SOMA
Service d'Oncologie Médicale Ariana

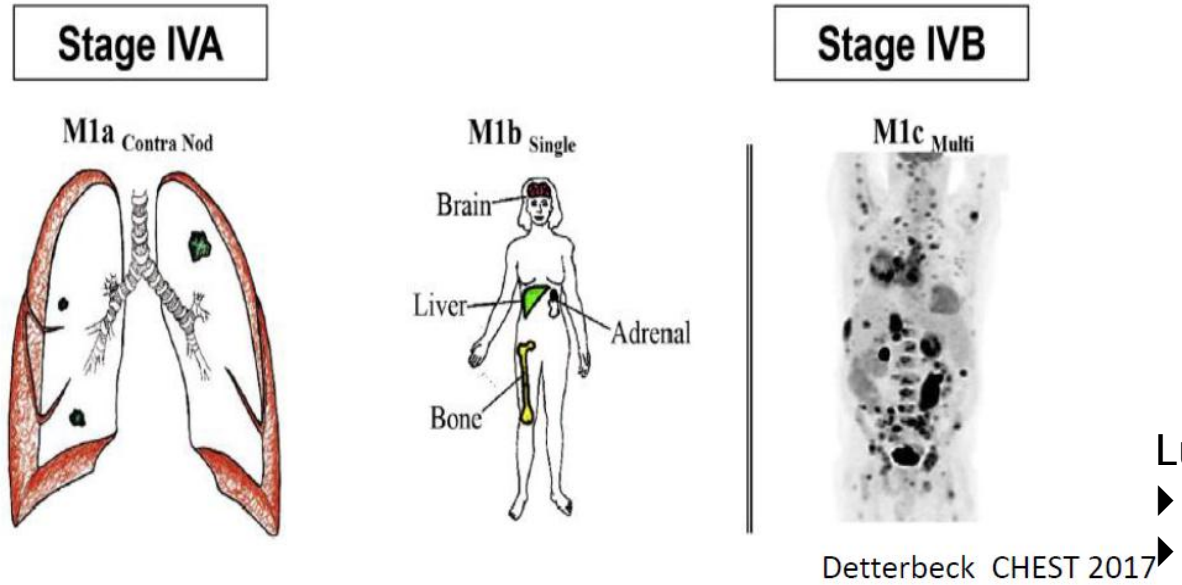
Cancer du poumon oligométastatique: un casse tête dans la prise en charge?

Nesrine Mejri, MD
Service d'oncologie médicale de l'Ariana (SOMA)

18-19 Octobre 2019

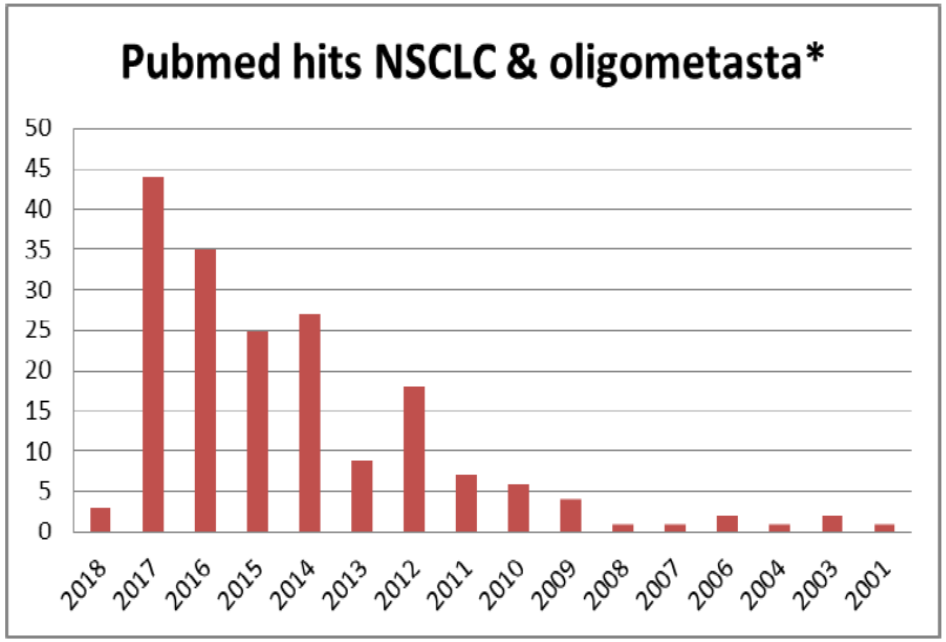
C’est une entité maintenant reconnue

Different outcome in oligometastatic disease in lung and other organs
(recognised in TNM version 8)



Detterbeck CHEST 2017

Première mention 1995 Hellman and Weichselbaum (J Clin Oncol, 1995)

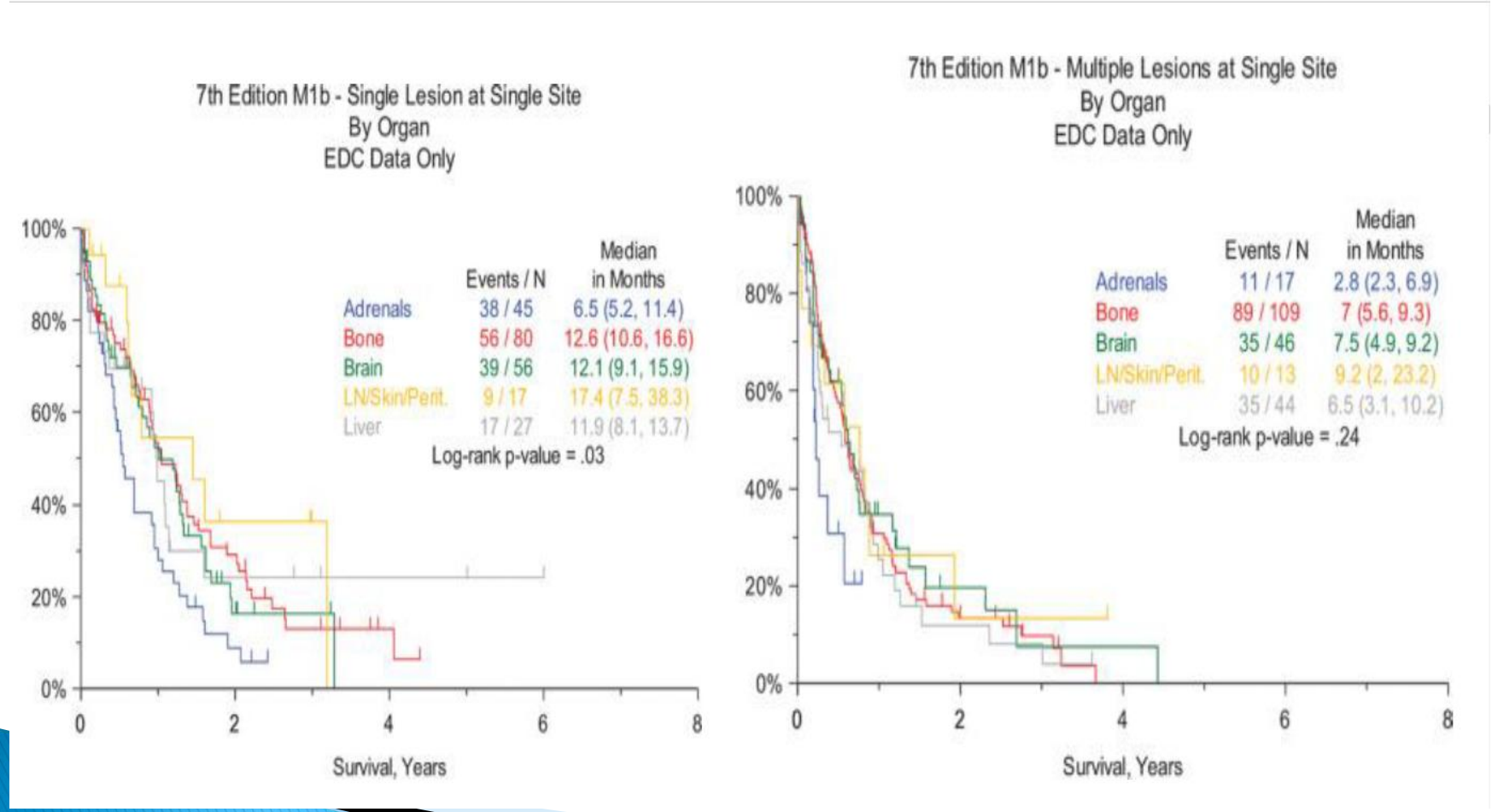


Lung Cancer TNM 8th edition

- M1a Separate tumor nodule(s) in a contralateral lobe
- M1b Single extrathoracic metastasis
- M1c Multiple extrathoracic metastasis

SOMA
Service d’Oncologie Médicale Ariana

Tous les Oligo métastatiques ne se comportent pas de la même façon!



-Le foie c'est le pire

-Le cerveau pas particulièrement de mauvais pronostic

SOMA
Service d'Oncologie Médicale Ariana

Indulgence

- Très peu de données robustes
- La majorité des études sont des études observationnelle
- Pas d'essai clinique phase III
- Mais le futur est prometteur!

La définition d'une MOM?

- Est-ce une question de nombre? Il existe différentes définitions, 1 à 5 organes, 1 à 5 lésions dans un organe
- Est-ce une question de faisabilité? Toutes les lésions sont traitables de façon curative avec toxicité acceptable
- Est-ce une question de disponibilité de moyens thérapeutiques permettant un traitement efficace du primitif et des métastases

La plus grande méta analyse

Individual Patient Data Meta-Analysis: 757 patients with 1-5 synchronous or metachronous metastases

Median OS **26 months**, 1-year OS 70.2%, and 5-year **OS 29.4%**

Surgery was commonest treatment for both primary (84%) and metastases (62%)

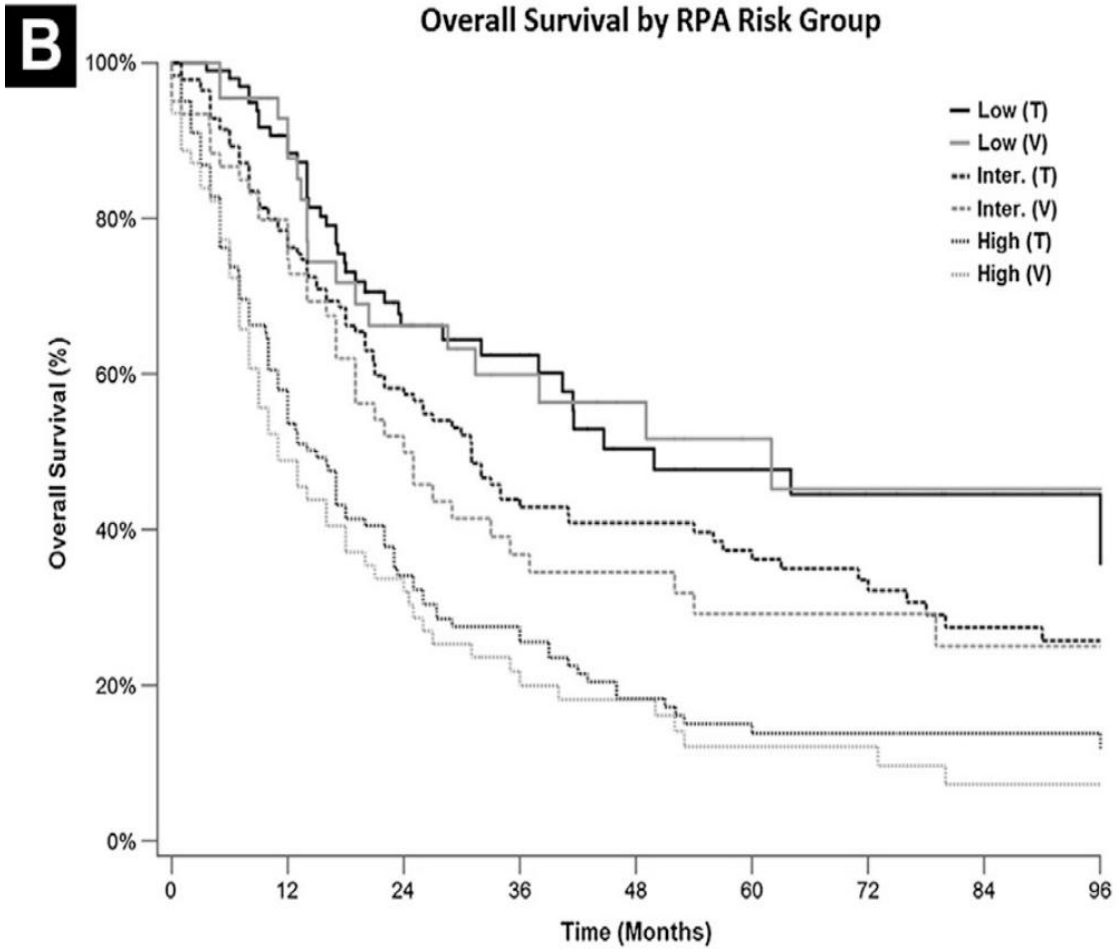
Recursive Partitioning Analysis for risk groups;

Low risk: metachronous metastases (5-year OS 48%)

Intermediate risk: synchronous metastases, N0 disease (5-year OS 36%)

High risk: synchronous metastases, N1/N2 disease (5-year OS 14%)

Treated with surgical metastasectomy, stereotactic radiotherapy or radical EBRT and curative treatment of the primary lung cancer



Ashworth et al., Clin Lung Cancer 2014

Pour avancer sur la sélection des malades

MOM Synchrone

MOM metachrone

Oligo-récidive

MOM persistante

MOM Oligo-progression

- A la présentation ou métastases **synchrones**
- **Oligorecidive** métastastatique après une période de maladie sous contrôle (metachrone)
- Maladie **oligopersistante** après une réponse au traitement systémique pour une maladie disséminée
- Maladie **Oligoprogressive** dans le cadre d'un traitement systémique qui permet un contrôle partiel de la maladie

MOM Fake

SOMA
Service d'Oncologie Médicale Ariana

MOM Synchrone

Risque intermédiaire

MOM metachrone

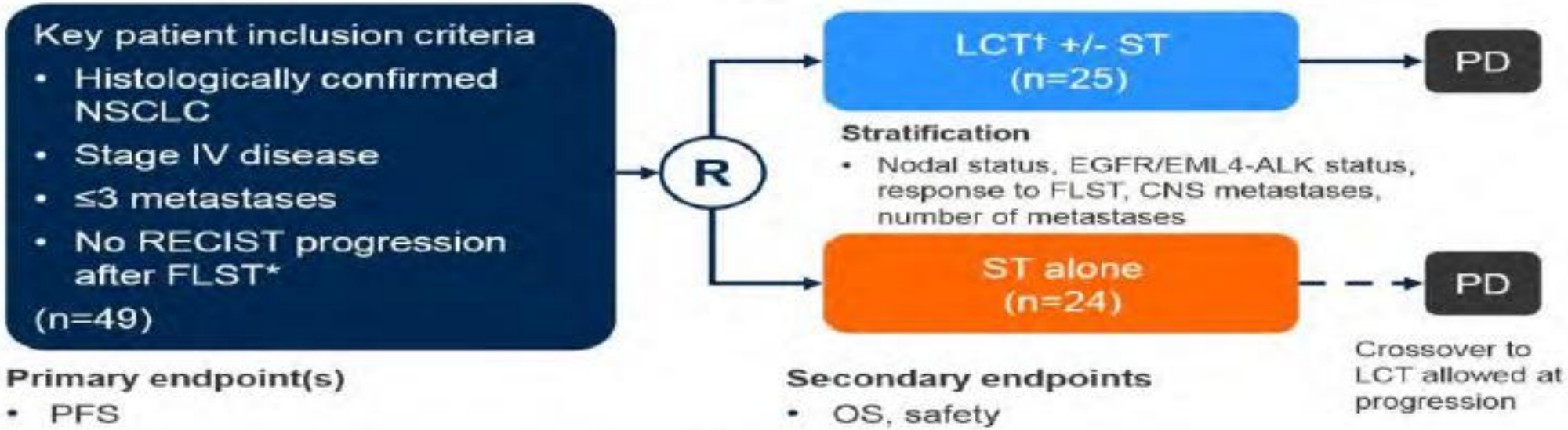
Oligo-récidive

MOM persistante

MOM Oligo-progression

9004: Local consolidative therapy (LCT) to improve progression-free survival (PFS) in patients with oligometastatic non-small cell lung cancer (NSCLC) who receive induction systemic therapy (IST): Results of a multi-institutional phase II randomized study – Gomez D et al

- **Study objective**
  - To investigate the effect of aggressive LCT in patients with oligometastatic NSCLC who did not progress after front-line systemic therapy (FLST)*



*≥4 cyc afatinib therapy [chemo

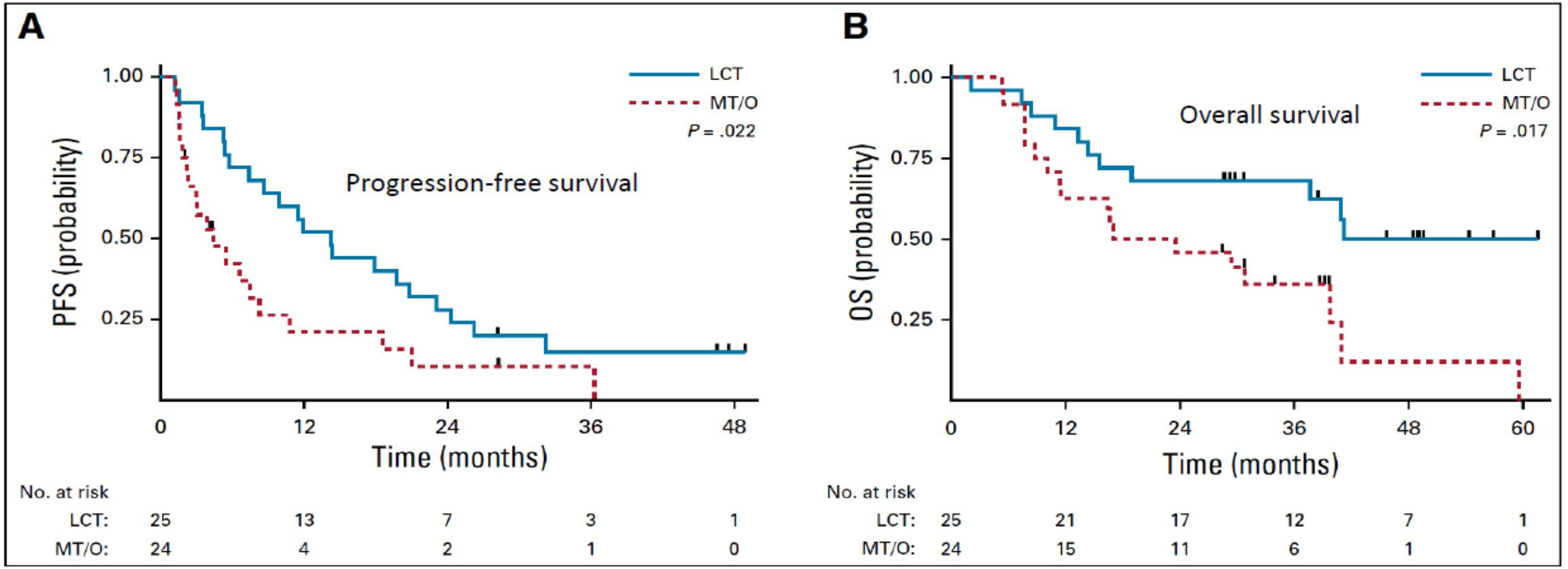
*≥4 cycles of platinum-doublet chemotherapy, ≥ 3 months of erlotinib, afatinib or gefitinib therapy if EGFR mutation or ≥ 3 months of crizotinib therapy if EML4-ALK fusion; †LCT, local consolidative therapy (i.e. [chemo]radiation or surgical resection of all sites); ST, systemic therapy

; 34 (suppl): abstr 9004

Gomez, Lancet Oncol 2016

SOMA
Service d'Oncologie Médicale Ariana

Oligometastatic NSCLC without progression after first-line systemic therapy: A randomised, phase 2 study



Type of local consolidative therapy used

- Hypofractionated RT or SABR in 48%
- Surgery and RT for 24%
- Chemo-RT for 8%
- Hypofractionated RT and CT-RT for 12%
- Surgery only for 4%

Gomez DR, JCO 2019

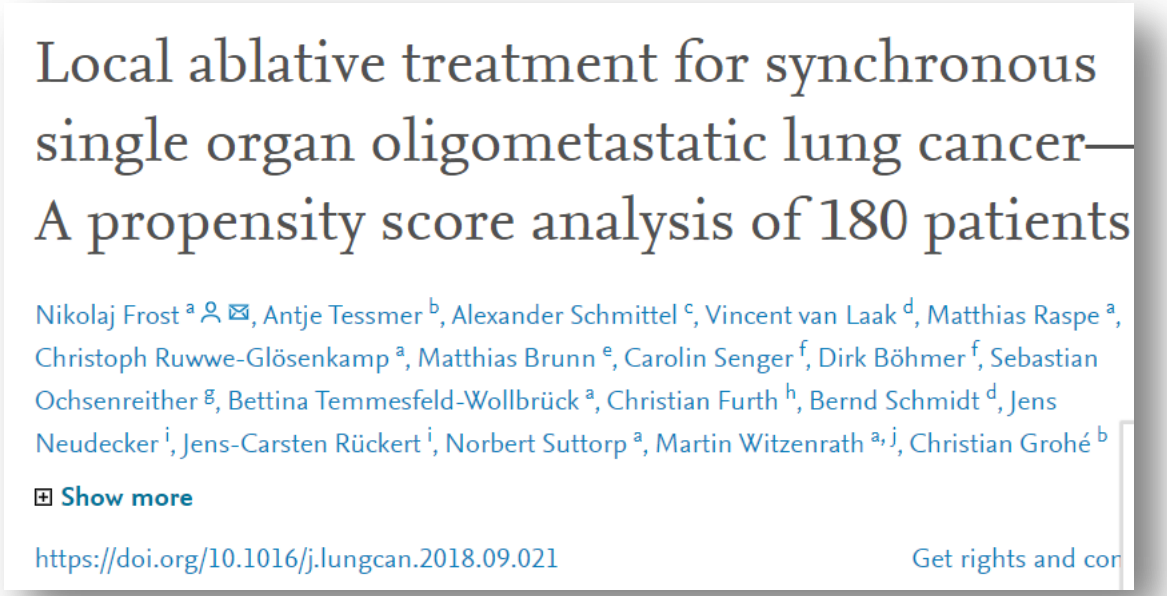
Deux principaux essais randomisés

- Gomez et al., JCO 2019
- Iyengar P et al. JAMA Oncol 2018

Deux essais sont en cours (SBRT in oligometastatic NSCLC)

- STOP trial (NCT02756793)
- HALT (NCT03256981

	Gomez D, Lancet Oncol 2016	Iyengar P, JAMAOncol 2017
Design	Randomized	Randomized
Number of patients	48	29
PFS	11.9 months (5.7–20.9) vs 3.9 months (2.3 – 6.6)	9.7 months vs 3.5 months
Median OS	37 vs 9.4, p=0.034	
	Closed by IDMC	Closed by IDMC



Local ablative treatment for synchronous single organ oligometastatic lung cancer—A propensity score analysis of 180 patients

Nikolaj Frost [a], Antje Tessmer [b], Alexander Schmittel [c], Vincent van Laak [d], Matthias Raspe [a], Christoph Ruwwe-Glösenkamp [a], Matthias Brunn [e], Carolin Senger [f], Dirk Böhmer [f], Sebastian Ochsenreither [g], Bettina Temmesfeld-Wollbrück [a], Christian Furth [h], Bernd Schmidt [d], Jens Neudecker [i], Jens-Carsten Rückert [i], Norbert Suttorp [a], Martin Witzenrath [a, j], Christian Grohé [b]

Show more

https://doi.org/10.1016/j.lungcan.2018.09.021

Get rights and cor

Prognostic factors: T1a, N0-2, ADK, ECOG-PS 0-1

- Progression-free survival (25.1 vs. 8.2 months), HR: 0.30; 95% CI, 0.21-0.43; $p < 0.001$
- Overall survival: 60.4 vs. 22.5 months, HR: 0.42; 95% CI, 0.28-0.62 $p < 0.001$

Frost N et al, Lung Cancer, 2018

SOMA
Service d'Oncologie Médicale Ariana

Nodule pulmonaire controlatéral isolé

ACCP 2013 guidelines (contralateral lobe)

- in patients with a contralateral lobe tumor nodule(s), **resection of each lesion is suggested**, provided the patient has adequate pulmonary reserve (Grade 2C).

Lung mets – strategy

- contralateral metastasis or second primary?
- which one is metastasis?
- sequence: primary first or metastasis first?
- for metastasis: surgery or SBRT?

SOMA
Service d'Oncologie Médicale Ariana

Nodule surrénalien

- Méta surrénalienne: ou incidentaloma, besoin de confirmation?
- Séquence: primitif en premier temps?

- Surrénalectomie laparoscopique: mortalité <1% et 6% de morbidité, préférée pour les petites lesions, moins de complications post-op, moins de séjour à l'hopital et plus d'épargne de sang.

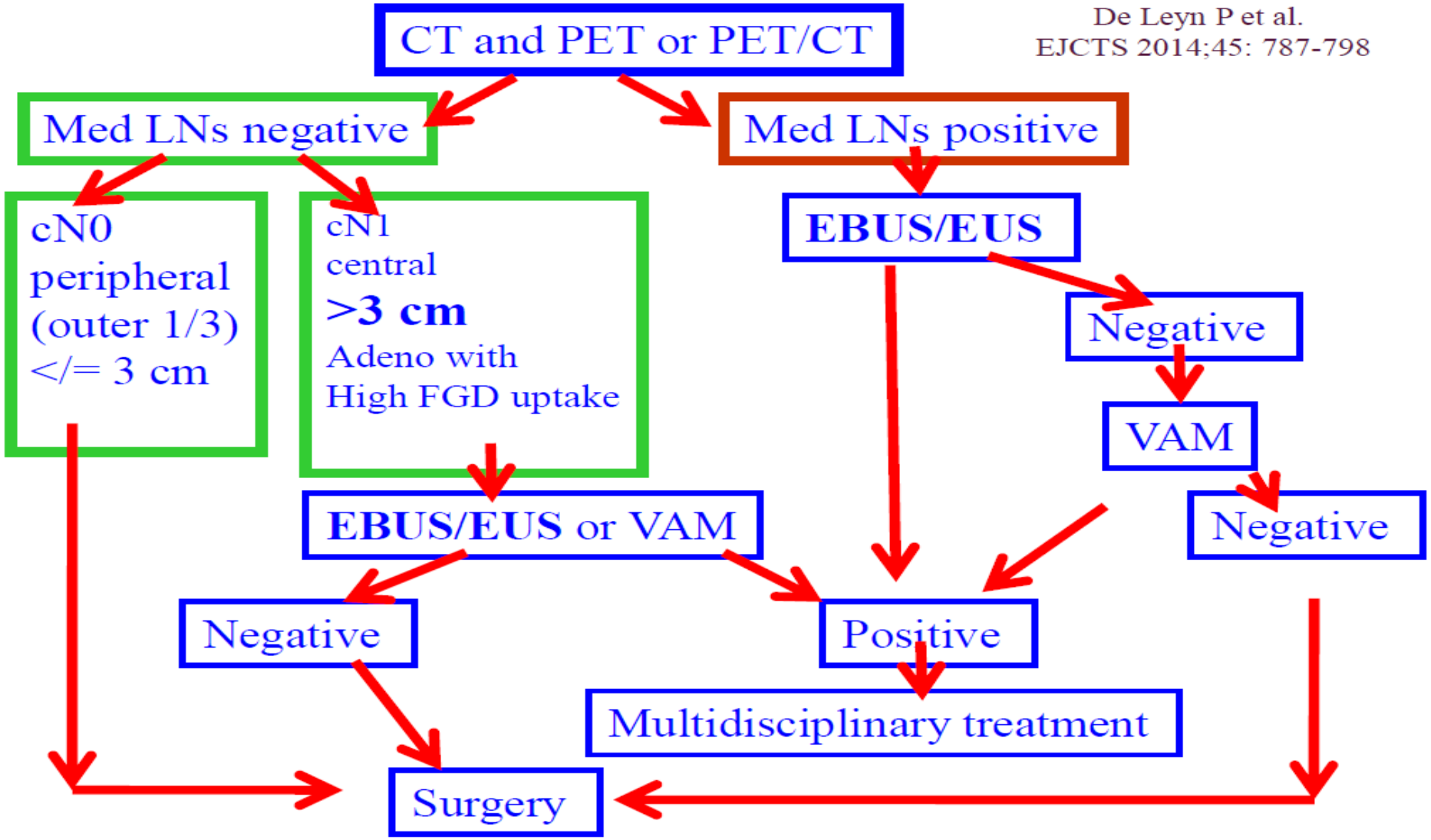
Thompson, Surgery 1997, Arenas et al., World J Surg 2014

SOMA
Service d'Oncologie Médicale Ariana

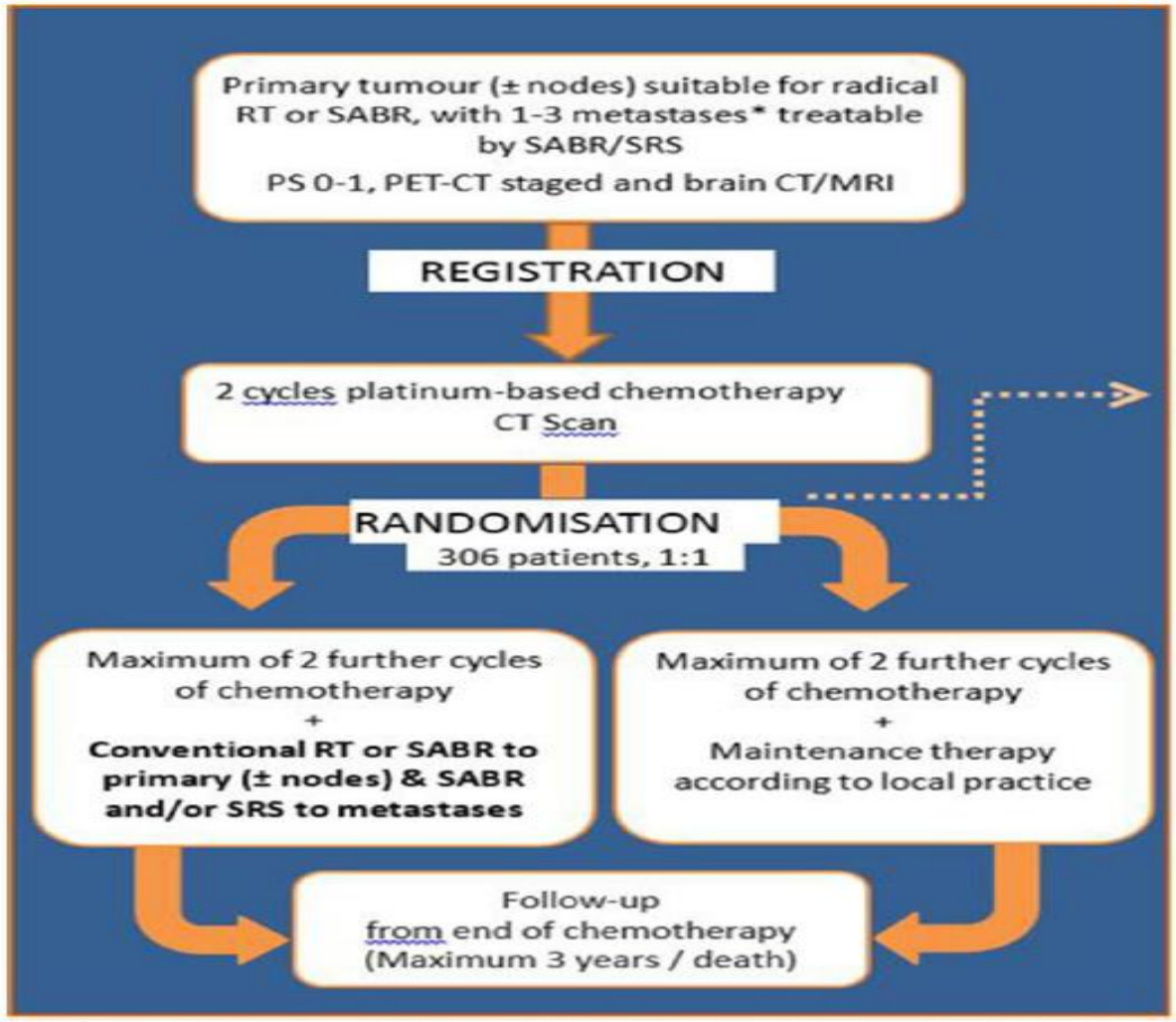
Métastases cérébrales

- Quelle séquence? Primtif ou métastastase en premier?
- Chirurgie ou RT stéreotaxique?
- Tout depend de l'anatomie, du nombre et de la balance bénéfice risque opératoire.

La stadification médiastinale est très importante!!



Essais cliniques en cours: SARON



*Brain metastases can be included if at least one extra-cranial metastasis is also present.

SOMA
Service d'Oncologie Médicale Ariana

ESMO Clinical Practice Guidelines for NSCLC

- Stage IV patients with 1-3 **synchronous** metastases at diagnosis may experience long-term DFS following systemic therapy and local consolidative therapy (**high-dose RT or surgery**) [III, B]. Because of the limited evidence, these patients should be discussed within a multidisciplinary tumour board [II, B], and inclusion in clinical trials is preferred

Planchard D, Ann Oncol updated in 2019

MOM Synchrone

MOM metachrone

Oligo-récidive

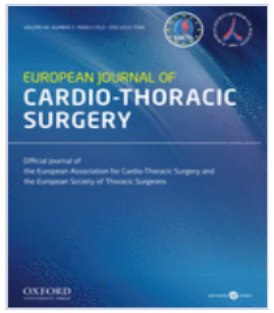
MOM persistante

MOM Oligo-progression

Faible risque

EUROPEAN JOURNAL OF
CARDIO-THORACIC SURGERY

Issues Subject More Content Author Hub Purchase About All European Journa Advanced Search



Volume 49, Issue 3

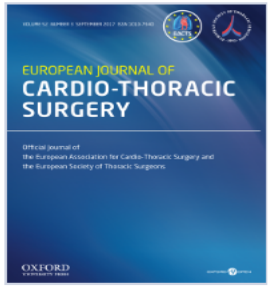
Postoperative oligo-recurrence of non-small-cell lung cancer: clinical features and survival† FREE

Tomoyuki Hishida ✉, Junji Yoshida, Keiju Aokage, Kanji Nagai, Masahiro Tsuboi Author Notes

European Journal of Cardio-Thoracic Surgery, Volume 49, Issue 3, March 2016, Pages 847–853,
https://doi.org/10.1093/ejcts/ezv249
Published: 22 July 2015 **Article history**

- 162 oligorecurrent NSCLC , 1 à 3 localisations (surrénale, os, foie, cerveau).
- Initial defintive local therapy increased progression free survival HR=0,44 CI[0,29-0,68]

EUROPEAN JOURNAL OF
CARDIO-THORACIC SURGERY



Volume 52, Issue 3
September 2017

Long-term survival outcome after postoperative recurrence of non-small-cell lung cancer: who is 'cured' from postoperative recurrence? FREE

Keigo Sekihara, Tomoyuki Hishida ✉, Junji Yoshida, Tomonari Oki, Tomokazu Omori, Shinya Katsumata, Takuya Ueda, Tomohiro Miyoshi, Masaki Goto, Syoko Nakasone ... Show more

European Journal of Cardio-Thoracic Surgery, Volume 52, Issue 3, September 2017, Pages 522–528,
https://doi.org/10.1093/ejcts/ezx127

- Prognostic factors: female [hazard ratio (HR) = 0.78], adenocarcinoma (HR = 0.77), locoregional (only) recurrence (HR = 0.59) and longer recurrence-free survival (HR = 0.99) were favorably associated with PRS
- 13% live more than 5 years

SOMA
Service d'Oncologie Médicale Ariana

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthi, Anand Swaminath, Neil Kopek, Mitchell Liu, Karen Moore, Suzanne Currie, Glenn S Bauman, Andrew Warner, Suresh Senan

- Phase 2, 99 patients

With oligo recurrent NSCLC

→ Standard of care

→ Standard of care+ SABR of all M+ sites

Interpretation SABR was associated with an improvement in overall survival, meeting the primary endpoint of this trial, but three (4·5%) of 66 patients in the SABR group had treatment-related death. Phase 3 trials are needed to conclusively show an overall survival benefit, and to determine the maximum number of metastatic lesions wherein SABR provides a benefit.

ESMO Clinical Practice Guidelines for NSCLC

Stage IV patients with limited **metachronous** metastases maybe treated with a radical local therapy (**high-dose RT or surgery**) and may experience long-term DFS [IV, B].

However, this is based mainly on retrospective data and inclusion in clinical trials is preferred.

Planchard D, Ann Oncol updated in 2019

MOM Synchrone

MOM metachrone

Oligo-récidive

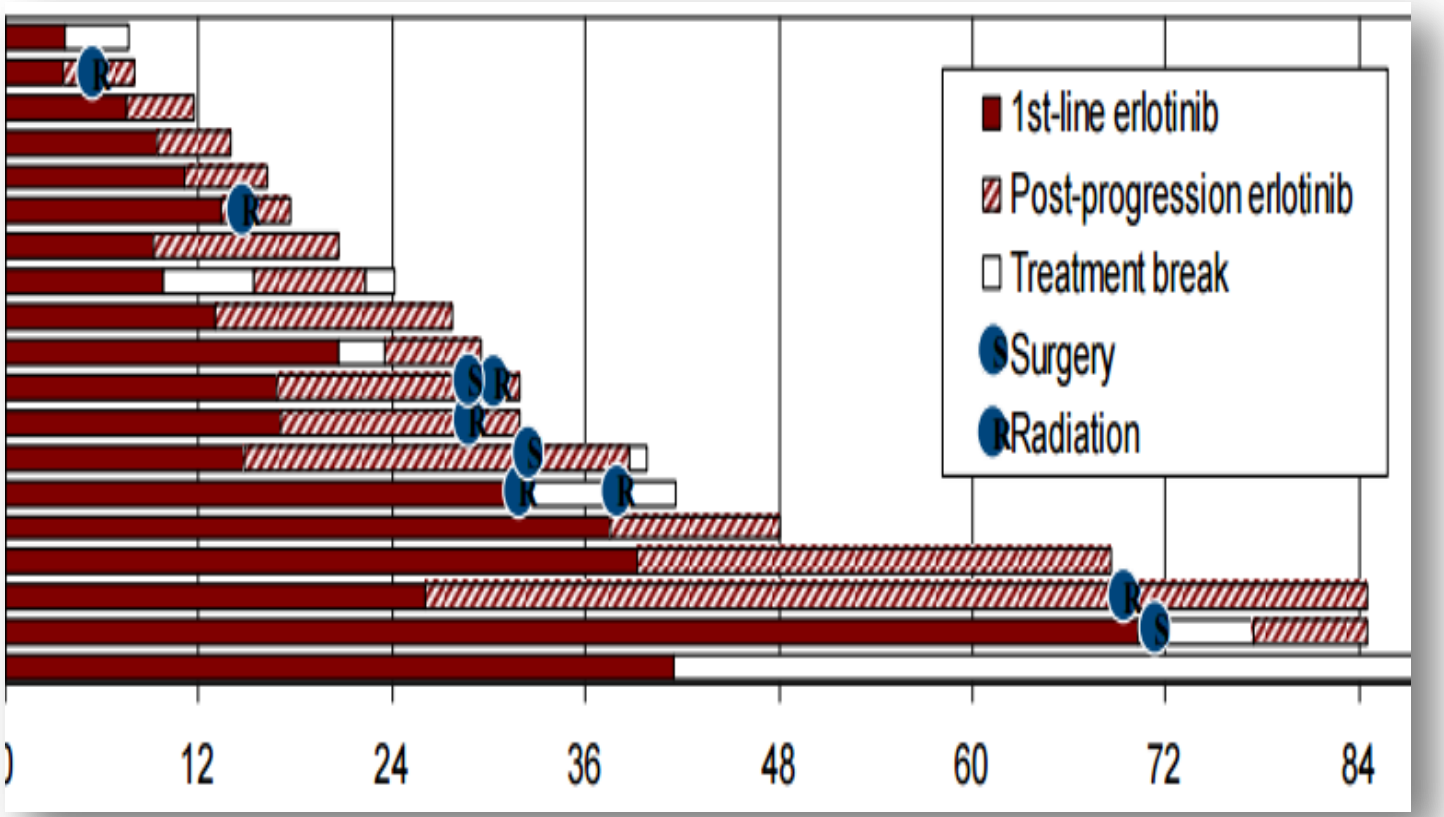
MOM persistante

MOM Oligo-progression

Haut risque

Post-progression?

Peut-on continuer?



42 patients, EGFR+, recevant Erlotinib dans 3 essais cliniques phase 3

19 patients (45%) ➔ retarder la CT> 3 mois

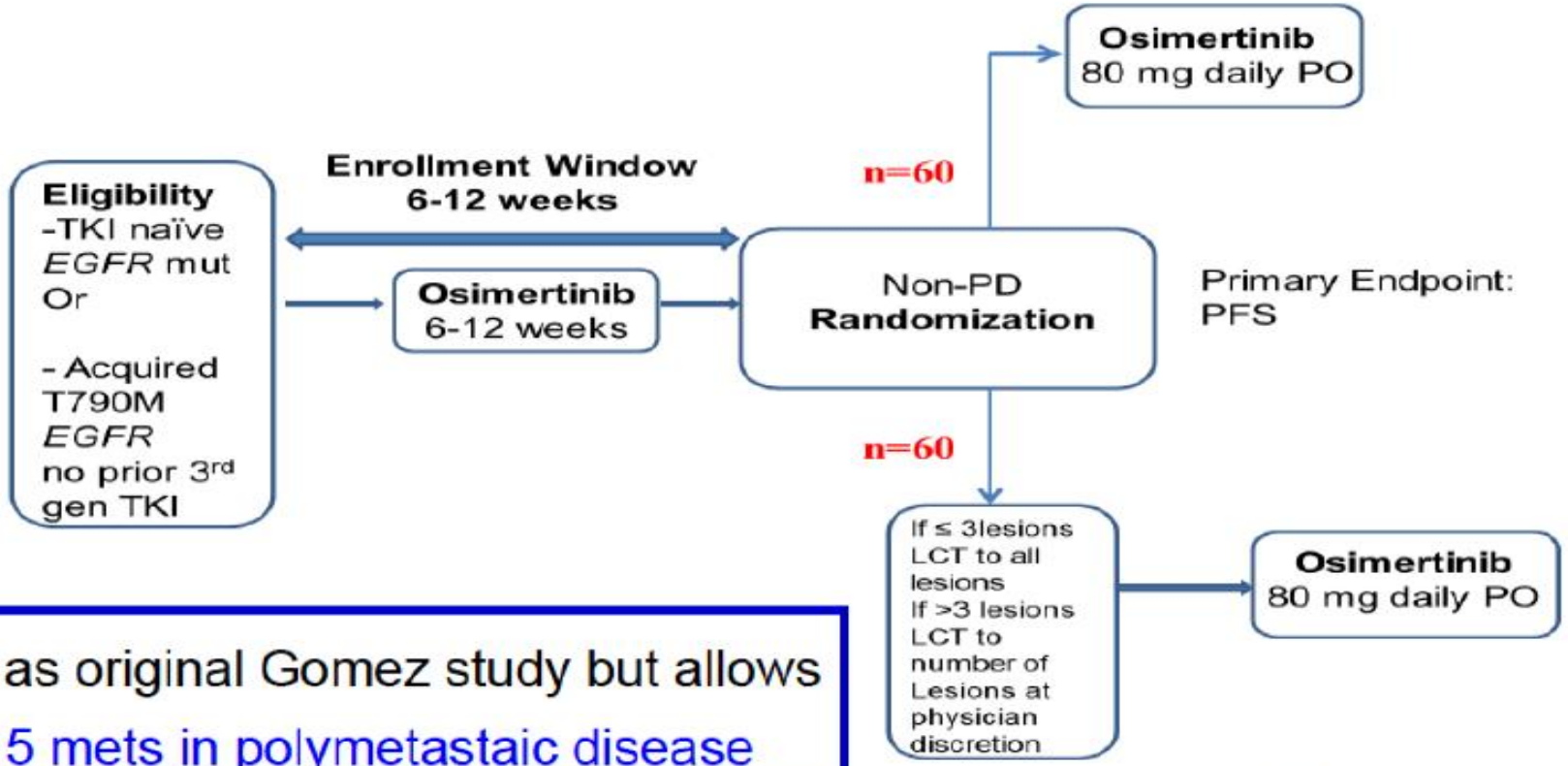
9 patients (21%) ➔ retarder la CT >12 mois

Oxnard et al. ASCO 2012/Park, JAMA oncol 2015

SOMA
Service d'Oncologie Médicale Ariana

NORTHSTAR (synchronous EGFR+ lung)

Randomized phase II trial of osimertinib with or without local consolidation therapy for patients with EGFR-mutant metastatic NSCLC



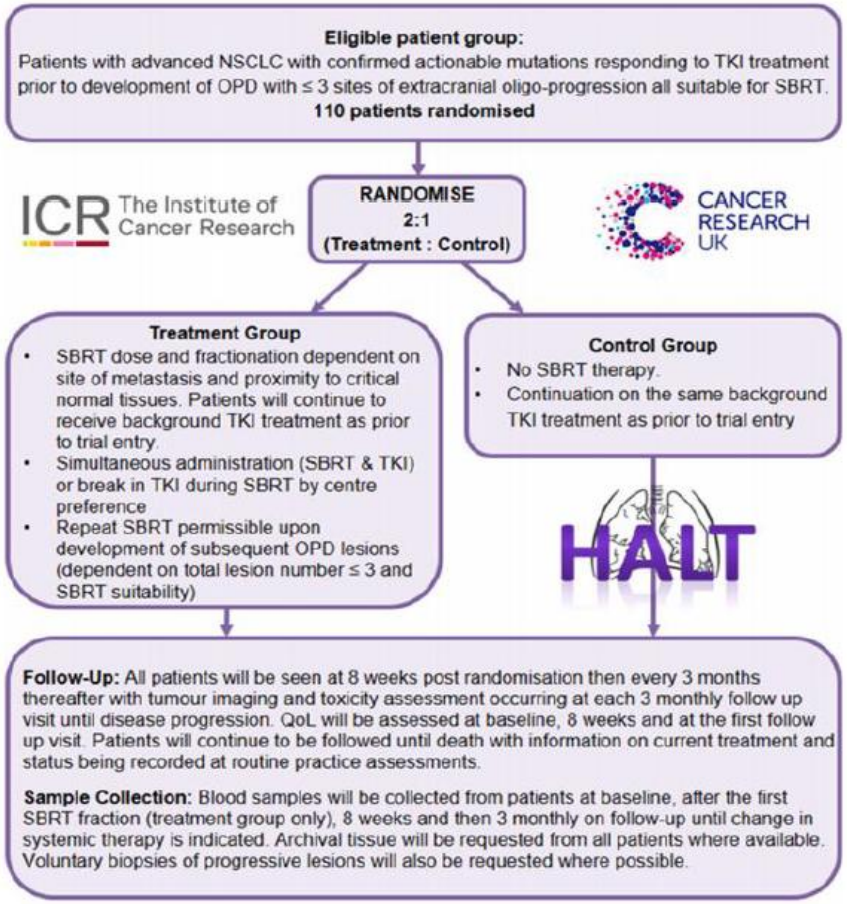
Same design as original Gomez study but allows for tx of up to 5 mets in polymetastaic disease

Slide courtesy D Gomez MDACC

SOMA
Service d'Oncologie Médicale Ariana

Essais cliniques en cours: HALT

HALT: randomized phase II/III trial of targeted therapy with or without dose-intensified RT in oligo-progressive disease in oncogene addicted lung tumors



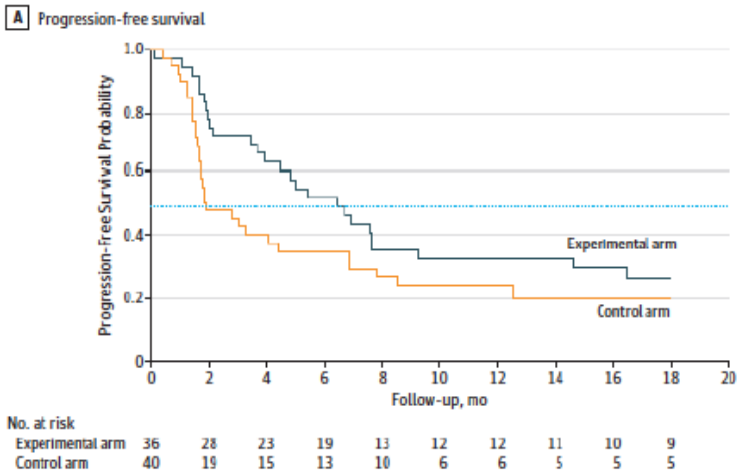
SOMA
Service d'Oncologie Médicale Ariana

Immunotherapy ± radiotherapy

Randomized phase II PEMBRO-RT study

3 fractions of 8 Gy
BED_{10} = 43 Gy

	ORR at 12 wks	Median PFS	Median OS
Control arm (n = 40)	18%	1.9 months (95%CI, 1.7-6.9 months)	7.6 months (95%CI, 6.0-13.9 months)
Experimental arm (n = 36)	36%	6.6 months (95%CI, 4.0-14.6 months)	15.9 months (95%CI, 7.1 months to NR)



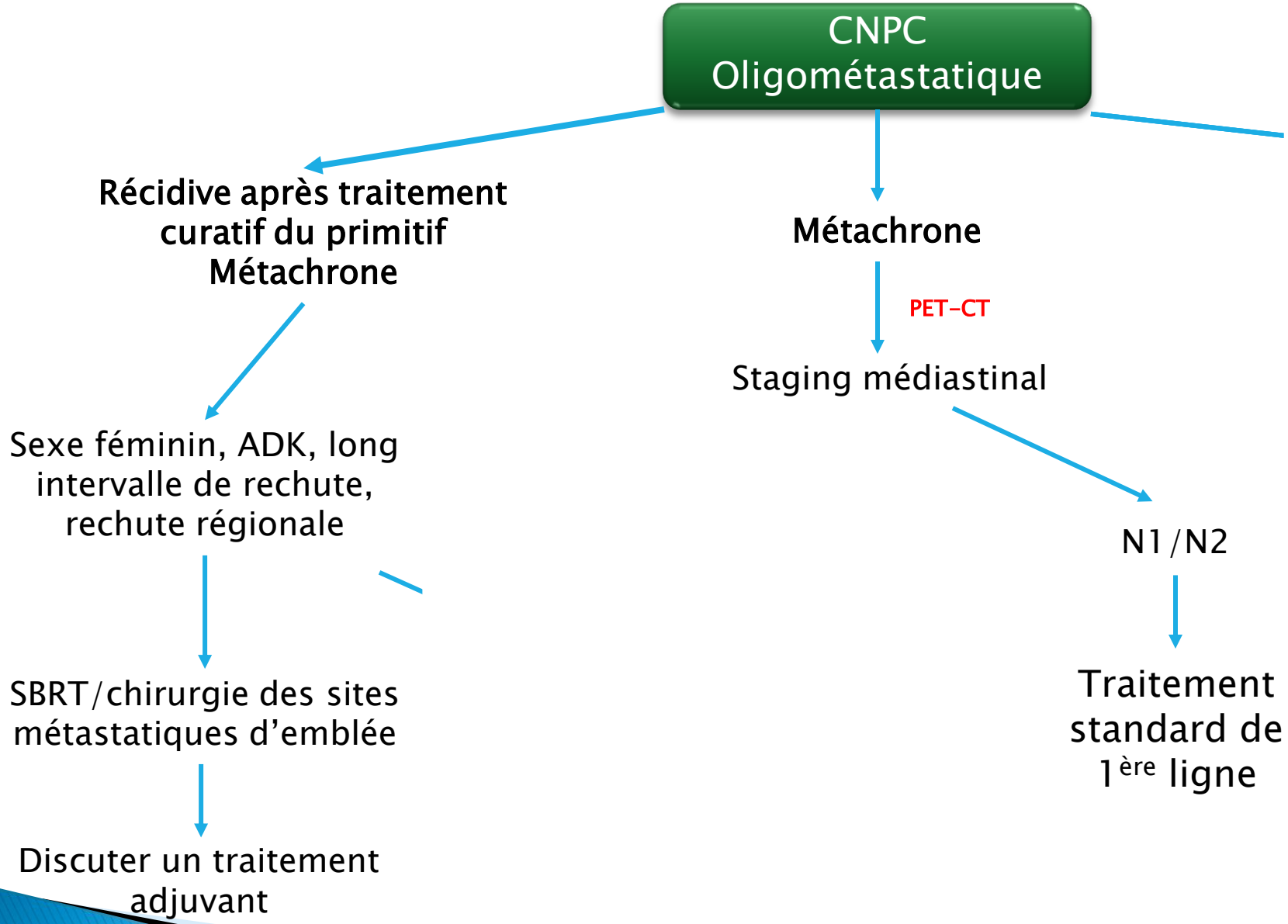
A doubling of the overall response rate; results did not meet the study criteria for meaningful clinical benefit

Subgroup analysis - largest benefit from the addition of radiotherapy was in patients with PD-L1–negative tumors

Abscopal effect

Theelen W, JAMA Oncol 2019

SOMA
Service d'Oncologie Médicale Ariana


CNPC
Oligométastatique
Récidive après traitement curatif du primitif Métachrone
Métachrone
PET-CT
Staging médiastinal
Sexe féminin, ADK, long intervalle de rechute, rechute régionale
N1/N2
SBRT/chirurgie des sites métastatiques d'emblée
Traitement standard de 1ère ligne
Discuter un traitement adjuvant

Le stade oligométastatique soulève beaucoup de questions

- Chez certains patients peut-on parler de guérison? survie 40% à 5 ans
- C'est rare mais c'est possible
- Les facteurs pronostiques existent mais les facteurs prédictifs non
- De plus en plus fréquente: moyens diagnostiques/thérapeutiques

- La surveillance après un traitement initial?

Merci

SOMA
Service d'Oncologie Médicale Ariana

One randomised study with Brain mets as focus

Séquelles pour les longs survivants

- Just another OMD site
- 1-4 asymptomatic BrMs
- chemotherapy starting within 3 weeks of SRS.
- Korea, recruited 105 patients over 5 years and closed early.

	SRS-CT	CT alone
OS mths	14.6	15.3
sym brain PD	18.4%	26.5%
RR in brain	57%	37%
RR	43	40%.

- This potential 8% improvement in symptomatic BrM progression might be clinically relevant but would need a large trial to document this.

Lim et al Ann Oncol 2015 ;26(4):762-8

2 essais cliniques/méta-analyses: pas de différence entre SRS+WBRT vs WBRT

SOMA
Service d'Oncologie Médicale Ariana