Cours du GOLF – CHU Purpan

Toulouse, le 8 Octobre 2019

Mésothéliome Pleural Malin :

Nouvelles recommandations et pistes thérapeutiques

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ERS

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2019 European Guidelines for Medical Treatment of Malignant Pleural Mesothelioma

(from ERS/ESTS/ESTRO/EACTS Taskforce)

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For more details…

Guidelines of the European Respiratory Society, the European Society of Thoracic Surgeons, the European Association for Cardio-Thoracic Surgery and the European Society for Radiotherapy and Oncology for management of Malignant Pleural Mesothelioma

SCHERPEREEL A, OPITZ I, BERGHMANS T, PSALLIDAS I, GLATZER M, RIGAU D, ASTOUL P, BOLÜKBAS S, BOYD J, COOLEN J, DE BONDT C, DE RUYSCCHER D, DURIEUX V, FAIVRE-FINN C, FENNELL D, GALATEAU-SALLE F, GRELLIER L, HODA MA, KLEPETKO W, LACOURT A, MCELNAY P, MASKELL NA, MUTTI L, PAIRON JC, VAN SCHIL P, VAN MEERBEECK JP, WALLER D, WEDER W, CARDILLO G AND PUTORA PM.

European Respiratory Journal 2019 (minor revision)

Conflict of interest disclosure

❑ **I have no real or perceived conflicts of interest that relate to this presentation.**

X I have the following real or perceived conflicts of interest that relate to this presentation:

Affiliation / Financial interest	Commercial Company
Grants/research support:	AS is an investigator in phases I, II & III clinical trials sponsored by AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Epizyme, Lilly, MSD, Roche… with no personal payment, all honoraria being perceived by my Institution (CHU de Lille, Clinical Research Center, France); research grants from Pierre Fabre, Roche to AS institution;
Honoraria or consultation fees:	participation to scientific or advisory Boards, organized by Astra-Zeneca, BMS, Boehringer-Ingelheim, MSD, Roche
Participation in a company sponsored bureau:	none
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Other support / potential conflict of interest:	AS was invited at some international oncology meetings (AACR, ASCO, WCLC) by A-Z, Roche, MSD, BMS

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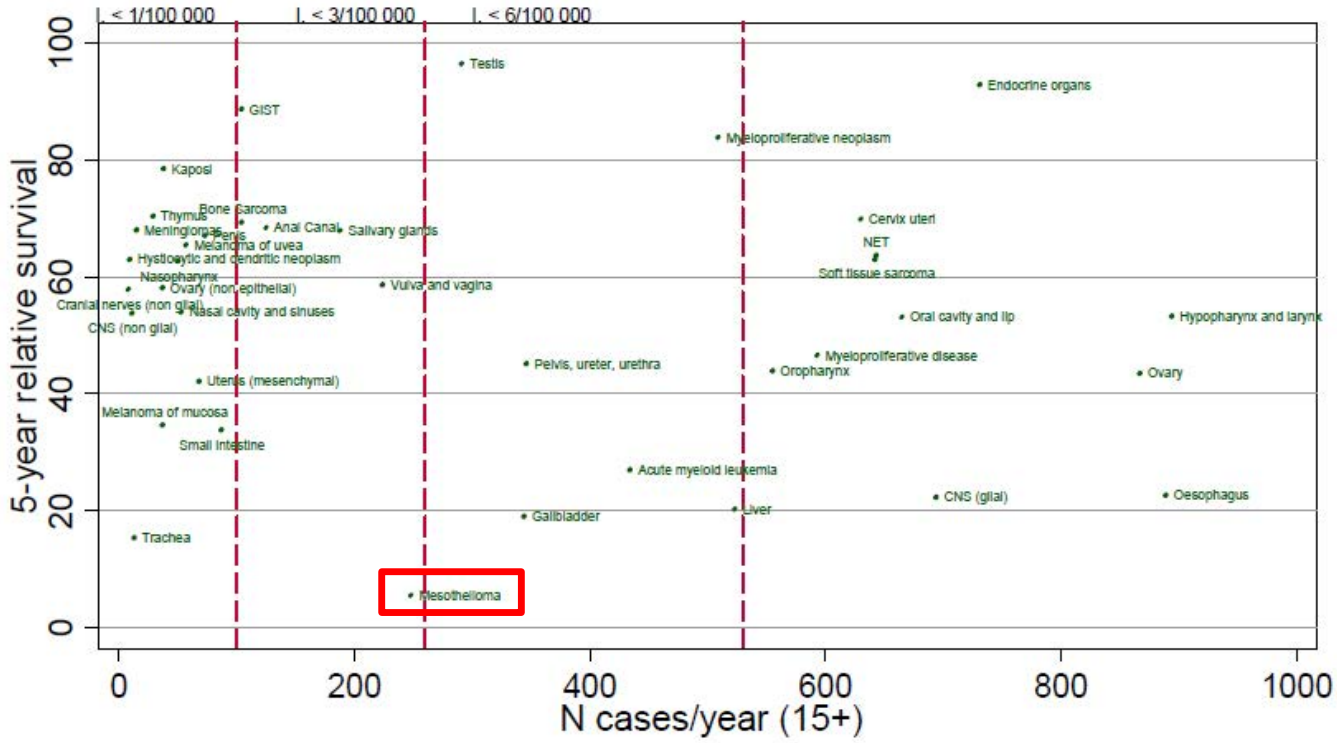
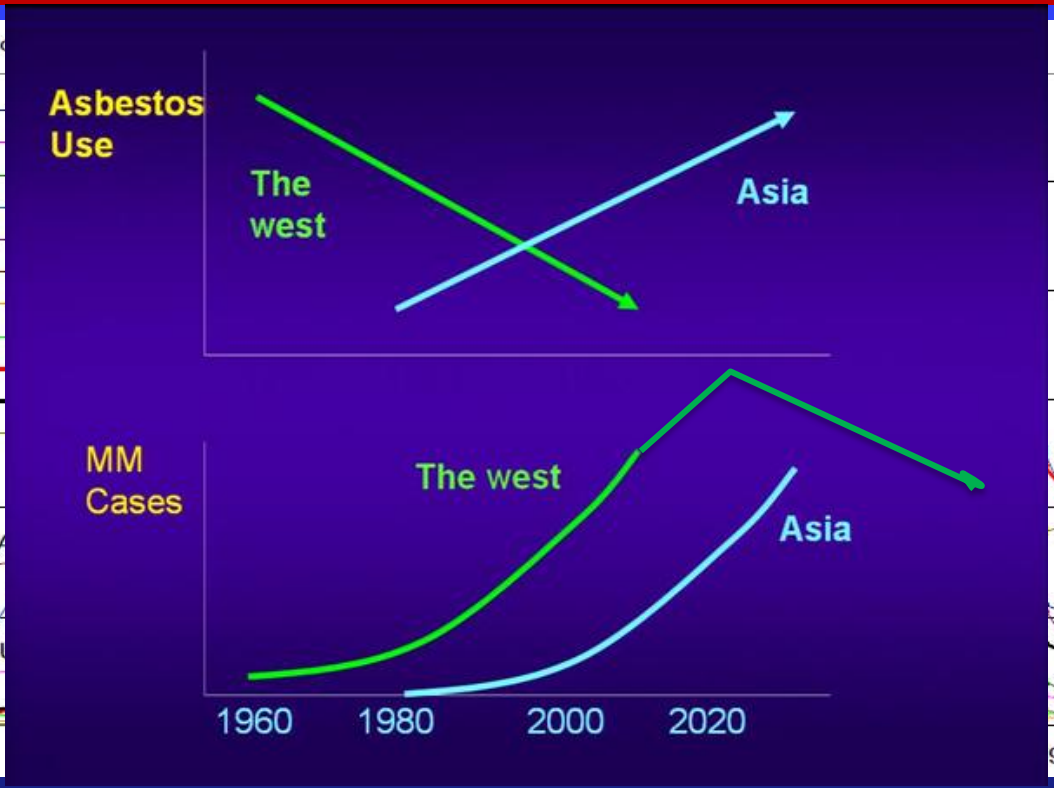
Le MPM : un cancer pas si rare (~1000/an en France), et de mauvais pronostic global…

Figure 2 - Incidence and 5 –year relative survival for all tumours grouped according to RARECARE layer 1 (< 1 000 new cases per year).



Méso en Asie : une épidemie à venir ?



De nombreuses recommandations pour le MPM

Scherpereel, ERJ 2010; ***ERS / ESTS Guidelines***

Woolhouse, BMJ Open and Thorax 2018;
BTS Guidelines

Baas, Annals of Oncology 2015; ***ESMO Guidelines***

Kindler, JCO 2018; ***ASCO Guidelines***

Sans compter celles du *NCCN* 2018 et bien sûr *AURA* 2019 en France

Universität Zürich

Pronostic et Stadification du MPM

Pronostic du MPM

Recommandations
La prise en compte des facteurs pronostiques suivants : sous-type histologique, PS, est un préalable nécessaire avant toute décision concernant la prise en charge d'un patient atteint de mésothéliome pleural malin. Le stade pTNM selon la classification de l'IMIG a une valeur pronostique reconnue chez les patients opérés.

Recommandations AURA 2019

- **Tout le monde est d'accord** pour les principaux facteurs pronostiques du MPM = **sous-type histologique, PS**;
  âge élevé et sexe Masculin plus mauvais ?
- BTS : suggestion du LENT score en routine (pleural LDH>1500UI, NLR, PS, type histo) (Clive et al, *Thorax* 2014) mais globalement comme les autres scores pas en routine, plutôt pour études prospectives

8th revision of TNM staging system for MPM

- Minor change in T1 category: collapse of both clinical and pathological T1a and T1b into a T1 classification
- Major change for N staging

Table 5. Final Recommendations for N Descriptors for the Eighth Edition of the AJCC/UICC Staging Handbook

Regional Lymph Nodes (N)	Definition
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes) lymph nodes
N2	Metastases in the contralateral bronchopulmonary, hilar, or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes

Stage Grouping for the 8th Edition of the TNM Classification for Malignant Pleural Mesothelioma
Proposed by the IASLC

STAGE	T	N	M
IA	T1	N0	M0
IB	T2, T3	N0	M0
II	T1, T2	N1	M0
IIIA	T3	N1	M0
IIIB	T1, T2, T3	N2	M0
	T4	N0, N1, N2	M0
IV	Any T	Any N	M1

J Thorac Oncol, 2018

Summary of staging algorithm for MPM patients

Recommandations

-L'évaluation de l'extension loco-régionale du mésothéliome pleural nécessite un scanner thoracique avec injection de contraste avec des coupes descendant jusqu'à la partie inférieure des piliers du diaphragme et une thoracoscopie.

-Dans une perspective chirurgicale, l'éventualité d'une atteinte ganglionnaire médiastinale doit être explorée par TEP au FDG, et/ou médiastinoscopie ou échographie endo-œsophagienne ou endo-bronchique.

-La recherche d'une atteinte extra-thoracique par TEP est indispensable lorsqu'une chirurgie radicale est envisagée.

OPTIONS :

L'atteinte du diaphragme peut être précisée par l'IRM mais sans certitude.

L'atteinte pariétale thoracique et/ou rachidienne (envahissement des trous de conjugaison…) est mieux appréciée par l'IRM.

The algorithm is a reasonable approach for pre-treatment staging investigations. However it is not intended as a recommendation for clinical practice

Scherpereel et al, *Eur Respir* J 2019 (in revision)

2019 European Recommmandations for MPM staging and prognosis

- **Use latest 8th edition of TNM staging classification**
- **If radical therapy is considered, exclude imaging-occult nodal and distant metastases**
- **Prognostic factors and scoring systems may help in the decision process… but cannot usually be applied per se on an individual basis outside clinical trials, as they were not validated for this purpose**

BTS recommendation, Thorax 2018

- Record staging of MPM according to the version 8 of the IASLC staging proposals. Grade D.

ASCO recommendation 2018: The current AJCC/UICC staging classification remains difficult to apply to clinical staging with respect to both T and N components and thus may be imprecise in predicting prognosis. (Evidence quality: high; Strength of recommendation: strong)

Recommandations

La classification TNM définie par l'IMIG a été réactualisée dans le cadre de la 8ème révision de la classification des cancers, entrainant une modification de la définition du T et du N ainsi que de la stadification, est désormais à utiliser même si l'évaluation reste délicate pour les patients non-chirurgicaux majoritaires, notamment pour préciser le T.

BTS recommendation, Thorax 2018

- Prognostic scores can provide useful survival information for patients and doctors, but should not be used in treatment decision-making. Grade D.

Scherpereel et al, *Eur Respir* J 2019 (in revision)

Perspectives pour l'évaluation du pronostic des patients MPM

- Valeur pronostique de :
  - L'évaluation du Volume Tumoral sur l'imagerie (TDM…)
  - L'épaississement Tumoral mesuré à 3 niveaux de l'hémithorax: haut, moyen, bas

- Scores pronostiques composites spécifiques du MPM :
  - Arbre décisionnel (*Brims, JTO 2016*): perte de poids, sous-type histologique, PS, Hb, albumine

- **Patient-reported outcomes (PROMS)**

Chirurgie du MPM

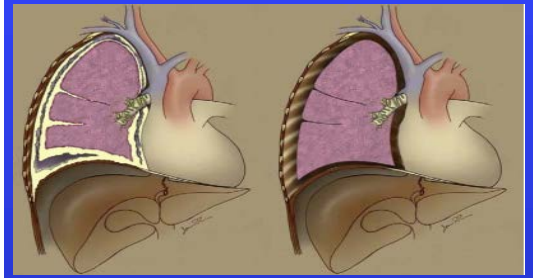
Chirurgie du MPM ((e)P/D)

Recommandations

La pleurectomie +/- décortication +/-élargie à visée de cytoréduction doit être discutée dans les stades I, éventuellement certains stades II et III A (TNM 8ème révision) en réunion de concertation pluridisciplinaire de recours MESOCLIN (régionale ou nationale).

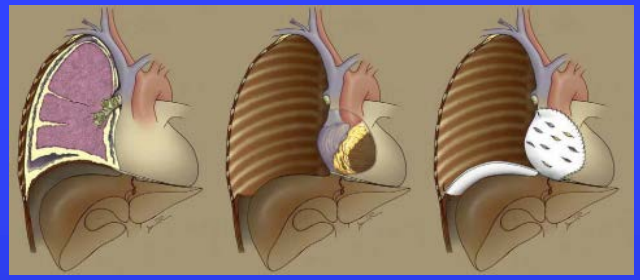
L'évaluation avant d'envisager une pleurectomie-décortication élargie doit préciser au mieux le stade :

- **scanner thoracique avec injection de contraste comportant des coupes descendant jusqu'aux piliers du diaphragme (et abdomen),**
- **recherche d'une invasion trans-diaphragmatique par IRM,**
- **appréciation de l'extension médiastinale par TEP au FDG avec contrôle histologique des adénopathies à caractère hypermétabolique par médiastinoscopie (7, 4R, 4L, 2R), écho-endoscopie œsophagienne ou bronchique, recherche d'une atteinte extra-thoracique par TEP-FDG.**



- **Tout le monde est d'accord** pour discuter la chirurgie (P/D…) uniquement par des équipes/RCP expertes (MESOCLIN…), en centres de recours...
- ASCO et NCCN : faire + facilement laparoscopie voire VATS controlatérale
- **indications plus discutées** : stades I-IIIA (mais + larges par ASCO/NCCN =ADP médiastinales homolat) ? épithélioïdes seuls (NCCN) ?

Chirurgie du MPM ((e)P/D et PPE)



Recommandations

La pleuro-pneumonectomie élargie ne doit être entreprise qu'après l'avis d'une RCP MESOCLIN nationale, par une équipe entraînée à ce type de chirurgie, si possible dans le cadre d'un essai clinique.

- Discordances :
  - ASCO et NCCN : PPE en accès libre; chimio (P/P) pré ou post-op hors essai
  - BTS : PPE enterrée depuis l'essai MARS ! P/D uniquement en essai clinique

PICO question: Should radical surgery (including EPP or P/D) be used in patients with MPM ? Same question for multimodal treatment ?

2019 European Recommendations:

- Patients considered for radical surgery should be either included in prospective, randomized, controlled clinical trials or in national/international surgical registries
- Same recommendation for multimodal treatment
- Remark: Surgery may be appropriate for carefully and highly selected MPM patients. This would usually be (E)P/D rather than EPP because of its lower comparative respiratory postoperative morbidity and preservation of quality of life, performed in centres of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoid predominant histology, N2 disease (8th edition TNM staging system) and/or stage IV should not be considered for radical surgery unless in the context of research. However, as no single prognostic factor influences treatment allocation then prognostic scores encompassing several prognostic factors should be preferred

Scherpereel , Opitz et al, *Eur Respir* J 2019 (in revision)

Chirurgie du MPM (palliative)

Recommandations
-Une symphyse pleurale doit être systématiquement proposée en cas de mésothéliome pleural malin avec épanchement pleural symptomatique, sauf si une chirurgie « radicale » (P/D ou PPE) est envisagée. -Le talcage sous thoracoscopie constitue la méthode de référence. -Le talcage doit être évité lors de la thoracoscopie initiale lorsqu'il n'existe pas de certitude diagnostique ou lorsqu'une pleurectomie est envisagée dans un 2ème temps. -Un cathéter pleural tunnélisé à demeure peut être envisagé en cas de pleurésie symptomatique et récidivante après talcage.

PICO question: Should partial pleurectomy compared to talc pleurodesis be used as palliative procedure in patients with symptomatic MPM ?

2019 European Recommendations:

- To control a recurrent MPM effusion, talc poudrage via thoracoscopy is the first choice to achieve pleurodesis in patients with expanded lungs *(strong recommendation, low quality of evidence)* [2nd choice: IPC]

- We suggest palliative VATS partial pleurectomy for selected patients fit enough to undergo surgery to obtain pleural effusion control in symptomatic patients who cannot benefit from (or after failure of) chemical pleurodesis or indwelling catheter *(weak recommendation, low quality of evidence)*

Scherpereel , Opitz et al, *Eur Respir* J 2019 (in revision)

Radiothérapie du MPM

Post-P/D or EPP Radiotherapy for MPM

PICO Question: Should adjuvant post-operative radiotherapy be used in patients with MPM ?

OPTION :

Après pleurectomie décortication (+/- élargie), l'irradiation externe de l'hémithorax atteint est conseillée afin de diminuer le risque de rechute loco-régionale. Les techniques en modulation d'intensité, la tomothérapie ou l'arc-thérapie sont fortement recommandées afin de limiter le risque de complications, en particulier sur le poumon restant.

Cette irradiation est à réaliser par une équipe experte du MPM, après validation en RCP MESOCLIN.

2019 European Guidelines → *Research priority*: RT after P/D or after EPP should be only considered within the context of clinical trials and/or included in national/international surgical registries

Prophylactic* Radiotherapy for MPM

PICO Question: What is the role of radiotherapy in the prevention of parietal seeding along the drainage tracts?

Characteristic	PIT	SMART
Sample size	374	203
Inclusion criteria		
Open thoracotomy	No	Yes
Thoracoscopy	Yes	Yes
Large-bore chest tubes (≥ 20 F)	Yes	Yes
Small-bore chest tubes (< 20 F)	Yes	No
Indwelling pleural catheters	No	Yes
Needle biopsy	No	No
RT field size	3-cm Lateral/inferior borders; variable superior border	2 cm all directions
RT dose/fractionation	21 Gy in three fractions over 3 days	21 Gy in three fractions over 3 days
Primary end point	Incidence of ipsilateral CWM at 6 months	Incidence of CWM within 7 cm of the margins of the procedure site at 12 months
Secondary end points	Time to CWM	Time to CWM
	Pain from CWM	Pain from CWM
	Toxicity of treatment	Toxicity of treatment
	Locality of metastases to RT field	Quality of life
		Incidence of CWM with indwelling catheters
		Effect of chemotherapy
		Semistructured qualitative interviews
		Health economic analysis
Follow-up	Clinic at 1, 3, 6, and 12 months; monthly telephone follow-up	Clinic at 1, 3, 6, 9, and 12 months; monthly telephone follow-up

Abbreviations: CWM, chest wall metastases; PIT, Prophylactic Irradiation of Tracts; RT, radiotherapy; SMART, Surgery for Mesothelioma After Radiation Therapy.

"SMART" trial: Clive et al, *Lancet Oncol* 2016
"PIT" trial: Bayman N et al. *J Clin Oncol* 2019)

Prophylactic Radiotherapy for MPM

Lancet Oncol. 2016 Aug;17(8):1094-1104. doi: 10.1016/S1470-2045(16)30095-X. Epub 2016 Jun 23.

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.

Clive AO[1], Taylor H[2], Dobson L[3], Wilson P[4], de Winton E[5], Panakis N[6], Pepperell J[7], Howell T[8], Stewart SA[9], Penz E[10], Jordan N[11], Morley AJ[11], Zahan-Evans N[11], Smith S[11], Batchelor TJP[4], Marchbank A[8], Bishop L[12], Ionescu AA[13], Bayne M[14], Cooper S[15], Kerry A[16], Jenkins P[17], Toy E[18], Vigneswaran V[19], Gildersleve J[20], Ahmed M[21], McDonald F[21], Button M[22], Lewanski C[23], Comins C[4], Dakshinamoorthy M[15], Lee YCG[24], Rahman NM[25], Maskell NA[26].

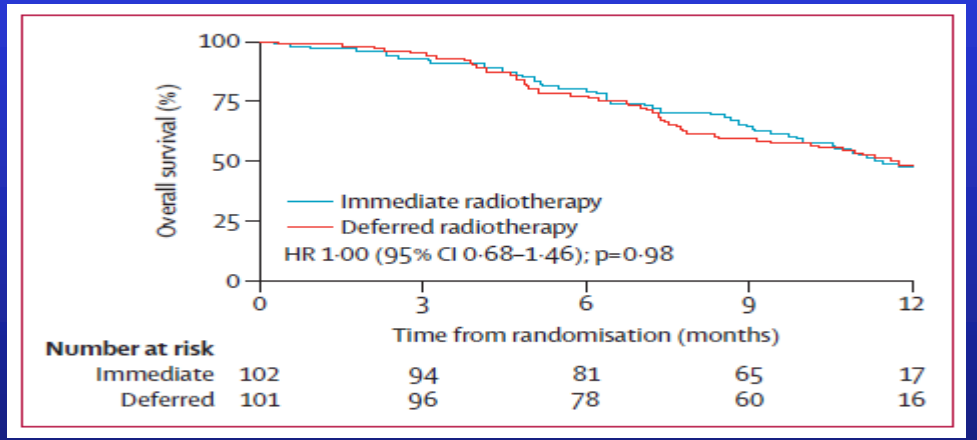
Bayman N[1], Appel W[2], Ashcroft L[1], Baldwin DR[3], Bates A[4], Darlison L[5], Edwards JG[6], Ezhil V[7], Gilligan D[8], Hatton M[6], Jegannathen A[9], Mansy T[10], Peake MD[5], Pemberton L[1], Rintoul RC[11], Snee M[12], Ryder WD[1], Taylor P[13], Faivre-Finn C[1,14].

"In MPM patients, prophylactic RT after large-bore pleural interventions did not reduce the incidence of PTM and confers no benefits in terms of symptom control, analgesia use, survival, or quality of life"

… however protocol deviations in some pts (technique, timing…), and trial in favor of this RT when pts had Pem-based chemo !

Zalcman et al, *Lancet Oncol* 2016

"SMART" trial: Clive et al, *Lancet Oncol* 2016



Prophylactic Radiotherapy for MPM

J Clin Oncol. 2019 Mar 28:JCO1801678. doi: 10.1200/JCO.18.01678. [Epub ahead of print]

Prophylactic Irradiation of Tracts in Patients With Malignant Pleural Mesothelioma: An Open-Label, Multicenter, Phase III Randomized Trial.

Bayman N[1], Appel W[2], Ashcroft L[1], Baldwin DR[3], Bates A[4], Darlison L[5], Edwards JG[6], Ezhil V[7], Gilligan D[8], Hatton M[6], Jegannathen A[9], Mansy T[10], Peake MD[5], Pemberton L[1], Rintoul RC[11], Snee M[12], Ryder WD[1], Taylor P[13], Faivre-Finn C[1,14].

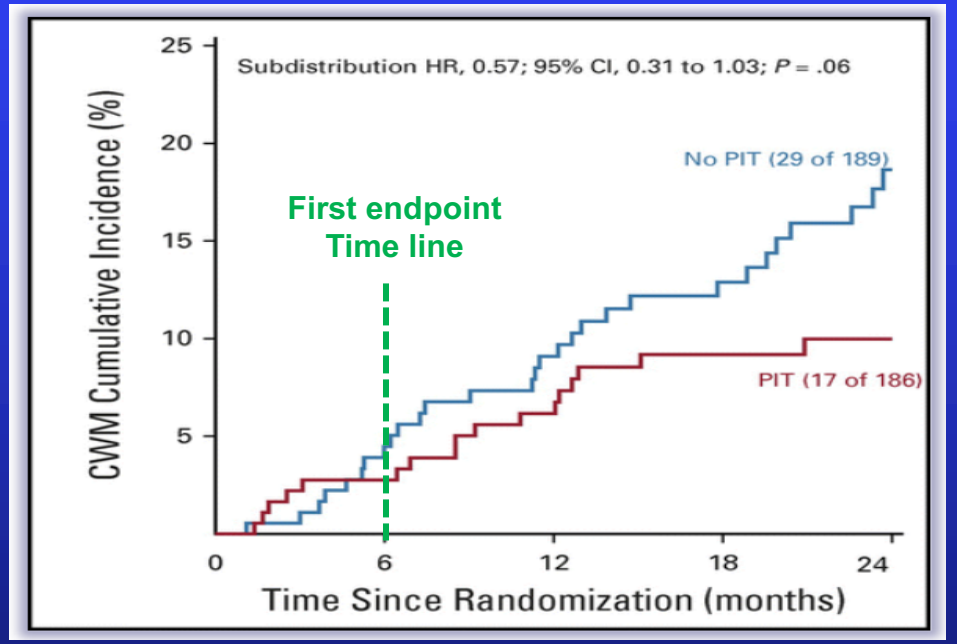
"PIT" trial: Bayman N et al. *J Clin Oncol* 2019

CONCLUSION: There is no role for the routine use of prophylactic irradiation to chest wall procedure sites in patients with MPM.

Auteur (ref)	N	Dose (Gy)	Fractions (N)	Récidive sur trajets, N (%)		P	HR/OR RT/contrôle
				Groupe RT	Groupe contrôle		
Boutin (80)	40	21	3	0	8 (40%)	<0.001	NR
Bydder (81)	58	10	1	2 (7%)	3 (10%)	0.53	NR
O'Rourke (82)	61	21	3	7 (23%)	3 (10%)	0.75	1.28 (0.29-5.73)
Clive (76) ITT	203	21	3	9 (9%)	16 (16%)	0.14	OR 0.51 (0.19-1.32)
Clive (76) PP				5 (6%)	16 (16%)	0.037	OR 0.33 (0.09-1.00)
Bayman (78) à 12 mois	375	21	3	15 (8.1%)	19 (10.1%)	0.59	HR*0.79 (0.36 – 1.69)
Bayman (78) à 18 mois				10 (10.1%)	19 (18.7%)	0.06	HR*0.57 (0.31– 1.03)

** : incidence cumulative, HR ajusté sur les facteurs de stratification*

ITT : intention de traiter PP : per-protocol (11% déications protocolaires excluses)



Prophylactic Radiotherapy for MPM

- **Discordances** :
  - **OPTION :** Une irradiation prophylactique (3x7Gy) dans les 6 semaines maximum après le geste pleural (drainage, thoracoscopie, thoracotomie) peut être proposée pour réduire la fréquence des nodules thoraciques de perméation. On l'envisagera notamment après une chirurgie du MPM avec mise en évidence d'un envahissement avéré (histologiquement) des orifices thoraciques précédents.
  - !

2019 European Guidelines → *Recommendation*: we do not recommend prophylactic drain site RT in routine clinical care *(strong recommendation, moderate quality evidence)*

Palliative Radiotherapy for MPM

PICO ents ?

- E
  (

Recommandations
La radiothérapie conserve une efficacité antalgique dans une optique palliative ; des traitements hypofractionnés à étalement court seront préférés à une irradiation plus étalée.

2019 European Guidelines → *Recommendation*: we suggest that palliative RT for pain relief should be considered in cases of painful sites of disease caused by infiltration of normal structures *(weak recommendation, low quality evidence).*

- **<u>Future directions</u>: which technique for RT in MPM among all recent innovations** (IMRT, proton therapy, SBRT...) ?

  → clinical trials recommended to assess the efficacy/toxicity ratio

Traitement Systémique du MPM: Chimiothérapie…

1rst Line Chemotherapy for MPM

PICO Question: Should first line chemotherapy consisting of platinum combined with pemetrexed be used in patients with MPM ?

➢**2019 European Guidelines (unchanged after 2009 ERS/ESTS guidelines*)**

→ *Recommendation*: we recommend first line combination chemotherapy consisting of Cisplatin, (otherwise Carboplatin) and Pemetrexed (with folic acid and vitamin B12 supplementation) in patients fitted for chemotherapy (good PS ECOG 0-2…) *(strong recommendation, low quality evidence)*

Remarks: (1) Start chemo after firm histologic diagnosis but do not wait for appearance of clinical signs (or clinical deterioration)
(2) Stop chemo if Progressive Disease, grade 3-4 toxicities or cumulative toxic doses, but continue up to 6 cycles if stable disease or tumor response

*Scherpereel et al, *ERJ* 2010

1rst Line Chemotherapy for MPM

PICO Question: Should targeted therapies (anti-VEGF Ab Bevacizumab*, other drugs…) be added to first line chemotherapy in patients with MPM ?

Recommandations

-L'introduction précoce de la chimiothérapie dans les formes non résécables paraît préférable à une mise en route différée à l'apparition des symptômes chez les patients non symptomatiques au moment du diagnostic.

➢**2019 European Guidelines (changed after 2009 ERS/ESTS guidelines**)**

→ *Recommendation*: we suggest Bevacizumab, if available, may be proposed in combination with Cisplatin/Pemetrexed in patients fitted for Bevacizumab and this chemotherapy (good PS ECOG 0-2…), but not MCR *(weak recommendation, moderate quality evidence)*

*Zalcman et al, *Lancet* 2016; **Scherpereel et al, *ERJ* 2010;

1rst Line Chemotherapy for MPM

- **All other recent guidelines agree about the value** of combining Bevacizumab to Cisplatin/Pemetrexed if no CI, based on IFCT MAPS trial data**) to increase mOS… even if, sadly, no general access to Bevacizumab yet
- However, ASCO and BTS guidelines suggest that chemo start may be delayed after clinical signs appearance

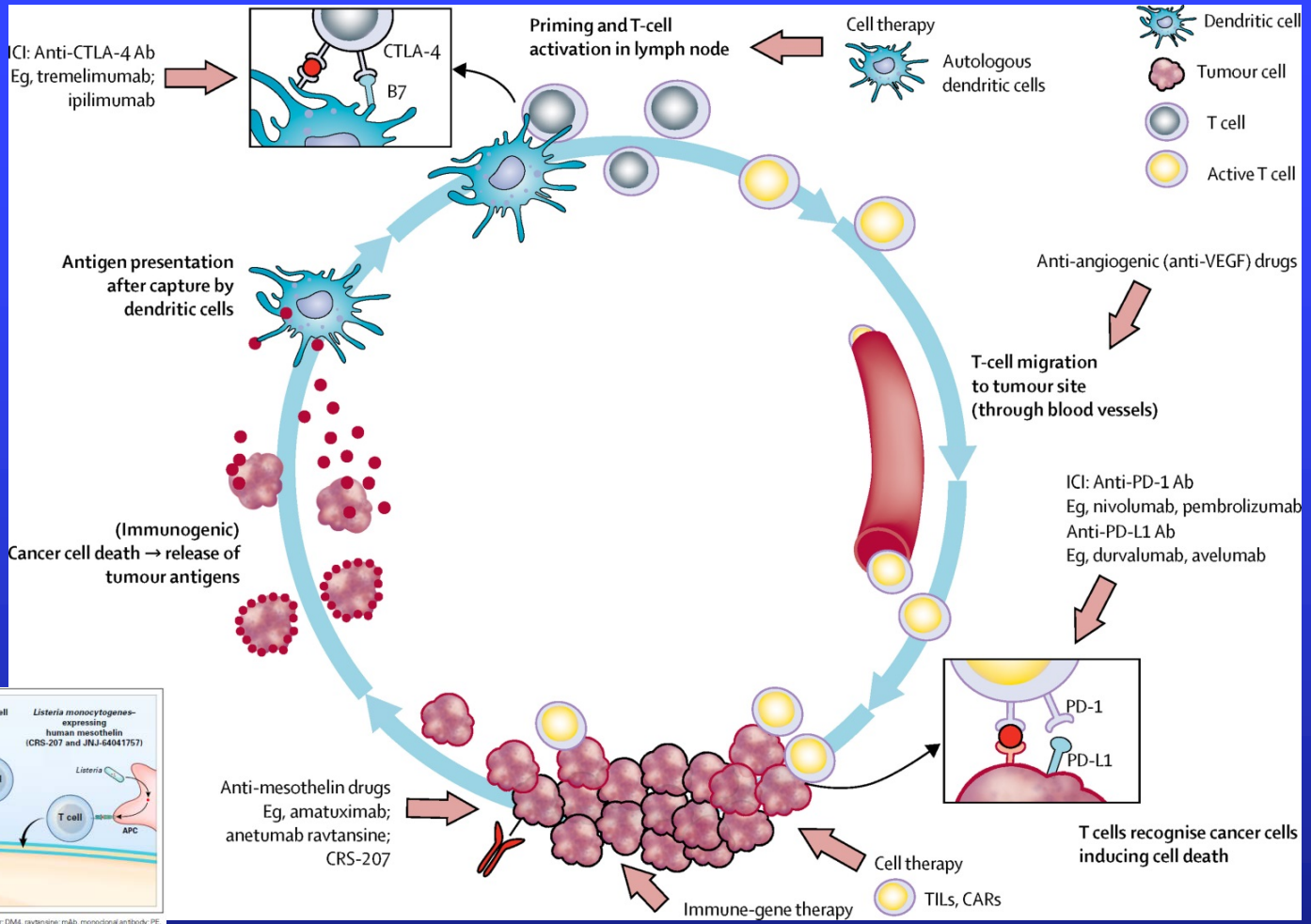
- **Globally, good consensus** including on the lack of evidence for maintenance treatment such as Pemetrexed** (except Bevacizumab)
- *Alternatives to standard 1rst Line:* Pemetrexed, Gemcitabine or Vinorelbine alone in old/frail patients [AURA 2018 : idem]

*Zalcman et al, *Lancet* 2016 ;**Dudek AZ et al, *ASCO* 2019 abstract 8517

Beyond 1rst Line Chemotherapy for MPM

PICO Question: Should immunotherapy be used as salvage therapy in patients with MPM who failed first line chemotherapy?

Scherpereel A and al, *The Lancet Oncol* 2018; 19: e161-72



Hassan R and al, *J Clin Oncol* 2016

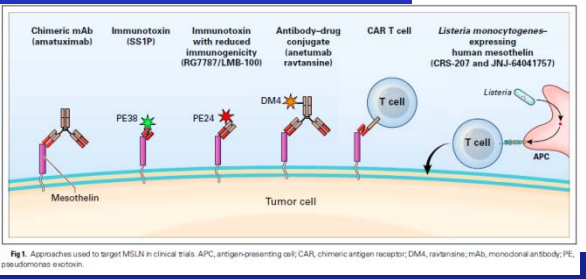


Fig 1. Approaches used to target MSLN in clinical trials. APC, antigen-presenting cell; CAR, chimeric antigen receptor; DM4, ravtansine; mAb, monoclonal antibody; PE, pseudomonas exotoxin.

First results of ICI as salvage therapy in MPM patients

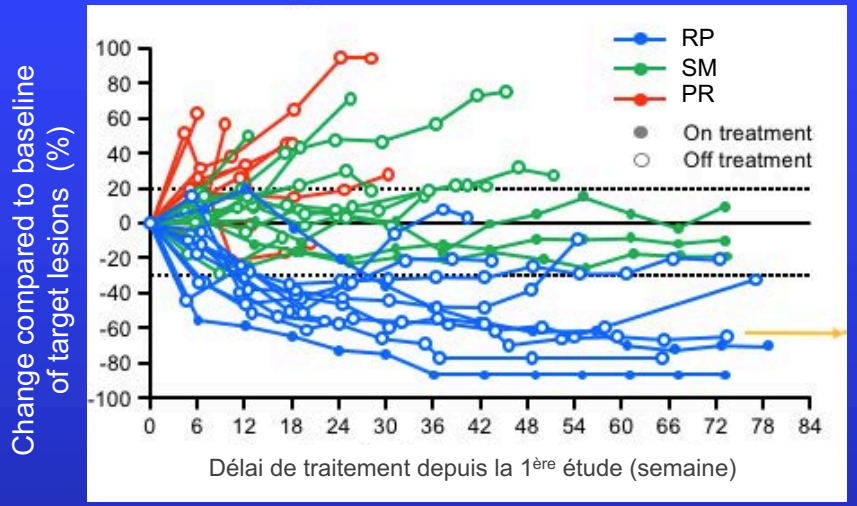
Molécule/ Etude	Ligne	RO(%)	SSP (mois)	SG (mois)	Impact de l'expression tumorale PDL1
Pembrolizumab (Keynote 028)	2	20%	5,4	18	Sélection sur PDL1+
Pembrolizumab (kindler)	2	21%	6,2	NR	Pas de corrélation avec RO
Pembrolizumab (Metaxas)	>2	18%	3,1	10,2	Corrélation avec réponse et SSP
Nivolumab (Quispel JTO 2018)	>1	24%	2,6	11,8	Pas de corrélation
Nivolumab MERIT (Goto, WCLC 2017)	>1		6,1	NR	
Avelumab (JAVELIN)	>1	9,4%	4,1	10,9	Pas à priori avec SSP, corrélation avec RO ? (18,8%/7,4%)
Durvalumab + Tremelimumab (NIBIT-MESO 1)	1-2	28%	5,7	16,1	Pas de corrélation avec RO, DCR, SSP ou survie
Nivolumab (MAPS2)	2-3	18,5%	4	11,9	Corrélation avec RO et DCR
Nivolumab + Ipilimumab (MAPS2)	2-3	25,9%	5,6	15,9	Corrélation avec RO et DCR
Cisplatine-pemetrexed+durvalumab (DREAM)	1	48%	6,9	NA	Pas de données

NR : Non rapportée - RO : Réponse Objective DCR : taux contrôle maladie – NA : Non Atteinte

Brosseau S et al; 2019 Scherpereel and al, *The Lancet Oncol* 2018 updated with Scherpereel and al, *The Lancet Oncol* 2019, and Forde P, *Curr Treat Options Oncol* 2019

MERIT trial in Japan : Nivolumab as salvage treatment

- Nivo as 2nd or 3rd line in 34 patients with unresectable MPM
- 1rst endpoint: ORR=29.4%; DCR=67.6%
- mOS= 17.3 months; mPFS= 6.1 months
- Efficacy not correlated to PD-L1 status or histologic subtype even if PD-L1>1% pts seemed to exhibit a better response
- No unexpected toxicity



The MERIT trial led to the approval by Japonese authorities of Nivolumab as second line treatment in MPM +++

Nakano T et al.- WCLC® 2018 - Abs.# OA08.01

Beyond 1rst Line Chemotherapy for MPM

PICO Question: Should immunotherapy be used as salvage therapy in patients with MPM who failed first line chemotherapy?

➢**2019 European Guidelines** → *Research priority*: novel insights in immunotherapy are promising but need further development and results from ongoing or planned phase III trials before to draw any definitive recommendation for their use in routine. Inclusion of patients in clinical trials is highly recommended.

NCCN already proposes **immunotherapy (Nivolumab ±Ipilimumab) as 2nd line treatment** according to IFCT MAPS-2 trial data*, in addition to chemo options beyond 1rst Line:

- Pemetrexed, in case of late relapse (≥6 months) after 1L Pem based CT
- otherwise Gemcitabine or Vinorelbine alone

*Scherpereel et al, *Lancet Oncol* 2019

Immunotherapies,Targeted therapies and intra-pleural treatments

- **All other recent international guidelines also agree** they are not indicated (yet!?) in routine
  → research recommendation = patients should be proposed to participate to clinical trials ++++++

- Many exciting drugs and strategies to follow in 2020 and beyond …

- … However some recent bad news modulating the hope for ICI in MPM

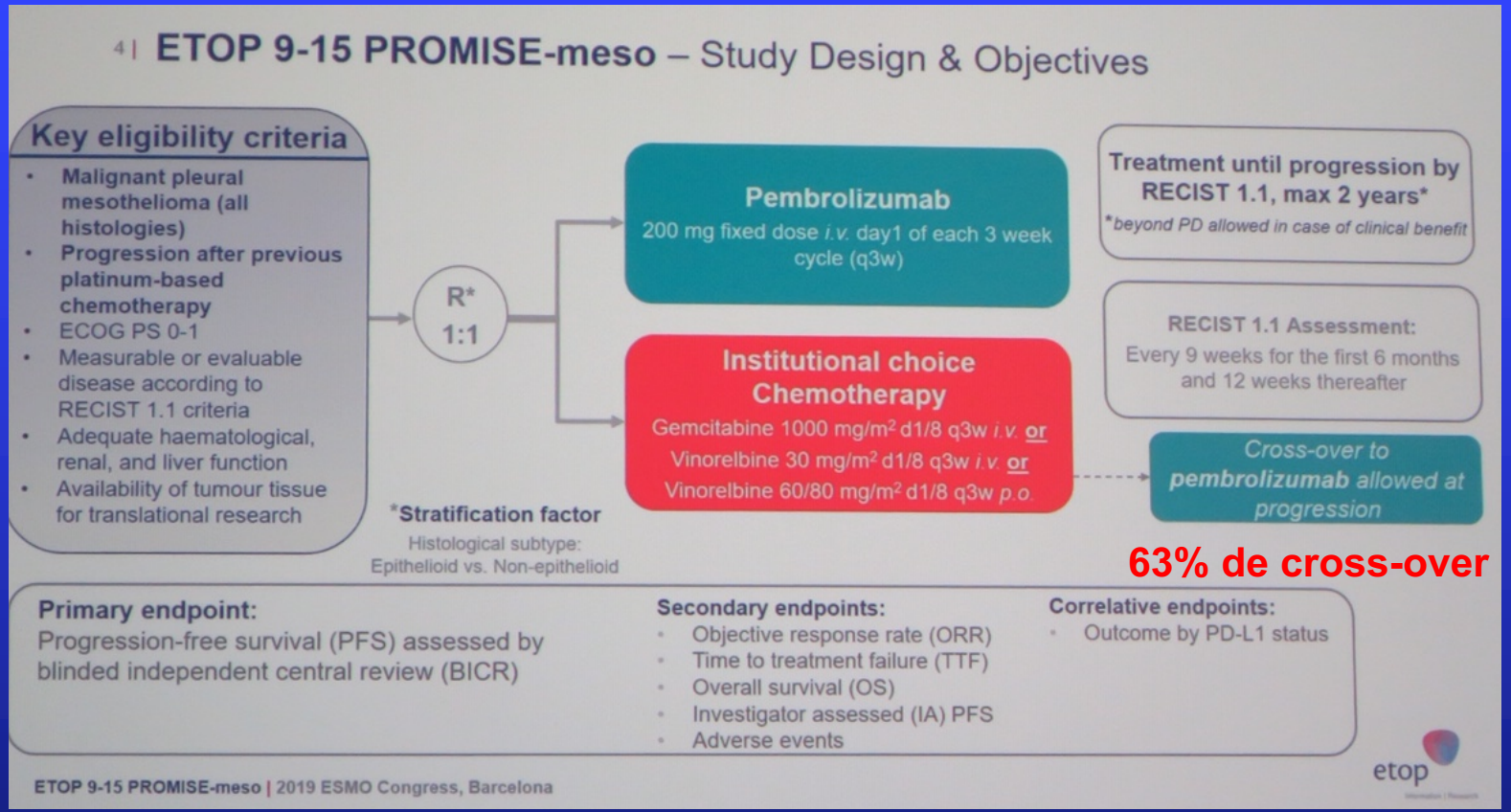
HPD in MAPS-2 trial

- **HPD pattern of progression does exist in Malignant Pleural Mesothelioma receiving 2L/3L immunotherapy but seems less frequent than in NSCLC : 6/125 or 11/125 = 4.8% - 8.8% depending of the definition *vs*.13.8% in NSCLC with IGR def.**
- TGR Gustave Roussy formula using volumes is difficult to use in MPM non-spheric tumor volumes and does not correlate with survival
- TGK Curie formula using single-dimensions mRECIST measures is easier to use in MPM
- HPD are observed in both MAPS-2 arms, but are slightly more frequent in the Nivo arm than the Nivolumab + Ipilimumab arm
- No pseudo-progression pattern was observed in MAPS 2 trial (n=125, small numbers)

Caution and early evaluation is needed in fast-progressing patients, with general condition deterioration (especially in 1rst line setting), to rapidly switch to pemetrexed-based 2, 3 or 4L

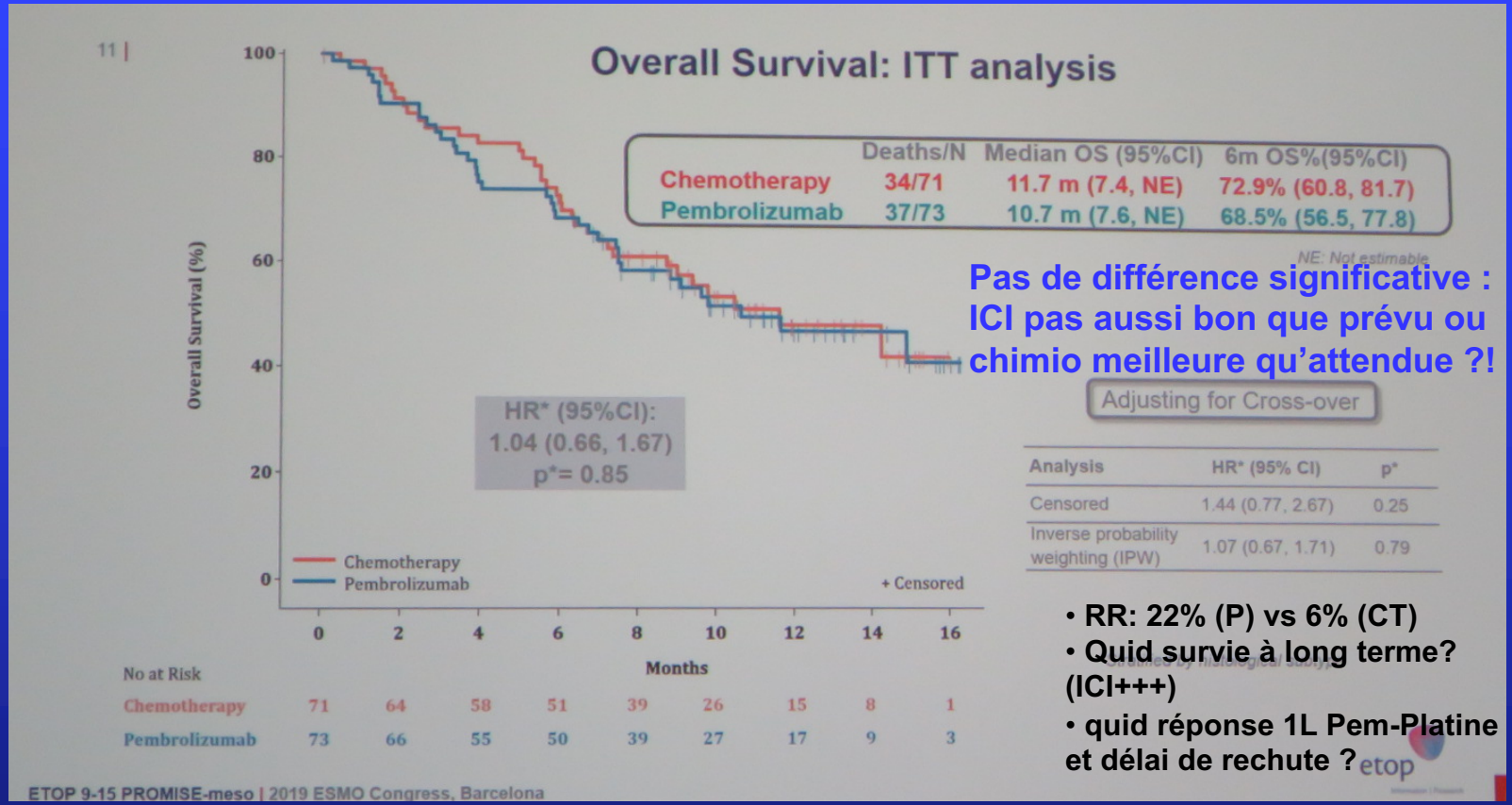
Gérard ZALCMAN, University Hospital Bichat-Claude Bernard, AP-HP, Paris, France

Essai de phase IIIr PROMISE Meso (ETOP)



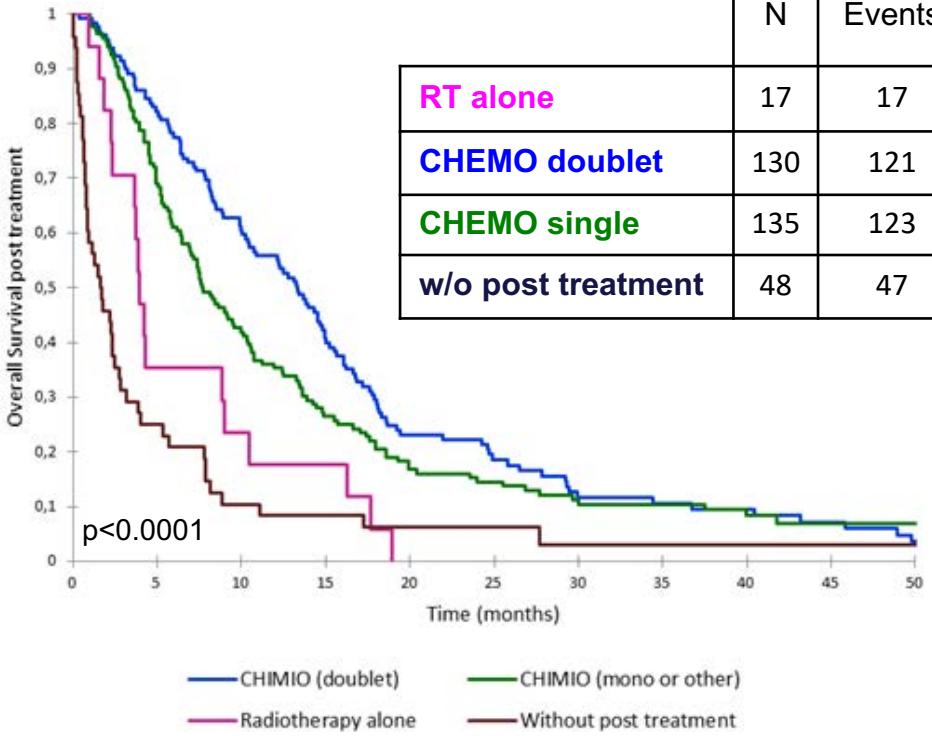
Popat S et al, ESMO 2019

Essai de phase IIIr PROMISE Meso (ETOP)



Popat S et al, ESMO 2019

IFCT MAPS trial: Overall Survival from the end of 1L treatment in patients who discontinued 1L for progression

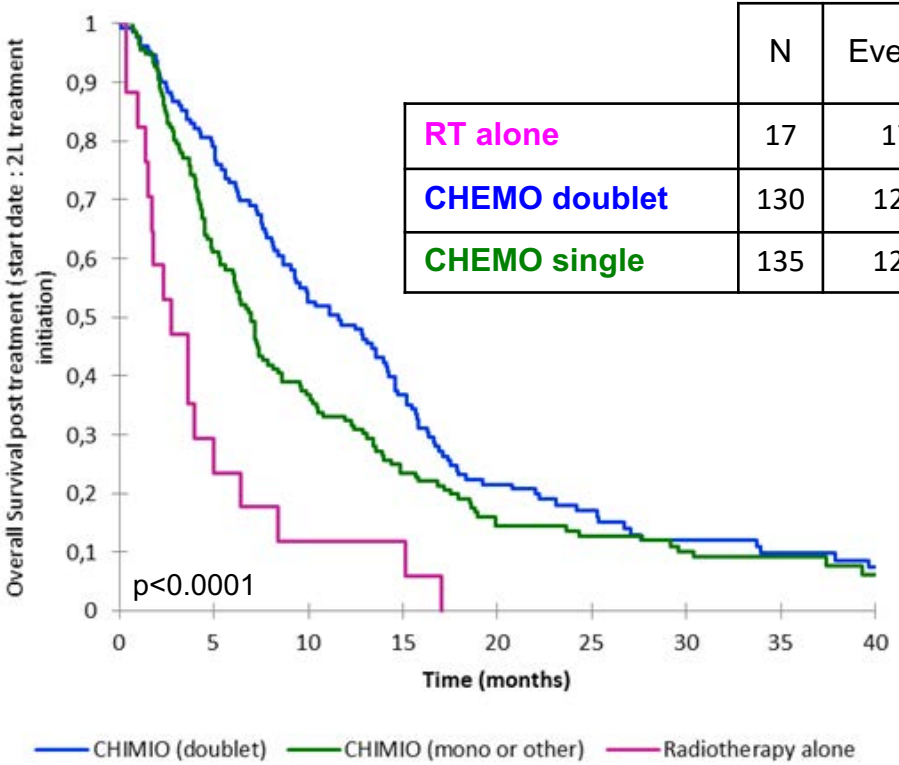


	N	Events	Median OS (months)	IC95%	1-year OS [IC95%]	2-years OS [IC95%]
RT alone	17	17	4.0	[2.3-9.0]	17.7% [4.3-38.3]	0%
CHEMO doublet	130	121	13.3	[10.3-15.0]	55.4% [46.4-63.4]	22.1% [15.4-29.7]
CHEMO single	135	123	7.7	[6.5-10.1]	35.6% [27.6-43.6]	14.6% [9.2-21.1]
w/o post treatment	48	47	1.7	[0.8-2.5]	8.3% [2.7-18.2]	6.3% [1.6-15.5]

⚠ Reminder:

Patients who received 2L doublet chemo were slightly **younger** (median 64.4 *vs.* 66.5yrs, p=0.038), had more frequently **epithelioid** rather than biphasic/sarcomatoid histology (88% *vs.* 79%, p=0.032) and more frequently Disease Control at 1L (59.2 vs. 54%, p<0.001) **although those differences were numerically weak**.

IFCT MAPS trial: Overall Survival from the start of 2L treatment in patients discontinued 1L for progression



	N	Events	Median OS (months)	IC95%	1-year OS [IC95%]	2-years OS [IC95%]
RT alone	17	17	2.7	[1.4-5.0]	11.8% [2.0-31.2]	0%
CHEMO doublet	130	121	11.1	[8.7-14.1]	48.4% [39.5-56.6]	17.9% [11.8-25.1]
CHEMO single	135	123	7.0	[5.6-8.1]	32.6% [24.9-40.5]	13.7% [8.5-20.6]

⚠ Reminder:

Patients who received 2L doublet chemo were slightly **younger** (median 64.4 *vs.* 66.5yrs, p=0.038), had more frequently **epithelioid** rather than biphasic/sarcomatoid histology (88% *vs.* 79%, p=0.032) and more frequently Disease Control at 1L (59.2 vs. 54%, p<0.001) **although those differences were numerically weak**.

pts with or w/o 2L Tt following MAPS 1L*	342 / 442 (77.4%)
Carbo or Cisplatin+ pemetrexed	125/442 (28.3%)
Carbo or Cisplatin or other + gemcitabine	36/442 (8.1%)
Carbo + other includin 1 pt with vinorelbine	4/442 (0.9%)
Pemetrexed + gemcitabine	1/442 (0.2%)
	Doublet chemo = 166 / 442 **(37.6%)**
Gemcitabine single agent	46 (10.4%)
Pemetrexed single agent	44 (10.0%)
Other (phase I trial or any single agent not listed)	39 (8.8%)
Vinorelbine single agent	16 (3.6%)
Bevacizumab single agent	12 (2.7%)
Pemetrexed + Beva	1 (0.2%)
	Single agent chemo = 158 / 442 **(35.7%)**
Radiotherapy alone	18 (4.1%)
No post-discontinuation treatment	100 (22.6%)

*6 patients still treated in 1L at time of data cut-off (bevacizumab maintenance)

But patients who received 2L doublet chemo were slightly younger (median 64.4 *vs.* 66.5yrs, p=0.038), had more frequently epithelioid rather than biphasic/sarcomatoid histology (88% *vs.* 79%, p=0.032) and more frequently Disease Control at 1L (59.2 vs. 54%, p<0.001).

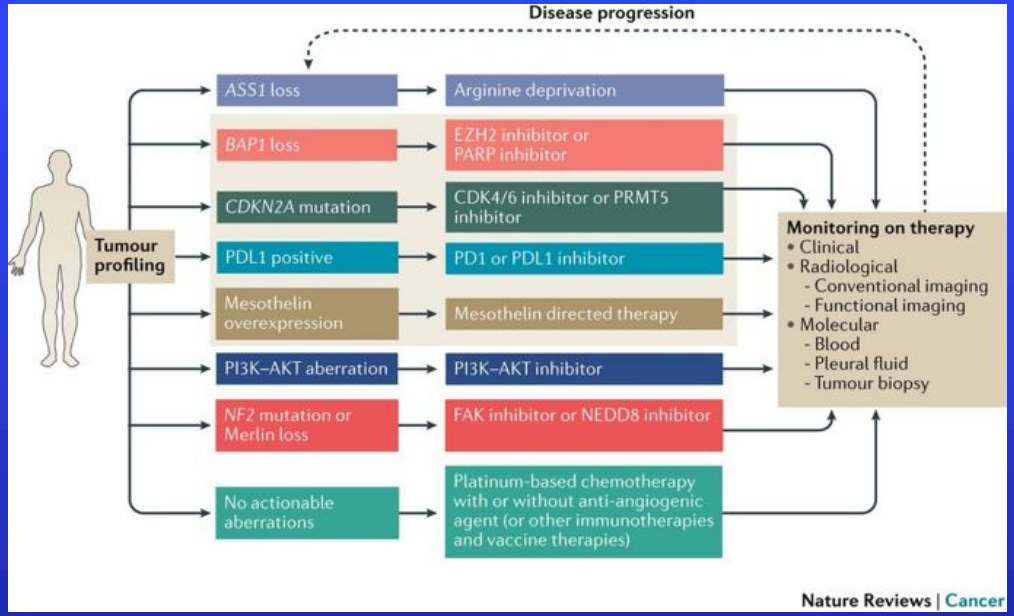
Second line treatment after 1L MAPS trial

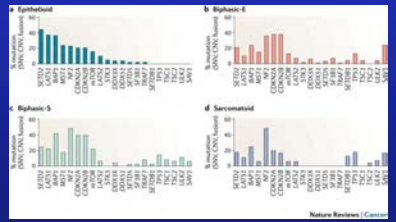
- MAPS trial definitively set a new standard of treatment for MPM not amenable to 'curative' surgery
- Long-term follow-up was reported for the very first time in a MPM clinical trial, showing 13% of patients alive at 5 years in the beva arm *vs*.7% in the chemo arm
- No unbalance occurred in frequency of 2L treatments between the MAPS two arms and 2L did not impact bevacizumab OS final results in MAPS
- 2L doublet chemo (pemetrexed-based or gemcitabin-based) gave a **13.3 mo OS**
- **2L single-agent** chemo led to only **7.7 mo** of OS, to be compared to Nivolumab (**11.9 mo**) and to Ipi+Nivo (**15.9 mo**) in MAPS2 trial

Prise en charge des patients MPM : Perspectives

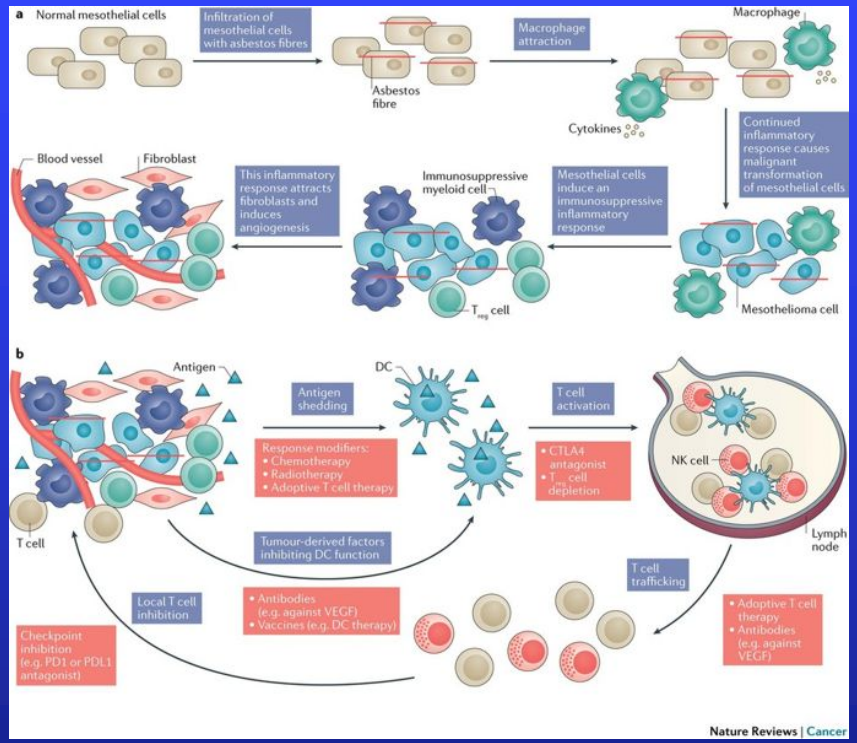
?

A better knowledge of MPM pathogenesis could provide us new efficient therapies such as immunotherapy or targeted therapies





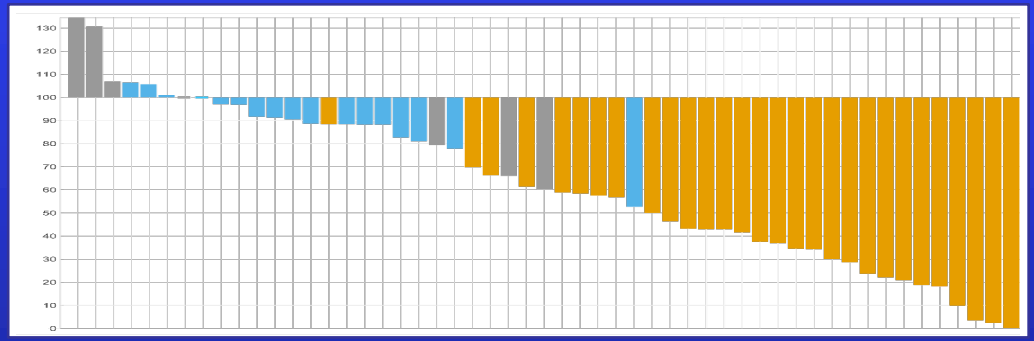
Review in Yap et al, *Nat Rev Cancer* 2017



DREAM trial: response to treatment PFS6, and tolerance

Responses	mRECIST (%)	iRECIST (%)
CR	**0**	**0**
PR	**26 (48%)**	**27 (50%)**
SD	**20 (37)**	**20 (37)**
PD	**8 (15)**	**7 (13)**
Total	**54**	**54**

Nowak AK et al. - WCLC® 2018 - Abs.# OA08.02



Median PFS, months (IC 95%)	
Chemotherapy + durvalumab	**6.2 (5.5-9.0)**
PFS6	**31/54 (57%)**

Tolerance: grade 3-5 in 36/54 pts (66%); 15% IrAE grade 3-4; 5 deaths under treatment (not related to Durva)

Conclusion: positive trial → a phase III trial (Australia/USA) will start in 2020

MPM I/O Strategy moving forward → other ongoing frontline trials

Frontline I/O Studies	Phase	NCT	Target	Population	Planned N	Primary endpoint
Nivolumab+Ipilimumab vs platinum-pemetrexed *(BMS CA209-743)*	**III**	02899299	**PD-1+CTLA4 inhibitors vs chemo**	**Frontline**	**600** (done)	**OS**
Durvalumab + cisplatin-pemetrexed *(PrE0505) (USA)*	**II**	02899195	**PD-L1 inhibitor + chemo**	**Frontline**	**55**	**OS**
Pembrolizumab + cis-pemetrexed vs cisplatin-pemetrexed *(Canadian Cancer Trials Group, Italia, IFCT France, UK)*	**II/III**	02784171	**Chemo +/- PD-1 inhibitor**	**Frontline**	**470**	**OS (Ph III)**
Atezolizumab + Bevacizumab + platin-pemetrexed vs Beva+platin-pemetrexed *(ETOP)*	**III**	03762018	**Chemo + anti-VEGF +/- PD-L1 inhibitor**	**Frontline**	**320**	**OS**

review in Scherpereel and al, *The Lancet Oncol* 2018; 19: e161-72; updated in 2019

Other active, randomized phase III trials with ICI in MPM as Salvage Therapy *(based on Clinical.Gov - May 28th, 2019)*

- *« Promise »* (ETOP): Pembrolizumab versus Standard Chemo for advanced **pre-treated** MPM *(NCT02991482); 144 randomized pts (all recruited yet)*
  → **NEGATIF !**

  à challenger avec :

- *« CONFIRM »* *(NCT03063450)* (UK) (*CheckpOiNt Blockade For Inhibition of Relapsed Mesothelioma*): Nivolumab vs Placebo in r**elapsed** Mesothelioma
  n= 336 patients; Fennell DA et al, Trials 2018

Examples of active, early phase Immunotherapy trials in Mesothelioma *(based on Clinical.Gov - May 28th, 2019)*

Anti-PD-1 + Cell Therapy

- Phase I trial of Pembrolizumab 4 wks after CAR T cells
- Phase I trial : autologous T Cells Genetically Engineered to Target the Cancer-Cell Surface Antigen Mesothelin
- Combination of Pembrolizumab Plus Autologous DC-CIK Cell Immunotherapy and Hyperthermia

Anti-PD-1 or PD-L1 combined with targeted therapies

- Phase I: Arginase Inhibitor INCB001158 alone or +Pembro in Pts With Advanced/Metastatic Solid Tumors
- Phase I of IPI-549 ± Nivolumab
- Phase 1/2 Study exploring INCAGN01876 + Nivo
- Phase II of Pembrolizumab evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)
- Phase I/IIA Study of FAKi (Defactinib) and Pembro
- *Mesothelioma Stratified Therapy (MiST):* A Stratified Multi-arm Phase IIa Clinical Trial (Rucaparib/ Abemaciclib/Pembro+ bemcentinib (AXL inh)/ Atezolizumab +Bevacizumab) (≥2nd line)

Window-of-opportunity Studies in Resectable MPM

- Phase I pilot of Pembrolizumab in Patients With Resectable MPM
- Phase II Study of Durvalumab alone or + Tremelimumab
- Feasibility Trial of Neoadjuvant Cis/Pem with Atezolizumab in Combination and in Maintenance

Anti-PD-1 or PD-L1 combined with Radiotherapy

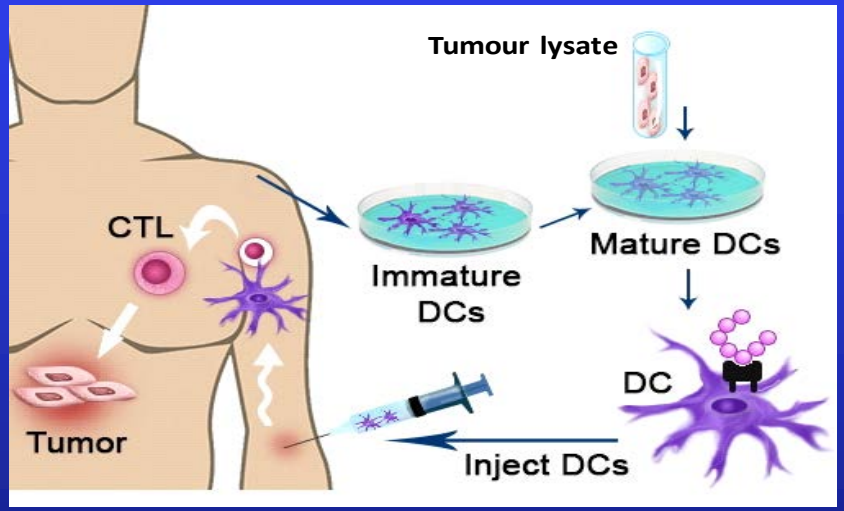
- Phase I Trial of Adjuvant Pembrolizumab After Radiation Therapy for Lung-Intact MPM
- Efficacy and Safety Study of Avelumab Plus SBRT in MPM

Anti-PD-1 + Therapy targeting Mesothelin

- Phase 1/2 Randomized Clinical Trial of Anetumab Ravtansine and Pembro vs Pembro Alone for Mesothelin-Positive MPM
- Phase II Study of the Anti-Mesothelin Immunotoxin LMB-100 Followed by Pembrolizumab in Meso (≥2nd line)
- Phase II Study of the Anti-Mesothelin Immunotoxin LMB-100 Followed by Pembrolizumab

Ongoing European randomized Phase 3 trial (MM04; "DENIM"): DC therapy with allogenic tumor cell lysate *("Mesopher")* as Maintenance (+BSC) versus BSC alone after standard 1rst line chemotherapy in unresectable, non-progressing MPM

(NCT03610360) – European Union H2020 funding



Accrual (June 2019): 50 / 230 planned patients (8/2018-)

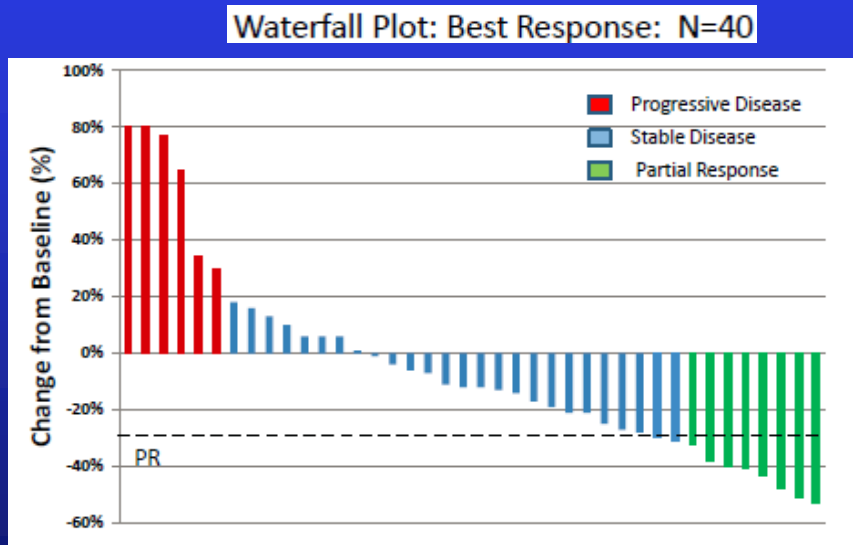
Centers: Rotterdam* (J Aerts, PI; Cornelissen), Antwerp* (J van Meerbeeck), Lille* (A Scherpereel), Amsterdam* (P Baas), Leicester (D Fennell), Ancona (R Berardi); *recruiting

First endpoint: mOS - hypothesis = 21 months after randomization for the MesoPher group vs 12 months for the control group (HR of 0.57)

Immuno-Thérapie Génique du MPM par délivrance intrapleurale d'un vecteur AdénoV-IFN-α combiné à la chimio

- 18 pts + 1rst line Pem-based chemo; 22 pts +2nd line chemo with Pem (n=7) or gemcitabine (n=15). All had AdV-IFN-a through IPC. Treatment well tolerated
- ORR = 25%; DCR = 88%
- **mOS: epithelioid vs non-epi MPM pts = 21 vs 7 months**
- mOS for 1st-line cohort = 12.5 months
- **mOS for 2nd-line cohort = 21.5 months** (32% of pts alive at 2 years); Pem>Gemci

→ **En 2019, essai multicentrique randomisé "Trizell" en 2/3e ligne par chimio -immunothérapie génique vs chimio standard (MPM sous-type épithélioïdes)**



Sterman et al, *Clin Cancer Res*. 2016

Intrapleural immunotherapies for MPM

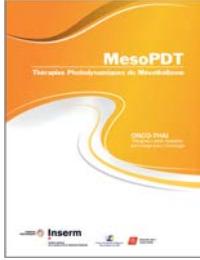
Various strategies, tested in 26 clinical trials identified for MPM and MPE[1]:

- **direct cytokine-mediated immunotherapies, innate immunomodulators (IL-2, IFN-γ…)**
- **Oncolytic virus therapy**
- **Gene-mediated cytotoxic immunotherapy**
- **Chimeric antigen receptor (CAR) T-cell therapy.** Ex: MSKCC phase I trial of intrapleural, fully humanized *anti-mesothelin CAR-T cells (*iCasM28z), after conditioning by cyclophosphamide in 19 patients → ORR=48% (up to 72% when Pembrolizumab combined in 11 pts)[2]

→ Globally, promising results in early phase trials with these quite well tolerated therapies, able to generate durable tumor-specific immune responses with possible clinical benefits deserving further investigation as part of multimodal treatment (plus chemotherapy and/or immunotherapy = ICI)

[1]Murthy et al, *Clin Respir J* 2018; [2]Adusumilli PS et al*; AACR* 2019: abstr. CT036.

Thérapie photodynamique intrapleurale et MPM



1ère Ligne : eP/D + PDT, puis chimio x6 max (C/P) + RT prophylactique

- **Essai de phase II de faisabilité à Lille « MesoPDT »** (n = 4) : **résultats positifs** avec à ce jour : 2 patients sans rechute à 33 et 37 mois; 3e rechute à 11M mais vivant à 25M sous Nivo; 4e DC à 24M; (**mSG = 30 mois**); bonne tolérance

  Soutien du Conseil Régional Hauts de France (PI : AS)

- **Essai de phase II contrôlé, randomisé, multicentrique « MesoPDT2 »**

  → essai randomisé en cours aux USA (UPENN, Roswell Park center; NCT02153229; n=102); projet prévu en France mais suspendu

  PHRC National Cancer 2013 (PI : AS)

2e Ligne ou + : PDT intrapleurale par thoracoscopie suivi d'un anti-PD-1 (Nivolumab IV; max 2 ans)

- **Essai de phase II de faisabilité prévu à Lille en 2020 « IMPALA »** (n =20)

Treatment allocation of MPM patients ?

➢**2019 European Guidelines** → *Research priority*:
we still recommend that patients who are considered for a multimodal approach should be adequately informed of its challenges and referred to expert centers in order to be included in a prospective (randomized) clinical trial or registered in a large institutional database.

Diagnosis → **Malignant Pleural Mesothelioma** → *Asbestos exposure ? MPM compensation according to state law*

Pre treatment Work-up

Minimal biology tests and cardiorespiratory evaluation
+ Basic staging for all patients fit for treatment:
Chest/Abdomen CT-scan (with iodine contrast)

Patients suitable for Multimodal Treatment including Surgery with MCR ?

YES

Further Staging and Patient allocation

Treatment

Multimodal treatment including MCR (in expert centers only, within a RCT if possible)

NO: **patients suitable for Medical treatment ?**

YES

Standard first line Chemotherapy (Platin/Pemetrexed)* +BSC or RCT

NO

BSC only, including palliative RT if necessary

RCT: randomized controlled trial
MCR: macroscopic complete resection
BSC: Best supportive care

*± bevacizumab if available and no contraindication

MPM patients Follow-Up after treatment

Recommandations
L'évaluation de la réponse à la chimiothérapie dans le mésothéliome malin doit être effectuée selon les critères RECIST modifiés 1.1, actualisés en 2018. De ce fait, un scanner pré-thérapeutique, avec injection de produit de contraste, réalisé après une symphyse pleurale est recommandé.

Most recent 2019 European guidelines consider the new and improved **mRECIST 1.1 criteria for MPM***, even if they were not prospectively validated yet, as the prefered method of mesuring tumor lesions and response to the treatment on CT-scan.

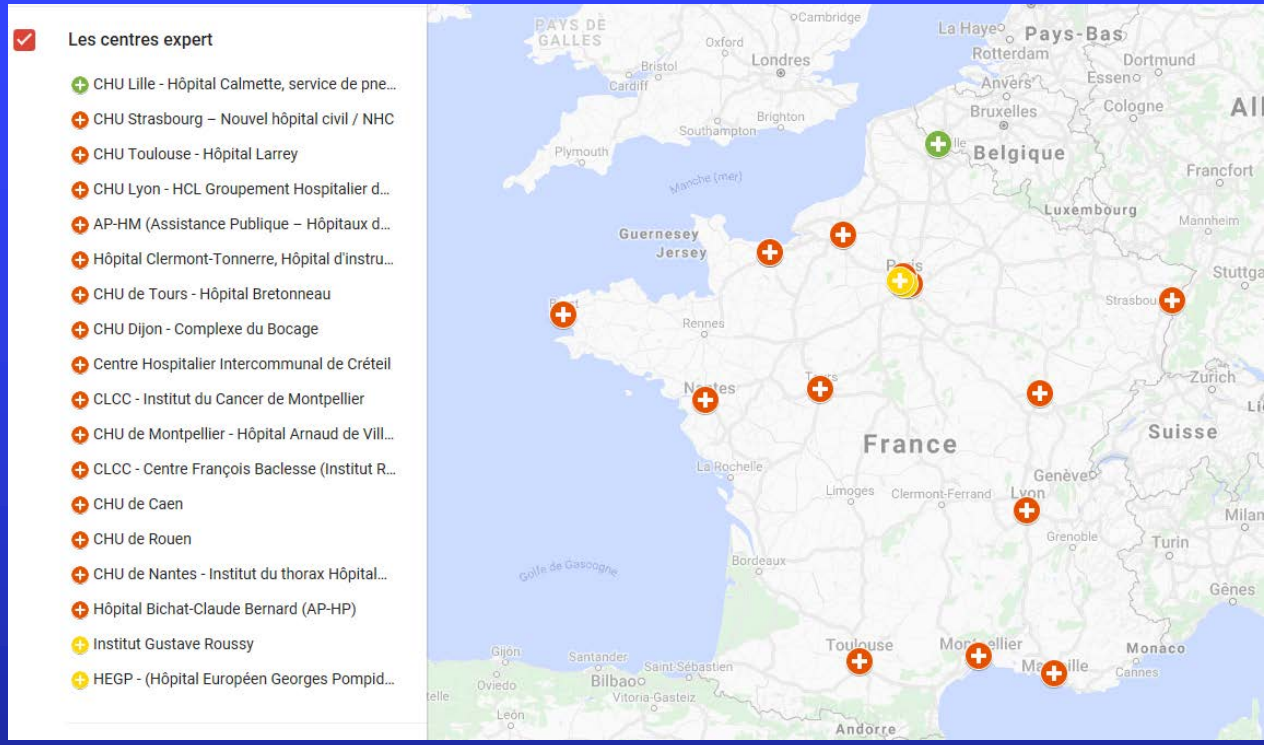
Pet-scan and biomarkers are still under investigation for the evaluation of response to treatment.

*Armato et Nowak, *JTO* 2018

MPM : messages à retenir

- Toujours beaucoup de questions sur la meilleure stratégie thérapeutique
  ⇒ **recruter les patients en essais cliniques +++**
- Suivre les Recommandations AURA 2019 en France et guidelines européennes ERS/EACTS/ESTS/ESTRO 2019 assez similaires
- Importance de centres experts et RCP du réseau MESOCLIN (associé à MESOPATH → NET MESO France) pour la prise en charge des patients en routine +++ et pour la recherche

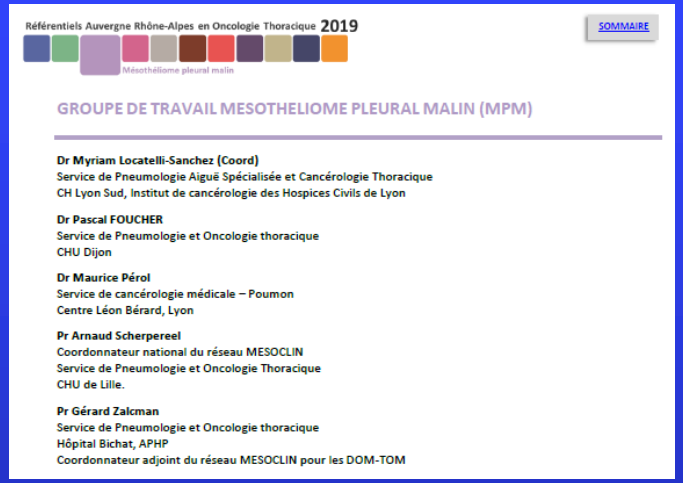
Site internet : https://www.mesoclin.fr/



BUTS :

- Avis d'experts par RCP dédiées régionales et/ou nationale
- Stimuler la Recherche Clinique et Translationnelle (essais, études via information, inclusion, *Mesobank*)
- DO, information (brochure patients, réunions de formation PS et/ou d'information associations)…

Remerciements


Référentiels Auvergne Rhône-Alpes en Oncologie Thoracique 2019

Mésothéliome pleural malin

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MESOCLIN
Réseau National Expert pour le Mésothéliome Pleural Malin

- Nos patients, leurs proches et associations
- Nos collègues impliqués dans les réseaux MESOCLIN, MESOPATH, l'IFCT, l'ERS et tous ceux qui prennent soin des patients et participent à la recherche sur le MPM
- Organisateurs et experts des reco AURA 2019 et ERS/ESTS/ESTRO/EACTS 2019

et Bienvenue au sein de l'iMig ! (www.imig.org)