ESMO PRECEPTORSHIP ON LUNG CANCER

Best strategy for advanced NSCLC with KRAS mutation

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DECLARATION OF INTERESTS

Laura Mezquita

Research grant/Funding: Amgen, Inivata, AstraZeneca, Gilead
Advisory/Consultancy: Roche, Takeda, MSD, Jannsen
Education activities: Bristol Myers Squibb, Takeda, Roche, Jannsen, MSD
Travel/Accommodation/Expenses: Roche, Takeda, Bristol Myers Squibb, Jannsen

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1. *KRAS* mut in patients with NSCLC
2. Profile of *KRAS* mutation
3. Therapeutic strategy for *KRAS* G12C
   - Focused on immunotherapy
   - Focused on targeted therapy
4. New challenges and future perspectives
5. Take home messages

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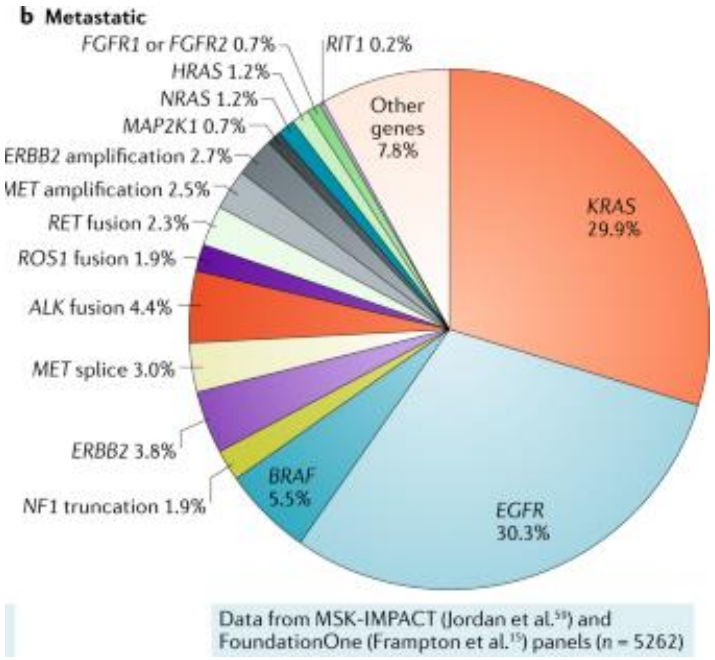
KRAS mutation in NSCLC

KRAS mut. is the most common mutation in NSCLC (~ 30%)



Sánchez Vega et al, Cell 2018

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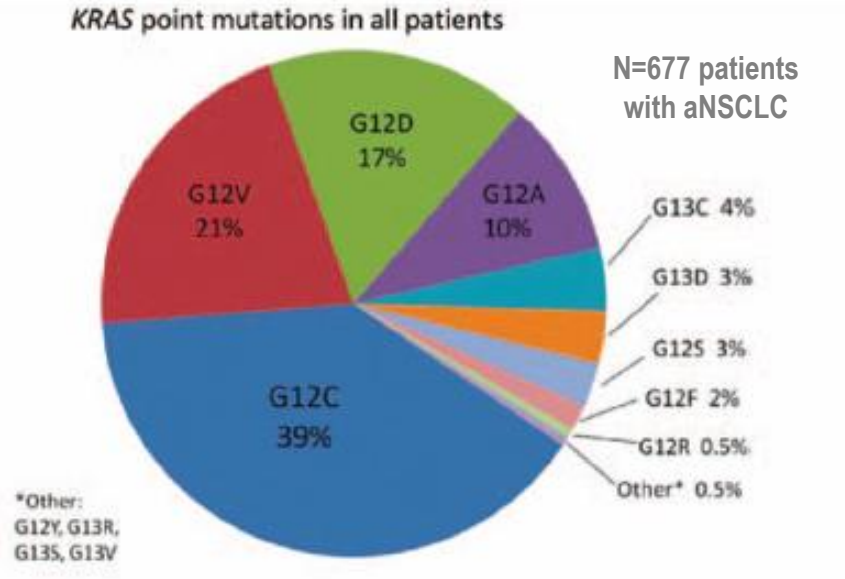
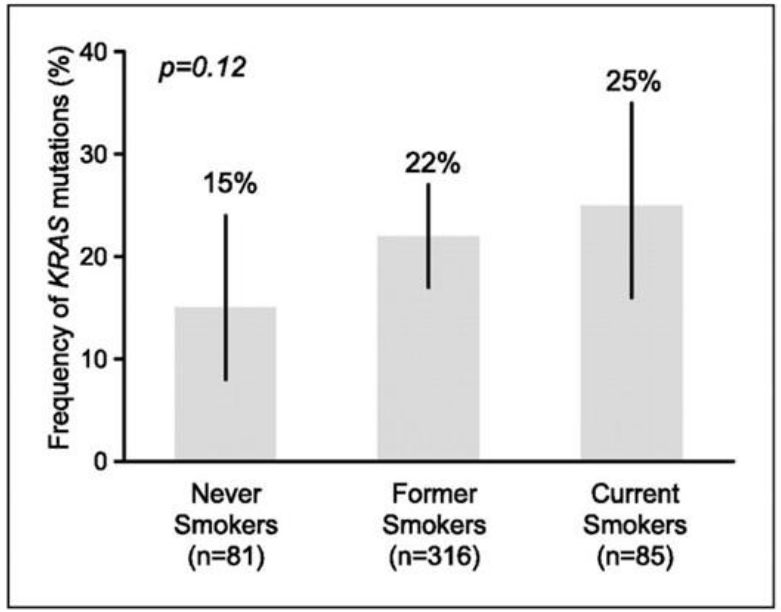
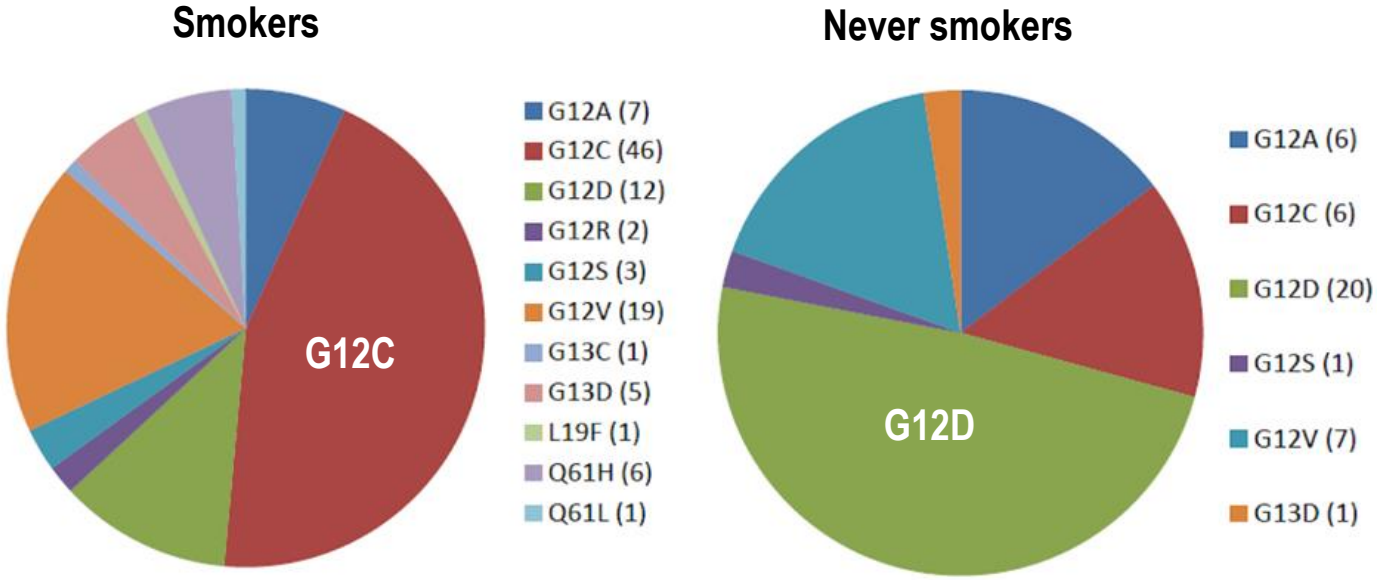


Yu et al, JTO 2015

KRAS mutation in NSCLC



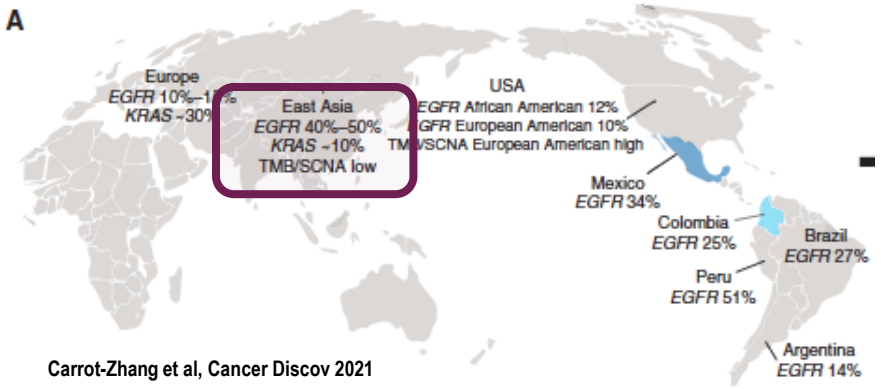


Riely et al. CCR 2008; Redig et al. ASCO 2016

- **Current/Former smoker +++**
- **Female population**
- **Agressive disease**
- **Mainly adenocarcinoma**

Janne, ESMO 2019

KRAS mutation in NSCLC: differences

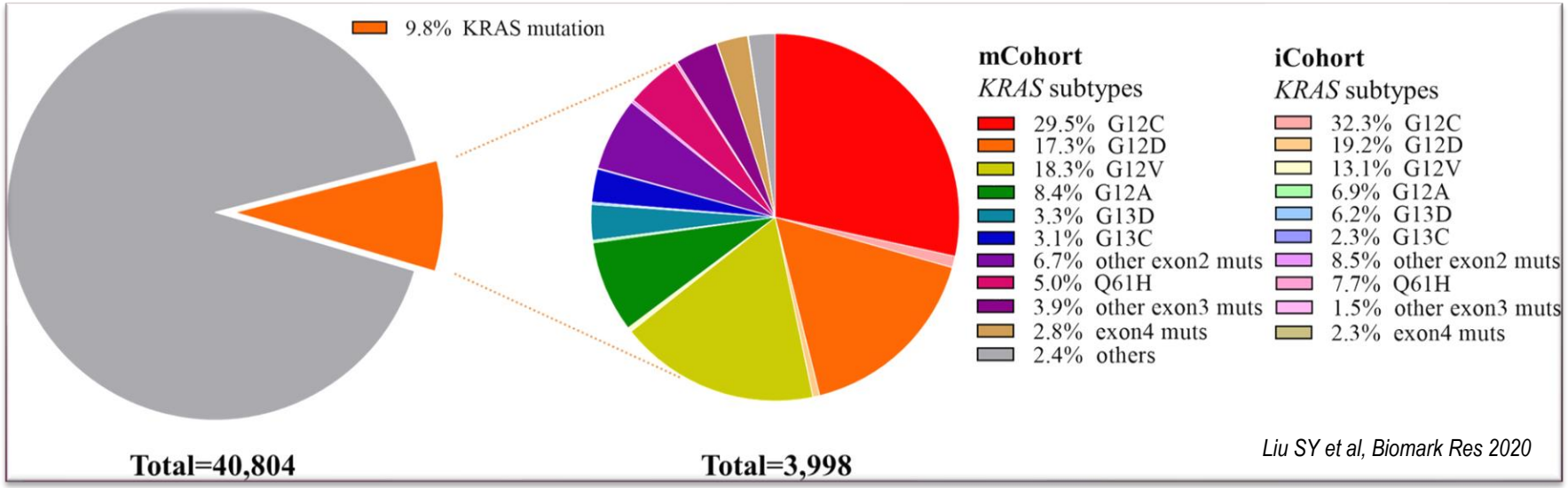


Carrot-Zhang et al, Cancer Discov 2021

Mutation	Germany	USA	China	India
KRAS	**33%**	**25%**	**8%**	**5%**
EGFR	11%	17%	49%	29%

Timar J & Kashofer K. Cancer Metastasis Rev 2020

Chinese Population with NSCLC



Liu SY et al, Biomark Res 2020

NGS recommendations, ESMO

ESMO Translational Research Working Group

ESCAT, ESMO

	Ready for routine use	Investigational	ypothetical target	Combination development	
ESCAT evidence tier	I: Alteration-drug match is associated with improved outcome in clinical trials	II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	X: lack of evidence for actionability
			: pre-clinical evidence of actionability		

Levels of accionability

NGS, advanced NSCLC

Gene	Alteration	Prevalence	ESCAT
EGFR	Common mutations (*Del19, L858R*)	15% (50%–60% Asian)	IA
	Acquired *T790M* exon 20	60% of *EGFR* mutant	IA
	Uncommon *EGFR* mutations (*G719X* in exon 18, *L861Q* in exon 21, *S768I* in exon 20)	NSCLC	IB
		10%	IIB
	Exon 20 insertions	2%	
ALK	Fusions (mutations as mechanism of resistance)	5%	IA
MET	Mutations *ex 14 skipping*	3%	IB
	Focal amplifications (acquired resistance on EGFR TKI in *EGFR*-mutant tumours)	3%	IIB
$BRAF^{V600E}$	Mutations	2%	IB
ROS1	Fusions (mutations as mechanism of resistance)	1%–2%	IB
NTRK	Fusions	0.23%–3%	IC
RET	Fusions	1%–2%	IC
$KRAS^{G12C}$	Mutations	12%	IIB
ERBB2	Hotspot mutations	2%–5%	IIB
	Amplifications		

Mateo J et al, Ann Oncol 2018; Mosele F Ann Onc 2020

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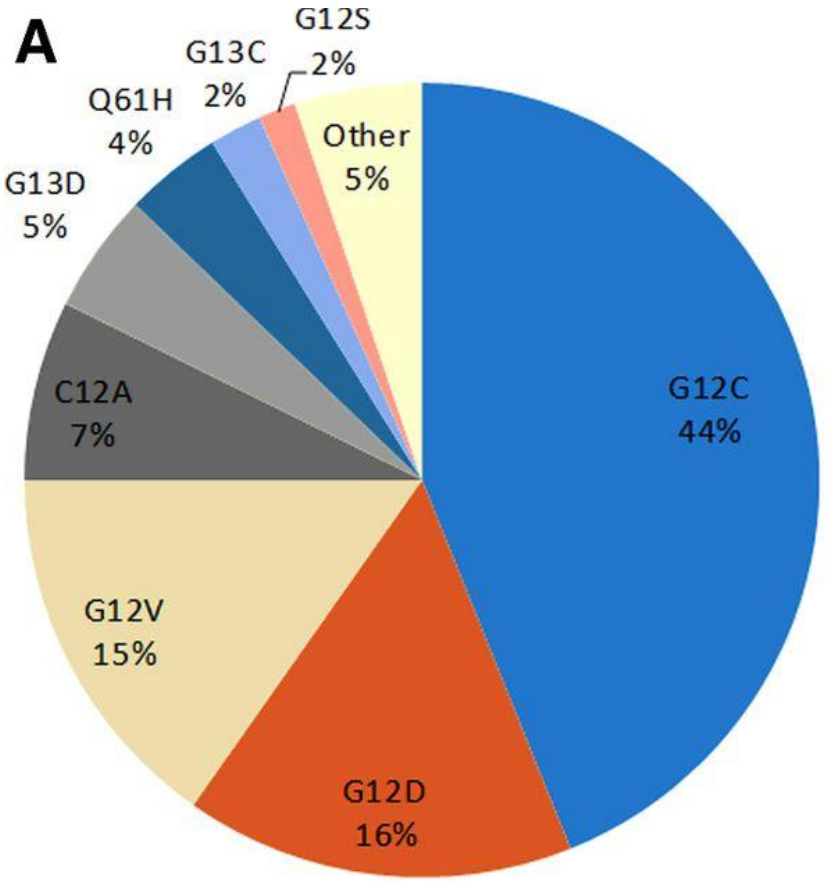
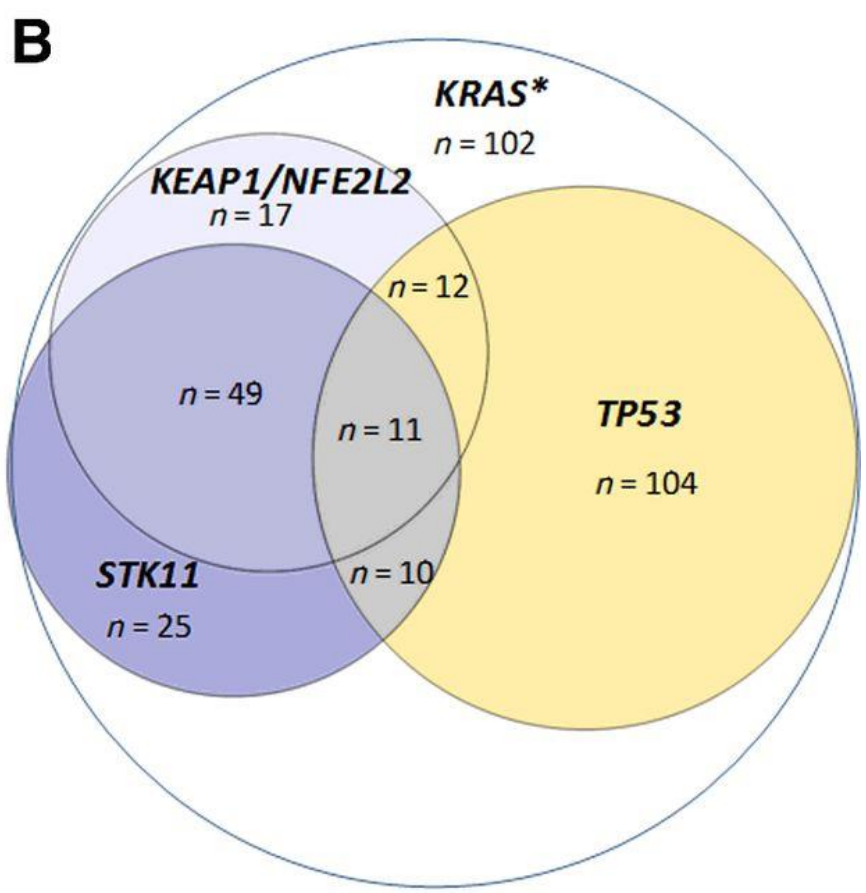
KRAS NSCLC: Heterogeneous disease

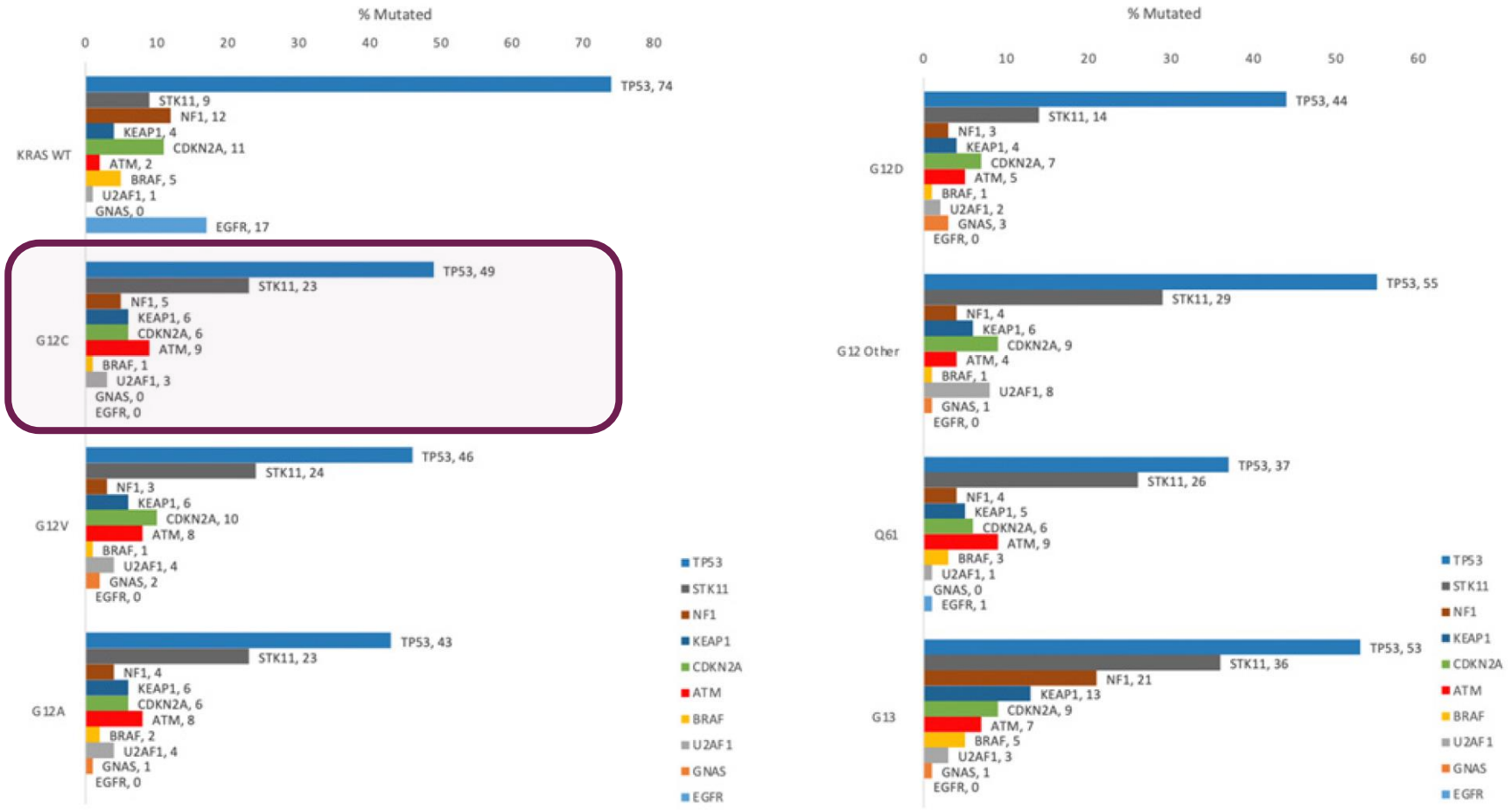




*KRAS (*n* = 102) listed above represents number of patients with *KRAS* mutations but without cooccurring mutations in *TP53*, *STK11*, *KEAP1* or *NFE2L2*

Arbour et al. Clin Cancer Res 2018

KRAS NSCLC: *Co-occurring mutations across the KRAS variants*

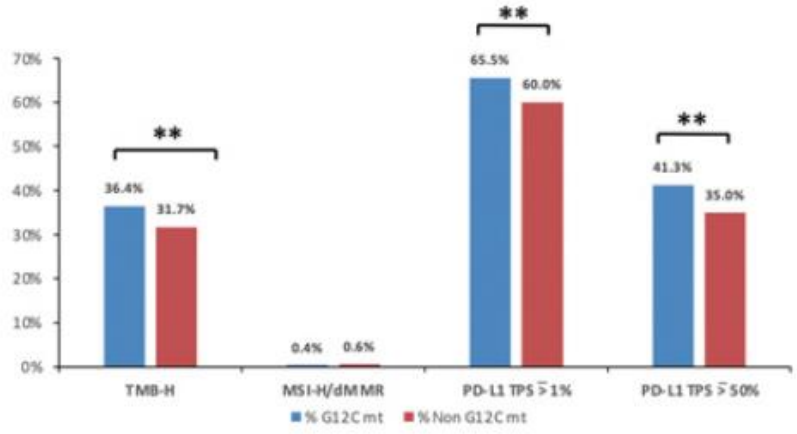


Judd J et al, Mol Cancer Ther 2021

KRAS MUT. IN LUNG CANCER: IMMUNE PROFILE

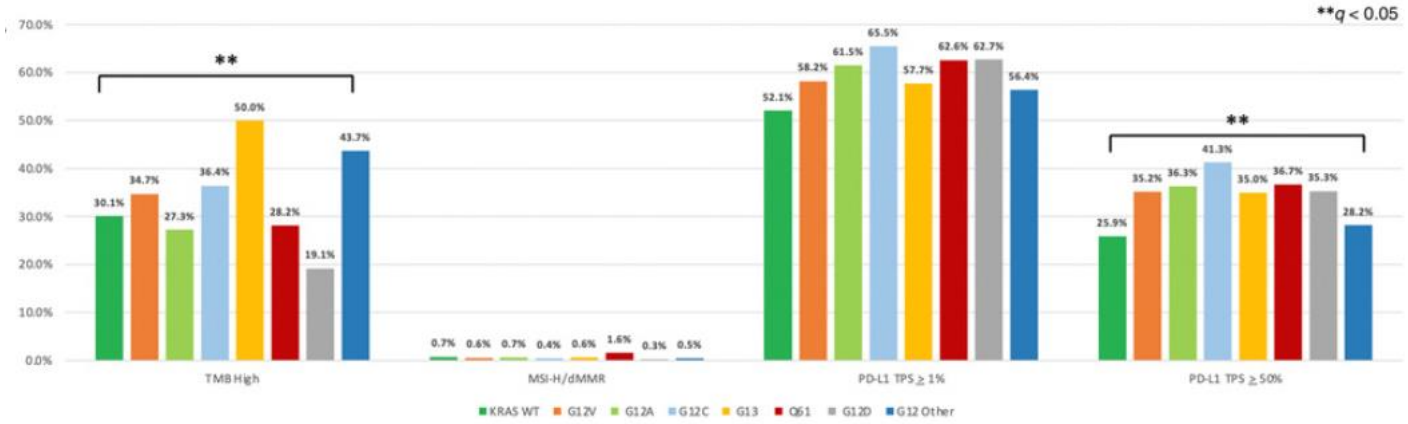
KRAS mut. G12C

↑↑ favorable immunomarkers



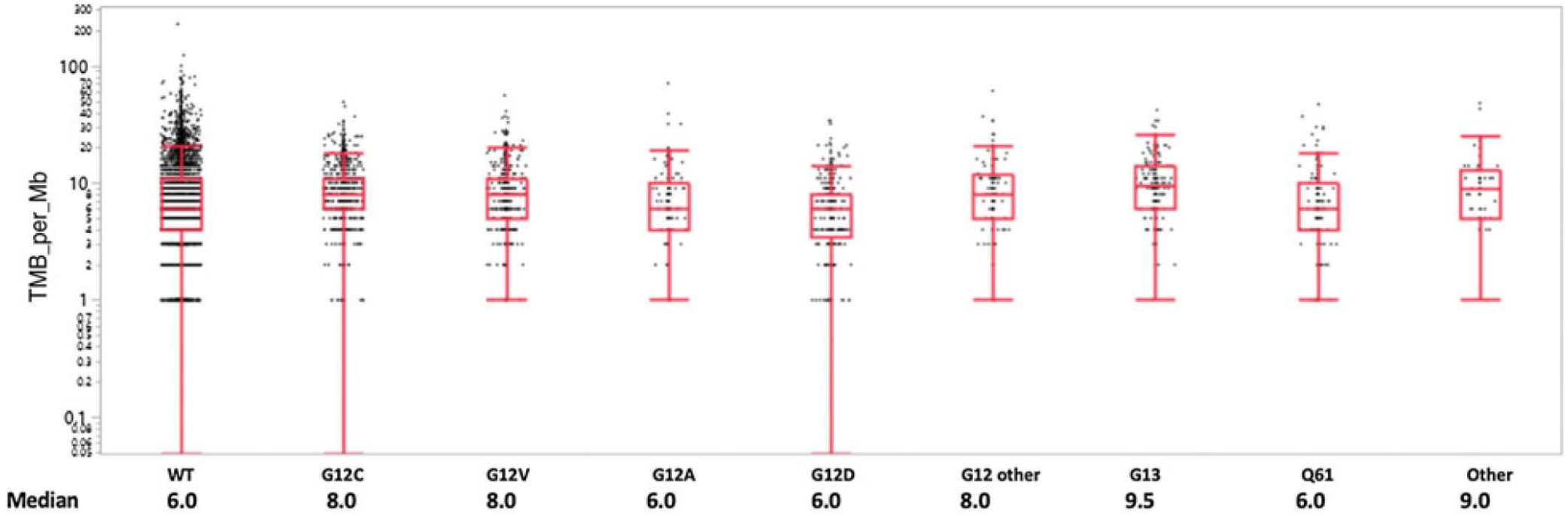
Other *KRAS* mut. variants:

Differences on immunomarkers



Judd J et al, Mol Cancer Ther 2021

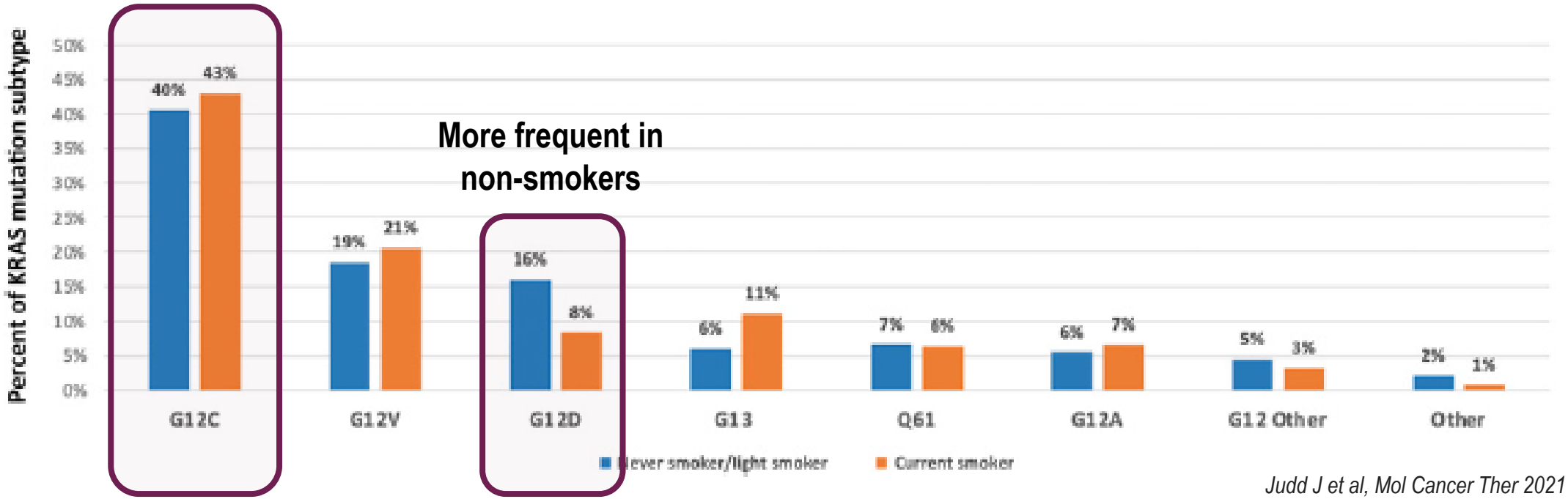
KRAS MUT. IN LUNG CANCER: IMMUNE PROFILE



Judd J et al, Mol Cancer Ther 2021

KRAS MUT. IN LUNG CANCER: SMOKING

KRAS mut. variant & Smoking status



Judd J et al, Mol Cancer Ther 2021

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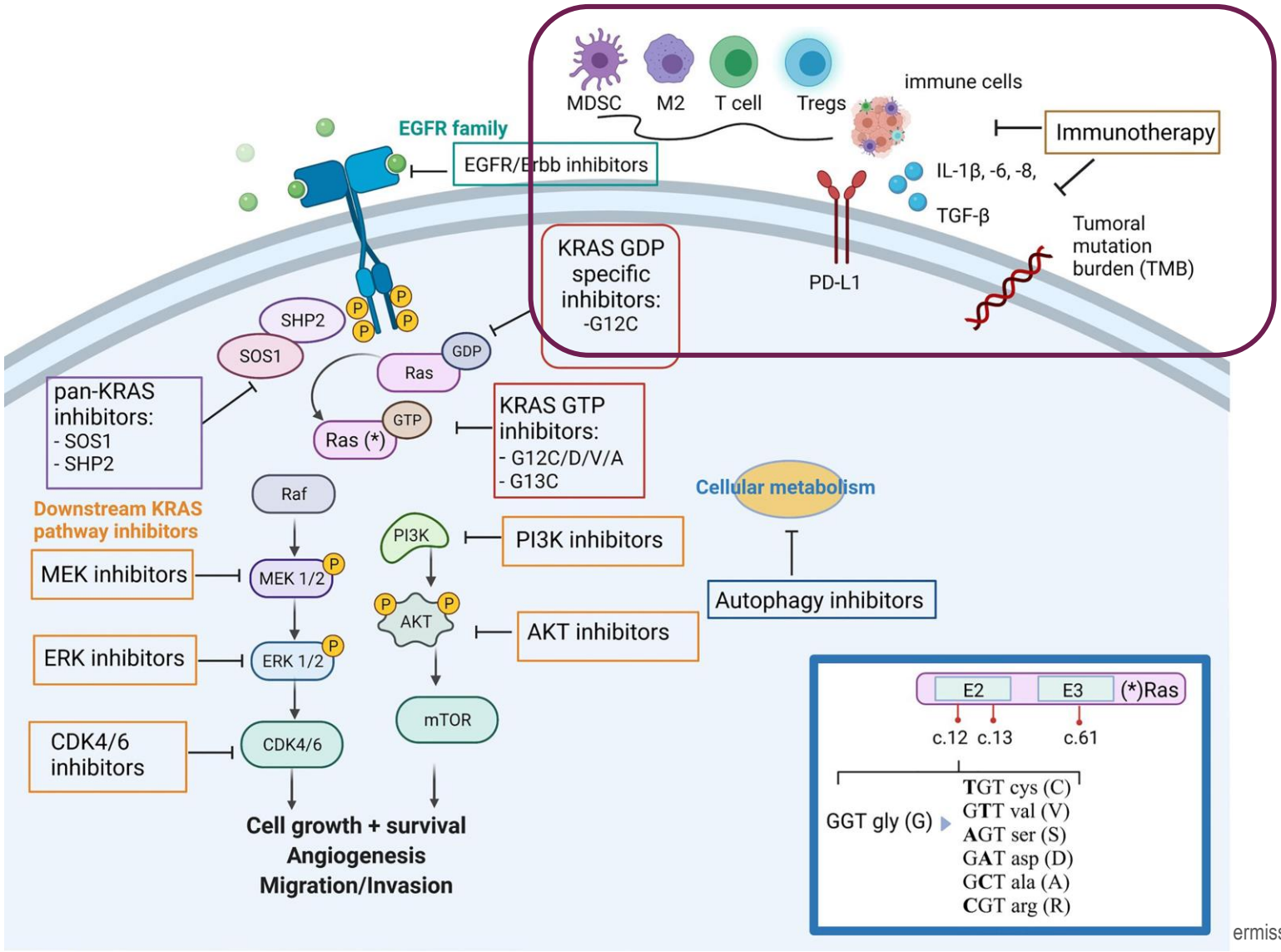
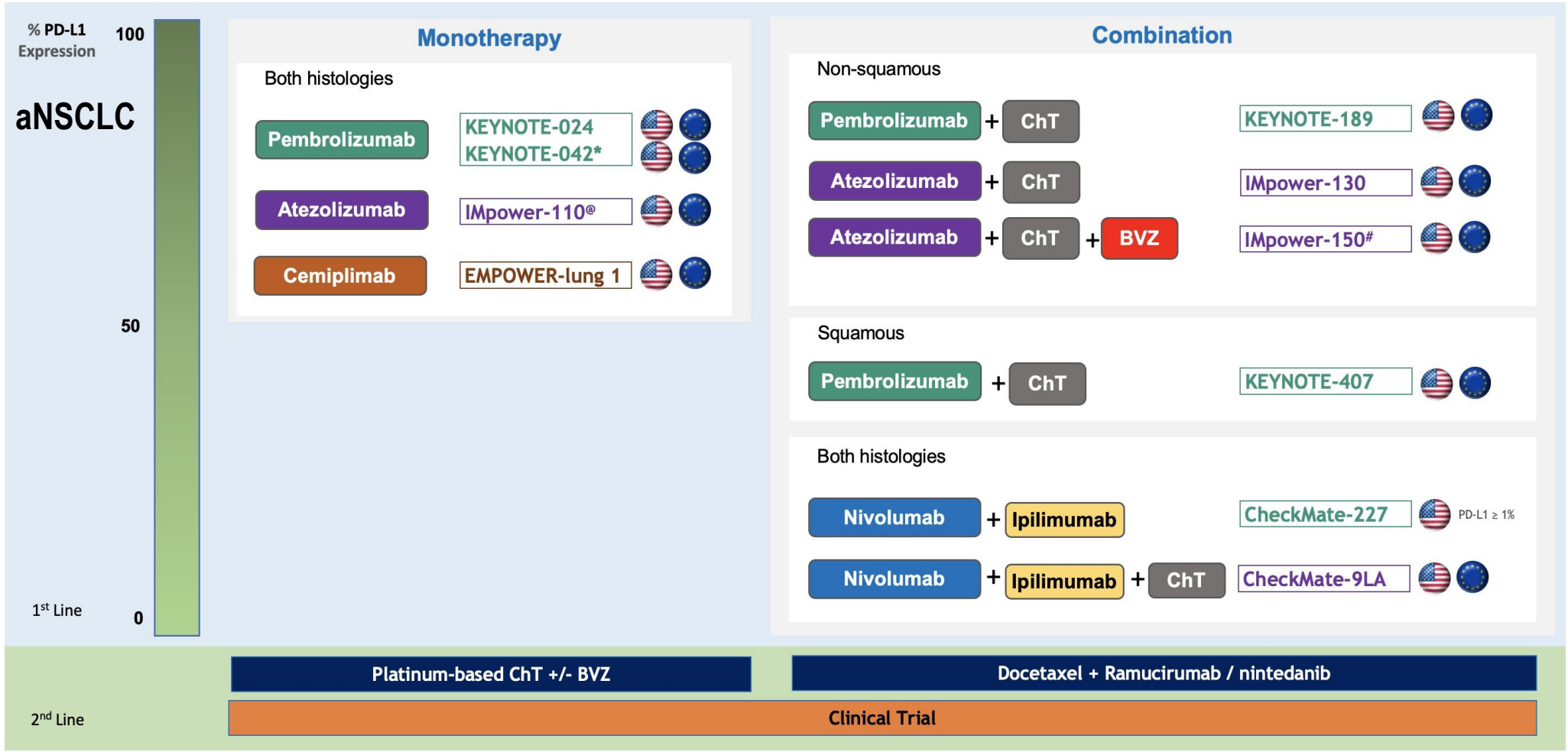
Targeting KRAS with immunotherapy



Cucurull M, et al Frontier Oncol 2022

Immunotherapy: SoC in advanced lung cancer

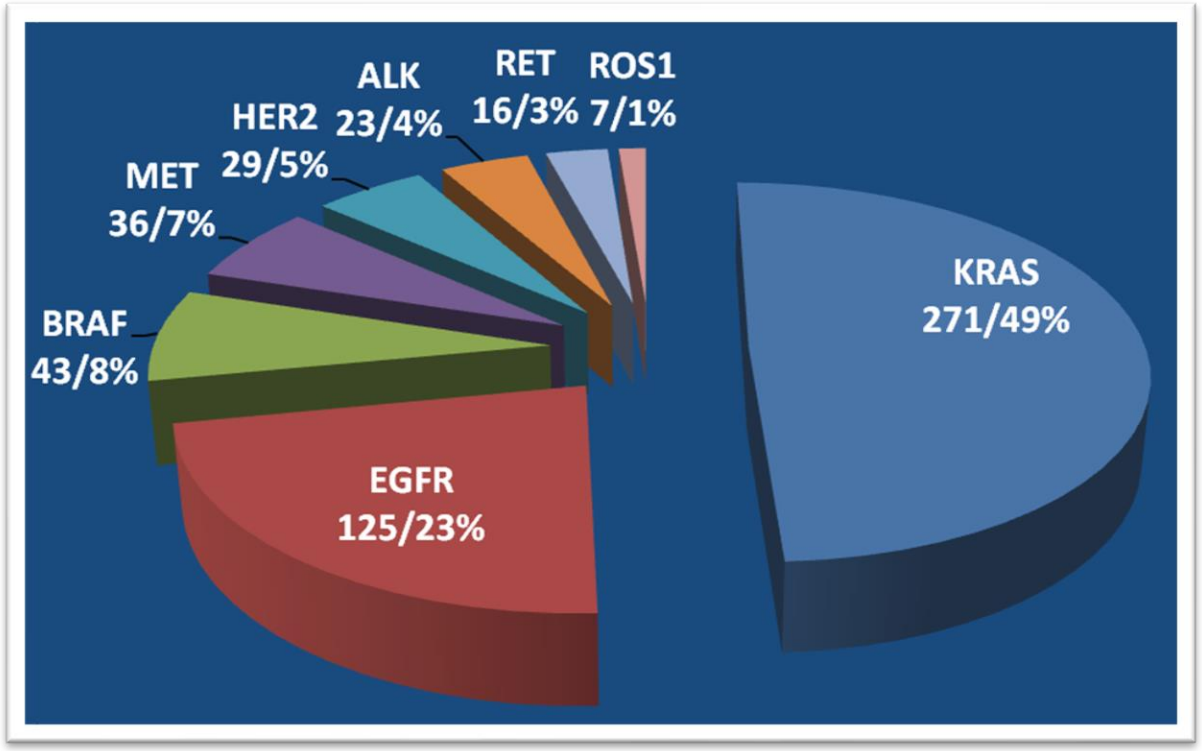


Reck M et al, J Clin Oncol 2022

KRAS mutation: Immunotherapy outcomes

Pretreated pop; Single agent

IMMUNOTARGET cohort (n=574)



Mazières et al , ASCO 2018, Mazièrez Ann Oncol 2018

Driver	PD	SD	CR/PR	PFS (m.)
BRAF	46%	30%	24%	3.1
MET	50%	34%	16%	3.4
KRAS	51%	23%	26%	3.2
HER2	67%	26%	7%	2.5
EGFR	67%	21%	12%	2.1
ALK	68%	32%	0	2.5
RET	75%	19%	6%	2.1
ROS1	83%	0	17%	-
TOTAL	57%	24%	19%	2.8

KRAS mutation: Immunotherapy outcomes

Pretreated pop; Single agent

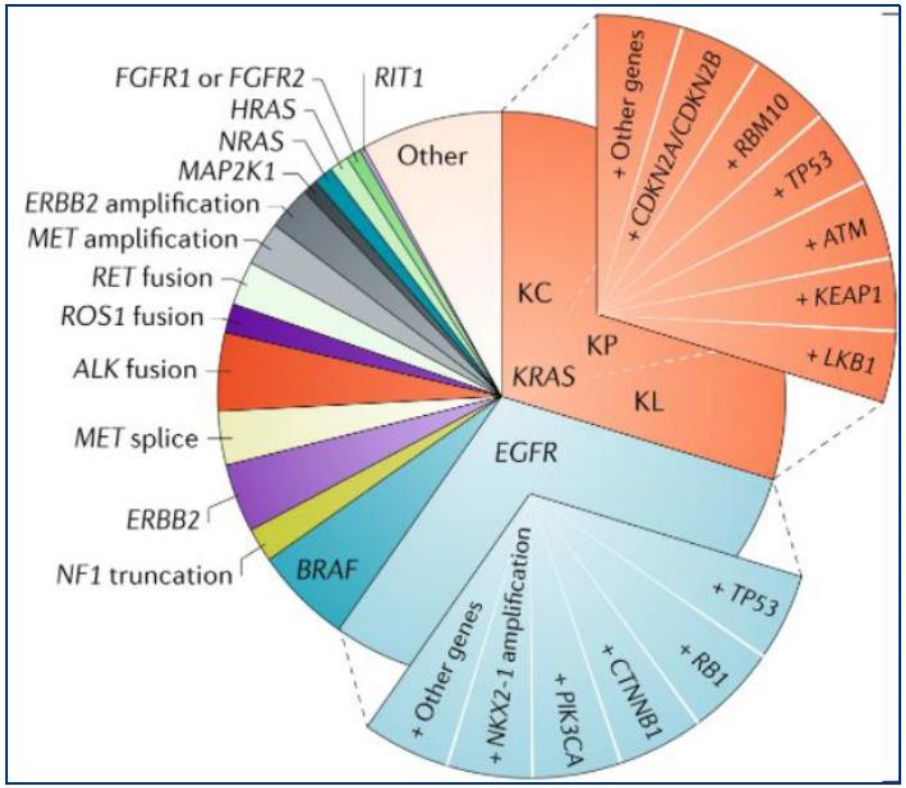
Table 2. Comparison of ICI Efficacy in *KRAS*-Mutant NSCLC and Other Types of NSCLC

Indicator	*KRAS*-Mutated NSCLC	Non-*KRAS*-Mutated NSCLC	OR or HR (95% CI)	*p* Value	NSCLC with Other Mutation	OR or HR (95% CI)	*p* Value	Wild-Type NSCLC	OR or HR (95% CI)	*p* Value
ORR	18.7%	14.4%	OR = 1.37 (0.71-2.63)	0.348	7.7%	OR = 2.76 (0.62-12.35)	0.184	16.3%	OR = 1.18 (0.6-2.34)	0.633
DCR	48.4%	49.2%	OR = 0.97 (0.6-1.57)	0.900	50%	OR = 0.94 (0.41-2.15)	0.879	48.9%	OR = 0.98 (0.58-1.64)	0.936
Mean PFS, mo (range)	3.09 (2.36-3.82)	2.66 (1.98-3.34)	HR = 0.93 (0.71-1.21)	0.584	2.66 (1.39-3.93)	HR = (0.62-1.6)	1.000	2.66 (1.71-3.62)	HR = 0.91 (0.69-1.21)	0.519
Mean OS, mo (range)	14.29 (9.64-18.95)	11.14 (7.4-14.9)	HR = 0.93 (0.68-1.29)	0.682	13.04 (7.71-18.37)	HR = 1.14 (0.64-2)	0.660	10.97 (4.74-17.21)	HR = 0.89 (0.62-1.24)	0.465
PFS >6 mo	30.2%	25.8%	OR = 1.25 (0.73-2.11)	0.417	25.9%	OR = 1.24 (0.49-3.12)	0.649	25.8%	OR = 1.25 (0.7-22.1)	0.451
PFS >12 mo	12.3%	11.7%	OR = 1.07 (0.52-2.21)	0.863	14.8%	OR = 0.81 (0.25-2.58)	0.722	10.8%	OR = 1.17 (0.52-2.62)	0.704

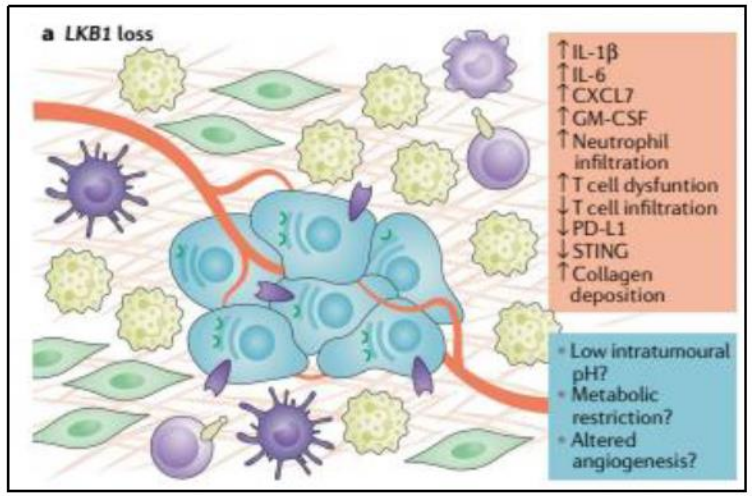
OR, odds ratio; HR, hazard ratio; CI, confidence interval; ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

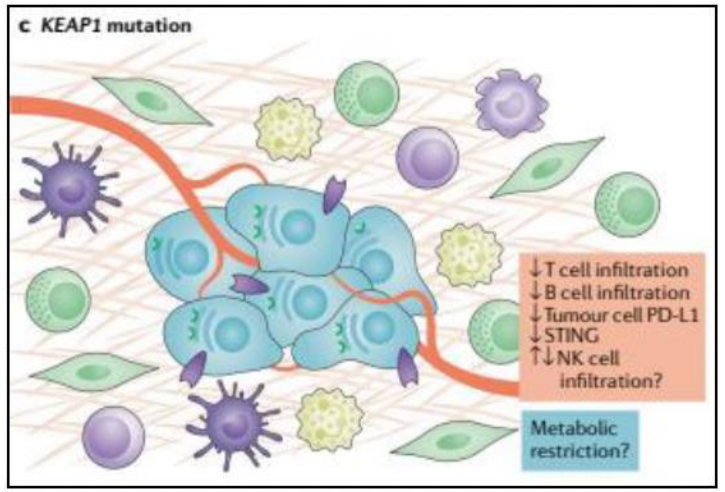
Jeanson et al, Clin Cancer Rev 2019

KRAS NSCLC: Inmunosuppresive TME



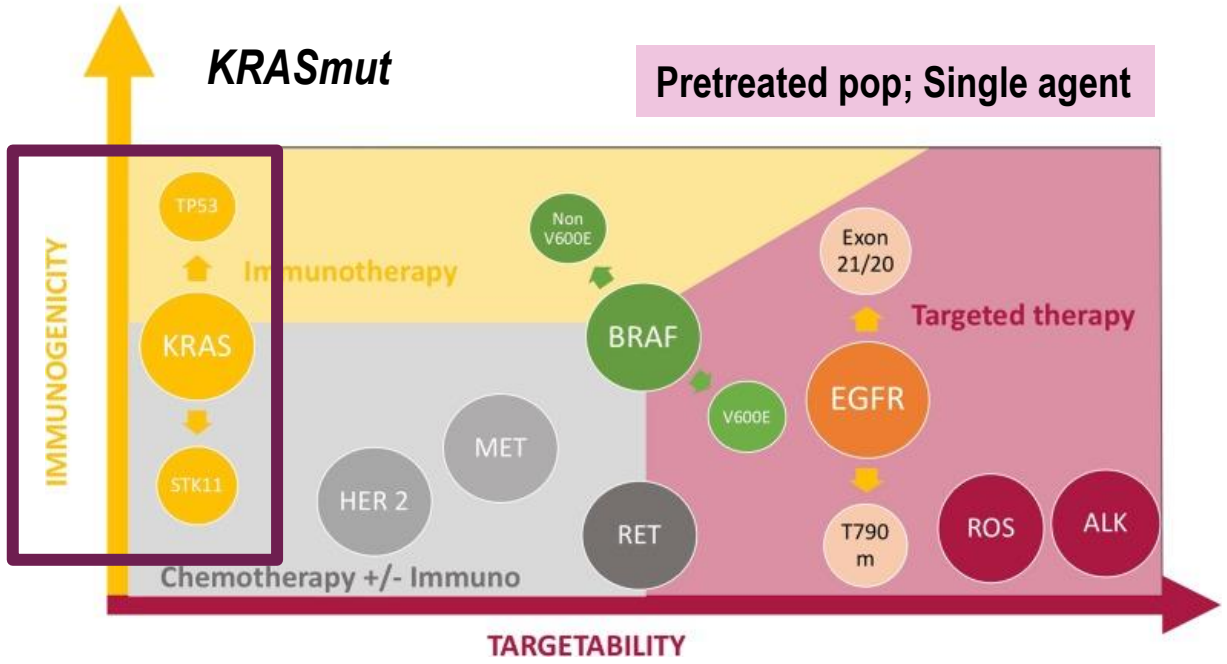
Co-occurring STK11/KEAP1 mutations



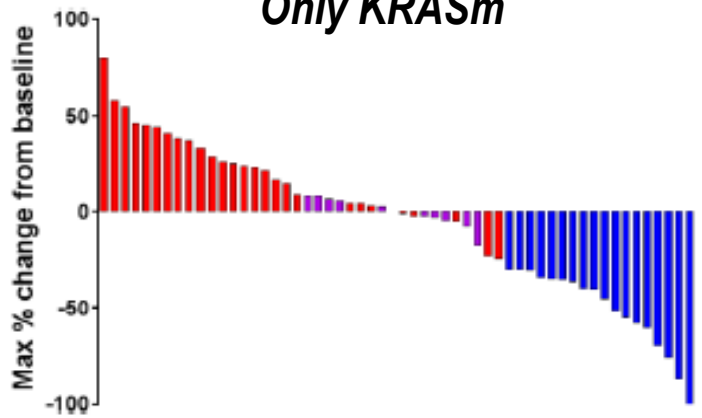


Skoulidis F. Nat Rev Cancer. 2019.

KRAS mutation: Immunotherapy outcomes

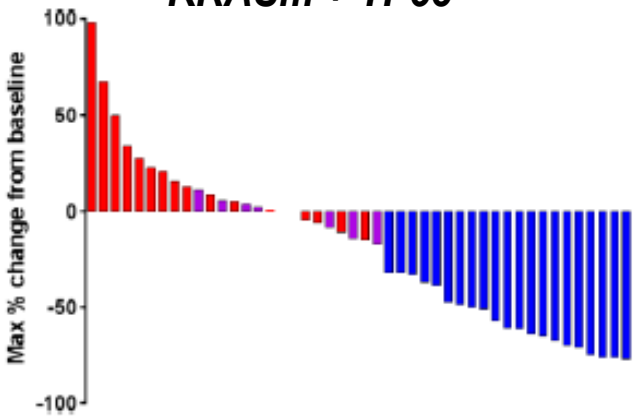


Only KRASm



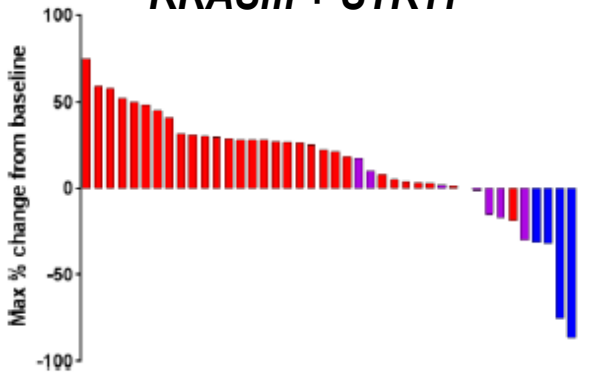
Co-Mutations

KRASm + TP53



C.

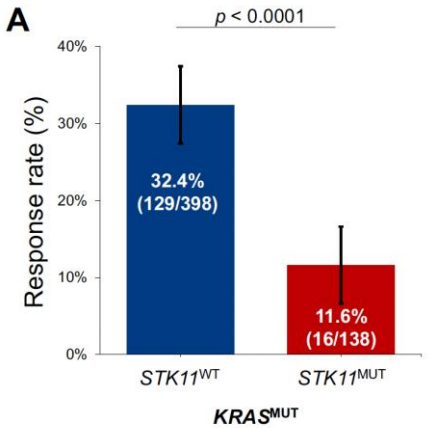
KRASm + STK11

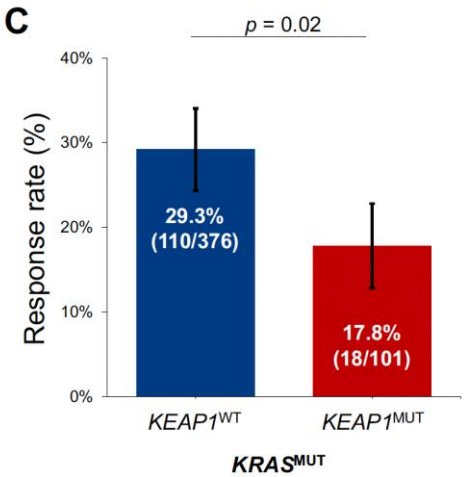


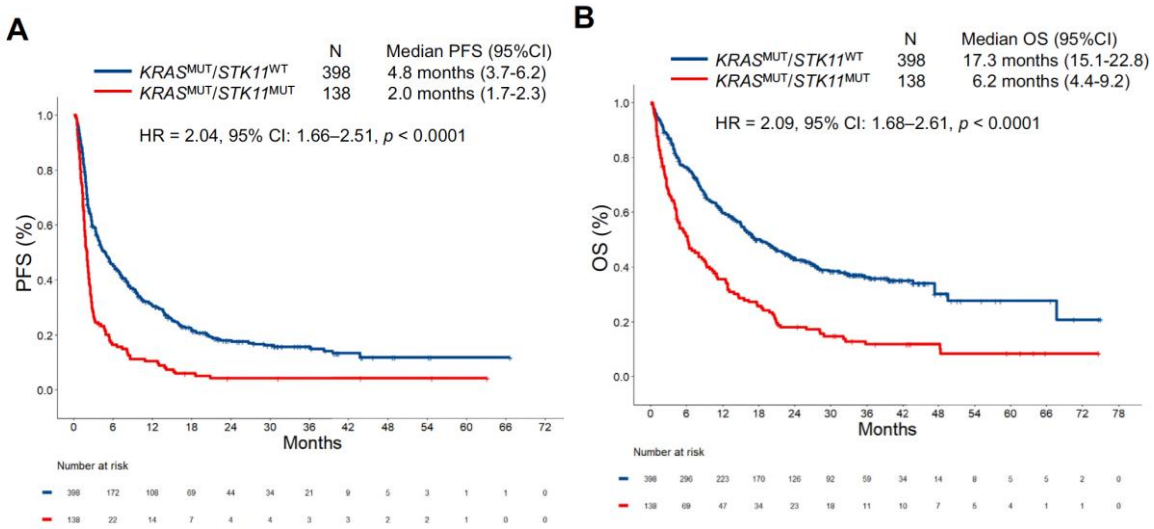
Mhanna et al, Current Treat Options Oncol 2019;
Skoulidis, Cancer Discovery 2018

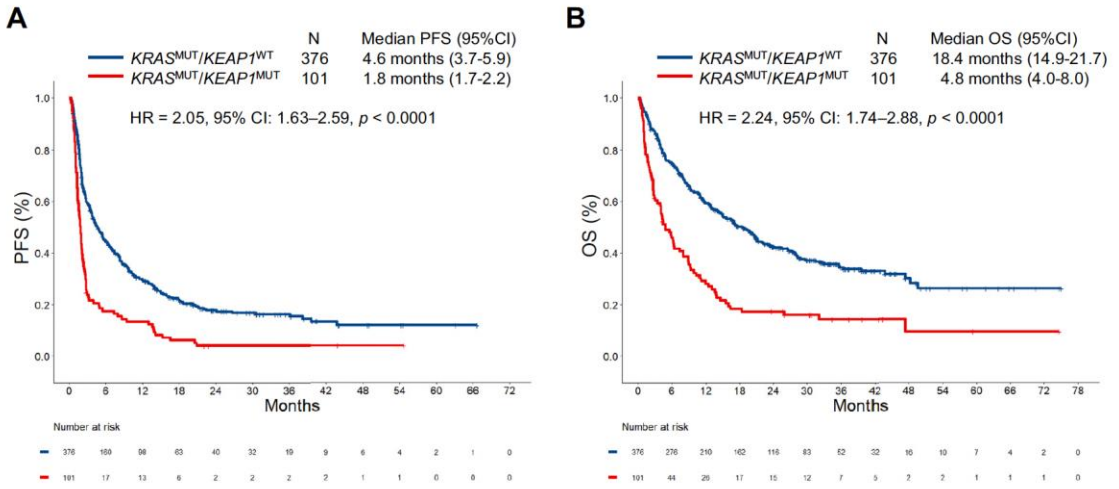
STK11/KRAS mut, *KEAP1/KRAS* mut: Immunotherapy outcomes

Pretreated pop; Single agent







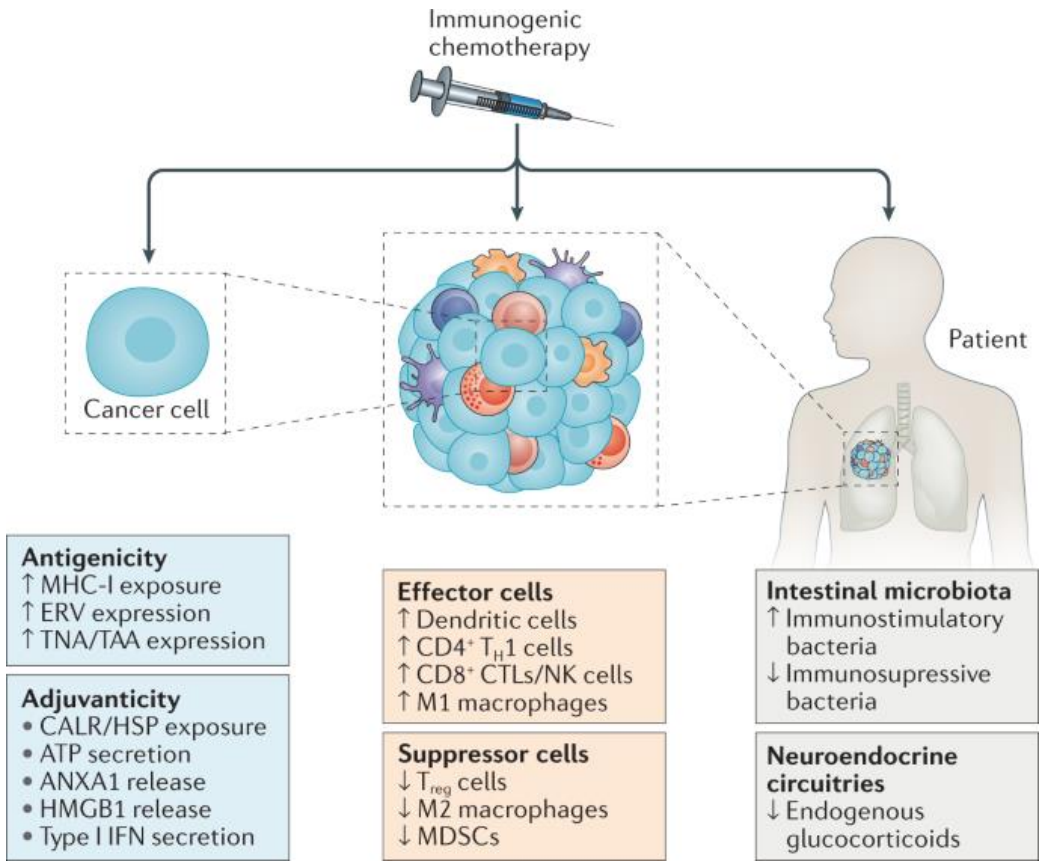


Ricciuti et al JTO 2021

KRAS mutation: Impact on outcomes upfront

Upfront; Combinations

Chemotherapy



Different Treatment options

Dr. Laura Mezquita

Galluzzi L et al, Nature Reviews Clin Oncol 2020

KRAS mutation: Chemo + Immuno outcomes

Upfront; Combinations

KRAS in KN-189

- **289 (47% of the overall population) patients pts had evaluable WES data for**
  - *KRAS* status
  - Tumor mutational burden (TMB)

→ **89 (31%) had *KRAS* mutation**
→ **37 (13%) had *KRAS* G12C mutation**

  - ↑ PD-L1 TPS (median 30% vs 5% WT)
  - ↑ TMB (median 204 mut/exome vs. 141 WT)

Outcomes: No significant differences

Empty Cell	With Any KRAS Mutation		With KRAS G12C Mutation		Without Any KRAS Mutation	
Empty Cell	Pembro + Chemo (N = 59)	Placebo + Chemo (N = 30)	Pembro + Chemo (N = 26)	Placebo + Chemo (N = 11)	Pembro + Chemo (N = 145)	Placebo + Chemo (N = 55)
ORR, % (95% CI)	40.7	26.7	50.0	18.2	47.6	10.9
	(28.1-54.3)	(12.3-45.9)	(29.9-70.1)	(2.3-51.8)	(39.2-56.0)	(4.1-22.3)
PFS, median, mo (95% CI)	9 (7-14)	5 (5-9)	11 (6-18)	5 (5-NR)	9 (7-14)	5 (4-5)
PFS, HR (95% CI)	0.47 (0.29-.77)		0.48 (0.22-.06)		0.40 (0.29-.57)	
OS, median, mo (95% CI)	21 (16-NR)	14 (8-NR)	18 (11-NR)	25 (8-NR)	23 (19-NR)	9 (7-17)
OS, HR (95% CI)	0.79 (0.45-1.38)		1.14 (0.45-2.92)		0.55 (0.37-0.81)	

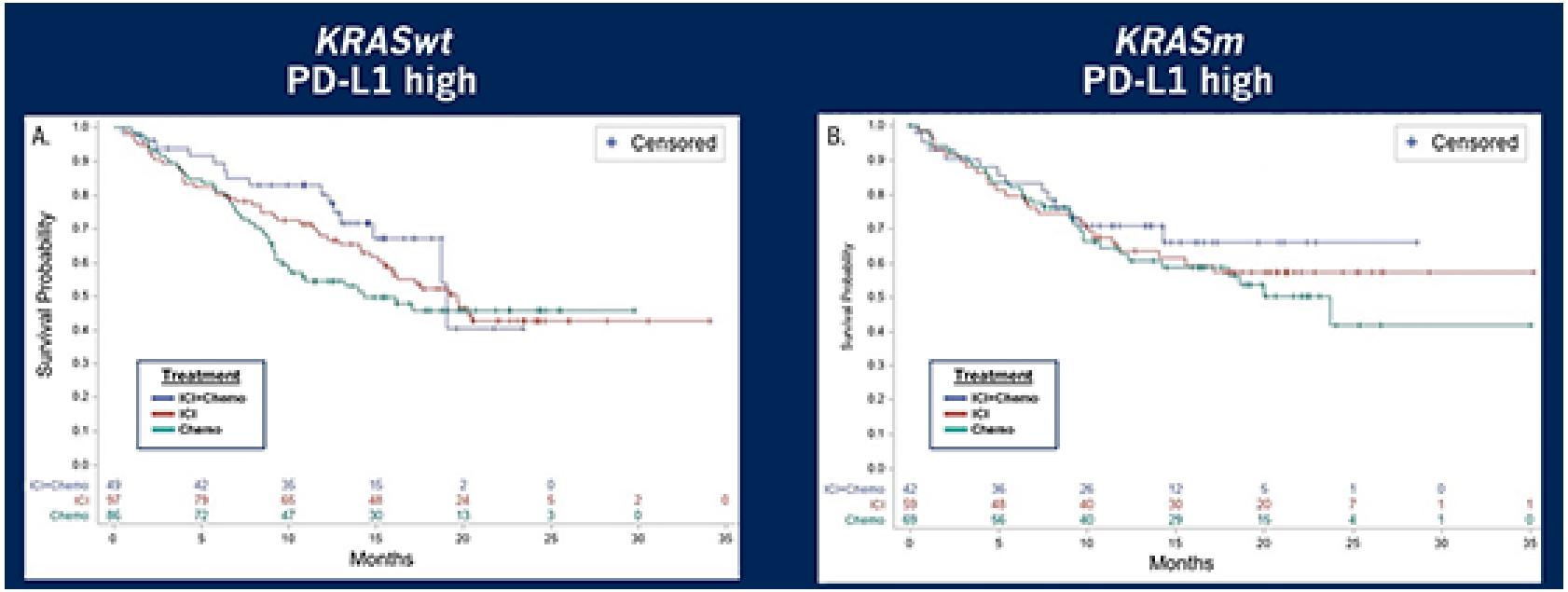
Gadgeel, ESMO 2019

KRAS mutation: Chemo + Immuno outcomes

Upfront; Combinations

KRAS in KN-042; KN-189; FDA-pooled

Treatment type	Study	Objective response rate		Median overall survival (mo)	
		*KRAS*m	*KRAS*wt	*KRAS*m	*KRAS*wt
Immunotherapy monotherapy	KN-042[8,a]	57%	29%	28 mo	15 mo
	FDA-pooled[10]	37%	33%	16 mo	16 mo
Chemoimmunotherapy	KN-189[9]	41%	48%	21 mo	23 mo
	FDA-pooled[10]	46%	51%	22 mo	19 mo



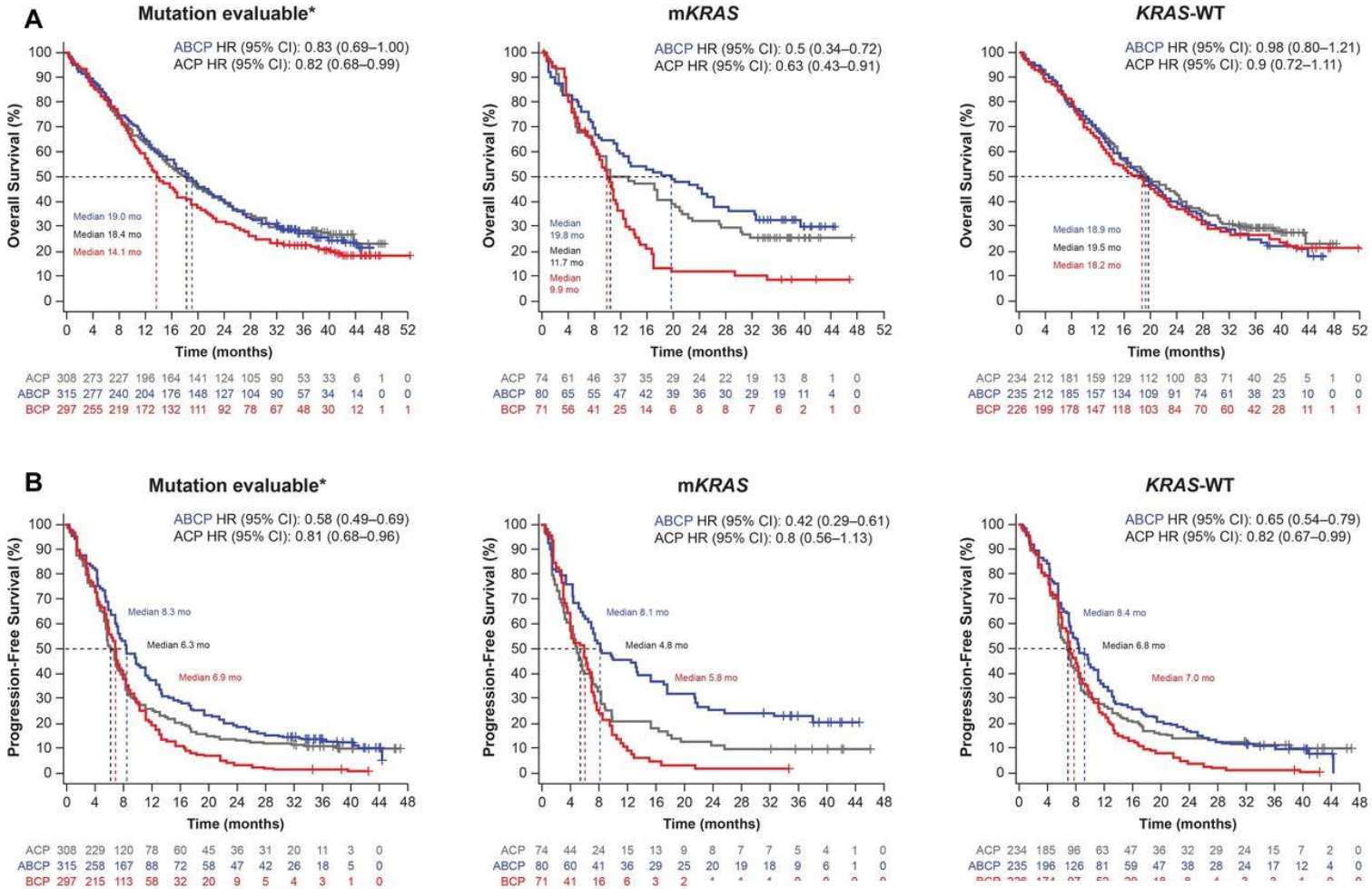
Sun, ; Marmarelis and Aggarwal, ASCO Daily News Sep 2022

KRAS mutation: Chemo + Immuno outcomes

Upfront; Combinations

KRAS in IMPOWER 150

A post hoc analysis in patients with *KRAS*, *STK11* and *KEAP1* mut.



Dr. Laura Mezquita

West et al, ESMO 2020

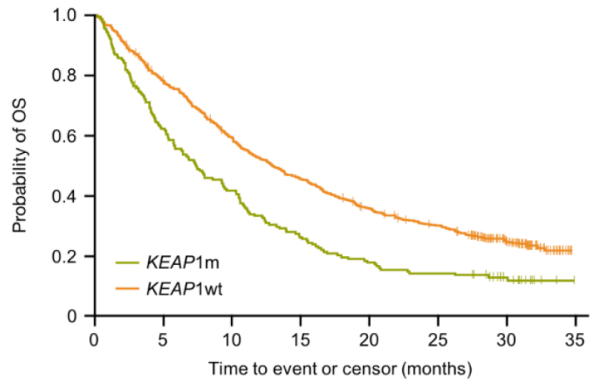
STK11/KEAP1 + *KRAS* mut.: Impact on outcomes upfront

KRAS in MYSTIC

Upfront; Combinations

*KEAP1*m vs *KEAP1*wt

	*KEAP1*m (n=170)	*KEAP1*wt (n=773)
mOS, months (95% CI)	7.4 (5.7–9.4)	12.9 (11.4–14.5)
HR (95% CI)	**1.64** (1.37–1.97)	

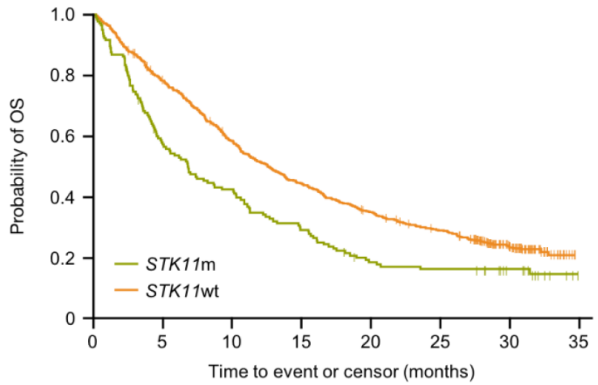


No. at risk

Mut	170	104	70	44	30	24	13	0
WT	773	592	447	345	267	220	94	0

*STK11*m vs *STK11*wt

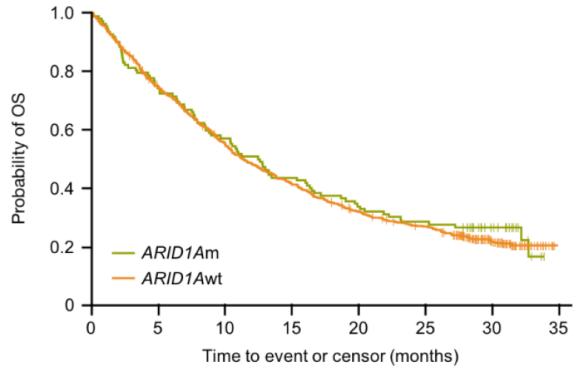
	*STK11*m (n=147)	*STK11*wt (n=796)
mOS, months (95% CI)	6.8 (4.9–10.0)	12.6 (11.1–13.8)
HR (95% CI)	**1.52** (1.25–1.85)	



	147	81	61	42	25	22	13	0
	796	615	456	347	272	222	94	0

*ARID1A*m vs *ARID1A*wt

	*ARID1A*m (n=114)	*ARID1A*wt (n=829)
mOS, months (95% CI)	12.6 (8.8–16.4)	11.4 (10.4–12.7)
HR (95% CI)	**0.94** (0.74–1.17)	



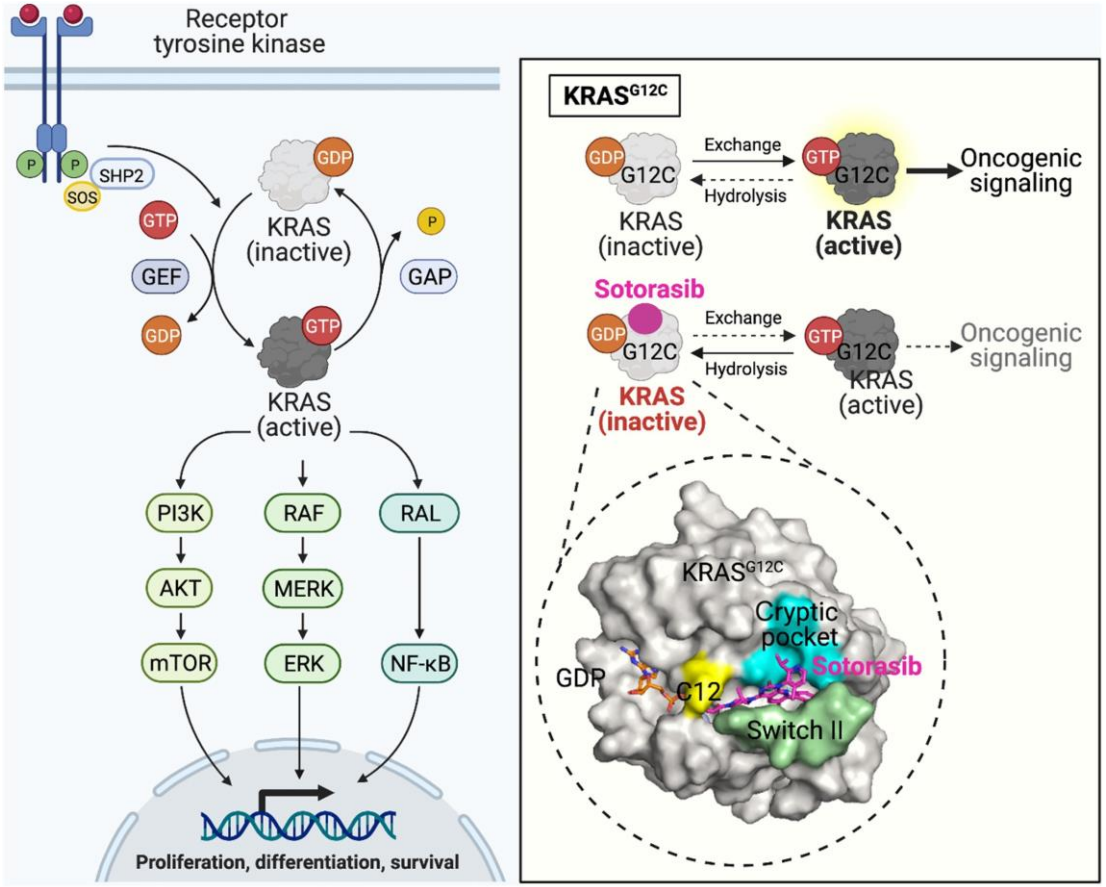
	114	83	64	49	38	32	17	0
	829	613	453	340	259	212	90	0

Rizvi, WCLC 2019

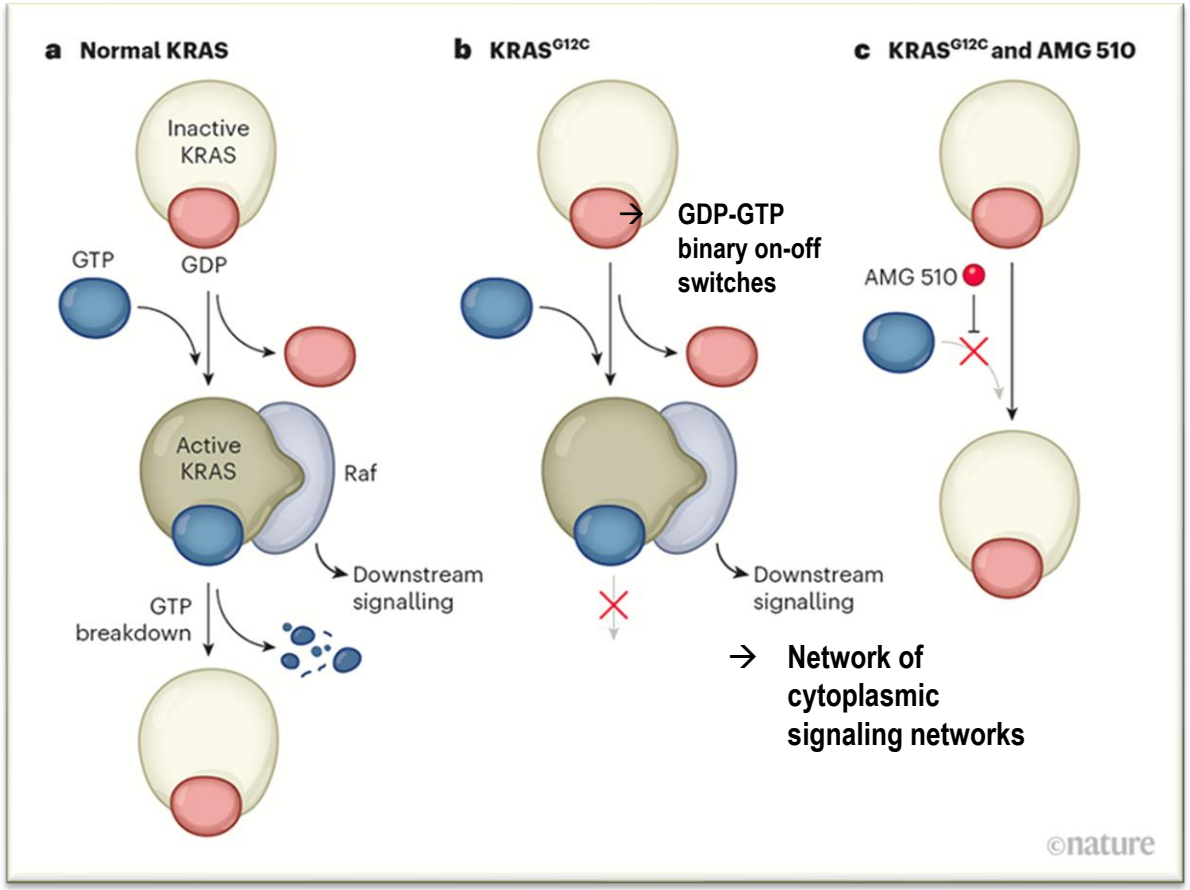
OUTLINE

1. *KRAS* mut in patients with NSCLC
2. Profile of *KRAS* mutation
3. **Therapeutic strategy for *KRAS* G12C**
   - Focused on immunotherapy
   - **Focused on targeted therapy**
4. New challenges and future perspectives
5. Take home messages

KRAS G12C covalent inhibitors in NSCLC

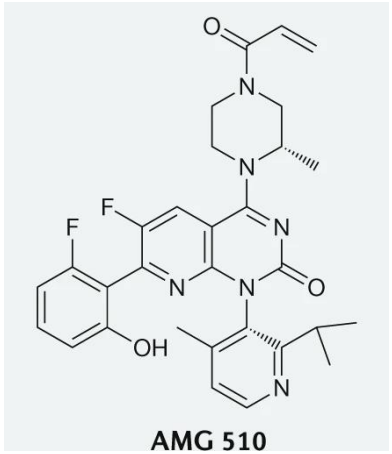


Ganguly, et al. Cell. 2020 [5]

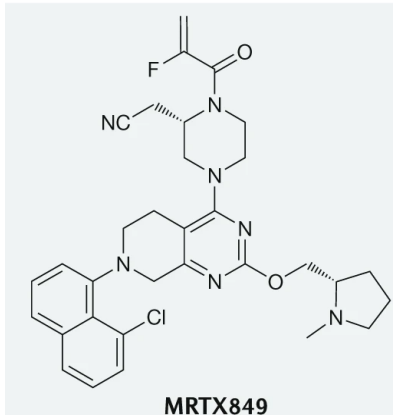


Herbs & Schlessinger, Nature 2019

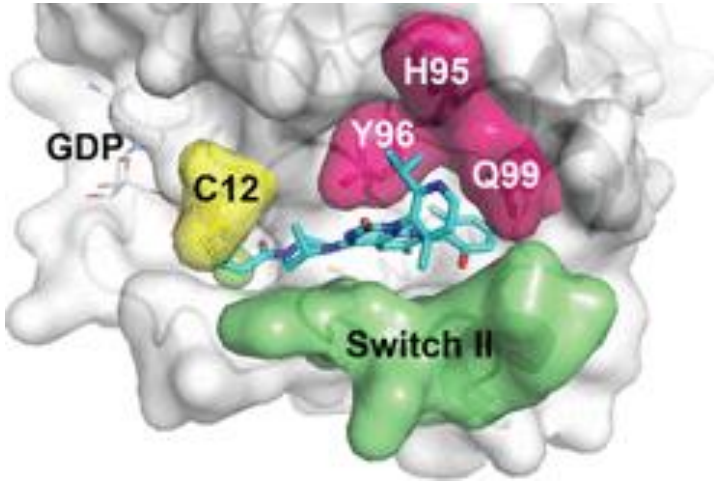
KRAS G12C covalent inhibitors

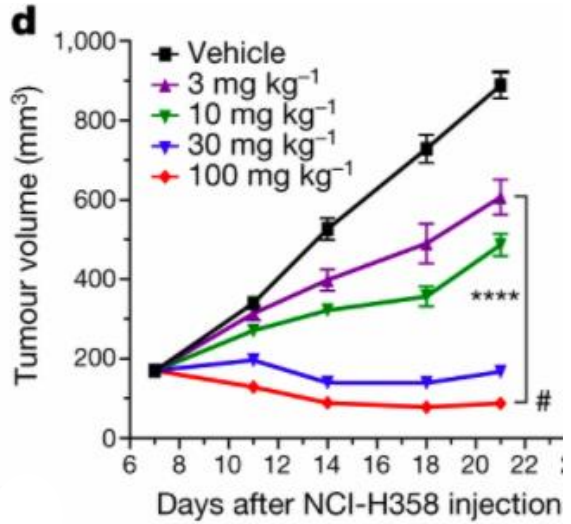


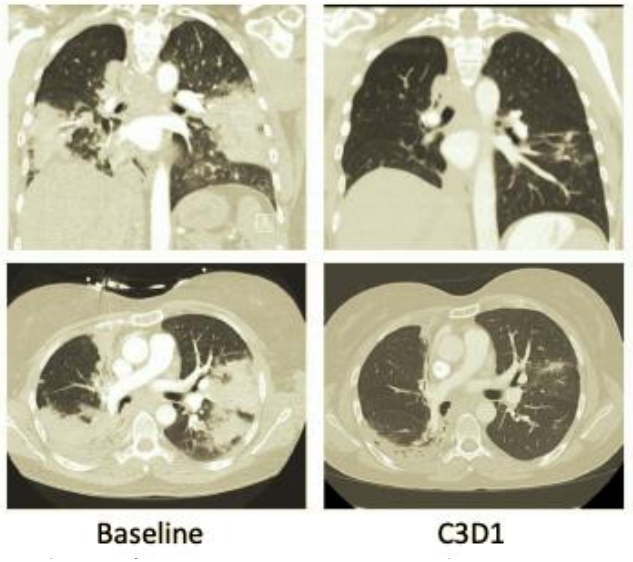
Sotorasib



Adagrasib



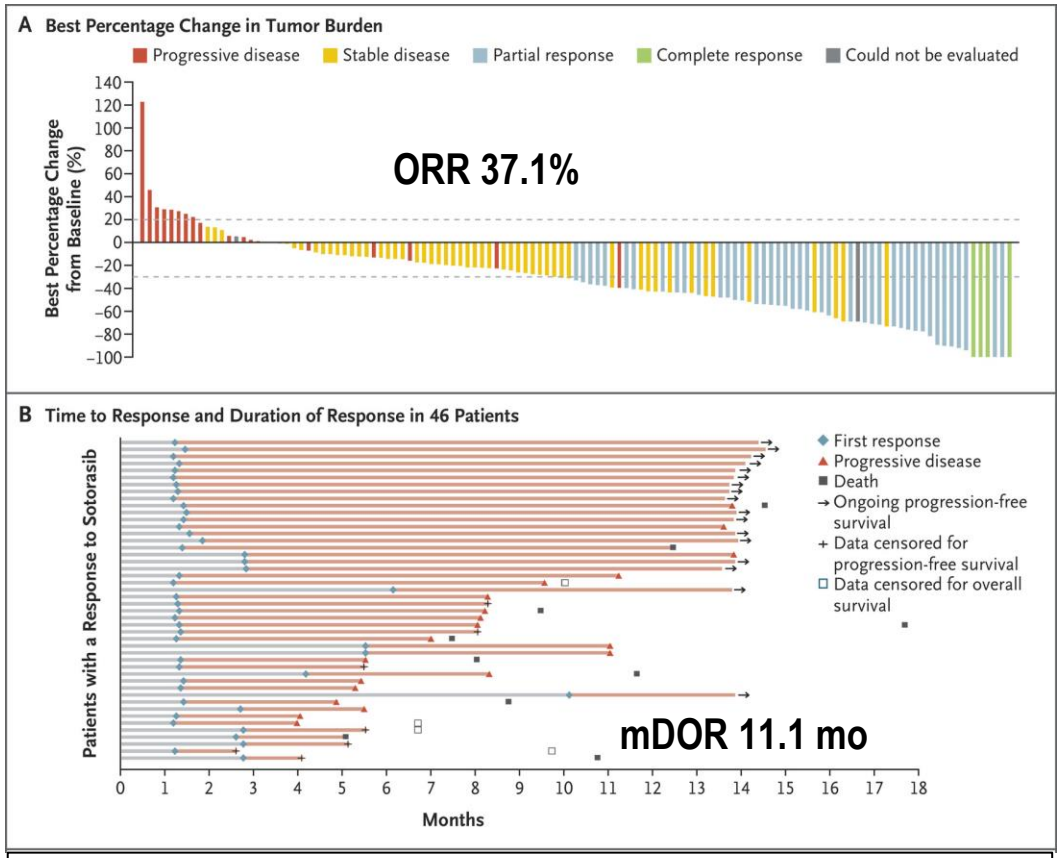




Hallin et al. Can Disc 2019, Canon et al Nature 2019

KRAS G12C covalent inhibitors in NSCLC

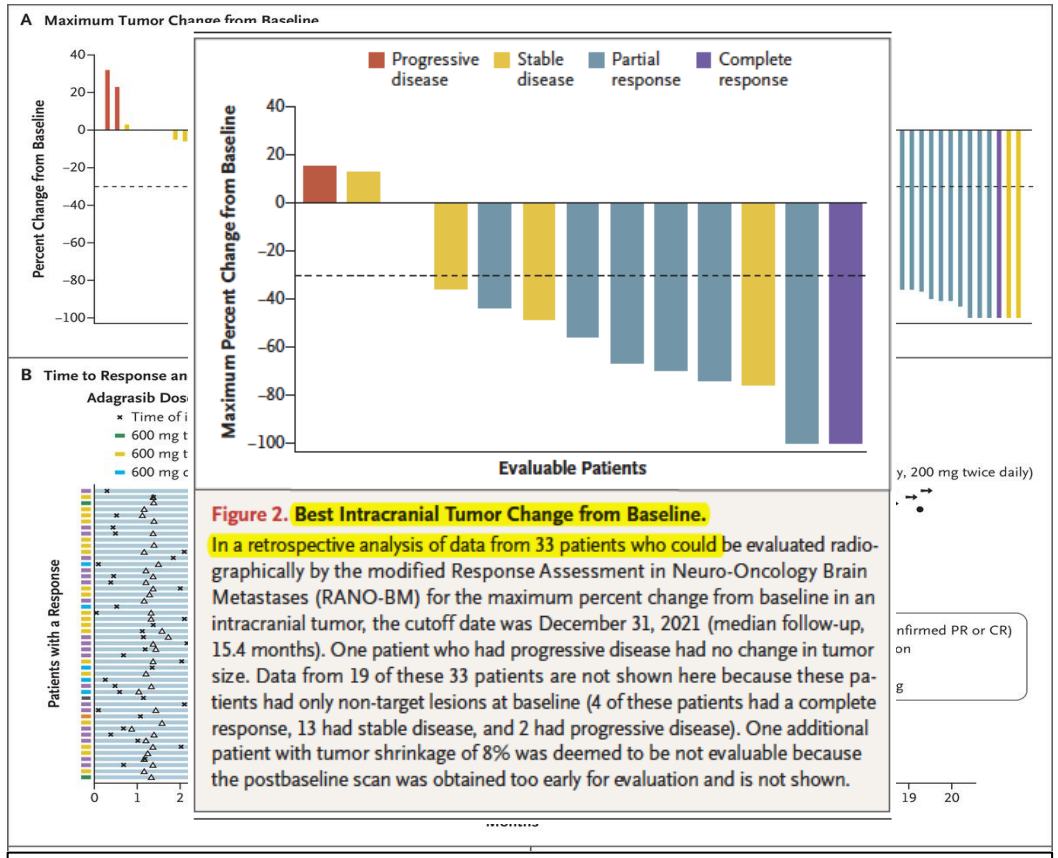
Sotorasib, CodeBreak 100



mPFS 6.8 mo; **mOS** 12.5 mo

Skoulidis, F, et al. N Engl J Med 2021

Adagrasib, *KRYSTAL-1*



mPFS 6.5 mo; **mOS** 12.6 mo

Jänne,P, et al. N Eng J Med 2022, Sabari Clin Cancer Res 2022

CodeBreak 200, Ph3: Sotorasib for *KRAS* G12C NSCLC

Key eligibility criteria
- Locally advanced/unresectable or metastatic *KRAS* G12C-mutated NSCLC
- **≥ 1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor***
- **No active brain metastases**
- ECOG performance status ≤ 1

Stratification factors
- Prior lines of therapy (1 vs 2 vs > 2)
- Race (Asian vs non-Asian)
- History of CNS involvement (yes vs no)

Randomisation 1:1 (N = 345)

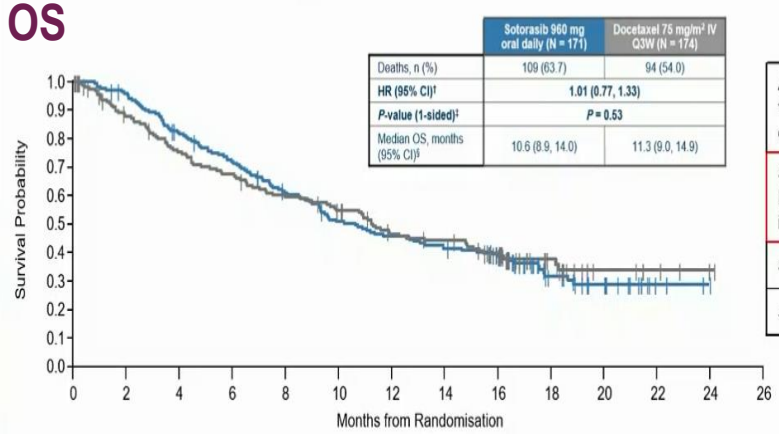
- Sotorasib 960 mg oral daily N = 171
- Docetaxel 75 mg/m² IV Q3W N = 174

Primary Endpoint: PFS by BICR
Secondary Endpoints: Efficacy (OS†, ORR, DOR, TTR, DCR), **safety/tolerability, PRO**
ITT population analysis included all randomised patients

Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

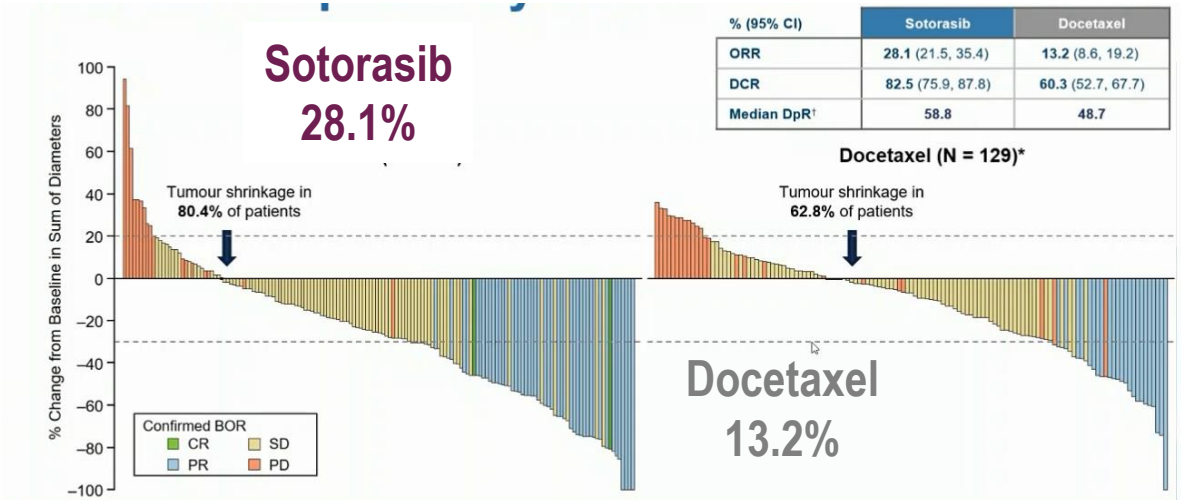
Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.

OS



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent KRAS^{G12C} inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

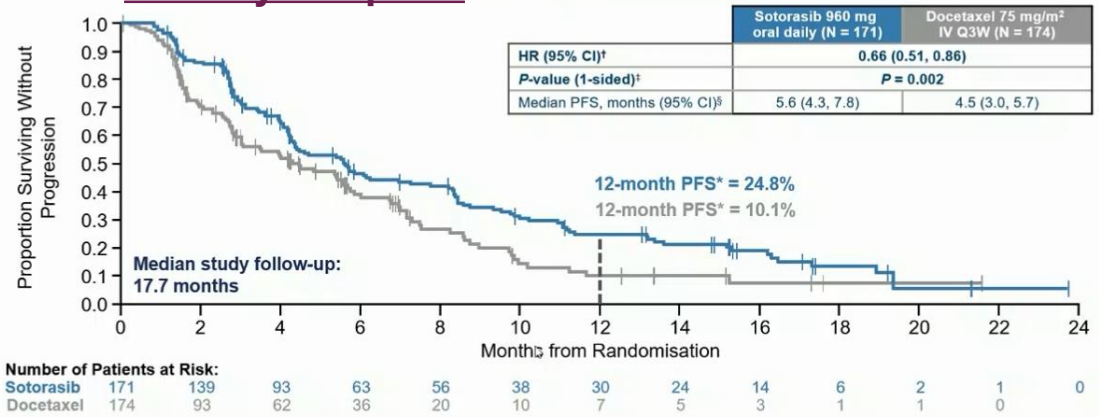


% (95% CI)	Sotorasib	Docetaxel
ORR	28.1 (21.5, 35.4)	13.2 (8.6, 19.2)
DCR	82.5 (75.9, 87.8)	60.3 (52.7, 67.7)
Median DpR†	58.8	48.7

Docetaxel (N = 129)*

Response rate was significantly higher with sotorasib versus docetaxel (*P* < 0.001)

Primary Endpoint: PFS



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

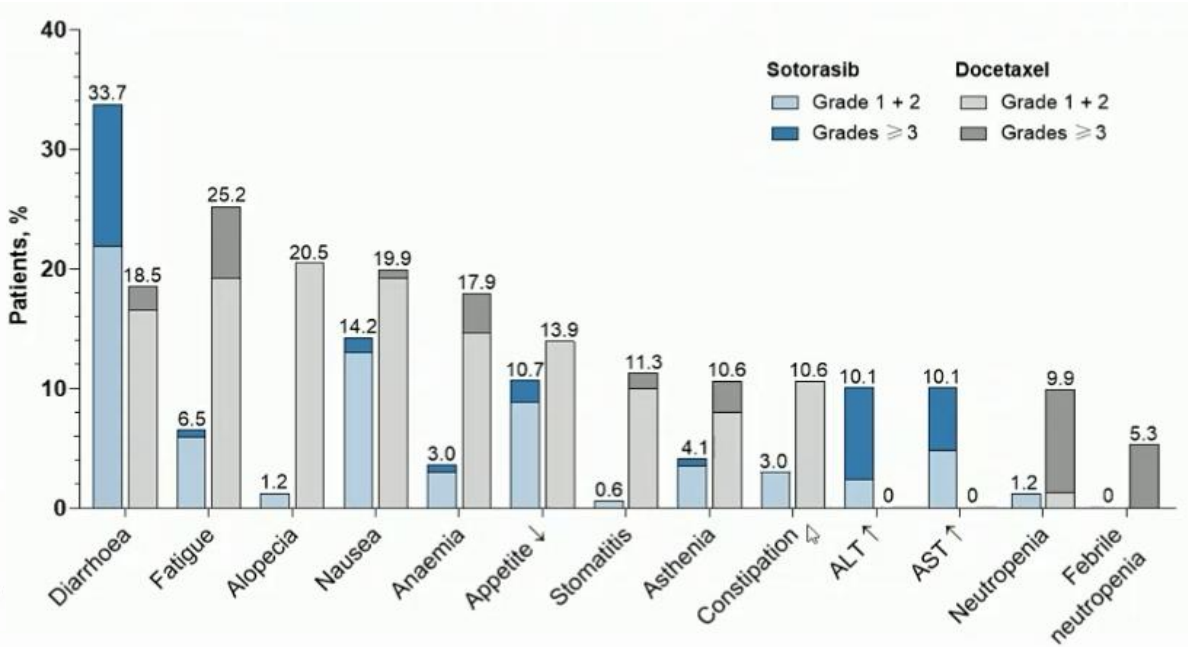
Johnson M, ESMO 2022

CodeBreaK 200, Ph3: Sotorasib for *KRAS* G12C NSCLC

	Sotorasib 960 mg oral daily (N = 169)	Docetaxel 75 mg/m² IV Q3W (N = 151)
TEAEs, n (%)	**166 (98.2)**	**148 (98.0)**
Grade ≥3	121 (71.6)	91 (60.3)
TRAEs, n (%)	**119 (70.4)**	**130 (86.1)**
Grade ≥3	56 (33.1)	61 (40.4)
Serious	18 (10.7)	34 (22.5)
Leading to dose interruption*	60 (35.5)	23 (15.2)
Leading to dose reduction†	26 (15.4)	40 (26.5)
Leading to discontinuation‡	16 (9.5)	17 (11.3)
Fatal TRAEs§, n (%)	**1 (0.6)**	**2 (1.3)**
Duration of treatment, weeks, median (range)	**20 (0.4, 101)**	**12 (3, 101)**

Sotorasib was well-tolerated with a lower incidence of grade ≥3 and serious TRAEs vs docetaxel

*For sotorasib, diarrhoea (n=22), increased ALT (n=9), and AST (n=7), and for docetaxel, fatigue and pneumonia (both n=3), hypersensitivity and myalgia (both n=2) were the most common.
†For sotorasib, diarrhoea (n=14), increased ALT (n=6), and AST (n=3), and for docetaxel, neutropenia (n=7), fatigue (n=6), febrile neutropenia, peripheral neuropathy, and asthenia (n=4 each) were the most common.
‡For sotorasib, increased ALT (n=6), blood bilirubin (n=4), AST and blood alkaline phosphatase (both n=2), and drug-induced liver injury (n=2), and for docetaxel, fatigue (n=3) and febrile neutropenia (n=2) were most common.
§Fatal TRAEs were observed in 1 patient in the sotorasib group (interstitial lung disease) and 2 patients in the docetaxel group (ileus and multiorgan failure).

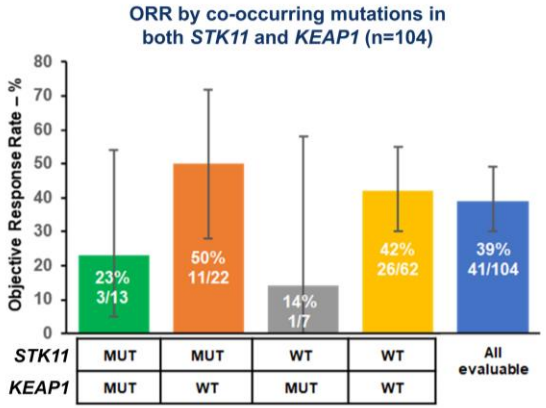


Sotorasib = SoC in pretreated population

Johnson M, ESMO 2022

Co-occurring mutations: KRAS G12C inhibitors

Sotorasib



PFS and OS by co-occurring mutations in both *STK11* and *KEAP1* (n=104)

STK11 status	*KEAP1* status	n	mPFS month (95% CI)	mOS month (95% CI)
MUT	MUT	13	2.6 (1.4, 11.1)	4.8 (2.1, 10.8)
MUT	WT	22	11.0 (2.8, NE)	15.3 (4.8, NE)
WT	MUT	7	5.5 (0, 7.0)	7.5 (0, NE)
WT	WT	62	6.8 (4.0, 11.0)	NE (NE, NE)
All evaluable	All evaluable	104	6.3 (4.1, 8.3)	13.1 (9.5, NE)

Analyses were conducted retrospectively in patients who had available biomarker data. ORR: objective response rate; MUT: mutant; WT: wild type; mPFS: median progression-free survival; mOS: median overall survival; NE: not evaluable; CI: confidence interval.

Improved efficacy with sotorasib was seen in *STK11*-mutant group with concurrent wild-type *KEAP1*, whereas *KEAP1*-mutant groups appeared to derive less benefit, with limitations of small sample size and exploratory nature

Presented By: Ferdinandos Skoulidis, M.D., Ph.D.
Data cutoff: March 15, 2021; Median follow-up time: 15.3 months

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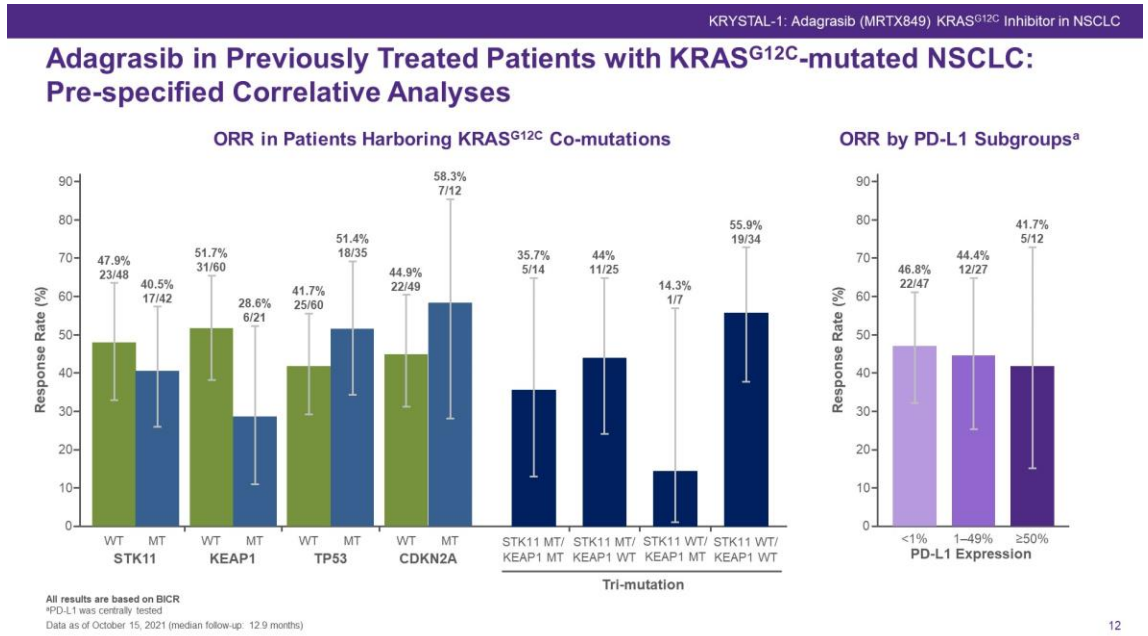
2021 ASCO ANNUAL MEETING

Adagrasib

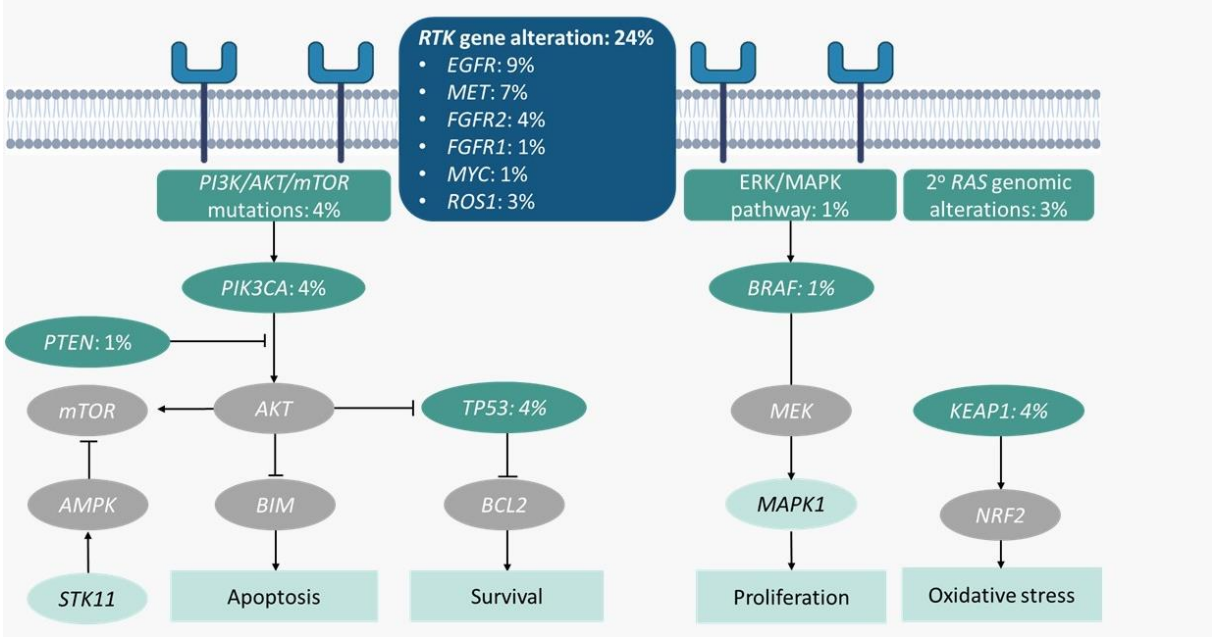


F Skoulidis et al ASCO Annual Meeting 2021
A Spria et al ASCO Annual Meeting 2022

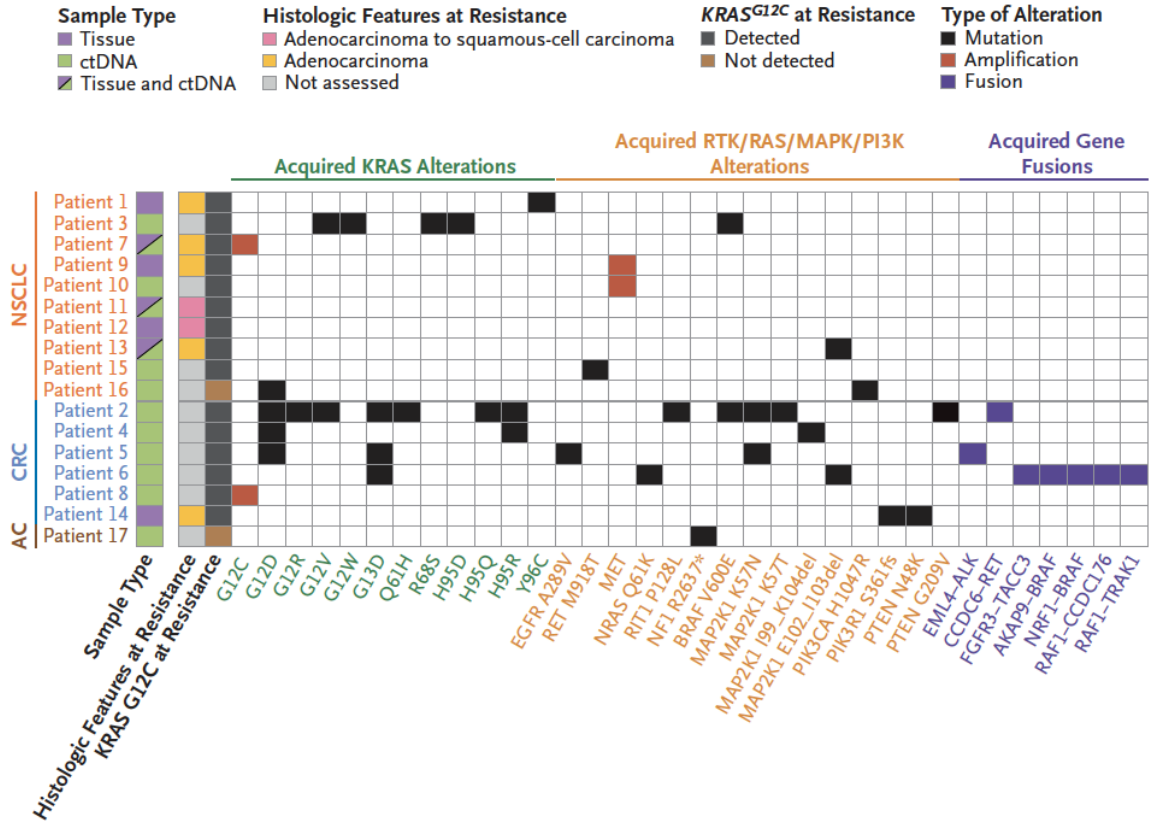
ESMO

Resistance mechanisms to KRAS G12C inhibitors

Sotorasib



Adagrasib



BT Li et al ASCO Annual Meeting 2022
Awad, MM et al. N Engl J Med 2021
Begum, et al. JTO, 2021

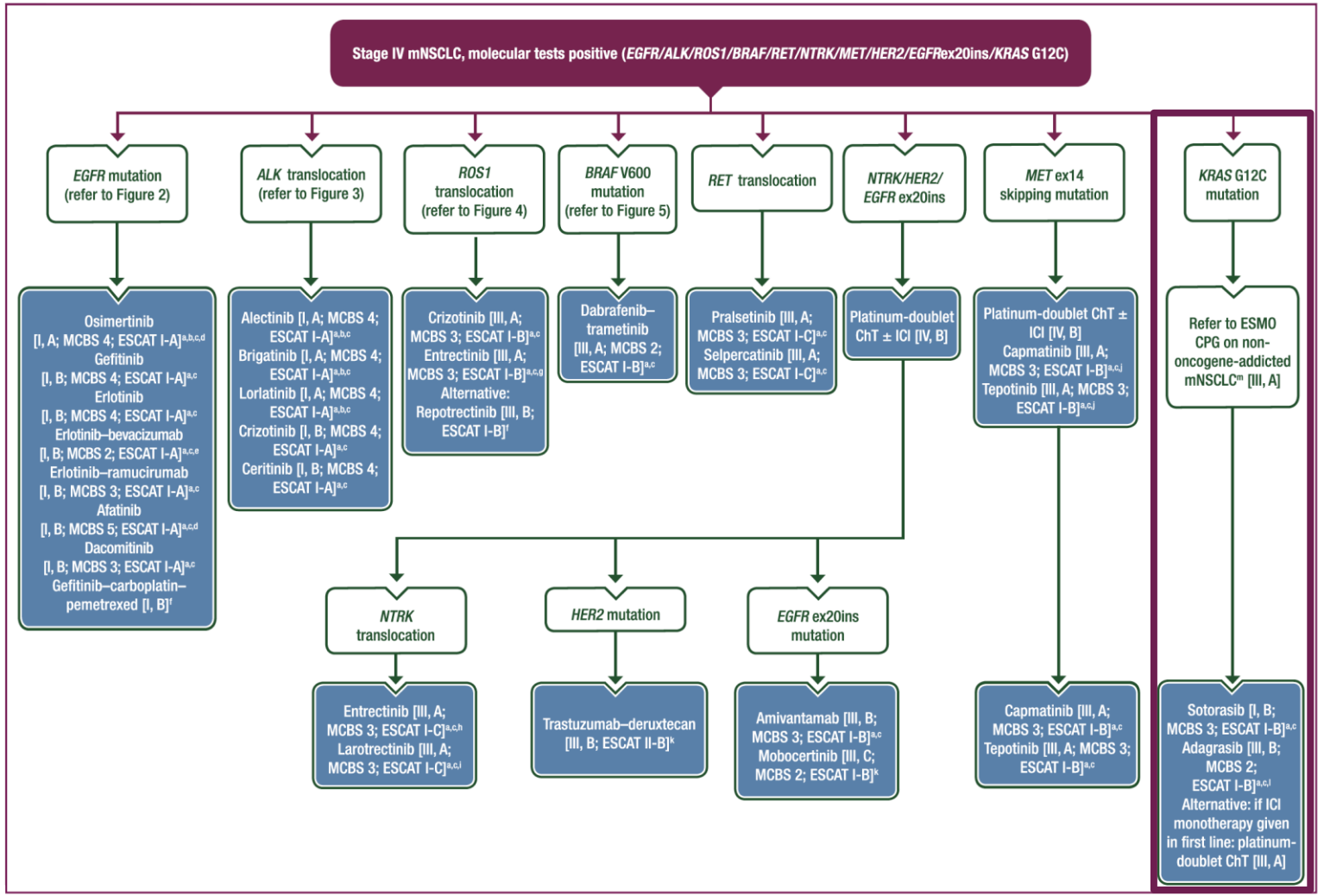
KRAS G12C covalent inhibitors combinations

Table 1. $KRAS^{G12C}$ Inhibitor Combination Strategies under Evaluation.*

Agent	Sotorasib†	Adagrasib	JDQ433	BI 1823911‡	GDC-6036§	LY3537982¶	MK-1084‖
PD-1 or PD-L1 inhibitor	AMG-404, pembrolizumab, atezolizumab**	Pembrolizumab**††‡‡	Spartalizumab,§§ tislelizumab		Atezolizumab	Pembrolizumab	Pembrolizumab
Chemotherapy	Carboplatin, pemetrexed+docetaxel**						
EGFR inhibitor	Afatinib**	Afatinib**††	Cetuximab¶¶		Cetuximab, erlotinib	Cetuximab, erlotinib	
SHP2 inhibitor	RMC-4630, TNO155	TNO155‖	TNO155		GDC-1971	TNO155	
SOS1 inhibitor		BI 1701963***		BI 1701963			
MEK or ERK inhibitor	Trametinib		Trametinib¶¶			Temuterkib	
VEGF inhibitor					Bevacizumab		
mTOR inhibitor	Everolimus						
CDK4/6 inhibitor	Palbociclib		Ribociclib¶¶			Abemaciclib	
PI3K inhibitor					Inavolisib		
Aurora kinase inhibitor						LY3295668	

Passaro, A, Peters, S. N Engl J Med 2022

ESMO guidelines, advanced *KRAS* G12C mut. NSCLC



Hendrriks, Ann Oncol 2023

OUTLINE

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2. Profile of *KRAS* mutation
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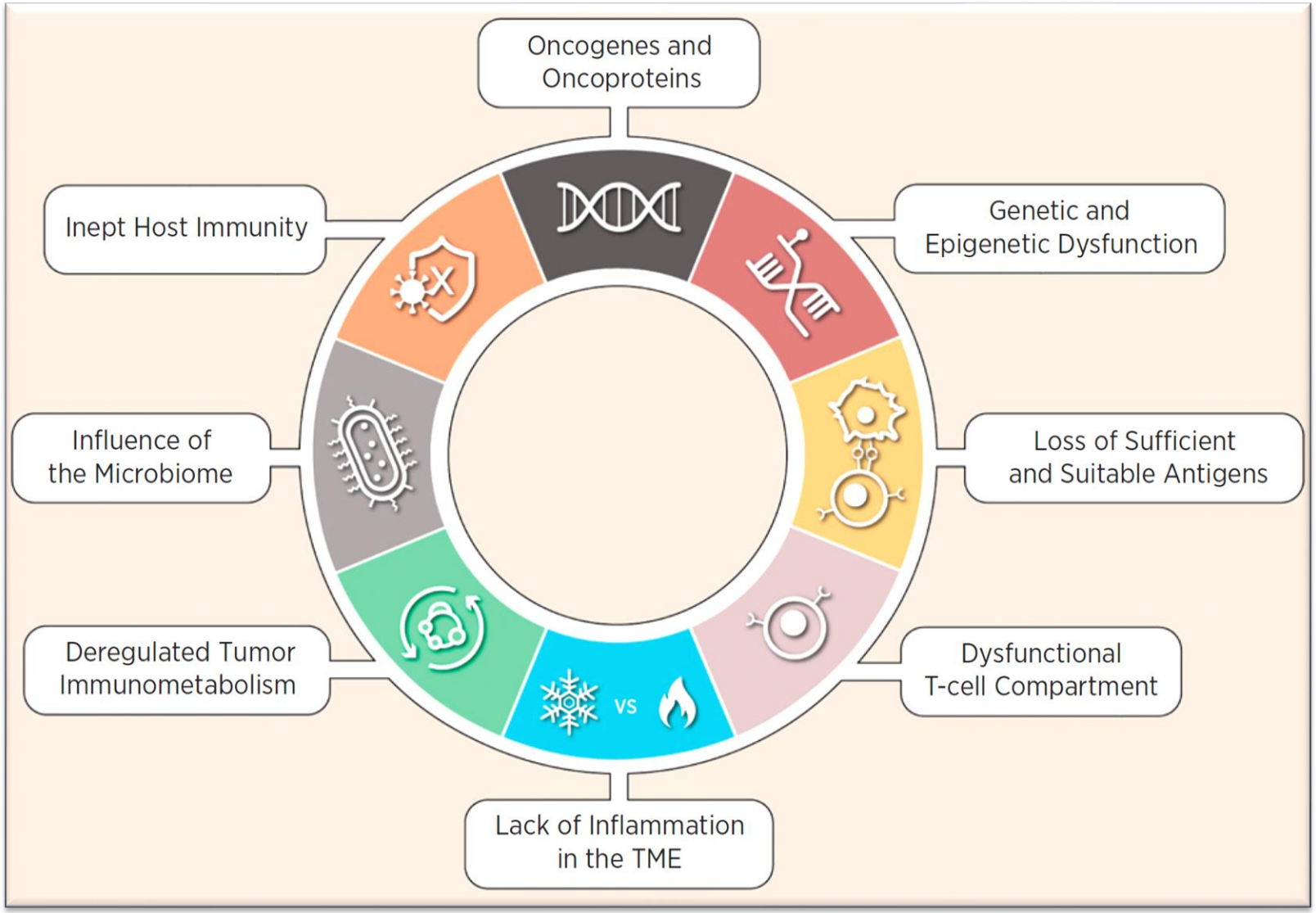
Hallmark of the Resistance to immunotherapy



Karasarides et al, Cancer Immuno Res 2022

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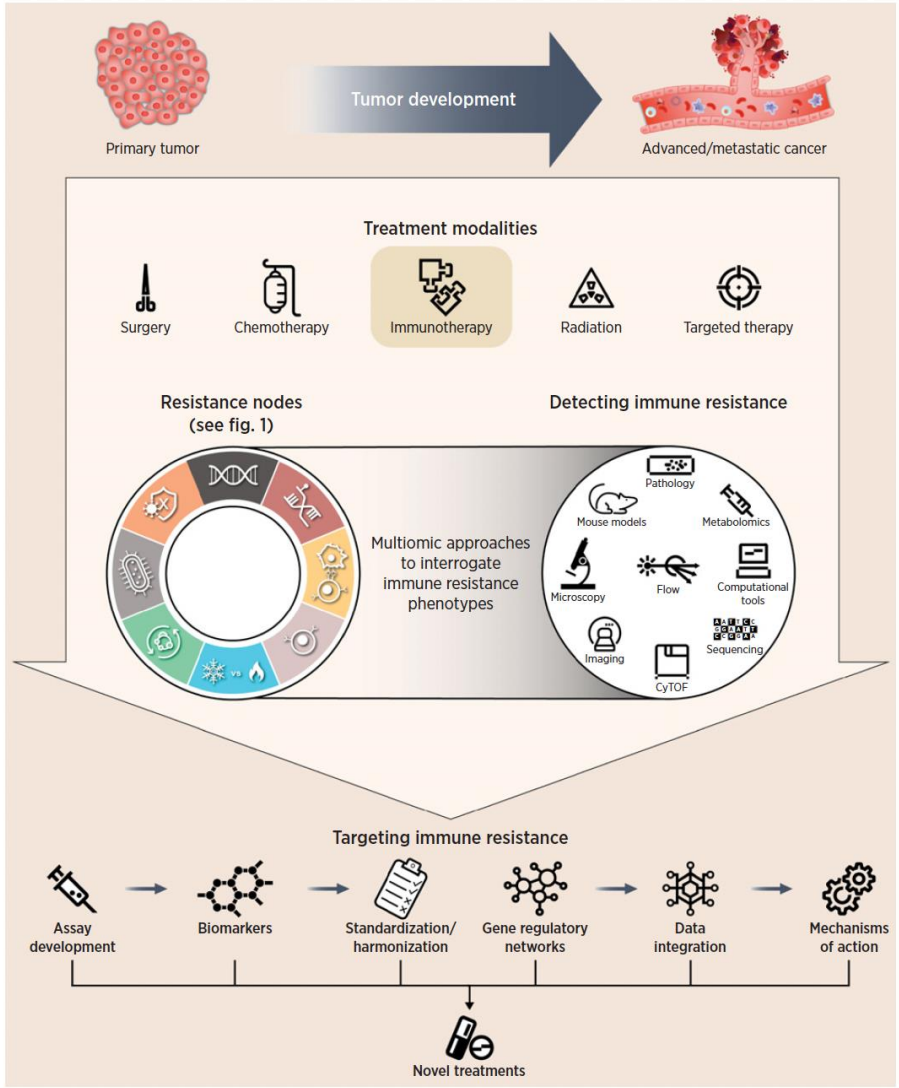


MULTIOMICS
Biomarkers of resistance

Novel drugs
to overcome resistance

Karasarides et al, Cancer Immuno Res 2022

KRAS G12C inhibitors reverse immunosuppression

→ **IMMUNOSUPPRESSION**

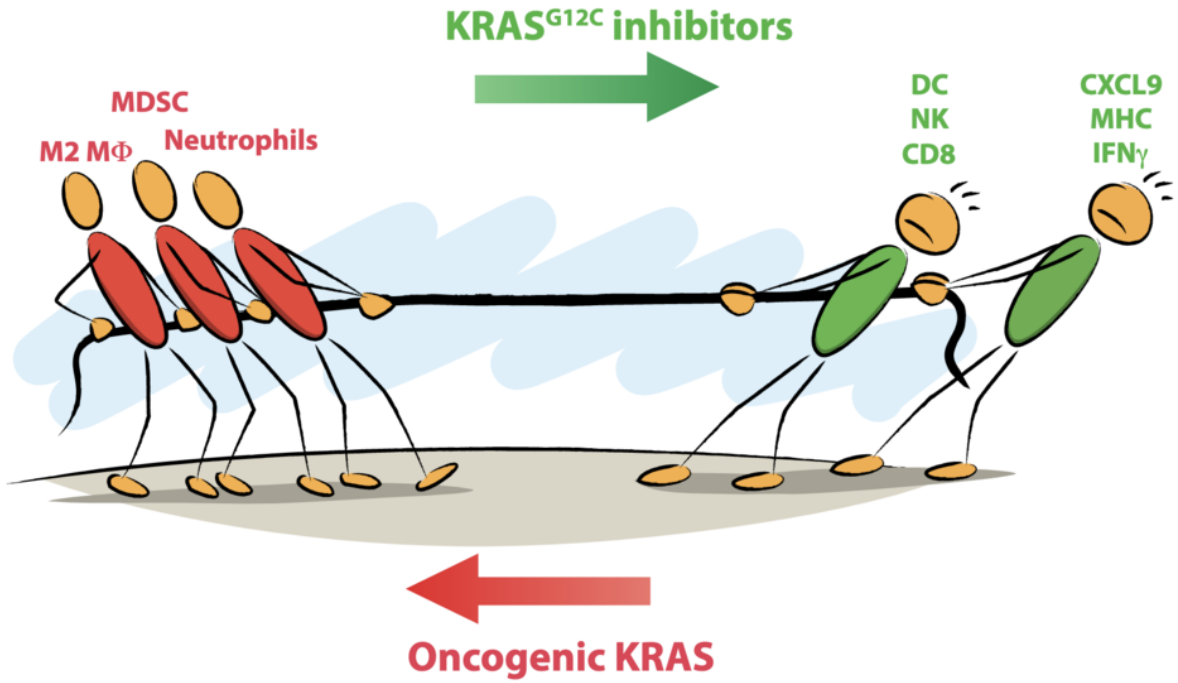
MULTIPLE mechanisms, including:

- Driving the expression of **myeloid cells**
- Inhibition of **antigen presentation**
- Inhibition of **tumour-intrinsic interferon** (IFN) signalling

→ **KRAS^{G12C} inhibition reversed KRAS-mediated immunosuppression remodelling the TME**

- ↓ **monocytes & neutrophils** infiltration
- ↑ **T cells** with improved cytotoxic functions
- ↑ **antigen uptake & T cell** secretion by dendritic cells

KRAS G12C-mediated immunosuppression is released by KRAS G12C inhibitors



Mugarza E, et al, Science Advances 2022; Boumelha J, et al; Cancer 2022

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SHP2 inhibitor	RMC-4630, TNO155	TNO155‖	TNO155		GDC-1971	TNO155	
SOS1 inhibitor		BI 1701963***		BI 1701963			
MEK or ERK inhibitor	Trametinib		Trametinib¶¶			Temuterkib	
VEGF inhibitor					Bevacizumab		
mTOR inhibitor	Everolimus						
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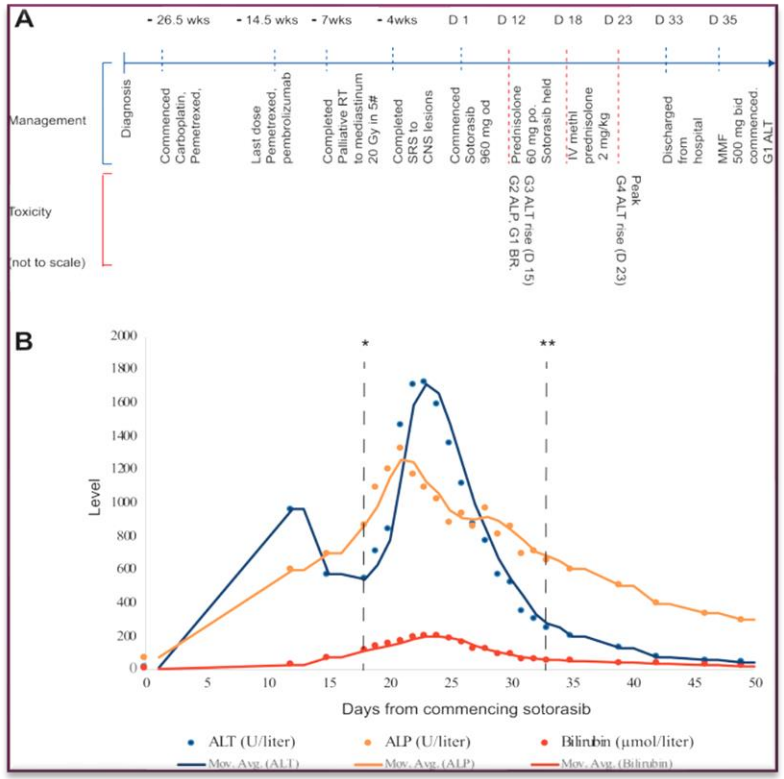
PI3K inhibitor					Inavolisib		
Aurora kinase inhibitor						LY3295668	

Passaro, A, Peters, S. N Engl J Med 2022

KRAS G12C + immunotherapy: safety profile

Severe Immune Checkpoint Inhibitor Hepatitis in KRAS G12C-Mutant NSCLC Potentially Triggered by Sotorasib: Case Report

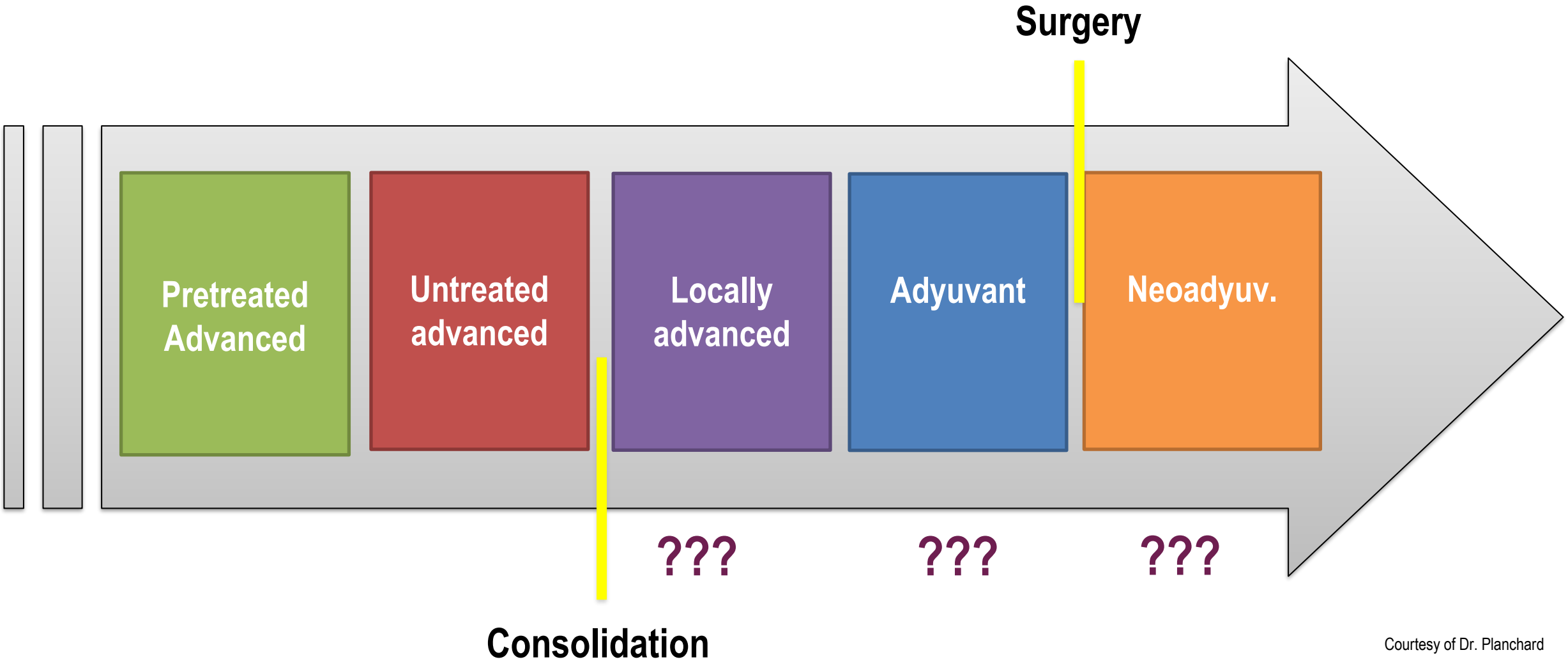


Safety profile (!!!):

- Overlap toxicities: Immunotherapy → KRASi
- Concomitant toxicities

Begum P et al, JTO Clin Res Rep 2021

Management of *KRAS* G12C
Early & locally advanced NSCLC



Courtesy of Dr. Planchard

OUTLINE

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   - Focused on targeted therapy
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TAKE HOME MESSAGES

- ***KRAS*-mutant NSCLC, most common genomic alteration in NSCLC**
- ***KRAS* mutant NSCLC ~** immunosuppresive TME & heterogeneous disease
- **Biomarkers:** PD-L1 high, TMB high, no dMMR
- **Strategy focused on immunotherapy: ICI +/- chemo outcomes:**
  - → No differences between *KRAS* pop vs WT pop
  - → Co-mutation *SKT11/KEAP1*: poor outcomes
- **Strategy focused on targeted therapies:** KRAS G12C selective inh
- **Challenges & future perspectives:**
  - → Combo with KRASi: synergies, but also safety!
  - → Understand resistance mechanisms – optimize the clinical development
- **The best strategy for *KRAS*-mutant NSCLC needs to be established**

Thanks for your attention!

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