Mésothéliome Pleural Malin :

Etat des lieux et Perspectives

Cours du GOLF

Strasbourg, le 18 Novembre 2015

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FACULTE DE MEDECINE HENRI WAREMBOURG

ONCO LILLE
Site de Recherche Intégrée sur le Cancer

Université de Lille 2 DROIT ET SANTÉ

Conflits d'intérêts potentiels

- Investigateur (ou coinvestigateur) principal en France pour les essais cliniques dans le MPM :
  - MedImmune
  - Verastem
  - Morphotek
  - Bayer
  - IRIS
  - MAPS et MAPS-2 (IFCT)
  - MesoPDT

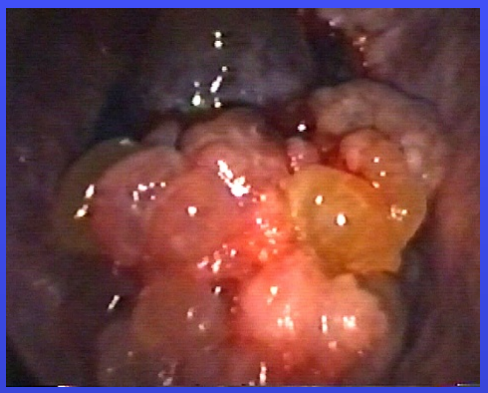
- Financements Recherche pour mon service ou laboratoire :
  - Roche
  - Amgen
  - Teva
  - *INCa* (PHRC National cancer 2013, PHRC Mesothel…)
  - Conseil Régional Nord - Pas de Calais

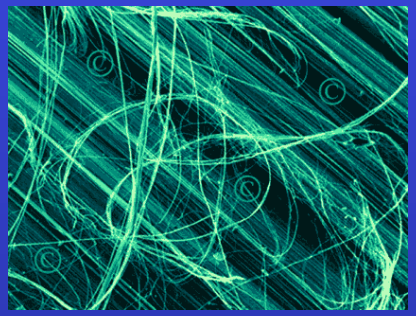
INSTITUT NATIONAL DU CANCER

Plan de la présentation

- Brève introduction sur le MPM
- Quelles armes thérapeutiques disponibles ?
- Le traitement multimodal et son actualité
- Autres thérapies innovantes
- Messages à retenir

Mésothéliome Pleural Malin

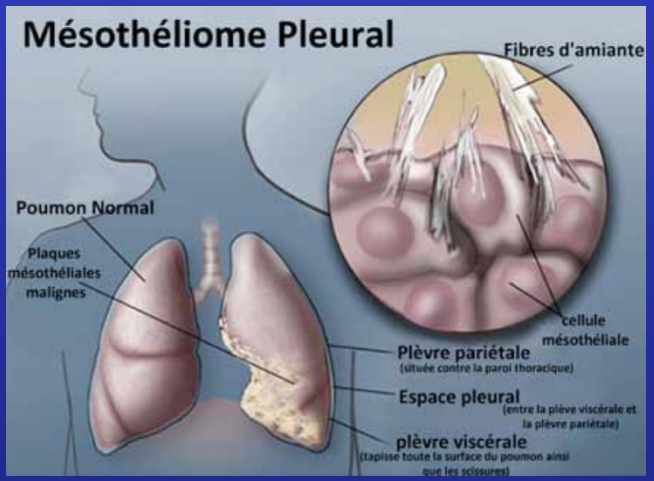




• **Tumeur très agressive** issue des cellules mésothéliales tapissant la plèvre (MPM : 80% des cas), la cavité péritonéale, le péricarde

• **Facteurs de risque : AMIANTE** (**H>F**);

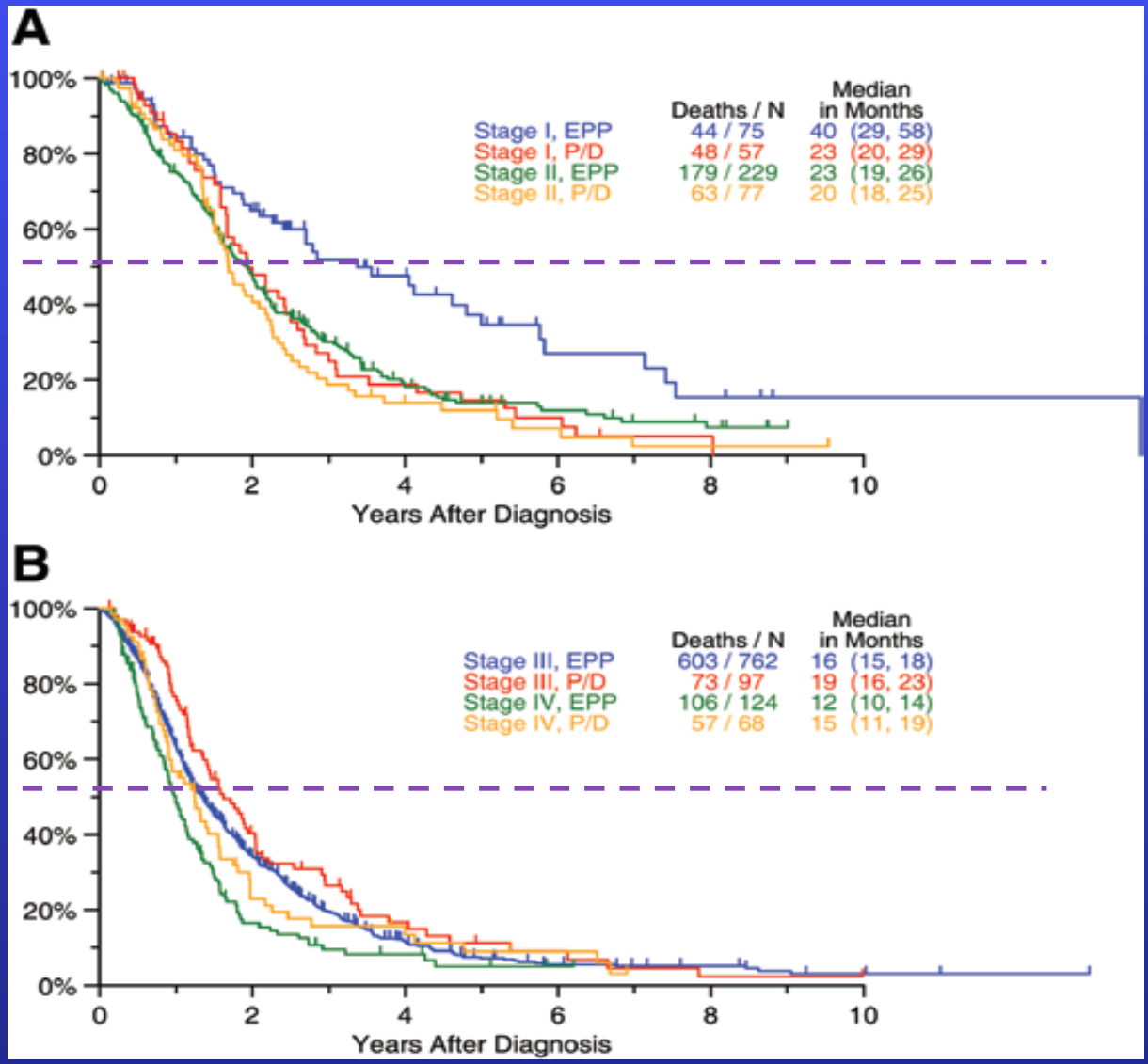
Prédisposition génétique possible : mutations du gène de **BAP1** (*BRCA1-associated protein 1*), délétion de p16…



IASLC mesothelioma database retrospective analysis

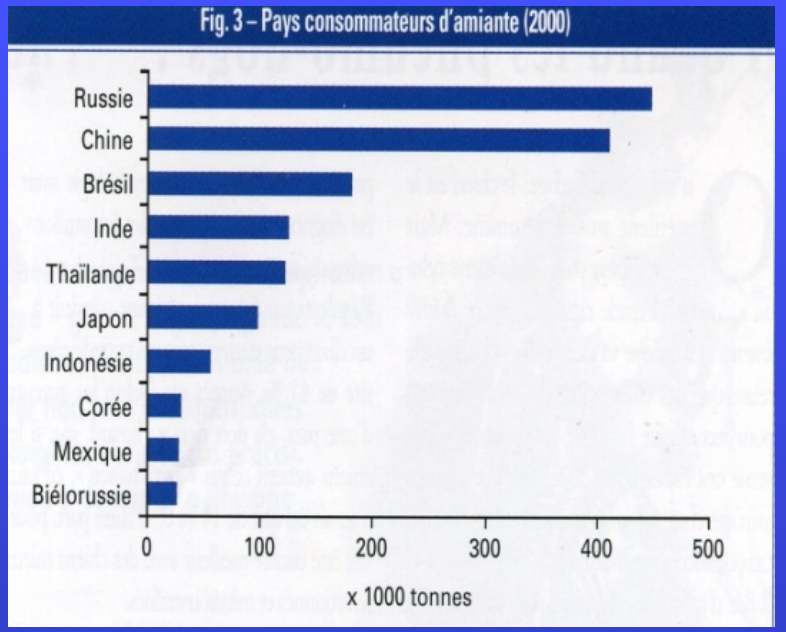
Pronostic du MPM :

- Médiane de survie ≤ 12 mois…
- …un peu mieux pour les patients opérés selon l'IASLC mais en fait patients très sélectionnés (de « meilleur » pronostic : épith…) donc interprétation prudente
- PAS de traitement CURATIF validé à ce jour…

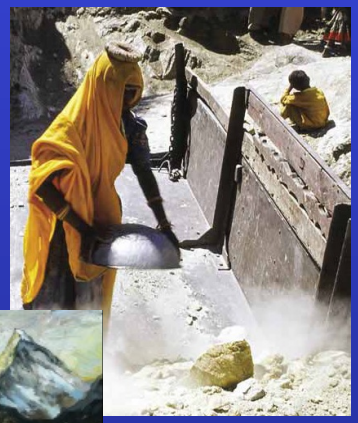


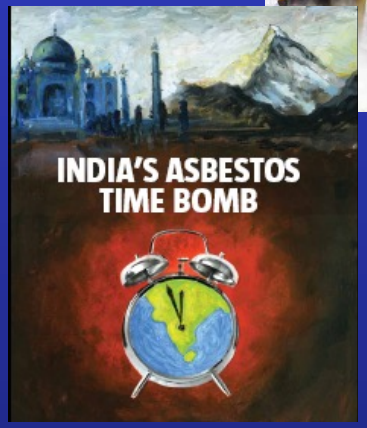
Rusch et al, *JTO* 2012

Épidémiologie du MM



- **Tumeur rare** (~1000 cas/an en France)
- **Latence du mésothéliome : 30-40 ans** après exposition à l'amiante
- **Incidence croissante**: **pic** NON atteint (INVS 2015) prévu en France vers **2020** (1200 cas/an) car pic utilisation = années1970
- **Pays occidentaux** : plateau atteint ? (USA, UK…)
- **Amiante interdite en France en 1997… et dans l'UE** (01/2005) **mais problème des pays émergents et PVD** !





Nouveautés dans le diagnostic du MPM

- Il reste basé sur **l'histologie avec IHC** (≥ 2 marqueurs + et 2 -)
- **Thoracoscopie** avec biopsies multiples profondes = méthode de référence > biopsies guidées (US/CT) …> cytoblocs (>cytologie)
- **Nouvelle classification OMS 2015** : toujours sous-type Epithélioïde >> Mixte (ou biphasique) > Sarcomatoïde… mais certaines entités + spéc de pronostic très ≠ (papillaire > autres)
- **Distinction MPM vs plèvre « bénigne »** (hyperplasie mésothéliale atypique…) : nouveaux marqueurs performants = **mutation du gène de BAP-1** (IHC) **et délétion de p16** (Bio Mol) **uniquement dans le MPM +++** *… intérêt thérapeutique à terme ?*

(A Churg, BS Scheffield, F Galateau-Sallé; *Arch Pathol Lab Med*. 2015)

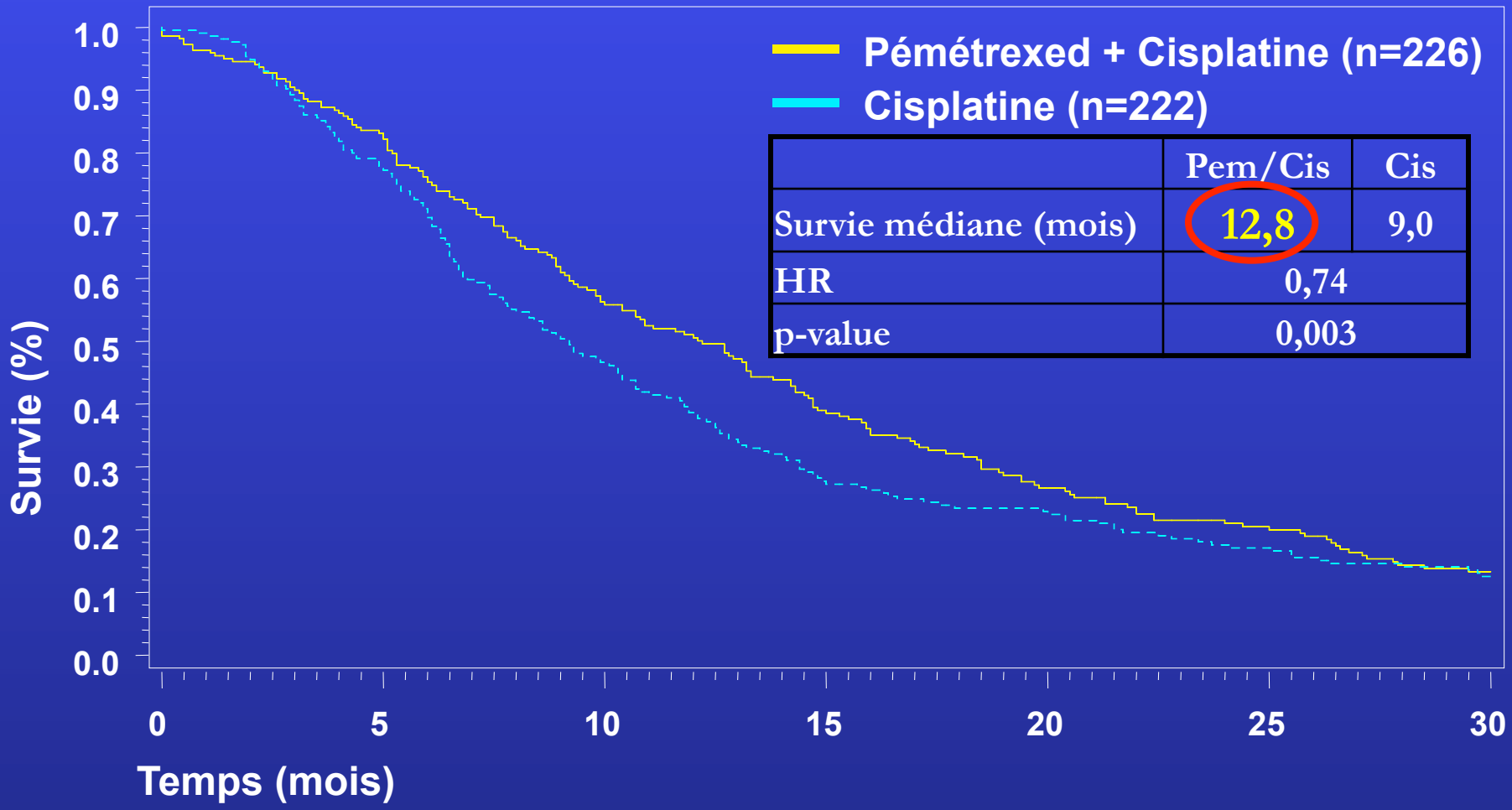
!* Ne pas oublier : validation Mesopath et DO MPM -> Mesoclin *!

Traitement de 1ère Ligne du MPM

Toujours la Chimiothérapie (Cis-Pem) seule (hors BSC) ?…

…ou combinée à d'autres traitements ?

Essai de Phase III randomisé : Cisplatine+Pémétrexed vs Cisplatine dans le MPM



	Pem/Cis	Cis
Survie médiane (mois)	12,8	9,0
HR	0,74	
p-value	0,003	

Vogelzang, *JCO* 2003 and *WCLC* 2005, updated survival

Chimiothérapie de 1ère Ligne pour les patients MPM

- **2009 ERS/ESTS Guidelines:** Scherpereel et al, *Eur Respir J* 2010
  - "when a decision is made to treat patients with CT alone, patients in a good PS (<3) should be treated with ***first line combination of platinum and pemetrexed ...*** (1B)"
  - "Alternatively, patients could be included in first (and 2nd) -line clinical trials"
- **2013 Australian Guidelines:** www.clinicalguidelines.gov.au
  - first line = combination of (cis or carbo)platin and pemetrexed (A)
- **2015 ESMO statements:** Baas et al, *Ann Oncol* 2015
  - first line = combination of (cis or carbo)platin and pemetrexed

… Mais depuis essai MAPS présenté à l'*ASCO* 2015 !

Radiothérapie dans le MPM

- **De 2009 (ERS/ESTS) à 2013 (Australian Guidelines) et 2015 (ESMO):**
  - peu de détails; plus de RT prophylactique malgré toujours un niveau de preuve faible... mais 2 essais en cours (SMART UK...)
  - également développement des nouvelles techniques de RT à suivre (IMRT, protonthérapie...)

Recommendations		Grade*
34.	Mesothelioma is sensitive to moderately high radiation doses and radiotherapy is advocated for palliation of symptomatic tumour masses arising from the pleural cavity or metastases in other locations.	C
35.	For doses greater than 50 Gy, advanced radiotherapy technologies with strict constraints for contralateral lung doses are recommended to avoid excessive toxicity.	C
36.	The administration of prophylactic radiotherapy following pleural interventions in patients with mesothelioma has no significant effect on changing the disease course and is not recommended.	C

Chirurgie du MPM

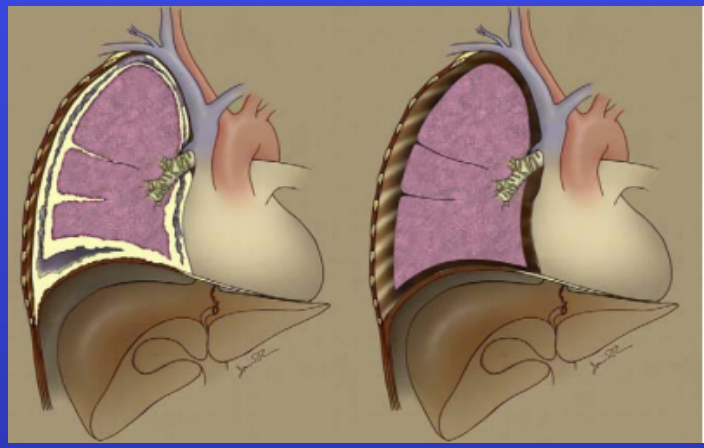
- **De 2009 (ERS/ESTS guidelines)**

  … à 2013 (Australian Guidelines)

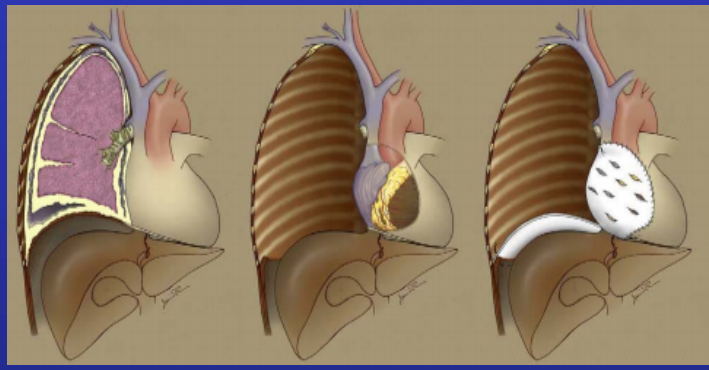
  ou 2015 (ESMO statements) :

  très peu de changements…

(e)P/D



PPE



Globalement, beaucoup d'études petites, non randomisées et rétrospectives, sans compter des techniques chirurgicales très inhomogènes jusque récemment, et un recrutement très sélectionné des patients

Rice D et al, Ann of Diagn Path 2009

Chirurgie du MPM : quelles tendances en 2015 ?

1. « La fin » de la Pleuro-Pneumonectomie Elargie (EPP) ?!

- Phase II EORTC 08031 trial : CT+EPP+RT : OS 18.4M; PFS 13.9M mais « treatment success rate » = 42% des patients seulement dû aux EI...
  (Van Schil et al, *ERJ* 2010)
- ... et données de survie similaires avec la chimio seule dans les stades précoces du MPM ! (Hillerdal et al, *JTO* 2009; Bolovato et al, *JTO* 2014)
- MARS trial (UK) (chemo then EPP+RT vs ∅EPP): négatif mais discutable
  (Treasure et al, *Lancet* 2011)

2. « Le retour » de la Pleurectomie/Décortication étendue (eP/D) ?

Contrôle local < EPP mais sans impact de survie, et morbidité-mortalité << EPP;
à combiner avec la chimio et/ou des « thérapies ciblées » (+RT ?) ? Essais +++

Survie médiane : eP/D > EPP

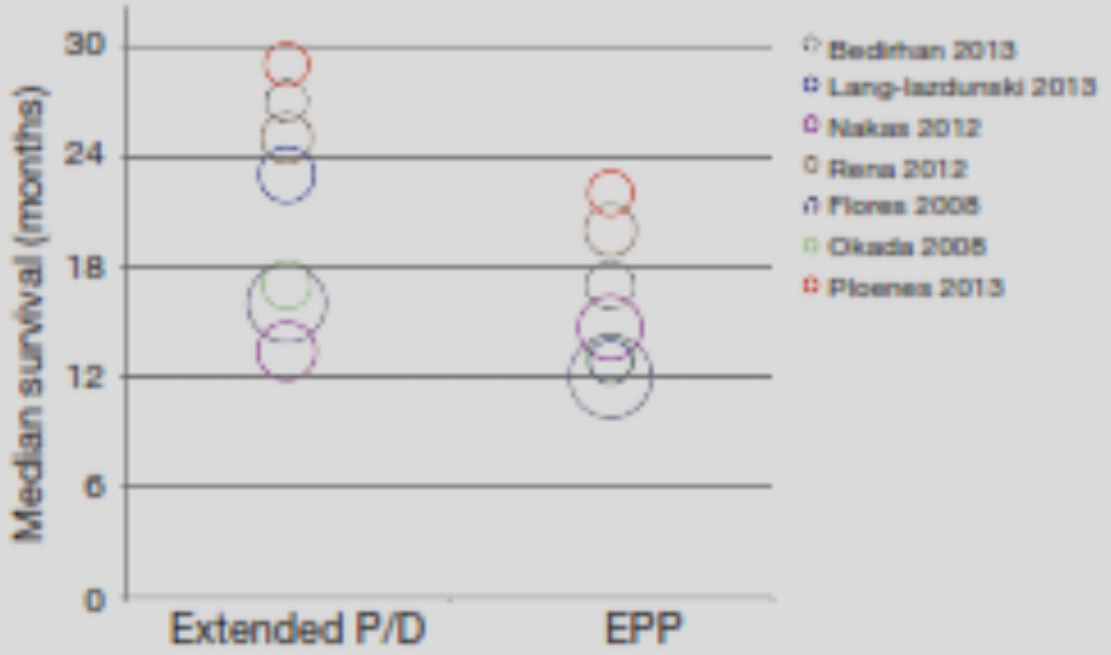
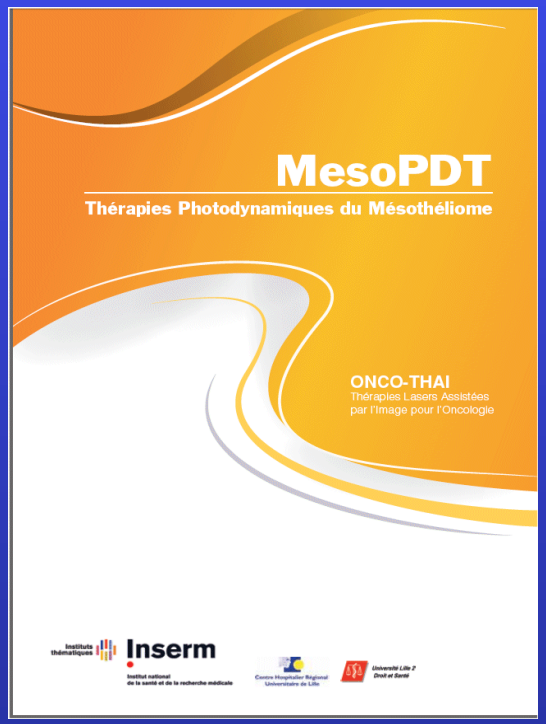


Figure 3 Summary of median overall survival outcomes for patients with malignant pleural mesothelioma who underwent extended pleurectomy/decortication (eP/D) or extrapleural pneumonectomy (EPP). Circle radius is logistically proportional to the size of individual studies. Solid lines indicate survival measured from the date of diagnosis, and dotted lines indicate survival measured from the date of surgery. From Cao *et al.* 2014 (59).

Opitz I, *J Thorac Dis* 2014; Cao et al, *Lung Cancer* 2014

Photothérapie dynamique (PDT) associée à la chirurgie du MPM



PRESENT (J Friedberg – *Philadelphia, USA*) … et FUTUR ? (S Mordon – *Lille, France*)

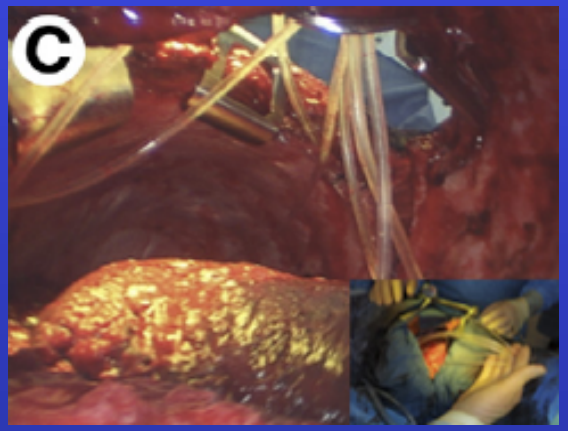
PDT dans le traitement du MPM : principes (USA)

- Injection IV produit photosensibilisateur > 48h avant
- Chirurgie d'exérèse maximale : eP/D ++ ou (PPE)
- Illumination de la cavité pleurale par une source laser

Photofrin ®

- Dérivé de l'hématoporphyrine
- Approuvé par la FDA pour le MPM en décembre 2011
- Dose : 2m/kg IV 24-48h avant illumination
- Lumière rouge à 630nm

Dosimétrie



Friedberg, Sem in Thor and Cardiovasc Surg 2009

Zhu JNCCN 2012

Résultats PDT dans le traitement du MPM (USA)

Chirurgie (14 eP/D +14 PPE) + PDT + chimiothérapie (C/P); (stades III-IV : 85%)

	Survie globale médiane (mois)	Survie sans progression médiane (mois)
eP/D	**> 25,2**	22,8
PPE	**8,5**	7,2
p	0.009	0.15

Friedberg et al Ann Thorac Surg 2011

Chirurgie (38 eP/D) + PDT + chimiothérapie (C/P); (stades III-IV : 97%)

	Survie globale médiane (mois)	Survie sans progression médiane (mois)
eP/D	**31,7**	9,6

Friedberg et al Ann Thorac Surg 2012

Projet MesoPDT

= 2 Essais cliniques + études ancillaires

* Essai de phase II de faisabilité à Lille :

Soutien du Conseil régional du Nord Pas de Calais

traitement multimodal : eP/D avec PDT, puis chimio x 6 maximum (Cis/ Carboplatine + pémétrexed) (n = 6)

* Essai de phase III contrôlé, randomisé, multicentrique en France :

PHRC National Cancer 2013 (PI : Pr A Scherpereel)

comparaison d'un traitement multimodal : eP/D avec ou sans PDT, puis chimio x6 max (Cis/Carbo + pémétrexed) (n = 45 x2)

Traitement Multimodal : en résumé ésumé

- Traitement multimodal indiqué dans les stades « limités »

= I - III ? ≤ cT3N2M0 ?*... Mais quel système de stade TNM ?*

(AJCC 8e édition ? mineurs) quel bilan pré-opératoire ?

- Traitement multimodal dans les stades « limités »

cœlioscopie, EBUS…)? *résécabilité*

cœlioscopie, EBUS…)? *? (TEP-TDM,*

- chirurgie de « debulking » maximal par

eP

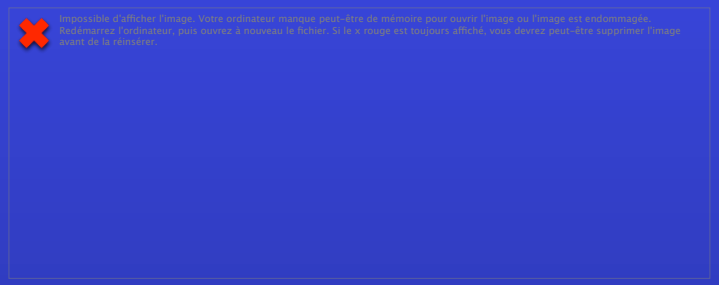
- Chimiothérapie d'induction ? /D versus EPP ?

Van Schil et al, *Eur*

Traitement Multimodal du MPM : Traitements Multimodaux du MPM : principaux essais cliniques en cours

1. « Mesothelioma And Radical Surgery » (MARS) 2 trial (UK):

   Plat/Pem x 2 cycles then **R**: eP/D + P/P x4 **vs** P/P x4 alone

   (early stage MPM pts)

3. PDT (USA), bientôt en France = MesoPDT

   PDT then adjuvant chemo (C/P)

4. NCT00797719 (Toronto): IMRT then EPP

5. NCT 01644994 (Zurich): intracavitary chemotherapy after EPP

6. NCT01265433 (MSKCC, NYC): WT1 vaccine after P/D

Quelle traitement de 2ème ligne (et plus) doit être proposée aux patients MPM ?

… Y-a-t-il quelque chose de valable après une 1ère ligne de chimiothérapie par sels de Platine et Pémétrexed ?

... hormis la reprise du Pémétrexed (± Platine) si la rechute est tardive (~ ≥6 mois) *

→ essais cliniques +++

***Selon les recommandations ERS/ESTS 2009 et Australiennes 2013**

Chimiothérapie ≥ 2nde ligne

TREATMENT	N pts	RR	Survival
Doxorubicin	11	9%	4.5 months
ZD0473	43	0	6.7 months
Oxaliplatin/Raltitrexed	14	0	3.2 months
Doxorubicin versus Cyclophosphamide	6 5	0 0	-
Pemetrexed	28	21	9.8 months
Pemetrexed/Carboplatin	11	18	8.6 months
CDDP/MMC/Irinotecan	10	20	7.3 months
Erlotinib/Bevacizumab	24	0	5.8 months

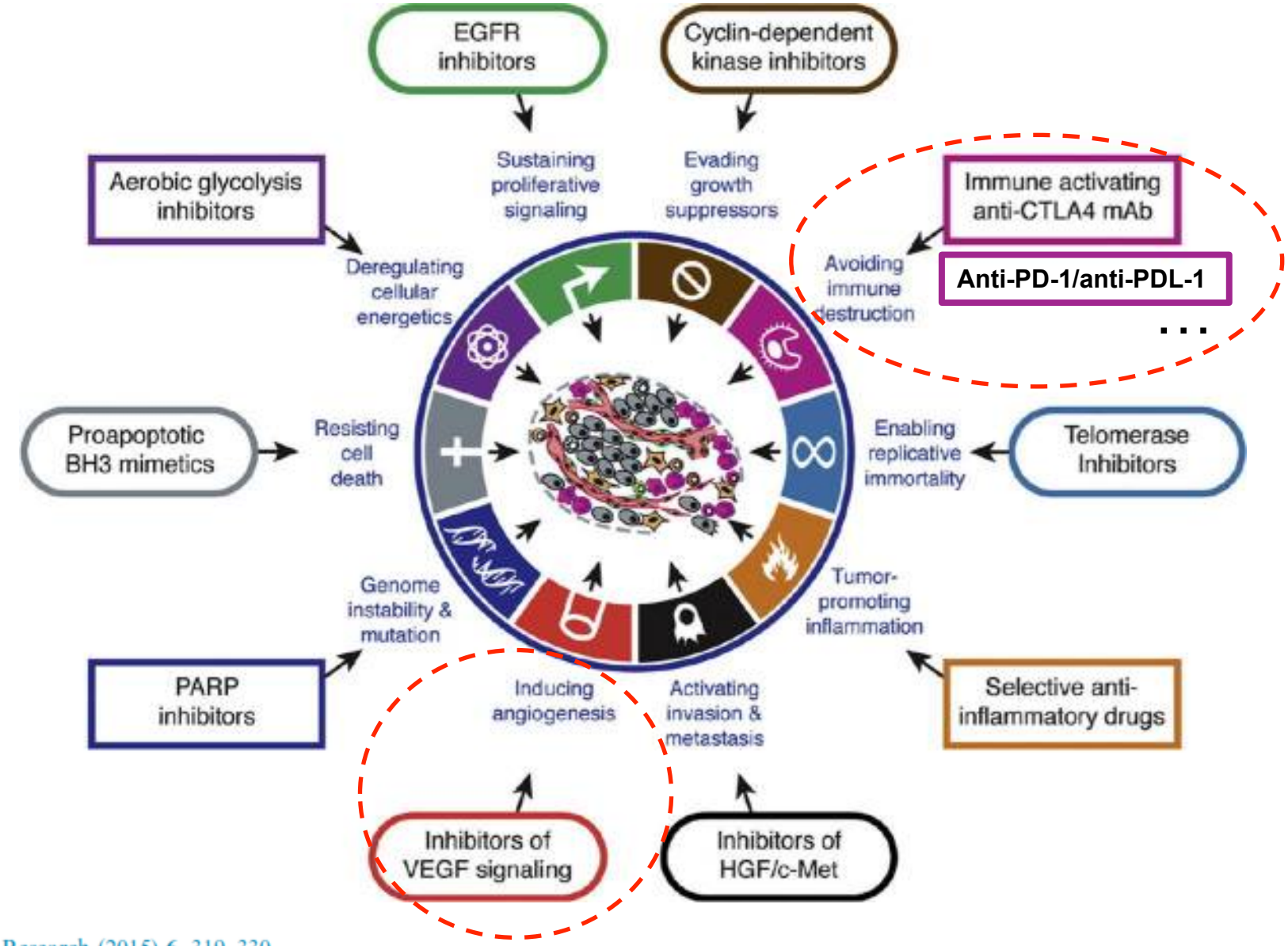
A Scherpereel, P Astoul, P Baas et al, *Eur Respir J* 2010

Traitements innovants du MPM

(en développement)

Mesothelioma treatment: Are we on target?
A review

Birgitta I. Hiddinga *, Christian Rolfo, Jan P. van Meerbeeck



Journal of Advanced Research (2015) 6, 319–330

Why trying to target VEGF in MPM using anti-VEGF humanized monoclonal antibody (bevacizumab) ?

1. VEGF is not only the main endothelial growth factor (GF) but also an autocrine GF for malignant mesothelioma cells

2. MPM cells highly express VEGF and its receptors (VEGF-R)

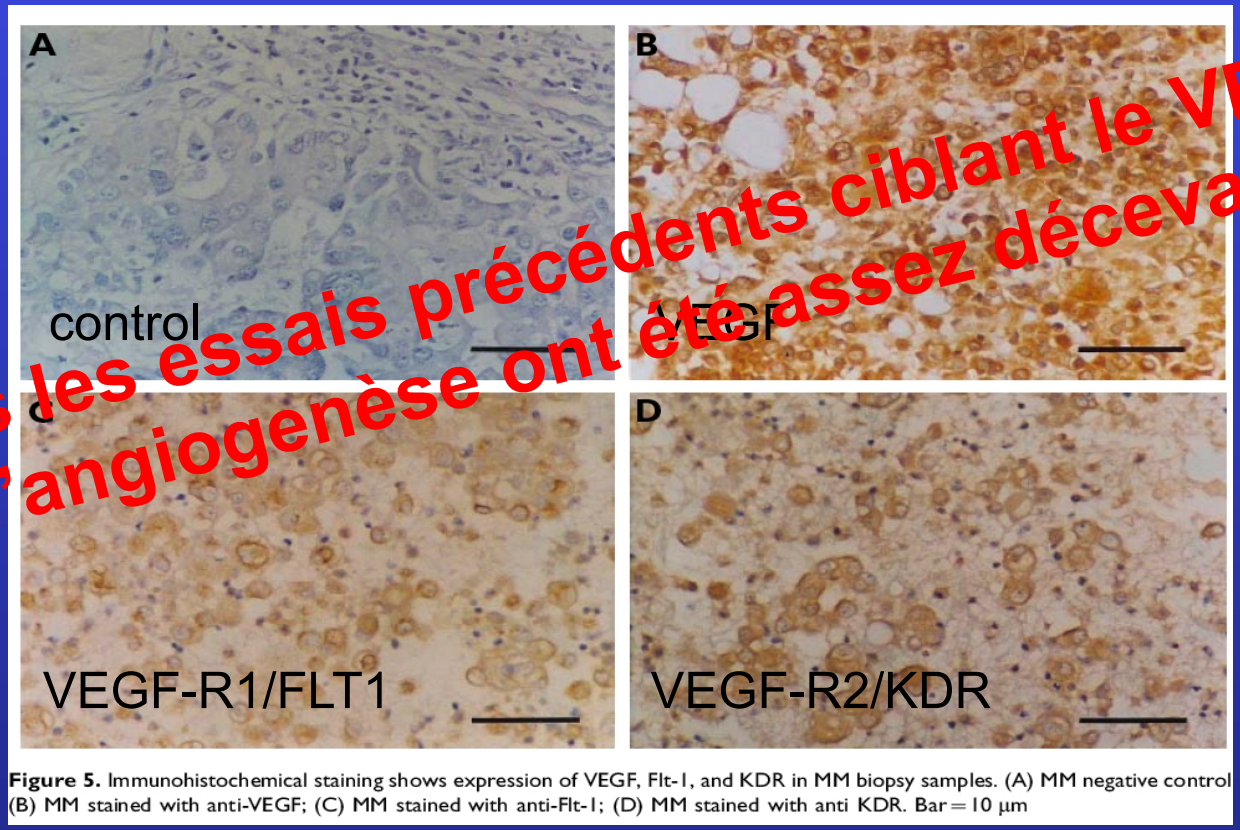


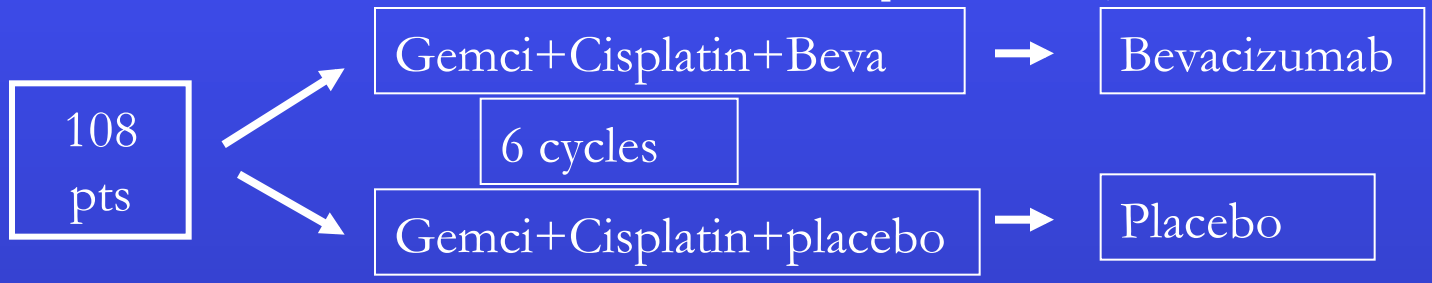
Figure 5. Immunohistochemical staining shows expression of VEGF, Flt-1, and KDR in MM biopsy samples. (A) MM negative control (B) MM stained with anti-VEGF; (C) MM stained with anti-Flt-1; (D) MM stained with anti KDR. Bar = 10 μm

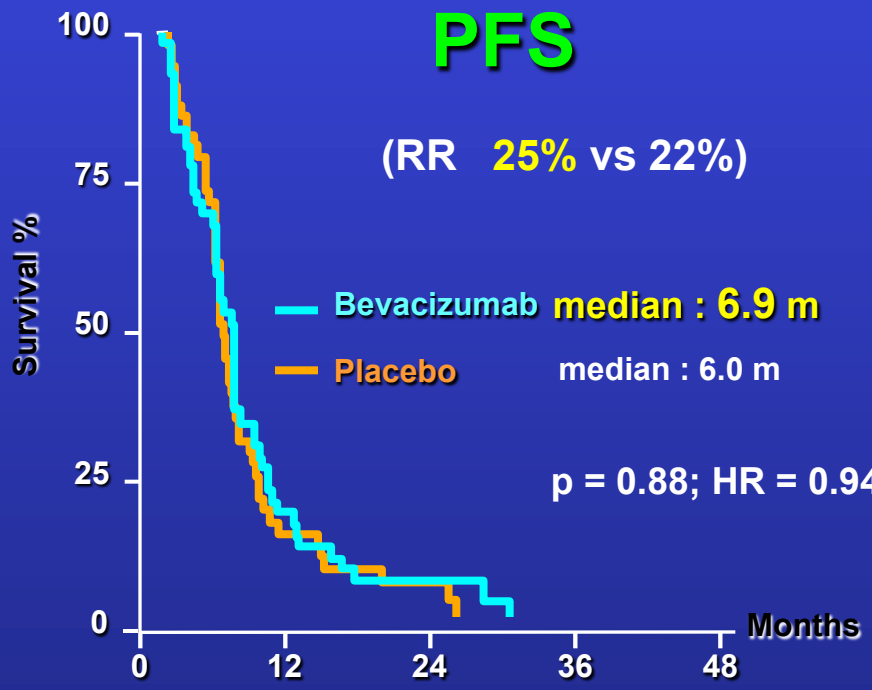
Mais les essais précédents ciblant le VEGF ou l'angiogenèse ont été assez décevants

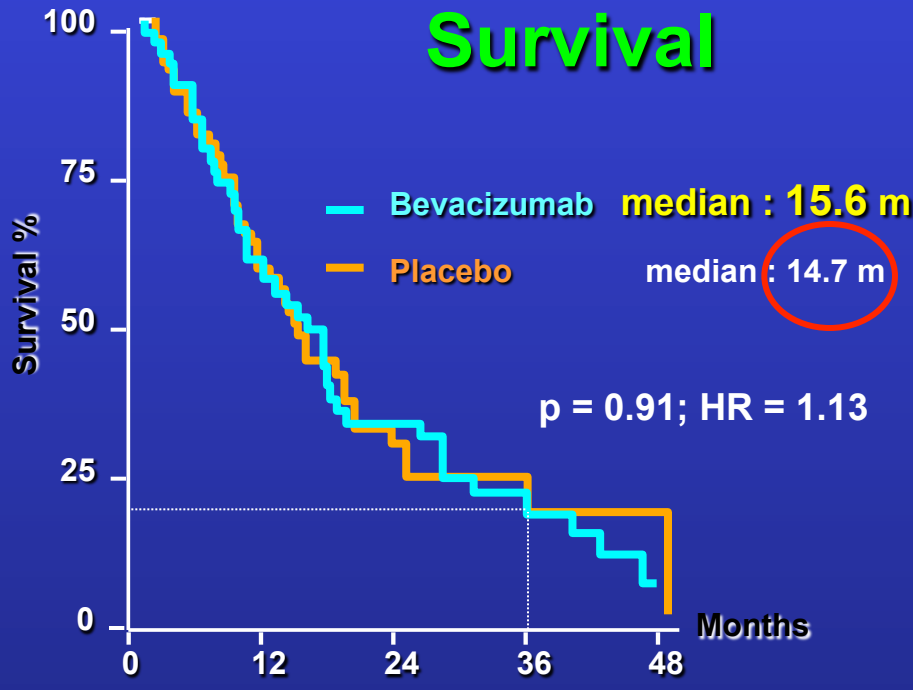
Strizzi L et al. J. Pathol. 2001; 193:468-7

Double-blind, Placebo-controlled Randomized Phase II trial of Bevacizumab in MM : tendances intéressantes mais pas d'amélioration significative de la PFS (obj principal) ou OS avec le Beva

[Kindler et al, WCLC 2007 and *J Clin Oncol* 2012]

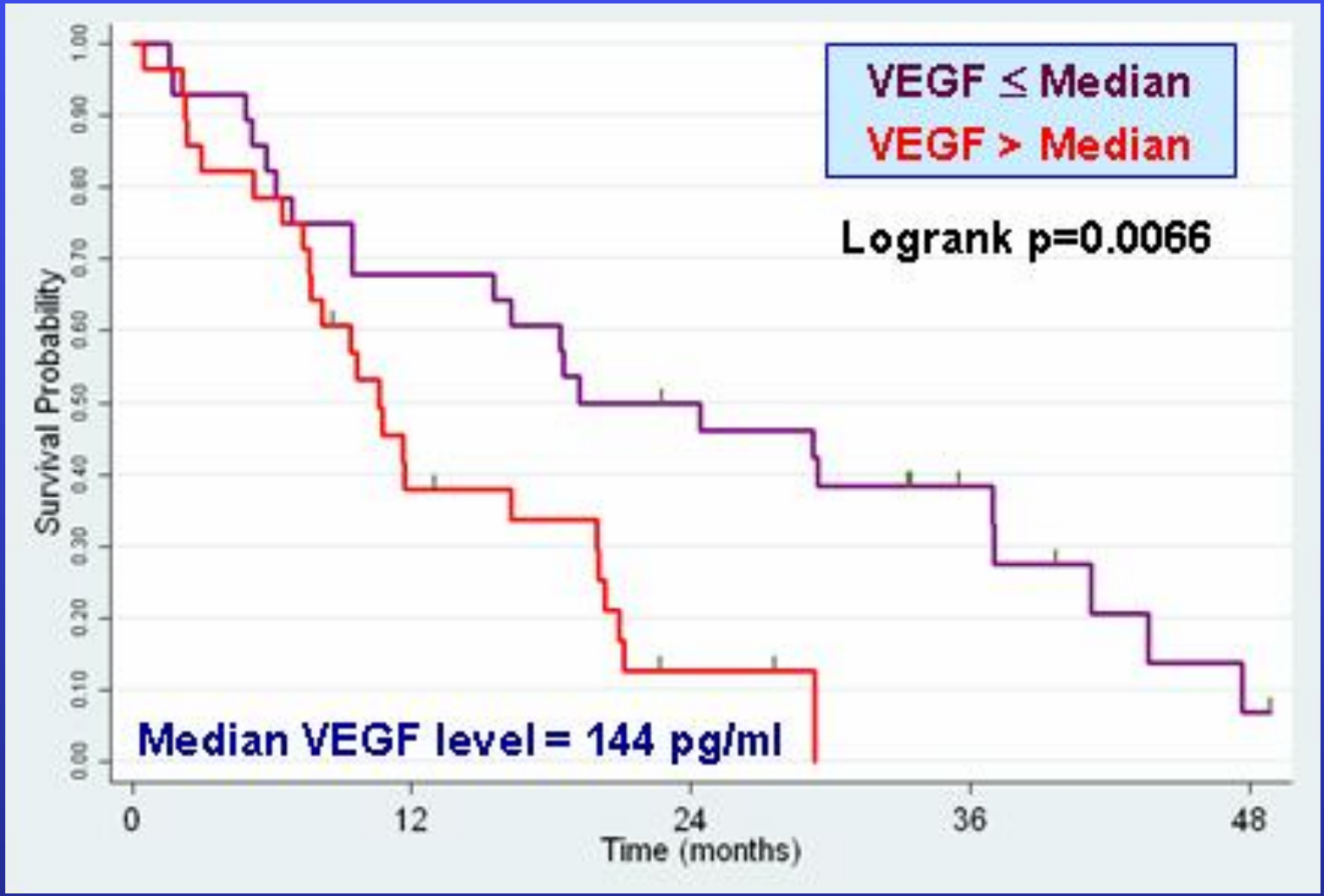






Survie : influence probable d'une 2ème ligne par Pémétrexed

Survie globale selon le taux sanguin initial de VEGF



Karrison JCO 2007 Abstract 7526

IFCT-GFPC-0701 trial: MAPS

IFCT-GFPC-0701 trial: MAPS

Mesothelioma Avastin-cisplatin Pemetrexed Study

biopsies (thoracoscopy...)

- Written informed consent

- PS 0 - 2
- Chemonaïve patients
- not candidate to curative intent surgery according to Multidisciplinary Board

not candidate to curative intent surgery according to Multidisciplinary Board

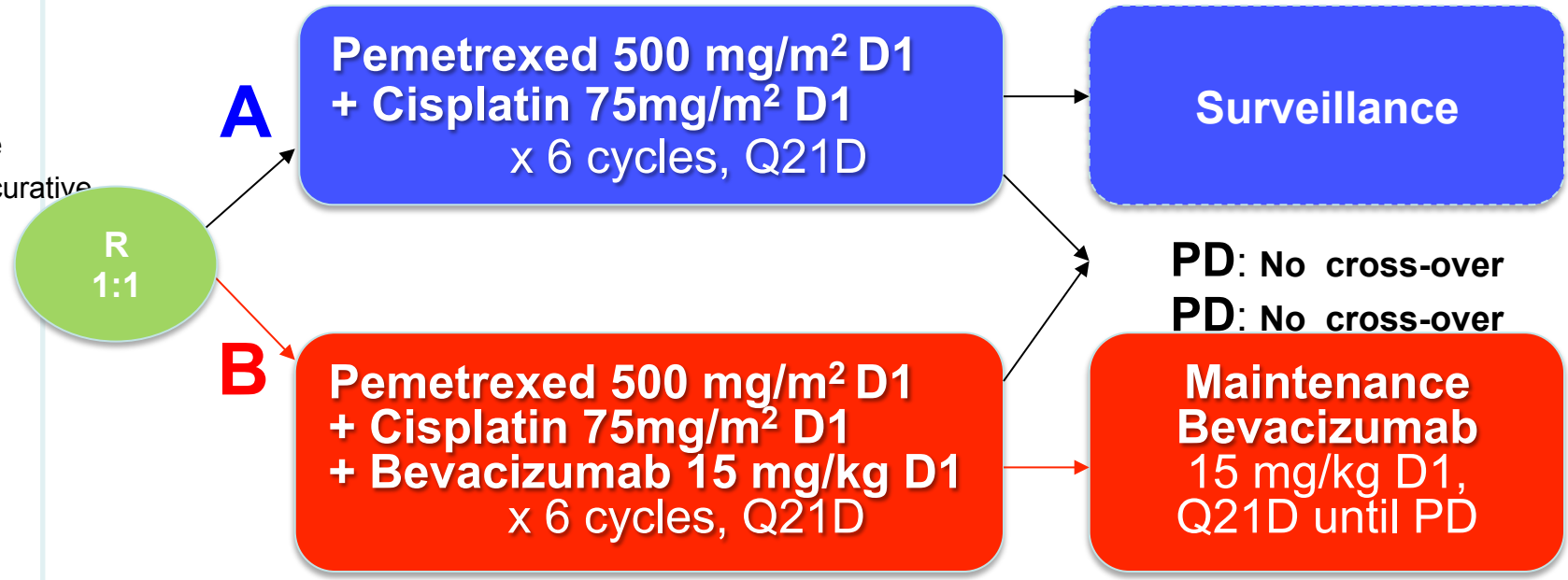
chemo or beva contra-indications

(HTA, GI perforation…)

(3 x 7 Gy) before chemo

Prophylactic radiotherapy

IFCT-sponsored, open-label, multi-centre randomized phase II-III trial (*bevacizumab*)



CT-scan Q 3 cycles in both arms; Response assessed with modified RECIST criteria for MPM

CT-scan Q 3 cycles in both arms; Response assessed with modified

➔ ***Phase 3 primary goal*** **= OS;** 2nd goals: PFS, QoL,

Stratification: *center, histology (epithelioid vs sarcomatoid/mixed), PS (0-1 vs 2), smoking status*

G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

Patient Disposition

Randomized
n = 448

From Feb. 2008 to Jan. 2014

Ineligible (*n=4*)
- No Consent (n=1)
- Previous cancer < 5 years (n=1)
- Final diagnosis = NSCLC, NOS (n=1)
- Previous ADK > 5 years (n=1)

Ineligible (*n=3*)
- Previous cancer < 5 years (n=1)
- Final diagnosis= NSCLC, NOS (n=1)
- Previous ADK> 5 years (n=1)

A	B
Allocated Pemetrexed plus Cisplatin *n = 225*	**Allocated Pemetrexed plus Cisplatin plus Bevacizumab** *n = 223*
Received treatment *n = 224* Including n=155 under surveillance	**Received treatment *n = 222*** Including *n=146 receiving Bevacizumab maintenance*
Did not received allocated treatment: Consent withdrawal (n=1)	Did not received allocated treatment: internal jugular veins Thrombosis (n=1)
Study withdrawn (n=217): **Disease Progression (*n=188*)**, **Toxicity (n=13)**, **Death (n=6)**, Other (n=10)	Study withdrawn (n=218): **Disease Progression (*n=137*)**, **Toxicity (n=47)**, **Death (n=5)**, **Patient's choice (n=1)**, **Protocol violation (n=1)**, Other (n=27)
Ongoing *n = 7*	Ongoing *n = 4*

Data cut-off: Jan 15, 2015

Patients baseline characteristics : 2 well-balanced arms

	Arm A (n=225)	Arm B (n=223)	Total (n=448)
Gender			
Male	170 (75.6%)	168 (75.3%)	338 (75.4%)
Female	55 (24.4%)	55 (24.7%)	110 (24.6%)
Age			
Mean +/- SD	64.7 +/- 7.7	65.2 +/- 6.6	65.0 +/- 7.2
Median	65.6	65.7	65.7
Range	[34.7 - 75.9]	[38.5 - 75.8]	[34.7 - 75.9]
Histology★			
Epithelioid	182 (80.9 %)	179 (80.3 %)	361 (80.6 %)
Sarcomatoid-Mixed	43 (19.1 %)	44 (19.7 %)	87 (19.4 %)
Performance Status★			
0-1	217 (96.4)	216 (96.9)	433 (96.7)
2	8 (3.6)	7 (3.1)	15 (3.3)
Smoking status★			
Smoker	127 (56.4)	124 (55.6)	251 (56.0)
Never Smoker	98 (43,6)	99 (44,4)	197 (44.0)

★ blue: stratification variables

G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

Toxicity

Patients with maximal grade 3-4 toxicity

	Arm A (PC) (n=224)	Arm B (PCB) (n=222)	p-value
No	85 (37.9%)	64 (40.4%)	0. 04
Yes	**139** (62.1%)	**158** (71.2%)	

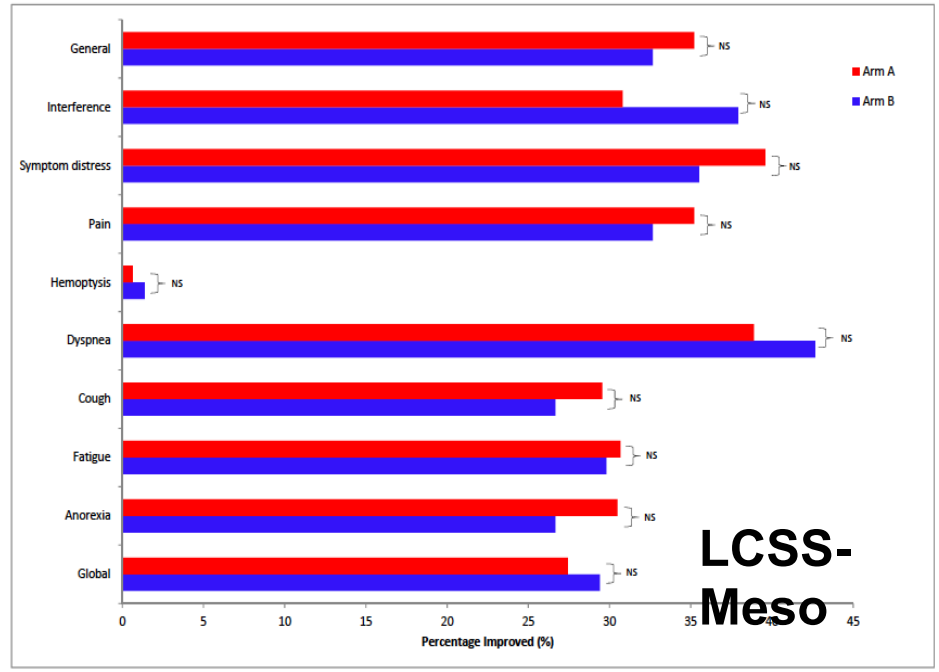
- Almost no significant difference between arms for hematological toxicities
  (except more anemia in PC arm vs PCB)

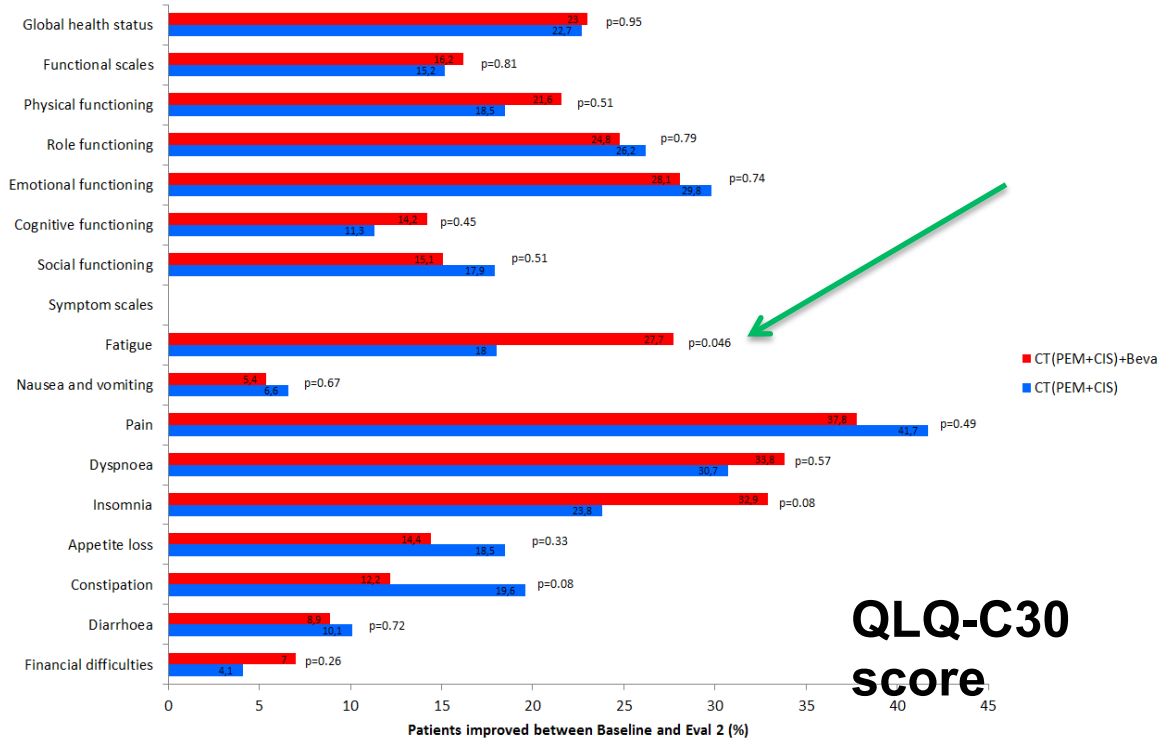
- Non-hematological toxicities: some significant differences with more hypertension, arterial and venous thrombo-embolic events, and (low grade) hemorrhage in PCB arm vs PC

G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

Quality of Life (QoL)

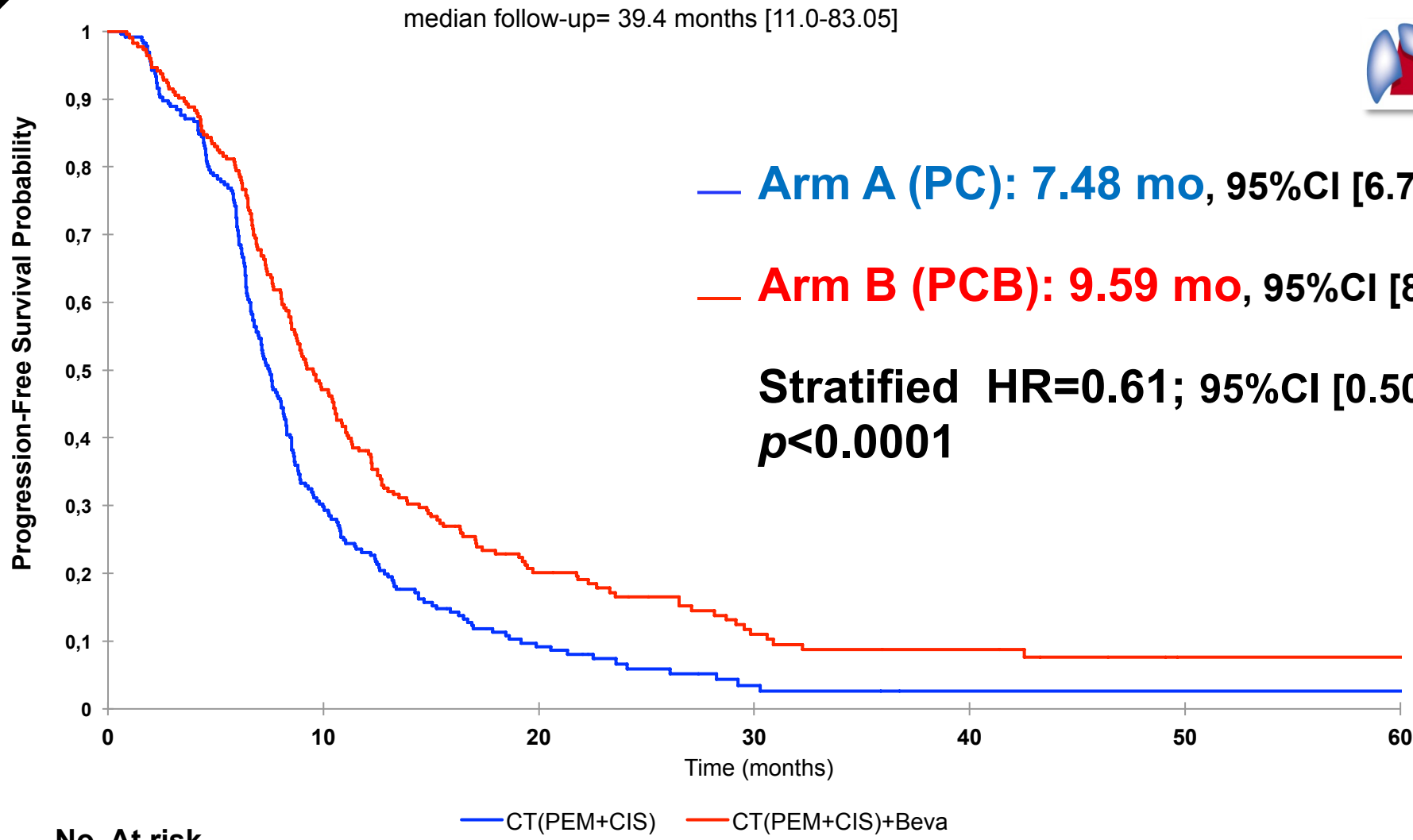
- At baseline, the QoL items measured were balanced
- QoL in terms of individual symptoms was **generally stable or improved** throughout treatment in both arms, with no significant difference between arms
- Patients receiving **PCB** had **significantly greater improvement** in **fatigue score** (p=0.046) vs **PC**, but the other QLQ-C30 items did not differ according to the treatment arm





G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

Efficacy: ITT median Progression-free Survival (PFS)



Arm A (PC): 7.48 mo, 95%CI [6.79-8.13]

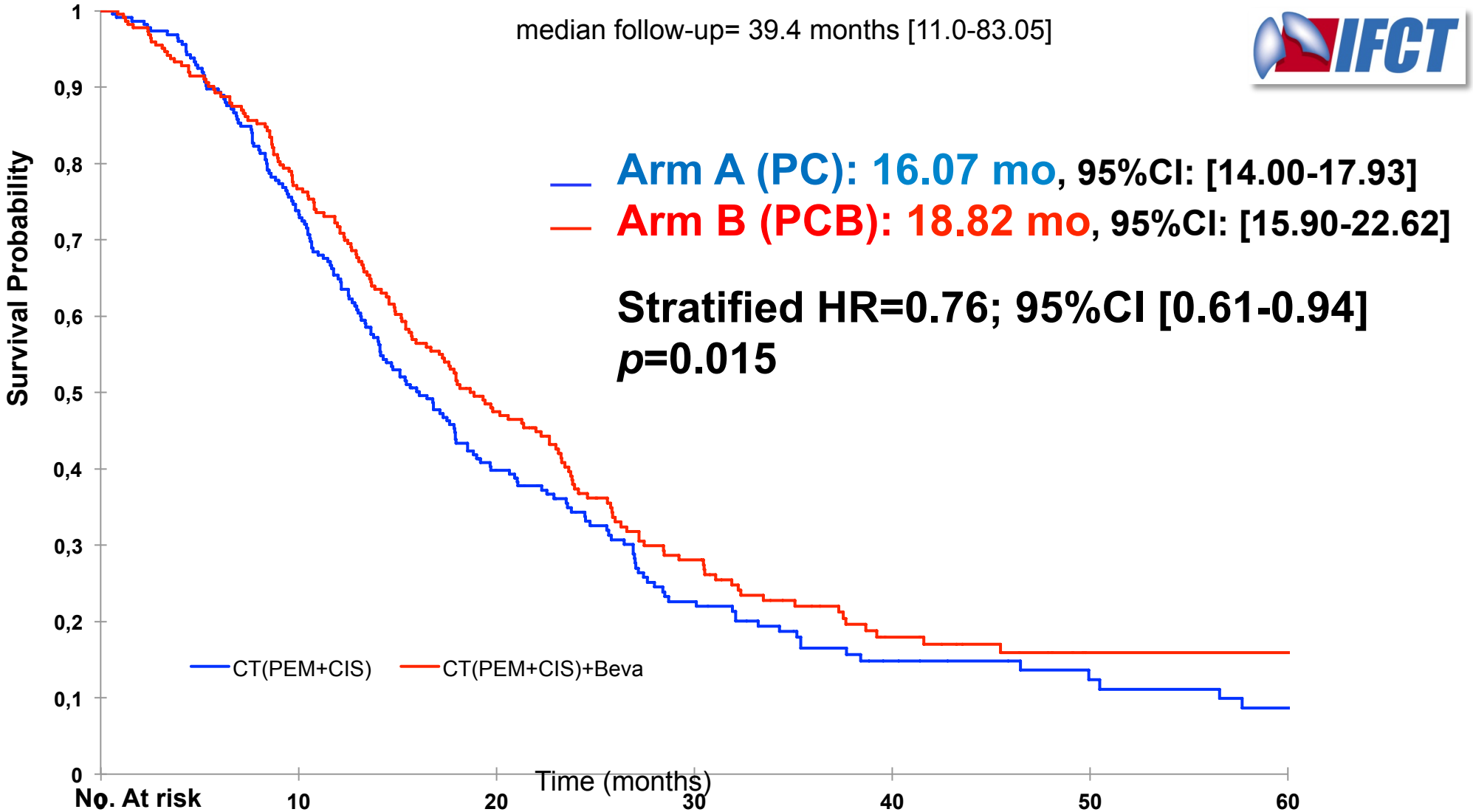
Arm B (PCB): 9.59 mo, 95%CI [8.49-10.59]

Stratified HR=0.61; 95%CI [0.50-0.75]
***p*<0.0001**

IFCT 0701 'MAPS' randomized phase 3 trial

G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

Efficacy: ITT median Overall Survival (OS)



Arm A (PC): 16.07 mo, 95%CI: [14.00-17.93]

Arm B (PCB): 18.82 mo, 95%CI: [15.90-22.62]

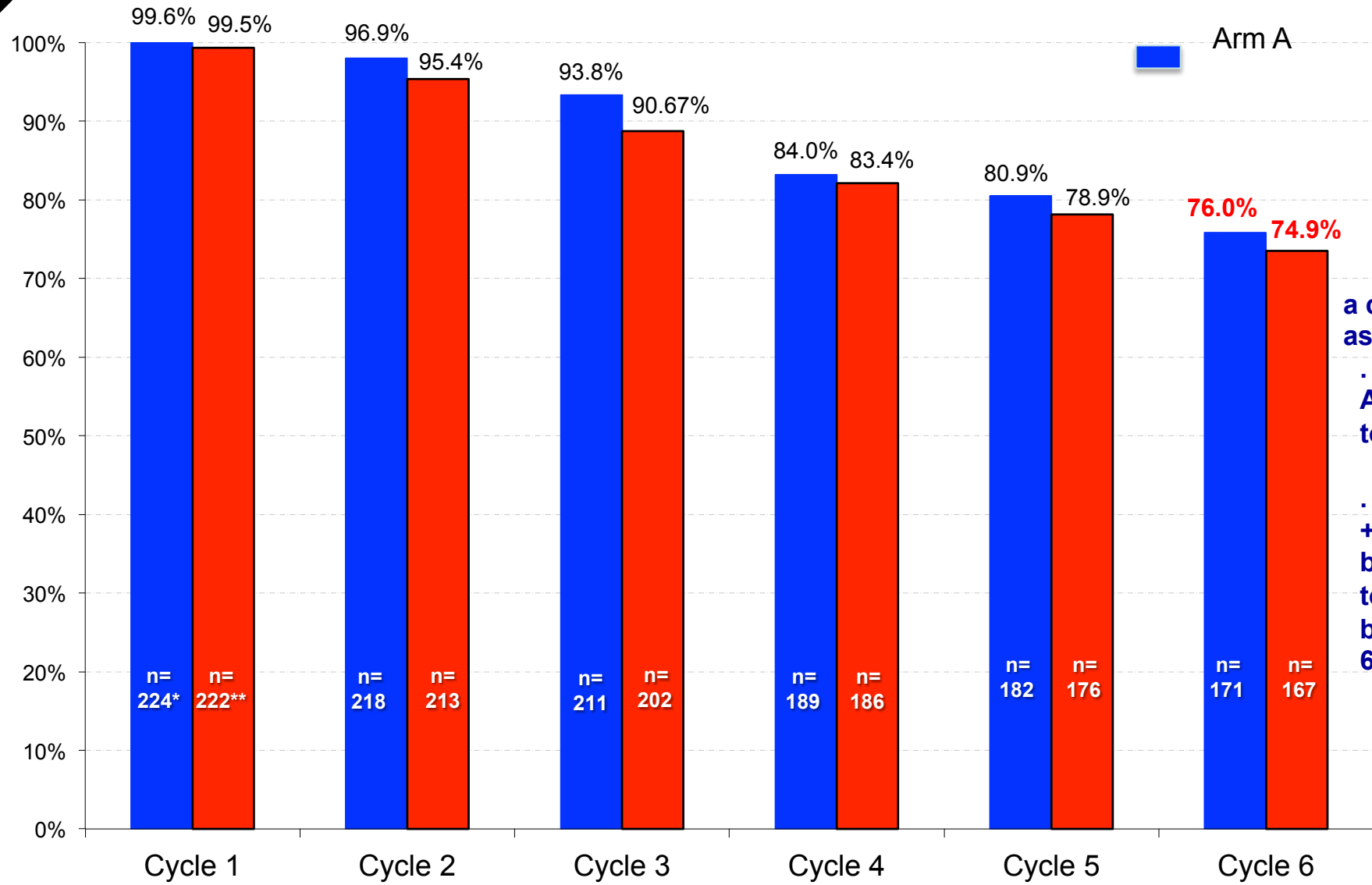
Stratified HR=0.76; 95%CI [0.61-0.94]

***p*=0.015**

G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

Drug Delivery

Proportion of delivered cycles (n=448 ; Arm A=225 – Arm B = 223)



a cycle was considered as completed if:

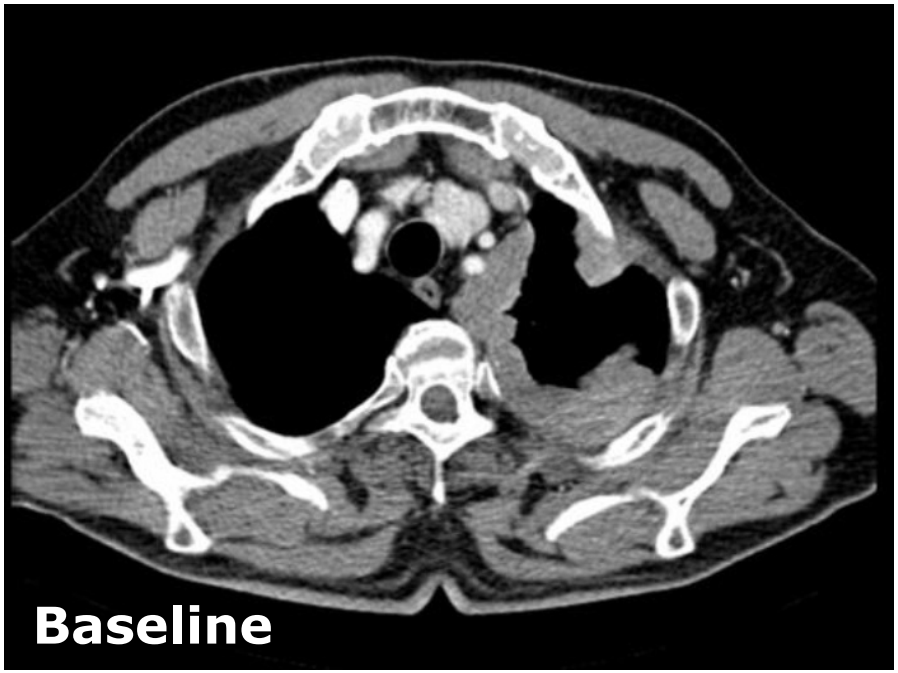
. Arm A : pemetrexed AND platinum cycle 1 to 6

. Arm B : pemetrexed + platinum + bevacizumab, cycle 1 to 5 and at least bevacizumab at cycle 6

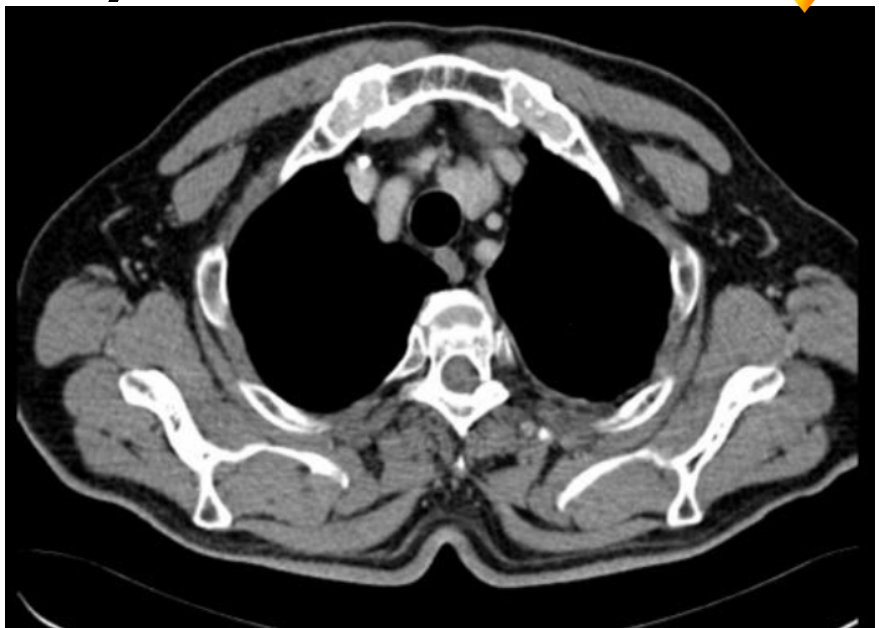
***Patient 7701 (arm A): Ineligible**
****Patient 05604 (arm B): no treatment since jugular vena thrombosis on D1,**

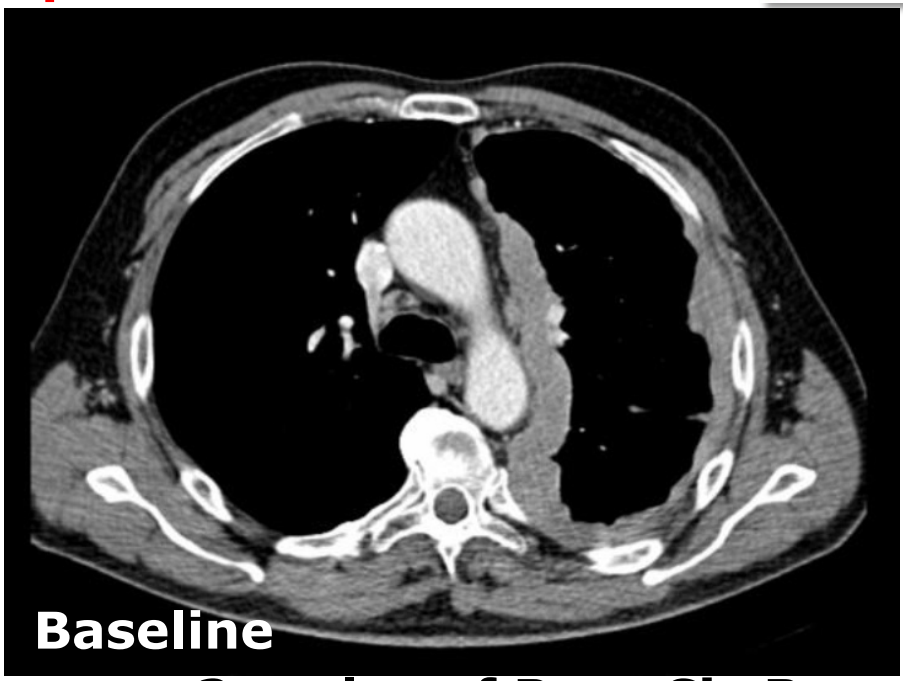
G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

Some Major Stricking Responses observed



2 cycles of Pem-Cis Beva





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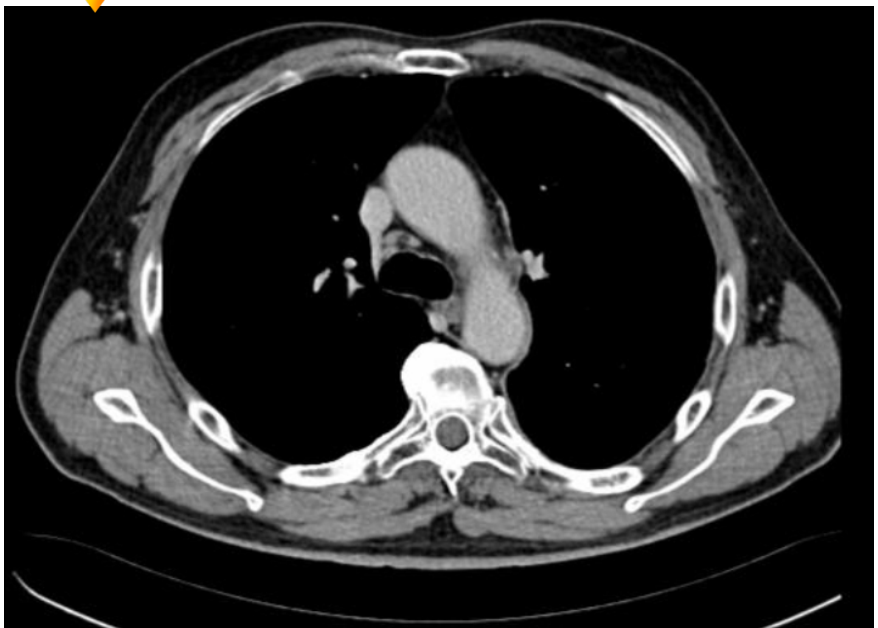


Systemic post-discontinuation therapy

	Arm A N=210	Arm B N=208	p-value
Second-line systemic therapy	**152 (72.4%)**	**129 (62.0%)**	**0.02**
pemetrexed	79	65	
gemcitabine	44	33	
Carboplatine/Oxali	66	40	
cisplatine	15	21	
bevacizumab	**0**	11*	
Other treatments (phase I)	24	21	

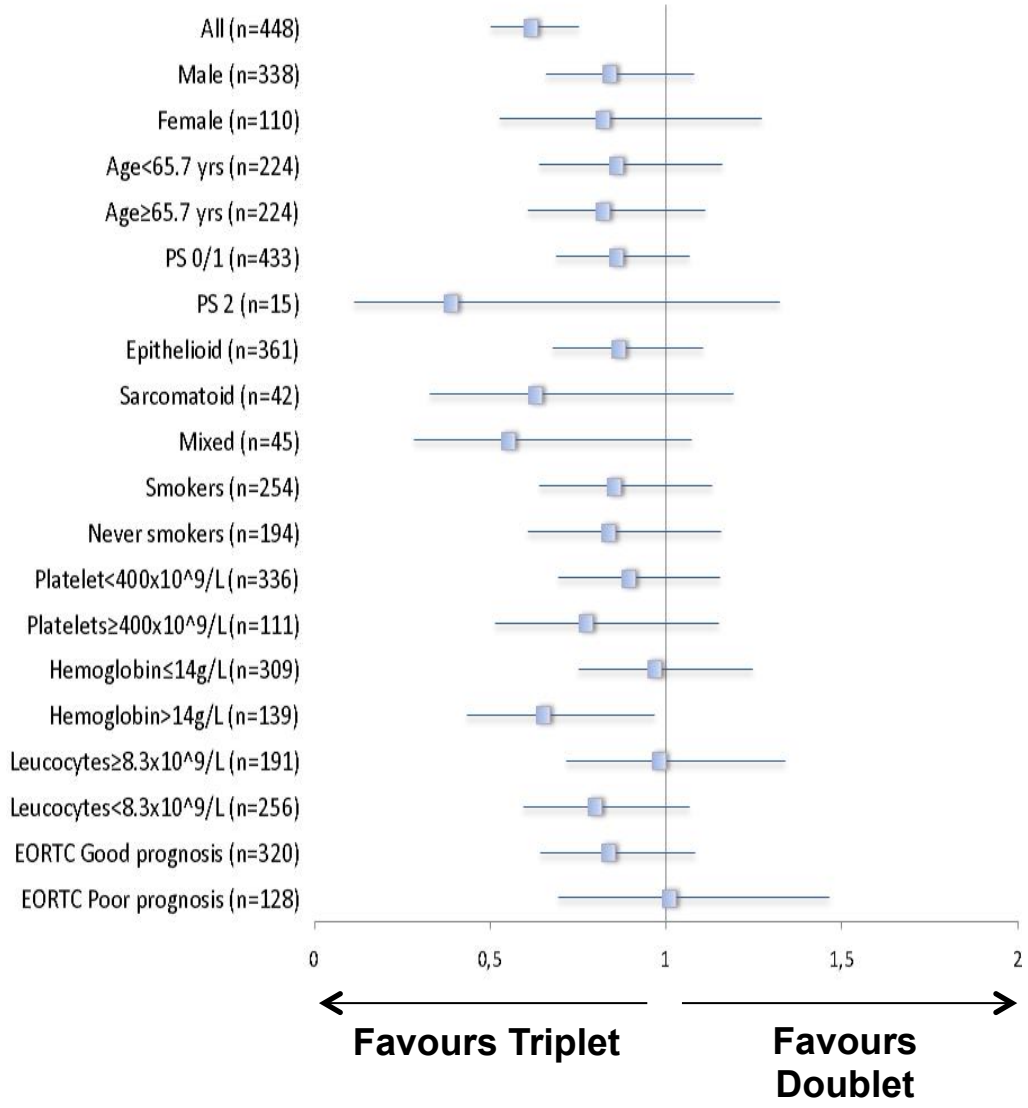
* off-label, off protocol

IFCT 0701 'MAPS' randomized phase 3 trial

G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

MAPS trial: predictive factors

Forest Plot *(OS, Univariate)*



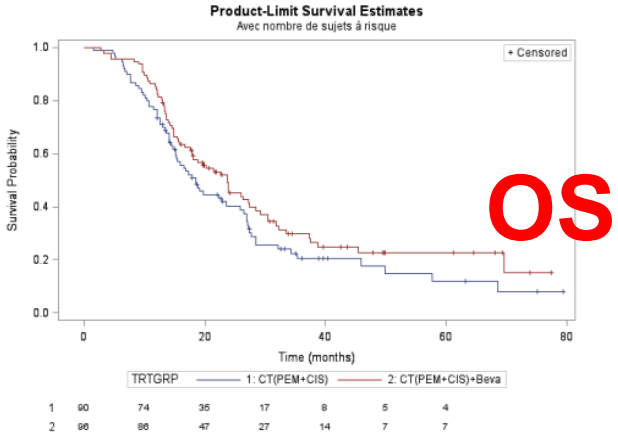
G Zalcman et al, *ASCO* 2015; Scherpereel et al, *WCLC* 2015

Blood VEGF level as a potential biomarker ?

*Serum VEGF level assessed in **372**/448 pts (83%) as continuous value or /median value=374 pg/ml*

VEGF<median

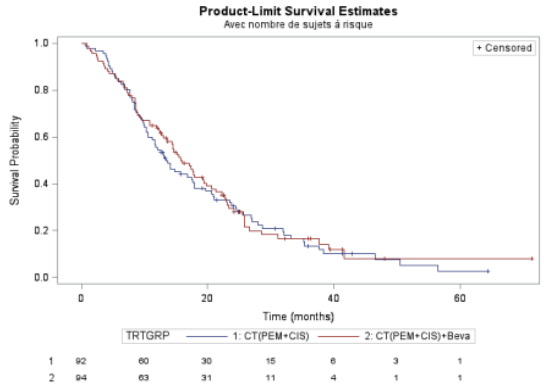
VEGF<median
HR=0.77 [0.55-1.08] $p = 0.13$
mOS (Arm A)= 18.5 [15.1-25.8]
mOS (Arm B)= 23.7 [18.0-28.4]



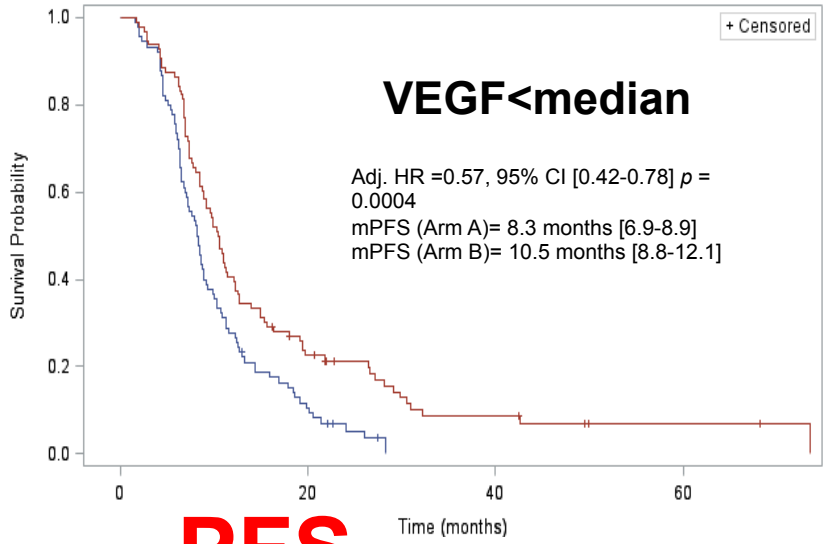
OS

VEGF≥median

VEGF≥median
HR =0.94 [0.68-1.29] $p = 0.69$
mOS (Arm A)= 13.4 [10.6-17.9]
mOS (Arm B)= 15.7 [12.6-19.8]

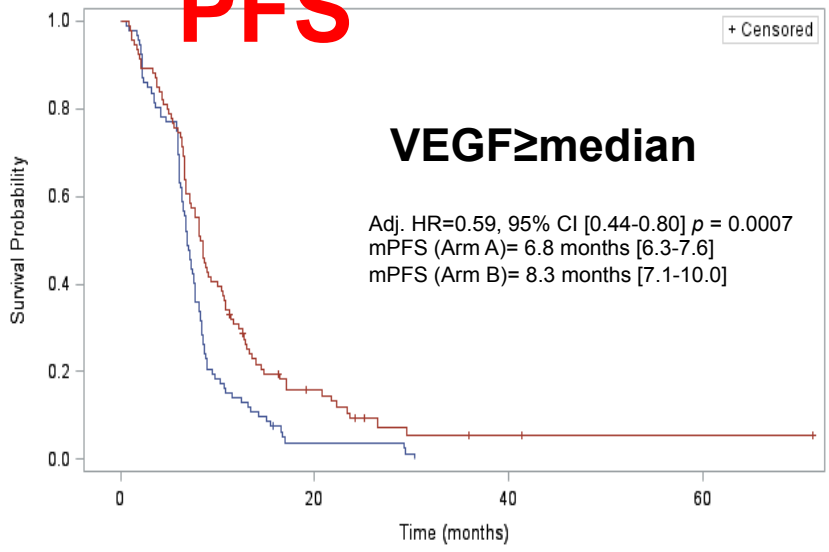


VEGF<median



PFS

VEGF≥median



- Similarly to H. Kindler and al findings on 56 patients (*JCO* 2012), **higher serum VEGF levels** before treatment were associated with **poorer survival in both arms (OS / PFS)** in the MAPS trial

Scherpereel et al, *WCLC* 2015

Blood VEGF level as a potential biomarker ?

MAPS trial

*Serum VEGF level assessed in **372**/448 pts (83%) as continuous value or /median value=374 pg/ml*

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HR=0.77 [0.55-1.08] $p = 0.13$
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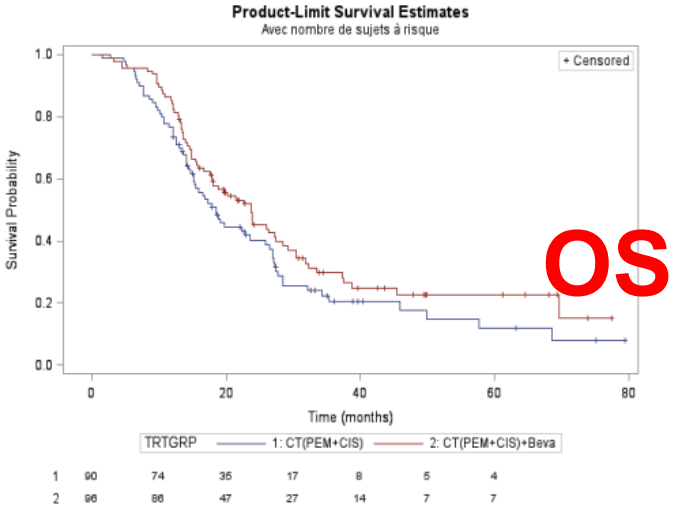

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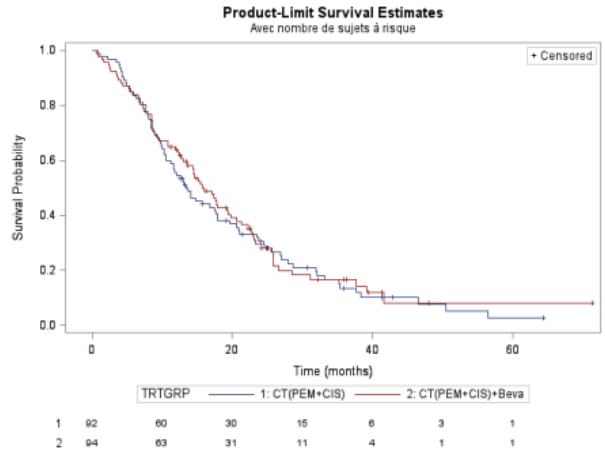


- However, **VEGF did not predict bevacizumab efficacy** in MPM
  ... even if only patients with lower baseline VEGF levels derived a longer OS with PCB versus PC (HR 0.69; p=0.035)
- Further results awaited from the large ongoing study **("BioMAPS")** on other soluble (mesothelin, endocan...) and tissue markers

Scherpereel et al, *WCLC* 2015

- L'association du bevacizumab au pémétrexed–cisplatine augmente significativement la **PFS (de 2 mois)** **ET** l'**OS (de 2,75 mois)** avec seulement une **augmentation faible et manageable de la toxicité**
- De plus, le bevacizumab n'avait pas d'effet délétère sur la **QoL**, malgré sa toxicité élevée **spécifique**
- Pas de différence significative entre les bras pour le % drogue délivrance ou le % de 2ème ligne traitement
- Dans cet essai, les patients du bras standard (P+C) avaient une survie globale (OS) > aux patients des séries historiques ou des essais antérieurs : rôle des critères d'éligibilité pour le bevacizumab? Talcage pleural?... *mais ceci était vrai pour les 2 bras et malgré cela, le bras bevacizumab restait le meilleur !*
- Pas de **marqueur prédictif clinique/biologique** identifié à ce jour (étude en cours)

=> Le triplet pémétrexed+cisplatine+bevacizumab est un nouveau paradigme de traitement pour les patients MPM éligibles pour le beva, non candidats à une chirurgie "curative" → nouveau SOC ?

Voies de signalisation cellulaire / Apoptose

- Un MPM peut être induit chez la souris KO en inhibant l'expression des gènes suivants :
  - **P53**
  - **P16 ^{INK4A}**: encodé par CDKN2A, dont la perte peut aussi induire un MPM, qui inhibe CDK4 : cible thérapeutique par les **CDK4 inhibiteurs**; *essai en cours (UK)*
  - **NF2 ⇒ *Focal Adhesion Kinase* (FAK) inhibiteurs;** *essai COMMAND*

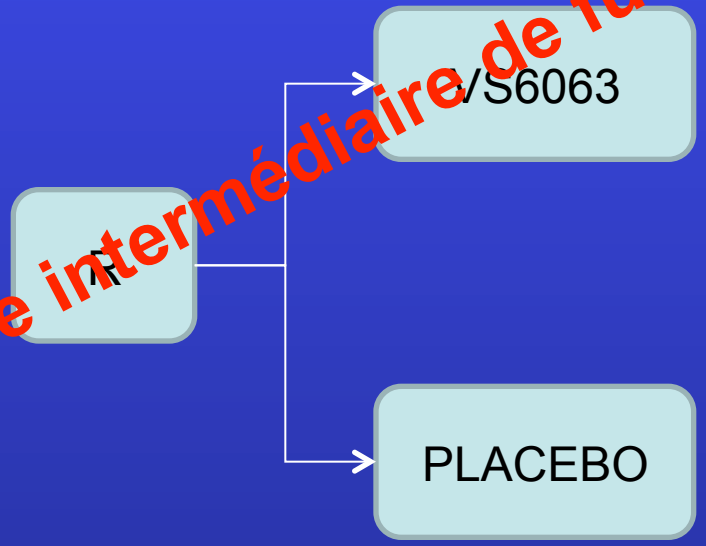
- Apoptose restaurable, *in vitro* et *in vivo,* dans les cellules de MPM par les **HDAC inhibiteurs, seuls ou combinés avec des inhibiteurs de la méthylation (ttt épigénétiques et/ou CT); inhibiteurs du protéasome aussi (bortezomib)** *essai en cours*

Vandermeers F et al, *Clin Can Res* 2009; Leclercq S et al, *Eur Respir J*. 2011

The COMMAND trial

A randomised phase II trial of maintenance by VS6063 (FAK inhibitor) versus placebo after standard first line chemotherapy

Histologically confirmed MPM
4-6 cycles of pemetrexed/platinum
Disease control post chemotherapy



PFS/OS
Merlin

Essai stoppé après analyse intermédiaire de futilité fin 2015 !

Study initiated September 2013
Oral administration 2 x 400 mg daily
(PI France : A Scherpereel)

Courtesy, Pr Dean Fennel

Marqueurs du MPM et autres cibles tumorales potentielles

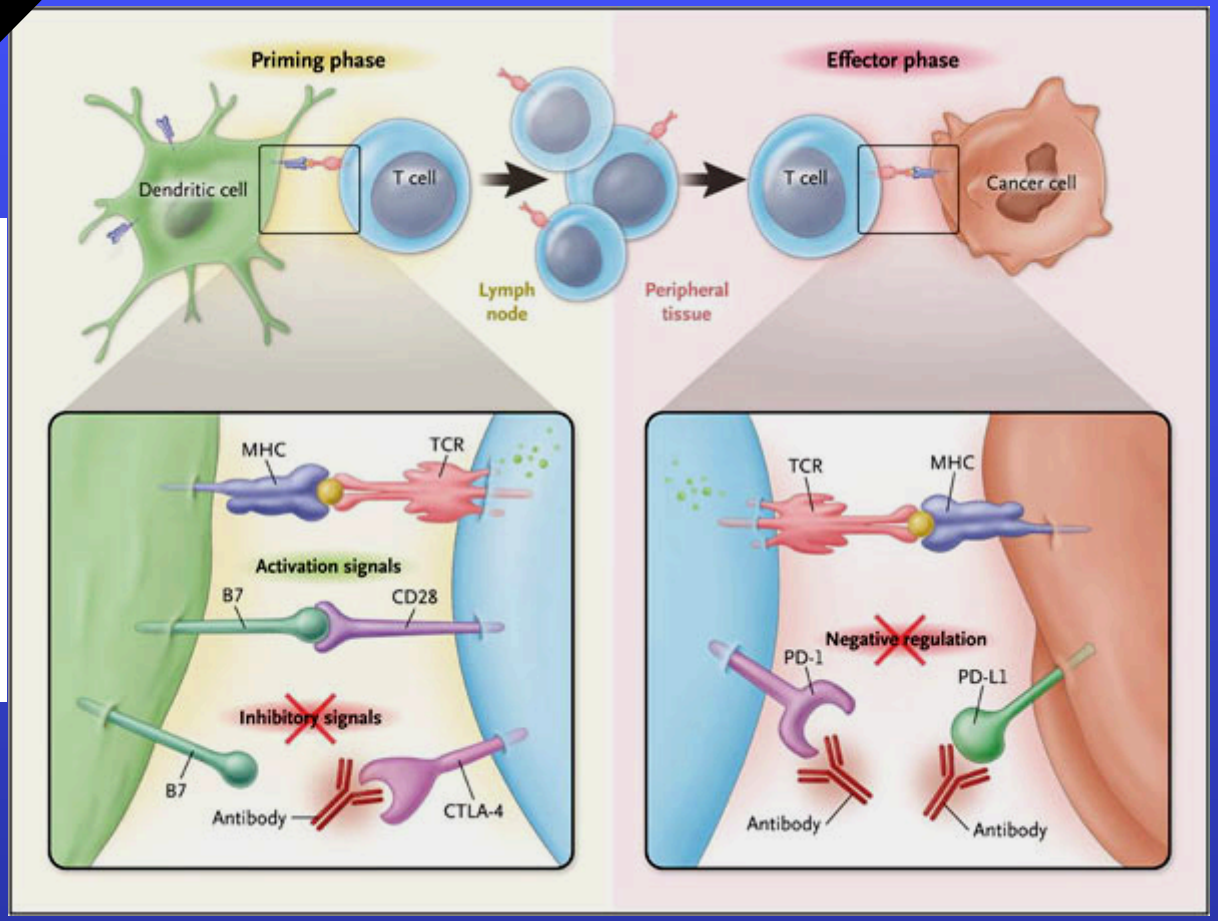
- Epithelial growth factor receptor (**EGFR**): *negative trials*
- **PDGF/PDGFR**: no success so far, *ongoing (Phase I - MD Anderson)*
- Downstream proteins within the EGFR signaling pathway, such as **PI3K and AKT**, are utilized by other tyrosine kinase receptor growth factor pathways, including the **c-MET receptor** and **IGF-1R** pathways: *ongoing*
- **PI3K/AKT/mTOR pathway**: *ongoing*
- **Inhibition of HSP90:** induces mitochondrial apoptosis : *ongoing trial (CR-UK MESO2)*

[Review by Astoul et al, *Respiration* 2012]

Marqueurs du MPM et autres cibles tumorales potentielles - Immunothérapie

- Cyclo-oxygenase 2 (**COX2**), over-expressed in 59–100% of MPM tumor samples (IHC): *ongoing trials with* **COX2 inhibitors**
- **Anti-CTLA-4 Ab**, stimulating the T cell immune response : *ongoing*
- **Anti-PD-1/PD-L1 Ab**, stimulating the T cell immune response : *ongoing*
- **Measles Virus Vaccine** : *ongoing phase 1 trial – Mayo Clinic (USA)*
- **Mesothelin**: immunotoxin SS1P: promising results from R Hassan et al *(WCLC 2013 and Sci Transl Med. 2013)*

Immune Checkpoint Inhibitors



Ribas et al NEJM 2012

- **mAb** stimulating the T cell immune response
- mAb active in different tumor types, inducing **durable clinical benefit** (even after initial PD); **potential late response**
- treatment commonly associated with **novel autoinflammatory side effects (irAEs)** resulting directly from its mechanism of action

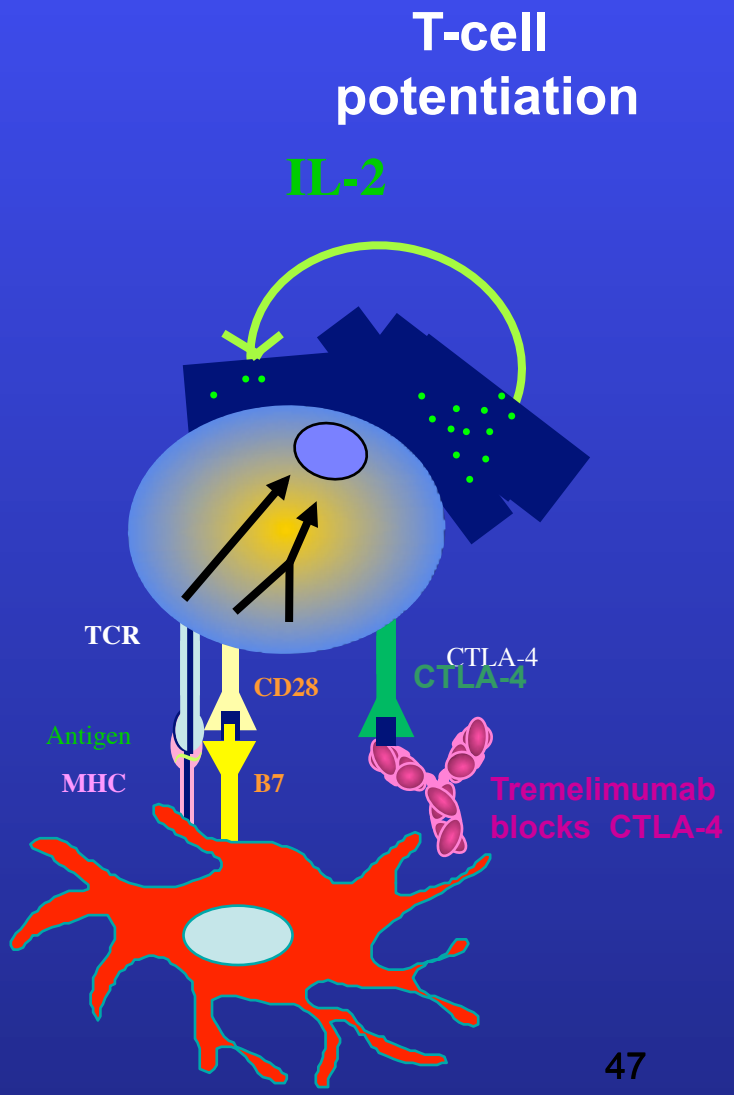
Ongoing phase I and II trials:

- **Anti-CTLA-4** (Ipilumimab, Tremelimumab)
- **Anti-PD-1** (Pembrolizumab, Nivolumab…) and **anti-PD-L1** (Medi-4736; BMS-936559…): *better if PD-L1+ tumor ? combination with anti-CTLA-4…?*

Anti-CTLA-4 Monoclonal Antibody

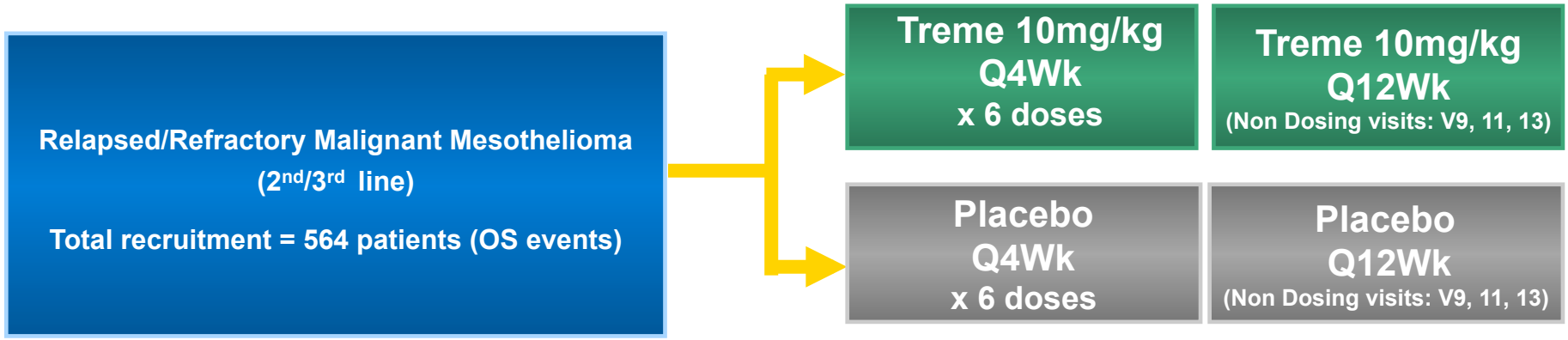
Tremelimumab is a fully human anti-CTLA-4 mAb that potentiates the anti-tumor immunity

- **Anti-CTLA-4 vs placebo in 2nd or 3rd line MPM patients (after Platinum/Pem failure):** ph II single arm **clinical trial**
- promising trends → to be confirmed by a randomized trial ended



Kindler HL, *WCLC* 2013
Calabrò L and al, *Lancet Respir Med* 2015)

Ph.2b Double-Blinded Randomized trial “Determine”



- **Primary endpoint is Overall Survival (OS)**
- **Randomized TREME: PLACEBO 2:1 (376/188)**
- **Stratification Factors**
  - European Organization for Research and Treatment of Cancer (EORTC) status (low-risk vs high-risk)
  - Line of therapy (second vs third)
  - Anatomical site (pleural vs peritoneal)
- **2 Interim Analysis**
  - **1st IA: 128 OS events from the first 180 subjects, expected to be reached after approximately 12 months of accrual and 11 months of follow-up.**
  - **2nd IA: 342 OS events for the second interim analysis are expected to be reached after approximately 32 months of accrual of all 564 subjects.**
  - **The IDMC will review the unblinded interim data and inform the sponsor whether the study has crossed interim boundaries**
- **Primary Analysis:**
  - **of OS performed after 456 events (Deaths) from the all 564 randomized subjects**
  - **90% power , HR 0.71 (m OS 7 vs 9.3)**

Recrutement de l’essai terminé en 2015: résultats attendus...

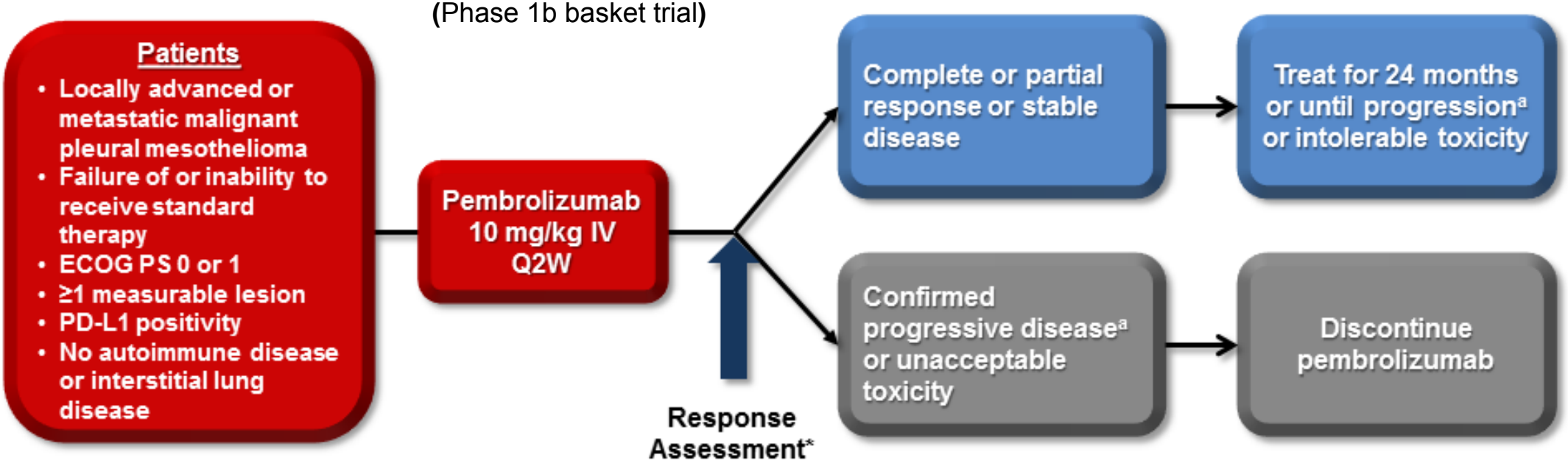
Rationale for targeting PD-1/PD-L1 in MPM

- T-cell inflamed phenotype and PD-L1 expression found in MPM (Mansfield and al, *JTO* 2014)
- PD-L1 expression associated with poor prognosis in mesothelioma: (Cedrés and al, *PLoS One* 2015)
  - Median OS: 5.0 months for PD-L1+ vs 14.5 months for PD-L1-
  - PD-L1 positivity is an independent risk factor for OS: RR 1.71
- Anti-tumor activity of anti-PD-1/anti-PD-L1 demonstrated in other tumors: malignant melanoma, NSCLC…

49

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors

(Phase 1b basket trial)



***Response assessment**: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety

Secondary end points: PFS, OS, duration of response

[a]If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later.

E. Alley
Presented September 7, 2015 at WCLC.

(E Alley and al, *AACR* 2015 and *WCLC* 2015)

Baseline Characteristics

Characteristic, n (%)	N = 25
Median age, years (range)	65.0 (32–86)
Male	17 (68.0)
Race	
White	21 (84.0)
Asian	2 (8.0)
Not specified	2 (8.0)
ECOG performance status	
0	9 (36.0)
1	16 (64.0)

Characteristic, n (%)	N = 25
Histology	
Epithelioid	18 (72.0)
Sarcomatoid	2 (8.0)
Biphasic	2 (8.0)
Not specified	3 (12.0)
Prior therapies[a]	
Cisplatin/carboplatin	22 (88.0)
Pemetrexed	21 (84.0)
Gemcitabine	4 (16)
Vinorelbine	1 (4)

[a]Patients could have received ≥1 type of prior therapy.
Data cutoff date: June 24, 2015.

E. Alley
Presented September 7, 2015 at WCLC.

→ **Mostly 2nde line pts, epithelioïd subtype, and all PDL-1+ tumors**

Treatment-Related Adverse Events

Any Grade, Occurring in ≥2 Patients	N = 25 n (%)
Any	15 (60.0)
Fatigue	6 (24.0)
Nausea	6 (24.0)
Arthralgia	5 (20.0)
Pruritus	4 (16.0)
Dry mouth	3 (12.0)
Diarrhea	2 (8.0)
Headache	2 (8.0)
Pyrexia	2 (8.0)
Rash maculopapular	2 (8.0)

Grade 3-4, Occurring in ≥1 Patient	N = 25 n (%)
Any	4 (16.0)
ALT increased	1 (4.0)
Thrombocytopenia	1 (4.0)
Iridocyclitis (uveitis)	1 (4.0)
Pyrexia	1 (4.0)
AEs of Interest Based on Immune Etiology Ocurring in ≥1 Patient	**N = 25 n (%)**
Erythema multiforme[a] (grade 1)	1 (4.0)
Iridocyclitis (uveitis)[a] (grade 3)	1 (4.0)

- Median follow-up duration: 11.5 mo (range, 1.4-13.1)
- No treatment-related deaths

[a]Occurred in the same patient.
Data cutoff date: June 24, 2015.

E. Alley
Presented September 7, 2015 at WCLC.

→ **Well tolerated treatment…**

Antitumor Activity
(RECIST v1.1, Investigator Review)

Best Overall Response	n	%	95% CI
Complete response[a]	0	0	0.0–13.7
Partial response[a]	7	28.0	12.1–49.4
Stable disease	12	48.0	27.8–68.7
Progressive disease	4	16.0	4.5–36.1
No assessment[b]	2	8.0	1.0–26.0

Objective response rate[a]: 28.0% (95% CI, 12.1–49.4)

Disease control rate[a]: 76.0% (95% CI, 54.9–90.6)

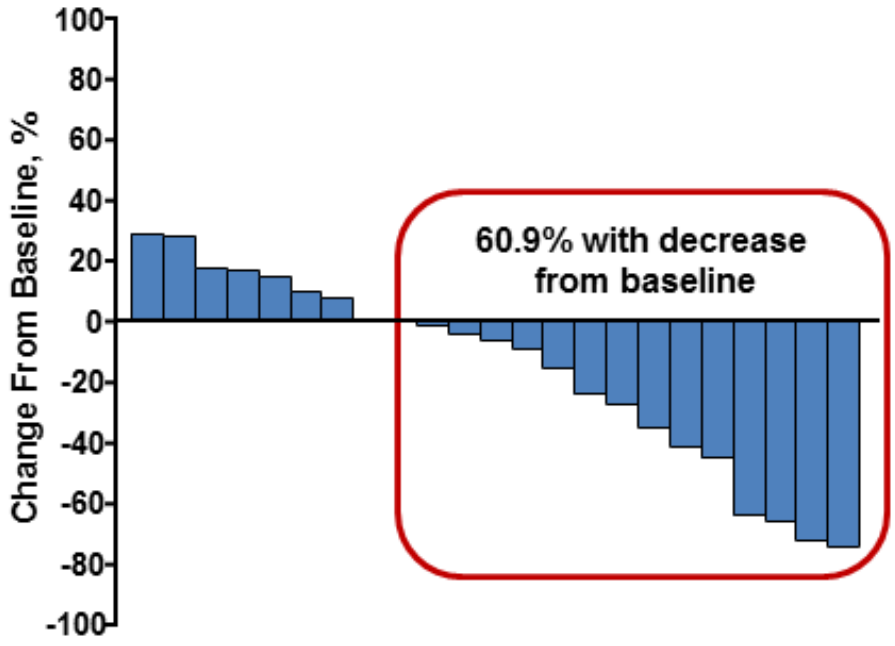
[a]Both confirmed and unconfirmed responses are included.
[b]Includes patients who discontinued therapy before the first post-treatment scan due to progressive disease.
Data cutoff date: June 24, 2015.

E. Alley
Presented September 7, 2015 at WCLC.

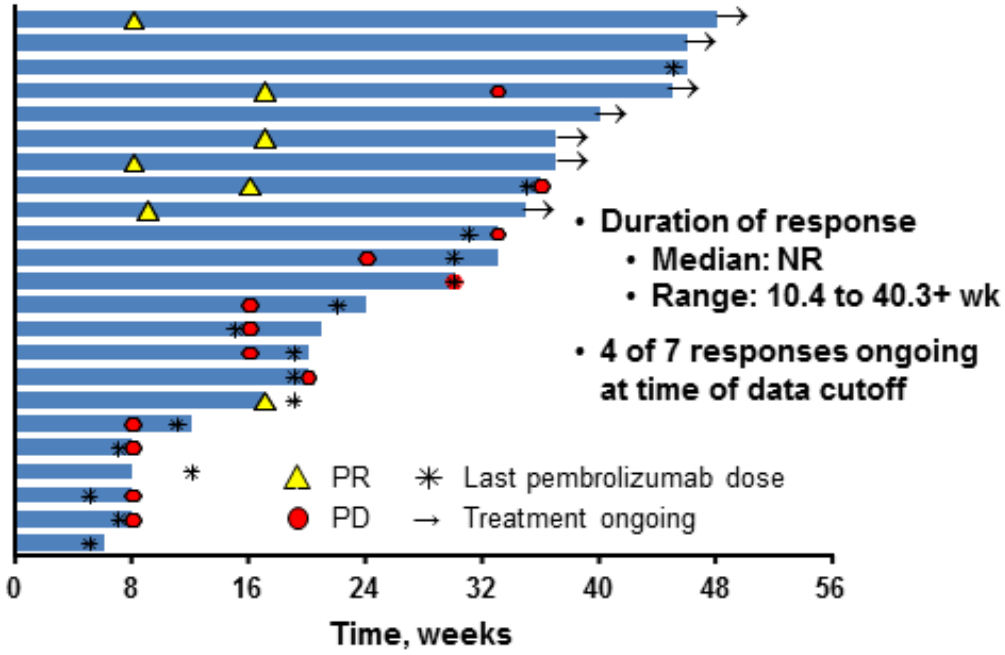
→ …and impressive results: ORR 28% - DCR 76% !!!

Antitumor Activity
(RECIST v1.1, Investigator Review)

Change From Baseline in Tumor Size



Treatment Exposure and Response Duration[a]



[a]Bar length is equivalent to the time to the last imaging assessment. Includes patients with ≥1 postbaseline tumor assessment (n = 23). Data cutoff date: June 24, 2015.

E. Alley
Presented September 7, 2015 at WCLC.

→ prolonged immune responses or stability (even after initial PD) as usually

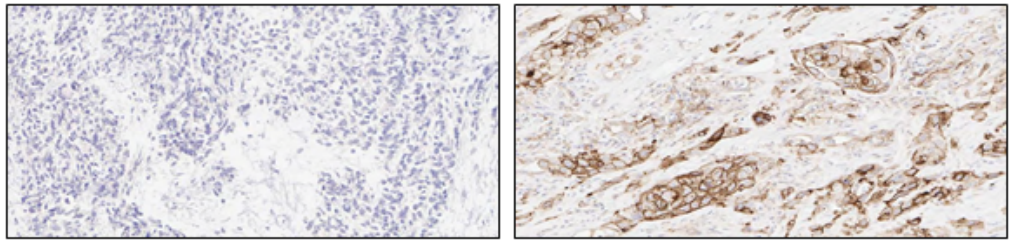
PFS

Median, mo (95% CI)	5.8 (3.4-8.2)
6-mo rate, %	50.0

Level of PD-L1 expression and response to anti-PD-1

- Samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: performed at a central laboratory using a prototype assay and the 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of tumor and associated inflammatory cells or positive staining in stroma
- MPM cohort: of 80 evaluable samples, 38 PD-L1 positive (45.2%)

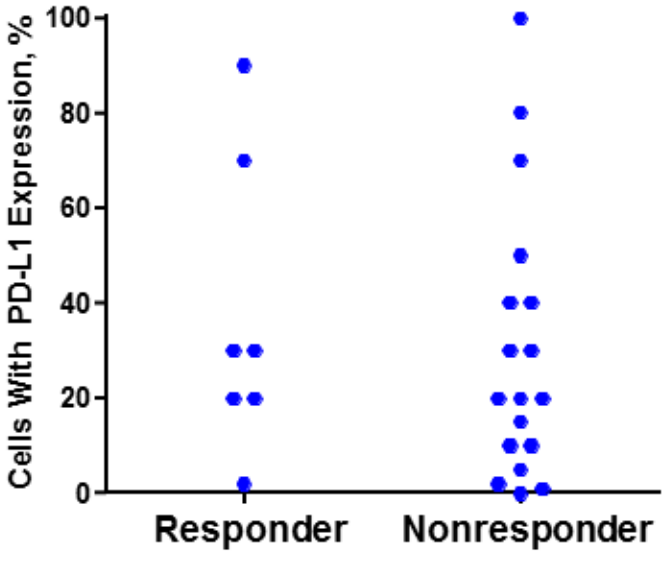
Examples of PD-L1 Staining in MPM Specimens from KEYNOTE-028



PD-L1 Negative | PD-L1 Positive

→ but NO relationship between PD-L1 expression and response to treatment

- Using prototype IHC assay, no relationship between level of PD-L1 expression on tumor and immune cells within tumor nests and frequency of response
  - One-sided $P = 0.284$ by logistic regression



E. Alley
Presented September 7, 2015 at WCLC.

Anti-PD-1 in MPM - Summary

- **Pembrolizumab (anti-PD-1)**
  - **phase Ib KEYNOTE-028** basket trial: **n= 25 pts only but impressive results and manageable safety profile – no predictive biomarker**
  - **10 mg/kg Q2W only tested so far in 2nde line mostly (PDL-1+ tumors)**
  - **ongoing phase II (Chicago) in pts after 1rst line treatment** (NCT 02399371)
- **other trials starting soon or ongoing:**
  - **Pembrolizumab:** alone or +FAK inhibitor (defactinib, UK), or +chemo…?
  - **Nivolumab:** alone or in combination (anti-CTLA-4…): « MAPS-2 »…
  - **MEDI-4736 (anti-PD-L1):** + Tremelimumab (NIBIT-MESO-1)...

Starting 2016

MAPS-2 trial
Mesothelioma Anti-PD-1 Study 2 - IFCT 1402

(PI: A Scherpereel)

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

- **Unresectable Malignant Pleural Mesothelioma**
- **Documented progression after previous 1 or 2 lines of chemotherapy including a pemetrexed + platinum doublet (baseline CT-scan)**
- **Measurable disease**
- **Histological diagnosis (thoracoscopy)**
- **ECOG PS 0-1**
- **Weight loss <10%**
- **Age > 18 years (M or F)**
- **available tumor tissue (archival or fresh)**

R

57 patients

Anti-PD-1 Nivolumab
3 mg/kg (1h IV)
every 2 weeks

PR/SD → **Nivolumab** 3mg/kg every 2 weeks *until progression (or 2 years max)*

week 12 (1rst CT-scan reassessment)

57 patients

Anti-PD-1 Nivolumab
3 mg/kg
every 2 weeks
+ Anti-CTLA4 Ipilimumab
1mg/kg IV D1-D42,
every 6 weeks

PR/SD → **Nivolumab** 3mg/kg every 2 weeks **+ Ipilimumab** 1mg/kg every 6 weeks *until progression (or 2 years max)*

week 12 (1rst CT-scan)

Stratification factors :

- epith *vs.* sarcomatoid + biphasic (mixed)
- 2nd *vs* 3rd line
- Chemo-S (progression > 3 mo) vs. Chemo-R (progression <3 mo)

Endpoint: DCR at 3 months (week 12)

Power =95%; one-sided α=5% P0= 20% P1=40%

Innovative therapies targeting *mesothelin*

± combined with chemo (Cis/Pem)

1. **SS1P:** mAb Fv fragment targeting mesothelin + truncated portion of Pseudomonas exotoxin – phase I trial done (1rst line +CP…)

2. **MORAb (Amatuximab):** chimeric IgG1 antibody targeting mesothelin – ongoing trial (1rst line +CP…) after 1rst promising results

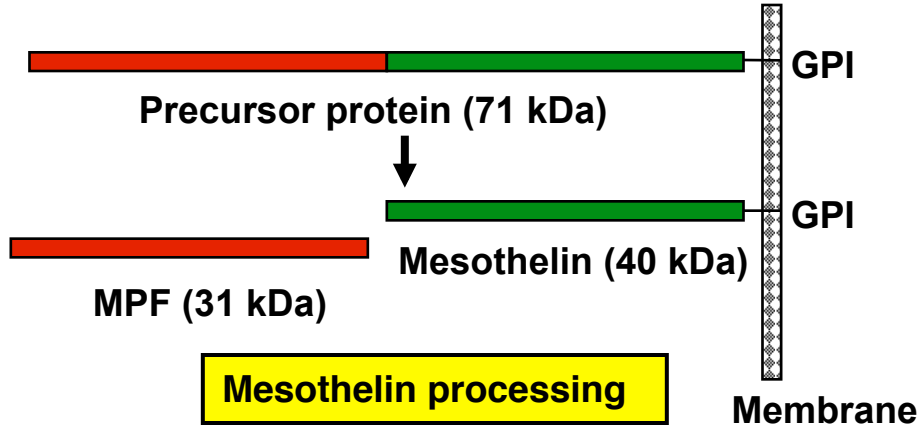
3. **Anetumab Ravsantine: ADC:** Ab targeting mesothelin + anti-tubulin – planned trial in 2016 (2nd line vs Vinorelbine)

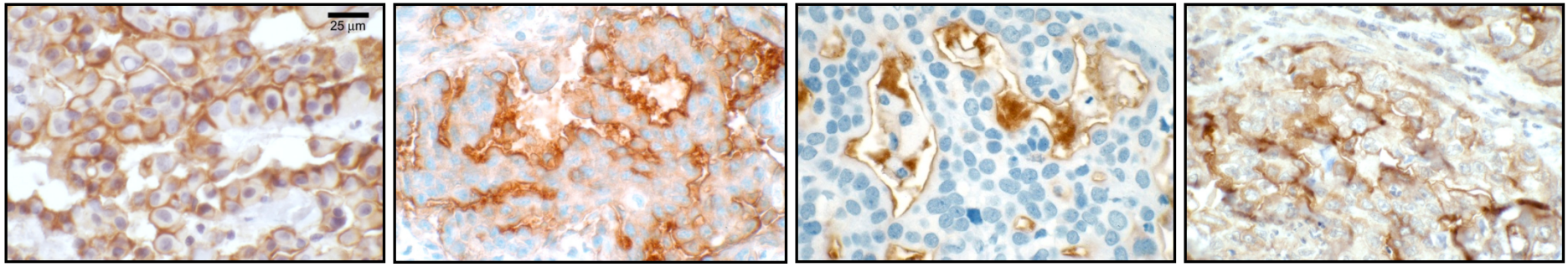
4. **Immunotoxin CRS-207:** mAb fragment of SS1P + attenuated live Listeria toxin – phase IB done (1rst line +CP)…

R Hassan et al, *Sci Transl Med.* 2013

Mesothelin: a target in MPM

- Cell surface glycoprotein
- Normal expression in human tissues is limited to mesothelial cells of pleura, peritoneum & pericardium
- Mesothelin is highly expressed in many cancers



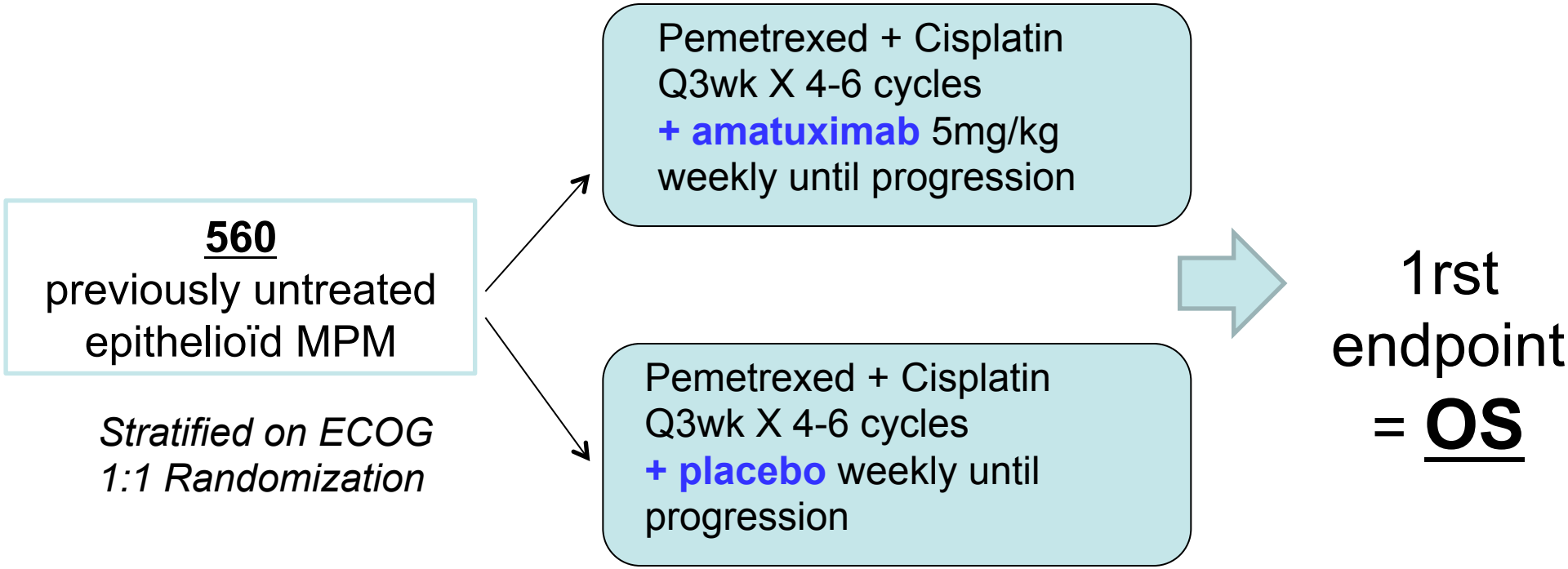


Mesothelioma | Ovarian Cancer | Pancreatic Cancer | Lung Cancer

Hassan et al. Clin. Cancer Res., 2004

Courtesy of Pr R Hassan (Bethesda, USA)

MORAb-009-201 ongoing trial

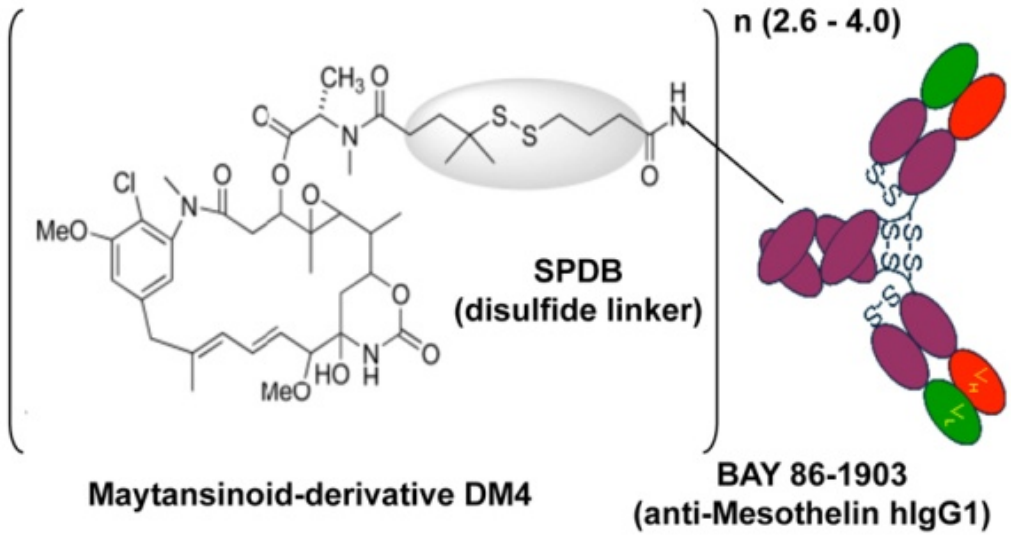


- 80% power to detect a statistically significant treatment effect at a 2 sided $\alpha=0.05$
- Interim analysis for futility after approx. 86 OS events

1er patient recruté en France (Lille) il y a 10 jours !

Courtesy of Pr R Hassan (Bethesda, USA)

Anti-mesothelin antibody-drug conjugate anetumab ravtansine (BAY 94-9343)



- Fully human anti-mesothelin antibody conjugated to DM4
- Targeted delivery of the potent anti-proliferative toxophore DM4 (tubulin inhibitor) to tumor cells expressing mesothelin

Golfier S et al. *Mol. Cancer Ther*. 2014

-> Phase I trial results

R Hassan et al - WCLC 2015 (Denver, USA) – présentation 1574

Courtesy of Pr R Hassan (Bethesda, USA)

Anetumab ravtansine phase I study: objective tumor response at the MTD (6.5 mg/kg q3w)

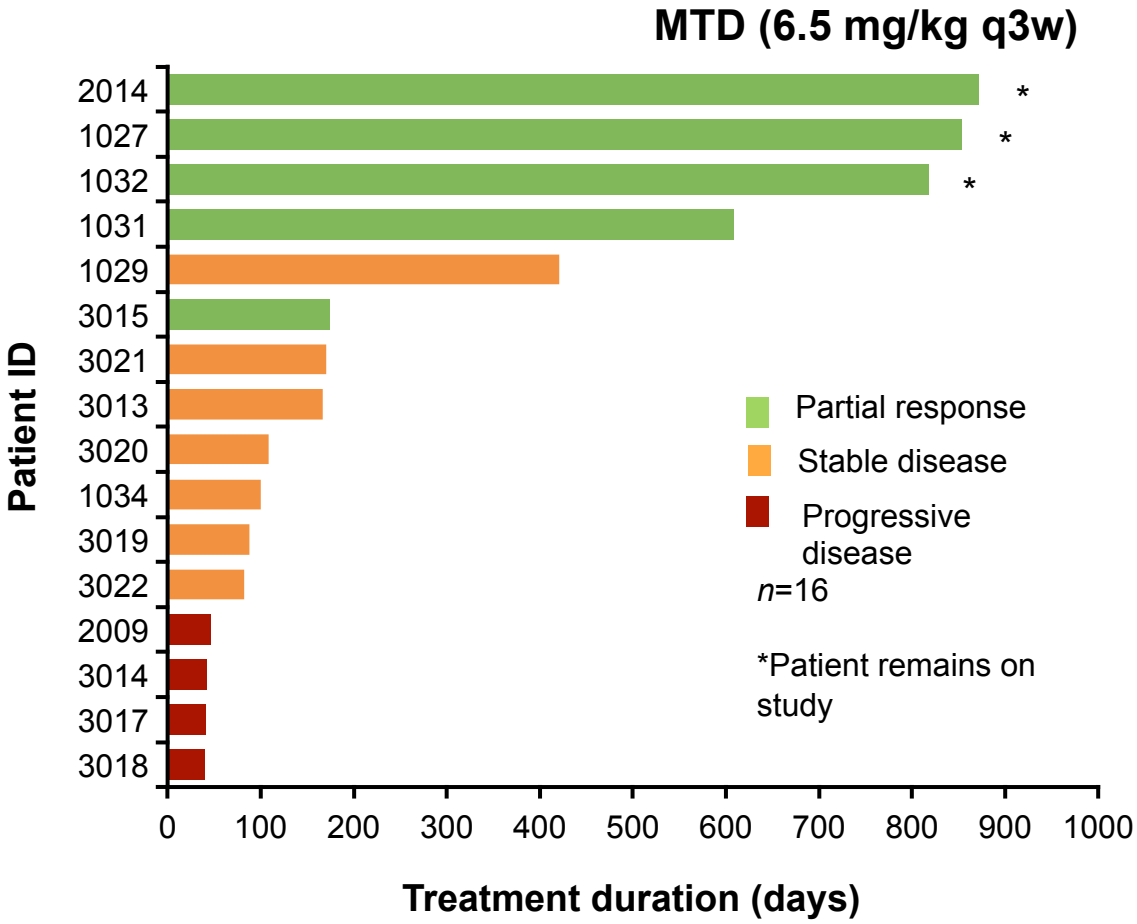
n (%)	All patients treated at MTD (*n*=38)	Mesothelioma patients treated at MTD	
		All patients (*n*=16)	1 prior line of systemic cytotoxic treatment (*n*=10)
Best overall response, RECIST[a]			
Complete response (CR)	0	0	0
Partial response (PR)	7 (18.4)	**5 (31.3)**	**5 (50.0)**
Stable disease (SD)	18 (47.4)	7 (43.8)	4 (40.0)
Progressive disease (PD)	10 (26.3)	4 (25.0)	1 (10.0)
Overall response (CR or PR)	7 (18.4)	5 (31.3)	5 (50.0)
Disease control rate (CR, PR, or SD)	25 (65.8)	**12 (75.0)**	**9 (90.0)**

[a]1 patient had non-complete response / non-progressive disease, and 2 patients were not evaluable
RECIST, Response Evaluation Criteria in Solid Tumors

Courtesy of Pr R Hassan (Bethesda, USA)

R Hassan et al - WCLC 2015 (Denver, USA) – presentation 1574

Anetumab ravtansine response *vs* duration of treatment in patients with mesothelioma



- **Encouraging efficacy with durable partial responses**

- **further studies in MPM are warranted (planned in 2016)**

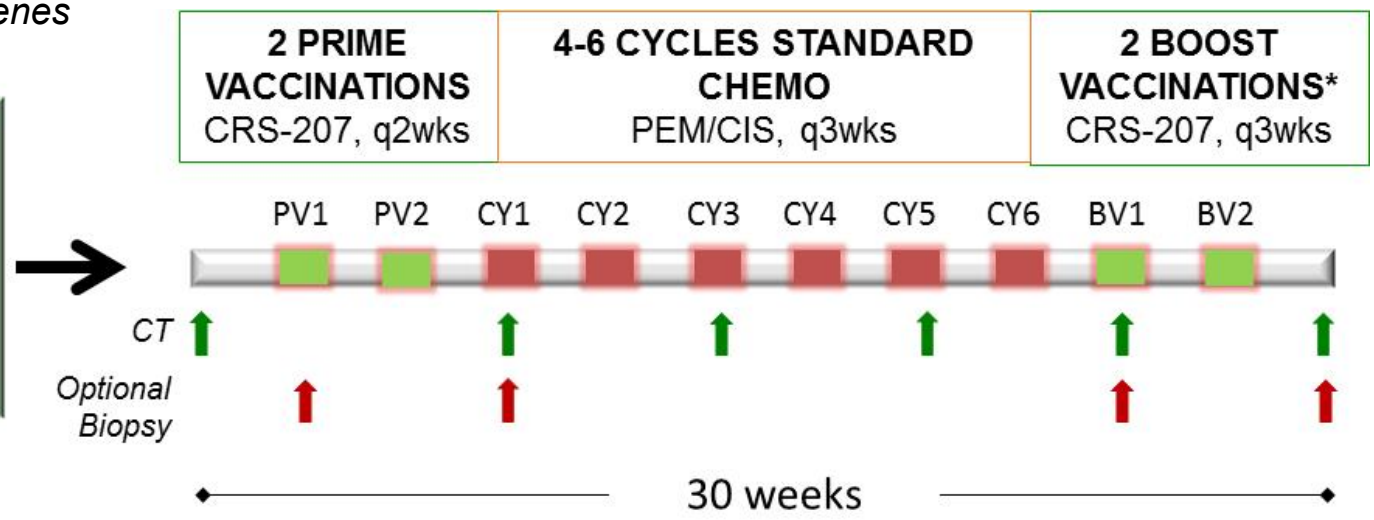
Essai randomisé de phase II : ouvre en France (Lille…) début Février 2016 : Anetumab ravsantine vs Vinorelbine en 2e ligne

Courtesy of Pr R Hassan (Bethesda, USA)

Anti-mesothelin Vaccine CRS-207 + Chemotherapy as Front-Line Treatment for MPM

[CRS-207 is live-attenuated, double-deleted (LADD) *Listeria monocytogenes (Lm)* engineered to express human mesothelin]

Planned N = 14-16
Single Arm Study
- **Stage III or IV unresectable pleural mesothelioma**
- **No prior chemotherapy**
- **ECOG 0-1**



* Subjects may continue CRS-207 q8wks if clinically stable

Phase 1B Study Design

Primary Endpoint

- Safety
- Induction of mesothelin-specific T cell responses

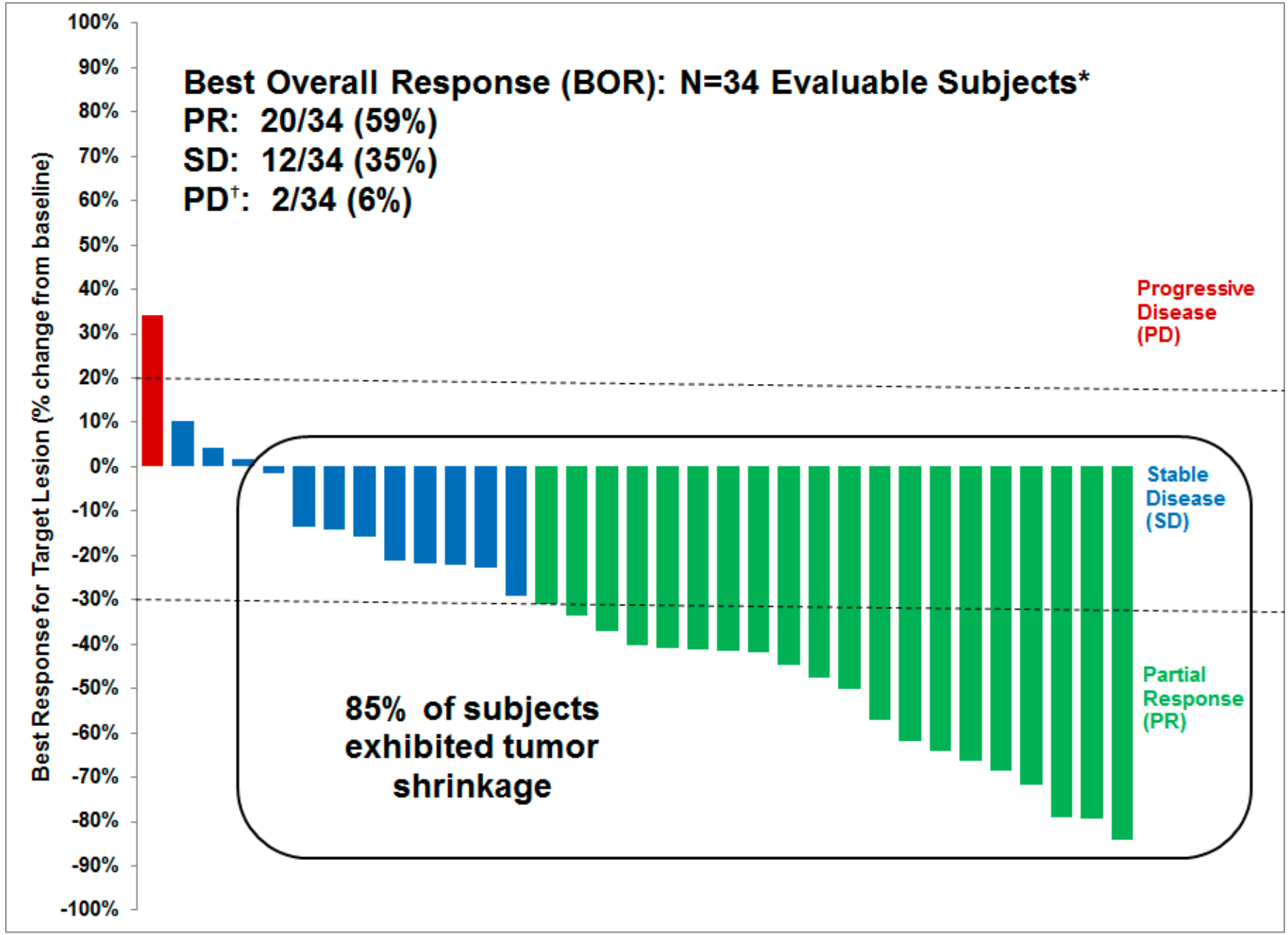
Secondary/Exploratory Endpoints

- Objective tumor responses by modified RECIST
- Time-to-progression
- IHC/gene expression analysis of tumor tissue

Courtesy of Pr R Hassan (Bethesda, USA)

R Hassan et al, *ASCO* 2014 and *ESMO* 2015

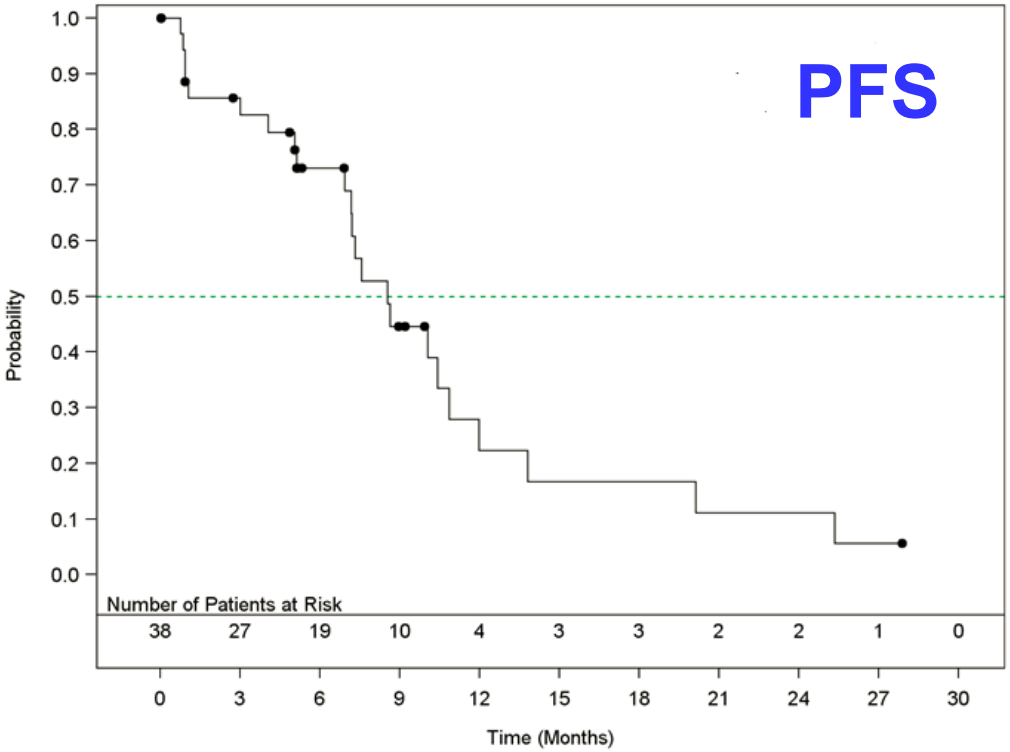
[redacted]-207 +Cis/Pem trial: BEST OVERALL RESPONSE AND WATERFALL PLOT

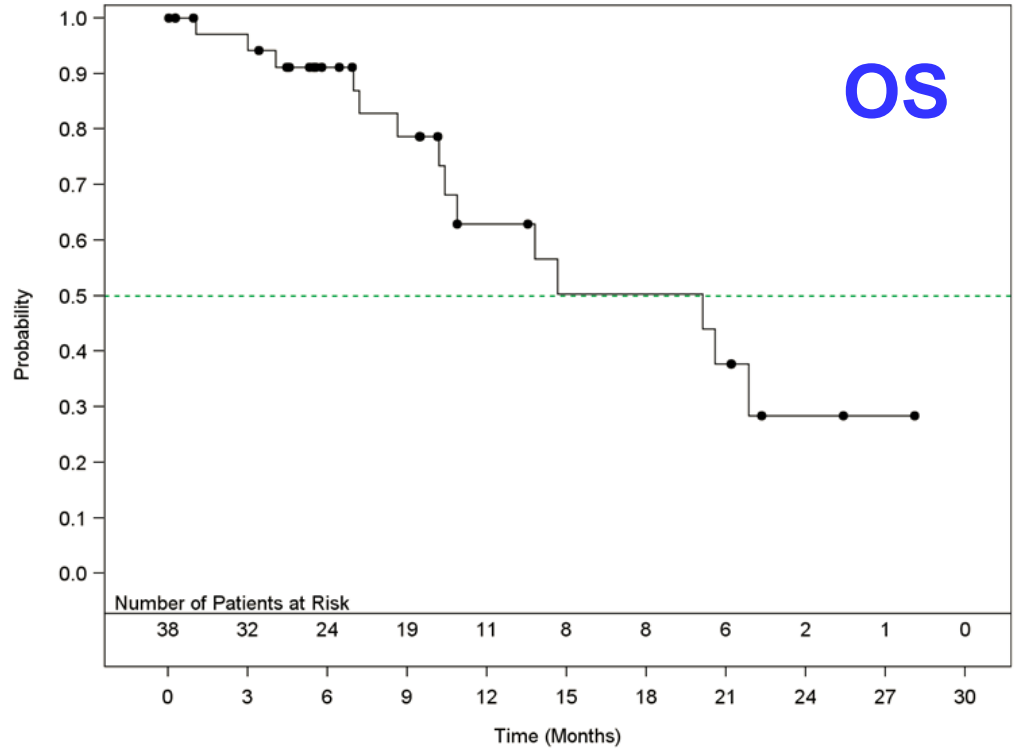


R Hassan et al, *ESMO* meeting 2015

Data cut-off is 31 July 2015; Results presented for subjects enrolled in Cohort 1 only

CRS-207 +Cis/Pem phase IB trial: PFS and OS





Estimated Median PFS:

8.5 months

(95% CI: 6.9-10.8)

Events: 23/38 (60.5%)

Estimated Median Overall Survival:

20.1 months

(95% CI: 10.4-N/A)

Events: 14/38 (36.8%)

R Hassan et al, *ESMO* meeting 2015

Data cut-off is 31 July 2015; Results presented for subjects enrolled in Cohort 1 only

Summary CRS-207 trial

- Based on patients treated to date, CRS-207 appears to be safe to administer in a sequence with chemotherapy (SOC Cis/Pem) with no additive or cumulative toxicities
- Toxicities attributable to CRS-207 were transient, mild and self-limited
- Encouraging objective response rates are being observed with the vaccine/chemotherapy combination (59%) compared to published data of Cis/Pem alone (25-40%) – DCR>90% !
- ORR appears to translate to durable response and survival benefit
- CRS-207 will be evaluated in a randomized phase III trial in front line setting, starting 2016

Courtesy of Pr R Hassan (Bethesda, USA)

Messages à retenir (1)

- **Suivre les recommandations** 2009 de l'ERS/ESTS, peu modifiées en 2013 par les Australiens et l'ESMO en 2015
- Une **mise à jour** est prévue en 2017 par une nouvelle taskforce Européenne (ERS/EACTS/ESTS/ESTRO...) + IMIG
- Connaitre les **nouveautés dans le diagnostic du MPM**

Messages à retenir (2)

- Toujours beaucoup de questions sur la meilleure stratégie thérapeutique :
  - Traitement multimodal vs chimio seule pour des pts similaires? (MARS 2 trial)
  - Quels sont les bons candidats en termes de stade, d'histologie...?
  - Quelles combinaisons de traitements (ciblés/standards)? quelles modalités ?

⇒ nécessité de travailler tous ensemble pour répondre à ces questions cruciales et développer d'autres outils (bioMol...) et traitements !

→ Aider nous à recruter les patients en essais cliniques +++

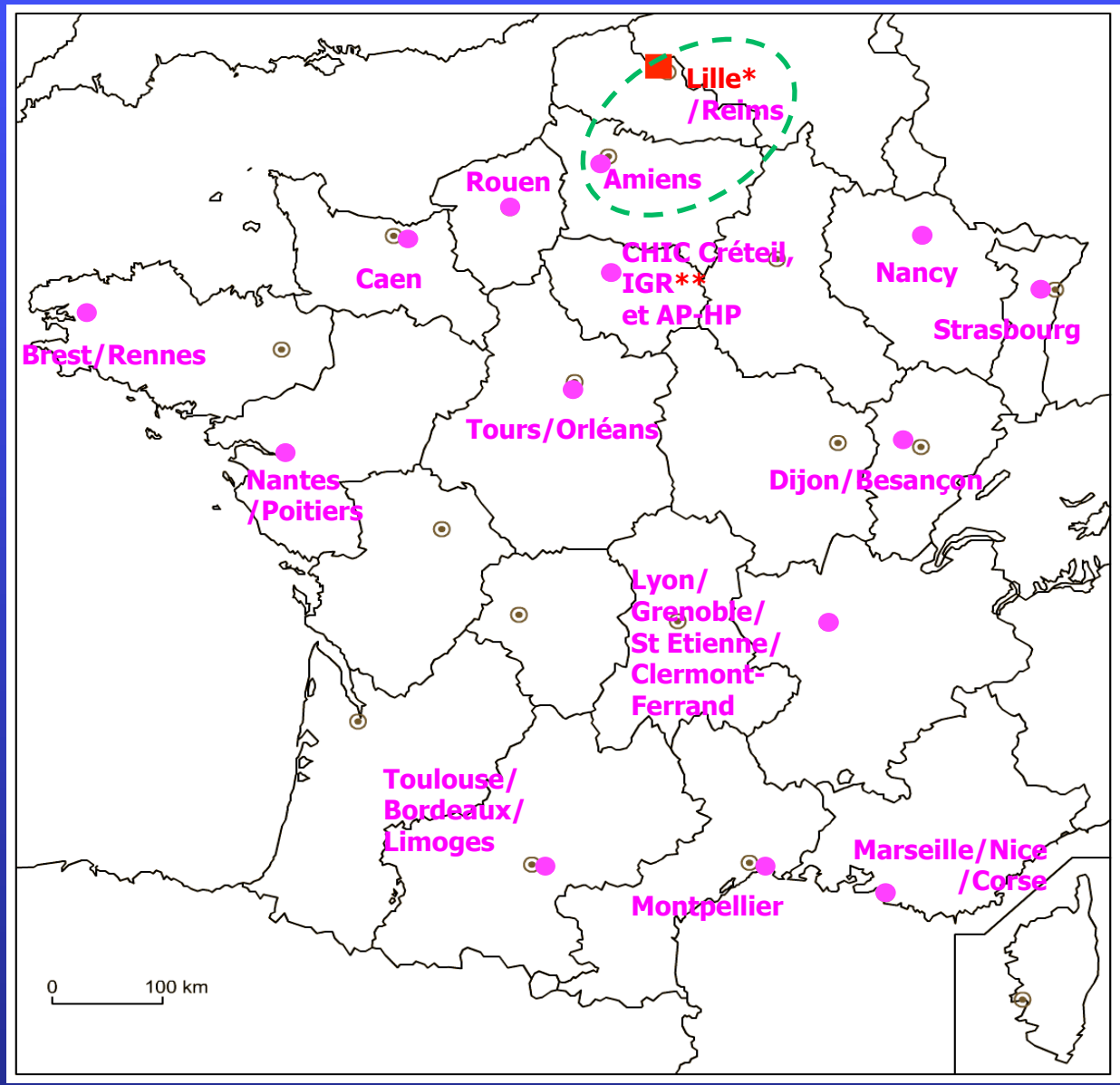
→ Rôle du réseau MESOCLIN pour la routine et la recherche !

MESOCLIN

Réseau National Expert
pour le Mésothéliome Pleural Malin

Centre expert National

Centre expert Régional



BUTS :

- Avis experts par RCP régionales et/ou nationale (soumission des patients par internet de n'importe quel médecin en France)
- Stimuler la Recherche Clinique et Translationnelle (essais, études via information , inclusion, *Mesobank* …)
- DO, information …

(démonstration Logiciel au CPLF 2015)

« Il n'existe que deux choses infinies, l'univers et la bêtise humaine … mais pour l'univers, je n'ai pas de certitude absolue » (*Albert EINSTEIN*)

Merci pour votre attention !

et Bienvenue au sein de l'IMIG

www.imig.org

prochain meeting à Birmingham, UK

du 1 au 4 Mai 2016

iMig

International Mesothelioma Interest Group

Devoted to the biology & pathology of mesothelial cells.