IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Updates in KRAS and MET-targeted therapies for advanced NSCLC

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UCSF

Best of IASLC-WCLC 2022
San Francisco

November 12, 2022

DISCLOSURES

Company	Relationship(s)
AstraZeneca	Research Support
Novartis	Research Support
Roche Spectrum	Research Support
Mirati	Research Support
Takeda	Research Support
Pfizer	Research Support
Janssen	Consultant
Bayer	Consultant
Amgen	Consultant
Oncocyte	Consultant

Presented studies

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 Phase I study:

- 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.*

METexon14 skipping NSCLC:

- OA03.05. Tepotinib in Patients with MET Exon 14 (METex14) Skipping NSCLC: Primary Analysis of the Confirmatory VISION Cohort C. *Thomas et al.*
- MA05.07. Intertumoral molecular heterogeneity of MET exon14+ NSCLC. Y. *Han et al.*
- MA05.08. *MET* Exon 14 Skipping Mutation in Non-Small Cell Lung Cancer (NSCLC) by Specific Mutation, Histology, and Smoking History. *J. Marks et al.*

Targeting KRAS-G12C in advanced NSCLC

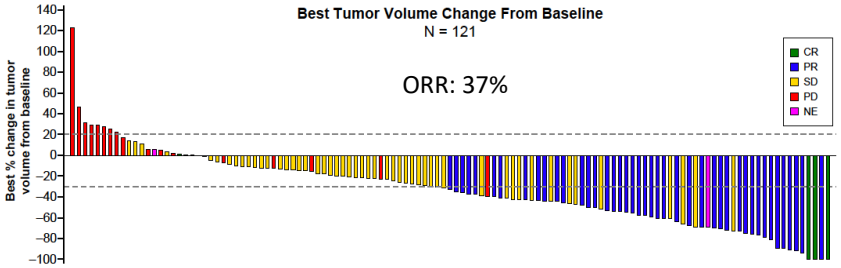
- ✓ KRAS p.G12C mutation in ~13% of NSCLC.
- ✓ **Sotorasib:** first-in-class inhibitor, FDA & EMA approved
- ✓ **Adagrasib:** FDA breakthrough therapy designation, under review for approval
- ✓ Many new inhibitors and combination therapy trials in development

Skoulidis & Heymach, Nat Rev Cancer, 2019; Luo et al. ASCO Educ Book 2022

CodeBreaK 100 Trial of Sotorasib for KRAS p.G12C mutated NSCLC

Depth of Tumor Response

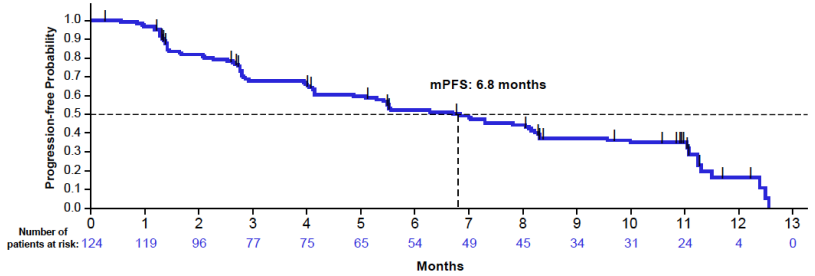
Tumor shrinkage of any magnitude was observed in 81% of patients (101/124)
Median percentage of best tumor shrinkage among all responders was 60%



Li et al. WCLC 2020

Progression-Free Survival

Median progression-free survival was 6.8 months (95% CI: 5.1, 8.2)



Li et al. WCLC 2020

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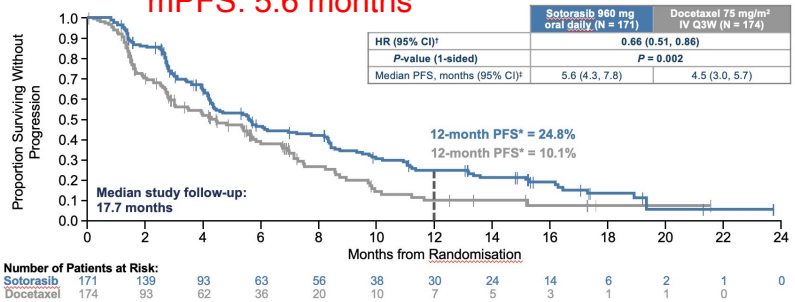
CodeBreaK 200 Trial of sotorasib vs. docetaxel for KRAS p.G12C mutated NSCLC

Primary Endpoint: PFS by BICR

mPFS: 5.6 months



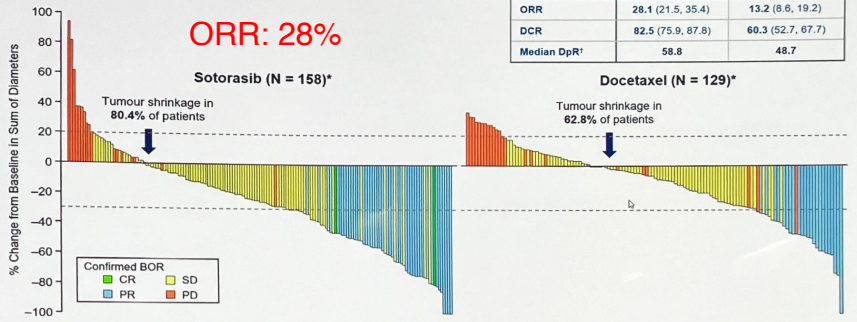
	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)	*P* = 0.002	
Median PFS, months (95% CI)‡	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model; *P*-value calculated using a stratified log-rank test.
‡Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

Tumour Response by BICR

ORR: 28%



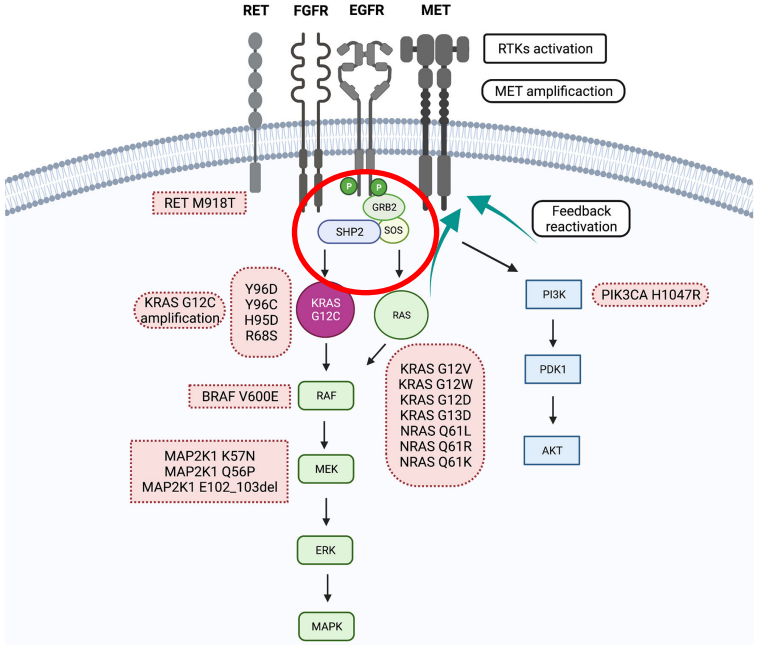
% (95% CI)	Sotorasib	Docetaxel
ORR	28.1 (21.5, 35.4)	13.2 (8.6, 19.2)
DCR	82.5 (75.9, 87.8)	60.3 (52.7, 67.7)
Median DpR†	58.8	48.7

Response rate was significantly higher with sotorasib versus docetaxel (*P* < 0.001)

*Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown.
†Median of best percent change from baseline in sum of diameters for confirmed responders.

PARIS 2022 ESMO congress
Melissa L. Johnson, MD
Twitter: @MLJohnsonMD2

Resistance to KRAS G12C inhibitors through RTK activation may be overcome by SHP2 inhibition



Front. Oncol., 24 December 2021
Sec. Thoracic Oncology
https://doi.org/10.3389/fonc.2021.787585

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

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

Screening/Enrollment

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

PART 1: Dose Exploration (N = 27)

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

*Prior systemic therapy for advanced/metastatic disease (other tumor types).
DCR, disease control rate; DOR, duration of response; ECG, electrocardiogram; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, per oral; Q7D, every 7 days; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, Treatment-emergent adverse event; TRAE, treatment-related adverse event; TTR, time to response.

Most Common Treatment-Related Adverse Events (TRAEs)

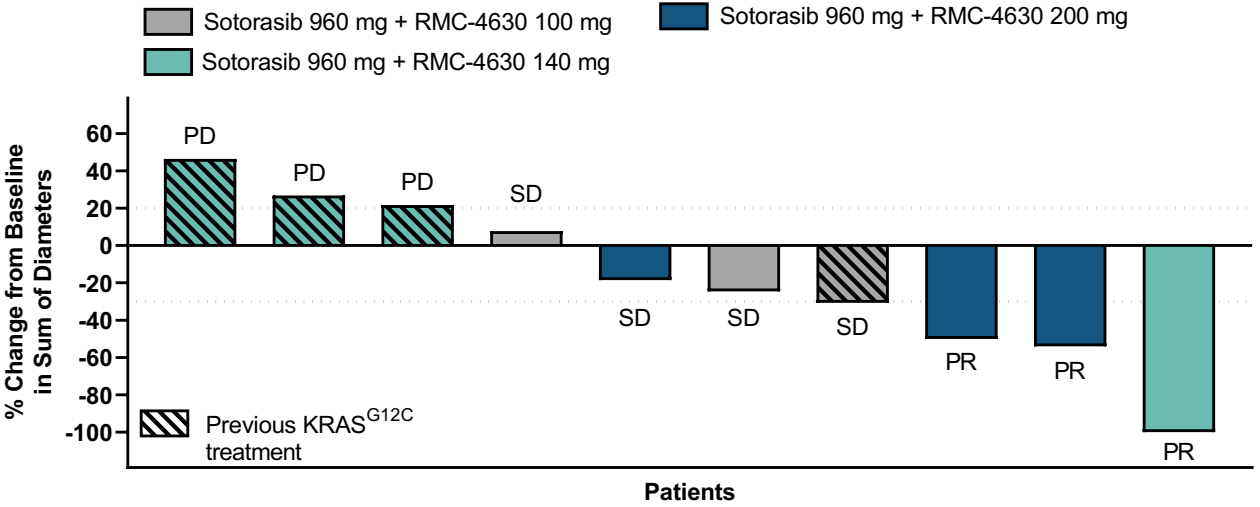
Variable, n (%)	Sotorasib + RMC-4630 (N = 27)*					
	Related to Sotorasib		Related to RMC-4630		Related to Sotorasib + RMC-4630	
	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Total TRAE	**15 (56)**	**6 (22)**	**17 (63)**	**6 (22)**	**17 (63)**	**6 (22)**
Edema†	7 (26)	0	6 (22)	0	8 (30)	0
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.

Tumor Response* in NSCLC

At the two highest doses, responders included 3 of 4 patients who were KRAS^{G12C} i-naïve



*One patient with PD was not included in tumor response due to data entry error.

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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)

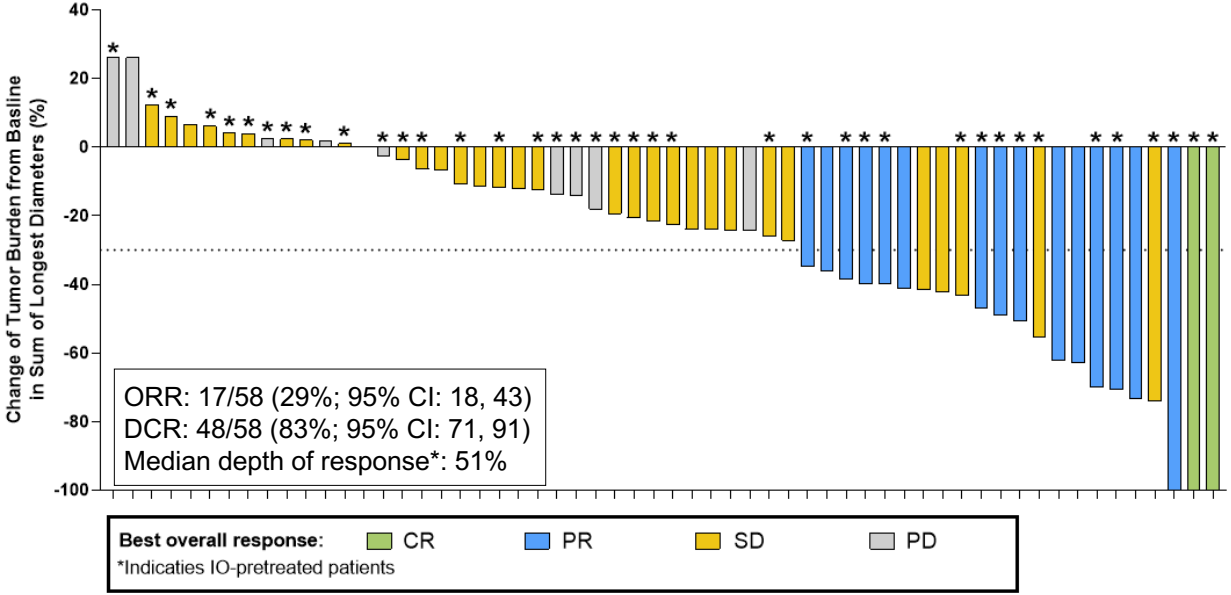
Safety Summary: Lead-in versus Concurrent

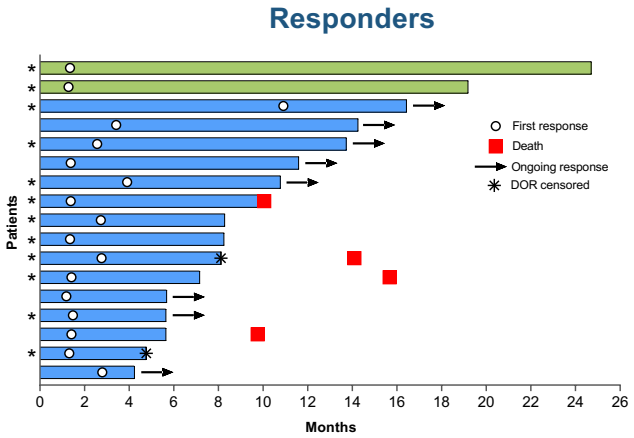
	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading 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**

Hepatotoxicity included ALT increased, AST increased, ALP increased, bilirubin increased, GGT increased; also hepatitis, liver function test increased, drug-induced liver injury, transaminases increased for sotorasib+atezolizumab; also hepatic enzyme increased, immune-mediated hepatitis for sotorasib lead-in+pembrolizumab; also autoimmune hepatitis for sotorasib+pembrolizumab concurrent.
*Grade 4 TRAEs were ALT increased (n = 1; related to sotorasib and atezolizumab), and AST increased (n = 1; related to sotorasib).
‡Duration of combination calculated for patients receiving both sotorasib and IO; one patient in a lead-in cohort did not receive IO and not included
†DLT window was 21 days following initiation of combination treatment. IO, immune-oncology

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**

*Median depth of response among responders. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

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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

N=6 N=5 N=10 N=6

Max Admin Dose

NSCLC N=27

DOSE EXPANSION

GDC-6036 oral QD, 21-day cycles

400mg

NSCLC N=32

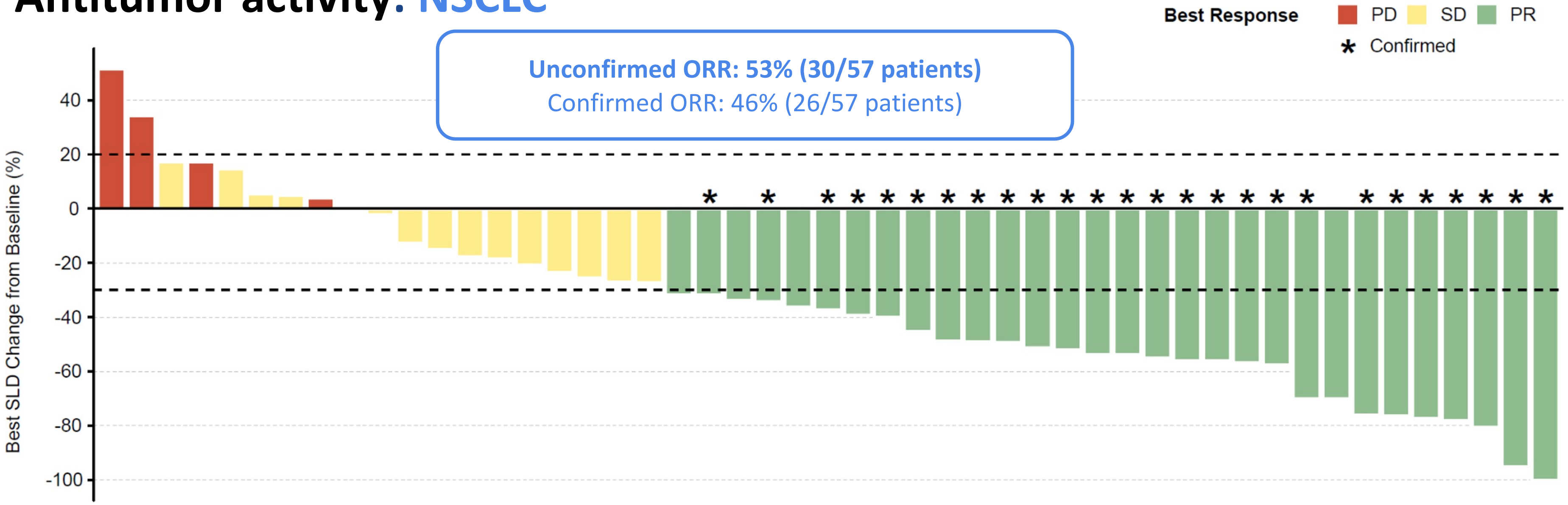
KEY ENDPOINTS

- 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**

Antitumor activity: NSCLC

Unconfirmed ORR: 53% (30/57 patients)
Confirmed ORR: 46% (26/57 patients)



Dose Level (mg)	50	50	200	50	200	200	400	200	400	100	400	400	200	400	100	400	400	400	400	400	400	400	200	400	400	400	400	400	200	400	100	100	400	200	400	400	50	200	400	400	200	400	100	400	400	400	400	400	400
Baseline SLD (mm)	68	35	52	315	122	75	41	100	83	46	47	73	34	86	48	34	62	54	106	104	85	107	35	99	75	66	11	53	22	102	130	41	23	82	119	15	50	41	51	196	10	30	21	142	101	32	31	21	49
Days on Treatment	19	38	92	34	40	91	80	42	255	345	127	180	346	123	165	61	543	199	126	71	85	42	126	93	100	256	143	147	252	150	417	514	265	116	207	274	303	293	199	64	453	72	359	166	119	143	95	276	388
Active on Treatment	N	N	N	N	N	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y

8 of 57 patients are not represented in waterfall plot, n=1 discontinued before first tumor assessment and n=7 ongoing without first tumor assessment by CCOD. All 8 patients treated with 400mg QD.

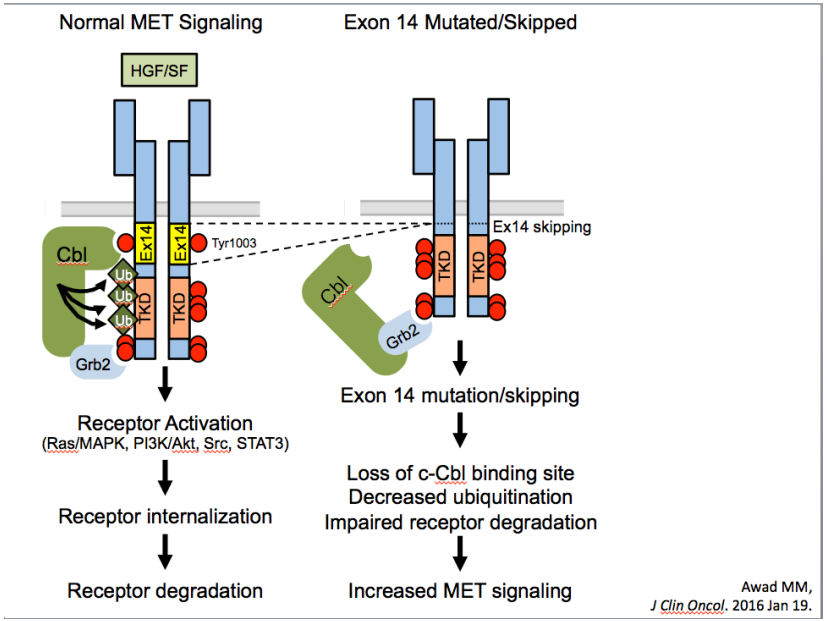
Conclusions: KRAS targeted therapies

- Combination of sotorasib + SHP2i RMC-4630 appears tolerable, but unclear efficacy at sotorasib acquired resistance. **May be better to combine upfront**.

- Sotorasib + atezolizumab/pembrolizumab results in **high degree of liver toxicity**. Lead-in and lower dose of sotorasib may reduce this risk.

- Monotherapy with **GDC-6036 has encouraging anti-tumor activity** in NSCLC patients with *KRAS G12C* mutation not previously treated with KRAS-G12C inhibitor.

Targeting METexon14 skipping NSCLC



METex14 alterations

- ✓ In 3-4% of NSCLCs
- ✓ More common in older patients (≥70 years), women, and smokers
- ✓ Concurrent MET amplification in approx. 20% of METex14-aberrant NSCLC
- ✓ Capmatinib, Tepotinib – FDA approved (ORR 41–46% in previously-treated populations)

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Tepotinib is a once daily and highly selective MET TKI approved for *MET*ex14 skipping NSCLC based mainly on Cohort A of the multi-cohort Phase II VISION study[1]

Key inclusion criteria

- Advanced NSCLC (*EGFR/ALK* wild-type, all histologies)
- Central confirmation of *MET*ex14 skipping by liquid and/or tissue biopsy
- First, second, or third line of therapy

Cohort A*
***MET*ex14 skipping (primary)**

Cohort C†
***MET*ex14 skipping (confirmatory)**

Tepotinib 500 mg‡ once daily

Selected endpoints

Primary:
Objective response by IRC (RECIST v1.1)

Secondary:
DOR, PFS, OS, Safety

Exploratory RANO-BM analysis§:
BOR per RANO-BM (patients with ≥1 evaluable post-baseline tumor assessment): disease control was defined as CR/PR/SD, or non-CR/non-PD

Here, we report the primary analysis (>9-months' follow-up) of the independent confirmatory Cohort C; data cut-off February 20, 2022‡

*Cohort A enrollment began on September 13, 2016. †Cohort C enrolment began on August 8, 2019. ‡500 mg tepotinib hydrochloride hydrate (active ingredient) contains 450 mg tepotinib free base (active moiety). §Composite of radiographic responses, corticosteroid use, and clinical status, giving a more comprehensive overview of the patient compared with RECIST.[2] For patients with non-measurable lesions only (enhancing and non-enhancing NTLs), non-CR/non-PD was defined as a best objective response of disease control, i.e. persistence of at least one non-progressing NTL. Brain imaging had no mandatory schedule and, as such, data for this analysis were incomplete, and confirmation of response was not required.

ALK, anaplastic lymphoma kinase; BOR, best overall response; CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRC, independent review committee; MET, mesenchymal-epithelial transition factor; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; NTL, non-target lesion; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease; TKI, tyrosine kinase inhibitor.

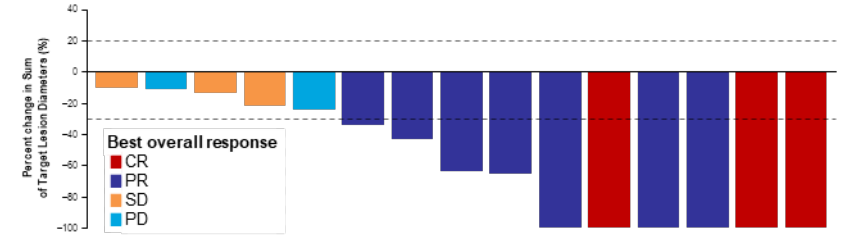
1. Paik PK, et al. *N Engl J Med.* 2020;383(10):931–943; 2. Lin NU, et al. *Lancet Oncol.* 2015;16(6):e270–e278.

Overall efficacy in Cohort C and Cohort A was robust and durable across therapy lines

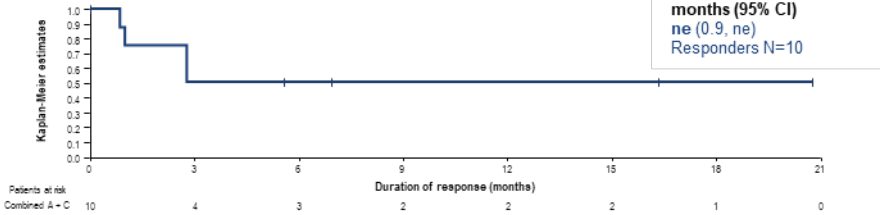
	1L* (T+ and/or L+)		2L+ (T+ and/or L+)	
	Cohort C (n=95)	Cohort A (n=69)	Cohort C (n=66)	Cohort A (n=83)
ORR, % (95% CI)	60.0 (49.4, 69.9)	50.7 (38.4, 63.0)	47.0 (34.6, 59.7)	43.4 (32.5, 54.7)
Median DOR, months (95% CI)	ne (13.4, ne)	46.4 (7.2, ne)	12.6 (5.1, ne)	12.4 (8.4, 18.5)
Median PFS, months (95% CI)	15.9 (10.4, ne)	10.3 (8.0, 15.3)	12.1 (6.9, ne)	10.9 (8.2, 12.7)
Median OS, months (95% CI)	21.1 (12.7, ne)	19.1 (9.9, 25.9)	18.8 (13.5, ne)	19.8 (15.0, 22.3)

Tepotinib showed promising intracranial activity in patients with brain metastases (RANO-BM analysis)

Intracranial response in patients with target lesions (n=15)



Intracranial duration of response



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Intertumoral molecular heterogeneity of non-small cell lung cancer with MET Exon 14 Skipping

Yuchen Han
Shanghai Chest Hospital
China

The flowchart of retyping MET Exon 14 skipping molecular and Significant differentially expressed genes among the 4 molecular subtypes

2017.4-2020.12 10525 cases NSCLC

DNA-based NGS detected METex14 skipping mutation

(n=133)

The sample was detected by Amoydx RNA based targeted NGS panel

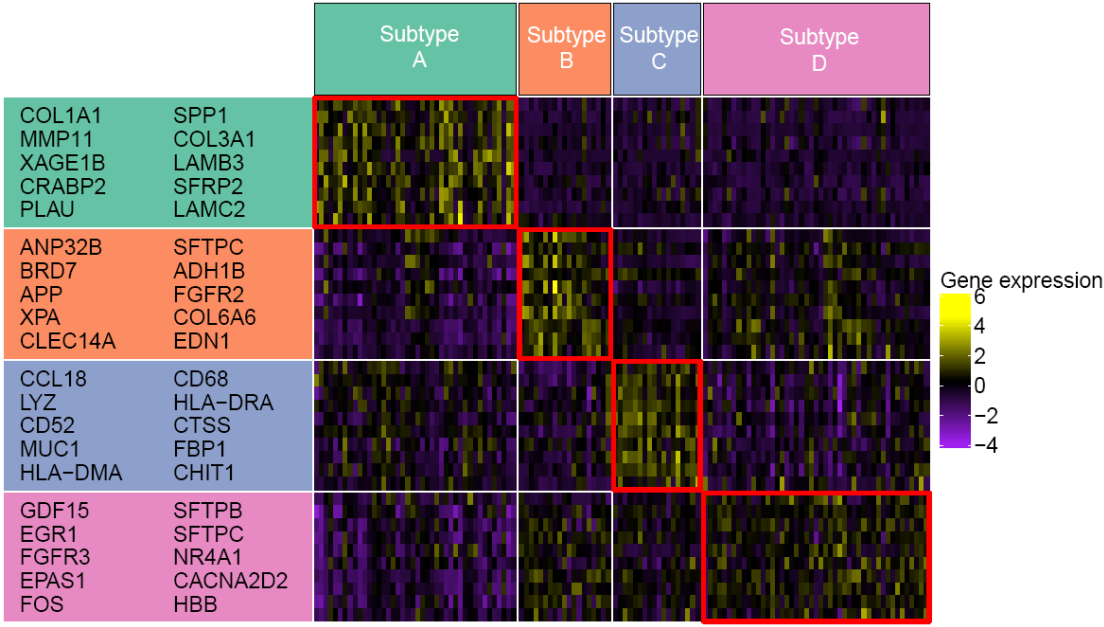
4 cases were excluded because the quality control did not meet the requirements

METex14 skipping wildtype

(n=3)

METex14 skipping mutation

(n=126)



Take home message

- Disclosed the clinical-relevant intertumoral heterogeneity of NSCLCs driven by MET exon 14 skipping.

Subtype A MET driven	Subtype B Mix	Subtype C Immune activated	Subtype D Bypass activated
More sensitive to MET-TKIs	Unremarkable	Might be more vulnerable to immunotherapy	Putatively primary resistant to MET-TKIs, Combination of MET-TKIs with bypass gene inhibitors, such as PIK3CA inhibitors, may improve efficacy

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MET Exon 14 Skipping Mutation in Non-Small Cell Lung Cancer (NSCLC) by Specific Mutation, Histology, and Smoking History

Jennifer A. Marks[1], Jun Yin[2], Balazs Halmos[3], Lyudmila Bazhenova[4], Suresh Ramalingam[5], Melina Marmarelis[6], Joanne Xiu[2], Phillip Walker[2], Matthew J. Oberley[2], Patrick C. Ma[7], Stephen V. Liu[1]

[1]Georgetown University, [2] Industry Support, [3]Montefiore Medical Center, [4]University of California San Diego, [5]Emory University, [6]University of Pennsylvania, [7]Penn State Cancer Institute

Results

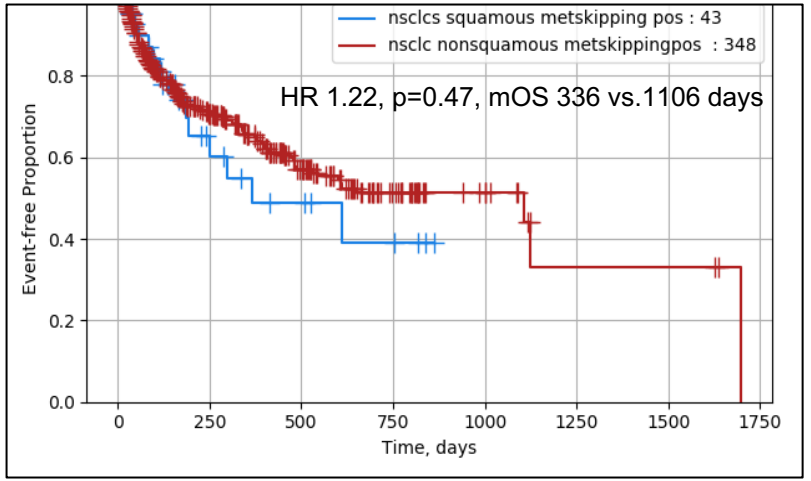
METex14 cases	Smokers	Non-Smokers
n=93	79 (84.9%)	14 (15.1%)

Smoking Status (n=93)	Squamous (n=8)	Non-Squamous (n= 85)
Smokers (n=79)	5 (6.3%)	74 (93.7%)
Non-Smokers (n=14)	3 (21.4%)	11 (78.6%)

Co-mutation by Histology

Features	Squamous	Non-Squamous
NGS-TP53	90.40% (p<0.001)	60.70% (p<0.001)
NGS-KMT2D	17.87% (p<0.05)	2.72% (p<0.05)
NGS-POT1	0.89% (p<0.05)	1.53% (p<0.05)
NGS-PIK3CA	10.71% (p=0.06)	4.31% (p=0.06)
CNA-TLX1	0.51% (p=0.07)	0.47% (p=0.07)
CNA-MDM2	0.87% (p=0.08)	2.09% (p=0.08)
NGS-SMAD4	2.08% (p=0.09)	2.77% (p=0.09)

Overall Survival



Conclusions: MET targeted therapies

- Tepotinib confirmed **60% ORR in 1st line setting** with promising intracranial activity.
- Gene expression profiling identified **4 subtypes of MET exon14+ NSCLC** that may have differential sensitivity to MET inhibitors and immunotherapies.
- Concurrent tumor genomic **alterations differ between squamous and non-squamous** MET exon14+ NSCLC and may influence response to MET inhibitors.