Phase 2 study of poziotinib in NSCLC with *EGFR exon20* insertions

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on behalf of ZENITH20 Study Group

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2020 AACR Virtual Annual Meeting Plenary Clinical Trial Abstract: 10189 CT081

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Disclosures

- Consultant/advisory: Eli Lilly, AstraZeneca, EMD Serono
- Research funds: Eli Lilly, Boehringer Ingelheim, Spectrum

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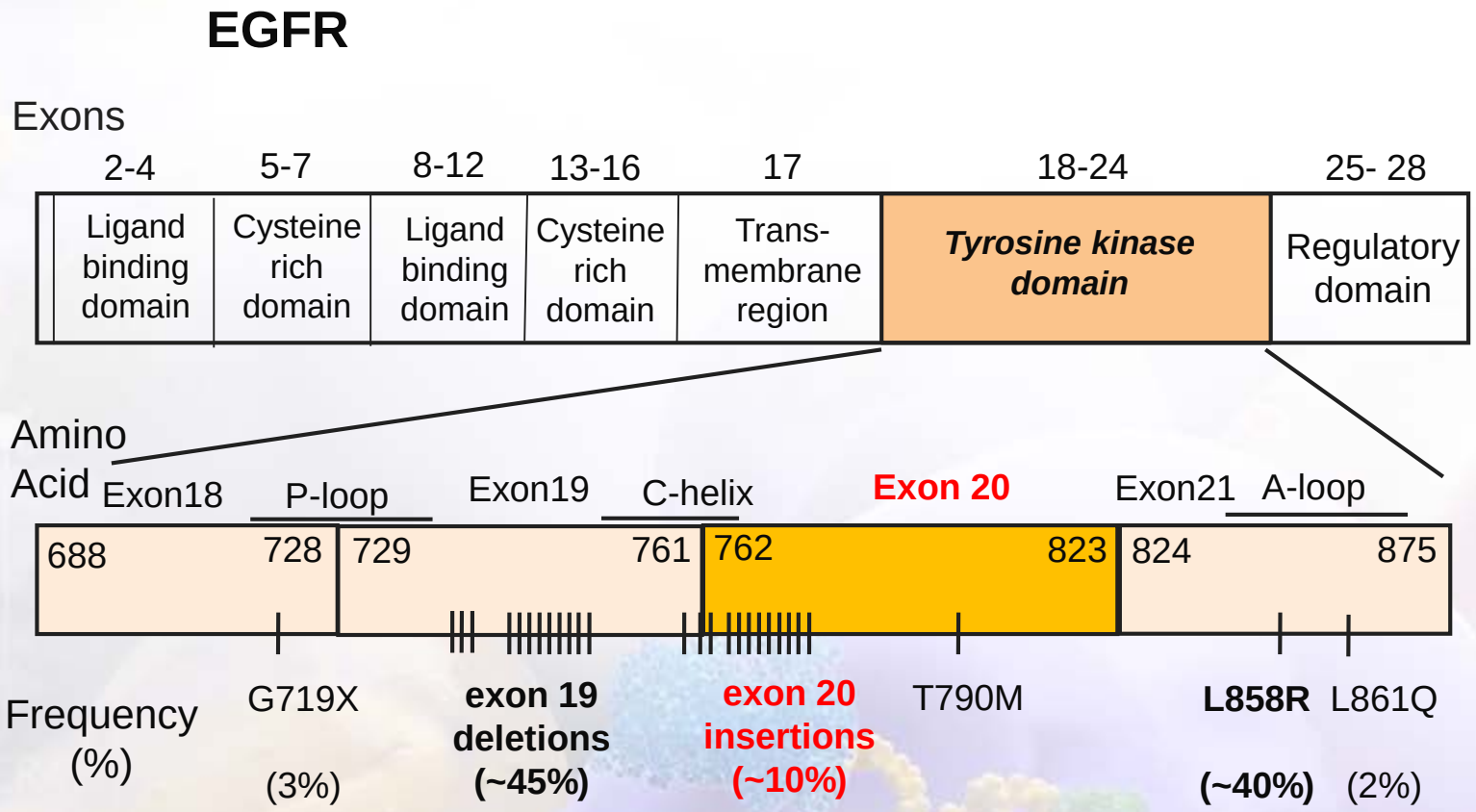
EGFR exon20 insertions in NSCLC

- EGFR is an oncogene driver for NSCLCs, most common being the classic sensitizing mutation L858R (40%) and deletion exon19 (45%)[1,2,3].
- EGFR exon 20 insertions account for approximately 10% of all EGFR mutations.
- EGFR exon 20 insertions are commonly located between amino acid positions 762-773 in the kinase domain of EGFR.
- No approved targeted therapy.

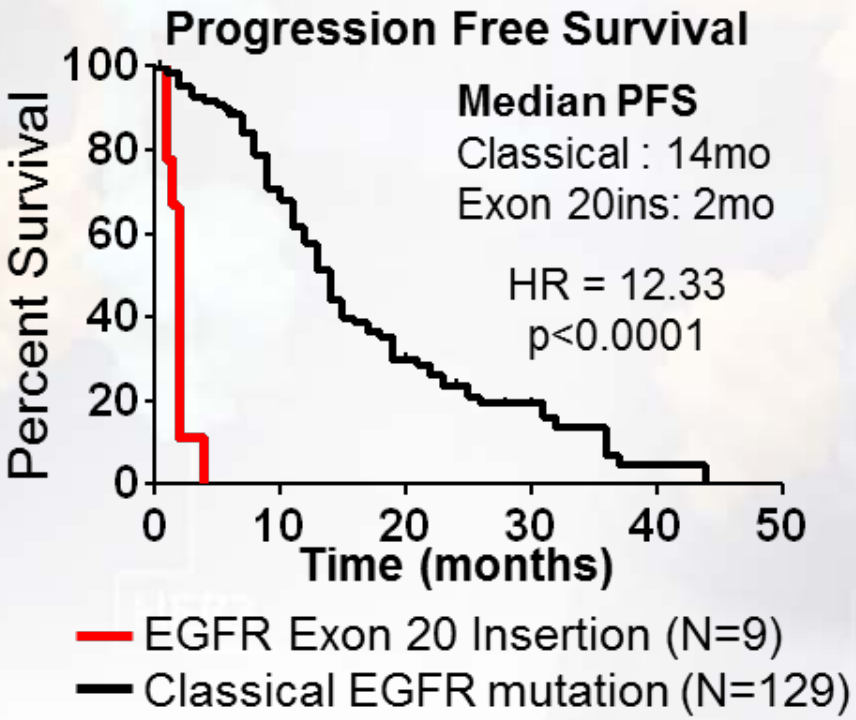


Adapted from Yasuda, Kobayashi, Costa Lancet Oncol (2012)

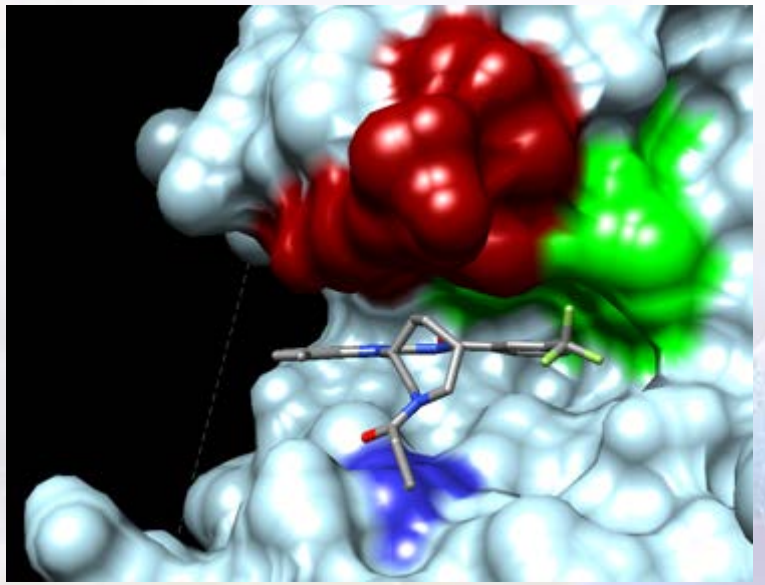
[1] Paez et al Science; [2] Lynch et al NEJM; [3] Pao et al PNAS (2004)

EGFR exon20 insertions in NSCLC

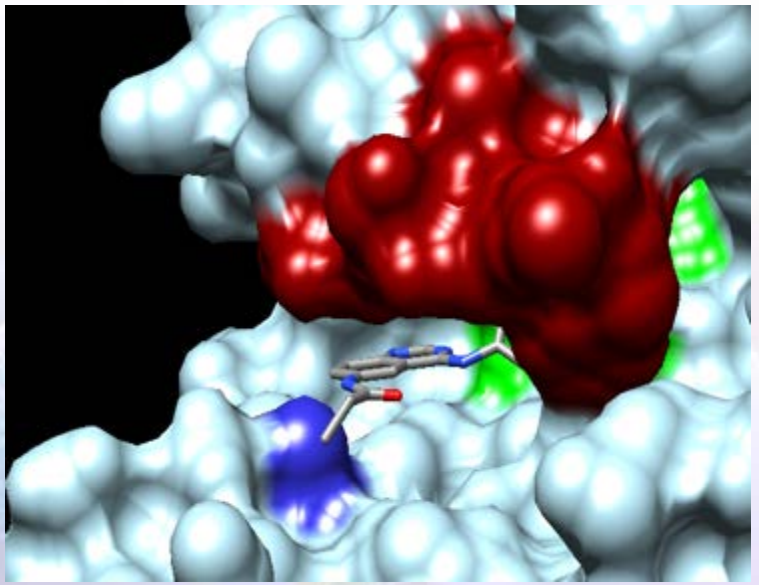
- EGFR exon20 insertions are resistant to other EGFR TKIs
- Due to the reduced overall binding pocket volume, compared to sensitizing mutations



EGFR T790M
Osimertinib



EGFR 770insNPG
Poziotinib

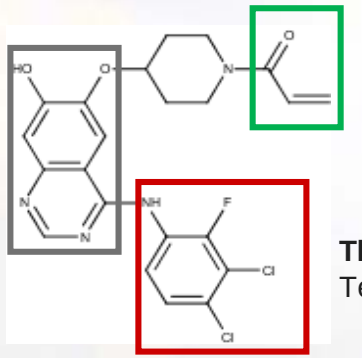


Robichaux, Heymach et al. Nat Med 2018

Poziotinib is a quinazoline-based EGFR inhibitor

The small size and shape of poziotinib can fit to the binding pocket of exon20

Poziotinib

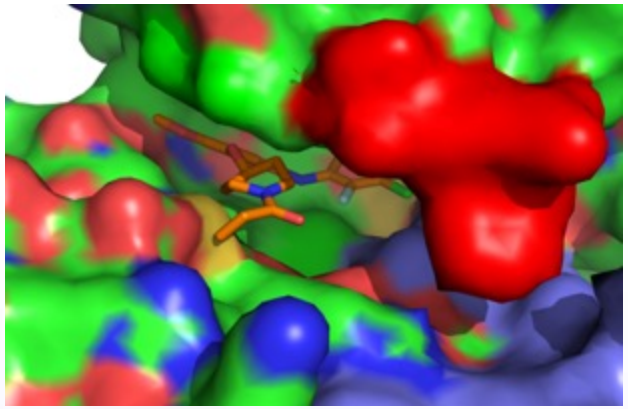


The body:
Quinazoline Core
(ATP mimetic)

The Arm:
Reactive Group (covalent bond to C797)

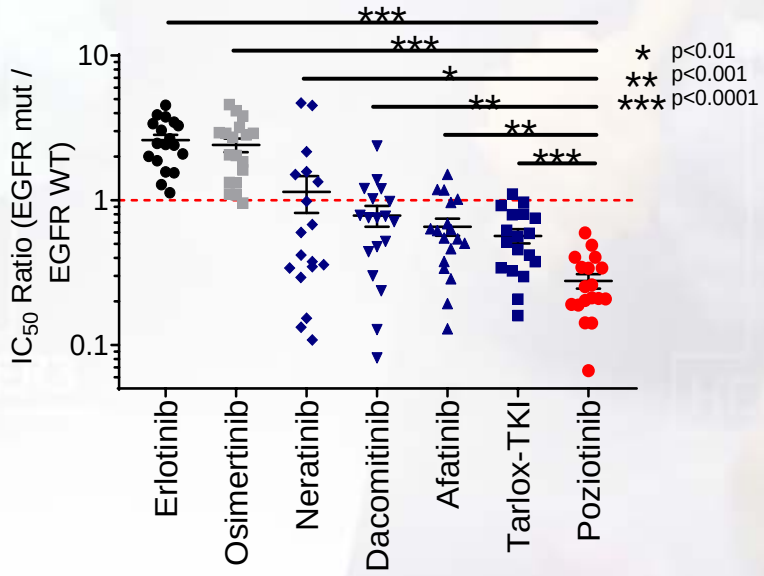
The feet:
Terminal group

EGFR D770insNPG

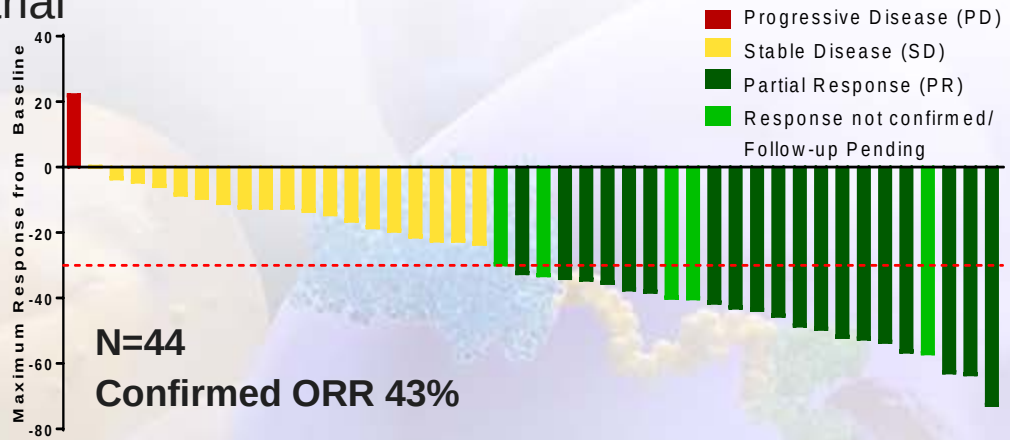


In vitro efficacy

EGFR Ba/F3 Selectivity Index
(N=20 cell lines)



Clinical efficacy in a single-center phase 2 trial



Robichaux, Heymach et al. Nat Med 2018, Heymach WCLC 2018

ZENITH20: a pivotal multi-center phase 2 study in North America and Europe

NSCLC patients with EGFR or HER2 exon 20 insertions

Key Eligibility Criteria

- NSCLC EGFR or HER2 exon20 insertions
- Point mutations, including T790M, are not allowed
- Brain mets are allowed if stable

Cohort 1
EGFR - previously treated
(N = 87)

Cohort 2
HER2 - previously treated
(N = up to 87)

Cohort 3
EGFR – treatment naive
(N = up to 70)

Cohort 4
HER2 – treatment naive
(N = up to 70)

Oral daily dose
28-day cycle

Poziotinib
16mg QD

Primary Endpoint
- Objective Response Rate (RECIST 1.1 by IRC)

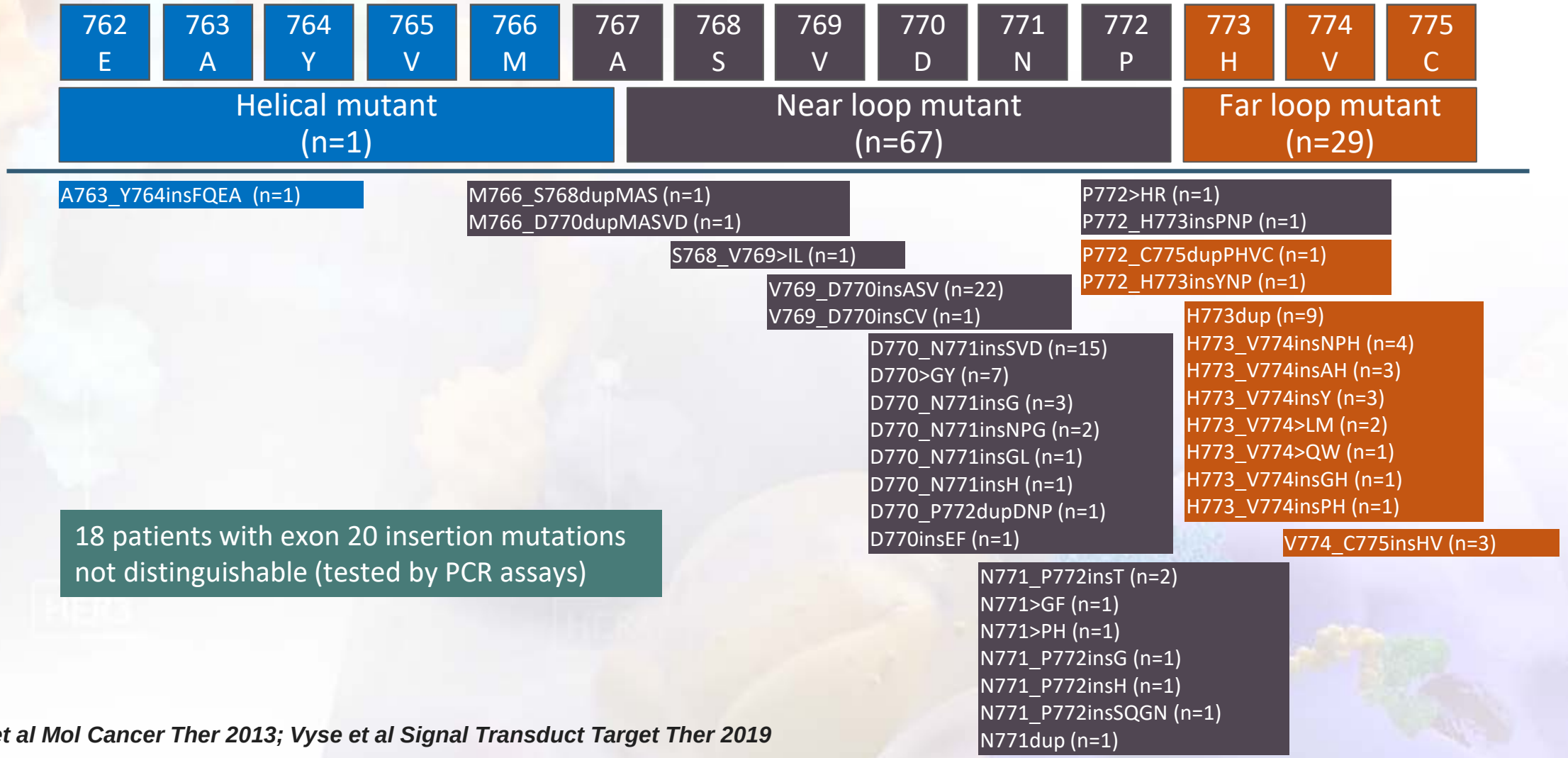
Secondary Endpoints
- Disease Control Rate (DCR)
- Duration of Response (DoR)
- PFS (exploratory)
- Safety

Baseline patient and tumor characteristics (N=115)

Characteristic		N (%)
Median age, years (range)		61 (33, 83)
Sex	Female	77 (67)
Race	White	77 (67)
	Asian	18 (16)
Smoking history	Never smoker	79 (69)
	Former smoker	2 (2)
	Regular smoker	34 (30)
Prior lines of therapy	1	49 (43)
	2	29 (25)
	≥3	37 (32)
Prior EGFR TKI therapy	Yes	29 (25)
	No	86 (75)

Characteristic		N (%)
Histopathological classification	Adenocarcinoma	112 (98)
	Squamous	3 (3)
	Mixed pathology	0
Disease stage at study entry	III	7 (6)
	IV	105 (91)
Brain metastases	None	103 (90)
	Present	12 (10)
ECOG PS	0	53 (46)
	1	62 (54)

Baseline *EGFR exon20* insertion distribution



18 patients with exon 20 insertion mutations not distinguishable (tested by PCR assays)

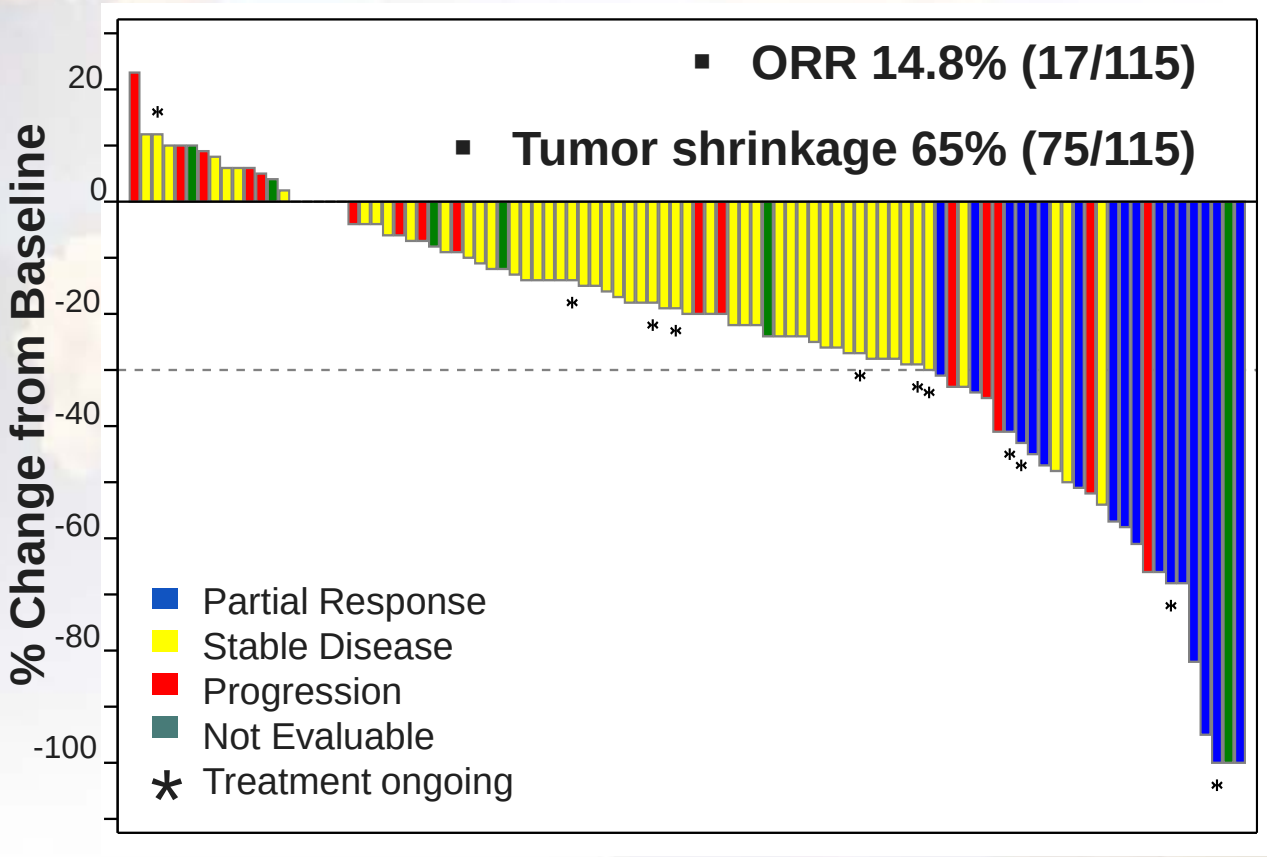
Arcila et al Mol Cancer Ther 2013; Vyse et al Signal Transduct Target Ther 2019

Efficacy

Best Overall Response	Intent to treat (N=115) N (%)
Objective Response Rate (ORR) by independent review committee (IRC) 95% Confidence Interval	**17 (14.8%)** (8.9 - 22.6%)
Disease Control Rate (DCR=CR+PR+SD) 95% Confidence Interval	**79 (68.7%)** (59.4 - 77.0%)
Duration of Response, Median (months) 95% Confidence Interval	**7.4** (3.7, 9.7)
Progression-free Survival, Median (months) 95% Confidence Interval	**4.2** (3.7, 6.6)

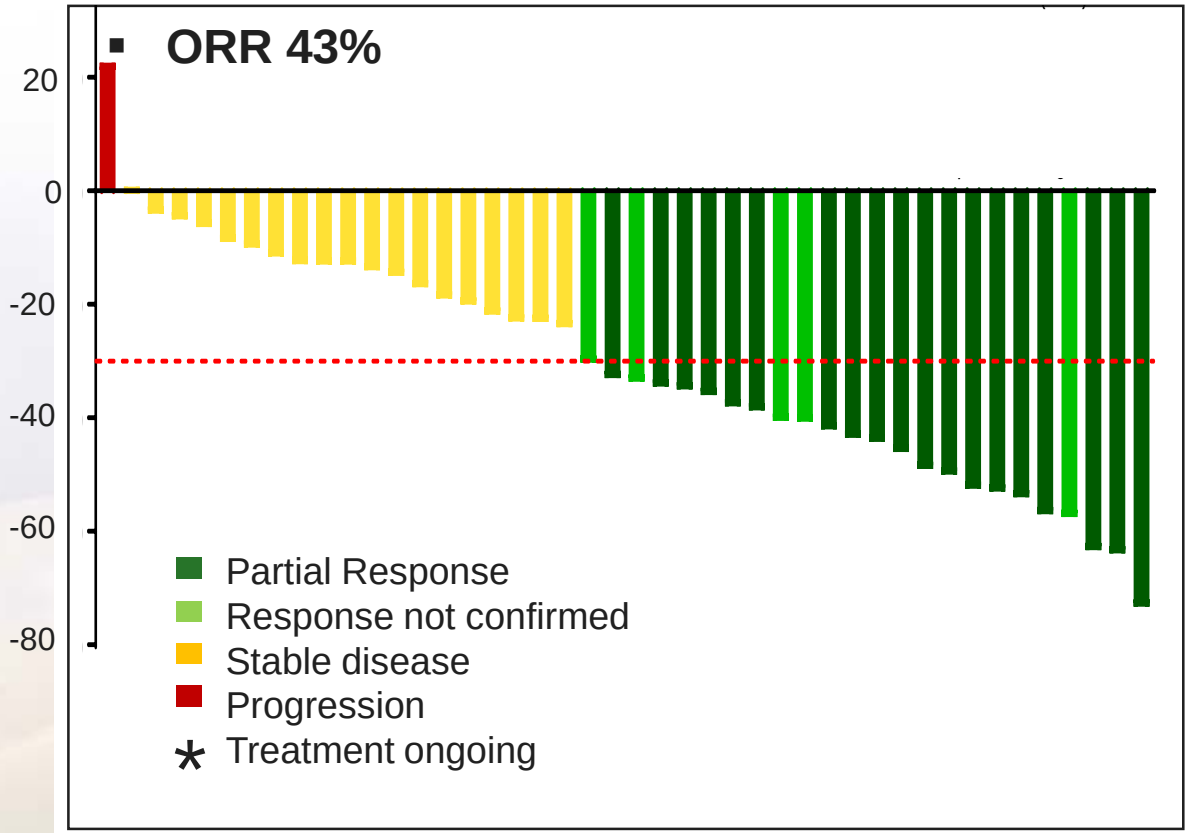
Efficacy: tumor size reduction

Best change (%) in the sum target lesions
ZENITH20 cohort 1 (N=97)



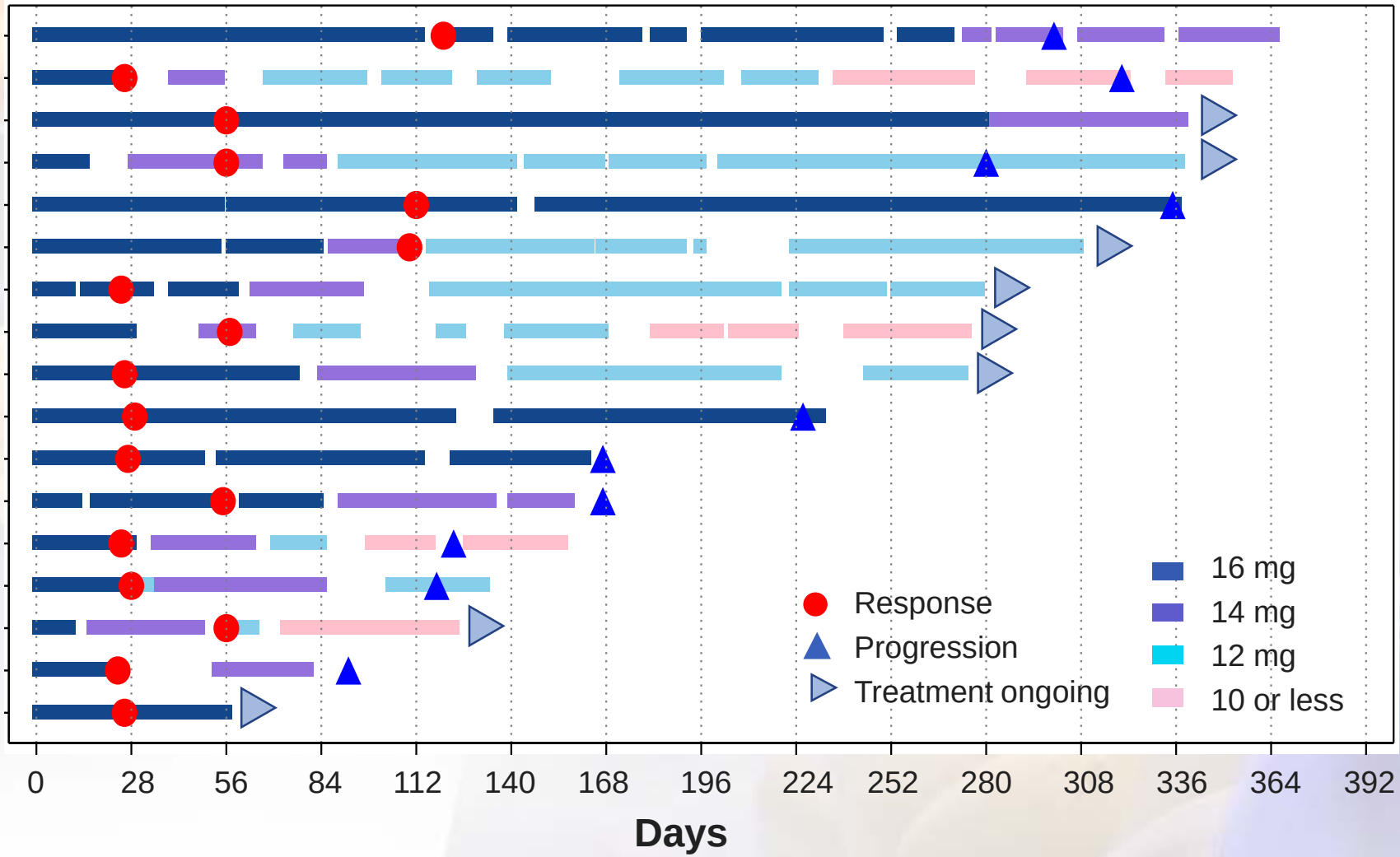
Reviewed by Independent Review Committee (IRC)

MDACC single-center study (N=44)



Elamin in preparation, Heymach WCLC 2018

Efficacy: duration of response



- Median duration of response: 7.4 months (95% CI 3.7,9.7)
- Responses occurred early and were durable
- A significant portion of patients had dose interruption or dose reduction
- Responses can be maintained on a lower dose than 16mg

Efficacy: subgroup analyses

Subgroup		N	ORR (%)	Time on Treatment (months) Median (range)
Prior lines of therapy	1	49	14.3	4.6 (0.3, 11.3)
	2	29	13.8	3.7 (0.2, 13.8)
	≥3	37	16.2	3.5 (0, 14.0)
Prior EGFR TKI therapy	Yes	29	6.9	3.5 (0, 14.0)
	No	86	17.4	4.4 (0, 13.8)
Brain metastases	Yes	12	8.3	4.1 (1.2, 8.2)
	No	103	15.5	4.0 (0, 14.0)
ECOG PS	0	53	18.9	6.3 (1.0, 14.0)
	1	62	11.3	2.3 (0, 11.2)

Safety: treatment-related adverse events

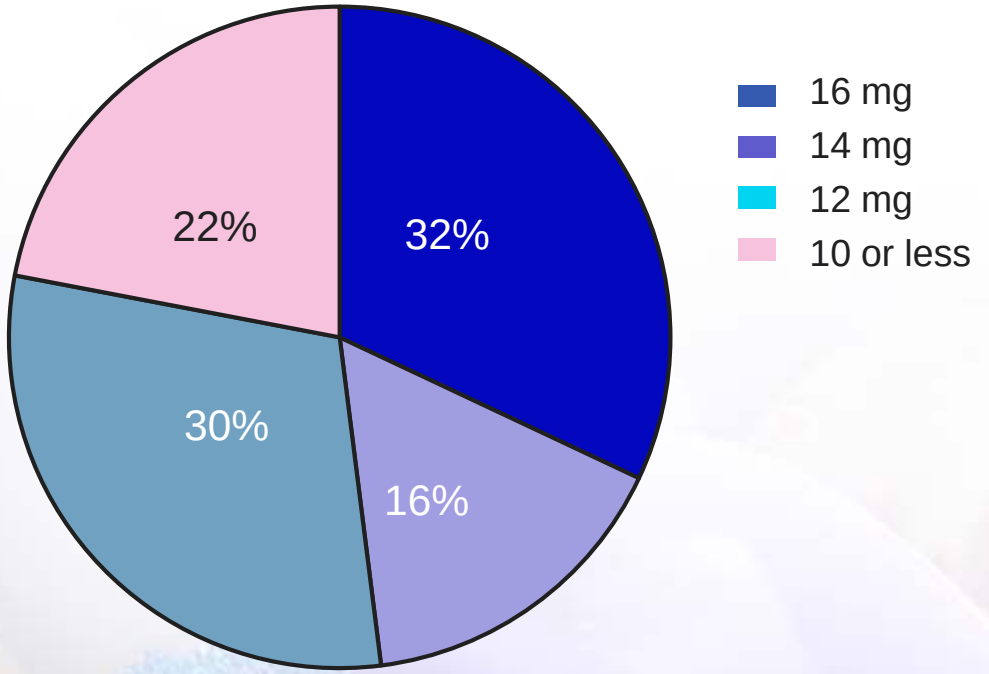
Treatment-related AE	N=115		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any TRAE	114 (99)	70 (61)	2 (2)
Diarrhea	91 (79)	29 (25)	1 (1)
Rash	69 (60)	32 (28)	0
Stomatitis	60 (52)	10 (9)	0
Paronychia	52 (45)	7 (6)	0
Nausea	44 (38)	3 (3)	0
Decreased appetite	36 (31)	2 (2)	0
Mucosal inflammation	34 (30)	8 (7)	0
Dry skin	33 (29)	3 (3)	0
Vomiting	33 (29)	1 (1)	0
Alopecia	31 (27)	0	0
Dermatitis acneiform	30 (26)	8 (7)	1 (1)
Fatigue	30 (26)	6 (5)	0
Pruritus	29 (25)	5 (4)	0

- No Grade 5 treatment-related AEs
- Most common treatment-related AEs (any grade) include:
  - Rash
  - Diarrhea
  - Stomatitis
  - Paronychia

Safety: drug compliance and dose reduction

- Dose reduction rate 68%
- Median relative dose intensity (%, range)

  = 72% (7-100%)
- Drug interruption
  - 97 patients (88%)
  - Median day first dose interruption = 16 days
    - 1-7 days = 21 (18%)
    - 8-14 days = 25 (22%)
    - >15 days = 55 (48%)
- Permanent discontinuation due to treatment-related AE = 12 (10%)



Afatinib (Lux-Lung 3): 52% dose reduction, 8% discontinuation[1]

Dacomitinib (Archer1050): 67% dose reduction, 10% discontinuation[2]

[1] Sequist et al JCO 2013; [2] Wu Lancet Oncol 2017

ZENITH20: continued enrollment with new cohorts

NSCLC patients with EGFR or HER2 exon 20 insertions

Key Eligibility Criteria

- **NSCLC EGFR or HER2 exon20 insertions**
- Point mutations, including T790M, are not allowed
- Brain mets are allowed if stable

Osimertinib-resistant with EGFR mutations

Atypical EGFR or HER2 mutations

Cohort 1
EGFR - previously treated

Cohort 2
HER2 - previously treated

Cohort 3
EGFR – treatment naive

Cohort 4
HER2 – treatment naive

Cohort 5
EGFR or HER2 exon 20 (N=180)

Cohort 6
EGFR osimertinib failure (N=30)

Cohort 7
Atypical EGFR or HER2 mutations (N=30)

Oral daily dose
28-day cycle

16mg QD with dose reduction

8mg BID

Randomized to 10mg QD, 6mg BID, 8mg BID

8mg BID

Primary Endpoint
- Objective Response Rate (RECIST 1.1)

Secondary Endpoints
- Duration of response
- Disease control rate
- PFS (exploratory)
- Safety

Conclusions

- Poziotinib has demonstrated clinical activity in previously treated NSCLC patients with EGFR exon 20 insertions
  - Objective response rate of 14.8%
  - Disease control rate of 69%
  - Tumor shrinkage in 65% of patients
  - Median duration of response of 7.4 months
  - Median PFS 4.2 months
- Toxicity profile was similar to those of other second-generation TKIs
  - Rash and diarrhea are most common
  - 68% dose reduction
  - 10% discontinuation due to AE
- ZENITH20 is ongoing with 3 new cohorts and adjustment of dosing to BID

Acknowledgements

We thank all the patients and their families

We thank all the ZENITH20 investigators and the study teams at each participating center

The trial is sponsored and overseen by Spectrum Pharmaceuticals, USA