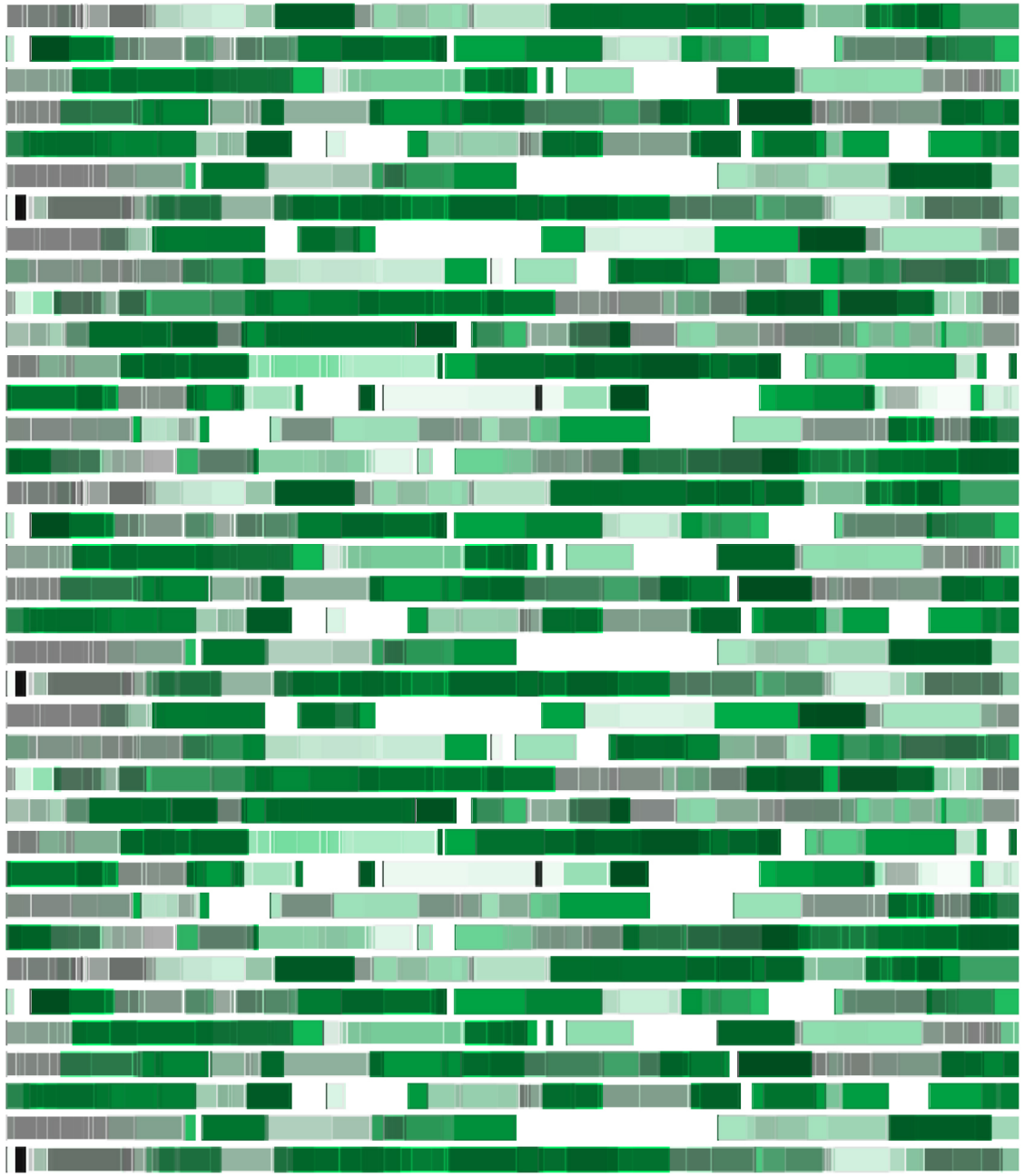
III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026



AVANCES EN LA ENFERMEDAD KRAS ¿NUEVOS INHIBIDORES, MONOTERAPIA O ASOCIACIÓN CON INMUNOTERAPIA?

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HENDERE HEALTHCARE

COI

Honoraria as consultant on advisory boards: Pfizer, Astellas, Janssen, MSD, Bayer, Roche, BMS, AstraZeneca, Ipsen, Novartis, Recordati, BeOne and Merck.

Honoraria as speaker: Lilly, Astellas, Bayer, Roche, Ipsen, Janssen, Takeda, Merck, MSD, Pfizer, Novartis, BeOne, Recordati, Regeneron and AstraZeneca.

Travel grants: Roche, Bayer, Ipsen and AstraZeneca.

BACKGROUND

Background: KRAS Biology

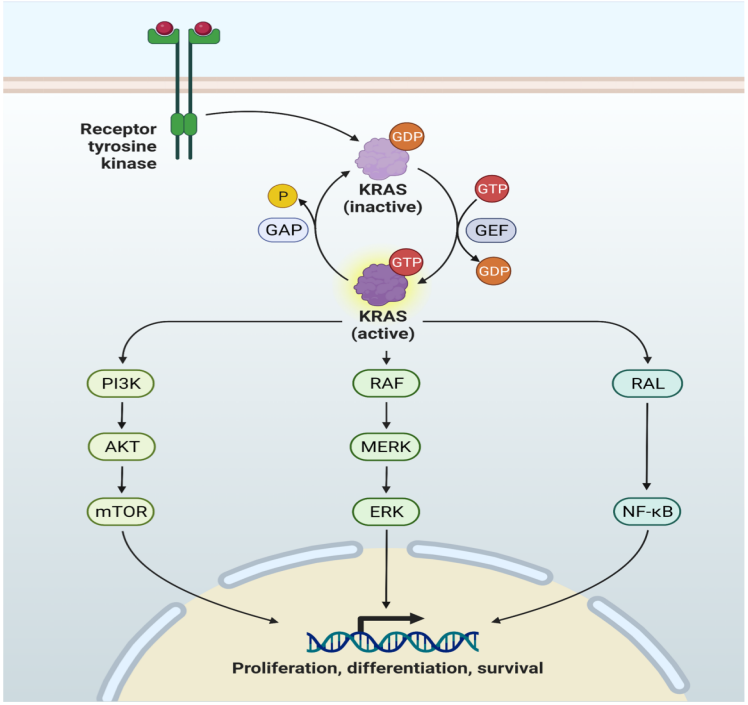
- KRAS is GTPase protein
- Acts as a cellular switch for extracellular stimuli (e.g. growth factors)
- 2 different states of KRAS:

INACTIVE → GDP-bound

ACTIVE → GTP-bound

- + common mutated oncogene in human cancer (≈20%)
- 80% of KRAS mutations → codon 12 (G12C, G12V, G12D)

12–14% Overall prevalence of *KRAS* G12C in NSCLC[3,4]



Prevent GTP hydrolysis → Constitutional activation of KRAS (GTP-bound)

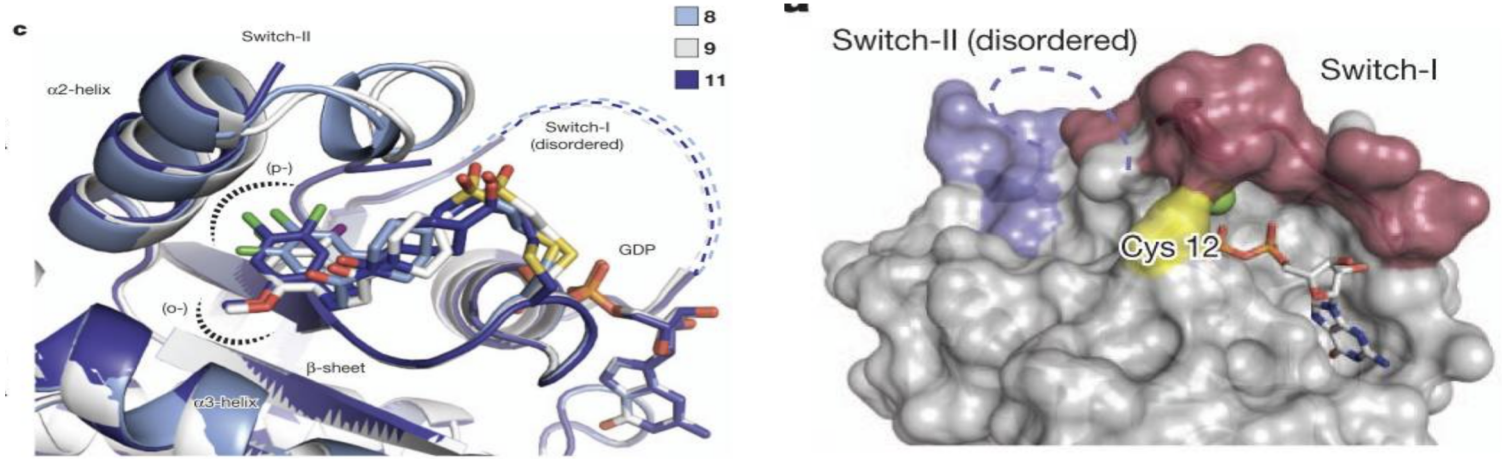
Downward J. Nat Rev Cancer. 2003 Jan;3(1):11-22.
Veluswamy R, et al. J Mol Diagn. 2021 May;23(5):507-520

Background: KRAS mutations in NSCLC

- KRAS: historically, thought to be an untreatable oncogene

✓ ⬆ affinity (pM) for GTP
✓No allosteric regulatory sites

- 2013: Discovered a **regulatory cysteine pocket** of **KRAS^{G12C}** ➡ **targetable!**

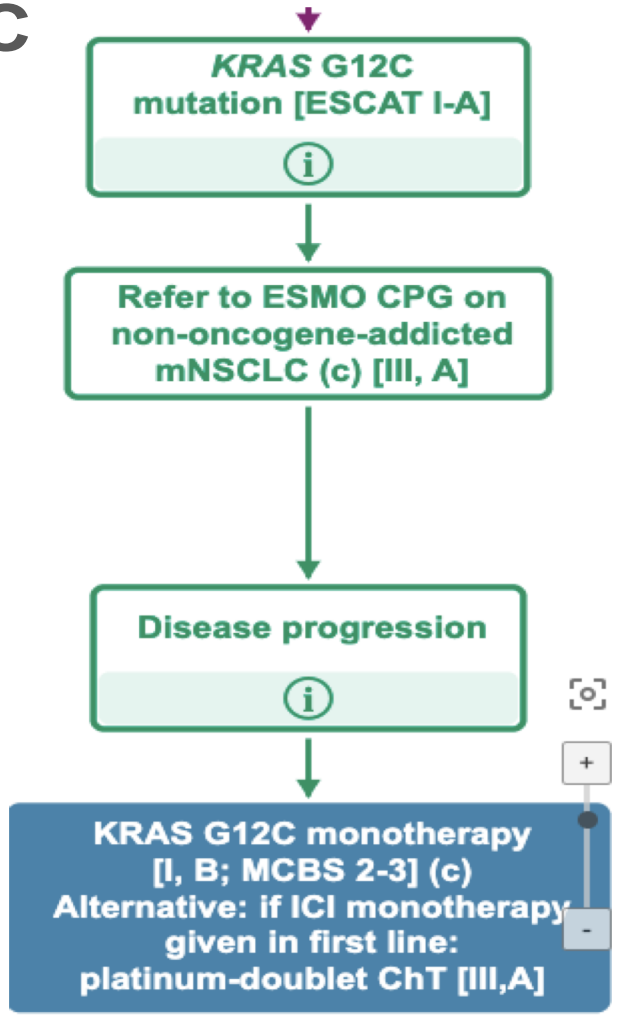


Ostrem JM, et al. Nature. 2013;503(7477):548-51. doi: 10.1038/nature12796.

KRAS mutant NSCLC

KRAS is a challenging therapeutic target

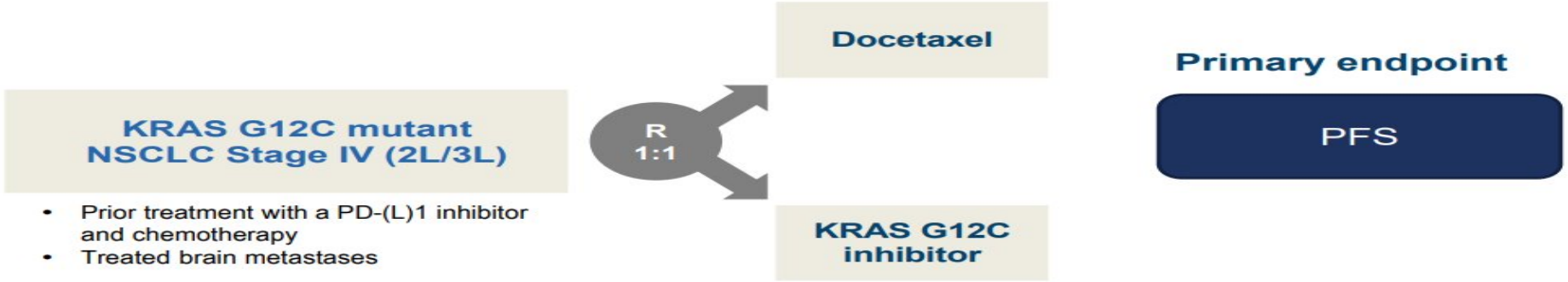
- First line vs. Previously treated patients
- KRAS G12Ci vs. Combination therapy (ICI?Chemo?)
- Allele specific vs. PanRAS inhibition
- KRAS on inhibitor vs KRAS off inhibitor



ESMO guidelines updated Jan 2025

KRAS G12C INHIBITORS

KRAS G12C inhibitors: what we know



KRAS G12C inhibitors: open questions

PFS ….is 1.5 months enough?

Safety profile ….docetaxel is not the best example

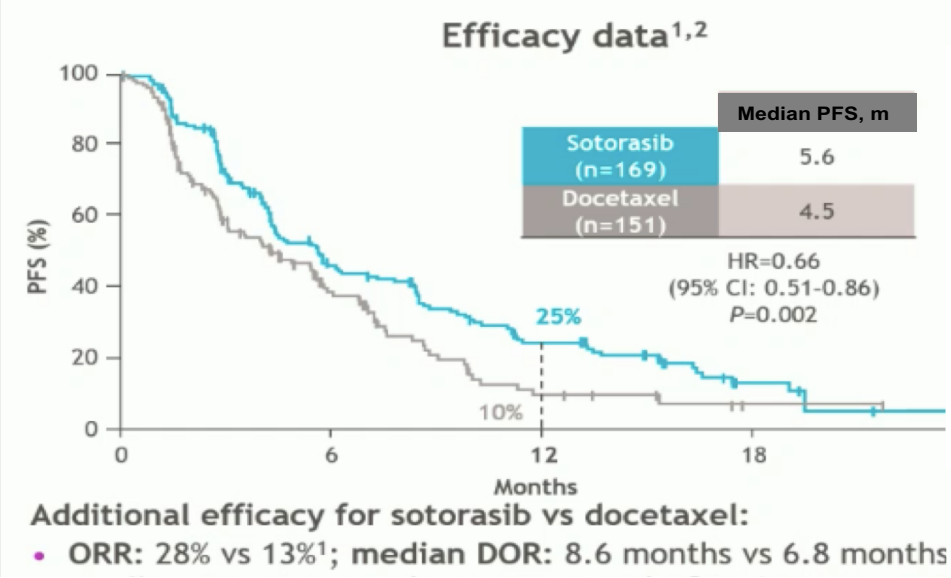
OS benefit

High ORR ….resistance mechanism

Better inhibitors? Combination therapy?

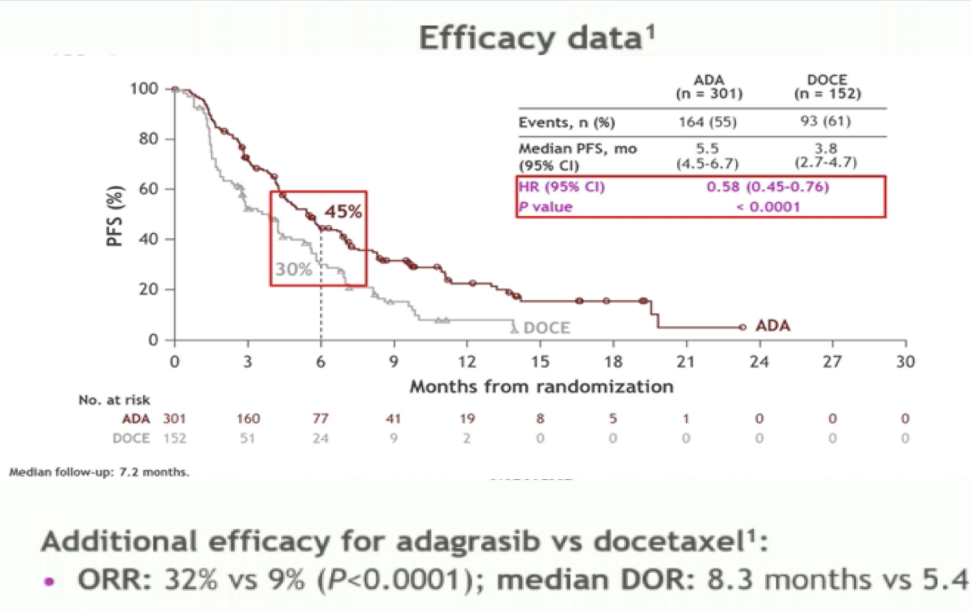
KRAS G12C inhibitors with data from global phase III trials in NSCLC that led to regulatory approvals

CodeBreak 200: Sotorasib



Safety
33% ≥G3 TRAEs
15% Dose reduction
10% Discontinuation

KRYSTAL-12: Adagrasib

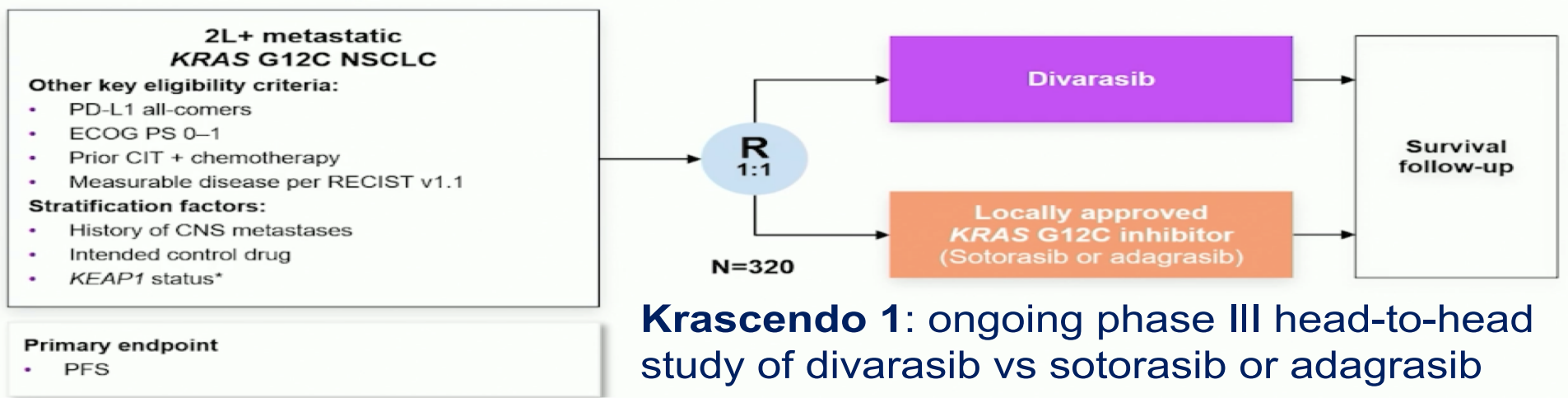


Safety
47% ≥G3 TRAEs
48% Dose reduction
8% Discontinuation

De Langen AJ et al. Lancet 2023
Dingemans AC et al. ASCO 2023.
Mok T et al. ASCO 2024

Other KRAS G12Ci with phase I/II monotherapy data in 2L+

	OLOMORASIB n=39	GARSORASIB n=123	GLECIRASIB n=119	FULZERASIB n=116	DIVARASIB n=65
ORR, %	41	52	48	49	56
DCR, %	82	89	86	91	92
Any grade TRAEs, %	65	96	98	92	94



Krascendo 1: ongoing phase III head-to-head study of divarasib vs sotorasib or adagrasib

KRAS G12CI COMBINATIONS

Moving to 1st line...KRAS G12Ci+IO

KRYSTAL-7 (Ph 2)
Adagrasib + pembro (n=148)

44%

n/N: 35/51
Based on these data, the phase 3 component of KRYSTAL-7 was initiated

CodeBreak 101 (Ph 1)
Lead-in with or concurrent sotorasib + atezo or pembro (N=58; 21% 1L)

29%

n/N: 17/58
Based on these and other data, it was determined that sotorasib + I-O is not viable[4]

LOXO-RAS-20001 (Ph 1)
Olomorasib + pembro (n=16)

77%

n/N: 13/17
Olomorasib + pembro + chemo is also currently under investigation[7]

MK-1084-001 (Ph 1)
MK-1084 + pembro (n=24)

71%

n/N: 21/24

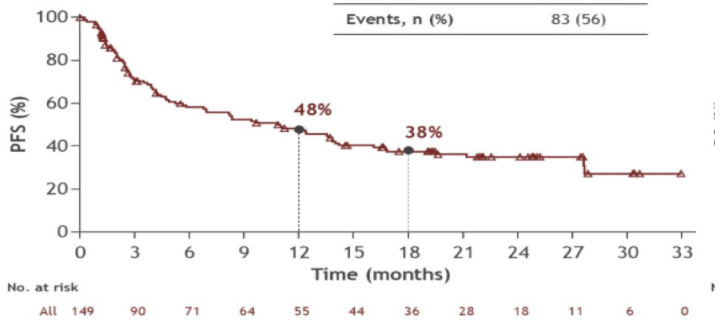
Bob T Li. ASCO 2024
Pasi Jänne. ASCO 2025

1L setting KRAS G12Ci+IO combination

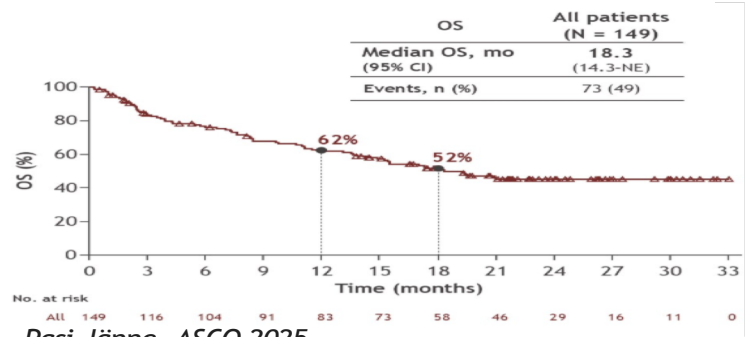
KRYSTAL-7: Adagrasib+ Pembrolizumab

ORR
36% PD-L1 <1%
41% PD-L1 1-49%
61% PD-L1 ≥50%

PFS	All patients (N = 149)
Median PFS, mo (95% CI)	11.0 (5.8-14.0)
Events, n (%)	83 (56)



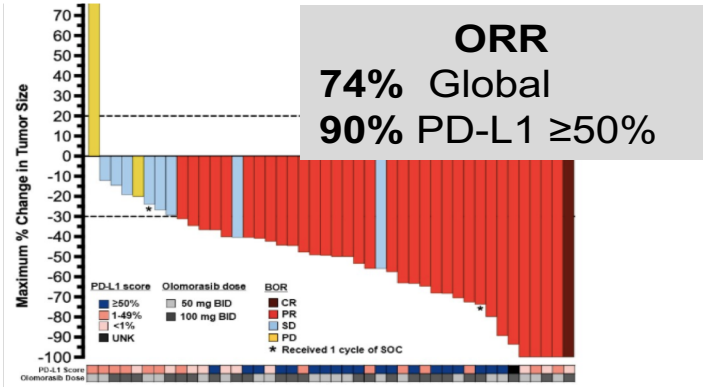
OS	All patients (N = 149)
Median OS, mo (95% CI)	18.3 (14.3-NE)
Events, n (%)	73 (49)



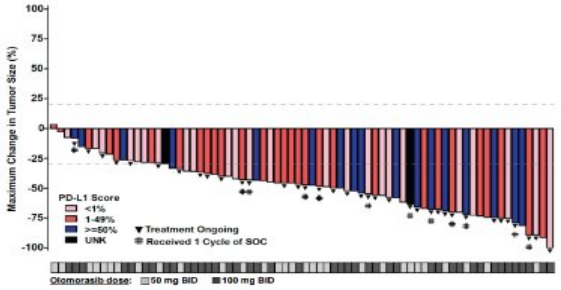
Pasi Jänne. ASCO 2025

Loxo-RAS 20001 Olomorasib+ Immunotehrapy

ORR
74% Global
90% PD-L1 ≥50%



Efficacy of 1L Olomorasib + Pembrolizumab + Pemetrexed + Platinum



Olomorasib + Pembrolizumab + Pemetrexed + Platinum				
Efficacy Evaluable Patients[a]	All pts PD-L1 0-100% N = 77[b]	Pts with PD-L1 <1% N = 26	Pts with PD-L1 1-49% N = 31	Pts with PD-L1 ≥50% N = 18
ORR, (%) (95% CI)	61 (49.2, 72.0)	50 (29.9, 70.1)	68 (48.6, 83.3)	67 (41.0, 86.7)
BOR, n (%)				
CR	1 (1)	-	1 (3)	-
PR[c]	46 (60)	13 (50)	20 (65)	12 (67)
SD	22 (29)	9 (35)	8 (26)	5 (28)
PD	3 (4)	2 (8)	-	-
NE	5 (7)	2 (8)	2 (7)	1 (6)
DCR, (%) (95% CI)	90 (80.6, 95.4)	85 (65.1, 95.6)	94 (78.6, 99.2)	94 72.7, 99.9)

Alexander Spira. ASCO 2025
Marcelo V Negrao. WCLC 2025

Moving to 1st line...KRAS G12Ci+Chemo or Cetuxi

CodeBreak 101 (Ph 1)

Sotorasib + Carboplatin + Pemetrexed → Sotorasib + Pemetrexed (N=37)

ORR65%

mPFS 10.8m ITT
mPFS 11.9m PD-L1<1%

SCARLET (Ph 2)

Sotorasib + Carboplatin + Pemetrexed → Sotorasib + Pemetrexed (N=27) NSQ

ORR89%

mPFS 6.6m ITT
mPFS 9.7m PD-L1<1%

Chemo free option

KROCUS (Ph 2)

Fulzerasib+Cetuximab (N=33)

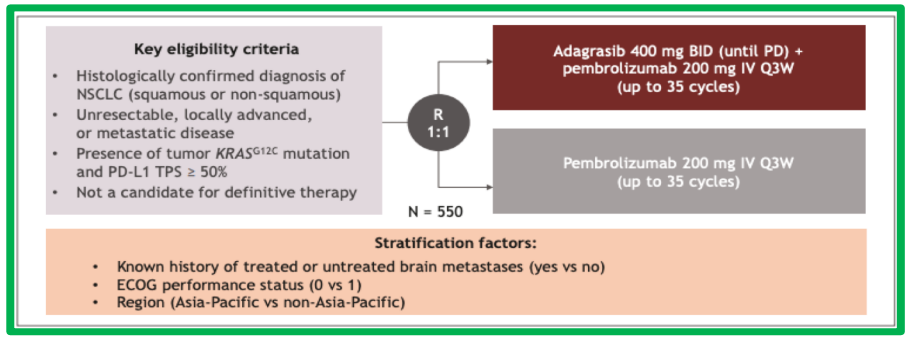
ORR82%

mPFS 12.6m

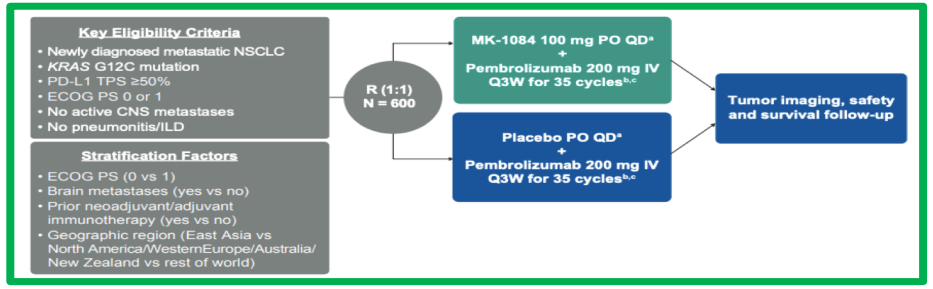
Li B et al. ASCO 2024
Yosioka H et al. ASCO 2024
Gregorc V et al ASCO 2024
Majem et al. ASCO 2025

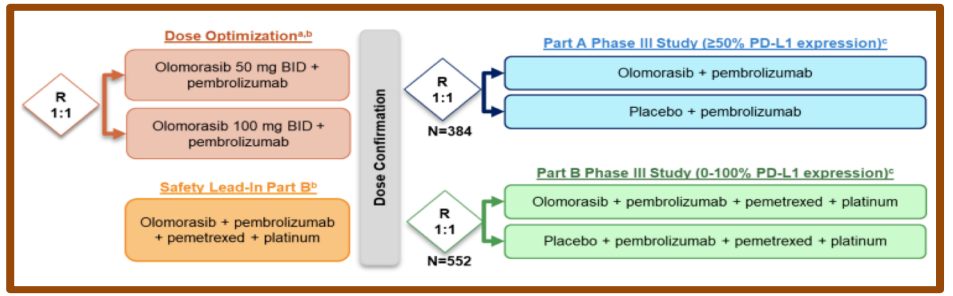
PHASE III TRIALS in 1st line

Addition of KRAS G12C off inhibitors could prolong PFS

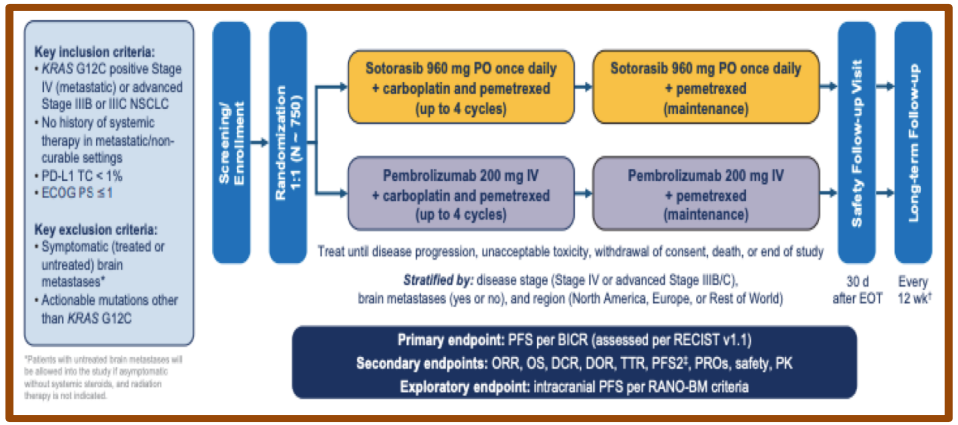


IO combinations



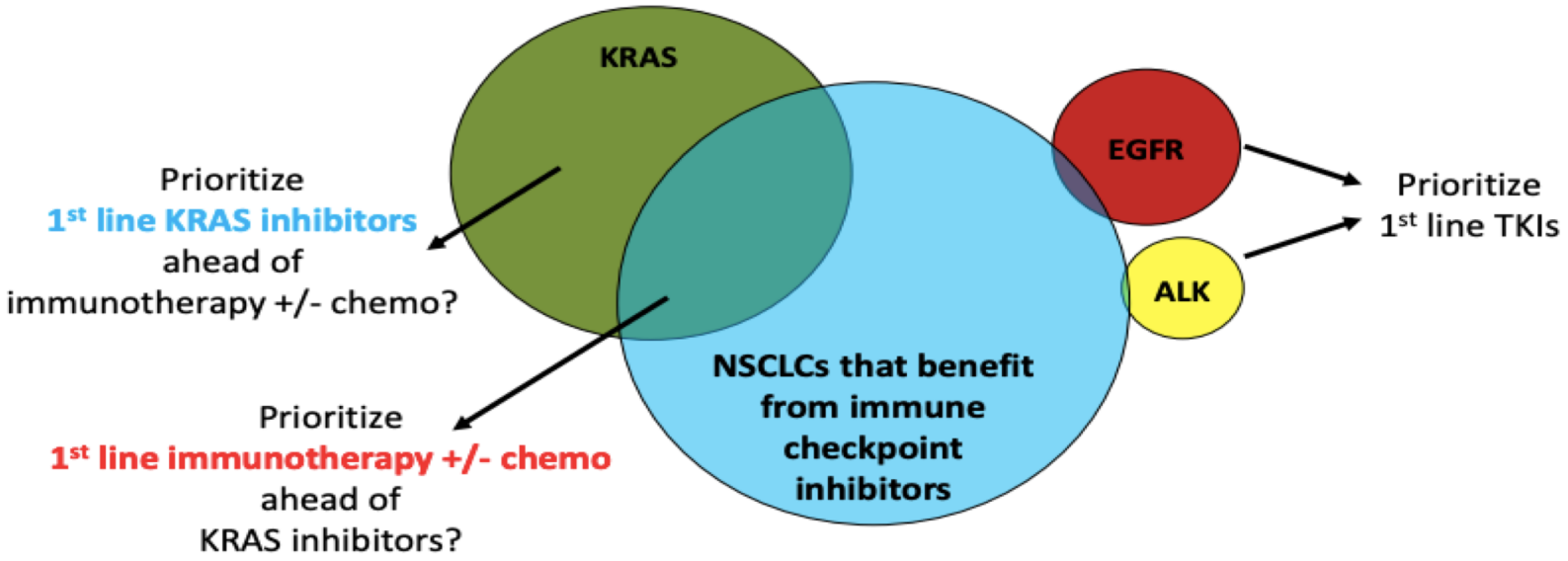


Chemo combinations



Garasino MC. ESMO 2023 y ESMO 2024. Negrao MV. ASCO 2024. Li BT. ASCO 2024

Moving to 1st line...combination therapy



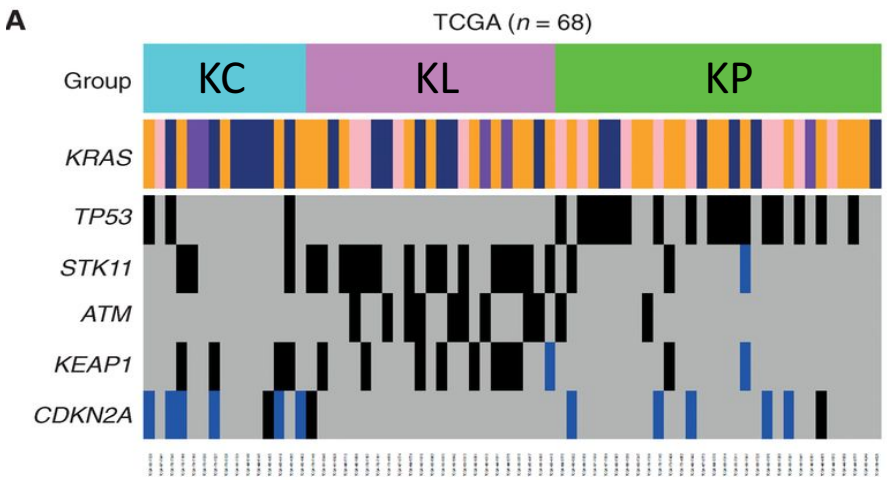
Biomarkers of ICI and KRASi efficacy in NSCLC?

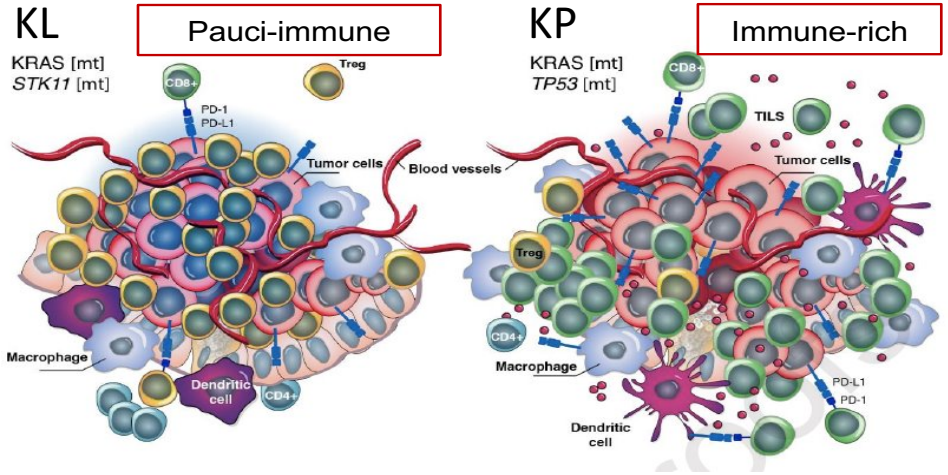
Do all need combination therapy?

Mark Awad Esmo 2024.

CONCOMITANT GENOMIC ALTERATIONS

Concomitant genomic alterations in KRAS mutant NSCLC



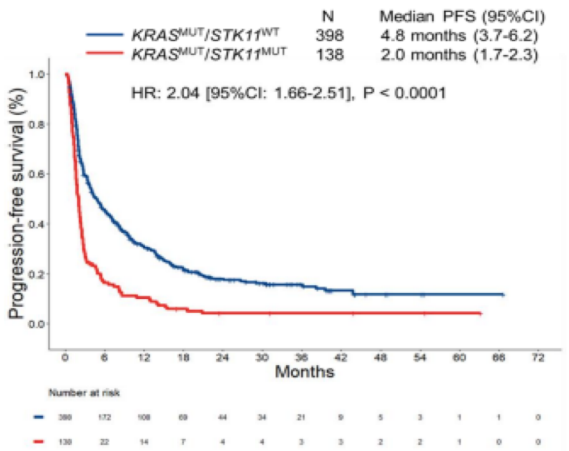


53% of tumours harboured at least one additional genomic alteration

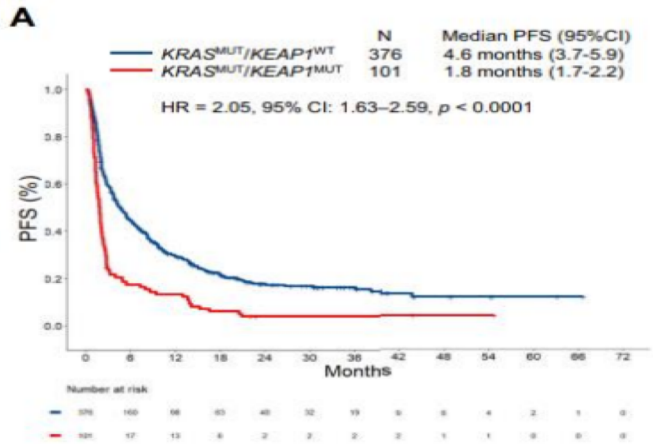
KRAS alone: ~30%; KRAS/TP53: ~30%; KRAS/LKB1: ~ 30%; KRAS/TP53/LKB1: < 5%

Ding et al. Nature 2008; Skoulidis et al. Cancer Discovery 2015

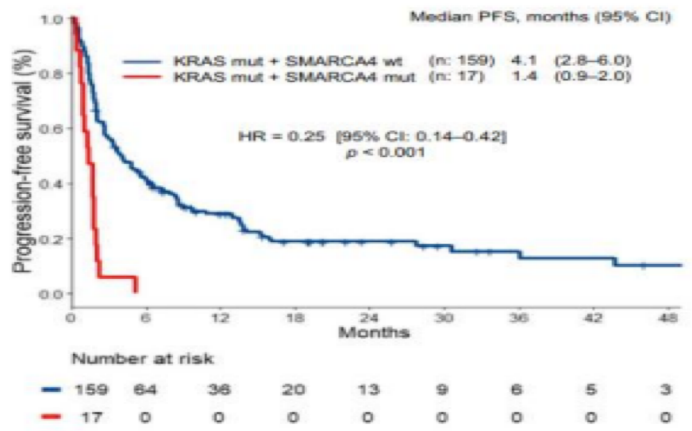
Genomic co-mutations: *STK11*



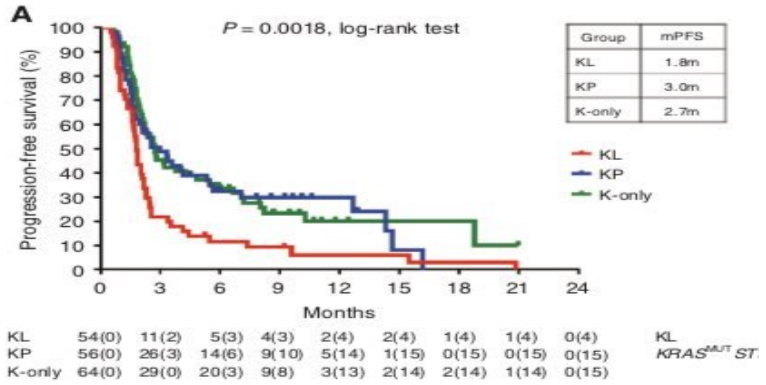
Genomic co-mutations: *KEAP1*



Genomic co-mutations: *SMARCA4*



Genomic co-mutations: *LKB1*

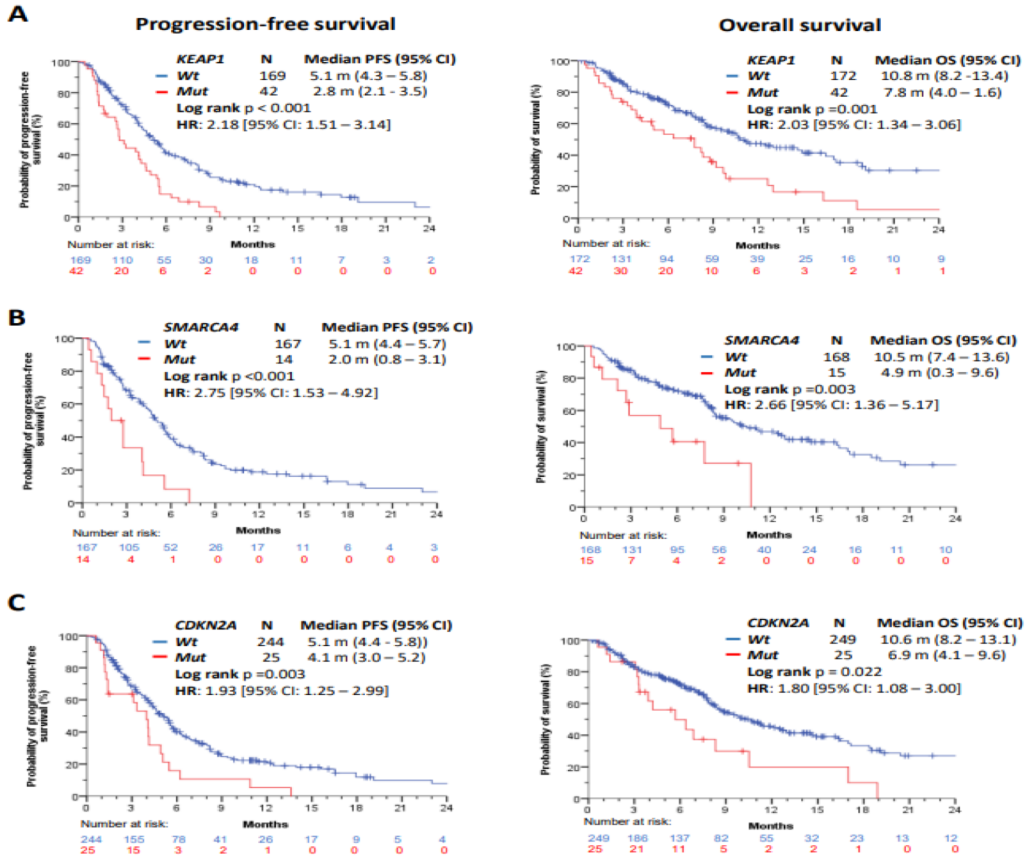


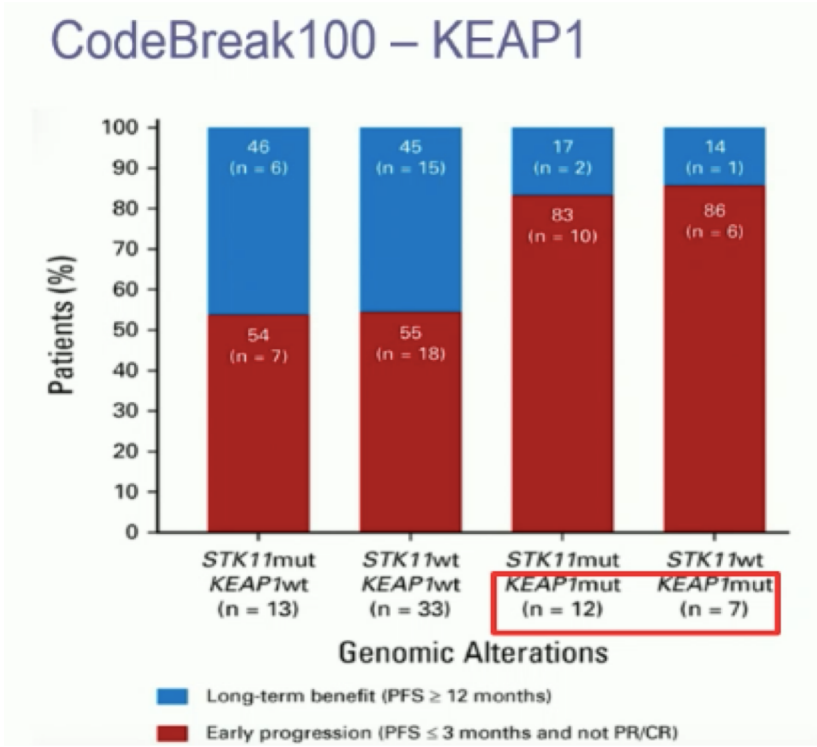
Ricciuti B, et al, J Thorac Oncol. 2021
Alessi JV, et al, J Thorac Oncol. 2021 Jul;16(7):1176-1187

PRIMARY RESISTANCE

Primary Resistance to KRAS G12Ci

Clinical outcomes with KRAS G12Ci therapy according to co-mutation status





Dy G et al. J clin oncol. 2023
Negrao MV. Cancer discov 2023

Primary Resistance mechanism

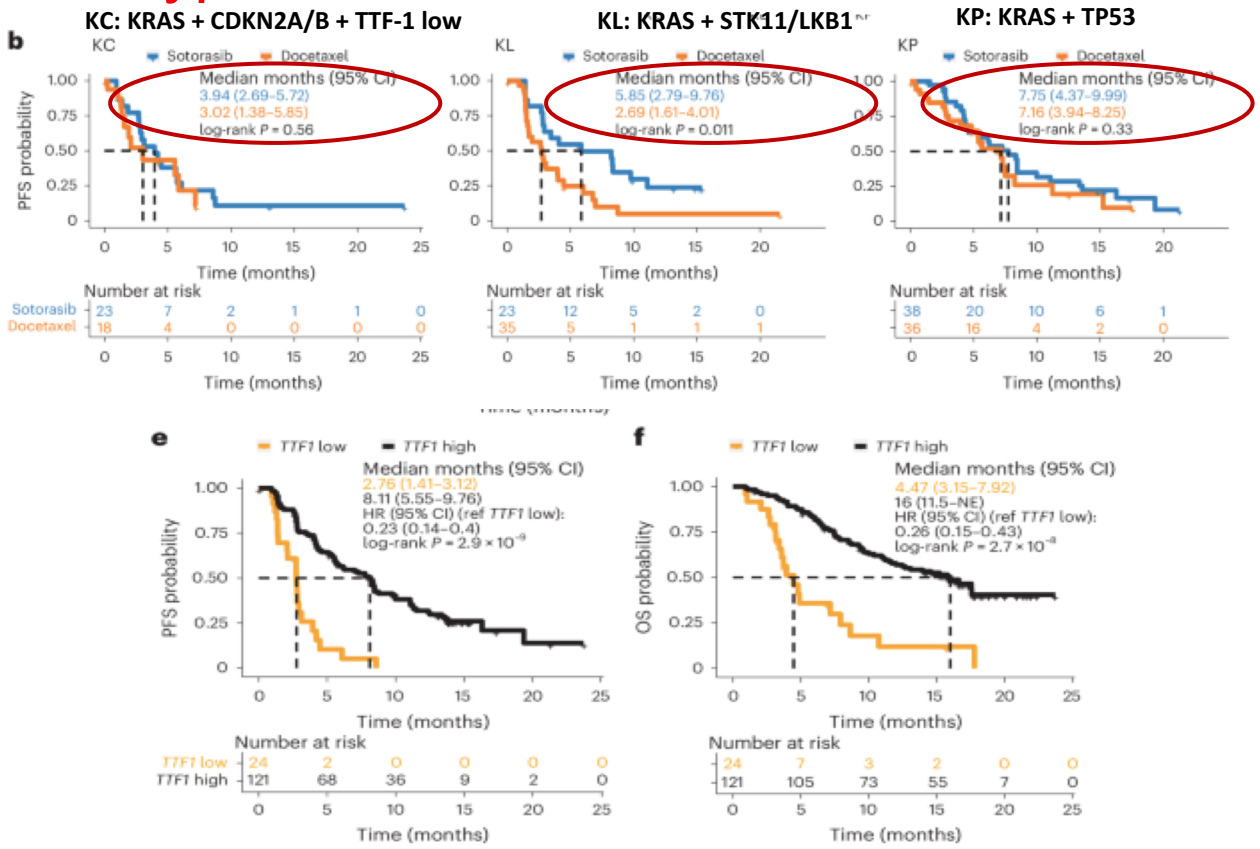
3 subtypes: KP/KC/KL

KL: <u>More benefit Sotorasib:</u>

- Cold TME
- Lack PD-L1

KC: <u>Worse prognosis:</u>

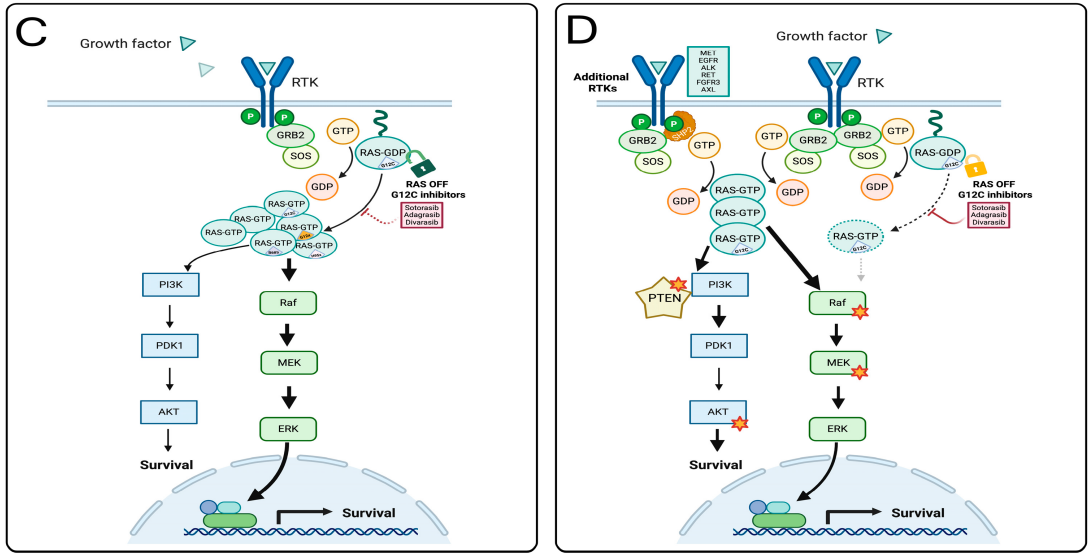
- TTF 1 low
- CDKN2a/2b loss
- Mucinous



Skoulidis et al. CAncer discov 2015.Skoulidis et al. Nat Med 2025

ACQUIRED RESISTANCE

Acquired Resistance mechanism



Resistance Mechanism	NSCLC Prevalence (%)	Notes
Secondary KRAS mutations	20–25	Y96C/D/S, G13D, Q99, etc.
KRAS amplification	22	More frequent in NSCLC than CRC
RAS/MAPK pathway alterations	26	Includes *NRAS*, *BRAF*, *MAP2K1*, *EGFR*, *MET*, *HER2*, *PI3KCA*, etc.
Multiple concurrent events	23	Often a combination of the above mutations
EGFR pathway activation	10–15	Key adaptive resistance driver, especially in CRC
MET amplification	1–6	Notable in NSCLC, less frequent in CRC
PI3K pathway activation	8–10	Includes *PI3KCA*, *PTEN*, *mTOR* alterations

Vitiello, P.P.et al Cancers 2025,

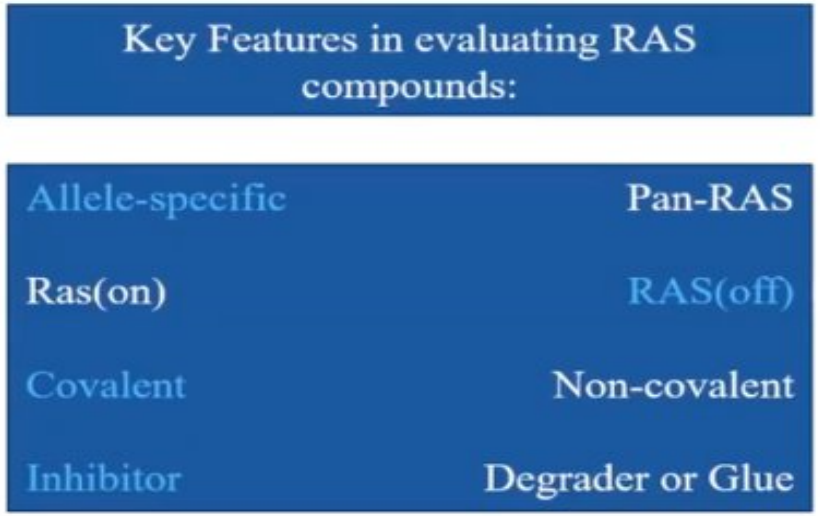
FUTURE DIRECTIONS

Potential future directions

KRAS G12Ci COMBINATIONS

Novel RAS inhibitors (pan-RAS, tricomplex, and ON-state inhibitors)

- Other KRAS alleles
- Active GTP-bound state
- **Co-mutations such as STK11 and KEAP1**



RAS(ON) inhibitors

RMC-6236
RAS(ON) multi-selective inhibitor

daraxonrasib

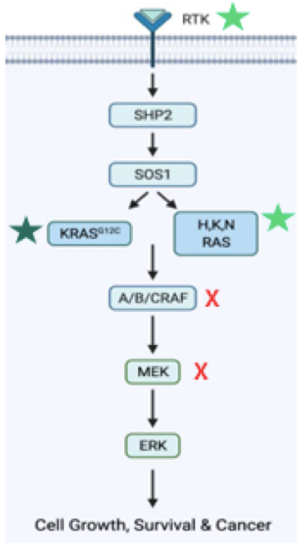
- Noncovalent, selective inhibitor with potent activity vs mutant and wild-type RAS(ON) proteins
- Orally bioavailable, generally well-tolerated in patients at active doses
- Clinical monotherapy anti-tumor activity observed across diverse RAS cancer mutations†
- Potential backbone of RAS(ON) inhibitor doublets with RAS(ON) mutant-selective inhibitors

†NCT05379985

Mutant RAS amplification
SWII binding pocket mutations

RAS(ON) Rescue Mechanisms
- Potential sensitivity to RMC-6236
- Potential sensitivity to RMC-6236 or RMC-6291

Schulze, et al. *Science* 2023
Holderfield et al. *Nature* 2024

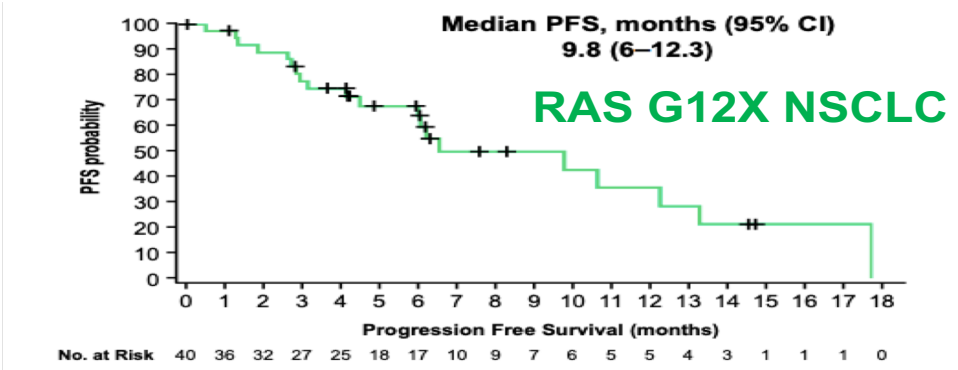


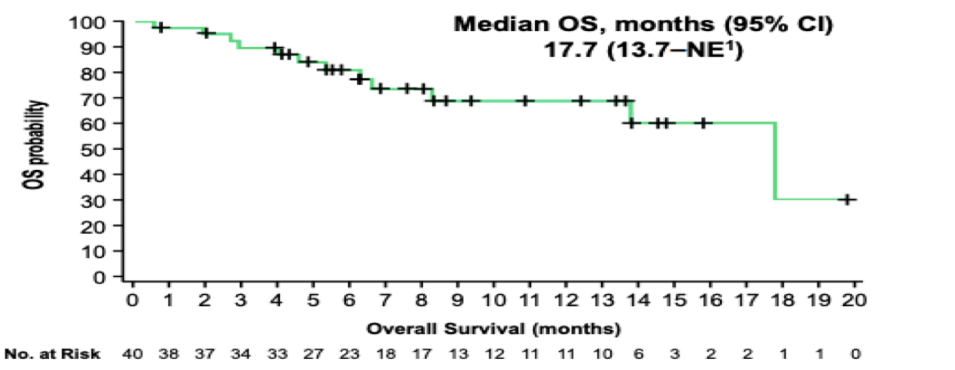
Upstream activation
RTK alterations

WT RAS activation
Oncogene switch mutations

Downstream pathway activation (X)

Awad and Aguirre et al., *New Engl J Med.* 2021
Tanaka et al. *Cancer Discovery* 2021
Zhao et al., *Nature* 2022
Sacher et al., *NEJM* 2023





Xing Wei, Ph.D. AACR 2024. Salman R Punekar. ELCC 2025

TAKE home messages

- **Historically difficult to develop therapies against KRAS; G12C inhibitors hold great promise; early clinical signs promising non G12C mutations**
  - Non-G12C mutants – more effective downstream inhibitor(s)
- **KRAS is a heterogenous cancer – different allelic variants and different co-mutations; all likely to impact future therapies**
- **These drugs and the research that underlies their development emphasizes the critical importance of fully genotyping all patients at diagnosis**
- **Future directions:**
  - Understanding resistance mechanisms
  - Improve the knowledge for patient selection (especially in treatment combinations)

Challenging questions: optimal dose of KRASi and intracranial activity

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