Lung Cancer UPDATES
ESMO HIGHLIGTHS
20-24 OCTUBRE 2023
Madrid, Spain

Iniciativa científica de:
GECP
lung cancer research

Enfermedad Metastática con alteraciones driver: RET, RAS, Her2

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NSCLC con fusiones de RET

- LIBRETTO-431: Selpercatinib

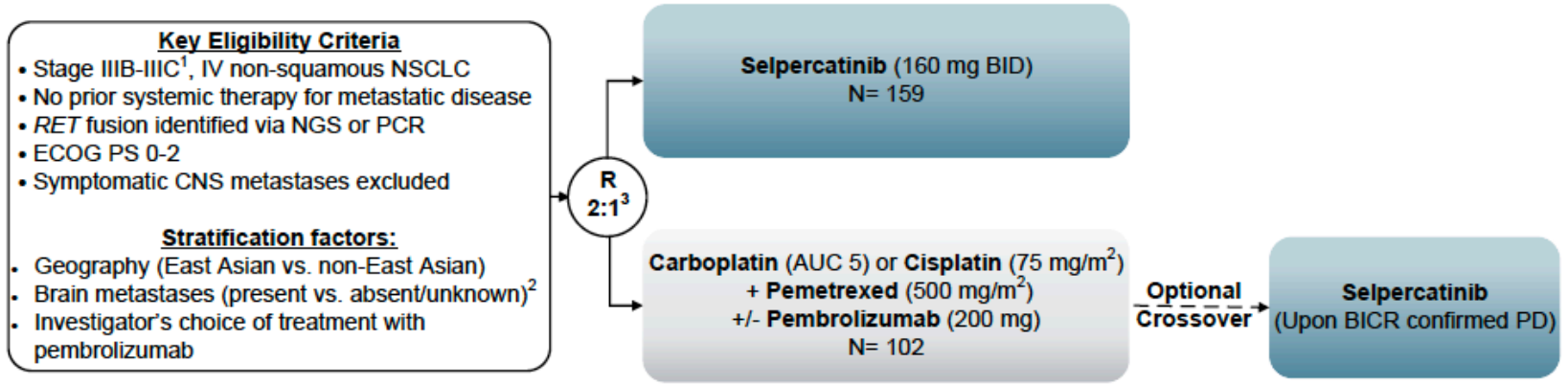
Iniciativa científica de: GECP lung cancer research

Randomized Phase 3 Study of First-line Selpercatinib versus Chemotherapy and Pembrolizumab in *RET* Fusion-positive NSCLC

LIBRETTO-431 (NCT04194944)

Herbert H. Loong, Koichi Goto, Benjamin J. Solomon, Keunchil Park, Maurice Pérol, Edurne Arriola, Silvia Novello, Ying Cheng, Andrea Ardizzoni, Milena P. Mak, Fernando C. Santini, Yasir Y. Elamin, Alexander Drilon, Jürgen Wolf, Baohui Han, Hongmei Han, Minji K. Uh, Tarun Puri, Viktoriya Soldatenkova, Caicun Zhou

LIBRETTO-431 phase 3 open-label study design



Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population
Secondary Endpoints:

- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time to progression][5])
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

NSCLC con fusiones de RET

- LIBRETTO-431: Selpercatinib

Iniciativa científica de: GECP lung cancer research

Randomized Phase 3 Study of First-line Selpercatinib versus Chemotherapy and Pembrolizumab in *RET* Fusion-positive NSCLC

LIBRETTO-431 (NCT04194944)

Characteristic		Selpercatinib N= 129	Control N= 83
Age, years	Median (range)	60.0 (31-84)	62.0 (31-83)
Sex, no. (%)	Female	65 (50.4)	48 (57.8)
	Male	64 (49.6)	35 (42.2)
Smoking status, no. (%)	Current/Former	44 (34.1)	24 (28.9)
	Never	85 (65.9)	59 (71.1)
Race, no. (%)	Asian	76 (58.9)	41 (51.9)
	White	49 (38.0)	37 (46.8)
	Other	4 (3.2)	1 (1.3)
Region of enrollment, no. (%)	East Asia	75 (58.1)	41 (49.4)
	Non-East Asia	54 (41.9)	42 (50.6)
Disease stage, no. (%)	Stage IIIB/C	7 (5.4)	7 (8.4)
	Stage IV	122 (94.6)	76 (91.6)
ECOG PS, no. (%)	0	45 (34.9)	27 (32.5)
	1	81 (62.8)	52 (62.7)
	2	3 (2.3)	4 (4.8)
Brain metastases, no. (%)	No/Unknown	104 (80.6)	65 (78.3)
	Yes	25 (19.4)	18 (21.7)
PDL-1 expression, no. (%)	Negative	31 (24.0)	12 (14.5)
	Positive (≥1%)	55 (42.6)	39 (47.0)
	Missing	43 (33.3)	32 (38.6)
RET fusion partner, no. (%)	*KIF5B-RET*	54 (41.9)	41 (49.4)
	CCDC6-RET	13 (10.1)	8 (9.6)
	Other	4 (3.1)	3 (3.6)
	Positive (partner undefined)	58 (45.0)	31 (37.3)

LIBRETTO-431 phase 3 open-label study design

Key Eligibility Criteria
- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2

R 2:1[3]

Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Optional Crossover → **Selpercatinib** (Upon BICR confirmed PD)

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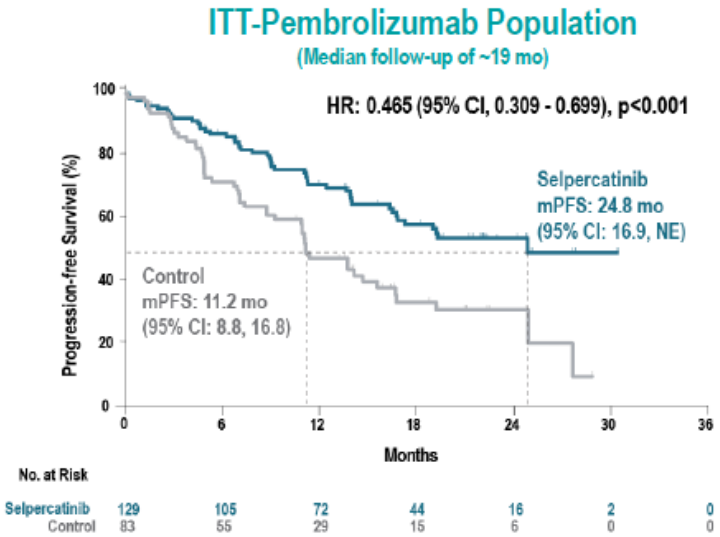
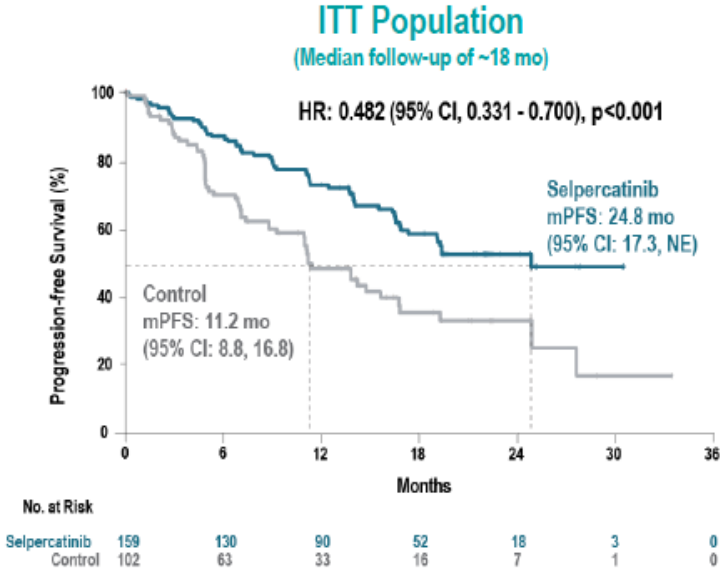
NSCLC con fusiones de RET

LIBRETTO-431: Selpercatinib → Eficacy

Primary Endpoint: PFS by BICR





Selpercatinib mejoró de forma estadísticamente significative en las poblaciónes pre-especificadas

ORR, DoR

Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

Mayor ORR y DoR con selpercatinib

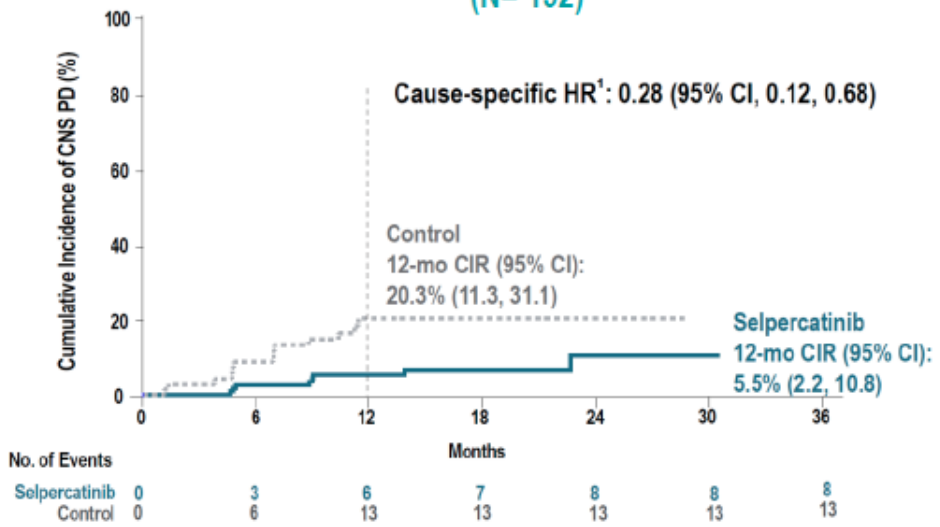
NSCLC con fusiones de RET

LIBRETTO-431: Selpercatinib → Eficacy

Iniciativa científica de: GECP lung cancer research

Incidencia acumulada de MTS cerebrales

Patients with and without Baseline CNS Metastases (N= 192)



Risk of CNS Progression

Without CNS Metastases at Baseline	Selpercatinib (N= 99)	Control (N= 51)
12-month CIR, % (95% CI)	1.1% (0.1, 5.2)	14.7% (5.7, 27.6)
Cause-specific HR[1] (95% CI)	0.17 (0.04, 0.69)	

With CNS Metastases at Baseline	Selpercatinib (N= 21)	Control (N= 21)
12-month CIR, % (95% CI)	25.7% (8.8, 46.7)	33.3% (14.3, 53.8)
Cause-specific HR[1] (95% CI)	0.61 (0.19, 1.92)	

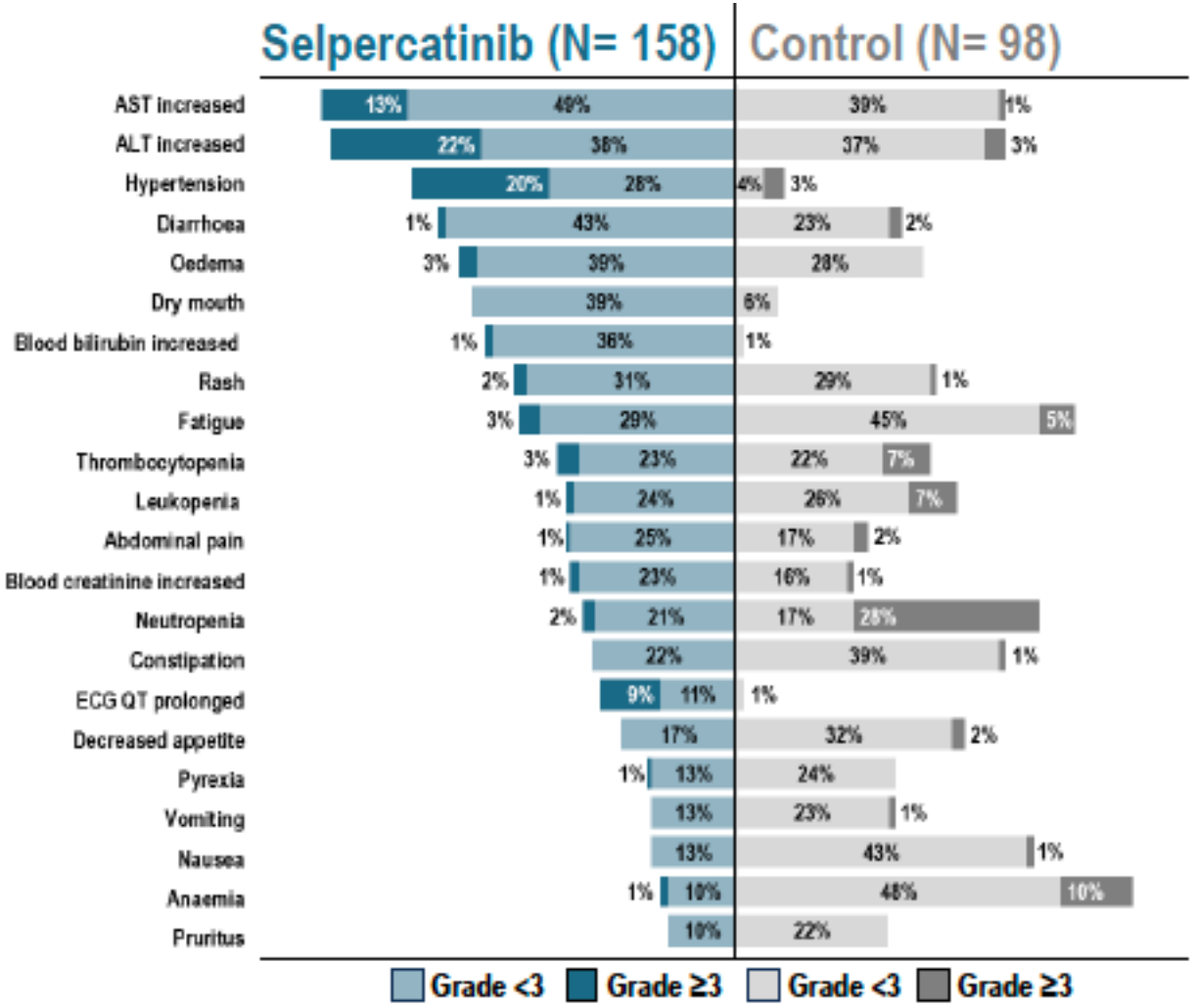
Intracraneal ORR, DoR y PFS

Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

NSCLC con fusiones de RET

LIBRETTO-431: Selpercatinib → Safety



	Selpercatinib N= 158	Control N= 98
Median time on treatment, months ± SD	**16.7 ± 8.3**	9.8 ± 7.2
Any AE, n (%)	158 (100.0)	97 (99.0)
AE Grade ≥3	111 (70.3)	56 (57.1)
Deaths due to AE, n (%)	7 (4.4)	0
Related AE (malnutrition and sudden death)	2 (1.3)	0
AEs leading to discontinuation, n (%)	16 (10.1)	2 (2.0)
AEs leading to any dose adjustment, n (%)	123 (77.8)	74 (75.5)
AEs leading to dose reduction	81 (51.3)	28 (28.6)

NSCLC con mutaciones de KRAS G12C

KRYSTAL-7

Iniciativa científica de: GECP lung cancer research

KRYSTAL-7: Efficacy and Safety of Adagrasib With Pembrolizumab in Patients With Treatment-Naïve, Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a KRAS^{G12C} Mutation

Marina C. Garassino[1], Willemijn S.M.E. Theelen[2], Robert Jotte[3], Janessa Laskin[4], Filippo de Marinis[5], Carlos Aguado[6], Firas Badin[7], Izabela Chmielewska[8], Maximilian J. Hochmair[9], Shun Lu[10], Ernest Nadal[11], Gyula Ostoros[12], Enriqueta Felip[13], Alexander I. Spira[14], Cassie Lane[15], Joyce He[15], Richard Chao[15], Pasi A. Jänne[16]

Study Design: Phase 2 Cohorts

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with KRAS^{G12C} mutation[a]
- No prior systemic therapy for locally advanced/ metastatic disease[b]
- Stable brain metastases allowed
- Known PD-L1 TPS score[c]

Cohorts 1a and 2[e]
Adagrasib 400 mg BID + Pembrolizumab 200 mg Q3W
N=148

Key Study Objectives

- Primary endpoint: ORR (RECIST v1.1 per investigator assessment)
- Secondary endpoints: DOR and PFS (per investigator assessment), OS, safety, PK

- We report safety in all treated patients (N=148) and efficacy in patients with PD-L1 TPS ≥50% (n=51[d]) from the KRYSTAL-7 study evaluating adagrasib[e] + pembrolizumab (200 mg IV Q3W) in treatment-naïve patients with NSCLC harboring a KRAS^{G12C} mutation
- Median follow-up for all treated patients, 8.7 months; PD-L1 TPS ≥50%, 10.1 months

Cohort 1a: PD-L1 < 1%
Cohort 2: PD-L1 ⩾ 1%

NSCLC con mutaciones de KRAS G12C

KRYSTAL-7

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Adagrasib 400 mg BID + Pembrolizumab 200 mg Q3W
N=148

Key Study Objectives

- Primary endpoint: ORR (RECIST v1.1 per investigator assessment)
- Secondary endpoints: DOR and PFS (per investigator assessment), OS, safety, PK

	Concurrent 400 mg BID Adagrasib + Pembrolizumab	
	All Patients (N=148)	PD-L1 TPS ≥50% (n=54)
Median age (range), years	67 (40–90)	66 (40–80)
Female, n (%)	71 (48)	28 (52)
Race, n (%)		
White	113 (76)	42 (78)
Black or African American	5 (3)	3 (6)
Asian / Other[a]	26 (18)	9 (17)
ECOG PS, n (%)		
0 / 1	57 (39) / 91 (61)	18 (33) / 36 (67)
Smoking history, n (%)		
Never smoker	2 (1)	0
Current smoker / former smoker	32 (22) / 114 (77)	12 (22) / 42 (78)
Baseline metastases, n (%)		
Bone	46 (31)	17 (31)
CNS	21 (14)	9 (17)
Adrenal	28 (19)	9 (17)
Liver	24 (16)	10 (19)

…d efficacy in patients with PD-L1 TPS ≥50% (n=51[d]) from the KRYSTAL-7 study
…IV Q3W) in treatment-naïve patients with NSCLC harboring a KRAS^{G12C} mutation
…hs; PD-L1 TPS ≥50%, 10.1 months

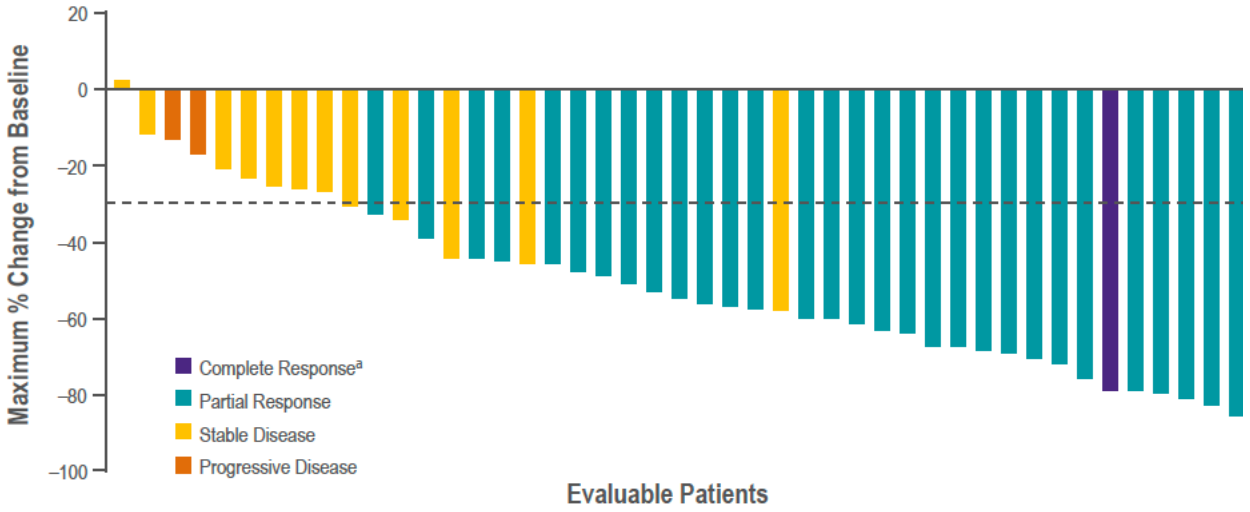
Cohort 1a: PD-L1 < 1%
Cohort 2: PD-L1 ⩾ 1%

NSCLC con mutaciones de KRAS G12C

KRYSTAL-7: Eficacy

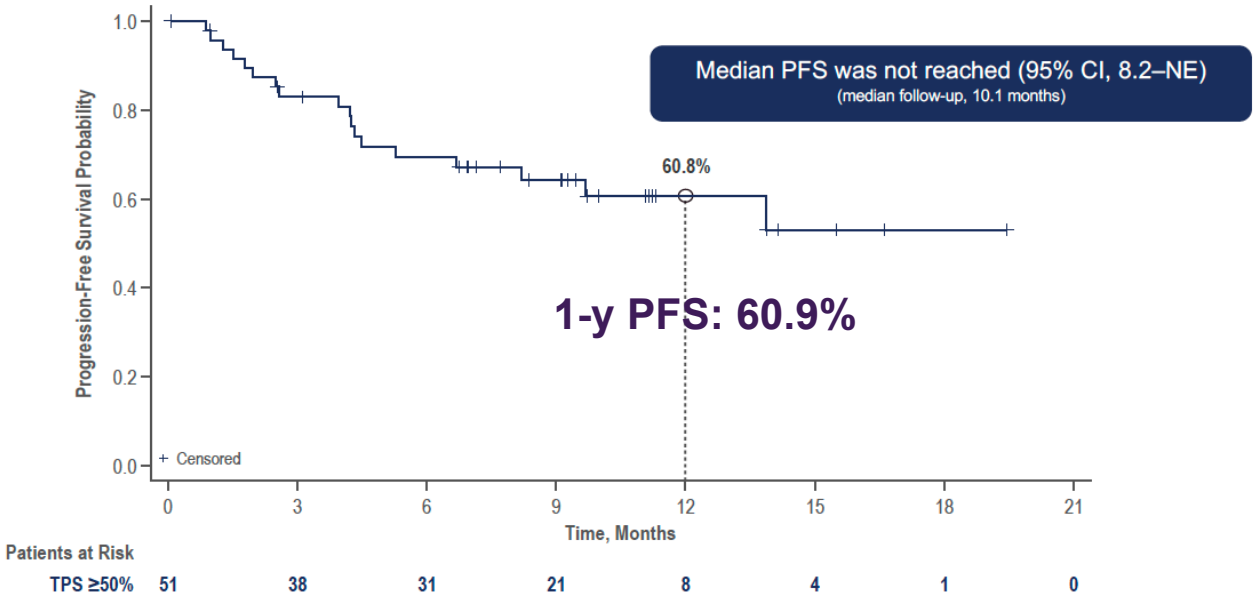
Iniciativa científica de: GECP lung cancer research

ORR in patients with PD-L1 ⩾ 50%



- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity[b], ORR was 70% (14/20; 95% CI, 46–88)

PFS in patients with PD-L1 ⩾ 50%



Mediant time to response 1.4 m
DoR not reached (95% CI, 12.6-NE)

NSCLC con mutaciones de KRAS G12C

KRYSTAL-7: Safety

Iniciativa científica de: GECP lung cancer research

TAES

Most Frequent TRAEs[a], %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51	28	20	3	0
Diarrhea	44	33	7	3	0
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Vomiting	29	17	11	1	0
Fatigue	26	12	10	4	0
Decreased appetite	24	14	9	1	0
Lipase increased	24	3	9	10	1

2 grado 5: neumonitis y neumonía
TAES 18%, grado ⩾3 en 5%
Reduccion de adagrasib 46%
Disontinuación adagrasib 5% y de pembrolizumab 11%

Liver treatment-related AEs

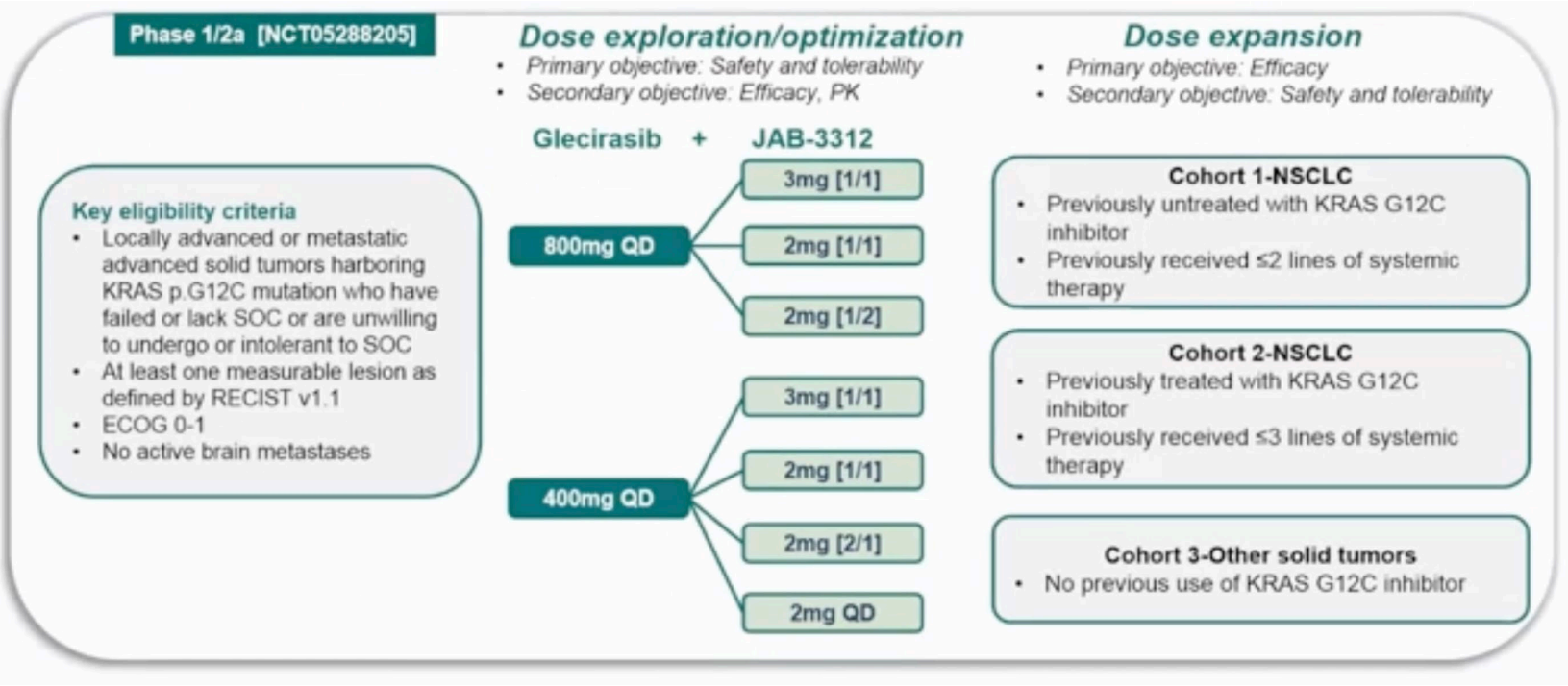
Most Frequent Liver TRAEs, %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Hepatitis	4	0	2	2	0
Hepatotoxicity[a]	1	0	1	1	0
Liver injury	1	0	1	0	0
Drug-induced liver injury	1	1	0	0	0
Hepatic failure	1	0	0	1	0
Acute hepatitis	1	0	1	0	0
Immune-mediated hepatitis	1	0	0	1	0

<10%
No razon para discontinuar
Tiempo medio para resolverse 22 días
24 (16%) fueron elevaciones AST/ALT ⩾3

NSCLC con mutaciones de KRAS G12C

Glecirasib (KRAS G12C inh) + JAB-3312 (SHP2 inh)

Estudio Fase 1



ORR NSCLC KAS G12C

ORR 62.1%
1L 65.5%
>1 L 55.2%

DCR 100%

Dosis 800 mg + 2 mg
ORR 86.7%

NSCLC con mutaciones de RAS

Glecirasib (KRAS G12C inh) + JAB-3312 (SHP2 inh)

Iniciativa científica de: GECP lung cancer research

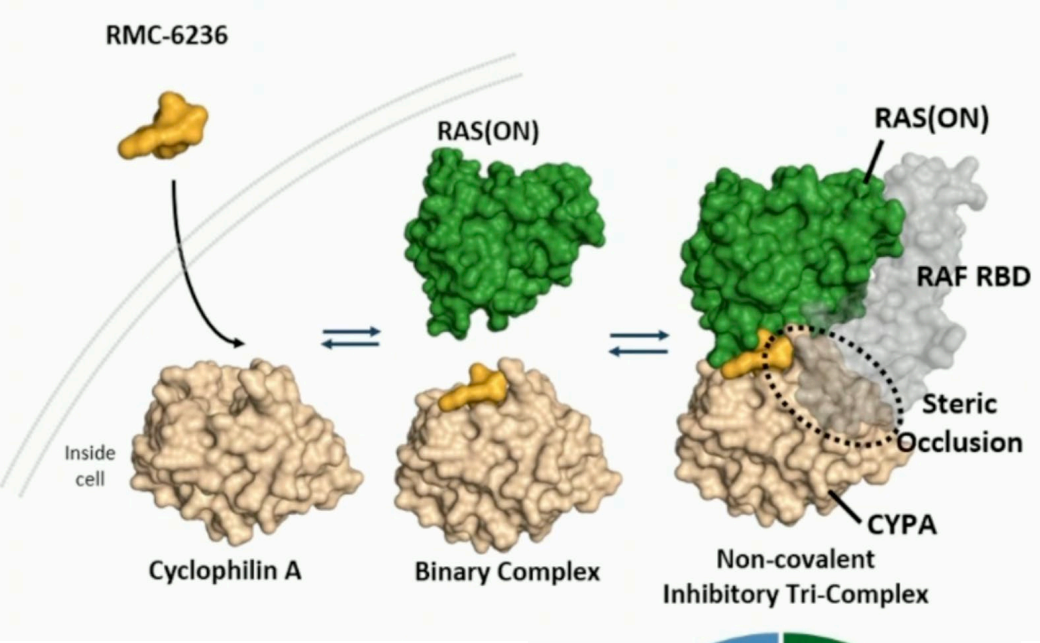
TRAE

Glecirasib	400mg QD		800mg QD
JAB-3312	2mg [1/1]	3mg [1/1]	2mg [1/1]
Patients enrolled**	(N=35)	(N=30)	(N=49)
TRAE	34 (97.1%)	28 (93.3%)	45 (91.8%)
Grade 3 or 4 TRAE	17 (48.6%)	10 (33.3%)	18 (36.7%)
SAE (related to treatment)	4 (11.4%)	1 (3.3%)	3 (6.1%)
TRAE leading to glecirasib discontinuation	0	0	1 (2.0%)
TRAE leading to JAB-3312 discontinuation	4 (11.4%)	1 (3.3%)	1 (2.0%)

Grado 3: hipertrigliceridemia, toxicidad hepática, neutropenia y edema

NSCLC con mutaciones de RAS

RMC-6236

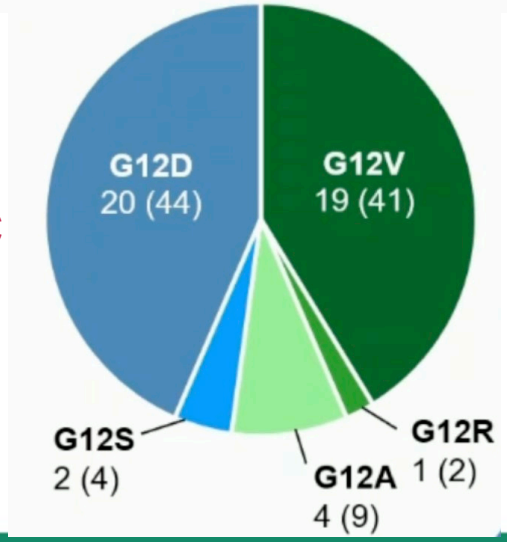


Estudio fase 1

RMC-6236 10-600 mg QD

	NSCLC[a] N = 46	PDAC[a] N = 65
Age, median (range), years	65 (31–83)	64 (30–86)
Female, n (%)	25 (54)	31 (48)
ECOG PS, n (%)		
0	11 (24)	20 (31)
1	35 (76)	45 (69)
Smoking status, n (%)		
Current	2 (4)	2 (3)
Past	28 (61)	14 (22)
Never	16 (35)	49 (75)
Number of prior anti-cancer therapies, median (range)	2 (1–6)	3 (1–7)
Select type of prior anti-cancer therapy/regimens, n (%)		
Checkpoint inhibitor[b]	44 (96)	–
Platinum-based chemotherapy	46 (100)	–
FOLFIRINOX	–	45 (69)
Gemcitabine + nab-paclitaxel	–	49 (75)

NSCLC



NSCLC con mutaciones de RAS

RMC-6236

Iniciativa científica de: GECP lung cancer research

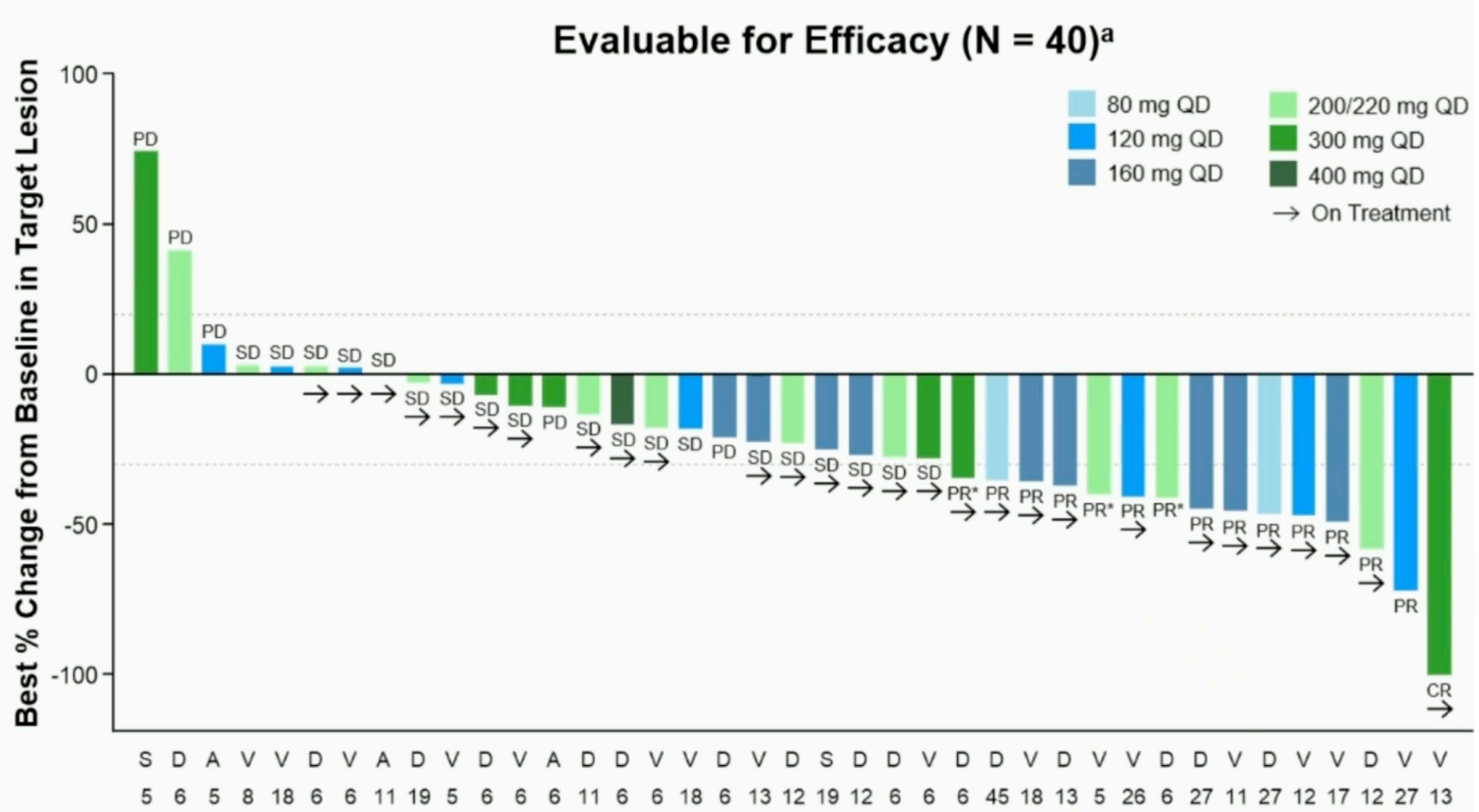
Patients with NSCLC and PDAC Treated at ≥80 mg QD (N = 111)					
Maximum severity of treatment-related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)					
Rash[a]	58 (52)	25 (23)	7 (6)	0	90 (81)
Nausea	40 (36)	11 (10)	0	0	51 (46)
Diarrhea	28 (25)	14 (13)	1 (1)	0	43 (39)
Vomiting	30 (27)	7 (6)	0	0	37 (33)
Stomatitis	13 (12)	9 (8)	2 (2)	0	24 (22)
Fatigue	11 (10)	6 (5)	0	0	17 (15)
Other select TRAEs, n (%)					
ALT elevation	8 (7)	1 (1)	0	0	9 (8)
AST elevation	8 (7)	0	0	0	8 (7)
Electrocardiogram QT prolonged	1 (1)	0	0	0	1 (1)
TRAEs leading to dose reduction[b], n (%)	0	10 (9)	5 (5)[c]	0	15 (14)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	1 (1)[d]	1 (1)

NSCLC con mutaciones de RAS

RMC-6236

Iniciativa científica de: GECP lung cancer research

KRAS G12X NSCLC patients



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
CR	1 (3)
PR	14 (35)
SD	19 (48)
PD	5 (13)
NE[b]	1 (3)
ORR, n (%)	15 (38)
Confirmed, n	12
DCR (CR+PR+SD), n (%)	34 (85)

Median time to response 1.4 m
Median time on treatment 3.1 m

NSCLC con mutaciones de RAS

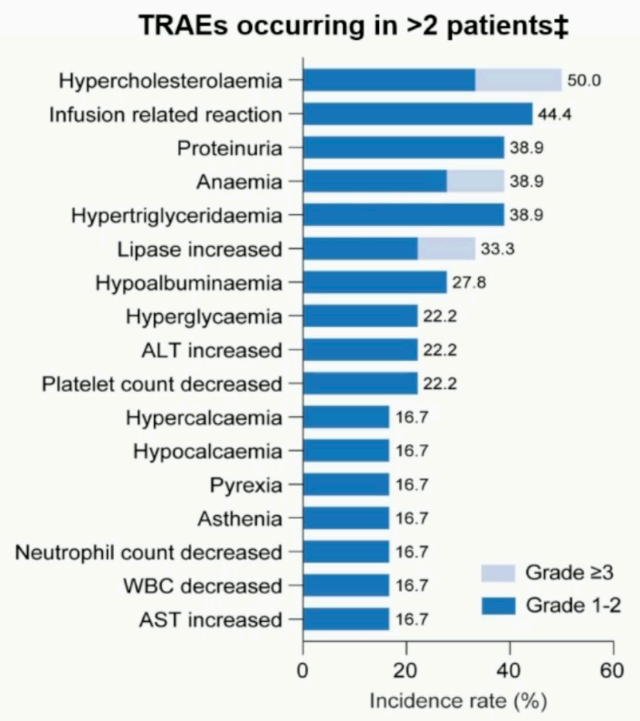
HRS-4642 KRAS G12D inhibitor

Phase 1 study N =18

Iniciativa científica de: GECP lung cancer research

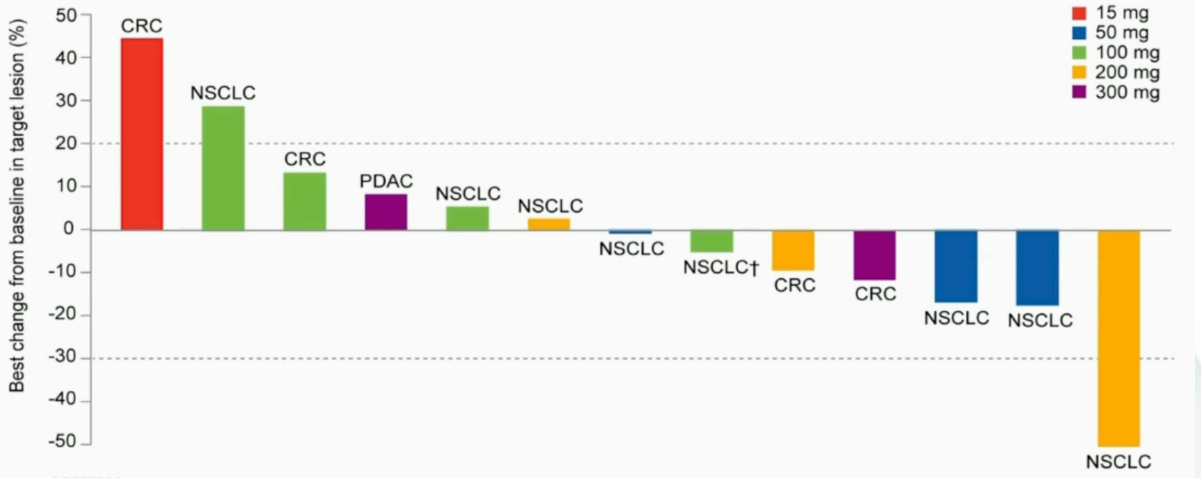
Safety

	All patients (n=18)
Any AE, n (%)	18 (100%)
Grade ≥3	9 (50.0%)
Any TRAE, n (%)	18 (100%)
Grade ≥3	6 (33.3%)*
Leading to dose reduction	0
Leading to dose interruption	8 (44.4%)
Leading to treatment discontinuation	0
Leading to death	0
Serious	1 (5.6%)†



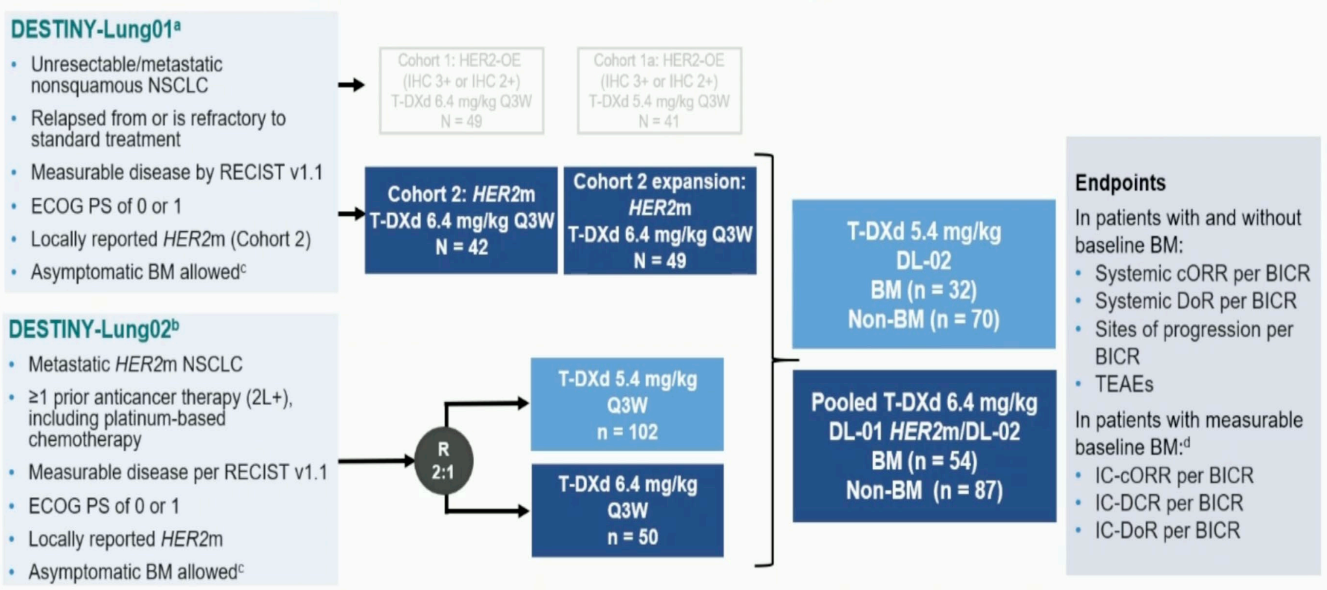
Eficay

	All tumors (n=18)	NSCLC (n=10)
BoR	1 PR, 11 SD, 2 non-CR/non-PD	1 PR, 7 SD, 1 non-CR/non-PD
DCR	77.8% (14/18)	90.0% (9/10)
Patient with target lesion shrinkage*	53.8% (7/13)	62.5% (5/8)



NSCLC con mutaciones HER2

DESTINY-Lung 01 & DESTINY-Lung02: Brain mets



Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM n = 14	Pooled T-DXd 6.4 mg/kg DL-01 *HER2m*/DL-02 BM n = 30
IC-cORR, n (%)[a]	**7 (50.0)**	**9 (30.0)**
95% CI[b]	23.0-77.0	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30.0)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE[c]	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%)[a]	**13 (92.9)**	**22 (73.3)**
95% CI[b]	66.1-99.8	54.1-87.7
IC-DoR, months[d]		
Median, (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response

Pacientes de similares características a la población general

Respuesta similar en pacients con o sin BM

Similar eficacia en BM tratadas o no en pacientes con BM basales

Conclusiones

- Selpercatinib nuevo estándar de tratamiento en pacientes con fusiones de RET
- Adagrasib + pembolizumab mayor eficacia que pembrolizumab en pacientes KRAS G12C con PD-L1≥ 50%
- Nuevos inhibidores de KRAS G12X con eficacia y seguridad
- Transtuzumab Deruxtecan eficaz en metástasis cerebrales

Iniciativa científica de:

GECP lung cancer research