Lung Cancer UPDATES
IASLC HIGHLIGTHS
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Iniciativa científica de:
GECP lung cancer research

TRATAMIENTO DIRIGIDO EN CPCNP – I (Mutaciones en *KRAS* y *EGFR*)

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Hospital de la Santa Creu i Sant Pau

- Agenda

CodeBreaK 100: Registrational Phase 2 Trial of Sotorasib in *KRAS* p.G12C Mutated Non-small Cell Lung Cancer

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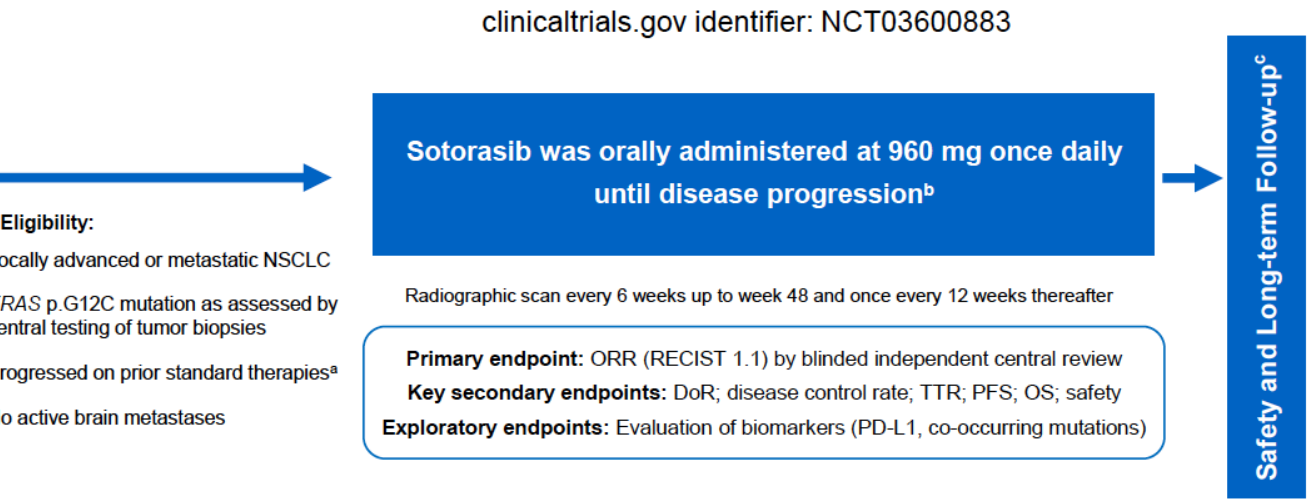
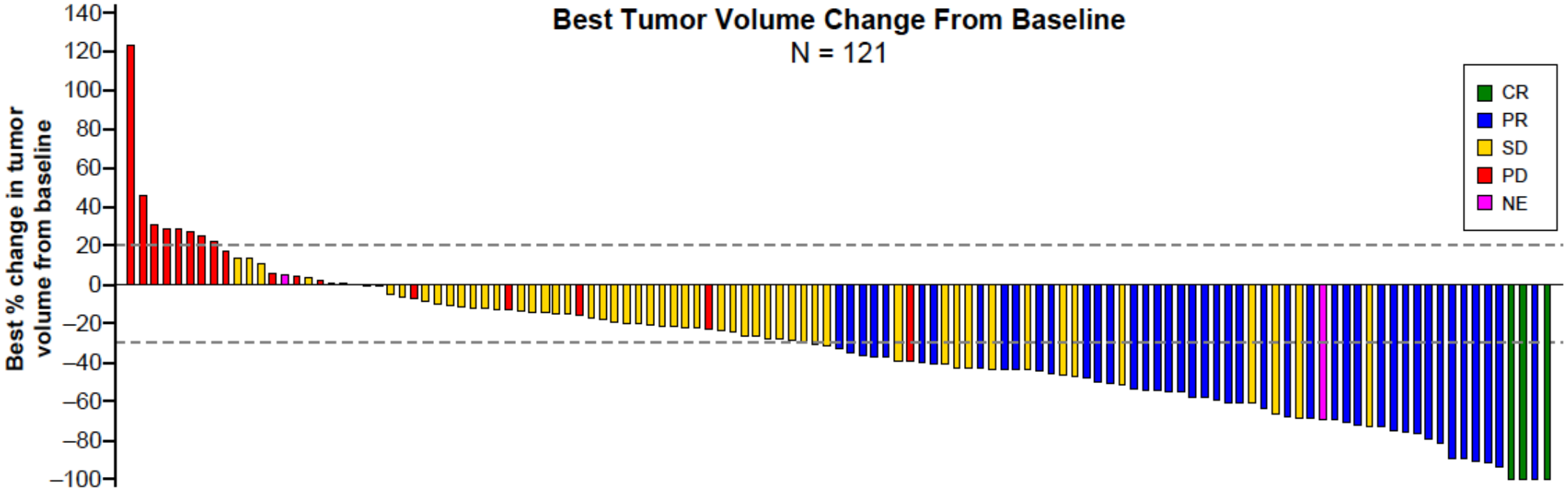


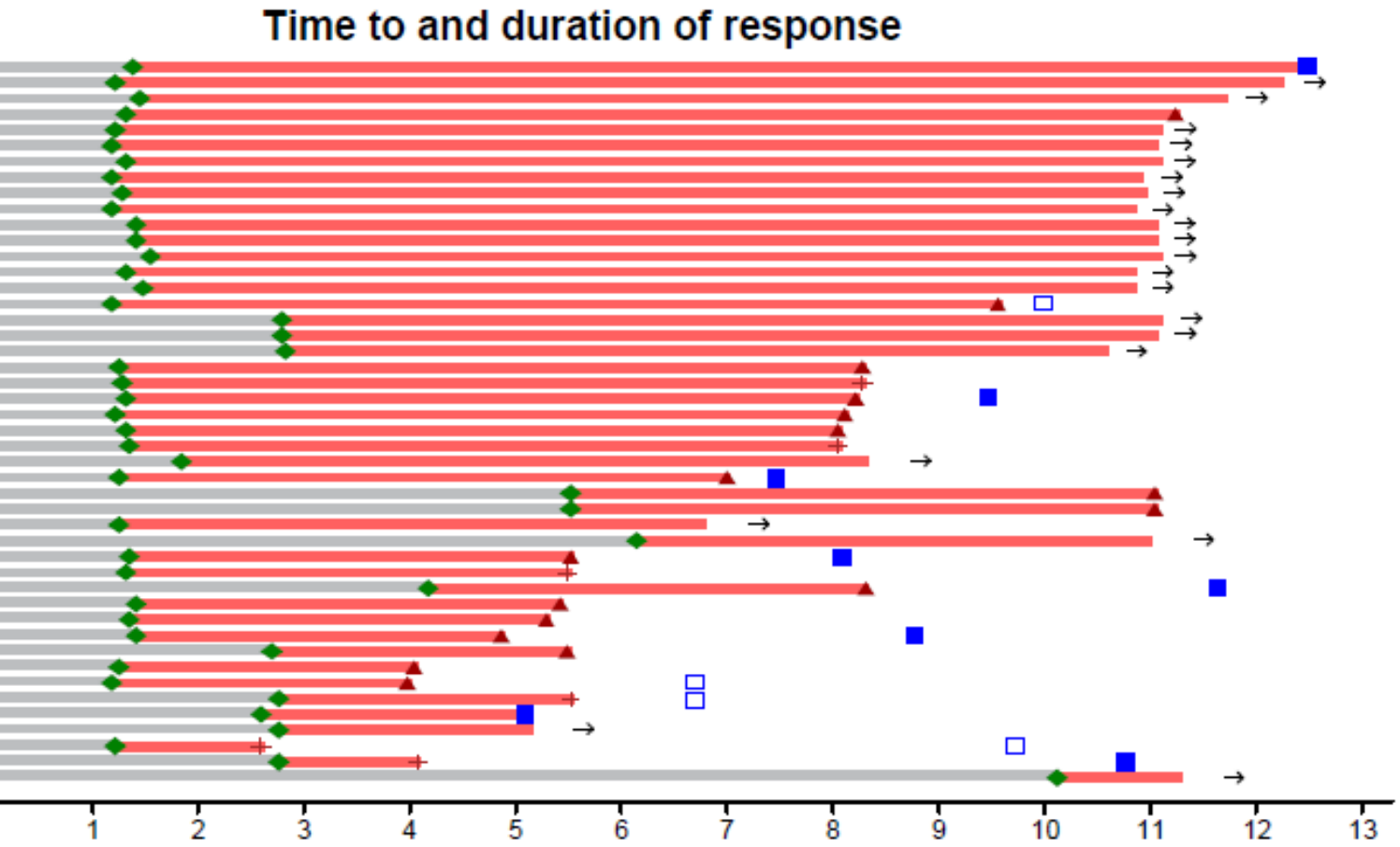
Follow up 12.2m

Baseline Characteristics	Sotorasib 9 N = 12
Median age – years (range)	63.5 (37–
Smoking history – n (%)[a]	
Never	6 (4.8
Current or former	117 (92.
ECOG performance status – n (%)	
0	38 (30.
1	88 (69.
Prior lines of systemic anticancer therapy – n (%)	
1	54 (42.
2	44 (34.
3	28 (22.
Types of prior systemic anticancer therapy[b] – n (%)	
Platinum-based chemotherapy	113 (89.
PD-1 or PD-L1 inhibitors	115 (91.
Platinum-based chemotherapy and PD1/L1 inhibitors	102 (81.



Response assessed by central review	Sotorasib 960mg, N = 124[a]
Confirmed objective response rate – % (95% CI)	**37.1 (28.6, 46.2)**
Best overall response – n (%)	
Complete response	3 (2.4)
Partial response	43 (34.7)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
"Not evaluable" or "Missing scan"[b]	4 (3.2)
Disease control rate – % (95% CI)	**80.6 (72.6, 87.2)**

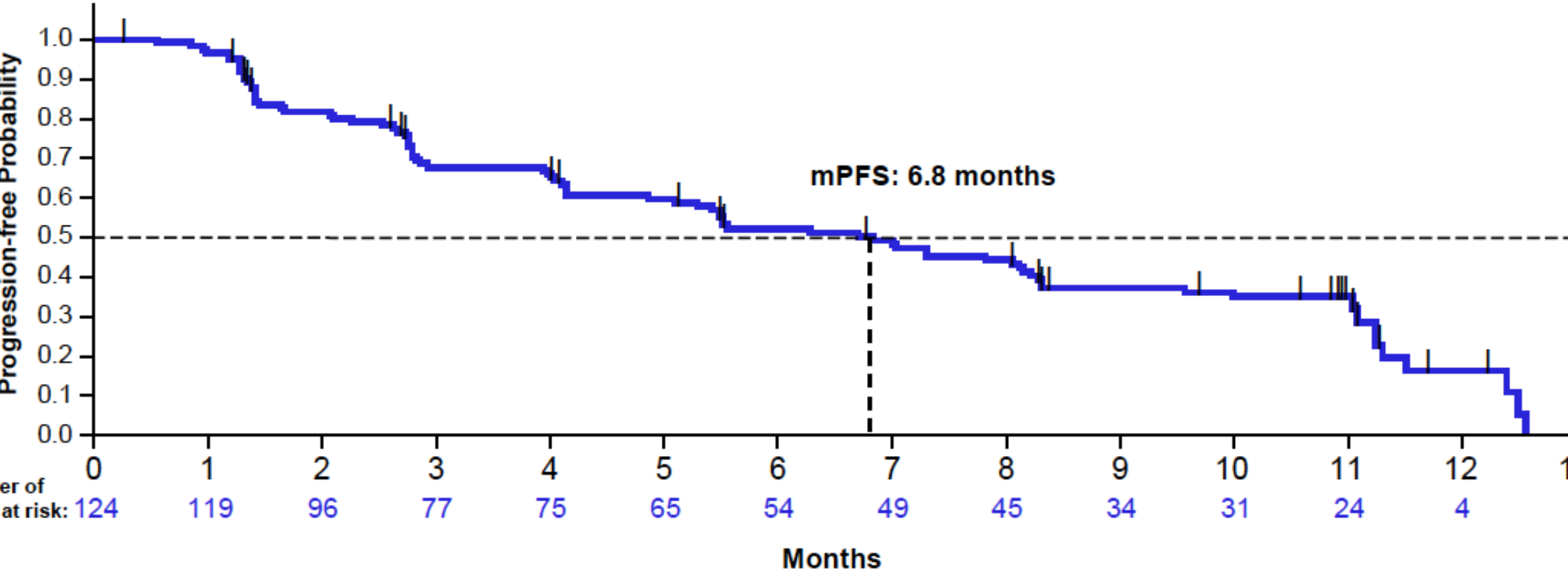
Responses to sotorasib were durable; 72% were seen at the first assessment



- Median duration of response: **10.0 months** (95% CI: 6.9, 11.1)
- Median time to objective response: **1.4 months**
- **43%** (20/46) of responders remained treatment without progression as of t data cutoff **(12.2 meses)**

ogression-Free Survival

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



eatment-Related Adverse Events

Treatment-related adverse events were generally mild and manageable

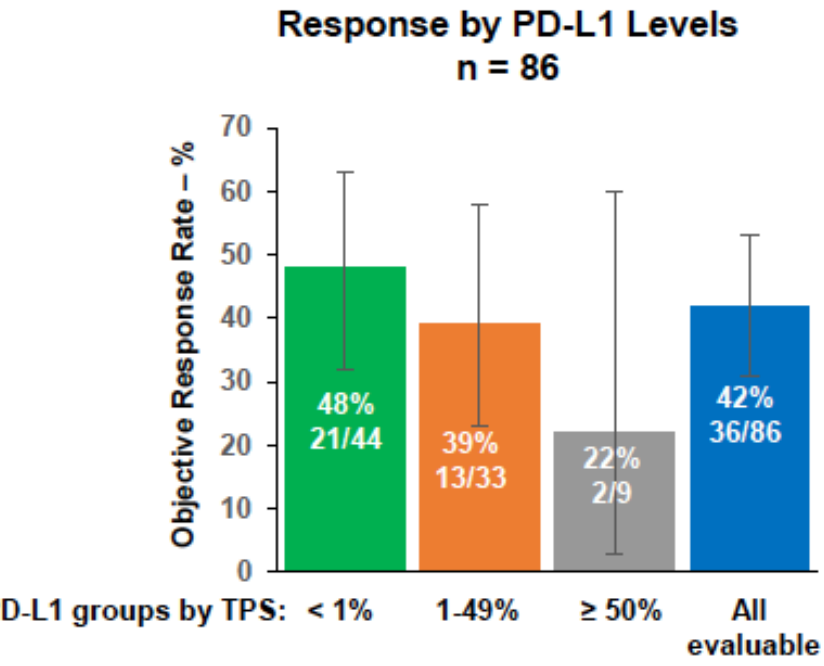
tment-related adverse events Es) occurring in >5%, n (%)	Any Grade N = 126	Grade 3 N = 126
event	**88 (69.8)**	**25 (19.8)**
hea	39 (31.0)	5 (4.0)
ea	24 (19.0)	0
increase	19 (15.1)	8 (6.3)
increase	19 (15.1)	7 (5.6)
ue	14 (11.1)	0
ting	10 (7.9)	0
d alkaline phosphatase increase	9 (7.1)	1 (0.8)
ulopapular rash	7 (5.6)	0

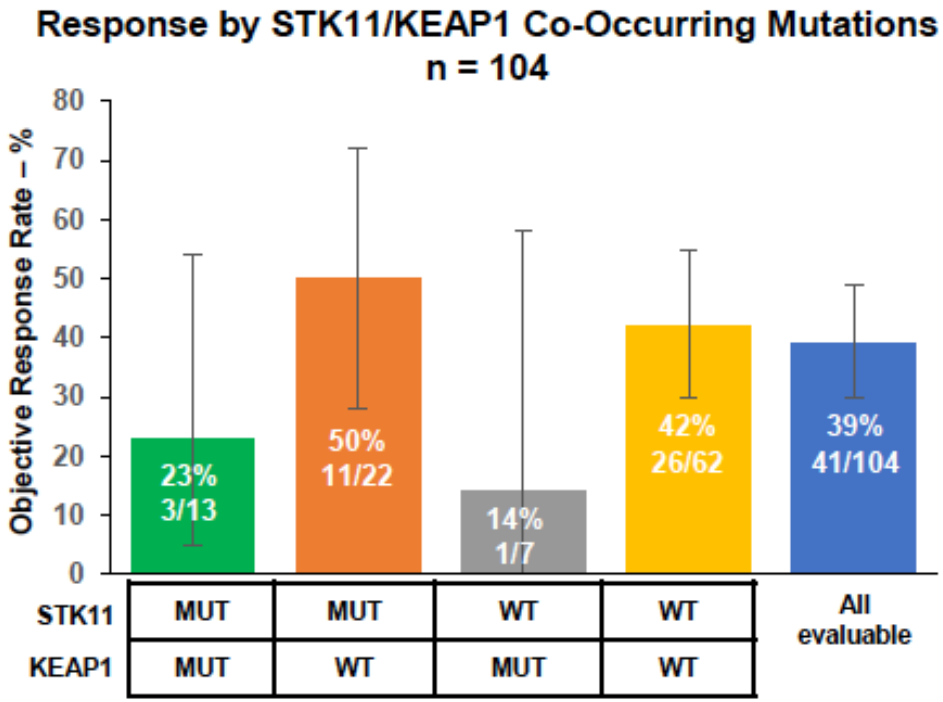
(0.8%) reported grade 4 TRAEs (pneumonitis and dyspnea)

- Most TRAEs were grade 1 or 2
- No fatal TRAEs occurred
- TRAEs led to treatment discontinuatio 7.1% of patients
- TRAEs led to dose modification in 22 of patients

mor Response by PD-L1 Levels and STK11/KEAP1 Co-Occurring Mutation

the exploratory biomarker analyses, responses to sotorasib were observed across the range o PD-L1 expression levels and STK11/KEAP1 co-occurring mutations





KRYSTAL-7: A Phase 2 Trial of Adagrasib (MRTX849) With Pembrolizumab in Patients With Advanced Non–Small-Cell Lung Cancer (NSCLC) With KRAS^{G12C} Mutation

Alexander I. Spira[1], William E. Lawler[2], Merrill Shum[3], Mark A. Socinski[4], Ronald Yanagihara[5], Sahar Roshan[6], Thian Kheoh[6], James G. Christensen[6], Richard C. Chao[6], Pasi A. Jänne[7], Marina Garassino[8].

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d

CLC

ons act as oncogenic drivers and occur in approximately 14% of NSCLC
as)[1-3]

on 12 of KRAS are associated with a poor prognosis, and although KRAS has
undruggable, KRAS^{G12C} can now be inhibited covalently[4,5]

emonstrate clinical activity of KRAS^{G12C} inhibitors in pretreated patients with
g KRAS^{G12C} mutations[6]

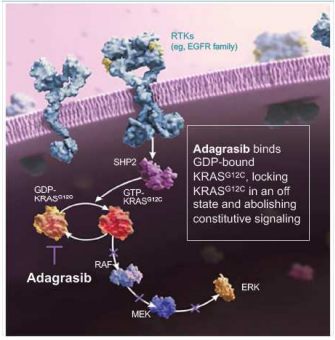
AS^{G12C} Cancers

valent inhibitor of
eversibly and
KRAS^{G12C} and locks it
P-bound state[6]

s KRAS^{G12C} mediated
ng and tumor growth

timized for desired
RAS^{G12C} inhibitor:
lent inhibition of
cellular IC_{50}: ~5 nM)
vity (>1000X) for the
S^{G12C} protein vs
T) KRAS
K properties,
l bioavailability, long
h), and extensive
bution[6]

Figure 1: Mechanism of Action (MOA) of Adagrasib

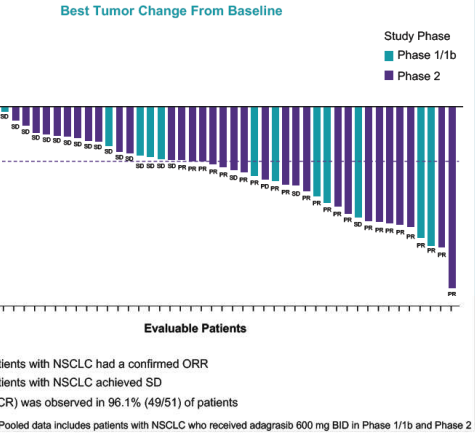


n KRYSTAL-1, a Phase 1/2 study, demonstrated antitumor activity and
grasib monotherapy across multiple tumor types harboring KRAS^{G12C} mutation,
with NSCLC previously treated with both platinum-based chemotherapy and
int inhibitors[6] **(Figure 2)**

sis of patients (n=110) from KRYSTAL-1, adagrasib was well tolerated, with few
ent-related AEs (TRAEs)[6]

ommon TRAEs included nausea, diarrhea, vomiting, and fatigue

0 mg BID in Patients With Pretreated NSCLC (KRYSTAL-1)[6]



ients with NSCLC had a confirmed ORR
ients with NSCLC achieved SD
CR) was observed in 96.1% (49/51) of patients

Pooled data includes patients with NSCLC who received adagrasib 600 mg BID in Phase 1/1b and Phase 2

Combination With Immune Checkpoint Inhibition

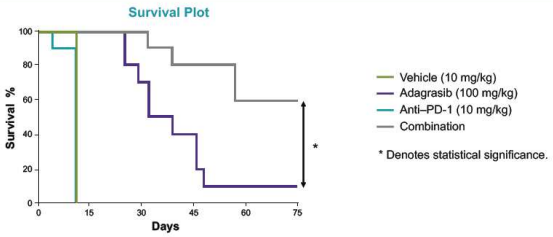
Synergy Between KRAS^{G12C} Inhibition and Immune Checkpoint Inhibition

- KRAS^{G12C} mutations are smoking-related transversion mutations associated with a relatively high tumor mutational burden (TMB) and PD-L1 positivity[7,8]
- Data suggest synergy between KRAS^{G12C} inhibition and immune checkpoint inhibition (CPI)[9]
- Adagrasib treatment alters tumor expression of factors implicated in the presentation of tumor antigens and/or mediates an immunosuppressive tumor microenvironment in multiple KRAS^{G12C} xenografts[9]
- These data support the rationale to further evaluate adagrasib in combination with CPIs in patients with first-line advanced/metastatic NSCLC
- The adagrasib + pembrolizumab combination (NSCLC) arm in KRYSTAL-1 has cleared the DLT observation period[10]

KRAS^{G12C} Syngeneic Mouse Model

- Adagrasib plus anti–PD-1 therapy led to durable complete responses (DCRs; cures) in the majority of mice and a survival advantage relative to either agent as monotherapy[7] **(Figure 3)**
- In mouse models showing complete response, reintroduction of tumor cell inoculum failed to result in re-formation of tumor, demonstrating durable antitumor immunity for the combination[7-9]

Figure 3. Preclinical Data Demonstrating Survival in a KRAS^{G12C} Syngeneic Mouse Model



Methods

Key Inclusion Criteria

- Aged 18 years or older and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Histologically confirmed diagnosis of NSCLC with KRAS^{G12C} mutation and known PD-L1 tumor proportion score (TPS)
- Unresectable or metastatic disease (ie, not a candidate for definitive therapy such as chemoradiation for locally advanced disease)
- Presence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1
- Expected availability of representative tumor specimen (fresh or archived) for central laboratory testing of correlative gene alterations

Key Exclusion Criteria

- Prior systemic treatment for locally advanced or metastatic NSCLC, including chemotherapy, CPI therapy, or a therapy targeting KRAS^{G12C} mutation
- Active brain metastases; patients are eligible if brain metastases are adequately treated and patients are neurologically stable for at least 2 weeks prior to the first dose of study treatment without the use of corticosteroids or are on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent)

Testing Procedures

Testing for PD-L1 Expression

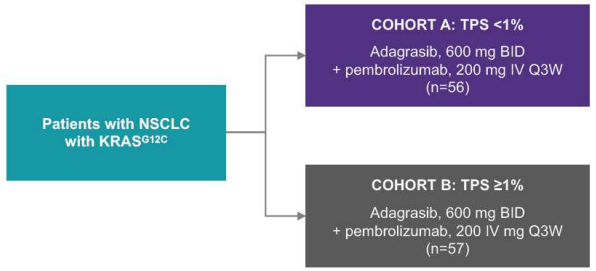
- Molecular testing for PD-L1 TPS should be performed centrally or locally using a sponsor-approved test and laboratory prior to or during the prescreening period
- Tumor tissue samples should be collected from the most recent biopsy or excision, preferably no more than 6 months earlier and without prior systemic treatment or radiation to the site of tissue collection

Detection of KRAS^{G12C} Mutation for Trial Eligibility

- The presence of KRAS^{G12C} mutation established using sponsor-approved methods and laboratories:
  - In tumor tissue, including polymerase chain reaction (PCR) and next-generation sequencing (NGS) platforms
  - In blood samples, for circulating tumor deoxyribonucleic acid (ctDNA) analysis, including NGS platforms

Methods

Figure 4. KRYSTAL-7 Study Design



BID, twice daily; IV, intravenously; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; TPS, tumor proportion score.

Study Design

- KRYSTAL-7 (849-007) is a global, open-label, Phase 2 study evaluating the clinical activity of adagrasib administered in combination with pembrolizumab as treatment for patients with advanced NSCLC harboring a KRAS^{G12C} mutation
- An estimated 120 patients will be enrolled into 2 cohorts based on PD-L1 TPS: Cohort A (TPS <1) and Cohort B (TPS ≥1%) **(Figure 4)**
- Patients will receive study treatment until disease progression, unacceptable tolerability, or investigator decision to terminate treatment
- This study was initiated November 2020

Study Treatments

- Adagrasib is to be dosed at 600 mg (BID) in 3-week cycles administered orally on a continuous basis until disease progression
- Pembrolizumab is to be dosed at 200 mg every 3 weeks (Q3W); if permitted by local labeling, after 9 months or more on study treatment, individual patients may switch to 400 mg administered every 6 weeks (Q6W), at the investigator's discretion
  - Pembrolizumab treatment may continue for up to 24 months or in accordance with approved local labeling

Primary Endpoint

- Objective response rate (ORR), as defined by RECIST 1.1

Secondary Endpoints

- Safety, including adverse events and laboratory abnormalities
- PK, including blood plasma levels of adagrasib and potential metabolite concentrations
- Secondary efficacy endpoints:
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - 1-Year survival rate
  - Overall survival (OS)

Exploratory Endpoints

- Proportion of selected cell populations (including subpopulations of T-cells and myeloid cells) in the blood before and after study treatment
- T-cell receptor repertoire in the blood before and after study treatment
- Gene alterations in tumor tissue and ctDNA before treatment and at disease progression

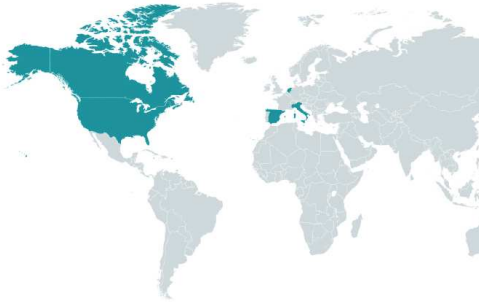
Statistical Methods

Simon's Optimal 2-Stage Design[11]

- Simon's optimal two-stage design will be used to calculate the sample size for each Phase 2 cohort
- The number of responses in the first stage of each Phase 2 cohort will be assessed for potential early study termination

Trial Progress

- Approximately 40 global sites are planned for this study
- Enrollment is currently ongoing at sites from the United States, Canada, Italy, the Netherl



Summary

- Adagrasib is a KRAS^{G12C}-selective covalent inhibitor with a long half-life and e target coverage throughout the dosing interval[6]
- The adagrasib + pembrolizumab combination (NSCLC) arm in KRYSTAL-1 ha DLT observation period
- KRYSTAL-7 is a global, open-label Phase 2 study designed to further evaluat activity of adagrasib in combination with pembrolizumab administered as first- patients with advanced NSCLC harboring a KRAS^{G12C} mutation
- ClinicalTrials.gov identifier: NCT04613596

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Acknowledgments

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- The clinical study teams for their work and contributions
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EGFR Exon 20 Insertion

Amivantamab in Post-platinum EGFR Exon 20 Insertion Mutant Non-small Cell Lung Cancer

ari[1], Catherine A. Shu[2], Keunchil Park[3], Natasha B. Leighl[4], Paul Mitchell[5], Sang-We Kim[6], Jong-Seok Lee[7], Dong-Wan Kim[8], [9], Alexander I. Spira[10], Ji-Youn Han[11], José Trigo[12], Chee Khoon Lee[13], Ki Hyeong Lee[14], Nicolas Girard[15], Tsung-Ying Yang[16], Goto[17], Rachel E. Sanborn[18], James Chih-Hsin Yang[19], Joshua C. Curtin[20], John Xie[20], Amy Roshak[20], Meena Thayu[20], Roland E. Knoblauch[20], Byoung Chul Cho[21]

Mobocertinib in NSCLC With *EGFR* Exon 20 Insertions: Results From EXCLAIM and Platinum-Pretreated Patient Populations

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ZENITH20 Trial: A Phase 2 International Trial

Updated efficacy, safety, and dosing management of poziotinib in previously treated EGFR and HER2 exon 20 NSCLC patients

R Cornelissen[1], MC Garassino[2], X Le[3], J Clarke[4], N Tchekmedyian[5], J Goldman[6], F Lebel[7], G Bhat[7], MA Socinski[8]

CHRYSALIS

NCT02609776

Amivantamab in Post-platinum EGFR Exon 20 Insertion Mutant Non-small Cell Lung Cancer

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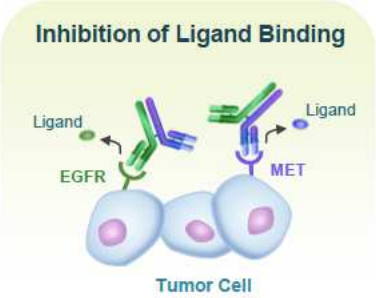
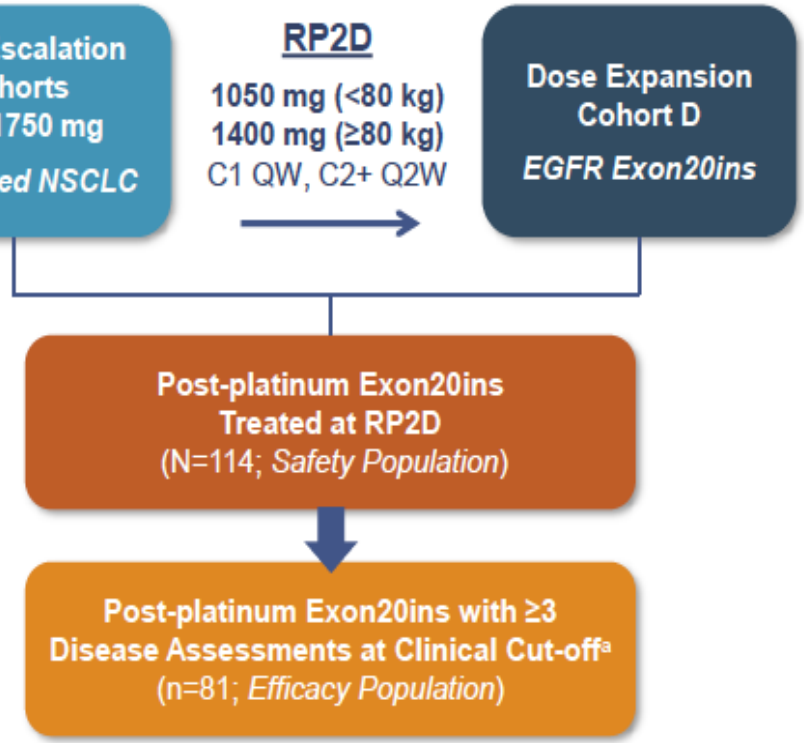




Efficacy End Points

Primary

- Overall response rate per RECIST v1.1

Key Secondary

- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

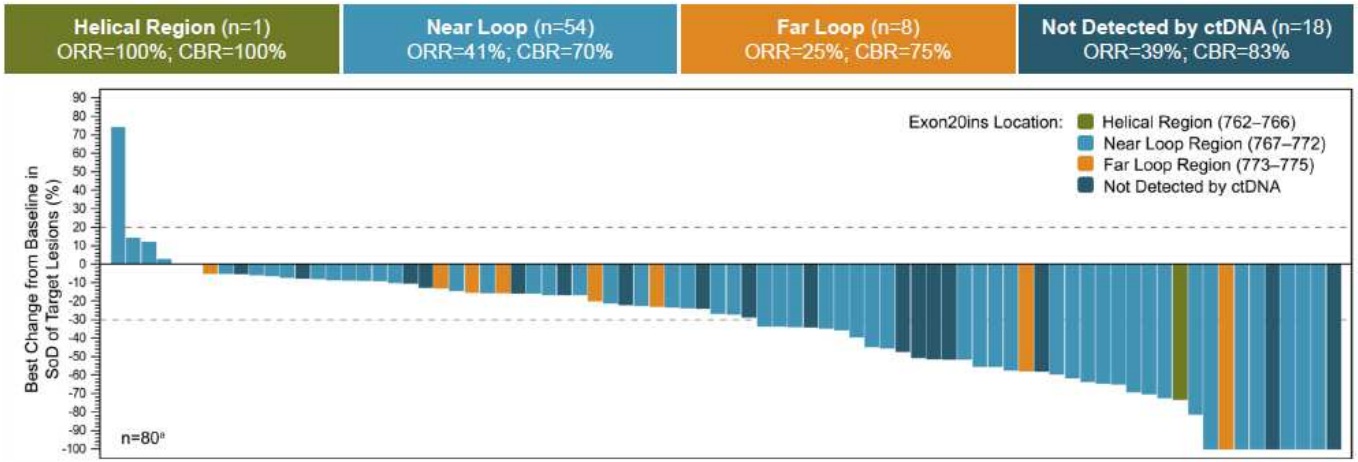
Characteristic, n (%)	Efficacy Popu (n=81)
History of brain metastases	18 (22)
Median number of prior lines (range)	2 (1–7)
Prior systemic therapy	81 (100
Platinum-based doublet chemotherapy	81 (100
Immuno-oncology therapy	37 (46)
EGFR TKI	20 (25)
1st-gen TKI	7 (9)
2nd-gen TKI	6 (7)
3rd-gen TKI	6 (7)
Poziotinib	1 (1)

BICR-assessed Response	Efficacy Population (n=81)
Overall response rate	**40%** (95% CI, 29–51)
Median duration of response	**11.1 months** (95% CI, 6.9–NR)
Best response, n (%)	
Complete response	3 (4)
Partial response	29 (36)
Stable disease	39 (48)
Progressive disease	8 (10)
Not evaluable	1 (1)
Clinical benefit rate[a]	74% (95% CI, 63–83)

Median follow-up: 9.7 months (range, 1.1–29.3)

- 15 of 32 (47%) patients remain on treatment at time of data cutoff
- 20 of 32 (63%) patients had responses of ≥6 months
- mPFS: 8.3 mo (95% CI, 6.5–10.9)
- mOS: 22.8 mo (95% CI, 14.6–NR)

Best ORR by Insertion Region of Exon 20 (detected by ctDNA)

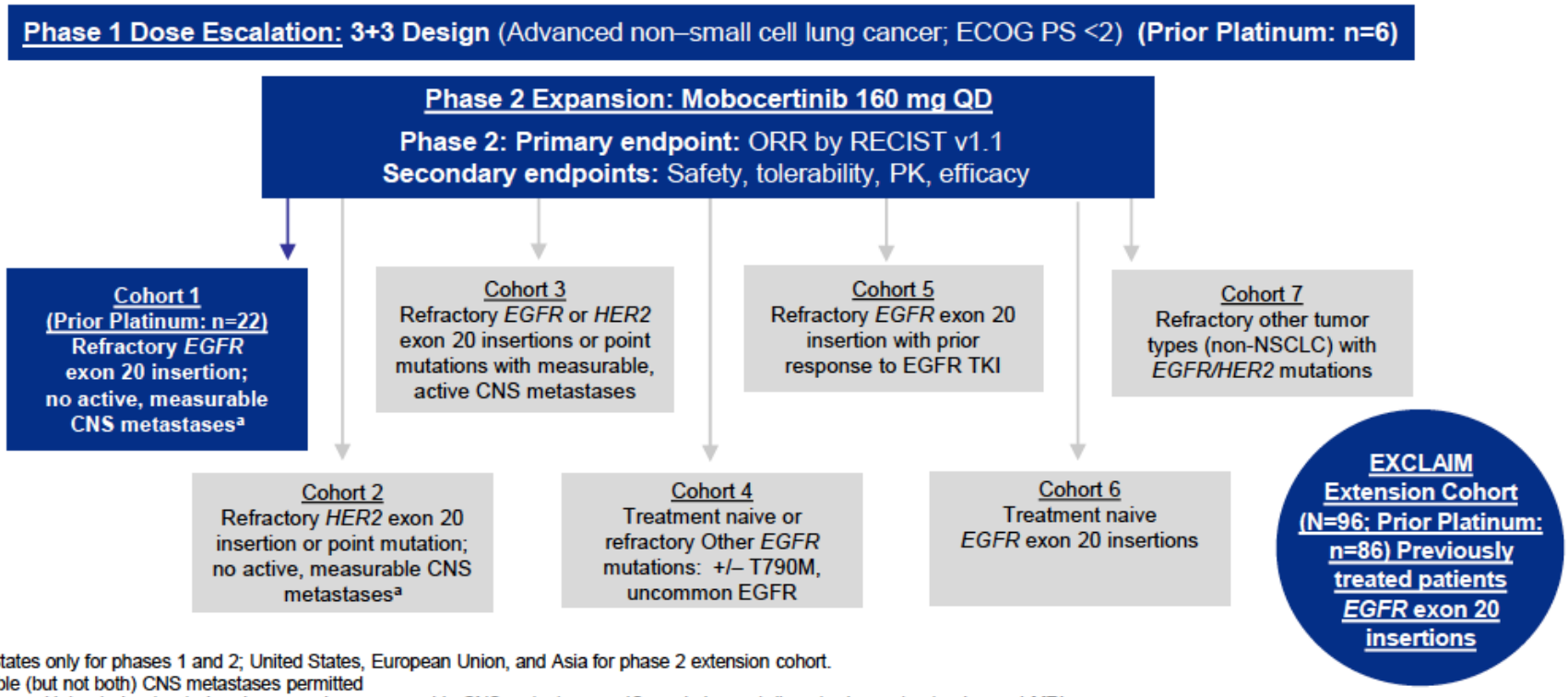


25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

[a]One patient in the efficacy population discontinued before any disease assessment and is not included in the plot. NGS, next-generation sequencing; SoD, sum of diameters

Mobocertinib in NSCLC With *EGFR* Exon 20 Insertions: Results From EXCLAIM and Platinum-Pretreated Patient Populations

Design and Patient Cohorts in Phases 1/2 and EXCLAIM

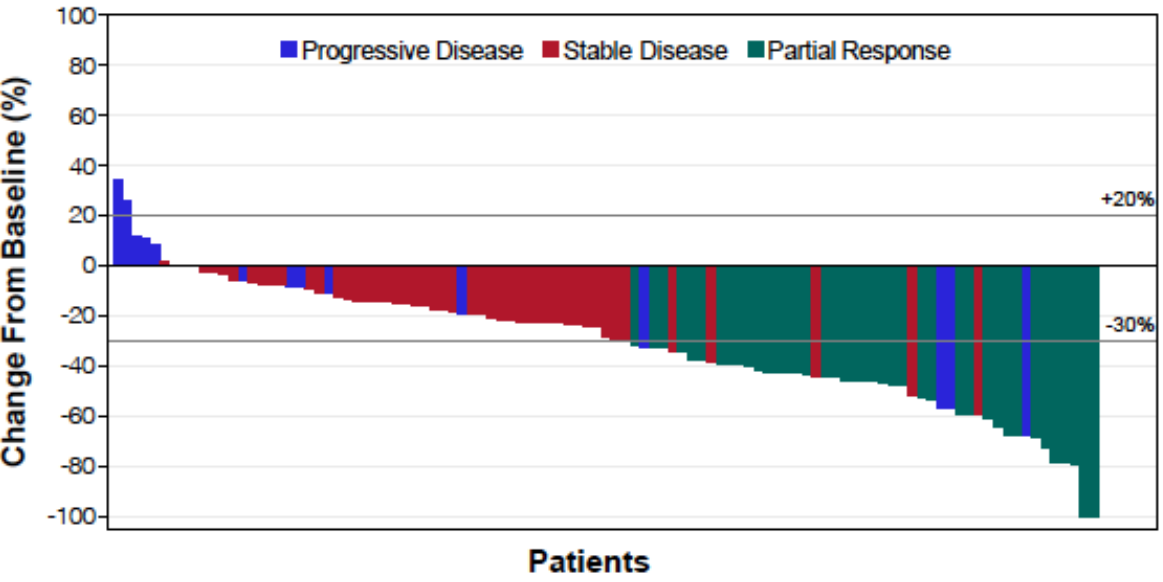


Locations: United States only for phases 1 and 2; United States, European Union, and Asia for phase 2 extension cohort.
[a]Active or measurable (but not both) CNS metastases permitted
Active CNS metastases: Untreated or treated and progressing; measurable CNS metastases: ≥10 mm in longest diameter by contrast-enhanced MRI
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor gene; *HER2*, human epidermal growth factor receptor 2 gene; MRI, magnetic resonance imaging; NSCLC, non–small cell lung cancer; ORR, objective response rate; QD, once daily; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor

arameter	PPP Cohort (N=114)	EXCLAIM Cohort (N=96)
ledian time on treatment, mo (range)	7.0 (0–31)	6.5 (0–14)
onfirmed ORR per IRC, n (%) [95% CI]	30 (26) [19–35]	22 (23) [15–33]
onfirmed ORR per investigator, n (%) [95% CI]	40 (35) [26–45]	31 (32) [23–43]
ledian DOR per IRC, mo [95% CI][a]	17.5 (8.3–NE)	NE (8.3–NE)
ledian DOR per investigator, mo [95% CI][a]	13.9 (5.6–NE)	NE (5.5–NE)
CR per IRC, n (%) [95% CI][b]	89 (78) [69–85]	73 (76) [66–84]
CR per investigator, n (%) [95% CI][b]	89 (78) [69–85]	72 (75) [65–83]
ledian PFS per IRC, mo [95% CI]	7.3 (5.5–10.2)	7.3 (5.5–10.2)
ledian PFS per investigator, mo [95% CI]	7.3 (5.5–8.1)	7.1 (5.6–7.8)

78% and 84% of patients had DOR >6 months in PPP and EXCLAIM cohorts, respectively (per IRC)

At the time of data cutoff, over 50% of responses were ongoing in both cohorts



94 patients (82%) had a reduction from baseline in the sum of target lesion diameter

ZENITH20 Trial: A Phase 2 International Trial

Updated efficacy, safety, and dosing management of poziotinib in previously treated EGFR and HER2 exon 20 NSCLC patients

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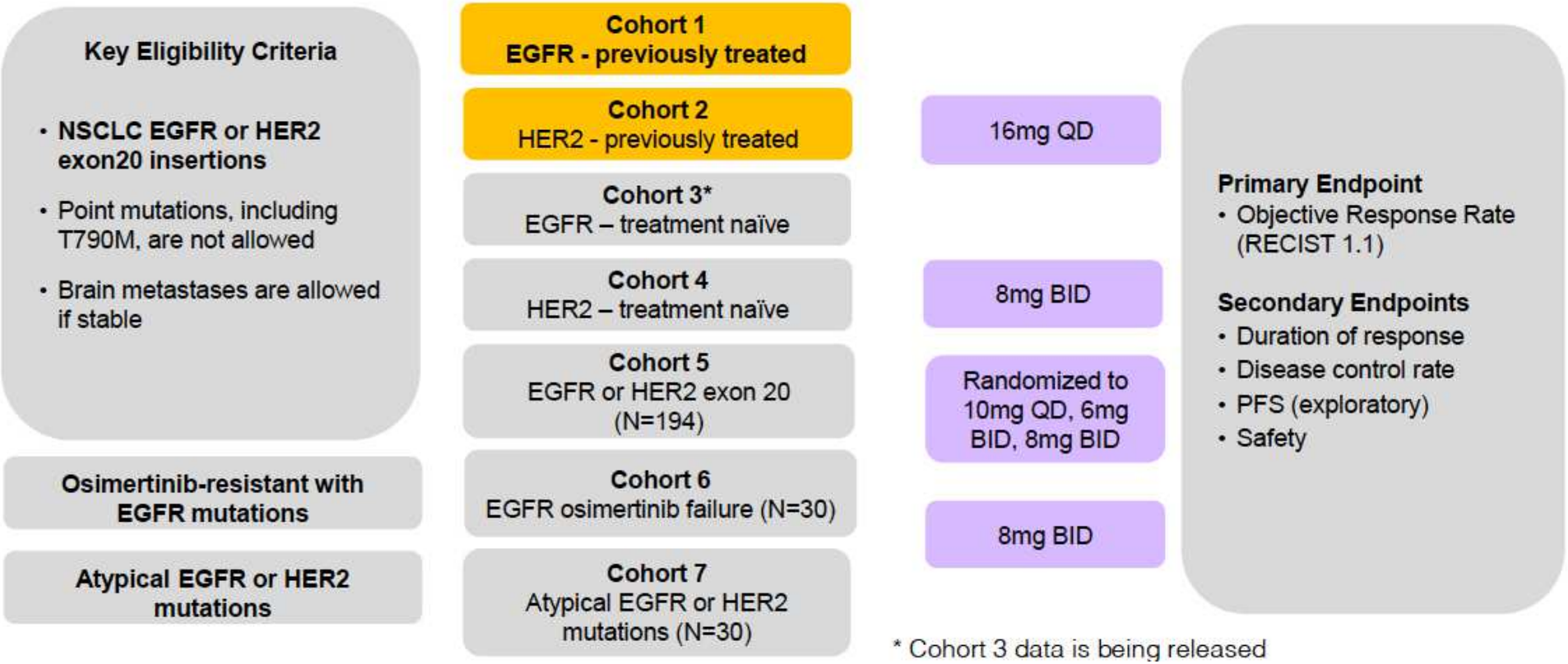
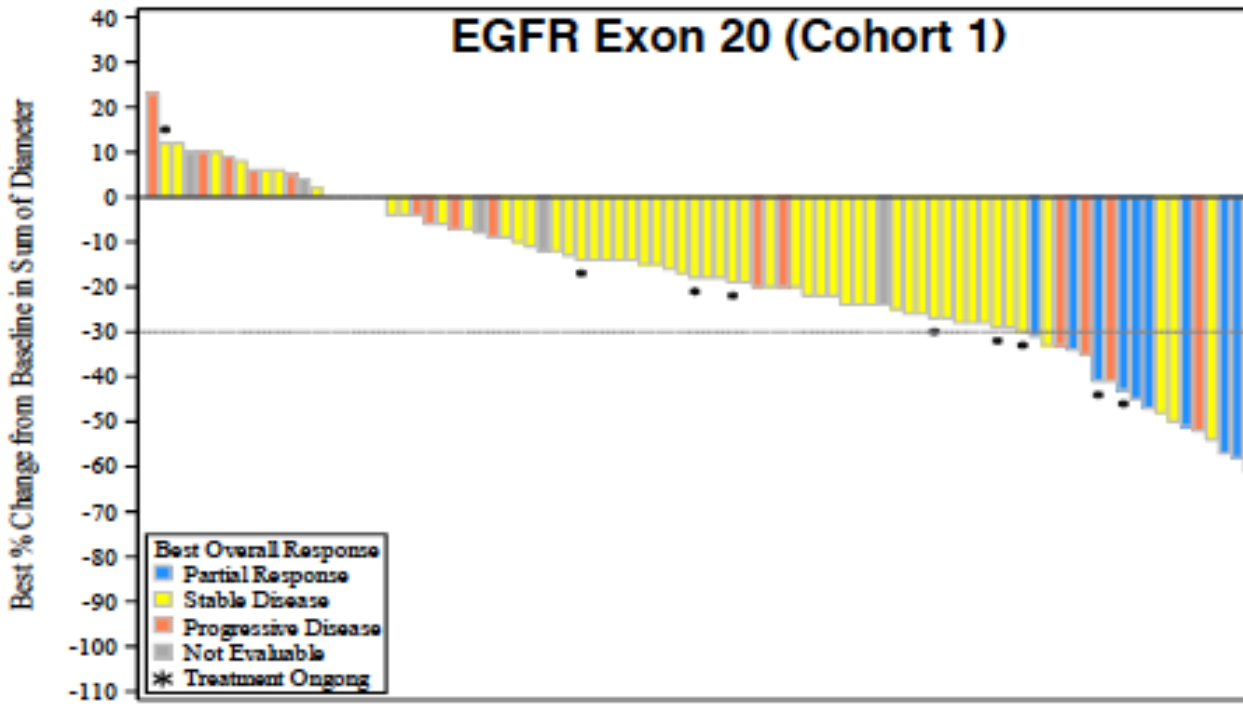


* Cohort 3 data is being released

	2L EGFR Exon 20 (N=115)
(n), [95% CI]	**14.8%** (17) [8.9, 22.6%]
onfirmed ORR (n), % CI]	**19.1%** (22) [12.4, 27.5%]
(n), % CI]	**68.7%** (79) [59.4, 77.0%]
, median (months), % CI]	**7.4** [3.7, 9.7]
, median (months), % CI]	**4.2** [3.7, 6.6]



- Higher response rates (38.7%) seen in heavily pre-treated HER2 cohort (≥3 lines of therapy)

EGFR Exon 20 Insertion: Eficacia

	AMIVANTAMAB (n: 81)	MOCERTINIB (n: 114)	POCIOTINIB (n: 115)
ORR	**40%**	26%	11.8%
DCR	**88%**	78%	68.7%
DOR	11m	**17.5m**	7.4m
PFS	**8.3m**	7.3m	4.2m
OS	22.8m		

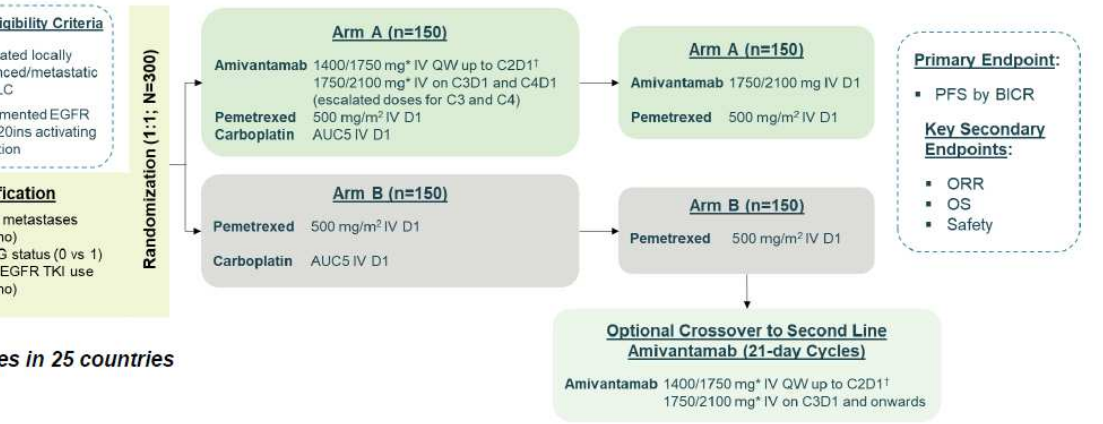
PAPILLON: A Randomized Phase 3 Study of Amivantamab Plus Chemotherapy vs hemotherapy Alone in EGFR Exon 20ins NSCLC

Trishala Agrawal, Eunice Artis, John Xie, Archan Bhattacharya, Nahor Haddish-Berhane, Tammy Gopen, Joshua C. Curtin, Jayaprakash Karkera, Amy Roshak, Roland E. Knoblauch, and Kiran Patel

Janssen Research & Development
USA

Abstract #3374

y Design



es in 25 countries

MARIPOSA: Randomized Phase 3 Study of Firs line Amivantamab + Lazertinib vs Osimertinib Lazertinib in EGFR-mutant NSCLC

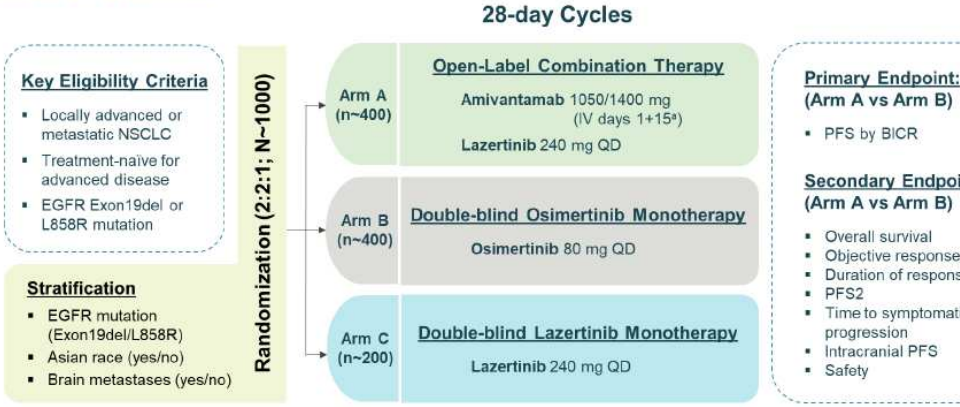
S. Martin Shreeve, Melissa Martinez, Remy B. Verheijen, Seema N. Sethi, Kellen Meadows, Renee Pierson, John Xie, Tao Sun, Nahor Haddish-Berhane Dona Pang, Joshua C. Curtin, Jayaprakash Karkera, Amy Roshak, Roland E. Knoblauch, and Kiran Patel

Janssen Research & Development, USA

Abstract #3380

METHODS: Study Design

262 sites in 27 countries

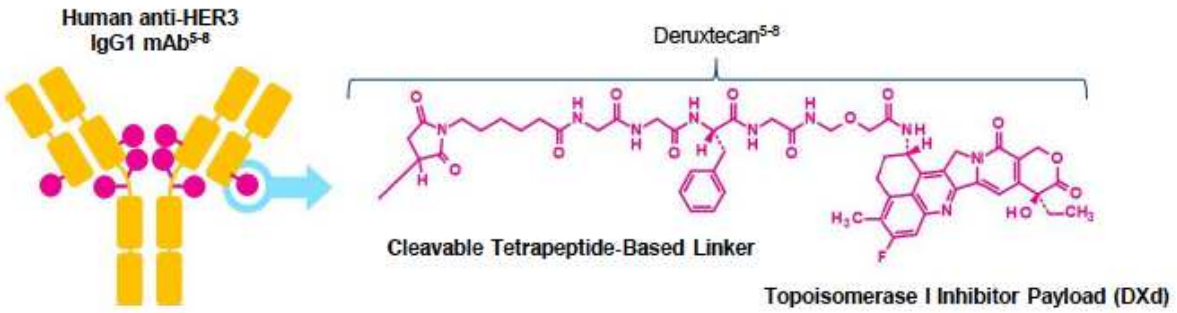


Efficacy and Safety of the Novel HER3 Directed Antibody Drug Conjugate Patritumab Deruxtecan (HER3-DXd; U3-1402) in *EGFR*-Mutated NSCLC

Helena A. Yu, MD
Memorial Sloan Kettering Cancer Center
New York, NY, USA

Helena A. Yu, Christina Baik, Kathryn Gold, Hidetoshi Hayashi, Melissa L. Johnson, Marianna Koczywas, Haruyasu Murakami, Makoto Nishio, Conor Steuer, Wu-Chou Su, James C. H. Yang, Samer Karam, Zhenhao Qi, Yang Qiu, Shuquan Chen, Channing Yu, Pasi A. Jänne

- Patients with advanced *EGFR*-mutated NSCLC have few treatment options after failure of EGFR TKIs and platinum-based chemotherapy[1,2]
- HER3 is expressed in most lung cancers, including in >80% of *EGFR*-mutated NSCLC, and overexpression has been associated with worse clinical outcomes[1,3-4]
  - HER3 therefore represents a promising therapeutic target; however, no HER3 directed therapies are currently approved[3,4]
- Patritumab deruxtecan (HER3-DXd; U3-1402) is a novel, investigational HER3 directed ADC comprising a fully human anti-HER3 IgG1 mAb (patritumab) covalently linked to a topoisomerase I inhibitor payload, an exatecan derivative, via a tetrapeptide-based cleavable linker[5-8]



Dose escalation[a]

Metastatic/unresectable **EGFR-*mutated* NSCLC** *either after progression on osimertinib or T790M-negative after progression on erlotinib, gefitinib, or afatinib*

HER3-DXd
5.6 mg/kg Q3W
n = 12

Dose expansion cohort 1[b]

Metastatic/unresectable ***EGFR*-mutated NSCLC** and treatment with ≥1 EGFR TKI and ≥1 prior platinum-based chemotherapy regimen

HER3-DXd
5.6 mg/kg Q3W
n = 45

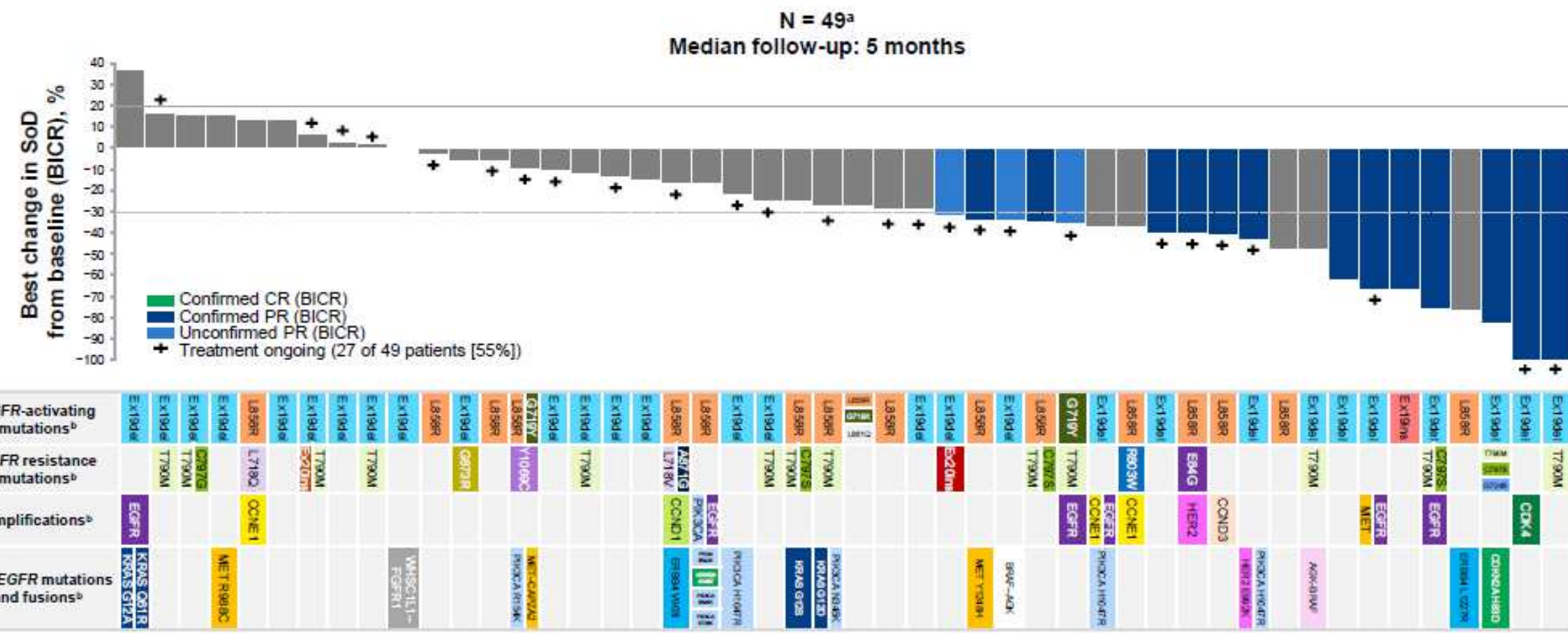
Primary objective:
Antitumor activity of HER3-DXd

Secondary objectives:
Safety and tolerability of HER3-DXd

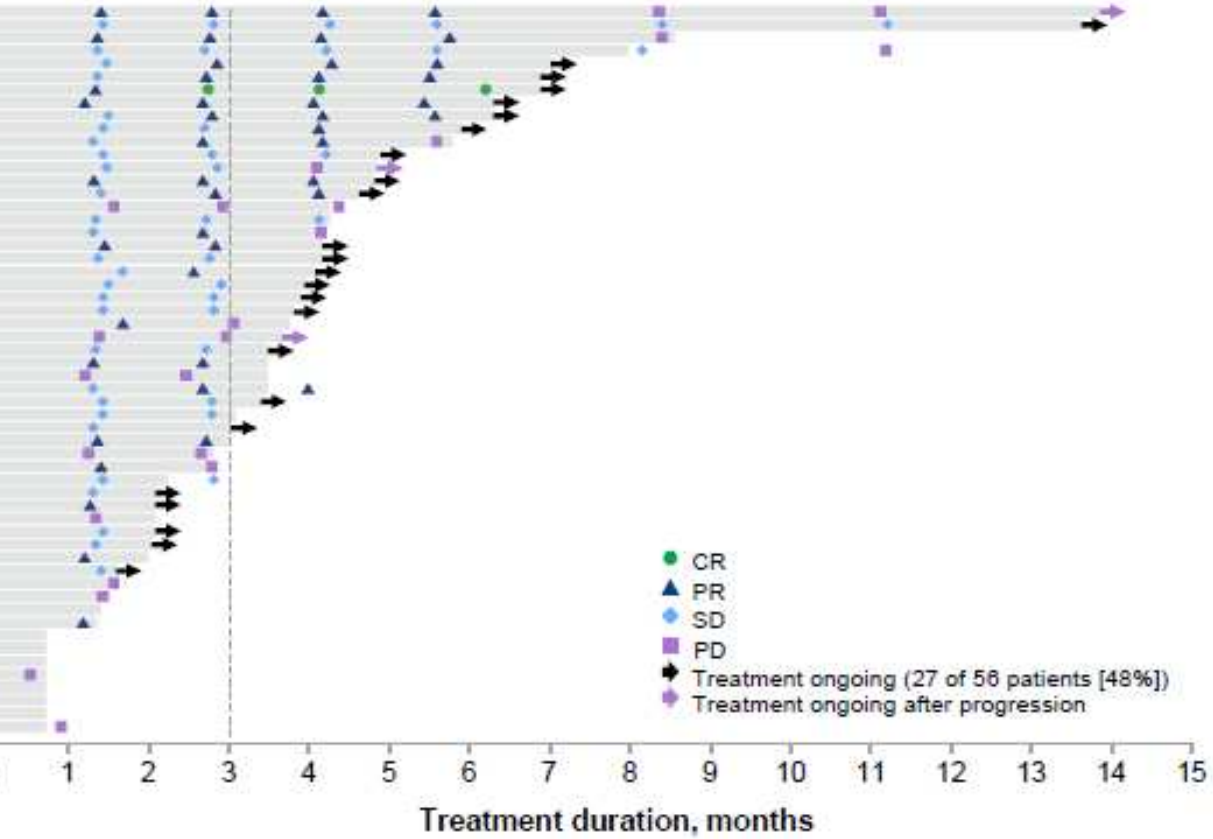
- Stable brain metastases were allowed
- Pretreatment tumor tissue (after progression on TKIs) required for retrospective analysis of HER3 expression

Median no. of therapies for advanced/metastatic disease (range)	4 (1-9)
Prior therapy, n (%)	
EGFR TKI	57 (100)
Osimertinib	49 (86)
Other EGFR-targeted therapy	3 (5)
Platinum-based chemotherapy	51 (90)
Anti–PD-1/PD-L1	23 (40)
History of CNS metastases, n (%)	27 (47)

HER3-DXd 5.6 mg/kg Demonstrated Antitumor Activity in *EGFR*-Mutated NSCLC With Diverse TKI Resistance Mechanisms



Antitumor Response Occurs Within 3 Months in Patients Treated With 5.6 mg/kg of HER3-DXd



Activity according to BICR evaluation (efficacy-evaluable population) N = 56[a]	
Confirmed BOR, n/N (%)	
CR	1/56 (2%)
PR	13/56 (23%)
SD	25/56 (45%)
PD	9/56 (16%)
NE	8/56 (14%)
Confirmed ORR, % (n/N; 95% CI)	25% (14/56; 14.4-38.4
DCR, % (n/N; 95% CI)	70% (39/56; 55.9-81.2
Median TTR, months (range)	2.0 (1.2-2.8)
Median DOR, months (range)	6.9 (3.0-7.0)

HER3-DXd 5.6 mg/kg Continues to Demonstrate a Manageable Safety Profile

he most common grade ≥3 TEAEs were thrombocytopenia (16 patients [28%]) and neutropenia (11 patients [19%])

EAEs associated with discontinuation (9%) included fatigue (n = 2), decreased appetite (n = 1), terstitial lung disease (n = 1), pneumonitis (n = 1), and URI (n = 1)

- No discontinuations were due to thrombocytopenia or neutropenia

hree (5.3%) interstitial lung disease events were adjudicated by an independent central review committee as being elated to treatment

here were no treatment-related TEAEs associated ith death

TEAEs (regardless of causality), n (%)	N = 57
TEAEs	57 (100)
Grade ≥3	38 (67)
Associated with discontinuation	5 (9)
Associated with dose reduction	10 (18)
Associated with dose interruption	17 (30)
Associated with death	3 (5)
Treatment-emergent SAEs	21 (37)
Grade ≥3	18 (32)
Treatment related	11 (19)

TEAEs in ≥20% of patients, n (%)	N = 57	
	All grades	Grade ≥3
Fatigue	33 (58)	5 (9)
Nausea	31 (54)	2 (4)
Thrombocytopenia[a]	30 (53)	16 (28)
Decreased appetite	20 (35)	1 (2)
Neutropenia[b]	19 (33)	11 (19)
Vomiting	17 (30)	1 (2)
Alopecia	17 (30)	NA
Anemia[c]	15 (26)	5 (9)
Constipation	14 (25)	0

Neratinib in pretreated *EGFR* exon 18-mutant non-small cell lung cancer (NSCLC): initial findings from the SUMMIT basket trial

Valentina Boni,[1] Christophe Dooms,[2] Barbara Haley,[3] Santiago Viteri,[4] Amit Mahipal,[5] J. Marie Suga,[6] Lisa D. Eli,[7] Alshad S. Lalani,[7] Richard Bryce,[7] Feng Xu,[7] Naisargee Shah,[7] Fairooz Kabbinavar,[7] Jonathan W. Goldman[8]

***EGFR* exon 18-mutant Lung Cancer**

Open-label, single-arm cohort

Neratinib monotherapy (240 mg, oral daily)

Mandatory Loperamide prophylaxis: oral 4 mg TID days 1–14, 4 mg BID days 15–46; as needed PRN

Key inclusion criteria

- Histologically confirmed lung cancers for which no curative therapy exists
- Documented *EGFR* exon 18 mutation by local method (any CAP/CLIA-certified lab)
- **Prior treatment with EGFR or pan-HER TKI allowed (afatinib, dacomitinib, osimertinib, etc)**
- ECOG status of 0 to 2
- RECIST 1.1 disease only

Key exclusion criteria

- Patients who are receiving any other anticancer agents
- Symptomatic or unstable brain metastases
- Women who are pregnant or breast-feeding
- Known KRAS activating co-mutation

Study endpoints and trial design features

Primary endpoint

- Objective response rate at first post-baseline tumor assessment (Week 8) (ORR_{Wk8})

Secondary endpoints

- ORR (confirmed by RECIST criteria)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

Simon 2-stage design

- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

Tumor assessments

- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

Statistical methods

- ORR_{first}, ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI
- DOR

neter	Efficacy evaluable patients (n=11)	TKI pre-treated subgrou (n=10)
ctive response (confirmed),[a] n	**4** 0 4	**4** 0 4
R,[a†] % (95% CI)	**36** (11–69)	**40** (12–74)
overall response, n	**6** 0 6	**6** 0 6
t overall response rate, % (95% CI)	**54** (23–83)	**60** (26–88)
an DOR,[b] months (95% CI)	**7.5 (4.0–NE)** **(1.9*, 4.0, 7.5, 9.2*)**	**7.5 (4.0–NE)** **(1.9*, 4.0, 7.5, 9.2*)**
cal benefit,[c] n or PR ≥16 weeks ical benefit rate, % (95% CI)	**8** 4 4 **73** (39–94)	**8** 4 4 **80** (44–97)
an PFS[b] time to event, months (95% CI)	**6.9** (2.1–NA)	**9.1 (3.7–NA)**

ve response rate) defined as either a CR or PR that is confirmed no less than 4 weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis in safety population; [c]CBR (clinical benefit rate) defined as confirme
weeks (within +/– 7-day visit window); [†]Data for ORR at week 8 (ORR_{final}) and ORR (RECIST 1.1 confirmed) are identical and are only presented once. DOR, duration of response; PFS, progression-free survival, *response on