First-in-human study of HM95573, a novel oral RAF inhibitor, in patients with solid tumors

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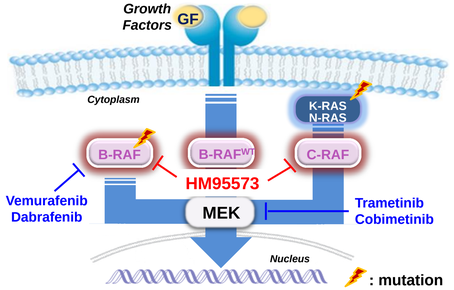
INTRODUCTION



- The RAF kinase is a key component of the MAPK signaling pathway that regulates cell proliferation and survival in various tissues.[1]
- HM95573 is a novel and selective RAF kinase inhibitor toward BRAF mutant and CRAF kinase.[2]
- HM95573 showed potent anti-tumor activity in BRAF, KRAS and NRAS mutant model *in vitro* and *in vivo*. Furthermore, HM95573 did not show a potential to paradoxical activation inducing tumor growth in mouse xenograft study using A431 cuSCC (cutaneous squamous cell carcinoma) cancer cell.[3]
- This phase 1 trial evaluates the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of HM95573 in patients with solid tumors (NCT02405065).
- Data included here are preliminary and cut off date is 31 March 2016.

STUDY DESIGN

Table 1. Objectives and Key Inclusion and Exclusion Criteria

Objectives
▪ Primary: To determine MTD and recommended phase 2 dose ▪ Secondary: Preliminary efficacy & PK ▪ Exploratory: Biomarker study & Pharmacogenetics

Key Inclusion and Exclusion Criteria	
▪ **Inclusion Criteria**	▪ **Exclusion Criteria**
Solid tumor harboring BRAF, NRAS or KRAS mutation Aged ≥ 19 years / ECOG 0-2	Symptomatic or uncontrolled CNS or brain metastasis

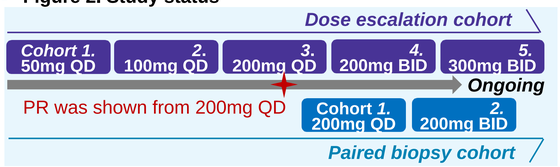
Figure 1. Study design

Dose escalation Cohorts		Expansion Cohorts
≥Initial Response Dose or MTD or RP2D		Tumor types for which the efficacy of HM95573 is shown in Dose escalation cohorts
Part A2	• Modified Fibonacci Scheme • Rolling Six Design	
Part A1	• PK-guided Rapid Escalation	

Paired Biopsy Cohorts (optional)

From 200mg QD which has shown tumor response in dose escalation.

Figure 2. Study status



RESULTS

Table 2. Baseline characteristics (n=35)

	No. (%)		No. (%)
Median age (range)	58 yrs (38-74)	**Gender**	
		Male	23 (66)
		Female	12 (34)
ECOG PS		**Mutation**	
0	12 (34)	*BRAF*	16 (46)
1	22 (63)	*KRAS*	14 (40)
2	1 (3)	*NRAS*	5 (14)
No. of Prior anticancer therapy		**Type of Cancer**	
0	3 (9)*	Colorectum	22 (62)
1	10 (29)	Melanoma	9 (26)
2	11 (31)	Lung	1 (3)
3	7 (20)	GIST	1 (3)
≥ 4	4 (11)	Bladder	1 (3)
		Sarcoma	1 (3)

* 3 naïve patients have melanoma.

Table 3. Best overall response (n=33)

Response	N (%)
PR	4 (12)
SD	12 (36)
PD	17 (52)

4 PRs

200mg QD: NRASm melanoma
200mg BID: NRASm melanoma, BRAFm GIST
300mg BID: BRAFm melanoma

- Tumor assessment was performed every 6 weeks.

Figure 3. Best tumor change from baseline in target lesion

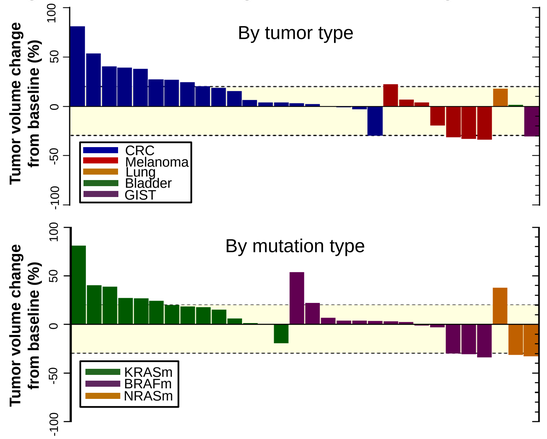


Figure 4. Duration of treatment and best overall response

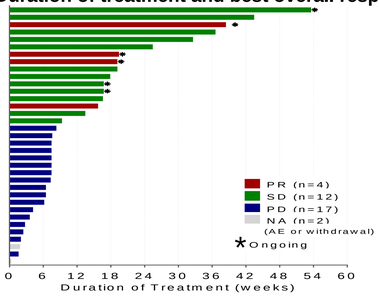
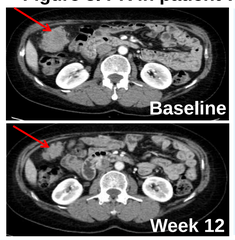


Figure 5. PR in patient with BRAFm(V600E) melanoma



- 52yrs/Female
- Vemurafenib treatment (Apr.2012- Oct.2015) : radiologic CR → PD
- Enrolled in this trial at acquired resistance with multiple metastases
- Best tumor volume change from baseline: -33.8%
- Dose: 300mg BID

Figure 6. $AUC_{24hr,ss}$ and $C_{max,ss}$ after continuous dosing

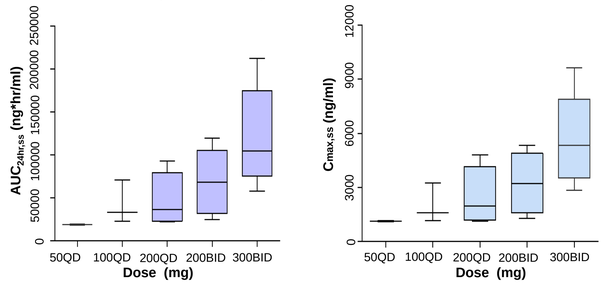


Table 4. Adverse events related to the IP in ≥ 5% of patients

ADR	G1	G2	G3	G4 or 5	Total
Rash	9	1	1	-	11 (31%)
Pruritus	4	-	-	-	4 (11%)
Nausea	3	-	-	-	3 (9%)
ALT increased	-	2	-	-	2 (6%)
ECG QT prolonged	1	-	1	-	2 (6%)
Decreased appetite	1	1	-	-	2 (6%)
Fatigue	1	1	-	-	2 (6%)

Dose limiting toxicity (DLT)

Only one DLT (grade 3 skin rash) was reported at 200mg BID. G3 Skin rash was recovered to G1 after 13 days of IP discontinuation.

SUMMARY

- The MTD was not reached so far and dose escalation is currently ongoing
- Most of ADRs were G1 or G2, except 2 cases (One G3 rash and one G3 QT prolonged)
- Drug exposure is continuously increasing as per HM95573 dose level
- Among 33 patients who are evaluable for tumor response, 4 patients experienced PR (including 1 confirmed PR) and 12 patients had SD

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2. YM. Lee et al., Cancer Res., 2015; 75(15 Suppl): Abstract #2607
3. R. Kudchadkar, K. Smalley et al., Clin Dermatol., 2013; 31; 200

Poster Presented at 2016 ASCO Annual Meeting, Chicago, IL, USA, 3 June - 7 June 2016

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