Lung Cancer UPDATES
IASLC HIGHLIGTHS
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Viena, Austria

Iniciativa científica de:
GECP
lung cancer research

TARGETED THERAPIES

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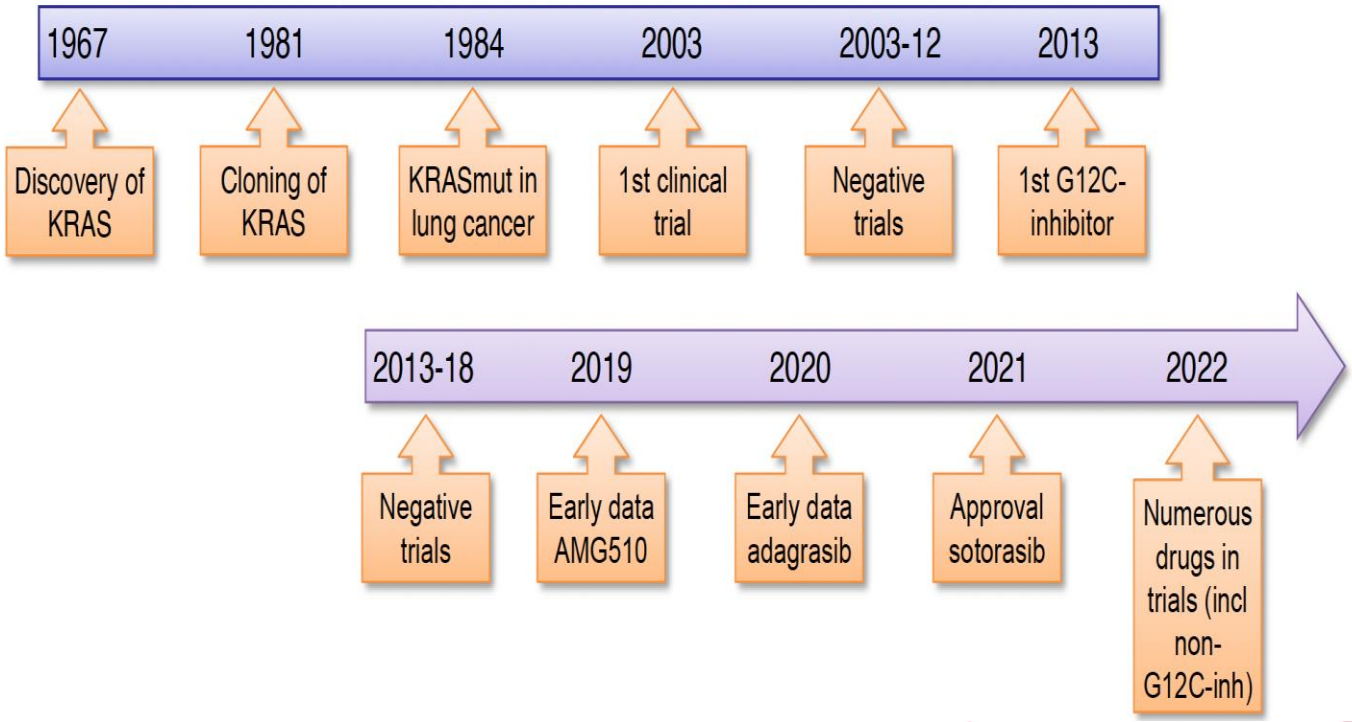
Disclosures

- Advisory boards: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda
- Consultancy: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda
- Speaker honoraria: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda

LET´S START WITH AN OLD FRIEND: KRAS



Current and Future challenges:

- -Efficacy limitations
- -Resistance mechanisms
- -Brain activity
- -Optimal dose
- -Combinations approaches
- -New Kras inhibitors

Sotorasib Combinations (Phase 1b studies):

- OA03.03. Sotorasib in Combination with RMC-4630, a **SHP2 Inhibitor**, in KRAS p.G12C-Mutated NSCLC and Other Solid Tumors. *Falchook et al.*
- OA03.06. CodeBreaK 100/101: First Report of Safety/Efficacy of Sotorasib in Combination with **Pembrolizumab or Atezolizumab** in Advanced KRAS p.G12C NSCLC. *Li et al.*

New KRAS^{G12C} inhibitor monotherapy studies (Phase I studies):

- OA03.04. Phase IA Study to Evaluate **GDC-6036** Monotherapy in Patients with Non-small Cell Lung Cancer (NSCLC) with KRAS G12C Mutation. *Sacher et al.*
- OA03.07. Safety and Efficacy of **D-1553** in Patients with KRAS G12C Mutated Non-Small Cell Lung Cancer: A Phase 1 Trial. *Lu et al.*

SOTORASIB+SHP2 INHIBITOR (RMC-4630)

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Study Design: Sotorasib + SHP2 Inhibitor (RMC-4630)

- Phase 1b multicenter, open-label study (NCT04185883); data cutoff: April 11, 2022

Screening/Enrollment → **PART 1: Dose Exploration (N = 27)**

Key eligibility criteria*
- Locally advanced or metastatic *KRAS* p.G12C solid tumors
- Prior anti-PD(L)1 and/or platinum-based chemo and targeted therapy (NSCLC)
- Allowed prior $KRAS^{G12C}$ inhibitor

Sotorasib (960 mg PO daily) + RMC-4630 (PO) at:
- 200 mg at days 1 and 2 Q7D
- 140 mg at days 1 and 2 Q7D
- 100 mg starting dose at days 1 and 2 or days 1 and 4 Q7D

Primary endpoints: Safety
- Dose-limiting toxicities
- TRAEs and TEAEs
- Changes in vital signs, ECGs, and clinical laboratory tests

Secondary endpoints
- Pharmacokinetics
- ORR, DOR, TTR, PFS, DCR, duration of stable disease per RECIST v1.1, OS

Baseline Characteristics

	NSCLC (N=11)	Total (all tumors)* (N=27)
Median age, years (range)	64 (51–78)	63 (43–78)
Male, n (%)	4 (36)	15 (56)
Smoking history, n (%)†	11 (100)	19 (70)
ECOG performance score, n (%)		
0	10 (90)	5 (19)
1‡	0	20 (74)
Brain metastasis, n (%)	7 (64)	13 (48)
Liver metastasis, n (%)	3 (27)	11 (41)
Median lines of prior therapies, n (range)	3 (1–6)	3 (1–6)
Prior $KRAS^{G12C}$ inhibitor, n (%)§	5 (45)	11 (41)
Prior anti-PD-(L)1, n (%)	10 (91)	15 (56)

Falchook G, et al OA 03.03

SOTORASIB+SHP2 INHIBITOR (RMC-4630)

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Most Common Treatment-Related Adverse Events (TRAEs)

Variable, n (%)	Sotorasib + RMC-4630 (N = 27)*					
	Related to Sotorasib		Related to RMC-4630		Related to Sotorasib + RMC-4630	
	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Total TRAE	15 (56)	6 (22)	17 (63)	6 (22)	17 (63)	6 (22)
Edema†	7 (26)	0	6 (22)	0	8 (30)	0
Diarrhea	7 (26)	2 (7)	5 (19)	2 (7)	7 (26)	2 (7)
Dry mouth	3 (11)	0	2 (7)	0	3 (11)	0
Fatigue	3 (11)	0	3 (11)	0	3 (11)	0
AST increased	1 (4)	1 (4)	2 (7)	1 (4)	2 (7)	1 (4)
Ascites	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
Colitis	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
Dyspnea	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
Hypertension	0	0	1 (4)	1 (4)	1 (4)	1 (4)
Pleural effusion	0	0	1 (4)	1 (4)	1 (4)	1 (4)

TRAEs consistent with known safety profile of sotorasib and RMC-4630
Edemas (peripheral and facial) were most common TRAE; all were Grade 1 or 2, and none led to discontinuation

*Related to either study drug across all doses. Includes TRAEs with >10% patient incidence across all grades and all grade ≥ 3 TRAEs; no Grade 4 or 5 TRAEs were reported.
†Includes general, peripheral, periorbital, and facial edema.

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Efficacy*

Response assessed by investigator	NSCLC	
	All enrolled (N = 11)	KRAS^{G12C} inhibitor-naïve (N = 6)
ORR, % (95% CI)	**27 (6, 61)**	**50 (12, 88)**
Best overall response, n (%)		
Partial response	3 (27)	3 (50)
Stable disease	4 (36)	3 (50)
Progressive disease	4 (36)	0
Disease control rate, n (%)	**7 (64)**	**6 (100)**

Other tumor types: 8 CRC (5 SD; 3 PD); 1 ovarian cancer (PR with an 81% reduction in tumor burden); 1 pancreatic adenocarcinoma (SD), and 2 other solid tumors (1 SD, 1 NE).

- Disease control in 7 of 11 patients with NSCLC and in all patients who were KRAS^{G12C} i-naïve
- Promising early efficacy observed in patients with NSCLC who were KRAS^{G12C} i-naïve

*Efficacy is summarized only for evaluable patients who were treated and had the opportunity for at least 1 post-baseline scan.
CRC, colorectal cancer; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

A study is underway (NCT05054725) to further define efficacy and safety of this combination in patients with mNSCLC who are KRAS^{G12C} inhibitor-naïve (WCLC 2022 e-poster #EP08.02-111)

SOTORASIB+PEMBROLIZUMAB OR ATEZOLIZUMAB

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CodeBreaK 100/101: First report of safety and efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced *KRAS* p.G12C NSCLC

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CodeBreaK 100/101 Study Design

- Phase 1b multicenter, open-label studies

Key Eligibility
- Advanced *KRAS* p.G12C-mutated NSCLC
- Received (or refused) prior standard therapies
- No prior $KRAS^{G12C}$ inhibitor
- No active brain mets

Screening/Enrollment →

Sotorasib* (oral daily) at:	Sotorasib lead-in 21d or 42d then combination (N = 29)	Concurrent treatment (N = 29)
960 mg	Atezolizumab 1200 mg Q3W (N = 10)	Atezolizumab 1200 mg Q3W (N = 10)
720 mg		
360 mg	OR	OR
240 mg	Pembrolizumab 200 mg Q3W (N = 19)	Pembrolizumab 200 mg Q3W (N = 19)
120 mg		

Primary endpoints: safety
Key secondary endpoints: ORR, DOR, DCR, PK

*Not all doses were tested for each cohort.
DCR, disease control rate; PK, pharmacokinetics; Q3W, every 3 weeks.

Snapshot: April 15, 2022

Here we present first data of lead-in and concurrent sotorasib with pembrolizumab or atezolizumab from CodeBreaK 100/101 with median follow-up time of 12.8 months (range: 1.6, 29.9)

Li B, et al. OA 03.06

SOTORASIB+PEMBROLIZUMAB OR ATEZOLIZUMAB

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Safety by Dose: Pembrolizumab Concurrent

TRAE, n (%)	Sotorasib 120 mg (N = 5)		Sotorasib 360 mg (N = 8)		Sotorasib 720 mg (N = 2)		Sotorasib 960 mg (N = 4)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	5 (100)	4 (80)	7 (88)	6 (75)	2 (100)	2 (100)	3 (75)	3 (75)
Hepatotoxicity	2 (40)	2 (40)	3 (38)	2 (25)	2 (100)	2 (100)	3 (75)	3 (75)
ALT increased	2 (40)	1 (20)	3 (38)	1 (13)	2 (100)	2 (100)	3 (75)	3 (75)
AST increased	2 (40)	2 (40)	3 (38)	0	2 (100)	2 (100)	3 (75)	1 (25)

- Higher rate of TRAEs than with either monotherapy[6–8], with no fatal TRAEs
- At lower doses of sotorasib, there was a trend towards less liver enzyme elevations, although sample sizes were limited
- Given the safety data for this combination, sotorasib lead-in was explored

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Safety Summary: Lead-in versus Concurrent

	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading to sotorasib and/or IO discontinuation, n (%)	1 (10)	5 (50)	6 (32)	10 (53)
Median duration of sotorasib, months (min, max)	6.5 (1, 18)	4.4 (1, 14)	2.8 (1, 15)	4.9 (2, 30)
Median duration of combination, months (min, max)‡	1.5 (0, 18)	2.5 (1, 14)	0.7 (1, 15)	2.3 (1, 9)
Hepatotoxicity grade ≥ 3, median onset, days (range)	50 (28, 93)	67 (36, 147)	73 (45, 127)	51 (29, 190)

- Lead-in had lower incidence of Grade 3-4 TRAEs and TRAEs leading to discontinuation than concurrent
- Grade 3-4 hepatotoxicity first occurrence was outside DLT window† in 88% of patients; 97% of events resolved with corticosteroids, treatment modification, and/or discontinuation
- The incidence of hepatotoxicity TRAEs was similar in IO-naïve versus IO-pretreated patients

Li B, et al. OA 03.06

SOTORASIB+PEMBROLIZUMAB OR ATEZOLIZUMAB

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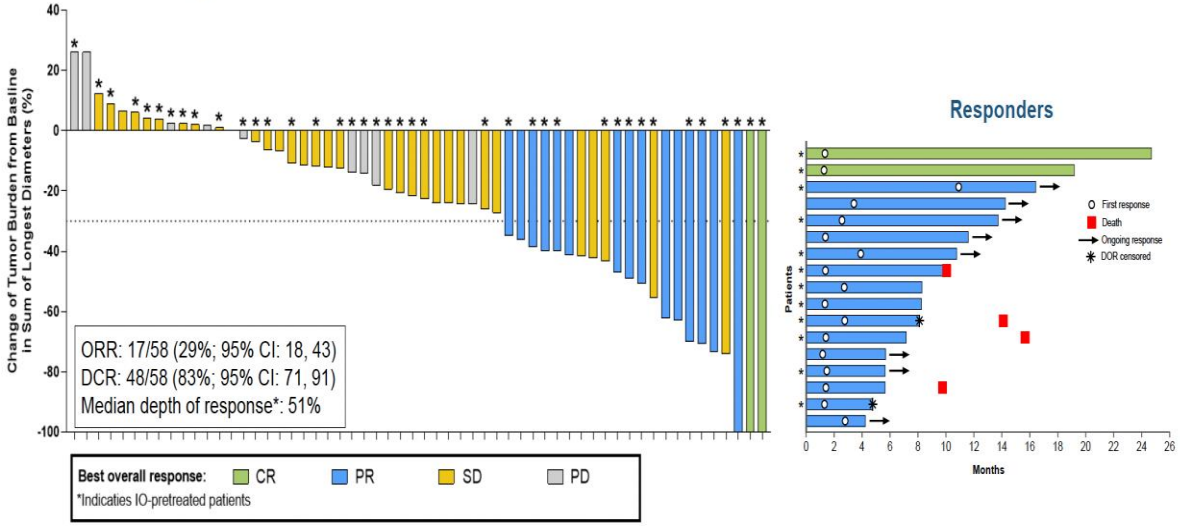
Efficacy



- Deep and durable responses were observed for this combination across all cohorts, including at low doses
- Among the 17 responders, median duration of response was 17.9 months (95% CI: 5.6, NE)
- Response was similar in IO-naïve and IO-pretreated patients

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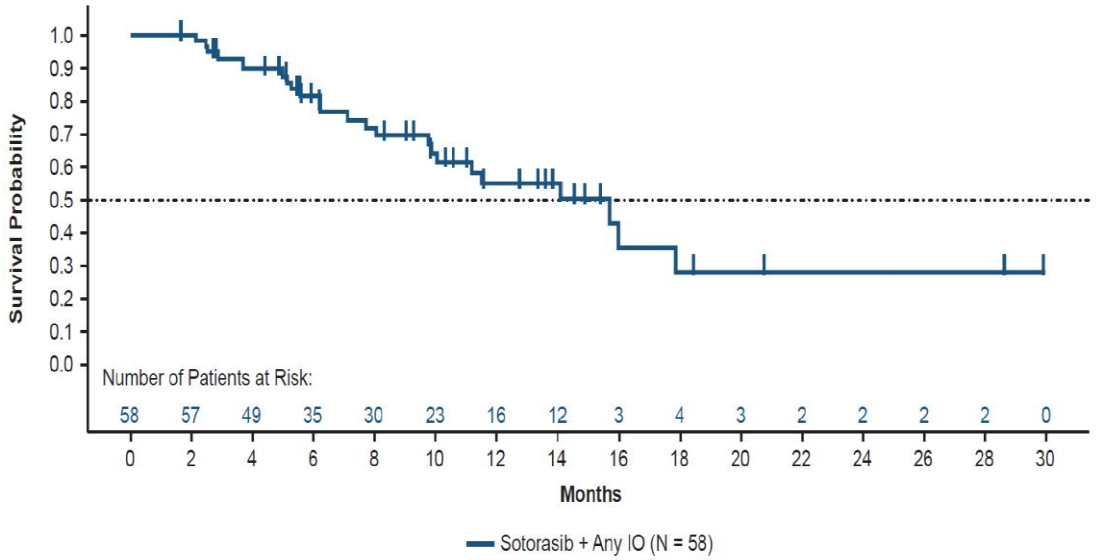
Overall Survival: Sotorasib + any IO



Median OS: 15.7 months (95% CI: 9.8, 17.8)

ORR 29%
DCR 83%
mOS: 15.7m

Time from ICIs to Sotorasib use correlates with risk of hepatotxicity in NSCLC

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Baseline demographics

Grade 3 Hepatotoxicity	No (N=22)	Yes (N=10)	Total (N=32)	p value
Age at diagnosis, years, median (range)	67 (43- 77)	69 (49- 81)	68(43- 81)	0.405
Male gender, n(%)	6 (27.3%)	3 (30.0%)	9 (28.1%)	0.874
Smoking, pack yrs, median (range)	30 (7-60)	28 (3-60)	30 (3-60)	0.500
Histology, n(%)				0.354
Adenocarcinoma	18 (81.8%)	10 (100.0%)	28 (87.5%)	
NSCLC NOS	1 (4.5%)	0 (0.0%)	1 (3.1%)	
Squamous	3 (13.6%)	0 (0.0%)	3 (9.4%)	
Duration of sotorasib treatment, days, median (Range)	82.5 (7.0, 264.0)	131.5 (31.0, 254.0)	95.0 (7.0, 264.0)	0.309
Prior ICI use, N(%)	18 (81.8%)	10 (100.0%)	28 (87.5%)	0.149
Time from prior ICI to sotorasib initiation, days, median (range)	131.0 (15.0, 542.0)	39.0 (4.0, 70.0)	68.5 (4.0, 542.0)	0.001

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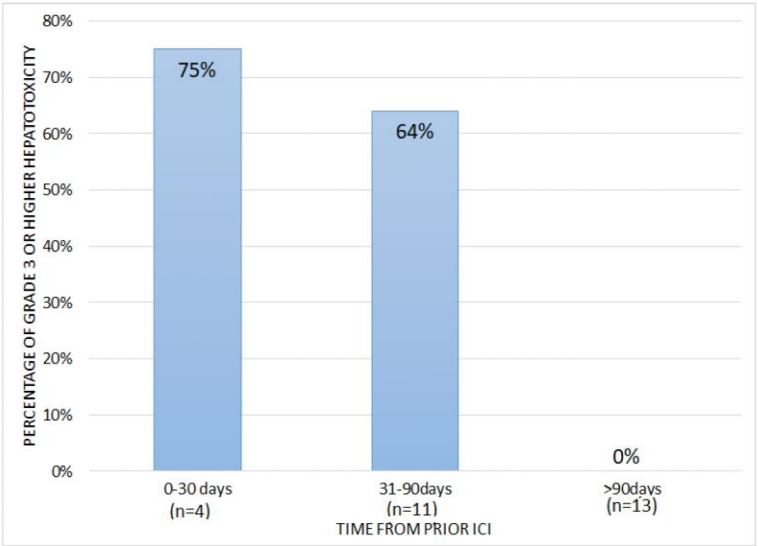
Rate of ≥ grade 3 hepatoxicity is higher in patients who received prior ICI within 90 days



Rakshit S, et al. MA 13.09

PHASE Ia GDC-6036

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Phase Ia study to evaluate GDC-6036 monotherapy in patients with non-small cell lung cancer (NSCLC) with *KRAS G12C* mutation

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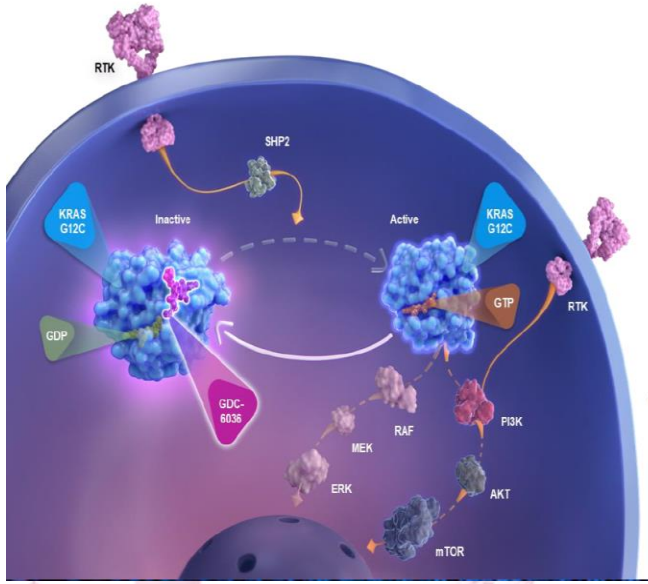
GDC-6036 is a potent, selective, covalent inhibitor of KRAS G12C



- *KRAS G12C* is one of the most common oncogenic mutations in NSCLC
- GDC-6036 is an oral, highly potent, and selective KRAS G12C inhibitor that irreversibly locks the protein in an inactive state to turn off its oncogenic signaling
- GDC-6036 has been shown to be more potent and selective *in vitro* than sotorasib and adagrasib[1]

[1]Purkey et al. AACR 2022.

PHASE Ia GDC-6036

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Phase I study evaluates single agent GDC-6036 in advanced or metastatic solid tumors with *KRAS G12C* mutation

KEY ELIGIBILITY CRITERIA

- Locally advanced or metastatic solid tumors, including NSCLC, harboring a *KRAS G12C* mutation
- At least one prior treatment or intolerability of standard therapy
- Measurable or evaluable disease per RECIST
- Previously treated brain metastases only
- No prior KRAS G12C inhibitor treatment

DOSE ESCALATION

GDC-6036 oral QD, 21-day cycles
50mg → 100mg → 200mg → 400mg *Max Admin Dose*
N=6 N=5 N=10 N=6
NSCLC N=27

DOSE EXPANSION

GDC-6036 oral QD, 21-day cycles
400mg
NSCLC N=32

KEY ENDPOINTS

- Safety
- Pharmacokinetics
- Preliminary antitumor activity

GO42144, NCT04449874 - Data presented as of CCOD 13 May 2022: **N=135 patients across indications and N=59 NSCLC patients**

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Disposition and baseline demographics: NSCLC

NSCLC patients enrolled	**N=59**
NSCLC patients enrolled at 400 mg	38 (64%)
NSCLC patients discontinued from study treatment	25 (42%)

Reasons for treatment discontinuation:

- Progressive disease 15 (25%)
- Adverse event 4 (7%)
- Physician decision 3 (5%)
- Clinical progression 2 (3%)
- Withdrawal by subject 1 (2%)

	NSCLC patients N=59
Age, median (range), years	67 (43 - 82)
Sex, female	33 (56%)
Smoking status, current or former	55 (93%)
ECOG 0 vs 1	21 (36%) vs 38 (64%)
PD-L1 positive (based on local test results), % (N=45)	56%
Median number of prior therapies in metastatic setting (N=58)	1 (0 - 5)
Prior checkpoint inhibitor	51 (86%)
Prior platinum chemotherapy	53 (90%)
Time on treatment, median (range), months	4.2 (0 - 18.1)

Sacher A, et al. OA 03.04

PHASE Ia GDC-6036

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Summary of adverse events: NSCLC and all solid tumors

TREATMENT-RELATED AEs (≥10 PATIENTS) OVERALL & CORRESPONDING GRADE 3-5 AEs	NSCLC Patients N=59		All Patients N=135	
	Related AEs	Related Grade 3-5 AEs	Related AEs	Related Grade 3-5 AEs
Patients with at least one AE	52 (88.1%)	10 (16.9%)	119 (88.1%)	15 (11.1%)
Nausea	45 (76.3%)	0	94 (69.6%)	0
Diarrhea	36 (61%)	2 (3.4%)	82 (60.7%)	5 (3.7%)
Vomiting	32 (54.2%)	0	68 (50.4%)	0
Fatigue	14 (23.7%)	1 (1.7%)	26 (19.3%)	1 (0.7%)
Decreased appetite	9 (15.3%)	0	16 (11.9%)	0
Alanine aminotransferase increased	8 (13.6%)	4 (6.8%)	12 (8.9%)	4 (3%)
Aspartate aminotransferase increased	6 (10.2%)	3 (5.1%)	11 (8.1%)	3 (2.2%)
Dyspepsia	4 (6.8%)	0	10 (7.4%)	0

TREATMENT-RELATED AEs	NSCLC Patients N=59	All Patients N=135
Patients with AEs resulting in GDC-6036 modification (interruption/reduction/withdrawal)	21 (36%)	31 (23%)
Patients with AEs resulting in GDC-6036 reduction	11 (19%)	14 (10%)
Patients with AEs resulting GDC-6036 withdrawal	3 (5%)	3 (2%)

- Common treatment-related AEs: nausea, vomiting, and diarrhea
  - Most events Grade 1, occurred early in study treatment
- No dose-limiting toxicities reported
- Grade 5 events in 7 patients, all related to disease progression and none related to drug
- Overall, AEs were manageable with supportive medications and dose modifications

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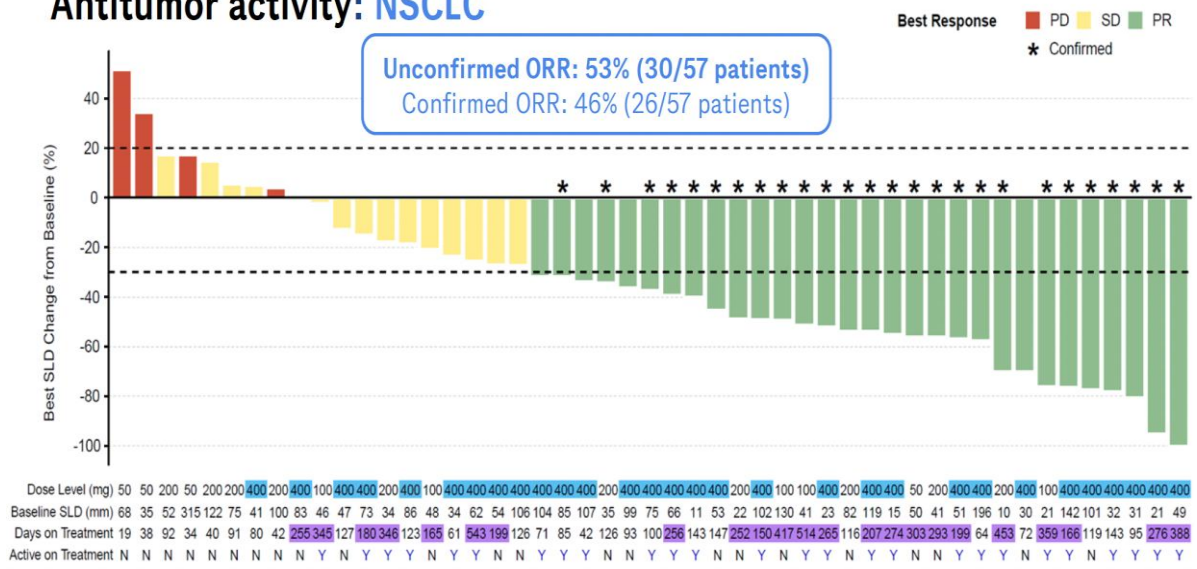
Antitumor activity: NSCLC



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GDC-6036 Development

- GDC-6036 is also being investigated in combination with other anti-cancer therapies in this study:

GDC-6036 + atezolizumab	GDC-6036 + cetuximab	GDC-6036 + bevacizumab	GDC-6036 + erlotinib	GDC-6036 + GDC-1971 (SHP2 inhibitor)	GDC-6036 + inavolisib (PI3K alpha inhibitor)
NSCLC	CRC	SOLID TUMORS	NSCLC	SOLID TUMORS	SOLID TUMORS

- A **Phase II/III study** is recruiting NSCLC patients for treatment with GDC-6036 vs. docetaxel (**BFAST**; NCT03178552)

www.clinicaltrials.gov/ct2/show/NCT03178552

Sacher A, et al. OA 03.04

Phase I trial D-1553 in patients with KRAS G12C mutated NSCLC

Study Design

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- D-1553 is an orally bioavailable inhibitor of KRAS G12C that selectively and irreversibly binds KRAS G12C mutated protein in an inactive GDP-bound state.
- Here we present the safety and efficacy phase 1 data of D-1553 in patients with KRAS G12C mutated NSCLC.

Study Population

- Locally advanced, unresectable and/or metastatic NSCLC
- KRAS p.G12C mutation assessed by historical result
- Progressed or intolerant on prior standard therapies
- No active brain metastases
- Measurable disease for Phase 1b

Endpoints

- Safety and PK parameters.
- ORR, DCR, PFS and DOR, evaluated according to RECIST 1.1 by investigator.

Baseline Characteristics of Patients with NSCLC

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Baseline Characteristics	All Doses, n=79*	600 mg BID, n=66**
Age – median (range), years	65 (30-86)	66 (48-86)
Asian, n (%)	79 (100)	66 (100)
Female, n (%)	9 (11.4)	8 (12.1)
ECOG PS, n (%)		
0	5 (6.3)	5 (7.6)
1	74 (93.7)	61 (92.4)
Prior lines of systemic anticancer therapy, n (%)		
1	34 (43.0)	32 (48.5)
2	17 (21.5)	15 (22.7)
≥3	28 (35.4)	19 (28.8)
Prior anti-PD1/L1 therapy, n (%)	50 (63.3)	40 (60.6)
Prior platinum-based chemo, n (%)	67 (84.8)	54 (81.8)
Metastasis, n (%)	75 (94.9)	62 (93.9)
Bone metastasis	30 (38.0)	25 (37.9)
Brain metastasis	12 (15.2)	8 (12.1)
Liver metastasis	12 (15.2)	11 (16.7)

Lu et al. OA 03.07

Progression-free Survival and Duration of Response

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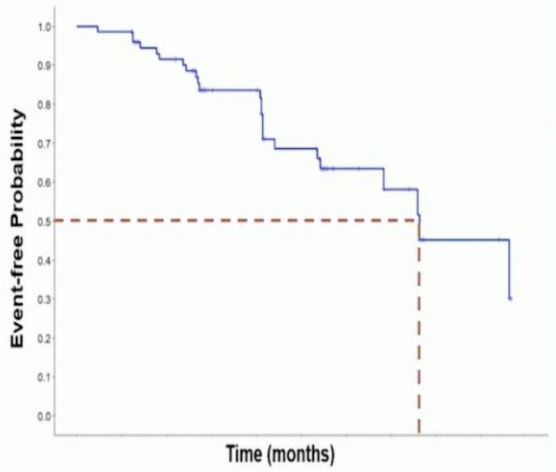
	All Doses (n=74)	600 mg BID (n=62)
Median duration of follow-up, months	6.7 (1.6, 12.4)	6.2 (1.6, 9.9)
mPFS & 95% CI, months	7.6 (5.4, NA)	6.8 (4.1, NA)
No. of Events, n (%)	24 (32.4)	20 (32.3)
PFS ≥ 3 Months (%)	83.6	82.1
PFS ≥ 6 Months (%)	63.4	53.5
mDOR & 95% CI, months	6.2 (4.2, NA)	5.4 (4.1, NA)
DOR ≥ 3 Months (%)	92.3	90.9
DOR ≥ 6 Months (%)	42.7	30.3



- Median PFS: 7.6 (range 5.4 to NA) months. Data is still immature since 68% events are censored.

Best Overall Response and Tumor Burden Change

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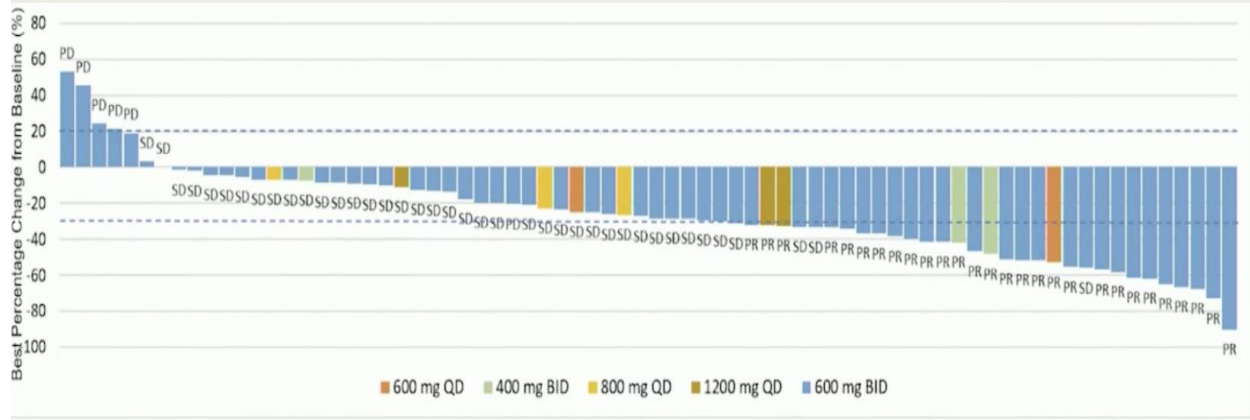

Evaluable Patients	All Doses (n=74)	600 mg BID (n=62)
Best overall response, n		
Partial response	28	23
Stable disease	40	33
Progressive disease	6	6
Objective response rate, n (%)	28 (37.8)	23 (37.1)
Disease control rate, n (%)	68 (91.9)	56 (90.3)

- 600 mg BID was selected as Phase II dose in NSCLC.
- 65 patients (87.8%) had tumor shrinkage from baseline at the first assessment.

ORR 37.8%
DCR 91.9%
mPFS: 7.6 m

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SOME NOTES TO CONCLUDE

- Kras G12C, a new druggable target
- Kras combinations with SHP2i , ICIs: a new potential strategy, toxicities-efficacy balanced must be addressed
- Next generation KRAS G12C inhibitors, potent and tolerable
- Do we really need more ”me too drugs”?