

## CASSE-TÊTE DES MALADIES OLIGO-MÉTASTATIQUES : QUELLES MODALITÉS DE PRISE EN CHARGE ?

21/11/2025

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**Angoulême**

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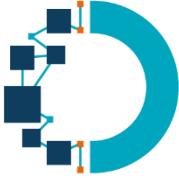
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Oncologue médical - Praticien Hospitalier

CHU Bordeaux

5e rencontre d'oncologie thoracique en nouvelle-aquitaine

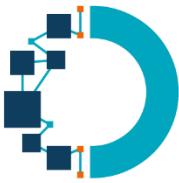




# Liens d'intérêts

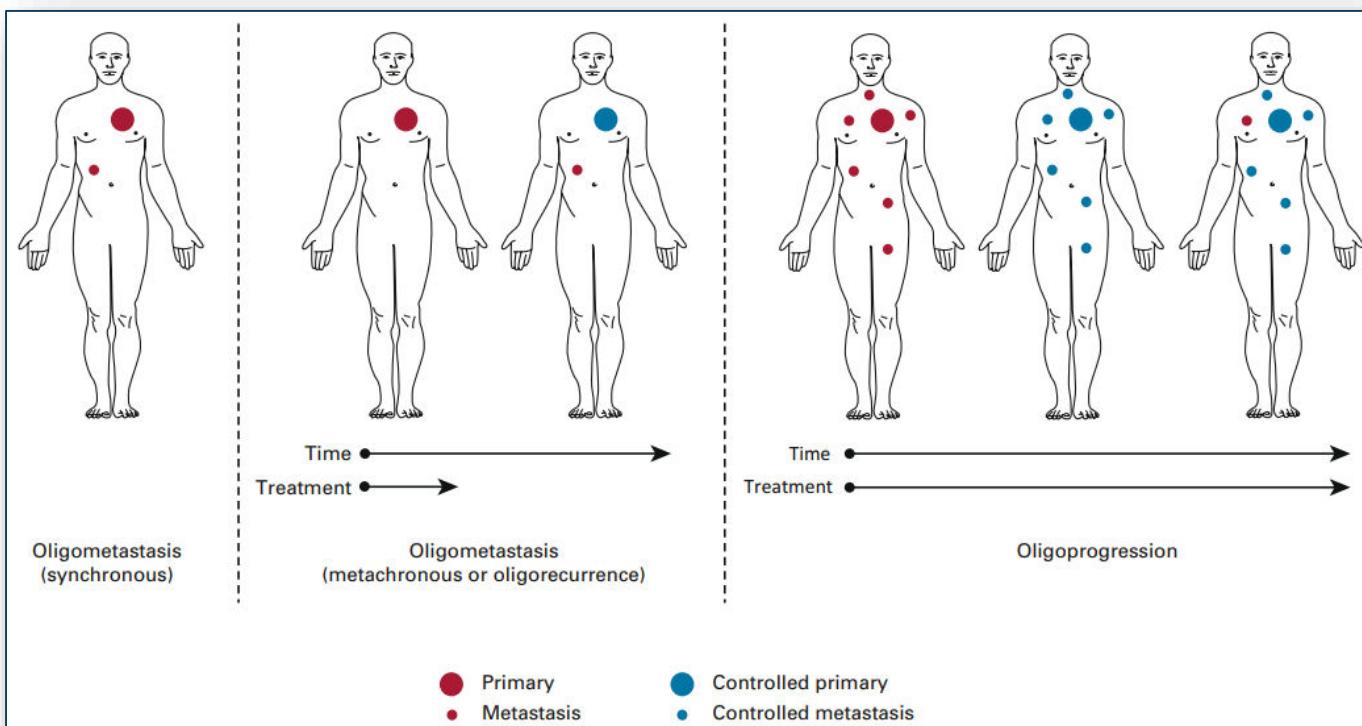
- Participation à des congrès (ASCO, ESMO, WCLC) :
  - Roche, Amgen, Lilly, Boehringer-Ingelheim, Pfizer, MSD, Bristol-Myers Squibb
- Board local d'experts ; animations ou interventions (réunions d'experts, post-congrès)
  - Roche, Astra-Zeneca, Bristol-Myers Squibb, MSD, Pfizer, Takeda, Sanofi, Astra-Zeneca
- Consultant
  - Janssen
- Honoraires investigateurs dans le cadre de recherche clinique :
  - Roche, Astra-Zeneca, Takeda, Abbvie, Merck-Serono, Bristol-Myers Squibb, GSK, Novartis, Janssen, Gilead, Sanofi



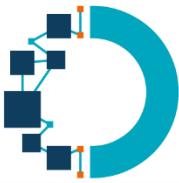


# Définition d'une maladie oligométastatique

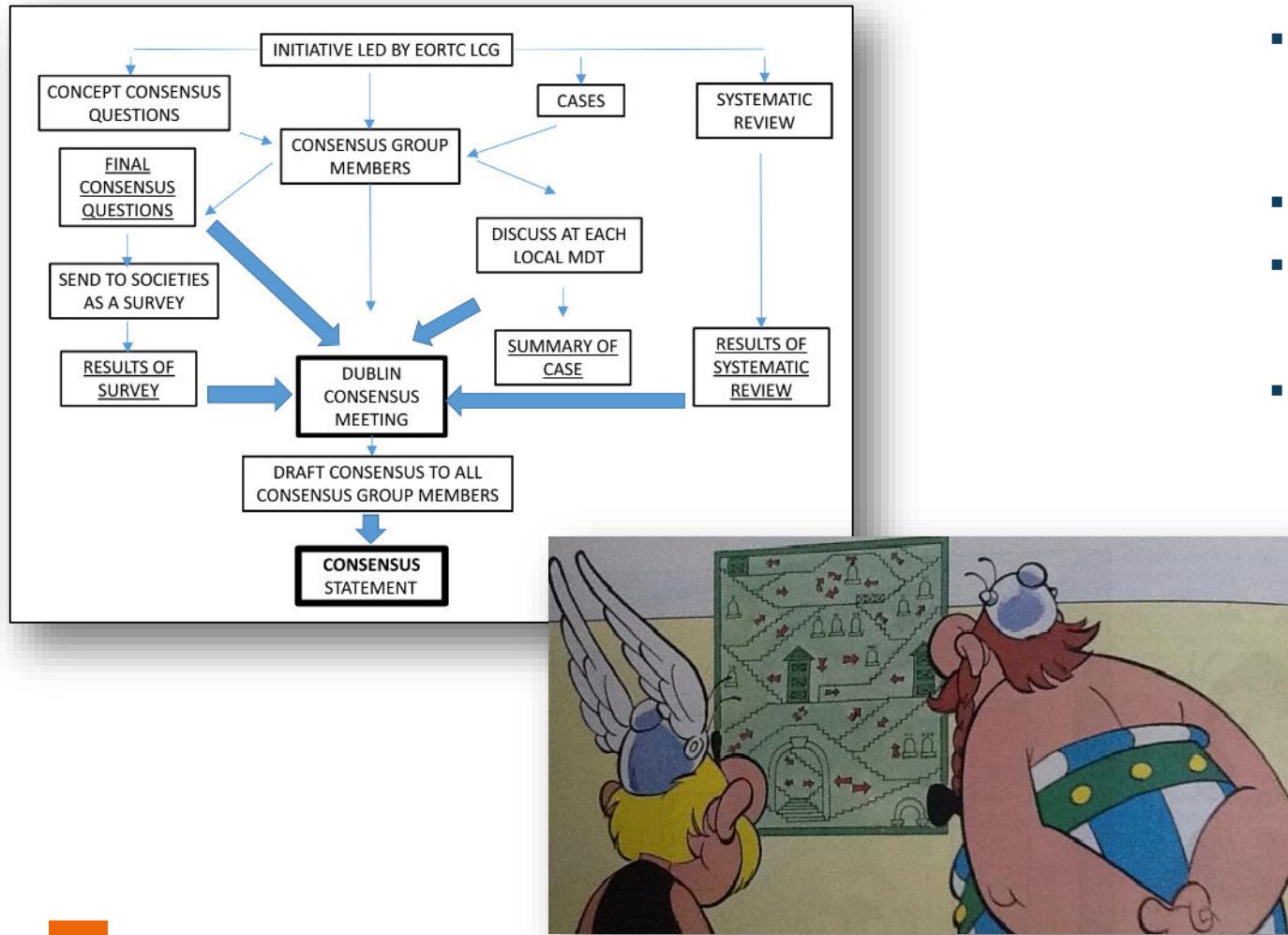
- Oligométastatique Synchrone vs Métachrone
- Oligopersistance / Oligoprogression



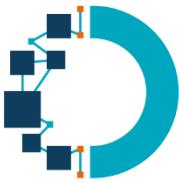
Jasper et al. JCO 2022 ; 40 : 635-664



# Définition (JTO)

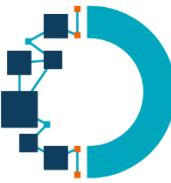


- Réunion de consensus : 35 experts
- Situation où un traitement radical est techniquement faisable sur tous les sites tumoraux
- Maximum 5 métastases / 3 organes
- Adénopathies médiastinales non comptabilisées
- Bilan par
  - TEP et IRM cérébrale
  - IRM hépatique si lésion hépatique unique en TDM et TEP
  - Thoracoscopie si lésion pleurale « unique »



# Définition (EORTC)

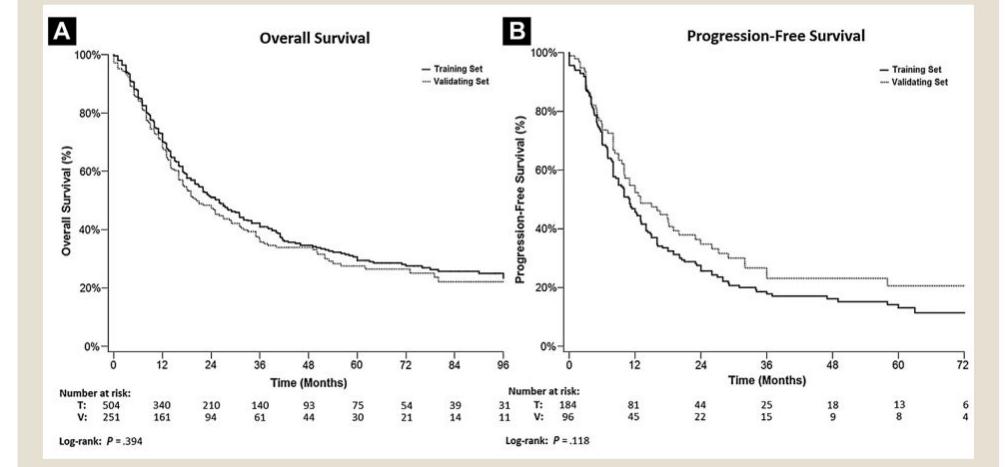
- Basée sur 11 cas cliniques donnés à des experts en 2017
  - Comparaison avec les réponses données par des experts en 2012
  - Comparaison avec les traitements effectivement proposés (puis reçus)
- Notion d'atteinte synchrone (au diagnostic)
- Patients bilantés par TDM, TEP et IRM cérébrale
- 100% des cas considérés oligométastatiques présentent  $\leq 5$  métastases
- 90% des cas considérés oligométastatiques présentent  $\leq 3$  métastases
- Pas de précision sur la prise en compte des ganglions médiastinaux
- Prise en compte de la possibilité d'irradier toutes les lésions



# Métaanalyse ?

- 1985 – 2012
- 757 patients / 20 centres
- Synchrones / Métachrones
- Inclus en essais cliniques : 1 à 5 métastases
- 668 patients (88%) avec 1 seule métastase (hors T et N)
- 269 métastases Cérébrales (35%), 254 pulmonaires (34%) 98 surrénales (13%)
- 339 patients (62%) avec métastases traitées par résection chirurgicale.
  
- Médiane survie globale : 26 mois
- Taux de survie 70% à 1 an ; 51% à 2 ans ; 29% à 5 ans ; 23% à 8 ans

Figure 1 Kaplan-Meier Estimates of (A) Overall Survival and (B) Progression-Free Survival in the Training Set (T); n = 505, and in the Validating Set (V), n = 252





# Recommandations ESMO

## **Patients with oligometastatic disease**

- Patients with oligometastatic NSCLC (synchronous, metachronous, oligoprogressive) should be staged with FDG-PET-CT and brain imaging [IV, B].
- LRT in addition to systemic treatment is recommended as it may increase PFS and OS [II, B].
- The choice of LRT (RT, surgery) should be discussed in the MTB as both are safe and effective [III, B].
- Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous second primary tumours and, if possible, treated with curative-intent therapy [IV, B].

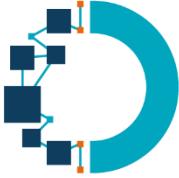
- Bilan par TEP et IRM cérébrale
- Ajouter un traitement local au traitement systémique
- Choix du traitement local (chirurgie vs radiothérapie) à discuter en RCP
- Une lésion unique pulmonaire controlatérale doit être considérée comme un 2nd primitif

**Oligometastases.** ‘Oligometastatic’ refers to a state of a limited number of metastases in a limited number of organs.<sup>96</sup> Different types of oligometastatic disease exist (for example, synchronous, metachronous, oligopersistent/induced and oligoprogressive; for a detailed description see Guckenberger et al.<sup>97</sup>). The prognosis of patients with metachronous metastases is superior to those with synchronous metastases, and mediastinal involvement is a negative prognostic factor.<sup>98</sup>

To consider a disease oligometastatic, the most accepted maximum number of metastatic lesions is five, even if in the majority of studies patients with only one to two distant lesions were included.<sup>99</sup> A special situation is the case of a solitary lesion in the contralateral lung (second primary versus metastasis); for differentiation, these patients should be discussed in the multidisciplinary team (MDT).

In the trials addressing oligometastatic local ablative concepts, all metastases, the primary tumour and, if applicable, involved mediastinal lymph nodes had to be eligible for radical treatment by local therapy [radiotherapy (RT), resection or both]. Of note, not all completed trials mandated baseline FDG-PET-CT and brain imaging, while these are both recommended in the European Organisation for Research and Treatment of Cancer (EORTC) synchronous oligometastatic NSCLC consensus.<sup>99</sup>

Trial data evaluating local radical therapy (LRT) in synchronous oligometastatic NSCLC are limited. A single-arm phase II trial ( $N = 40$ ; 87% with a single metastasis, one patient with a known EGFR mutation) reported 5- and 6-year survival rates of 8% and 3%, respectively.<sup>101</sup> Two phase II RCTs ( $N = 49$ , including eight patients with an oncogenic driver and  $N = 29$ ) showed that PFS improved with the addition of LRT to systemic therapy in patients with oligometastatic NSCLC that responded to induction systemic therapy (ChT or tyrosine kinase inhibitor, no ICI used). Of note, both trials were closed prematurely due to impressive PFS benefits,<sup>102,103</sup> and one trial also demonstrated an OS benefit (other trial no OS data reported yet):



# Référentiels AURA : succinct

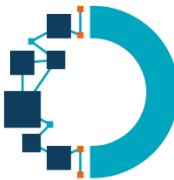
## 5.9. Oligométastases

- Les patients oligométastatiques constituent un groupe à part avec un pronostic différent des patients multi-métastatiques (1,64).
- Il est conseillé de se reporter au référentiel correspondant édité par les réseaux du Grand-Est et Ile de France.
- De manière générale, le traitement des patients oligométastatiques doit comprendre :
  - o une chimiothérapie avec ou sans immunothérapie, avec ou sans poursuite d'une chimiothérapie et/ou immunothérapie de maintenance
  - o et/ou un traitement local (chirurgie / radiothérapie / autre) bifocal qui peut être mené de manière séquentielle.
  - o La stratégie complète et l'ordre des séquences doivent être définis en RCP (→ référentiels métastases osseuses et cérébrales).

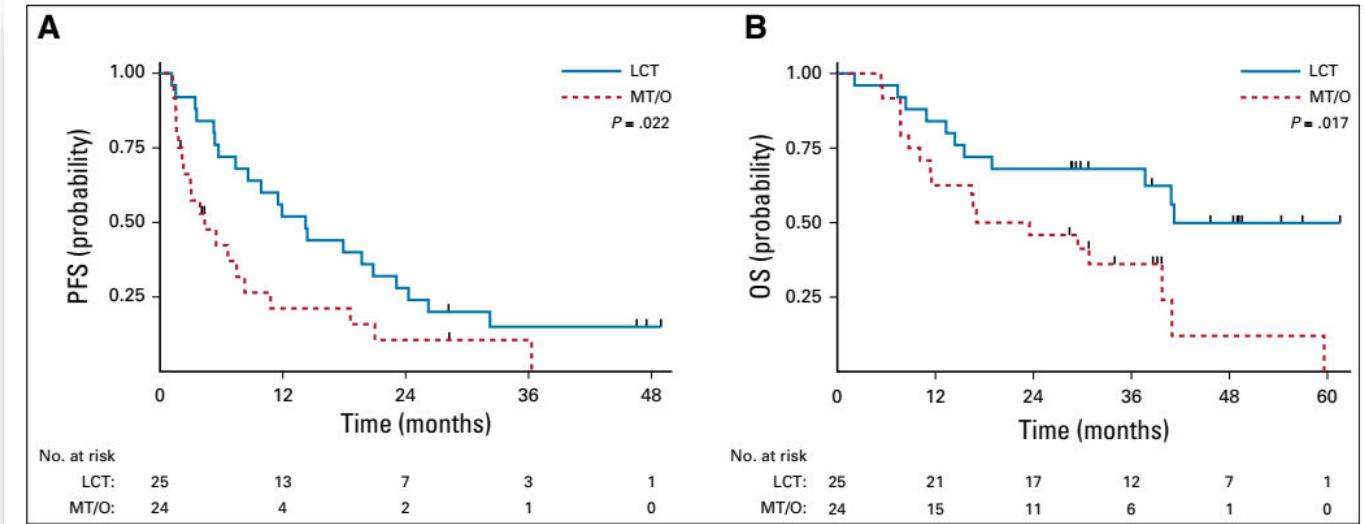
### Recommandation

Les patients présentant une maladie oligo-méstatique doivent être identifiés et discutés en RCP pour envisager la stratégie thérapeutique optimale.

<http://referentiels-aristot.com/>



# Etude randomisée



**FIG 1.** (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non-small-cell lung cancer.

- CBNPC métastatique (2012-2016)
- $\leq 3$  site métastatiques (en plus de la tumeur primitive ; adénopathies médiastinales comptant pour un site)
- Maintenance vs traitement local
- 49 patients (25/24) (étude stoppée précocement, trop grande différence en SSP)
- Survie sans progression médiane **14 vs 4,4 mois** ( $p=0,022$ )
- Sur 39 progressions : 15 re-traitements locaux (6 du bras ttt et 9 du bras observation/maintenance)
- Survie globale médiane **41 vs 17 mois** ( $p=0,017$ )

Gomez et al. Lancet Oncol 2016 ; 17 : 1672-82  
Gomez et al. JCO 2019 ; 37 :1558-1565

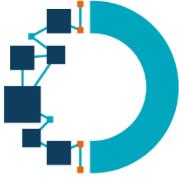


# Point d'étape

■ Définition...

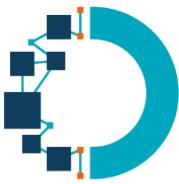
- Synchrone / Métachrones / Oligoprogression / Oligoresistance
- Nb métastases
- Ganglions ?

- Essais cliniques datant de l'aire pré-immunothérapie pré-thérapies ciblées
  - Fin de traitement prévu (4-6 cycles de chimiothérapie)
  - Net bénéfice de l'impact des traitements locaux
- Perspective :
  - Addictions oncogéniques
  - Immunothérapies



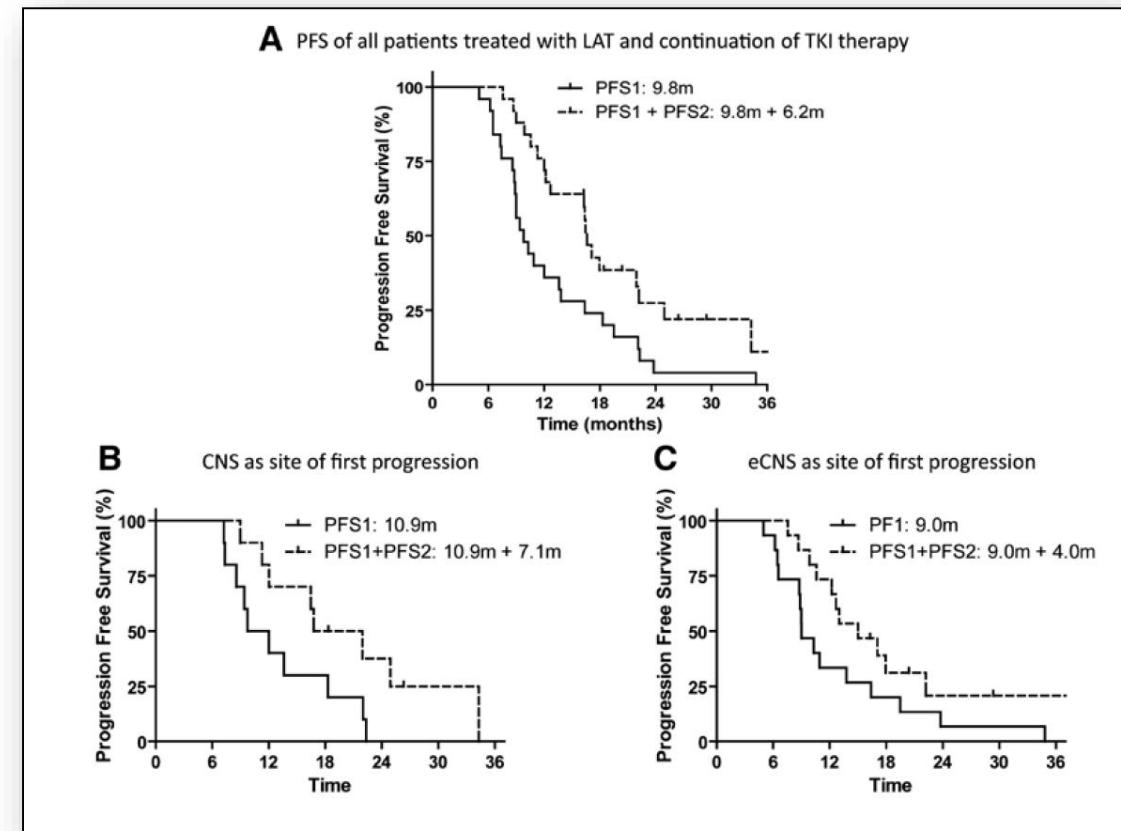
# Addiction oncogénique

- Les taux de réponse sous thérapie ciblée sont bons
- Prise en charge de l'oligoprogression
- En situation synchrone :
  - il ne faut pas qu'un traitement local retarde l'initiation de la thérapie ciblée
- En situation de réponse (oligopersistance)
  - éradiquer une maladie résiduelle

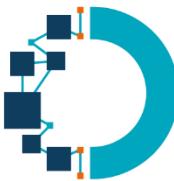


# Oligoprogression

- 25 patients sous TKI ALK ou EGFR
- Traitements locaux (radiothérapie)
- Gain de 4 à 7 mois avant nouvelle progression



Weickhardt, et al. JTO 2012 ; 7 : 1807-1814.



# Oligoprogression

- Patients mutés EGFR sous TKI
- Cohorte prospective
- Protocole de rebiopsie à progression sous TKI
- 18 patients : progression oligométastatique (<5 sites)
- Diagnostic → traitement local : 26 mois (médiane)
- 13 progressions : 1 seule progression locale (pleuro-pneumonectomie extra pleurale) ; 12 progressions à distance ; 8 décès
- Médiane SSP : 10 mois (1-51) (IC95% : 2-27)
- Médiane de temps jusqu'à changement de traitement systémique : 22 mois
- Médiane OS : 41 mois (1 – 65+) (IC 95% : 26 – NA)

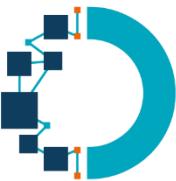
ORIGINAL ARTICLE

Local Therapy with Continued EGFR Tyrosine Kinase Inhibitor Therapy as a Treatment Strategy in EGFR-Mutant Advanced Lung Cancers That Have Developed Acquired Resistance to EGFR Tyrosine Kinase Inhibitors

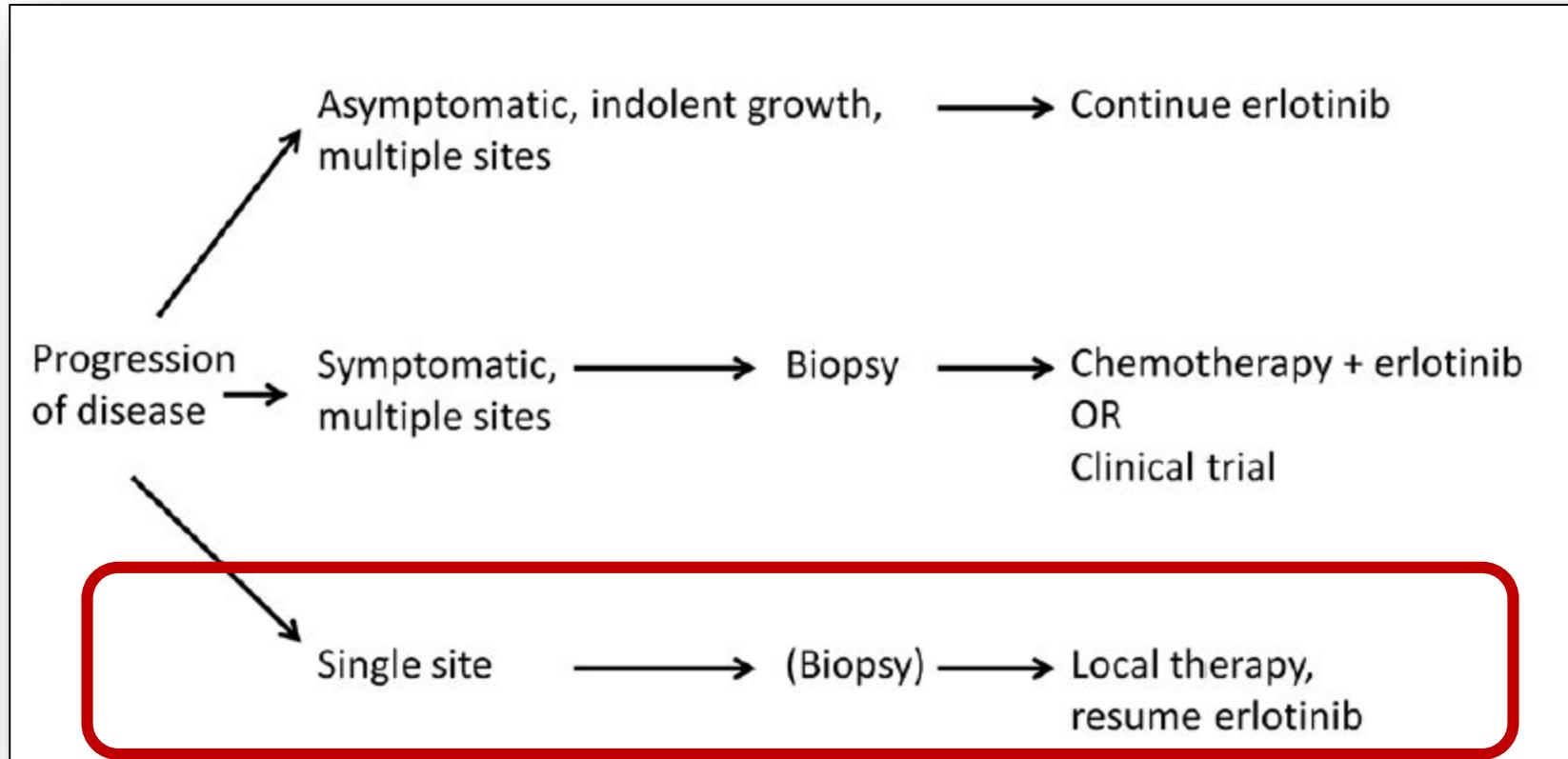
TABLE 2. Procedures

Performed

Total	18
Lung	15
Radiofrequency ablation	2
Stereotactic radiotherapy	1
Radiation therapy	1
Lobectomy	7
Wedge resection	1
Pneumonectomy	3
Lymph node (supraclavicular)	
Radiation therapy	1
Adrenal gland	
Adrenalectomy	2

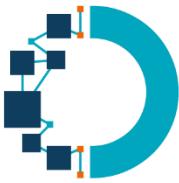


# Prise en charge de la progression sous TKI ?



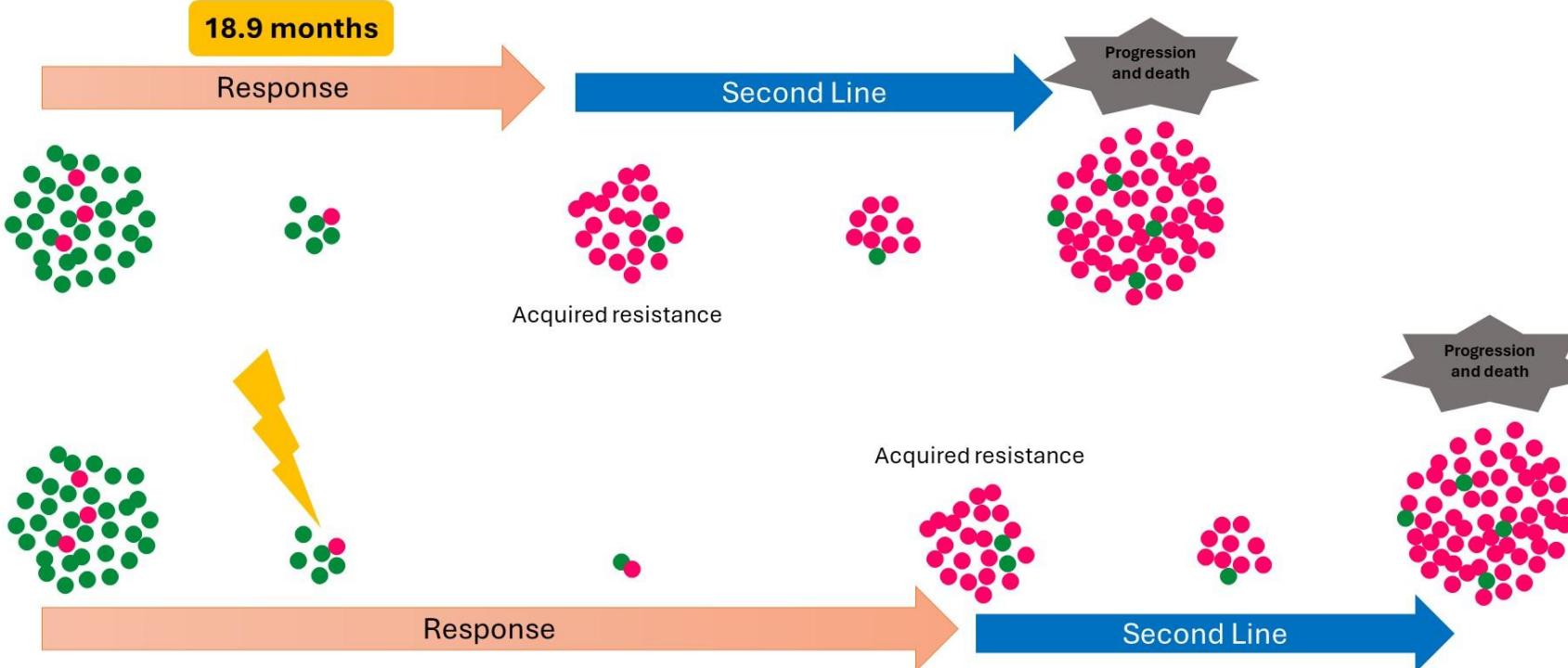
**FIGURE 3.** An approach to management of patients with acquired resistance to EGFR TKI therapy

*Yu, et al ; JTO 2013 ; 8 : 346-351*



# Prévenir l'oligopersistance

## Background



2024 ASCO  
ANNUAL MEETING

#ASCO24

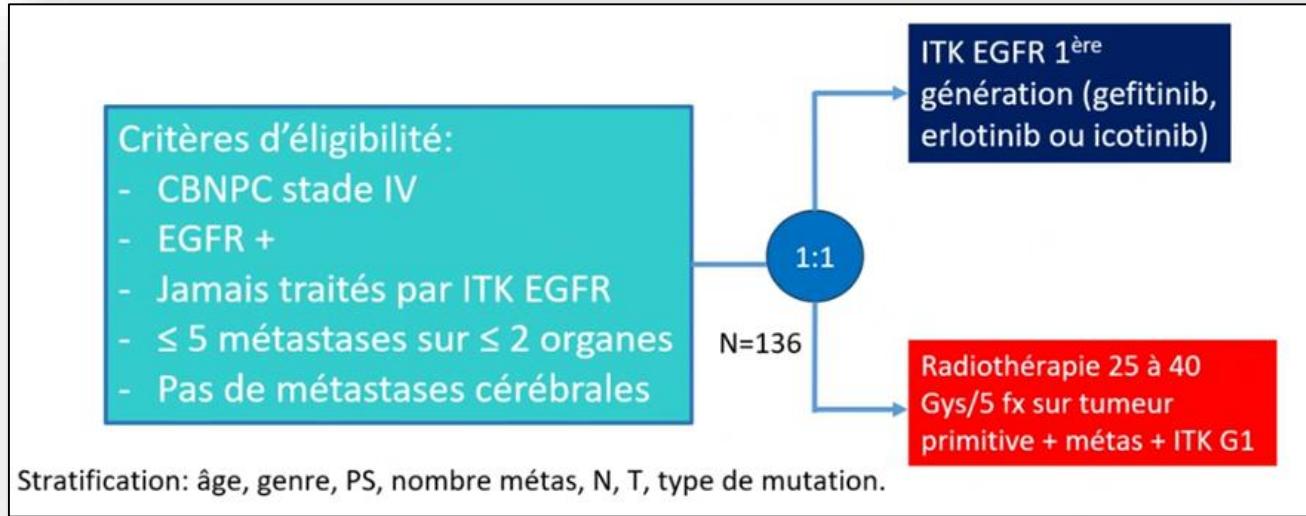
PRESENTED BY: Sawsan Rashdan, MD

Presentation is property of the author and ASCO. Permission required for reuse; contact [permissions@asco.org](mailto:permissions@asco.org).

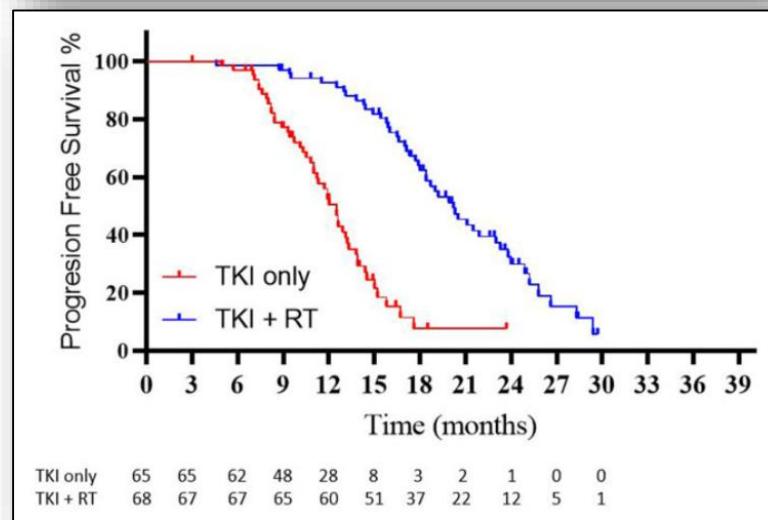
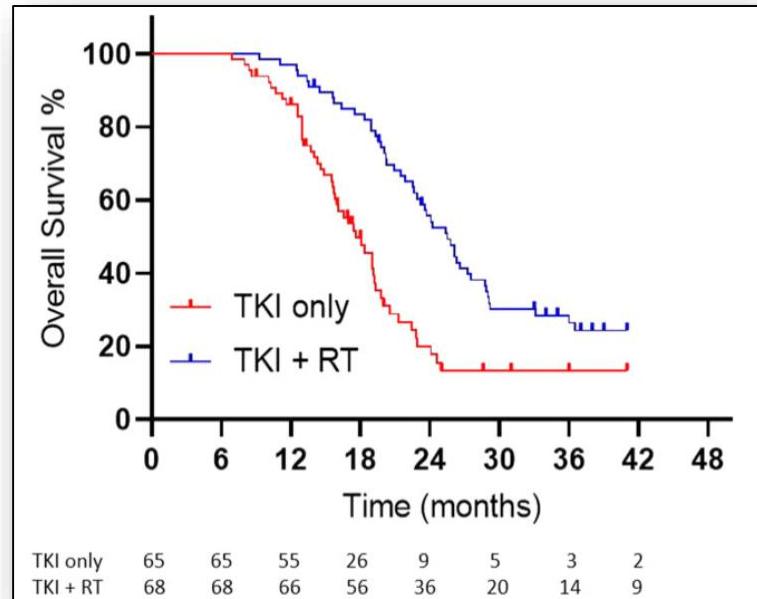
ASCO® AMERICAN SOCIETY OF  
CLINICAL ONCOLOGY  
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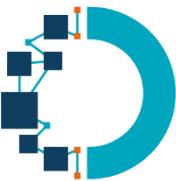


# Exemple d'étude : SINDAS

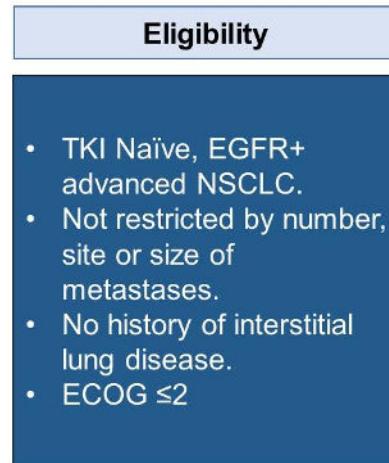


- Bilan extension n'imposant pas TEP et IRM
- Dose radiothérapie sous optimales
- Inhibiteurs de 1<sup>ère</sup> génération
- **Timing radiothérapie ?**

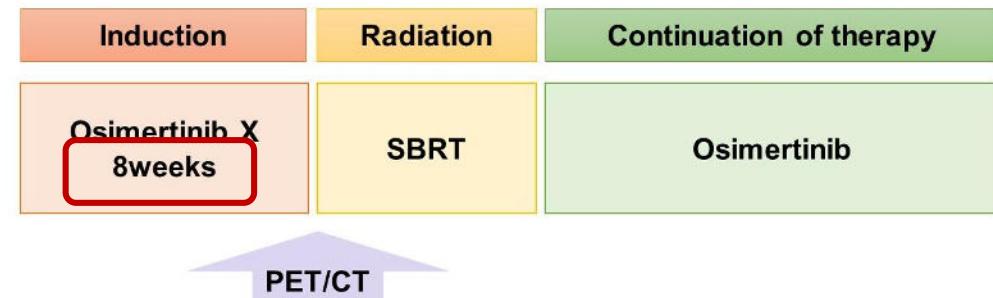




# Exemple

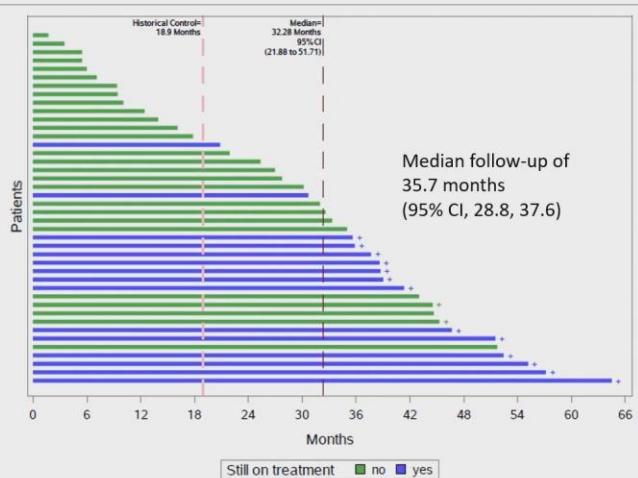


Multicenter, single arm phase 2 IIT



## Results

### Progression-free Survival

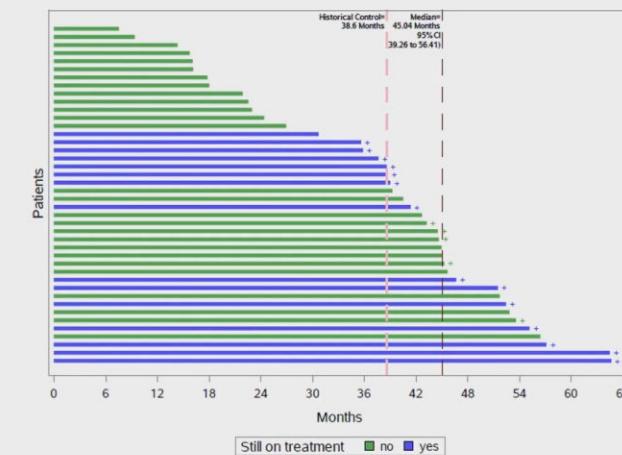


Median PFS 32.3 months exceeds published historical standard FLAURA trial for first line treatment 18.9 months

Comparison of separate trials for discussion only. The presented data are not meant to be viewed as head-to-head trial data

## Results

### Overall Survival

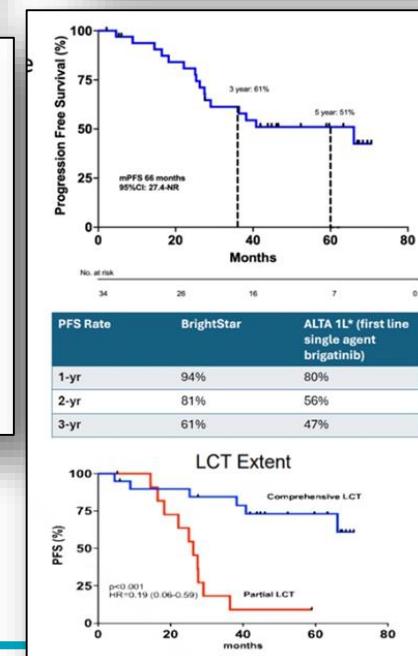
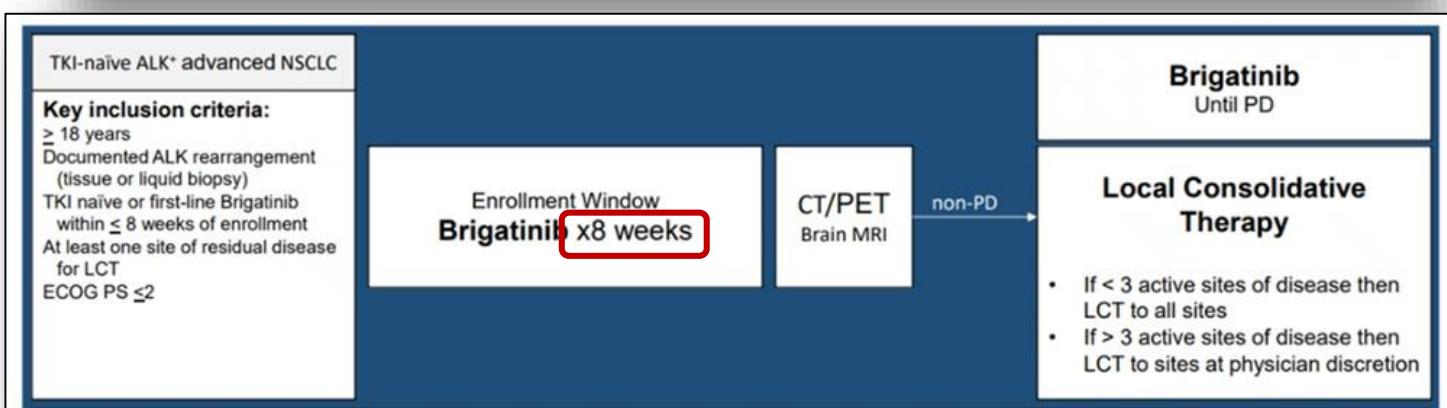
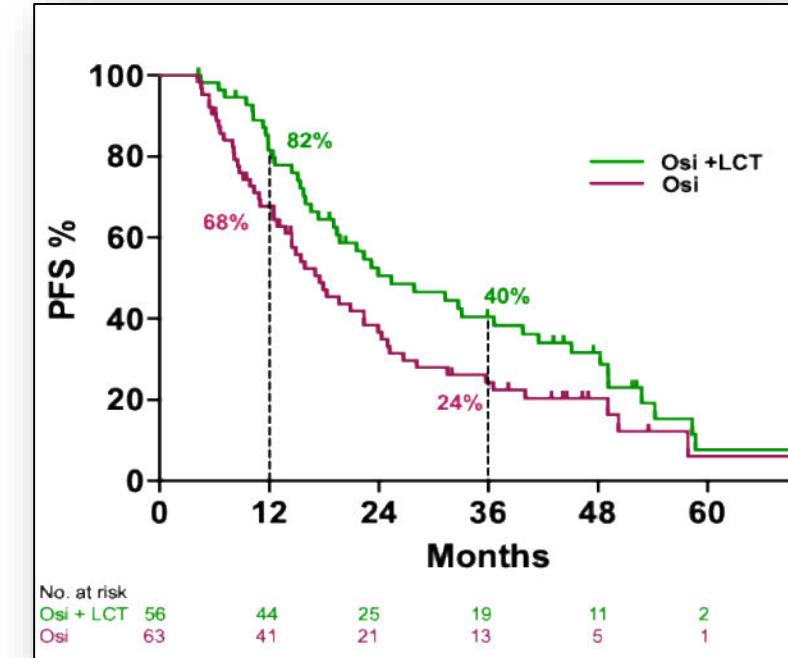
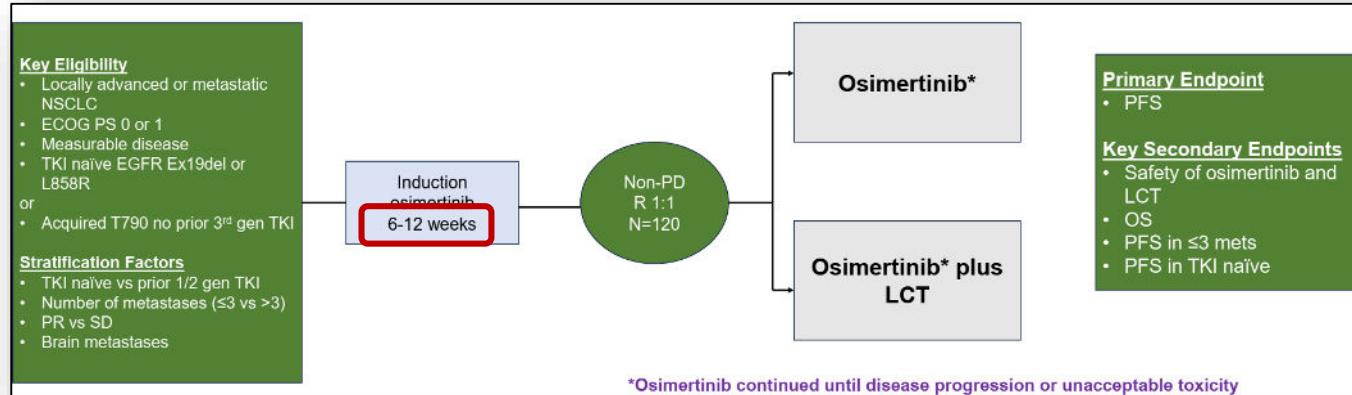


Median OS 45 Months exceeds published historical standard FLAURA trial for first line treatment 38.6 months

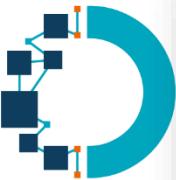
Comparison of separate trials for discussion only. The presented data are not meant to be viewed as head-to-head trial data



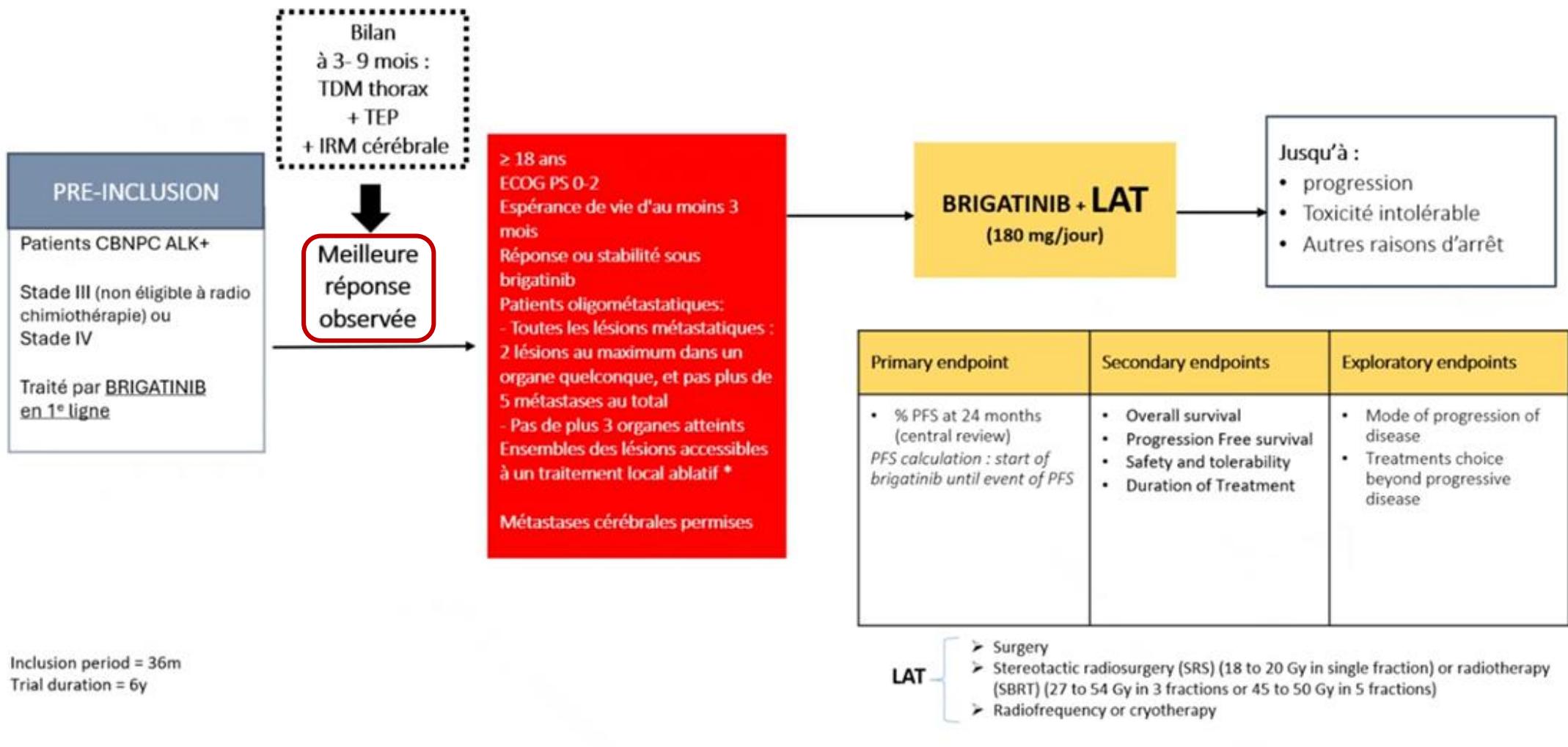
# Exemple : Northstar

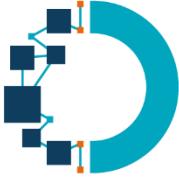


Elamin, ESMO 2025  
Elamin, WCLC 2025



# OPTALK GFPC 07-2023 : design



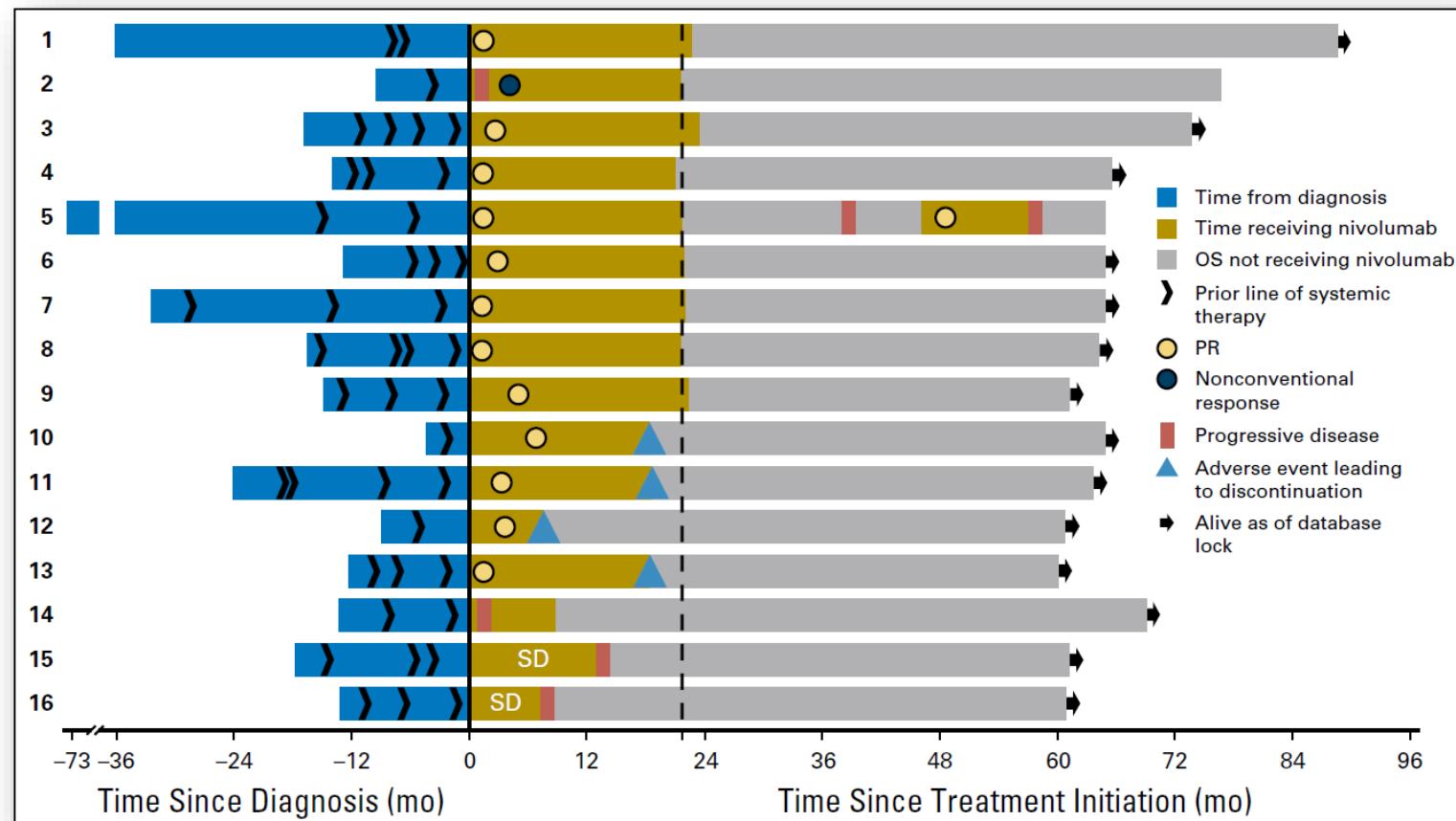


# Addiction oncogénique

- Faut il traiter l'oligopersistance ?

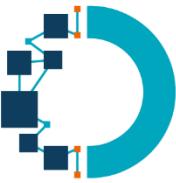


# Apport de l'immunothérapie

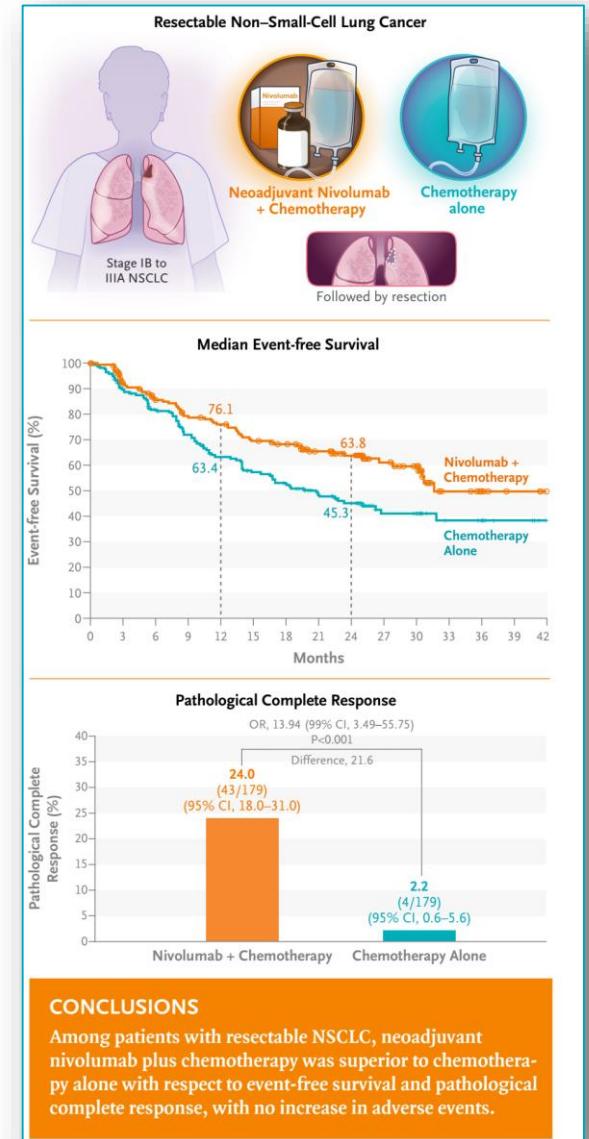
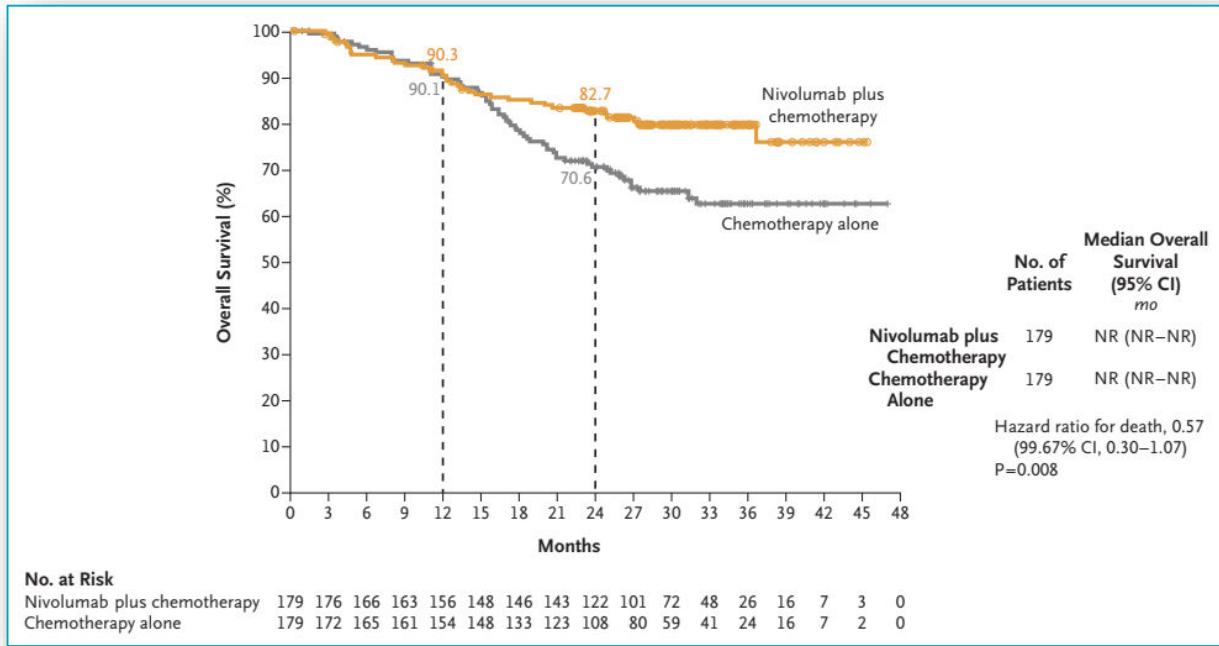


- À 5 ans

Gettinger et al. JCO 2018 ; 36 : 1675-1684



# Apport de l'immunothérapie



- Maladie oligo métastatique :
  - Immunothérapie (+/-) chimiothérapie
  - Puis traitement local
- ≈ néoadjuvant ?

Forde et al. NEJM 2022 ; 386 : 1973-85



# Apport de l'immunothérapie

NRG-LU002: randomized phase II/III trial of maintenance systemic therapy versus local consolidative therapy (LCT) plus maintenance systemic therapy for limited metastatic non-small cell lung cancer

- Stades IV
- 4 cycles chimio-immunothérapie
- Exclusion patients EGFR/ALK
- Éligibilité si
  - Absence de progression
  - ≤ 3 sites extra-cérébrales
  - Au moins 1 site accessible à un traitement ablatif local: SBRT/radiothérapie +/- chirurgie

N=218

Analyse arrêtée à la 1<sup>ère</sup> analyse intermédiaire (fin de la phase 2)

- Evénements indésirables grade ≥2 : 84% vs 73%
- Pneumopathies : 10% vs 1%



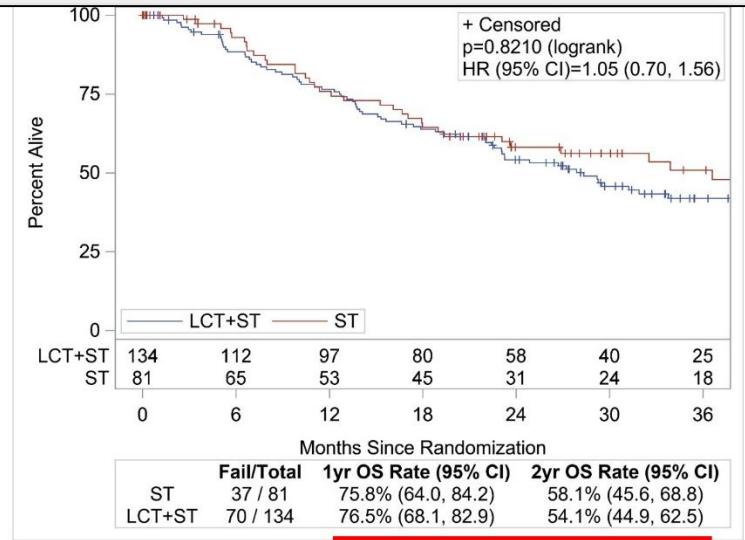
## Results – OS

Median Follow-up:

All patients – 21.9 mo

Surviving patients – 29.4 mo

Of 185/215 patients treated with IO-containing systemic therapy regimens, the OS HR remained 1.05 (95% CI: 0.68, 1.63).



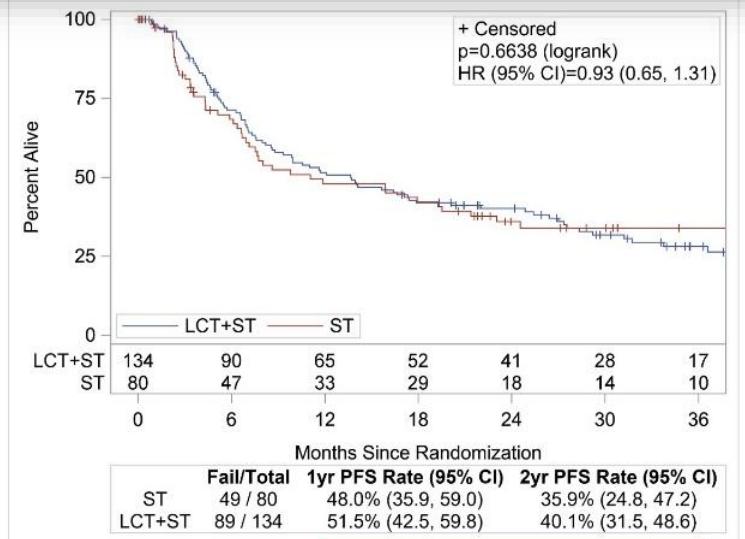
## Results – PFS

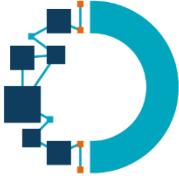
Median Follow-up:

All patients – 21.9 mo

Surviving patients – 29.4 mo

Of 185/215 patients treated with IO-containing systemic therapy regimens, the PFS HR was 0.90 (95% CI: 0.61, 1.32).

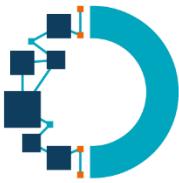




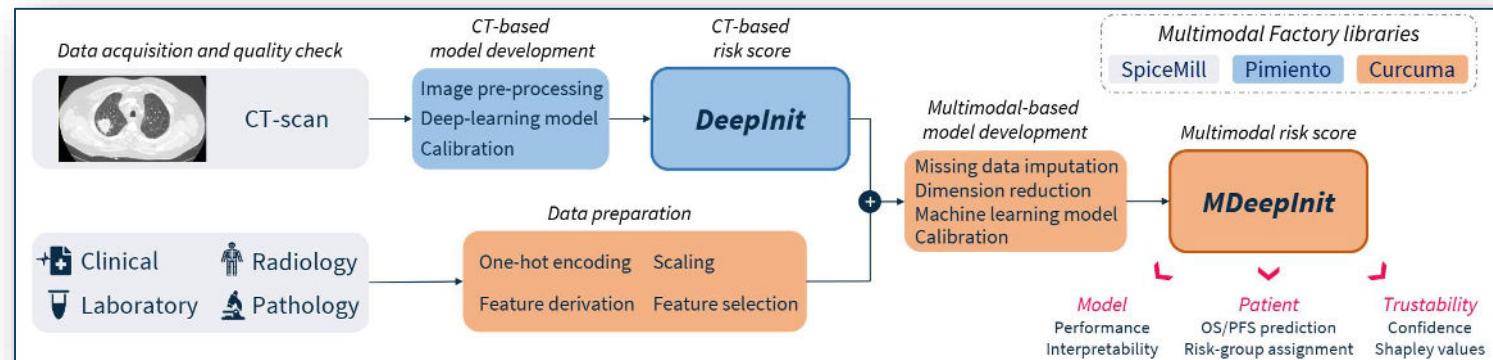
## Place de l'immunothérapie

- Amélioration de l'efficacité du traitement systémique
- Traitements locaux à des patients potentiellement guéris ?
- Souhait d'augmenter le nombre de long répondeur
  
- Qui est l'adjuvant de qui ?
  
- Comment choisir les patients à qui proposer des traitements locaux...

# Place de l'IA ?



## DEEP-LUNG IV

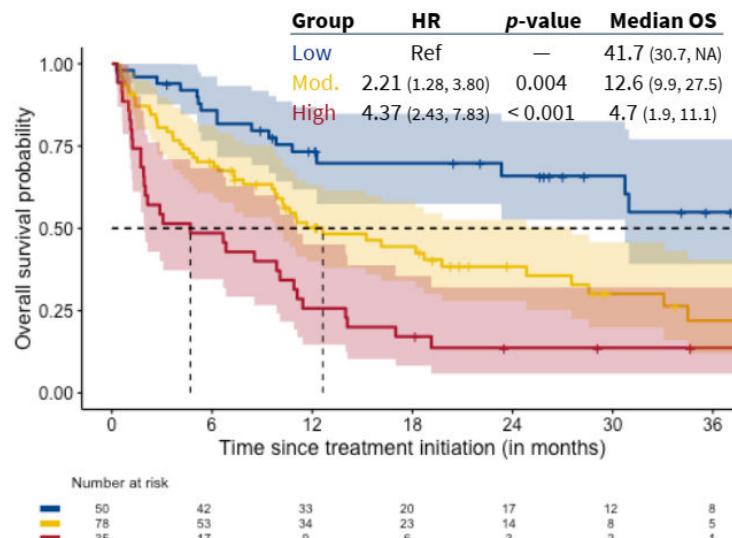


### Risk-group stratification

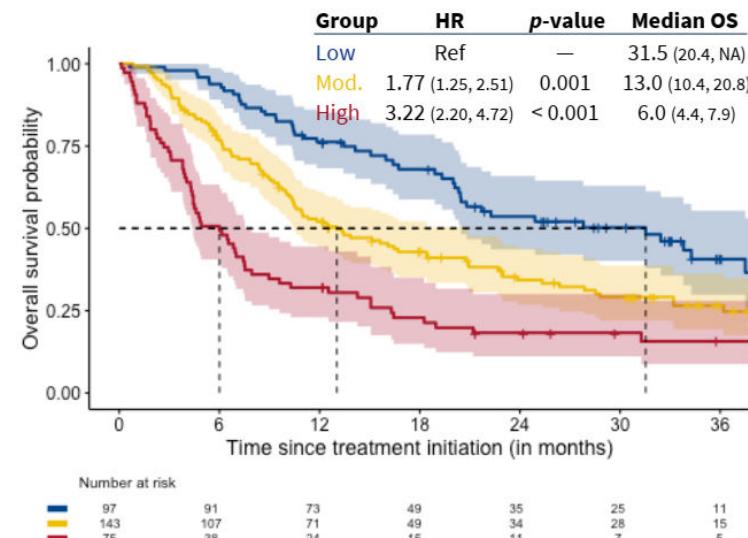
**Figure 4.** Kaplan-Meier OS curves stratified by *MDeepInit*-based risk groups, for P and P+CTx testing cohorts.

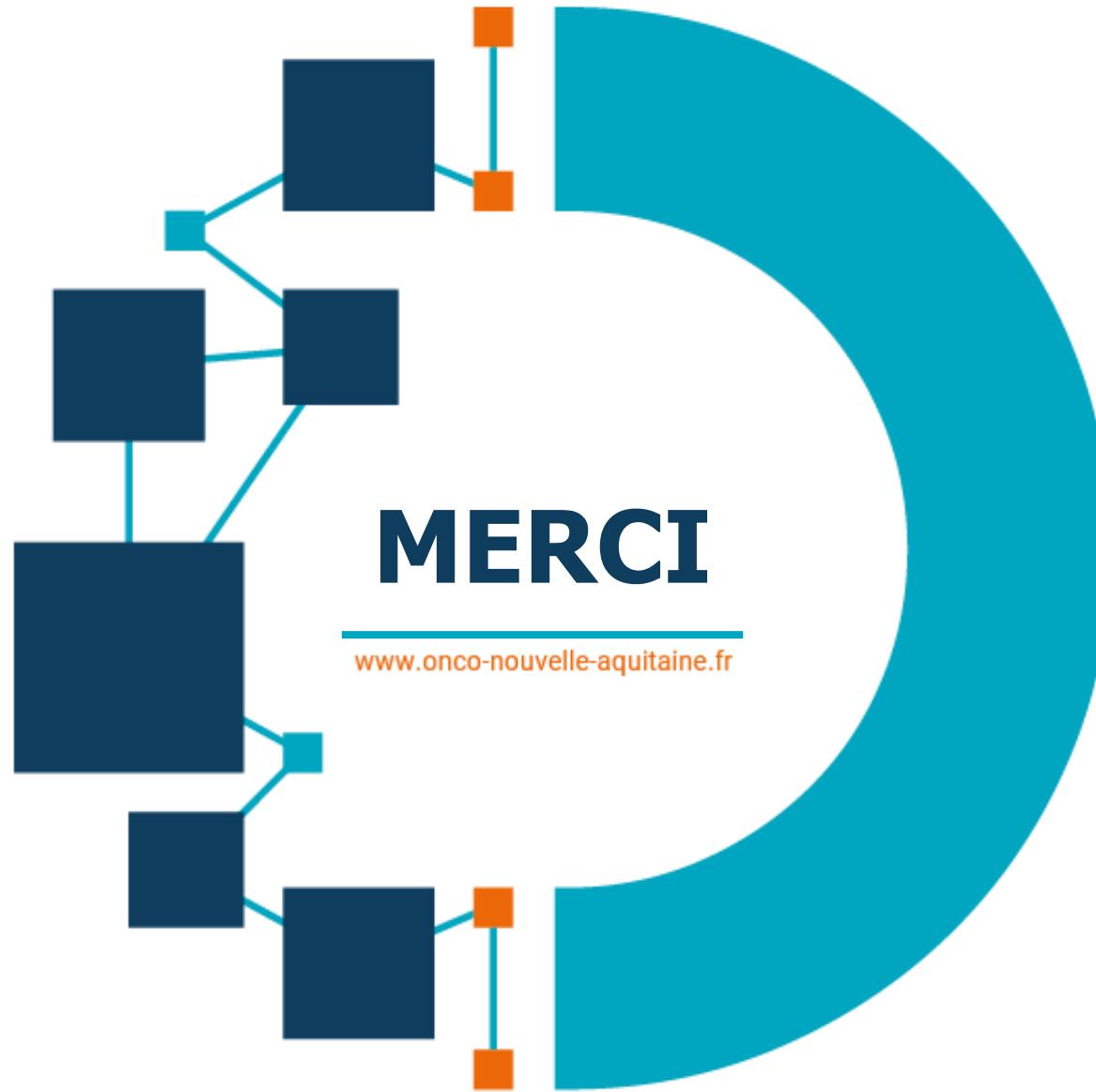
HR stands for hazard ratio.  
95% CIs are given in parentheses.

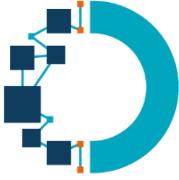
#### Cohort P – Testing



#### Cohort P + CTx – Testing





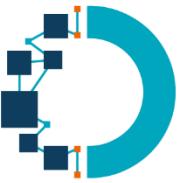


# Atteinte cérébrale (référentiels AURA-aristot)

- 1 métastase :
  - résection chirurgicale
  - option : radiothérapie stéréotaxique
- 2-4 métastases :
  - Radiothérapie stéréotaxique
  - Option : traitement combiné chirurgie/radiothérapie
- Traitement systémique à discuter en RCP
- Séquence thérapeutique : privilégier le traitement de l'atteinte cérébrale



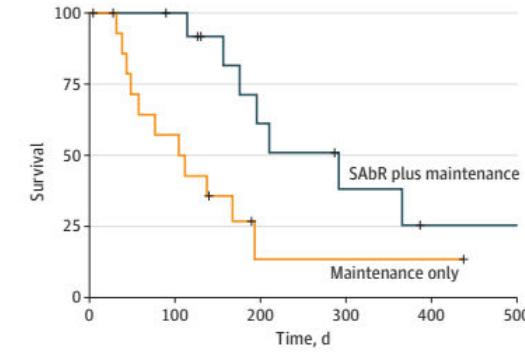
<http://referentiels-aristot.com/>



# Etude randomisée

- Phase II
- 2014 - 2016
- Après induction bithérapie (sels de platine)
- Jusqu'à 6 lésions extra-cérébrales
  - Primitif + 5 métastases max
  - Pas plus de 3 lésions pulmonaire ou hépatique
  - Métastases cérébrales exclues (ou traité avant l'induction)
- randomisation maintenance vs Irradiation + maintenance
- Irradiation lésion primitive et toutes les métastases
- Bras maintenance : 10 rechutes ; 7 sur un site déjà connu
- Bras radiothérapie : 4 rechutes, sites non irradiés
- SSP médiane **9,7 vs 3,5 mois** (HR 0,3)
- SG médiane : non atteinte vs 17 mois (2 cross-over)
- En regardant les irradiations effectivement réalisées : pas plus de 3 sites irradiés

Figure 2. Analysis of Progression-Free Survival

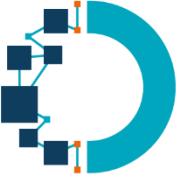


	No. at risk				
	SAbR plus maintenance	Maintenance only	14	12	6
			14	12	6
			15	8	1

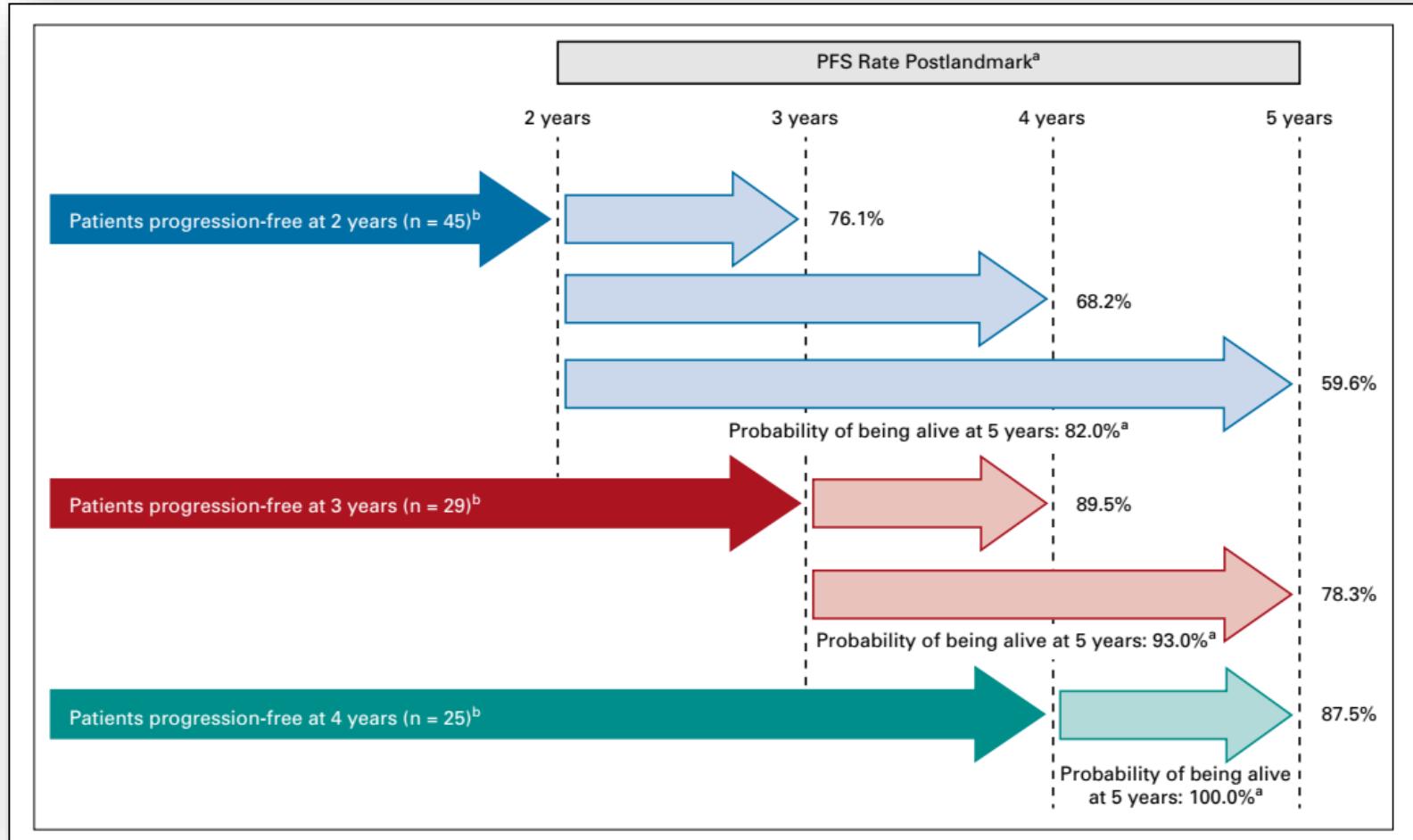
Log-rank testing reveals a statistically significant benefit in progression-free survival for SAbR-plus-maintenance chemotherapy (hazard ratio, 0.304; 95% CI, 0.113-0.815;  $P = .01$ ). SAbR indicates stereotactic ablative radiotherapy.

Table 1. Comprehensive Demographics of 29 Patients

Characteristic	SAbR Plus Maintenance	Maintenance Only	P Value
Sex			
Male	9 (64.3)	11 (73.3)	
Female	5 (35.7)	4 (26.7)	
Median (range) age, y	63.5 (51.0-78.0)	70.0 (51.0-79.0)	.13
Histology			
Squamous	1 (7.1)	3 (20.0)	
Nonsquamous	13 (92.9)	12 (80.0)	
Sites of disease prior to induction chemotherapy, median No. (range)	3 (2-6)	2 (2-5)	.58
Previously treated brain metastases			
Yes	6 (42.9)	5 (33.3)	
No	8 (57.1)	10 (66.7)	
Induction chemotherapy, median cycles (range)	4.5 (4-6)	4 (4-6)	.31



# Apport de l'immunothérapie



- CM 017 et 057 : Nivolumab vs Docetaxel
- Probabilité d'être vivant à 3, 4 et 5 ans selon la survie sans progression

Borghaei et al. JCO 2021 ; 39(7):723-733