

CANCERS BRONCHIQUES NON À PETITES CELLULES MÉTASTATIQUES AVEC ADDICTION ONCOGÉNIQUE

Quelles données suivre en 2019
pour préparer l'édition 2020 ?

(EGFR, BRAF, HER2, ALK, ROS et autres)



Radj Gervais
Catherine Dubos
Pascal Dô
Delphine Lerouge
Serge Danhier

Dingyu Xiao
Pierre Rousselot
Léo Peschard

Charlotte Raboutet
Marie-Aude Thenint

Comité Thorax
Centre François Baclesse, Caen

29 mars 2019, Nice



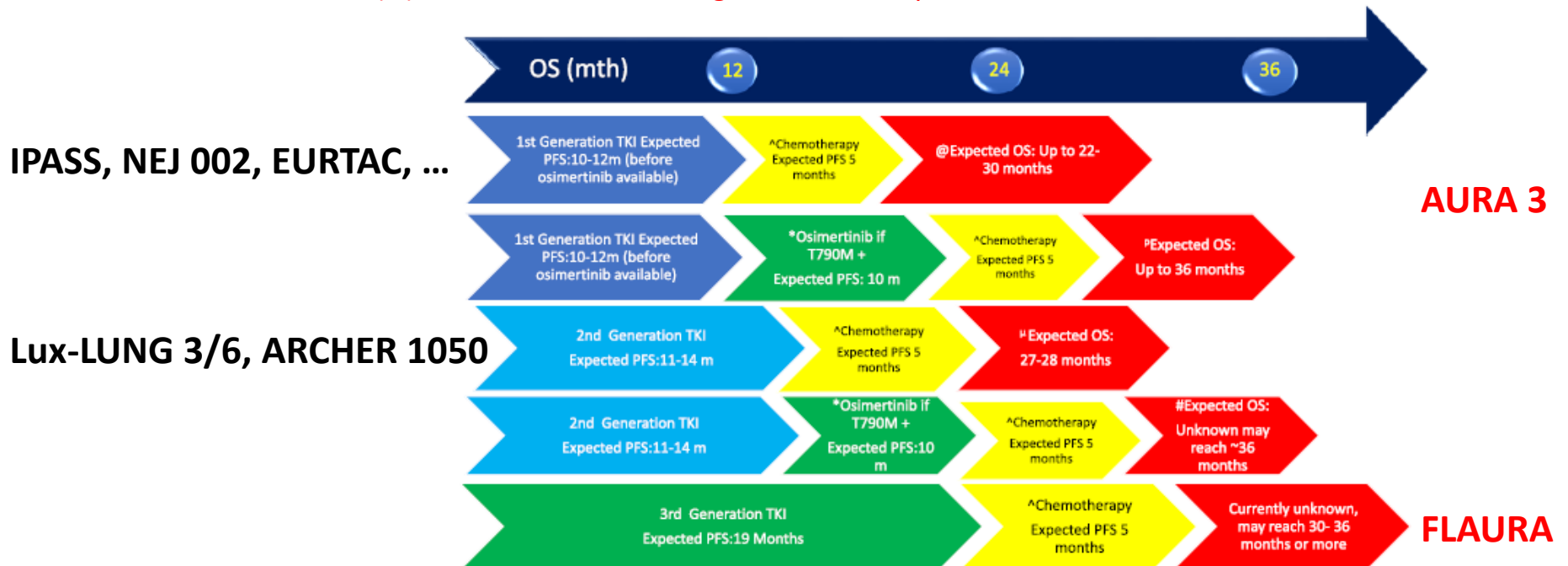
Liens d'intérêt

- Boehringer-Ingelheim, Astra-Zeneca, Roche, Pfizer, Novartis, Takeda

EGFR

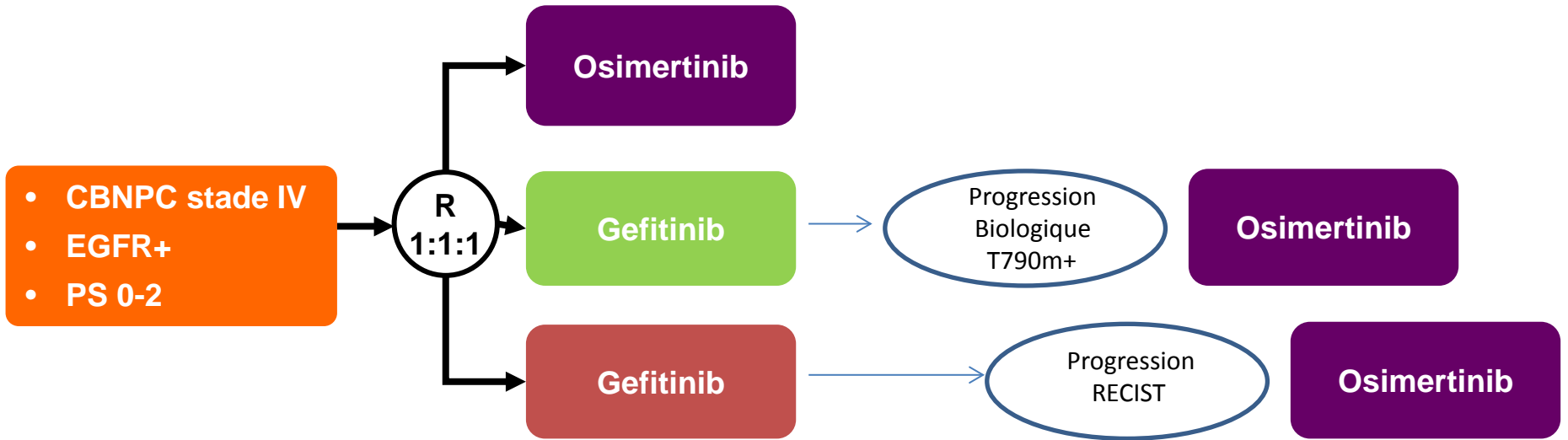
EGFR

- « L'essai FLAURA (...) Les résultats en survie globale ne sont pas encore matures »



EGFR

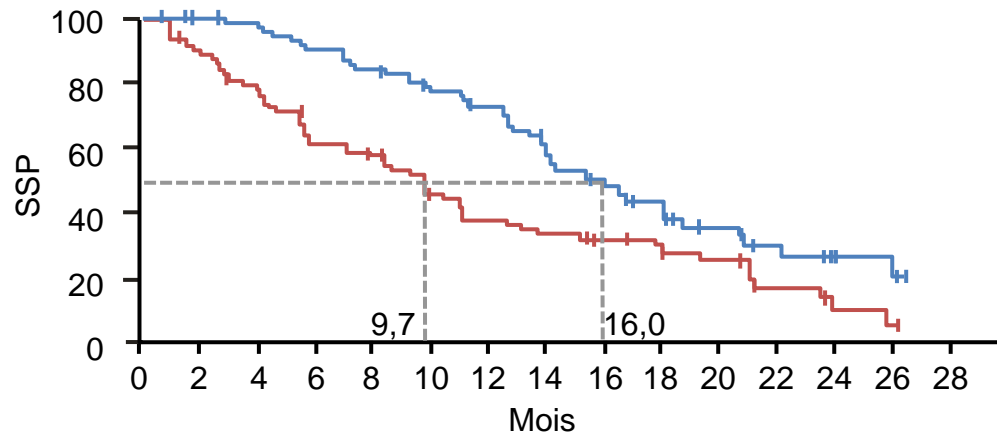
APPLE [NCT02856893](#)



Obj I: % SSP à 18 mois

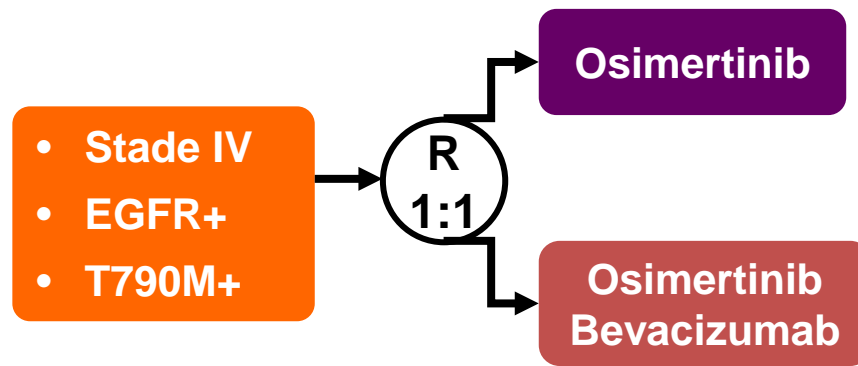
osi + bevacizumab > osi ?

- « L'association erlotinib-bevacizumab a démontré un bénéfice en SSP par rapport à l'erlotinib seul »



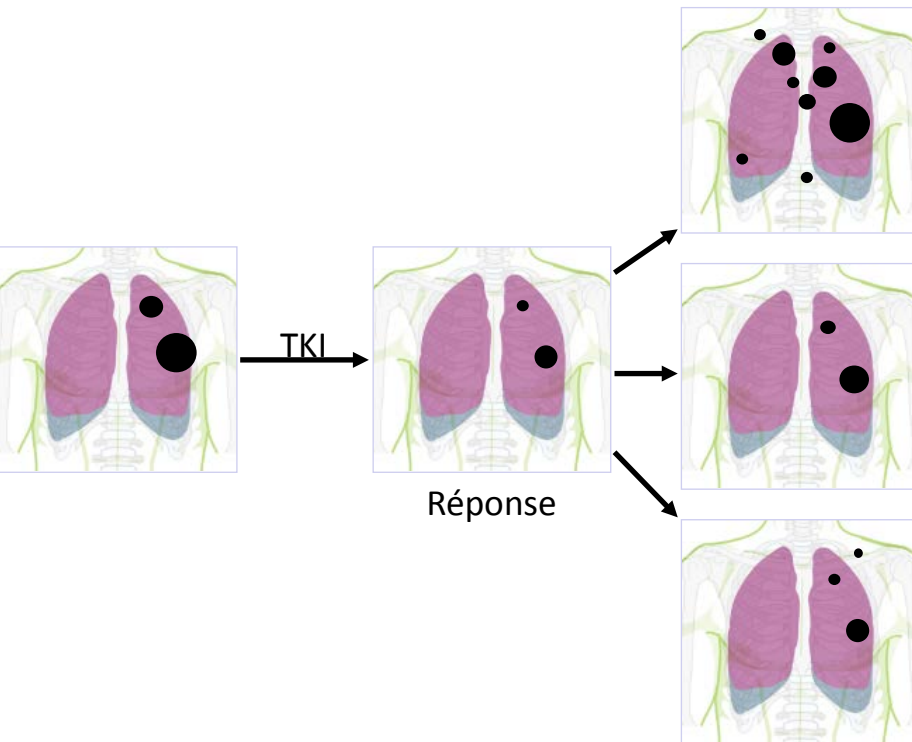
Seto et al. Lancet Oncol 2014; 15:1236-44

- [NCT03133546](#)



osi + SBRT > osi ?

- « En cas de progression sur un seul site accessible à un traitement local, il doit être discuté en Réunion de Concertation Pluridisciplinaire la réalisation de ce traitement local et la poursuite de l'ITK »



Accepted Manuscript

Phase II Study of Stereotactic Radiosurgery for the treatment of patients with oligoprogression on Erlotinib

Jared Weiss , Brian Kavanagh , Allison Deal , Liza Villaruz , James Stevenson , Ross Camidge , Hossein Borghaei , Jack West , Padmini Kirpalani , David Morris , Carrie Lee , Chad Pecot , Timothy Zagar , Thomas Stinchcombe , Nathan Pennell

PII: S2468-2942(18)30186-2
DOI: <https://doi.org/10.1016/j.ctarc.2019.100126>
Article Number: 100126
Reference: CTARC 100126

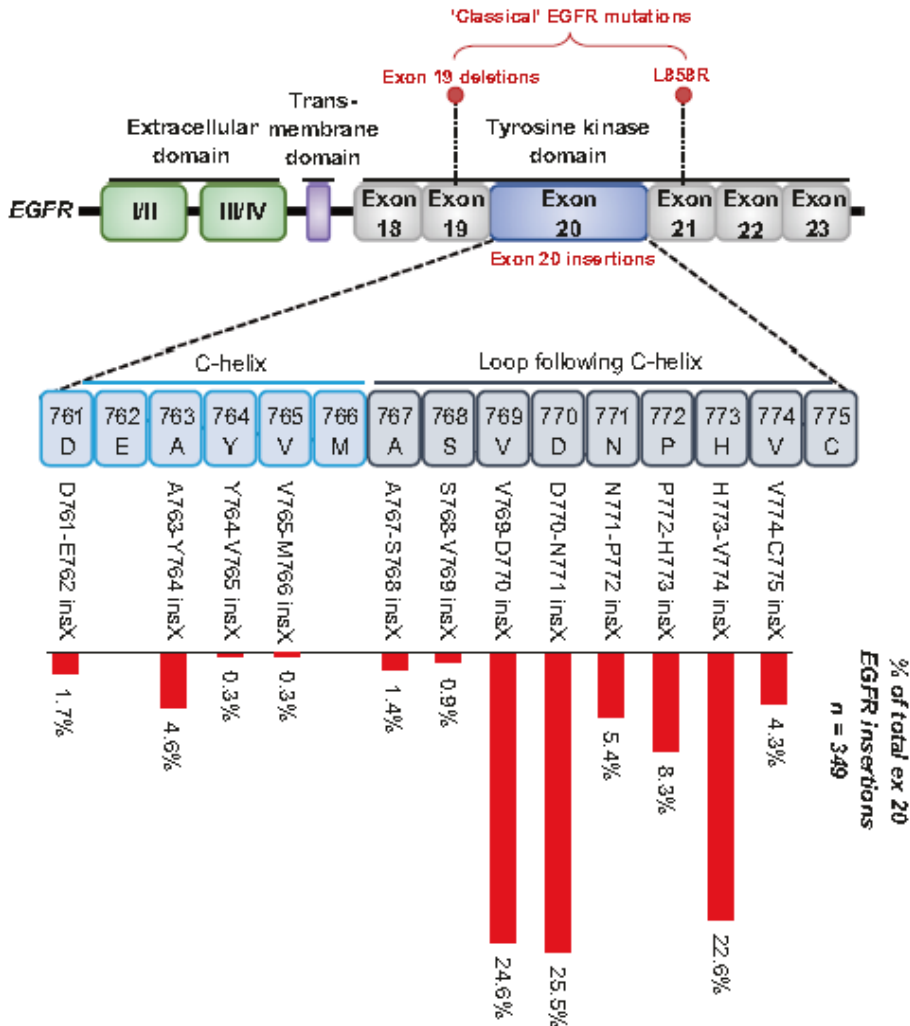


Etude non menée à son terme cf arrivée osimertinib

- [NCT03667820](#) Osimertinib and Stereotactic Body Radiation Therapy in Treating Patients with EGFR Mutant Advanced Non-small Cell Lung Cancer
- [NCT02759835](#) Local Ablative Therapy for Treatment of Oligoprogressive, EGFR-Mutated, Non-Small Cell Lung Cancer After Treatment With Osimertinib
- [NCT02314364](#) Stereotactic Body Radiation Therapy in Treating Patients with Stage IV Oncogene-Driven Non-small Cell Lung Cancer Receiving Selected Targeted Therapy
- [NCT03535363](#) Osimertinib and Stereotactic Radiosurgery in Treating Patients with Brain Metastases from EGFR-Positive Non-Small-Cell Lung Cancer
- [NCT03410043](#) Osimertinib, Surgery, and Radiation Therapy in Treating Participants with Stage IIIB or IV Non-small Cell Lung Cancer with EGFR Mutations

Insertions exon 20

- « En cas de mutation *EGFR* «rare», il est recommandé de se référer au site <https://www.mycancergenome.org/> »



- [NCT03191149](#)

- [NCT03414814](#)

Osimertinib insertions exon 20 EGFR

- [NCT03066206](#)

- [NCT03318939](#)

Poziotinib EGFR exon 20 or HER2 Exon 20 Mutation

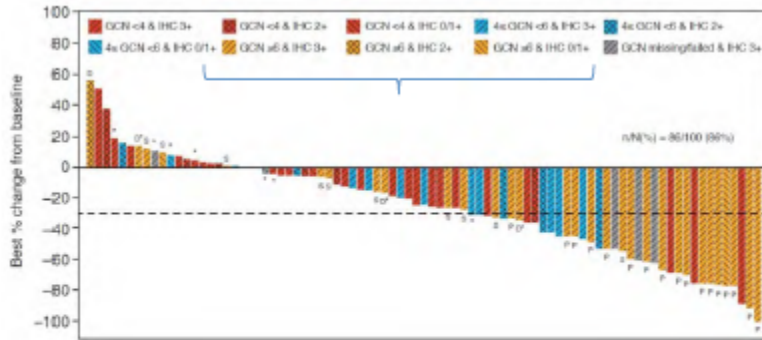
- [NCT02716116](#)

TAK-788 (AP32788) EGR exon 20 ou Her2 exon 20 mutation

- [NCT03805841](#)

Tarloxotinib (TH-4000) EGFR or HER2 Exon 20 Insertion Mutation

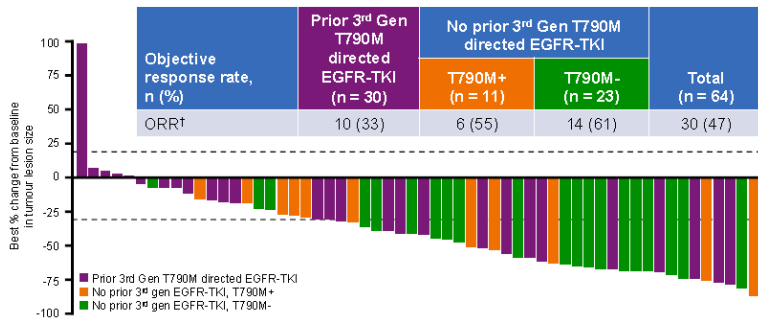
Résistance TKI EGFR+ amplification de cMet



ORR: 47% in patients with MET gene copy number ≥ 6

Wu J Clin Oncol 2018
Capmatinib + Gefitinib

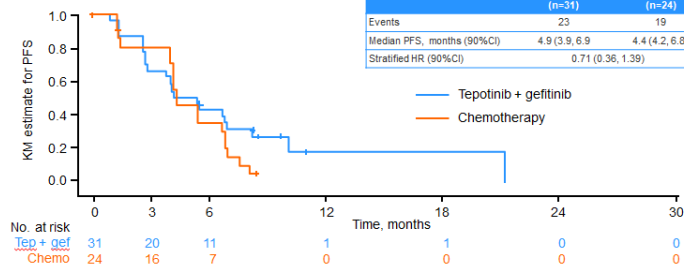
[NCT02143466](#) Osimertinib + savolitinib
wclc 2017 Ahn **TATOON => SAVANNAH**



Key results

Investigator-assessed PFS (ITT population)

	Tepotinib + gefitinib (n=31)	Chemotherapy (n=24)
Events	23	19
Median PFS, months (90%CI)	4.9 (3.9, 6.9)	4.4 (4.2, 6.8)
Stratified HR (90%CI)	0.71 (0.36, 1.39)	



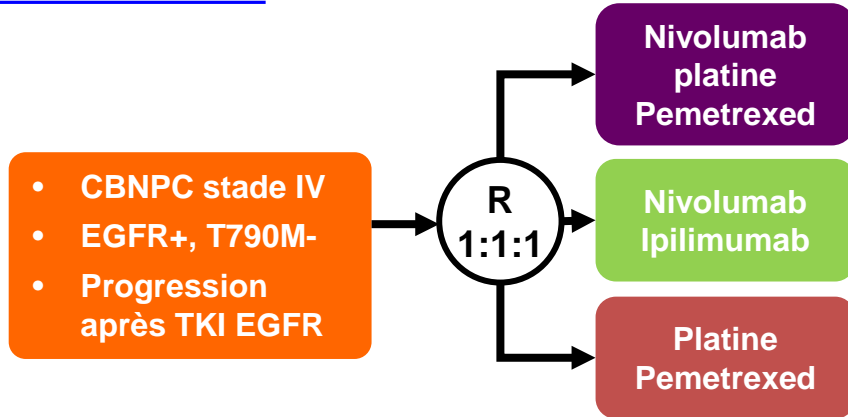
Gefitinib + tepotinib vs platine pemetrexed
Wu, ESMO 2018 abstr 13770

[NCT01982955](#)

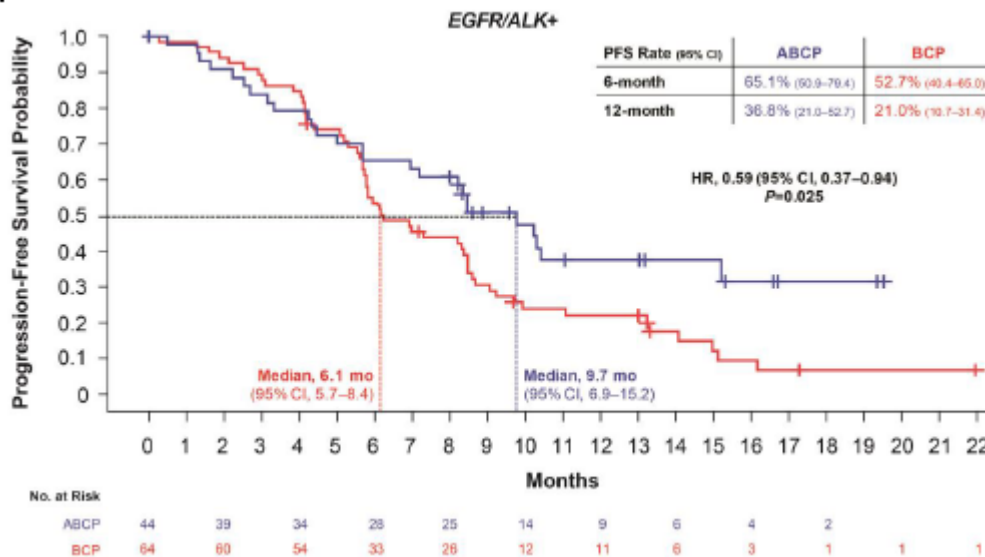
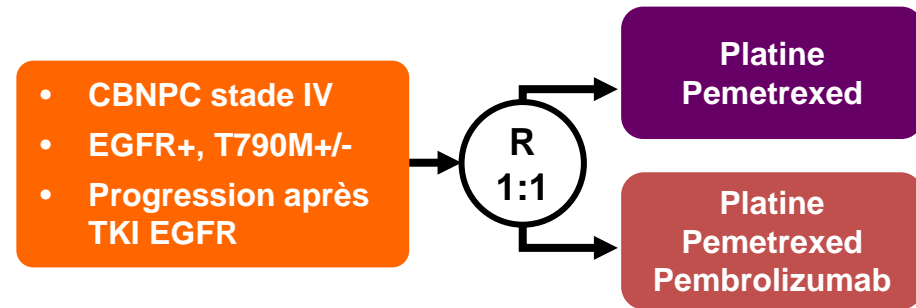
IO: TKI EGFR « exhausted »

« l'utilisation de l'immunothérapie seule chez ces patients, peut être considérée après traitement par ITK puis chimiothérapie à base de sels de platine (...) et chez les patients PDL1+ après nouvelle(s) recherche(s) de la mutation T790M pour ceux n'ayant pas reçu l'osimertinib en 1ère ligne »

[NCT02864251](#) Checkmate 722

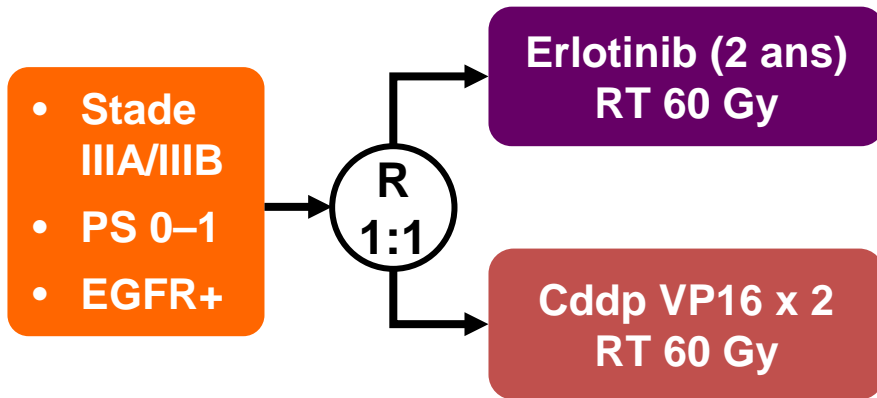


Keynote 789 [NCT03515837](#)



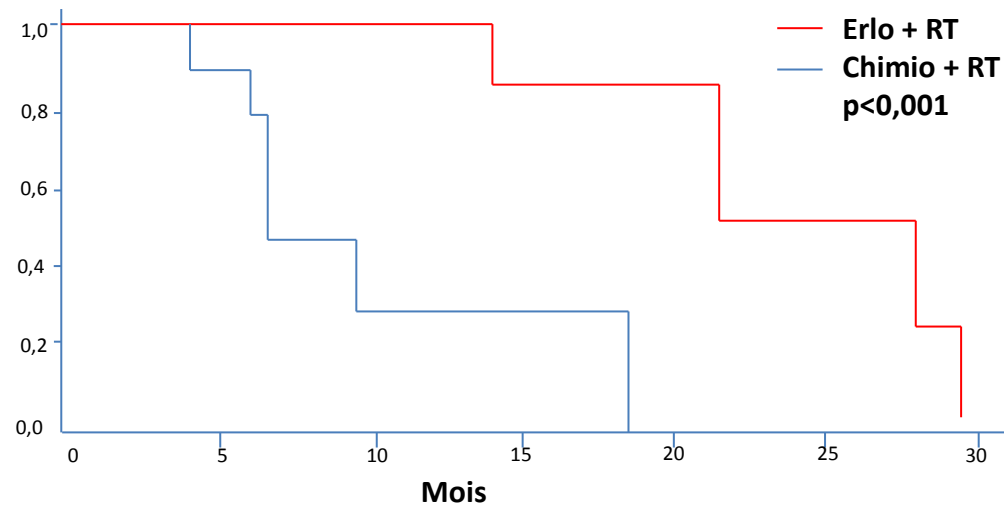
IMPOWER 150
EGFR+/ALK+

EGFR IIIA IIIB



n=41

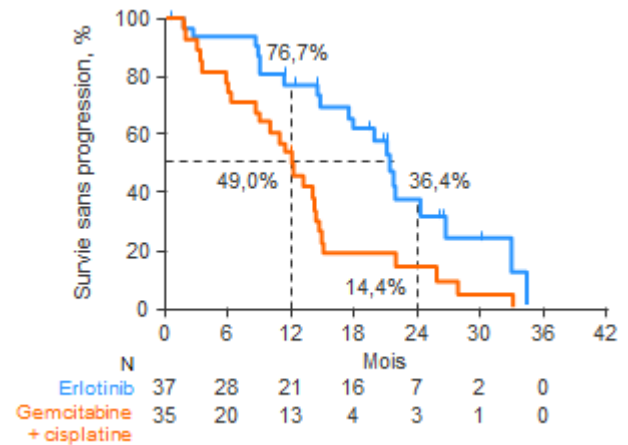
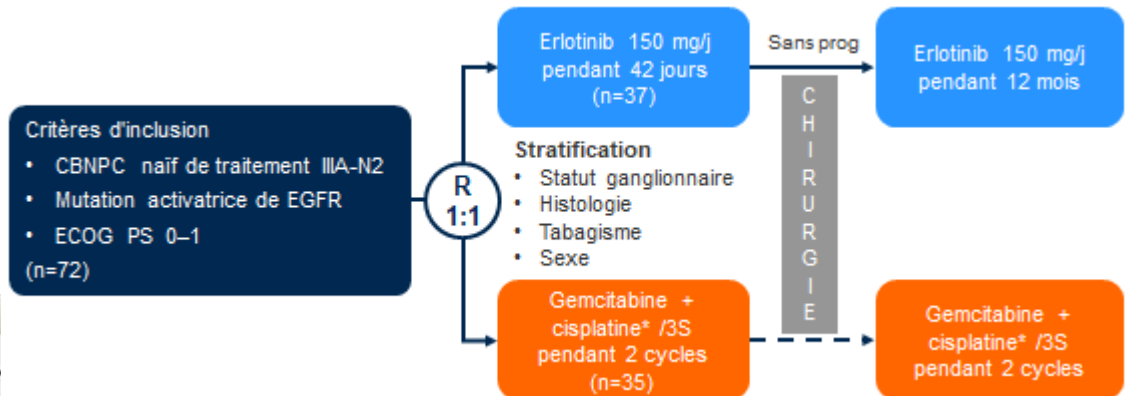
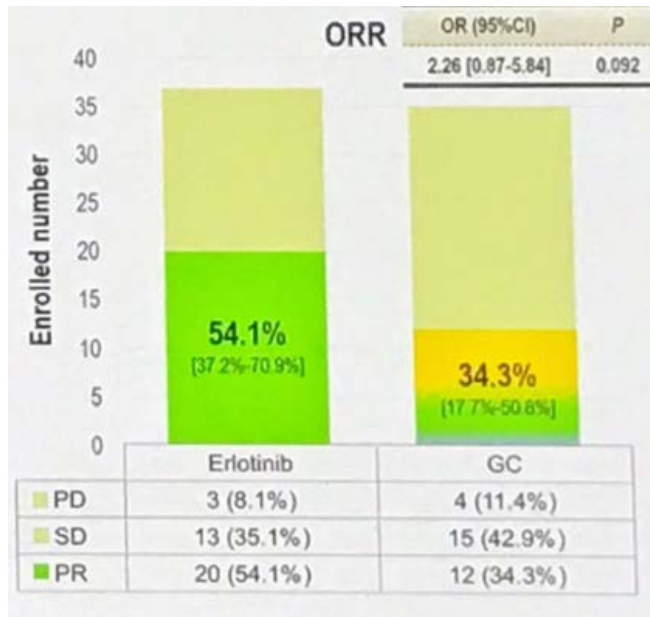
Xing et al, ASCO 2017; Abstr 8531



- [NCT01553942](#) Afatinib Dimaleate, Combination Chemotherapy, and Radiation Therapy in Treating Patients with Stage IIIA or Stage IIIB Non-small Cell Lung Cancer (phase 2)
- [NCT03521154](#) A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer (LAURA, phase 3)

EGFR Péri opératoire (1)

CTONG 1103
Wu, ESMO 2018



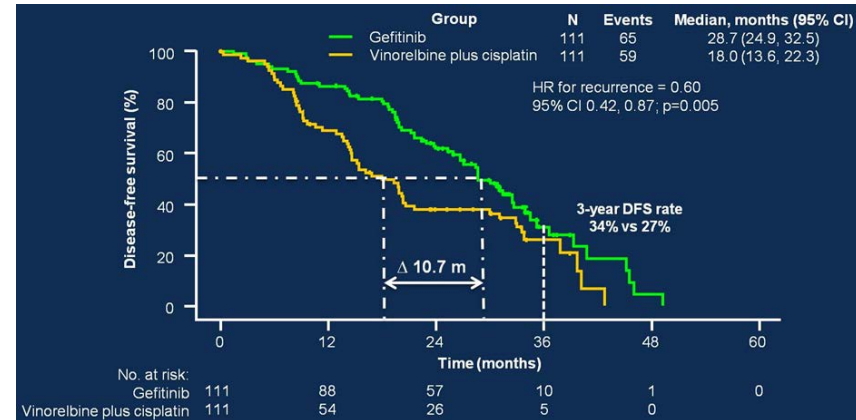
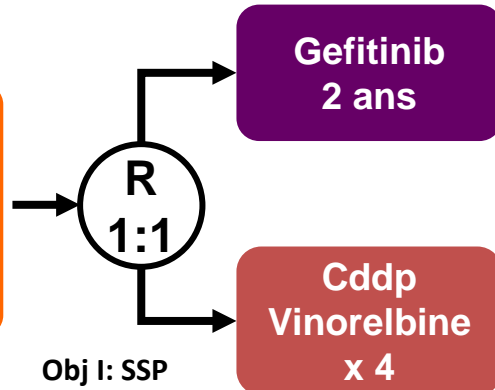
[NCT03433469](https://clinicaltrials.gov/ct2/show/study/NCT03433469)

Osimertinib in Treating Participants with Stage I-IIIa EGFR-mutant Non-small Cell Lung Cancer before Surgery

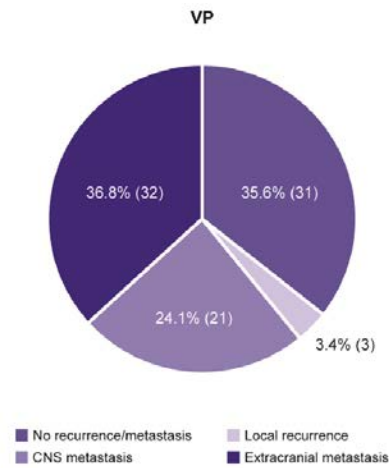
(phase 2)

EGFR Péri opératoire (2)

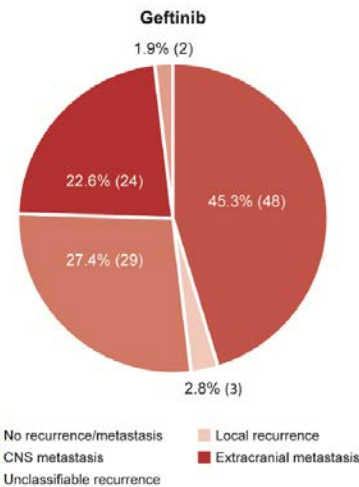
- Stade II/IIIA
- résection complète
- PS 0-1
- EGFR+ (exon19/21)



Zhong et al, Lancet Oncol 2018

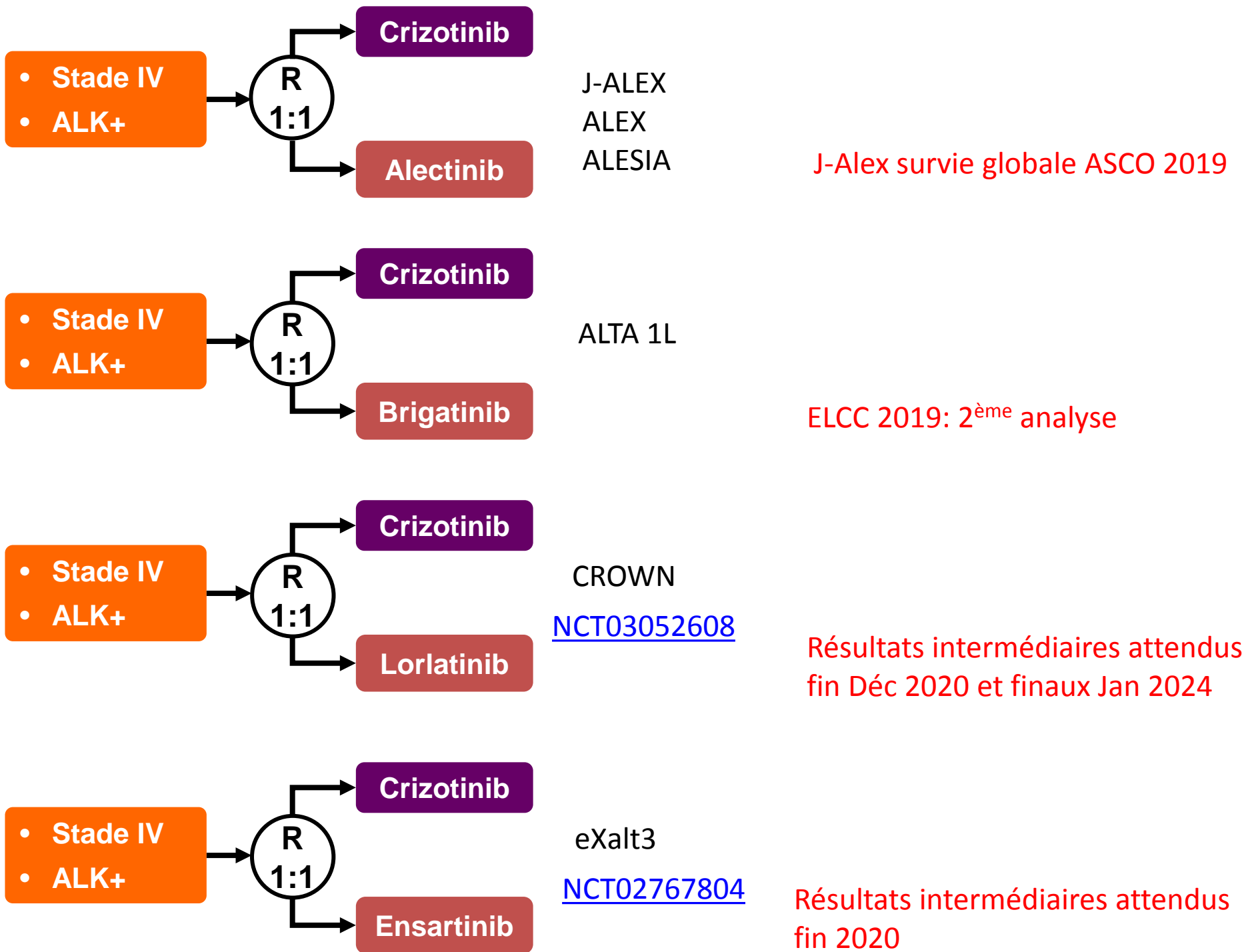


Xu et al, J Thor Oncol 2019



[NCT02511106](#) Osimertinib Versus Placebo in Patients With Stage IB-III A Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA)

ALK



ITK ALK + thérapie ciblées

Alectinib

+

Cobimetinib

[NCT03202940](https://clinicaltrials.gov/ct2/show/study/NCT03202940)

Résultats ASCO 2019

Ceritinib

+

Trametinib

[NCT03087448](https://clinicaltrials.gov/ct2/show/study/NCT03087448)

Ceritinib

+

Ribociclib

[NCT02292550](https://clinicaltrials.gov/ct2/show/study/NCT02292550)

Ceritinib

+

Everolimus

[NCT02321501](https://clinicaltrials.gov/ct2/show/study/NCT02321501)

Alectinib

+

Bevacizumab

[NCT02521051](https://clinicaltrials.gov/ct2/show/study/NCT02521051)

Résultats ASCO 2019

ITK ALK + IO

« l'Immunothérapie seule, hors essais cliniques, semble être à considérer avec précaution dans cette indication »

Crizotinib

+

**Nivolumab ou
Ipilimumab**

[NCT01998126](#)

Crizotinib

+

Pembrolizumab

[NCT02511184](#)

Alectinib

+

Atezolizumab

[NCT02013219](#)

**Crizotinib
ou
Lorlatinib**

+

Avelumab

[NCT02584634](#)

Ensartinib

+

Durvalumab

[NCT02898116](#)

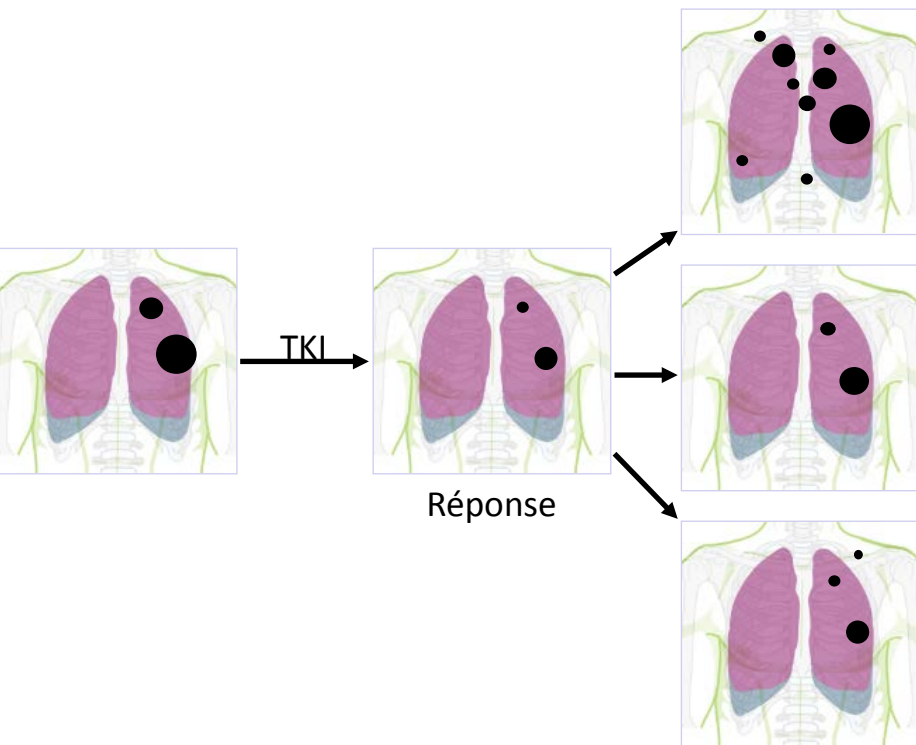
Ceritinib

+

Nivolumab

[NCT02393625](#)

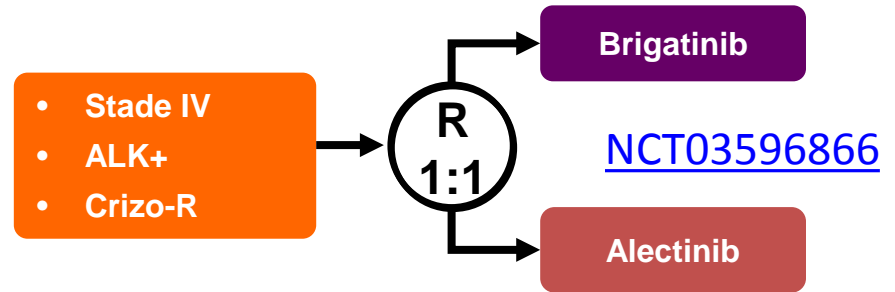
« En cas de progression sur un site accessible à un traitement local, il doit être discuté en RCP la réalisation de ce traitement local avec la poursuite de l'ITK »



- [NCT02513667](#) **Ceritinib** and Stereotactic Body Radiation Therapy in Treating Patients with ALK-Rearranged Metastatic Lung Cancer
- [NCT02314364](#) Stereotactic Body Radiation Therapy in Treating Patients with Stage IV Oncogene-Driven Non-small Cell Lung Cancer Receiving Selected Targeted Therapy
- [NCT03707938](#) Local Consolidative Therapy and **Brigatinib** in Treating Patients with Stage IV or Recurrent Non-small Cell Lung Cancer

« En cas de première progression sous ITK, il est possible d'adapter le traitement au profil moléculaire de résistance si celui-ci est disponible. En l'absence de données moléculaires, il est recommandé d'utiliser l'alectinib s'il n'a pas été utilisé auparavant, ou le ceritinib, ou le brigatinib »

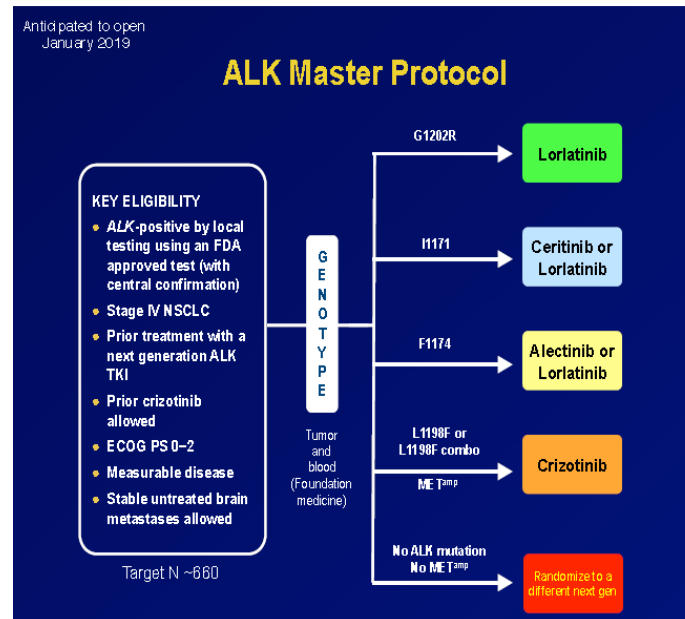
« Pour les progressions ultérieures, il est recommandé d'adapter le traitement au profil moléculaire de résistance si celui-ci est disponible et/ou d'utiliser un traitement par ITK non-utilisé jusqu'alors »



Cellular ALK Phosphorylation mean IC50 (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4 – ALK V1	38.6	4.9	11.4	10.7	2.3
EML4 – ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4 – ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4 – ALK I1171S	94.1	3.8	117.0	17.8	30.4
EML4 – ALK I1171T	51.4	1.7	33.6a	6.1	11.5
EML4 – ALK F1174C	115.0	38.0a	27.0	18.0	8.0
EML4 – ALK L1196M	339.0	9.3	117.6	26.5	34.0
AML4 – ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4 – ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4 – ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4 – ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4 – ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4 – ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4 – ALK D1203N + F1174C	338.8	237.8	75.1	123.4	69.8
EML4 – ALK D1203 + E1210K	153.0	97.8	82.8	136.0	26.6

- IC50 ≤ 50 nmol/L
- IC50 > 50 < 200 nmol/L
- IC50 ≥ 200 nmol/L



[NCT03737994](#)

[NCT03535740](#) A Study of Brigatinib in Participants With Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non-Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib

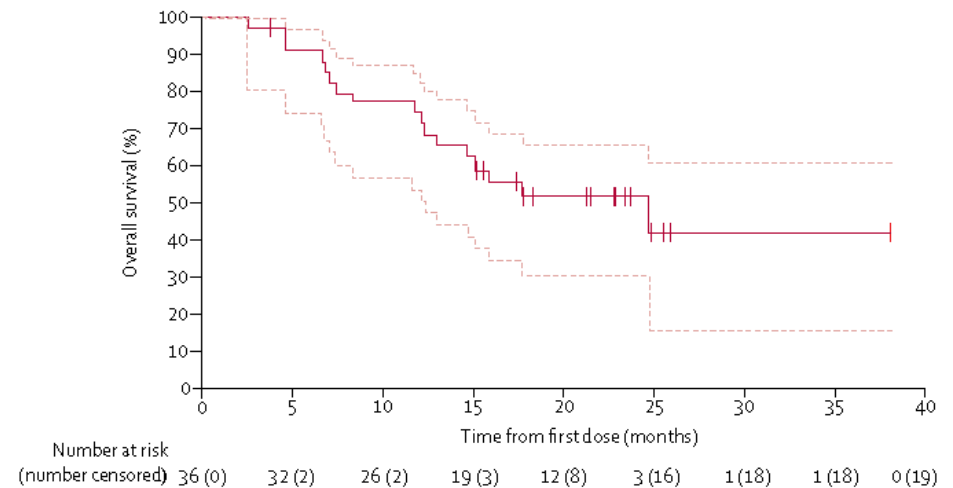
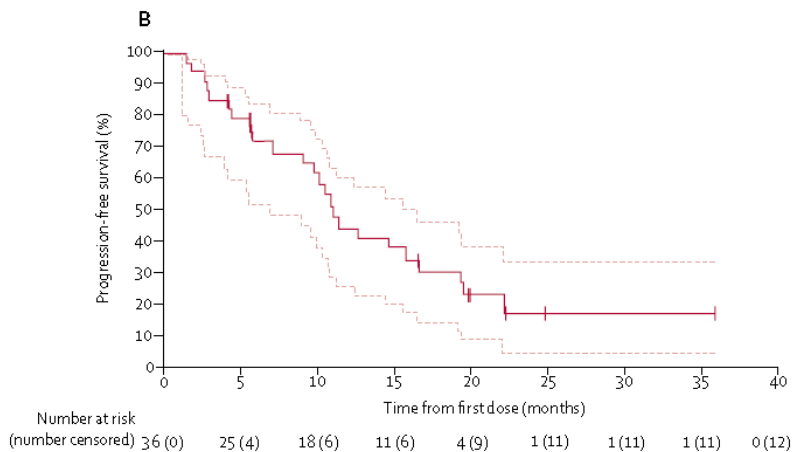
ALK+ Péri opératoire

- [NCT03088930](#) **Crizotinib** before Surgery in Treating Patients with ALK, ROS1, or MET Mutation Positive Stage IA-III A Non-small Cell Lung Cancer That Can Be Removed by Surgery (phase 2)
- [NCT02201992](#) ALCHEMIST **Crizotinib** adjuvant (phase 3)
- [NCT03456076](#) ALINA **Alectinib** adjuvant (phase 3)

ROS, Braf, Her2, cMet, RET

Braf

- Dabrafenib 300 mg x 2/j + Trametinib 2 mg x 1/j
- Taux de réponse, de contrôle, SSP mais pas de SG
- 2020: données réactualisées de survie globale
- Nouvelle demande de remboursement fin mars, avec données de vie réelle



cMet

	Amplification	Exon 14		
Crizotinib	X Camidge, ASCO 2018 Abstr 9062	X Drilon, WCLC 2018 OA12.02	NCT00585195	
Tepotinib		X Felip, WCLC 2018 OA12.01	NCT02864992	Fin en 2019
Capmatinib	X Schuler, ASCO 2016 Abstr 9067	X Wolf, ESMO 2018 LBA 52	NCT02414139	ASCO 2019 PFS (exon 14)
Savolitinib		X	NCT02897479	Congrès 2019
Merestinib		X	NCT02920996	Fin en 2020

Ac Her2

Trastuzumab Emtansine (TDM-1)

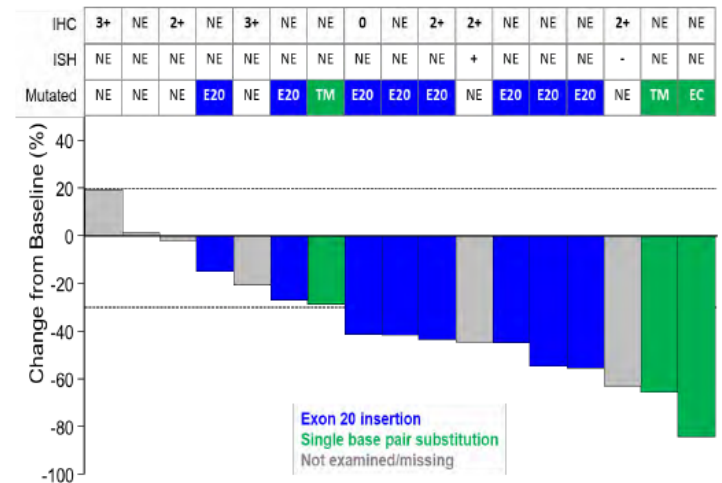


Stinchcombe ASCO 2017

[NCT02675829](#)

in HER2 Amplified or Mutant Advanced Cancers

Trastuzumab Derutexcan (DS-8201a)



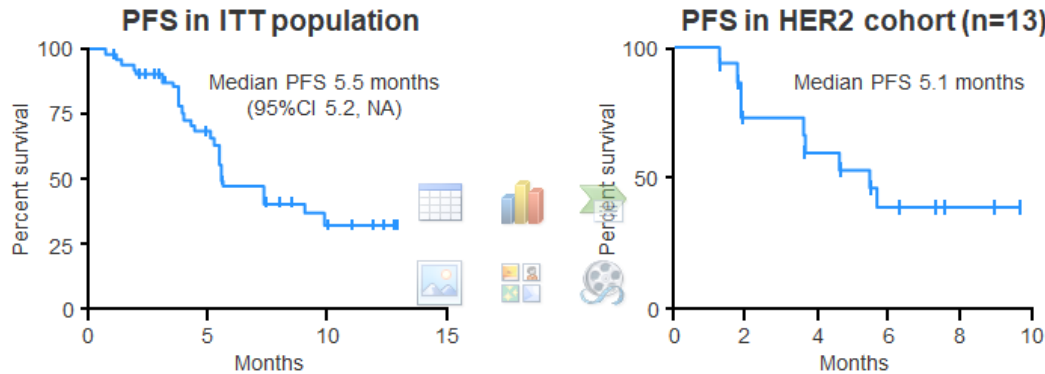
Junji Tsurutani, WCLC 2018

[NCT03505710](#)

in (HER2)-Expressing or -Mutated Non-Small Cell Lung Cancer

TKI Her2

OA02.06: A Phase II Trial of Poziotinib in EGFR and HER2 exon 20 Mutant Non-Small Cell Lung Cancer (NSCLC) Heymach JV, et al



Adapted from Heymach JV. OA 02.06 (WVLC 2018)

- [NCT03318939](#) Phase 2 Study of Poziotinib in Patients With NSCLC Having EGFR or HER2 Exon 20 Insertion Mutation
- [NCT03066206](#) Poziotinib in Treating Patients with Stage IV Non-small Cell Lung Cancer with EGFR or HER2 Exon 20 Mutation
- [NCT02716116](#) A Trial of TAK-788 (AP32788) in Non-small Cell Lung Cancer (NSCLC)
- [NCT03805841](#) tarloxotinib (TH-4000) in Patients With NSCLC Having EGFR or HER2 Exon 20 Insertion Mutation
- [NCT03284723](#) Phase 1 PF-06804103 in patients with HER2 positive solid tumors.

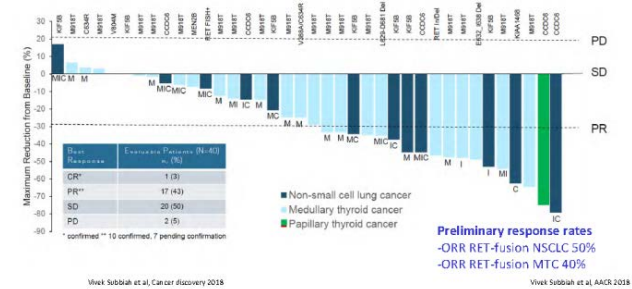
ROS1

Drug	Trial
Entrectinib	NCT02568267
Cabozantinib	NCT01639508
Repotrectinib	NCT03093116
DS-66051b	NCT02279433

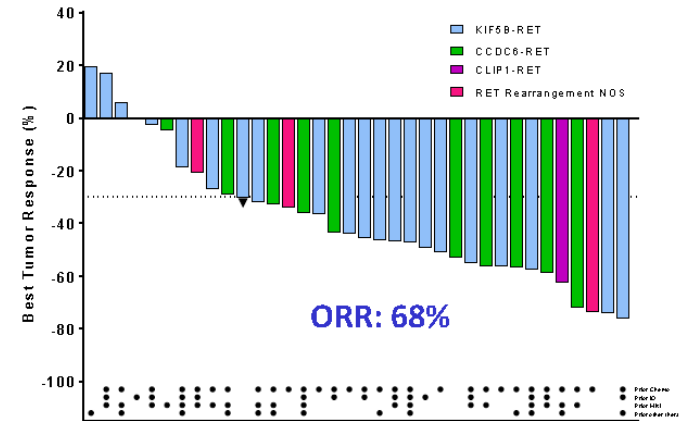
[NCT03088930](#) Crizotinib before Surgery in Treating Patients with ALK, ROS1, or MET Mutation Positive Stage IA-III A Non-small Cell Lung Cancer That Can Be Removed by Surgery (**Résultats 2020**)

RET: phases ½ pan tumeurs

NCT03037385 BLU-667



NCT03157128 LOXO-292



NCT03780517 BOS172738

Merci de votre attention!