



Traitements des CBNPC de stades avancés avec addiction oncogénique

DES Pneumologie



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(Support initial Pr J Cadranel)
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Liens d'intérêt Dr Vincent Fallet

- **Invitation à des congrès médicaux avec hospitalité :** Amgen (ESMO 2022) Jansen (virtual WCLC 2021), Pfizer (virtual ASCO et ESMO 2021), AstraZeneca (virtual ASCO 2020), Takeda (ESMO 2019), Boehringer Ingelheim (virtual ESMO 2020, EMSO 2018, CPLF 2017), Novartis (ERS 2018, WCLC 2022), LVL (CPLF 2023)
- **Hospitalité lors de réunion :** Lilly, Chiesi, BMS, Novartis, AstraZeneca, Takeda, Leo Pharma, InterMune, Boehringer Ingelheim, MSD, Mundipharma, Icomed, SOS Oxygène, Roche, Pfizer, Pierre Fabre, LVL Médical, GSK, Amgen, ISIS Médical
- **Rémunération pour activités de conseil, animation symposium, conférences, board:** Bristol-Myers Squibb (2018, 2020- 2022), Boehringer Ingelheim (2019-2020), Takeda (2019, 2021-2023), AstraZeneca (2019-2023), Sanofi (2021), Jansen (2021, 2022), Roche (2020- 2021), Pfizer (2019-2023), MSD (2022) Novartis (2023)
- Le contenu et/ou les opinions exprimées lors de cette présentation, notamment celui ou celle(s) relatifs à la stratégie thérapeutique ont été réalisés en toute indépendance et les recommandations française et internationales en vigueur

Plan

- Addiction oncogénique – définition
- Quelles addictions oncogéniques dans les CBNPC?
- Séquences thérapeutiques dans les CBNPC avec addiction EGFR, ALK, ROS1
- Gestion des progressions en cas d'addiction
- Toxicités
- Autres addictions
- Conclusions

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Plan

- **Addiction oncogénique – définition Talon d'Achille du cancer**
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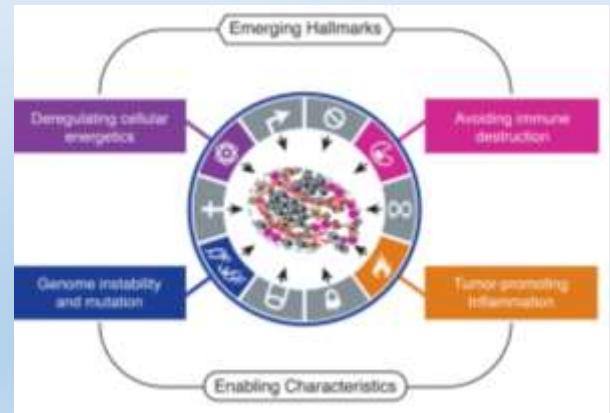
« The Hallmarks of cancer »



Processus impliqués dans l'oncogenèse



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(Hanahan 2000 et 2011)

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Preuve du concept en oncologie moléculaire

- Thérapeutiques ciblées sur des anomalies moléculaires **causes**
 - Directement responsables de la transformation néoplasique, précoces et constantes
 - Exemple LMC
- Thérapeutiques ciblées sur des anomalies moléculaires **plus tardives**, fréquentes mais non constantes,
 - Contribuent à la progression tumorale mais ne constituent pas l'étape initiale de la transformation
- Thérapeutiques ciblées sur des cibles moléculaires ne jouant pas un rôle direct dans la transformation tumorale

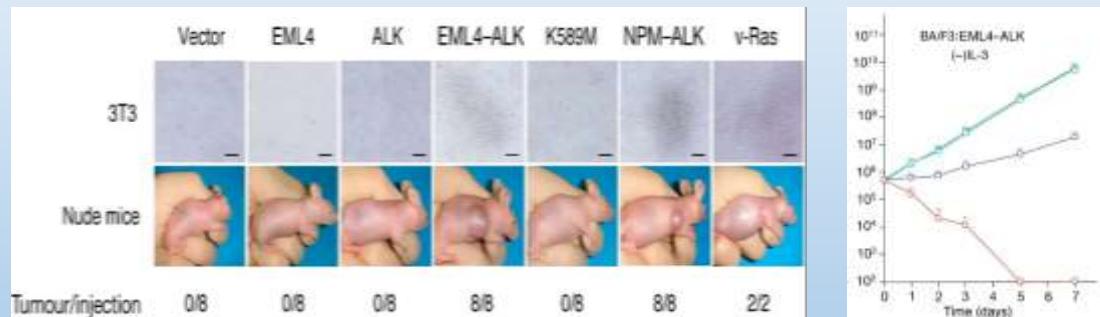
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Preuve du concept en oncologie moléculaire

Préclinique ALK - crizotinib



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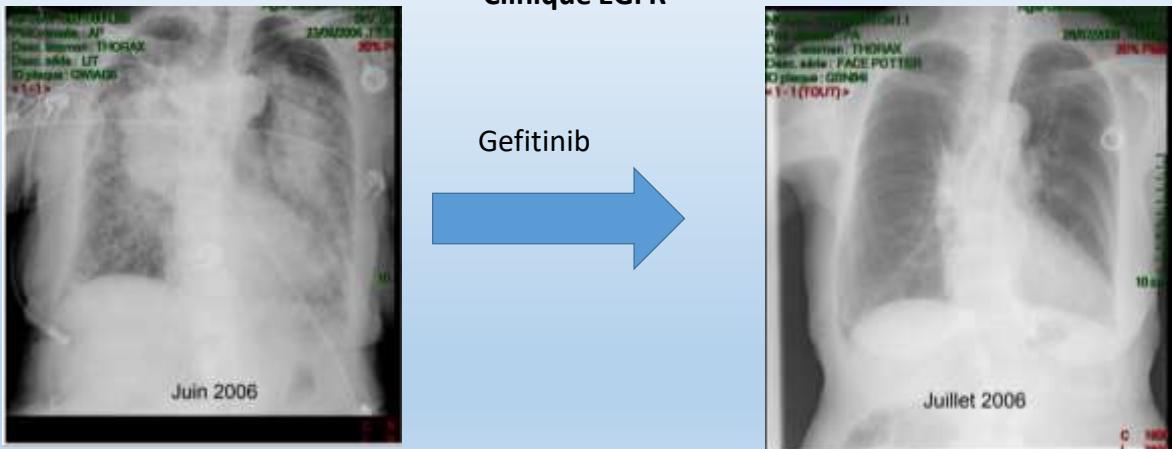
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(Soda et al. 2007)

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Preuve du concept en oncologie moléculaire

Clinique EGFR



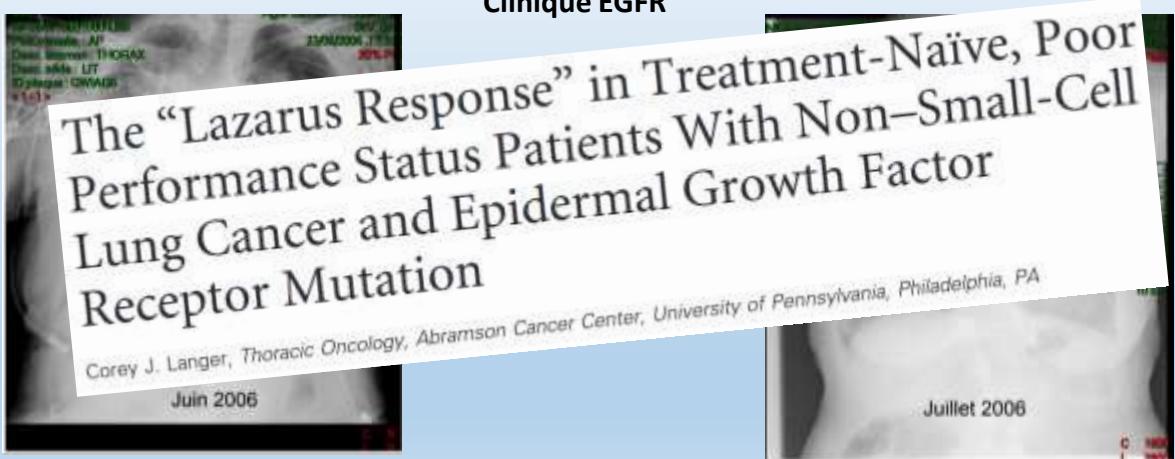
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Preuve du concept en oncologie moléculaire

Clinique EGFR



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Plan

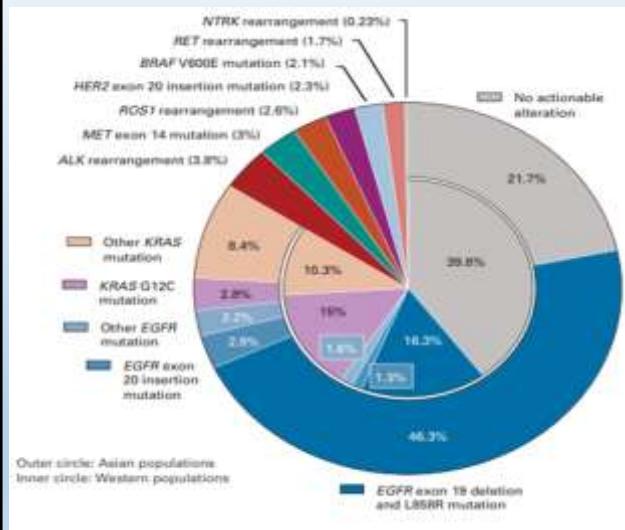
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Altérations moléculaires ciblables et CBNPC



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From Solange Peters ESMO 2020

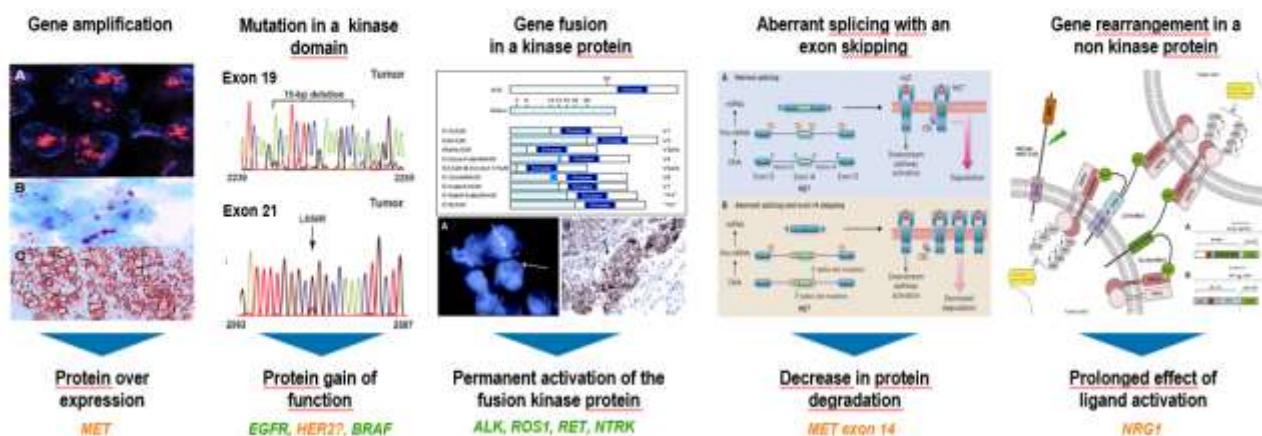
BM et CBNPC de stade avancé:

- ✓ CBNPC non épidermoïde
- ✓ CBNPC épidermoïde non fumeur

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Les différents types de dépendance oncogénique

2010-2023

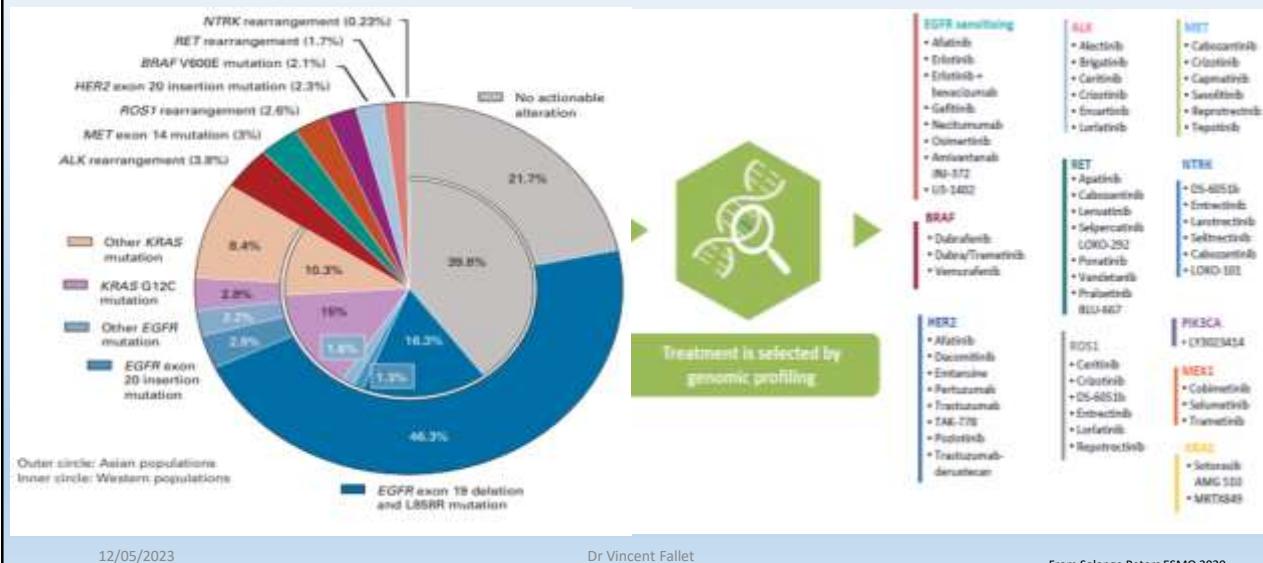


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Altérations moléculaires cibles et CBNPC



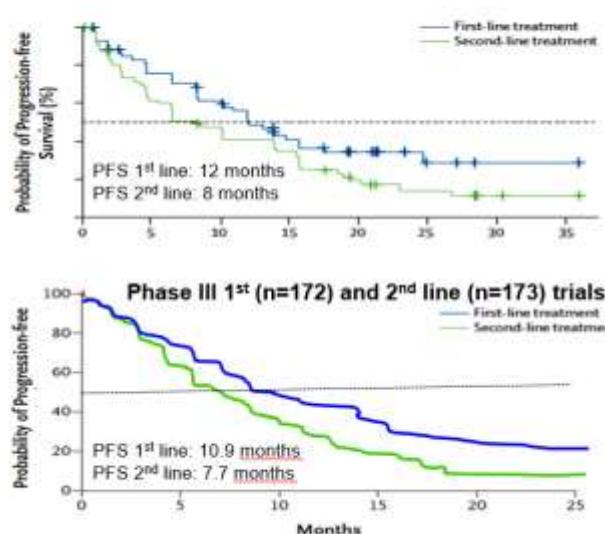
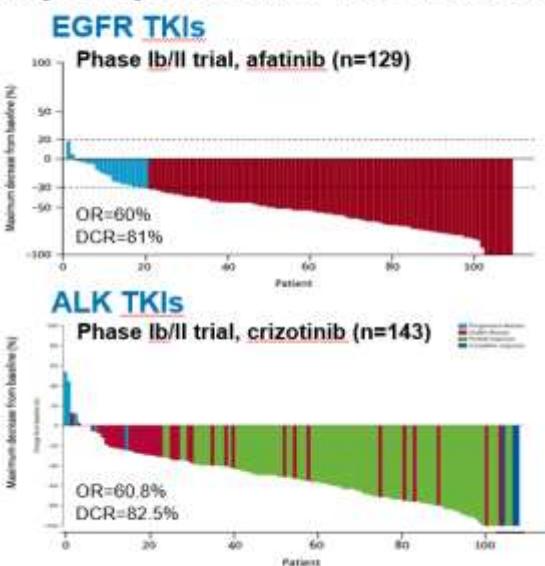
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From Solange Peters ESMO 2020

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Impact prédictif d'une addiction oncogénique



Yang JC, Lancet Oncol 2012; 13:539; Camidge DR, Lancet Oncol, 2012;13:1011; Shaw AT, N Engl J Med 2013, 368:2385; Solomon BJ, N Engl J Med 2014, 371:2167

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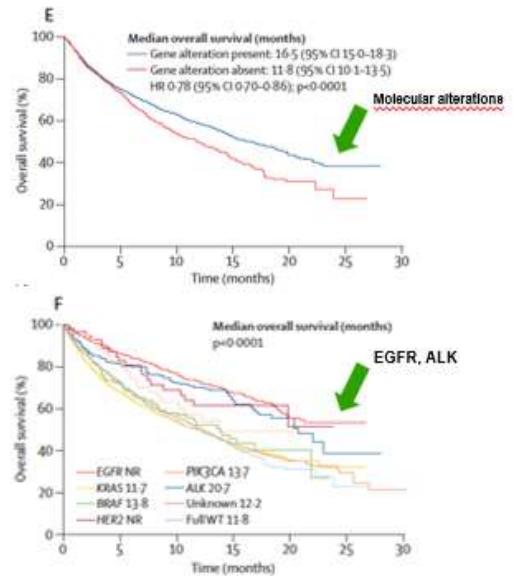
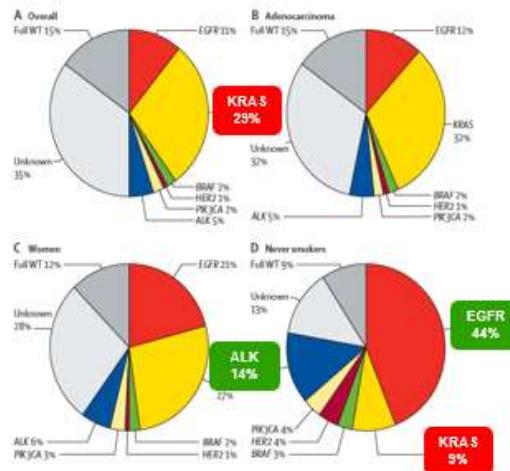
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Impact pronostique du traitement adapté

IFCT Biomarqueurs France cohort

1 year testing for EGFR, ALK, KRAS, BRAF, HER2, PI3K
alterations in 17 664 consecutive patients



Barlesi F, Lancet 2016, 387:1415

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Diagnostic moléculaire « minimal » CBNPC avancé

Stades IA	Stades IB	Stades II A	Stades II B	Stades IIIA réséqués	Stades IIIB non réséqués à IIC	Stades IV Avant I3	Stades IV A.I3 / Avant I2	Stades IV A.I2 et plus
PDL1						IHC		
EGFR					Non recommandé à l'IHC	Non recommandé à l'IHC		
KRAS								
BRAF								
HER2								
MET ex14								
Autres MET								
ALK					Non recommandé à l'IHC	Non recommandé à l'IHC		
ROS1								
RET								
NTRK1/2/3								
NRG1								
RB1						IHC / TNEx		
STK11						TNE		
TP53						TNE		
KEAP1						TNE		



Recommandé En option
IHC : Immuno-histochimie ; TNE : Tumeurs neuro-endocrines ; Non-épi : Non épidermoïde ; IT : Immunothérapie.
Figure 4 – Proposition de panel minimal de biologie moléculaire pour les CBNPC de stade avancé

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Plan

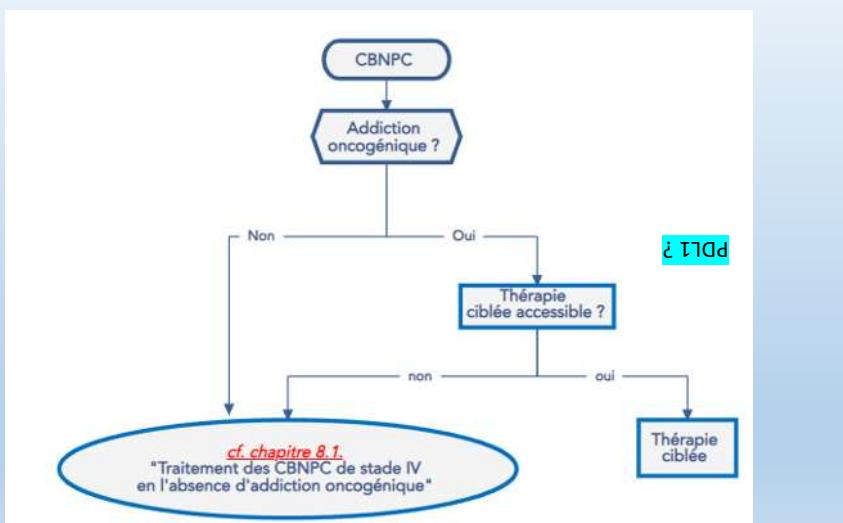
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 - Conclusions et accès à l'innovation

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Modalité du traitement de 1^{ère} ligne – CBNPC avancé

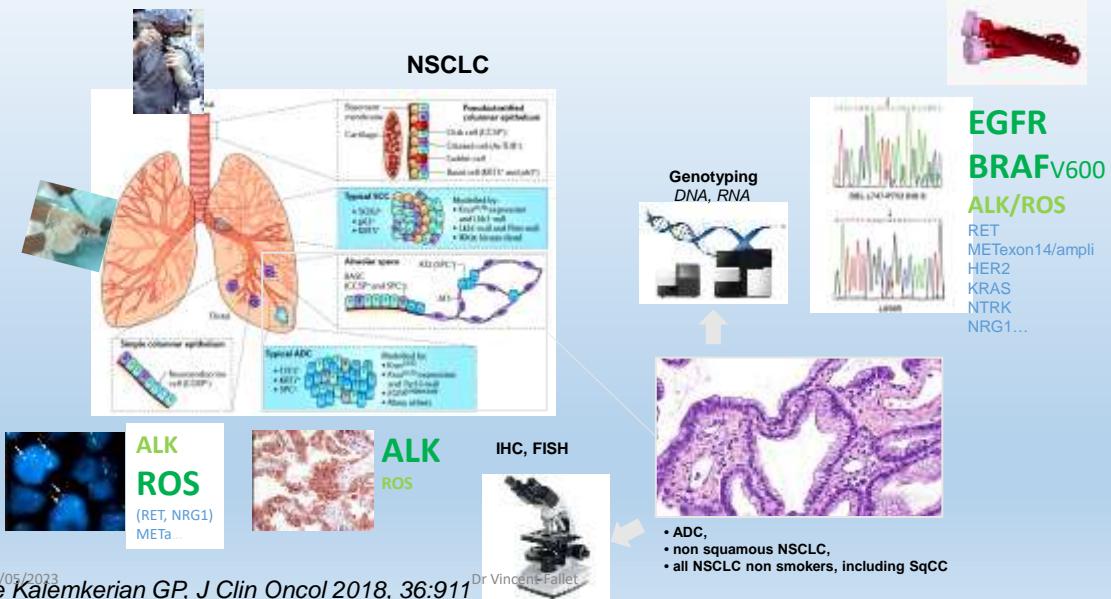


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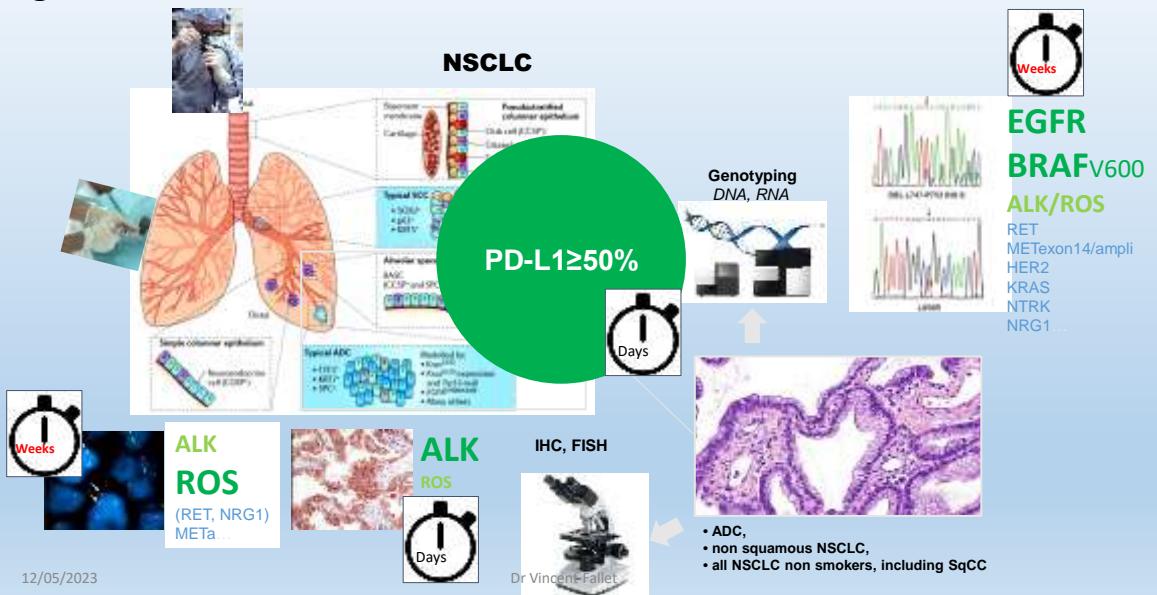
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Diagnostic histo-moléculaire des CBNPC étendus



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Diagnostic histo-moléculaire des CBNPC étendus



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Diagnostic histo-moléculaire des CBNPC étendus

PD-L1
≥50%



Mucinous/signet ring ADC
Female
Asian
Non smoker; light/former smoker
(No need for emergency treatment)

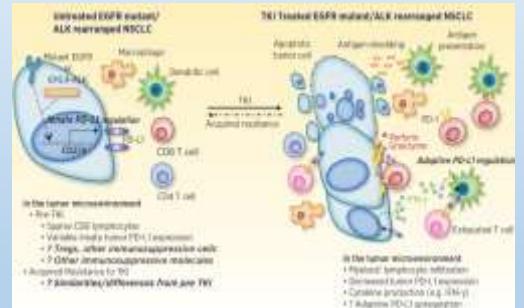
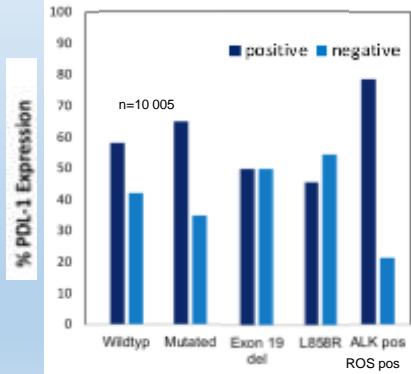


Molecular testing

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Berghoff A, ESMO Open 2019, 4:e000498; Gettinger S, Clin Cancer Res Discov 2016, 22:4539

Relationship between oncogene alteration and PD-L1 expression



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Diagnostic histo-moléculaire des CBNPC étendus

PD-L1
≥50%



Mucinous/signet ring ADC
Female
Asian
Non smoker; light/former smoker
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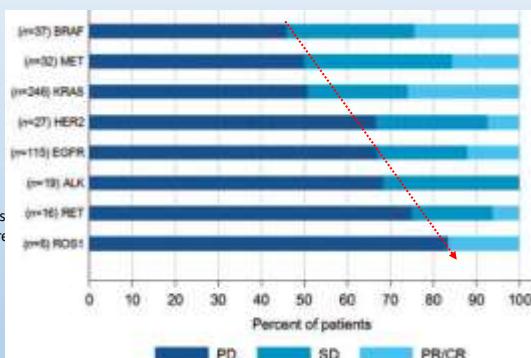


Molecular testing

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Mazières J, Ann Oncol 2019, 30:1321; Mhanna L, Rev Mal Respir 2019, 11:476; Adderley H, Cancer Immunol Immunot 2021, 70:589

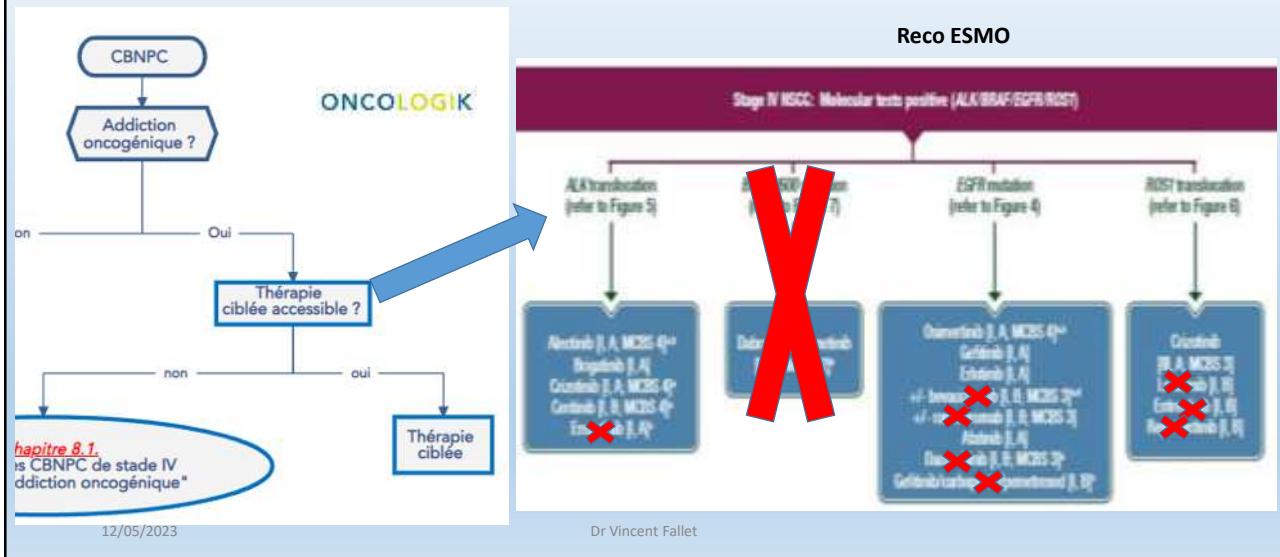
En cas d'addiction, le statut PD-L1 n'impacte pas la séquence thérapeutique



- Increased toxicity of TKI and IO associations
- Increased toxicity of TKIs after the IO then TKI sequence

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Modalité du traitement de 1^{ère} ligne – CBNPC avancé



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EGFR, BRAF, ALK, ROS convergences et divergences

EGFR

- ≈ 10% in Caucasian, 40% in Asian
- Female more frequent
- Non or former light smoker
- Adenocarcinoma
- Frequent brain metastasis at diagnosis (20-30%) and at disease progression (35-44%)

ALK

- ≈ 3-7% general population, Caucasian = Asian
- Female equal male; younger
- Non smoker
- Adenocarcinoma; signet ring morphology
- Frequent brain metastasis at diagnosis (15-40%) and at disease progression (>60%)

BRAF

- ≈ 0.5-3% general population, Caucasian > Asian?
- Female more frequent (depending of BRAF subtypes)
- Smoker > non smoker (depending of BRAF subtypes)
- Adenocarcinoma; micropapillary
- Less frequent brain metastasis at diagnosis / frequent intrathoracic metastasis

ROS

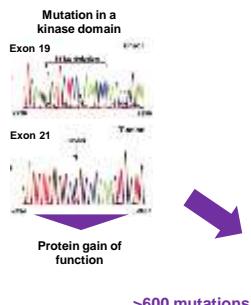
- ≈ 0.5-2% general population, Caucasian = Asian
- Female more frequent; younger
- Non smoker
- Adenocarcinoma; signet ring morphology
- Pneumonic-type; thromboembolism(?)
- Less frequent brain metastasis at diagnosis / progression
- Pemetrexed high responsiveness(?)

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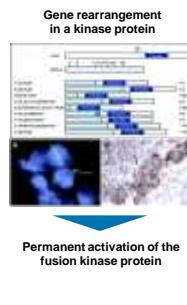
EGFR, BRAF, ALK, ROS convergences et divergences

Impact sur les décisions thérapeutiques : oui, EGFR; non, ALK

EGFR gene tyrosine kinase domain mutations



ALK gene rearrangement with variable partners



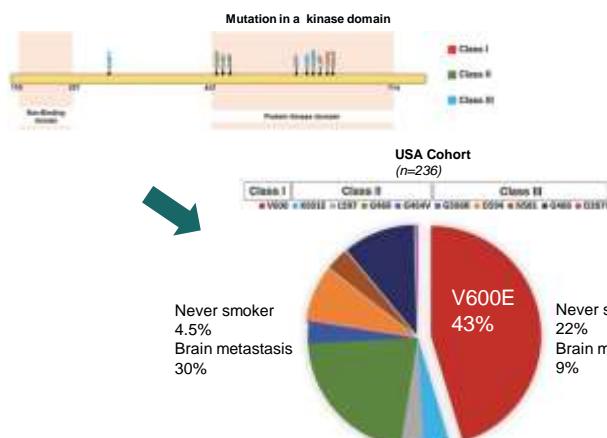
Leduc C, Ann Oncol 2017, 28:2715; Lin J, J Clin Oncol 2018, 36:1199

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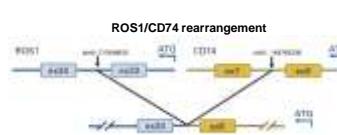
EGFR, BRAF, ALK, ROS convergences et divergences

Impact sur les décisions thérapeutiques : oui, BRAFV600; non, ROS

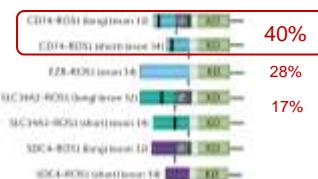
BRAF gene kinase domain mutations



ROS gene rearrangement with variable partners



China Cohort (n=47)



Dagogo Jack, Clin Cancer Res 2019, 25:158; Drilon A, Nature Rev Clin Oncol 2021, 18:35; Zhang L, Oncotarget 2016, 7:75145

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EGFR, BRAF, ALK, ROS convergences et divergences

Les IK sont le standard de traitement de 1^{ère} ligne

Phase III trials comparing 1st generation EGFR TKIs vs CT

Trial	Trial design (phase, primary end point and treatment arms, including number of patients harbouring EGFR mutations)*	Outcomes (ORR, median PFS and median OS)
First generation		
iASSIST		
WJTOG3405		
NEJ002		
OPTIMAL (C-TONG-R)		
ENSURE		
EURTAC		
Mutations communes		
		ORR: 62-85% vs 18-47%
		PFS: 9.2-13.1 vs 4.6-6.3 months
		Better QoL and less toxicities
		OS: 19.3-34.8 vs 19.5-37.3 months
		+ORR: 62.6% versus 37.5%; +PFS: 10.9 months versus 7.2 months [HR 0.47, $P < 0.0001$]; +OS: 34.8 months versus 19.5 months [HR 1.54, $P = 0.01$]
		+ORR: 85.0% versus 47.0%; +PFS: 13.1 months versus 6.3 months [HR 0.42, $P < 0.0001$]; +OS: 34.0 months versus 19.5 months [HR 1.54, $P = 0.01$]
		+ORR: 85.0% versus 47.0%; +PFS: 13.1 months versus 6.3 months [HR 0.42, $P < 0.0001$]; +OS: 34.0 months versus 19.5 months [HR 1.54, $P = 0.01$]
		+ORR: 85.0% versus 47.0%; +PFS: 13.1 months versus 6.3 months [HR 0.42, $P < 0.0001$]; +OS: 34.0 months versus 19.5 months [HR 1.54, $P = 0.01$]

Phase III trial comparing crizotinib vs CT

Drug	Phase	Treatment	Sample size	ORR	DCR ^a	PFS	OS
Crizotinib	III	First-line	473 vs 473	74% vs 45%	80% vs 67%	10.9 vs 7.0 months	NR vs 47.5 months

ORR: 74% vs 45%

PFS: 10.9 vs 7.0 months

Better QoL and less toxicities

OS: NR vs 47.5 months

Recondo G, Nature Rev Clin Oncol 2018, 15:694

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EGFR, BRAF, ALK, ROS convergences et divergences

Les IK sont le standard de traitement de (1^{ère}) ligne

Phase II non comparative trials with crizotinib

ROS1 TKI	Drug	Phase	Treatment	Sample size	ORR	DCR ^a	PFS	OS
ROS1 TKI-naïve	Crizotinib	II	First-line	66	65%	80%	19.3 months	51.4 months
				100	65%	80%	15.9 months	—
				100	65%	80%	20.0 months	—
				100	65%	80%	22.5 months	17.2 months
				100	65%	80%	22.8 months	—

ORR: 65-72%

PFS: 19.0-24.7 months

OS: 51.4 months

Phase II non comparative trials with dabrafenib/trametinib

Drug	Phase	Treatment	Sample size	ORR	DCR ^a	PFS	OS
Dabrafenib + Trametinib ^b	II	First-line	6 and 9.7	61%	80%	8.6 months	NR
Dabrafenib + Trametinib ^b	II	First-line	6 and 9.7	63%	80%	8.6 months	NR

ORR: 63%

PFS: 8.6-10.9 months

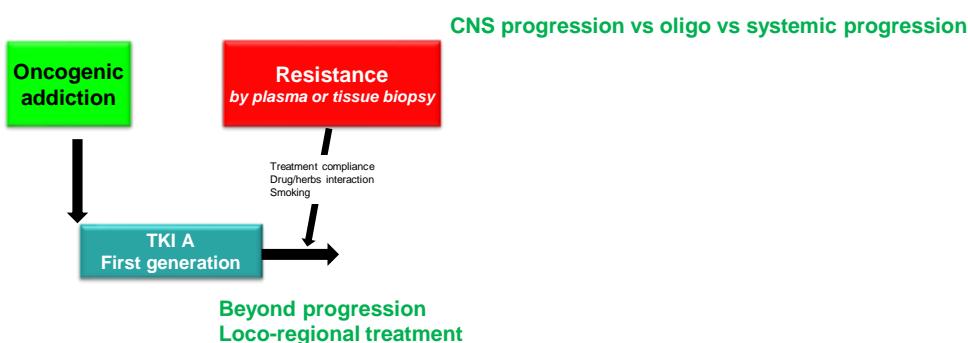
OS: 24.6 months

Drilon A, Nature Rev Clin Oncol 2021, 18:35; Bustamante Alvarez JG, Drugs in Context 2019, 8:212566

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EGFR, BRAF, ALK, ROS convergences et divergences

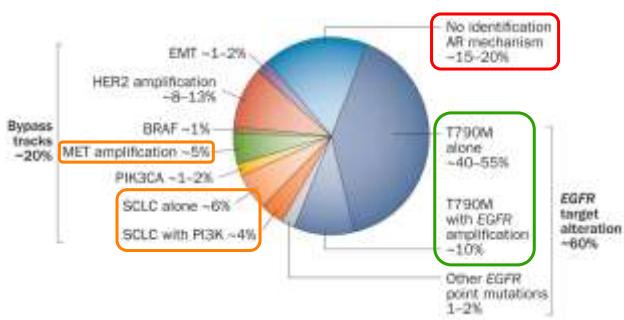
Stratégie thérapeutique chez les malades avec addiction



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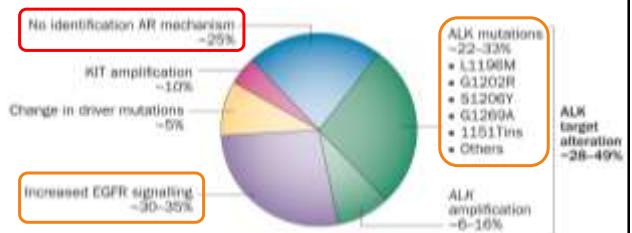
EGFR et ALK convergences et divergences

EGFR molecular resistance, 1st/2nd generation TKIs



Less frequent T790M selection in the CNS
More MET alterations (amplification, HGF expression)

ALK molecular resistance, crizotinib



Include also loss of ALK rearrangement

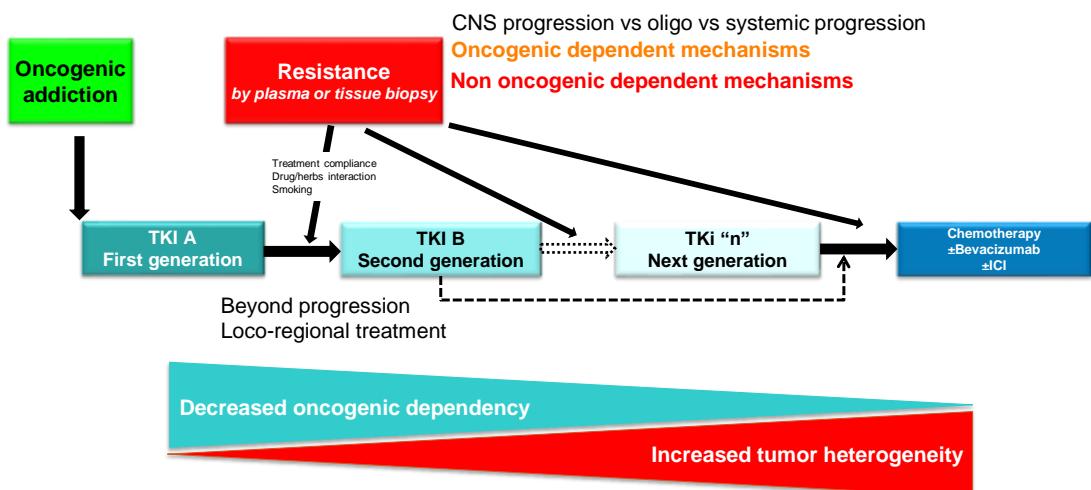
Impact sur les décisions thérapeutiques : oui pour EGFR, ? pour ALK

Camidge R, Nat Rev Clin Oncol 2014, 11:473; Gainor JF, Cancer Discov 2016, 6:1118

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EGFR, BRAF, ALK, ROS convergences et divergences

Stratégie thérapeutique chez les malades avec addiction



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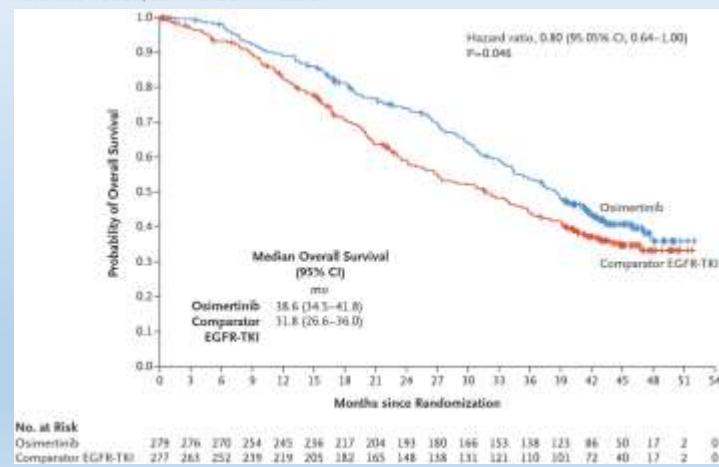
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Osimertinib = traitement de L1 CBNPC EGFRm

FLAURA Phase III 1st line treatment, osimertinib vs gefitinib/erlotinib

Advanced NSCLC, common EGFR mutation



L'osimertinib est l'ITK de choix en 1^{ère} ligne

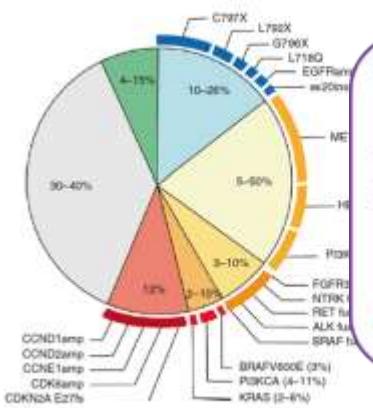
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Mutations EGFR – résistances post osimertinib

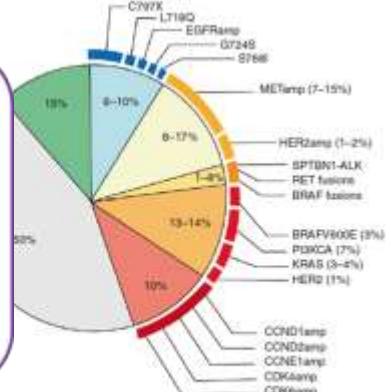
Resistance mechanisms to second-line osimertinib



- Platinum doublet CT ± bevacizumab
 - (Carbo-paclitaxel, atezolizumab, bevacizumab)
 - IO
- Carboplatinate etoposide ± TKI
- Case reports of targeted therapy (ib or ab)
 - monotherapy
 - combination
 - ± osimertinib continuation

• Trials

Resistance mechanisms to first-line osimertinib



Other EGFR tertiary mutations include G719X, G734S AND I516L
Mutations have also been reported

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(Leonetti et al. 2019)

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Evolution des séquences thérapeutiques – algorithme pour EGFR

Stage IV NSCLC

Common EGFR mutation

1L

Osimertinib

Pharmacology?

Oligo-progression

Diffuse progression
plasma AND tissue biopsies

≥2L

Increase dose
change TKI?

TKI
beyond progression

All/no molecular alterations
platinum doublet
± bevacizumab

SCLC
ddp etoposide
TKI pursuit?

Other alteration
Trials/
molecular board

PDL1 +
ICI?

T790M-/ADC
Carbo-platinaxel
+ beva + atezo

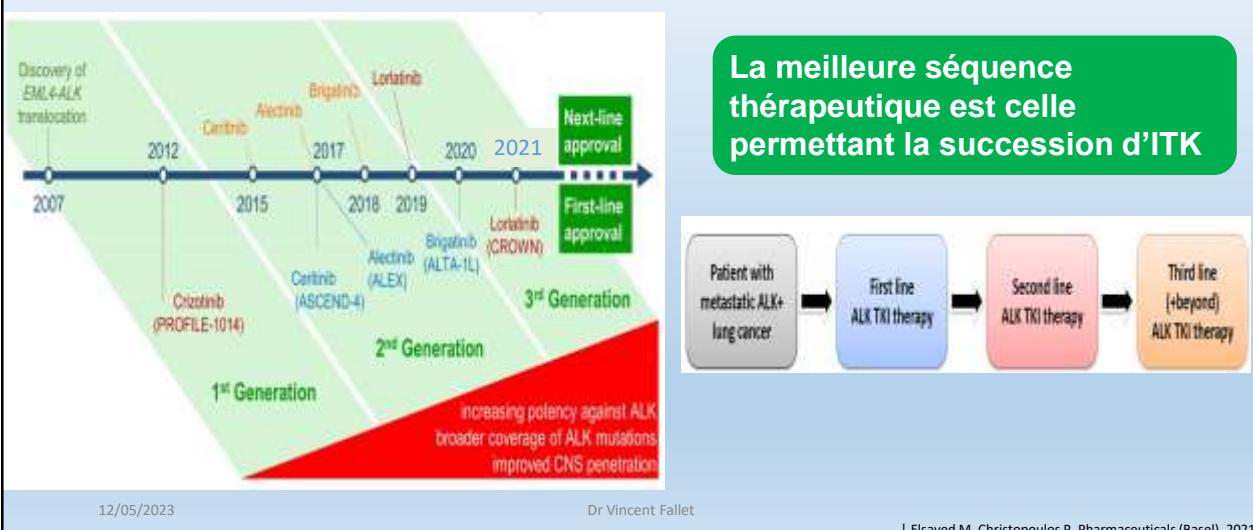
?

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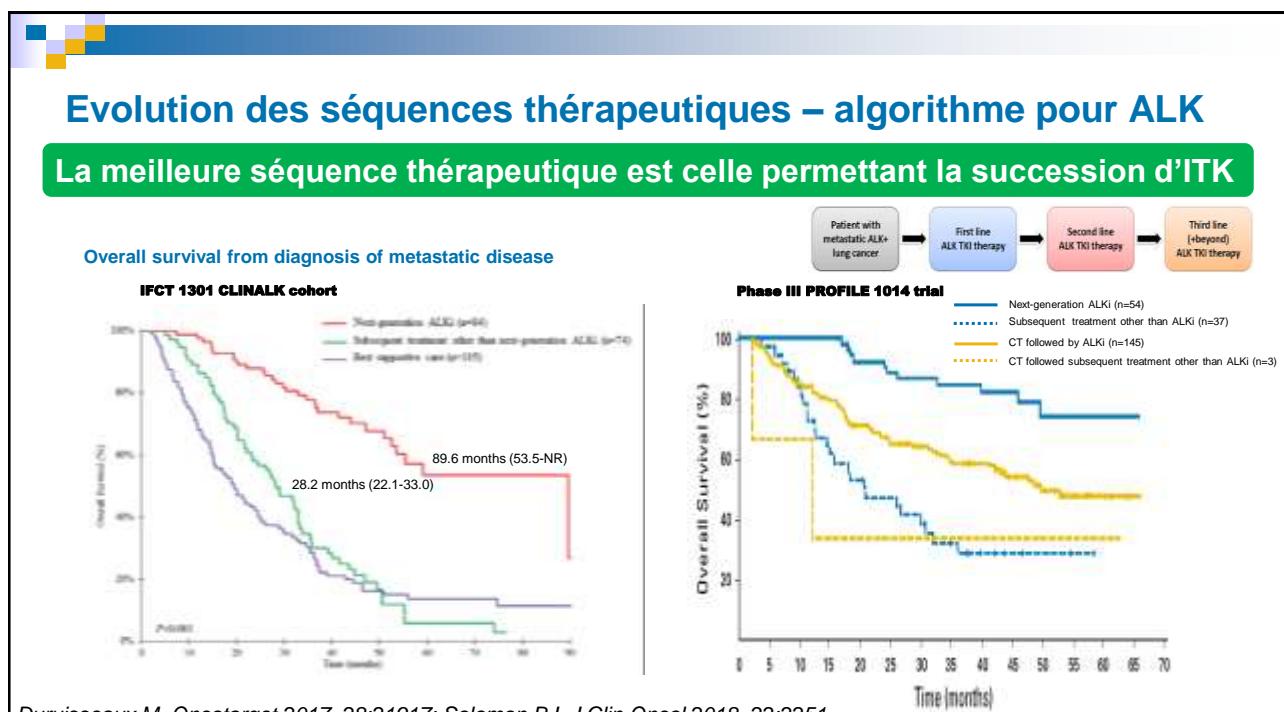
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Stratégie thérapeutique CBNPC ALK+

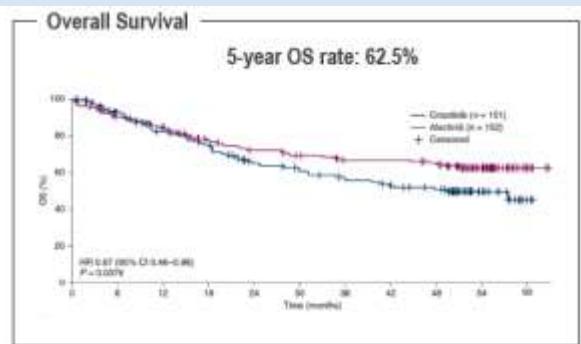
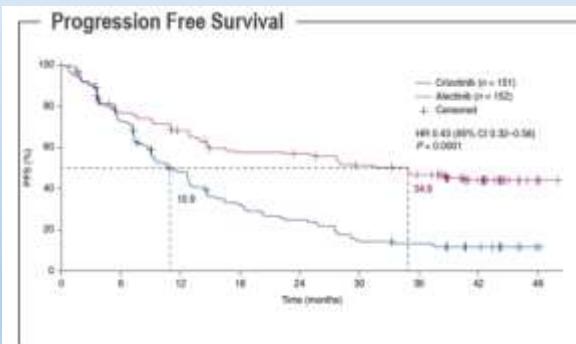
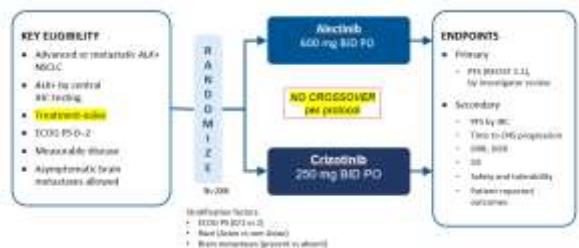


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Alectinib L1 - ALEX

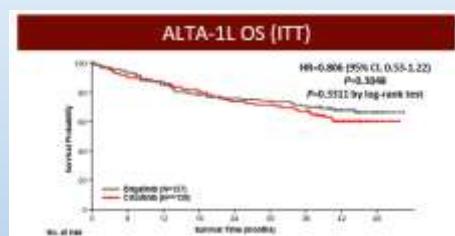
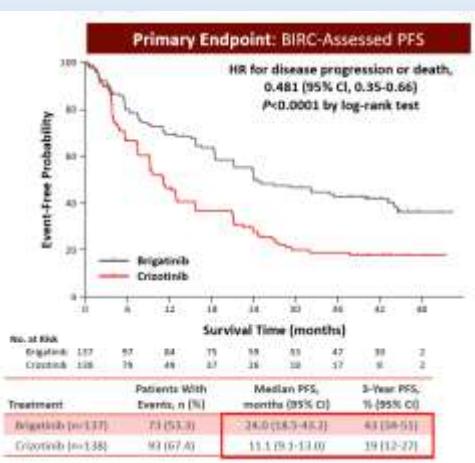


mPFS Alectinib 34.8 months vs Crizotinib 10.9 months

Mok T, et al. Ann Oncol 2020

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Brigatinib L1 - ALTA-1L



65 patients (47.1%) discontinued crizotinib and crossed over to receive brigatinib study drug according to the protocol:
Crossover occurred in 46% (19/41) of patients who had brain metastases at baseline per investigators
23/65 patients (35%) remained on brigatinib up to study end

BIRC mPFS brigatinib 24 months vs Crizotinib 11 months

Camidge DR et al., Journal of Thoracic Oncology (2021)

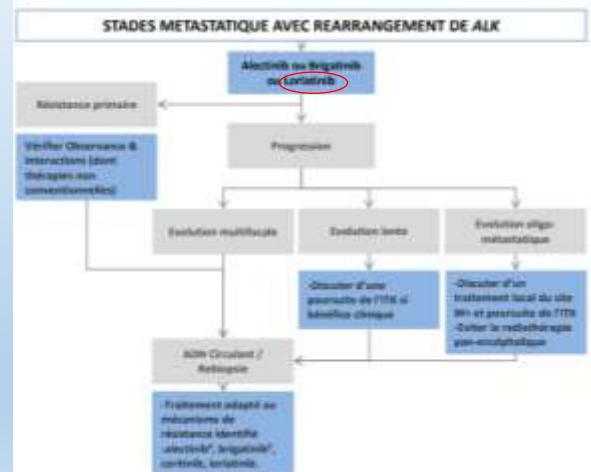
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Stratégie thérapeutique CBNPC ALK+



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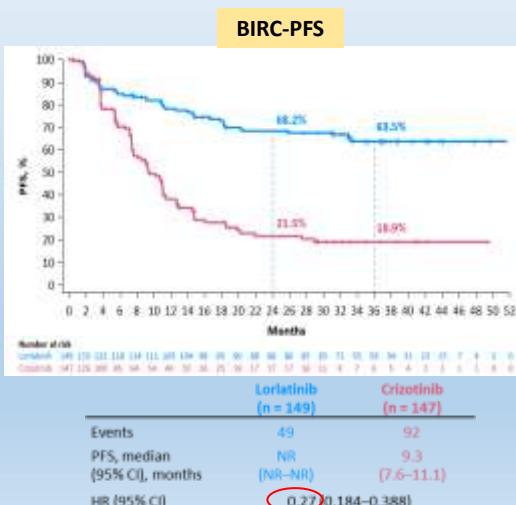
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| Esayed M, Christopoulos P. Pharmaceuticals (Basel). 2021

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Lorlatinib L1 - CROWN



Shaw AT, et al. N Engl J Med. 2020 ; Solomon et al. Lancet Resp Med. 2023

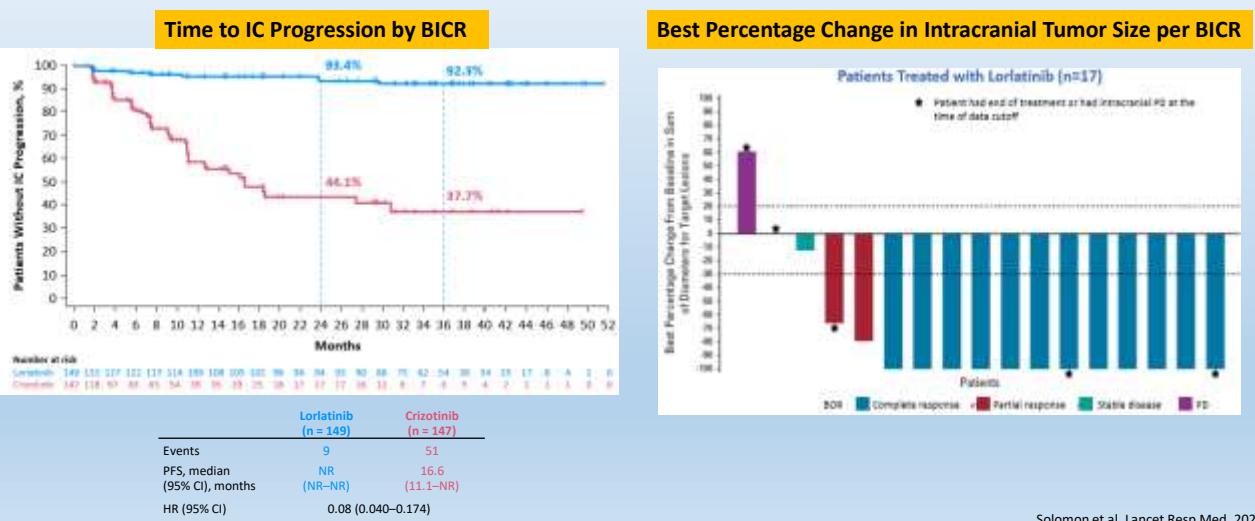
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Tableau de synthèse – profil d'efficacité des ITK ALK en 1^{ère} ligne

	Crizotinib PROFILE 1014	Ceritinib ASCEND-4	Alectinib ALEX	Brigatinib ALTA-1L	Lorlatinib CROWN
ORR	74%	73%	83%	74%	76%
mPFS (months)	10,9	16,6 (IRC) 10,7 (baseline BM) 26,3 (no baseline BM)	25,7 (IRC) 34,6 (INV) 25,4 (baseline BM) 38,5 (no baseline BM)	24 (IRC) 30,8 (INV) 24 (baseline BM) NA (no baseline BM)	NE
PFS-HR	0,45 (IRC)	0,55 (IRC)	0,50 (IRC) 0,43 (INV) 0,37 (baseline BM (INV))	0,48 (IRC) 0,43 (INV) 0,29 (baseline BM (IRC))	0,28 (IRC) 0,21 (INV) 0,20 (baseline BM) 0,32 (no baseline BM)
mOS	NE HR=0,346 (After crossover adjustment)	NE	1-year OS: 84,3% 2-year OS: 72,5% 3-year OS: 67% 4-year OS: 65,3% 5-year OS: 62,5%	1-year OS: 85,3% 2-year OS: 76% 3-year OS: 71% 4-year OS: 66% 5-year OS: NA	OS HR=0,72

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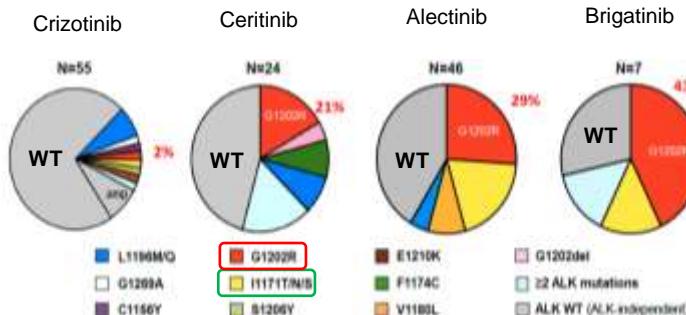
Contrôle cérébral sous Lorlatinib - CROWN



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Evolution des séquences thérapeutiques – algorithme pour ALK

ALK dependant resistance mechanism at progression



ALK-ogram for therapeutic strategy?

Mutation status	Cellular ALK 20% inhibition mean IC ₅₀ (nM)				Lorlatinib
	Crizotinib	Control	Alectinib	Brigatinib	
Positive DelT	1000	300	300	370	10000
DEL4-ALK	100	0.5	11.4	10.7	0.5
DEL4-ALK G1202R	100	0.5	11.4	10.7	0.5
DEL4-ALK G1202del	0.4	0.5	17.5	22.8	0.5
DEL4-ALK G1202del G1202R	0.4	0.5	17.5	22.8	0.5
DEL4-ALK F1174C	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L G1202R	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L G1202del	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L G1202del G1202R	100	0.5	11.4	10.7	0.5
DEL4-ALK F1174C G1202R	100	0.5	11.4	10.7	0.5
DEL4-ALK F1174C G1202del	0.5	0.5	17.5	22.8	0.5
DEL4-ALK F1174C G1202del G1202R	0.5	0.5	17.5	22.8	0.5
DEL4-ALK V1180L F1174C	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L F1174C G1202R	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L F1174C G1202del	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L F1174C G1202del G1202R	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L V1180L G1202R	100	0.5	11.4	10.7	0.5
DEL4-ALK V1180L V1180L G1202del	0.5	0.5	17.5	22.8	0.5
DEL4-ALK V1180L V1180L G1202del G1202R	0.5	0.5	17.5	22.8	0.5

Gainor JF, Cancer Discov 2016, Epub October;

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Tableau de synthèse tolérance ITK ALK en L1

	ALK-Alectinib (n=152)	ALK-Brigatinib (n=136)	ALK-Lorlatinib (n=149)
Any-grade AEs in >10% of patients	Anemia: 22% Increased blood bilirubin: 19% Peripheral edema: 10% Increased ALT: 17% Nausea: 10% Increased AST: 10% Myalgia: 16% Diarrhea: 13%	Diarrea: 49% Increased blood creatine kinase level: 39% Nausea: 26% Cough: 25% Hypertension: 23% Increased alanine aminotransferase level: 19% Increased lipase level: 19% Vomiting: 18% Constipation: 15% Increased amylase level: 14% Pruritis: 13% Rash: 10%	Hypochromic anemia: 70% Hyperglycemia: 64% Edema: 55% Increased weight: 38% Peripheral neuropathy: 34% Cognitive effects: 21% Diarrea: 21% Anemia: 19% Fatigue: 19% Hypertension: 18% Vision disorder: 18% Increase ALT: 17% Constipation: 17% Mood effects: 16% Nausea: 15% Increased AST: 14% Vomiting: 13% Hyperlipidemia: 11% Dysgeusia: 5%
Grade 3-5 AEs in >5% of patients	None	Increased blood CPK: 18% Increased lipase level: 13% Hypertension: 10% Increased amylase level: 5%	Hypochromic anemia: 15% Hyperglycemia: 12% Edema: 4% Increased weight: 17%
Dose reduction due to AEs, %	16	29	21
Dose interruptions due to AEs, %	22	Not reported	49
Discontinuation due to AEs, %	13	12	7
Fatal AEs, %	4	5	5

Updates on ALK: TKI and beyond presented by Myung-Ju Ahn, M.D. ELCC 2022
RCP Alectinib, Brigatinib, Lorlatinib

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Plan

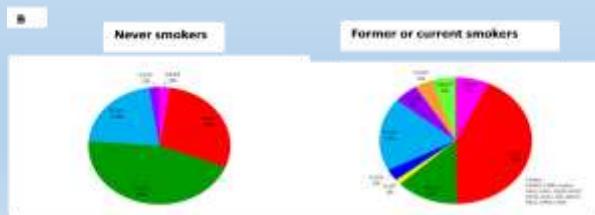
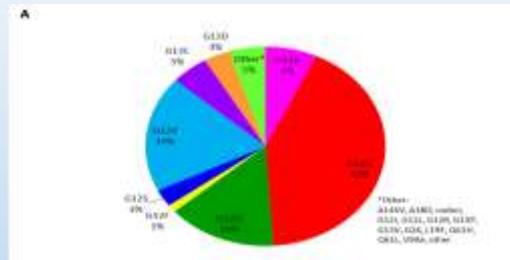
- Addiction oncogénique – définition
- Quelles addictions oncogéniques dans les CBNPC?
- Séquences thérapeutiques dans les CBNPC avec addiction EGFR, ALK, ROS1
- Gestion des progressions en cas d'addiction
- Toxicités
- **Autres addictions**
- Conclusions

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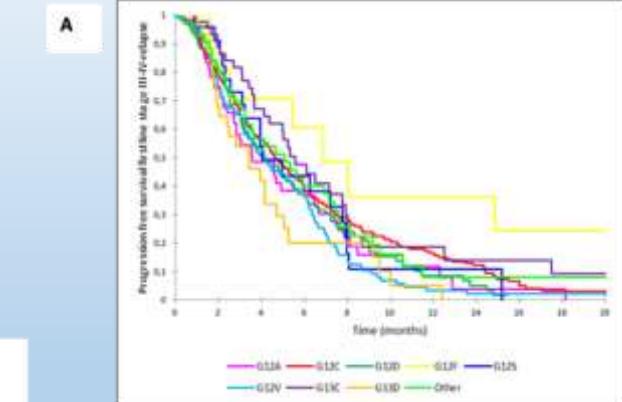
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Mutation KRAS



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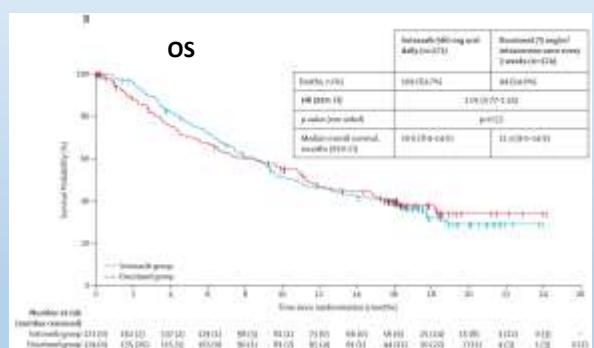
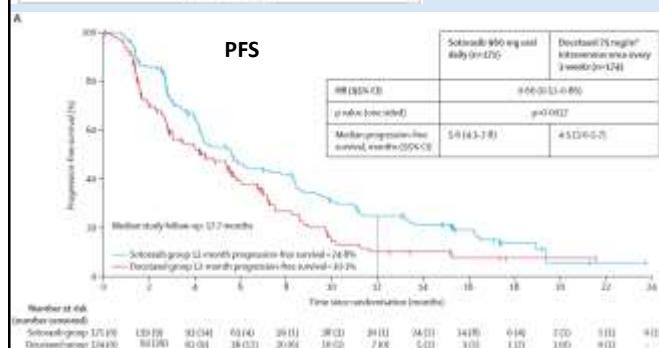
Ruppert AM, JTO CCR 2020

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Mutation KRAS G12C: sotorasib



AMM sotorasib en L2 CBNPC G12C
Disponible en AP



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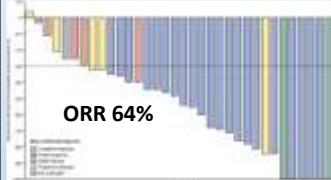
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Hong DS 2020 ; (de Langen et al. 2023)

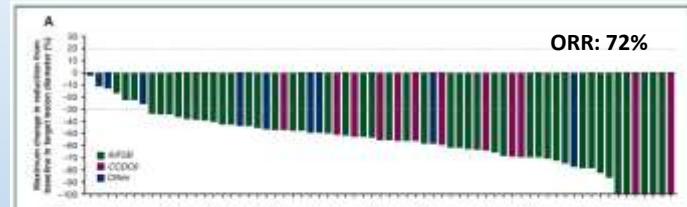
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Autres addictions potentiellement ciblables...

Dabrafenib trametinib in previously untreated BRAF V600E

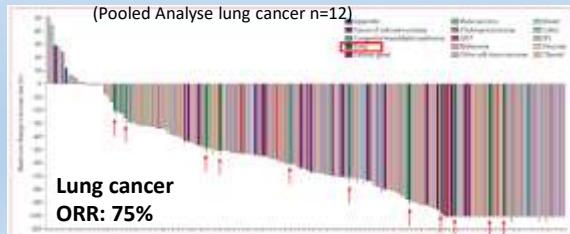


Praseltinib in previously untreated RET rearrangement

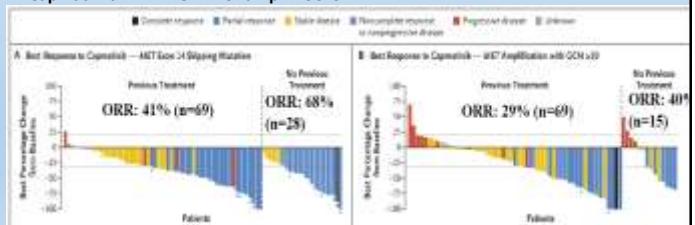


Larotrectinib in NTRK rearrangement tumors

(Pooled Analyse lung cancer n=12)



Capmatinib in MET ex 14 or ampli NSCLC



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Planchard et al. Lancet Oncol . 2017; Drilon et al. JCO Precis Oncol 2022; Griesinger et al. Annal Oncol Nov 2022; Wolf et al. N Engl J Med 2020;383:944

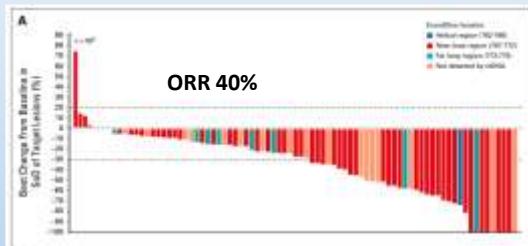
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Autres addictions potentiellement ciblables...

Mobocertinib in EGFRm ins ex 20



Amivantanib in EGFRm ins ex 20



T-DXd in HER2m NSCLC



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Park et al. JCO 2021; Zhou et al. JAMA Oncol. 2021; Li et al. N Engl J Med 2022; 386:241

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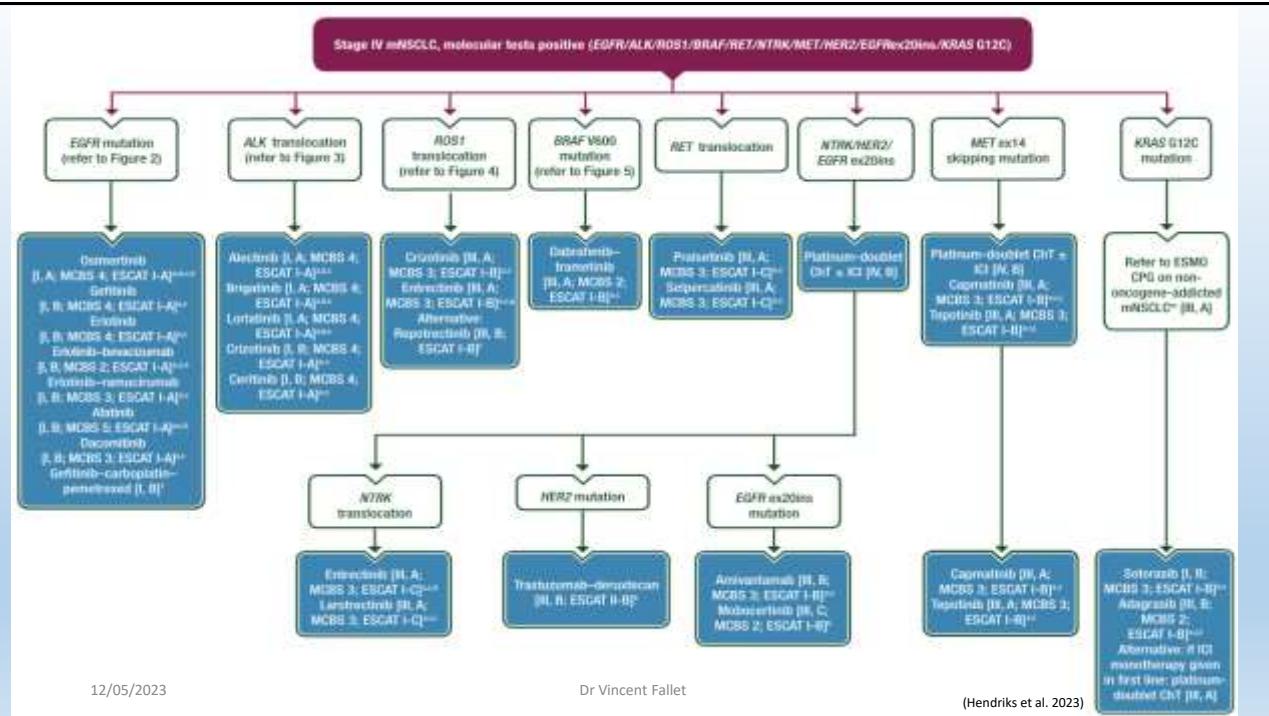
Conclusion Take Home Messages

- Recherche anomalies moléculaires **EGFR ALK ROS1** avant L1 pour tout CBNPC non épidermoïde ou épidermoïde du non fumeur même si PDL1>50%
- Testing moléculaire élargi avant L2
 - NGS
- Mutation activatrice EGFR -> L1 **OSIMERTINIB**
- Réarrangement de ALK -> L1 **ALECTINIB** ou **BRIGATINIB** ou **LORLATINIB**
- Réarrangement de ROS1 -> L1 **CRIZOTINIB**
- A progression: rechercher si possible un mécanisme de résistance (Biopsie ou ADNtc) / Penser au dosage
- Si oligo progression: traitement local si possible et poursuite ITK
- Problématique de l'accès aux thérapies ciblées -> AP -> Essai clinique -> **RCP moléculaire**
- Gestion des EI et qualité de vie des patients... **maladie chronique – pas d'arrêt du traitement...**

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(Hendriks et al. 2023)

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Merci pour votre attention

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