GFPC
Groupe Français de Pneumo-Cancérologie
French Lung Cancer Group

GROUPE FRANÇAIS DE PNEUMO-CANCÉROLOGIE

16ème réunion Clinico-Pathologique en Oncologie Thoracique

Session 2
Anatomopathologie et biologie moléculaire

Mutation TP53, KEAP1, STK11 : *en tenir compte ou pas ?*

JOURNÉES GFPC 2022

Présenté par :

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APHP Paris & UVSQ, Université Paris-Saclay

Hôpital Ambroise-Paré AP-HP

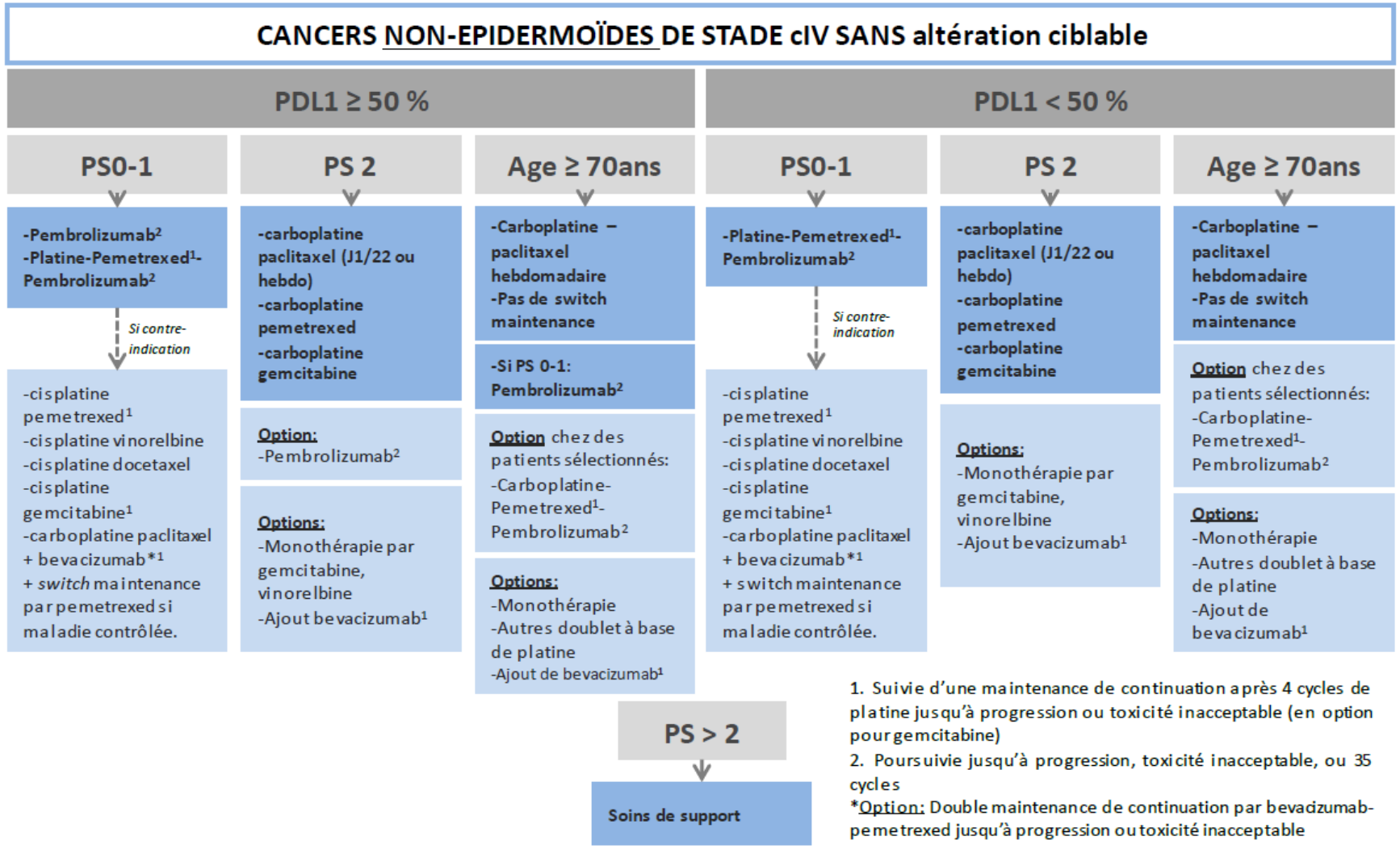
UVSQ université PARIS-SACLAY

Liens d’intérêts

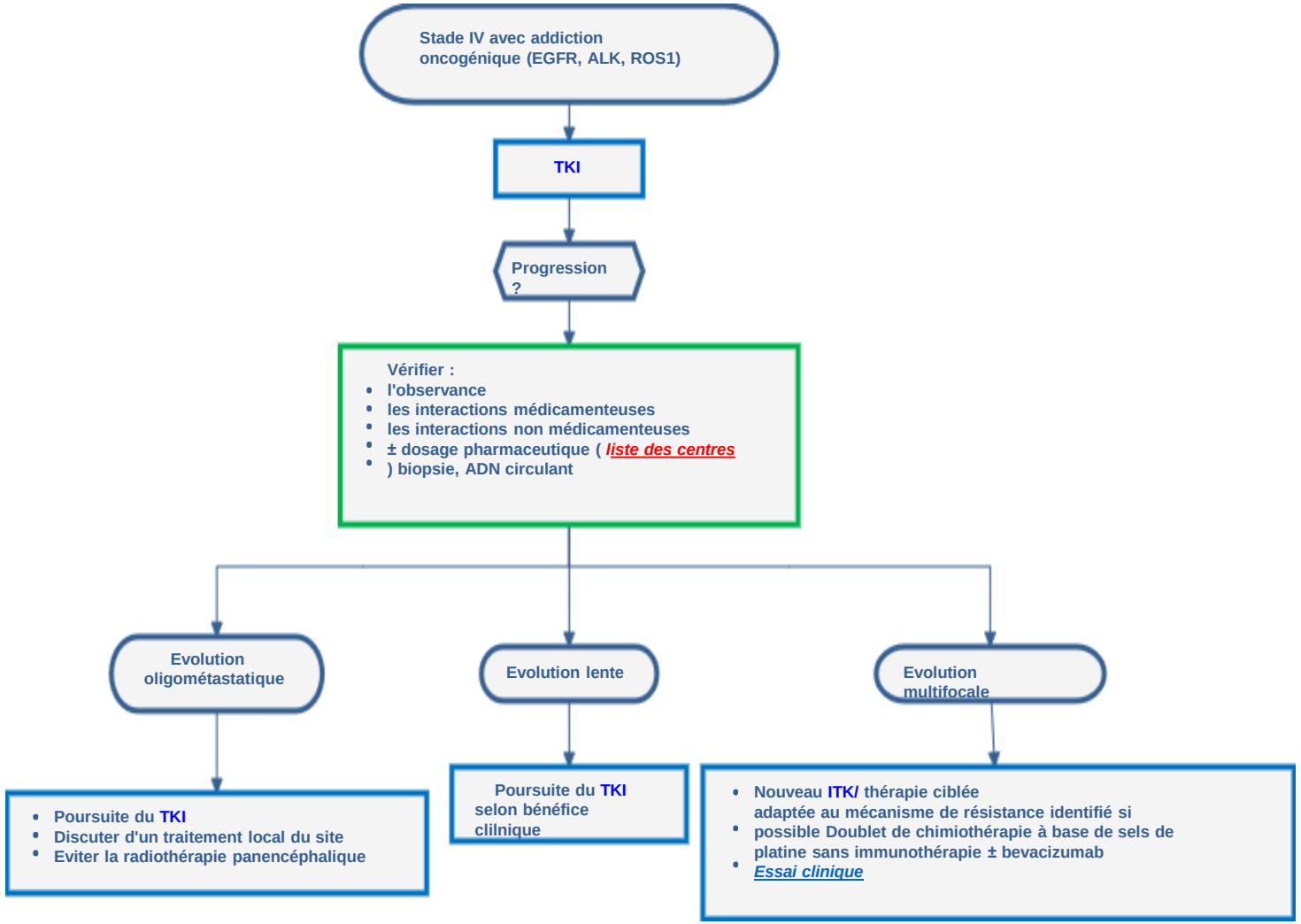
- Honoraria/advisory board : Amgen, AstraZeneca, Bristol-Myers-Squibb, Ipsen, Janssen, Lilly, MSD, Novartis, Oncodesign, Pfizer, Roche, Sanofi, Takeda

- Research grants (institution) : AstraZeneca, Bristol-Myers-Squibb, Replimune, Roche

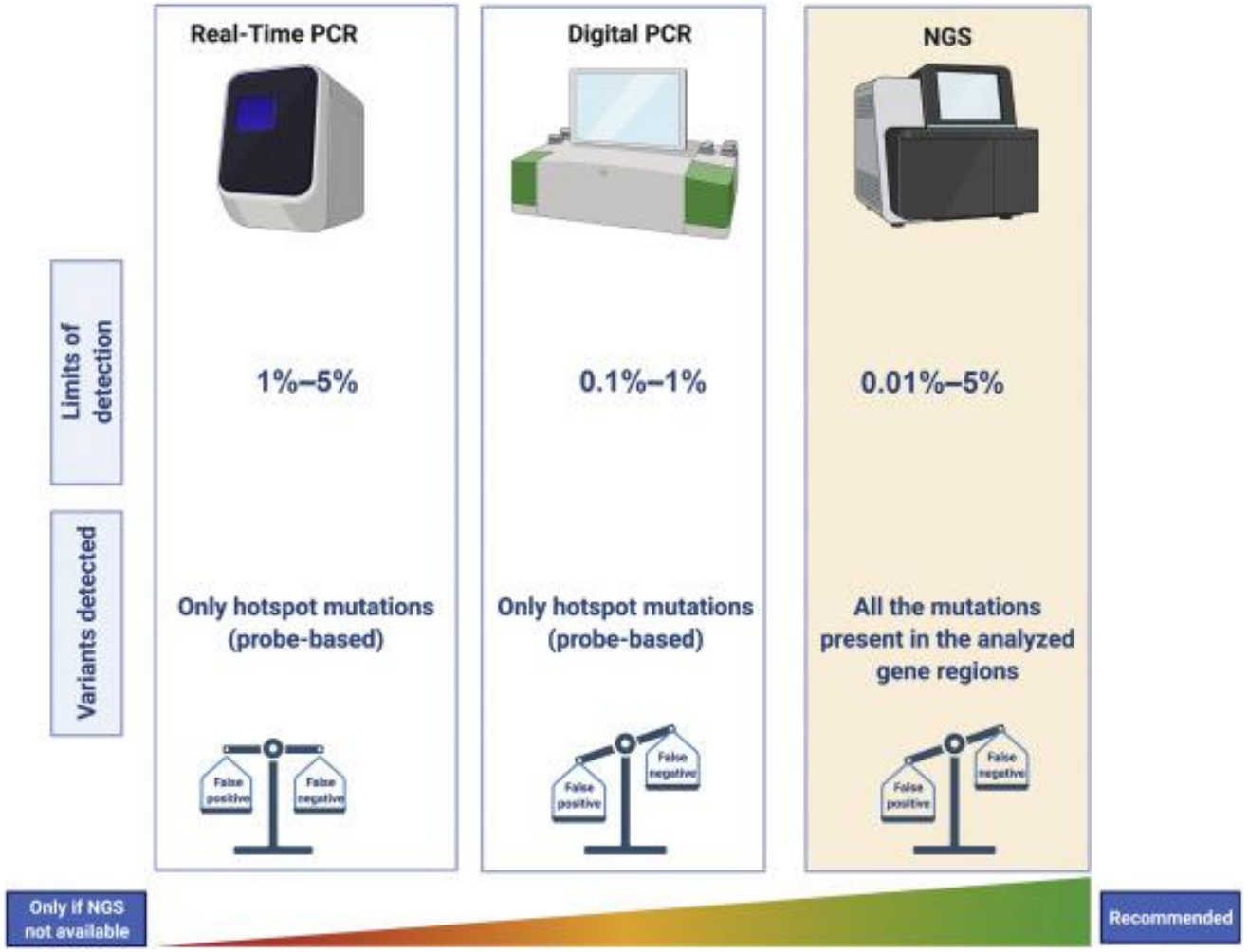
Contexte

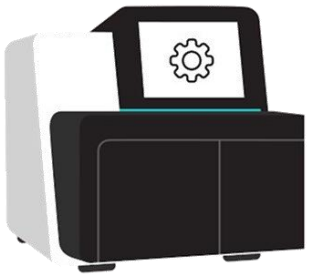

CANCERS NON-EPIDERMOÏDES DE STADE cIV SANS altération ciblable
PDL1 ≥ 50 %
PDL1 < 50 %
PS0-1
PS 2
Age ≥ 70ans
PS0-1
PS 2
Age ≥ 70ans
-Pembrolizumab2
-Platine-Pemetrexed1-Pembrolizumab2
Si contre-indication
-cisplatine pemetrexed1
-cisplatine vinorelbine
-cisplatine docetaxel
-cisplatine gemcitabine1
-carboplatine paclitaxel + bevacizumab*1
+ switch maintenance par pemetrexed si maladie contrôlée.
-carboplatine paclitaxel (J1/22 ou hebdo)
-carboplatine pemetrexed
-carboplatine gemcitabine
Option:
-Pembrolizumab2
Options:
-Monothérapie par gemcitabine, vinorelbine
-Ajout bevacizumab1
-Carboplatine – paclitaxel hebdomadaire
-Pas de switch maintenance
-Si PS 0-1: Pembrolizumab2
Option chez des patients sélectionnés:
-Carboplatine-Pemetrexed1-Pembrolizumab2
Options:
-Monothérapie
-Autres doublet à base de platine
-Ajout de bevacizumab1
-Platine-Pemetrexed1-Pembrolizumab2
Si contre-indication
-cisplatine pemetrexed1
-cisplatine vinorelbine
-cisplatine docetaxel
-cisplatine gemcitabine1
-carboplatine paclitaxel + bevacizumab*1
+ switch maintenance par pemetrexed si maladie contrôlée.
-carboplatine paclitaxel (J1/22 ou hebdo)
-carboplatine pemetrexed
-carboplatine gemcitabine
Options:
-Monothérapie par gemcitabine, vinorelbine
-Ajout bevacizumab1
-Carboplatine – paclitaxel hebdomadaire
-Pas de switch maintenance
Option chez des patients sélectionnés:
-Carboplatine-Pemetrexed1-Pembrolizumab2
Options:
-Monothérapie
-Autres doublet à base de platine
-Ajout de bevacizumab1
PS > 2
Soins de support
1. Suivie d'une maintenance de continuation après 4 cycles de platine jusqu'à progression ou toxicité inacceptable (en option pour gemcitabine)
2. Poursuivie jusqu'à progression, toxicité inacceptable, ou 35 cycles
*Option: Double maintenance de continuation par bevacizumab-pemetrexed jusqu'à progression ou toxicité inacceptable

Contexte


Stade IV avec addiction oncogénique (EGFR, ALK, ROS1)
TKI
Progression ?
Vérifier :
l'observance
les interactions médicamenteuses
les interactions non médicamenteuses
± dosage pharmaceutique (liste des centres
) biopsie, ADN circulant
Evolution oligométastatique
Evolution lente
Evolution multifocale
Poursuite du TKI
Discuter d'un traitement local du site
Eviter la radiothérapie panencéphalique
Poursuite du TKI selon bénéfice clilnique
Nouveau ITK/ thérapie ciblée adaptée au mécanisme de résistance identifié si possible Doublet de chimiothérapie à base de sels de platine sans immunothérapie ± bevacizumab
Essai clinique

Contexte

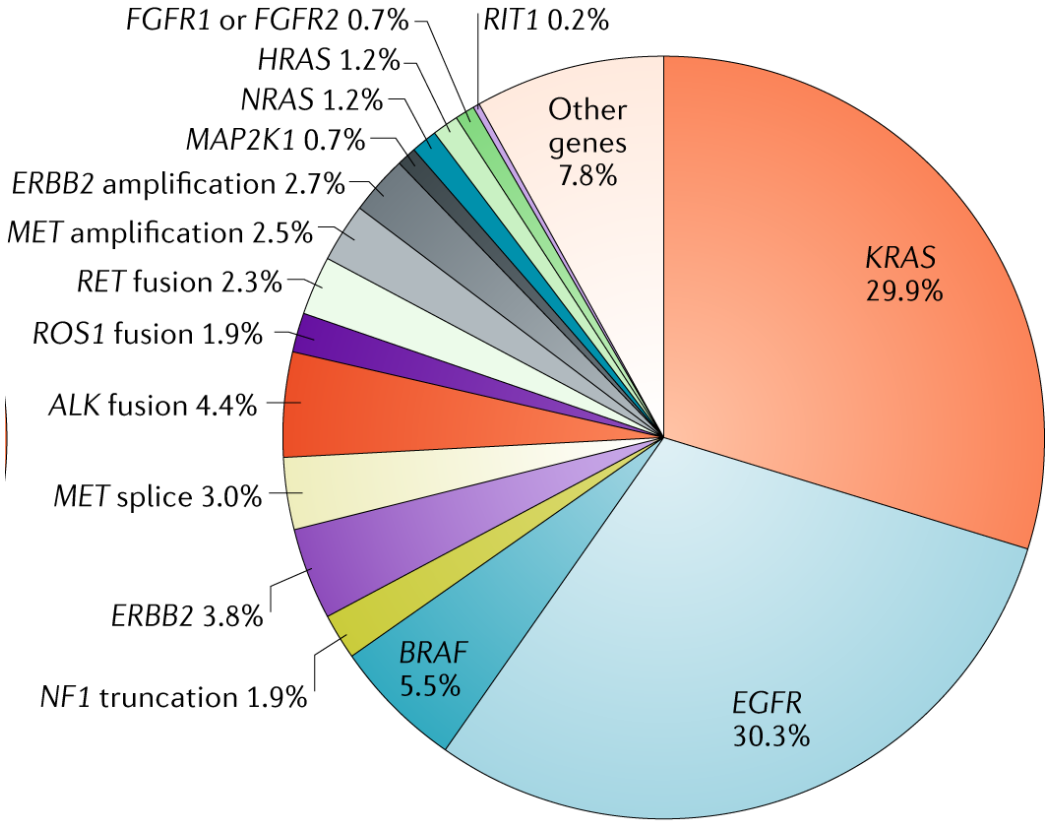




NGS DATA ANALYSIS

Rolfo et al. JTO 2021

Contexte



Skoulidis et al. Nat Rev Cancer 2019

Hôpitaux universitaires Paris-Sud

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: Dr MARTIN SEROR

Analyse génétique des tumeurs

Nom de Nais
Nom Usuel :
Prénom :
Né(e) le :

Indication : Biopsies pulmonaires : localisation d'un adénocarcinome mucosécrétant TTF1+
Cellules tumorales % : 40 %

Méthode d'analyse :

- Analyse réalisée à partir d'un prélèvement de copeaux de paraffine fixé au formol (10%) après macrodissection de la zone d'intérêt.
- Méthode d'extraction de l'ADN génomique tumoral: QIASymphony QIAGEN
- Préparation de librairies par la technologie « QIASeq Targeted DNA Custom Panel » adaptée au séquençage sur MiSeq (Illumina)
- Analyse des données par le logiciel d'analyse bioinformatique de la plateforme MOABI AP-HP G-route et Leaves
- Le seuil de détection des variants est fixé à 5%. Des résultats positifs et négatifs sont rendus pour des profondeurs de séquençage minimum de 500X
- Les gènes pour lesquels les CNV sont évaluées sont mentionnés dans la liste des cibles en annexe : **+ CNV**

Résultat :

Résultat de l'analyse par séquençage haut débit (NGS):

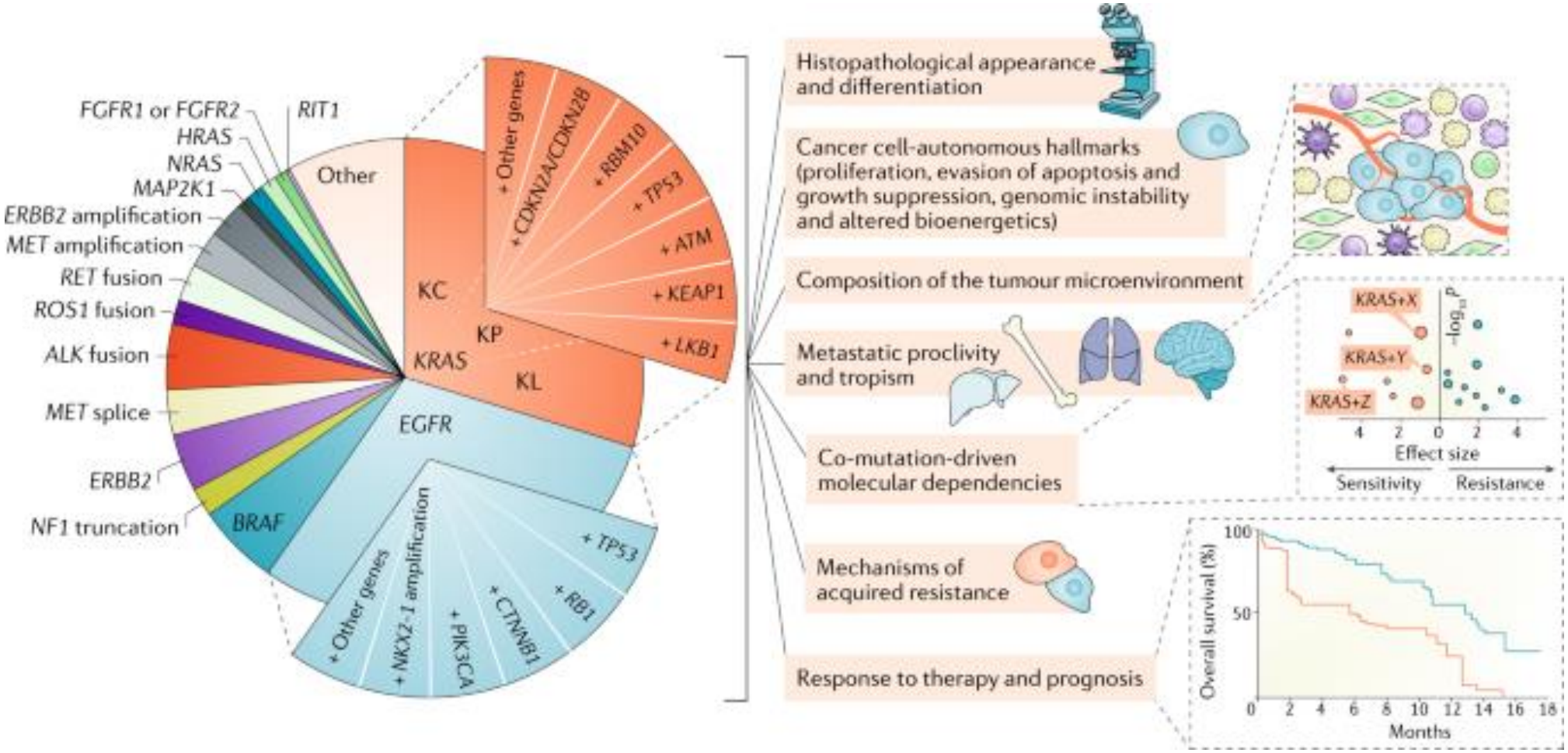
Gène	Région de gène	Anomalie
KRAS (NM_033360)	Exon 02	c.34G>T ; p.(Gly12Cys)
STK11 (NM_000455)	Exon 06	c.738_742del ; p.(Asn247fs)

Commentaires et conclusion :

Anomalies potentiellement délétères identifiées :

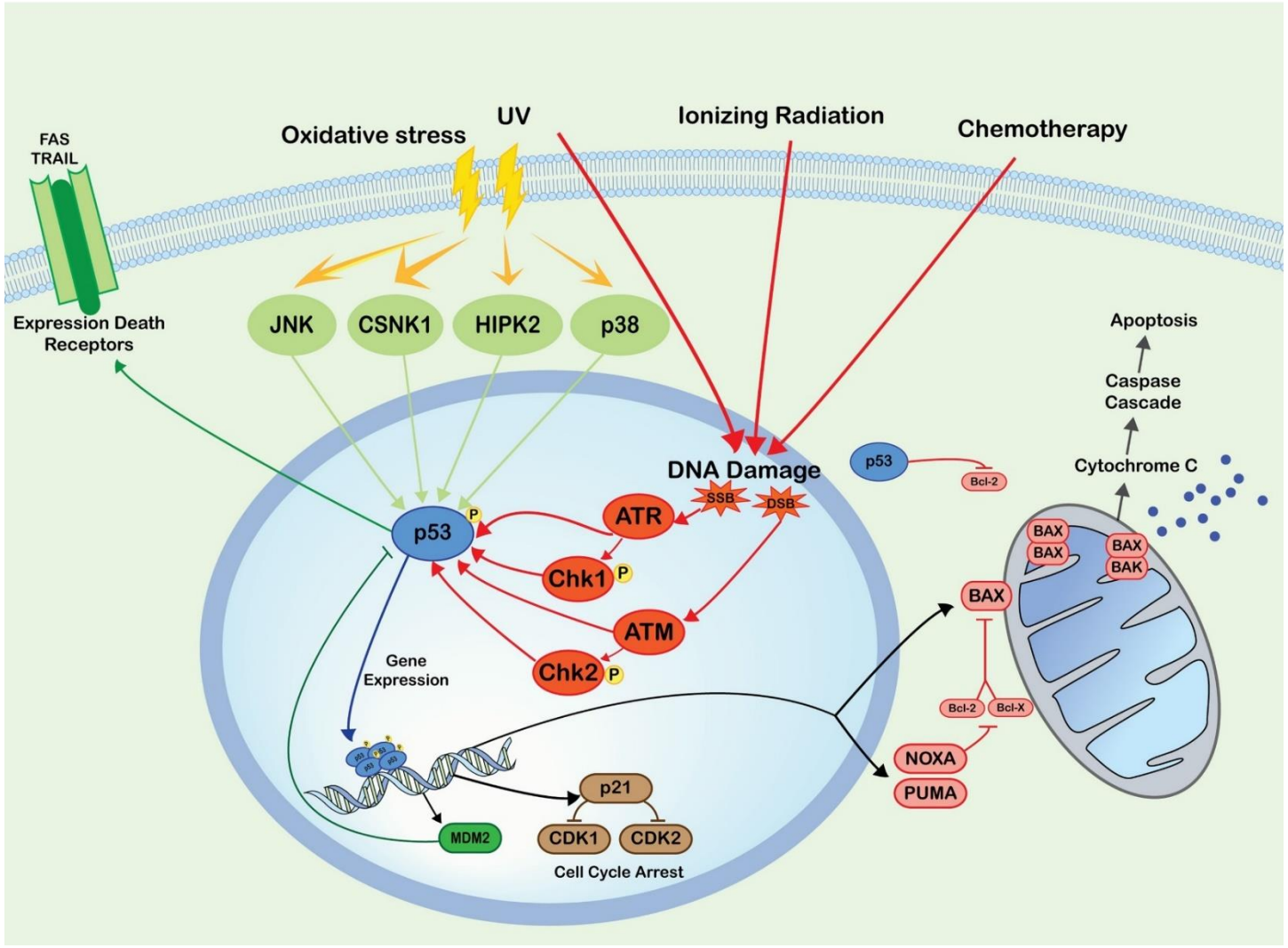
- KRAS p.(Gly12Cys)
- STK11 p.(Asn247fs)

Importance des co-mutations dans le CBNPC



Skoulidis et al. Nat Rev Cancer 2019

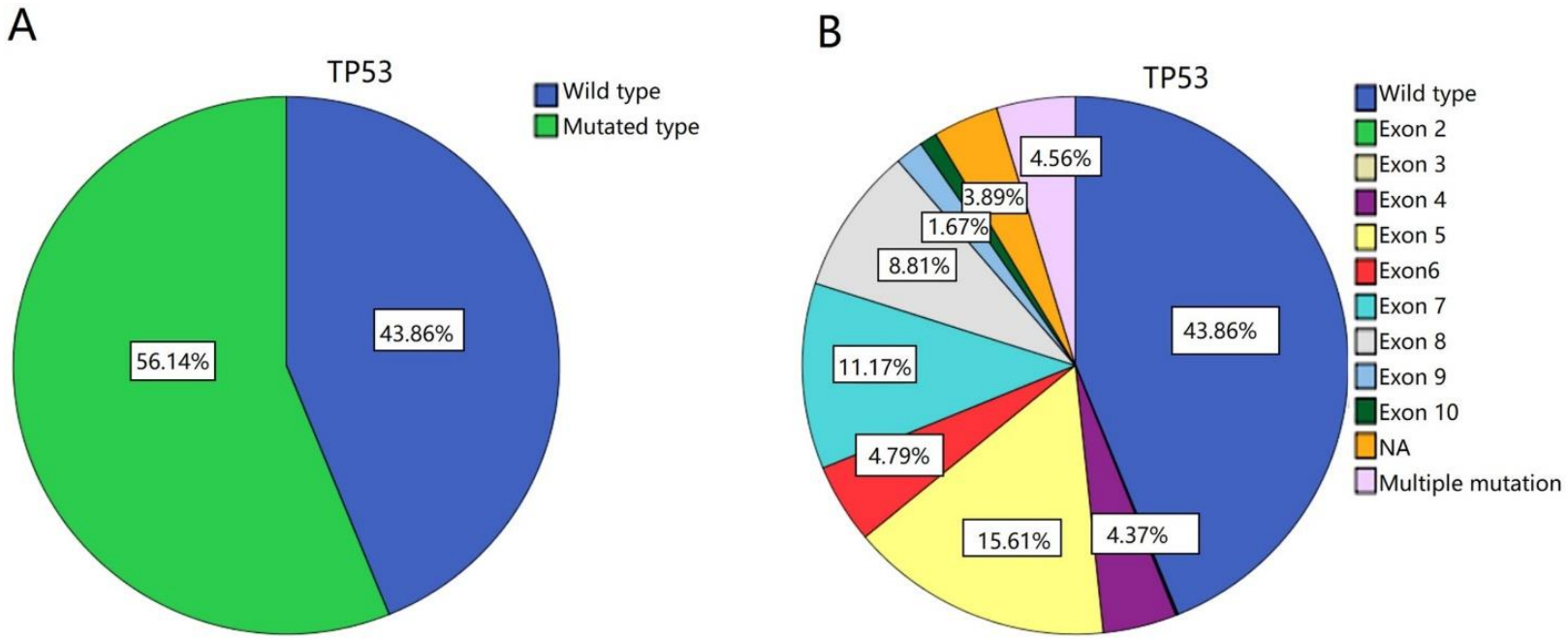
Mutations TP53



Deben et al. Crit Rev Oncol Hematol 2016

Mutations TP53 et CBNPC

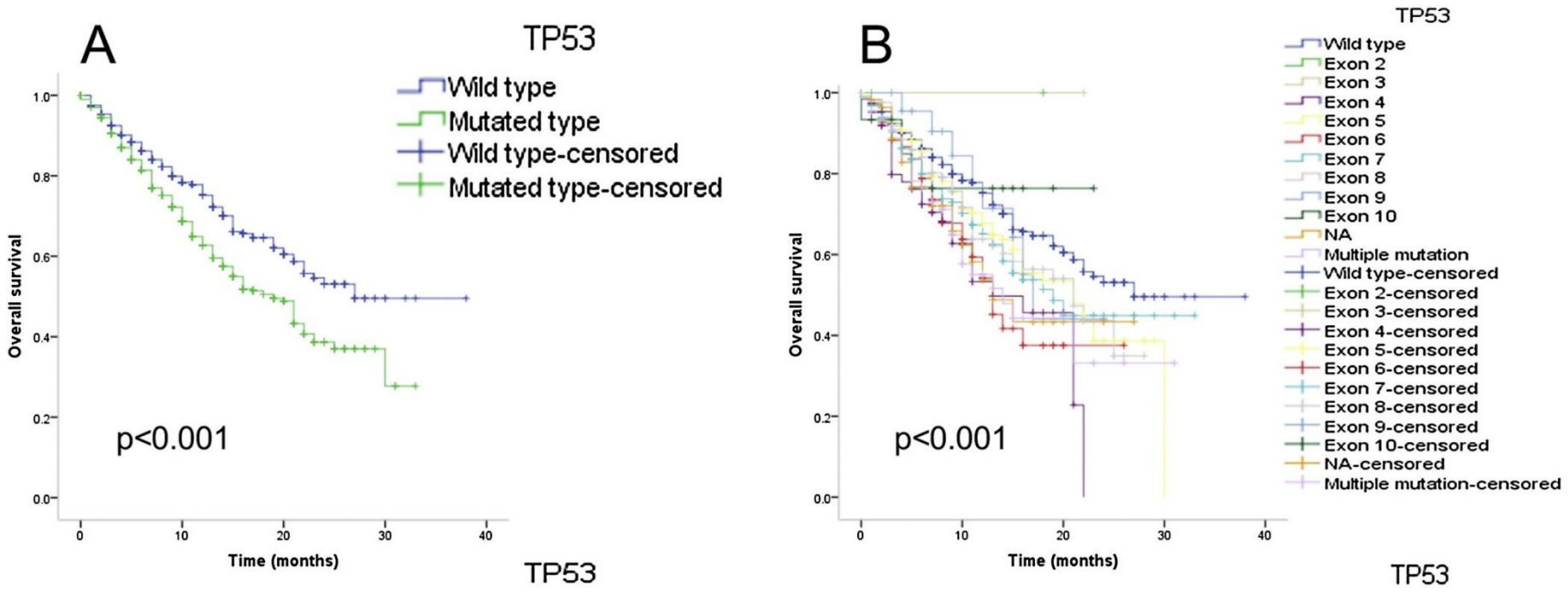
Cancer Genome Atlas Database (n=1441, NSCLC stade 4)



Jiao et al. Lung Cancer 2018

Mutations TP53

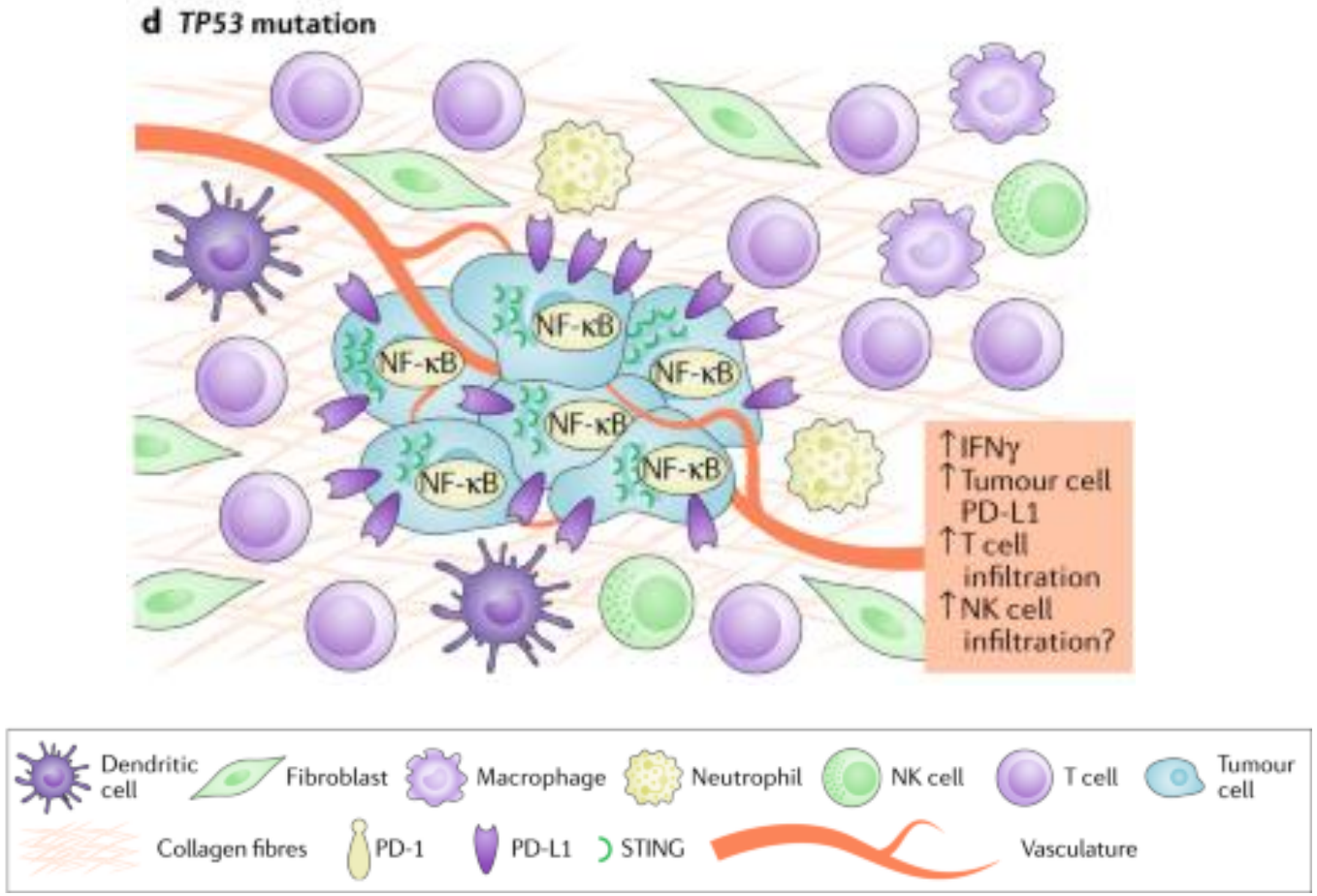
Cancer Genome Atlas Database (n=1441, NSCLC stade 4)

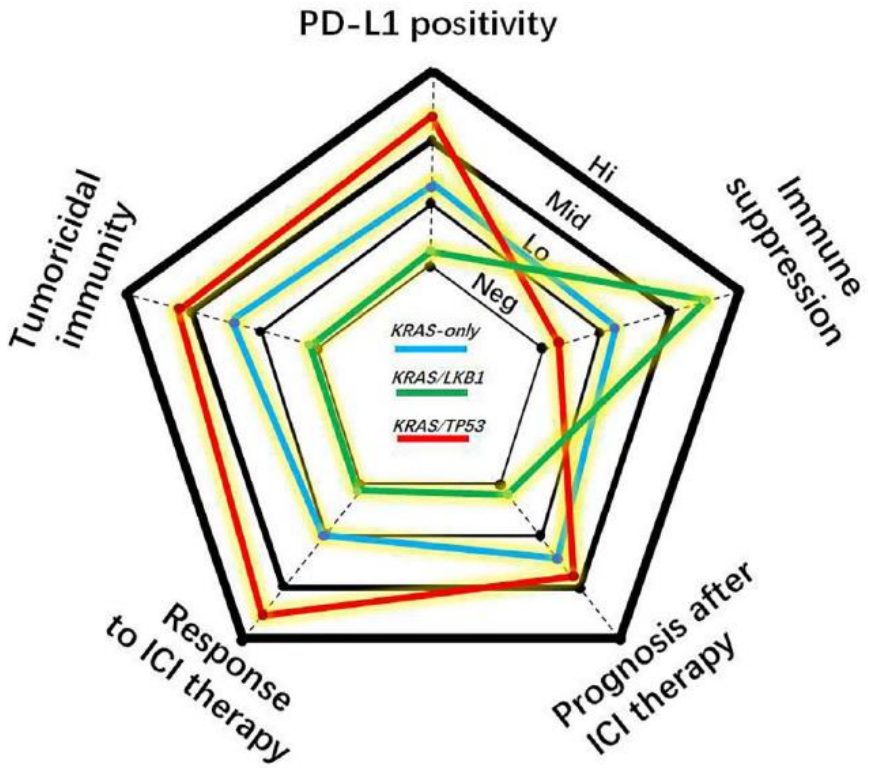


Les mutations de TP53 sont très majoritairement inactivatrices et sont associés globalement à un mauvais pronostic

Jiao et al. Lung Cancer 2018

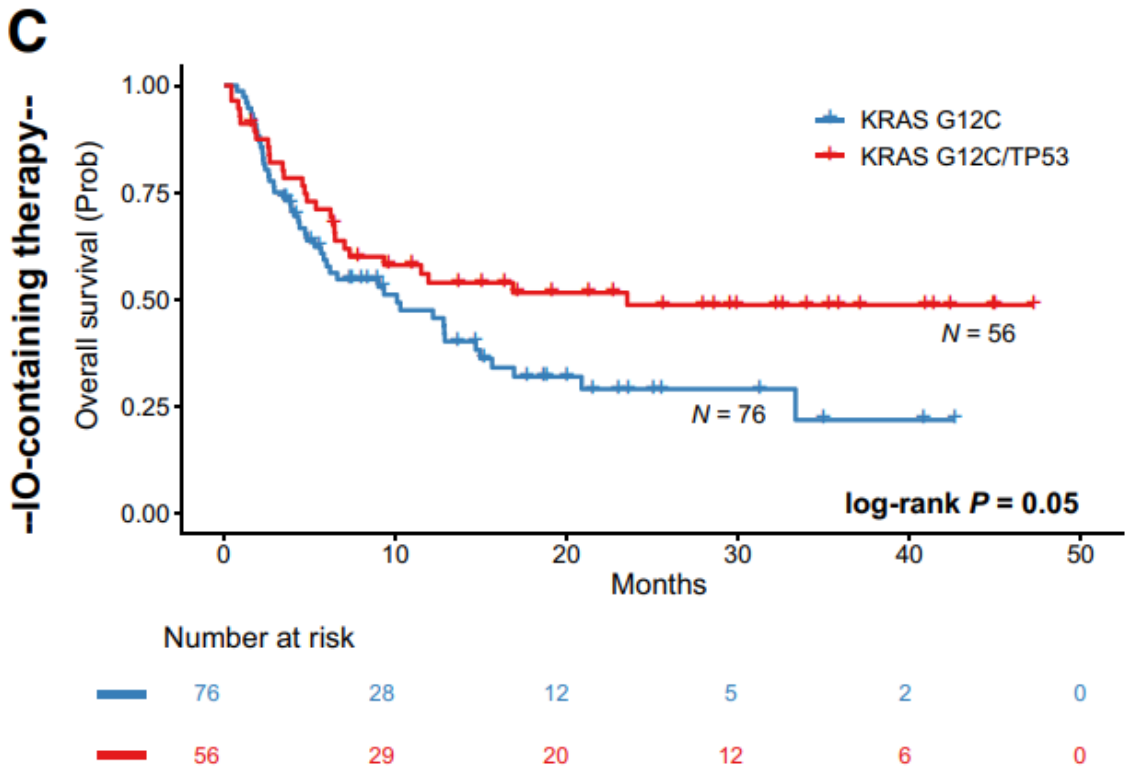
Mutations TP53 et contexte inflammatoire





Skoulidis et al. Nat Rev Cancer 2019; Gu et al. Ther Adv Med Oncol 2021

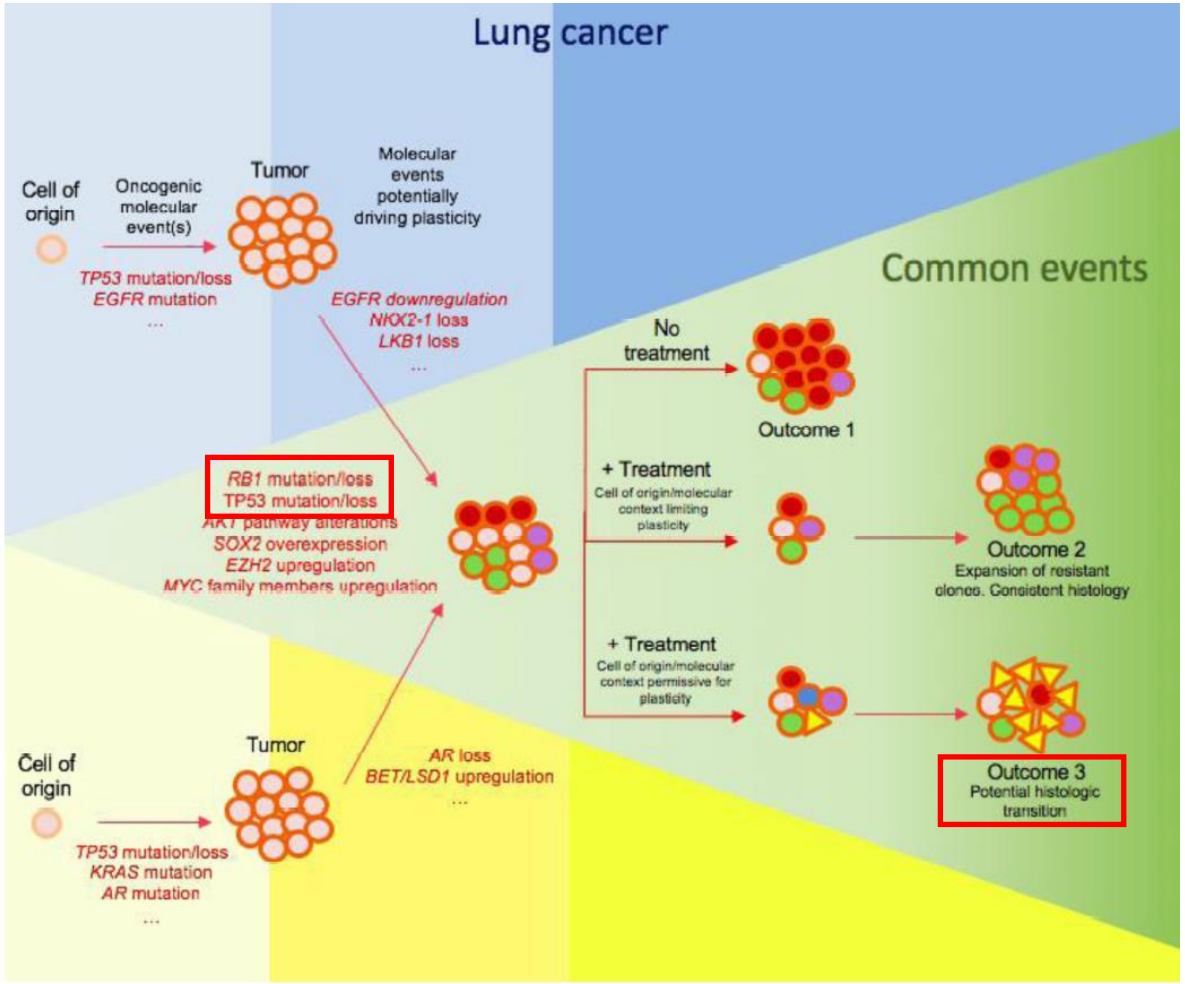
Co-mutation KRAS –TP53 et IO

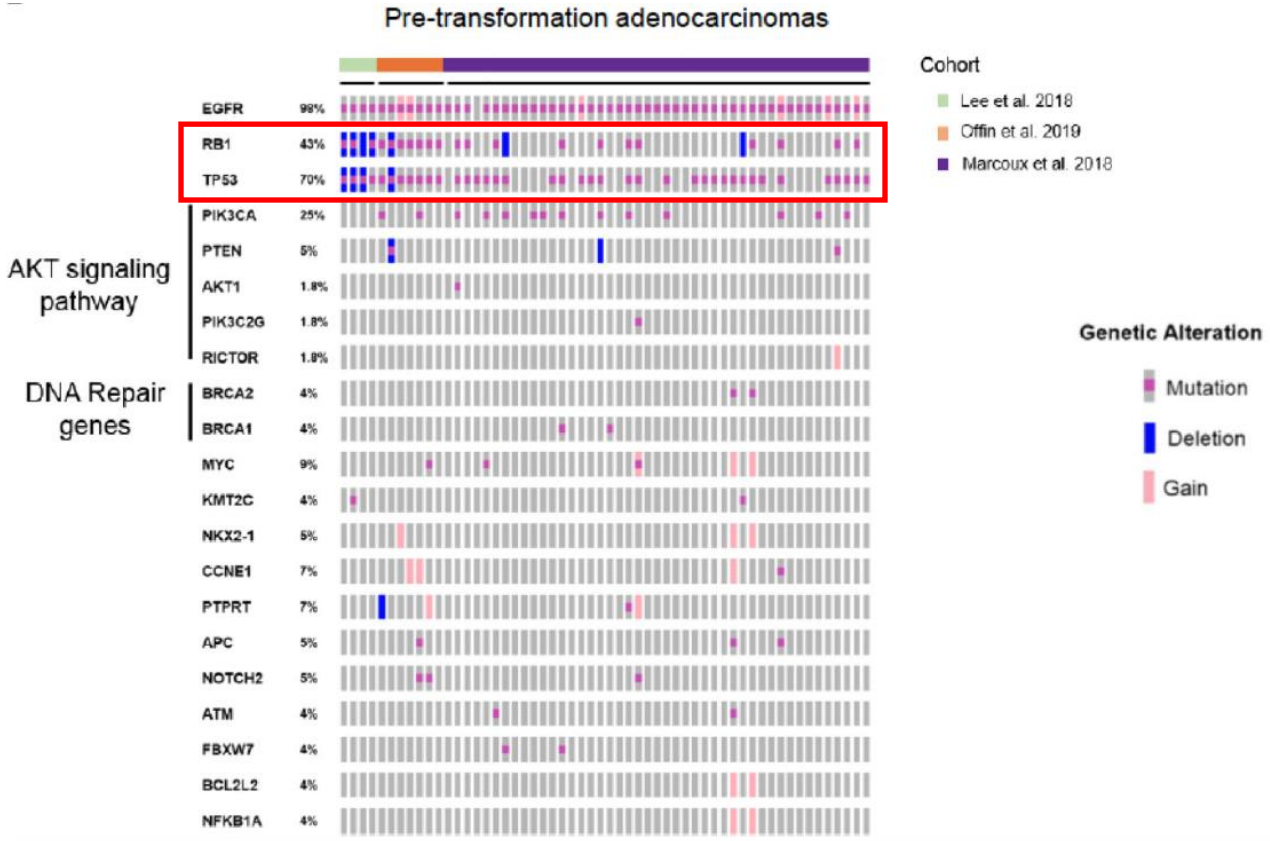


La présence d'une co-mutation KRAS-TP53 est associée à une meilleure efficacité des IO

Scharpf et al. Cancer Res 2022

Mutations TP53 et mutations EGFR

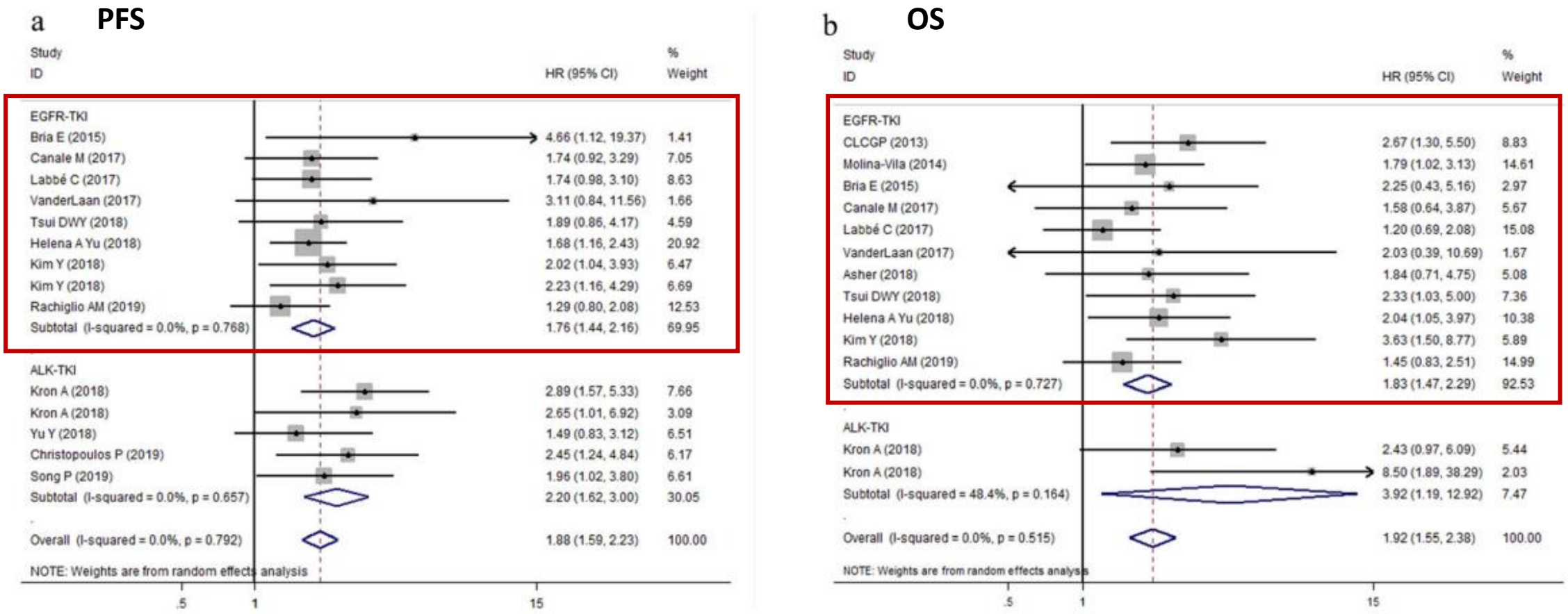




La présence d'une co-mutation TP53 – RB1 est associée à un risque accru de transformation histologique en CBPC dans les adénocarcinomes EGFRm

Quintanal-Villalonga et al. Nat Rev Clin Oncol 2021

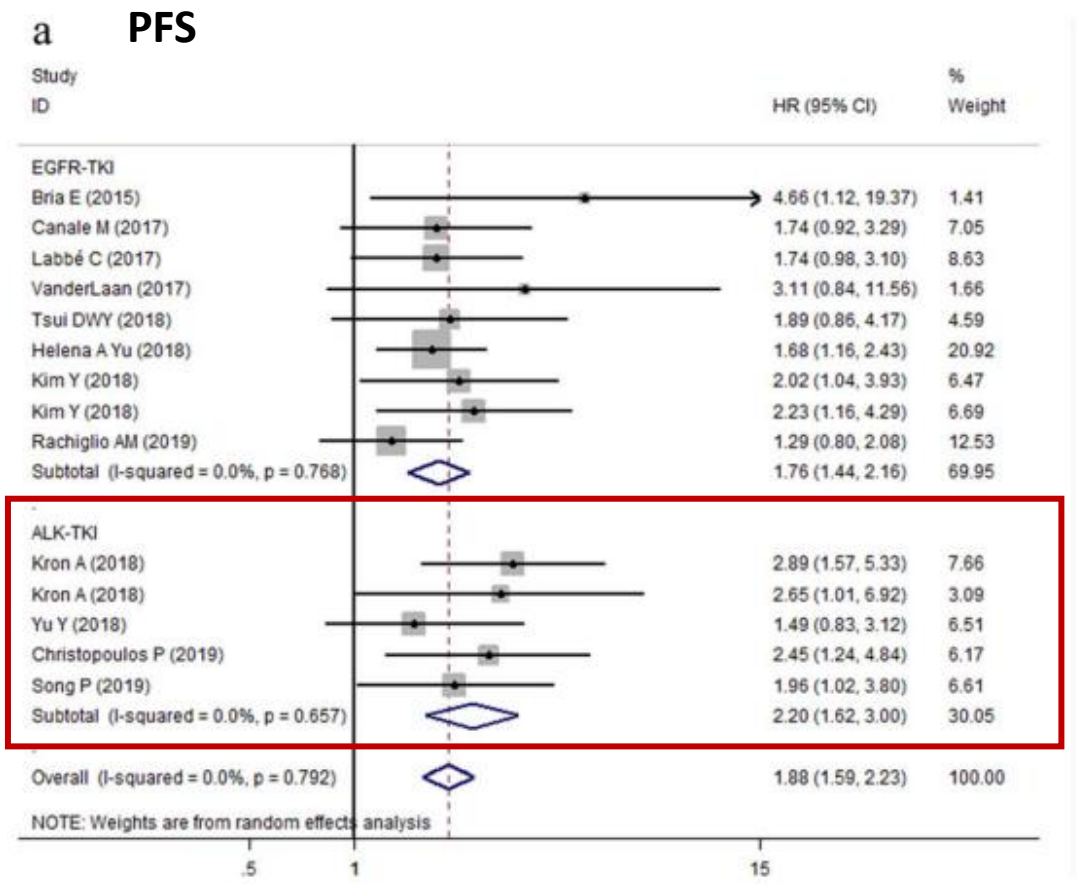
Mutations TP53 et efficacité des TKI EGFR

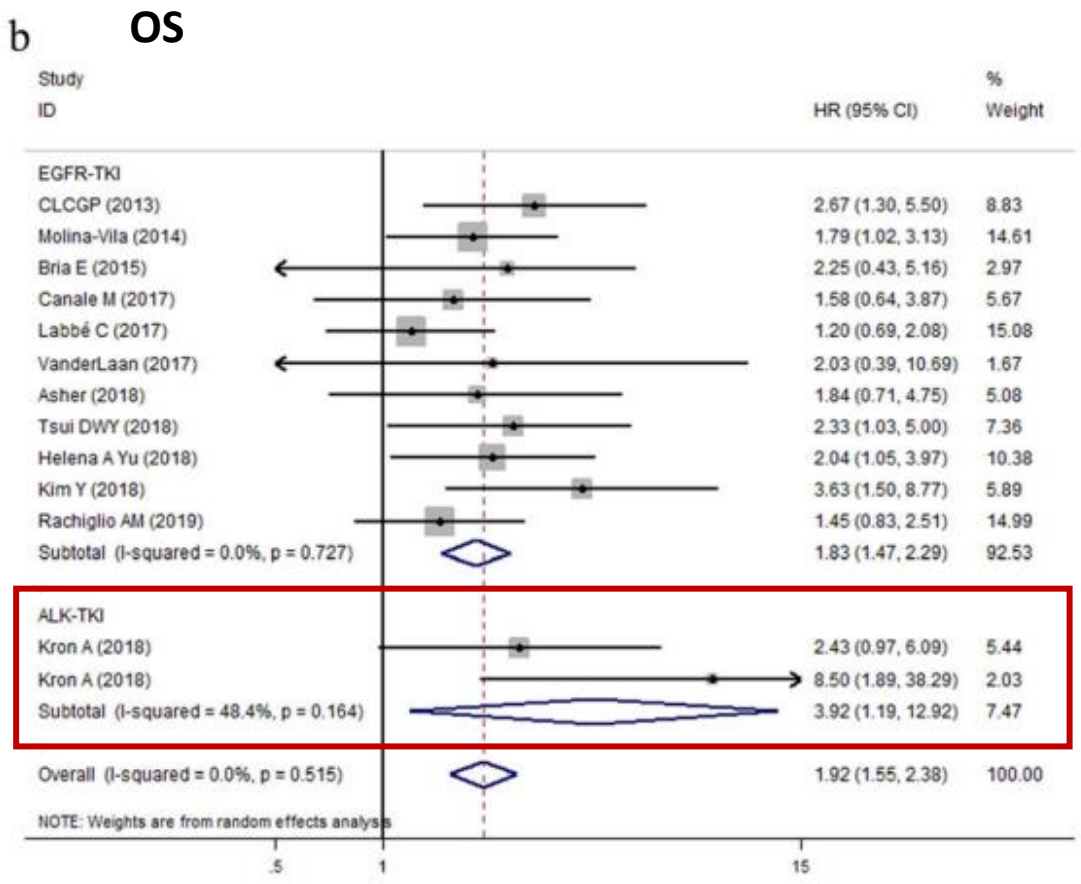


La présence d'une mutation TP53 est associée à un mauvais pronostic dans les adénocarcinomes EGFRm

Qin et al. BMC Cancer 2020

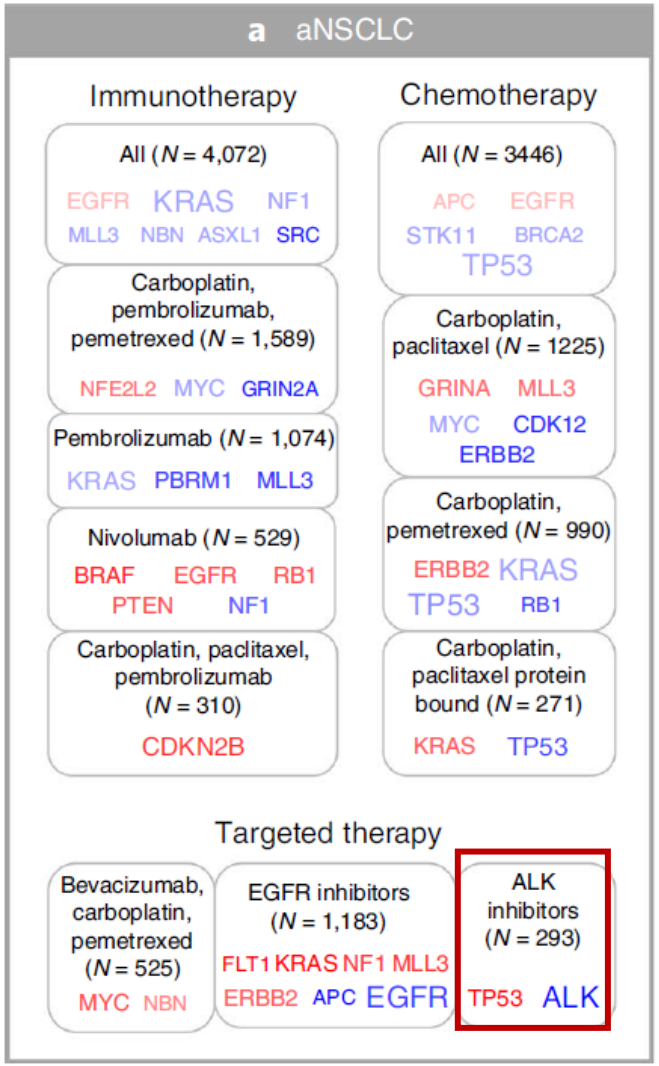
Mutations TP53 et fusions ALK

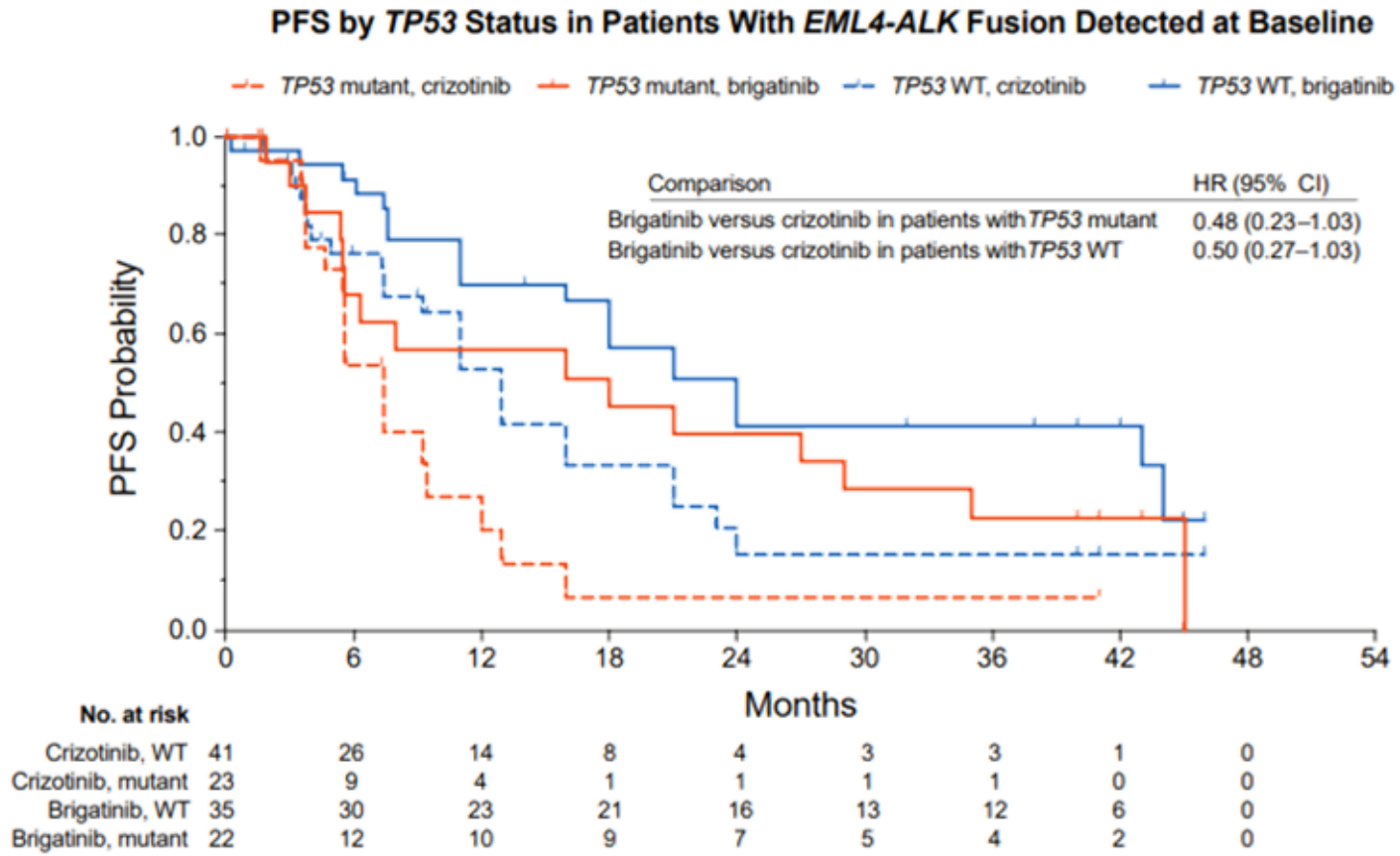




Qin et al. BMC Cancer 2020

Mutations TP53 et fusions ALK

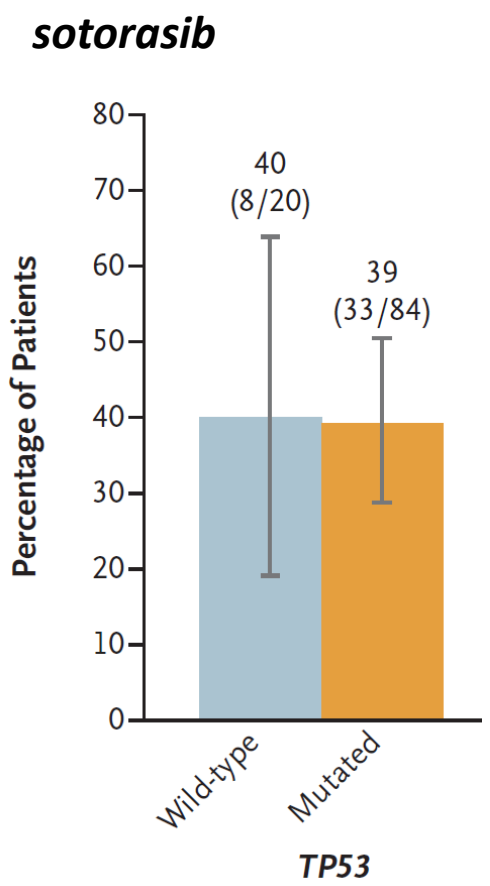


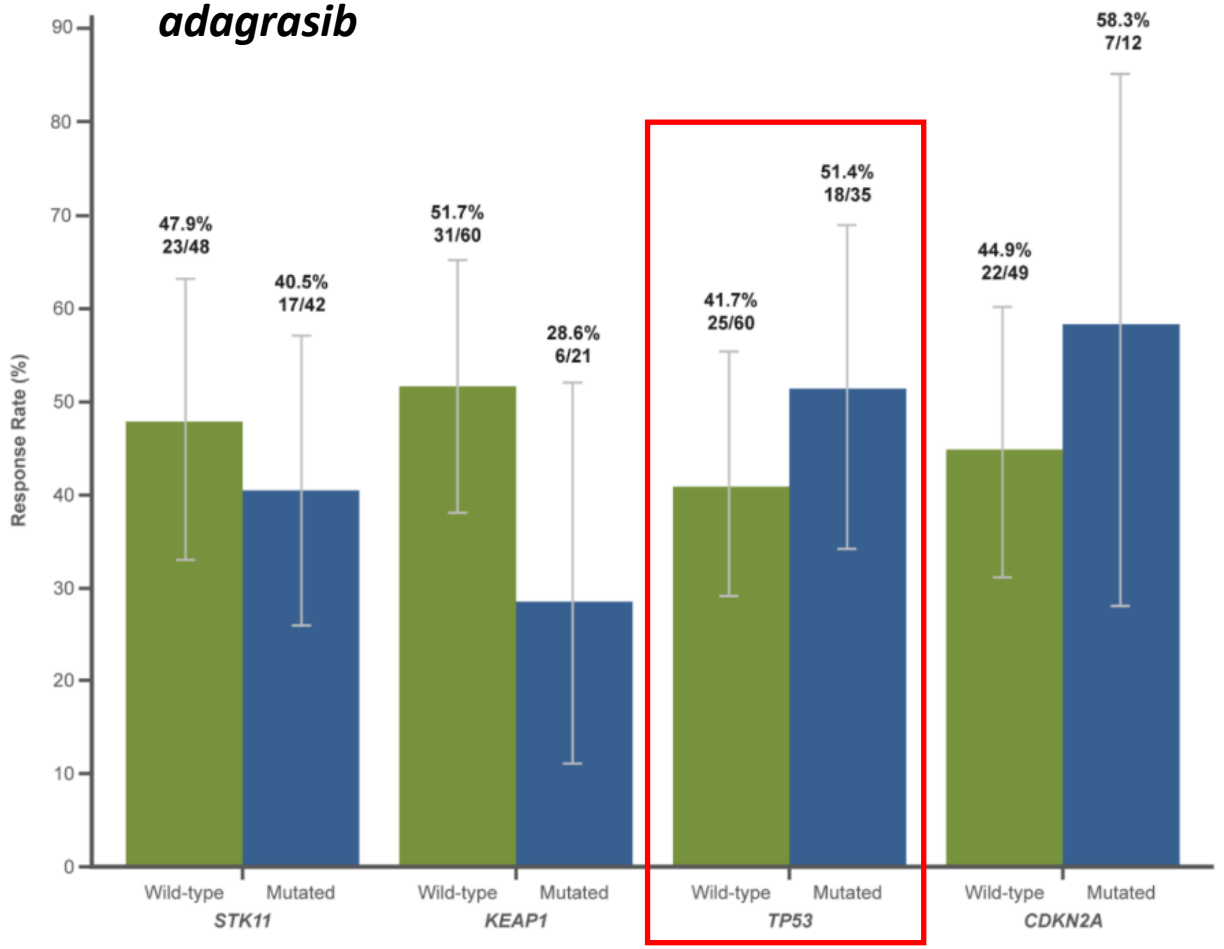


La présence d'une mutation TP53 est associée à un mauvais pronostic dans les CBNPC ALK+

Liu et al. Nat Med 2022; Camidge et al. J Thorac Oncol 2021

Co-mutations KRAS G12C –TP53 et inhibiteurs de KRAS





Skoulidis et al. NEJM 2021

Jänne et al. NEJM 2022

Mutations TP53 et CBNPC

Marqueur de mauvais pronostic global

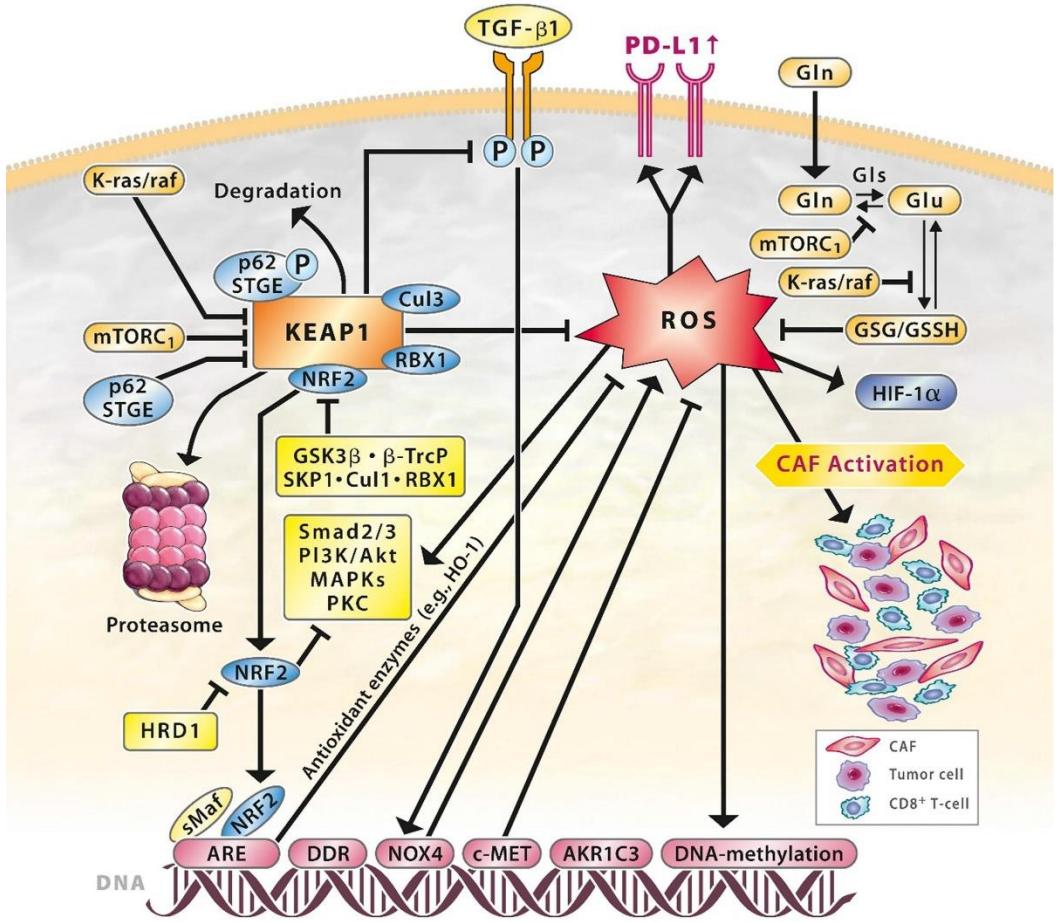
Co-mutation Kras-TP53: meilleure efficacité de l'IO

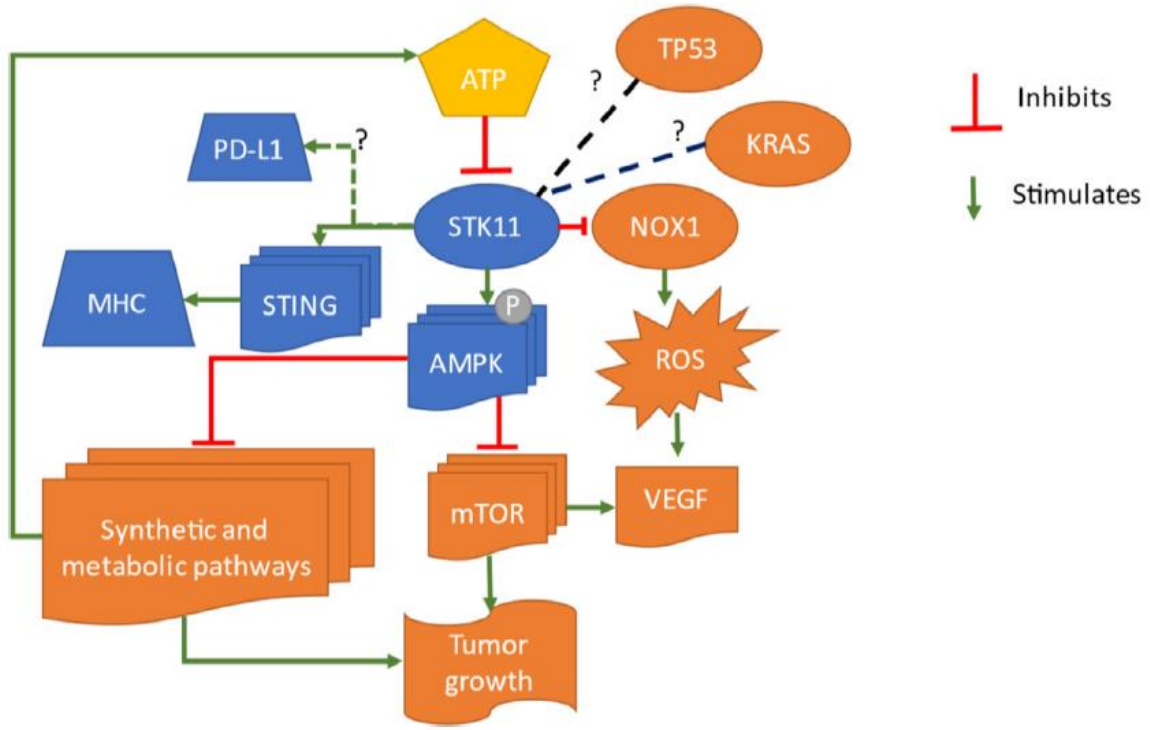
TP53 et addictions oncogéniques : moindre efficacité des TKI, survies plus courtes

Co-mutation TP53 et RB1 dans les CBNPC EGFRm: FDR de transformation en CBPC

Co-mutation Kras G12C -TP53: pas d'impact sur l'efficacité des KRASi

KEAP1 / STK11





KEAP1 : kelch- like ECH-associated protein 1
NRF2 : Nuclear Factor Erythroid 2-related factor 2
ROS : reactive oxygen species

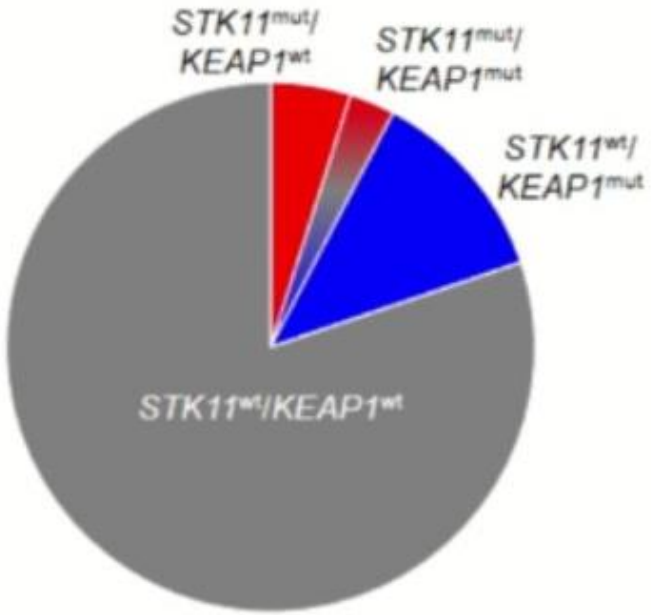
STK11 : serine/threonine kinase 11
AMPK : AMP-activated protein kinase

Dempke et al. Lung Cancer 2021; Hellyer et al. J Thorac Oncol 2020 ; Farooq et al. Semin Oncol 2022

STK11 and *KEAP1* Mutation Prevalence

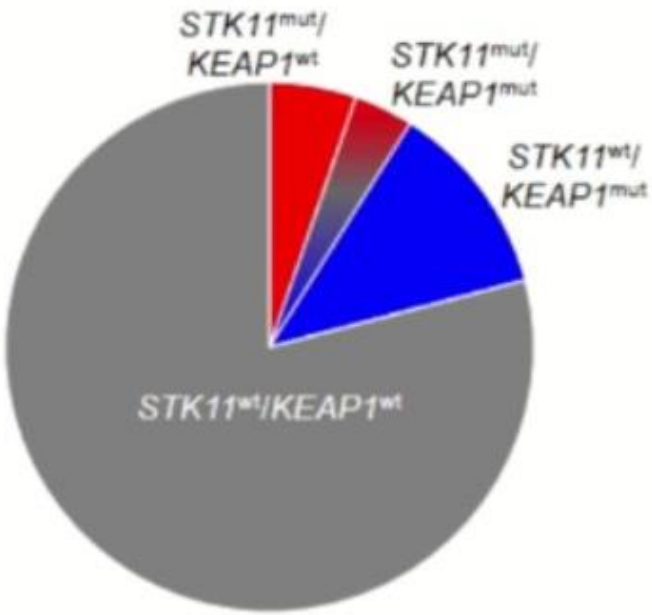
Keynote -042

Any Histology (N = 429)



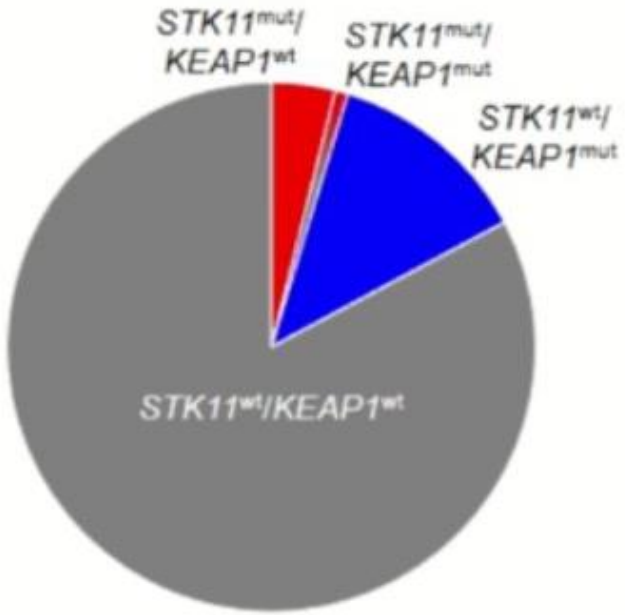
- Any *STK11* mutant: 7.7%
- Any *KEAP1* mutant: 14.9%
- *STK11* and *KEAP1* mutant: 2.8%

Nonsquamous (n = 301)



- Any *STK11* mutant: 9.0%
- Any *KEAP1* mutant: 15.6%
- *STK11* and *KEAP1* mutant: 3.7%

Squamous (n = 128)



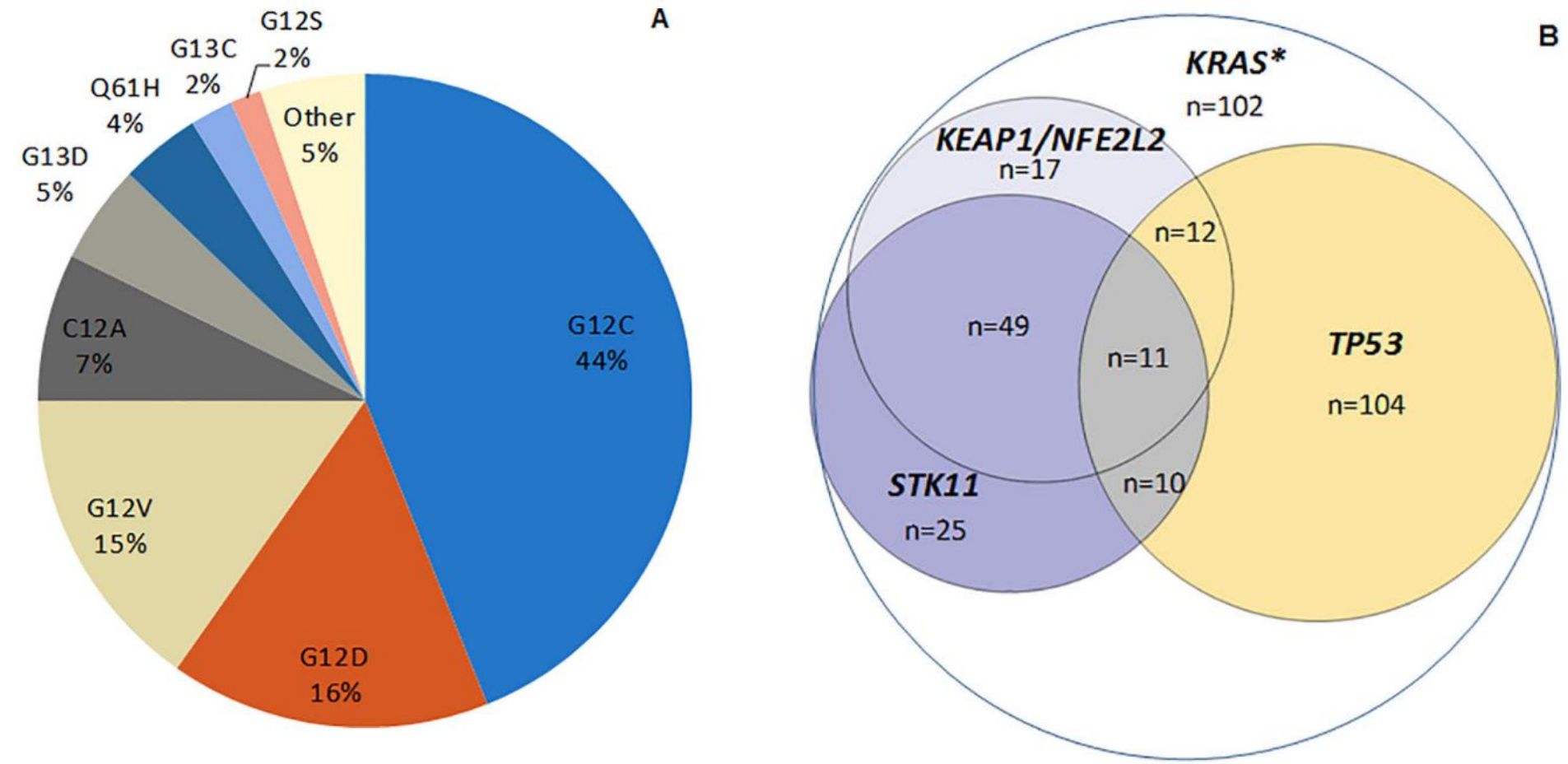
- Any *STK11* mutant: 4.7%
- Any *KEAP1* mutant: 13.3%
- *STK11* and *KEAP1* mutant: 0.8%

All participants had PD-L1-positive tumors (TPS ≥1%).
Data cutoff date: Sep 4, 2018.

Cho et al. AACR 2020

Fréquence des co-mutations KRAS-KEAP1-STK11

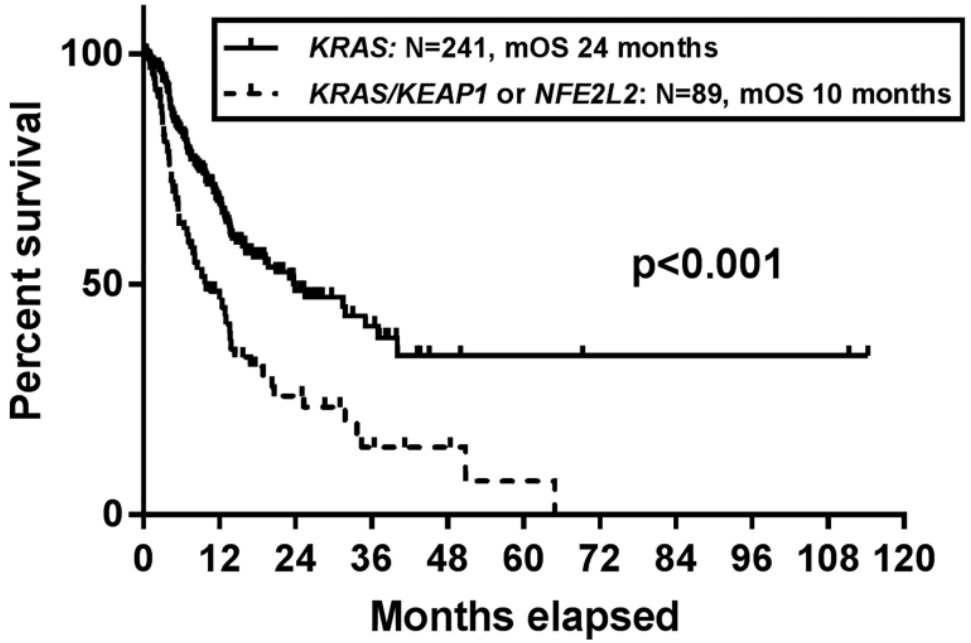
Cohorte de 330 CBNPC mutés KRAS (MSKCC)

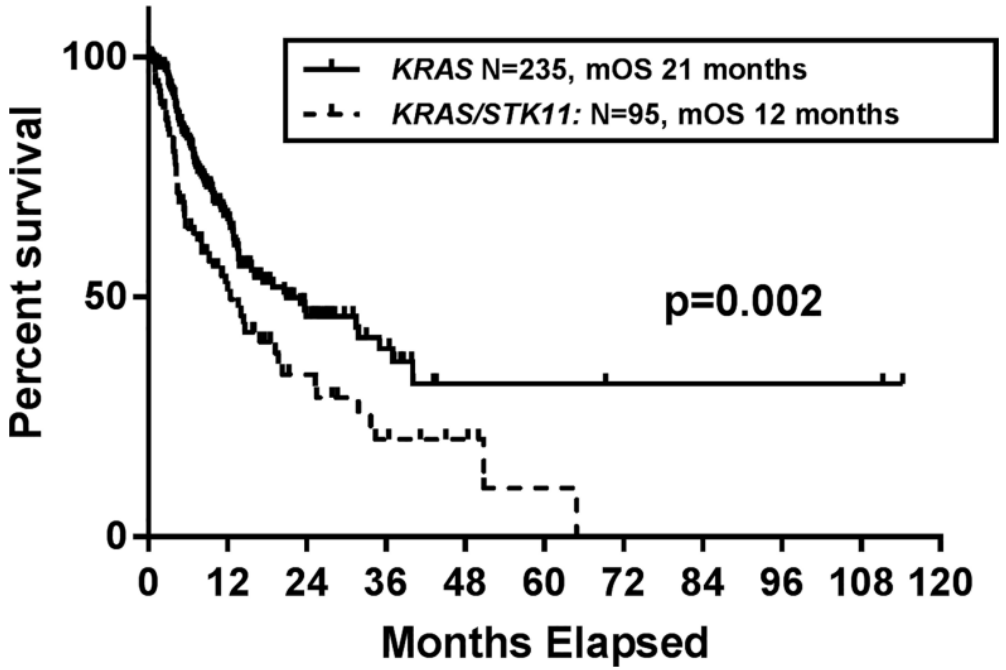


TP53 (41%), STK11 (28%), KEAP1 (24%)

Arbour et al. Clin Cancer Res 2018

Co-mutations KRAS-KEAP1-STK11

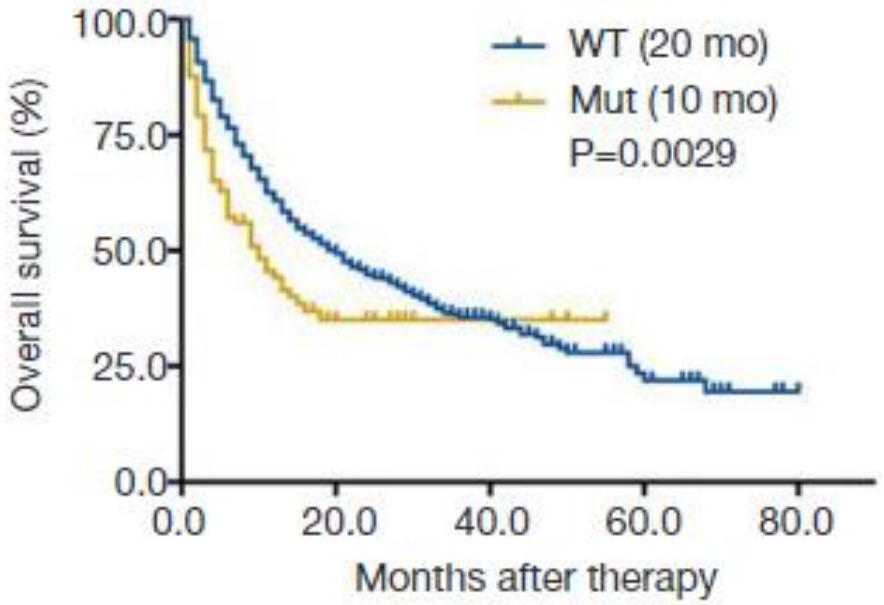




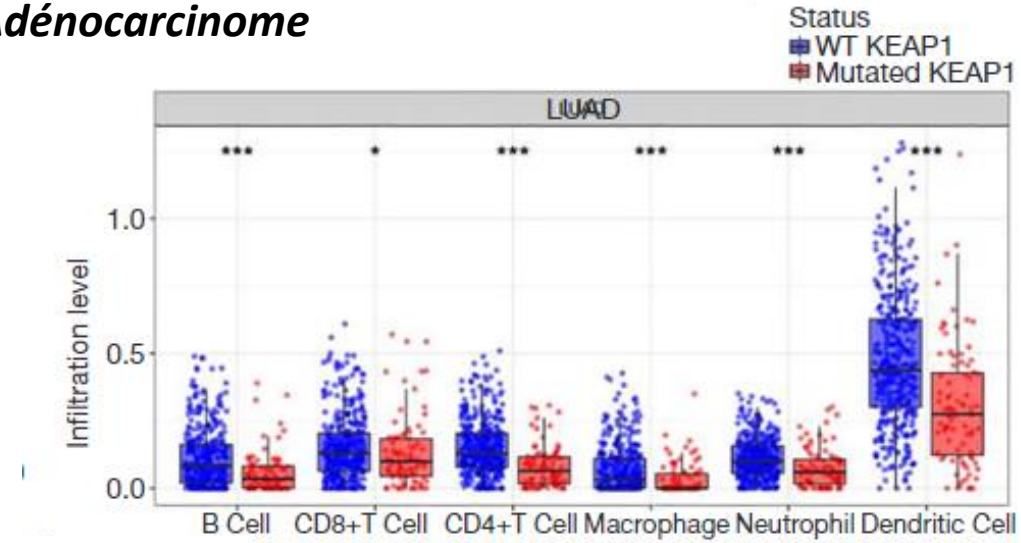
La présence d'une co-mutation KRAS-KEAP1 ou KRAS-STK11 est associée à un mauvais pronostic global dans les CBNPC de stade 4

Arbour et al. Clin Cancer Res 2018

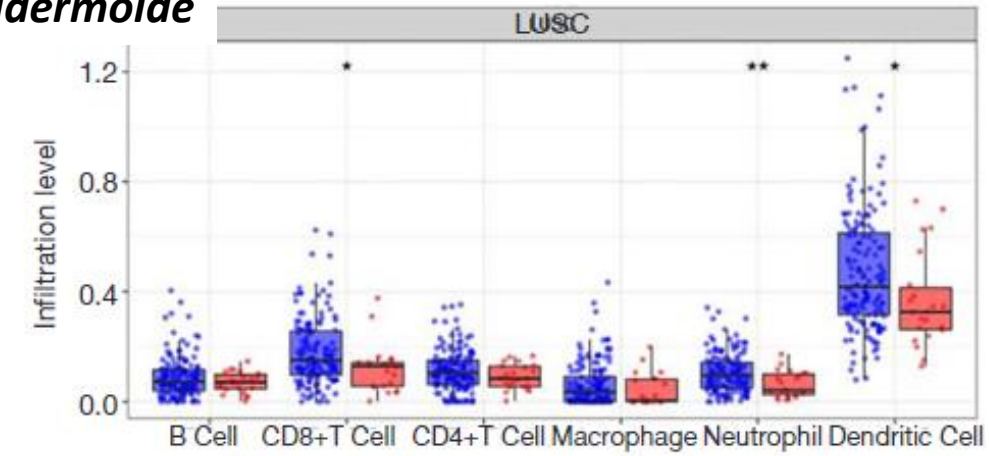
Mutations KEAP1 et résistance aux IO ?



Adénocarcinome

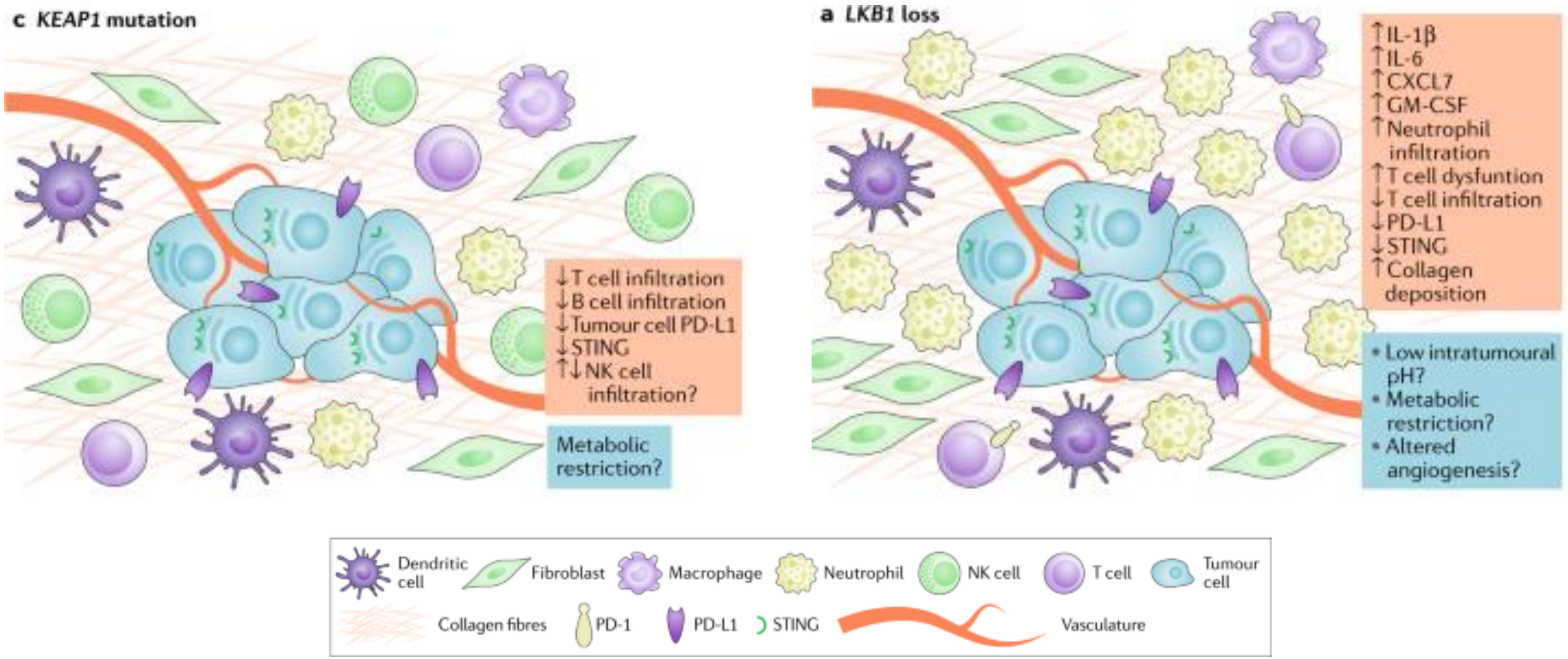


Épidermoïde



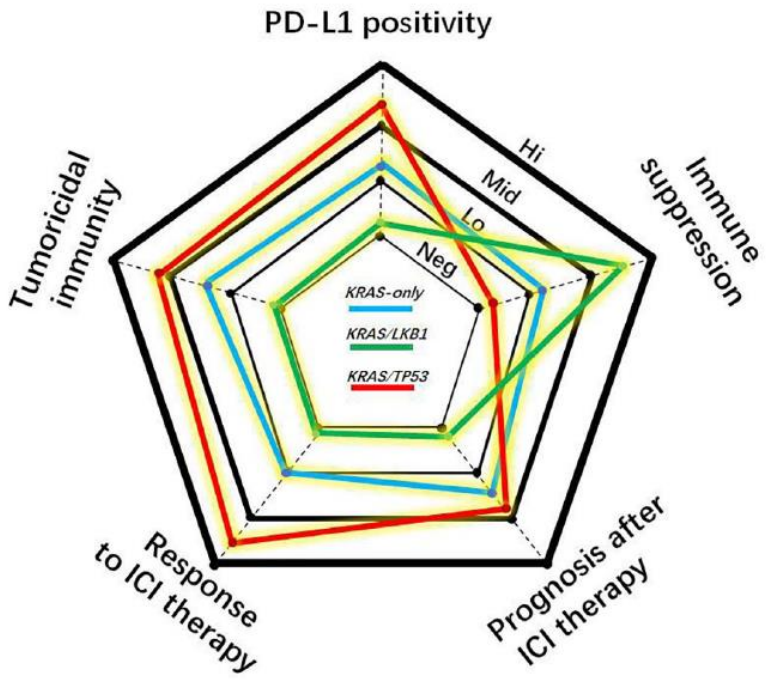
Chen et al. Ann Transl Med 2020

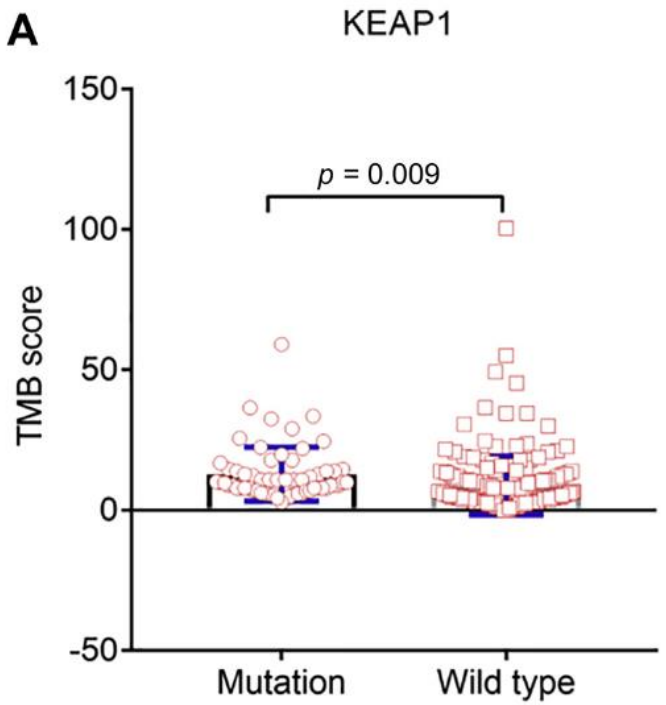
Mutations KEAP1/STK11 et résistance aux IO ?

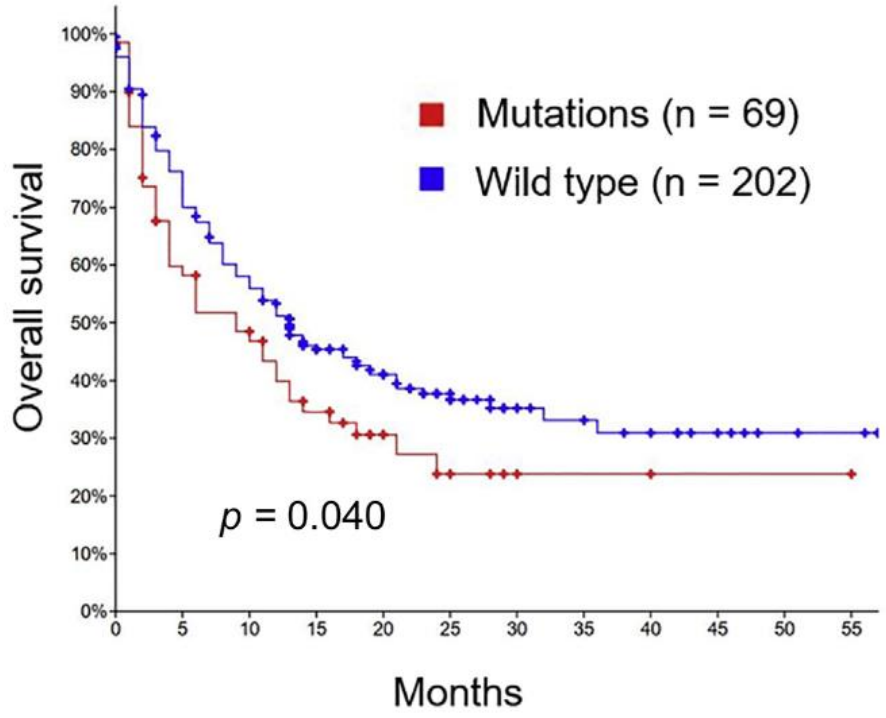


Skoulidis et al. Nat Rev Cancer 2019

Mutations KEAP1/STK11 et résistance aux IO ?







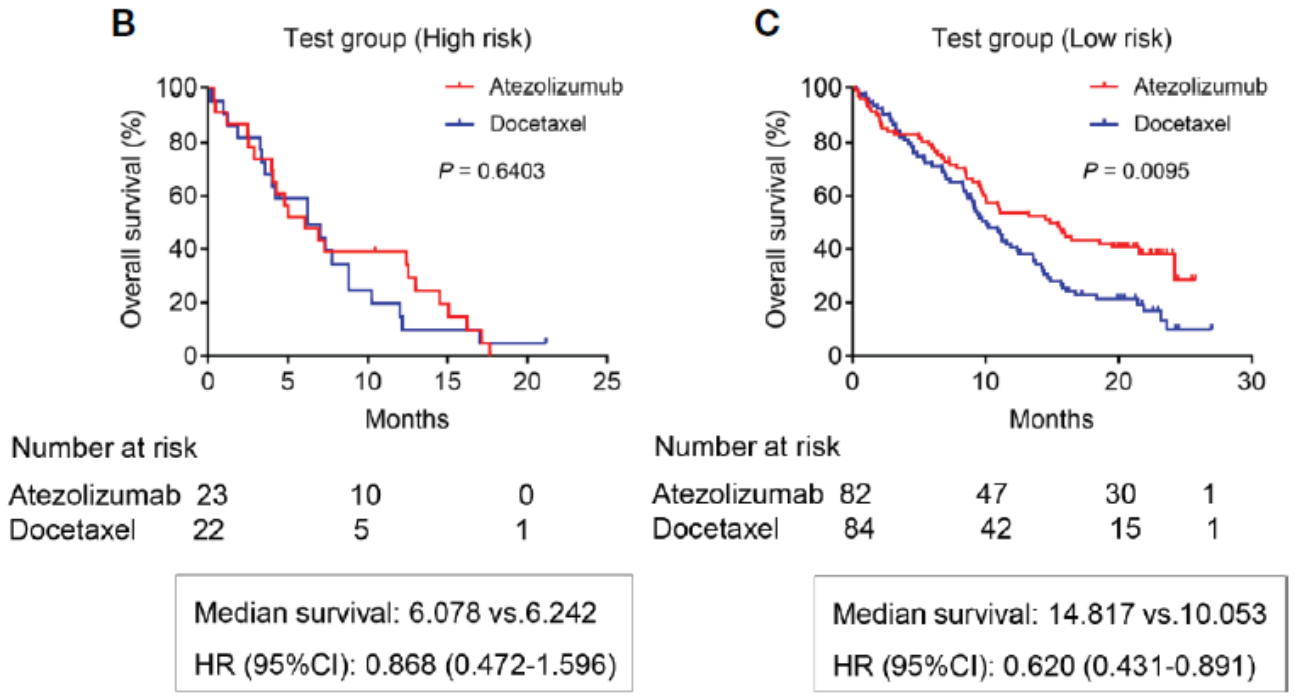
Zhang et al. J Thorac Oncol 2020 ; Gu et al. Ther Adv Med Oncol 2021

Mutations KEAP1/STK11 et résistance aux IO ?

A 5-Genomic Mutation Signature Can Predict the Survival for Patients With NSCLC Receiving Atezolizumab

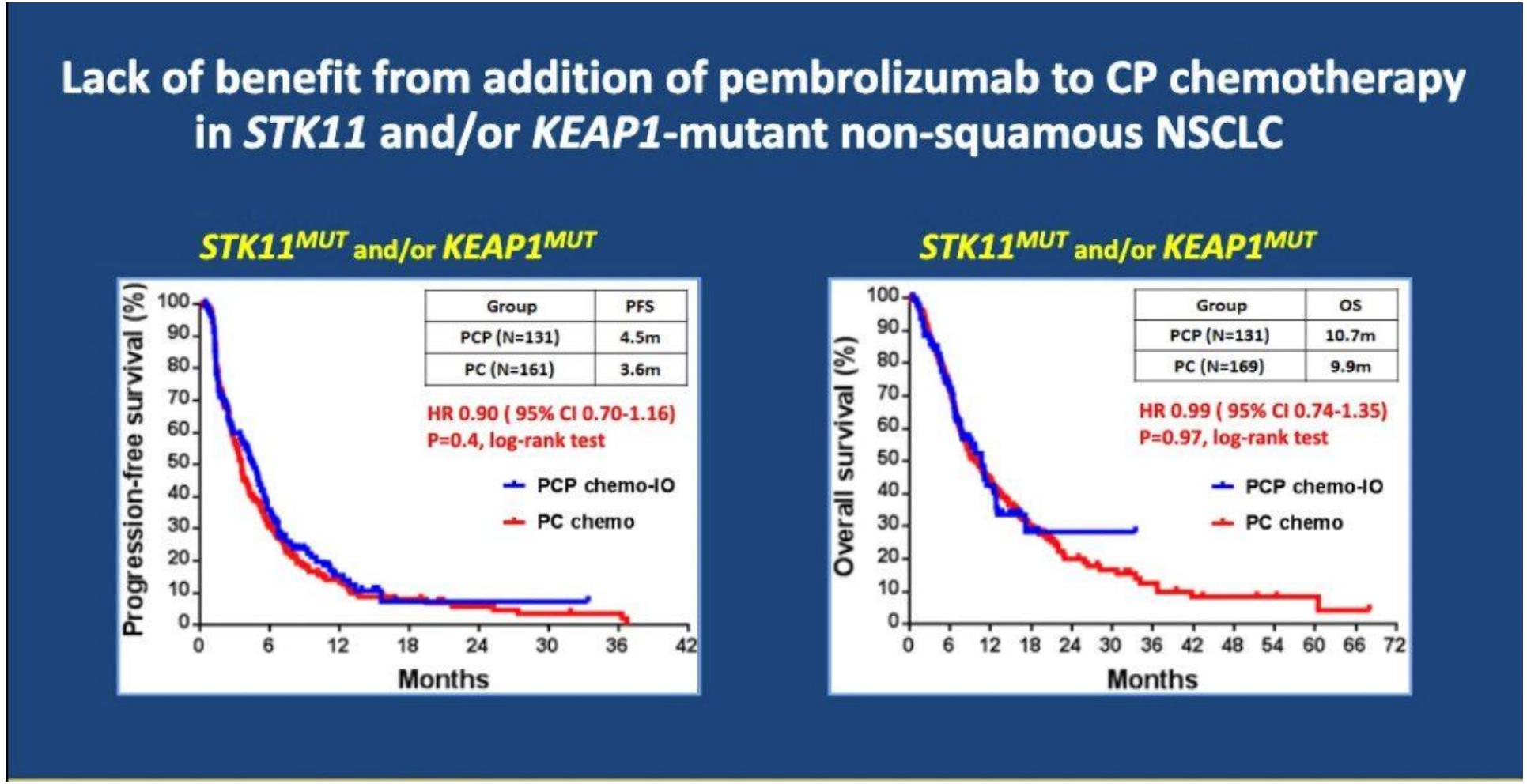
Gene	Coefficient
CREBBP	0.292711
KEAP1	0.306608
RAF1	-0.05406
STK11	0.023995
TP53	0.065909

Etude POPLAR (atezolizumab vs docetaxel)



Lin et al. Front Immunol 2021

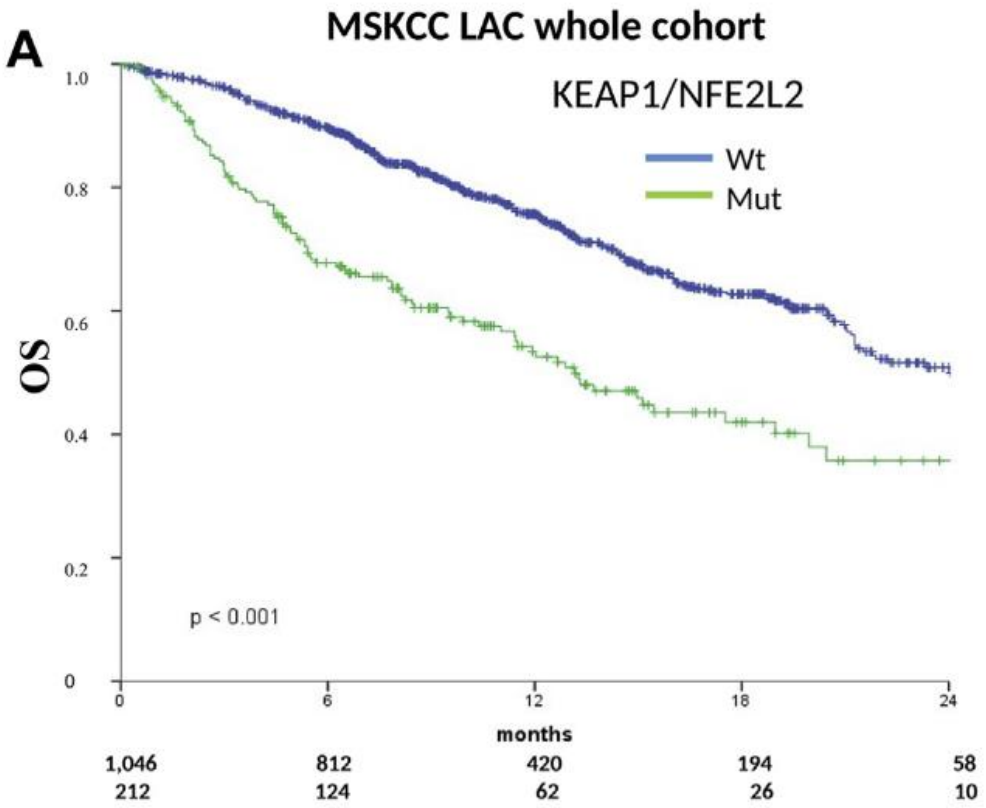
Mutations KEAP1/STK11 et résistance aux IO ?



Skoulidis et al. ASCO 2019

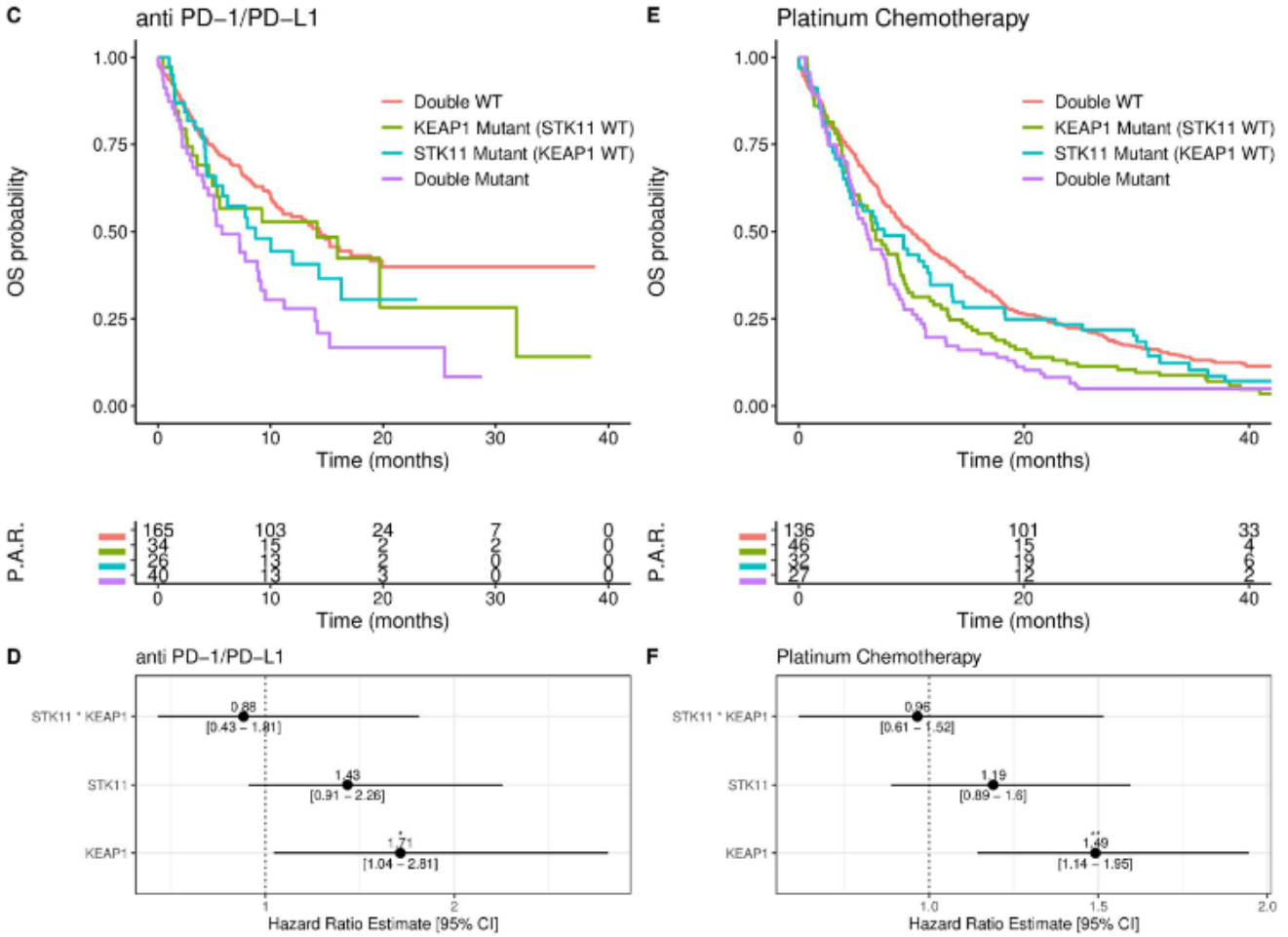
…mais pas qu'aux IO ?

Adénocarcinomes stade 4 traités par CT



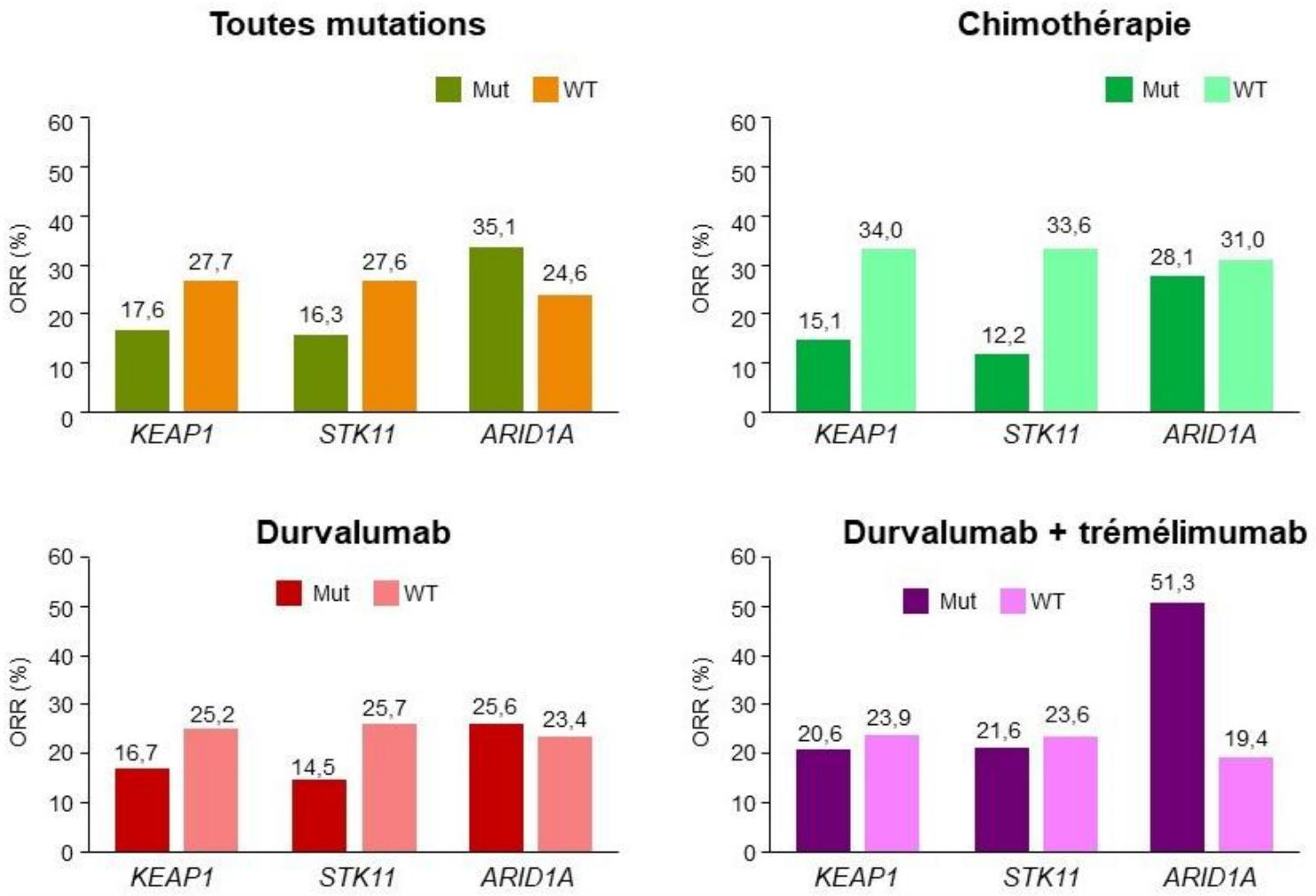
Goeman J Thorac Oncol 2019

Cohorte « vraie vie » CBNPC L1



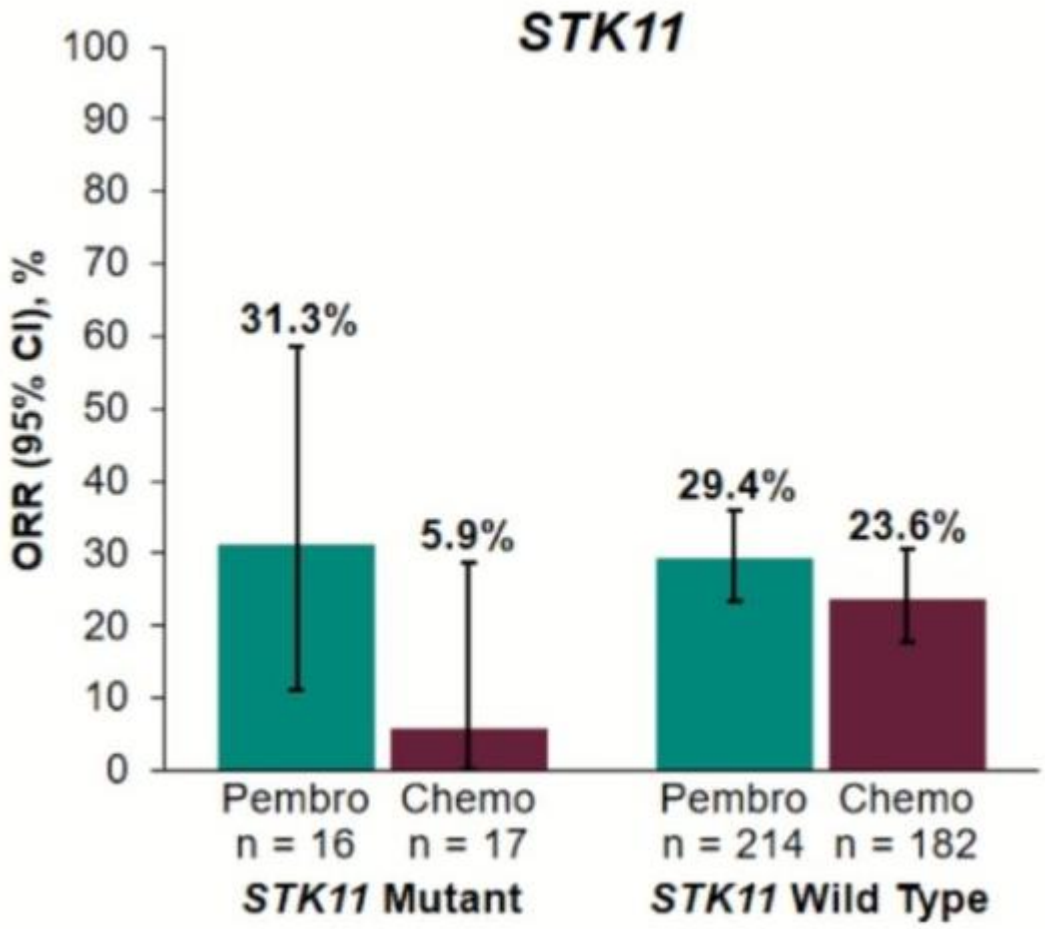
Papillon-Cavanagh et al. ESMO Open 2020

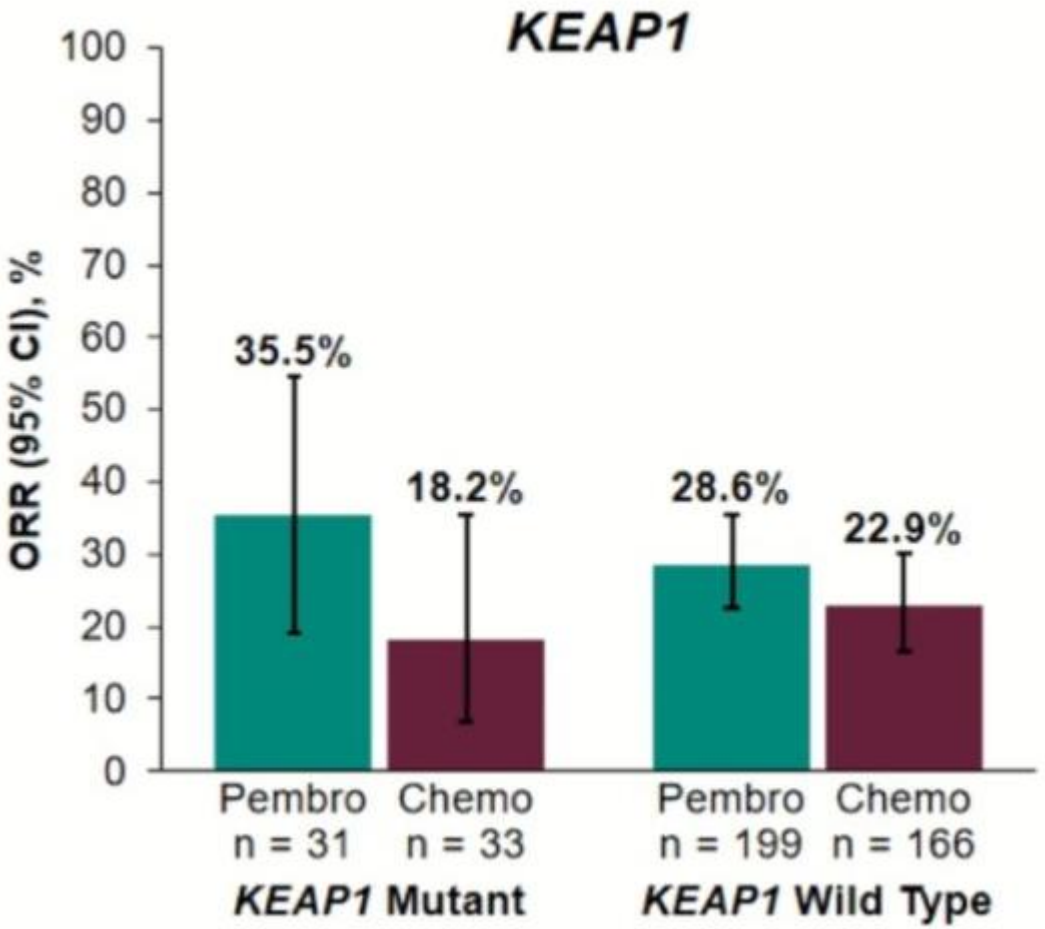
Analyses post-hoc MYSTIC



Rizvi et al. WCLC 2019

Analyses post-hoc Keynote-042





Cho et al. AACR 2020

Analyses post-hoc Keynote-042

Table. KEYNOTE-042 Efficacy Outcomes According to *STK11* and *KEAP1* Mutation Status and Treatment

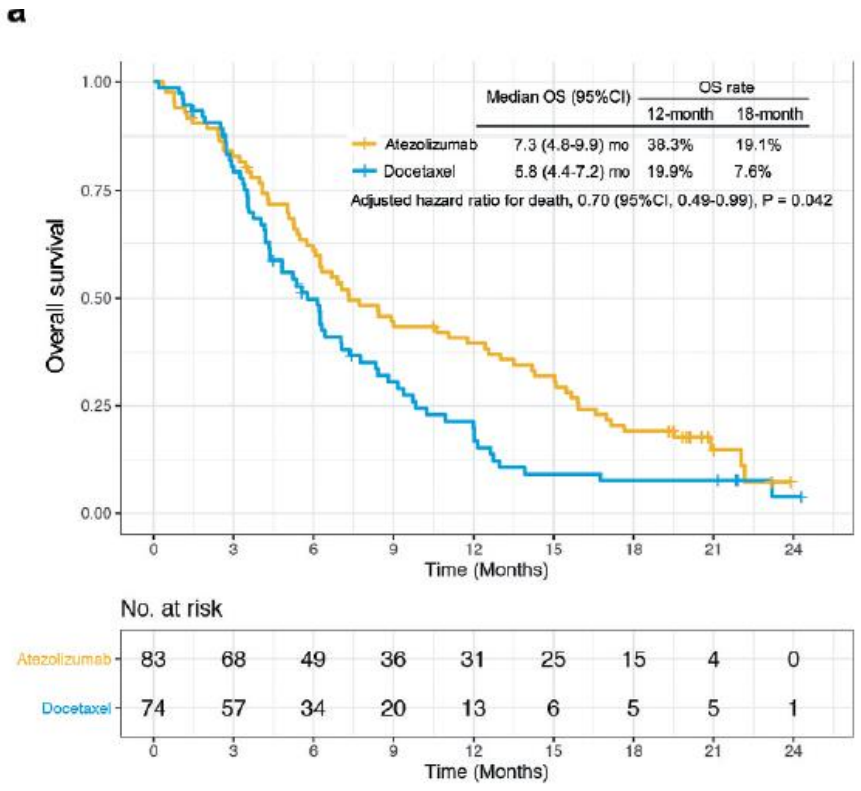
Efficacy Outcome	*STK11* Mutation				*KEAP1* Mutation			
	Present		Absent		Present		Absent	
	Pembro (16 patients)	Chemo (17 patients)	Pembro (214 patients)	Chemo (182 patients)	Pembro (31 patients)	Chemo (33 patients)	Pembro (199 patients)	Chemo (166 patients)
ORR, %	31.3	5.9	29.4	23.6	35.5	18.2	28.6	22.9
Median PFS, mos (95% CI)	5 (2-NR)	5 (4-11)	6 (4-7)	6 (6-7)	6 (4-24)	6 (4-7)	6 (4-6)	6 (6-8)
PFS, HR (95% CI)	0.75 (0.36-1.57)		0.91 (0.74-1.13)		0.67 (0.38-1.17)		0.96 (0.77-1.20)	
Median OS, mos (95% CI)	18 (10-NR)	8 (6-13)	17 (13-23)	12 (11-15)	17 (7-NR)	9 (7-26)	17 (13-23)	12 (11-15)
Median PFS, mos (95% CI)	0.37 (0.16-0.86)		0.83 (0.65-1.05)		0.75 (0.42-1.35)		0.78 (0.61-0.99)	

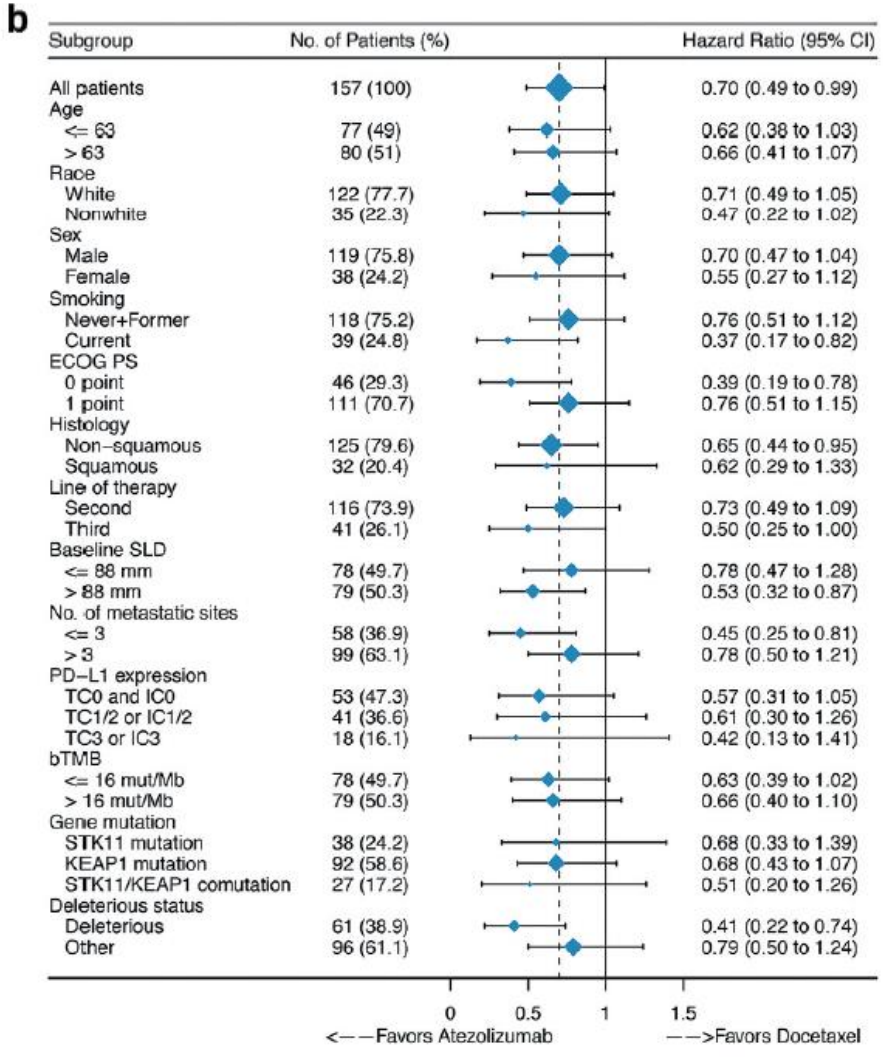
Abbreviations: CI, confidence interval; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Cho et al. AACR 2020

Analyses post-hoc OAK et POPLAR

N=157 avec mutations KEAP1/STK11

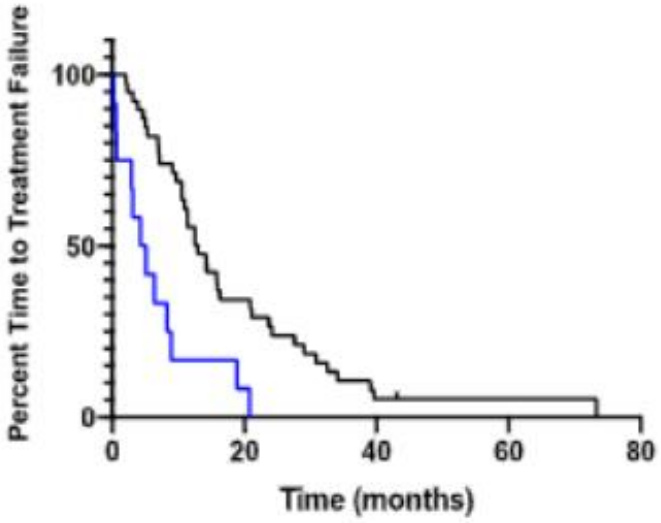




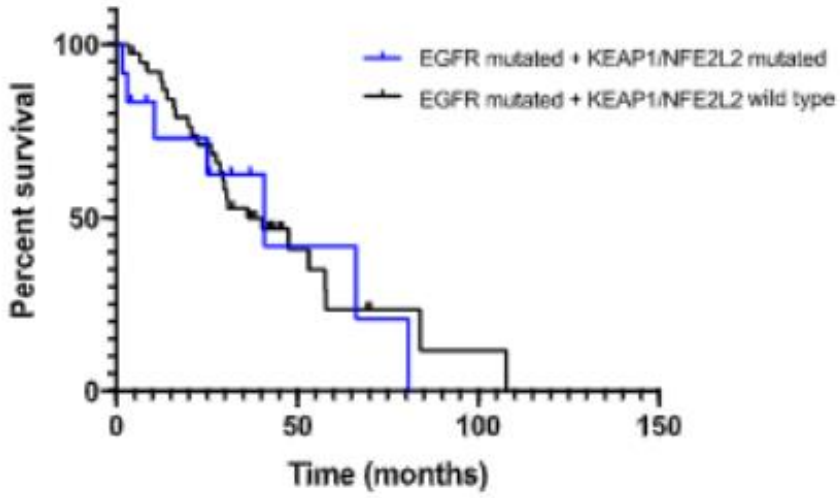
L'IO reste le TTT de choix même en cas de mutation KEAP1/STK11

Nie et al. OncoImmunol 2021

Mutations KEAP1 et mutations EGFR



Median TTF 4.7 vs 13.0 months
HR = 2.8 (95% CI 1.1 – 7.2), *p= 0.0014*



Median OS 41 vs 36 months
HR = 1.3 (95% CI 0.56 – 3.1) *p = 0.48*

Hellyer et al. Lung Cancer 2019

Ciblage mutations KEAP1

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Table 1. Ongoing and Upcoming Trials Targeting *KEAP1-NFE2L2*-Mutant Tumors

Trial	NCT Number	Phase	N	Study Group	Treatment Regimen	Primary End Point
CB-839	NCT04265534	2	120	Stage IV *KEAP1* mutant, nonsquamous NSCLC	Randomized Arm 1: CB-839 with chemo + pembro Arm 2: chemo + pembro	Progression-free survival and safety
Sapanisertib (TAK-228)	NCT02417701	2	40	Stage IV squamous cell or *KRAS*-mutant lung cancers with mutation in *KEAP1-NFE2L2*	Sapanisertib PO daily days 1-28	Overall response rate
Lung-MAP	NCT04267913	2	94	Stage IV squamous cell lung cancer with mutations in *KEAP1-NFE2L2*	Randomized Arm 1: docetaxel and sapanisertib Arm 2: docetaxel ± ramucirumab	Progression-free survival
BeGIN	NCT03872427	2 Basket Trial	108	Stage IV *KEAP1-NFE2L2*, *STK11/LKB1*, or *NF1*-mutant solid neoplasms	CB-839 PO twice daily on days 1-28	Best overall response rate at 6 mo
CB-839 + Sapanisertib	NCT04250545	1/1B	85	Dose escalation: patients with stage IV NSCLC Dose expansion: stage IV lung squamous cell carcinoma with *KEAP1* or *NFE2L2* mutations or lung adenocarcinoma with *KRAS/KEAP1* or *KRAS/NFE2L2* mutations	CB-839 PO twice daily plus sapanisertib PO daily on days 1-28	Phase 1: maximum tolerated dose Phase 1B: response rate and progression-free survival

Hellyer et al. J Thorac Oncol 2020

Ciblage mutations STK11

Recent and current clinical trials for STK11 altered non–small-cell lung cancer.

Study name (NCT identifier)	Study title	Status	Phase	Experimental arm
CodeBreaK 201 NCT04933695	A study of Sotorasib (AMG 510) in stage IV NSCLC whose tumors harbor a KRAS p.G12C mutation in first line treatment.	Recruiting	Phase II	Sotorasib (KRAS inhibitor)
LUNG-MAP NCT04173507	Combination treatment (Talazoparib plus avelumab) for stage IV or recurrent nonsquamous NSCLC with STK11 gene mutation	Active, not recruiting	Phase II	Talazoparib (PARP inhibitor) and Avelumab (PDL1 inhibitor)
KEAPSAKE NCT04265534	A study of Telaglenastat (CB-839) with standard of care chemoimmunotherapy in 1L KEAP1-NRF2-mediated non-squamous NSCLC	Active, not recruiting	*Phase II*	*Telaglenastat (Glutaminase inhibitor) and Pembrolizumab (PDL1 inhibitor) and Carboplatin/Pemetrexed and Placebo + Pembrolizumab + Carboplatin/Pemetrexed*
NCT05234307	PBF-1129 and Nivolumab for the treatment of recurrent or metastatic NSCLC	Not yet recruiting	Phase I	*Adenosine A2B Receptor Antagonist PBF-1129*
NCT05054725	Combination study of RMC-4630 and Sotorasib of NSCLC with KRASG12C mutation after failure of prior standard therapies	Recruiting	Phase II	RMC-4630/ SAR442720 (SHP2 inhibitor; Tyrosine-protein phosphatase nonreceptor type 11) *v* Sotorasib (KRAS inhibitor)
NCT04471415	First in human study of DRP-104 (Sirpiglenasta) as single agent or in combination with atezolizumab in patients with advanced solid tumors	Recruiting	Phase I/II	Sirpiglenasta (glutaminase inhibitor) and atezolizumab (PDL1 inhibitor)
KRYSTAL-1 NCT03785249	Study of MRTX849 in patients with cancer having KRAS G12C mutation	Recruiting	Phase I/II	MRTX849/Adagrasib (KRAS inhibitor)
BUNCH NCT04518137	A study of evaluating the safety and efficacy of ATG-008 for advanced solid tumors	Recruiting	Phase II	ATG-008/onatasertib (Dual inhibitor of mammalian target of rapamycin- mTOR)

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Farooq et al. Seminar Oncol 2022

Conclusion

MUTATIONS TP53 :
Biomarqueur **pronostique**
ET prédictif (**+** pour IO / **-** pour TKI EGFR et ALK)

MUTATIONS KEAP1 et STK11 :
Biomarqueur plus **pronostique** que prédictif

→ faut-il en tenir compte ?

Probablement pour le suivi des patients
Probablement pas pour le choix des traitements