Phase II trial of poziotinib for EGFR and HER2 exon 20 mutant NSCLC

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DISCLOSURES

Advisory Committees – AstraZeneca, Boehringer Ingelheim, Exelixis, Genentech, GSK, Hengrui, Lilly, Novartis, Spectrum, EMD Serono, and Synta
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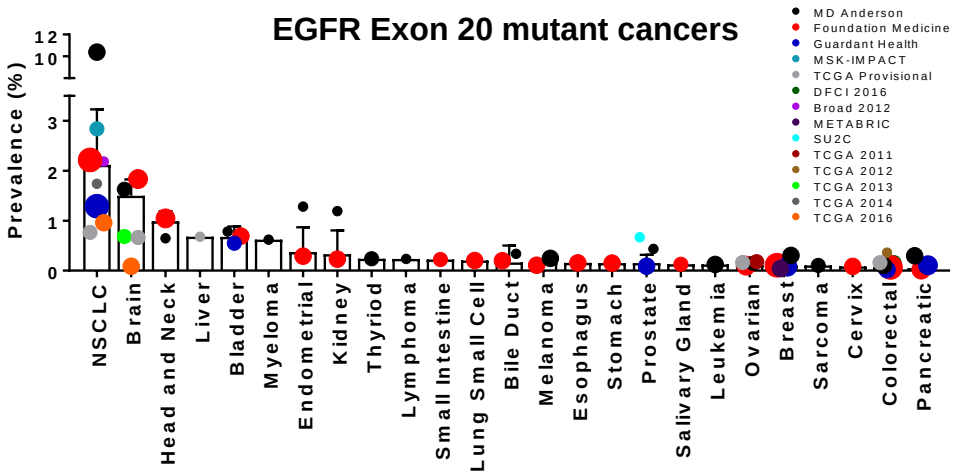
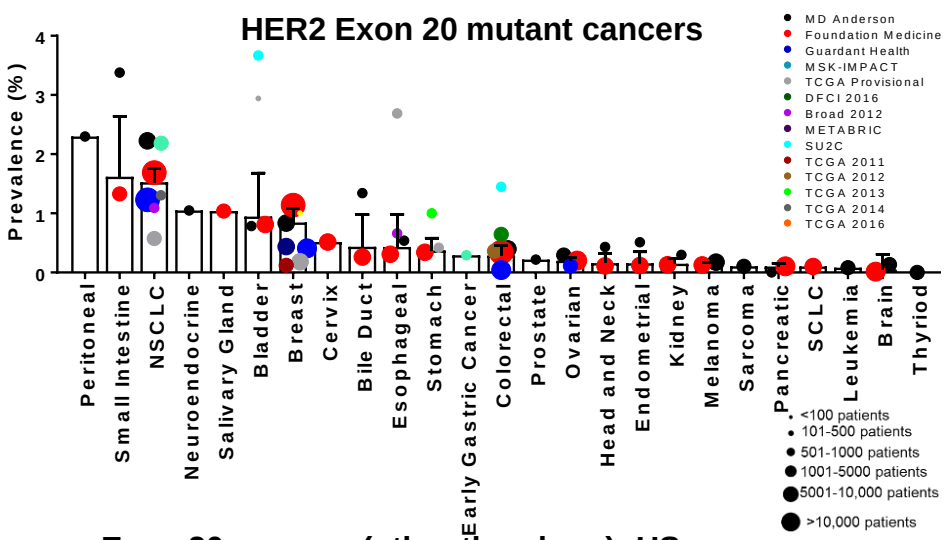
EGFR and HER2 exon 20 mutations occur in NSCLC and many other cancer types (N=390,000 pts)





Exon 20 NSCLC: US and China

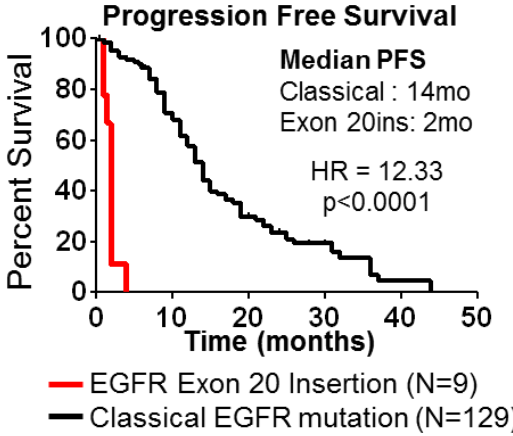
		Exon 20 Frequency	Total Number of NSCLC Patients/year	
United States	EGFR	2.1%	3.6%	7700
	HER2	1.5%		
China	EGFR	2.4%	6.3%	41100
	HER2	3.9%		

Exon 20 cancers (other than lung): US

	Exon 20 frequency (%)	Total Exon 20 patients/year	
EGFR	3710 (0.2%)	0.6%	8400
HER2	4691 (0.4%)		

Patients with EGFR or HER2 exon 20 NSCLC have poor response rates to TKIs

EGFR exon 20			
	N	PR	ORR
Gefitinib/erlotinib	26	0	0%
Gefitinib/erlo* (with 763FQEA)	28	2*	7%
Afatinib	9	1	11%
		1	**3% (w/o 763insFQEA)**
Total for EGFR TKIs	**37**	**3**	**8% (w/ 763insFQEA)**
Luminespib (AUY922)	29	5	17%
HER2 exon 20			
Neratinib	11	0	0%
Afatinib	11	2	18%
Afatinib	6	2	33%
Dacomitinib	26	3	11.5%
Lapatinib	5	0	0%
Total for HER2 TKIs	**59**	**7**	**11.9%**
TDM-1	11	6	55%

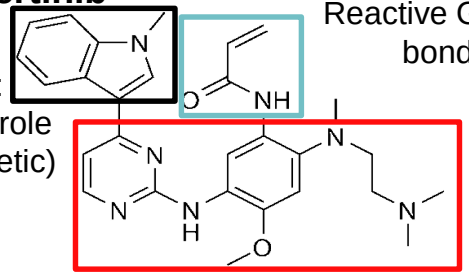


Non-targeted standard 2L therapies	
	ORR%
Docetaxel	9-13%
PD-1/PD-L1 inhibitors	3.6-19%

*both responders were known 763insFQEA. Robichaux *et al* 2018 Nat Med; Piotrowska JTOsupp 12:11S2, 2017; Kris et al, Ann Oncol 2015; Li et al, JCO 2018; Mazieres et al, Ann Oncol 2015; Peters et al, JTO 2018; Hyman et al, Nature 2018; Gainor CCR 2016; Borghaei NEJM 2015; Hanna JCO 2004; Herbst Lancet 2016; Rittmeyer Lancet 2017

The size and shape of poziotinib overcome the hindered binding pocket

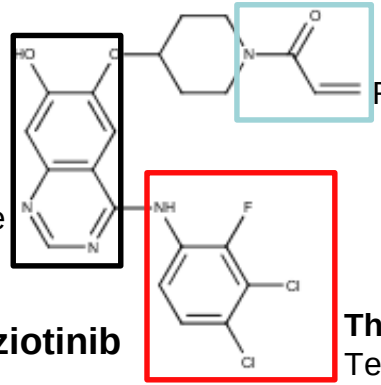
Osimertinib



The body: Benzo-pyrrole (ATP mimetic)

The Arm: Reactive Group (covalent bond to C797)

The feet: Terminal group



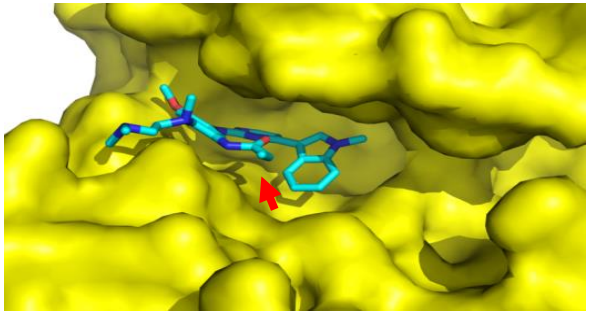
The body: Quinazoline Core (ATP mimetic)

The Arm: Reactive Group (covalent bond to C797)

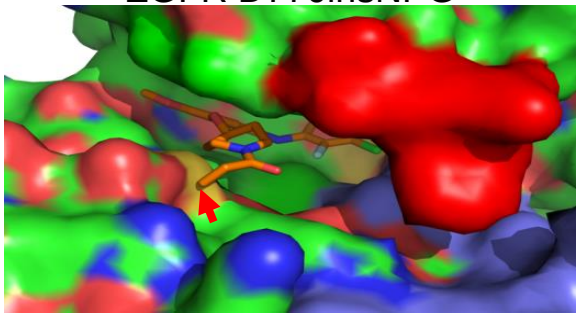
Poziotinib

The feet: Terminal group

EGFR T790M



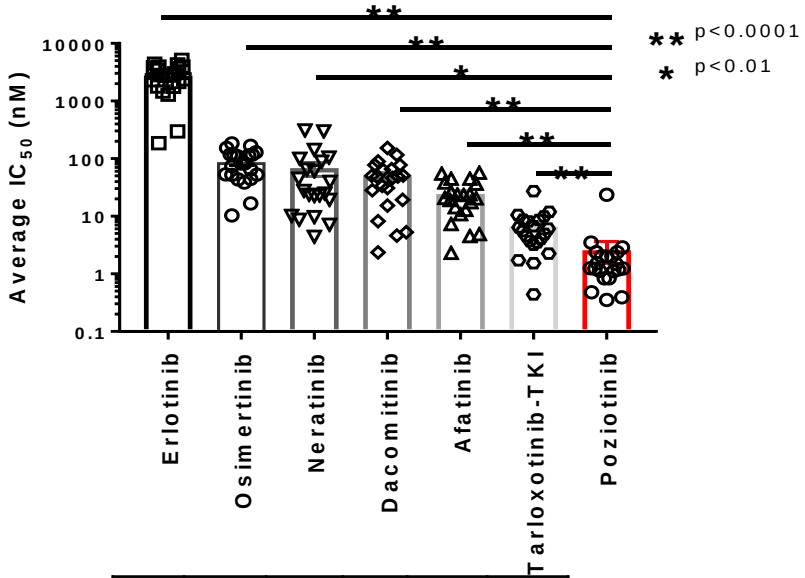
EGFR D770insNPG



Robichaux *et al* 2018 Nature Medicine

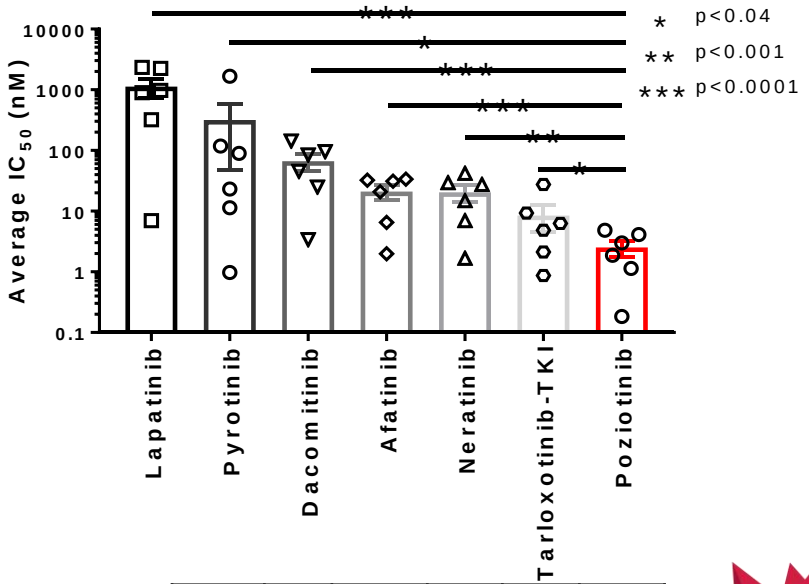
Poziotinib is a potent inhibitor of EGFR and HER2 exon 20 mutations *in vitro*

Ba/F3 EGFR Exon 20
(N=20 cell lines)



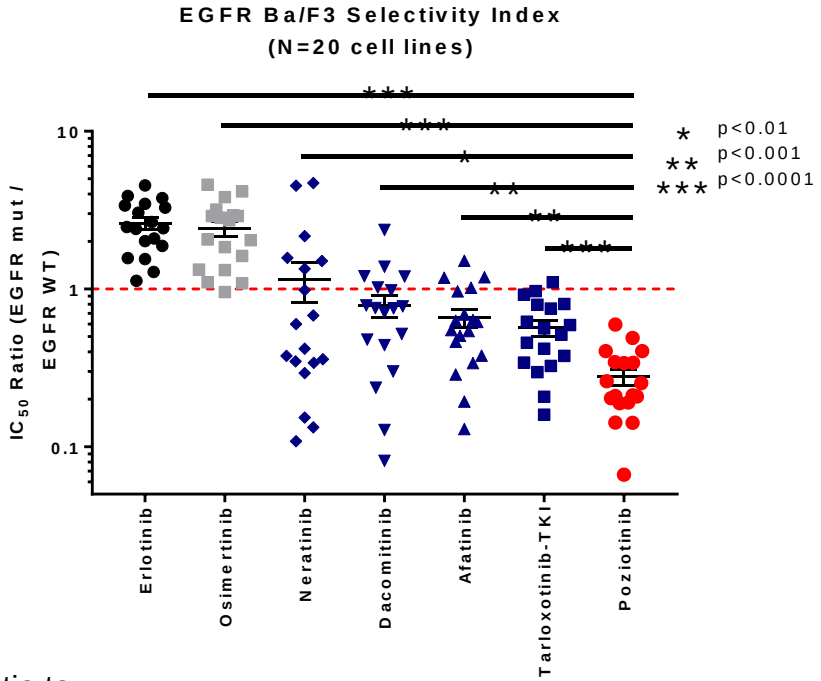
Ratio IC_{50} to Poziotinib	1075	34.8	27.3	19.7	9.7	2.7

Ba/F3 HER2 Exon 20
(N=6 cell lines)

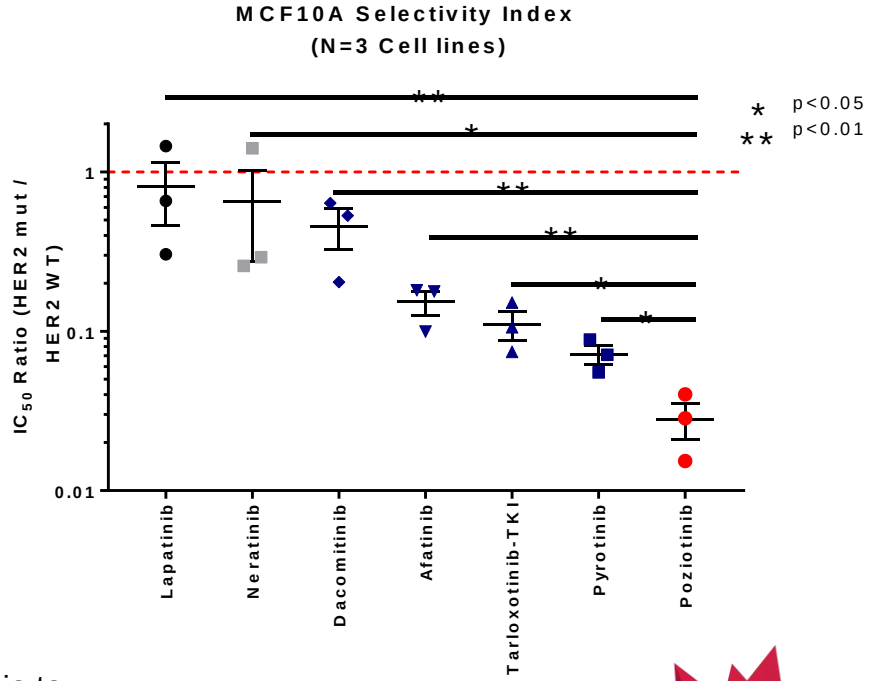


Ratio IC_{50} to Poziotinib	452	127	26.5	8.4	8.2	3.4

Poziotinib is a selective (mut vs wt) inhibitor of EGFR and HER2 exon 20 mutations *in vitro*



Ratio to Poziotinib	9.4	8.7	4.1	2.8	2.4	2.0



Ratio to Poziotinib	28.7	23.3	16.3	5.4	4.0	2.6

Phase 2 trial design

Design: Investigator-initiated, open label 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). Target ORR ≥20%.

Secondary objectives: PFS, OS, disease control rate, duration of response, safety and toxicity

Eligibility:
1. EGFR or HER2 exon 20 insertion or point mutation excluding acquired T790M
2. One or more prior systemic therapy (amended to include treatment-naïve patients).
3. Brain metastases permitted if asymptomatic and stable, without escalating steroids or anticonvulsants.

Treatment: 16 mg PO QD, dose reductions to 12mg and 8mg allowed

Patient Characteristics

	EGFR cohort	HER2 cohort
Characteristics*	**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)
Brain metastases	14 (28%)	4 (31%)
Mutation type		
Exon 20 insertion n (%)	46 (92%)	13 (100%)
Exon 20 point mutation	4 (8%)	0 (0%)
Prior systemic therapy		
Naïve	3 (6%)	2 (15%)
1 prior	13 (26%)	6 (46%)
2 prior	17 (34%)	2 (15%)
3 prior	11 (22%)	1 (8%)
≥4 prior	6 (12%)	2 (15%)
Prior platinum n (%)	43 (86%)	10 (77%)
Prior TKI n (%)	17 (34%)	2 (15%)
Prior PD1/PDL1 inhibitor n (%)	27 (54%)	8 (62%)

*From 8 different countries.

Safety Summary (N=63)

All Cause AE N(%)	N (%)
Grade 3-4	50 (79%)
Grade 5	12 (19%)
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%)**

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

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

- 59 YOF with 3 prior lines of treatment including RT, chemo, pembro, ipi/nivo presented with dyspnea and PD; ddx included lymphangitic spread, infection, vs pneumonitis. It was refractory to steroids and antibiotics. Outside treating physician attributed it as “possibly related” to drug vs PD.

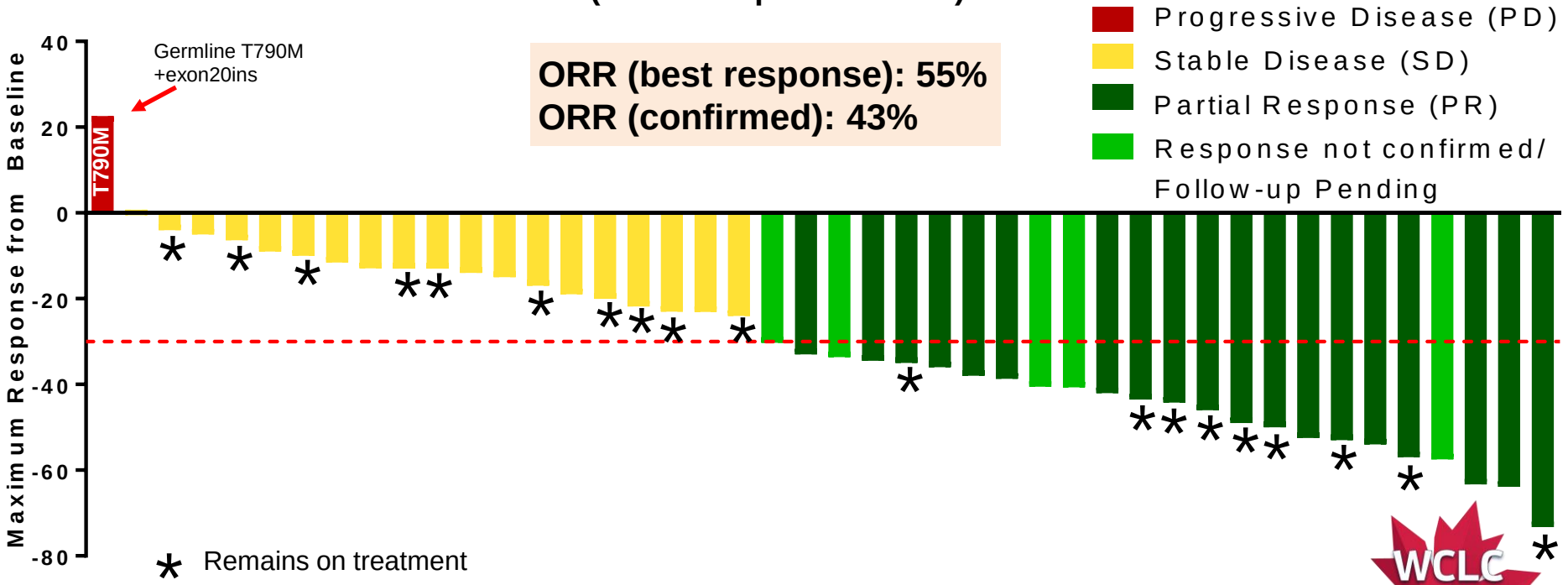
Sequist et al, JCO 2013; Wu et al, Lancet Oncol 2017

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

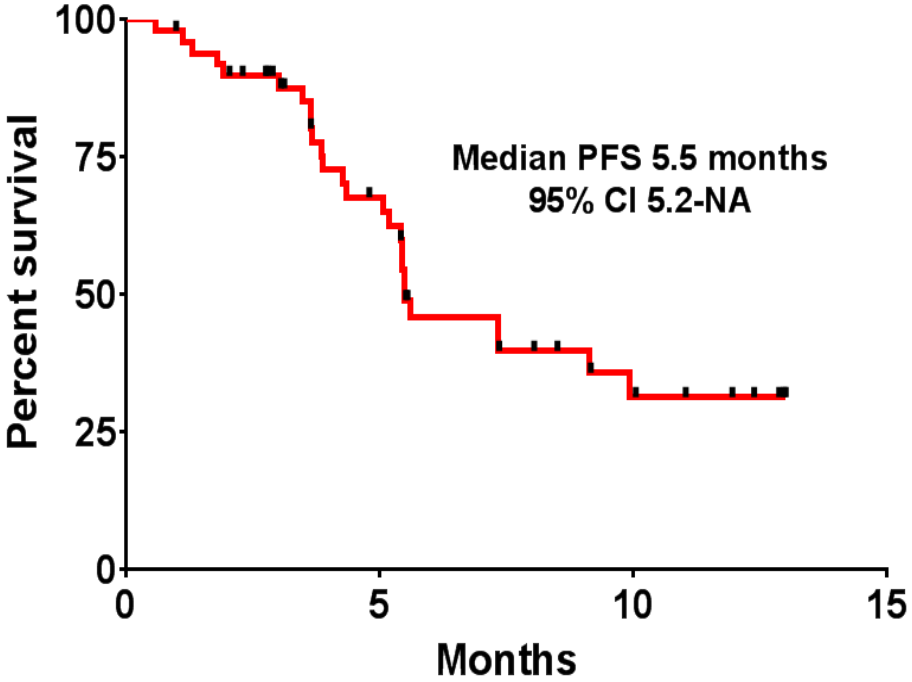
AE	All Grade N (%)	Grade 3-4 N(%)	Grade 5 N(%)
Diarrhea	44 (69.8%)	11 (17.5%)	-
Oral mucositis	44 (69.8%)	1 (1.6%)	-
Paronychia	38 (60.3%)	6 (9.5%)	-
Dry skin	37 (58.7%)	-	-
Skin rash	35 (55.6%)	22 (34.9%)	-
Alopecia	22 (34.9%)	-	-
Anorexia	19 (30.2%)	-	-
Nausea	15 (23.8%)	5 (7.9%)	-
Vomiting	13 (20.6%)	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%)	-
Hypokalemia	5 (7.9%)	2 (3.2%)	-

Poziotinib efficacy in EGFR Exon 20 mutant NSCLC

(Evaluable patients n=44)

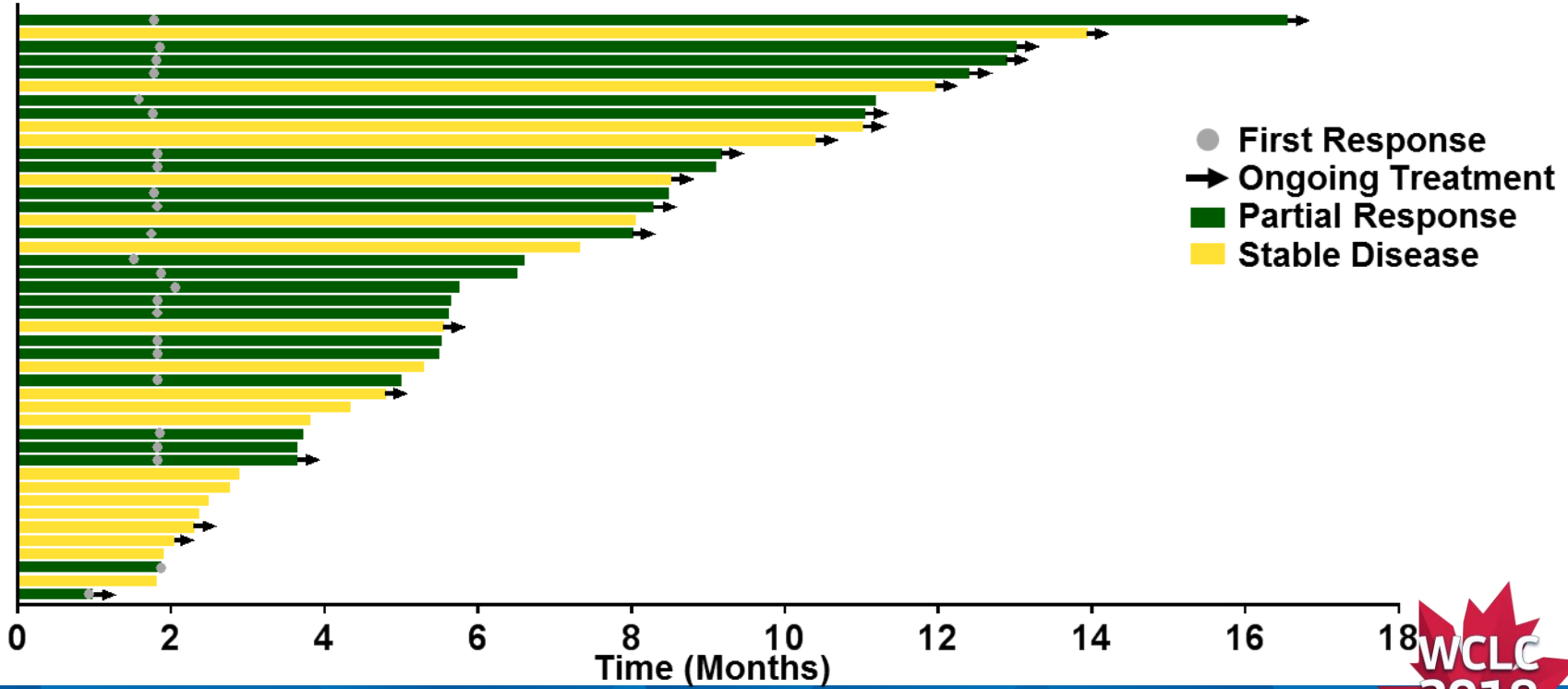


Progression Free Survival (ITT population)



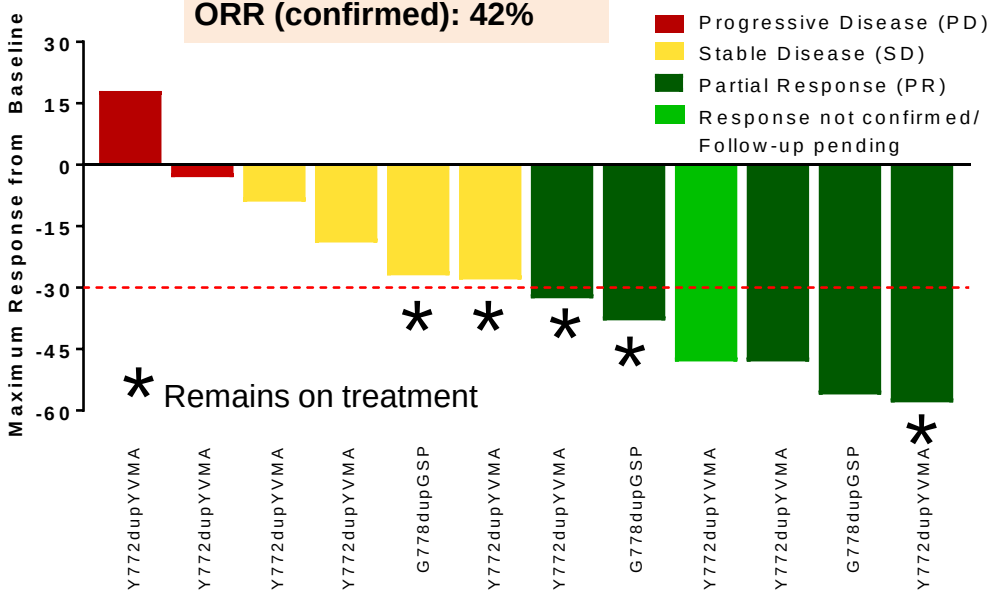
*19 patients remain on treatment as of data cutoff 9/12/2018

Duration of treatment: EGFR cohort

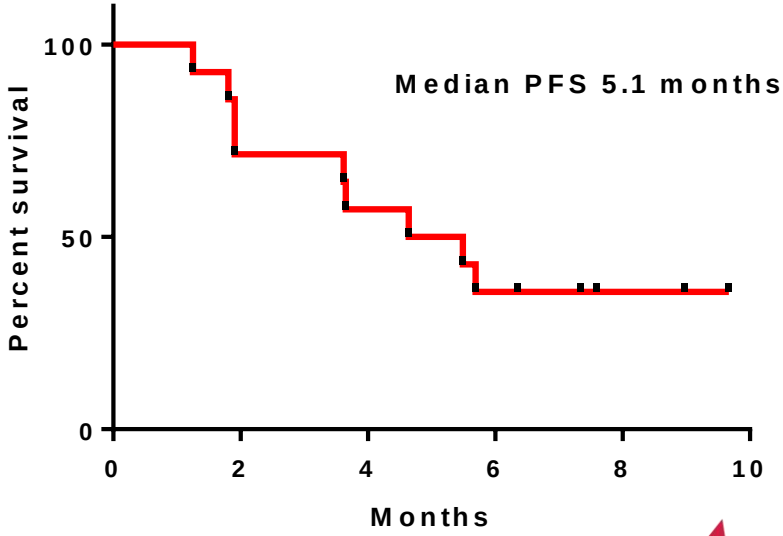


Poziotinib efficacy in HER2 Exon 20 insertion mutant NSCLC

12 evaluable patients
ORR (best response): 50%
ORR (confirmed): 42%



Progression-free Survival HER2 (All patients n=13)



Conclusions

1. This phase II study demonstrates high anti-tumor activity for poziotinib in metastatic, heavily pretreated EGFR exon 20 mutant NSCLC, a group for which no targeted agents have proven effective to date* with best response of PR in 55% of evaluable patients (43% confirmed ORR to date; 19 patients remain on treatment).

   -Median PFS 5.5m; durable responses observed with 6 treated for >1year thus far.

   -Compares favorably to historical ORR rates of <8% approved TKIs and <19% for standard of care 2L agents (docetaxel, PD-1/PD-L1 inhibitors).

2. Significant activity also observed in HER2 exon 20-mutant NSCLC with initial responses observed in 50% (6/12) evaluable patients and median PFS 5.1m.

3. EGFR-related toxicities (including rash, diarrhea, & paronychia) were manageable and required dose reductions in 60%. Discontinuation due to poor tolerance was rare (3%).

4. 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 separate pan-tumor basket study.

*other than patients bearing T790M or S768I mutations .

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