7e ÉDITION

# JOURNÉES DU **GFCO 2021**

## Biomarqueurs et analyses moléculaires en oncologie

Avec la participation scientifique du GFCO

# Actualités et Vision Projective en Oncologie thoracique

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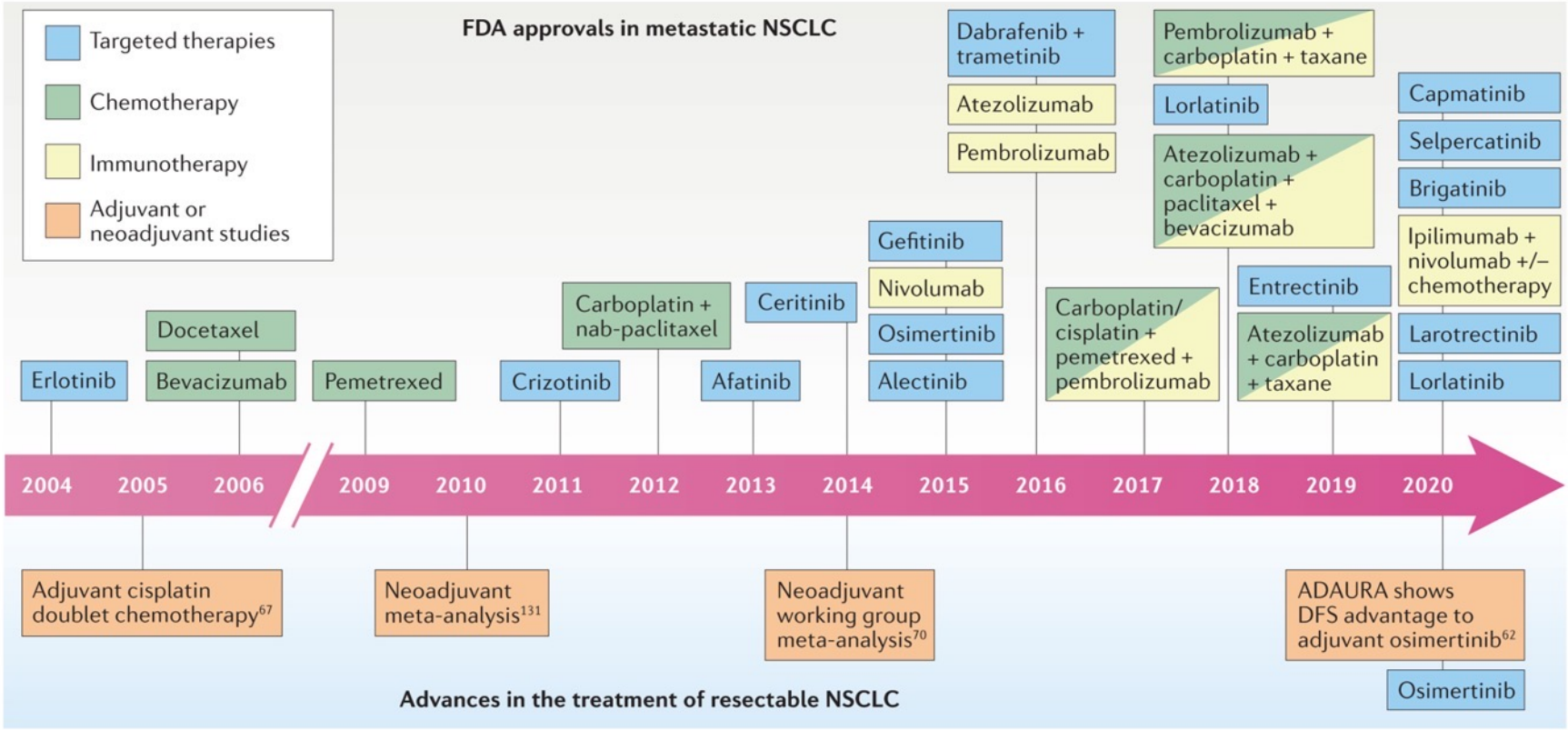
# Liens d’intérêt

- **Investigateurs essais thérapeutiques : AZ, Roche, BMS, MSD, Novartis**
- **Symposium : AZ, Roche, MSD, Pfizer, Amgen**
- **Expertise : AZ, Roche, MSD, Novartis**

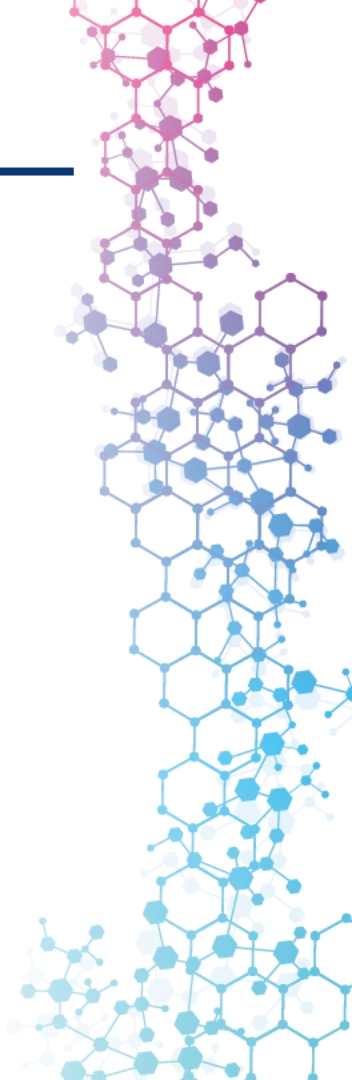
# Développement thérapeutique des CBNPC




Chaft, J.E., Rimner, A., Weder, W. et al. Evolution of systemic therapy for stages I–III non-metastatic non-small-cell lung cancer. Nat Rev Clin Oncol (2021).

# Disponiblité des thérapies ciblées

- **Autorisations de mise sous le marché (AMM)**
- **Autres accès :**
  - **Autorisations d'accès compassionnel** (AAC) délivrées par l'ANSM, sur demande d'un médecin ou d'une institution sanitaire pour un patient nommément désigné (**ex ATU nominative**)
  - **Autorisations d'accès précoce** (AAP) délivrées par la HAS, sur demande d'un laboratoire, prescrit à un groupe de patients (**ex ATU de cohorte**)
  - **Cadre de Prescription Compassionnelle** (CPC) délivrées par l'ANSM (ex RTU)



Courtesy K Leroy

# Thérapies ciblées disponibles en oncologie thoracique - sept. 2021

| | Fréquence | AMM | AAP | AAC | CPC | Essai |
|---|---|---|---|---|---|---|
| *KRAS (G12C)* | 10% | | sotorasib (2L) | | | |
| *EGFR* | 10-15% | gefitinib<br>erlotinib<br>osimertinib | osimertinib (adj) | | | |
| *EGFR Ins20* | | | amivantamab (2L) | mobocertinib (2L)<br>poziotinib (2L) | | |
| *MET ex14* | 3% | | capmatinib (2L) | tepotinib (2L) | crizotinib | |
| *BRAF (V600E)* | 1-2% | dabrafenib + trametinib (2L) | | | | |
| *HER2* | 2% | | | | | TKI-HER2<br>trastuzumab-deruxtecan |

Courtesy K Leroy

# Thérapies ciblées disponibles en oncologie thoracique - sept. 2021

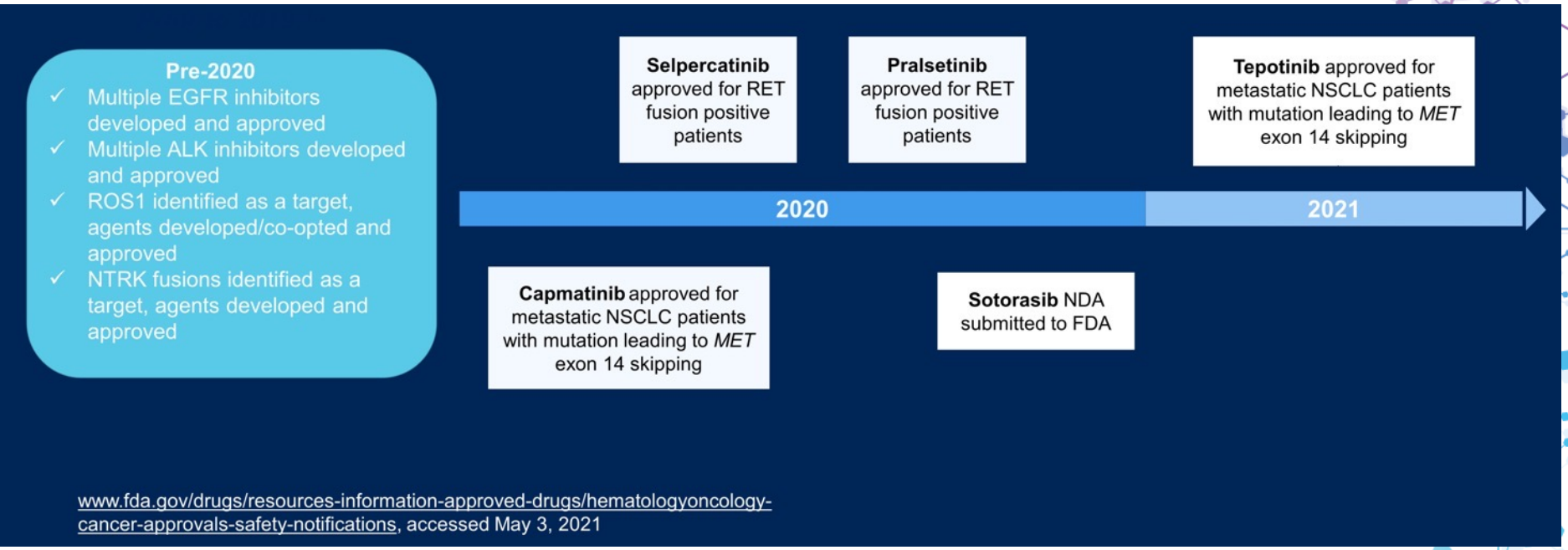
| | Fréquence | AMM | AAP | AAC | CPC | Essai |
|---|---|---|---|---|---|---|
| *ALK* | 5% | crizotinib<br>alectinib<br>brigatinib<br>ceritinib (2L)<br>lorlatinib (2L) | | | | |
| *ROS1* | 1-2% | crizotinb (2L) | | | | |
| *RET* | 1-2% | | praseltinib (2L) | selpercatinib (2L) | | |
| *NTRK* | 0,5% ? | | | | | larotrectinib<br>entrectinib<br>reprotectinib |

Courtesy K Leroy

Actualités

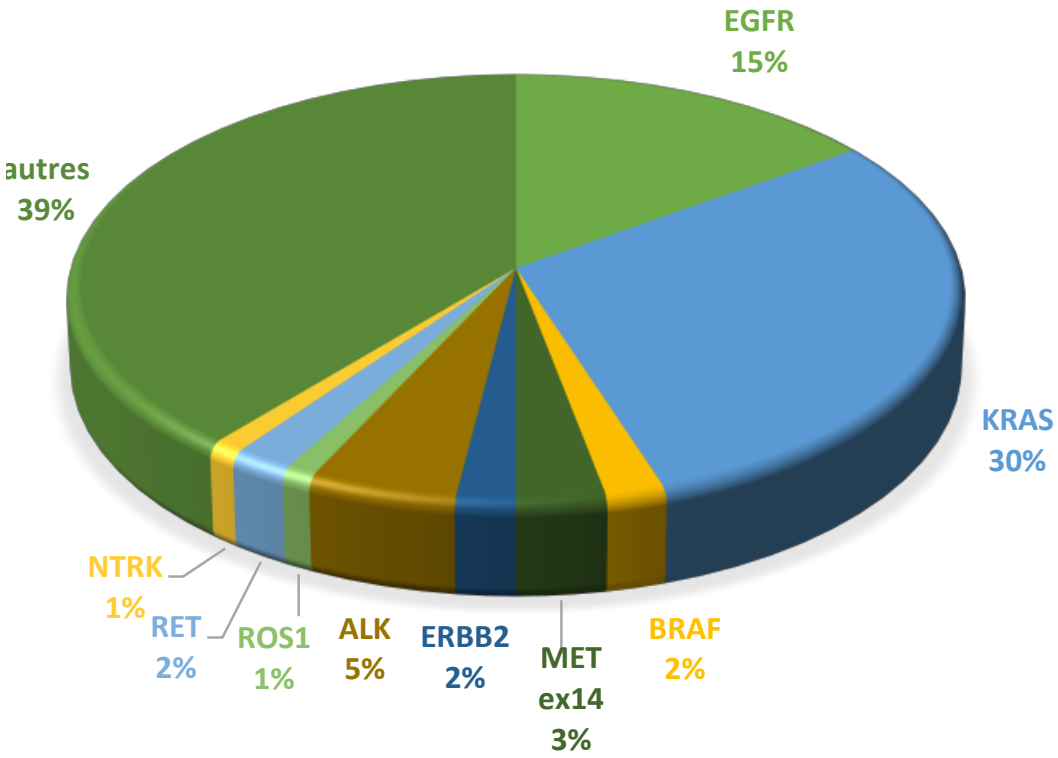
# Petites molécules inhibitrices

# Développement thérapeutique des CBNPC




www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications, accessed May 3, 2021

# Altérations génétiques CBNPC (adénocarcinomes)



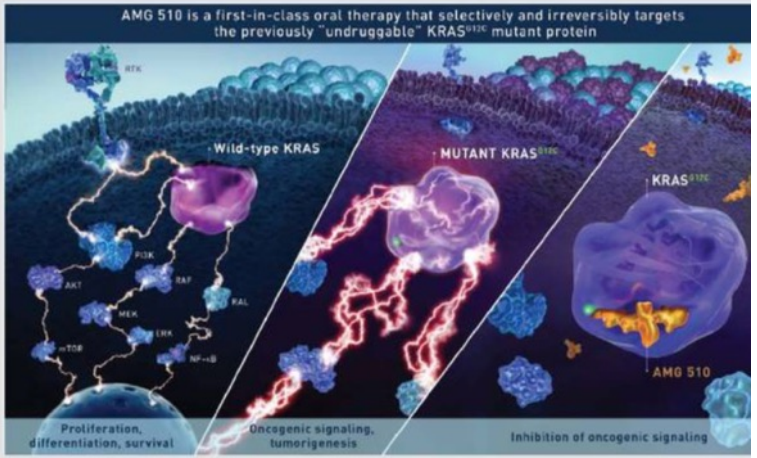

**Mutations « driver » mutuellement exclusives**

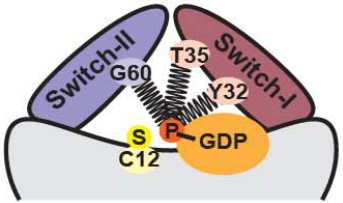
# Cibler *RAS G121C*

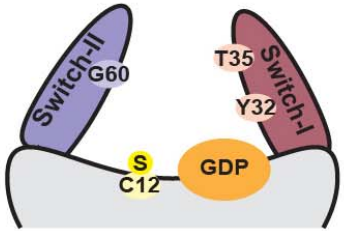
e 1 Study of AMG 510, a Novel KRAS$^{G12C}$ Inhibitor, in Advanced Solid Tumors With *KRAS p. G12C* Mutation: ESMO 2019

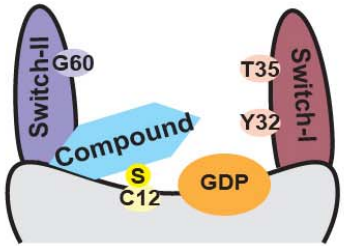
## AMG 510 IS A FIRST-IN-CLASS KRAS$^{G12C}$ INHIBITOR

- ***KRAS p. G12C*** **mutation is found in approximately 13% of lung cancer, 3% of colorectal cancer and appendix cancer, and 1%–3% of other solid tumors[1-3]**
- **Currently, there is no approved therapy targeting this mutation**
- **AMG 510 is a novel, first-in-class small molecule that specifically and irreversibly inhibits KRAS$^{G12C}$ by permanently locking it in an inactive GDP-bound state**

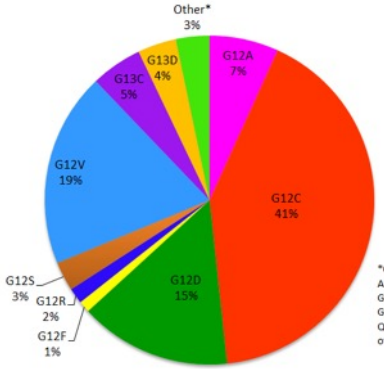




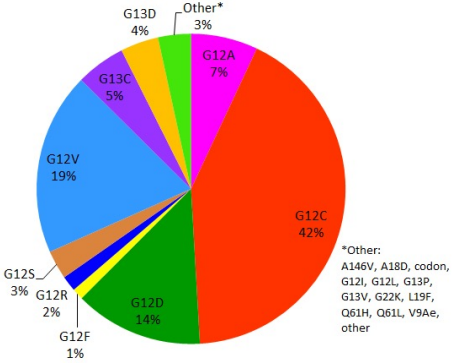



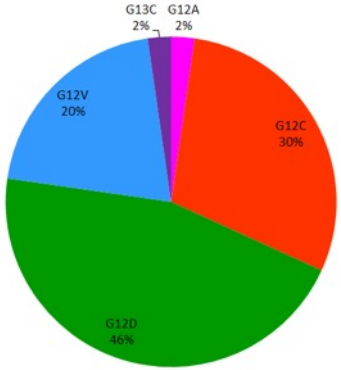

Ostrem LM, Nature 2013




Smokers




Non smokers

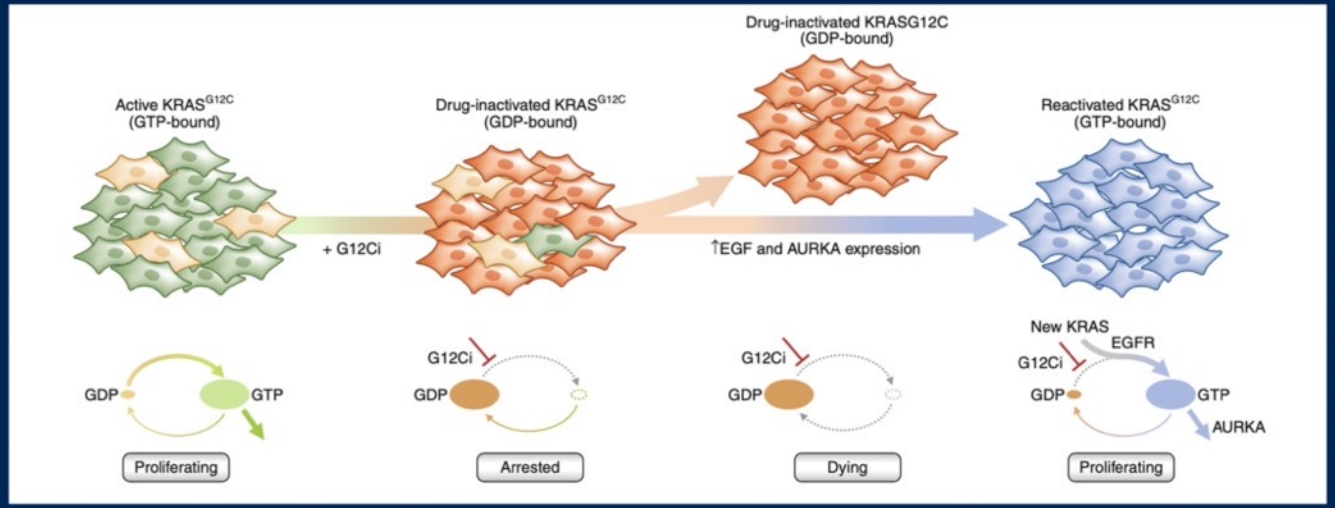



Outcomes of Patients With Advanced NSCLC From the Intergroupe Francophone de Cancérologie Thoracique Biomarkers France Study by *KRAS* Mutation Subtypes

Ruppert AM, JTO Clinical and Research Reports 2020

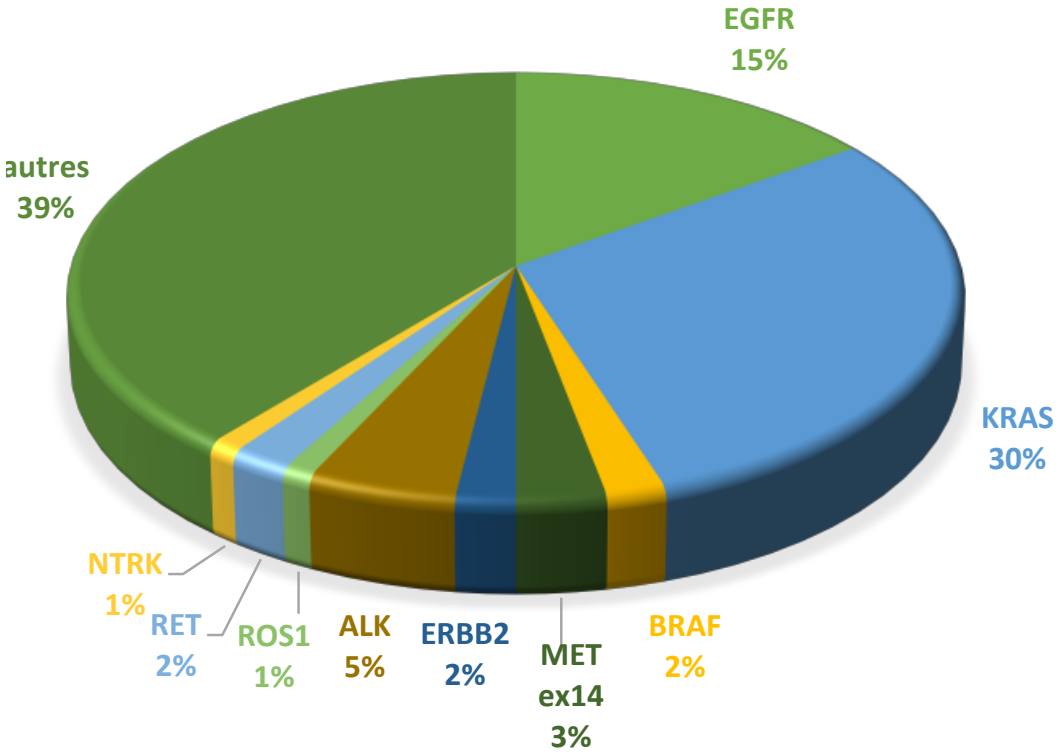
# Resistance Mechanisms for Small Molecule Inhibitors

- KRAS$^{G12C}$ – increased target production, escape pathway activation (EGFR with SHP2, Aurora kinase)




Hata AN, Shaw AT. Nat Med 2020;26:169-170.

# Altérations génétiques CBNPC (adénocarcinomes)



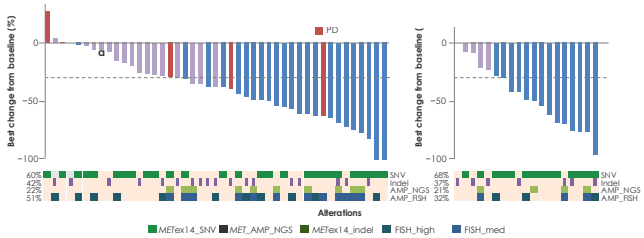

**Mutations « driver » mutuellement exclusives**

# Anti-MET : Capmatinib & Tepotinib

## Capmatinib CBNPC METex14

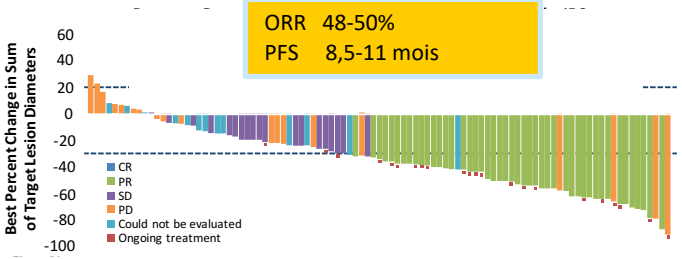
ORR 41-68%
PFS 5,4-12,4 mois

*Pré-traités* *Chimio-naïfs*



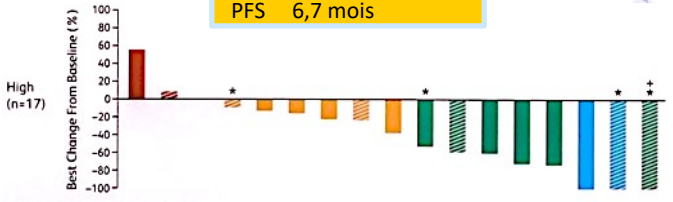

## Tepotinib CBNPC METex14

ORR 48-50%
PFS 8,5-11 mois




## Crizotinib CBNPC METamp (ratio ≥4)

ORR 40%
PFS 6,7 mois

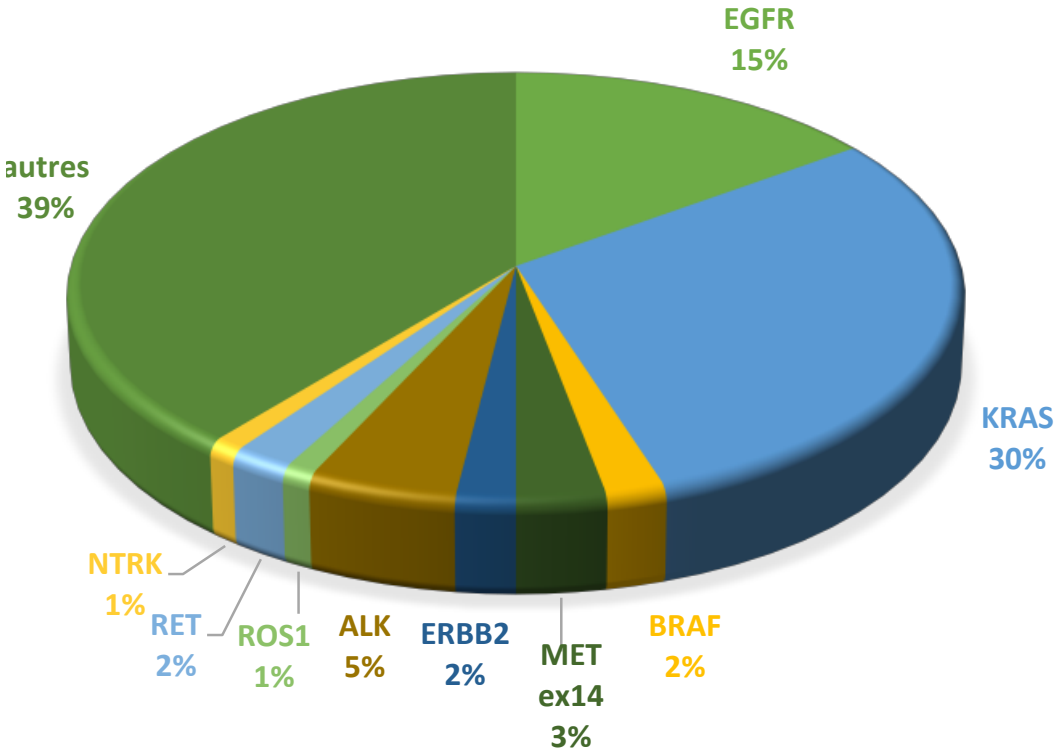



## Capmatinib CBNPC METamp (GCN ≥10)

| Responses assessed by BIRC in patients with high-level *MET* amplification[a] | Treatment-naive Subcohort 5a (n = 15) |
|---|---|
| ORR (95% CI), % | 40 (16–68) |
| DCR (95% CI), % | 67 (38–88) |
| Median DoR (95% CI), months | 7.5 (2.6–14.3) |
| Median PFS (95% CI), months | 4.2 (1.4–6.9) |

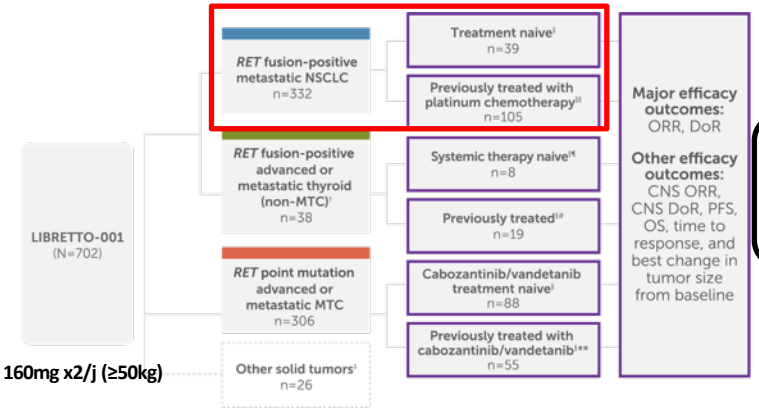
Wolf et al. NEJM 2020; Paik et al. NEJM 2020; Camidge et al. ASCO 2018

# Altérations génétiques CBNPC (adénocarcinomes)

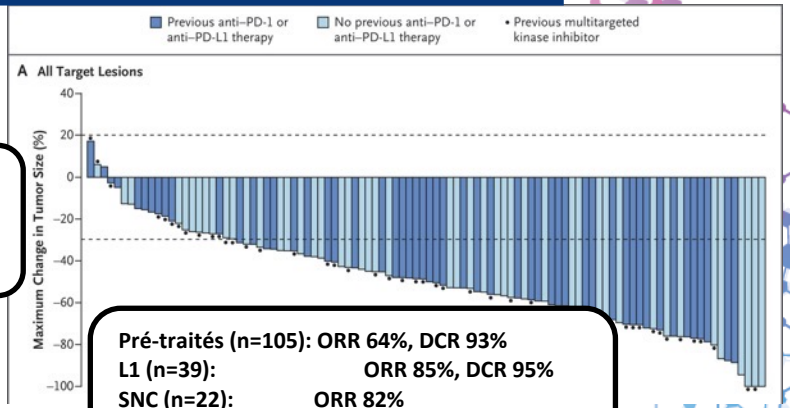



**Mutations « driver » mutuellement exclusives**

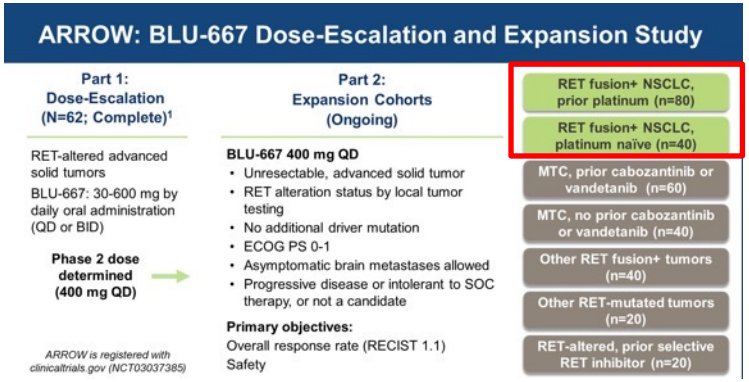
# Anti-RET : Selpercatinib & Pralsetinib



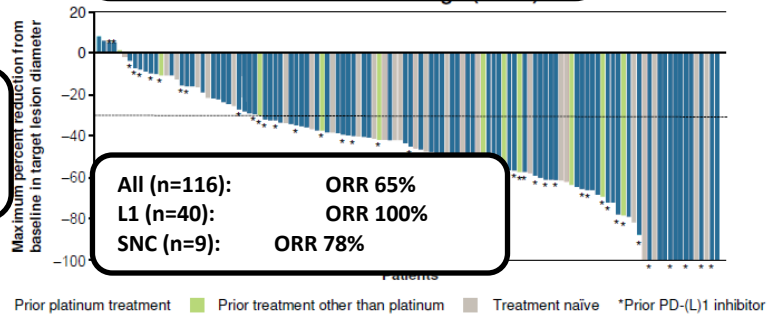

**Toxicité grade ≥3 :**
HTA (8%)
Cytolyse (6%)
Stop pour toxicité 1,7%




**Pré-traités (n=105): ORR 64%, DCR 93%**
**L1 (n=39): ORR 85%, DCR 95%**
**SNC (n=22): ORR 82%**
**mPFS 16,5 mois**




**Toxicité grade ≥3 :**
neutropénie (13%)
HTA (10%)
Stop pour toxicité 7%




**All (n=116): ORR 65%**
**L1 (n=40): ORR 100%**
**SNC (n=9): ORR 78%**

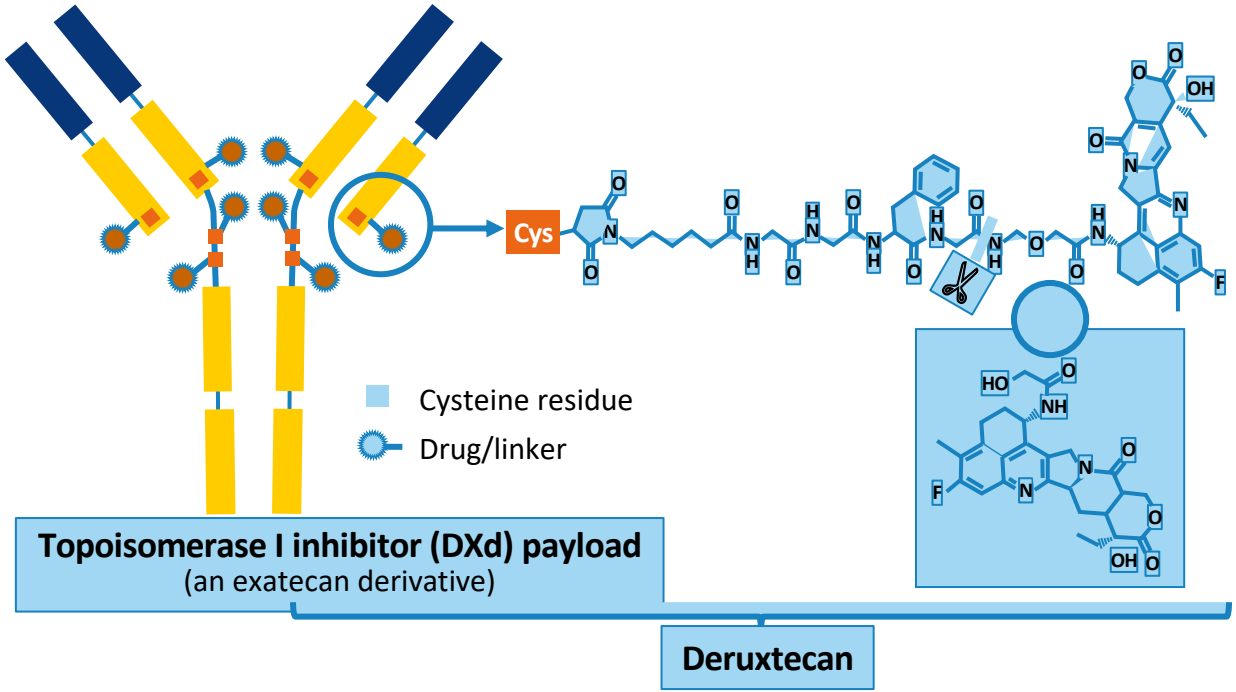
Drilon et al. N Engl J Med 2020; S ubbiah et al. ASCO 2020 abstr #9516; Gainor et al. ASCO 2019 abstr #9008; Gainor et al. NACLC 2020

Actualités

# ADC : Antibody-drug Conjugate

Conjugué anticoprs médicament

# HER2-Targeted ADC: Trastuzumab Deruxtecan T-DXd

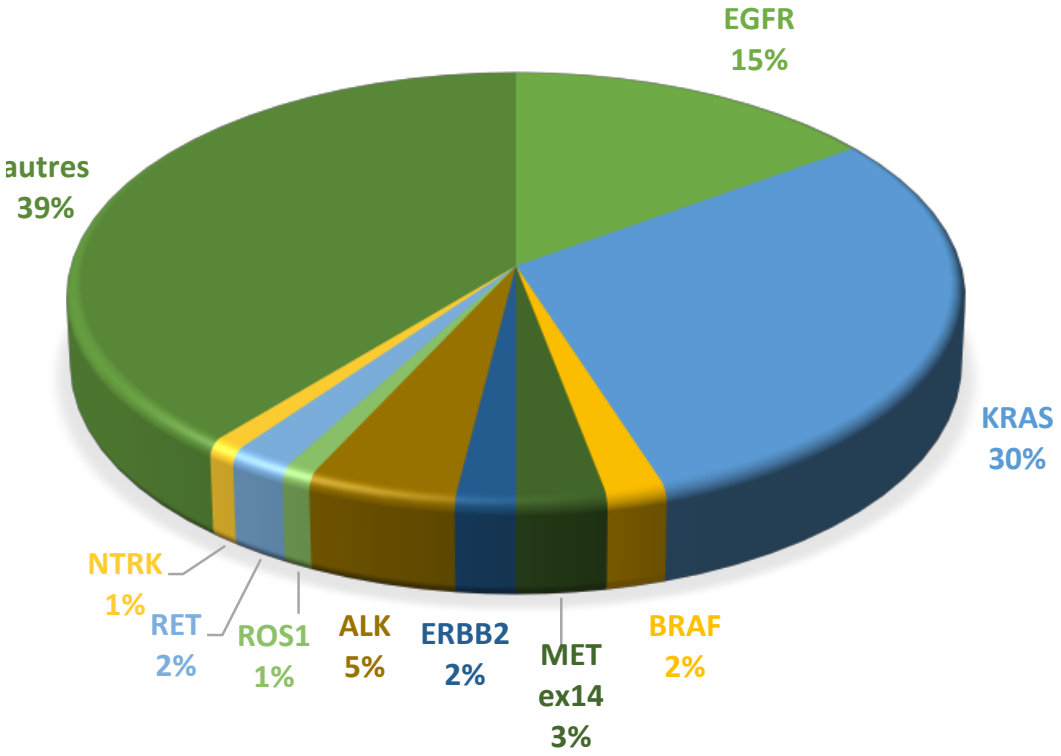



- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

- **DESTINY-Lung01:** Ongoing phase II study of T-DXd in *HER2*-mutated metastatic NSCLC

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

# Altérations génétiques CBNPC (adénocarcinomes)

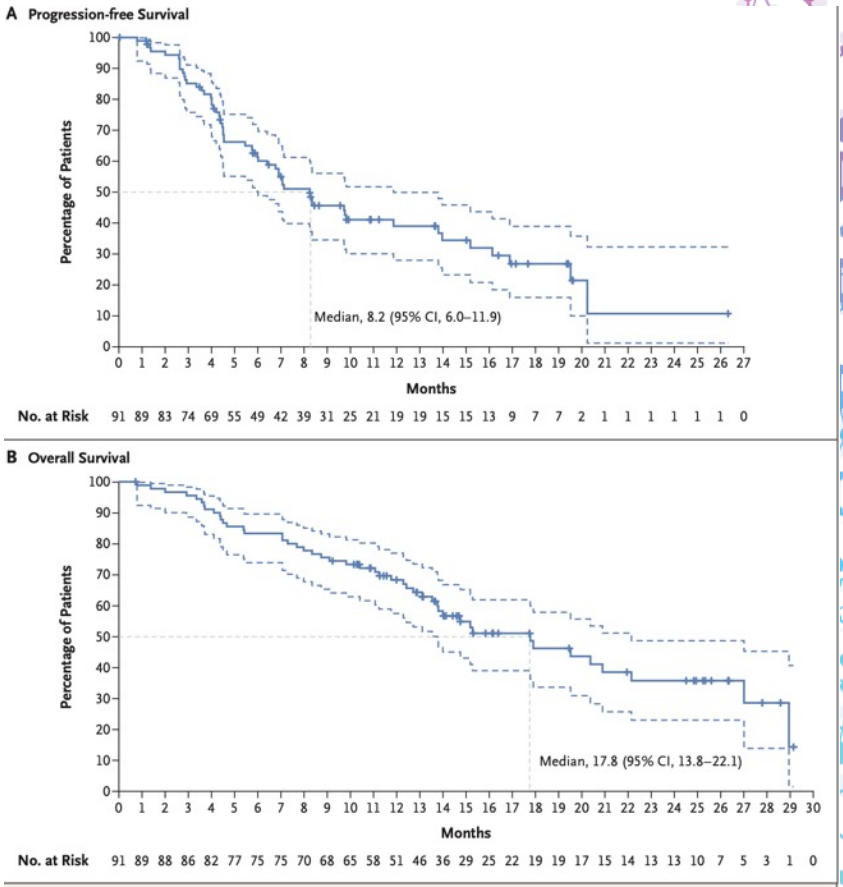



**Mutations « driver » mutuellement exclusives**

# DESTINY-Lung01: Response with T-DXd in *HER2*-Mutated Metastatic NSCLC

**Table 2. Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.**

| Response Assessment | Patients (N = 91) |
|---|---|
| Confirmed objective response* | |
| No. of patients | 50 |
| Percentage of patients (95% CI) | 55 (44–65) |
| Best response — no. (%) | |
| Complete response | 1 (1) |
| Partial response | 49 (54) |
| Stable disease | 34 (37) |
| Progressive disease | 3 (3) |
| Response could not be evaluated | 4 (4) |
| Disease control† | |
| No. of patients | 84 |
| Percentage of patients (95% CI) | 92 (85–97) |
| Median time to response (range) — mo‡ | 1.5 (1.2–9.3) |
| Median duration of response (95% CI) — mo‡ | 9.3 (5.7–14.7) |




Bob Li, NEJM 2021-

# DESTINY-Lung01: Interstitial Lung Disease with T-DXd in HER2-Mutated Metastatic NSCLC

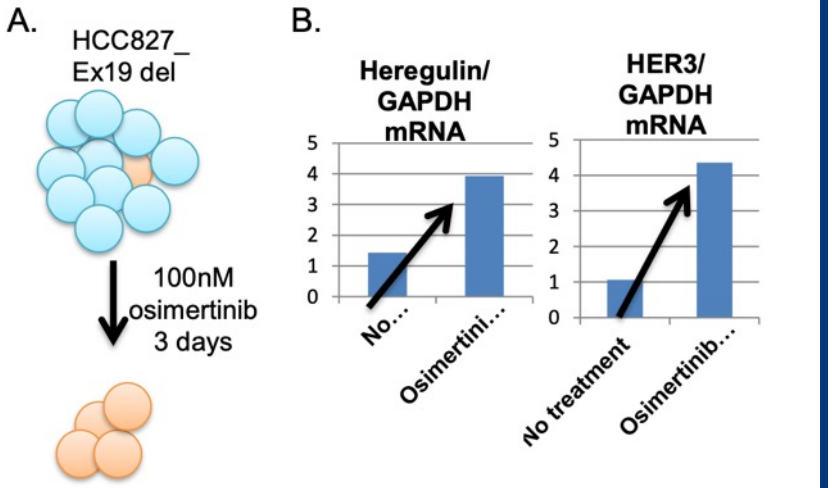
ILD 26%

**Table 3. Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).**

| Event | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 | Overall |
|---|---|---|---|---|---|
| | *number of patients (percent)* | | | | |
| Drug-related adverse event | 46 (51) | 37 (41) | 4 (4) | 1 (1)* | 88 (97) |
| Drug-related adverse events with ≥20% incidence | | | | | |
| Nausea | 58 (64) | 8 (9) | 0 | 0 | 66 (73) |
| Fatigue† | 42 (46) | 6 (7) | 0 | 0 | 48 (53) |
| Alopecia | 42 (46) | 0 | 0 | 0 | 42 (46) |
| Vomiting | 33 (36) | 3 (3) | 0 | 0 | 36 (40) |
| Neutropenia‡ | 15 (16) | 14 (15) | 3 (3) | 0 | 32 (35) |
| Anemia§ | 21 (23) | 9 (10) | 0 | 0 | 30 (33) |
| Diarrhea | 26 (29) | 2 (2) | 1 (1) | 0 | 29 (32) |
| Decreased appetite | 27 (30) | 0 | 0 | 0 | 27 (30) |
| Leukopenia¶ | 17 (19) | 4 (4) | 0 | 0 | 21 (23) |
| Constipation | 20 (22) | 0 | 0 | 0 | 20 (22) |

Bob Li, NEJM 2021-

# HER3-Targeted ADC : Patritumab Deruxtecan

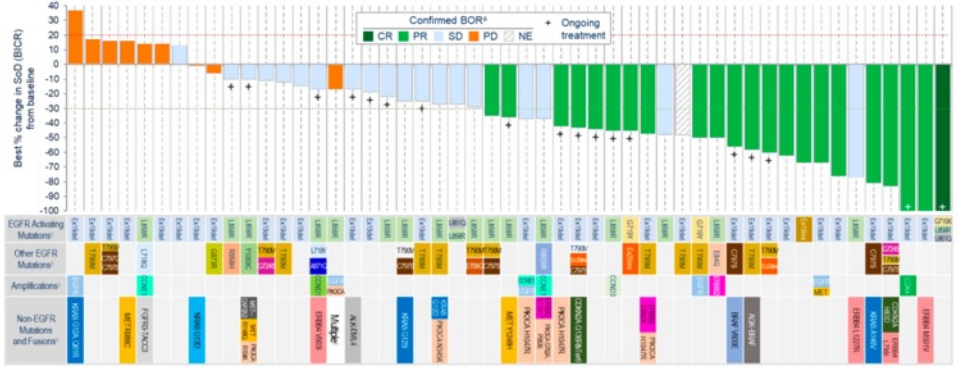



**Yonesaka, et.al, unpublished data**

Osimertinib upregulate HER3 and heregulin (HER3 ligand) of HCC827 cells.

**Pasi A Janne, et.al, ASCO 2021**

| Outcomes (BICR per RECIST 1.1)<br>Median Follow Up: 10.2 (range, 5.2-19.9) mo[a] | HER3-DXd 5.6 mg/kg<br>Prior TKI ± PBC<br>(N=57) | <br>Prior OSI and PBC<br>(N=44) |
|---|---|---|
| Confirmed ORR, % (95% CI) | 39 (26-52) | 39 (24-55) |
| Best overall response, n (%) | | |
| CR | 1 (2) | 1 (2) |
| PR | 21 (37) | 16 (36) |
| SD, Non-CR/Non-PD | 19 (33) | 13 (30) |
| PD | 9 (16) | 8 (18) |
| Not evaluable | 7 (12) | 6 (14) |
| Disease control rate, % (95% CI) | 72 (59-83) | 68 (52-81) |
| Time to response, median (range), mo | 2.6 (1.2-5.4) | 2.7 (1.2-5.4) |
| Duration of response, median (95% CI), mo | 6.9 (3.1-NE) | 7.0 (3.1-NE) |
| PFS, median (95% CI), mo | 8.2 (4.4-8.3) | 8.2 (4.0-NE) |



# Autres ADC en developpement

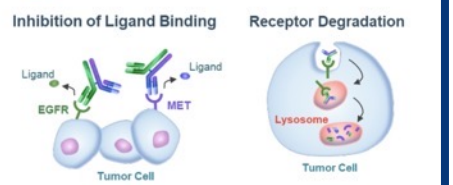
| Drug | Target | Payload | Main Target Population |
|---|---|---|---|
| Trastuzumab-DXd (DS-8201) | HER2 | Deruxtecan | HER2+ NSCLC |
| Patritumab-DXd (U3-1402) | HER3 | | EGFR mt NSCLC |
| Dapototamab-DXd (DS-1062) | Trop2 | | Wt NSCLC<br>Any oncogenic driver mt |
| CEACAM5-DM4 (SAR408701) | CACAM5 | DM4 | CECAM5+ NSCLC |
| Telisotuzumab-Vedotin (Teliso-V) | C-Met | Monomethyl Auristatin E (MMAE) | C-Met+ EGFRwt NSCLC |

Actualités

# Anticorps bispécifiques

# CHRYSALIS 01 – Design de l'étude

**Amivantamab: Fully human bispecific antibody that targets EGFR and MET**




**Lazertinib: 3rd gen EGFR TKI**

**Dose escalation cohorts**

**140-1750 mg CBNPC avancé**

**Monothérapie**
1050/1400 mg AMI

**Combinaison**
1050/1400 mg AMI
+ 240 mg LAZ ou
SOC Chimio

**Dose expansion cohorts**

- **Post EGFR TKI** (T790M+, C797S+)
- **Post EGFR TKI** (T790M-, C797S-)
- **Post osimertinib** (C797S+)
- **Post EGFR TKI** (MET amplified)
- **MET Exon14 skipping**
- **EGFR Exon20ins**
- **AMI + LAZ: EGFRm CBNPC,** Post-osimertinib
- **AMI + Chimio; CBNPC**

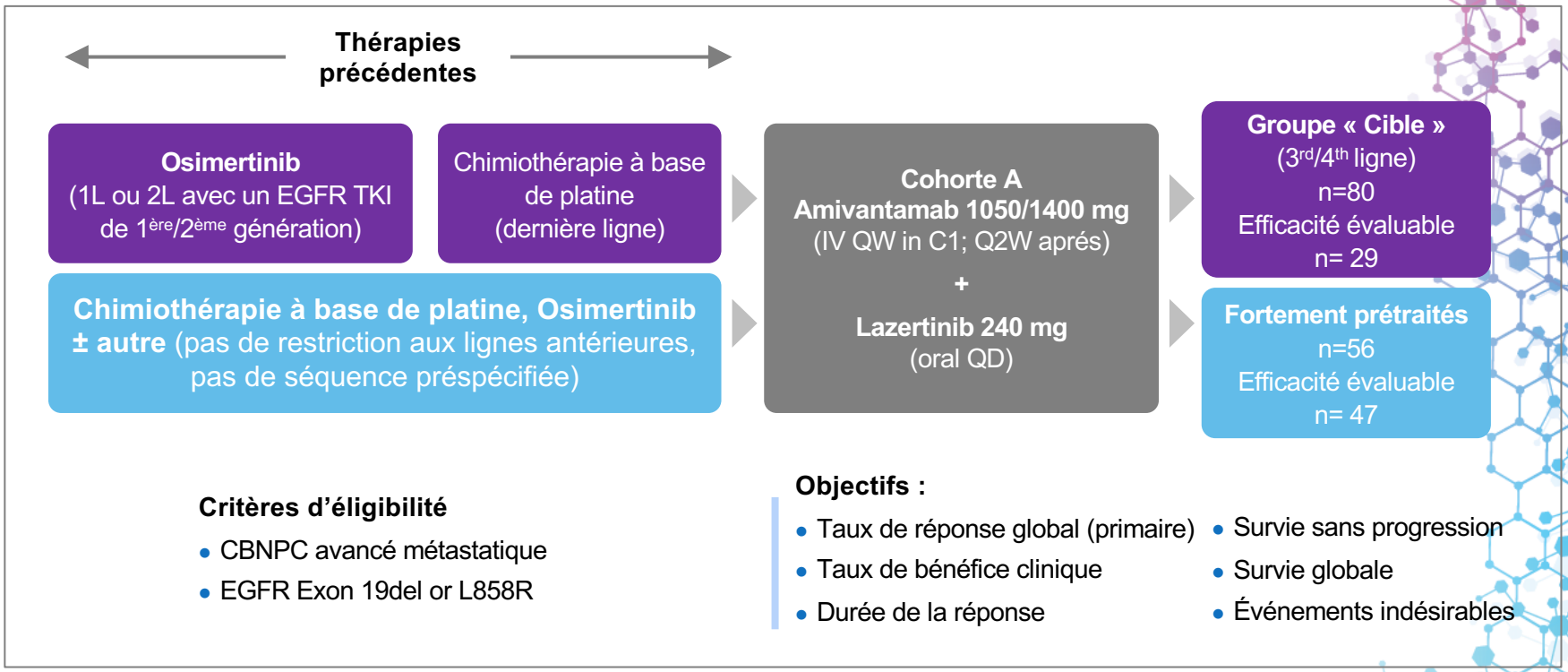
Toutes les cohortes fermées sauf MET Exon14 Skipping

**Post-osimertinib Cohorte AMI**
n=121
(Présélection de la majorité des biomarqueurs)

**Post-osimertinib Cohorte AMI + LAZ**
n=45
(Biomarqueurs non sélectionnés)

Leighl N.B., et al., ESMO® 2021, Abs #1192MO

# CHRYSALIS-2 : Design de l'étude




**Critères d'éligibilité**

- CBNPC avancé métastatique
- EGFR Exon 19del or L858R

**Objectifs :**

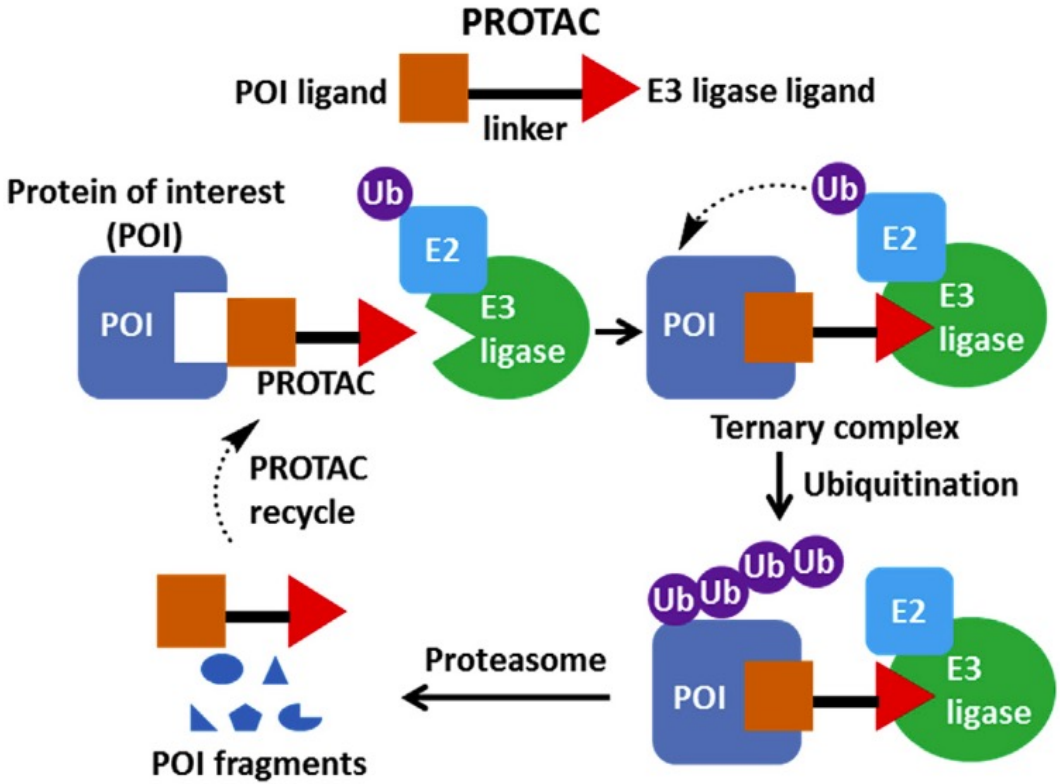
- Taux de réponse global (primaire)
- Taux de bénéfice clinique
- Durée de la réponse
- Survie sans progression
- Survie globale
- Événements indésirables

Shu C.A., et al., ESMO® 2021, Abs #1193MO

Perspectives

# PROTACs

# Proteolysis targeting chimera (PROTAC)



# Proteolysis targeting chimera (PROTAC)

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

## Discovery of potent epidermal growth factor receptor (EGFR) degraders by proteolysis targeting chimera (PROTAC)

Hao Zhang [a], Hong-Yi Zhao [a], Xiao-Xiao Xi [a], Yan-Jie Liu [a], Minhang Xin [a], Shuai Mao [a], Jun-Jie Zhang [b], A-Xin Lu [c], San-Qi Zhang [a, *]

[a] Department of Medicinal Chemistry, School of Pharmacy, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, PR China
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# Proteolysis Targeting Chimeras (PROTACs)

- Large molecular weight, orally bioavailable compounds
- Challenge: development of pharmacokinetic and pharmacodynamic assays due to catalytic function
- Potential in coupling E3 ligase protein (Von Hippel Lindau) to EGFR inhibitor
- Trials underway targeting androgen and estrogen receptors

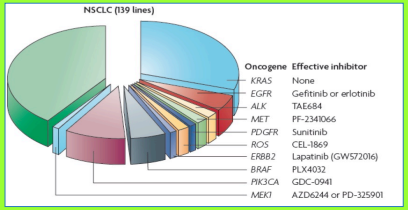
Burslem GM, et al. Cell Chem Biol 2018;25:67-77

# Quelle stratégie Poumon 1ière ligne ?

**CBNPC IIIB IV**

- **Non épidermoïde** → **Platine pemetrexed Pembro**
- **Epidermoïde** → **Platine Paclitaxel Pembrolizumab**
- **Addiction oncogénique**




  - **EGFR ALK ROS Braf NTRK**
  - **MET exon 14 RET NRG1…**
- **PD-L1 >50%** → **Pembro Ou Chimio Pembro**

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# MERCI DE VOTRE ATTENTION