

16th
CONGRESS
Lung **ON**
CANCER

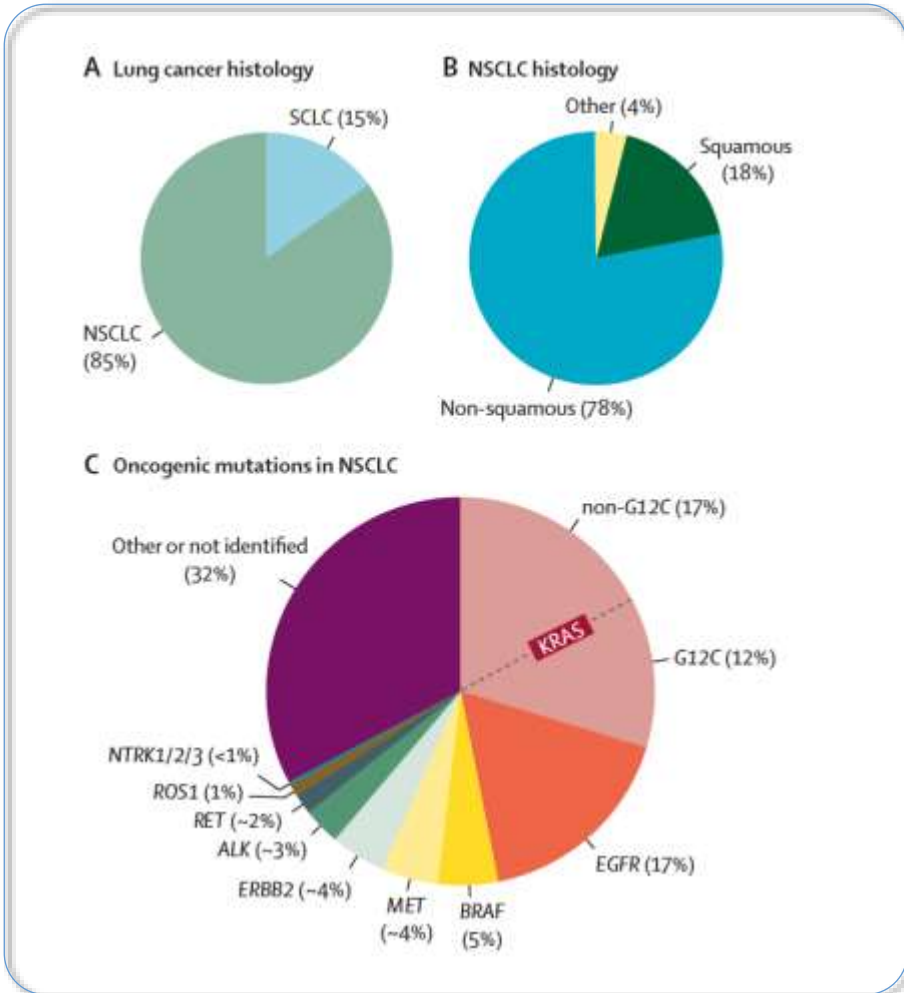
BARCELONA
27 / 28
NOVEMBER 2025

New insights in KRAS mutation

Miriam Molina-Arcas
The Francis Crick Institute

KRAS mutations in cancer

KRAS is the most common driver oncogene of NSCLC

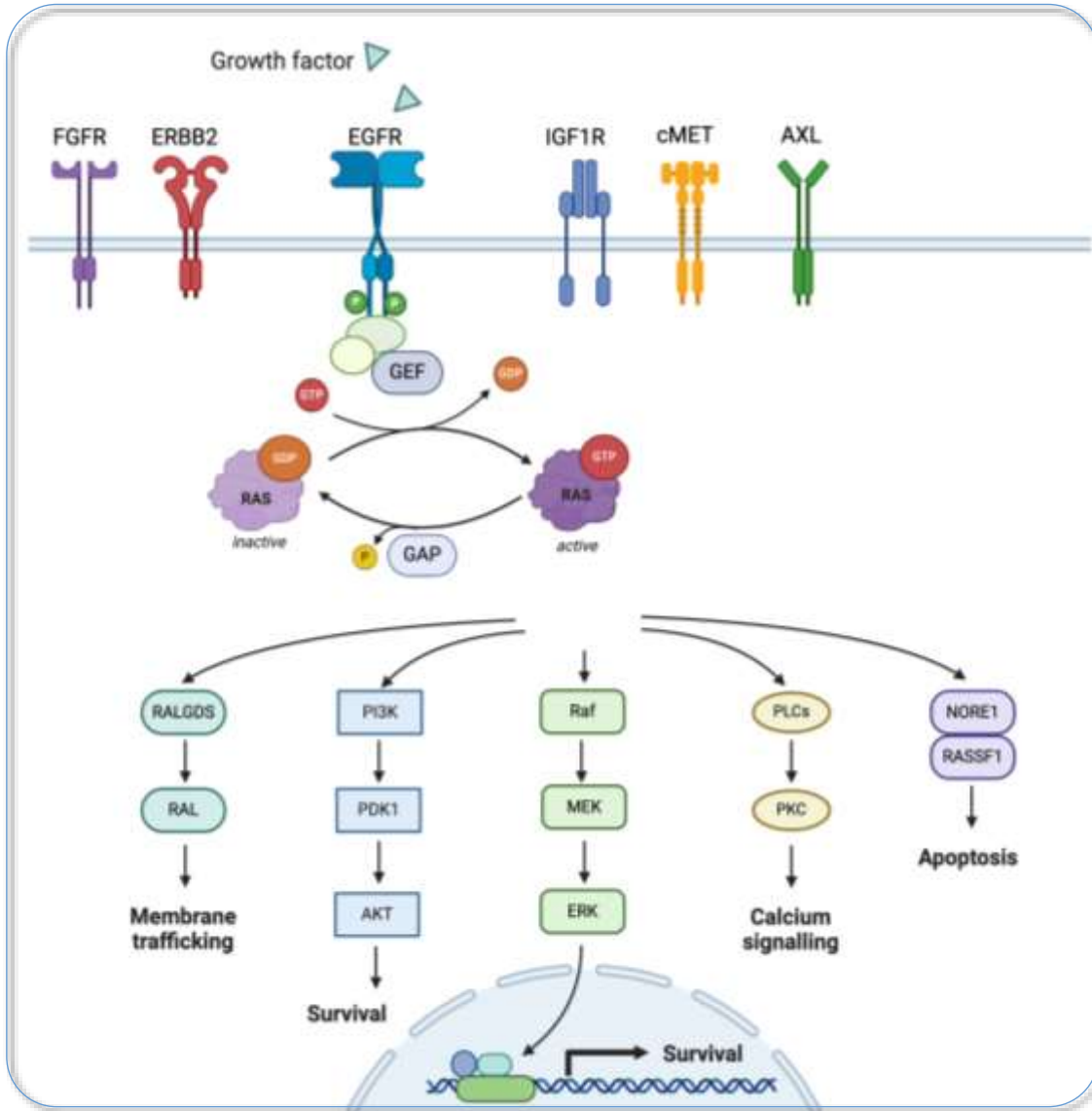


➔ *RAS biology*

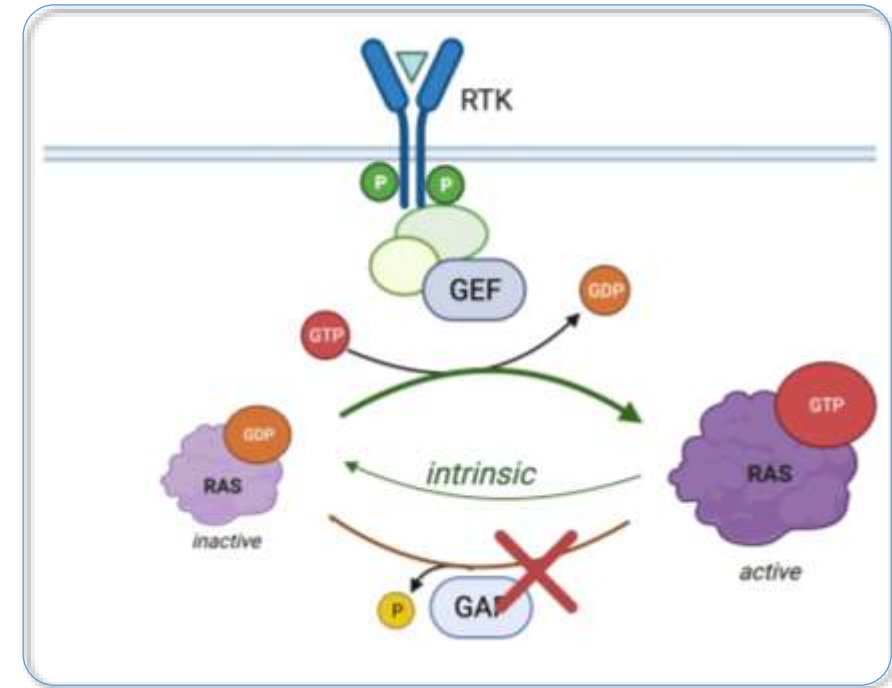
➔ *(K)RAS inhibitors*

➔ *Possible combinations: TME*

The RAS pathway



Oncogenic RAS



Oncogenic RAS mutations impair GAP protein binding and therefore GTP hydrolysis

Targeting Oncogenic (K)RAS

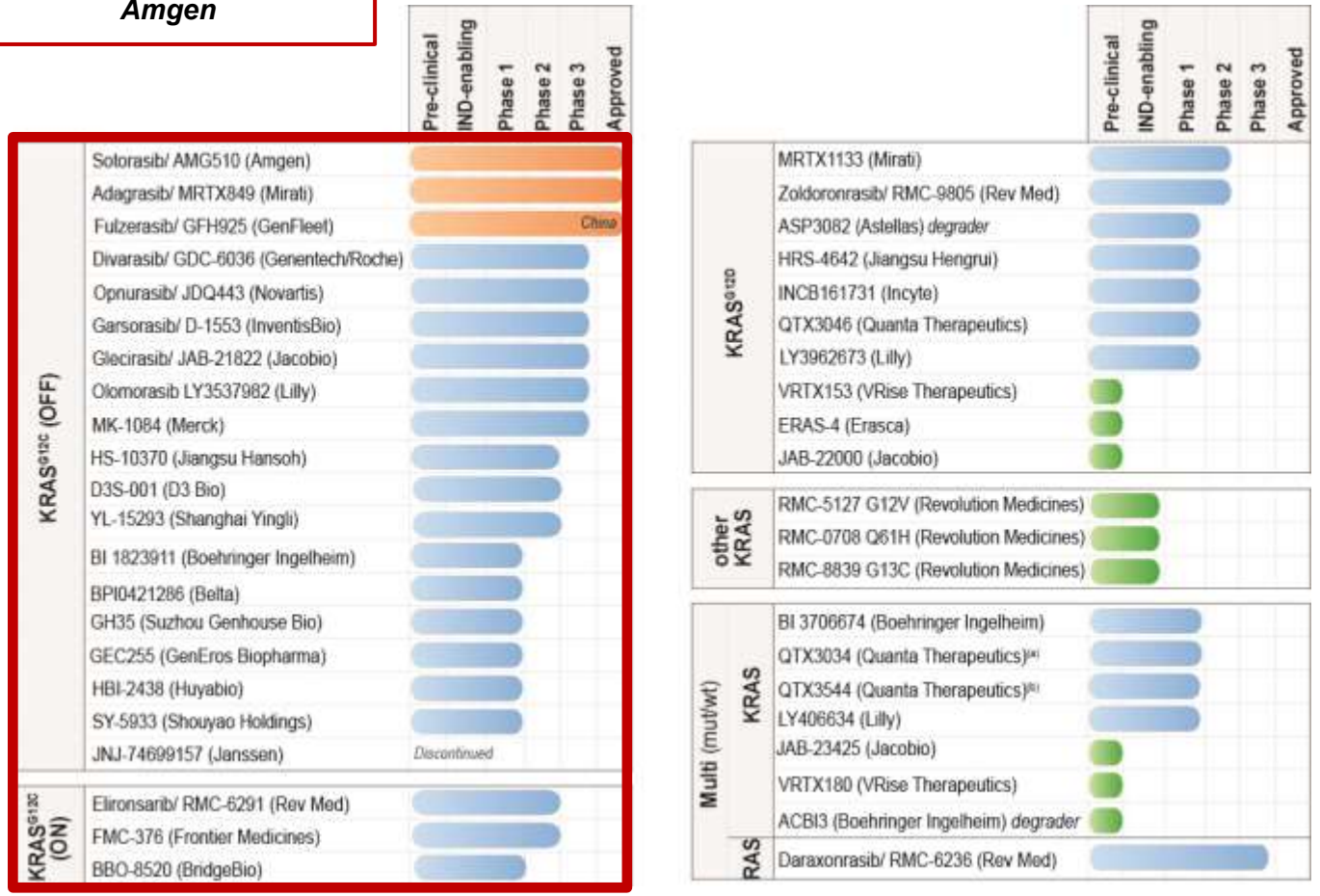


1982
KRAS cloned

2013
First inhibitor (chemistry)
Ostrem, Nature 2013

2019
First clinical trial starts
Amgen

2021
Sotorasib approval



Adapted from Molina-Arcas and Downward, Cancer Cell 2024

Targeting Oncogenic (K)RAS

1982

2013

2016

2018

2019

2020

2021

2022

2023

2024

KRAS cloned

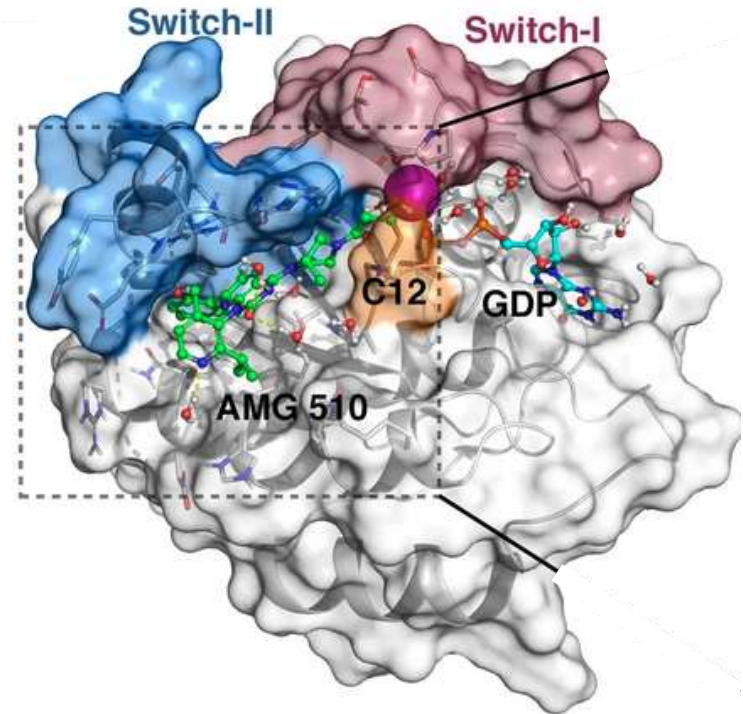
First inhibitor (chemistry)
Ostrem, Nature 2013

First clinical trial starts
Amgen

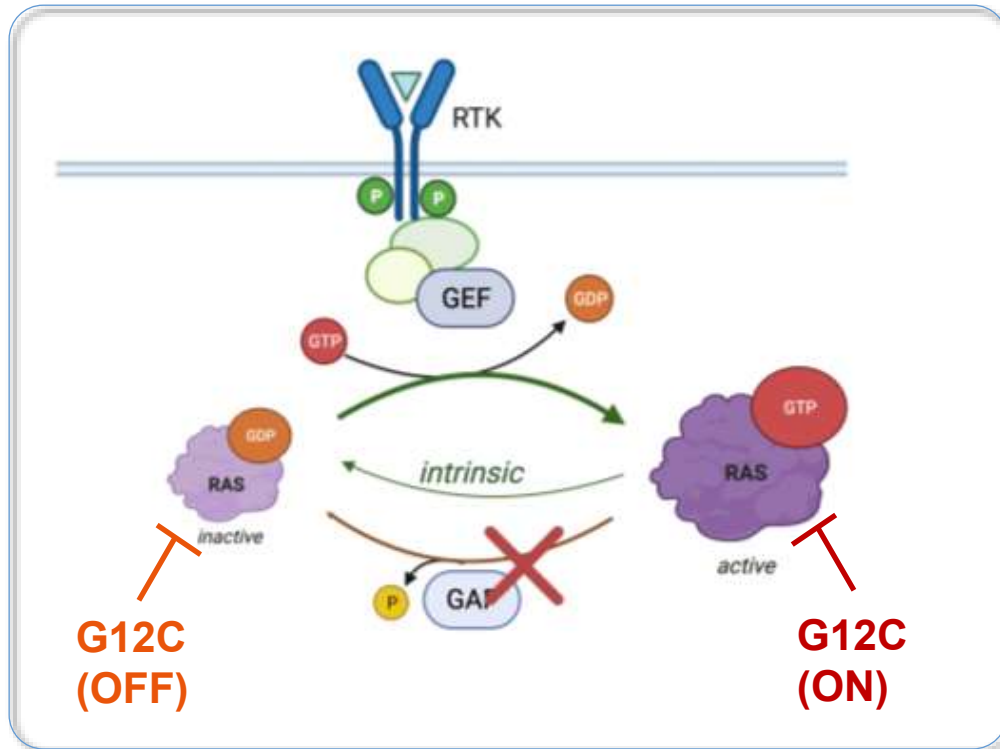
Sotorasib approval

KRAS^{G12C} inhibitors

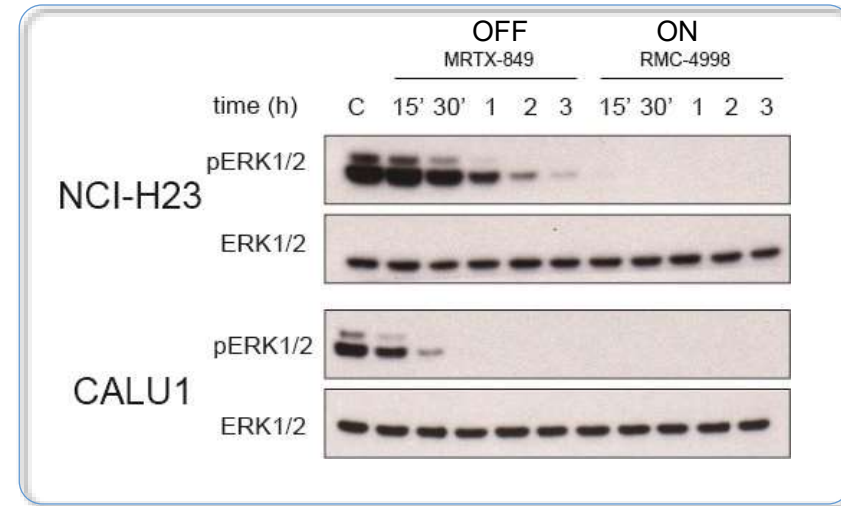
- bind covalently to the Cys12
- bind to the switch-II region
- only bind to inactive KRAS (GDP-bound)



KRAS-G12C inhibitors: ON vs OFF



KRAS-G12C(ON) inhibitors act more rapidly to block KRAS signalling and display higher potency

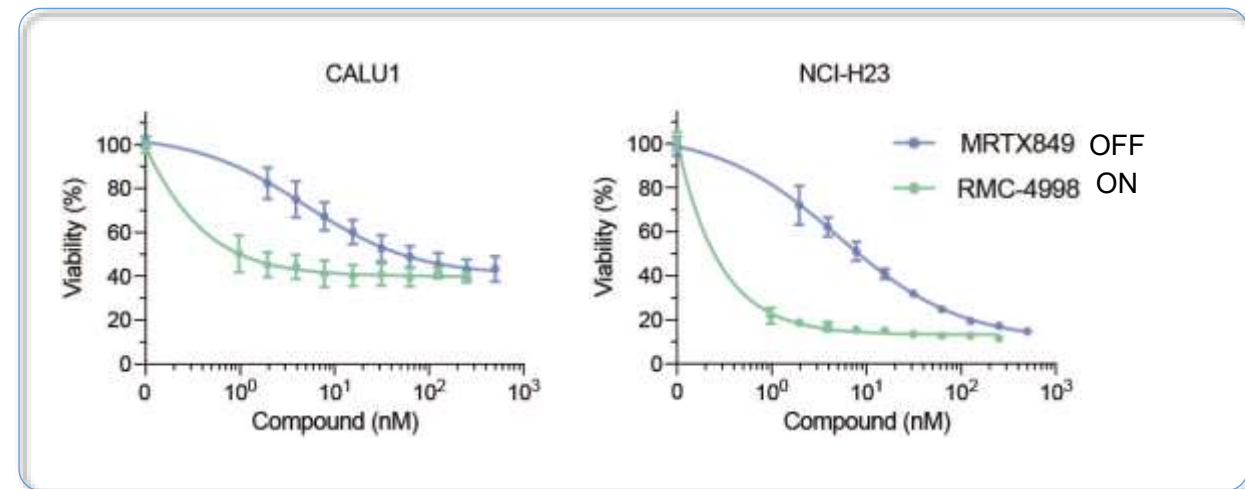


Sotorasib vs Elironrasib

Sotorasib and adagrasib target GDP-bound (OFF)

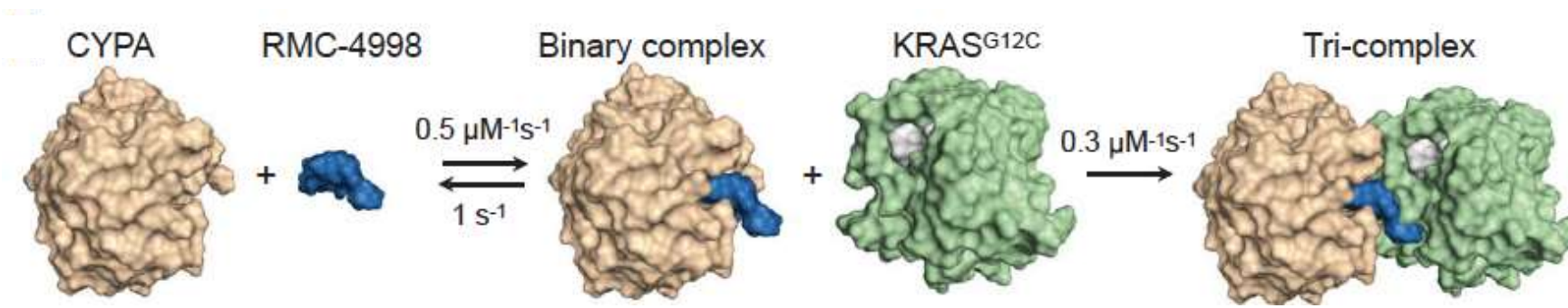
Elironrasib targets GTP-bound (ON)

BBO-8520 targets both GTP- and GDP-bound

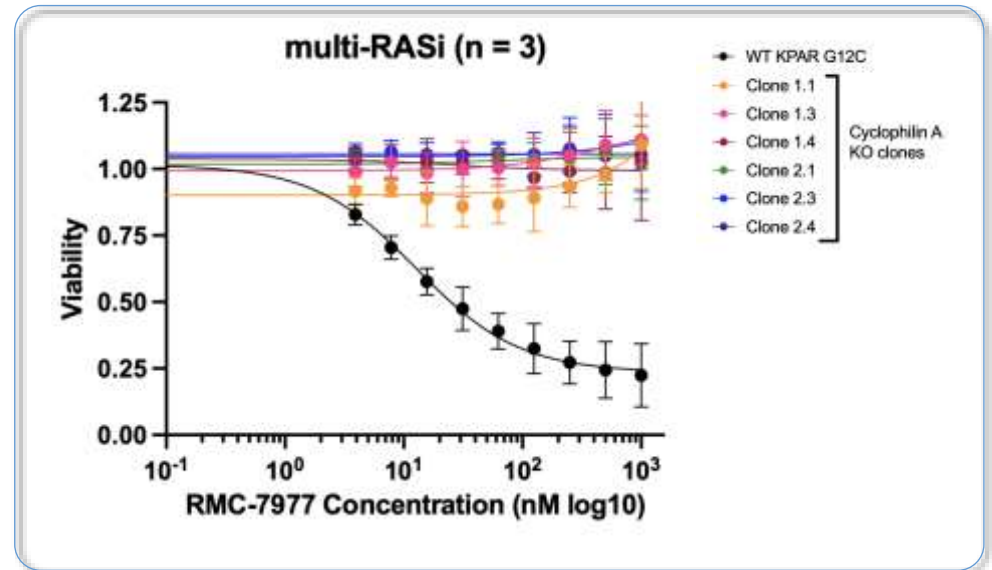


Revolution Medicines compounds

Revolution Medicines compounds target RAS through a tri-complex formation which allows targeting of the active-state



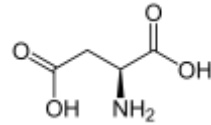
Elironrasib	RMC-6291	G12Ci	Phase 2
Zoldonrasib	RMC-9805	G12Di	Phase 2
Daraxonrasib	RMC-6236	multi-RAS	Phase 3
	RMC-5127	G12Vi	pre-clinical
	RMC-0708	Q61G	pre-clinical
	RMC-8839	G13Ci	pre-clinical



Revolution Medicines compounds require the expression of cyclophilin A

KRAS-G12D inhibitors

	Pre-clinical	IND-enabling	Phase 1	Phase 2	Phase 3	Approved
MRTX1133 (Mirati)						
Zoldonrasib/ RMC-9805 (Rev Med)						
ASP3082 (Asiellas) degrader						
HRS-4642 (Jiangsu Hengrui)						
INCB181731 (Incyte)						
QTX3046 (Quanta Therapeutics)						
LY3962073 (Lilly)						
VRTX153 (Vrise Therapeutics)						
ERAS-4 (Erisca)						
JAB-22000 (Jacobo)						

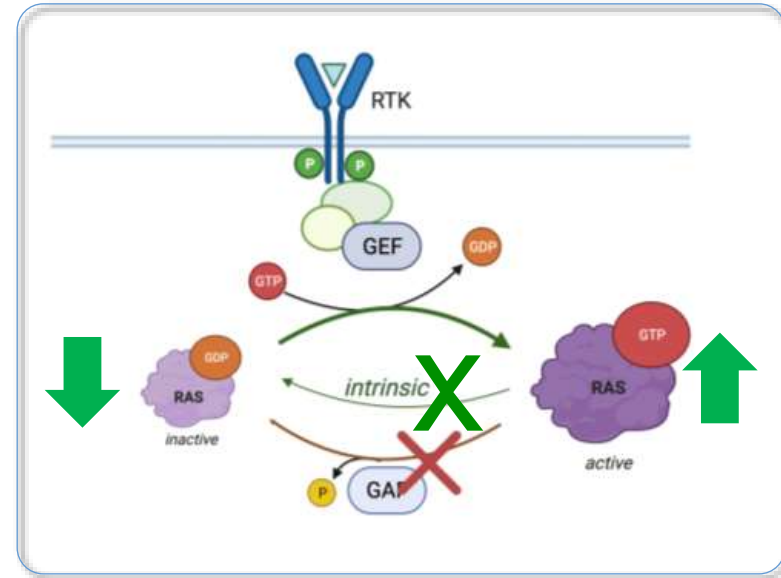


Asp is less reactive than Cys

MRTX1133 is non-covalent

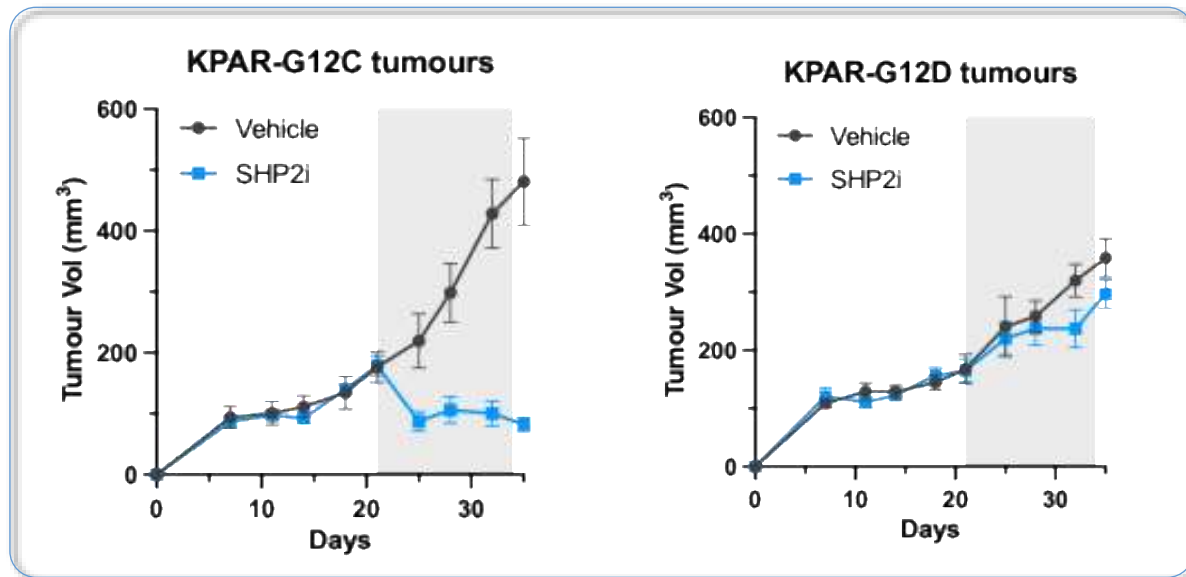
Zoldonrasib (RMC-9805) is covalent

Not all the mutations are the same:



Most G12D inhibitors target ON/OFF

Zoldonrasib targets ON



KRAS-G12C tumours, but not KRAS G12D, respond to SHP2i

Pan-KRAS and pan-RAS inhibitors

		Pre-clinical	IND-enabling	Phase 1	Phase 2	Phase 3	Approved	
Multi (mut/wt)	KRAS	BI 3706674 (Boehringer Ingelheim)	█					
		QTX3034 (Quanta Therapeutics) ^(a)	█					
		QTX3544 (Quanta Therapeutics) ^(b)	█					
		LY406634 (Lilly)	█					
		JAB-23425 (Jacobio)	█					
		VRTX180 (VRise Therapeutics)	█					
		ACBI3 (Boehringer Ingelheim) <i>degrader</i>	█					
RAS	Daraxonrasib/ RMC-6236 (Rev Med)	█						

pan-KRAS inhibitors can have different specificities

BI3706674 – preference for wild-type

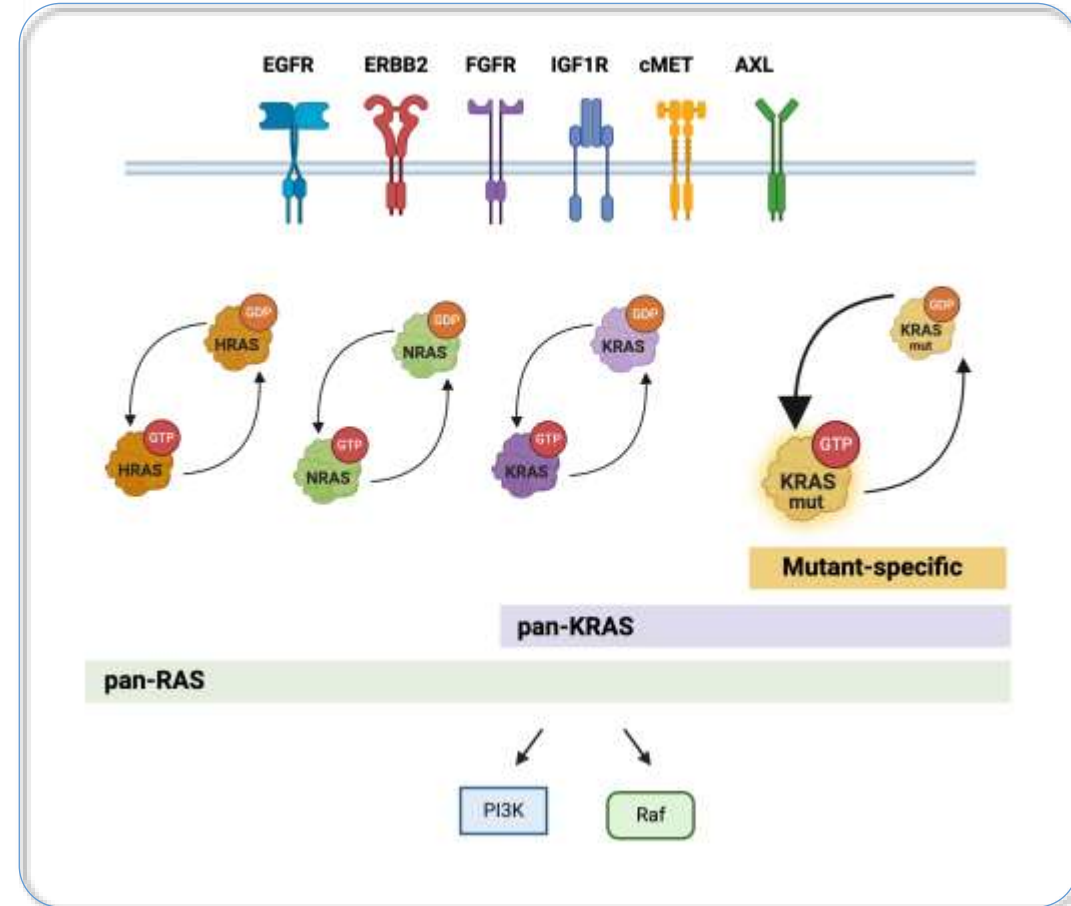
QTX3034 – preference for G12D

QTX3544 – preference for G12V

pan-RAS inhibitors:

Daraxonrasib (RMC-6236)

Other molecular glues: eg. ERAS-0015



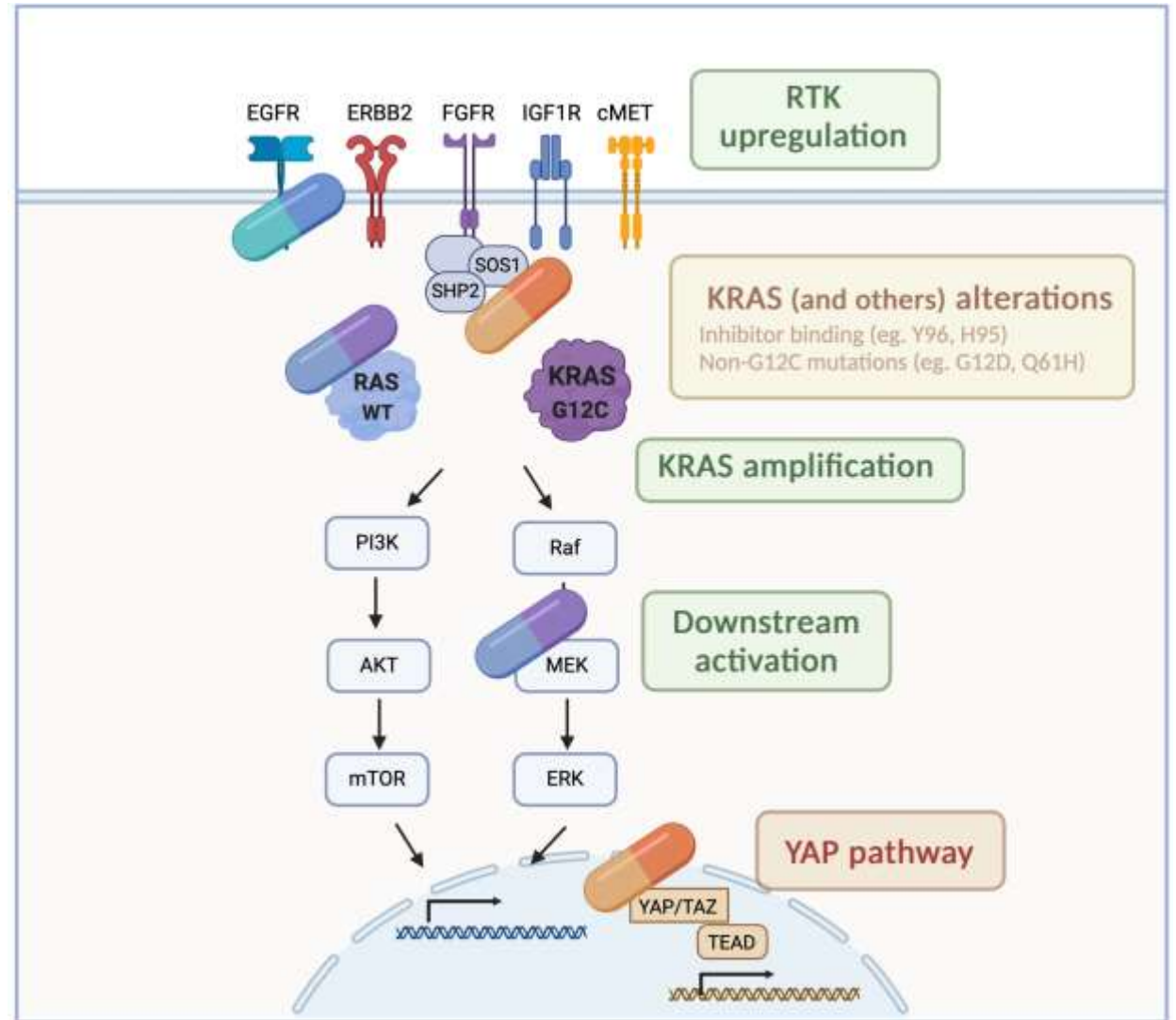
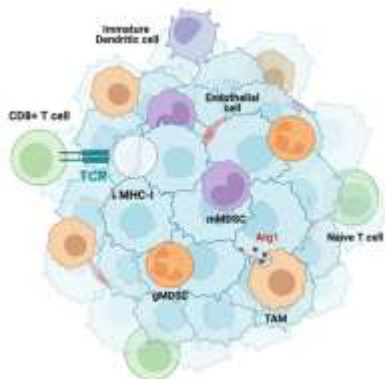
They will also inhibit non-tumoural cells

Targeting mechanisms of resistance

Inhibitor	Company	Trial/phase	DCR	ORR	mPFS
Sotorasib	Amgen	Codebreak 100 (phase 1/2)	84%	41%	6.3 mo
Adagrasib	Mirati / BMS	Krystal-1 (phase 1/2)	42.90%	50.50%	6.5 mo
Divarasib	Roche/Genentech	phase 1		53.40%	13.1 mo
Garsorasib	InventisBio	phase 1/2	91.90%	40.50%	8.2 mo
IBI351	Innovent Tech	phase 2	90.50%	46.60%	8.3 mo

Adapted from Singhal et al, Nature Medicine 2024

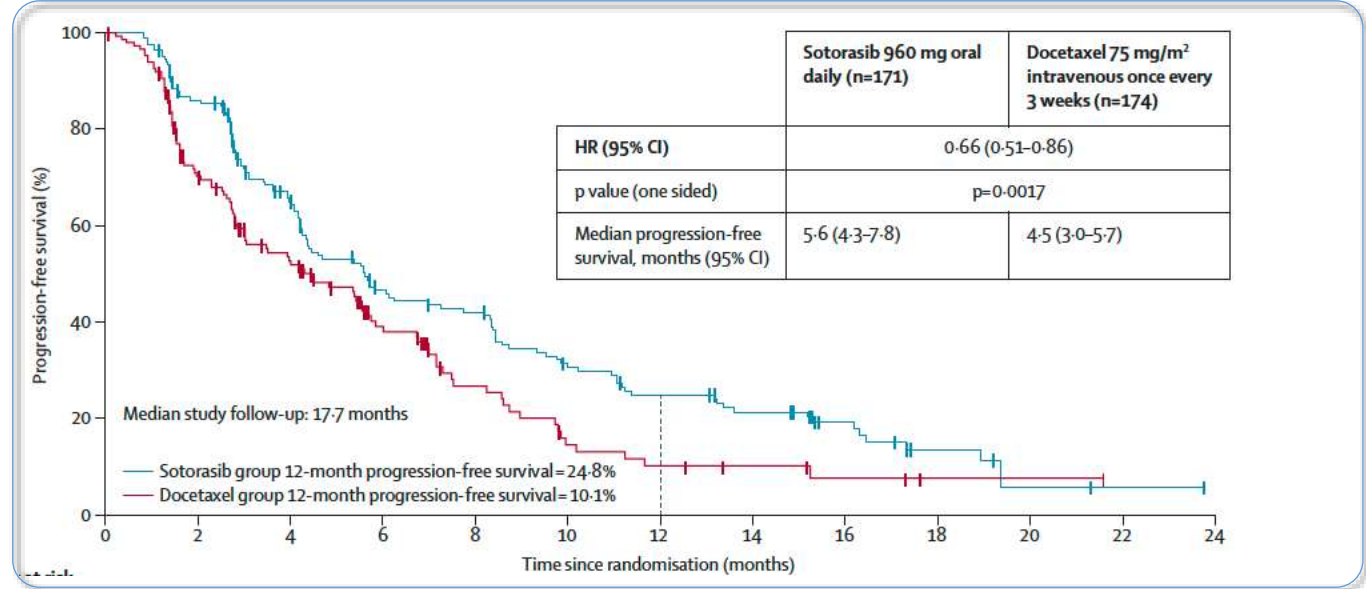
Engage the immune system



1- Tumours adapt to targeted agents and develop drug resistance

Targeted therapies

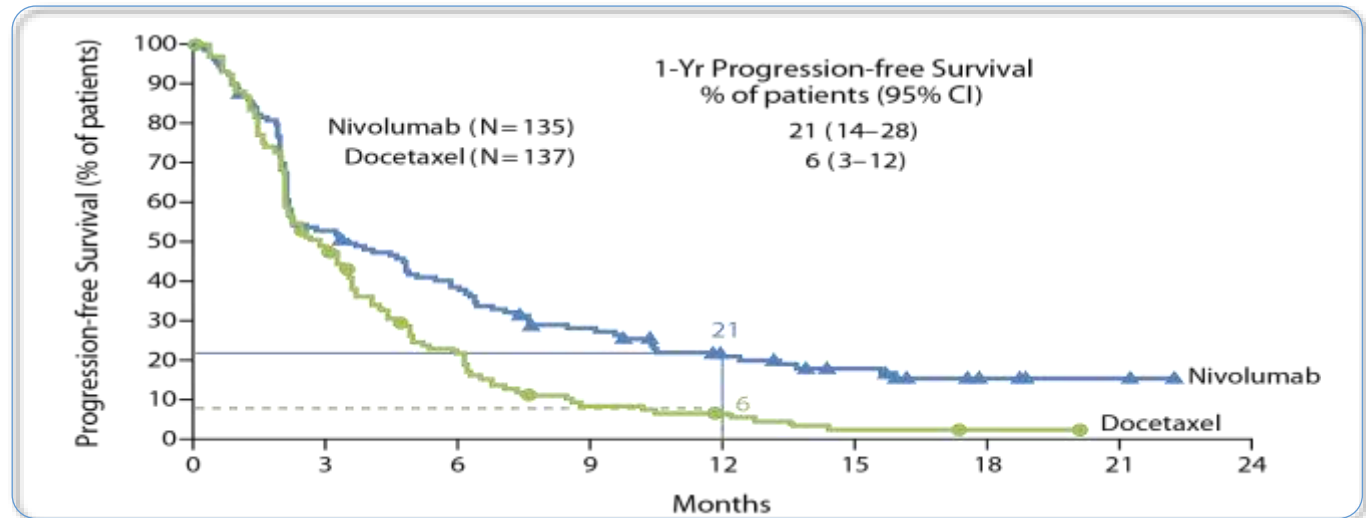
Transient regressions followed by drug resistance



de Langen, Lancet 2023

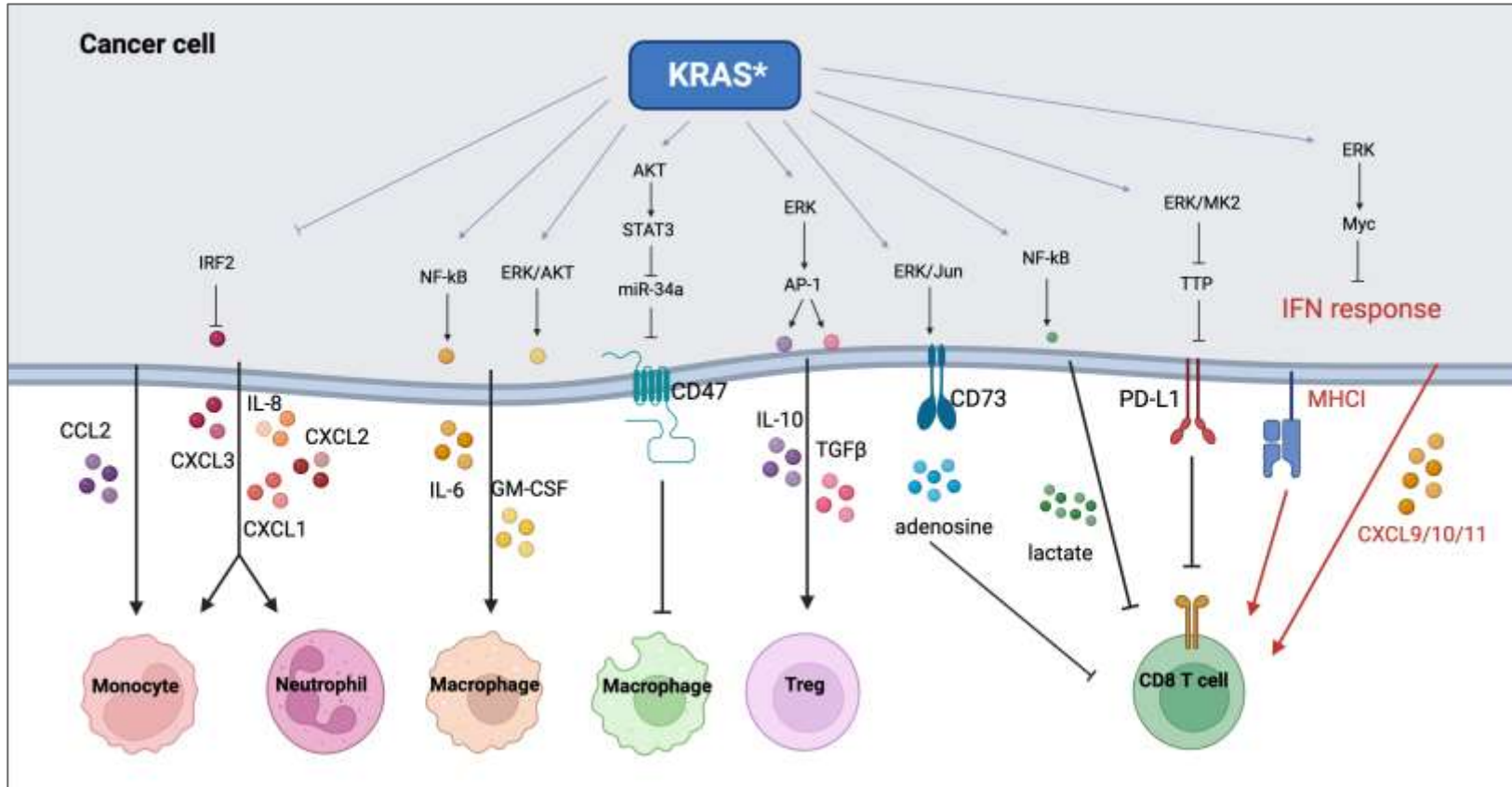
Immunotherapies

Durable clinical responses in some patients

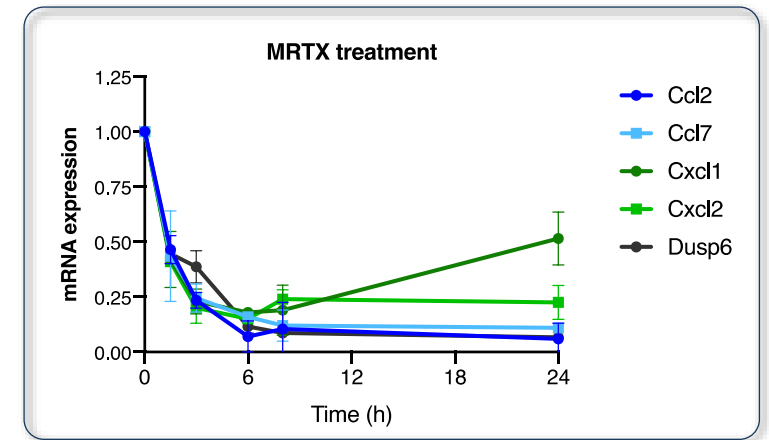
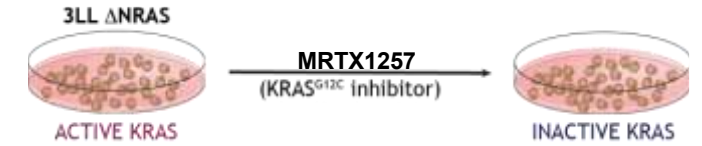


Brahmer et al, NEJM 2015

2- Oncogenic KRAS modulates the immune TME



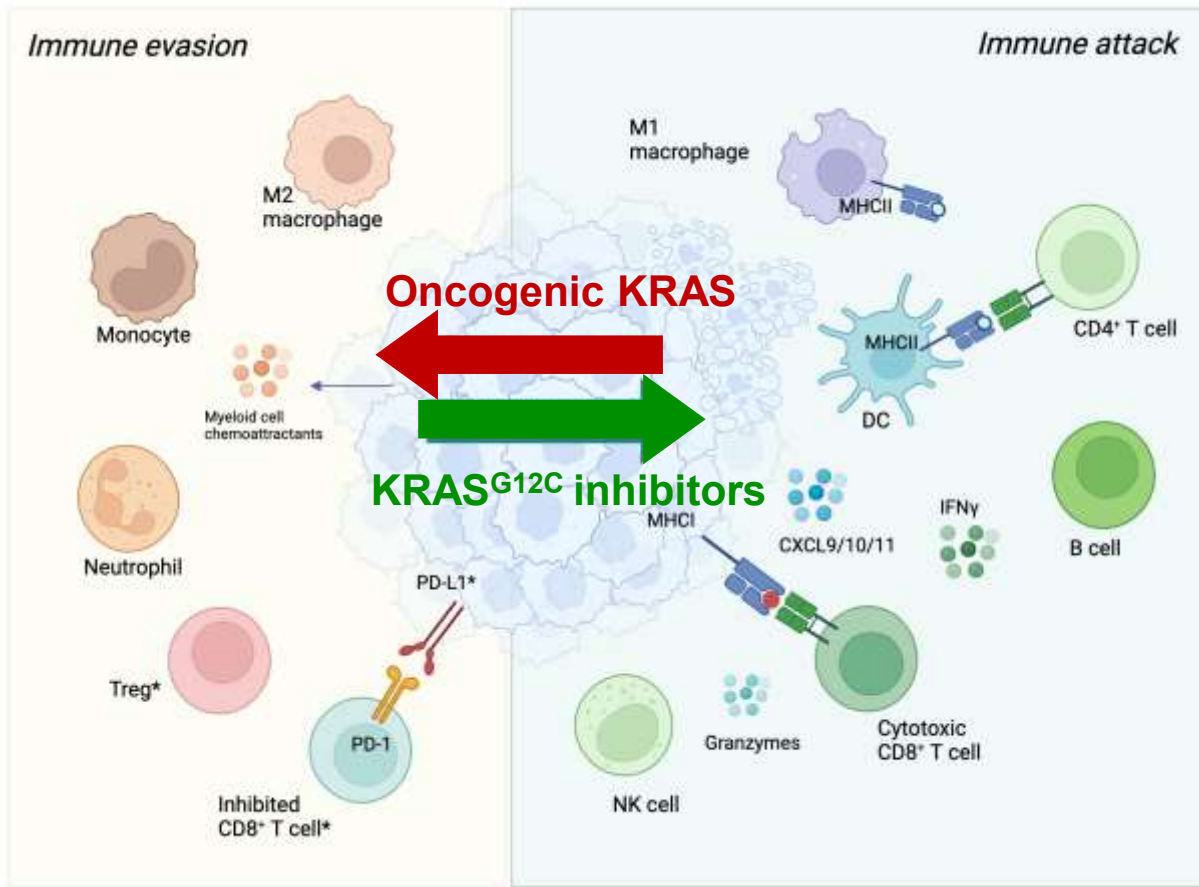
In vitro: Tumour cell intrinsic effects



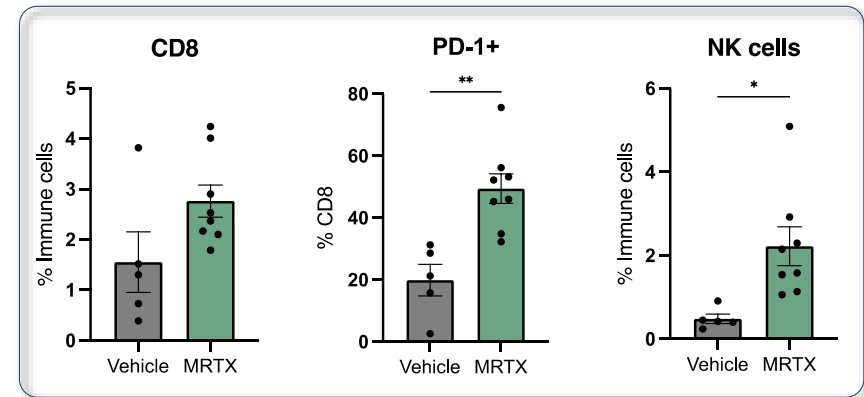
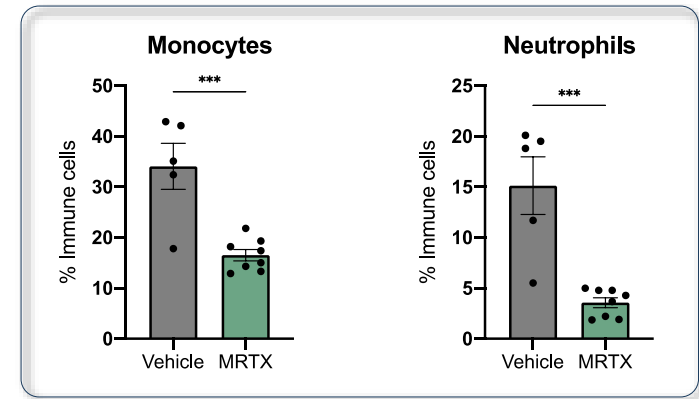
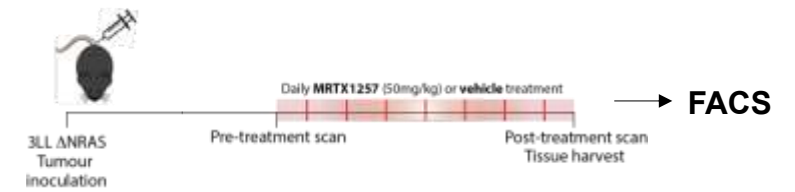
↓ *Monocyte and neutrophil chemoattractants*

Adapted from Molina-Arcas and Downward, Cancer Cell 2024

KRAS-G12C inhibition reverses immune suppression and increases inflammation



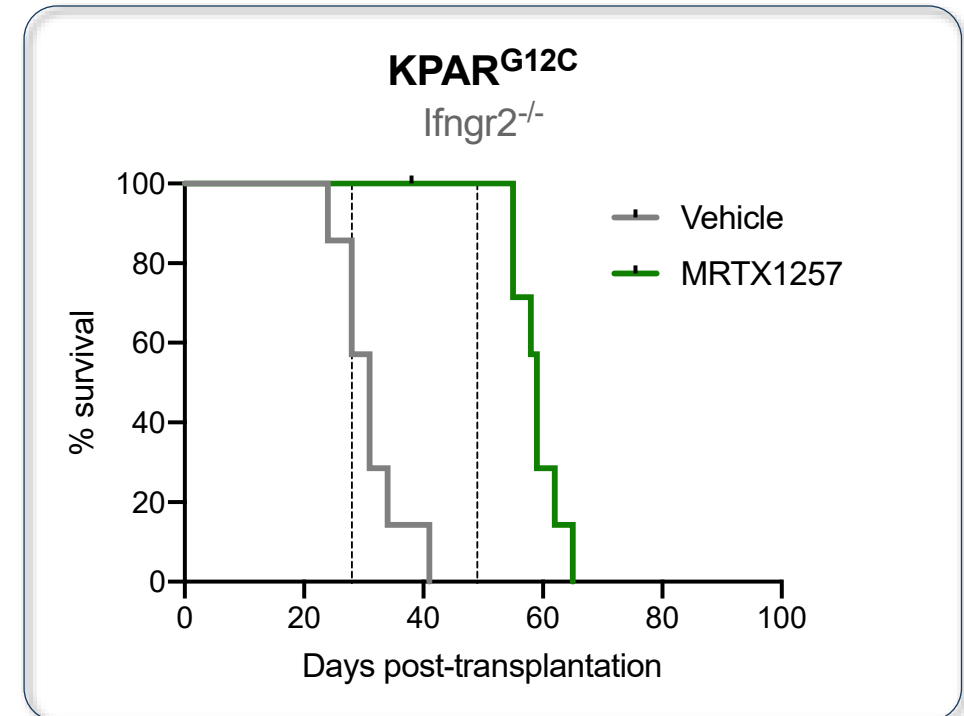
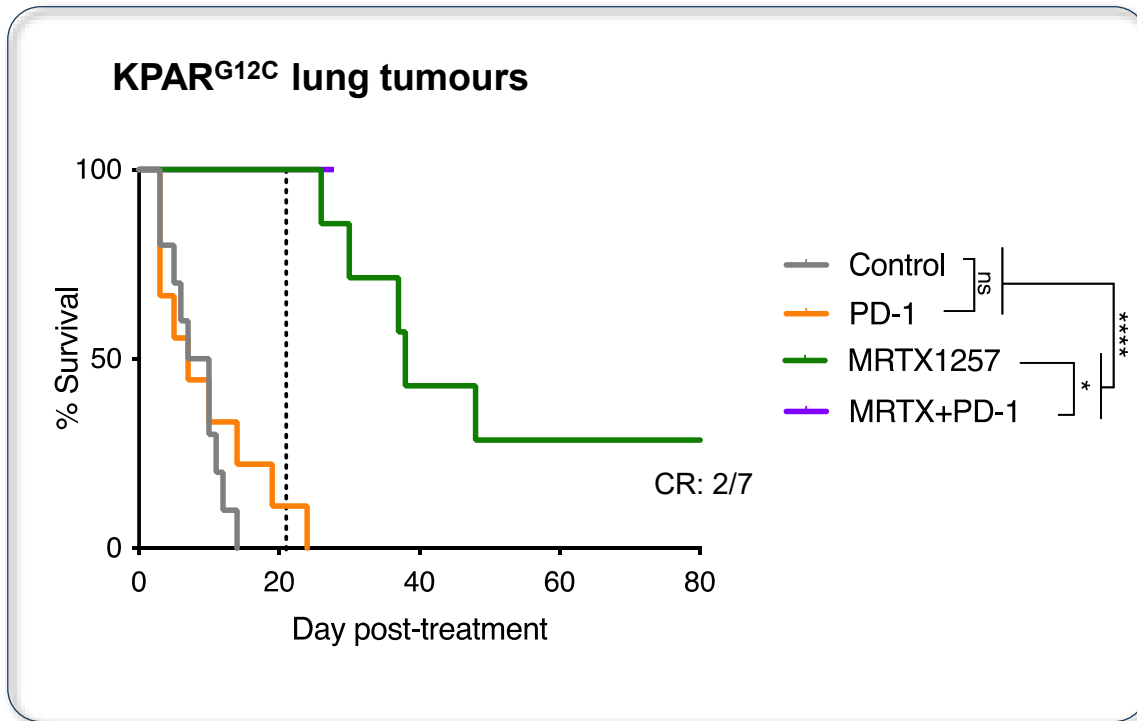
Molina-Arcas and Downward, *Cancer Cell* 2024



Mugarza, *Science Advances* 2022

KRAS-G12C inhibitors combine with anti-PD-1 (pre-clinical)

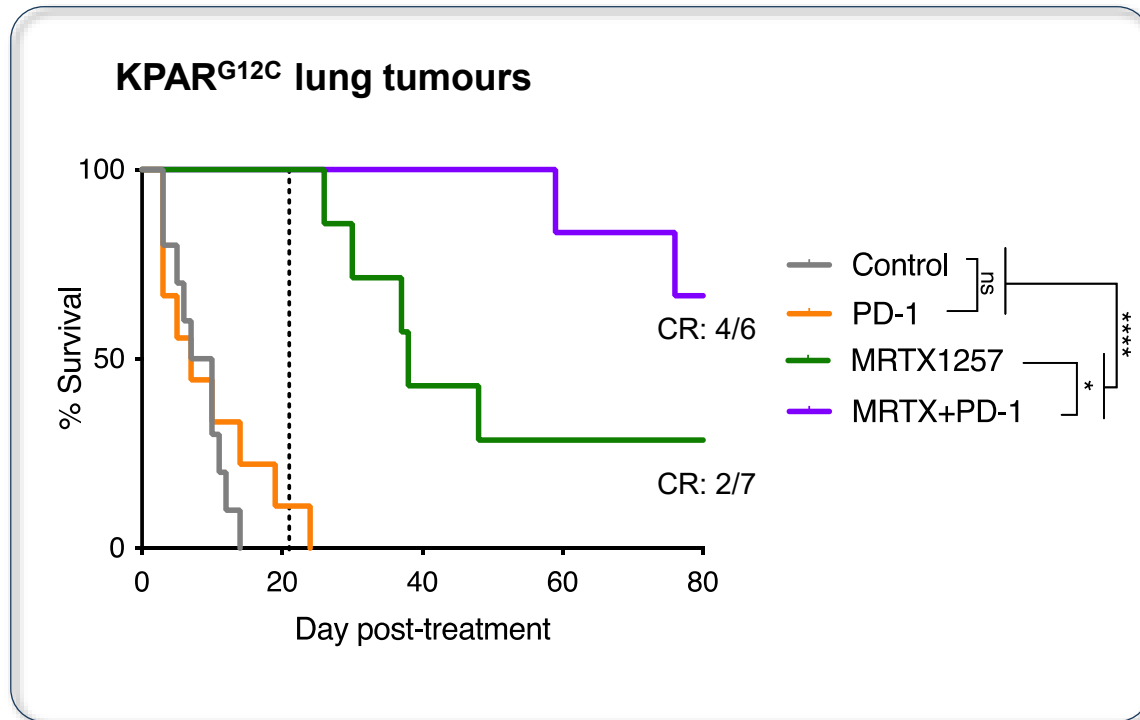
Immune-hot lung tumour model



Adaptive immunity contributes to the efficacy of KRAS^{G12C} inhibitors

KRAS-G12C inhibitors combine with anti-PD-1 (pre-clinical)

Immune-hot lung tumour model



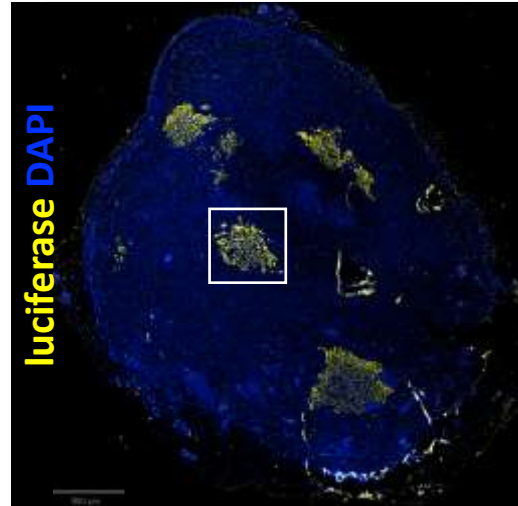
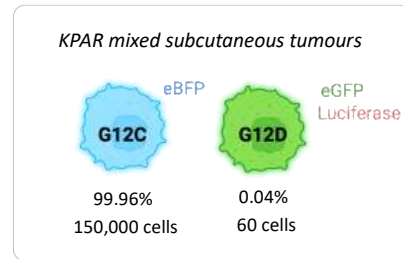
Clinical trials

Drug	Combination	Clinical trial	Phase
Sotorasib <i>Amgen</i>	Anti PD-1/PD-L1 ^(a)	CodeBreak 100 (NCT03600883)	Phase 1
Sotorasib <i>Amgen</i>	Pembrolizumab (PD-1) Atezolizumab (PD-L1)	CodeBreak 101 (NCT04185883)	Phase 1/2
Adagrasib <i>Mirati Ther</i>	Pembrolizumab (PD-1)	KRYSTAL-1 (NCT03785249)	Phase 1b
Divarasisb <i>Genentech</i>	Atezolizumab (PD-L1)	NCT04449874	Phase 1
Opnurasisb <i>Novartis</i>	Tislelizumab (PD-1) -/+ TNO155 (SHP2i)	KontRAsT-01 (NCT04699188)	Phase 1/2
Olomorasib <i>Eli Lilly</i>	Pembrolizumab (PD-1)	NCT04956640	Phase 1
MK-1084 <i>Merck</i>	Pembrolizumab (PD-1)	NCT05067283	Phase 1
IBI351 <i>Innovent Biol</i>	Sintilimab (PD-1) -/+ chemotherapy	NCT05504278	Phase 1/2
RMC-6291 (G12C) or RMC-6236 (multi) <i>RevMed</i>	Pembrolizumab (PD-1) -/+ chemotherapy	NCT06162221	Phase 1/2
Adagrasib <i>Mirati Ther</i>	Pembrolizumab (PD-1)	KRYSTAL-7 (NCT04613596)	Phase 2-3 (PD-L1 TPS ≥50%)
Adagrasib <i>Mirati Ther</i>	Nivolumab (PD-1)	Neo-Kan (NCT05472623)	Phase 2 (neoadjuvant)
Adagrasib <i>Mirati Ther</i>	Pembrolizumab (PD-1) +/- chemotherapy	NCT05609578	Phase 2 (PD-L1 TPS between ≥1% and <50%)

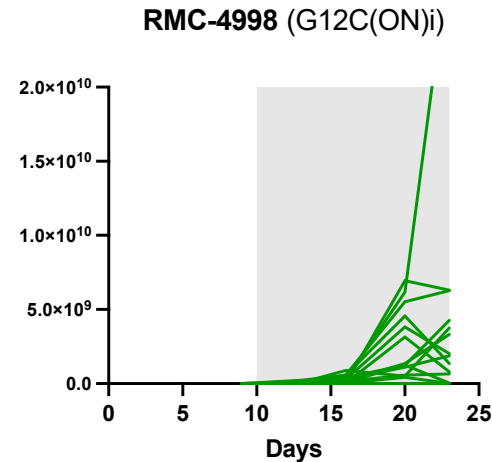
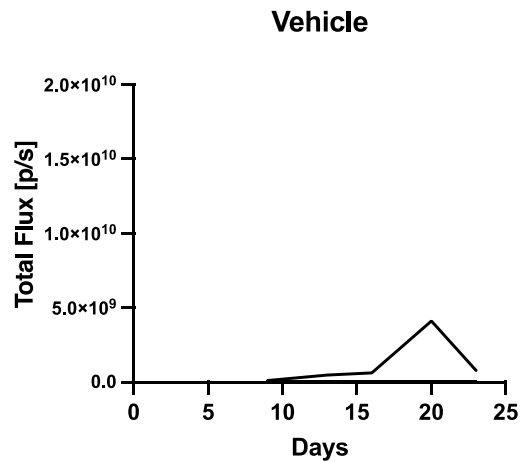
Can we target resistant cells by promoting an adaptive immune response?

RMC-4998

G12C(ON)i, 6 days



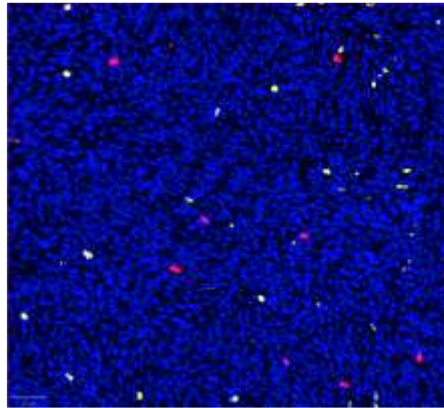
IVIS scans (G12D cells)



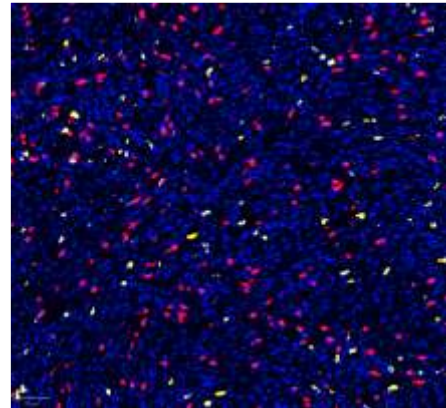
Can we target resistant cells by promoting an adaptive immune response?

Combinations that enhance immune responses

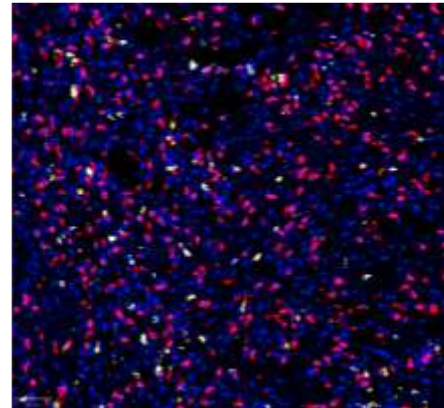
Vehicle



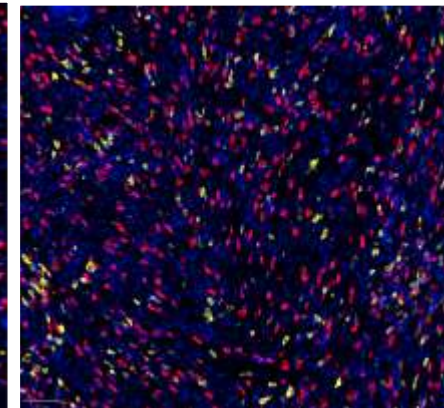
G12Ci



G12Ci + SHP2i



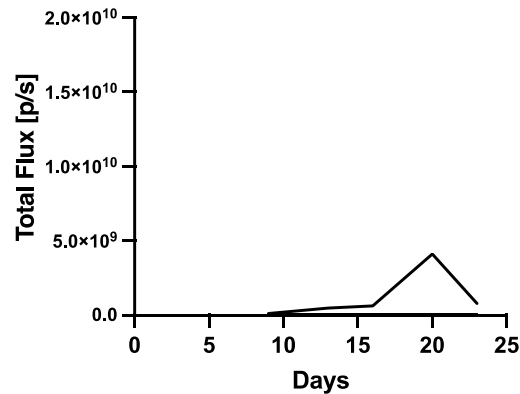
G12Ci + α PD-1



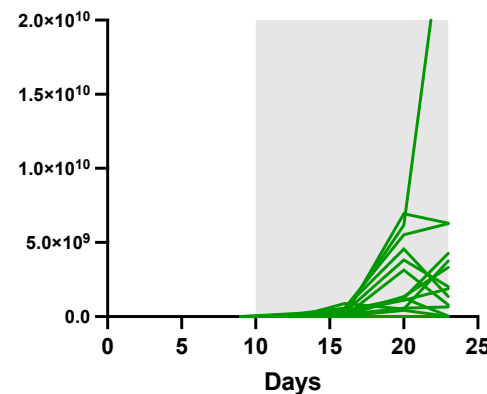
CD4
CD8
DAPI

IVIS scans (G12D cells)

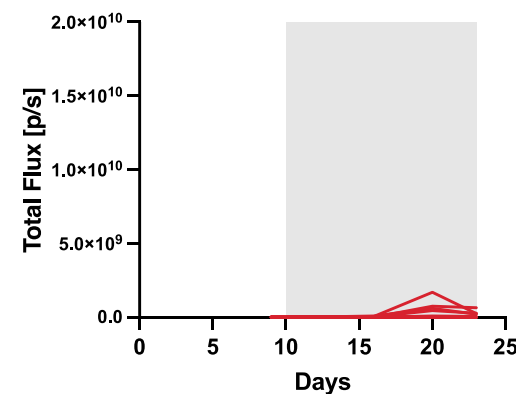
Vehicle



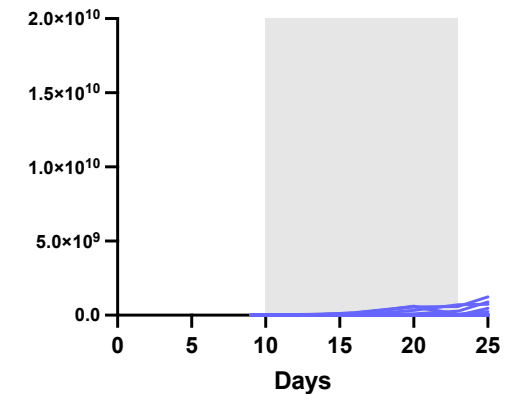
RMC-4998 (G12C(ON)i)



RMC-4998 + RMC-4550 (SHP2i)

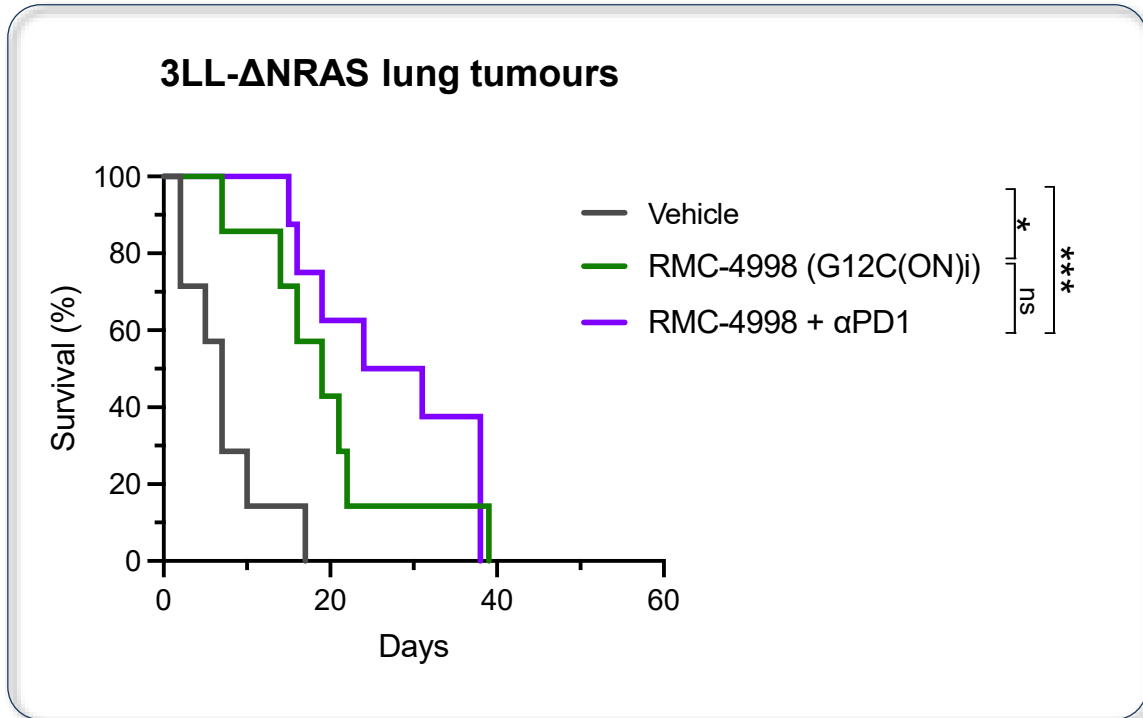


RMC-4998 + aPD-1



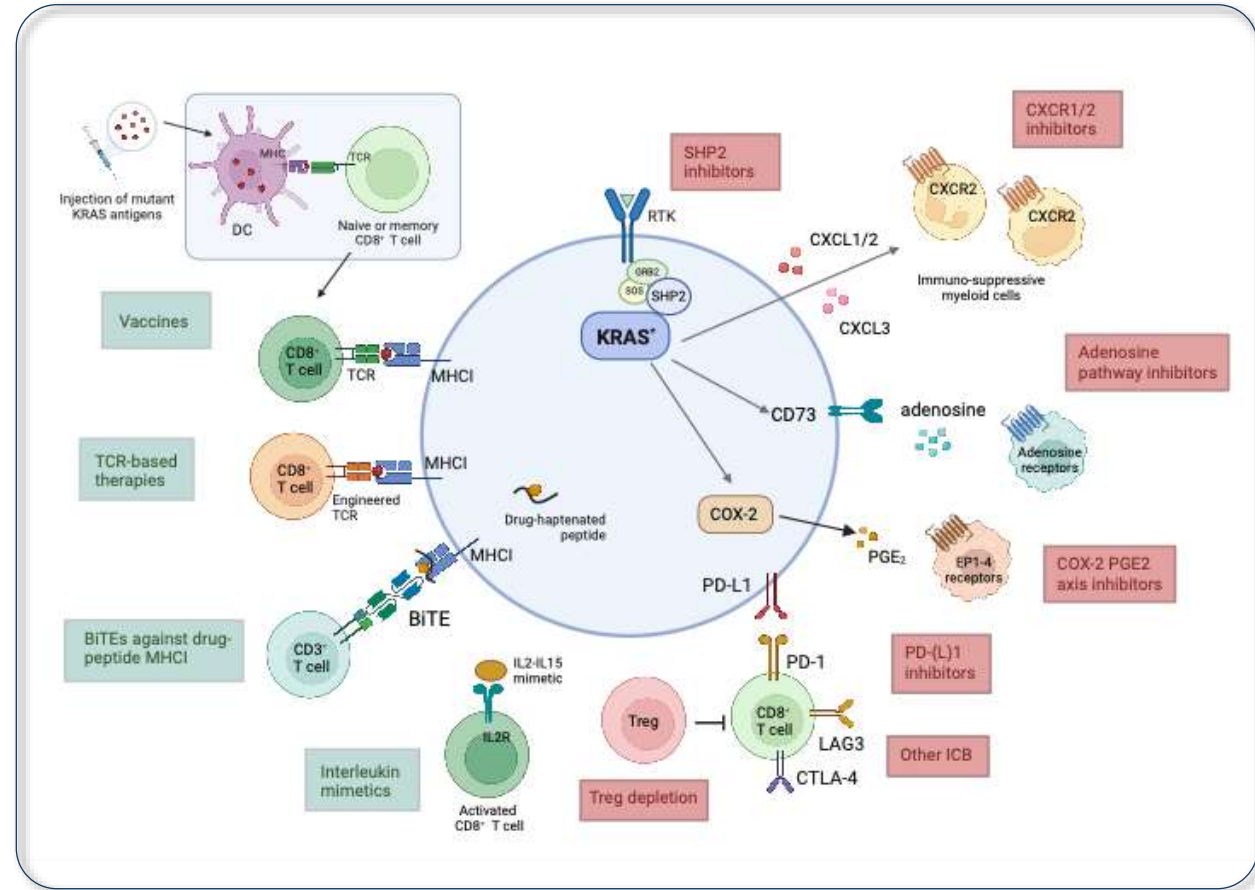
Not all the tumours will respond to the combinations with anti-PD-1

Immune-cold lung tumour model



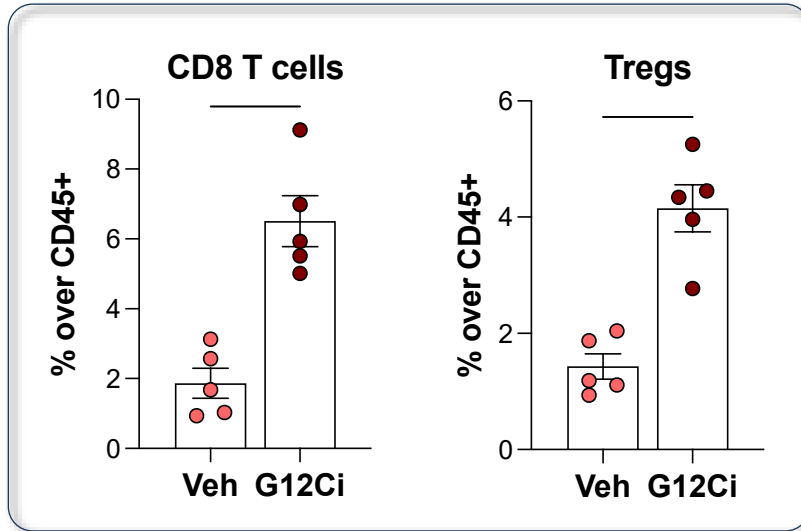
Anastasiou, Nat Comm 2024

Therapies beyond anti-PD-1

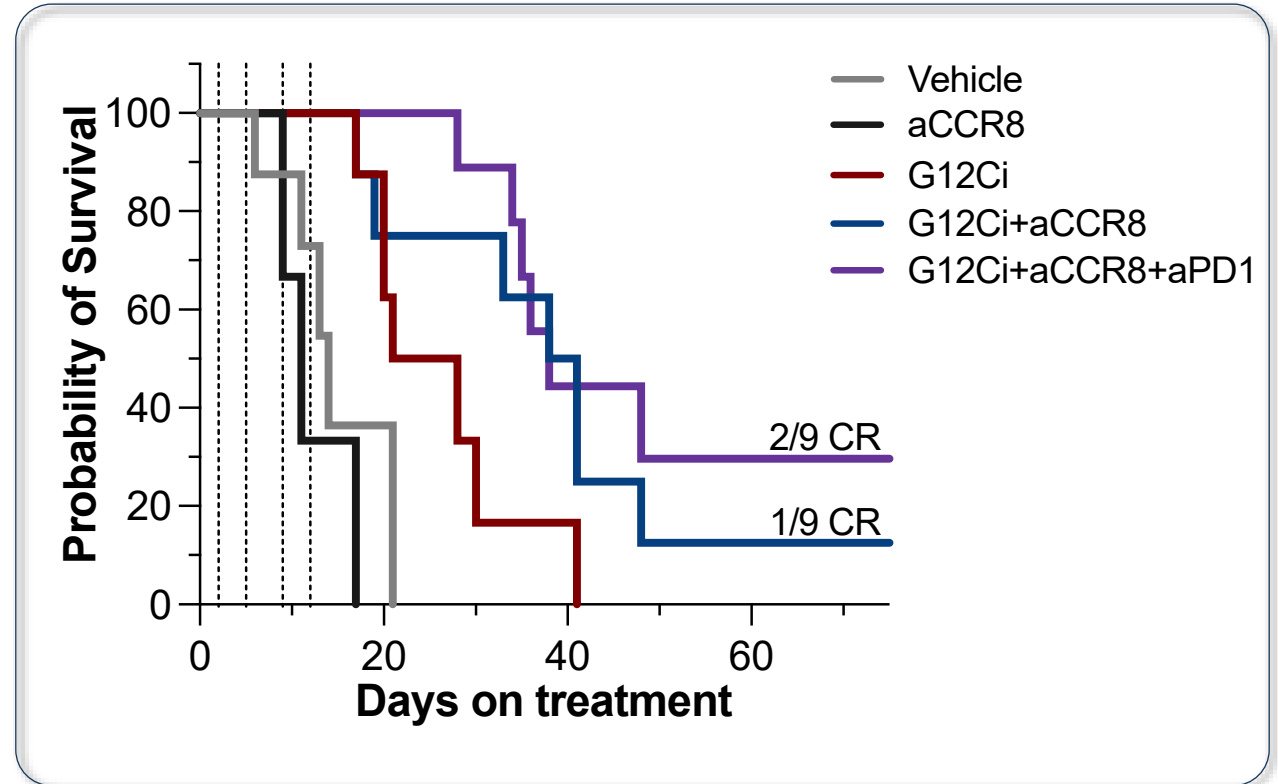
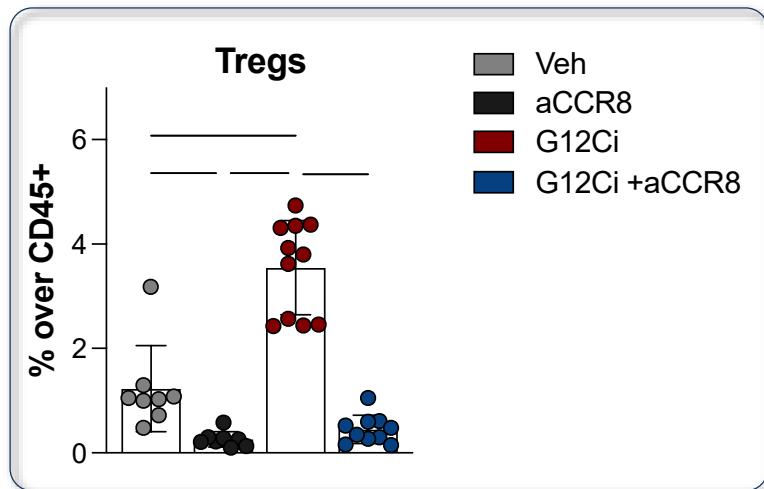


G12Ci combine with Treg depletion in immune cold tumour models

G12Ci increases Treg infiltration



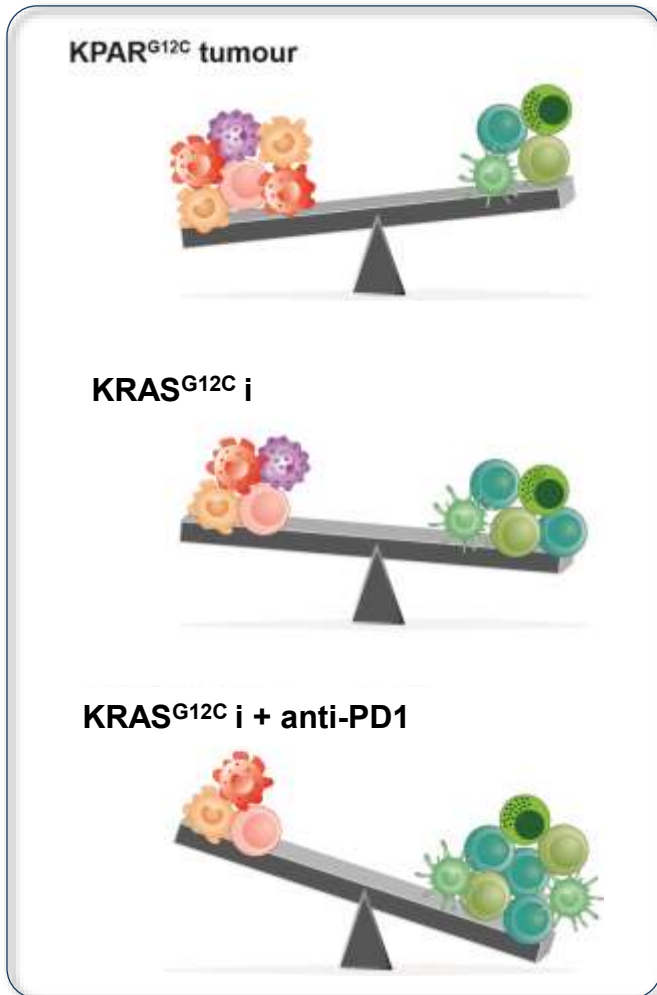
aCCR8 effectively depletes tumour-infiltrating Tregs



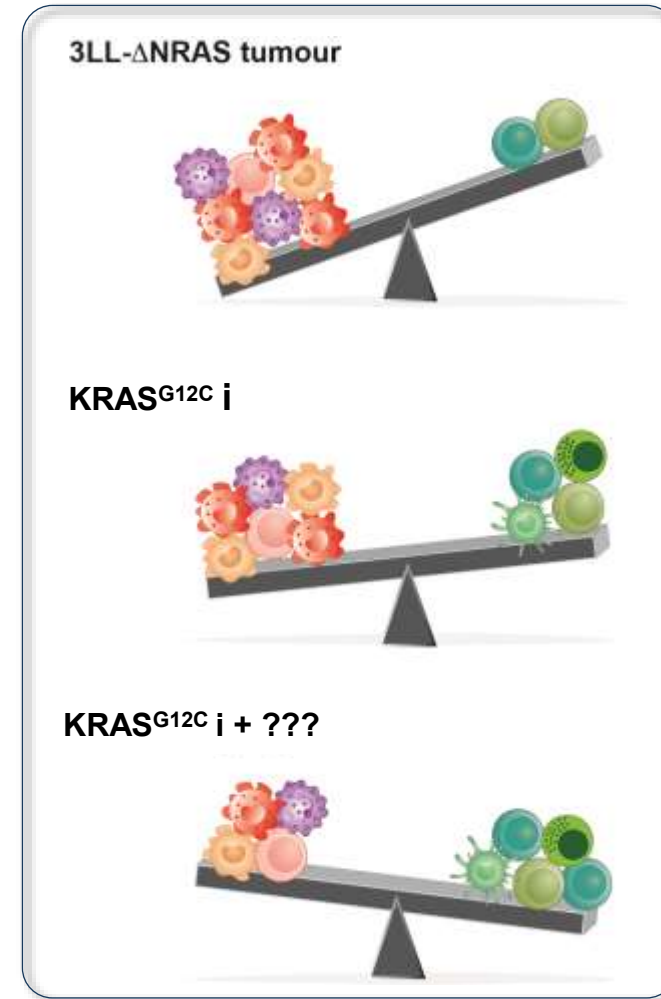
aCCR8 in combination with G12Ci hinders tumour progression

Need to identify the right immunotherapies

KPAR^{G12C} tumours (immunogenic)



3LL-ΔNRAS tumours (non-immunogenic)



- *The RAS pathway is very complex, with a lot of feed-back loops that allow pathway reactivation*
- *Not all mutations are the same*
- *Not all the inhibitors are the same*

- *We need to identify the best combination strategies*
- *Not all combinations will show efficacy in all tumours → need biomarkers*
- *Combinations that enhance the immune system could achieve durable responses*

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CRICK Core Facilities

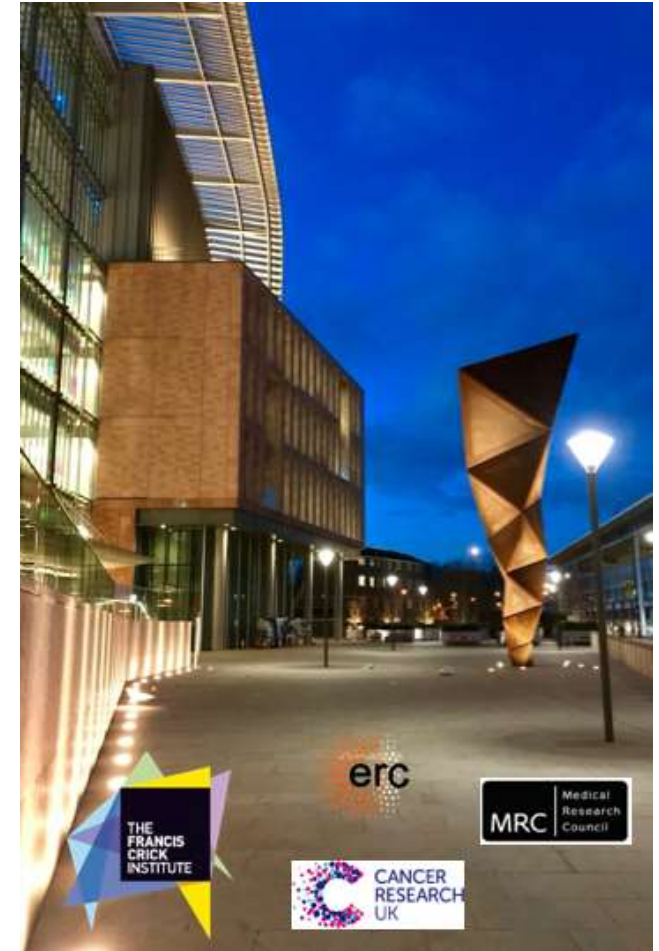
BRF (Biological Research Facility)
FACS Facility
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Advanced Sequencing Facility
In vivo imaging

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THANK YOU