Lung Cancer UPDATES
IASLC HIGHLIGHTS
08-14 SEPTIEMBRE 2021

Iniciativa científica de:
GECP
lung cancer research

Terapias dirigidas

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    - MA02.05 - A Phase I Study of Afatinib in Combination With Osimertinib in Patients After Failure of Prior Osimertinib. *Miura S, et al*
    - MA02.06 - Phase 1b Study of Pelcitoclax (APG-1252) in Combination With Osimertinib in Patients With EGFR TKI-Resistant NSCLC. *Zhang Z, et al.*
    - MA02.07 - T-DM1 and Osimertinib (TRAEMOS) To Target HER2 Bypass Track Resistance in EGFRm+ NSCLC: Interim Analysis of a Phase II Trial. *Jebbink M, et al*
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    - OA15.04 - Telisotuzumab Vedotin (teliso-v) Monotherapy in Patients With Previously Treated c-Met+ Advanced Non-Small Cell Lung Cancer. *Camidge R, et al.*

EGFR: Progresión a osimertinib

Phase 1 study of afatinib + osimertinib

Level 1 (n=6)
Afatinib 20mg/day
Osimertinib 80mg/day

DLT : 1 (16.7%)
77 y, F: grade 3 Diarrhea

Level 2 (n=7)
Afatinib 30mg/day
Osimertinib 80mg/day

DLT : 2 (33.3%)
75 y, F: persistent grade 2 Nausea/Vomit
76 y, F: grade 3 Diarrhea

Level 3
Afatinib 40mg/day
Osimertinib 80mg/day

After the observational period analysis
Intolerable toxicity: 2 (33.3%)
50 y, F: persistent grade 2 Diarrhea
70 y, F: grade 3 Rash

Table 1. Patient characteristics (n=13)

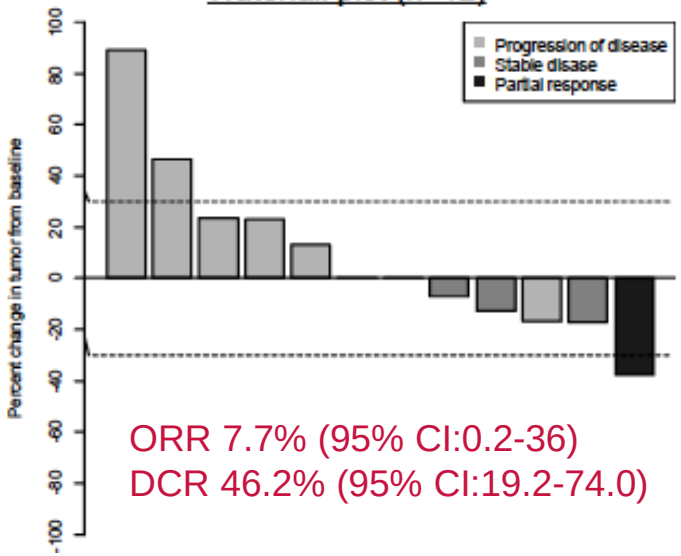
		n (%)
Age – years old	Median	67
	Range	50-76
Sex	Male	4 (30.8)
	Female	9 (69.2)
Smoking status	Never	6 (46.2)
	Current/former	7 (53.8)
ECOG-PS	0	5 (38.5)
	1	8 (61.5)
Histology	Adenocarcinoma	43 (100)
Clinical stage	IVA	4 (30.8)
	IVB	6 (46.2)
	Recurrence	3 (23.0)
EGFR mutation*	Exon 19 deletion	4 (30.8)
	+ T790M	2 (15.4)
	Exon 21 L858R	4 (30.8)
	+ T790M	2 (15.4)
	G719C+S768I	1 (7.7)
Treatment lines	2nd line	2 (15.4)
	3rd line	5 (38.5)
	≥ 4th line	6 (46.2)

* EGFR mutation status was collected at the prior osimertinib therapy.

Table 2. Safety

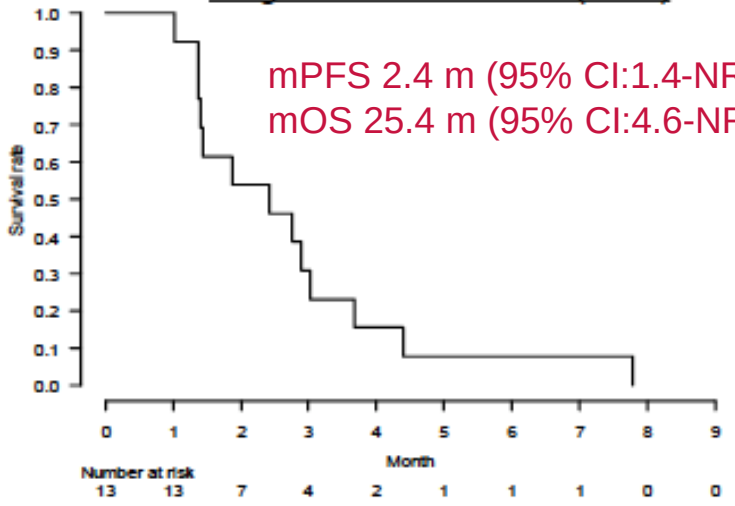
	All patients (n=13)				Level 2 (n=7)			
	All Gr		Gr 3-4		All Gr		Gr 3-4	
	n	(%)	n	(%)	n	(%)	n	(%)
Neutropenia	1	(7.7)	0	(0)	1	(14.3)	0	(0)
Anemia	10	(76.9)	0	(0)	4	(57.1)	0	(0)
Thrombocytopenia	2	(15.4)	0	(0)	1	(14.3)	0	(0)
Anorexia	5	(38.5)	1	(7.7)	3	(42.9)	0	(0)
Nausea	2	(15.4)	0	(0)	1	(14.3)[a]	0	(0)
Vomiting	3	(12,1)	0	(0)	2	(28.6)[a]	0	(0)
Diarrhea	10	(76.9)	2	(15.4)	6	(85.7)	1	(14.3)[a]
Oral mucositis	5	(38.5)	0	(0)	1	(14.3)	0	(0)
Paronychia	2	(15.4)	0	(0)	1	(14.3)	0	(0)
Skin rash	9	(69.2)	1	(7.7)	4	(57.1)	1	(14.3)
Fatigue	1	(7.7)	1	(7.7)	1	(14.3)	1	(14.3)
Increased ALT	1	(7.7)	0	(0)	1	(14.3)	0	(0)
Increased AST	1	(7.7)	0	(0)	1	(14.3)	0	(0)
Increased creatinine	2	(15.4)	0	(0)	1	(14.3)	0	(0)
Hyponatremia	1	(7.7)	2	(15.4)	1	(14.3)	1	(14.3)

Waterfall plot (n=12)



ORR 7.7% (95% CI:0.2-36)
DCR 46.2% (95% CI:19.2-74.0)

Progression free survival (n=13)



mPFS 2.4 m (95% CI:1.4-NR)
mOS 25.4 m (95% CI:4.6-NR)

EGFR: Progresión a osimertinib

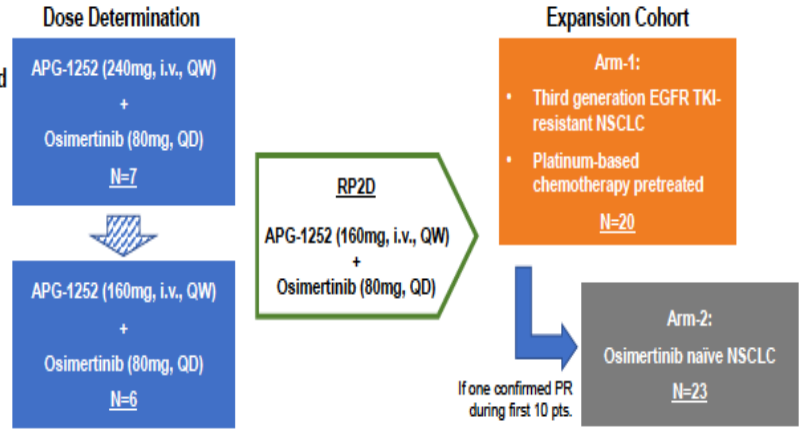
Phase 1b Study of Pelcitoclax (APG-1252) plus Osimertinib

Key inclusion criteria:

- Advanced EGFR-mutated NSCLC
- Progression on prior EGFR TKI treatment
- Measurable disease

Key objectives:

- Establish RP2D
- Safety, efficacy and PK characteristics

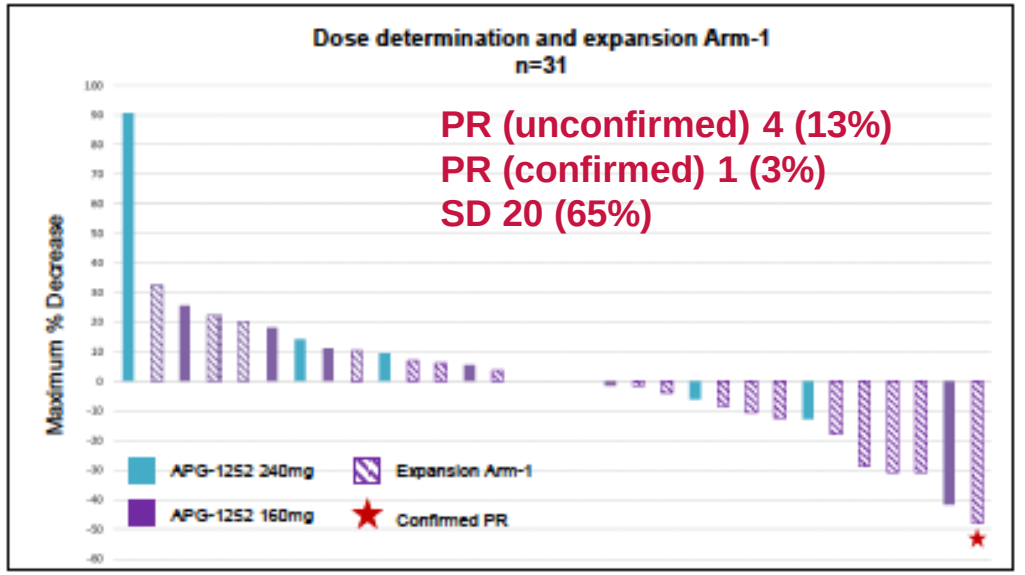


Safety: RP2D 160 mg

Treatment-related AEs (TRAE) by preferred term, n (%)	APG-1252+Osimertinib/80mg					
	160 mg QW N=49		240 mg QW N=7		Total N=56	
	All Grade	Grade 3 or Higher	All Grade	Grade 3 or Higher	All Grade	Grade 3 or Higher
Subjects with at least one TRAE	42 (85.7%)	4 (8.2%)	7 (100.0%)	4 (57.1%)	49 (87.5%)	8 (14.3%)
Aspartate aminotransferase increased	25 (51.0%)	1 (2.0%)	7 (100.0%)	3 (42.9%)	32 (57.1%)	4 (7.1%)
Alanine aminotransferase increased	23 (46.9%)	1 (2.0%)	7 (100.0%)	2 (28.6%)	30 (53.6%)	3 (5.4%)
Platelet count decreased	12 (24.5%)	0	6 (85.7%)	4 (57.1%)	18 (32.1%)	4 (7.1%)
Blood creatinine increased	12 (24.5%)	0	1 (14.3%)	0	13 (23.2%)	0
Amylase increased	9 (18.4%)	0	2 (28.6%)	0	11 (19.6%)	0
White blood cell count decreased	7 (14.3%)	1 (2.0%)	4 (57.1%)	0	11 (19.6%)	1 (1.8%)
Anaemia	8 (16.3%)	0	1 (14.3%)	0	9 (16.1%)	0
Decreased appetite	7 (14.3%)	0	0	0	7 (12.5%)	0

Patient Characteristics

Characteristics	Dose determination and expansion Arm-1 N=33	Expansion Arm-2 N=23
Median age, y (range)	56.0 (38 - 80)	57.0 (34 - 79)
Female, n (%)	18 (54.5%)	14 (60.9%)
ECOG PS (0/1), n (%)	10 (30.3%) / 23 (69.7%)	5 (21.7%) / 18 (78.3%)
Prior systemic treatment		
Lines, median (range)	4 (1 - 10)	0 (0 - 2)
Chemotherapy, n (%)	29 (87.9%)	2 (8.7%)
EGFR TKI, n (%)	33 (100.0%)	4 (17.4%)
Osimertinib	25 (75.8%)	0
1st or 2nd generation TKIs	33 (100.0%)	4 (17.4%)
Other	5 (15.2%)	0
Baseline brain metastasis, n (%)	21 (63.6%)	7 (30.4%)



EGFR: Progresión a osimertinib

Trastuzumab-emtansine and osimertinib (TRAEMOS)

Study design

Simons 2 stage minimax | **Study Phase I: classical 3+3 design** | **Study Phase II**

Sample size determination

ORR
H0=41%
H1>55%

80% power, one-sided type I error rate of 10%

Sample size: 58 patients

Cohort A ORR 16/36 in order to proceed to cohort B

Study population
EGFRm+ NSCLC, WHO PS≤2
positive for HER2-overexpression (IHC2+ ≥10%)
PD on EGFR TKI

Study treatment
T-DM1 3.0 and 3.6 mg/kg iv q3w
Osimertinib 80mg QD
(n=6)

Endpoints
Safety
RP2D for Phase II

Study treatment
T-DM1 3.0 or 3.6 mg/kg iv (RP2D) q3w
Osimertinib 80mg QD
(n=58)

Endpoints
Objective response rate (RECIST v1.1)
Safety, DCR after 12 weeks, PFS, OS

Fase I - Safety run in

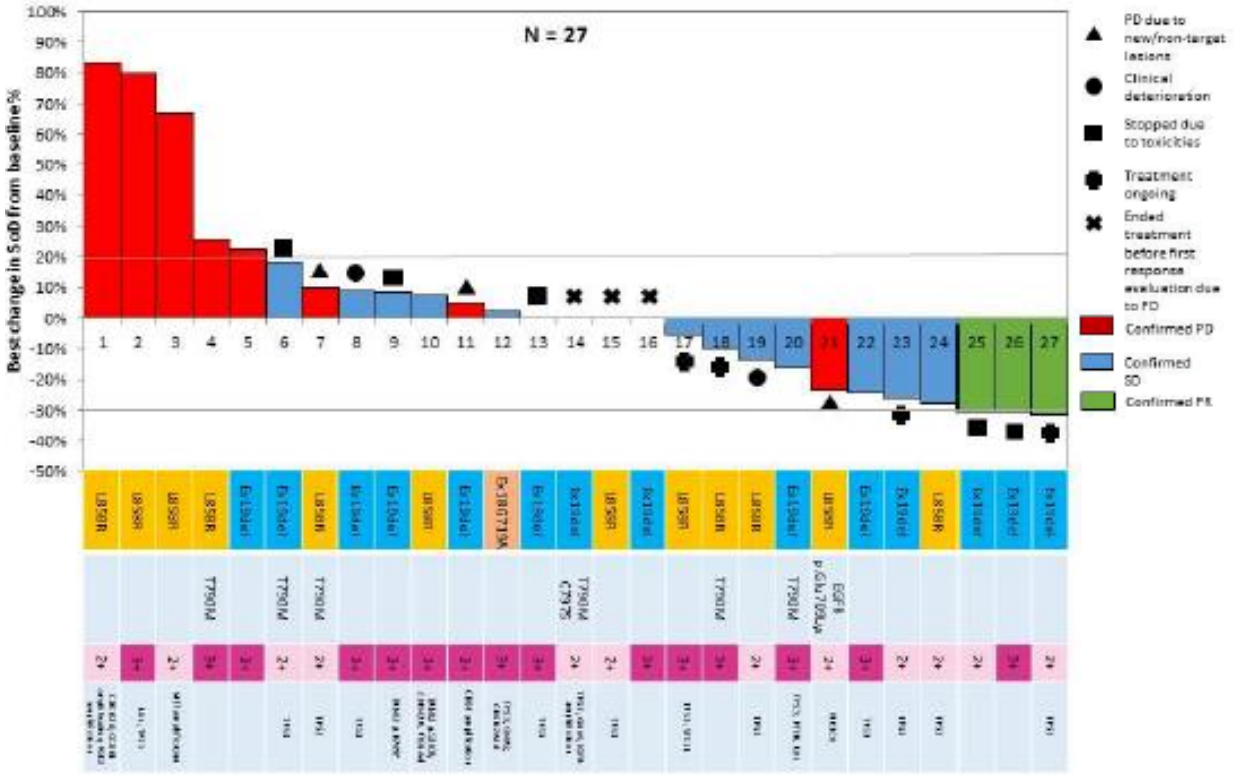
- None of 6 patients developed a DLT
- RP2D: T-DM1 3.6 mg/kg IV infusion q3w + osimertinib 80mg QD

Fase II - Safety and toxicity

- Median # cycles T-DM1: 4 (range 1-14)
- There were no grade 4 or 5 therapy-related AEs
- Grade 2: 30%; Grade 3: 19%

- 5 patients stopped due to toxicities
  - Pneumonitis: 2
  - LVEF decrease: 1
  - Nausea and vomiting: 1
  - Stomach pain/fatigue: 1

Fase II - Efficacy analysis



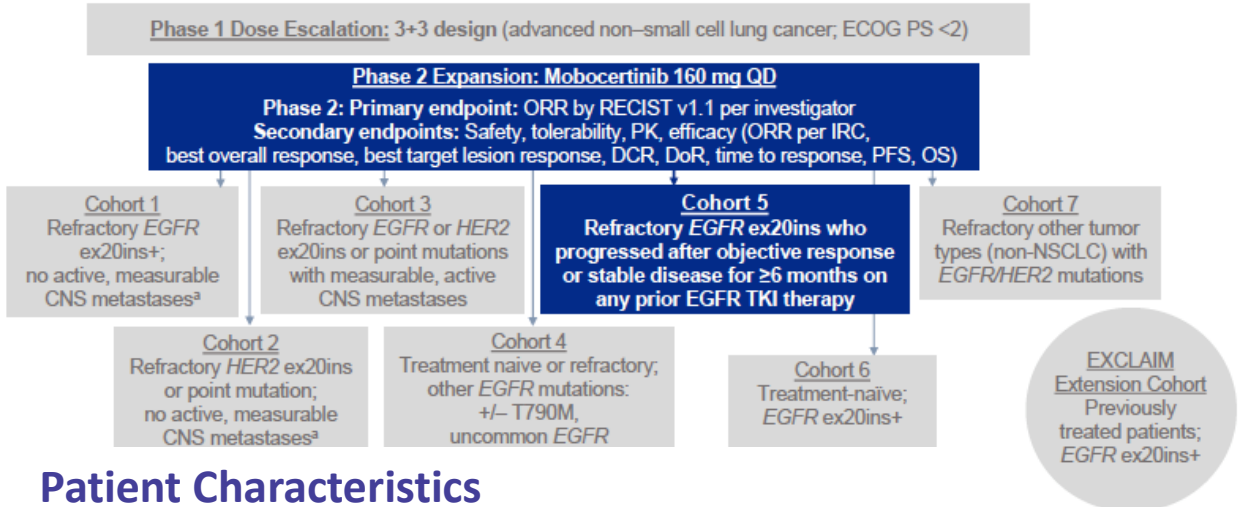
Median PFS: 2.7 months (95% CI, 2,1-3,5 months)

	All	HER2 IHC 2+	HER2 IHC 3+
ORR	11% (3/27)	17%	7%
DCR 12w	48% (13/27)	42%	53%

EGFR Exon 20 insertion

Mobocertinib

Phase 1/2 Study Design



Patient Characteristics

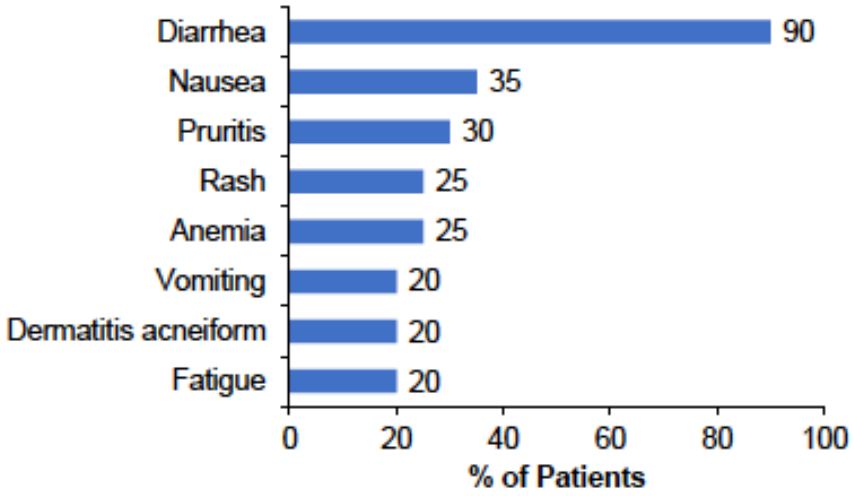
Characteristic	N=20
Median age, years (range)	61 (38–78)
Female, n (%)	11 (55)
Race: Asian/White/Black/unknown, n (%)	3 (15) / 15 (75) / 1 (5) / 1 (5)
ECOG PS 0/1, n (%)	7 (35) / 13 (65)
Median no. metastatic sites (range)	3.5 (1–6)
Baseline brain metastases, n (%)	10 (50)
History of smoking: never/current/former, n (%)	11 (55) / 1 (5) / 8 (40)
Median no. prior systemic anticancer regimens (range)	3 (1–7)
Prior systemic anticancer regimens: 1/2/≥3, n (%)	1 (5) / 5 (25) / 14 (70)
Prior platinum-based chemotherapy, n (%)	16 (80)
Prior immunotherapy, n (%)	13 (65)

Characteristic	N=20
Prior TKI therapy,[a] n (%)	20 (100)
Poziotinib	13 (65)
Osimertinib	4 (20)
Afatinib	4 (20)
Erlotinib	2 (10)
Investigational TKI	1 (5)
Median time on prior TKI therapy, months (range)	7.8 (4.0–37.6)
Investigator-assessed response to prior TKI therapy, n/N (%)	
Poziotinib	7/13 (54)
Osimertinib	2/4 (50)
Erlotinib	0/2 (0)
Investigational TKI	1/1 (100)

Safety

	n (%) N=20
Any TEAEs	20 (100)
Grade ≥3 TEAEs	10 (50)
Any TRAE	20 (100)
Grade ≥3 TRAE	4 (20)
Serious AEs	7 (35)
AEs leading to dosage reduction	4 (20)
AEs leading to treatment discontinuation	2 (10)

All-Grade TRAEs Observed in ≥20% of Patients (N=20)



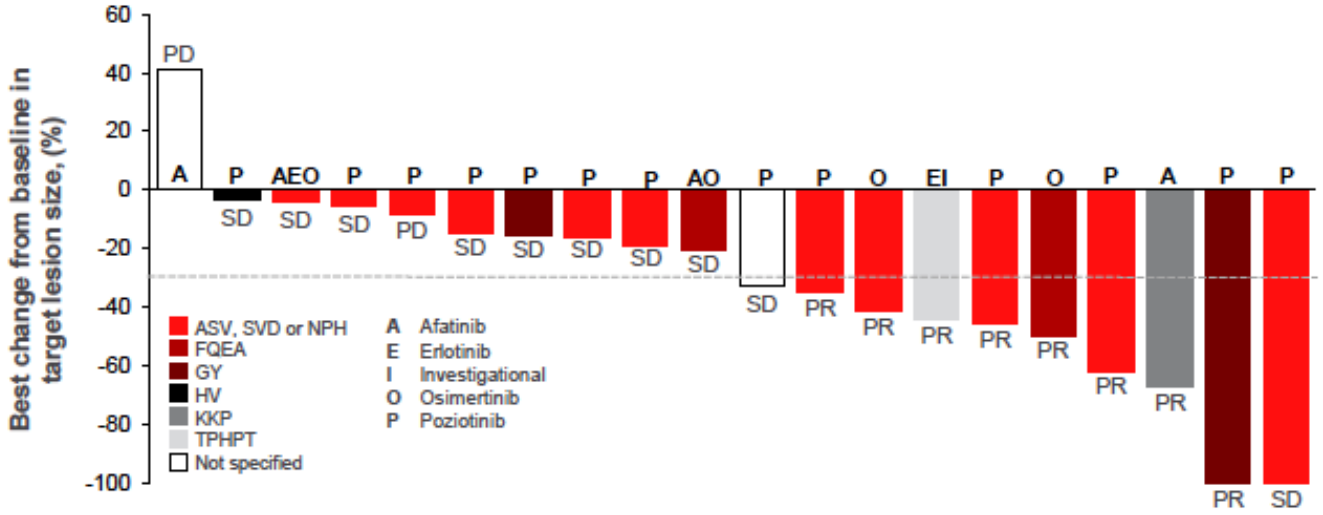
- Only 1 patient (5%) had Grade ≥3 diarrhea

EGFR Exon 20 insertion

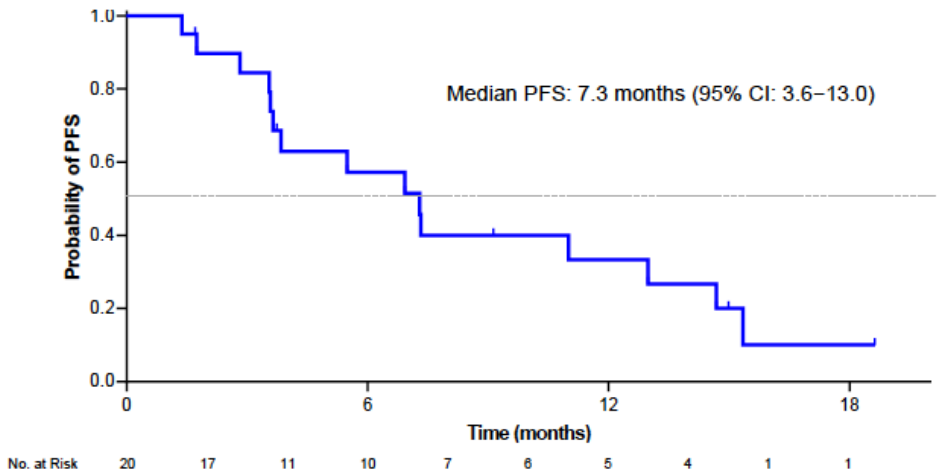
Mobocertinib

Efficacy

	IRC Assessment N=20
Confirmed ORR, n (%; 95% CI)	8 (40%; 19.1%–63.9%)
PR, n (%)	8 (40)
SD, n (%)	10 (50)
Confirmed ORR[a] on mobocertinib by prior TKI, n/N (%)	
Poziotinib	4/13 (31)
Osimertinib	2/4 (50)
Afatinib	1/4 (25)
Erlotinib	1/2 (50)
Investigational TKI	1/1 (100)



Progression-free survival per IRC Assessment

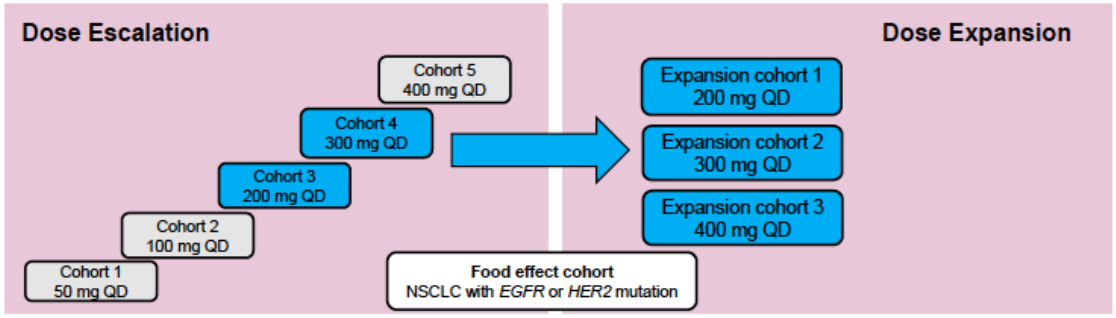


Median DoR 13 months
Median OS NR
6-months OS 94.7%
12-months OS 78.6%

EGFR Exon 20 insertion

DZD9008

Phase 1 Study Design Overview



Key inclusion criteria
- Previously treated advanced NSCLC with
  - *EGFR* or *HER2* mutation (escalation and food effect cohorts)
  - *EGFR* or *HER2* Exon20 insertion (expansion cohorts)
- Adequate organ system functions
- Patients with stable brain metastasis allowed

Objectives
- Primary objectives: Safety and tolerability
  - Secondary objectives:
    - Pharmacokinetics
    - *Anti-tumor activity: ORR; DoR; DCR; PFS

Patients Demographic and Baseline Characteristics

Characteristics	Safety set (n = 102)	Efficacy set (n = 56)	
		Escalation (n = 18)	Expansion (n = 38)
Median age, y (range)	59 (32 - 85)	60 (36. 85)	59 (32, 83)
Female, n (%)	57 (56)	11 (61)	22 (58)
Race (White/Asian), n (%),	17 (16.7)/85 (83.3)	3 (16.7)/15 (83.3)	5 (13.2)/33 (86.8)
ECOG (0/≥1), n (%)	38 (37.3)/64 (62.7)	6 (33.3)/17 (66.7)	12 (31.6)/26 (68.4)
Prior systemic anti-cancer treatment			
Lines, Median (range)	3 (1-10)	2.0 (1-6)	2 (1-10)
Chemotherapy, n (%)	93 (91.2)	18 (100)	34 (89.5)
EGFR TKIs[#], n (%)	47 (46.1)	11 (61.1)	14 (36.8)
Poziotinib	3 (2.9)	2 (11.1)	0 (0)
TAK-788	1 (1.0)	0 (0)	0 (0)
PD-1/PD-L1, n (%)	35 (34.3)	7 (38.9)	10 (26.3)
JNJ-61186372, n (%)	5 (4.9)	4 (22.2)	0 (0)
Others, n (%)	25 (24.5)	6 (33.3)	5 (13.2)
Baseline brain metastasis, n (%)	44 (43.1)	8 (44.4)	15 (39.3)
Prior brain radiotherapy	27 (61.4)	10 (55.6)	23 (60.5)

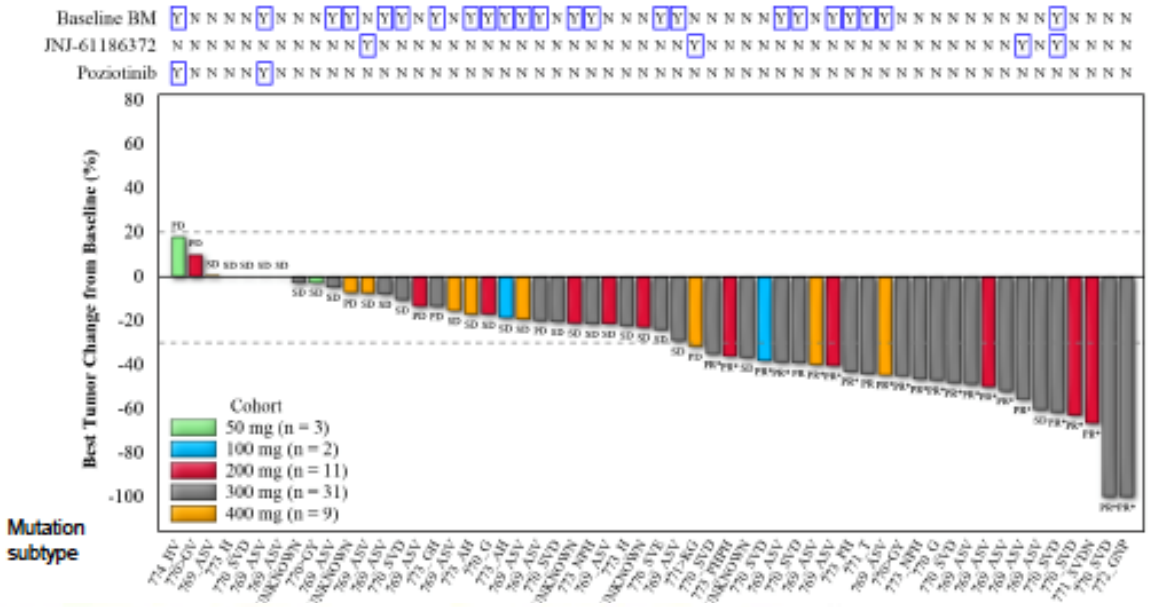
Safety Summary

AE summary n (%)	50 mg QD (n = 6)	100 mg QD (n = 9)	200 mg QD (n = 16)	300 mg QD (n = 51)	400 mg QD (n = 20)	All (n = 102)
Treatment emergent AE						
Any grade	6 (100.0)	9 (100.0)	16 (100.0)	51 (100.0)	20 (100.0)	102 (100.00)
≥ Grade 3	2 (33.3)	2 (22.2)	2 (12.5)	20 (39.2)	14 (70.0)	40 (39.2)
Drug-related AE						
Any grade	6 (100.0)	8 (88.9)	16 (100.0)	48 (96.1)	20 (100.0)	99 (97.1)
≥ Grade 3	1 (16.7)	1 (11.1)	1 (6.3)	17 (33.3)	14 (70.0)	34 (33.3)
Dose reduction due to drug-related AE	0 (0.0)	0 (0.0)	0 (0.0)	6 (11.8)	10 (50.0)	16 (15.7)
Dose interruption due to drug-related AE	0 (0.0)	1 (11.1)	1 (6.3)	14 (27.5)	8 (40.0)	24 (23.5)
Discontinuation due to drug-related AE	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.8)	2 (10.0)	6 (5.9)

EGFR Exon 20 insertion

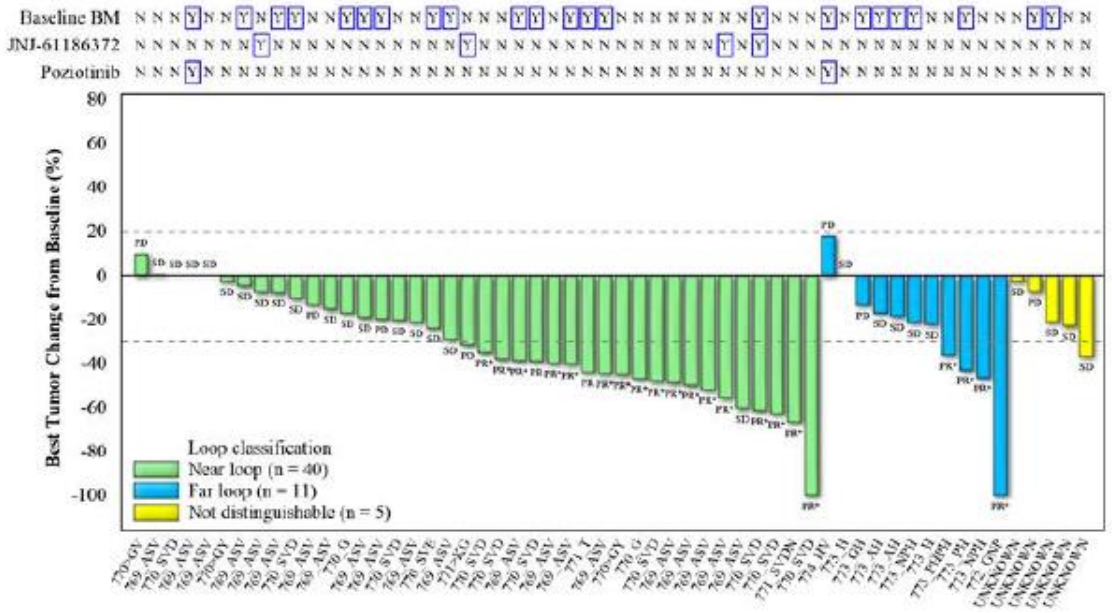
DZD9008

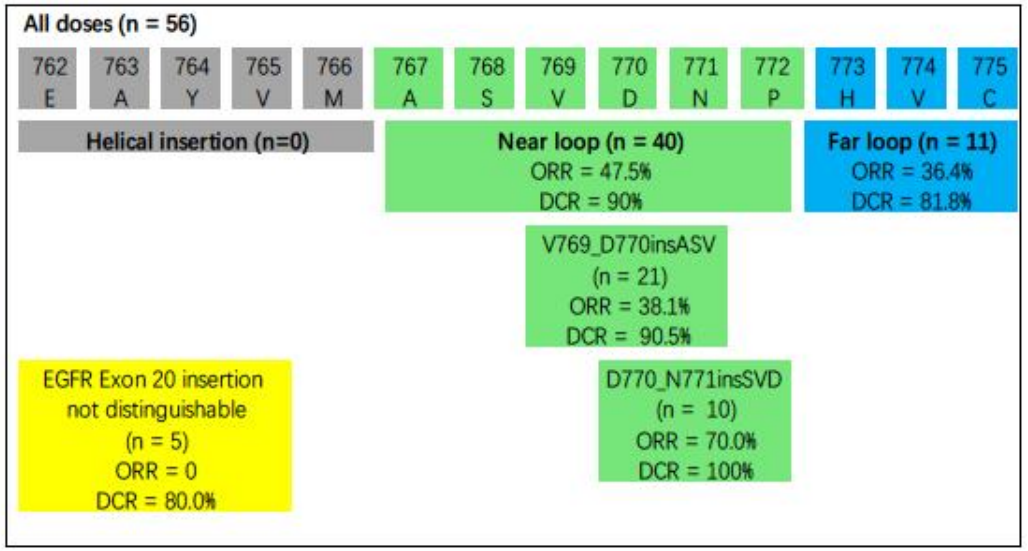
Antitumor activity



PR (unconfirmed) 23 (41%)
PR (Confirmed) 21 (37.5%)
SD 27 (48%)
DCR 48 (85.7%)

The longest DoR > 8 mo, median DoR >3.5 mo has not been reached
mPFS was > 4 mo and has not been reached



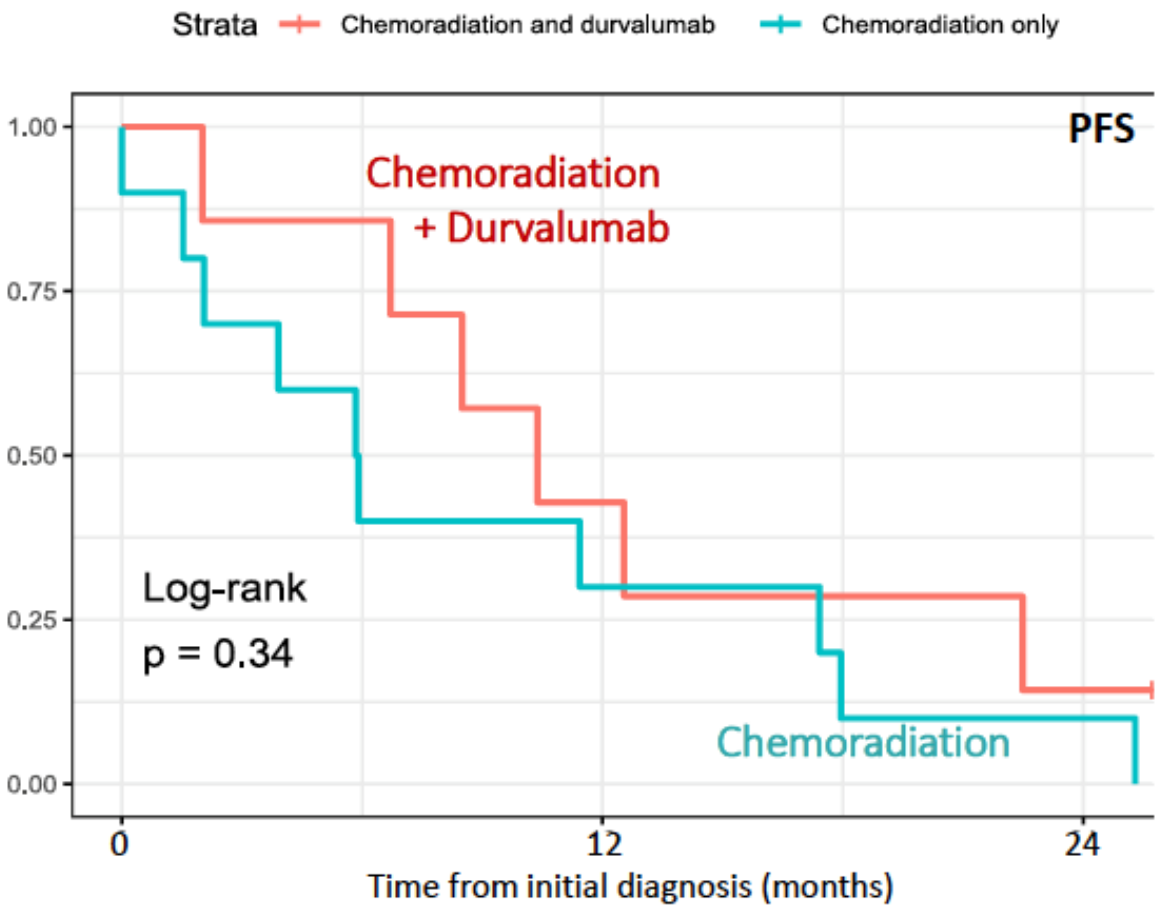


ALK

Outcomes of Early Stage ALK-positive

Unresectable stage III ALK+ patients treated with CT/RT +/- Durbalumab

- 10 patients treated with chemoradiation alone
  - 1 patient stopped chemorads because of toxicity
- 7 patients received chemoradiation + durvalumab
  - All patients completed chemorads
  - Median number of cycles of durva received: 8.5
  - Median time on durvalumab: 9.9 months
- Reasons to stop durvalumab were
  - Completed treatment n=2
  - Disease progression n=4
  - Durvalumab-related AEs n=1
- 16 of 17 patients have relapsed.
  - Median PFS 8.5 (95% CI: 5.8-18.7)



METex14

Amivantanab

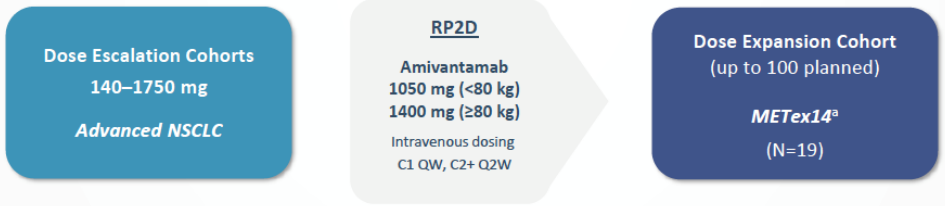
CHRYSALIS Phase 1 Study Design: METex14 Population
(NCT02609776)

Key Objectives

- Dose escalation: Establish RP2D
- Dose expansion: Safety and efficacy at the RP2D

Key Eligibility Criteria for METex14 Cohort

- Metastatic/unresectable NSCLC
- Measurable disease
- Progressed after or declined SOC
- Primary METex14 mutation by NGS of tumor or ctDNA



Characteristic, n (%)	N=19
Median number of prior lines (range)	2 (0–10)
Chemotherapy or other	13 (68)
Immune checkpoint inhibitor[a]	8 (42)
MET inhibitor[a]	8 (42)
Crizotinib	5 (26)
Capmatinib	2 (11)
Tepotinib	2 (11)
Anti-MET antibody (REGN5093)	1 (5)
Other[b]	3 (16)
Treatment-naive	4 (21)

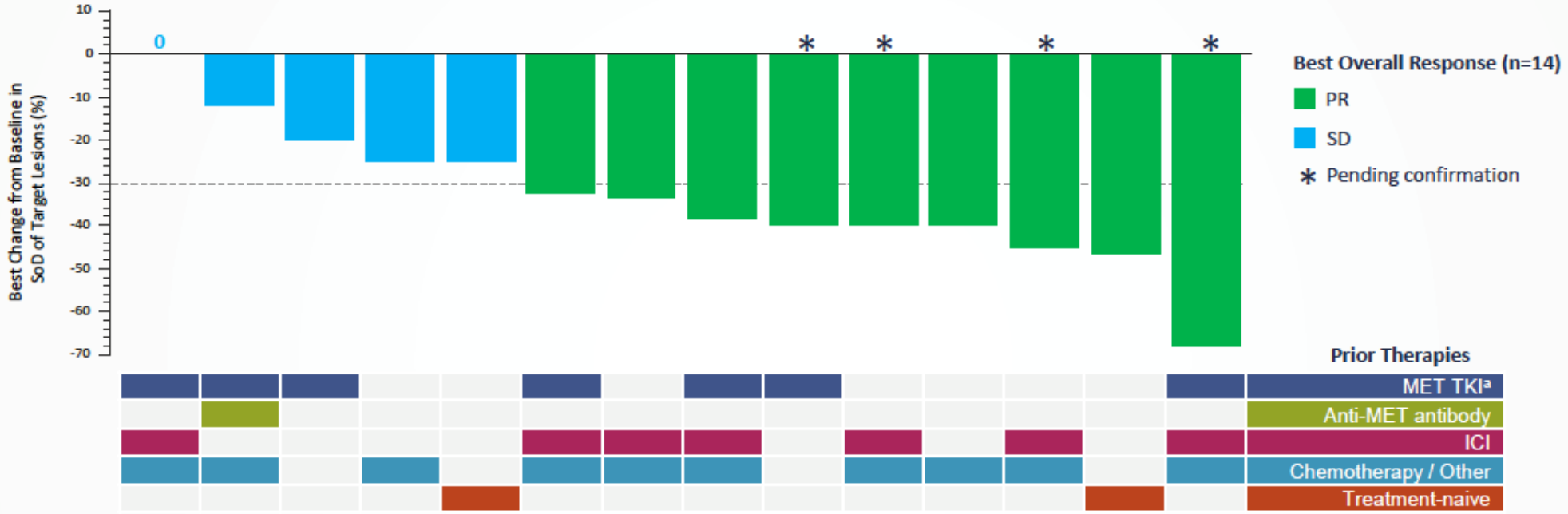
Safety

TEAEs (≥15%), n (%)	Treated at RP2D[a] (N=258)		METex14 (N=19)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Rash[b]	195 (76)	7 (3)	11 (58)	1 (5)
Infusion-related reaction	161 (62)	6 (2)	14 (74)	0
Paronychia	101 (39)	3 (1)	4 (21)	0
Hypoalbuminemia	59 (23)	4 (2)	3 (16)	1 (5)
Constipation	58 (23)	0	2 (11)	0
Nausea	54 (21)	1 (0.4)	4 (21)	0
Dyspnea	41 (16)	11 (4)	2 (11)	1 (5)
Stomatitis	50 (19)	0	5 (26)	0
Peripheral edema	48 (19)	2 (1)	2 (11)	0
Pruritus	49 (19)	0	3 (16)	0

METex14

Amivantanab

Antitumor Activity by Prior Therapies

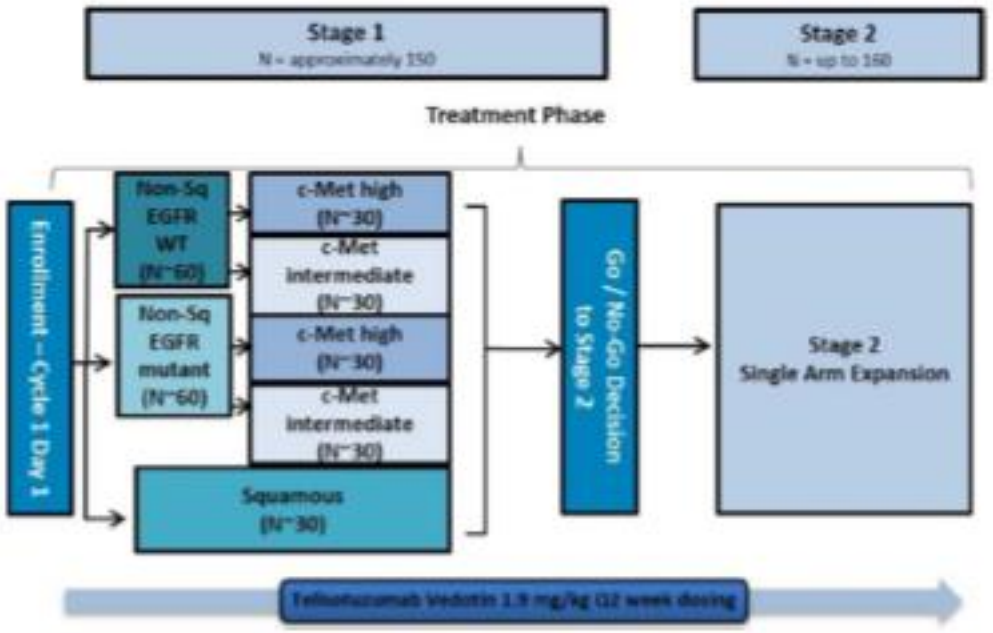


- Of 14/19 response-evaluable[b] patients, PRs were observed in 9 (64%), with 5 confirmed and 4 pending confirmation
- Activity observed in treatment-naïve and previously-treated, including 4 PRs in 7 previously treated with MET TKIs
  - Of 7 patients previously treated with MET TKIs, 2 had potential resistance mechanisms[c] identified
- Median time to first confirmed response was 4.1 months (range, 1.6–9.9)

MET+

Telisotuzumab vedotin in previously treated c-Met+

Study Design



Screening Rates for c-Met Expression by Cohort

	Patients	Percentage C-Met[+a]	Percentage c-Met high	Percentage c-Met Int
Non-Sq *EGFR* WT NSCLC	446	25	12	13
Non-Sq *EGFR* MU NSCLC	245	37	22	15
Sq NSCLC	150	39	–	–

Characteristic	NSQ EGFR WT NSCLC (N=37)	NSQ EGFR MU NSCLC (N=31)	SQ NSCLC (N=22)
Number of prior systemic cancer therapies, median [range]	2 [1-4]	2[1-4]	2[1-4]
Prior systemic cancer therapies, n (%)			
Immune checkpoint inhibitors	30 (71)	6 (16)	25 (93)
Platinum-based therapies	40 (95)	32 (84)	26 (96)
Docetaxel-based	4 (10)	0	1 (4)
c-Met inhibitor	3 (7)	0	0
EGFR TKI	0	37 (97)	1 (4)
1st/2nd generation	0	32 (84)	1 (4)
3rd generation	0	14 (37)	1 (4)
Time from initial diagnosis to study entry, weeks, median [range]	59.7 [17.0–245.6]	120.3 [32.7–976.3]	76.0 [30.4–465.7]

Safety

- In total, 96% of patients experienced a treatment-emergent adverse event (TEAE), and 72% experienced a TEAE related to teliso-v as assessed by investigators
  - TEAEs (any grade) occurring in ≥10% of total patients are summarized
- Grade ≥3 TEAEs occurred in 50 (44%) patients
  - The most frequent was malignant neoplasm progression occurring in 6% of patients
- The most common serious TEAEs were pneumonia (n=6, 5%), malignant neoplasm progression (n=4, 4%), and pneumonitis (n=4, 4%)
- Three patients died as a result of a TEAE considered possibly related to teliso-V by investigators (sudden death, dyspnea, pneumonitis, n=1 each)

MET+

Telisotuzumab vedotin in previously treated c-Met+

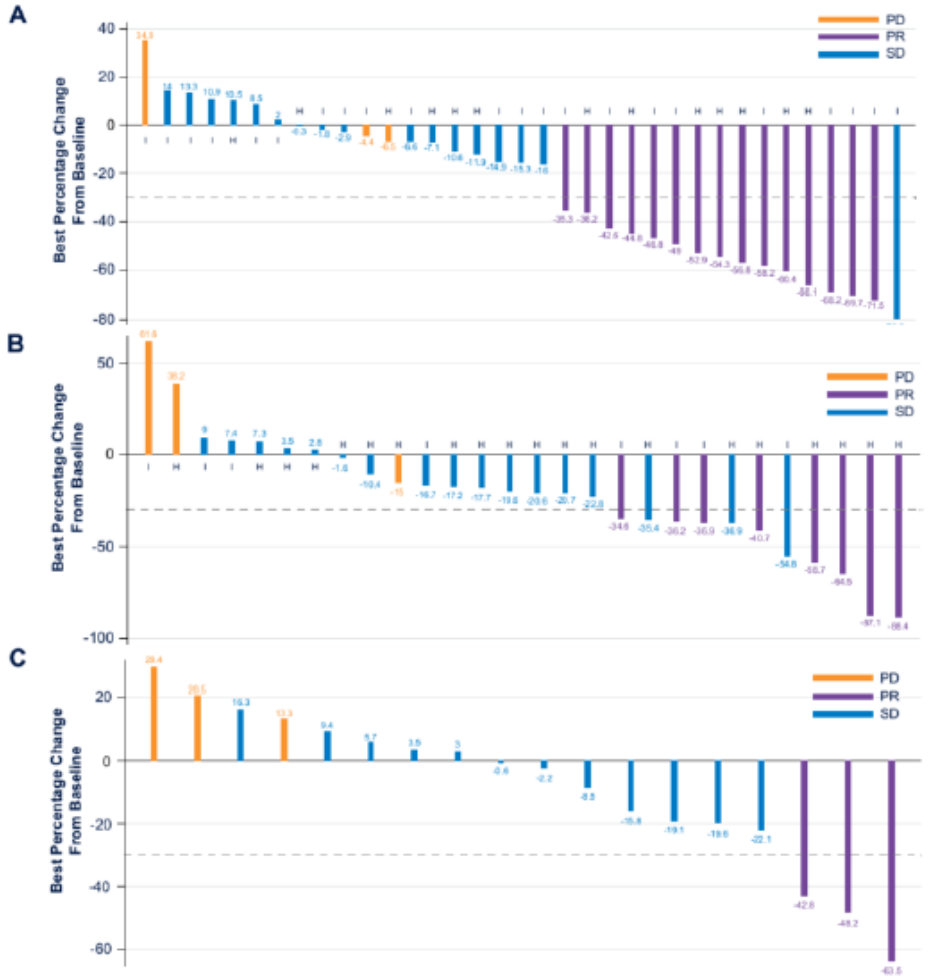
Efficacy Endpoints

Efficacy endpoints by NSCLC group

NSCLC Group	ORR (CR+PR)[a] by ICR, n/N (%) [95% CI]	ORR (CR+PR) by INV, n/N (%) [95% CI]	mDoR by ICR[b], months [95% CI]	mDoR by INV[c], months [95% CI]
NSQ EGFR WT	13/37 (35.1) [20.2, 52.5]	13/36 (36.1) [20.8, 53.8]	6.9 [3.8, -]	5.5 [4.2, 9.6]
c-Met high	7/13 (53.8) [25.1, 80.8]	6/12 (50.0) [21.1, 78.9]	---	---
c-Met int	6/24 (25.0) [9.8, 46.7]	7/24 (29.2) [12.6, 51.1]	---	---
NSQ EGFR MU	4/30 (13.3) [3.8, 30.7]	8/31 (25.8) [11.9, 44.6]	NA	5.9 [2.6, -]
c-Met high	4/22 (18.2) [5.2, 40.3]	8/22 (36.4) [17.2, 59.3]	---	---
c-Met int	0/8 (0) [-, -]	0/9 (0) [-, -]	---	---
SQ	3/21 (14.3) [3.0, 36.3]	1/22 (4.5) [0.1, 22.8]	4.4 [3.0, -]	4.4 [-, -]

- ORR was 13/37 (35.1%) in the non-squamous EGFR wild type cohort (7/13 (53.8%) in c-Met high group and 6/24 (25.0%) in c-Met intermediate group, but was modest in the non-squamous EGFR mutant and squamous cohorts
- At the time of this interim analysis, no patients had achieved a complete response, 26/88 (30%) had achieved a partial response, and 9/88 (10%) experienced disease progression

Best percentage change in size of target lesion from baseline in patients with ≥1 post-baseline tumor assessment in non-squamous *EGFR* wild type (A), non-squamous *EGFR* mutant (B), and squamous (C) cohorts



Conclusiones

- EGFR: Progresión a osimertinib
  - Poca actividad de las combinaciones
- EGFR inserciones exón 20
  - Nuevos agentes con actividad similar
  - Posible eficacia a nivel de MTS cerebrales
  - Diferente actividad según el tipo de mutación
- ALK
  - No beneficio de durvalumab en la CP-LA
- Alteraciones de MET
  - Amivantanab similar actividad a otros fármacos en METex14
  - Teliso-v sólo actividad en EGFRwt MET+ high


Gracias!