Lung Cancer UPDATES
ASCO HIGHLIGTHS
02-06 JUNIO 2023
Chicago, USA

Iniciativa científica de:
GECP
lung cancer research

CPNM KRAS mutado

Ernest Nadal

ICO Hospitalet (Barcelona) - IDIBELL

Conflictos de interés

Iniciativa científica de: GECP lung cancer research

Research funding: Roche, Pfizer, Merck-Serono, Bristol Myers Squibb

Advisory board or lectures: Roche, Bristol Myers Squibb, Merck Sharp Dohme, Merck-Serono, Sanofi, Pfizer, Lilly, Amgen, Boehringer-Ingelheim, AstraZeneca, Takeda, Sanofi, Pierre Fabre, Qiagen, Mirati, Janssen and Bayer.

CodeBreak 200 – Biomarker subgroup analysis

Exploratory analysis based on tissue and plasma NGS

Iniciativa científica de: GECP lung cancer research

CodeBreaK 200

2023 ASCO ANNUAL MEETING

Biomarker subgroup analyses of CodeBreaK 200, a phase 3 trial of sotorasib versus docetaxel in patients with pretreated *KRAS* G12C-mutated advanced non-small cell lung cancer (NSCLC)

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PRESENTED BY: Ferdinandos Skoulidis, MD, PhD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Skoulidis et al. Oral.

CodeBreak 200 – Biomarker subgroup analysis

Exploratory analysis based on tissue and plasma NGS

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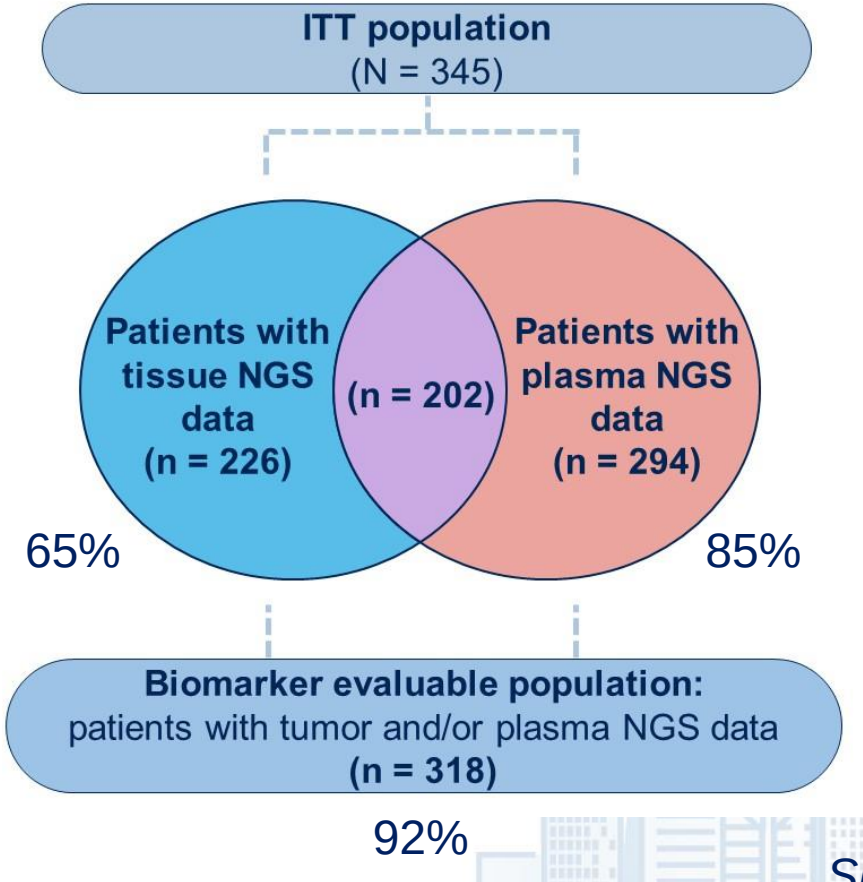
Biomarker Analysis Methodology

Pre-specified Subgroup Analyses

- Baseline tissue and/or plasma samples were analyzed for key genomic alterations* using central targeted NGS[7]
  - Tissue NGS: Tempus xT assay (648 genes)
  - Plasma NGS: Resolution ctDx Lung assay (23 genes)
- PD-L1 protein level was assessed by local standard of care testing



Skoulidis et al. Oral.

CodeBreak 200 – Biomarker subgroup analysis

Exploratory analysis based on tissue and plasma NGS

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Sotorasib Retained PFS Benefit Versus Docetaxel Across Key Co-alteration Subgroups*

	Number of Patients		Hazard Ratio (95% CI)
	Sotorasib	Docetaxel	
All patients	164	154	0.68 (0.52, 0.88)
TP53			
Altered	89	92	0.83 (0.58, 1.18)
Wild-type	75	62	0.48 (0.30, 0.75)
STK11			
Altered	60	60	0.68 (0.45, 1.05)
Wild-type	104	94	0.65 (0.46, 0.92)
KEAP1			
Altered	46	36	0.84 (0.48, 1.47)
Wild-type	118	118	0.62 (0.45, 0.84)
EGFR			
Altered	31	35	0.86 (0.47, 1.58)
Wild-type	133	119	0.63 (0.46, 0.86)
BRAF			
Altered	7	9	–
Wild-type	157	145	0.63 (0.48, 0.83)
ALK			
Altered	19	15	0.72 (0.33, 1.57)
Wild-type	145	139	0.70 (0.53, 0.93)
MET			
Altered	18	21	0.52 (0.21, 1.29)
Wild-type	146	133	0.73 (0.55, 0.97)

	Number of Patients		Hazard Ratio (95% CI)
	Sotorasib	Docetaxel	
ERBB2			
Altered	13	13	1.02 (0.40, 2.59)
Wild-type	151	141	0.67 (0.50, 0.88)
RET			
Altered	10	11	0.49 (0.16, 1.52)
Wild-type	154	143	0.68 (0.52, 0.90)
ROS1			
Altered	12	5	–
Wild-type	152	149	0.68 (0.52, 0.89)
NTRK1, 2, 3			
Altered	35	18	0.59 (0.29, 1.20)
Wild-type	129	136	0.66 (0.49, 0.88)
KRAS, NRAS			
Altered	11	17	0.62 (0.21, 1.82)
Wild-type	153	137	0.67 (0.50, 0.89)
PIK3CA			
Altered	16	14	0.88 (0.35, 2.21)
Wild-type	148	140	0.64 (0.49, 0.85)

Additionally, sotorasib retained ORR benefit versus docetaxel independent of key co-alteration subgroups*

Skoulidis et al. Oral.

CodeBreak 200 – Biomarker subgroup analysis

Primary resistance to sotorasib

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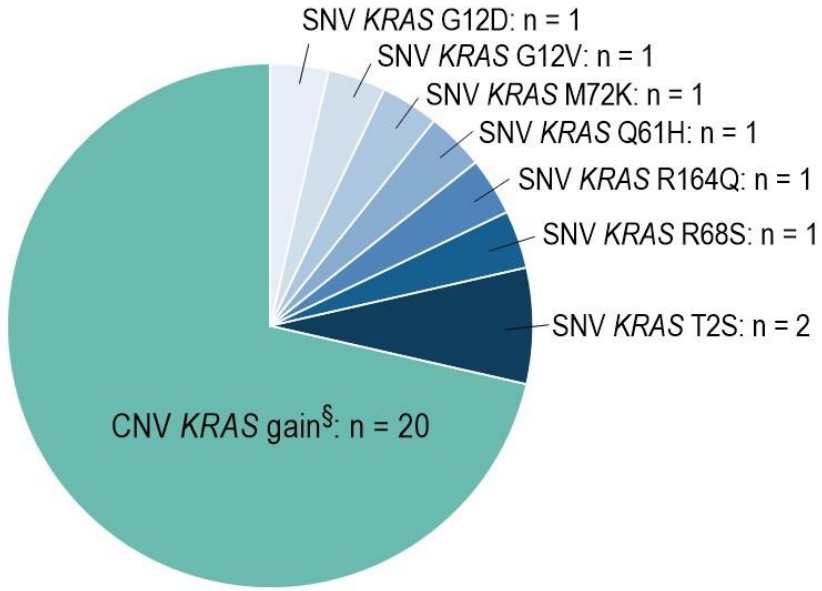
KRAS Co-alterations Were Potentially Associated with Primary Resistance Irrespective of Treatment

	Sotorasib (n = 164)	Docetaxel (n = 154)	Treatment Difference (*P*-value)
***KRAS* co-alteration*, n (%)**	**9 (5)**	**17 (11)**	
ORR†, n (%)	0	0	–
Median PFS (95% CI)†	1.8 (0.8, 3.0)	2.5 (1.4, 3.1)	0.016‡
HR (95% CI)‡	1.74 (0.84, 3.58)		



2 codón 12
1 codón 61
4 otros codones

- **No response observed in patients with additional *KRAS* co-alterations in either treatment arm**
- **Outcomes align with preclinical data suggesting some non-G12C *KRAS* alterations mediate sotorasib resistance[8]**

Skoulidis et al. Oral.

CodeBreak 200 – Biomarker subgroup analysis

Genomic alterations in early progressors to sotorasib

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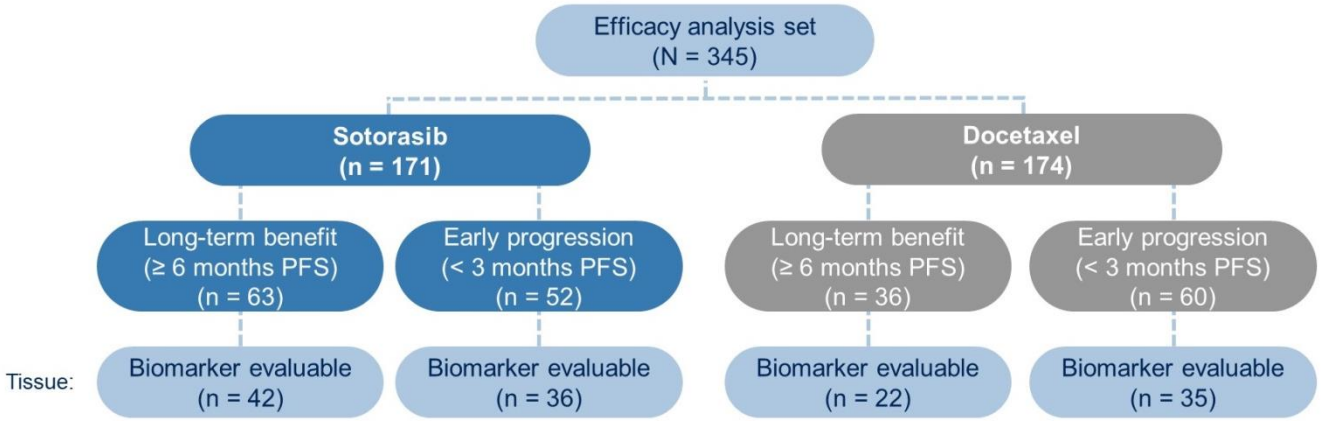
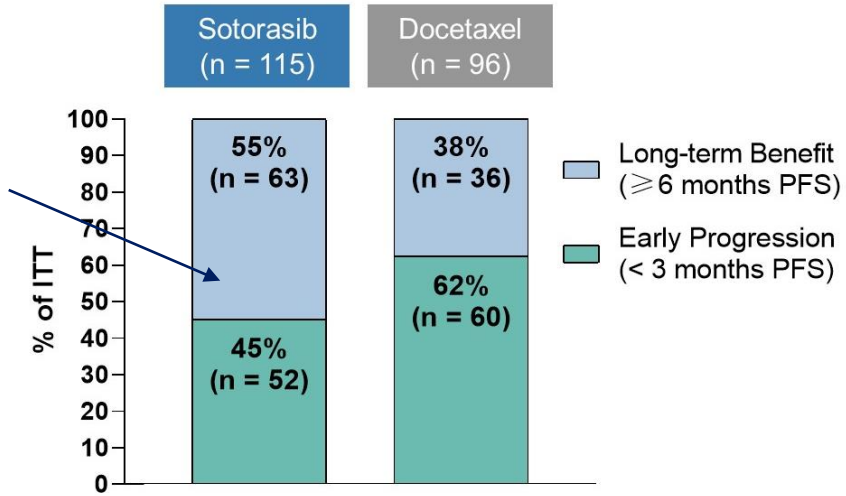
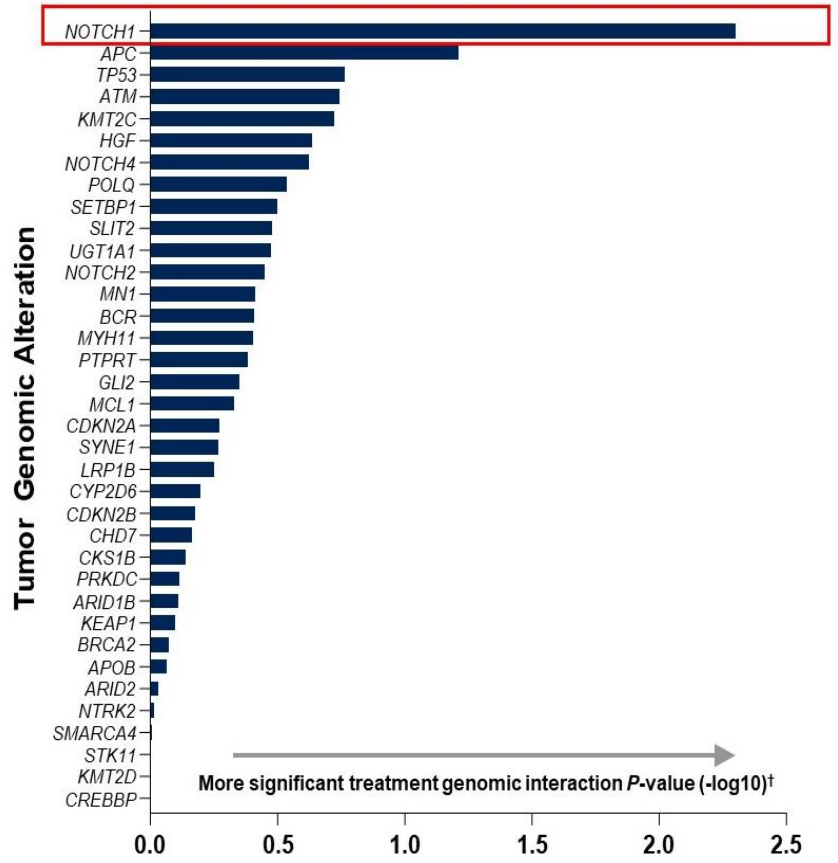


More patients obtained “long-term” benefit from sotorasib than docetaxel





***NOTCH1* was the most notable co-alteration associated with early progression or long-term benefit**

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CodeBreak 200 – Biomarker subgroup analysis

Early progressors to sotorasib were enriched for NOTCH1 mutations

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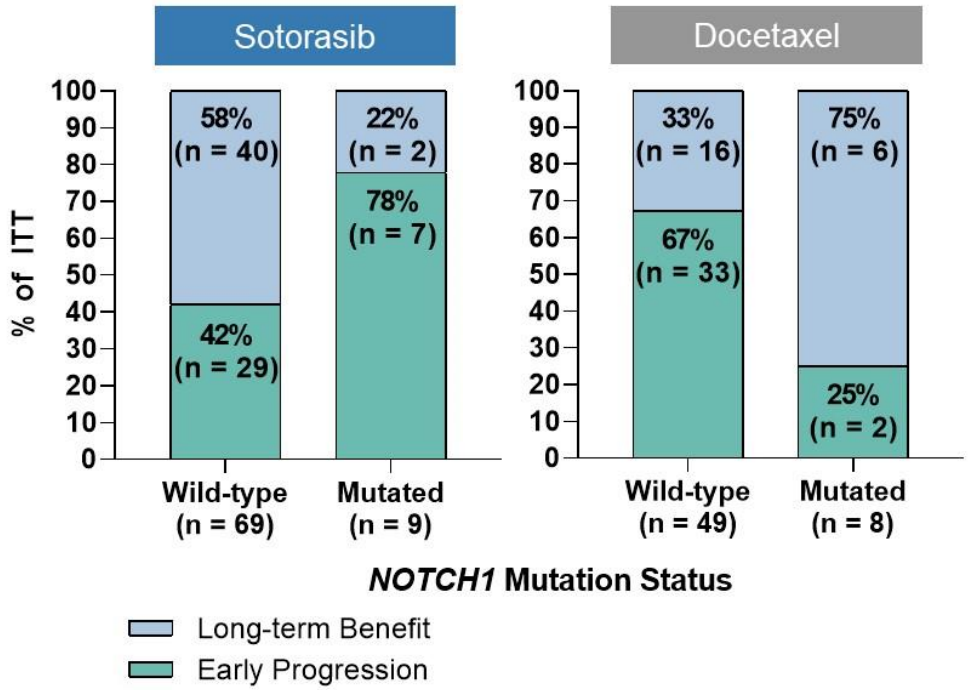
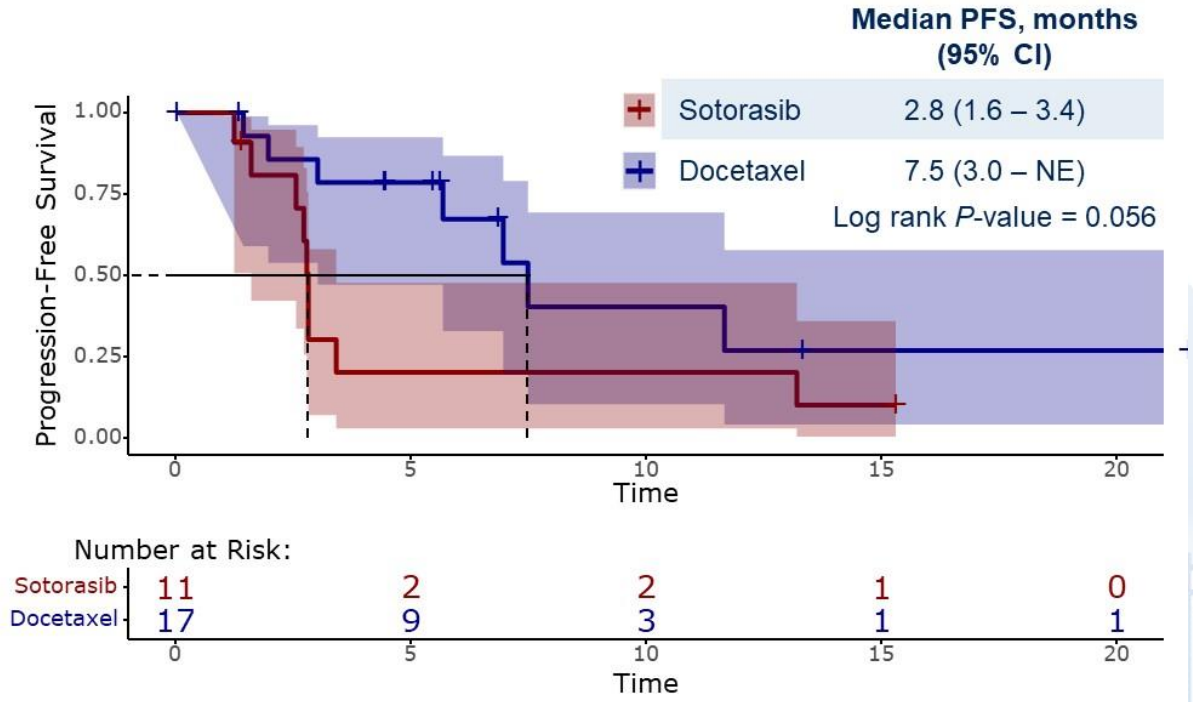
In a Limited Data Set, *NOTCH1m* Had an Early Progression Signal With Sotorasib That Warrants Further Exploration





Skoulidis et al. Oral.

CodeBreak 200 – Exploratory analysis in patients with Brain mets

Patients with brain mets previously treated were underrepresented in the study

Iniciativa científica de: GECP lung cancer research

ASCO 2023

Intracranial Efficacy of Sotorasib Versus Docetaxel in Pretreated *KRAS* G12C-Mutated Advanced Non-Small Cell Lung Cancer (NSCLC): Practice-Informing Data From a Global, Phase 3, Randomized, Controlled trial (RCT)

Anne-Marie C. Dingemans[1], Konstantinos Syrigos[2], Lorenzo Livi[3], Astrid Paulus[4], Sang-We Kim[5], Yuanbin Chen[6], Enriqueta Felip Font[7], Frank Griesinger[8], Kadoaki Ohashi[9], Gerard Zalcman[10], Brett Gordon Maxwell Hughes[11], Jens Benn Sørensen[12], Normand Blais[13], Carlos Gil Ferreira[14], Colin R. Lindsay[15], Rafal Dziadziuszko[16], Patrick J. Ward[17], Cynthia C. Obiozor[18], Yang Wang[18], Solange Peters[19]

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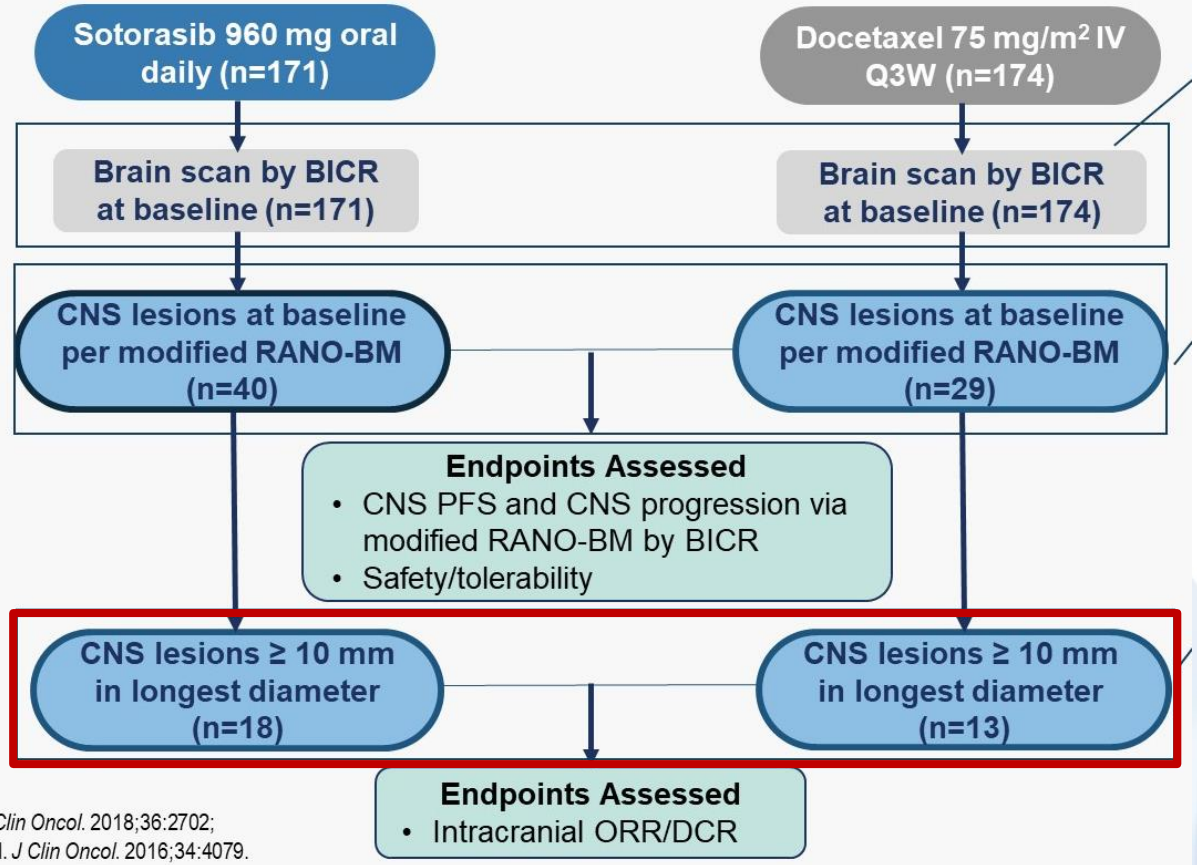

*Wu et al. *J Clin Oncol.* 2018;36:2702; Gadgeel et al. *J Clin Oncol.* 2016;34:4079.

Dingemans et al. Poster Discussion.

CodeBreak 200 – Exploratory analysis in patients with Brain mets

Better Time to intracranial progression or CNS PFS with sotorasib

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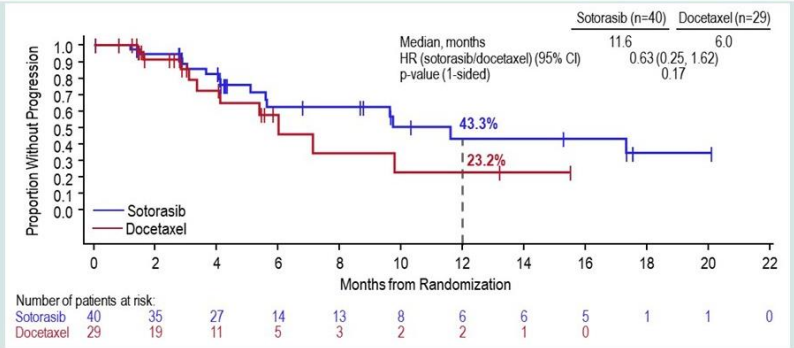
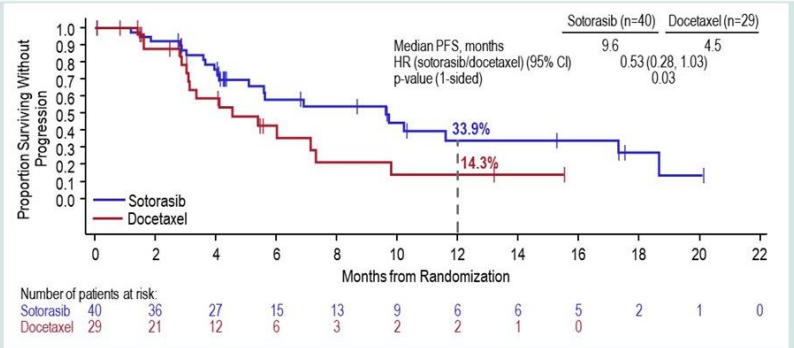
Time to CNS Progression in Patients with CNS Lesions at Baseline



Median time to CNS progression was delayed in patients treated with sotorasib compared with docetaxel (11.6 months vs 6.0 months; HR 0.63 [95% CI: 0.25, 1.62]; p=0.17)

CNS Progression-Free Survival in Patients with CNS Lesions at Baseline



Median time to CNS progression or all-cause death was longer in patients treated with sotorasib compared with docetaxel (9.6 months vs 4.5 months; HR 0.53 [95% CI: 0.28, 1.03]; p=0.03)

	Patients with Stable/Pretreated CNS Lesions at Baseline	
	Sotorasib n=18	Docetaxel n=13
Confirmed Objective Response Rate, n (%)	**6 (33.3)**	**2 (15.4)**
Complete Response	1 (5.6)	1 (7.7)
Partial Response	5 (27.8)	1 (7.7)
Stable Disease	9 (50.0)	9 (69.2)
Progressive Disease	1 (5.6)	2 (15.4)
Not Evaluable/Not Done†	2 (11.2)	0
Disease Control Rate, n (%)	15 (83.3)	11 (84.6)
Unconfirmed and Confirmed ORR, n (%)	9 (50.0)	2 (15.4)

Dingemans et al. Poster Discussion.

SCARLET- Sotorasib + CBDCA + PEM in KRAS G12C

Iniciativa científica de: GECP lung cancer research

2023 ASCO ANNUAL MEETING

The primary endpoint analysis of SCARLET study:

A single-arm, phase II study of sotorasib plus carboplatin-pemetrexed in advanced non-squamous, non-small cell lung cancer patients with KRAS G12C mutation: WJOG14821L

Shinya Sakata[1], Hiroaki Akamatsu[2], Koichi Azuma[3], Takehiro Uemura[4], Yuko Tsuchiya-Kawano[5], Hiroshige Yoshioka[6], Mitsuo Osuga[2], Yasuhiro Koh[2], Satoshi Morita[7], Nobuyuki Yamamoto[2]

[1]Kumamoto University Hospital, [2]Wakayama Medical University, [3]Kurume University School of Medicine, [4]Nagoya City University Graduate School of Medical Sciences, [5]Kitakyushu Municipal Medical Center, [6]Kansai Medical University, [7]Kyoto University Graduate School of Medicine, JPN

SCARLET- Sotorasib + CBDCA + PEM in KRAS G12C

Study design

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Umbrella-type, prospective studies @ WJOG
for advanced non-Sq, NSCLC patients with rare driver oncogenes

ALK-rearranged	KRAS G12C (SCARLET)	MET ex14 skipping	.....
ALK-TKI +/- platinum-doublet	Sotorasib + CBDCA / PEM	MET-TKI +/- platinum-doublet	

Key inclusion criteria

- Advanced non-Sq, NSCLC
- With KRAS G12C
- Naïve for Cytotoxic chemotherapy and KRAS inhibitor
- With measurable lesion
- ECOG PS 0-1
- Asymptomatic CNS mets allowed

Induction phase

Sotorasib 960mg
+ CBDCA (AUC5)/ PEM 500 mg/m ^{2}
[q3W, 4 cycles]
(n = 30)

Maintenance phase

Sotorasib + PEM
[q3W, until PD]

- Primary endpoint; ORR by blinded independent central review (BICR)
- Secondary endpoints; DCR, PFS, DOR, OS and AEs
- Translational research; NGS analysis (tissue and plasma [at baseline, 3 wks, and PD])

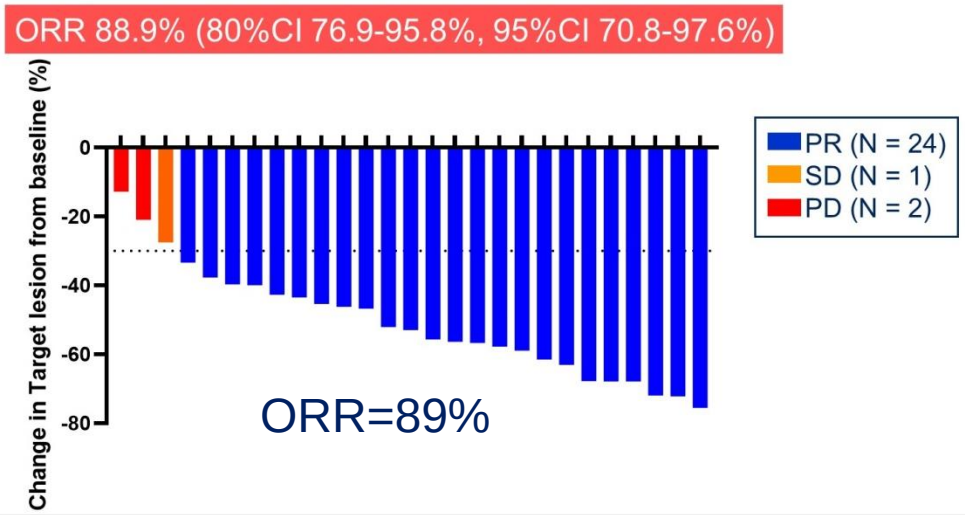
Sakata et al. Oral.

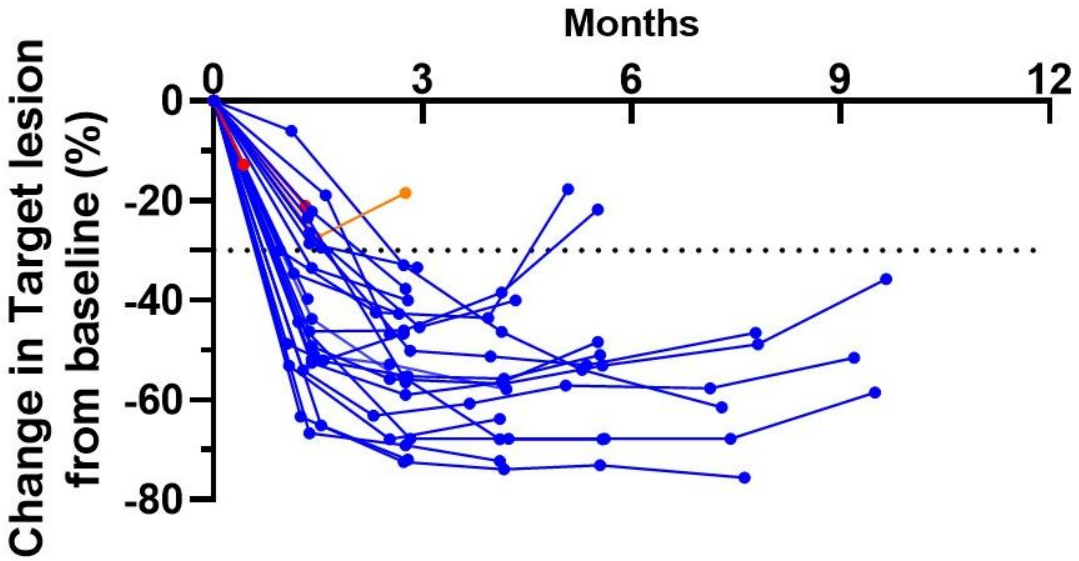
SCARLET- Sotorasib + CBDCA + PEM in KRAS G12C

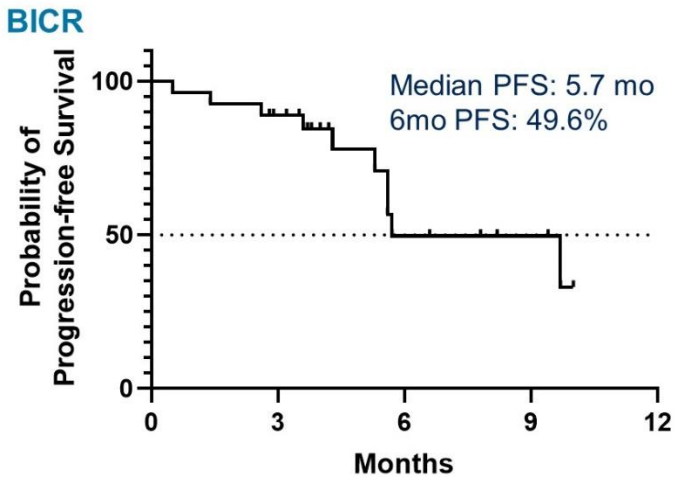
Promising efficacy results

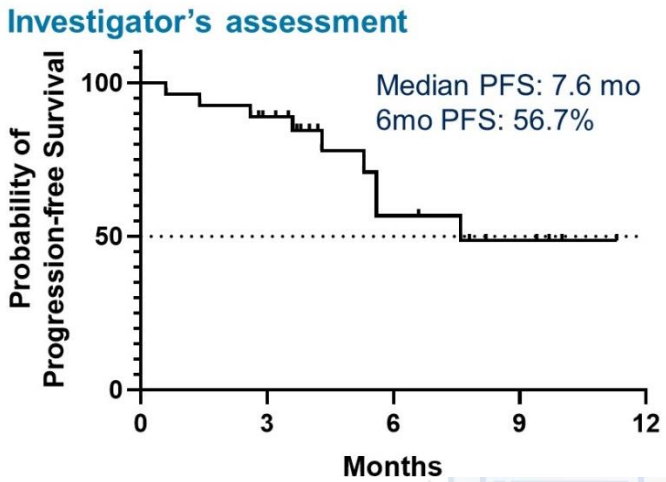
Iniciativa científica de: GECP lung cancer research

Primary endpoint: ORR by BICR







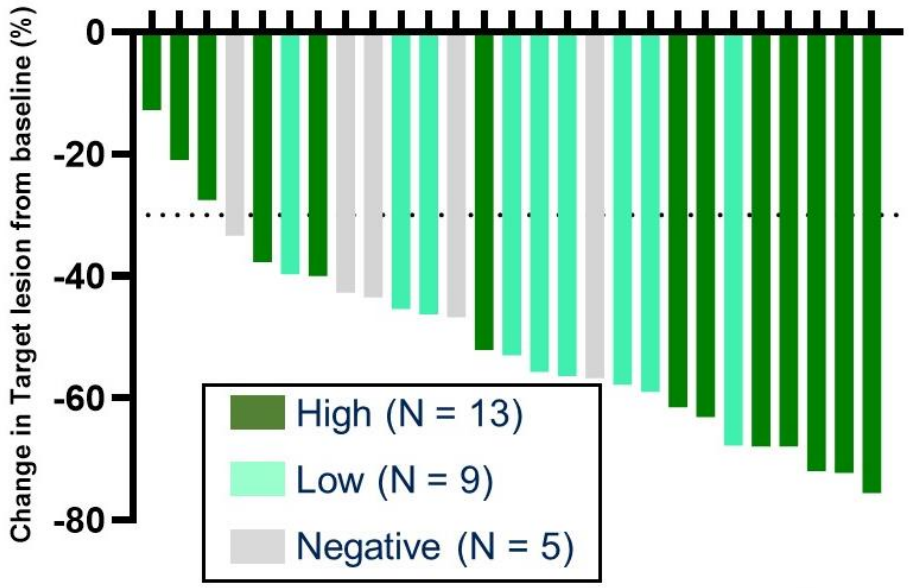


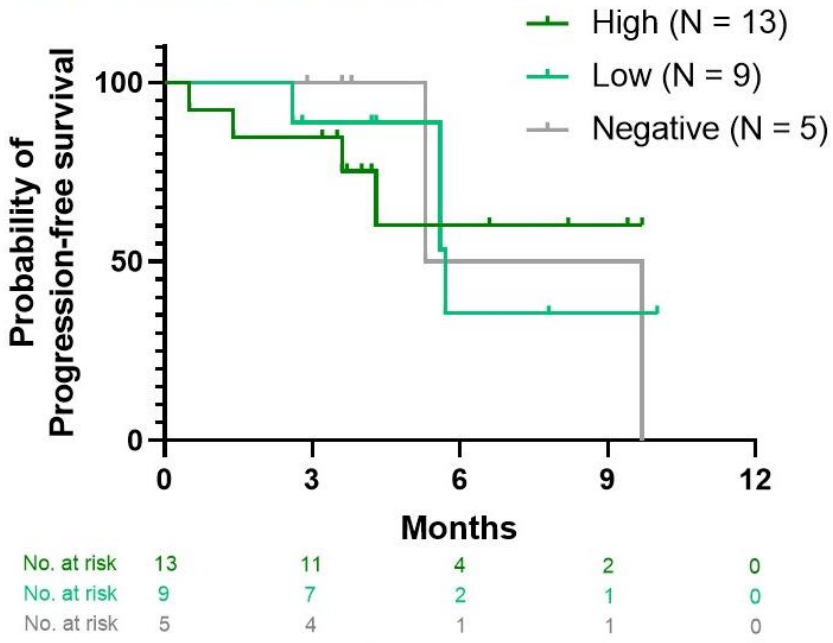
Sakata et al. Oral.

SCARLET- Sotorasib + CBDCA + PEM in KRAS G12C

Promising efficacy results

Efficacy by PD-L1 expression level





PD-L1 expression level	N	ORR	Median PFS (mo)
High (≥50%)	13	76.9% (95%CI 46.2-95.0%)	Not reached
Low (1-49%)	9	100% (95%CI 66.4-100%)	5.7
Negative (<1%)	5	100% (95%CI 47.8-100%)	7.5

Sakata et al. Oral.

SCARLET- Sotorasib + CBDCA + PEM in KRAS G12C

Acceptable safety profile

Iniciativa científica de: GECP lung cancer research

	Sotorasib	CBDCA	PEM
No. of cycles,			
Median (range)	5 (1-14)	4 (1-4)	5 (1-14)
Minimum dose level			
Level 0	960mg: 20 (69.0%)	AUC 5: 22 (75.9%)	500mg/m^2: 20 (69.0%)
Level -1	480mg: 8 (27.6%)	AUC 4: 5 (17.2%)	400mg/m^2: 5 (17.2%)
Level -2	240mg: 1 (3.4%)	Discontinuation: 1 (3.4%)	350mg/m^2: 3 (10.3%)
Reason for dose reduction			
Adverse event	9 (31.0%)	6 (20.7%)	8 (27.6%)
Other	0	0	1 (3.4%)
Patients required Dose Interruption	11 (37.9%)		
Duration of Dose Interruption,			
Median days (range)	12 (2-44)		

- Most grade ≥ 3 AEs associated with chemotherapy
- Low grade ≥ 3 ALT/AST (3.4% / 6.9%)
- One G4 ALT and 1 G5 pneumonia

Sakata et al. Oral.

KontRASt-01 update: JDQ443 efficacy and safety

Iniciativa científica de: GECP lung cancer research

2023 ASCO ANNUAL MEETING

KontRASt-01 update: Safety and efficacy of JDQ443 in *KRAS G12C*-mutated solid tumors including non-small cell lung cancer (NSCLC)

Philippe A Cassier,[1] Christophe Dooms,[2] Anas Gazzah,[3] Enriqueta Felip,[4] Neeltje Steeghs,[5] Kristoffer Staal Rohrberg,[6] Filippo De Braud,[7] Benjamin Solomon,[8] Martin Schüler,[9] Daniel SW Tan,[10] Noboru Yamamoto,[11] Herbert HF Loong,[12] Byoung Chul Cho,[13] Jürgen Wolf,[14] Chia-Chi Lin,[15] Marcelo V Negrao,[16] Lillian Werner,[17] Xiaoming Cui,[18] Anna F Farago,[17] María José de Miguel[19]

1. Centre Léon Bérard, Lyon, France; 2. University Hospitals Leuven, Leuven, Belgium; 3. Gustave Roussy, Villejuif, France; 4. Vall d'Hebron University Hospital, Barcelona, Spain; 5. The Netherlands Cancer Institute, Amsterdam, the Netherlands; 6. Department of Oncology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; 7. Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; 8. Peter MacCallum Cancer Centre, Melbourne, Australia; 9. West German Cancer Center, University Hospital Essen, Essen, Germany; 10. National Cancer Centre Singapore, Singapore; 11. National Cancer Center Hospital, Tokyo, Japan; 12. Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong; 13. Yonsei University College of Medicine, Seoul, Republic of Korea; 14. Department I of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany; 15. National Taiwan University Hospital, Taipei, Taiwan; 16. MD Anderson Cancer Center, Houston, TX, USA; 17. Novartis Institutes for BioMedical Research, Cambridge, MA, USA; 18. Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 19. START-CIOCC Hospital Universitario HM Sanchinarro, Madrid, Spain.

Dr. Philippe A Cassier

Scan to obtain presentation

https://bit.ly/CassierP9007

KontRASt-01 update: JDQ443 efficacy and safety

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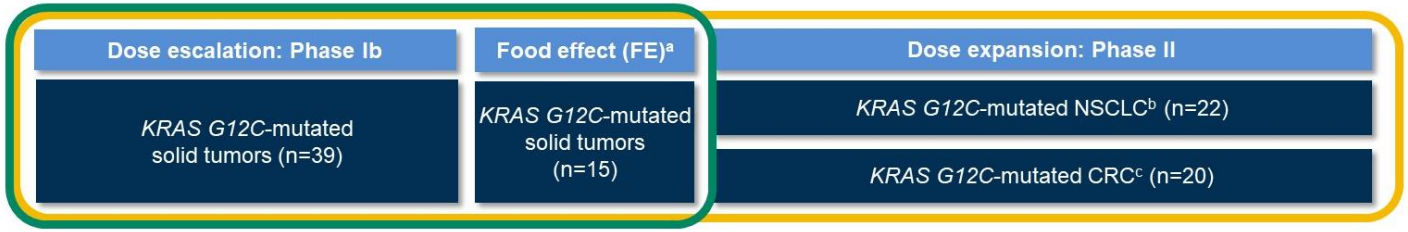
KontRASt-01: JDQ443 monotherapy

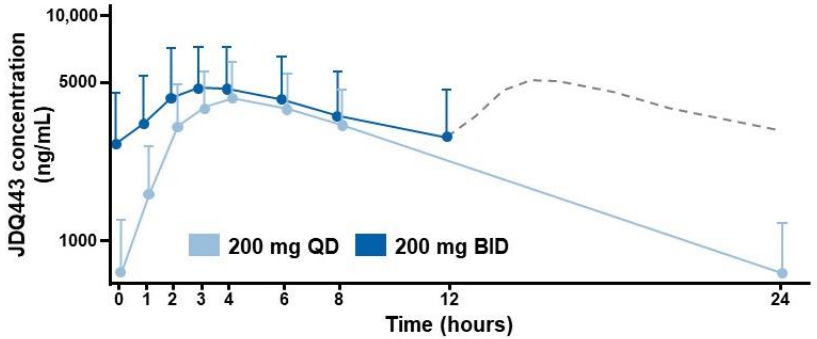


Safety data set: All patients (N=96) across dose escalation, FE and dose expansion cohorts

Efficacy data set: Patients with NSCLC (N=27) from dose escalation and FE cohorts

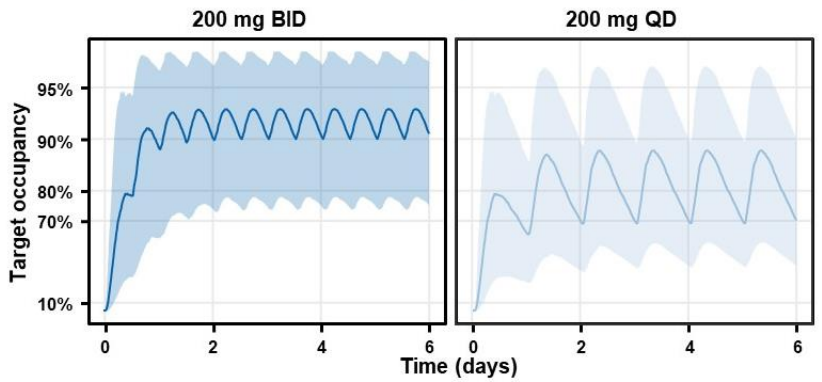
JDQ443 200 mg BID maximizes exposure and enables sustained KRAS^{G12C} target occupancy

Steady state plasma PK



For 200 mg BID continuous dosing, PK sampling is not performed during 12–24 hrs.
The dashed gray line represents the expected PK profile.

Predicted KRAS^{G12C} target occupancy[a]



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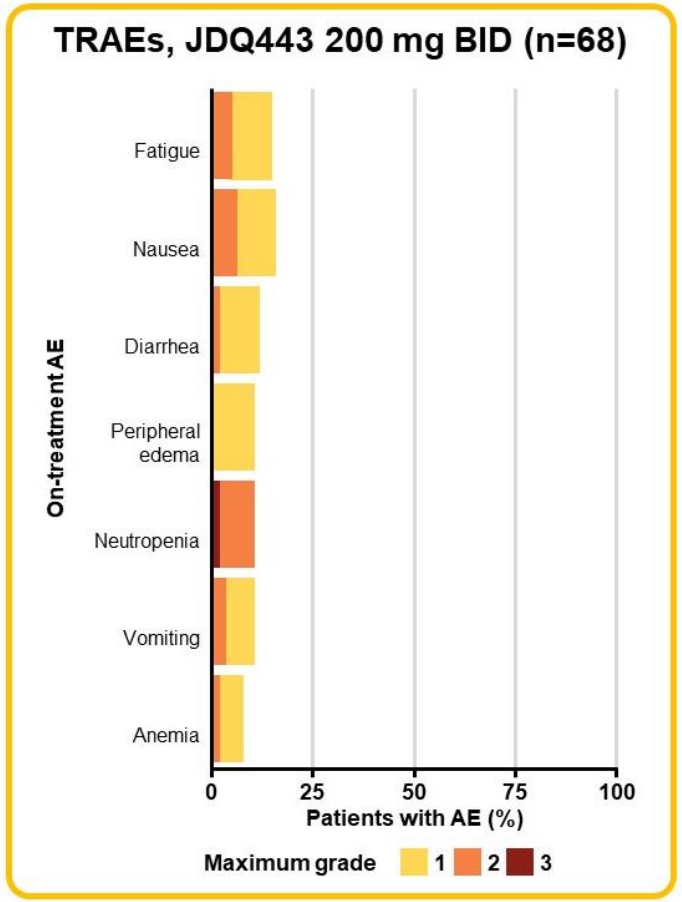
KontRASt-01 update: JDQ443 efficacy and safety

Iniciativa científica de: GECP lung cancer research

Treatment-related adverse events (≥10% of all patients)

	JDQ443 200 mg QD escalation (n=10)		JDQ443 400 mg QD escalation (n=11)		JDQ443 300 mg BID escalation (n=11)		JDQ443 200mg BID escalation + FE + expansion (n=68)		All dose levels, pooled (N=96)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Number of patients with at least one event, n (%)	**8 (80.0)**	**2 (20.0)**	**8 (72.7)**	**1 (9.1)**	**6 (85.7)**	**5 (71.4)**	**51 (75.0)**	**4 (5.9)**	**73 (76.0)**	**12 (12.5)**
Fatigue	5 (50.0)	2 (20.0)	3 (27.3)	–	4 (57.1)	1 (14.3)	11 (16.2)	–	23 (24.0)	3 (3.1)
Nausea	3 (30.0)	–	1 (9.1)	–	–	–	12 (17.6)	–	16 (16.7)	–
Diarrhea	2 (20.0)	–	2 (18.2)	–	1 (14.3)	–	9 (13.2)	–	14 (14.6)	–
Peripheral edema	2 (20.0)	–	2 (18.2)	–	1 (14.3)	–	8 (11.8)	–	13 (13.5)	–
Neutropenia	–	–	1 (9.1)	–	2 (28.6)	1 (14.3)	8 (11.8)	2 (2.9)	11 (11.5)	3 (3.1)
Vomiting	2 (20.0)	–	–	–	–	–	8 (11.8)	–	10 (10.4)	–
Anemia	2 (20.0)	–	2 (18.2)	–	–	–	6 (8.8)	–	10 (10.4)	–



- **TRAEs were low-frequency, low-grade events**
- **There were no Grade 4 or 5 TRAEs**
- **No nausea/vomiting/diarrhea higher than Grade 2**

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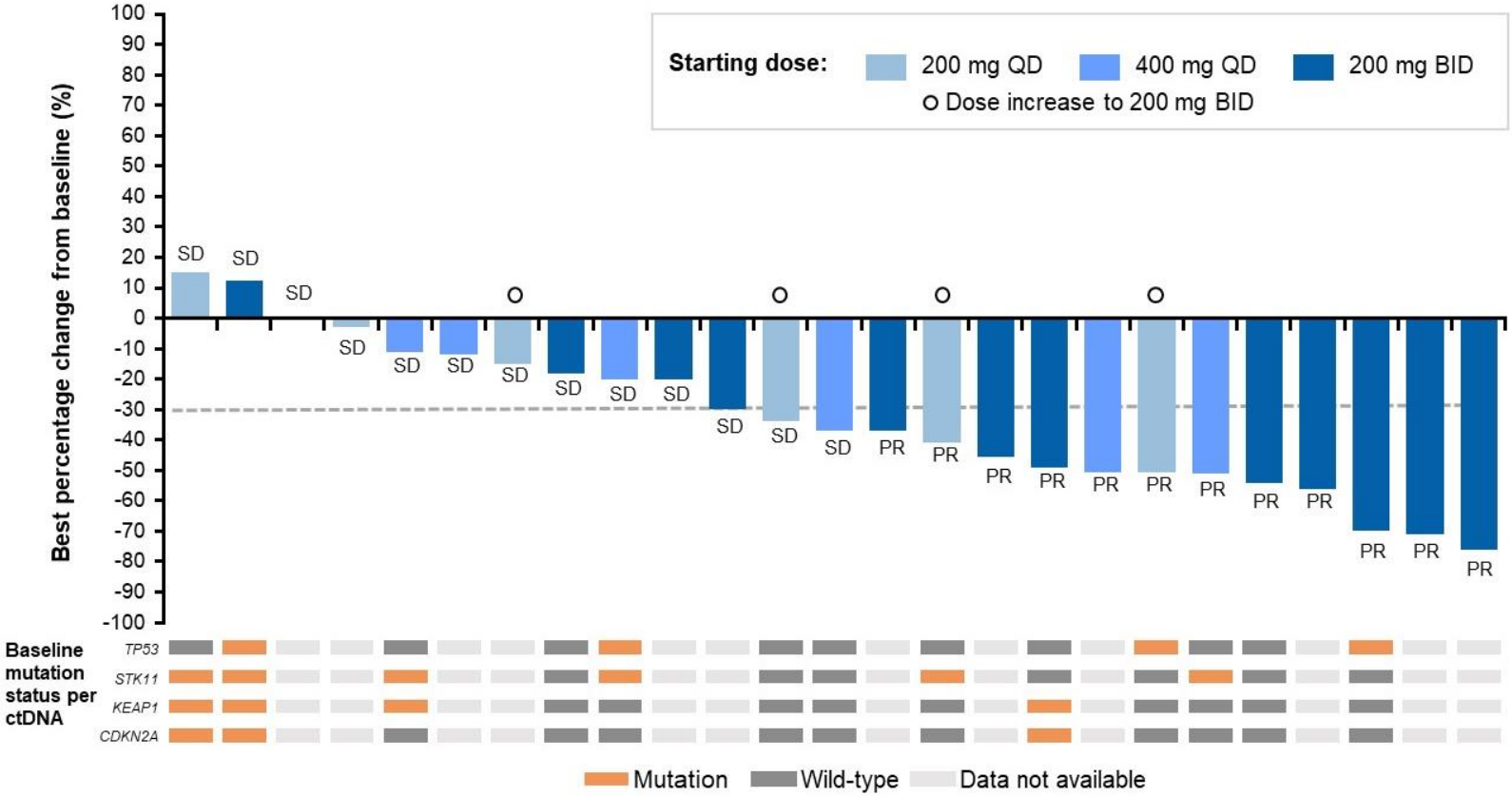

	JDQ443 200 mg BID (n=14)	JDQ443 All dose levels, pooled (n=27)
Confirmed ORR	**57.1%**	44.4%
DCR	**92.9%**	92.6%
BOR[a], n (%)		
PR	8 (57.1)	12 (44.4)
SD	5 (35.7)	13 (48.1)
PD	0	0
Unknown	1 (7.1)	2 (7.4)

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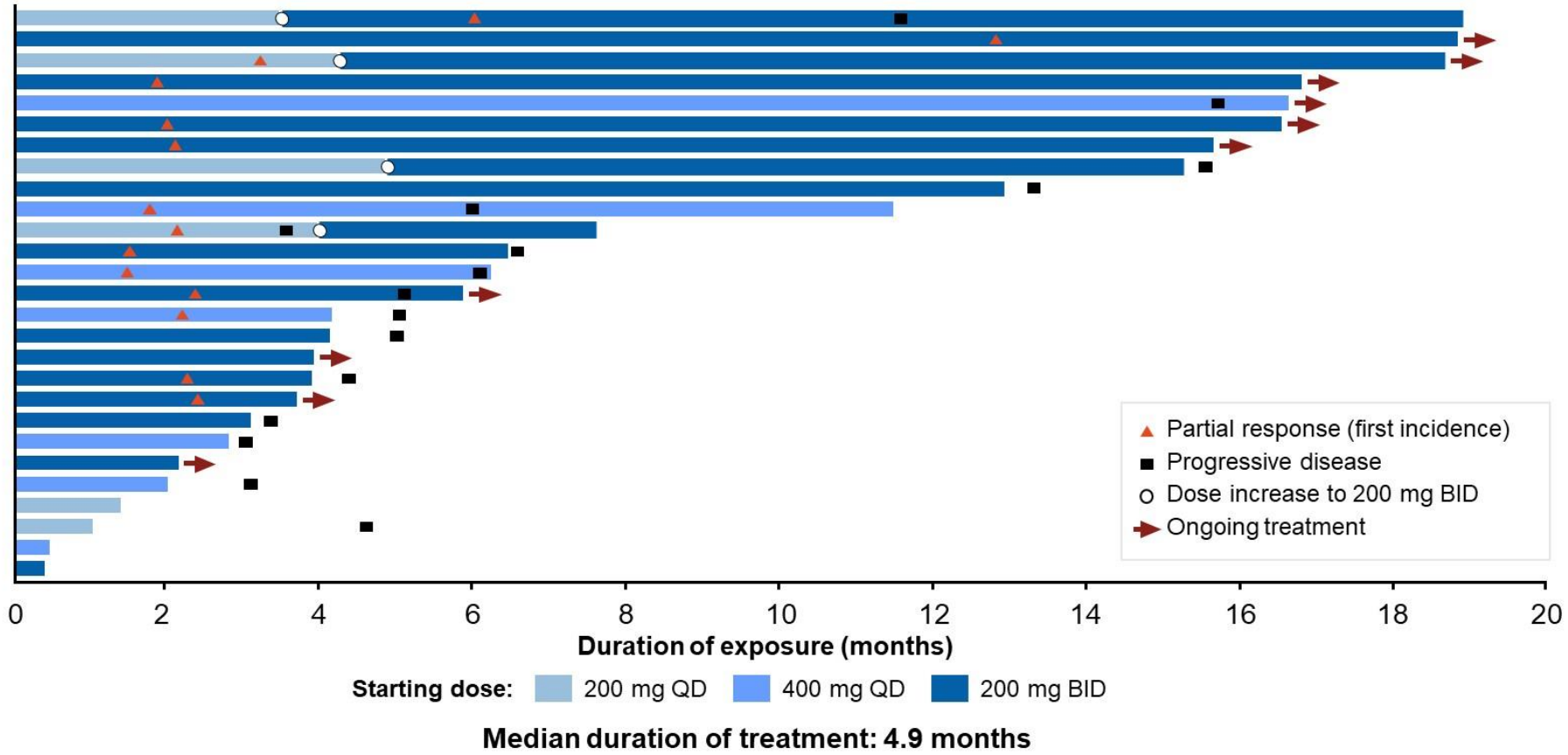
NSCLC: Duration of treatment and onset of response



Median duration of treatment: 4.9 months

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/Salut

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Gracias por vuestra atención

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