2021 ESMO congress

Efficacy and Safety of Poziotinib in Treatment-naïve NSCLC Harboring HER2 exon 20 Mutations: A Multinational Phase 2 Study (ZENITH20-4)

Robin Cornelissen, MD

Pulmonary Medicine, Erasmus MC

University Medical Center, Rotterdam, Netherlands

Erasmus MC
University Medical Center Rotterdam

DECLARATION OF INTERESTS

Robin Cornelissen

Commercial Interest	Relationship(s)
Speaker's fee	Roche, Pfizer, BMS
Advisory board	MSD, Roche, Spectrum

Background

- EGFR and HER2 exon 20 insertion mutations are rare subsets of accounting for approximately 10% each of all mutations and 2-4% each in NSCLC
- There is no approved therapy for either treatment-naïve or previously treated NSCLC with HER2 exon 20 mutations
- Currently utilized treatments include chemotherapy agents with or without checkpoint inhibitors and TKIs. None are specific to exon 20 mutations. Efficacy reported in literature is mostly from small uncontrolled studies and varies widely [1- 5]
  - Response rates range 6.9 – 35%
  - Median PFS range 3 to 7 months
- Poziotinib is an oral pan-HER TKI with activity in patients with EGFR or HER2 exon 20 mutated NSCLC[6]

[1]Zhou 2020; [2]Yang 2021; [3]Xu 2020; [4]Auliac 2019; [5]Yuan 2020; [6]Cornelissen, WLCLC 2021

ZENITH20: Multi-cohort Global Clinical Trial

Completed

Cohort 1
Previously treated NSCLC with EGFR exon 20 insertions

Cohort 2
Previously treated NSCLC with HER2 exon 20 insertions

Cohort 3
First-line NSCLC with EGFR exon 20 insertions

Objectives

- **Primary**
  - Objective Response Rate (ORR)
- **Secondary**
  - Disease Control Rate (DCR)
  - Duration of Response (DOR)
  - Safety & Tolerability
- ORR based on Central independent imaging review

Cohort 4: Primary Endpoint Criteria: ORR 95% CI Lower Bound >20%

Treatment:
- 16 mg QD in first 48 patients (complete)
- 8 mg BID in subsequent patients (enrolling)

Enrolling

Cohort 4
First-line NSCLC with HER2 exon 20 insertions

Cohort 5
Exploratory Previously Treated or First-line NSCLC with EGFR or HER2 exon 20 insertions

Cohort 6
EGFR Osimertinib Failures

Cohort 7
Atypical EGFR or HER2 mutations

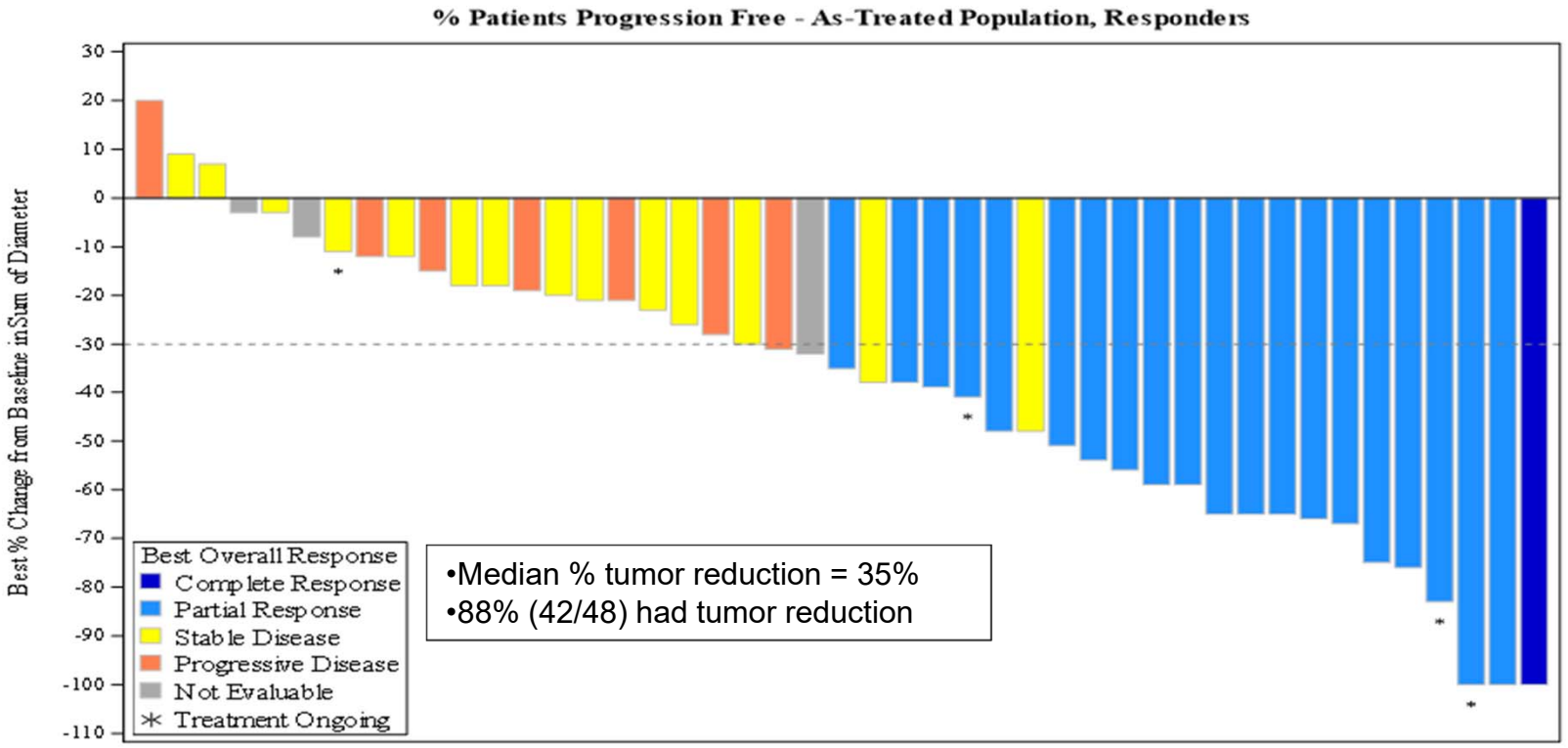
Preliminary safety and efficacy data from Cohort 4 QD dosing being presented here

ZENITH20 Cohort 4: Patient Characteristics

Disposition	1L HER2 exon 20	
	QD Dosing N=48 n (%)	BID dosing N=23* n (%)
Ongoing	4 (8)	14 (61)
Discontinued	44 (92)	9 (39)
Death	5 (10)	1 (4)
Disease progression	30 (63)	3 (13)
Adverse events	1 (2)	3 (13)
Other	8 (17)	2 (9)
Age, median (range)	60.5 (34, 87)	59 (27, 88)
Female / Male, n	26/22	13/10
White /Asian / Others, n	36/7/5	19/3/1
Smoker / Non-Smoker, n	15/33	5/18
ECOG Status: 0 / 1	17/31	7/13

* BID patients enrolling with majority ongoing

Best %Change from Baseline in Target Tumor Size



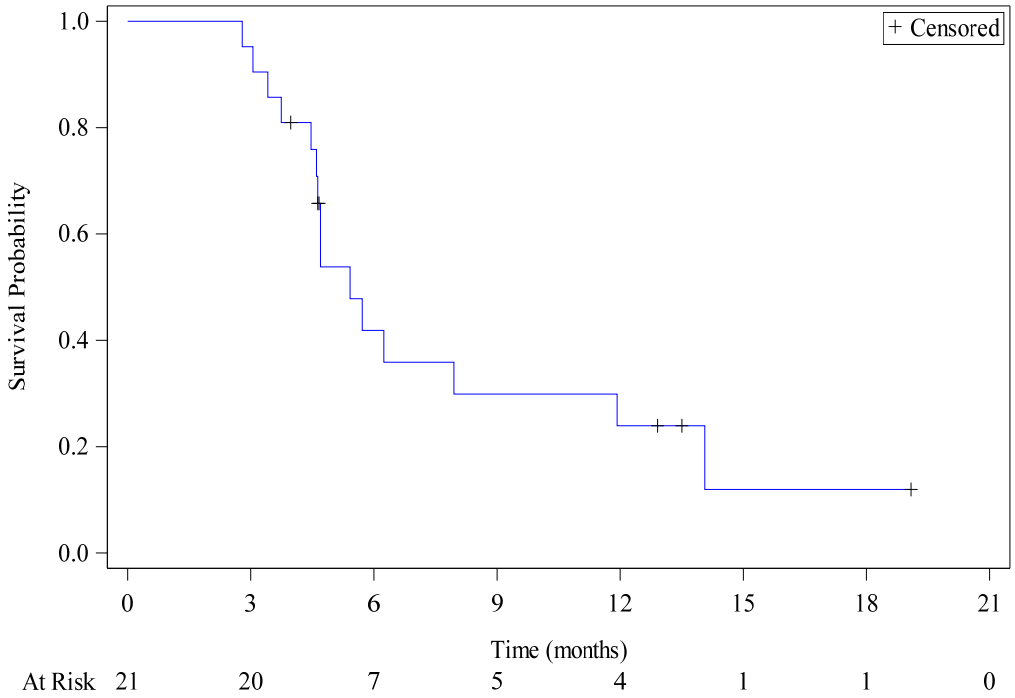
Efficacy of QD Dosing

	All treated N=48
Objective Response Rate (ORR)[1]	**21 (43.8%)**
95% confidence interval	**(29.5, 58.8)**
Responses, n	
Complete response	1 (2.1%)
Partial response	20 (41.7%)
Stable disease	15 (31.3%)
Progressive disease	7 (14.6%)
Not evaluable	5 (10.4%)
Disease Control Rate (DCR), n	36 (75.0%)
ORR including unconfirmed response[2], n	23 (47.9%)
95% confidence interval	(33.3, 62.8)

[1]By RECIST v1.1; [2]Two additional response not confirmed by subsequent imaging in ≥4 weeks

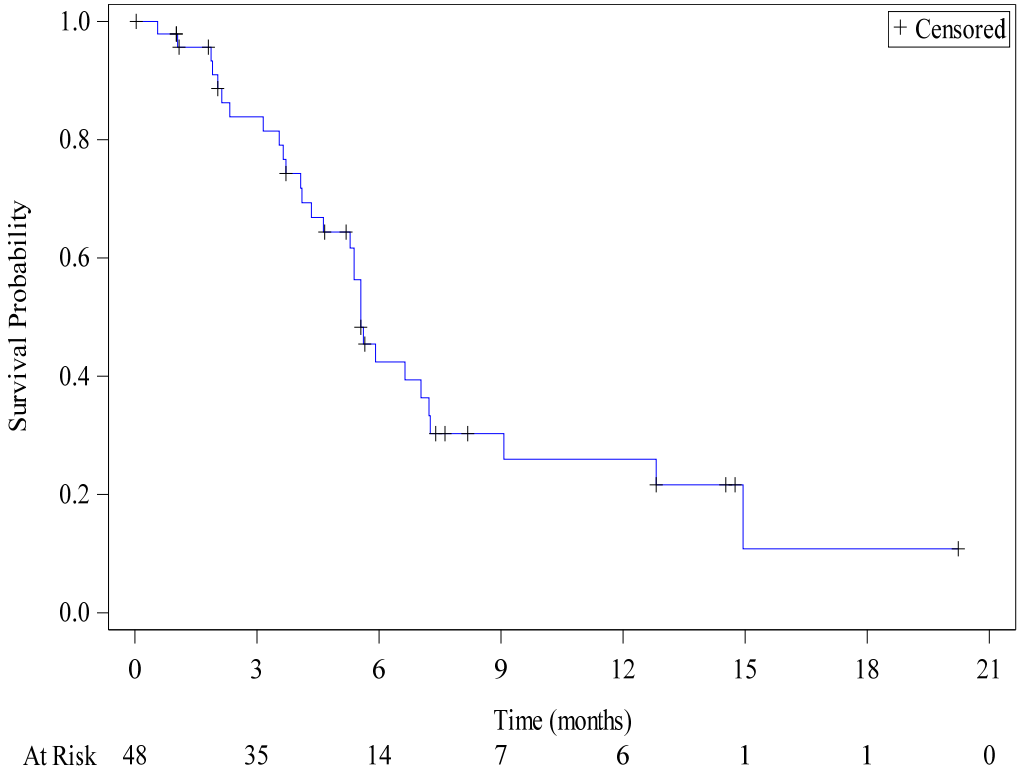
Duration of Response (DoR)

Median DoR (months) (range)	5.4 (2.8, >19.1)
Median follow up of response (months)	13.5
Response duration	
>6 months	42%
>12 months	24%



Progression-free-survival (PFS)

Median PFS (months) (range)	5.6 (0, >20.2)
PFS duration	
>6 months	42%
>12 months	26%



Exposure and Safety

	N=48
Treatment-related AE	48 (100%)
Treatment-related Serious AE	5 (10%)
Dose interruptions	42 (88%)
Dose reductions	37 (77%)
AE leading to permanent discontinuation	6 (13%)

	Any Grade	Grade 3	Grade 4 / 5
Diarrhea	40 (83)	7 (15)	0
Rash	34 (69)	17 (35)	0
Stomatitis / Mucosal Inflammation	39 (81)	10 (21)	0
Paronychia	22 (46)	4 (8)	0
Pneumonitis	2 (4)	1 (2)	0

Summary and Conclusions

- Poziotinib shows clinically meaningful efficacy for treatment-naïve NSCLC HER2 exon 20 mutations with QD dosing
  - Centrally reviewed confirmed response rate of 44% (unconfirmed 48%)
  - Tumor reduction in 88% of patients
  - Median DOR of 5.4 months with upper range >19.1 months
- Manageable toxicity profile, in line with previous poziotinib studies and other 2nd generation EGFR TKIs
  - Diarrhea and rash are the most common AEs; low rate of pneumonitis (G3 2%, no ≥G4)
- ZENITH20 Cohort 4 is ongoing with patients enrolling at 8 mg BID dosing
  - Improved tolerability and anti-tumor activity with 8 mg BID in Cohort 5 interim analysis[1]

[1]Le, AACR 2021

Acknowledgments

- We thank all the patients and their families
- We thank all the ZENITH20 investigators and the study teams at each participating center
- Authors:

  Cornelissen R; Sun S; Wollner M; Garassino M; Prelaj A; Haura E; Piotrowska Z; Socinski M; Dreiling L; Bhat G; Lebel F; Le X on behalf of ZENITH20 Study Group

2021 ESMO congress

Contacts ESMO

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org