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KRAS mutation in aNSCLC

Thoraxonkologie-Tag 2020

the *KRAS* gene

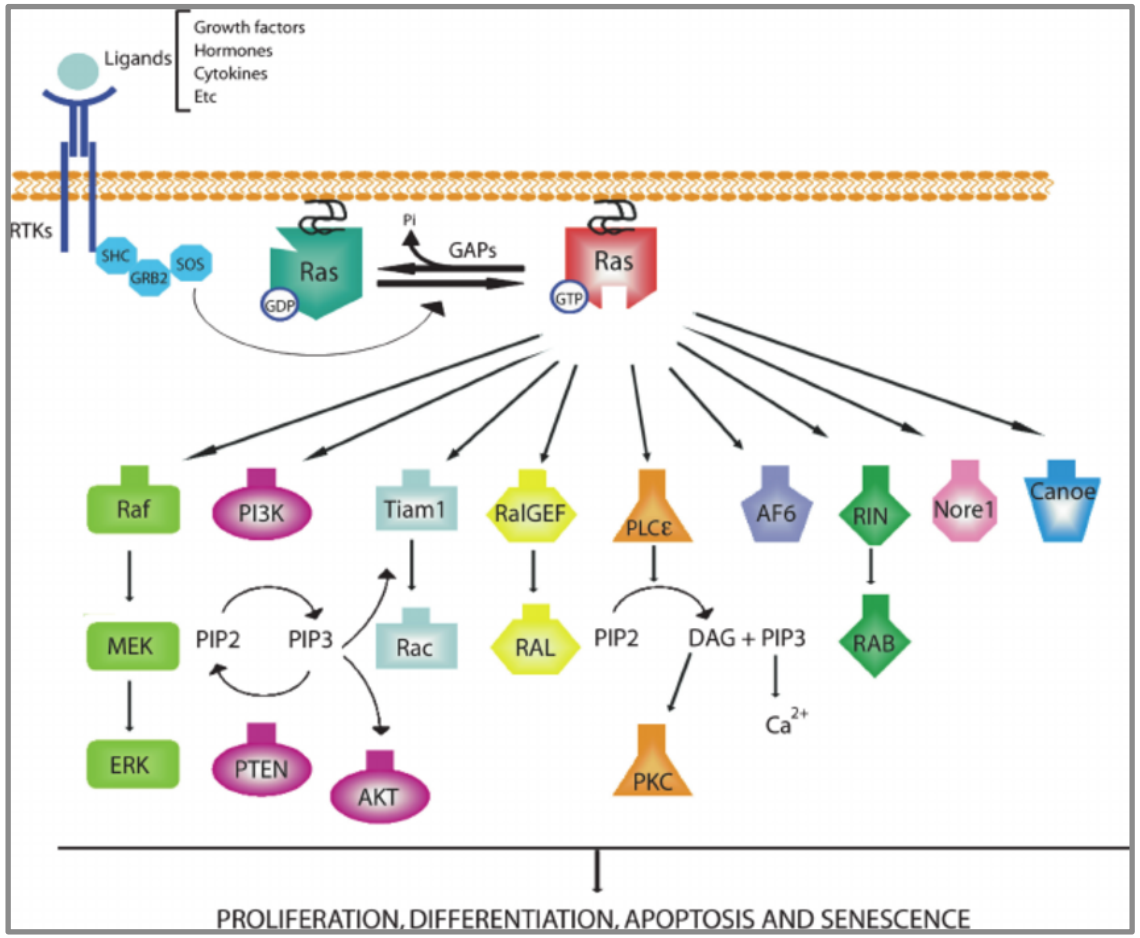
RAS family: *KRAS*, *HRAS*, *NRAS*

189 AA; cell-membrane, cytosol-facing

multi-purpose molecular switch active w/ GTP, inactive w/ GDP; regulated by GEFs/GAPs

very high GTP-affinity

pathways:
Raf-MEK-MAPK;
PI3K-AKT-mTOR, ...



- FROM: Castellano E., Downward J. (2010) Role of RAS in the Regulation of PI 3-Kinase. In: Rommel C., Vanhaesebroeck B., Vogt P. (eds) Phosphoinositide 3-kinase in Health and Disease. Current Topics in Microbiology and Immunology, vol 346. Springer, Berlin, Heidelberg. https://doi.org/10.1007/82_2010_56

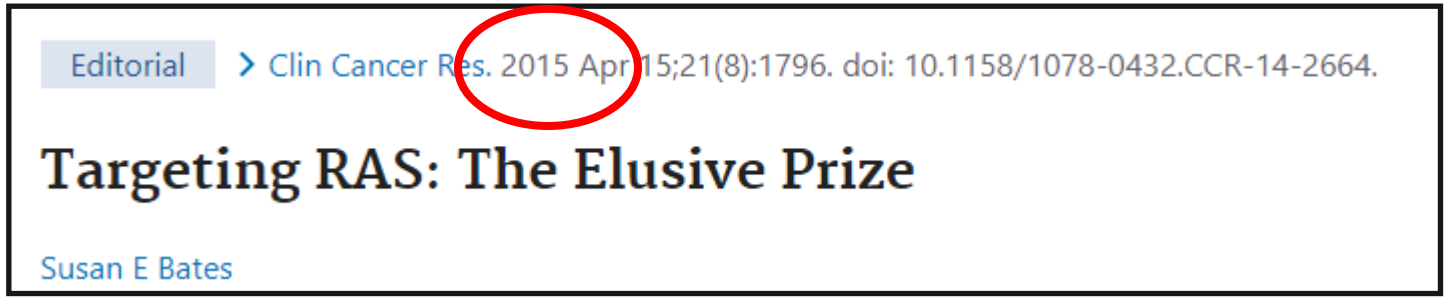
KRAS mutation – very common, „undruggable“

 # discovered 1982 „Kirsten *r*at sarcoma“

 # very common oncogene:
PDAC 90 %; NSCLC 35 %; CRC: 40 %

 # G12C mutation:
40 % of NSCLC *KRAS* mutations = 10-15 % absolute

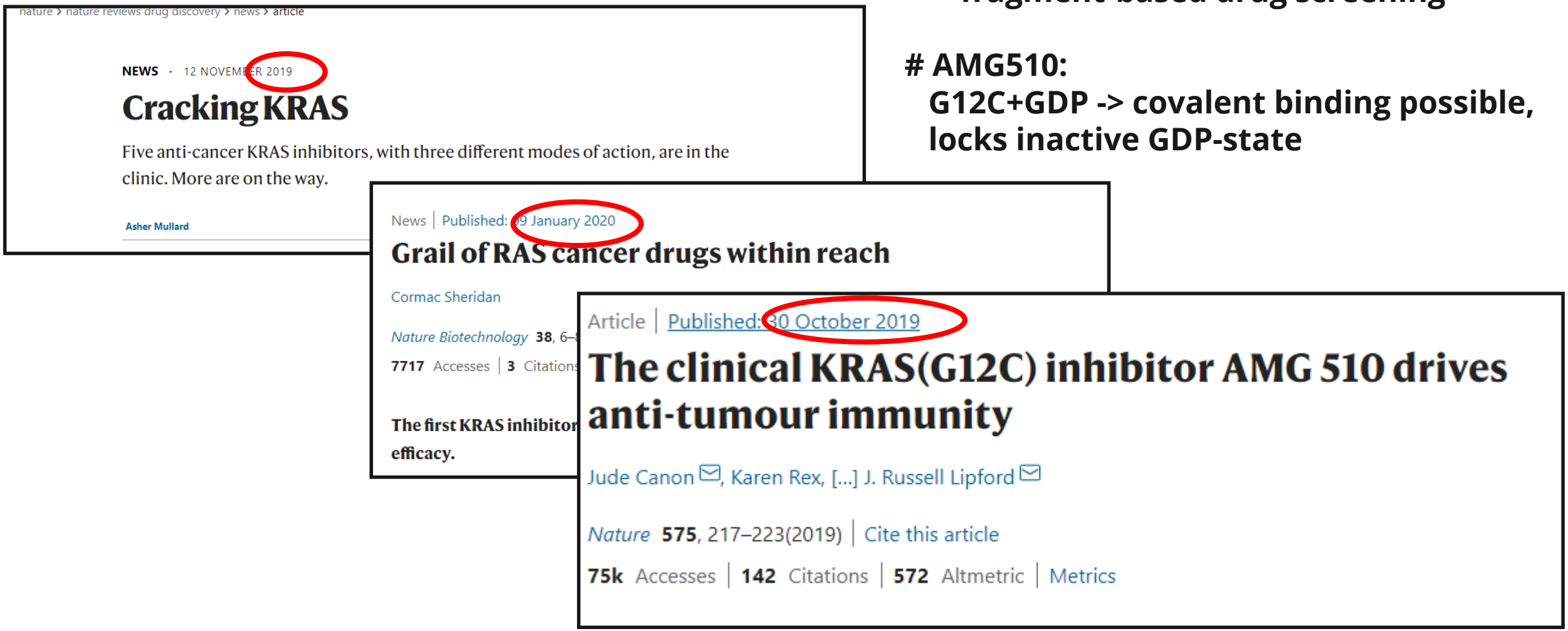
 # „undruggable“: high GTP affinity; side effects; rapid resistance



Progress 2020

 # technologies:
- **in silico docking**
- **covalent tethering**
- **fragment-based drug screening**

 # AMG510:
G12C+GDP -> covalent binding possible, locks inactive GDP-state



nature › nature reviews drug discovery › news › article

NEWS · 12 NOVEMBER 2019

Cracking KRAS

Five anti-cancer KRAS inhibitors, with three different modes of action, are in the clinic. More are on the way.

Asher Mullard

News | Published: 09 January 2020

Grail of RAS cancer drugs within reach

Cormac Sheridan

Nature Biotechnology **38**, 6–

7717 Accesses | **3** Citations

The first KRAS inhibitor
efficacy.

Article | Published: 30 October 2019

The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity

Jude Canon, Karen Rex, [...] J. Russell Lipford

Nature **575**, 217–223(2019) | Cite this article

75k Accesses | **142** Citations | **572** Altmetric | Metrics

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 24, 2020 VOL. 383 NO. 13

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

D.S. Hong, M.G. Fakih, J.H. Strickler, J. Desai, G.A. Durm, G.I. Shapiro, G.S. Falchook, T.J. Price, A. Sacher, C.S. Denlinger, Y.-J. Bang, G.K. Dy, J.C. Krauss, Y. Kuboki, J.C. Kuo, A.L. Coveler, K. Park, T.W. Kim, F. Barlesi, P.N. Munster, S.S. Ramalingam, T.F. Burns, F. Meric-Bernstam, H. Henary, J. Ngang, G. Ngarmchamnanrith, J. Kim, B.E. Houk, J. Canon, J.R. Lipford, G. Friberg, P. Lito, R. Govindan, and B.T. Li

Table 2. Adverse Events in All 129 Patients.

Events	Any Grade	Grade ≥3	Grade ≥4	Grade 5: Fatal
	number (percent)			
Adverse events of any cause that occurred during treatment				
Any	125 (96.9)	68 (52.7)	26 (20.2)	22 (17.1)
Serious	58 (45.0)	51 (39.5)	25 (19.4)	22 (17.1)
Resulting in discontinuation of treatment*	9 (7.0)	9 (7.0)	4 (3.1)	4 (3.1)
Adverse events of any cause that occurred during treatment in ≥10% of patients				
Diarrhea	38 (29.5)	5 (3.9)	0	0
Fatigue	30 (23.3)	3 (2.3)	0	0
Nausea	27 (20.9)	2 (1.6)	0	0
Vomiting	23 (17.8)	5 (3.9)	0	0
Abdominal pain	23 (17.8)	4 (3.1)	0	0
Dyspnea	21 (16.3)	3 (2.3)	1 (0.8)	1 (0.8)

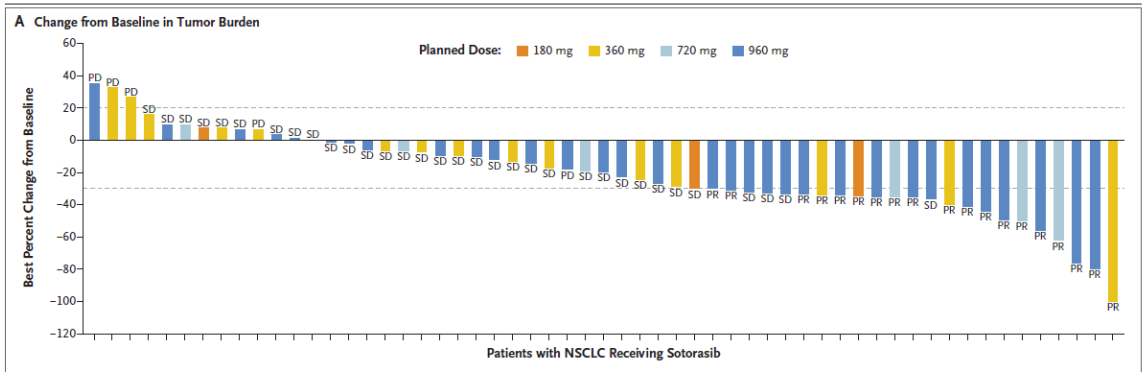


Table 3. Efficacy of Sotorasib in All Tumor Types.

	NSCLC (N=59)	Colorectal Cancer (N=42)	Other (N=28)
Best overall response — no. (%)			
Confirmed complete response	0	0	0
Confirmed partial response	19 (32.2)	3 (7.1)	4 (14.3)
Stable disease	33 (55.9)	28 (66.7)	17 (60.7)
Progressive disease	5 (8.5)	10 (23.8)	4 (14.3)
Could not be evaluated	1 (1.7)	0	1 (3.6)
No assessment*	1 (1.7)	1 (2.4)	2 (7.1)
Objective response — % (95% CI)†	32.2 (20.62–45.64)	7.1 (1.50–19.48)	14.3 (4.03–32.67)
Disease control — % (95% CI)‡	88.1 (77.07–95.09)	73.8 (57.96–86.14)	75.0 (55.13–89.31)

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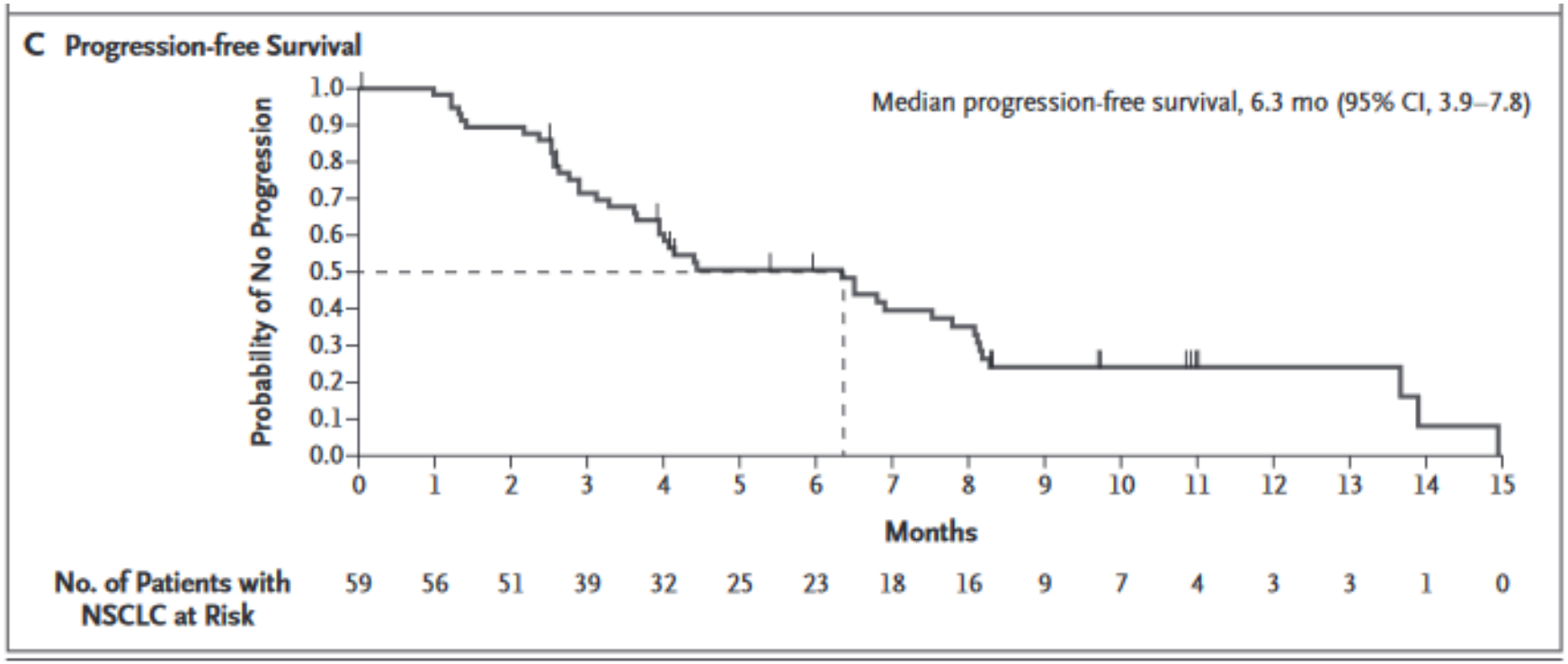

CASE: our best patient in expansion cohort

 # Pt, male, 52 years
 # aNSCLC ED 05/2016 cT3 cN0 cM0
 # ND COPD GOLD 3; current smoker

 # Tx:

2016 CTX/Sx/CTX
PD 12/2016 cM1(PUL) -> Nivolumab
PD 03/2017 -> Docetaxel/Nintedanib
PD 07/2017 -> Pemetrexed on/off
PD 06/2019 -> Gem/Vino
PD 09/2019 -> AMG510 960 mg p.o. expansion cohort
start 11/2019; Symptoms: dyspnea +++

CT-Bildgebung mit Ausgangsbefund und Therapieansprechen

CASE: *KRAS* G12C oral treatment, Pt now 53 yo

 # clinical response:
early improvement of dyspnoe, ECOG 0

 # AE:
mild pulmonary infection;
dermatological (low grade)

Next:

**# understand resistance,
overcome resistance**

 # synergy with IOT, CTX?

 # mutations other than G12C?