A phase II, single-arm, efficacy and safety study of Poziotinib (NOV120101) in Korean patients with advanced or metastatic lung adenocarcinoma who have acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors

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INTRODUCTION

- Poziotinib (NOV120101) is an oral, irreversible inhibitor of EGFR, HER2 and HER4.
- Preclinical studies conducted in cell lines and xenograft models of NSCLC revealed that Poziotinib has more potent activity than gefitinib, erlotinib and even afatinib in lung cancer models with activating EGFR mutations or T790M mutation[1].
- A phase I study to investigate the safety and maximum tolerated dose (MTD) of Poziotinib in genetically-unselected patients with advanced solid cancers including NSCLC showed that 14% (7/51) of patients experienced partial response (PR), with the MTD of 24 mg once daily and acceptable toxicity profile (unpublished data), supporting further clinical development of Poziotinib.
- This phase II open-label, single-arm study was conducted to explore the anti-cancer activity and safety of Poziotinib in patients with advanced or metastatic lung adenocarcinoma with activating EGFR mutations, who developed acquired resistance (AR) to EGFR TKIs based on the Jackman criteria[2].
- ClinicalTrial.gov identifier: NCT01718847

METHODS and MATERIALS

- Patients received Poziotinib at a dose of 16 mg once daily in 28-day cycles.
- The primary endpoint was progression-free survival (PFS).
- All tumor responses were evaluated by independent review and, in a supportive manner, by investigator.
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, X-ray, ECGs and LEVF by a multi-gated acquisition scan (MUGA) or echocardiogram.
- EGFR mutation analysis in tumor tissue and blood samples were conducted using Ion Torrent deep-amplicon sequencing and PANAMutyper™ R EGFR kit, respectively.
- MET amplification or overexpression in tumor tissue were assessed by FISH and immunohistochemistry

PATIENTS

- Eligible patients had documented activating *EGFR* mutations and developed AR after treatment with erlotinib or gefitinib based on Jackman criteria.

Table 1. Baseline characteristics (FAS)

Characteristic		
Age (years)	Median (range)	62 (43-84)
Gender	Male	10 (26%)
	Female	29 (74%)
Smoking	Never	30 (77%)
	Former	9 (23%)
	Current	0
Smoking pack year	Median (range)	15 (3.9-47)
ECOG PS	0	6 (15%)
	1	30 (77%)
	2	3 (8%)
The therapy line of previous EGFR TKI	First	27 (69%)
	Second	11 (28%)
	Third	0
	Fourth	1 (3%)
Duration of previous EGFR TKI (months)	Median (range)	13.1 (3.4-33.2)
Best response to previous EGFR TKI	CR	0
	PR	36 (92%)
	SD	3 (8%)

RESULTS

Efficacy

- Between December 2012 and September 2014, 39 patients received at least one dose of Poziotinib with at least one tumor assessment after baseline.

Table 2. Overall summary of efficacy (FAS)

	All (n=39)
Number of PFS events	34 (87%)
Estimated median PFS, months (95% CI)	2.7 (1.8-3.7)
Number of PFS events at week 16	24 (62%)
Estimated PFS at week 16, % (95%CI)	34 (19-49)
Deaths	20 (51%)
Estimated median OS, months (95% CI)	15.0 (9.5-not estimable)
Best response	
CR	0
PR	3 (8%)
SD	17 (44%)
PD	18 (46%)
Not evaluable	1 (3%)
ORR(CR+PR), % (95% CI)	8 (2-21)
DCR(CR+PR+SD), % (95% CI)	51 (35-68)
Estimated median duration of response, months (95% CI)	4.5 (3.7-4.6)
Estimated median duration of disease control, months (95% CI)	3.7 (1.8-3.8)

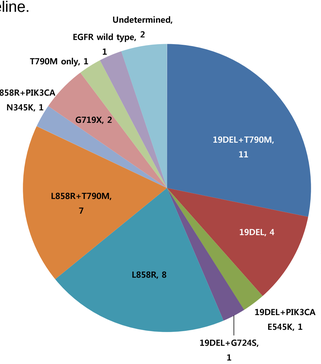
Safety and tolerability

- Most patients required at least one dose reduction ; 15 with one dose reduction; 15 with two dose reductions.
- Two events (one myositis and one rash) led to permanent discontinuation.
- There was no treatment-related death.

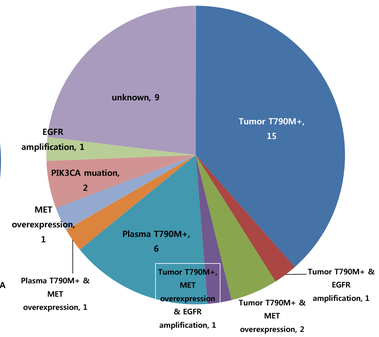
Table 3. All TEAEs by CTCAE grade reported in ≥10% of patients

Preferred Term	Any grade	Grade 1	Grade 2	Grade 3
Total with AEs	39 (100%)	39 (100%)	37 (95%)	37 (95%)
Diarrhoea	36 (92%)	30 (77%)	17 (44%)	4 (10%)
Rash	30 (77%)	14 (36%)	17 (44%)	23 (59%)
Pruritus	25 (64%)	10 (26%)	17 (44%)	2 (5%)
Stomatitis	23 (59%)	11(28%)	13 (33%)	7 (18%)
Paronychia	21 (54%)	8 (21%)	13 (33%)	2 (5%)
Decreased appetite	19 (49%)	12 (31%)	8 (21%)	5 (13%)
Mucosal inflammation	18 (46%)	8 (21%)	9 (23%)	10 (26%)
Dry skin	15 (38%)	8 (21%)	7 (18%)	1 (3%)
Fatigue	12 (31%)	7 (18%)	7 (18%)	1 (3%)
Dyspepsia	8 (21%)	6 (15%)	2 (5%)	0 (0%)
Hypokalaemia	7 (18%)	2 (5%)	2 (5%)	4 (10%)
Alopecia	6 (15%)	6 (15%)	0 (0%)	0 (0%)
Dermatitis acneiform	5 (13%)	2 (5%)	0 (0%)	4 (10%)
Weight decreased	5 (13%)	3 (8%)	2 (5%)	1 (3%)
Skin exfoliation	4 (10%)	3 (8%)	1 (3%)	0 (0%)

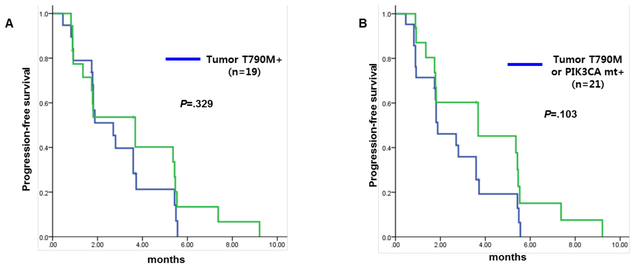
EGFR Mutational status in tumor tissue at baseline



The possible mechanism of AR to prior EGFR-TKIs

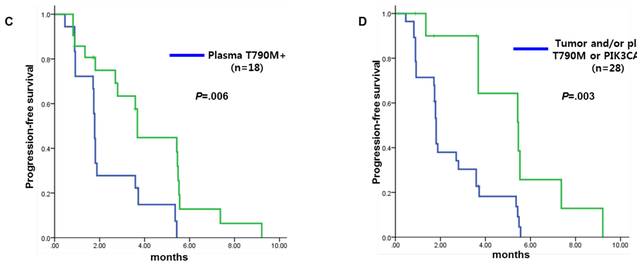


Progression-free survival for patients with EGFR T790M mutation in tumor(A); EGFR T790M or PIK3CA mutation in tumor(B); EGFR T790M mutation in plasma(C); EGFR T790M or PIK3CA mutations in tumor and/or plasma(D)



Tissue	Median PFS (95% CI)
T790M+ (n=19)	2.7 (1.4-4.0) mo
T790M- (n=18)	3.7 (1.3-6.0) mo

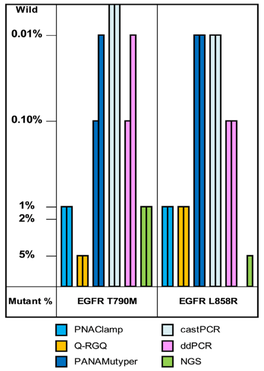
Tissue	Median PFS(95% CI)
T790M+ or PIK3CAmt+ (n=21)	1.9 (0.9-2.9) mo
T790M- and PIK3CAmt- (n=16)	3.7 (0.0-7.7) mo



Plasma	Median PFS (95% CI)
T790M+ (n=18)	1.8 (1.7-1.9) mo
T790M- (n=21)	3.7 (3.5-3.8) mo

Tissue or plasma	Median PFS(95% CI)
T790M+ or PIK3CAmt+ (n=28)	1.8 (1.7-1.9) mo
T790M- and PIK3CAmt- (n=11)	5.5 (3.1-7.8) mo

Performance of T790M mutation in plasma assay



T790M		Tissue			Total
		Positive	Negative	Unknown	
Plasma	Positive	11	6*	1	18
	Negative	8	12	1	21
	Total	19	18	2	39

*** Five out of 6 patients with tissue-/plasma+ showed PD to poziotinib.**

- Concordance: 63 %
- Sensitivity: 58 %
- Specificity: 68 %
- PPV: 65 %
- NPV: 62 %

CONCLUSION

- **Poziotinib showed modest efficacy in patients with EGFR-mutant lung adenocarcinoma who had progressed on erlotinib or gefitinib.**
- **As might be expected, most patients developed AR to prior EGFR-TKIs due to secondary acquisition of EGFR T790M mutations.**
- **These results suggesting that poziotinib may not overcome AR secondary to EGFR T790M mutation in EGFR mutant lung adenocarcinoma.**
- **The exploratory biomarker analysis suggest that plasma T790M assay may be more correlated with clinical benefit with Poziotinib.**
- **In subgroup analysis, noteworthy activity of Poziotinib was observed in patients without T790M or PIK3CA mutations in tumor or plasma.**

REFERENCES

1. Cha et al., Int J Cancer, 2012. 130(10): p.2445-54.
2. Jackman et al., J Clin Oncol, 2010. 28(2): p.357-60.

ACKNOWLEDGMENTS

We would like to thank all of the participating patients and their families, as well as study coordinators of all study sites.
This study was sponsored by National OncoVenture and Hanmi Pharmaceutical Co.,Ltd.

Presented at 2015 ASCO Annual Meeting, Chicago, IL, USA, 29 May-2 June 2015