Abstract # 1048

Phase I study of HM61713, a novel epidermal growth factor receptor (EGFR) mutant selective inhibitor, in non-small cell lung cancer (NSCLC) patients having an activating EGFR mutation but failed to prior EGFR tyrosine kinase inhibitor (TKI) therapy

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Background

- NSCLC patients having an activating EGFR mutation initially responded well to EGFR TKI but most of them experienced progressive disease due to various resistance mechanisms including T790M (~50% of cases) mutation[1,2,3,4]
- Disease progression occurs after 9-14 months of EGFR TKIs, generally[5]
- HM61713 is an orally active, novel EGFR mutant selective inhibitor showing an anti-cancer activity in several EGFR mutant lung cancer cell lines including T790M mutation harboring cell line
- Therefore, HM61713 might provide the potential clinical benefit to those who have an activating EGFR mutation but have failed previous EGFR TKI treatment

Preclinical data

- HM61713 is an orally active, novel EGFR mutant selective inhibitor showed a strong anti-cancer activity in several EGFR mutant lung cancer cell lines including T790M mutation harboring cell line
- Lower activity to EGFR WT cell suggests the possibility of reduction of adverse effects from high selectivity to EGFR mutant form

Figure 1. Response in *H1975 Xenograft study

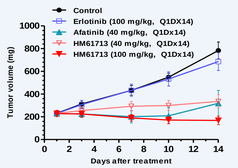


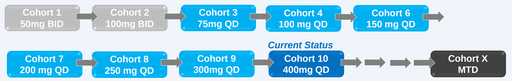
Table 1. *In vitro* growth inhibition in NSCLC

	Inhibition concentration (IC_{50}, nM)		
	H358	HCC827	H1975
	EGFR WT	$EGFR^{exon\ 19\ del}$	$EGFR^{L858R/T790M}$
Erlotinib	449	3.2	2,253
Afatinib	31	1.8	53
HM61713	2,225	9.2	10

*H1975 – Human NSCLC cell line harboring T790M and L858R mutations

Study design

- Objectives
  - Primary : Safety and tolerability
  - Secondary : Preliminary efficacy, PK of HM61713 and metabolites
  - Exploratory : Biomarker study
- Dose escalation study (3+3 dose escalation scheme, Tissue biopsy is not mandatory)



- Expansion study (Two arms, 30 pts/arm, Tissue biopsy is mandatory)

Arm A : 300mg QD
Failure of previous TKIs within 4 weeks

Arm B : 300mg QD
Failure of previous TKIs before 4 weeks or more

- Key inclusion criteria
  - Histological or cytological confirmation of NSCLC
  - EGFR mutation
  - 20+ years, ECOG 0-2
  - Dose escalation : Two or more prior chemotherapies including EGFR TKI
  - Expansion : One prior EGFR TKI , other lines of chemotherapy may have been given
    - Arm A : Failure of previous TKI within 4 weeks
    - Arm B : Failure of previous TKI before 4 weeks or more
- Key exclusion criteria
  - Active/symptomatic CNS metastases

Demography

- A total of 29 patients were enrolled (median age : 58 years [range 43-81])
- Most of patients treated with gefitinib (86.2%) previously
- Data were cut off at 12-Aug-2013

Table 2. Patient demographics and characteristics (N=29, NSCLC)

	No. (%)
Median Age (Range)	58 (43-81) yrs
Male	6 (20.7)
Female	23 (79.3)
ECOG	
0	3 (10.3)
1	24 (82.8)
2	2 (6.9)

	No. (%)
*Previous Chemotherapies	
2 regimens	10 (34.5)
3 regimens	7 (24.1)
4 regimens or more	12 (41.4)
Previous EGFR TKIs	
Gefitinib	25 (86.2)
Erlotinib	4 (13.8)
Afatinib	3 (10.3)

*Previous chemotherapies include EGFR TKIs

Safety

- 23 of 29 patients experienced drug related AEs, and most were Grade 1 or 2

Table 3. Adverse events related to study drug (≥5% of pts)

Adverse Event	N=29				
	Gr1 n(%)	Gr2 n(%)	Gr3 n(%)	Gr4 n(%)	Total n(%)
Skin exfoliation	11(37.93%)	1(3.45%)	-	-	12(41.38%)
Diarrhea	8(27.59%)	-	-	-	8(27.59%)
Rash	7(24.14%)	1(3.45%)	-	-	8(27.59%)
Nausea	6(20.69%)	1(3.45%)	-	-	7(24.14%)
Pruritus	3(10.34%)	3(10.34%)	-	-	6(20.69%)
↓ Appetite	3(10.34%)	1(3.45%)	1(3.45%)	-	5(17.24%)
Skin fissures	3(10.34%)	-	-	-	3(10.34%)
Abdominal pain	2(6.90%)	1(3.45%)	-	-	3(10.34%)
Anaemia	0(0.00%)	3(10.34%)	-	-	3(10.34%)
↑ALT	1(3.45%)	-	1(3.45%)	-	2(6.90%)
Alopecia	2(6.90%)	-	-	-	2(6.90%)
↑AST	1(3.45%)	-	1(3.45%)	-	2(6.90%)
Asthenia	2(6.90%)	-	-	-	2(6.90%)
Dermatitis acneiform	2(6.90%)	-	-	-	2(6.90%)
Dry mouth	2(6.90%)	-	-	-	2(6.90%)
Dry skin	2(6.90%)	-	-	-	2(6.90%)
Dyspepsia	2(6.90%)	-	-	-	2(6.90%)
Fatigue	1(3.45%)	1(3.45%)	-	-	2(6.90%)
Headache	1(3.45%)	1(3.45%)	-	-	2(6.90%)
Decreased Neutrophil count	-	2(6.90%)	-	-	2(6.90%)
Pyrexia	2(6.90%)	-	-	-	2(6.90%)
Stomatitis	1(3.45%)	1(3.45%)	-	-	2(6.90%)
Urticaria	-	2(6.90%)	-	-	2(6.90%)
Vomiting	2(6.90%)	-	-	-	2(6.90%)

Table 4. Adverse events related to study drug (Grade 3 or 4)

Adverse Event	N=29	
	Gr3 n(%)	Gr4 n(%)
*Drug induced idiosyncrasy	1(3.45%)	-
†↓ Appetite	1(3.45%)	-
‡↑Blood amylase	1(3.45%)	-
‡↑AST, ALT	1(3.45%)	-
‡↑ Lipase	-	1(3.45%)

* DLT (100mg bid) – Grade 3 drug induced idiosyncracy
Dypsnea and skin rash were occurred after 11 days of treatment
The symptoms were transient and improved after steroid treatment and supportive care
The events were judged as drug induced idiosyncracy by investigator

† Grade 3 decreased appetite (150mg qd)
Decreased appetite occurred at cycle 7
The events were judged by investigator not to be clinically significant or dose-limiting

‡ DLT (300mg qd) – Grade 3 increase of blood amylase, AST, ALT and Grade 4 increase of Lipase
These events were occurred after 10 days of treatment
These events may resulted from inflammation of pancreas or cholangitis
However, this case was determined as DLT
because it is hard to exclude the relationship of drug and these events

Pharmacokinetics

- PK exposures were dose-dependent
- Terminal half-lives ranged 8.2-11.3 hr
- Based on this PK results, dosing schedule was changed from twice daily to once daily

Figure 2. Mean plasma concentration (Day 1)

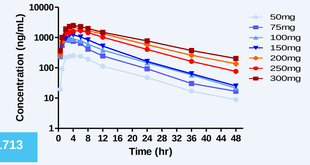


Table 5. Pharmacokinetic parameters of HM61713

Dose	50mg (n=3)	75mg (n=4)	100mg (n=6)	150mg (n=3)	200mg (n=3)	250mg (n=4)	300mg (n=6)
$AUC_{0\text{-}48hr}$ (ng*hr/ml)	3,574 ± 1,028	9,105 ± 6,460	12,322 ± 6,836	15,537 ± 10,183	36,618 ± 24,982	28339 ± 17556	42,198 ± 22,473
C_{max} (ng/ml)	267 ± 74	845 ± 673	932 ± 439	1226 ± 729	2565 ± 901	2043 ± 645	2432 ± 1092
T_{max} (hr) (median)	4.0	2.0	3.0	3.9	3.0	4.0	4.0
Half life (hr)	11.3 ± 1.2	8.2 ± 0.8	9.0 ± 1.4	8.6 ± 2.1	9.4 ± 2.2	8.6 ± 2.5	11.3 ± 1.3

Clinical activity

- 4 patients achieved PR and 2 of 4 PR patients harbored T790M
- *T790M status of 2 PR patients was unknown
- 3 PR cases were confirmed and 1 patient is awaiting confirmation
- All 4 patients had PR did not experienced Grade 3 or 4 drug related AEs

Figure 3. Best % change of tumor volume

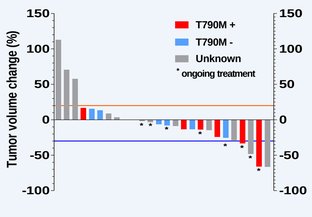
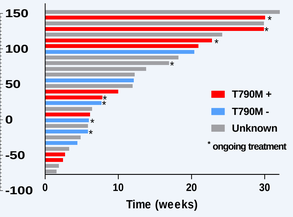


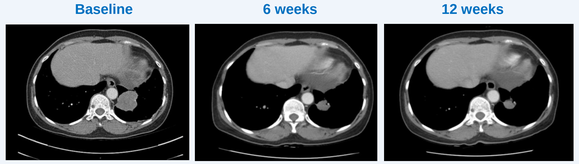
Figure 4. Duration of treatment



*T790M status was analyzed by PNAclamp™ method
PNAclamp™ : PNA(Peptide nucleic acid)-mediated clamping technology based on real time PCR with high sensitivity from small amount of clinical DNA samples

T790M Positive (N=8) : Proven T790M in tissue or blood sample
T790M Negative (N=6) : T790M not detected in tissue or blood after screening
Unknown (N=15) : Absence of tissue sample after screening
Tissue biopsy was not mandatory in dose escalation cohorts

Figure 5. Clinical response



- Patient with *T790M and L858R
- Treated with HM61713 200 mg QD
- Patient had prior 5 lines of chemotherapy including elotinib and BIBW2992
- PR has been maintaining until 30 weeks, currently ongoing
- -66.0% of size reduction from baseline

*T790M mutation was detected from blood sample at study entry

Dose escalation status

- PR was observed at 100mg qd or more
- The regimen was changed to once daily after PK analysis
- MTD is not defined yet, cohort with 400 mg qd is ongoing, currently
- The expansion cohort (300 mg qd, 60 patients) is ongoing with mandatory tissue biopsy for confirmation of efficacy in patients with T790M mutation

Table 6. Dose escalation status

Dose (mg)	50 bid	100 bid	75 qd	100 qd	150 qd	200 qd	250 qd	300 qd	Total
Enrolled pts	3	3	3	4	3	3	4	6	29
Efficacy Evaluable pts	3	3	2	4	3	2	4	5	26
Ongoing	-	-	-	-	2	1	2	3	8
PR	-	-	-	1	-	1	1	1	4

Table 7. Tumor responses

Response	Total (N=26)	100mg or more (N=18)
PR	4 (15.4%)	4 (22.2%)
PR+SD	19 (73.1%)	16 (88.9%)
Median PFS (weeks)	12.0 (95% CI, 6.1,23.9)	12.0 (95% CI, 6.1-36.0)

Conclusion

- To date, HM61713 has been well tolerated with promising anti-cancer activity in NSCLC patients with EGFR mutation who failed to prior EGFR TKI therapy
- HM61713 showed tumor shrinkage in T790M+ NSCLC patients
- These results support the therapeutic potential of HM61713 for NSCLC patients with activating EGFR mutations after development of resistance to EGFR TKI therapy
- Currently, dose escalation cohort with the dose of 400 mg and expansion cohorts with the dose of 300 mg are ongoing

References

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Acknowledgement

- We would like to thank all of the participating patients and their families, as well as study coordinators of the all study sites.
- Study sites participated;
  Seoul National University Hospital, Asan Medical center,
  National Cancer Center, Samsung Medical Center,
  Seoul National University Bundang Hospital,
  Seoul St. Mary's Hospital, Severance Hospital
- This study was sponsored by Hanmi Pharmaceutical.
  Clinical Trial.gov identifier : NCT01588145