Tratamientos dirigidos (ROS1, EGFR ex20 y HER2)

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Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Entrectinib in ROS1 fusion positive NSCLC (pooled analysis)

Integrated analysis

Efficacy population

53 *ROS1*+, ROS1 inhibitor-naïve NSCLC patients

Safety population

355 patients have received entrectinib (all tumour types and gene rearrangements)

STARTRK-2[1]
Phase II, multicenter, global basket study 600 mg QD, 28-day cycle
N=37 ROS1-positive patients

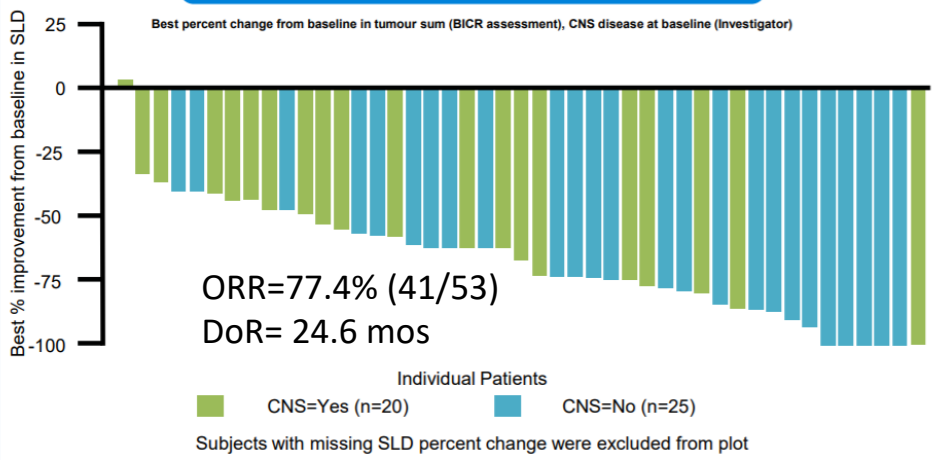
STARTRK-1[2]
Phase I dose escalation;
N=7 ROS1-positive patients

ALKA-372-001[2]
Phase I dose escalation;
N=9 ROS1-positive patients

Primary endpoints
ORR and DOR*

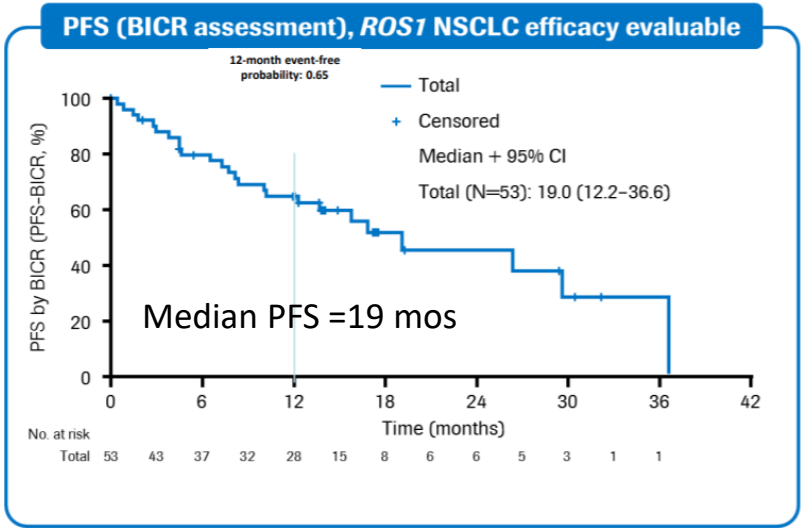
Secondary endpoints
CBR*
PFS and OS
Intracranial ORR*†
Intracranial DOR*
Safety and tolerability

Change in tumour size: *ROS1*+ NSCLC population (n=53) (BICR assessment)



Intracranial response – CNS metastases at baseline by BICR (n=20*)	
Intracranial ORR, n (%) (95% CI)	11 (**55**) (31.53, 76.94)
CR	**4 (20.0)**
PR	7 (35.0)
SD	0
PD	3 (15.0)
Non CR/PD-Non evaluable	6 (30.0)
Intracranial median DOR, months (95% CI)	**12.9** (5.6, NE)
Patients with event, n (%)	5 (45.5)
Disease progression, n	3
Death, n	2
6 months	
Patients remaining at risk	7
Event-free probability	0.71

Entrectinib in ROS1 fusion positive NSCLC (pooled analysis)



Most common (≥10%) treatment-related AEs, n (%)	Safety evaluable population (N=355)	
	All grades	Grade 3
Dysgeusia	147 (41.4)	1 (0.3)
Fatigue	99 (27.9)	10 (2.8)
Dizziness	90 (25.4)	2 (0.6)
Constipation	84 (23.7)	1 (0.3)
Nausea	74 (20.8)	0
Diarrhea	81 (22.8)	5 (1.4)
Weight increased	69 (19.4)	18 (5.1)
Paresthesia	67(18.9)	0
Blood creatinine increased	54 (15.2)	2 (0.6)
Myalgia	54 (15.2)	2 (0.6)
Edema peripheral	50 (14.1)	1 (0.3)
Vomiting	48 (13.5)	0
Anemia	43 (12.1)	16 (4.5)
Arthralgia	44 (12.4)	2 (0.6)
Aspartate Aminotransferase increased	39 (11.0)	4 (1.1)*

*One Gr 4 aspartate aminotransferase increased reported

AEs leading to discontinuation: 3.9%
and to dose reduction: 27.3%

TRIDENT1: Repotrectinib in ROS1 fusion positive NSCLC (phase 1)

Study Design / Eligibility
- Multicenter study in advanced/metastatic solid tumors harboring *ROS1/NTRK1-3/ALK* fusions
- Measurable disease (RECIST v1.1)
- No limit on prior lines of therapy (including prior TKIs)
- Asymptomatic treated or untreated CNS metastases/leptomeningeal disease allowed

Primary Objective
- Determine the maximum tolerated dose and recommended phase 2 dose

Secondary Objectives
- Safety and tolerability
- Food effect
- Preliminary objective response rate and clinical benefit rate

	Number of patients per dose level						
	40 mg QD	80 mg QD	160 mg QD	240 mg QD	160 mg BID	200 mg BID	Total
Safety population (*ROS1+, NTRK1-3+, ALK+* solid tumors)	13	12	23	10	12	2	**72**
Efficacy population (*ROS1+* NSCLC)	6	5	10	2	7	0	**30***

Characteristic	N=30*
Age, median (range)	52 (30, 75)
Sex, female n (%)	20 (67)
Race, Asian n (%)	17 (57)
CNS metastases at baseline, n/N (%)	16/30 (53)
TKI-naïve, n/N (%)	5/10 (50)
TKI-pretreated, n/N (%)	11/20 (55)
***ROS1* fusion detection method, n (%)**	
FISH	22 (73)
NGS	8 (27)
Median lines of prior systemic therapy (range)	2 (1, 8)
Prior ROS1 TKI, n (%)	20 (67)
Crizotinib only, n (%)	11 (37)
Median # of prior TKIs (range)	1 (0, 3)
No prior TKI(s), n (%)	10 (33)
1 prior TKI, n (%)	14 (47)
≥2 prior TKIs, n (%)	6 (20)
Prior chemotherapy, n (%)	27 (90)

TRIDENT1: Repotrectinib in ROS1 fusion positive NSCLC (phase 1)

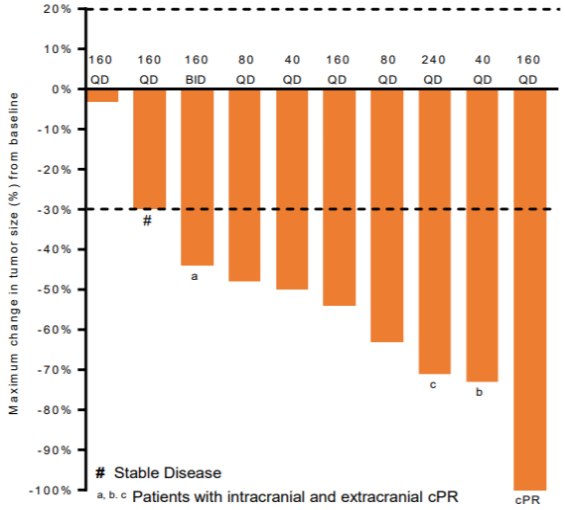
TKI-naïve (N=10)

Confirmed ORR, n/N (%)	**8/10 (80%)**
95% CI (%)	(44 – 97)
Time to response (TTR), mo	
Median	1.6
Range	1.4 – 3.3
Intracranial ORR, n/N (%) (measurable disease)	3/3 (100%)
95% CI (%)	(29 – 100)
CBR*, n/N (%)	10/10 (100%)
95% CI (%)	(69 – 100)

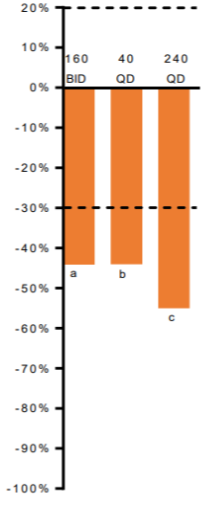
**Clinical benefit rate (CBR) = CR + PR + SD ≥ 2 cycles*

5 of 8 patients remain in cPR (3.7+ – 11.1+mo)

Overall Response (N=10)



Intracranial Response (N=3)



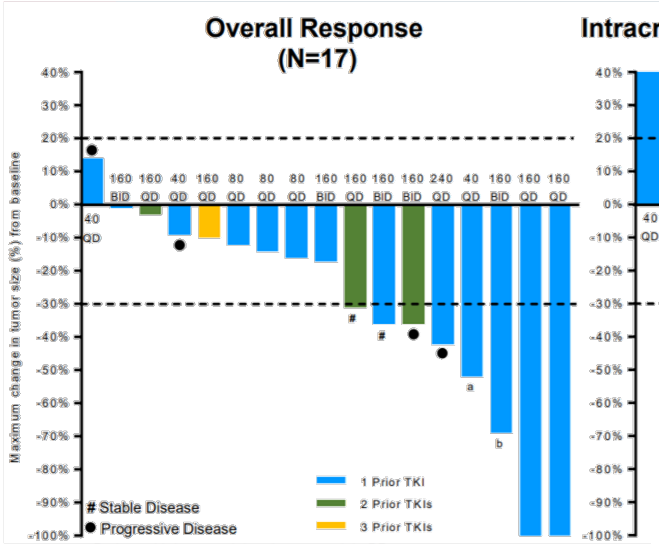
TKI-pretreated (N=17)

Confirmed ORR, n/N (%)	**3/17 (18%)**
95% CI (%)	(4 – 44)
ORR at 160 mg QD	**2/6 (33%)**
Time to response (TTR), mo	
Median	1.6
Range	1.5 – 1.8
Intracranial ORR, n/N (%) (measurable disease)	1/4 (25%)
CBR*, n/N (%)	13/17 (76%)
95% CI (%)	(56 – 97)

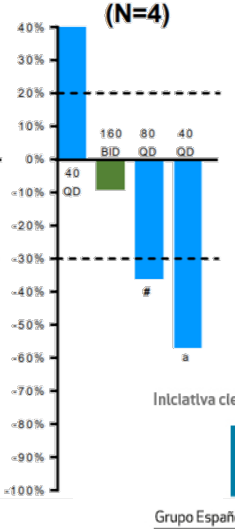
**CBR = CR + PR + SD ≥ 2 cycles*

1 of 3 patients remains in cPR (11.1+ mo)

Overall Response (N=17)



Intracranial Response (N=4)



Iniciativa científica de:

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Spanish Lung Cancer Group

OA 02.02 – J.Lin et al

TRIDENT1: Repotrectinib in ROS1 fusion positive NSCLC (phase 1)

Most common (>10%) treatment-related AEs	All Grades (%)	Grade 3# (%)
Any AE	60 (83.0)	
Dizziness	36 (50.0)	2 (2.8)
Dysgeusia	33 (45.8)	
Paresthesia	21 (29.2)	
Constipation	14 (19.4)	
Fatigue	13 (18.1)	
Anemia	9 (12.5)	3 (4.2)
Nausea	8 (11.1)	

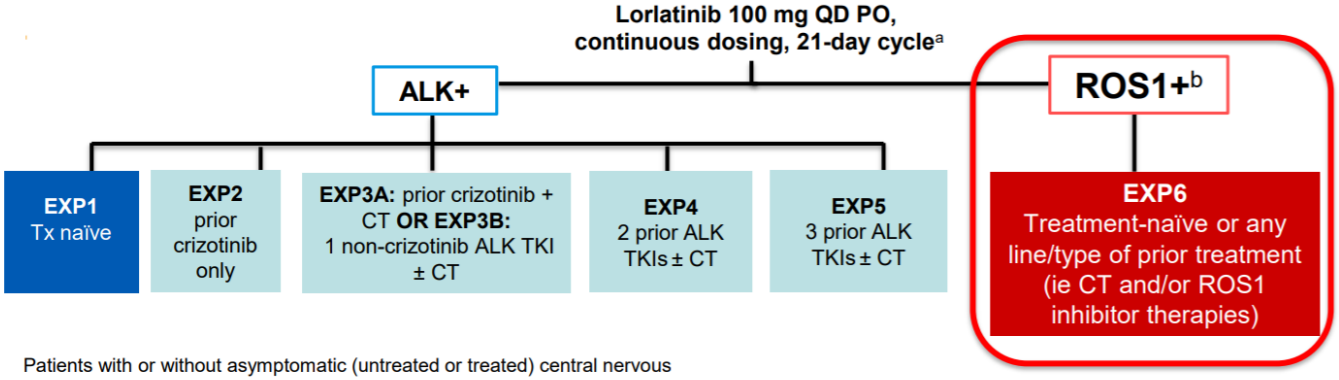
#Additional grade 3 treatment-related AEs: weight increased, dyspnea/hypoxia, pleural effusion, hypophosphatemia (1 each)

No grade 4 treatment-related AEs observed

- **Dose-limiting toxicities** (n=4)
  - **Grade 2 or 3 dizziness**
    - 160 mg BID (n=2)
    - 240 mg QD (n=1)
  - **Grade 3 dyspnea/hypoxia**
    - 160 mg BID (n=1)
- **Two deaths during study treatment**
  - 1 due to disease progression
  - 1 due to sudden death possibly related to study drug
- **RP2D determination is ongoing**

- The preliminary TRIDENT-1 phase 1 data warrant further clinical testing of Repotrectinib in ROS1+ NSCLC and other solid tumors harboring ROS1 fusions

Lorlatinib in ROS1 fusion positive NSCLC (expansion cohort)



Patients with or without asymptomatic (untreated or treated) central nervous system metastases were eligible.

[a]Treatment until PD or unacceptable toxicity; treatment beyond PD allowed if deriving benefit.

[b]*ROS1* rearrangement status was determined locally via fluorescence in situ hybridization, reverse transcriptase–polymerase chain reaction or next-generation sequencing, and confirmed by central laboratory testing.

The data cut-off date was February 2, 2018.

Primary Endpoint
- Overall and intracranial (IC) antitumor activity measured as confirmed overall and IC response by ICR

Secondary Endpoints
- Safety and tolerability
- Secondary measures of clinical efficacy

N= 47 pts
13 crizo-nave
34 crizo pretreated
53% brain mets

	Crizotinib-naïve (n=13)		Crizotinib-pretreated (n=34)
BOR, n (%)		BOR, n (%)	
CR	1 (7.7)	CR	2 (5.9)
PR	7 (53.8)	PR	7 (20.6)
SD	5 (38.5)	SD	16 (47.1)
PD	0	PD	3 (8.8)
IND	0	IND	6 (17.6)
ORR, n (%)	8 (61.5)	ORR, n (%)	9 (26.5)
95% CI	31.6, 86.1	95% CI	12.9, 44.4
Median TTR, mo	1.4	Median TTR, mo	2.5
Range	1.3–8.3	Range	1.4–4.2
Median DOR, mo	19.6	Median DOR, mo	NR
95% CI	4.0, 25.3	95% CI	7.1, NR
DOR ≥12 mo, n°/n (%)	5/8 (62.5)	DOR ≥12 mo, n°/n (%)	5/9 (55.6)
Median PFS, mo	21.0	Median PFS, mo	8.5
95% CI	4.2, 26.7	95% CI	4.4, 18.0

Lorlatinib in ROS1 fusion positive NSCLC (expansion cohort)

Safety Summary, n (%)	Total (N=47)
TRAEs	45 (95.7)
Grade 3–4 TRAEs	23 (48.9)
TRAEs leading to dose delay	17 (36.2)
TRAEs leading to dose reduction	11 (23.4)
TRAEs leading to discontinuation	0
TRAEs leading to death	0

TRAEs in ≥10% of Patients, n (%)	Total (N=47)	Grade 3	Grade 4
Hypercholesterolemia*	39 (83.0)	4 (8.5)	0
Hypertriglyceridemia*	28 (59.6)	9 (19.1)	0
Edema*	21 (44.7)	1 (2.1)	0
Peripheral neuropathy*	16 (34.0)	1 (2.1)	0
Cognitive effects*	11 (23.4)	0	0
Weight increased	10 (21.3)	3 (6.4)	0
Dizziness	7 (14.9)	2 (4.3)	0
Mood effects*	6 (12.8)	0	0
Lipase increased	6 (12.8)	3 (6.4)	0
Fatigue*	5 (10.6)	1 (2.1)	0
ALT increased	5 (10.6)	0	0
Arthralgia	5 (10.6)	0	0
Thrombocytopenia	5 (10.6)	0	1 (2.1)

Poziotinib in EGFR and HER2 ex20 mutant NSCLC (phase 2)

Phase 2 trial design

Design: Open-label, investigator-initiated, global, single center trial at MDACC
-Cohort 1: EGFR exon 20 mutant NSCLC (N=50)
-Cohort 2: Her2 exon 20 (planned N=30)

Primary objective: Assess objective response rate (ORR, RECIST 1.1)

Patient Characteristics

	EGFR cohort	HER2 cohort
Characteristic	**Total (n=50)**	**Total (n=13)**
Female/Male n(%)	30 (60%) / 20 (40%)	11 (85%) / 2 (15%)
Median age (range)	62 (29-77)	60 (54-64)
Mutation type		
Exon 20 insertion n (%)	46 (92%)	13 (100%)
Exon 20 point mutation	4 (8%)	0 (0%)
Median Prior systemic therapy (range)	2 (0-6)	1 (0-6)
Prior platinum n (%)	43 (86%)	10 (77%)
Prior TKI n (%)	17 (34%)	2 (15%)
Prior PD1/PDL1 inhibitor n (%)	27 (54%)	8 (62%)

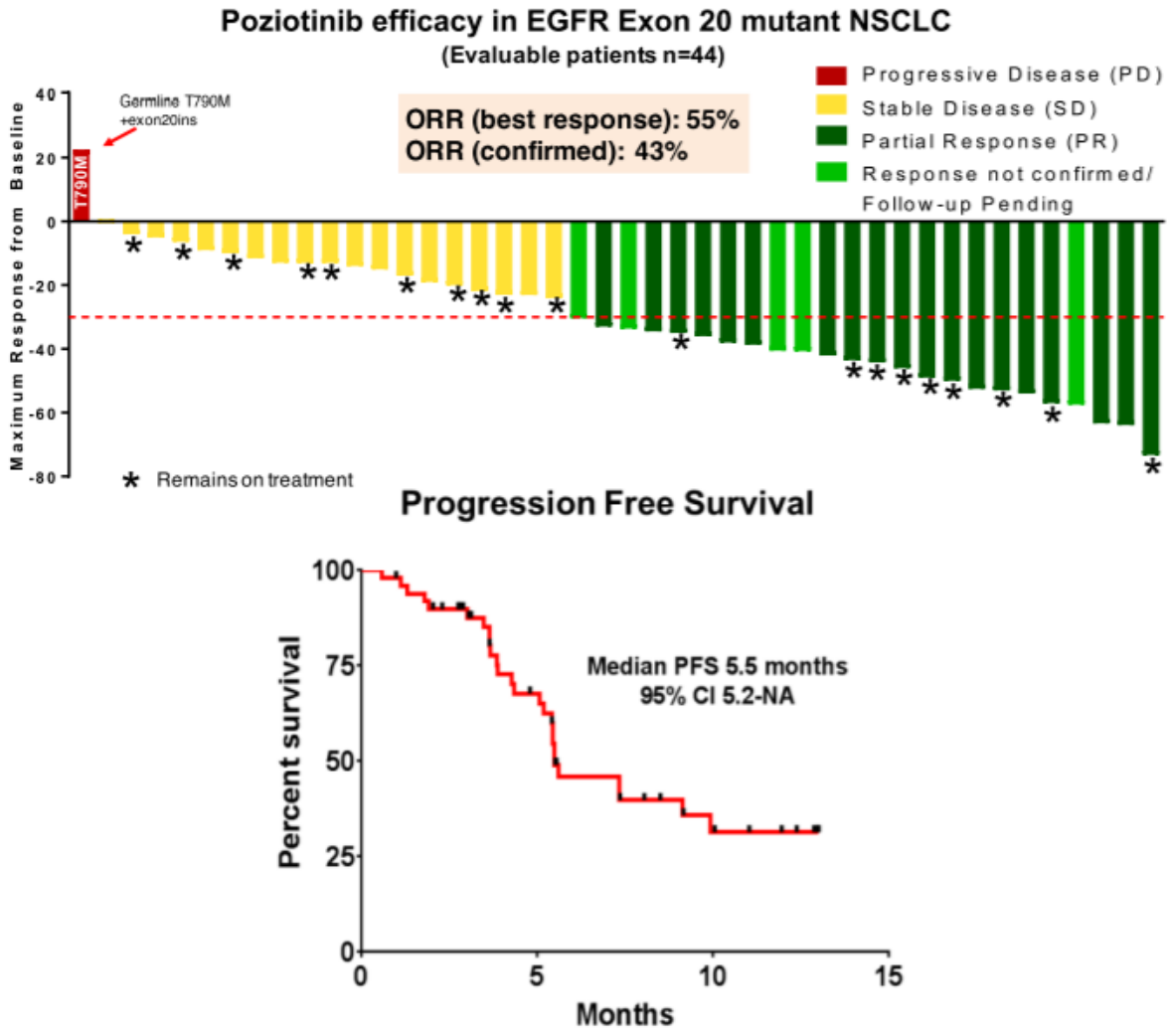
Safety Summary (N=63)

Treatment related AEs N (%)	
Grade 3-4	35 (56%)
Grade 5	1 (1.5%)
AE leading to treatment dose reduction N (%)	38 (60%)
AE leading to treatment discontinuation N (%)	**2 (3%)**

Treatment related AEs in >10% of patients (N=63)

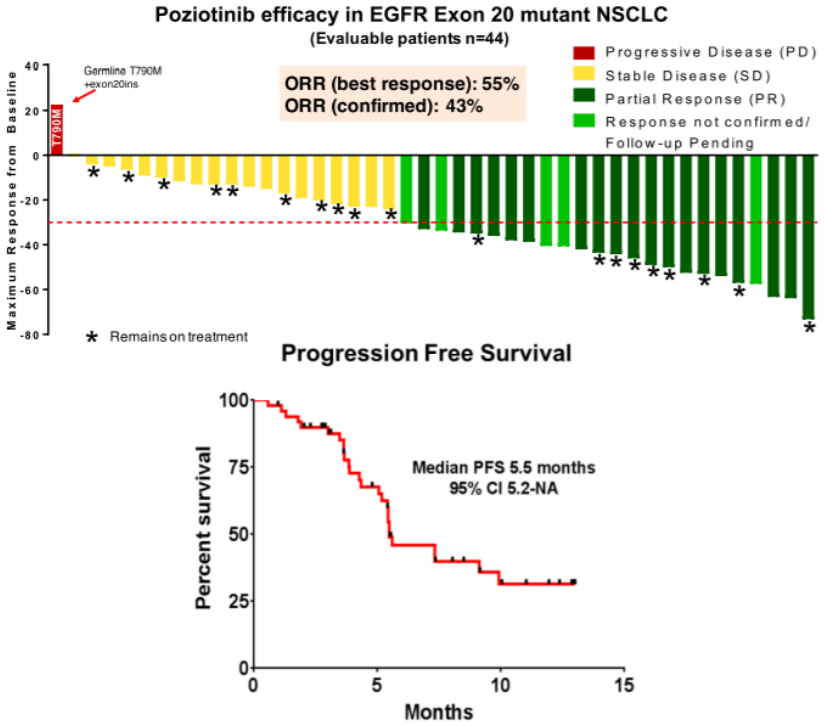
AE	All Grade N (%)	Grade 3-4 N(%)	Grade 5 N(%)
Diarrhea	44 (69.8%)	11 (17.5%)	-
Oral mucositis	44 (69.8%)	1 (1.6%)	-
Paronychia	38 (60.3%)	6 (9.5%)	-
Dry skin	37 (58.7%)	-	-
Skin rash	35 (55.6%)	22 (34.9%)	-
Alopecia	22 (34.9%)	-	-
Anorexia	19 (30.2%)	-	-
Nausea	15 (23.8%)	5 (7.9%)	-
Vomiting	13 (20.6%)	3 (4.8%)	-
Pruritus	9 (14.3%)	-	-
Weight loss	8 (12.7%)	3 (4.8%)	-
Weight loss	8 (12.7%)	3 (4.8%)	-
Fatigue	7 (11.1%)	3 (4.8%)	-

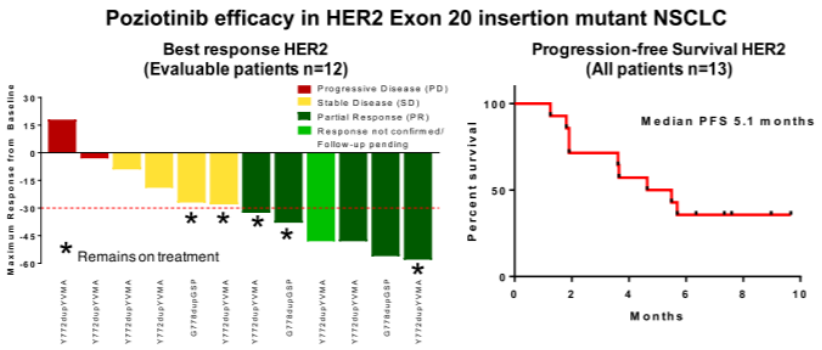
Poziotinib in EGFR and HER2 ex20 mutant NSCLC (phase 2)



Poziotinib in EGFR and HER2 ex20 mutant NSCLC (phase 2)

ORR= 50% (6/12)





Conclusions:

Encouraging activity has prompted a confirmatory, international, multicenter study in *EGFR* and *HER2* exon 20 mutant NSCLC patients which is currently enrolling (NCT03318939) including a first-line cohort and development of a pan-tumor basket study

Update on trastuzumab-deruxtecan (DS-8201a) in HER2 expressing NSCLC (expansion cohort)

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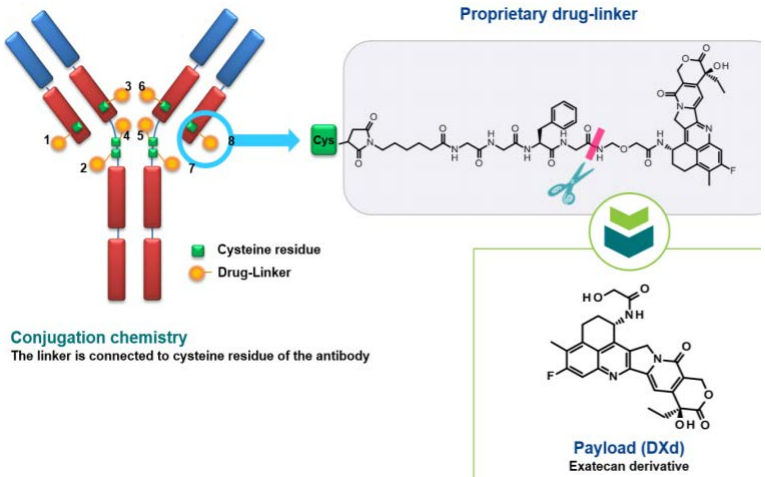

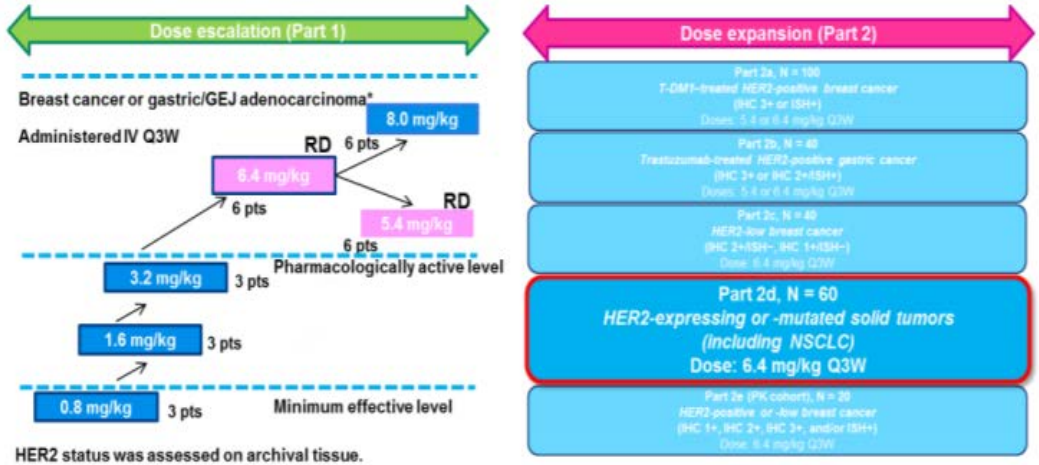

	NSCLC (N = 18)
Age (years), median (range)	58.0 (23.0–83.0)
ECOG performance status 0, n (%)	4 (22.2)
ECOG performance status 1, n (%)	14 (77.8)
HER2-mutated, n (%)	11 (61.1)
Exon 20 insertions	8 (44.4)
Single base pair substitutions (eg, L755S, V777L, S310F)	3 (16.7)
Transmembrane domain mutation (eg, G660D)	2 (11.1)
Extracellular domain mutation (eg, S310F)	1 (5.6)
Missing/not examined	7 (38.9)
Prior cancer regimens, median (range)	3.0 (1.0–10.0)
Tumor size (cm), median (range)	7.3 (2.0–17.0)

Update on trastuzumab-deruxtecan (DS-8201a) in HER2 expressing NSCLC (expansion cohort)

LUNG CANCER UPDATES
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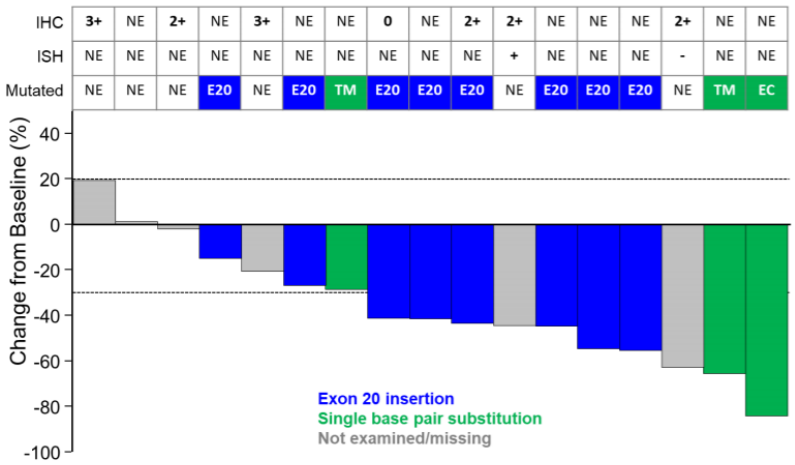
23-26 SEPTIEMBRE 2018, TORONTO

Efficacy Outcomes (Efficacy Evaluable Subjects)

	Confirmed ORR*, % (n/N)	DCR, % (n/N)	DOR, median (range), months	TTR, median (range), months	PFS, median (range), months
HER2-expressing or HER2-mutated NSCLC N = 18	58.8% (10/17)	83.3% (15/18)	9.9 (0.0+, 11.5)	1.4 (1.0, 4.2)	14.1 (0.9, 14.1)
HER2-mutated NSCLC n = 11	72.7% (8/11)	100% (11/11)	11.5 (0.03+, 11.5)	1.4 (1.0, 4.2)	14.1 (4.0+, 14.1)



IHC by local laboratory testing.
E20, exon 20 insertion; EC, single base pair substitution at extracellular domain; IHC, immunohistochemistr

Adverse Events of Special Interest

	Overall 5.4 or 6.4 mg/kg (N = 247)		NSCLC (N = 18)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
AST increased	51 (20.6)	4 (1.6)	1 (5.6)	0
ALT increased	38 (15.4)	2 (0.8)	0	0
Blood bilirubin increased	5 (2.0)	0	0	0
Ejection fraction decreased	2 (0.8)	0	0	0
Electrocardiogram QT prolonged	12 (4.9)	1 (0.4)	0	0
Interstitial lung disease	10 (4.0)	2 (0.8)	1 (5.6)	0
Pneumonitis	21 (8.5)	6 (2.4)	1 (5.6)	1 (5.6)
Infusion-related reactions	3 (1.2)	0	0	0