et versé une subvention de recherche à l'IFCT pour les études biomarqueurs de l'essai MAPS-2**	**Invitations et hébergement lors de congrès internationaux (ASCO, ESMO, ERS, AACR, WCLC)** : Roche, MSD, BMS, Astra-Zeneca, Lilly, Pfizer Honoraires personnels pour **participation a des conseils scientifiques ou "advisory boards"**: organisés par Lilly, Astra-Zeneca, BMS, Pfizer, Roche, MSD, Boerhinger, Inventiva **L'ensemble des sommes perçues n'excède pas 5000 euros au cours des 10 dernières années**

Sommaire

1ère partie: Epidémiologie: petite histoire de l'amiante

2ème partie: diagnostic, TNM

3ème partie: traitements loco-régionaux

4ème partie: traitements systémiques: du pémetrexed au bévacizumab

5ème partie: immunothérapie: retour vers le futur

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Bichat - Claude-Bernard

1ère partie: Epidémiologie histoire de l'amiante au XXème siècle

université PARIS DIDEROT PARIS 7

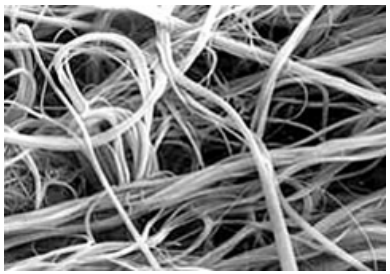
IFCT

Principaux types de fibres d'Amiante Commercialisées: **friction et isolation thermique**

« Fibres serpentine »

95% of all asbestos

Chrysotile - White
fine, silky, flexible

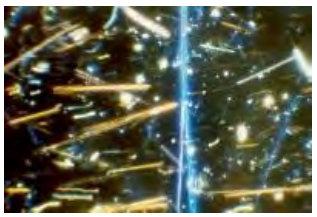


« Fibres amphibole »

5% of all asbestos consumed

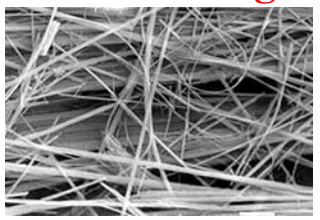
Afrique du Sud

Amosite - **Brown**
straight, brittle fibers

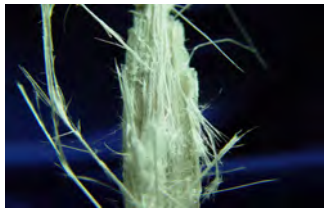


Afrique du Sud
Australie

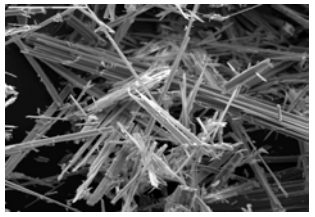
Crocidolite-
Blue & straight



Finlande, USA



Anthophyllite
White, brittle fibers



+ Tremolite and Actinolite, Anthophyllite is found mainly as a contaminant in other minerals.

Les risques liés à l'amiante

- Facteurs de risque liés aux fibres

  - dose cumulée (en f/ml x années)
  - dose en rétention (en f/g poumon)

    ---> biopersistance
  - granulométrie (longueur, diamètre)
  - type (amphiboles> chrysotile)
  - métaux de surface? (Fe, Mg)

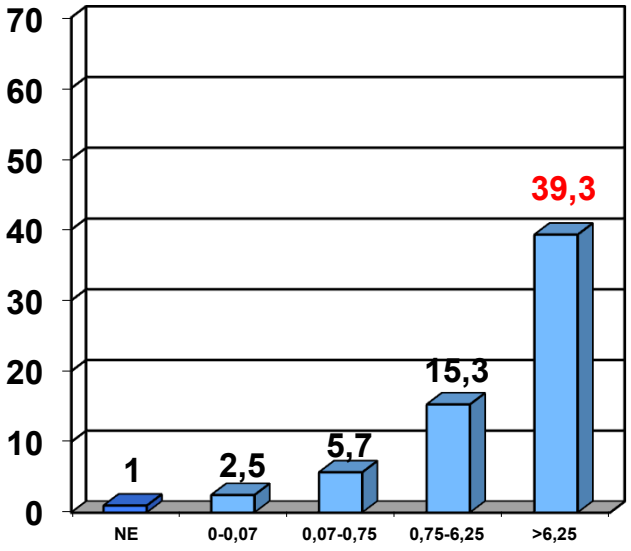
- Facteurs de risque individuels

  - susceptibilité génétique? (BAP1….)
  - co-expositions (autres aérocontaminants professionnels ?)

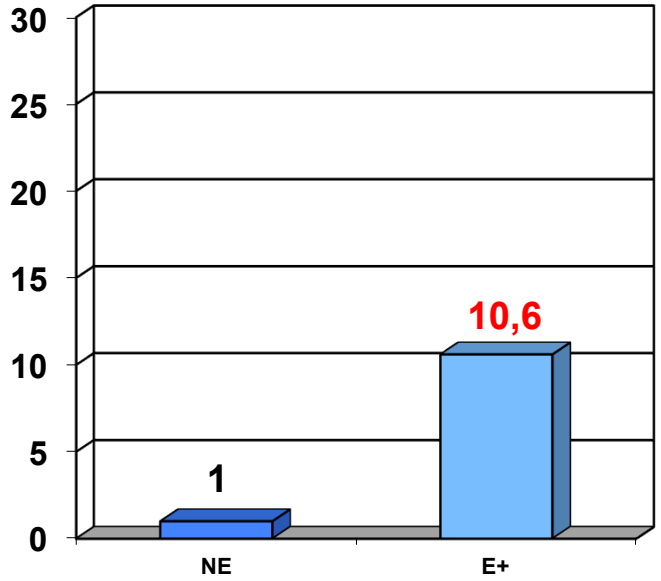
Exposition professionnelle à l'amiante

(données du Programme National de Surveillance du Mésothéliome)

RR Hommes



RR Femmes



Exposition cumulée
(f/ml x années)

Fraction de risque attribuable :
83 % [IC95% : 74,5%-92%]

Fraction de risque attribuable :
42% [IC95% : 25%-58 %]

Expositions indirectes (para-professionnelles)
Autres expositions ??

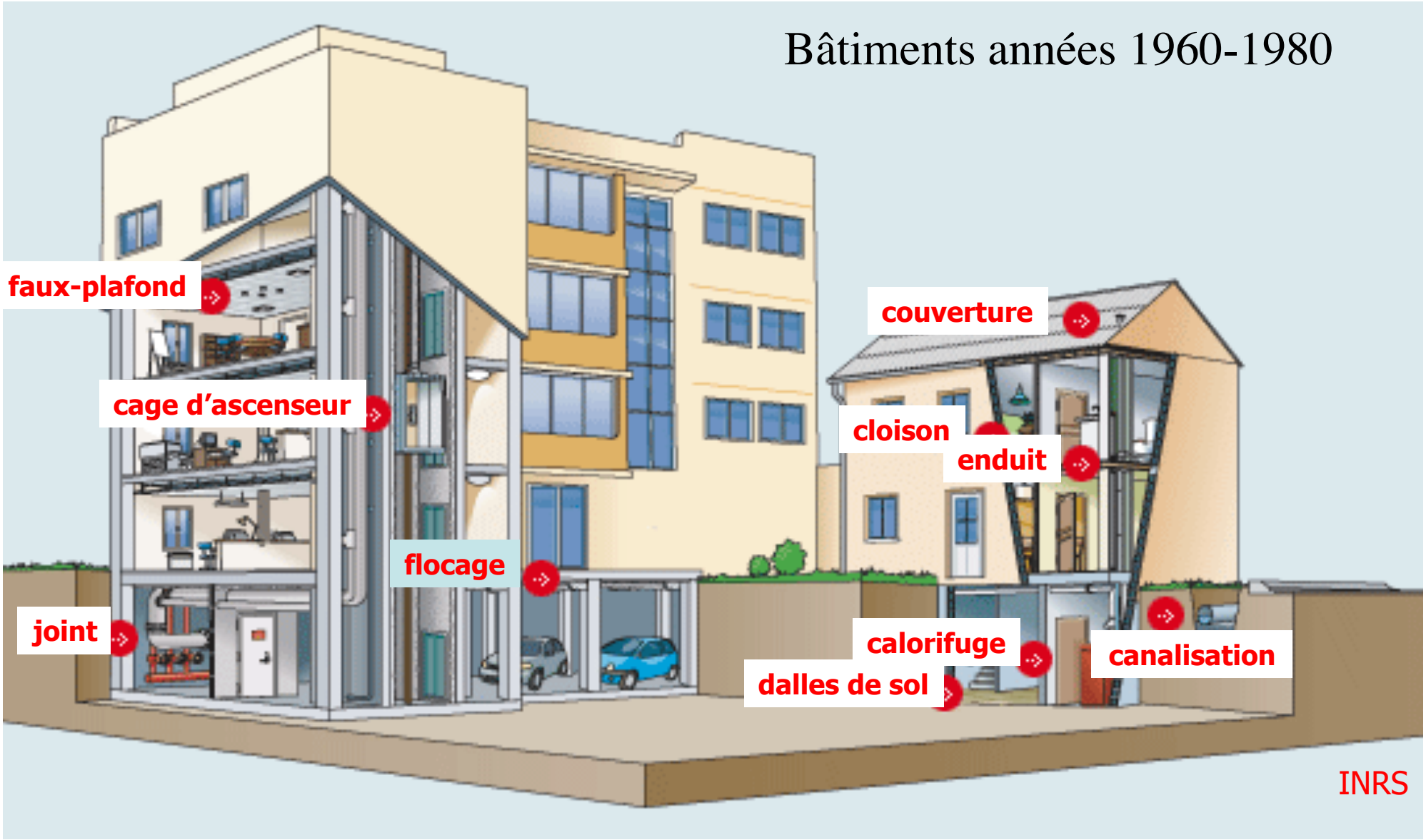
Talc cosmétique: USA (Talc Colgate)
Environnemental (sols) ex: Nevada, Sicile, Corse

Canada (Quebec)

Toiture en éternit


1953 – Le Rocray – Imprégnation et autoclaves

Ouvriers du bâtiment /déconstruction



Niveaux d'exposition mesurés dans différents Secteurs d'activité entre 1987 et 2009

anses
agence nationale de sécurité sanitaire
alimentation, environnement, travail

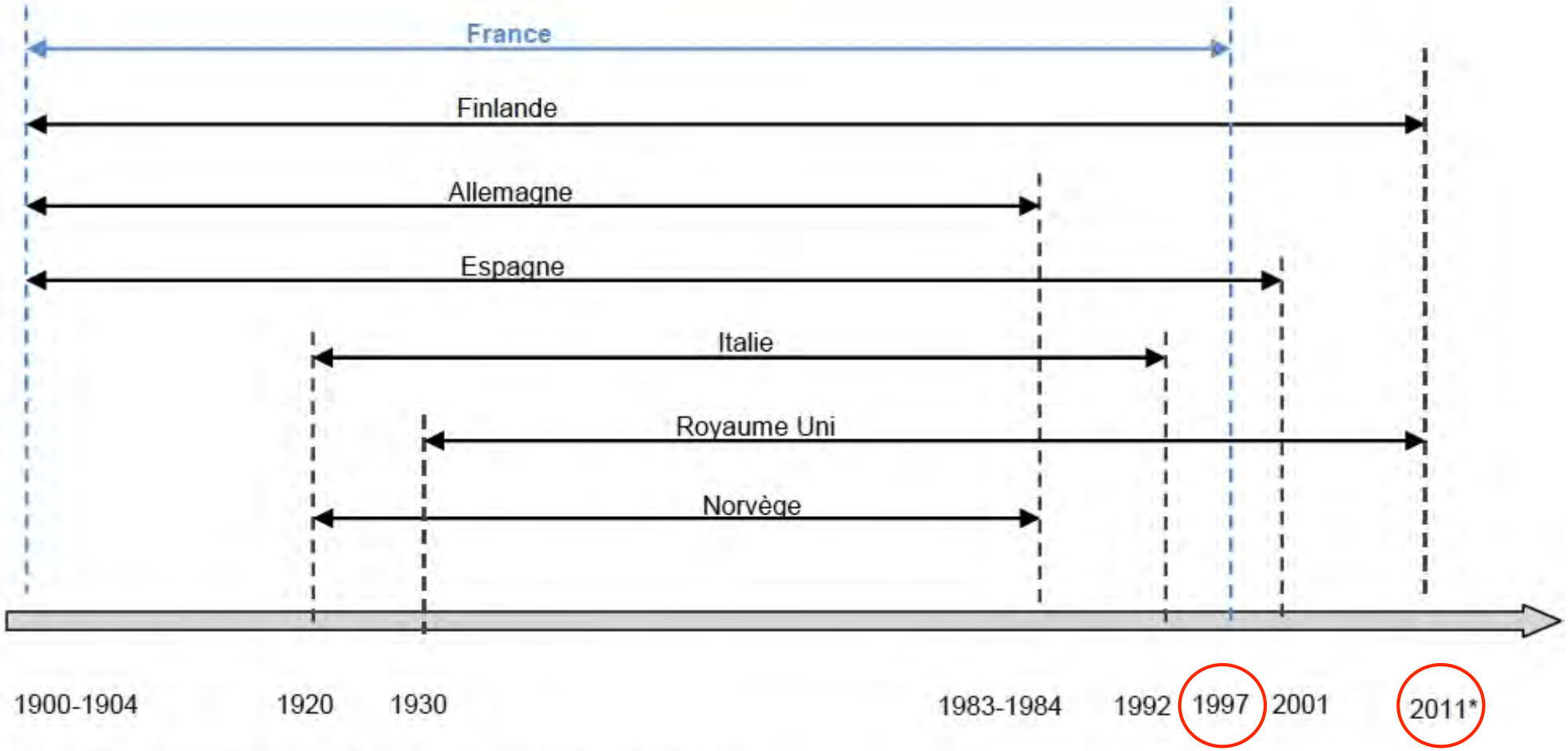
Secteur d'activité	Type de mesurages	Moyenne des mesures en fibres/cm^3
métallurgie	ambiance	0,06
	individuel	0,76
fabrication autres matériels de transport	ambiance	0,11
	individuel	0,29
installation électrique	ambiance	0,21
	individuel	0,25
travaux de plomberie et installation de chauffage	ambiance	0,65
	individuel	0,5
entretien et réparation de véhicules automobiles	ambiance	2,04
	individuel	3,15
production, transport et distribution d'électricité	ambiance	0,08
	individuel	0,35
démolition et préparation de sites	ambiance	0,12
	individuel	7,29
travaux d'installation : électrique, plomberie et autres travaux d'installation	ambiance	0,54
	individuel	0,49
construction de bâtiments résidentiels et non résidentiels	ambiance	11,94
	individuel	10,66
construction de locomotives et autres matériels ferroviaires roulants	ambiance	0,04
	individuel	0,04

Professions par ordre de % d'exposition forte à l'amiante

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
Autres conducteurs de fours de 2eme fusion et fours à réchauffer
Electricien de navire
Conducteur de four de verrerie
Autres ajusteurs-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

Il y a 20 ans la France interdisait l'utilisation de l'amiante dans l'industrie

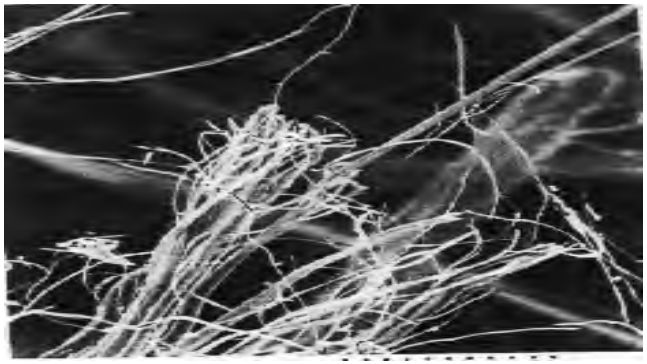
anses
agence nationale de sécurité sanitaire
alimentation, environnement, travail



* *Pour les pays considérant les travaux de désamiantage*

Périodes temporelles identifiées par les pays ayant répondu à l'enquête Anses en réponse à la question sur l'historique d'utilisation de l'amiante

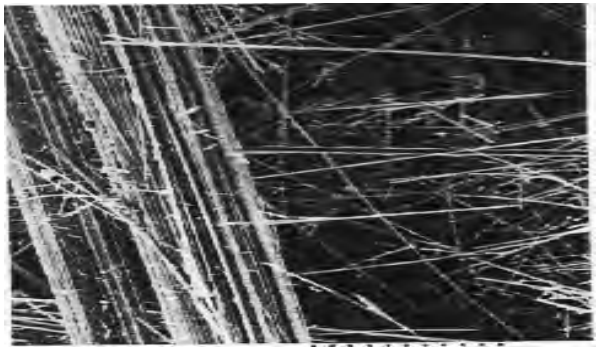
Données Epidémiologiques (4)



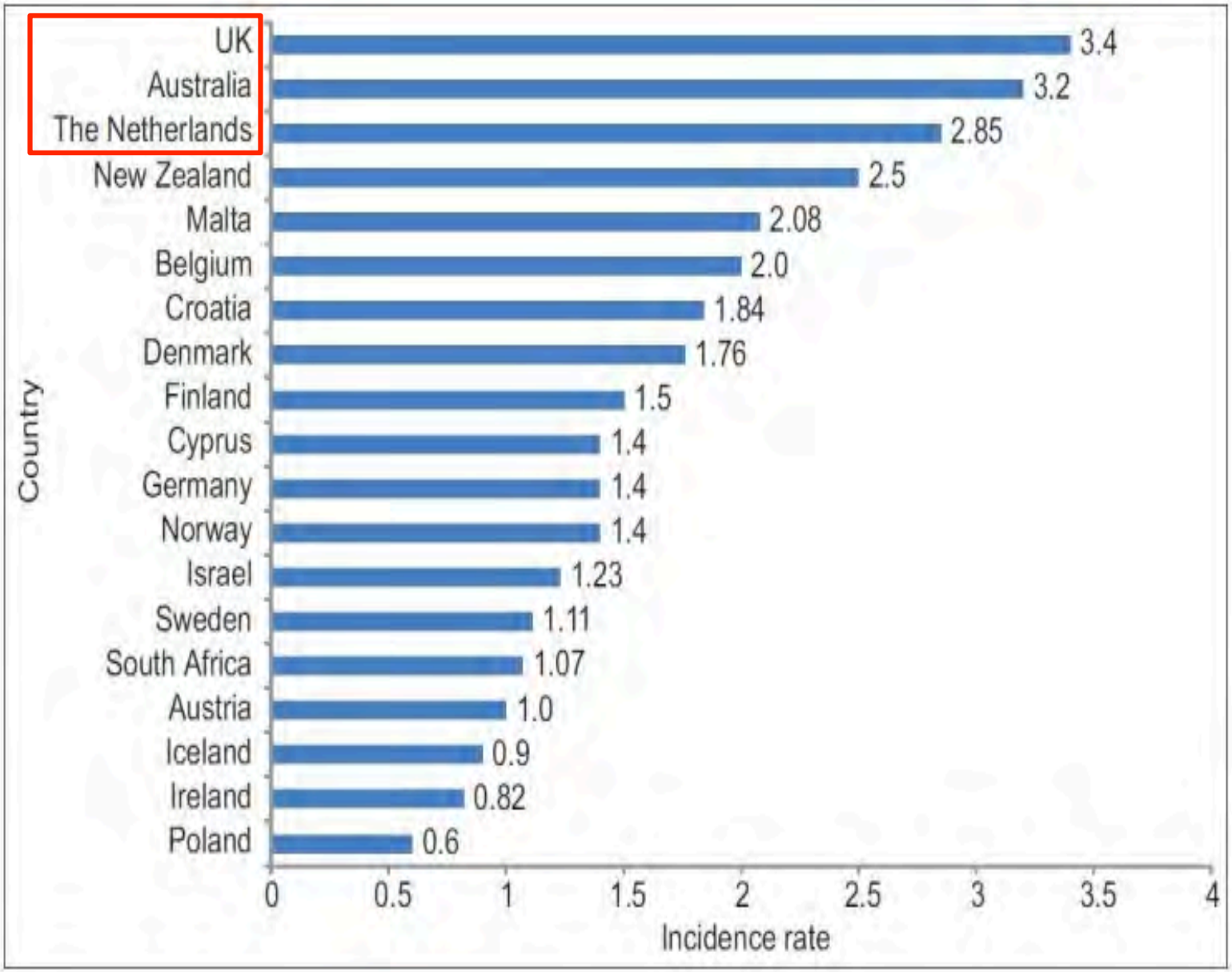
Pays Occidentaux

- 3000 décès en 2020 en GB
- Equivalent au nombre de décès par maladie de Hodgkin aux USA
- 250 000 cas estimés dans les 35 prochaines années

Pays	Cas par an	Cas par million par an
Finlande	75 (2002)	18
France	870 (2000)	18
Allemagne	1094 (2001)	16
Grande-Bretagne	1862 (2002)	39
Italie	1050 (2000)	21
Paysbas	389 (2000)	30
Norvège	57 (2000)	16
Suède	149 (2003)	20



Epidemiology



Global mesothelioma epidemic: Trend and features

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

Exposition professionnelle au fibres réfractaires céramiques

Fibres **longues** nanotubes de carbone

TABLE 4 Effect of the cumulative index of exposure to asbestos on pleural mesothelioma risk in subjects exposed to asbestos only and subjects exposed to both asbestos and refractory ceramic fibres (RCF)

Cumulative index of exposure fibers·mL^{-1}·year^{-1}	Exposed to asbestos only	Exposed to asbestos and RCF
0.0000875	1.0	1.0
0.1	1.0 (1.0–1.0)	1.0 (1.0–1.0)
1	1.1 (1.0–1.1)	1.2 (1.1–1.4)
10	1.9 (1.4–2.5)	5.9 (2.1–16.4)
25	1.9 (1.5–2.4)	13.7 (4.0–46.7)
50	1.9 (1.4–2.5)	12.8 (4.7–35.1)
75	2.6 (1.9–3.4)	12.4 (4.6–33.7)

Data are presented as OR (95% CI). The odds ratio was derived from a logistic regression model with cumulative index of exposure to asbestos (four-knot restricted cubic spline), age at diagnosis for cases and interview for controls (three-knot restricted cubic spline) and birth year (three-knot restricted cubic spline).

Cas-témoins, 988/ 1125

Lacourt A. *et al*. *Eur Respir J*. *2014 , 44(3):725-33*.

Chernova T. *et coll*. *Curr. Biology* 2017

Données Epidémiologiques (3)

En France

- ✓ Le plateau d'incidence a été atteint chez l'homme en 2005 et l'incidence a diminué depuis

1073 cas en

- ✓ L' incidence continue à croître chez la femme

➠ Moindre exposition ... en France qu' au... Bretagne

31ème maladie à Déclaration Obligatoire depuis 2012
Décret n° 2012-47 du 16 janvier 2012

IJC
International Journal of Cancer

Evolution of pleural cancers and malignant pleural mesothelioma incidence in France between 1980 and 2005

N. Le Stang[1,2,3], A. Belot[4,5,6,7], A. Gilg Soit Ilg[1,8], P. Rolland[1,9], P. Astoul[10], S. Bara[11], P. Brochard[12,13], A. Danzon[11], P. Delafosse[11], P. Grosclaude[11], A.-V. Guizard[11], E. Imbernon[8], B. Lapôtre-Ledoux[11], K. Ligier[11], F. Molinié[11], J.-C. Pairon[14,15,16], E.-A. Sauleau[11], B. Trétarre[11], M. Velten[11], N. Bossard[4,5,6], M. Goldberg[8], G. Launoy[2,3], F. Galateau-Sallé[1,2,3]

Conséquences médico-sociales des mésothéliomes liés à l'amiante à l'échelon individuel

- Reconnaissance en **maladie professionnelle**
- Indemnisation par le FIVA
- Identification entreprises à risque (souvent sous-traitants, ou entreprises n'existant plus….)

Ex: sous-traitants AREVA (La Hague)
site de Wonder (Rouen)

Plaques pleurales et risque de mésothéliome

- Population APEXS : 5 287 sujets de sexe masculin, avec TDM thoracique interprétable et suivis depuis TDM jusqu'au 31-03-2011

- 20,4 % ont des plaques pleurales
  71,2% plaques pleurales « typiques » (bilatérales, épaisseur > 2 mm et étendue > 1 cm)

- 17 cas incidents de mésothéliome pleural (14 confirmés par Mésopath, 3 incertains, ou inclassables, aucun exclu)

Pairon et al, J Natl Cancer Inst 2013;105 (4):293-301

Plaques pleurales et risque de mésothéliome

		Hazard Risk [IC 95%]	
	n	brut	Ajusté sur la latence et l'IEC à l'amiante
Absence de plaques	5	1 (réf)	1 (réf)
Plaques pariétales typiques ou diaphragmatiques	10	8,9 [3,0-26,5]	6,8 [2,2-21,4]
Autres plaques moins typiques	2	4,9 [0,9-25,5]	4,0 [0,7-21,2]

Conclusion : La présence de plaques pleurales apparaît être un facteur de risque indépendant pour la survenue du mésothéliome pleural

Pairon et al, J Natl Cancer Inst 2013;105 (4):293-301

En fait témoigne probablement de fortes expositions ++++

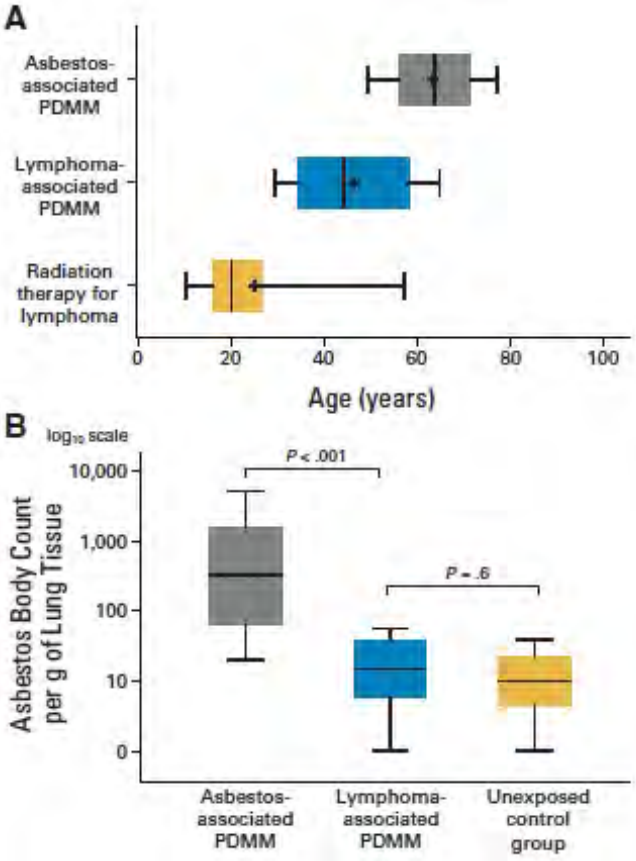
VOLUME 31 · NUMBER 36 · DECEMBER 20 2013

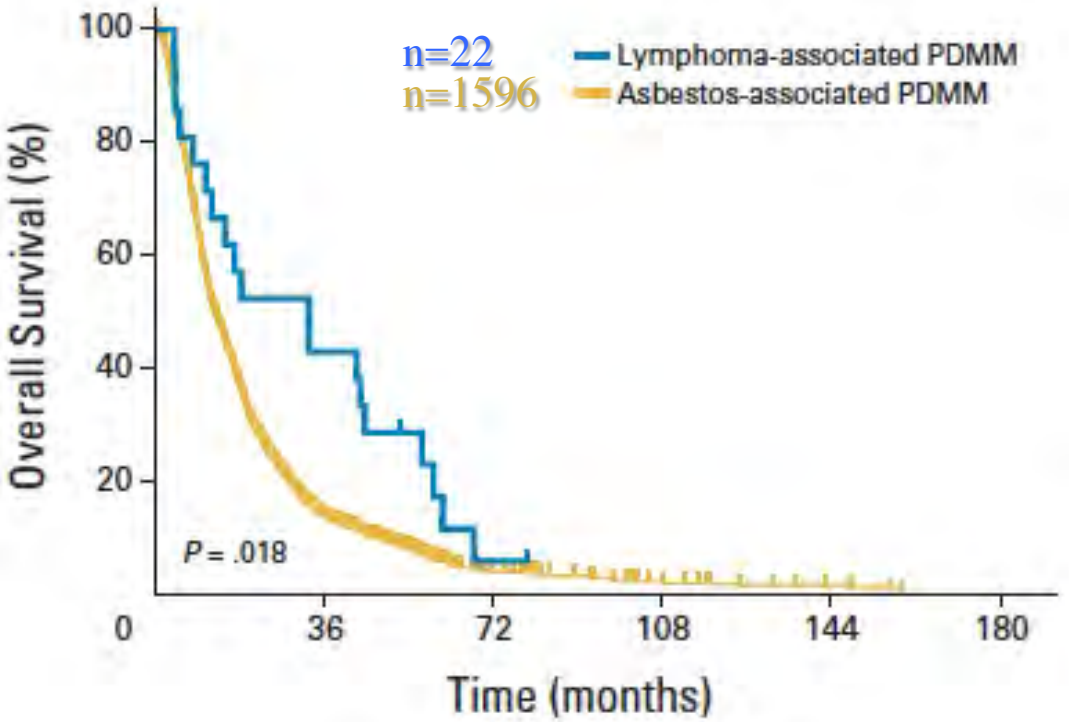
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinicopathologic Characteristics of Malignant Mesotheliomas Arising in Patients With a History of Radiation for Hodgkin and Non-Hodgkin Lymphoma

Lucian R. Chirieac, Justine A. Barletta, Beow Y. Yeap, William G. Richards, Tamara Tilleman, Raphael Bueno, Elizabeth H. Baldini, John Godleski, and David J. Sugarbaker





Malignant pleural mesothelioma (MPM) pathogenesis - Inflammation

Pleural trapping of inhaled fibers

↓

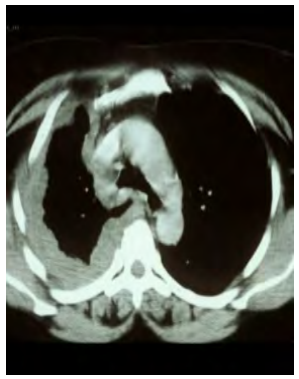
Frustrated phagocytosis

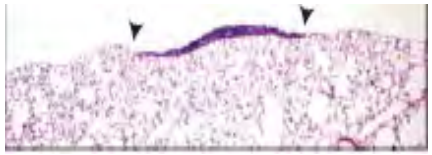
↓

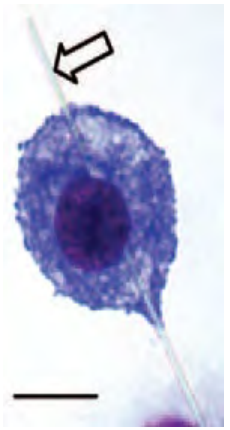
Pleural chronic inflammatory response

↓

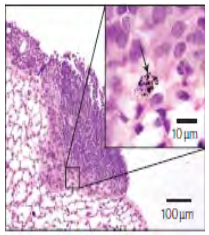
MPM

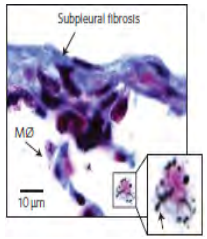






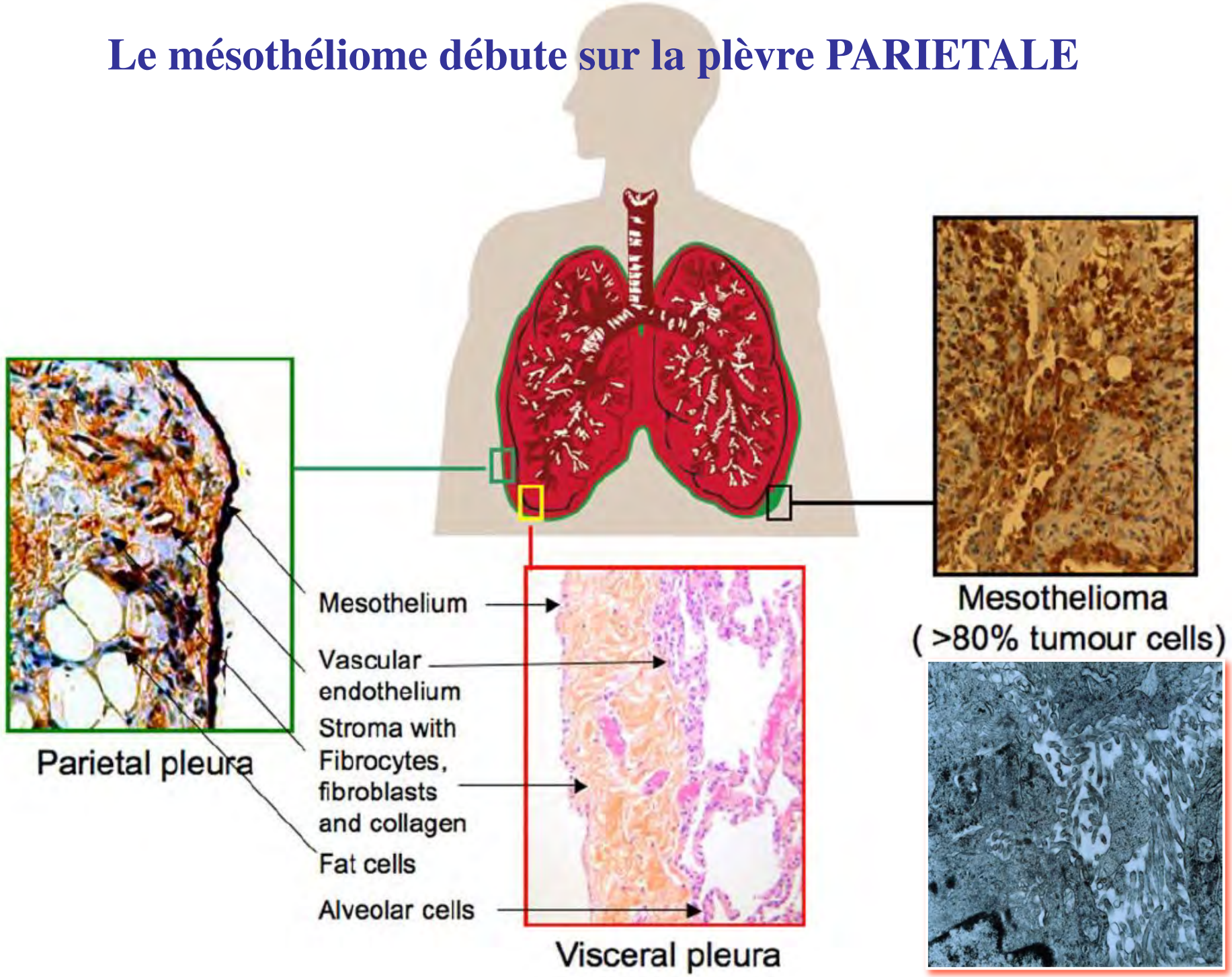
Principal facteur biologique de la carcinogénèse: longueur des fibres





Poland CA. *Nature Nanotech* 2008
Ryman-Rasmussen JP. *Nature Nanotech* 2009
Chernova T. et coll. *Curr. Biology* 2017

Le mésothéliome débute sur la plèvre PARIETALE



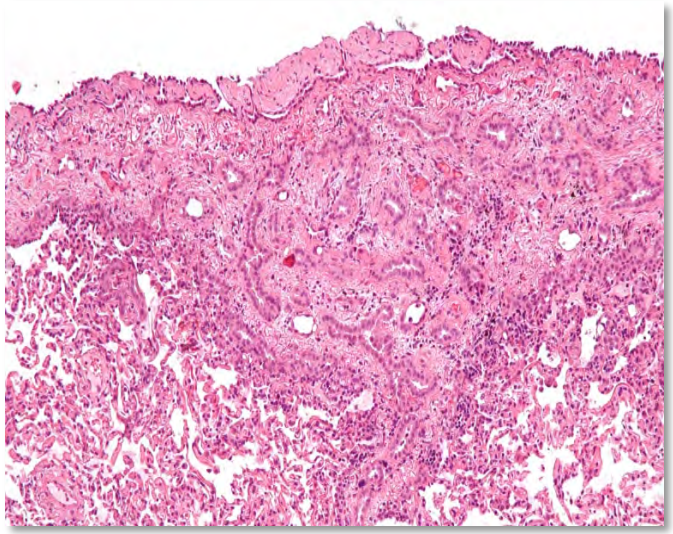
Diagnosis of mesothelioma – **WHO Classification**

IASLC

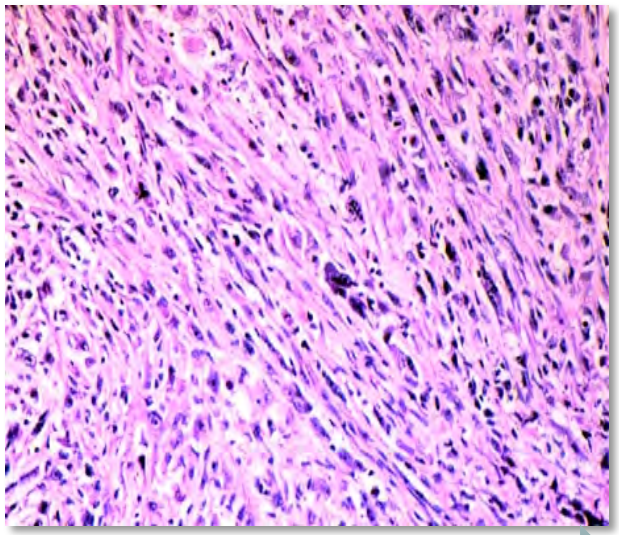
The 2015 World Health Organization Classification of Tumors of the Pleura: Advances since the 2004 Classification

Francoise Galateau-Salle, MD,[a,b] Andrew Churg, MD,[c] Victor Roggli, MD,[d] William D. Travis, MD,[e,*] on behalf of the World Health Organization Committee for Tumors of the Pleura

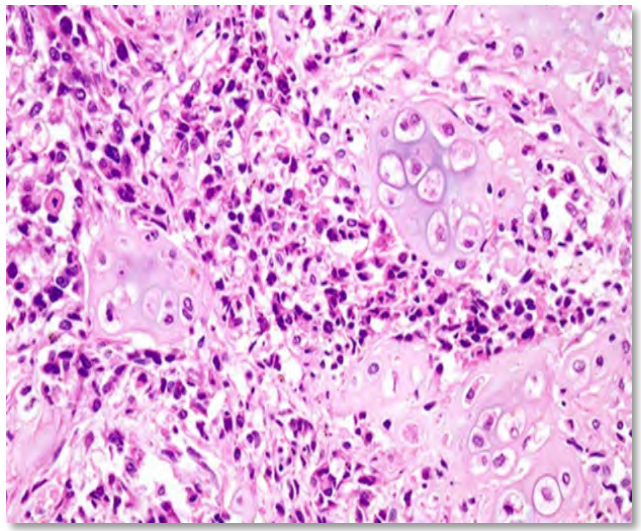
74% EPITHELIOID



15% BIPHASIC

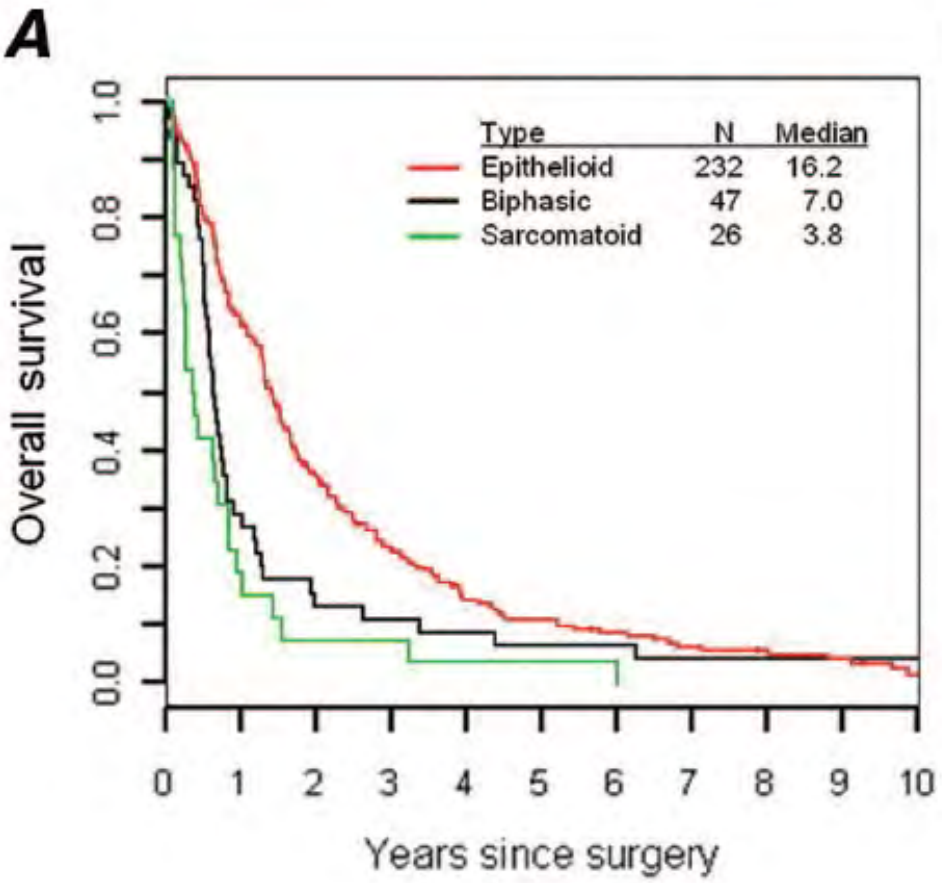


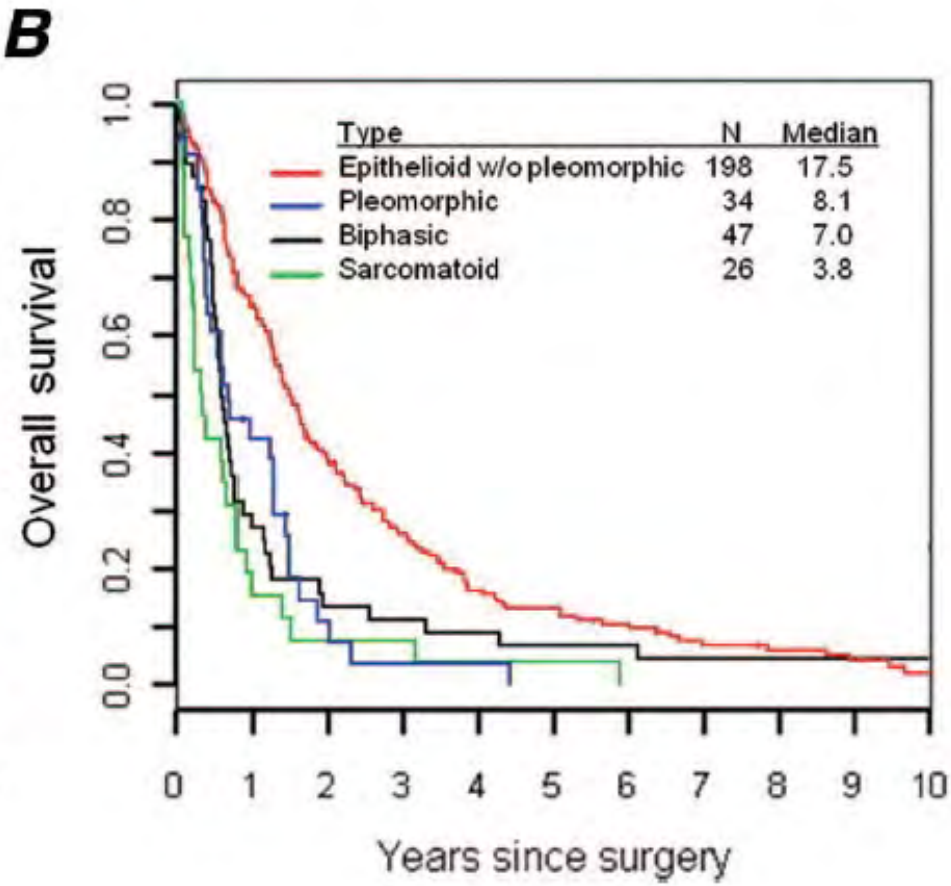
11% SARCOMATOID



Aggressiveness

Valeur pronostique du type histologique
(série chirurgicale)

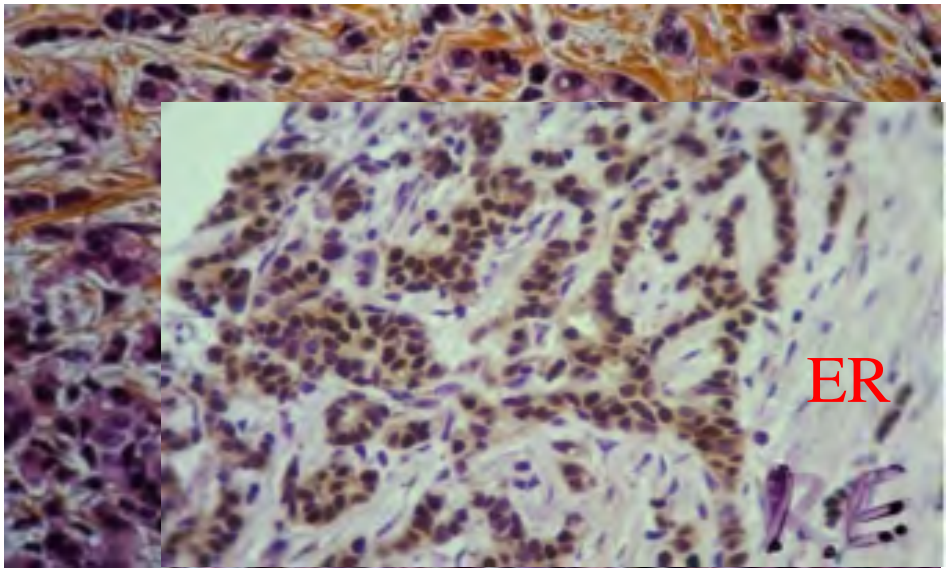




Kadota K et coll. J. Thorac. Oncol. 2011, 6: 896-904

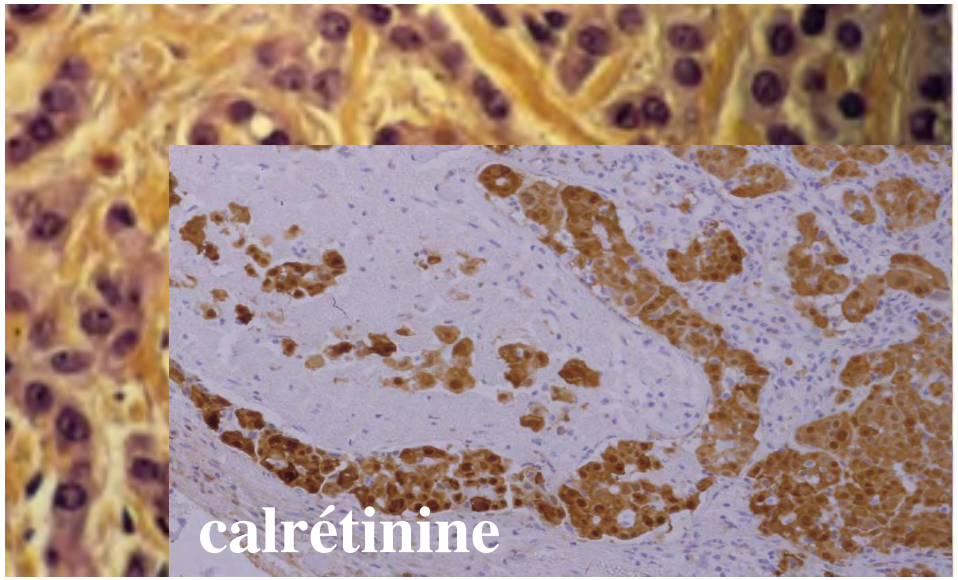
Le problème est que la cellule mésothéliale peut se différencier et mimer virtuellement toutes les cellules épithéliales de l'organisme, d'où un problème de diagnostic différentiel

Noyaux hyperchromatiques sans nucléole



Cancer du sein métastique à la plèvre

Halo clair périnucleaire



Mesothéliome épithélioïde

Absolue nécessité: *i)* de marquages immunohistochimiques
ii) d'une relecture centralisée d'expertise

D'après F. Galateau-Sallé, MESOPATH

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude-Bernard

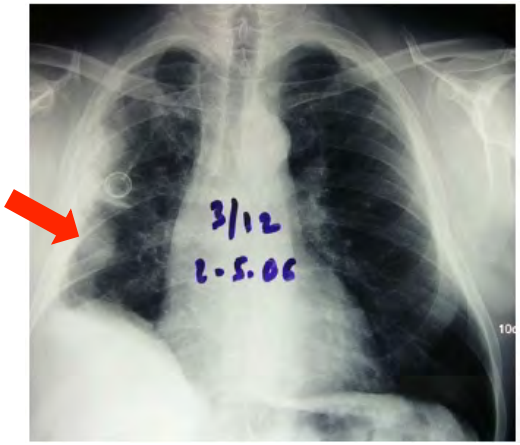
2ème partie: Clinique, Diagnostic
TNM
Pronostic

(rapide !)

université PARIS DIDEROT PARIS 7

IFCT

Tableau Clinique



Signes Révélateurs:

- Douleurs thoraciques +++ dans 60% des cas
- Dyspnée (60%), toux en cas de pleurésie liquidienne
- AEG: amaigrissement
- Fièvre au long cours, sueurs nocturnes (30%)

Dans un contexte connu ou non **d'exposition professionnelle** à l'amiante: **Temps moyen jusqu'au diagnostic= 2-3 mois**

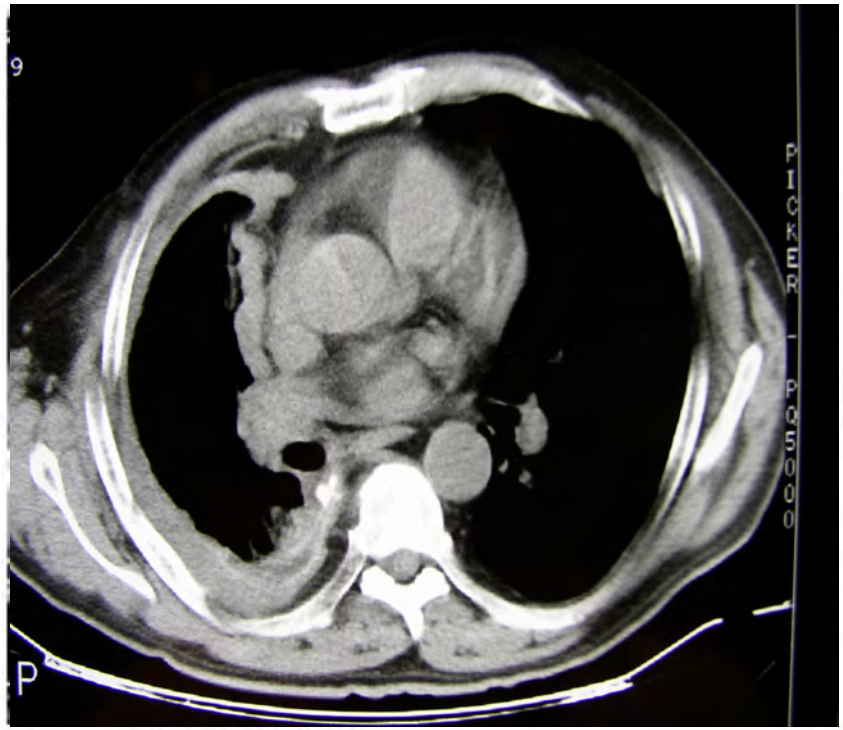
A l'examen:

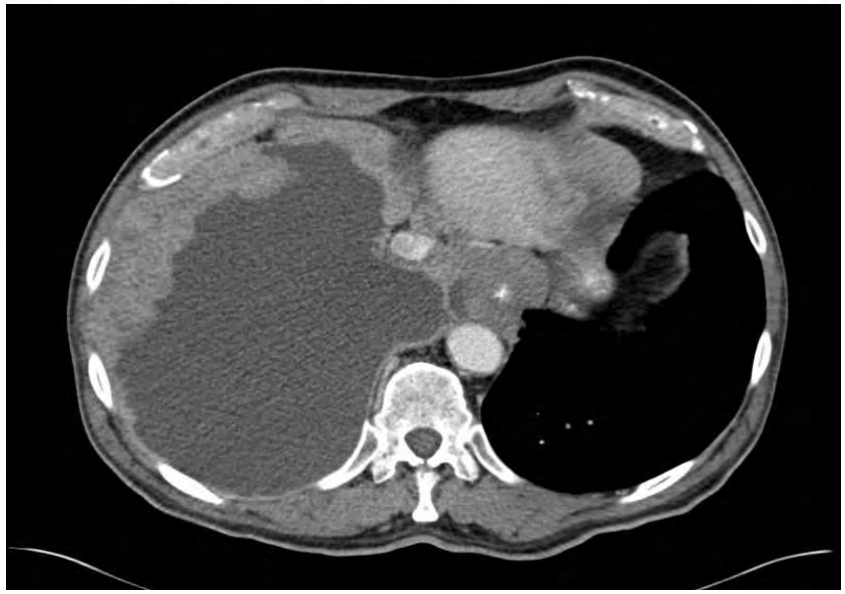
- Syndrome pleural clinique (matité, abolition MV, VV) dans 95%

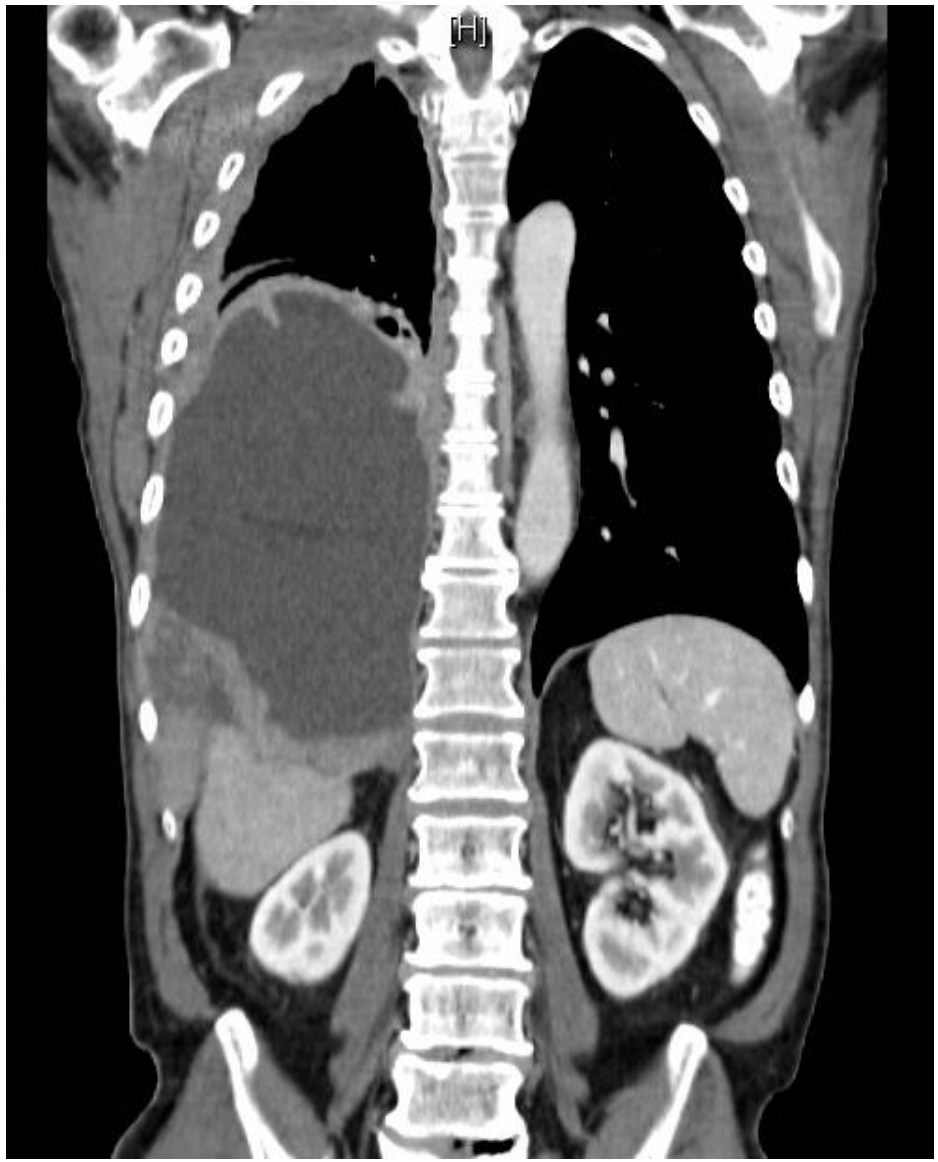
Biologiquement: syndrome inflammatoire, thrombocytose, hyperleucocytose….

Robinson et al. Lancet 2005: 366 (9483): 397 – 408

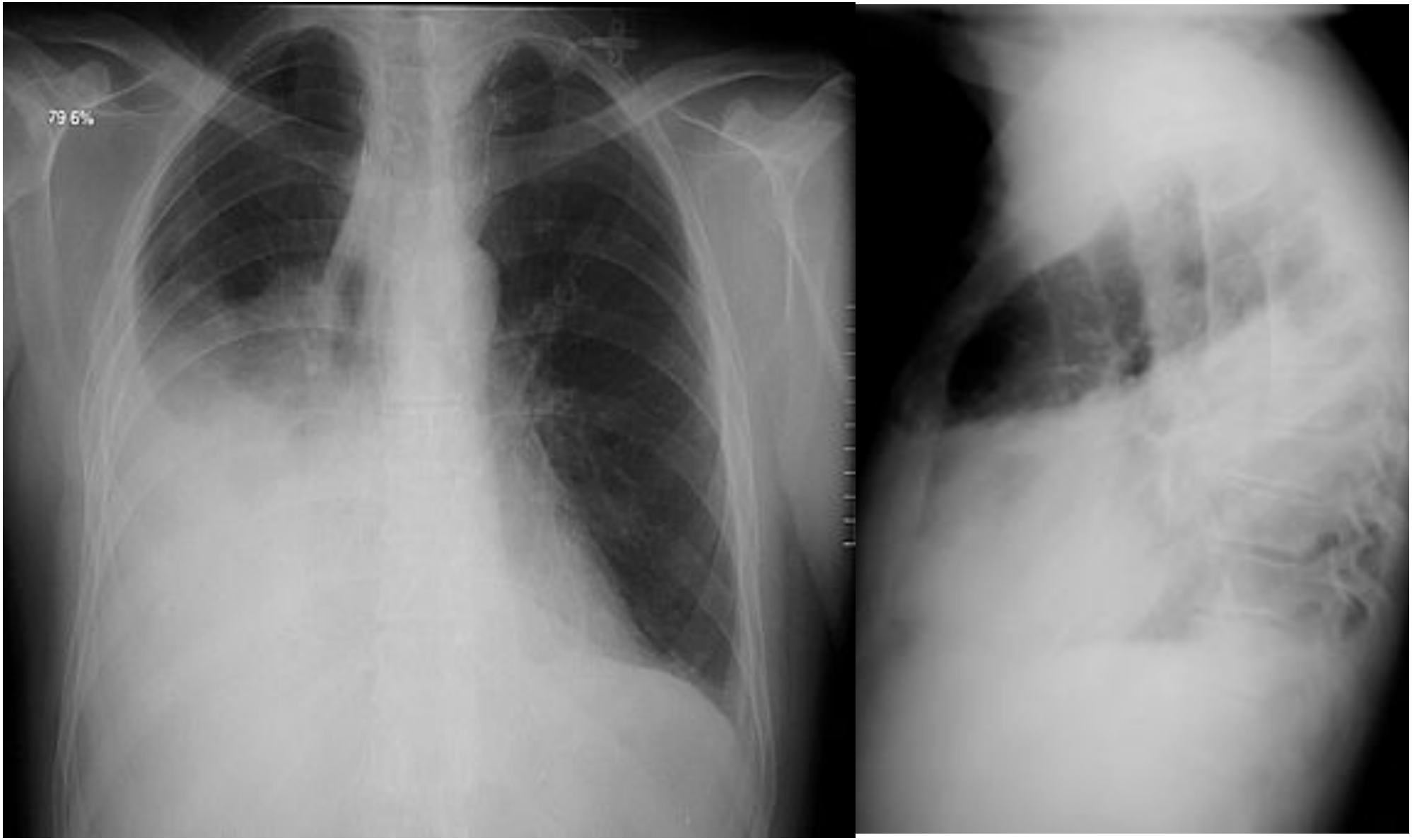
Examen-Clé: le scanner thoracique injecté







Parfois une simple pleurésie nue +/- abondante



Conduite à tenir diagnostique

- Devant une pleurésie et un **contexte d'exposition** identifiée à l'amiante, *A fortiori* si mammelonnement pleuraux, ou plaques pleurales calcifiées ou non, notamment controlatérales….

- NE PAS SE PRECIPITER SUR L'AIGUILLE !!!

- Si ponction, repérer le point de ponction (feutre indélébile + adhésif, ou tatouage) et ponctionner **sur ligne axillaire moyenne** (**pas dans le dos !!**) dans le 5ème espace intercostal

Exsudat très riche en protéines, liquide visqueux ou séro-hémorragique

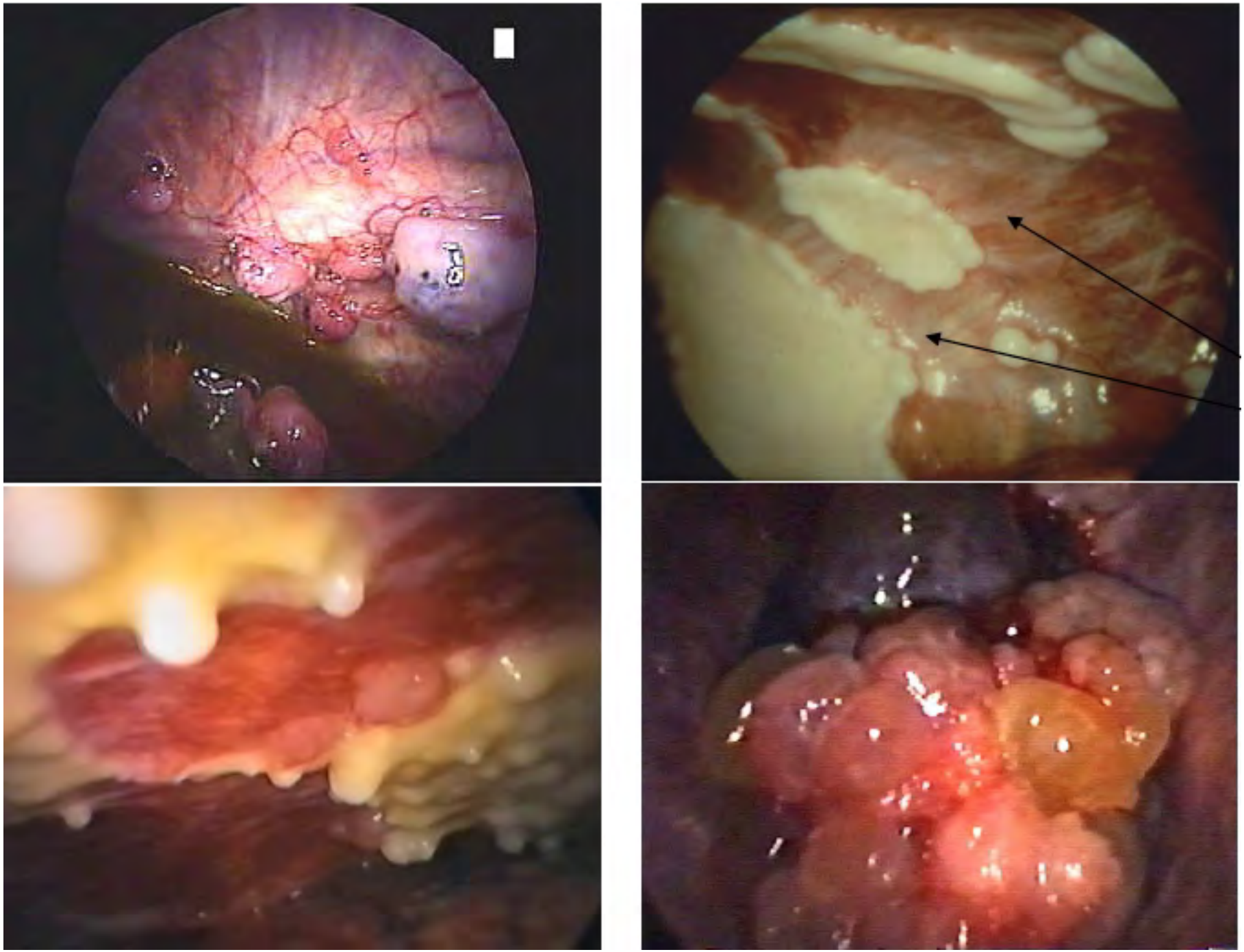
PAS de diagnostic cytologique !!! (seules les formes épithélioides desquament …et alors miment n'importe quel adénoK !!)

Conduite à tenir diagnostique

- Biopsies de large taille **guidées à la vue:**
- **Thoracoscopie** médicale ou chirurgicale (vidéo-chirurgie) ++++
- Permet une symphyse par talc dans le même temps
- Orifices (x 2 ou 3) regroupés dans le même espace intercostal
- Relecture histologique obligatoire par le panel MESOPATH (Caen => Lyon, CRLCC Léon Bérard)

=> Irradier dans les 3 semaines les orifices (voir plus loin)
(sur la seule présomption diagnostique)

MESOTHELIOME : Biopsie de large taille: pleuroscopie +++

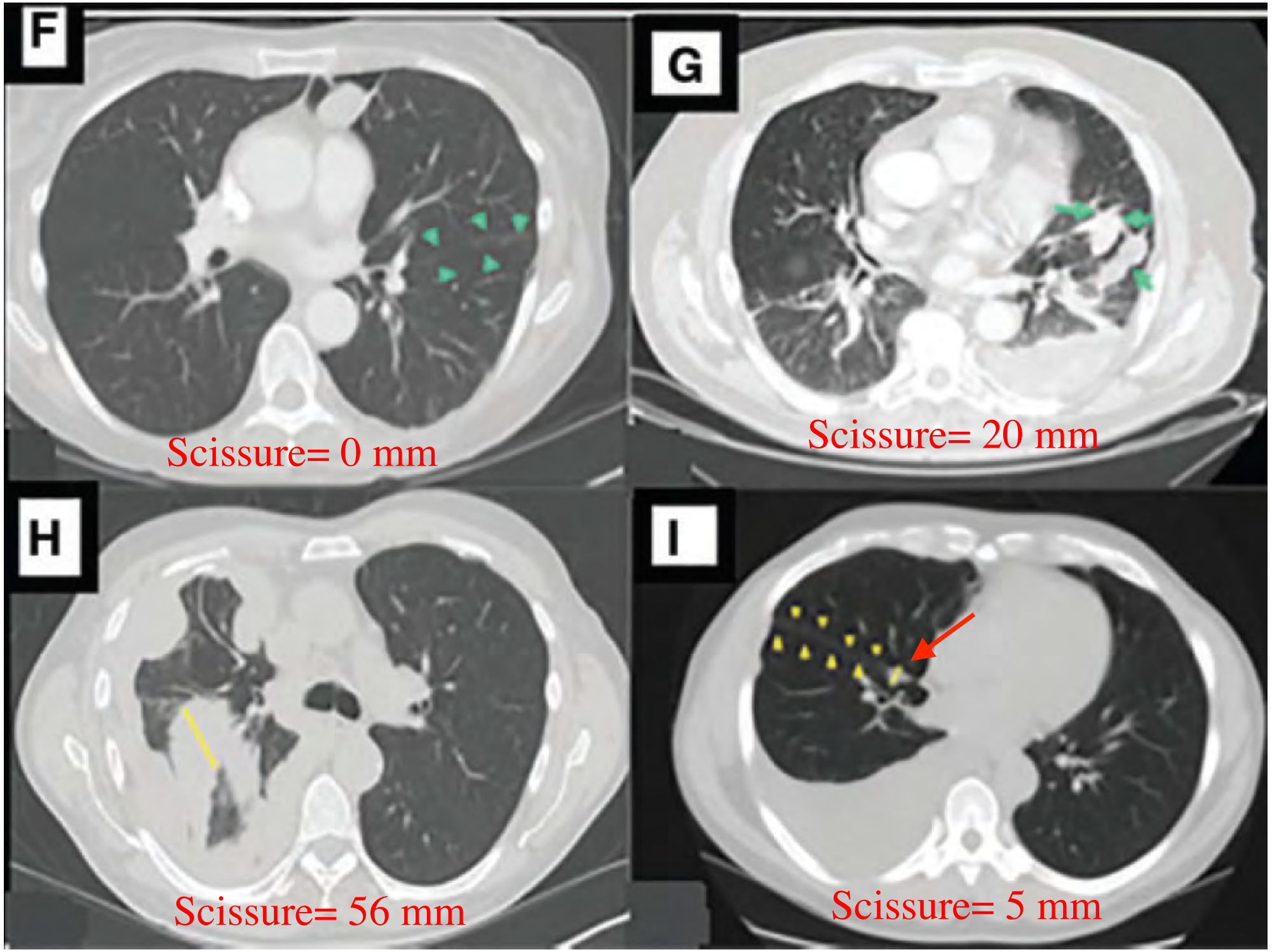


Inadéquation du TNM actuel de l'IASLC (V. Rush)

" It is nearly impossible to clinically distinguish between T1a (parietal pleural involvement), T1b (minimal visceral pleural involvement), and T2 (involvement of all pleural surfaces, plus the diaphragm, fissures, or pulmonary parenchyma), nor is it possible to clinically ascertain those features required for a T3 designation, such as endothoracic fascia or nontransmural pericardial involvement.

So it comes as no surprise that up to 80% of the patients clinically thought to have stage I or II disease were subsequently upstaged at surgery."

Hedy Lee Kindler, J. Thorac. Oncol. Nov 2012


F
Scissure= 0 mm
G
Scissure= 20 mm
H
Scissure= 56 mm
I
Scissure= 5 mm

Mieux que le cTNM, la quantification volumétrique TDM ?

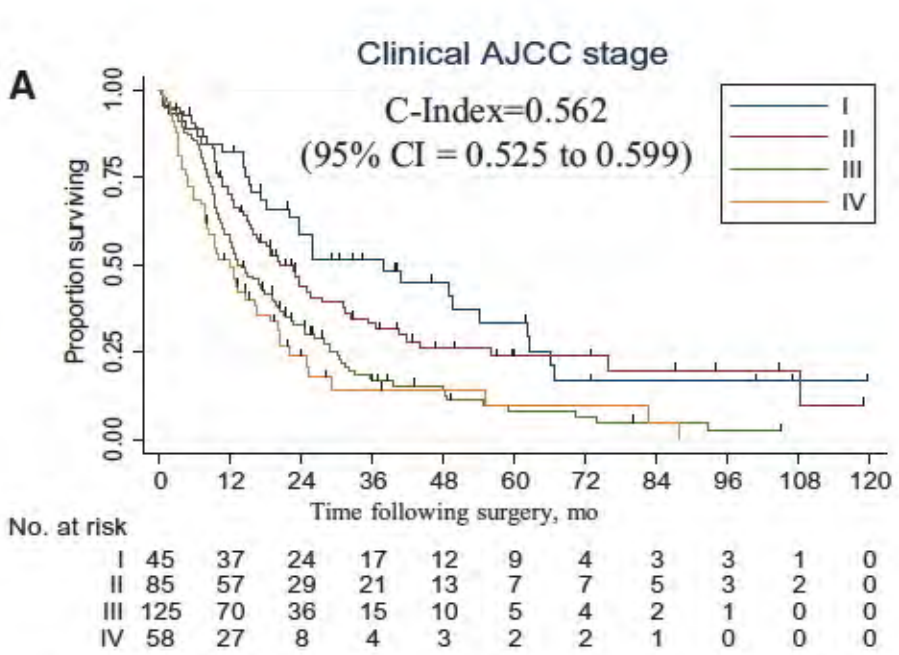
Gill RR *et al*. JNCI 2018

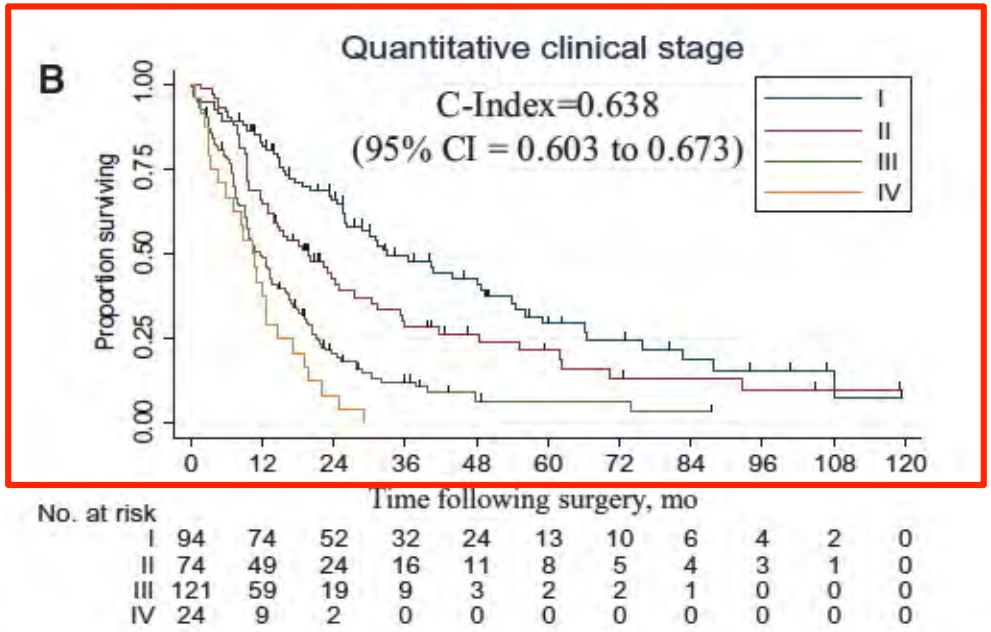
Quantitative clinical stage groupings*

Quantitative stage groupings	VolCT (cc) and Fmax (mm)
Stage I	VolCT ≤ 150 and Fmax ≤ 5
Stage II	VolCT ≤ 150 and Fmax > 5 or VolCT > 150 and VoCT ≤ 500 and Fmax ≤ 5
Stage III	VolCT > 150 and VoCT ≤ 500 and Fmax > 5 or VolCT > 500 and VoCT ≤ 1200
Stage IV	VolCT > 1200

*Fmax = maximal fissural thickness; VolCT = tumor volume assessed from three-dimensional reconstruction of computed tomography scans.

Basée sur le volume tumoral et l'épaississement de la scissure





Histoire Naturelle

- Espérance de vie médiane ≤ 10 mois avant l'ère du pemetrexed

- < 5% de patients en vie à 5 ans

- Rares cas de patients vivants sur une longue durée, indépendemment du traitement reçu.

(*7 des 64 patients non traités de la série de Law survivent à plus de 4 ans entre 1971 et 1980 avec une médiane d'espérance de vie…de 18 mois!)*

➠ Mésothéliome vrai ou hyperplasie mésothéliale atypique?

L'indolence supposée du MPM reste très rare !!

Facteurs Pronostiques
(avant ère pémetrexed)

(Validation des scores prédictifs du CALGB et de l'EORTC)

5 Variables	**Groupe favorable**
Histologie	MS = 10.8 mois
Hb	(40% à 1 an)
GB	**Groupe défavorable**
P.S	MS = 5.5 mois
Sexe	(12% à 1 an)

Les femmes ayant un MPM ont une espérance de vie trois fois supérieure à celle des hommes

- Registre Nord-Américain du SEER (**1973**-2009)
- 14 228 cas de Mésothéliomes
- Dont 3196 femmes (22%)

⇒ Espérance de vie à 5 ans :

13,4% chez les femmes *vs*. 4,5% chez les hommes

(% faible de traitement « moderne » à base de pemetrexed)

Effet pronostique persistant en analyse multivariée (âge, TNM, race, traitement): HR= 0,78

Taioli E et coll. Ann. Thorac Surg. 2014, 98: 1020-4

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude-Bernard

3ème partie: Traitements loco-régionaux Radiothérapie et Chirurgie

université PARIS DIDEROT PARIS 7

IFCT

Prévention des rechutes sur trajet de ponction ou talcage: Un essai randomisé “historique” positif

RT: 3 x 7 Gy en 3 jours consécutifs, avec bolus cutané en utilisant des électrons d’énergie adaptée (de 12 à 15 Mev) à la profondeur
Sur toutes les cicatrices de ponction ou de drainage, dans les 3 semaines après ponction.

	Surveillance	3 x 7 Gy
N	20	20
Rechute cutanée	8 (40%)	0

P< 0.001

Boutin, Chest, 1995; 108: 754

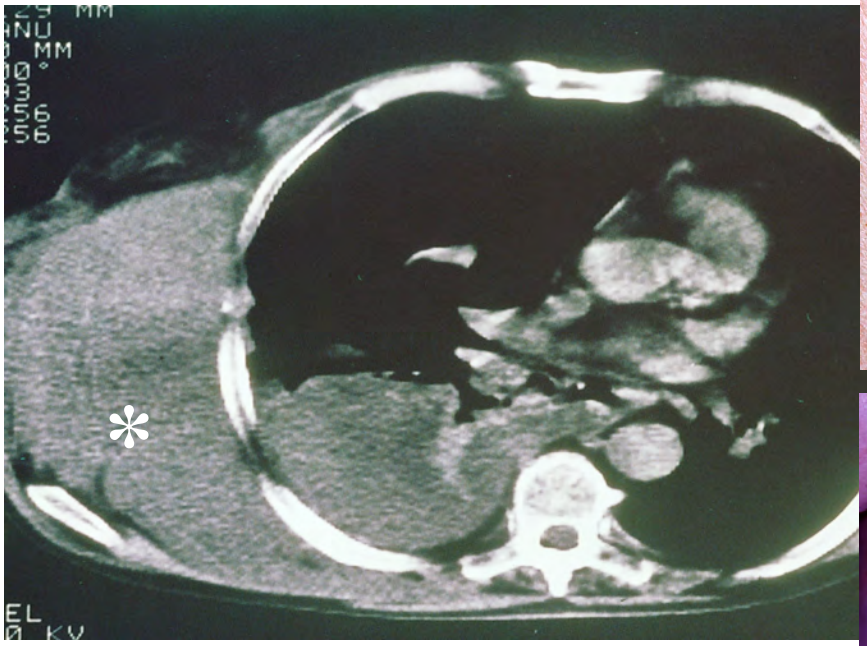
Prévention des rechutes sur trajet de ponction ou talcage:

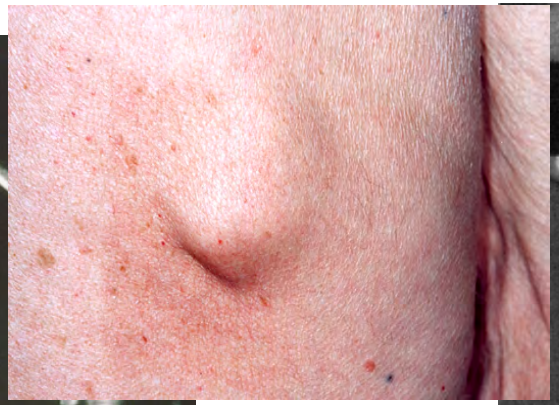
Plusieurs séries ou « essais » méthodologiquement tous contestables

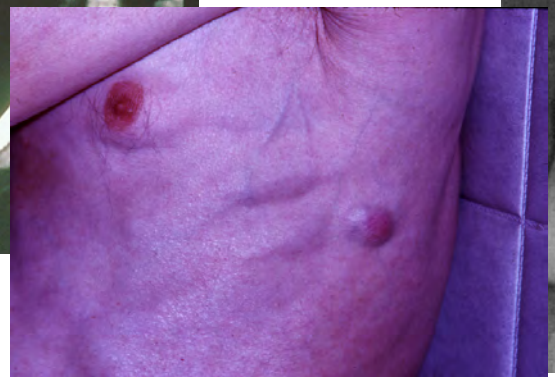
Details about prophylactic radiation therapy in malignant pleural mesothelioma from reported randomized and non-randomized studies and from current study.

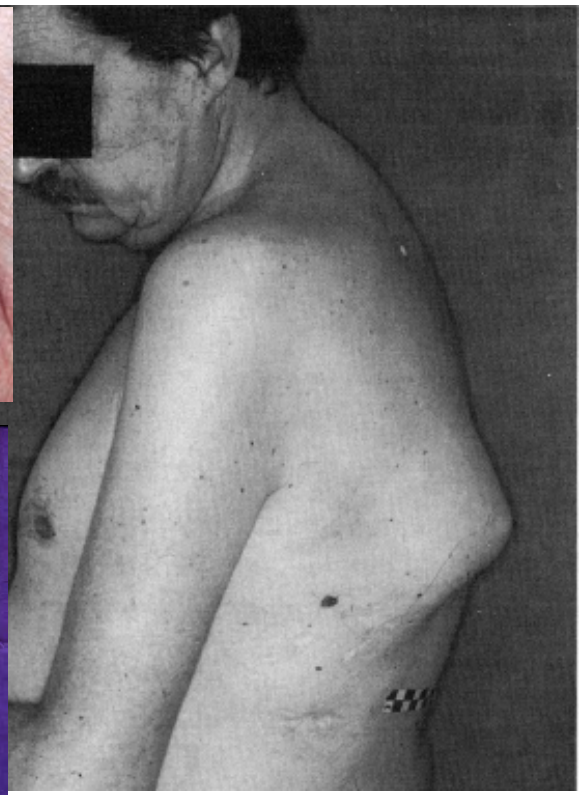
Author	Procedure	Time interval before RT (days)	EBRT schedule/ energy	N./ type of study	Procedure tract metastases after EBRT	Adverse effects from EBRT
Boutin 1995	Thoracoscopy	10 to 15	21 Gy in 3 fr/from 12.5 to 15 MeV electrons	20 vs. 20*/ randomized	0% vs. 40%	No inflammation or edema
Low 1995	Thoracoscopy	Within 15	21 Gy in 3 fr/ 140 KV or 250 KV photons	19**/ retrospective	0%	No side effects
Cellerin 2004	Aspiration, needle biopsy, chest drain, surgical incision	10 to 123 (median 37)	Several not specified	33 vs. 25*/ retrospective	21% vs. 48%	NR
Bydder 2004	Needle biopsy, FNA, thoracoscopy, thoracic drain	Within 15	10 Gy in 3 fr/9 MeV electrons	43**/ randomized	7% vs. 10%	No patients with RTOG/EORTC Grade 2–4 toxicities
West 2005	Needle biopsy, thoracoscopy, chest drain	6 to 42 (median 26)	21 Gy in 3 fr/10 MeV electrons, 6 MV photons with bolus, 200 KV photons without bolus	37/ retrospective	0%***	NR
O'Rourke 2007	Thoracic drain, thoracoscopy, pleural biopsy	Within 21	21 Gy in 3 fr/9–12 MeV electrons or 250 KV photons	31 vs. 30*/ randomized	13% vs. 10%****	Three patients with erythema/discoloration, one vomiting, one chest discomfort
Di Salvo 2008	Thoracoscopy, pleurectomy, thoracic drain, FNA	11 to 60	21 Gy in 3 fr/ 12 MeV electrons	32/ retrospective	0%	Eleven patients with erithema G1/ no late adverse effects

Les nodules métastatiques sur les trajets de ponctions









Fréquence réelle ?

- 40% dans le bras contrôle de l'essai Marseillais (Boutin, 40 patients)
-10% dans le bras contrôle de l'essai Australien (Bydder, 43 patients)
- de 4% après ponction sous TDM, à 16% après thoracoscopie et 24% après thoracotomie dans une série radiologique rétrospective canadienne (Argawal, n=100 patients avec MPM et procédure)
- 11% dans l'essai randomisé écossais (O'Rourke, 61 patients)
- 10% dans la série de 119 cas Caennais consécutifs (1993-2003): avec RT !

Boutin et al., Chest, 1995; 108: 754
Bydder et al. Brit. J. Cancer 2004: 9-10
Poret , thèse de médecine, UFR de Caen 2004
Agarwal et al. Radiology 2006; 2: 589-94
O'Rourke et al. Radioth. Oncol. 2007;84:18-22

Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial

Lancet Oncol 2016
Published Online
June 23, 2016
http://dx.doi.org/10.1016/S1470-2045(16)30095-X

Amelia O Clive, Hazel Taylor, Lee Dobson, Paula Wilson, Emma de Winton, Niki Panakis, Justin Pepperell, Timothy Howell, Samuel A Stewart, Erika Penz, Nikki Jordan, Anna J Morley, Natalie Zahan-Evans, Sarah Smith, Timothy J P Batchelor, Adrian Marchbank, Lesley Bishop, Alina A Ionescu, Mike Bayne, Samantha Cooper, Anthony Kerry, Peter Jenkins, Elizabeth Toy, Vallipuram Vigneswaran, James Gildersleve, Merina Ahmed, Fiona McDonald, Mick Button, Conrad Lewanski, Charles Comins, Muthukumar Dakshinamoorthy, Y C Gary Lee, Najib M Rahman, Nick A Maskell

- **Mesotheliome Pleural Malin (MPM)**
- Histologiquement prouvé
- PS= 0-3
- Chimio-naïf ou pas
- Age<78
- drain, pleuroscopie medicale ou chir, thoracotomie, pleur-X

R 1:1

A → **RT Immédiate des orifices**
(dans les 42 jours)
3x 7 Gys + bolus cutané
7cmx 7cm (3cm de marge circonférencielle)
électrons hte énergie(>12MeV)

B → **RT à l'émergence d'un nodule**
3x 7 Gys + bolus cutané
7cmx7cm dans les 42 jours suivant l'émergence

H: décroitre de **15%** dans le bras RT différée à **2%** l'incidence des métastases de reperméation

=>102 patients x 2 pour puissance = 90%, α=5%, avec 3 % de perdus de vue

Interpretation Routine use of prophylactic radiotherapy in all patients with mesothelioma after large-bore thoracic interventions is not justified.

OR= 0,51; p=0,14

Prophylactic radiotherapy to prevent procedure-tract metastases

Amelia Clive and colleagues' article[1] in *The Lancet Oncology* reports on a randomised trial comparing the use of early systematic radiotherapy for the prevention of procedure-tract metastases (PTM) to deferred radiotherapy in patients with malignant pleural mesothelioma. We think that the main conclusion of their study, emphasised by the accompanying Comment title,[2] could in eight patients, and three other patients receiving their first fraction beyond the 42-day limit, which is already twice the delay used in the seminal study by Boutin and colleagues.[7] Hence, the per-protocol prespecified analysis clearly showed a significant difference of PTM from 16 (16%) of 99 patients in the deferred radiotherapy group to five (6%) of 84 patients in the immediate radiotherapy group(p=0·037). Supporting this finding, the mean volume of PTM in the deferred radiotherapy group was larger by 1·5 cm, although the distance between the procedure site and the edge of

GZ participated in advisory boards for Roche, Eli Lilly, Bristol-Myers Squibb, Clovis Oncology, AstraZeneca, Boehringer Ingelheim, and Pfizer, all outside the submitted work, and received a research grant from Roche. AS reports grants from Roche. He was an advisory board member for Merck Sharp & Dohme, Bristol-Myers Squibb, Seattle Genetics, Roche, and AstraZeneca; he received research grants from Amgen, Teva, and Roche and received travel grants from Boehringer Ingelheim, all outside the submitted work. SB declares no competing interests.

*G Zalcman, S Brosseau, A Scherpereel
gerard.zalcman@aphp.fr

Department of Thoracic Oncology, Centre d'Investigation Clinique 1425, Hospital Bichat-Claude Bernard, Assistance Publique-Hôpitaux de Paris, Paris-Diderot University, Paris, France (GZ, SB); and Pulmonary and Thoracic Oncology Department, Centre Hospitalier Universitaire Lille, University of Lille, Lille, France (AS)

Partly SMART or partly flawed ?

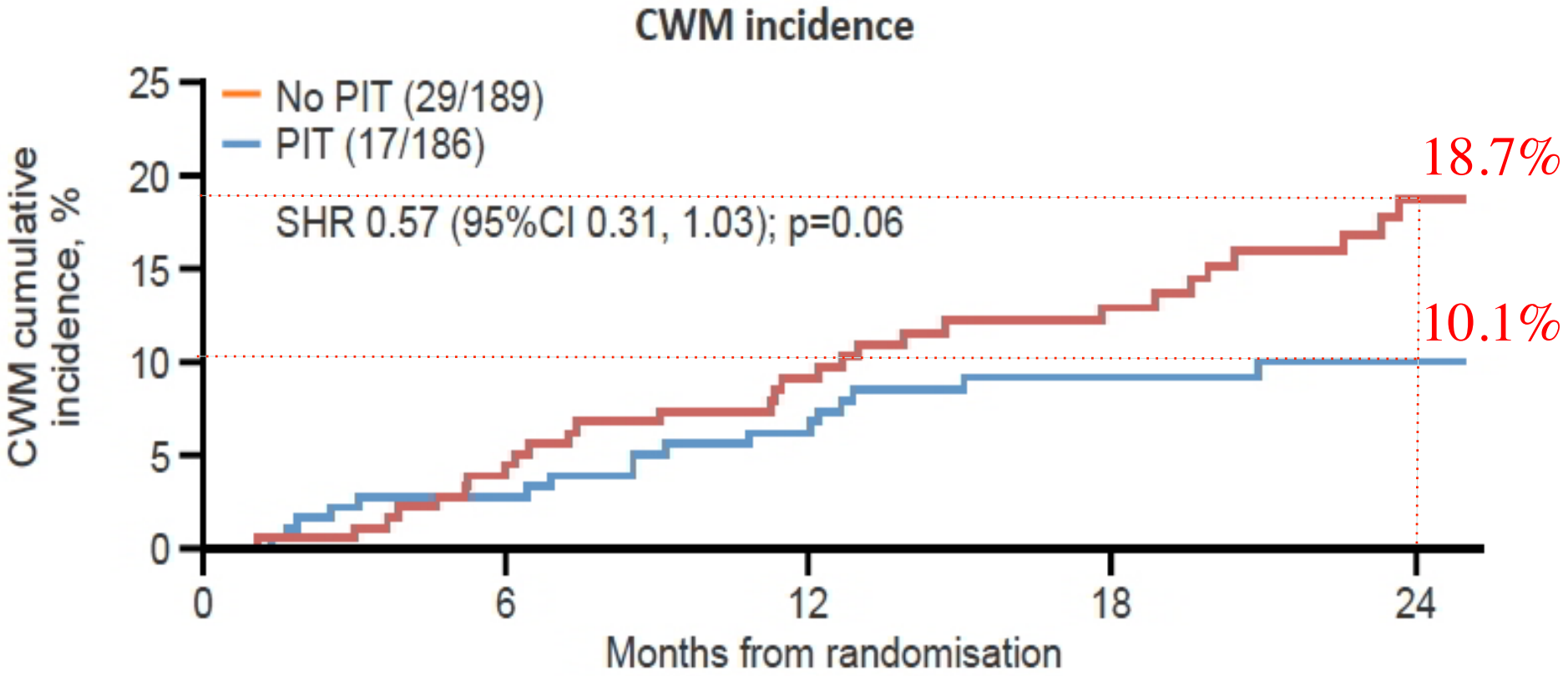
Zalcman G., Brosseau S, Scherpereel A. Lancet Oncol 2016

11% de violations majeures de protocole ! (> 42j, < 7cm, meV < 12meV)

Analyse per-protocole: 16% *vs*. 6% (OR= 0,33; p= 0.037)

Analyse chez les patients ne recevant pas de chimio: OR= 0,16 (p<0,021)

2ème essai britannique (PIT): 375 patients randomized, primary endpoint at….6 months
« large thoracotomies, needle biopsy sites were excluded…only VATS, chest drains »
Cumulative incidence at 24 months was 18.7% vs. 10.1%



- The cumulative incidence of CWM at 6 or 12 months was 3.2% with PIT vs. 5.3% without at 6 months and 8.1% vs. 10.1% at 12 months, respectively
- The most common radiotherapy-related AE in the PIT arm was mild skin toxicity

Bayman N et al. J Thorac Oncol 2017;12(suppl):Abstr OA 02.03

Chirurgie du Mésothéliome

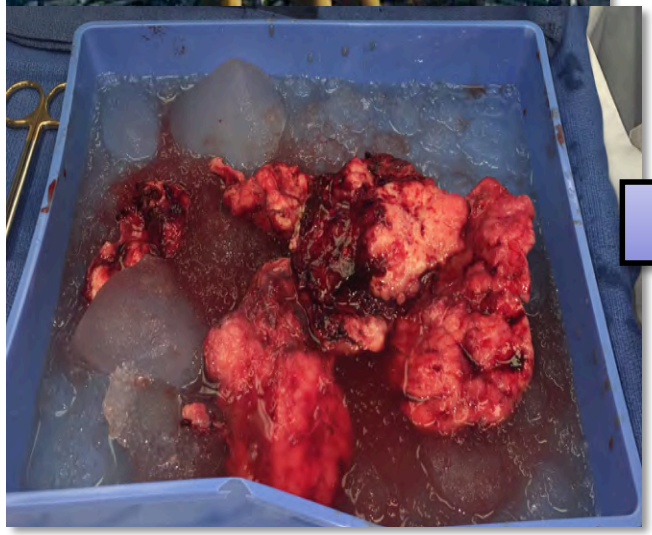
2011: La fin de la « chirurgie de l'impossible » (PPE) ?
...l'avènement de la chirurgie de « débulking » ou de « cytoreduction »

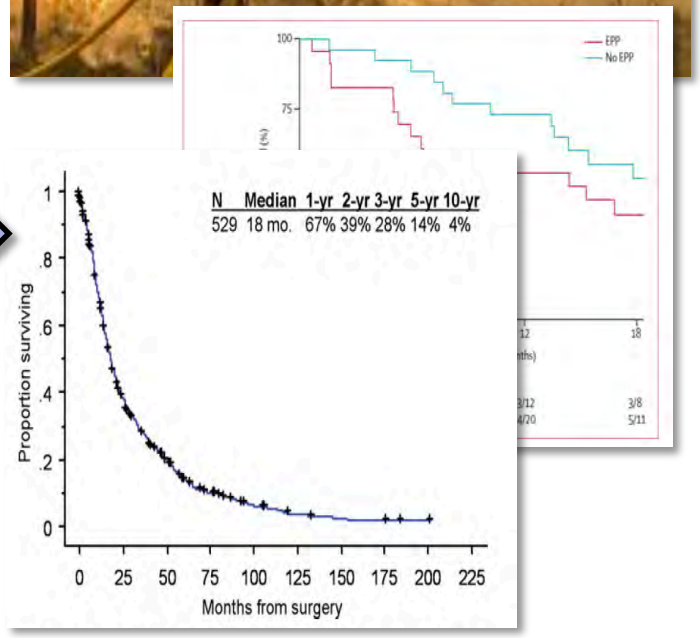
Harvey Pass, ASCO 2011
Valerie Rush, WCLC 2011

Do Facts Matter?

Climate Change

Surgery for Mesothelioma



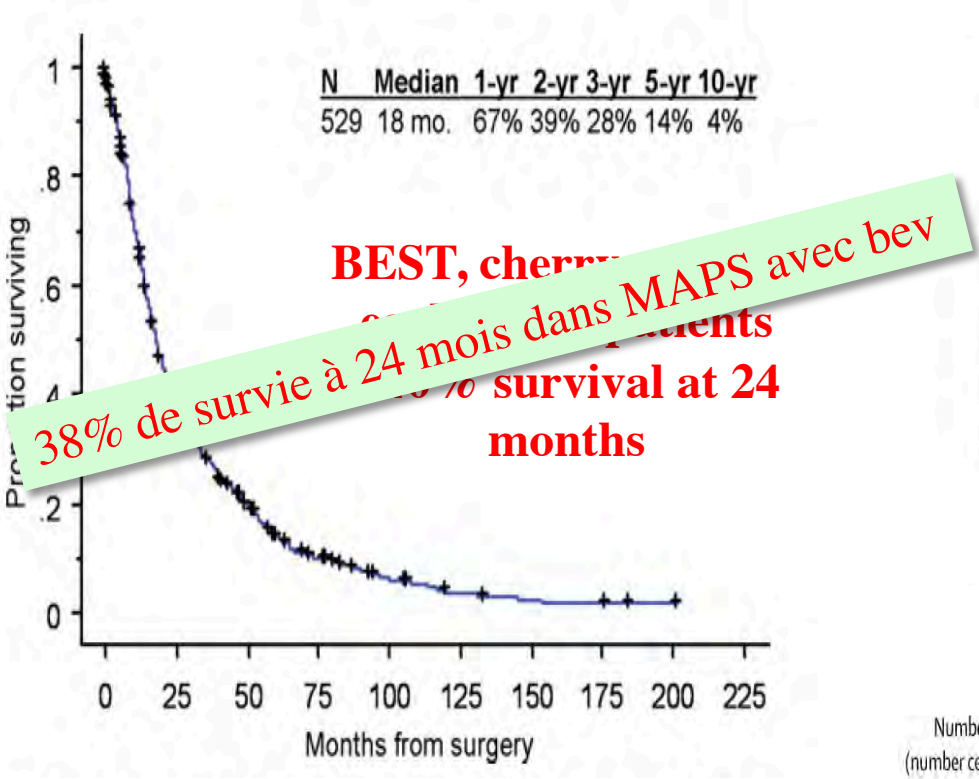


R0/R1 Resection?

David Jablons MD, University of California San Francisco, USA, WCLC 2018

Early Checkpoint Inhibitor Experience Survival as "Good" as EPP

Sugarbaker/Bueno EPP Series
529 Patients with Epithelioid MPM

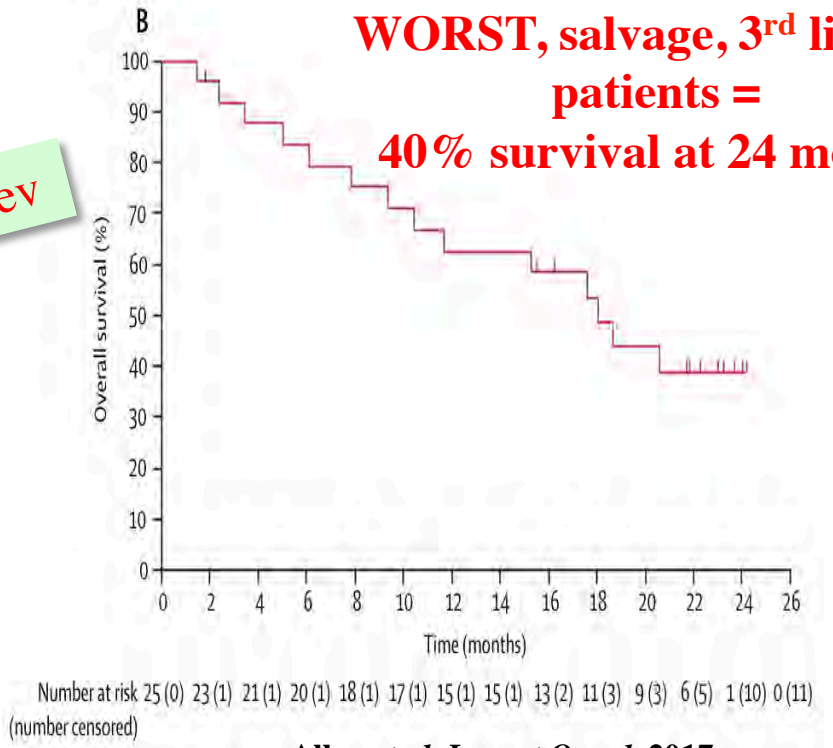


38% de survie à 24 mois dans MAPS avec bev

BEST, cherry
ients
% survival at 24 months

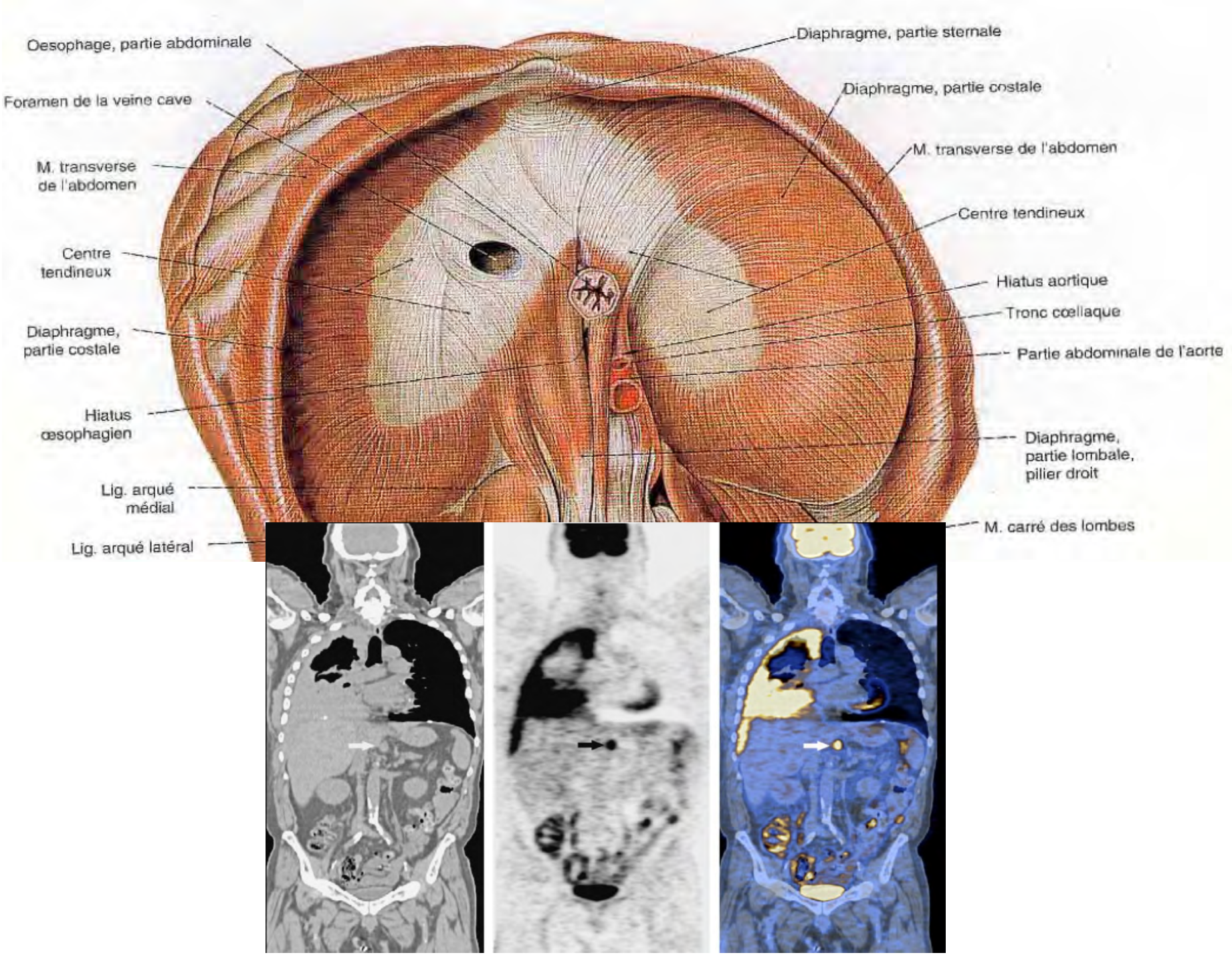
Sugarbaker *et al. Ann Surg*. 2014 Oct;260(4):577-80.

KEYNOTE – 028
25 MPM Patients on Pembrolizumab



WORST, salvage, 3rd line Rx patients = 40% survival at 24 months

Alley *et al. Lancet Oncol*. 2017 May;18(5):623-630.

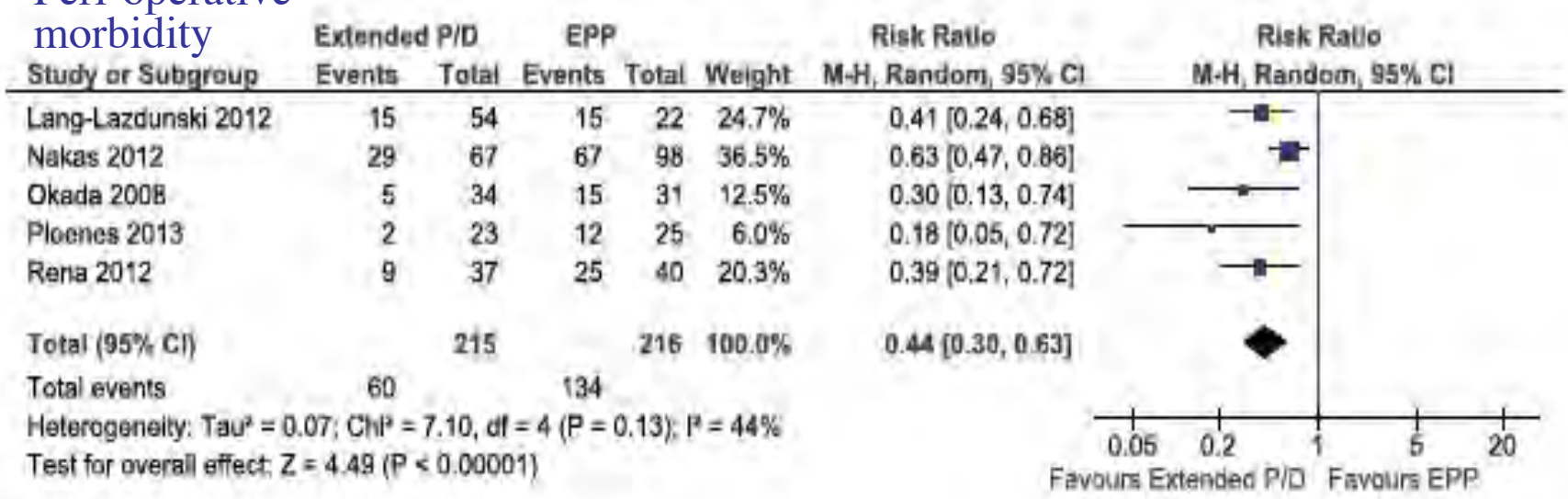

Oesophage, partie abdominale
Foramen de la veine cave
M. transverse de l'abdomen
Centre tendineux
Diaphragme, partie costale
Hiatus œsophagien
Lig. arqué médial
Lig. arqué latéral
Diaphragme, partie sternale
Diaphragme, partie costale
M. transverse de l'abdomen
Centre tendineux
Hiatus aortique
Tronc cœliaque
Partie abdominale de l'aorte
Diaphragme, partie lombale, pilier droit
M. carré des lombes

Méta-analyse 2014: EPP vs. P/D

Summary of study characteristics comparing extended pleurectomy/decortication (E P/D) to extrapleural pneumonectomy (EPP) in the treatment of malignant pleural mesothelioma; NR, not reported.

Author (ref no.)	Year of publication	Study period	Institution	Study size		Follow-up (months)	
				E P/D	EPP	E P/D	EPP
Bedirhan	2013	2001–2013	Yedikule Hospital, Turkey	20	31	25.0	23.7
Lang-Lazdunski	2012	2004–2011	Guy's Hospital, UK	54	22	15.7	12.9
Nakas	2012	1999–2010	Glenfield Hospital, UK	67	98	16.2	20.5
Rena	2012	1998–2009	Maggiore of Charity University Hospital, Italy	37	40		NR
Flores	2008	1990–2006	Memorial Sloan-Kettering Cancer Center, USA	278	385		17
Okada	2008	1986–2006	Hyogo Cancer Center, Japan	34	31		9
Ploenes	2013	NR	Freiburg University Medical Center, Germany	23	25		NR

Peri-operative morbidity



Cao C. et al. Lung Cancer, 2014, 83: 240-45

Risks and Benefits of Extended Pleurectomy Decortication for Mesothelioma

A Review of the Largest Institutional Series in the UK

Study objective

- To assess the efficacy and safety of extended pleurectomy decortication (EPD) in patients with mesothelioma

Study design

- Retrospective analysis of case notes and pathological reports of **266 patients** who underwent EPD within the previous 15 years
- Duration of hospital stay, complication rates and survival were investigated

Key results

- Across all patients studied the median OS was 12.2 months
- Epithelioid pNO disease was the most favourable subgroup with longer survival rate at 1, 3 and 5 years and longer overall median duration of survival

	OS rate (%)			
	1 year	3 years	5 years	**Median OS (months)**
All patients	48.0	10.3	2.7	**12.2**
Epithelioid pNO	64.9	17.5	5.2	**23.1**

Sharkey et al. J Thorac Oncol 2015; 10 (suppl 2): ORAL26.02

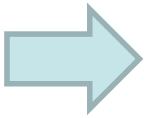
Phase II tri-modality trials with chemotherapy - EPP - adjuvant radiation

	Pts	Excluded from surgery	Treatment completed	Median survival ITT analysis	Median survival when radiation is completed
Weder	61	26%	59%	20 mo	NA
Flores	19	58%	42%	19 mo	33.5 mo
Krug	77	26%	57%	17 mo	29 mo
Van Schil	58	26%	66%	18 mo	33 mo
Hasegawa	42	22%	40%	20 mo	39.4 mo
Federico	54	17%	41%	16 mo	NA
Overall	**311**	**25%**	**53%**	**16 - 20 mo**	**29 - 39 mo**

Marc De Perrot, 2018

(Canadian) Evolution in multimodality therapy approach

Chemotherapy
EPP
Hemithoracic radiation



Hemithoracic radiation
EPP
± Adjuvant chemotherapy
(SMART trial)

Rational:

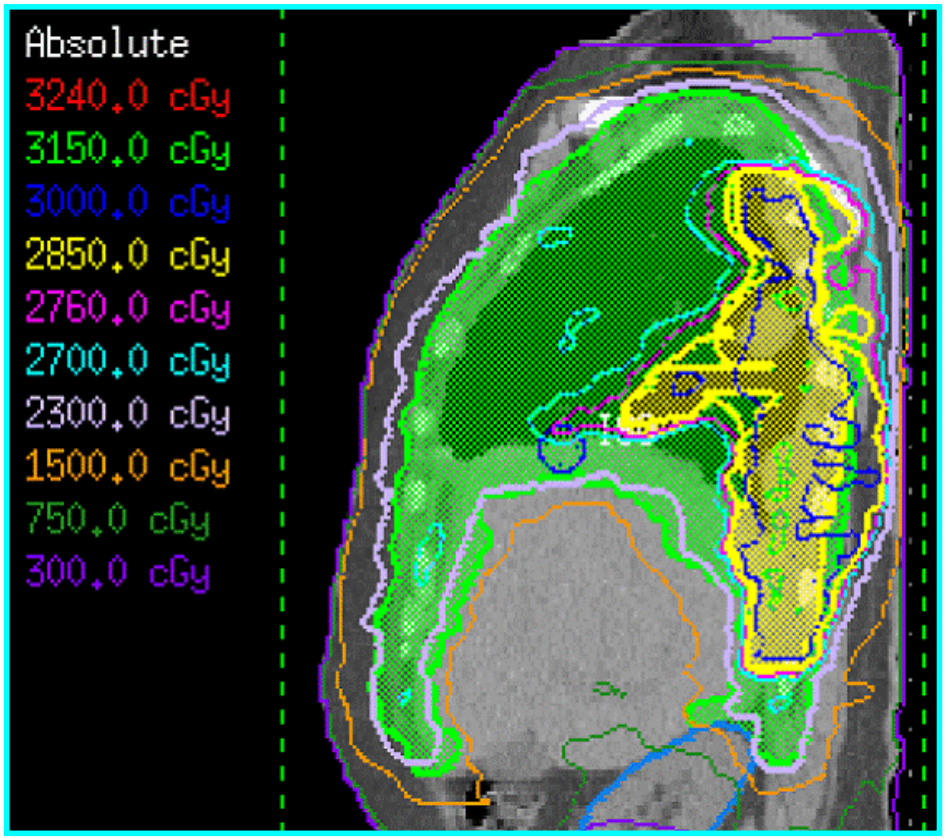
Two new concepts in SMART

- Induction radiation before surgery
- Hypofractionated hemithoracic radiation (IMRT)

Marc De Perrot

SMART trial

Surgery for Mesothelioma After Radiation Therapy



Study Schema

Histologically Proven, Previously Untreated Malignant Pleural Mesothelioma (cT1-3 N0 M0) Baseline Investigations, Informed Consent

Neoadjuvant Hemithoracic Intensity Modulated Radiotherapy (25 Gy/5 fx +/- concomitant 5 Gy boost over 1 week) — IMRT

1 week post-RT

Extrapleural Pneumonectomy

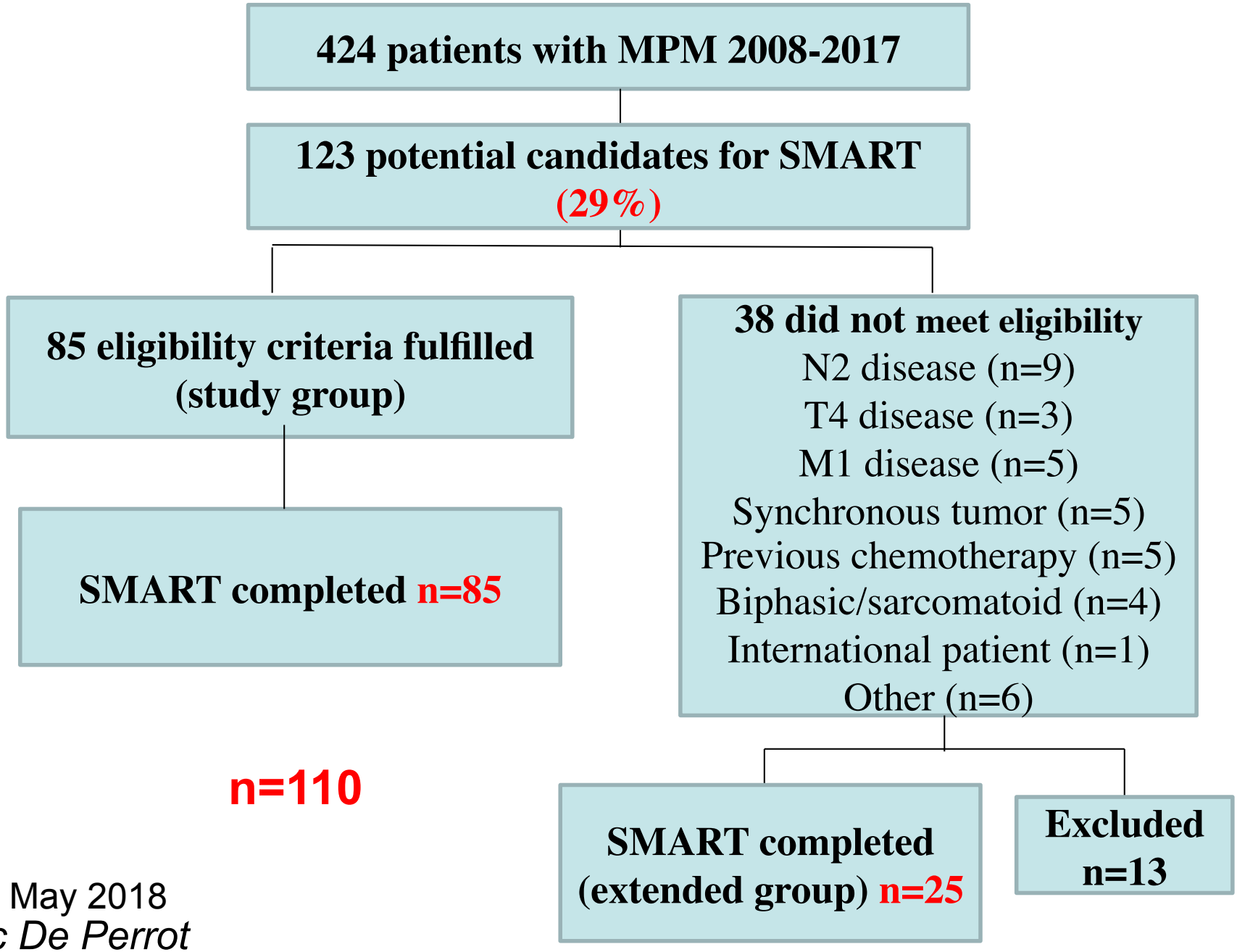
<26 weeks post-op

ypN0-1 — Observation

ypN2 — dans les 6 mois — Adjuvant Chemotherapy

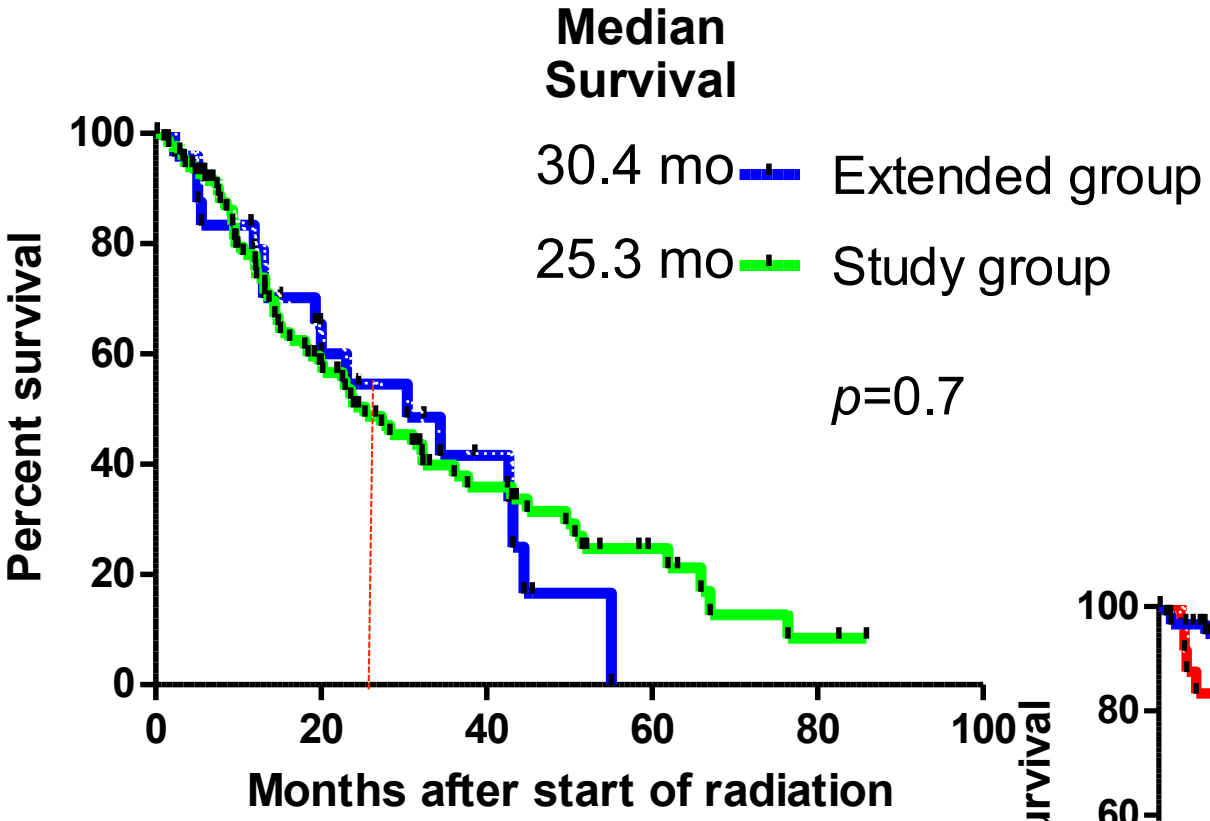
Cho et al *J Thorac Oncol* 2014;9:397-402

Flow diagram



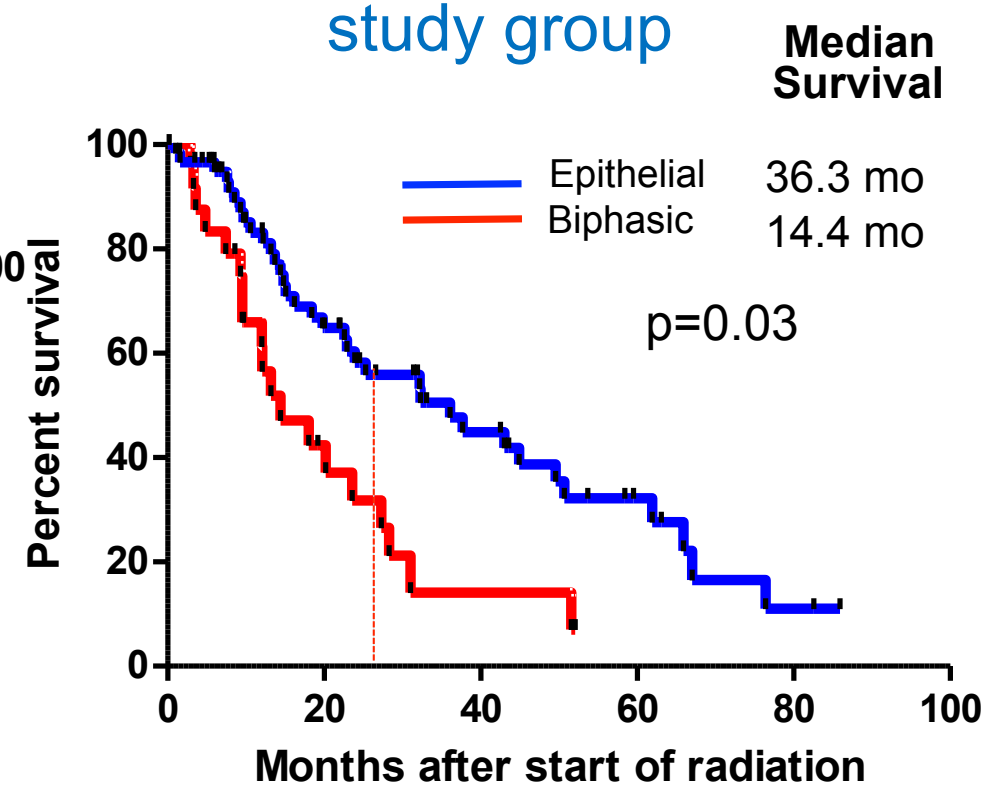
IMiG May 2018
Marc De Perrot

Overall survival after SMART



3.6% 90-days mortality
(n=4/110)

study group

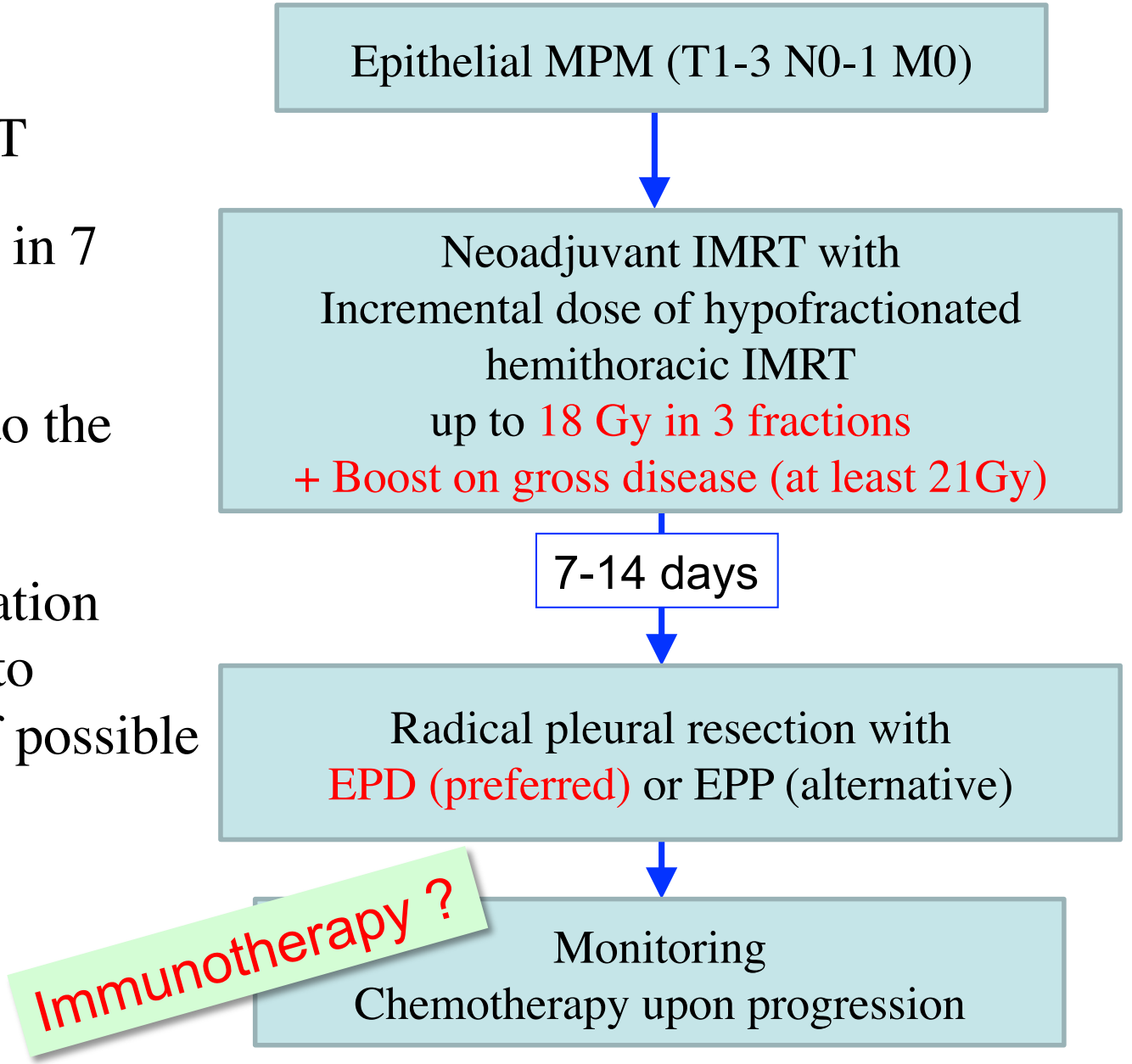


Marc De Perrot
IMiG May 2018

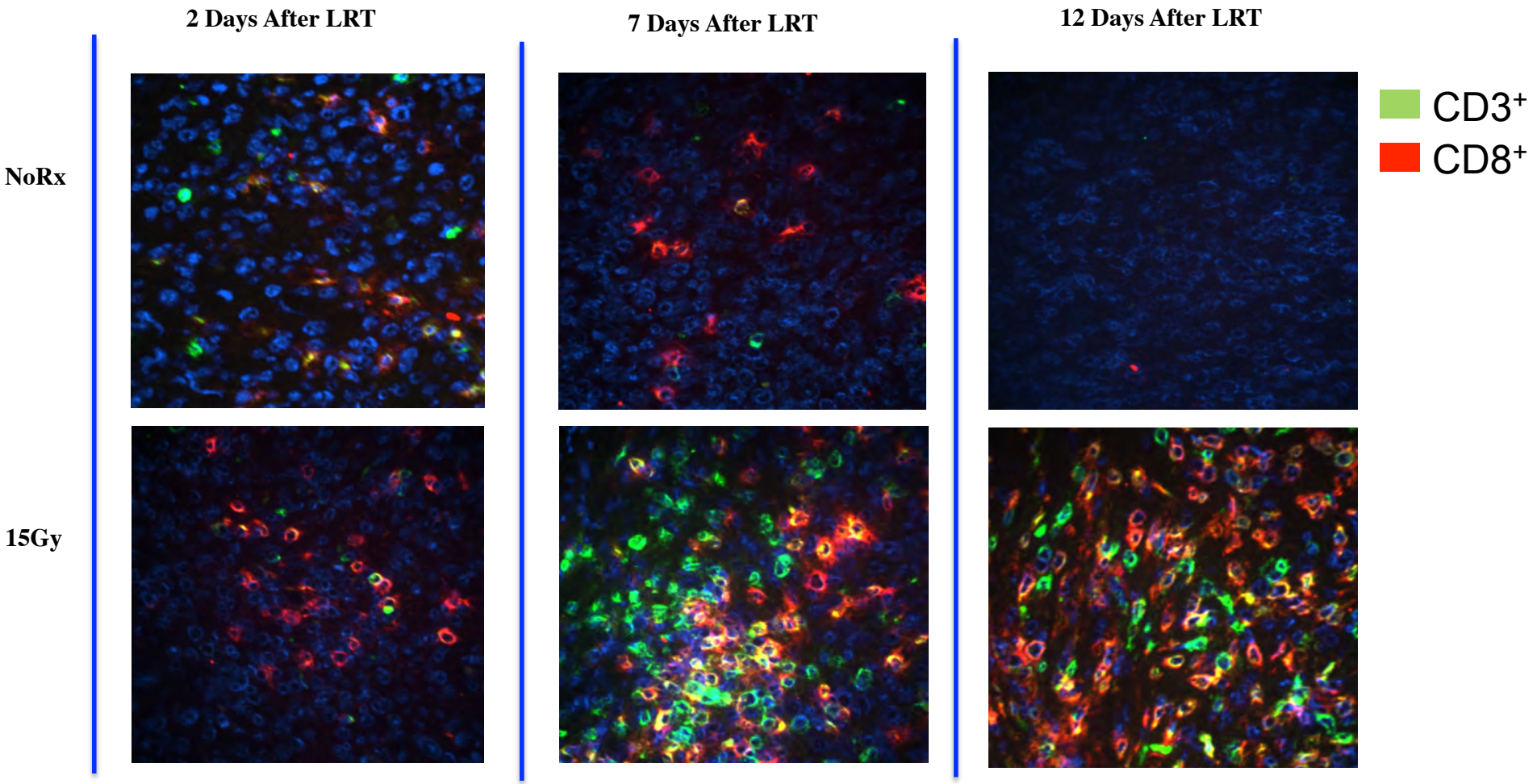
SMARTER trial

Changes from SMART

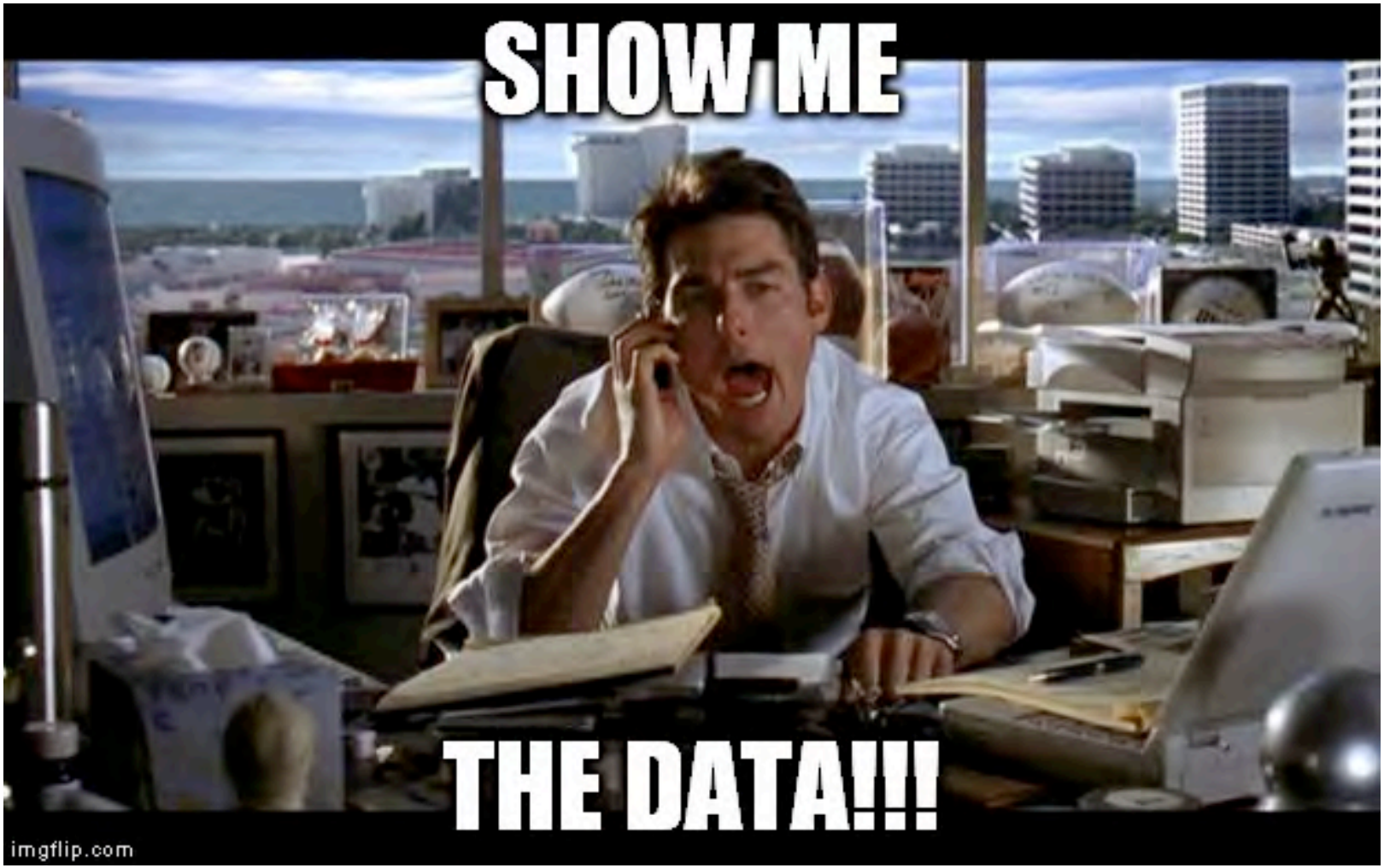
- Total of 3 fractions in 7 days
- Increase the boost to the gross disease
- Decrease total radiation dose on the pleura to preserve the lung if possible



Local RT induces upregulation of tumor infiltrating T cells (in mice)



De La Maza/ de Perrot et al Clin Cancer Res 2017;23:5502-13


SHOW ME
THE DATA!!!
imgflip.com

Alors la chirurgie radicale, STOP ?

...en tous cas, patients hyper-sélectionnés

Plus d'essai en cours en France

Fabrice Barlési

Donc : OUI , on arrête !!

Questions en suspense: SMARTER (EPD)+immunothérapie
Immunotherapie néo-adjuvante avant EPD

Neoadjuvant → Pembrolizumab, Nivolumab
SWOG 1619 (chemo-atezolizumab)

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude-Bernard

4ème partie: Traitements Systémiques
Du pémétrexed au bévacizumab

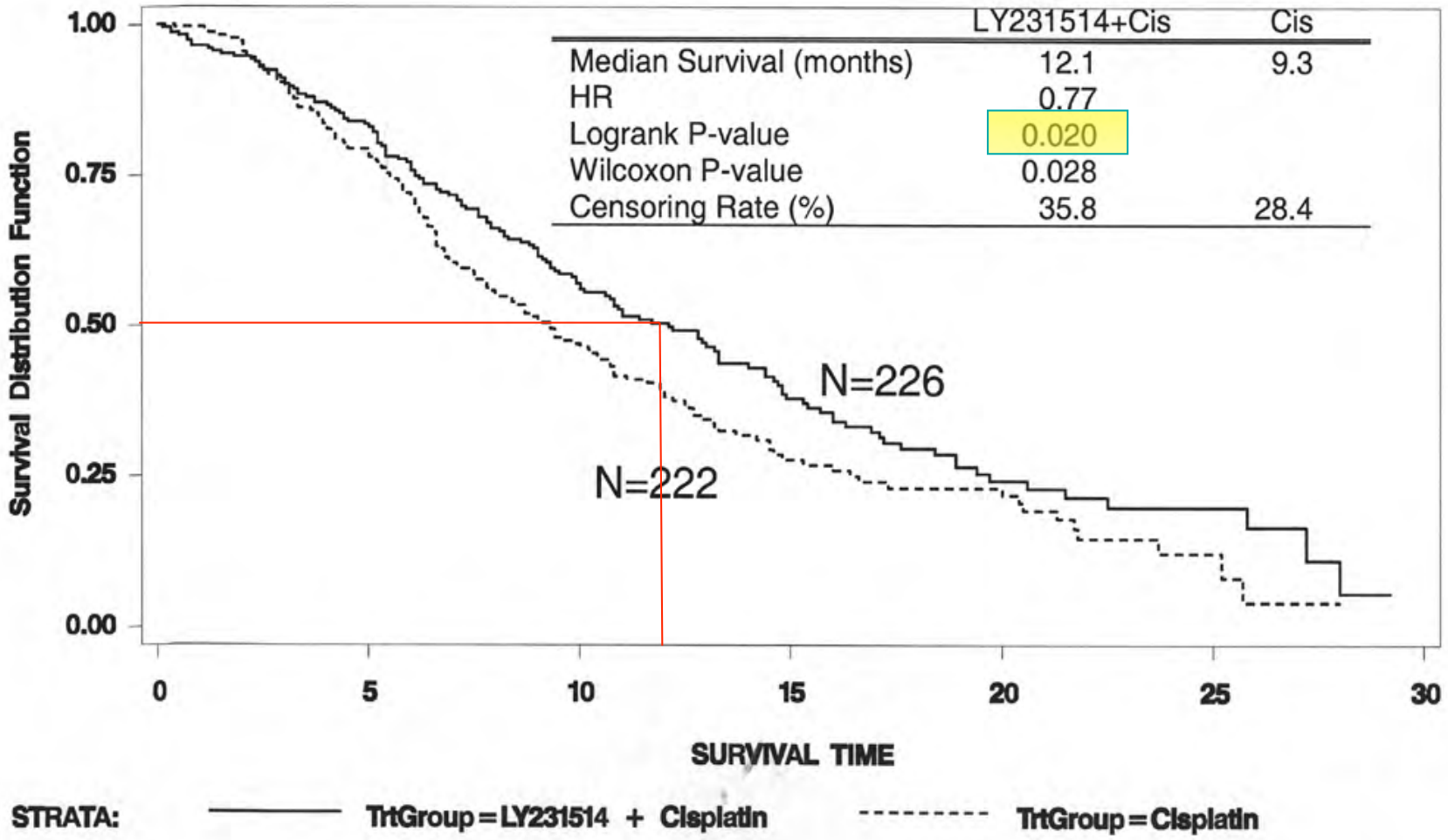
université PARIS DIDEROT PARIS 7

MESOCLIN
Réseau National Expert pour le Mésothéliome Pleural Malin

IFCT

Le Pemetrexed a changé l'histoire naturelle de la maladie

n=448



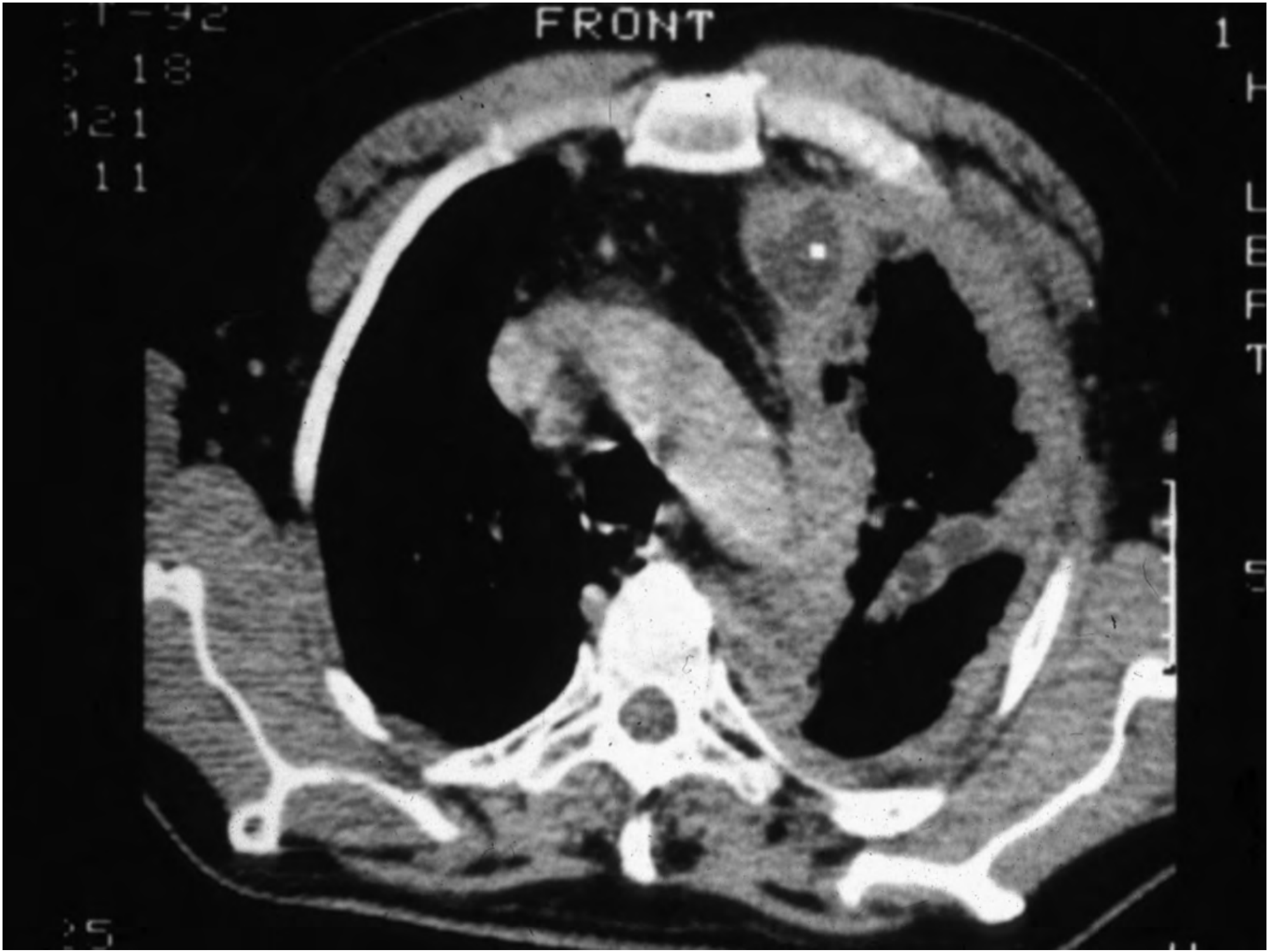
Vogelzang N et al. JCO 2004; 21:2636-44

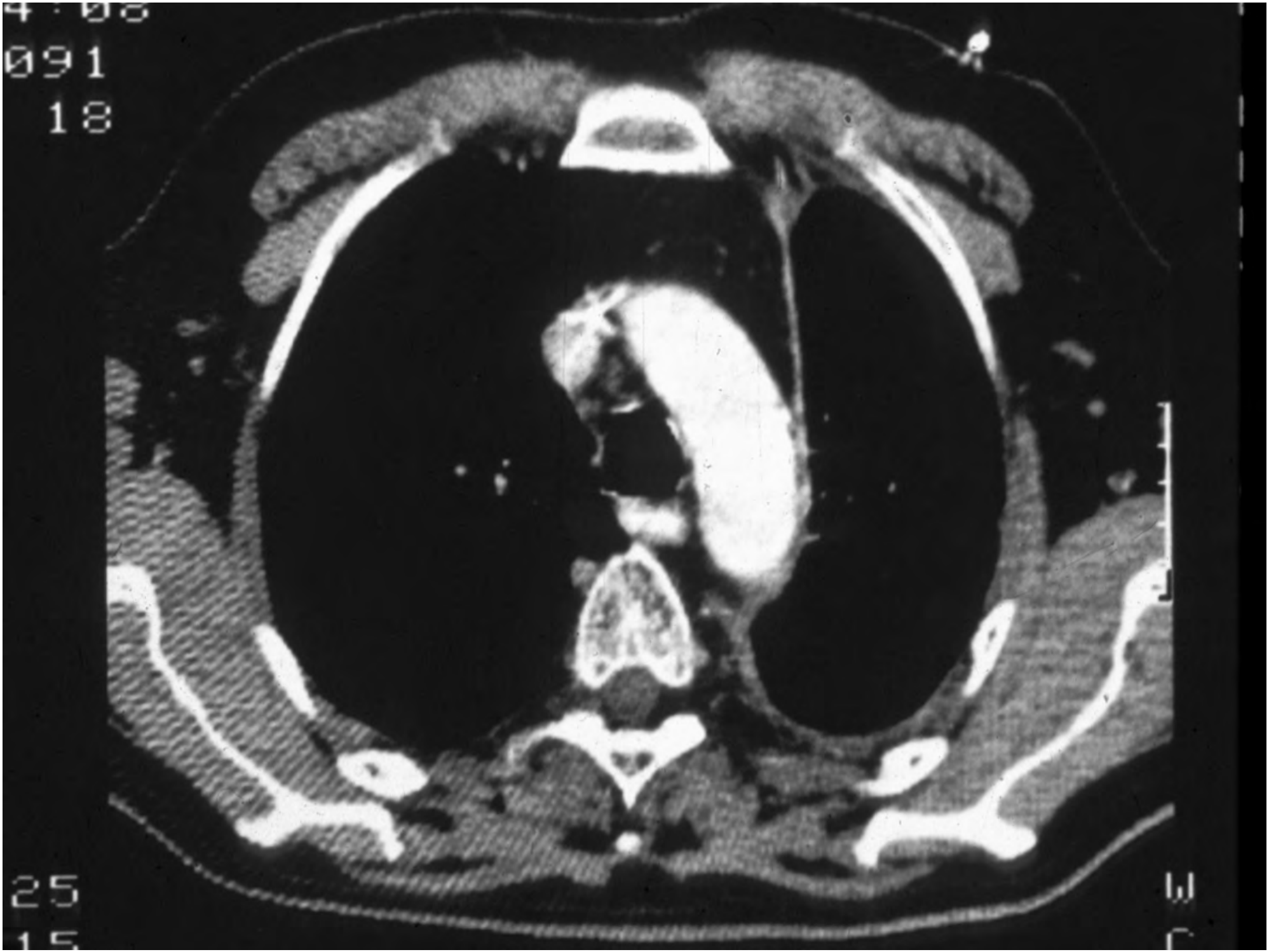
Phase III
Alimta + Cisplatine *versus* Cisplatine

RESULTATS

	Tous Patients		Supplémentés		Non Supplémentés	
	Bras A	**Bras B**	**Bras A**	**Bras B**	**Bras A**	**Bras B**
Nb (pts)	225	222	167	163	58	59
MS (M)	12.1	9.3	**13.3**	10.0	9.5	7.2
T.T.P (M)	5.7	3.9	6.1	3.9	4.6	2.8
RP (%)	41.3	16.7	45.5	19.6	29.3	8.5
Nb **(Cycles)**	6	4	6	4	2	2

Vogelzang N et al. JCO 2004; 21:2636-44

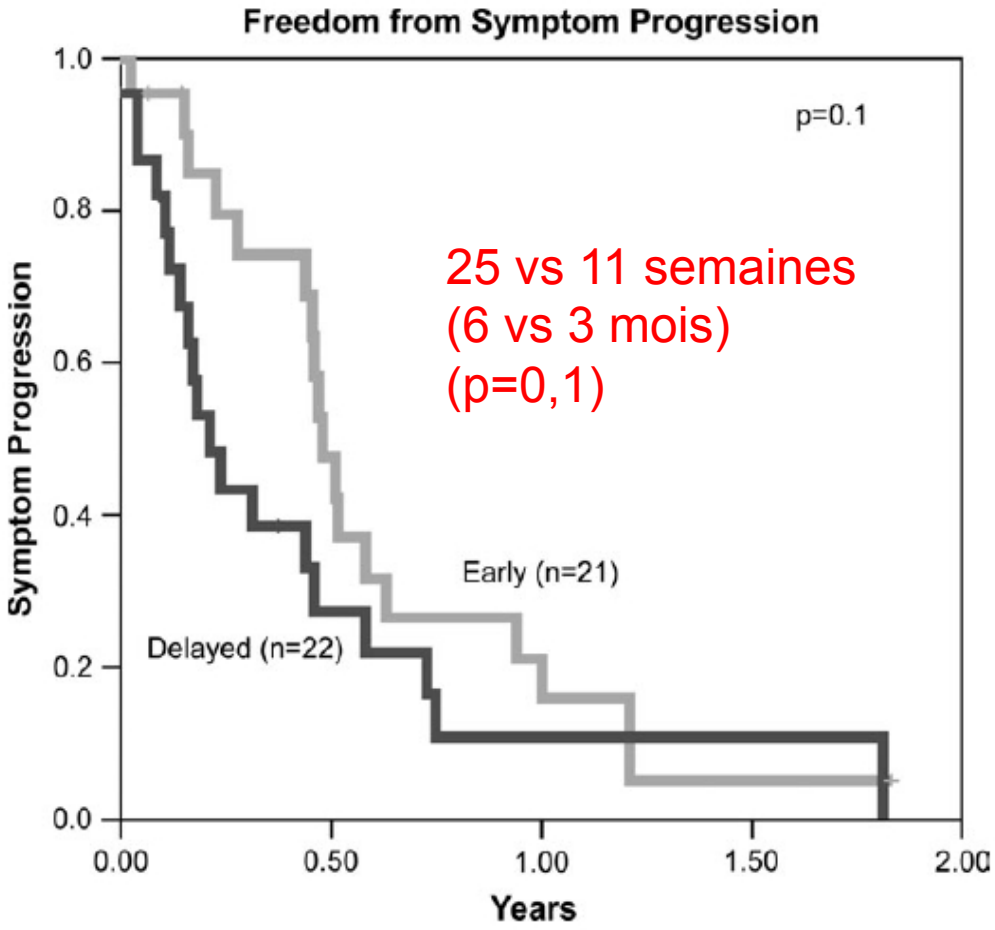

FRONT


4:08
091
18
25
15
W

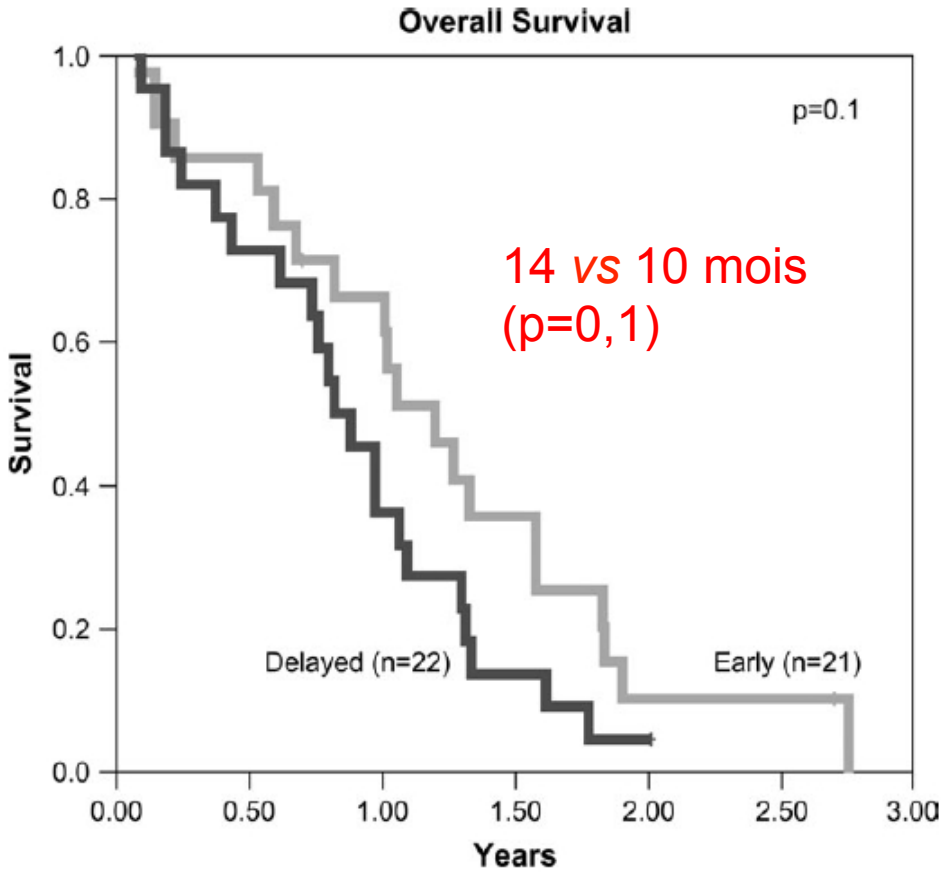
Faut-il traiter un mésothéliome asymptomatique immédiatement ou en cas de symptôme ?

Phase II randomisée: 43 patients

BSC puis CT lorsque SF *vs.* BSC+CT immédiate: MVP !



Symptom progression-free survival for all patients.



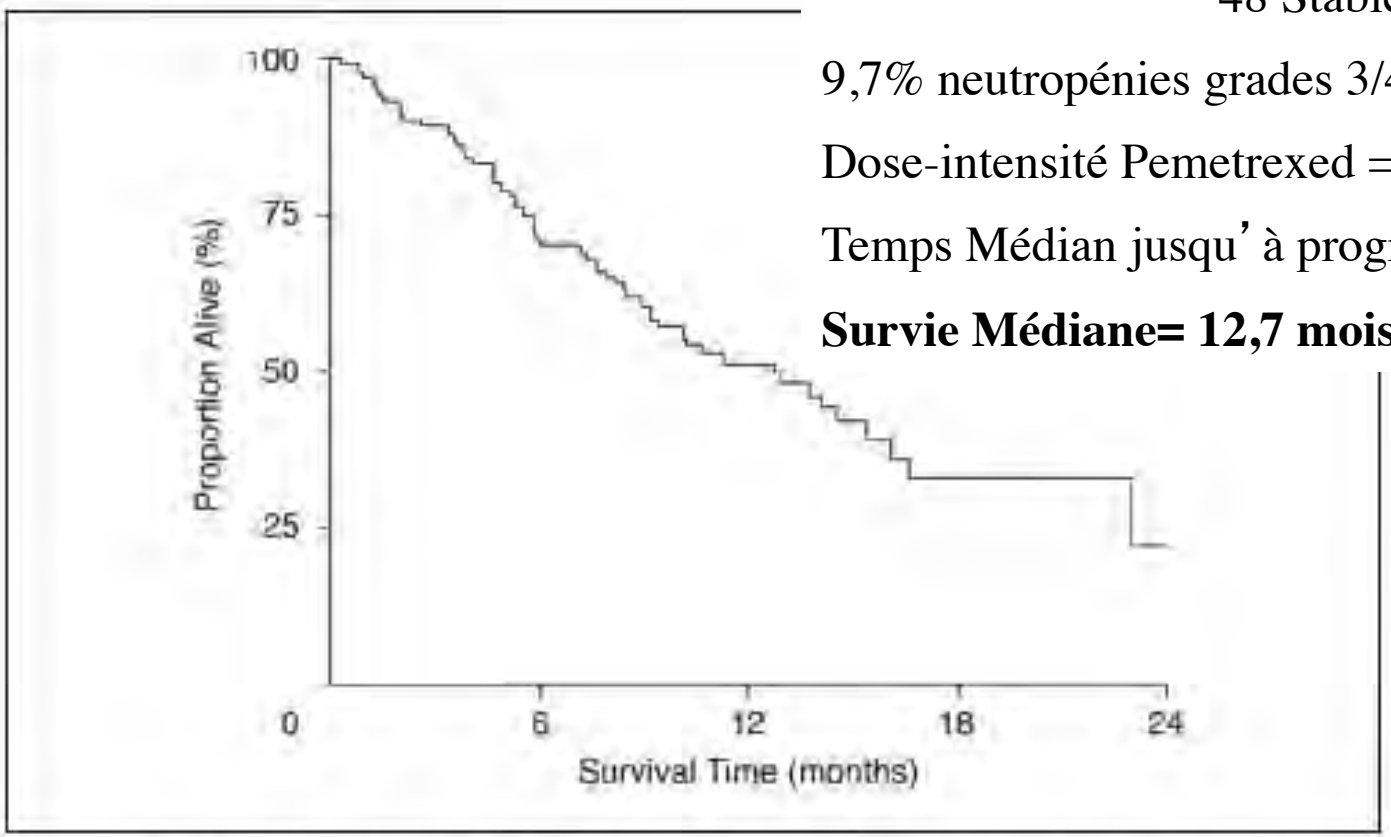
Overall survival (measured from the date of randomisation). Patients treated early survived longer. Median survival is 14 months for the 'early' group compared with 10 months for the 'delayed' group.

O' Brien, Ann. Oncol. 2006, 17: 270-275

Alimta-carboplatine fait-il aussi bien que Alimta-cis ?

Phase II 102 patients PS 0-2 : Pemetrexed-Carbo AUC 5 (+vitB12+folates)

19 RO (17 RP+2 RC) = 18,6%
48 Stables (48%)



Kaplan-Meier curve of overall survival time for all patients (median overall survival time, 12.7 months).

9,7% neutropénies grades 3/4

Dose-intensité Pemetrexed = 97% Carbo = 98%

Temps Médian jusqu'à progression: 6,5 mois

Survie Médiane= 12,7 mois

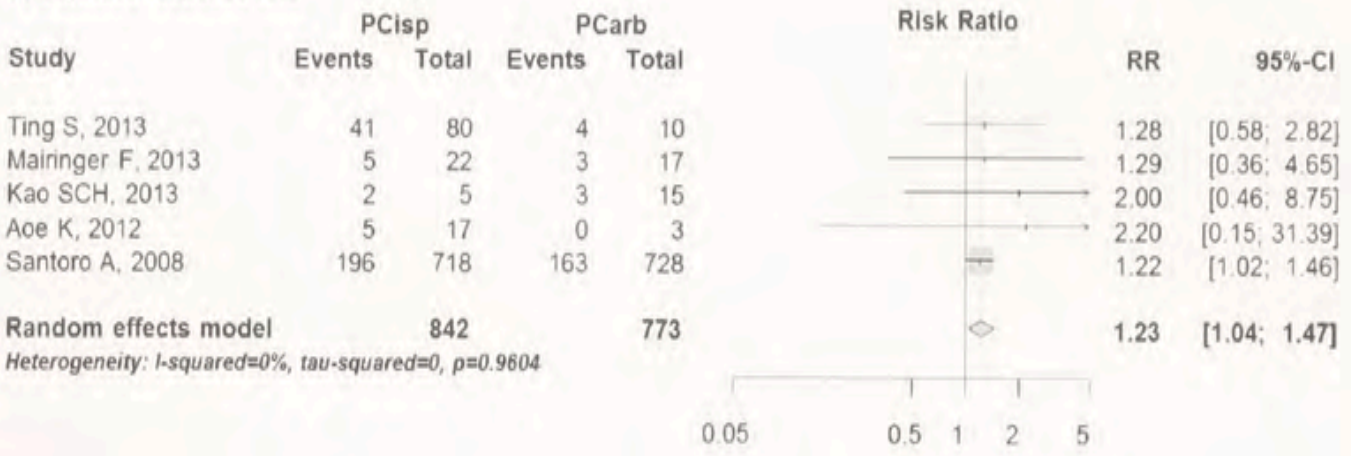
Ceresoli GL et al. J. Clin. Oncol. 2006; 24: 1443-48

Pemetrexed in Combination with Cisplatin Versus Carboplatin as First-line Therapy in Patients with Advanced-Stage Malignant Pleural Mesothelioma (MPM): A Systematic Review and Meta-analysis

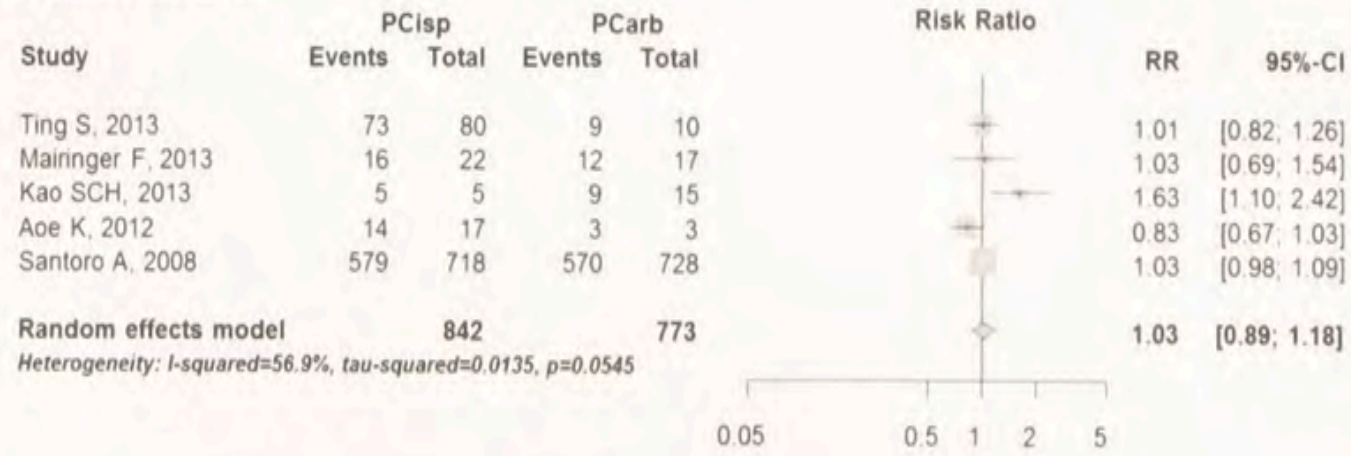
Samer A. Srour[1,2] and Julie A. Stoner[3]

Figure 1

A Objective response rate



B Disease control rate



Meilleur Taux de réponse avec le cisplatine

Mais taux de contrôle tumoral (réponses+ stabilisations) identiques

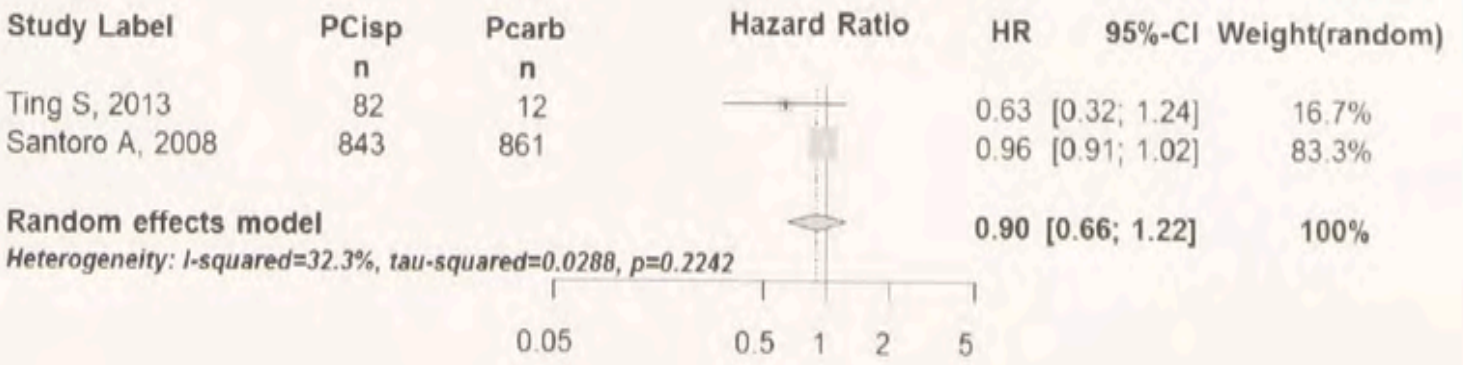
JCO 34 (15) suppl (May 2016):8554-8554.

Pemetrexed in Combination with Cisplatin Versus Carboplatin as First-line Therapy in Patients with Advanced-Stage Malignant Pleural Mesothelioma (MPM): A Systematic Review and Meta-analysis

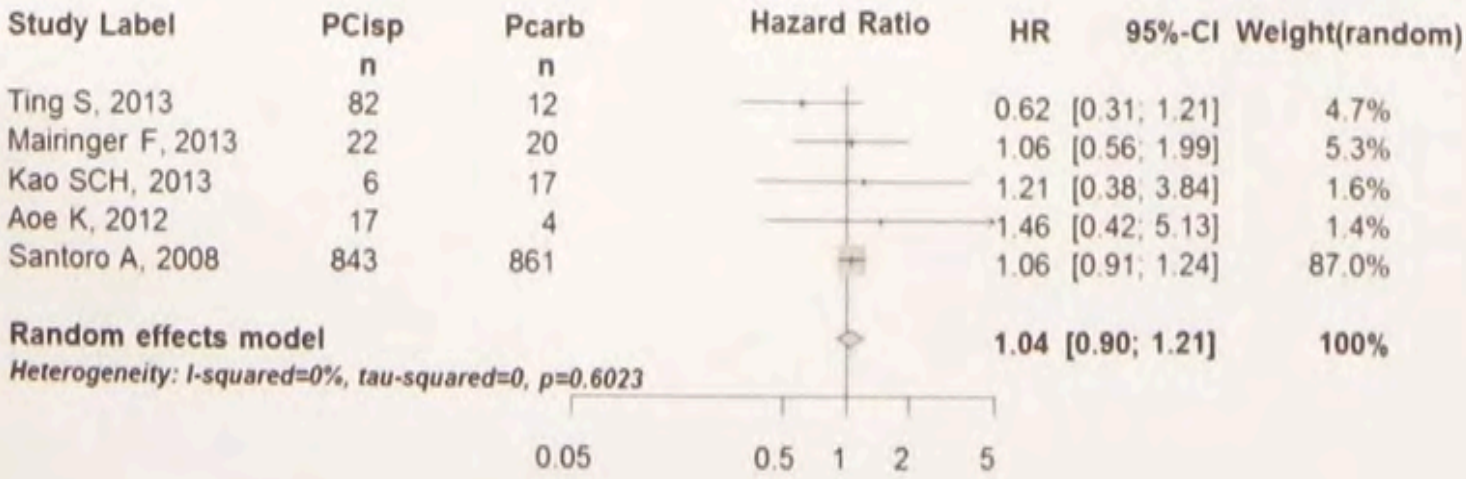
Samer A. Srour[1,2] and Julie A. Stoner[3]

Figure 2

A Progression-free survival



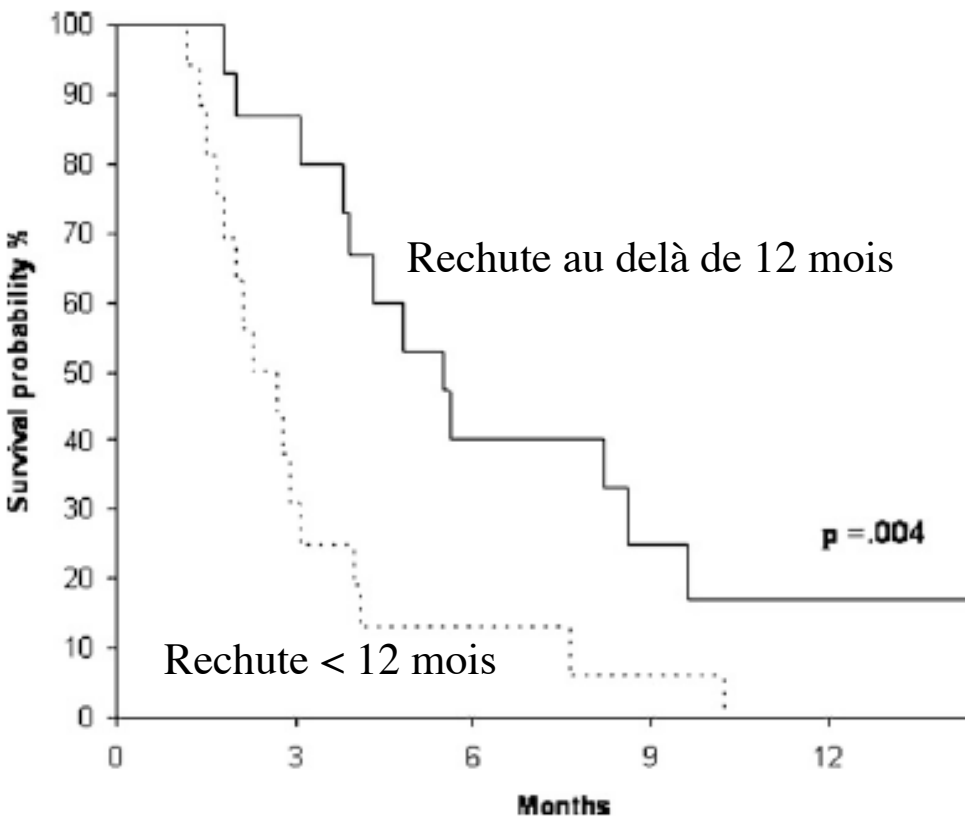
B Overall survival

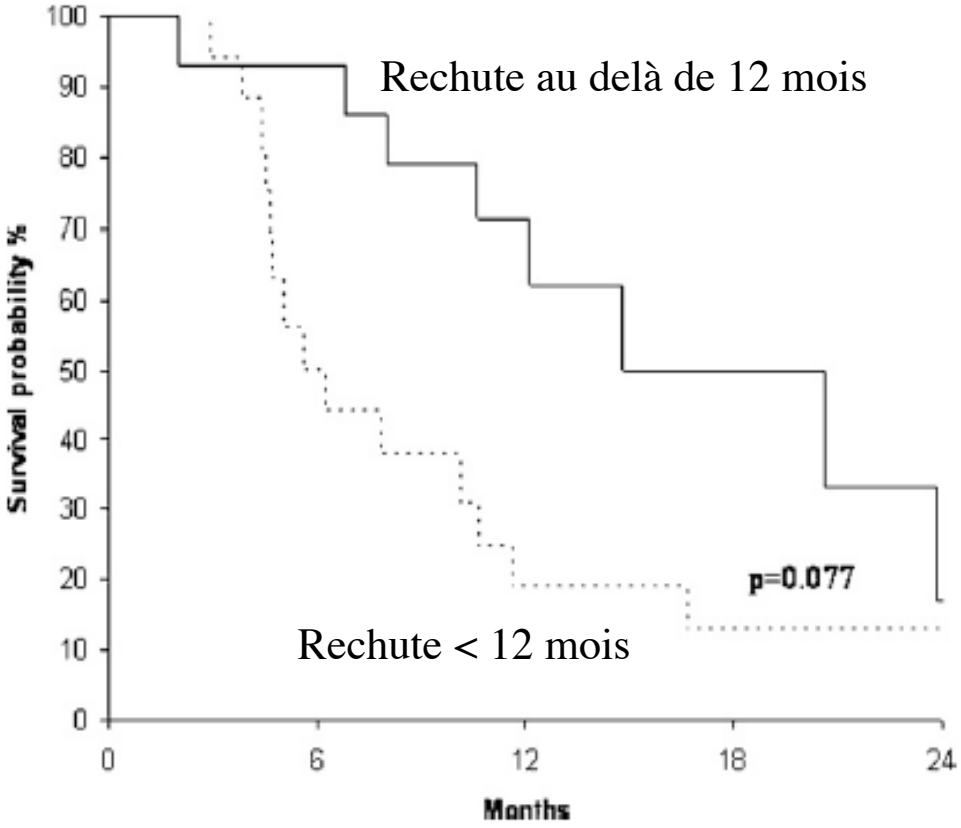


Pas de différence de Survie sans progression ou de Survie globale

JCO 34 (15) suppl (May 2016):8554-8554.

Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma☆

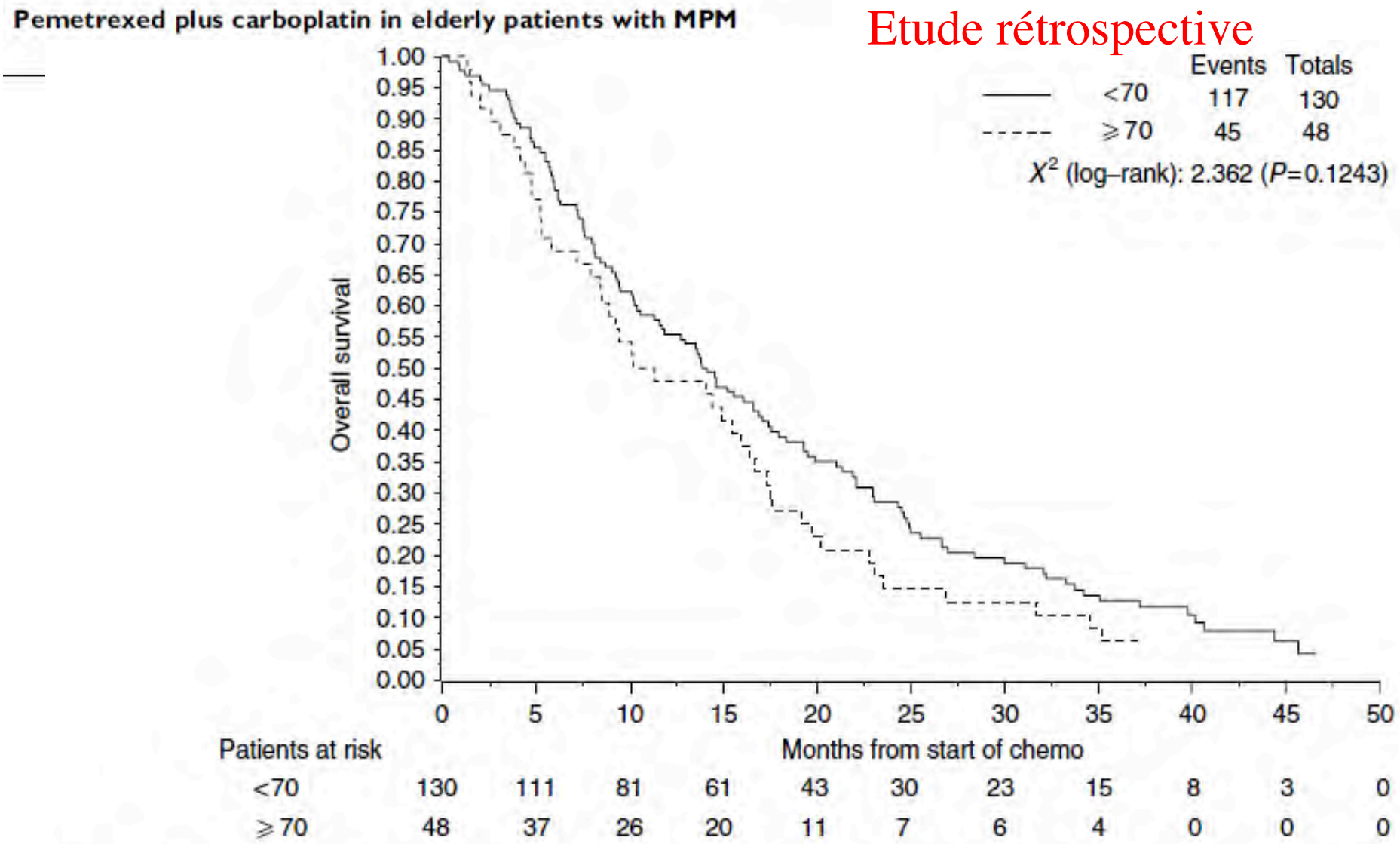




Editorial

Pemetrexed re-challenge in pleural malignant mesothelioma: An option for a subset of patients initially treated with pemetrexed-platinum doublets in the first-line setting? *G. Zalcman, Lung Cancer 2011*

Sujets âgés > 70 ans

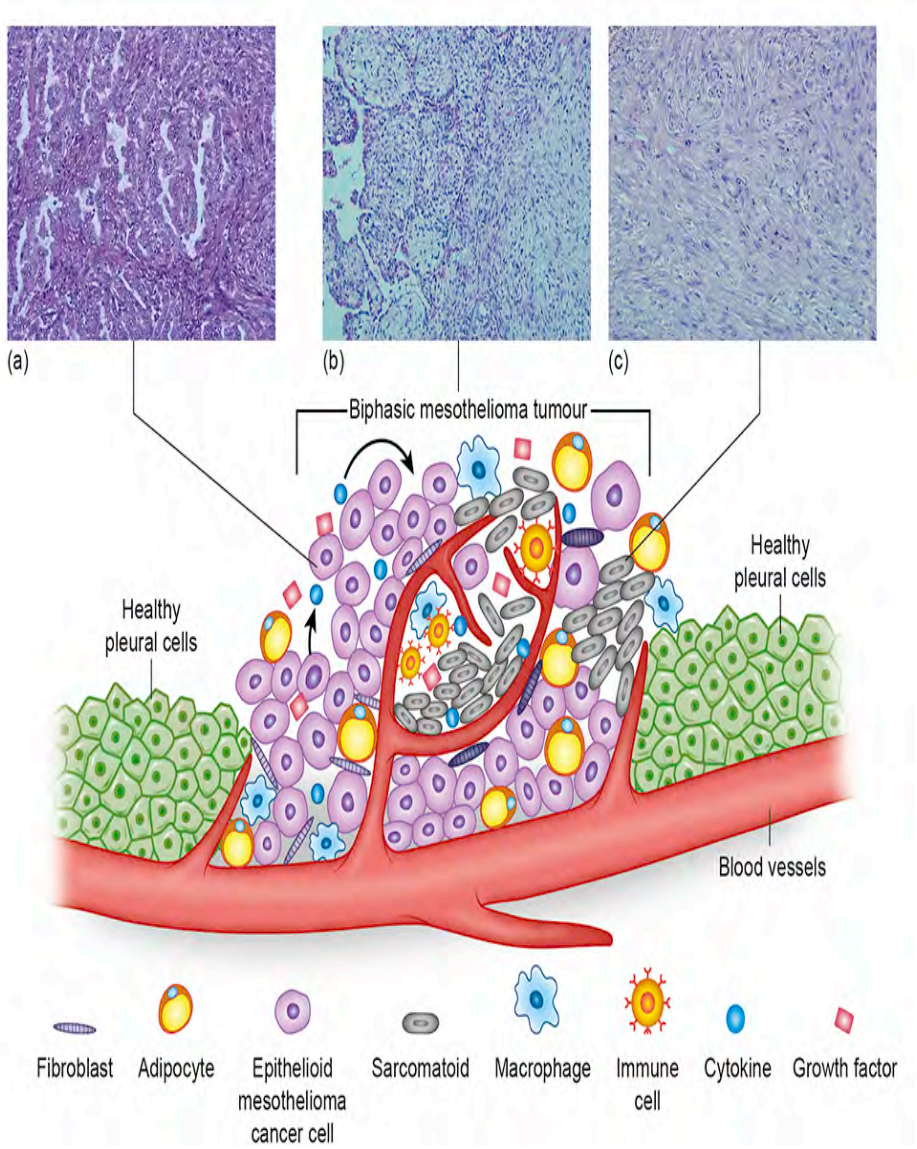


Kaplan–Meier curve of overall survival time for younger (solid line) and elderly (dotted line) patients ($P = 0.12$).

Ceresoli et al. Br. J. cancer 2008

Angiogenèse & mésothéliome

- MPM = stroma inflammatoire aussi associé à une néo-angiogenèse par activation de facteurs pro-angiogéniques
- VEGF-A, VEGF-C, VEGFR sont fortement exprimés dans les MPM[1,2]
- VEGF est un **facteur de croissance autocrine** des cellules de MPM[3,4]
- Un taux élevé de VEGF tissulaire pourrait être un facteur indépendant de mauvais pronostic dans les MPM[5]
- Un taux élevé de VEGF dans est un facteur de mauvais pronostic dans les MPM[6]
- La chute des taux sériques de VEGF sous traitement pourrait être corrélée avec la réponse au traitement [6]



Chia PL et al. Expert Rev Anticancer Ther. 16 (12), 1235-1245. 2016 Oct 12

1. Ohta Y et al. Br J Cancer 1999; 2. Konig et al. Virchows Archive 1999; 3. Strizzi L et al. J Pathol 2001; 4. Konig J-E et al. Respiration 2000; 5. Demirag F et al. Chest 2005; 6. Kao et al. Lung Cancer 75 (2012) 248–254

Au delà de son rôle en tant que principal facteur de croissance des cellules endothéliales , le VEGF est un facteur de croissance autocrine des cellules mesothéliomateuses

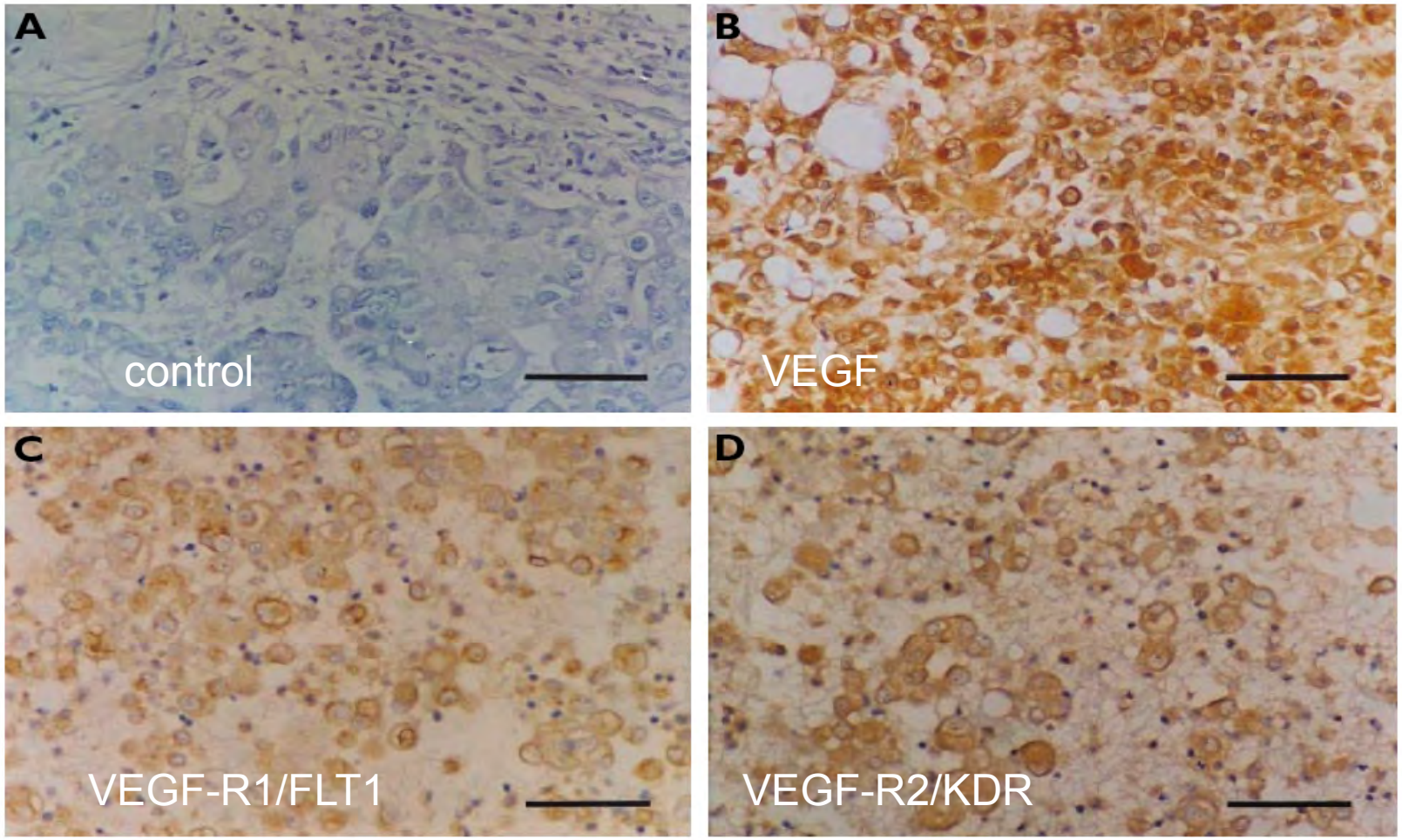
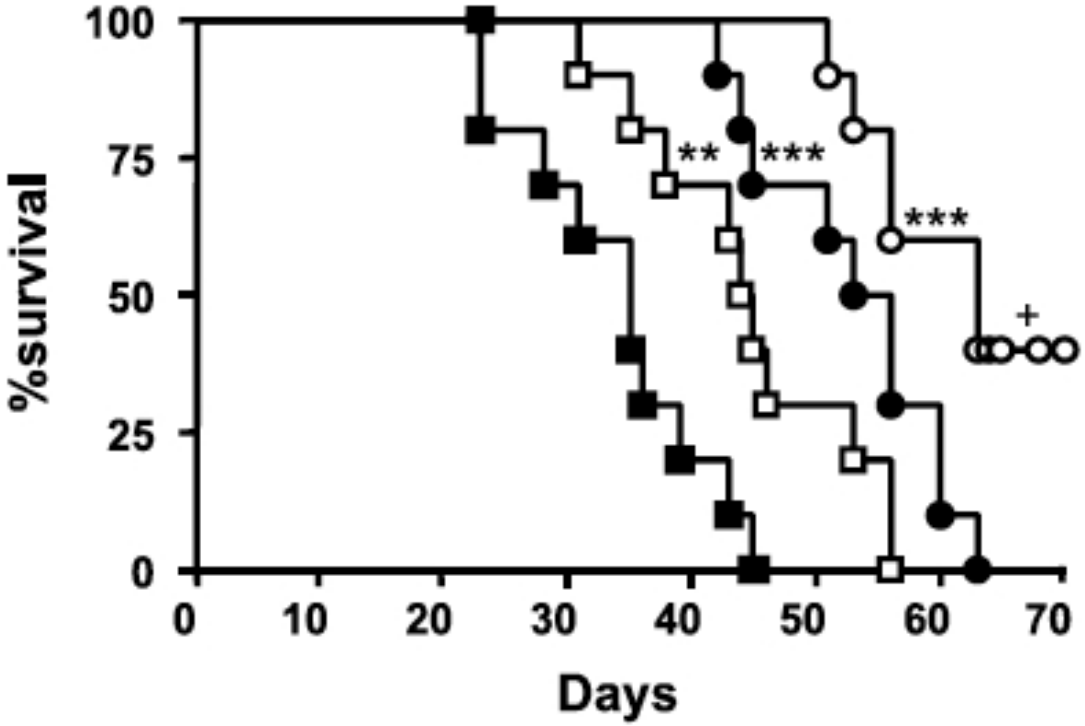


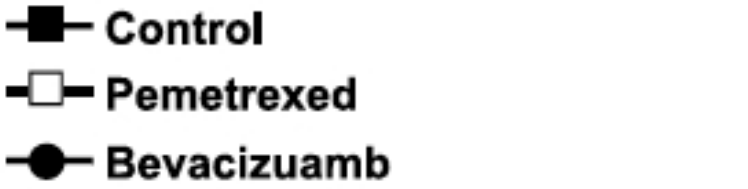
Figure 5. Immunohistochemical staining shows expression of VEGF, Flt-1, and KDR in MM biopsy samples. (A) MM negative control (B) MM stained with anti-VEGF; (C) MM stained with anti-Flt-1; (D) MM stained with anti KDR. Bar = 10 μm

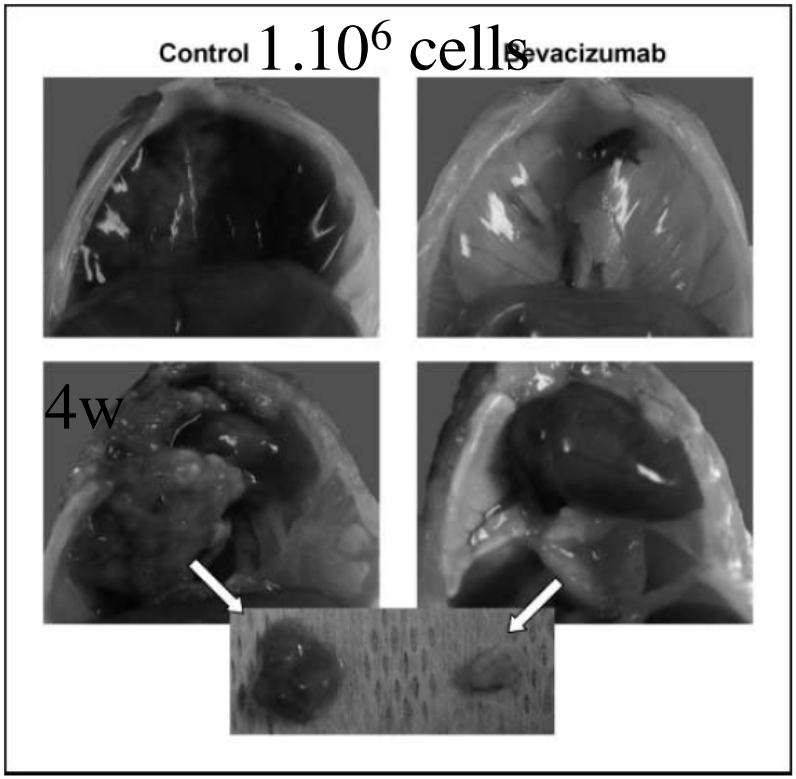
Les Mesothéliomes expriment un haut niveau de VEGF & et de VEGF-R

Strizzi L et al. J. Pathol. 2001; 193:468-73

Efficacité du doublet Bevacizumab + Pemetrexed chez des souris SCID avec greffe orthotopique de MPM humain







Li et al. CCR 2007, 13: 5918-25

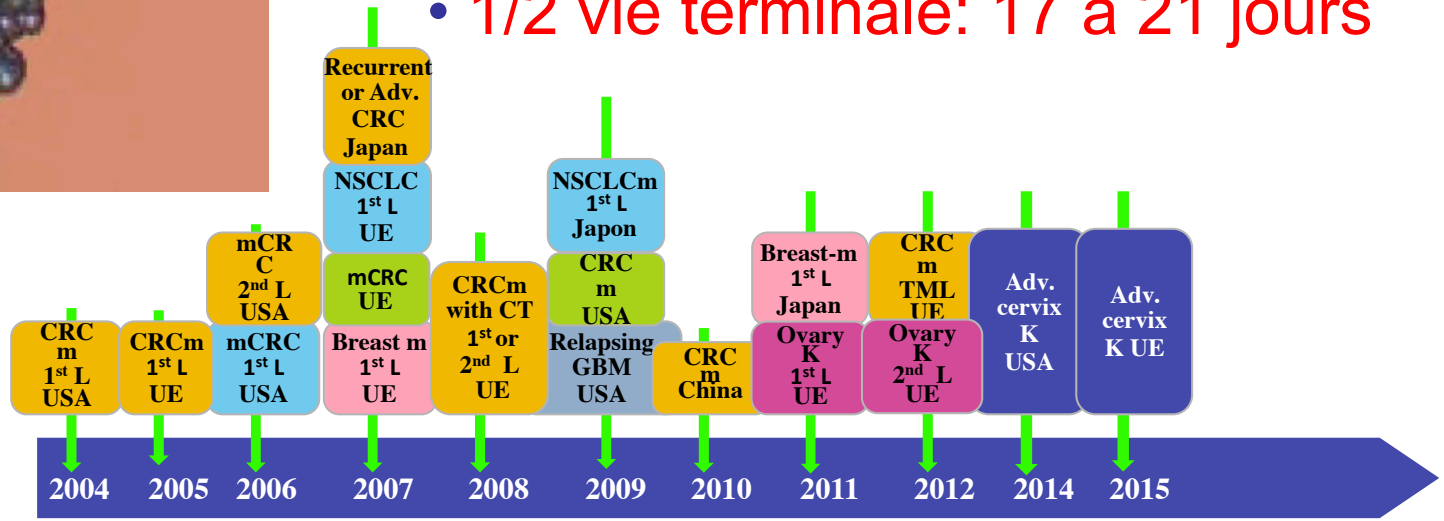
Targeting angiogenesis in Mesothelioma

Agent 2ème ligne	N	PR/CR	SD	OS (median)
Sunitinib[1] (australiasan)	53	12%	65%	6.1 m
Sunitinib[2] (NCIC)	17	0%	65%	8.3 m
Sorafenib[3]	53	6%	56%	9 m
Sorafenib[4] (CALGB)	51	6%	54%	9.7 m
Vatalinib[5]	47	11%	66%	10 m
Cediranib[6] (SWOG S0509)	54	9%	33%	10 m
BNC105P[7]	30	3%	43%	8.2 m
Thalidomide switch maintenance[8] (Dutch, Lilly)	222 (RCT)			10.6 *vs*. 12.9 (HR= 1.2, p=0.21)
NGR-hTNF[9]	57	2%	46%	12.1 m

L'anticorps monoclonal recombinant humanisé anti-VEGF (bevacizumab) Avastin® :

- protéine recombinante synthétique
- 7 % murine : région hypervariable liant un peptide antigénique du VEGF
- 93% humain: fragment Fc portant l'immunogénicité d'espèce
- liant toutes les isoformes du VEGF (ABCDE)
- 1/2 vie terminale: 17 à 21 jours

Approuvé dans sept types de cancers [1–12]



1. Sandler A et al. NEJM 2006 Dec 14;355:2542-50; 2. Reck M et al. JCO 2009;27:1227-34; 3. Hurwitz H et al. NEJM 2004;350:2335-42; 4. Giantonio BJ et al. JCO 2007 ;25:1539-44; 5. Escudier B et al. Lancet 2007;370:2103-11; 6. Miller K et al. NEJM 2007 ;357:2666-76; 7. Gray R et al. JCO 2009;27:4966-72; 8. Miles DW et al. JCO 2010 ;28:3239-47; 9. Friedman HS et al. JCO 2009;27:4733-40; 10. Burger RA et al. NEJM 2011;365:2473-83; 11. Perren TJ et al. NEJM 2011;365:2484-96; 12.Tewari KS et al. NEJ M 2014; 370:734-743

IFCT-GFPC-0701 trial: MAPS

Mesothelioma **A**vastin cisplatin **P**emetrexed **S**tudy

Phase 2-3

promotion IFCT, essai ouvert, multicentrique randomisé de phase II-III

Roche a fourni gracieusement le bevacizumab

- **Mesotheliome Pleural Malin (MPM)**
- Histologiquement prouvé
- PS= 0-2
- Sans comorbidité
- cardiovasculaire
- Chimio-naïf (1ère ligne)

R 1:1

A → **Pemetrexed 500 mg/m² J1**
Cisplatine 75mg/m² J1
6 cycles, tous les 21 jours
→ **Surveillance**

Pas cross-over autorisé

B → **Pemetrexed 500 mg/m² J1**
Cisplatine 75mg/m² J1
Bevacizumab 15 mg/kg J1
6 cycles, tous les 21 jours
→ **Maintenance de Bevacizumab** 15 mg/kg J1, tous les 21 jours jusqu'à progression ou tox

- Supplémentation par acide folique p.o.(400µg) et vitamine B12 IM (1,000 µg tous les 3 cycles) dans les 2 bras
- Scanner tous les cycles dans les 2 bras
- Réponse évaluée avec les critères RECIST modifiés pour le mesothéliome

<u>Stratification:</u> centre, histologie (épithelioide vs. sarcomatoide/mixte), PS (0-1 vs. 2), statut tabagique (fumeur vs. jamais -fumeur)

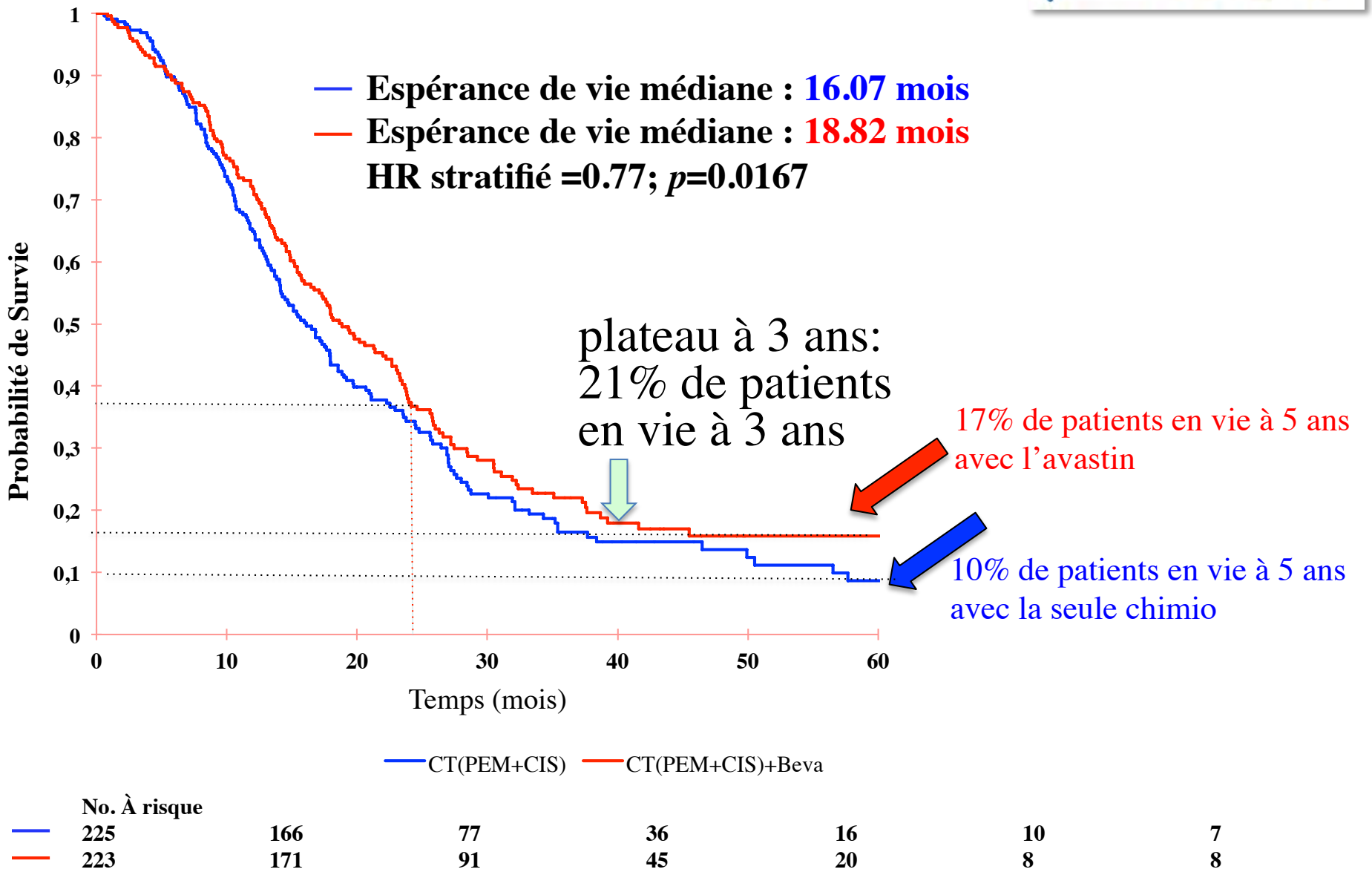
Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial

Gérard Zalcman, Julien Mazieres, Jacques Margery, Laurent Greillier, Clarisse Audigier-Valette, Denis Moro-Sibilot, Olivier Molinier, Romain Corre, Isabelle Monnet, Valérie Gounant, Frédéric Rivière, Henri Janicot, Radj Gervais, Chrystèle Locher, Bernard Milleron, Quan Tran, Marie-Paule Lebitasy, Franck Morin, Christian Creveuil, Jean-Jacques Parienti, Arnaud Scherpereel, on behalf of the French Cooperative Thoracic Intergroup (IFCT)

The Lancet
Published Online
January 14, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)00004-0

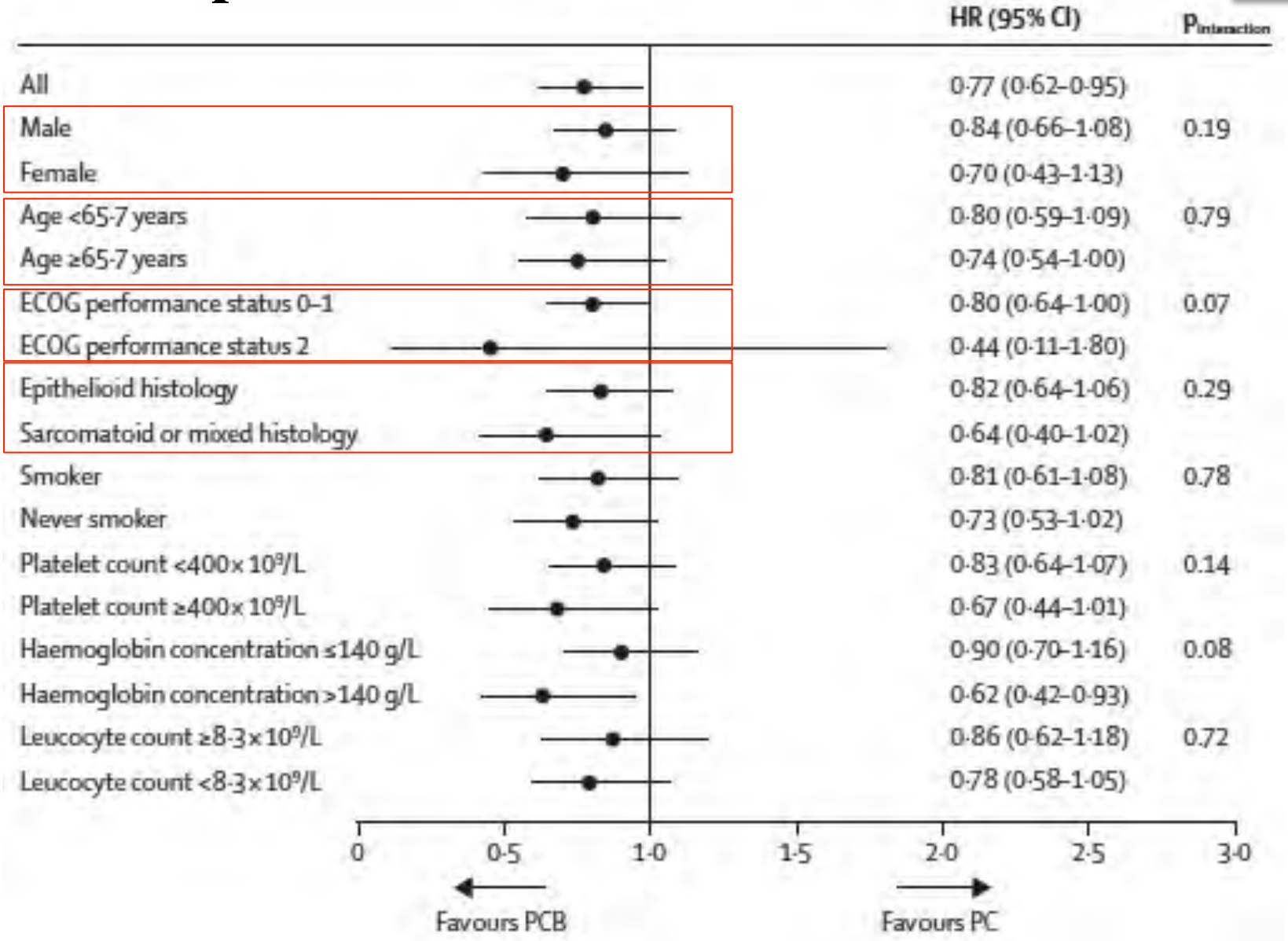
Essai MAPS, efficacité: Espérance de vie

suivi médian = 39.4 mois [11.0-83.05]



Essai de phase 3 randomisé IFCT 0701 'MAPS'

Facteurs prédictifs d'efficacité du bévacizumab



L'Avastin est efficace chez tous les sous-groupes de patients, y compris ceux ayant le moins bon pronostic, y compris ceux avec le taux de VEFG sanguin le plus élevé !

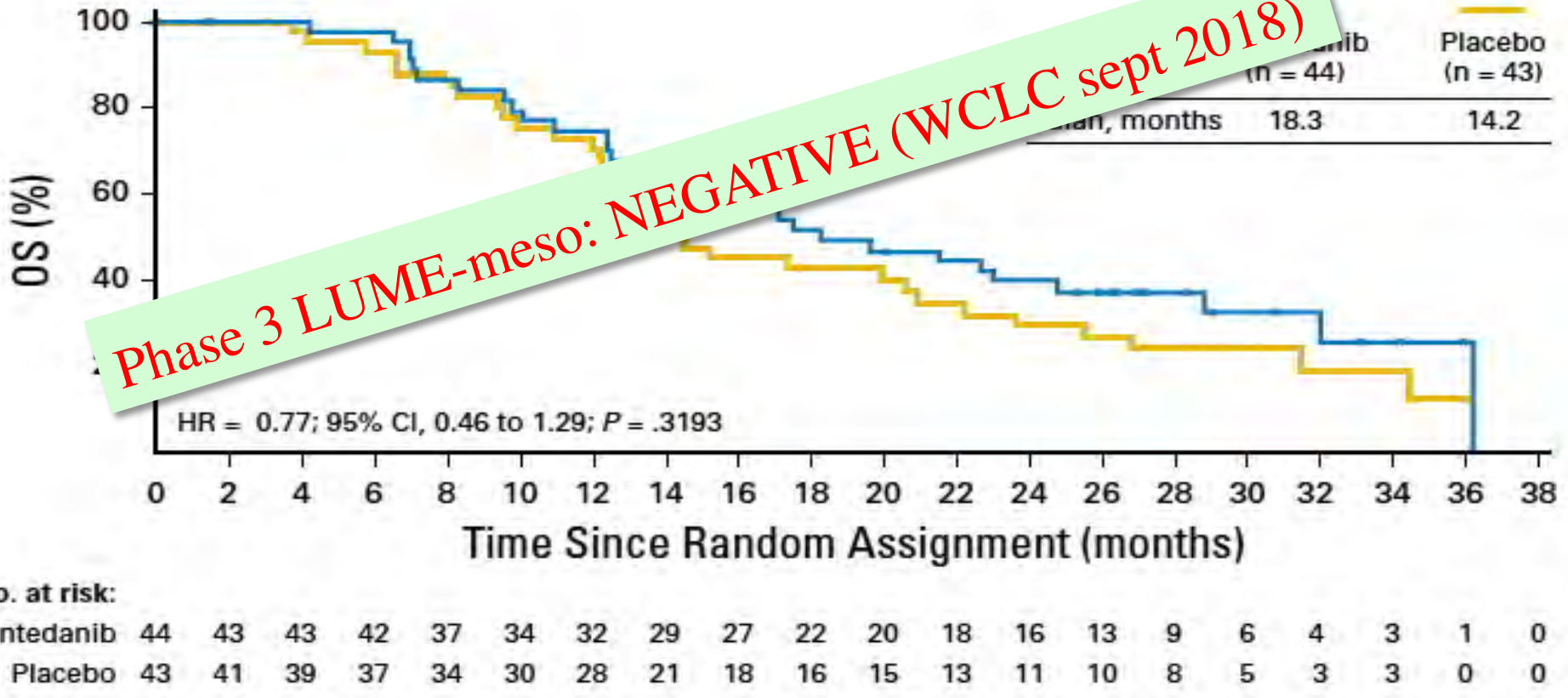
Nintedanib Plus Pemetrexed/Cisplatin in Patients With Malignant Pleural Mesothelioma: Phase II Results From the Randomized, Placebo-Controlled LUME-Meso Trial

Federica Grosso, Nicola Steele, Silvia Novello, Anna K. Nowak, Sanjay Popat, Laurent Greillier, Thomas John, Natasha B. Leighl, Martin Reck, Paul Taylor, David Planchard, Jens Benn Sørensen, Mark A. Socinski, Ute von Wangenheim, Arsène Bienvenu Loembé, José Barrueco, Nassim Morsli, and Giorgio Scagliotti

J. Clin. Oncol 2017

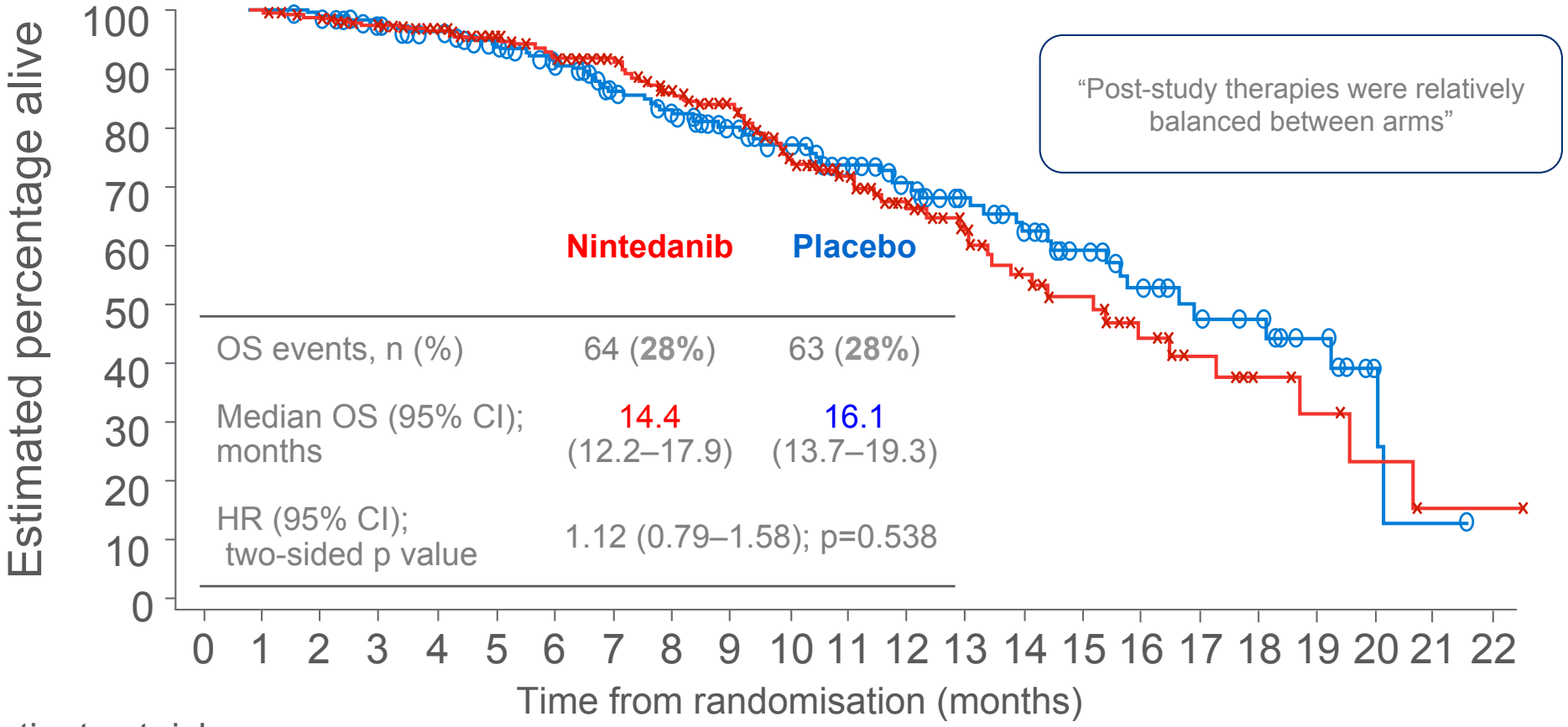
n=87

C



WCLC 2018, Toronto

OS (interim analysis) LUME MESO phase 3



Patients at risk

Nintedanib	229	222	208	195	179	160	146	128	113	90	71	57	44	33	24	18	12	8	5	3	1	1	0
Placebo	229	226	215	196	185	165	143	127	110	99	77	65	53	44	32	25	19	15	10	4	1	0	

NCCN Guidelines Version 3.2016
Malignant Pleural Mesothelioma

NCCN Guidelin
MPM Table of C
Dis

PRINCIPLES OF CHEMOTHERAPY (1 of 2)

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

- Pemetrexed* 500 mg/m^2 day 1
  Cisplatin 75 mg/m^2 day 1
  Administered every 3 weeks (category 1)[1]
- Pemetrexed 500 mg/m^2 day 1
  Cisplatin 75 mg/m^2 day 1
  Bevacizumab 15 mg/kg day 1
  Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression[2,**]
- Pemetrexed* 500 mg/m^2 day 1
  Carboplatin AUC 5 day 1
  Administered every 3 weeks[3-5]
- Gemcitabine 1000–1250 mg/m^2 days 1, 8, and 15
  Cisplatin 80–100 mg/m^2 day 1
  Administered in 3- to 4-week cycles[6,7]
- Pemetrexed* 500 mg/m^2 every 3 weeks[8]
- Vinorelbine 25–30 mg/m^2 weekly[9]

SECOND-LINE CHEMOTHERAPY

- Pemetrexed* (if not administered as first-line) (category 1)[10]
  Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted[11]
- Vinorelbine[12,13]
- Gemcitabine[13-15]

INITIAL EVALUATION[a]

Management by a multidisciplinary team with experience in MPM recommended

See Pretreatment Evaluation (MPM-2)

*Pemetrexed-based chemotherapy may also be used for malignant peritoneal mesothelioma and tunica vaginalis testis mesothelioma.[16]
**The combination regimen of pemetrexed/cisplatin/bevacizumab is only for unresectable disease.

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HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude-Bernard

5ème partie: Immunothérapie du mésothéliome

Retour vers le futur

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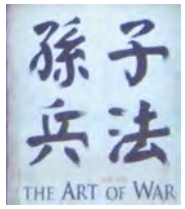
MESOCLIN
Réseau National Expert pour le Mésothéliome Pleural Malin

IFCT

Comment aller plus loin et augmenter le nombre de patients vivants au-delà de 3 ans ?

L'excellence suprême consiste à casser la résistance de l'ennemi…sans combattre

Sun Tzu (544-496 av JC)

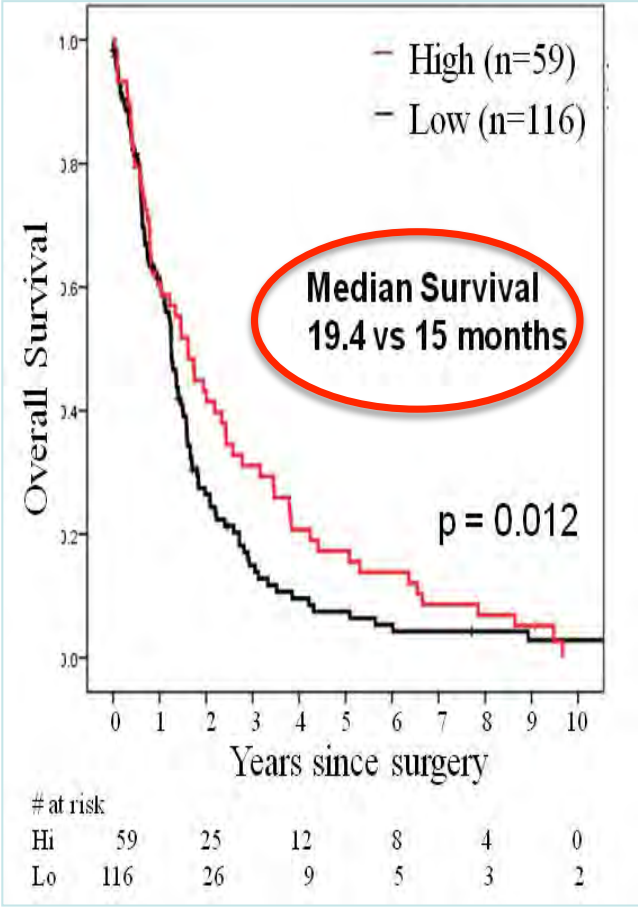


=> Renforcer la réponse immunitaire de l'organisme contre le cancer

Inflammatory responses improve outcome in epithelioid MPM

- Acute / chronic inflammation assessed in tumor / stroma
  - Epithelioid MPM (n = 175) H&E slides
  - Chronic inflammatory infiltrate in the stroma is independent predictor of survival (HR 0.70 (0.51 – 0.96)

Parameter	HR (95% CI)	p-value
Stromal inflammation	0.70 (0.51 - 0.96)	0.028
Age (>65 vs <65)	1.41 (1.06 – 1.88)	0.018
Laterality (R vs L)	1.34 (0.99 - 1.81)	0.056
Lymphatic invasion	1.52 (1.10 - 2.10)	0.010
Morphology	1.65 (1.07 – 2.56)	0.025



Suzuki K, Adusumilli PS.
Cancer Immunol Immunother 2011

MPM highly express PD-L1 (B7-H1)

Analysis of Expression of Programmed Cell Death 1 Ligand 1 (PD-L1) in Malignant Pleural Mesothelioma (MPM)

Susana Cedrés[1]*, Santiago Ponce-Aix[2], Jon Zugazagoitia[2], Irene Sansano[3], Ana Enguita[4], Alejandro Navarro-Mendivil[1], Alex Martinez-Marti[1], Pablo Martinez[1], Enriqueta Felip[1]

PLOS ONE | March 2015

B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis

Aaron Scott Mansfield, M.D.[1], Anja C. Roden, M.D.[2], Tobias Peikert, M.D.[3], Yuri M. Sheinin, M.D.[4,5,6], Susan M. Harrington[4], Christopher J. Krco, Ph.D.[5], Haidong Dong, M.D., Ph.D.[4], and Eugene D. Kwon, M.D.[4]

J. Thorac. Oncol 2014, July

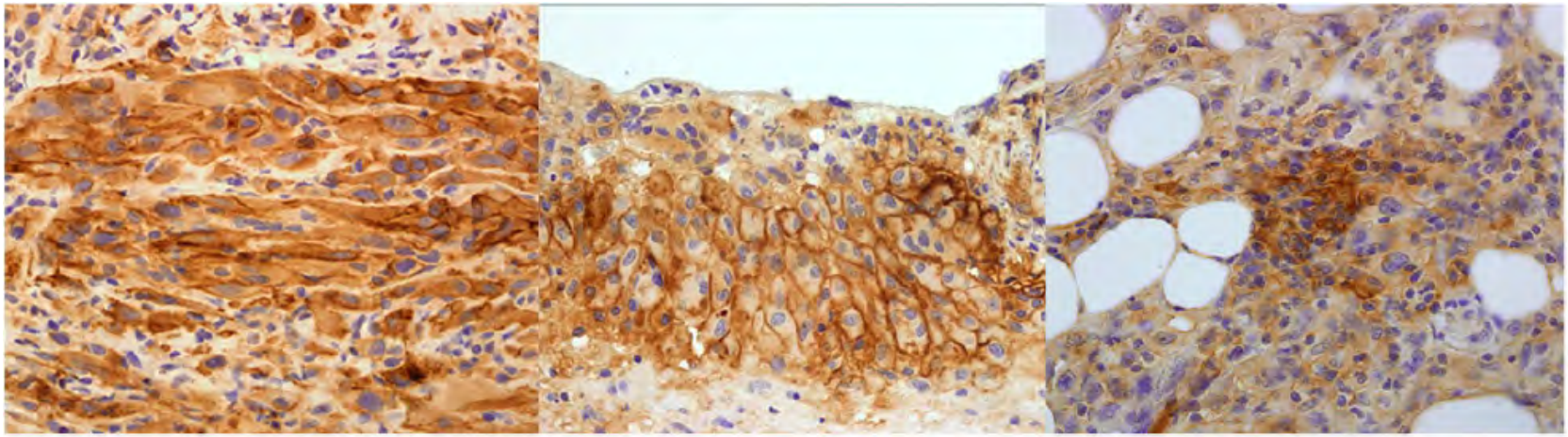
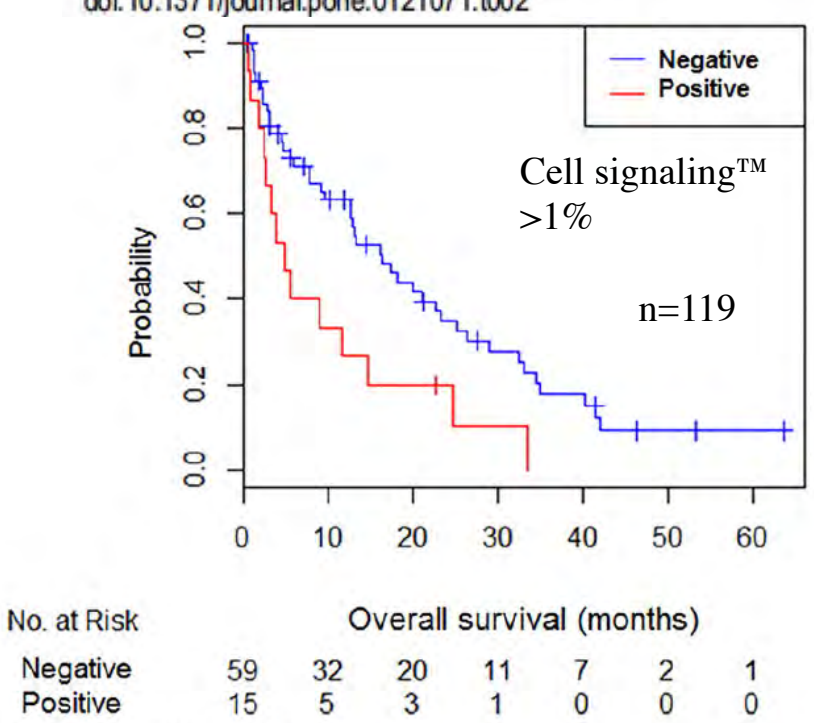


Table 2. Patients characteristics according PD-L1 expression.

Characteristic	PD-L1 + (n,%)	PD-L1 - (n,%)	P
Median age	69	66	0.6
Sex			0.38
Male	11 (68)	43 (70)	
Female	5 (32)	18 (30)	
Histology			0.003
Epithelial	7 (43.7)	46 (77.7)	
No epithelial	9 (56.2)	15 (28.3)	
Smoker	10 (63)	33 (54)	0.61
Asbestos exposure	5 (32)	31 (51)	0.14
Stage III-IV	13 (81)	48 (79)	0.26
Chemotherapy	10 (63)	45 (74)	0.3

20% de positivité

doi:10.1371/journal.pone.0121071.t002



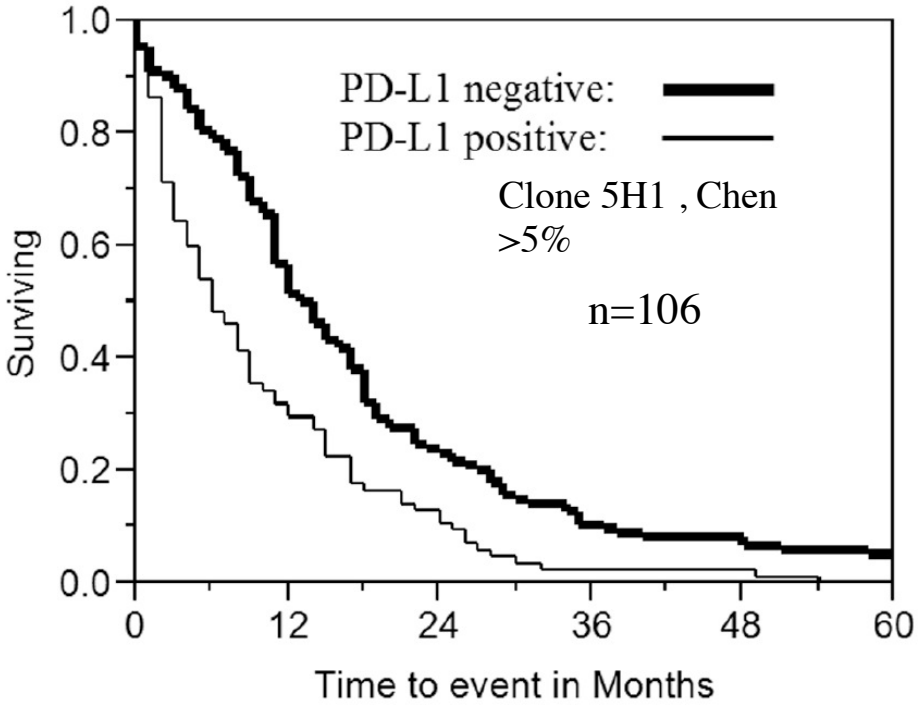
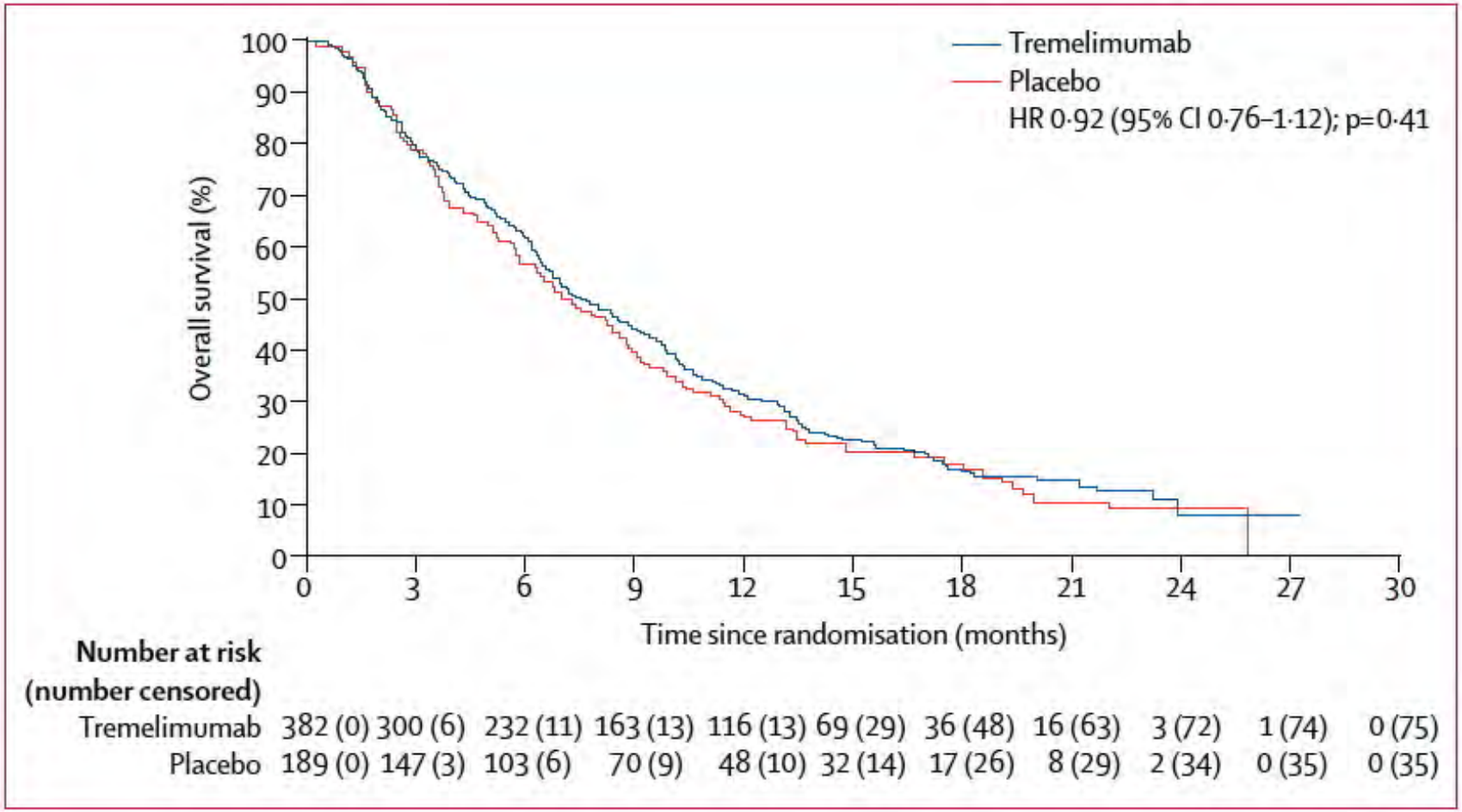


Fig 3. Kaplan-Meier overall survival according to PD-L1 expression

Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial

Michele Maio, Arnaud Scherpereel, Luana Calabrò, Joachim Aerts, Susana Cedres Perez, Alessandra Bearz, Kristiaan Nackaerts, Dean A Fennell, Dariusz Kowalski, Anne S Tsao, Paul Taylor, Federica Grosso, Scott J Antonia, Anna K Nowak, Maria Taboada, Martina Puglisi, Paul K Stockman, Hedy L Kindler

Lancet Oncol 2017; 18: 1261–73

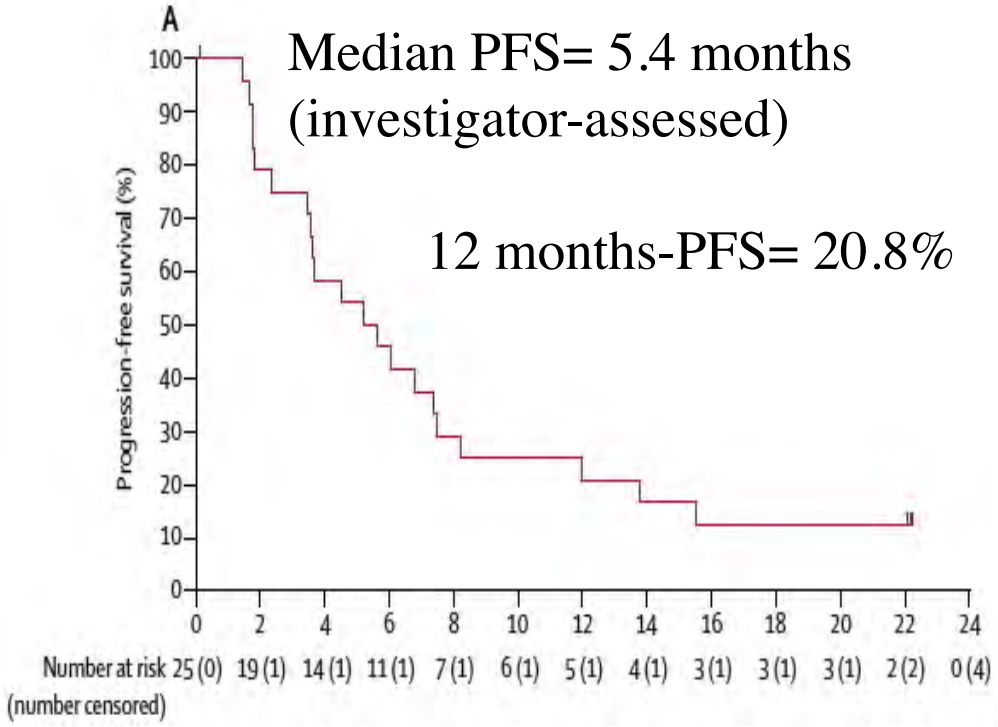


Number at risk (number censored)											
Tremelimumab	382 (0)	300 (6)	232 (11)	163 (13)	116 (13)	69 (29)	36 (48)	16 (63)	3 (72)	1 (74)	0 (75)
Placebo	189 (0)	147 (3)	103 (6)	70 (9)	48 (10)	32 (14)	17 (26)	8 (29)	2 (34)	0 (35)	0 (35)

Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial

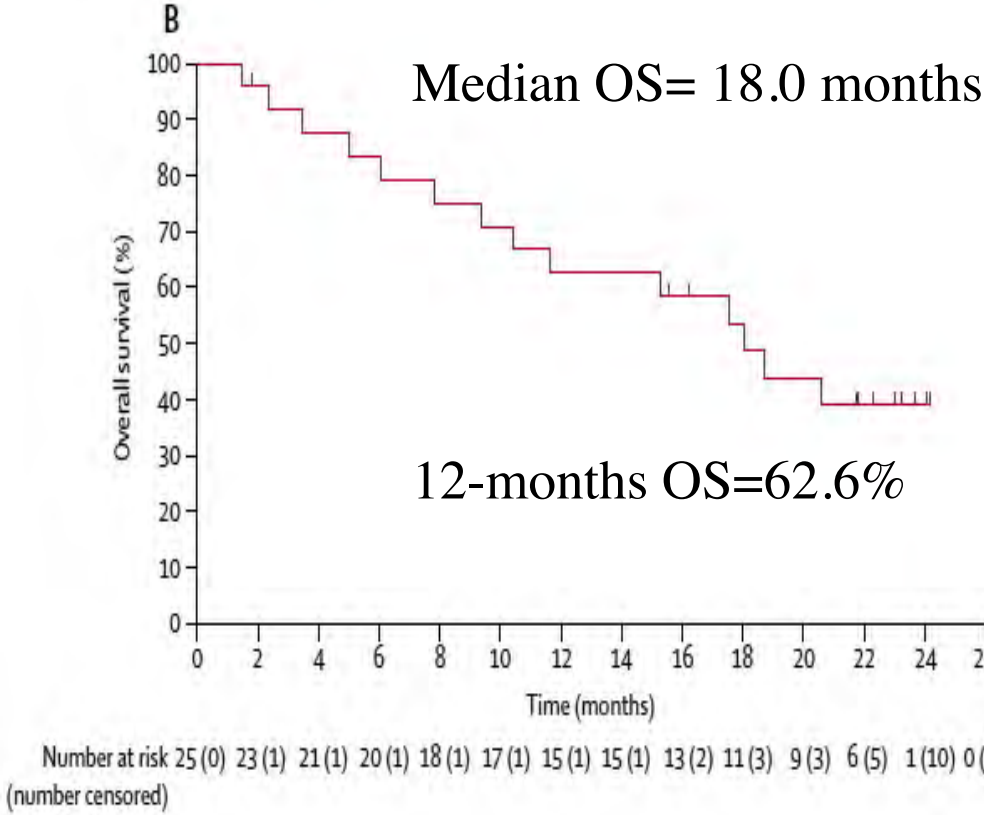
n=25

Evan W Alley, Juanita Lopez, Armando Santoro, Anne Morosky, Sanatan Saraf, Bilal Piperdi, Emilie van Brummelen



Median PFS= 5.4 months (investigator-assessed)

12 months-PFS= 20.8%



Median OS= 18.0 months

12-months OS=62.6%

NivoMes: Study Design

N=34

Key Eligibility Criteria

- Recurrent malignant pleural mesothelioma[1]
- ECOG PS ≤1[1]
- PD after ≥1 prior lines of chemotherapy[1] with a platinum-based doublet[2]
- No CNS metastases[1]
- No autoimmune disease[1]
- No pulmonary fibrosis, pneumonitis, or GI disorders[2]

No HIV[2]

→ **Nivolumab[1]** 3 mg/kg Q2W →

Nivolumab treatment until PD[1] or unacceptable toxicity[2]; ipilimumab treatment up to 4 doses[2]

Study Start Date[1]: July 2015
Estimated Completion Date[1]: July 2017
Estimated Primary Completion Date[1]: July 2017
Sponsor[1]: The Netherlands Cancer Institute
PI: Paul Baas

Primary Outcome Measure: DCR at 12 weeks
Secondary Outcome Measures[1]: PFS, OS, TTP, ORR, Safety and tolerability, DCR

Hypothesis

DCR at 12 wks will increase from 20%* to 40%

Sample size

Power 80%
Significance level 5% (α = 0.05)

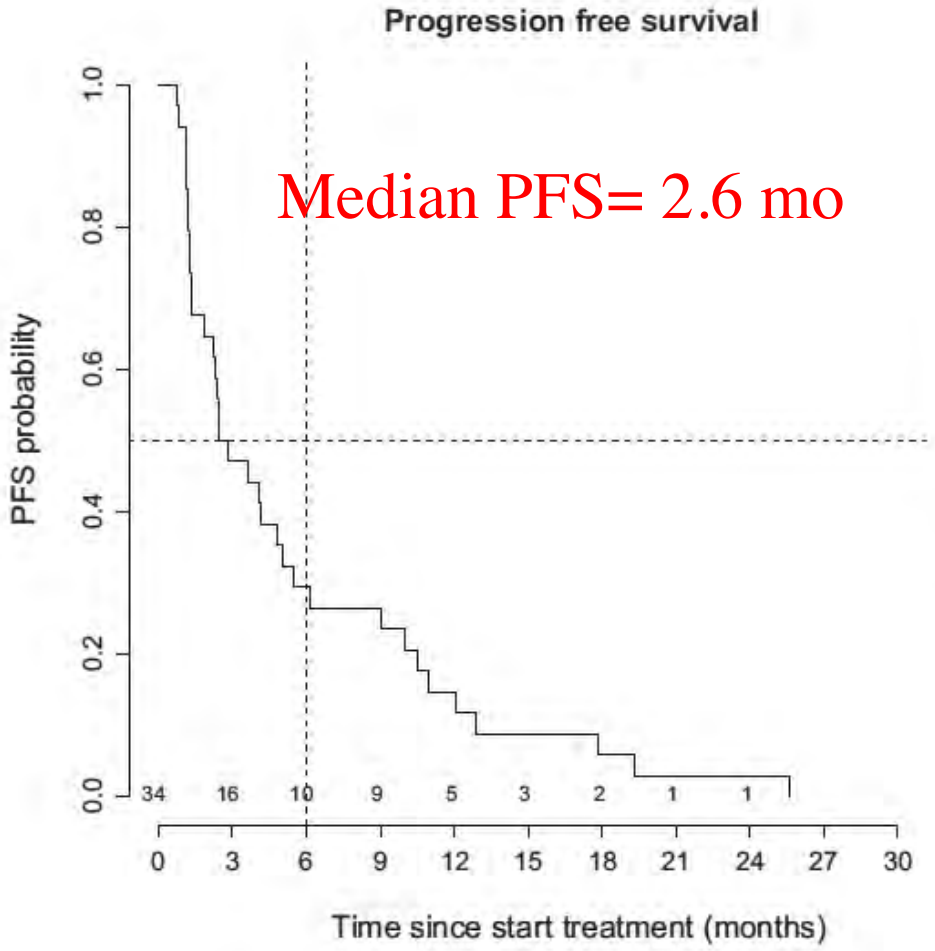
33 patients needed

* Based on Jassem *et al*, JCO 2008

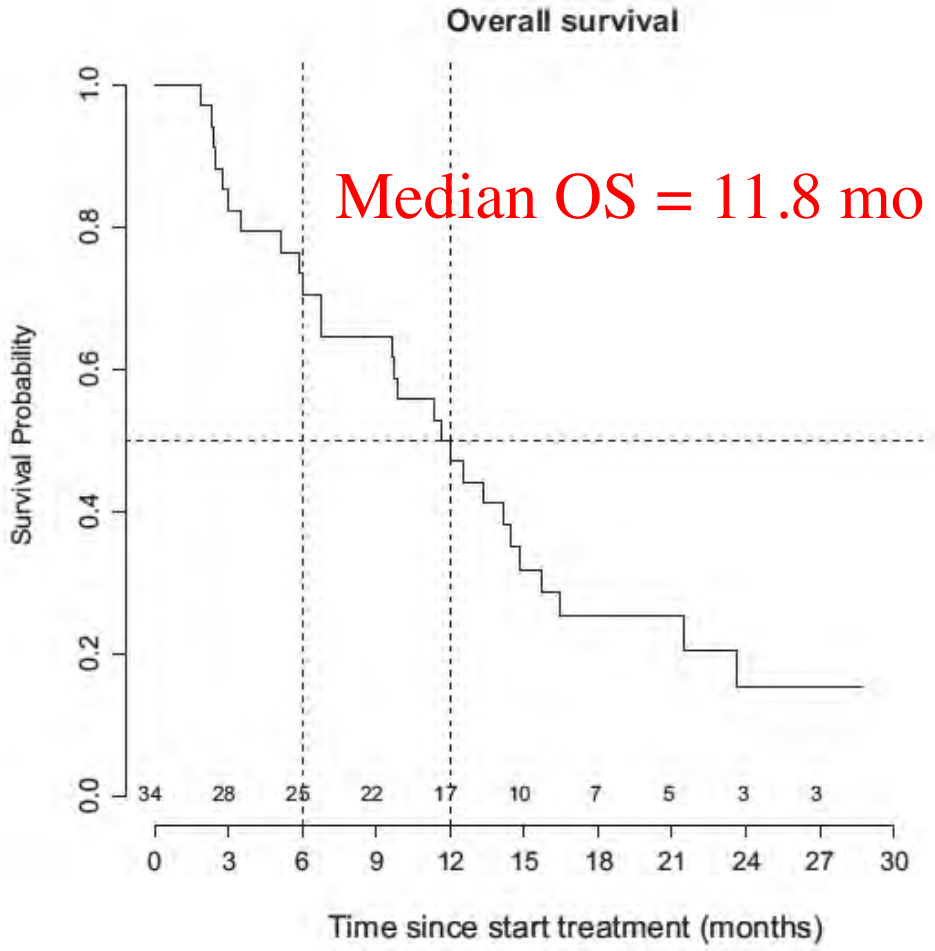
Baas P et al. Oral Presentation at WCLC 2016. OA13.01.

NivoMes: Results (27.5 months median follow-up)

Primary endpoint reached: 50% DCR



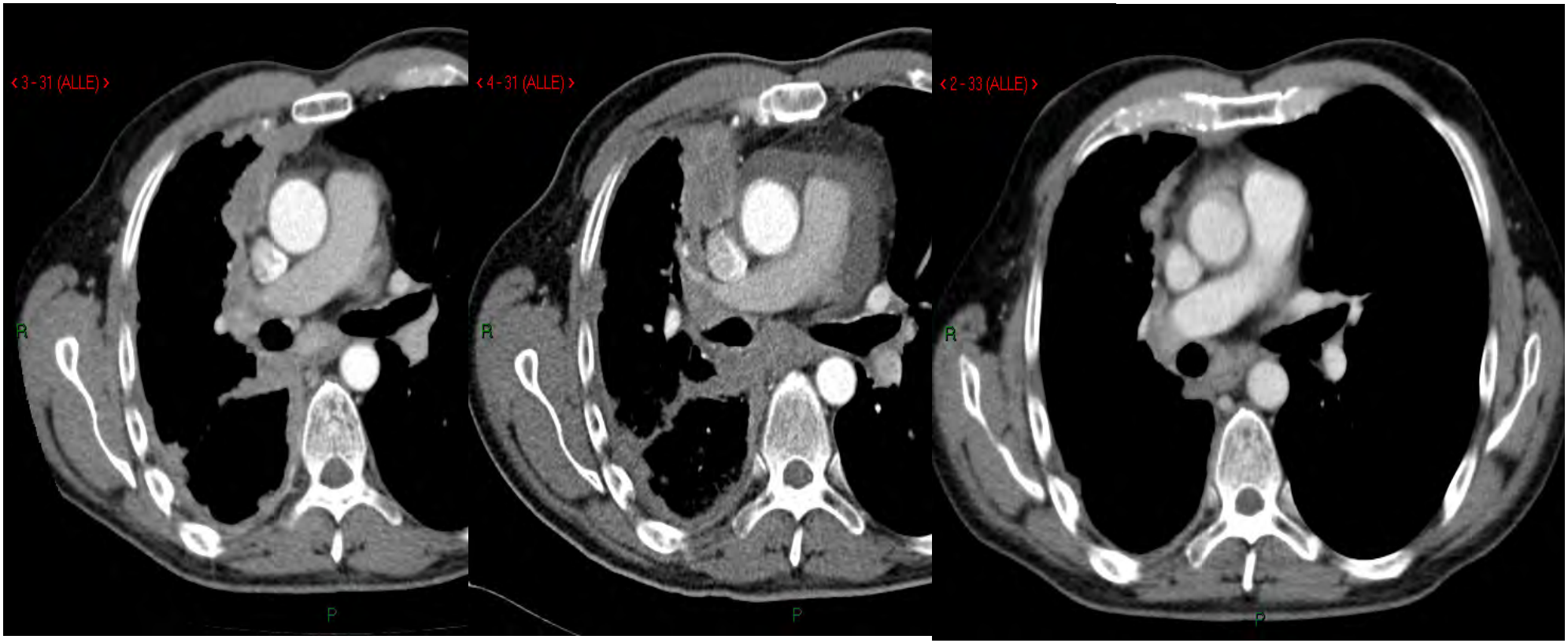
Median PFS= 2.6 mo



Median OS = 11.8 mo

Quispel-Janssen J et al. JTO 2018, Jun 14

Remarkable case….



Pre-treatment

After 2 courses

After 12 courses

Second or 3rd line Nivolumab (Nivo) OR Nivo plus Ipilimumab (Ipi) in Malignant Pleural Mesothelioma (MPM) patients: up-dated results of the IFCT-1501 MAPS2 randomized phase 2 trial.

EUDRACT N°2015-004475-75
- ClinicalTrials.gov : NCT 02716272

Gérard ZALCMAN, Julien MAZIERES, Laurent GREILLER, Sylvie LANTUEJOUL, Pascal DO, Olivier BYLICKI, Isabelle MONNET, Romain CORRE, Clarisse AUDIGIER-VALETTE, Denis MORO-SIBILOT, Myriam LOCATELLI, Olivier MOLINIER, Luc THIBERVILLE, Thierry URBAN, David PLANCHARD, Catherine LIGEZA-POISSON, Elodie AMOUR, Franck MORIN and Arnaud SCHERPEREEL,

on behalf of the French Cooperative Thoracic Intergroup (IFCT)

Presented by: Gérard ZALCMAN, M.D. Bichat Hospital (APHP), Paris, France

MAPS-2 trial
Mesothelioma Anti-PD-1 Study 2 - IFCT 1501

Randomized, non-comparative phase 2 trial - One-step Fleming design (each arm independently)

- **Histological diagnosis of Malignant Pleural Mesothelioma**
- **Unresectable cancer with documented progression after maximum 1 or 2 previous lines of chemotherapy including a pemetrexed/platinum doublet**
- **Measurable disease (mRECIST)**
- **ECOG PS 0-1**
- **Weight loss <10%**
- **Age : ≥ 18 years**
- **Life expectancy > 12 weeks**
- **Available tumor tissue (at least 4 slides)**

R 1:1

57 patients

Anti-PD-1 Nivolumab
3 mg/kg IV / 2 weeks

until progression or unacceptable toxicity (or 2 years max)

57 patients

Anti-PD-1 Nivolumab
3 mg/kg IV / 2 weeks
+ Anti-CTLA4 Ipilimumab
1mg/kg IV / 6 weeks

until progression or unacceptable toxicity (or 2 years max)

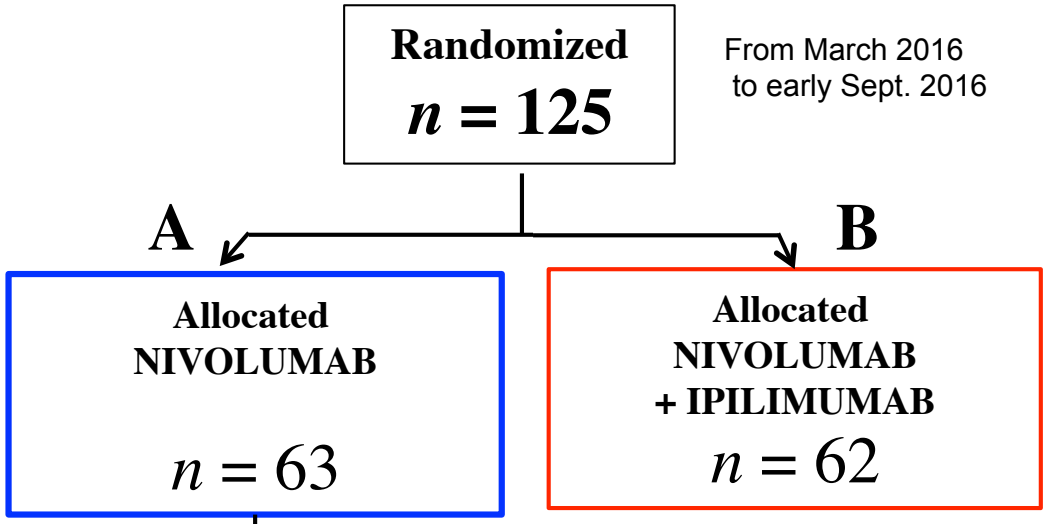
125 Inclusions en 4 mois !

→ **Primary Endpoint = Disease control rate (DCR) at 12 weeks in the first 2x 54 accrued eligible patients in each arm separately: 57 pts to be included assuming 5% ineligibility**

H0: P≤20% *vs*. H1: P≥40%

Data cut-off: July 31th, 2017
Database export: August 21th, 2017

Patient Disposition



Ineligible (*n*=5)
- No progression to inclusion (n=1)
- Received 3 or more treatment lines before inclusion (n=3)
- No histological evidence (n=1)

Ineligible (*n*=2)
- No progression to inclusion (n=1)
- Received 3 or more treatment lines before inclusion (n=1)

Study withdrawn (n=54)
- **Disease Progression (*n*=46, 85.2%)**
- **Toxicity (n=3, 5.6%)**
- Death (n=1, 1.8%)
- Second cancer (n=1, 1.8%)
- Intercurrent disease (n=1, 1.8%)
- Patient's choice (n=1, 1.8%)
- Other : Progr+Tox (n=1, 1.8%)

Did not receive allocated treatment
- Death (n=1)

Study withdrawn (n=54)
- **Disease Progression (*n*=35, 63.6%)**
- **Toxicity (n=13, 23.6%)**
- Death (n=5, 9.3%)
- Intercurrent disease (n=1, 1.8%)

Patients baseline characteristics (2)	Nivo Arm (n=63)	Nivo+Ipi Arm (n=62)
TNM (1995)*		
Stages III-IV n (%)	56 (89.0%)	51 (83.4%)
Leucocytes		
< 8.3 x 10^9/L	43 (68)	41 (66)
≥ 8.3 x 10^9/L	20 (32)	21 (34)
Hemoglobin		
> 12 g/L	33 (52)	37 (60)
≤ 12 g /L	30 (48)	25 (40)
Platelets		
< 350 x 10^9/L	46 (73)	43 (69)
≥ 350 x 10^9/L	17 (27)	19 (31)
PD-L1 status available (28.8 mAb, Dako PharmDX™)	50 (79%)	49 (79%)
Negative	31 (62%)	27 (55%)
≥1%	19 (38%)	22 (45%)
≥ 25%	2 (4%)	5 (10%)
≥50%	0	3 (6%)

All p-values: not significant

Drug-related Adverse Events (AE)

AE	Nivo Arm (n=63)	Nivo+Ipi Arm (n=61)
All grade	56 (88.9%)	57 (93.4%)
Grade 3	8 (12.7%)	14 (22.9%)
Grade 4	0 (0%)	2 (3.3%)
Grade 5	0 (0%)	3 (4.9%)*

Treatment related deaths as reported by local investigators:

*1 fulminant hepatitis , 1 encephalitis and 1 acute kidney failure

Presented by: Gérard ZALCMAN, M.D. Bichat Hospital (APHP), Paris, France

Tumor Response at 12 weeks assessment

By a blinded, independent panel of 3 Radiologists

Tumor assessment % [IC95%](n pts)	NIVO Arm (n=54)	NIVO+IPI Arm (n=54)	NIVO Arm (n=63)	NIVO+IPI Arm (n=62)
Objective response	18.5% [8.2-28.9%] (10)	27.8% [15.8-39.7%] (15)	17.5% [8.1-26.8%] (11)	25.8% [14.9-36.7%](16)
Stable Disease	25.9% [14.2-37.6%] (14)	22.2% [11.1-33.3%] (12)	22.2% [12.0-32.5%](14)	25.8% [14.9-36.7%](16)
Disease control rate	**44.4%** [31.2-57.7%] (24)	**50.0%** [36.7-63.3%] (27)	**39.7%** [27.6-51.8%] (25)	**51.6%** [39.2-64.1%] (32)
Disease Progression	51.9 [38.5-65.2%] (28)	42.6% [29.4-55.8%] (23)	57.1% [44.9-69.4%] (36)	37.1% [25.1-49.1%] (23)
Not evaluable/not done /missing	3.7% [0.0-8.7%] (2)	7.4% [0.4-14.4%] (4)	3.2% [0.0-7.5%] (2)	11.3% [3.4-19.2%] (7)

in the **first 108 eligible pts**

in the **ITT population (125 pts)**

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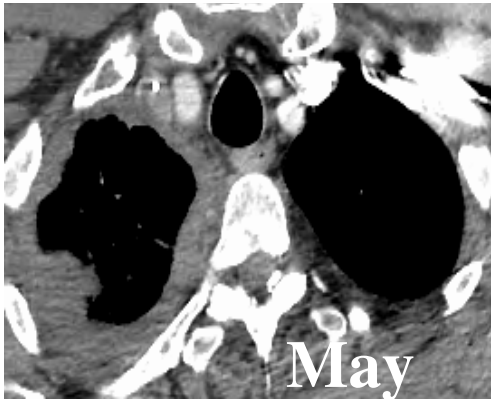
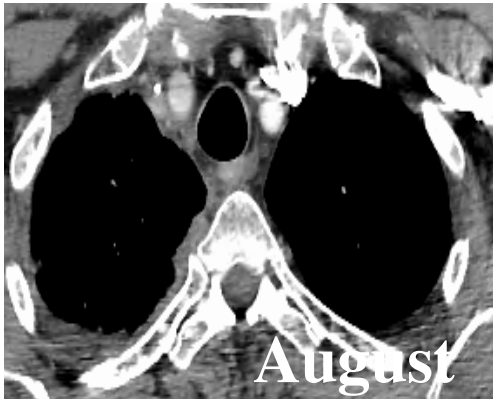
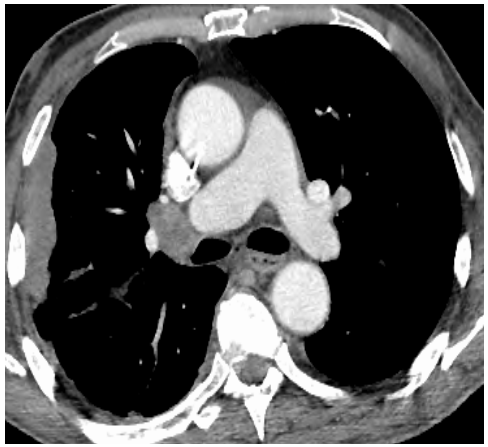
MADRID 2017 ESMO congress

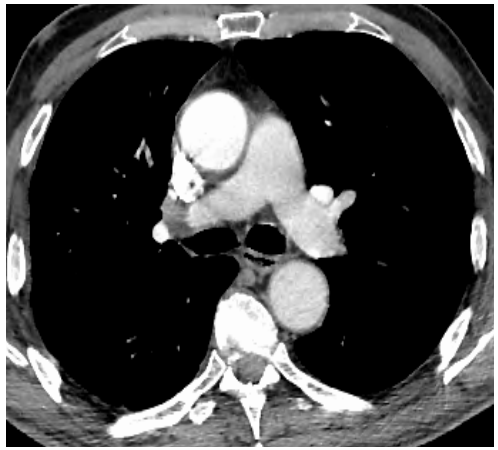
IFCT

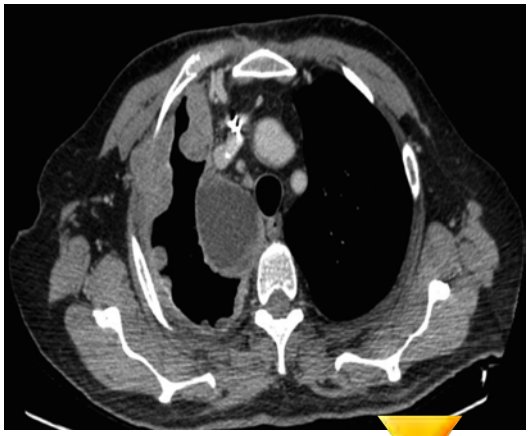
Some major Objective Responses…

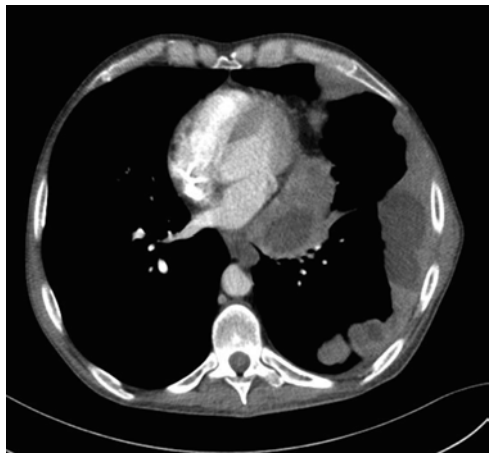


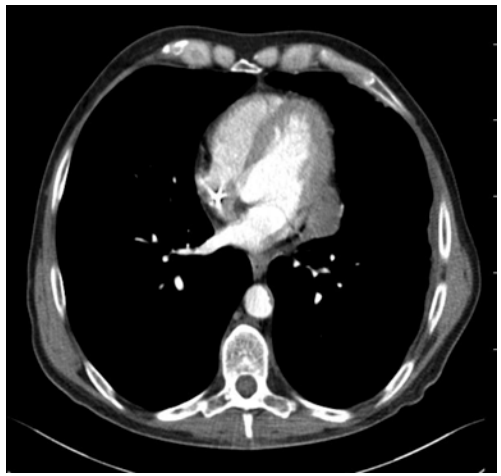


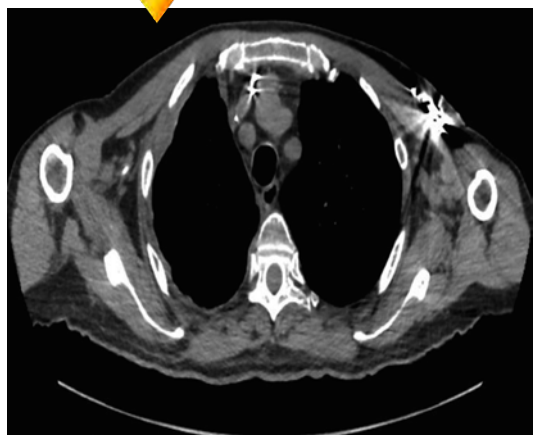












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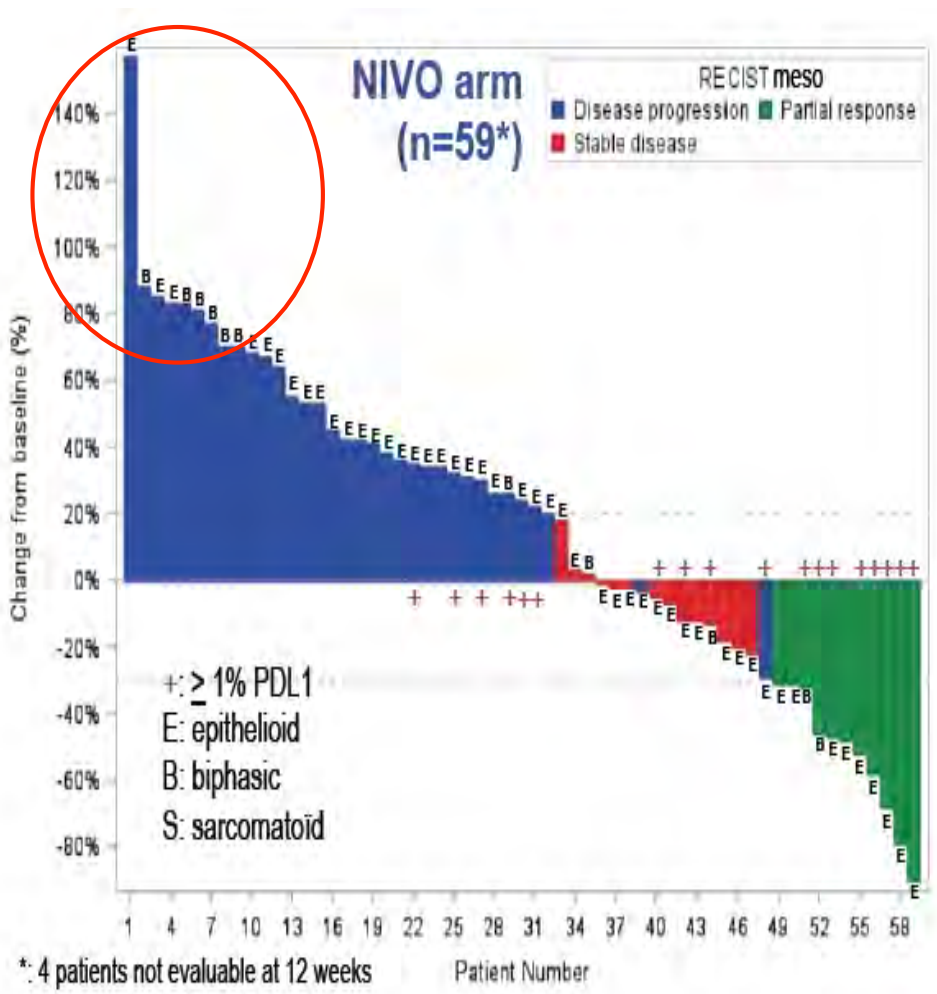
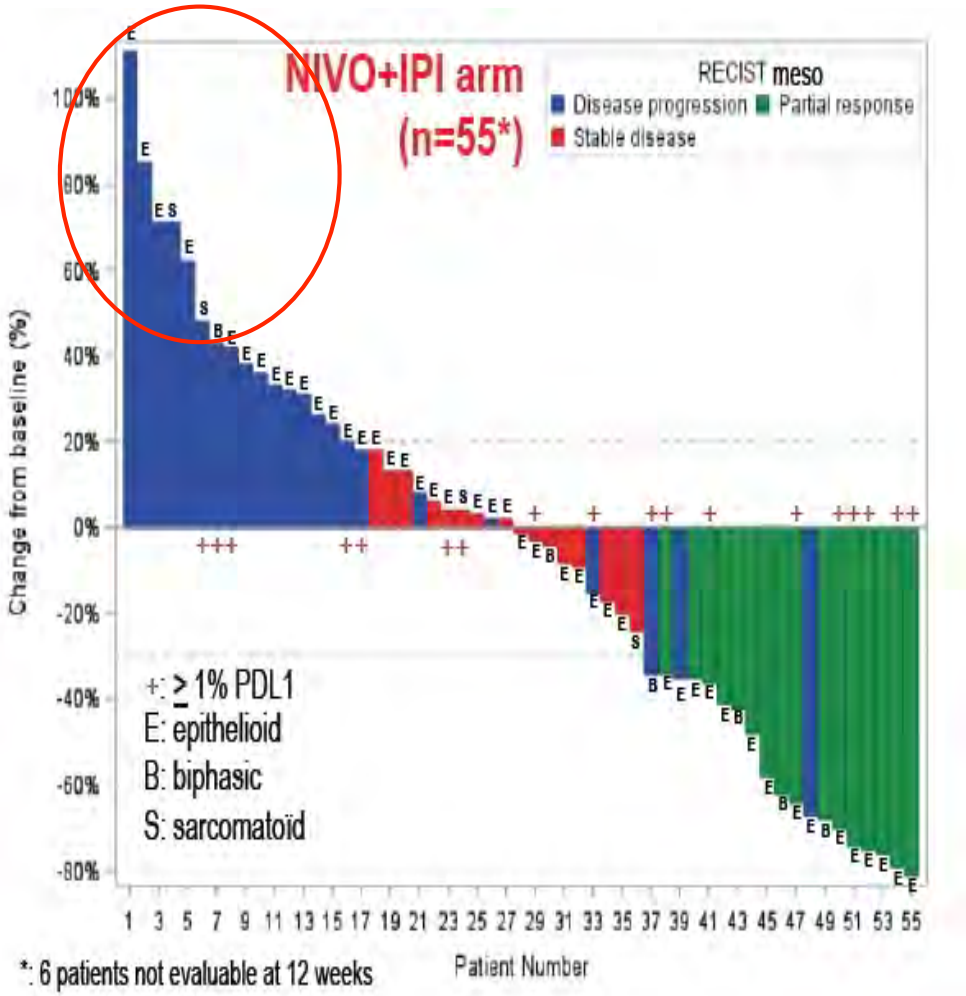
Waterfall plots of percentage change from baseline in tumour size for individual patients at 12 weeks in the Nivo group and the Nivo+Ipi group

In the 114 patients evaluable at 12 weeks

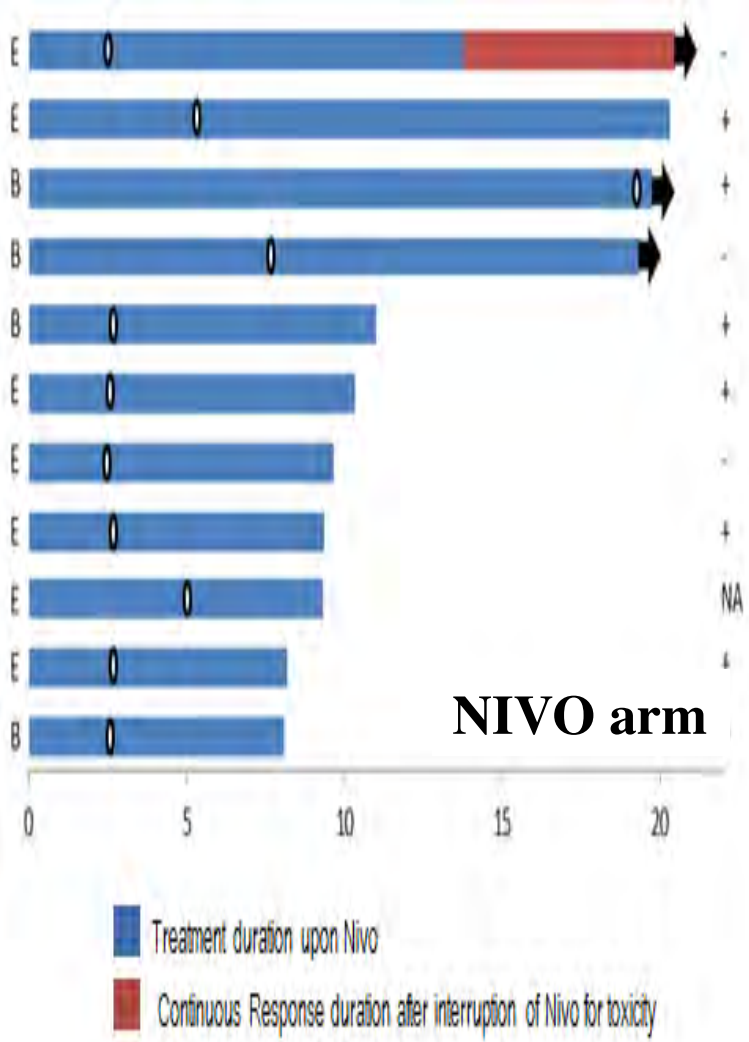


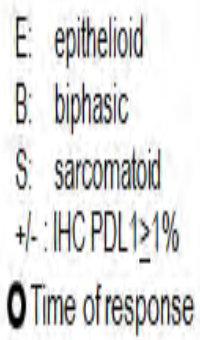


Presented by: Gérard ZALCMAN, M.D. Bichat Hospital (APHP), Paris, France

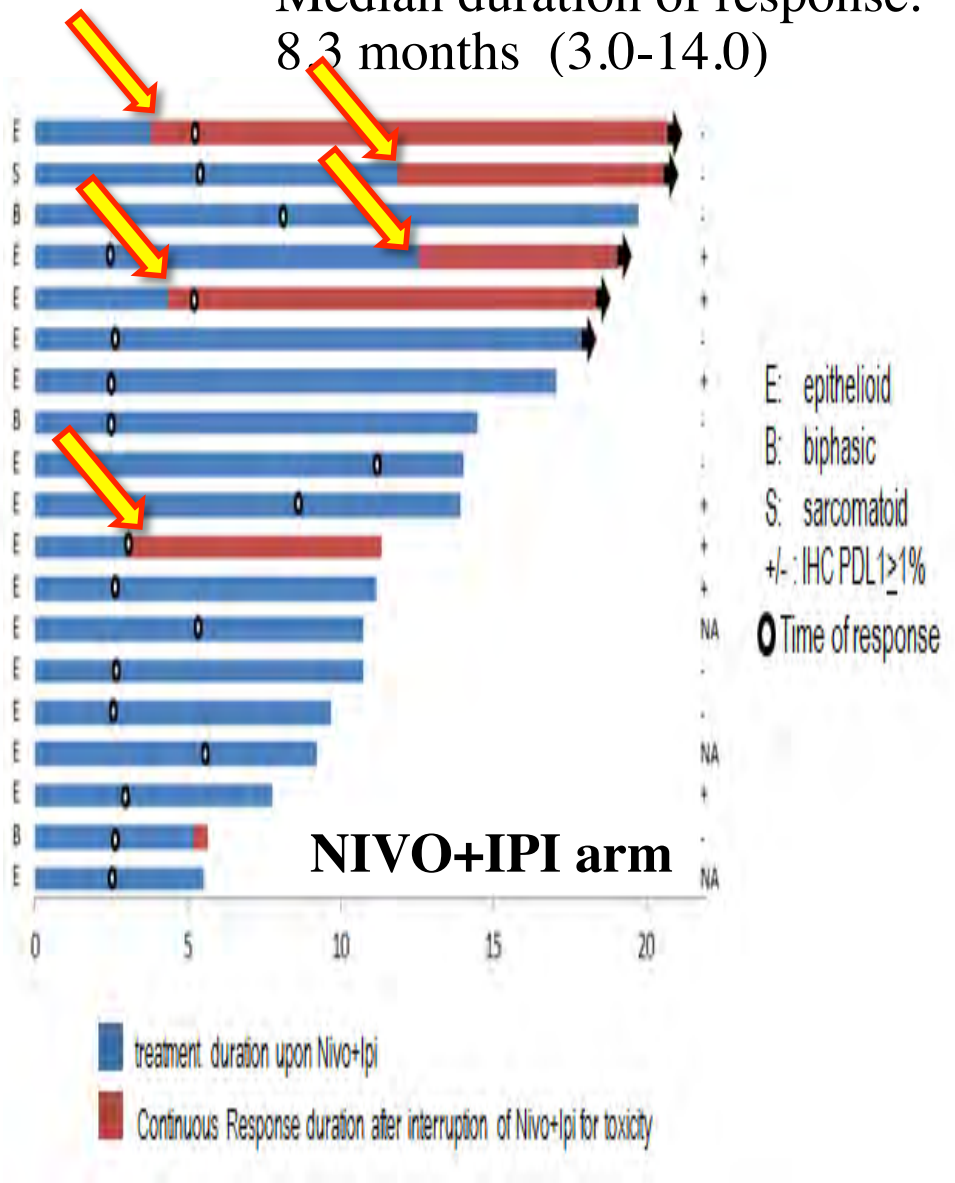
Treatment durations and Time to and duration of response in patients with an objective response (swimmer plots)

Median duration of response:
7.4 months (4.1-11.9)



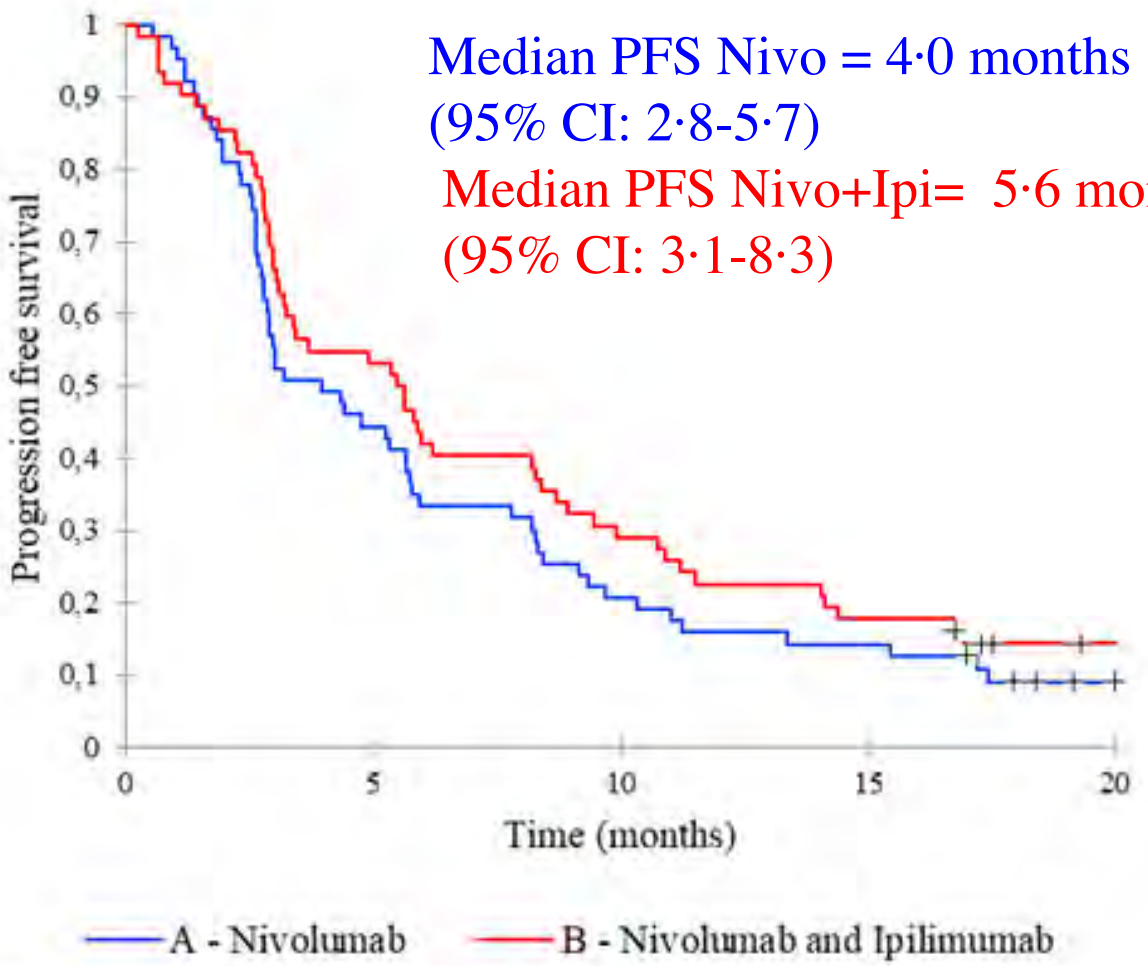


Median duration of response:
8.3 months (3.0-14.0)



Efficacy: PFS as centrally-assessed

median follow-up= 20.1months, (IQR: 18·4–20·8)



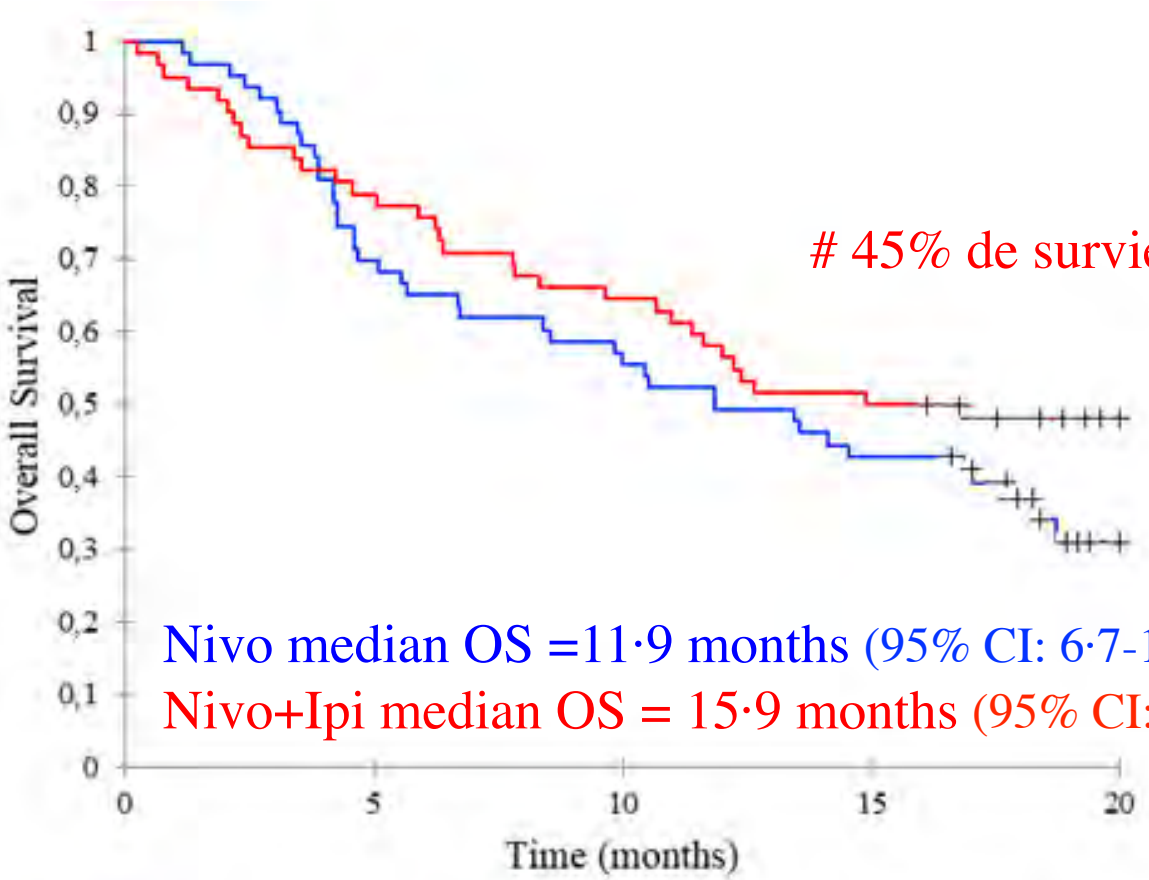
Median PFS Nivo = 4·0 months
(95% CI: 2·8-5·7)

Median PFS Nivo+Ipi= 5·6 months
(95% CI: 3·1-8·3)

Number at risk (number censored)					
Nivo Arm	63 (0)	28 (0)	13 (0)	9 (0)	1 (6)
Nivo+Ipi Arm	62 (0)	34 (0)	19 (0)	12 (0)	1 (9)

Efficacy: ITT median Overall Survival (OS)

median follow-up= 20.1months, (IQR: 18·4–20·8)



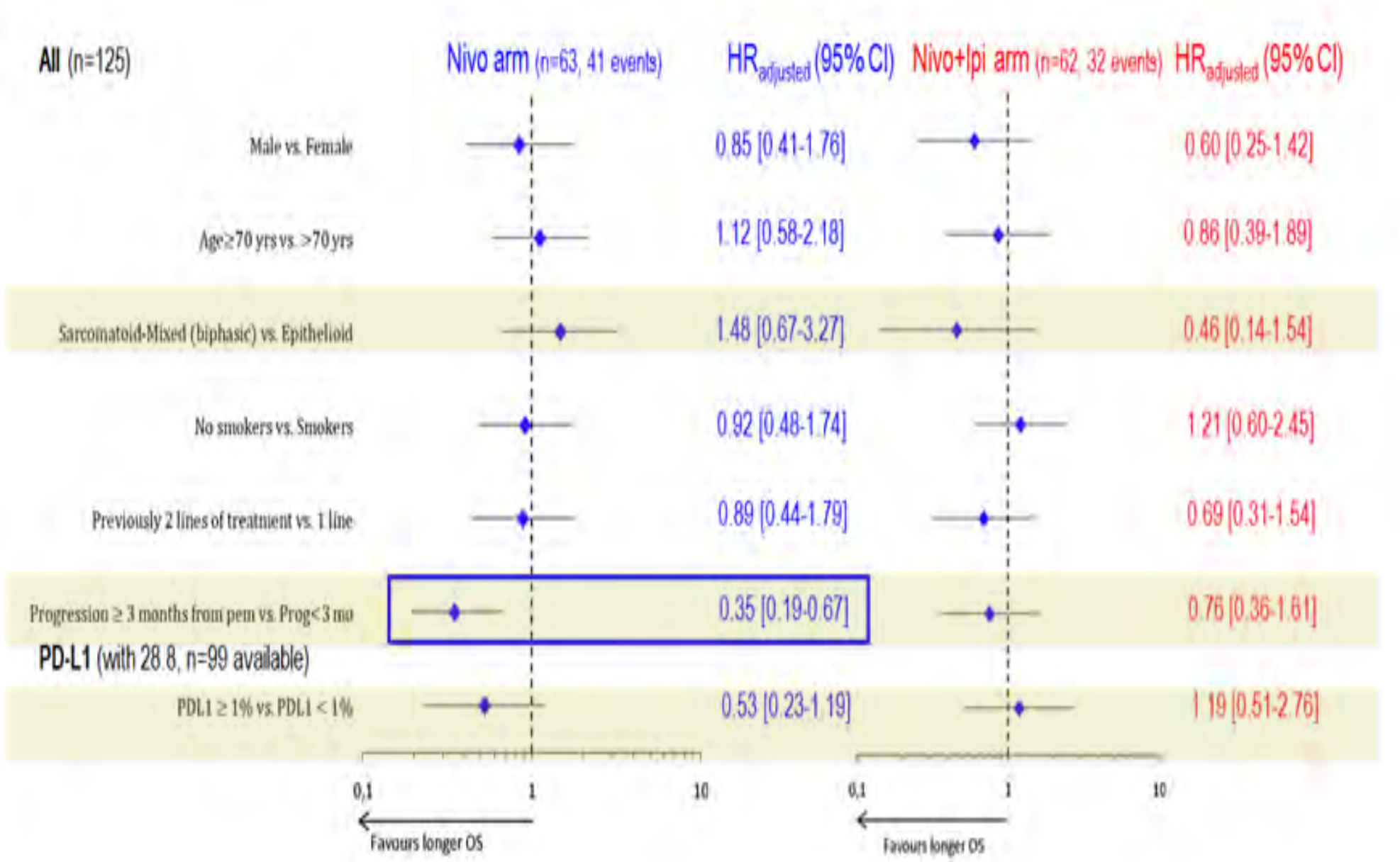
45% de survie à 20 mois

Nivo median OS =11·9 months (95% CI: 6·7-17·7)

Nivo+Ipi median OS = 15·9 months (95% CI: 10·7-NR)

Number at risk (number censored)					
Nivo Arm	63 (0)	44 (0)	35 (0)	27 (0)	6 (16)
Nivo+Ipi Arm	62 (0)	49 (0)	40 (0)	32 (0)	8 (23)

Exploratory Forest Plot: adj.HRs (95%CI) for OS (stratified)



MAPS-2 trial conclusions

- Both Nivo monotherapy Arm, and Ipi+Nivo Arm reached their 1rst endpoint in 2nd/3rd line MPM pts, increasing **meaningfully 12 weeks DCR,** compared to data from patients in historical series, or in previous non-immunotherapy clinical trials.
- Toxicity was **globally** manageable, **despite** 3 potential toxic deaths observed in the combo arm.
- QoL at 12 weeks favors, although not significantly, the monotherapy arm for global, pain, anorexia, interference items, and the combo for general, symptom distress scales, but **long-term and longitudinal QoL** studies (TUDD) are pending.
- Overall survival data are still immature one year after accrual of the last patient, with a median OS at **15.9** months for the Combo, while OS was **11.9** months in the Nivo arm.
- PD-L1 tumor expression could favor response and longer OS in the Nivo arm but did not influence OS of patients receiving the combo.

→ MAPS2 up-dated results support the recent National Comprehensive Cancer Network (NCCN) panel decision to recommend the monotherapy or the combination therapy as options for 2nd/3rd line therapy in relapsing malignant pleural mesothelioma patients

Lancet Oncol 2018, accepted

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Malignant Pleural Mesothelioma

NCCN Guidelin
MPM Table of C
Dis

PRINCIPLES OF CHEMOTHERAPY (1 of 2)

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

- Pemetrexed* 500 mg/m^2 day 1
  Cisplatin 75 mg/m^2 day 1
  Administered every 3 weeks (category 1)[1]
- Pemetrexed 500 mg/m^2 day 1
  Cisplatin 75 mg/m^2 day 1
  Bevacizumab 15 mg/kg day 1
  Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression[2,**]
- Pemetrexed* 500 mg/m^2 day 1
  Carboplatin AUC 5 day 1
  Administered every 3 weeks[3-5]
- Gemcitabine 1000–1250 mg/m^2 days 1, 8, and 15
  Cisplatin 80–100 mg/m^2 day 1
  Administered in 3- to 4-week cycles[6,7]
- Pemetrexed* 500 mg/m^2 every 3 weeks[8]
- Vinorelbine 25–30 mg/m^2 weekly[9]

SECOND-LINE CHEMOTHERAPY

- Pemetrexed* (if not administered as first-line) (category 1)[10]
  Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted[11]
- Vinorelbine[12,13]
- Gemcitabine[13-15]
- Nivolumab+/_Ipilimumab[16]
- Pembolizumab[17]

INITIAL EVALUATION[a]

Management by a multidisciplinary team with experience in MPM recommended

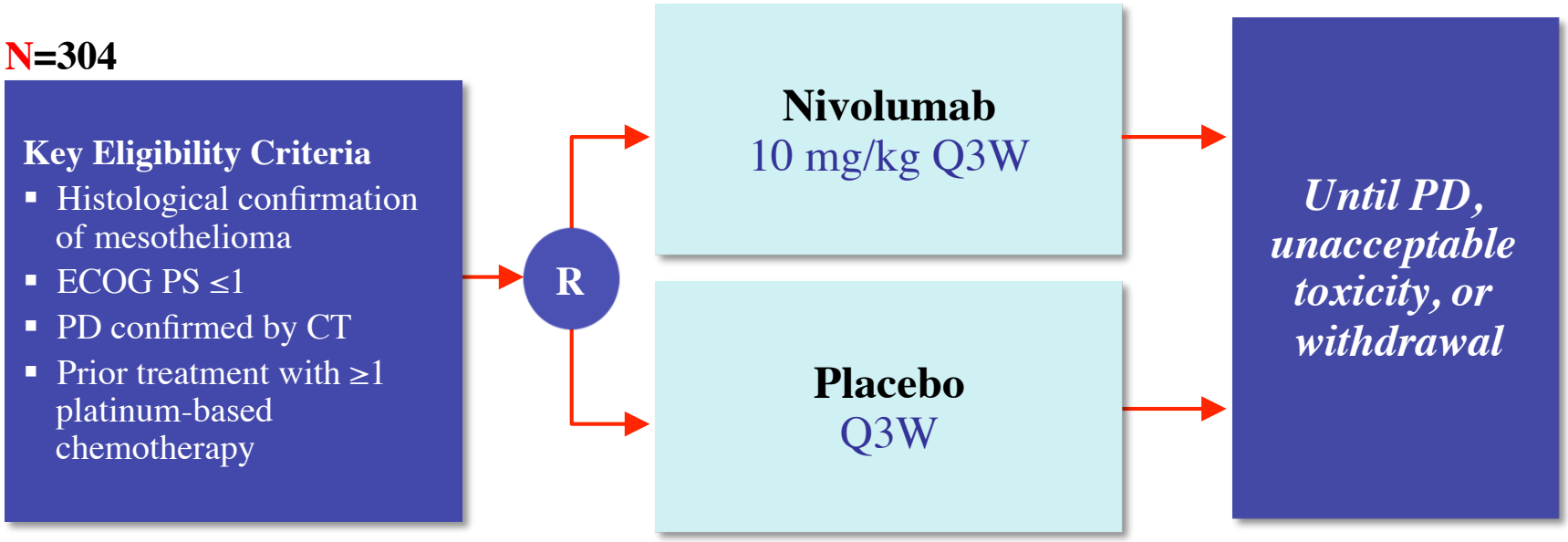
See Pretreatment Evaluation (MPM-2)

*Pemetrexed-based chemotherapy may also be used for malignant peritoneal mesothelioma and tunica vaginalis testis mesothelioma.[16]
**The combination regimen of pemetrexed/cisplatin/bevacizumab is only for unresectable disease.

Ref. 16: MAPS2
Ref. 17: Keynote-028

CONFIRM: Study Design

- **Phase III trial** to evaluate the efficacy of nivolumab in relapsed mesothelioma



- **Study Start Date: N/A**
- **Estimated Completion Date: N/A**
- **Estimated Primary Completion Date: N/A**
- **Status: Approved, protocol in development**
- **Sponsor: Southampton Univesity**
- **PI: Dean Fennell**

- **Primary Outcome Measure: OS**
- **Secondary Outcome Measures: PFS, toxicity, QoL and cost-effectiveness**

INITIATE: Study design

- **Phase II** trial of nivolumab + ipilimumab in patients with unresectable malignant pleural mesothelioma after previous platinum-based therapy

N=33

Key Eligibility Criteria

- Histologically confirmed recurrent MPM
- One previous line of Pt-based systemic treatment
- ECOG PS ≤1
- No uncontrolled pleural/ peritoneal/pericardial effusion

→

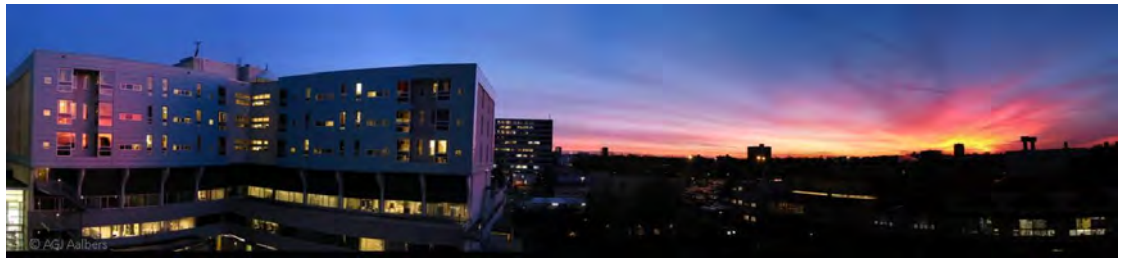
Nivolumab
240 mg Q2W
+
Ipilimumab
1 mg/kg Q6W x4 cycles

→

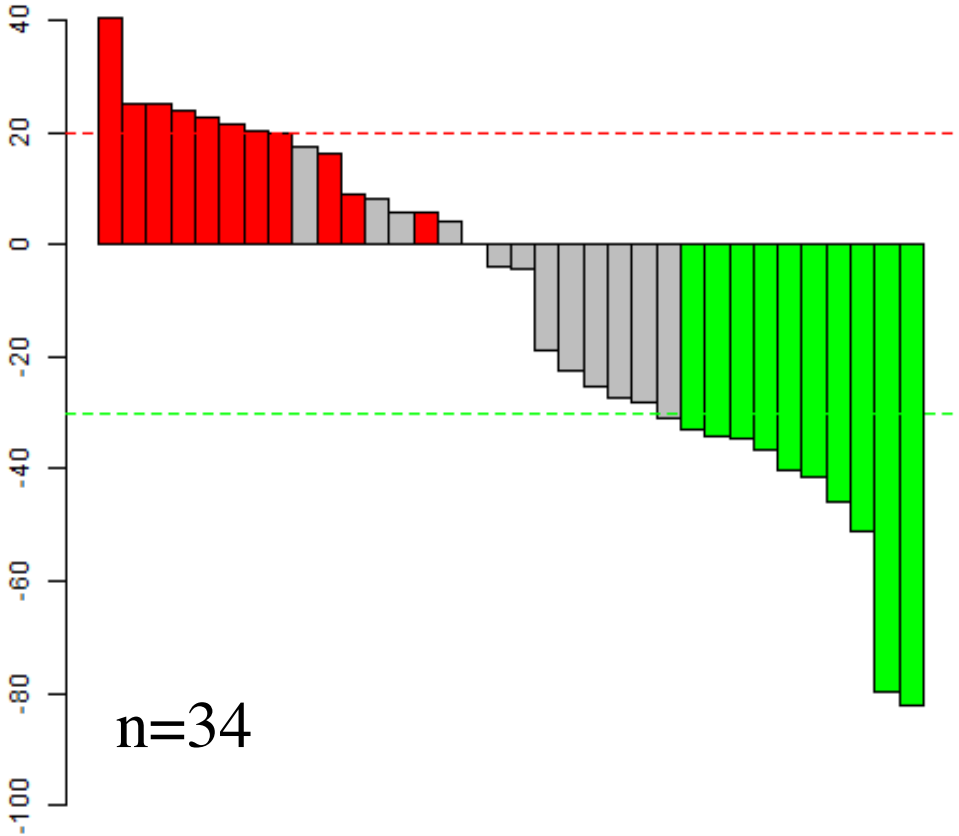
Treatment until PD, unacceptable toxicity, withdrawal of consent, or death

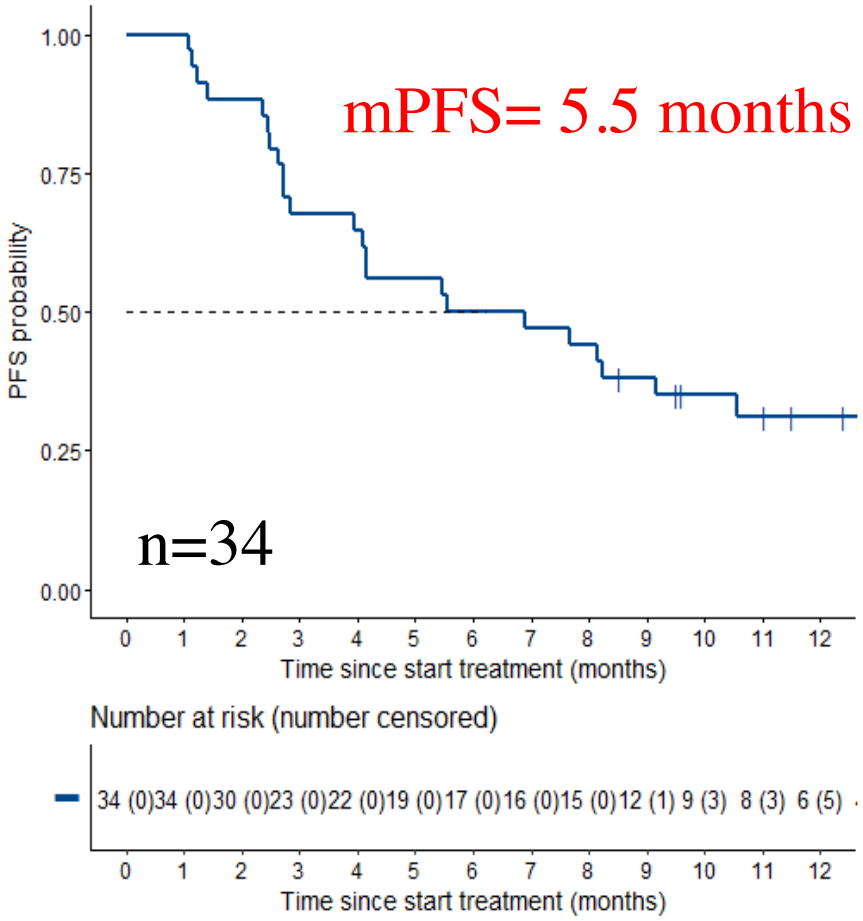
Study Start Date: September 2016
Estimated Completion Date: September 2018
Estimated Primary Completion Date: September 2018
Status: Recruiting
Sponsor: The Netherlands Cancer Institute
PI: Paul Baas

Primary Outcome Measure: DCR at 12 weeks
Secondary Outcome Measures: Safety, DCR at 6 months, PFS, OS, ORR



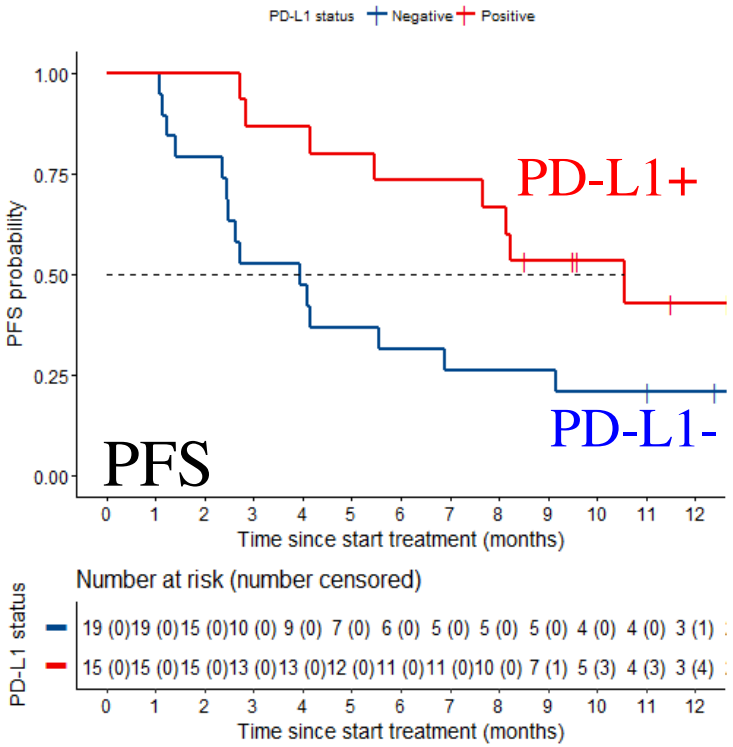
Phase II trial of Nivolumab and Ipilimumab in patients with malignant mesothelioma

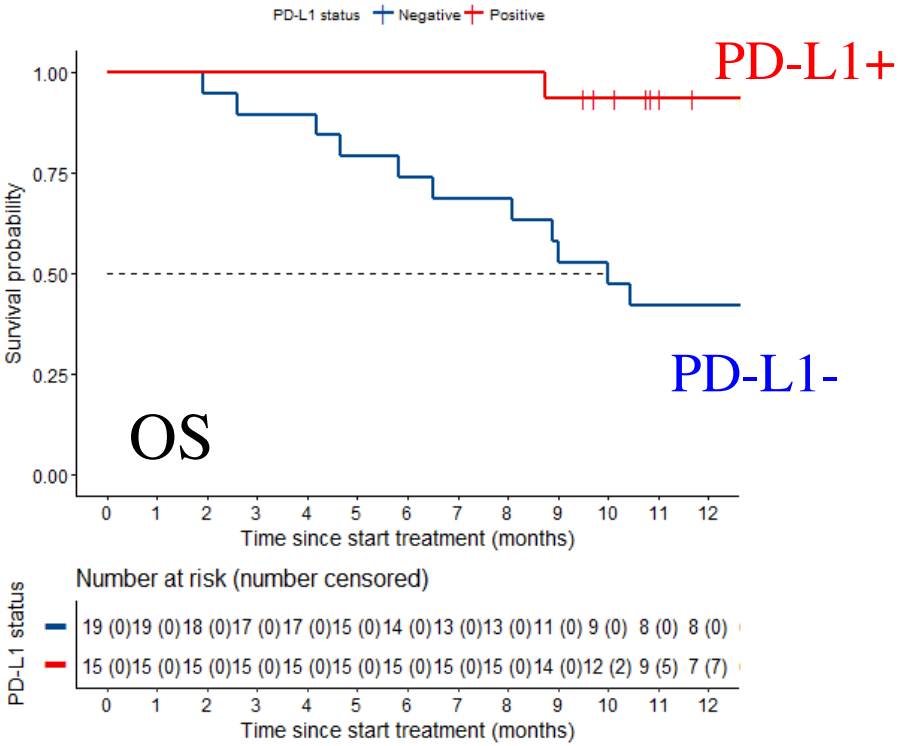


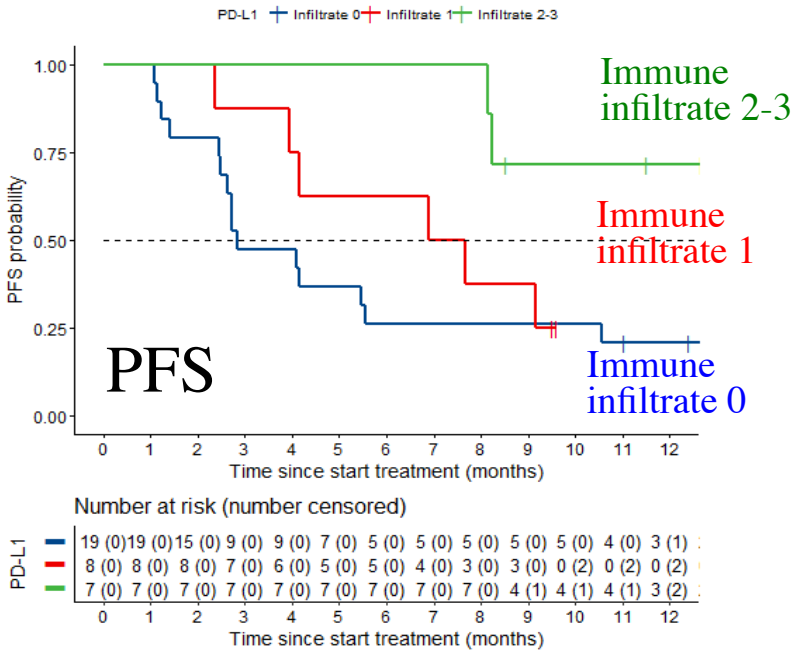


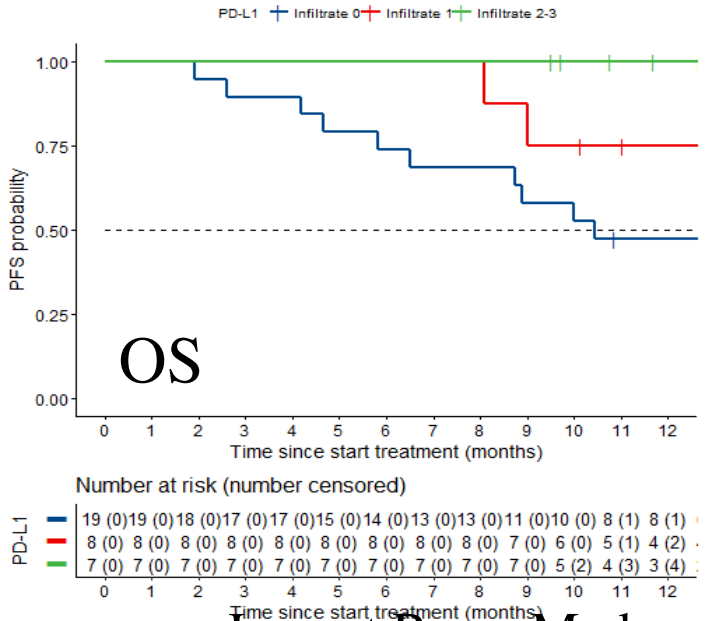
Radiological response at twelve weeks	
Complete response	0
Partial response	10 (29%)
Stable disease	13 (38%)
Progressive disease	11 (32%)
Disease control rate	23 (68%) 95% CI 50% – 83%)

Lancet Resp. Med, *accepted*









Lancet Resp. Med, *accepted*

Checkmate743: Study Design

- **A phase III,** randomized, open label trial of nivolumab in combination with ipilimumab versus pemetrexed with cisplatin or carboplatin as **first line** therapy in unresectable pleural mesothelioma

N=600

Key Eligibility Criteria

- Unresectable untreated pleural mesothelioma
- Available tumor sample
- ECOG PS 0-1
- No prior chemotherapy for pleural mesothelioma

Stratification Factors

- Histology (epithelioid vs. sarcomatoid or mixed histology subtypes)

R

Ipilimumab 1 mg/kg Q6W
+
Nivolumab 3 mg/kg Q2W
(up to progression/toxicity*)

Cisplatin 75 mg/m^2 or carboplatin AUC 5
+
Pemetrexed 500 mg/m^2
Q3W, ≤6 cycles

Study Start Date: October 2016
Estimated Completion Date: September 2021
Estimated Primary Completion Date: October 2020
Status: Recruiting
Sponsor: Bristol-Myers Squibb

Primary Outcome Measures: OS, PFS
Secondary Outcome Measures: ORR, DCR, PRO, association between PD-L1 expression and efficacy measures

DREAM

Final results of a phase 2 trial of **Du**R**v**alumab with first line ch**E**mother**A**py in **M**esothelioma

Anna K. Nowak, Peey Sei Kok, Willem Joost Lesterhuis, Brett G.M. Hughes, Chris Brown, Steven Chuan-Hao Kao, Deme Karikios, Tom John, Nick Pavlakis, Kenneth O'Byrne, Sonia Yip, Wei-Sen Lam, Karen Briscoe, Christos S. Karapetis, Martin R. Stockler on behalf of ALTG (Australasian Lung Cancer Trials Group and NHMRC Clinical Trials Centre)

DREAM

Final results of a phase 2 trial of **Du**R**v**alumab with first line ch**E**mother**A**py in **M**esothelioma

Trial design – Single-arm, multicentre phase II trial with a safety run-in, N= 56

Population

1st line MPM

Non-surgical

No prior RT to measurable disease

ECOG PS 0-1

No PD-L1 selection

Induction

Cisplatin 75mg/m^2 + Pemetrexed 500mg/m^2 + Durvalumab 1125mg q3w

6 cycles

Maintenance

Durvalumab 1125mg q3w x 52 w

To total 17 cycles durvalumab

Outcomes

PFS6*

OTRR (CR + PR)* Toxicity
PFS*
OS

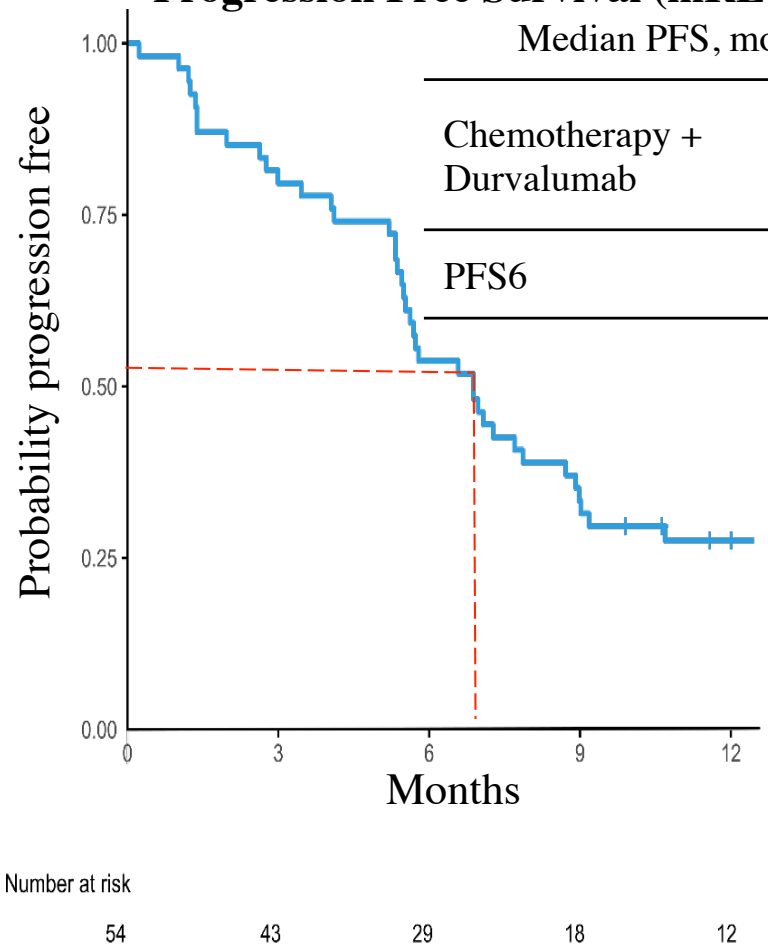
* mRECIST for MPM, mirRC

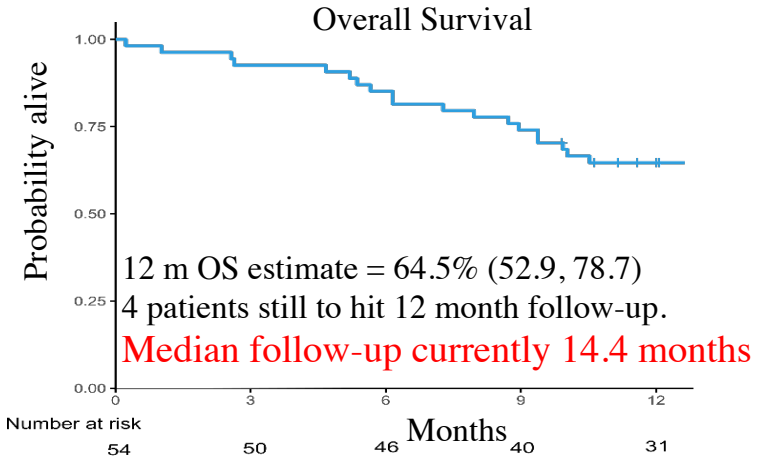
DREAM

Final results of a phase 2 trial of **DuR**valumab with first line ch**E**mother**A**py in **M**esothelioma

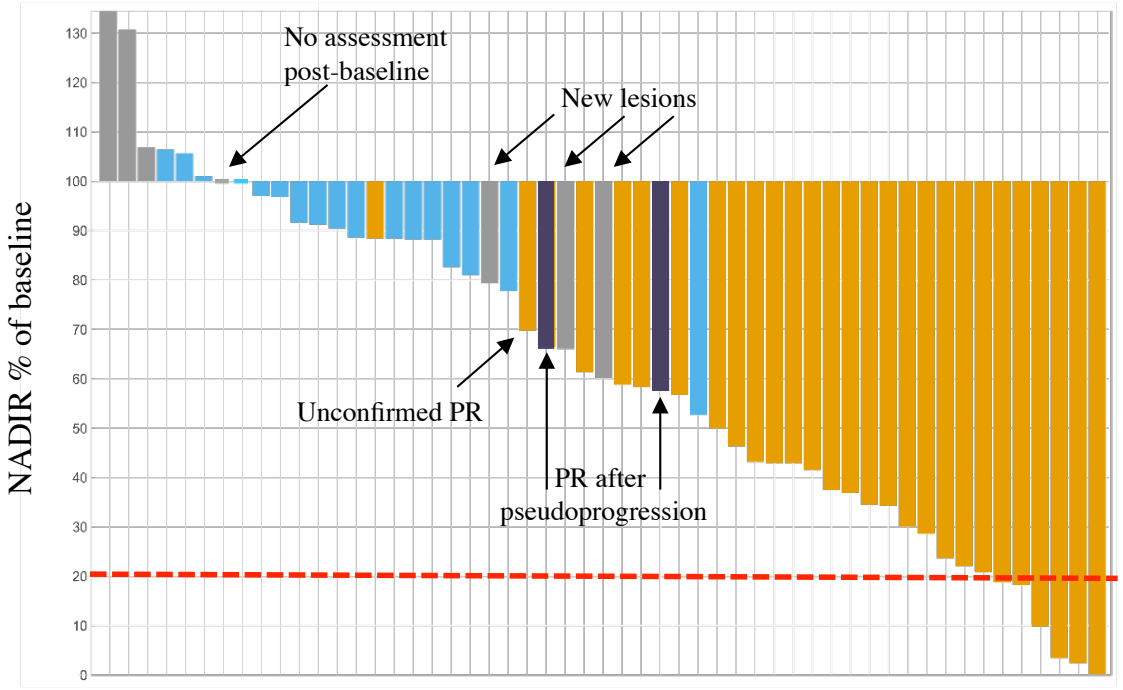
Progression Free Survival (mRECIST)

	Median PFS, mo (95% CI)
Chemotherapy + Durvalumab	6.2 (5.5-9.0)
PFS6	31/54 (57%)





12 m OS estimate = 64.5% (52.9, 78.7)
4 patients still to hit 12 month follow-up.
Median follow-up currently 14.4 months



Confirmed ORR= 48% (mRECIST)
DCR= 85%

Messages à emporter chez soi

1. Maladie rare mais à forte connotation sociétale: tout progrès dans cette maladie a un grand retentissement.
2. Pas de marqueur évident autre que le PDL1 pour les i.o. dans le mésothéliome (TMB faible)
3. Diagnostic= Thoracoscopie d'emblée, larges biopsies, relecture systématique/DO MESOPATH
4. Irradier les points de ponctions dans les 3 semaines: *2 mauvais essais UK restent 2 mauvais essais* ☹
5. Pem-cis Beva15 = Tt de réf 1ère ligne (<75ans)
6. Bithérapie Nivo/Ipi en 2ème ligne: OUI ! => RTU ???

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DU 8 AU 11
OCTOBRE 2018
ILE-DE-FRANCE
ESPACE SAINT-MARTIN • PARIS

Une « réussite » 2016 :
-le Bevacizumab

Un espoir 2018:
-Les anti-PD1+/- anti-CTL4
- L'assoc. anti-PD1/PDL1 + chimio

Mais la route est encore longue !!

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

gerard.zalcman@aphp.fr

Merci...