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Promising efficacy as combination therapy of DFP-14323, protease inhibitor, with *EGFR*-TKI in patients with metastatic NSCLC harboring *EGFR* mutation.

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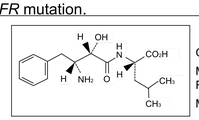
Background

DFP-14323(INN: Ubenimex) is protease inhibitor of aminopeptidase N (also called CD13), originated from *Streptomyces olivoreticuli* have been used for maintenance therapy of AML in Japan. Aminopeptidase N is well known as one of prognostic factors for several cancer patients, including non-small-cell lung cancer (NSCLC). Otherwise, afatinib is one of the standard treatments in non-small-cell lung cancer (NSCLC) patients with *EGFR* mutation, but the toxicities often require dose adjustment. Recently, it is suggested that reducing afatinib doses can decrease treatment-related adverse events without affecting efficacy. We aimed to examine efficacy of DFP-14323 with low-dose afatinib by conducting phase II study in patients with metastatic NSCLC harboring *EGFR* mutation.

What's DFP-14323 ?

- ✓ The same active ingredient as bestatin with the indication of "extension of survival by combination with maintenance-enhancing chemotherapy after induction of complete remission for adult acute non-lymphocytic leukemia".
- ✓ DFP-14323 is a drug confirmed to be bioequivalent to bestatin capsules. In development to obtain new indication in this clinical trial.
- ✓ It binds to aminopeptidase N (CD13) present on the surface of immunocompetent cells and exhibits a nonspecific immunostimulatory action.
- ✓ In vitro, the activation and growth inhibitory effects of caspase 3 (single and combined) on cancer cell lines have been confirmed.
- ✓ It has been observed in vitro that it promotes differentiation of bone marrow cells, enhances induction of macrophages and T cells, and enhances cytokine production.



Generic Name	:	Ubenimex
Molecular Formulation	:	C16H24N2O4
Molecular Wt.	:	308.37

Figure 1 . Property of DFP-14323

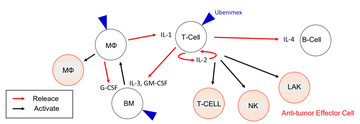


Figure 2 . DFP-14323 MOA

Methods

This study was a multi-center, single-arm, open-label phase II trial. Stage III/IV and treatment-naïve patients with common *EGFR* mutation-positive(L858R or Del19) NSCLC were treated with afatinib at a starting dose of 20 mg/day and DFP-14323 at a fixed dose of 10mg/day until disease progression or intolerable toxicity. Primary endpoint is disease control rate (DCR) defined by sum of CR, PR and SD (RECIST1.1) and secondary endpoints include progression-free survival, overall response rate and safety. A sample size of 26 patients was estimated based on α error of 0.05 (two sided), β error of 0.20, expected DCR 90% and threshold DCR 70% used the Simon's two stage design. From July 2018 to March 2020, 26 patients were enrolled. Data cut-off was July 2020.

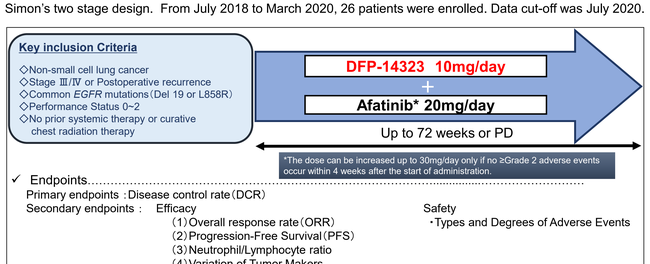


Figure 3 . Study design

Results

Baseline Characteristics		N=26
Gender	Male (%)	5 (19.2)
	Female (%)	21 (80.8)
Age	mean (SD)	72.2 (7.1)
	median (IQR)	72.8 (66.9 — 77.3)
Performance status	0 (%)	10 (38.5)
	1 (%)	16 (61.5)
	2 (%)	0 (0)
Smoking history	Yes (%)	0 (0)
	No (%)	16 (61.5)
	Past (%)	10 (38.5)
Metastases	brain (%)	10 (38.5)
	bone (%)	11 (42.3)
	liver (%)	3 (11.5)
	lymph (%)	7 (26.9)
	other (%)	16 (61.5)
	no (%)	1 (3. 8)
EGFR gene mutation	Del19 (%)	13 (50)
	L858R (%)	13 (50)
	Other (%)	0 (0)
Histological type	adenocarcinoma (%)	25 (96.2)
	large cell carcinoma (%)	0 (0)
	non-small cell lung cancer (%)	1 (3.8)
	other (%)	0 (0)
Stage	III (%)	1 (3.8)
	IV (%)	17 (65.4)
	Postoperative recurrence (%)	8 (30.8)

Table 1. Baseline Characteristics

Median age was 72.8 years. 21 patients (80.8%) were female, and 16 patients (61.5%) were never-smokers. Mutation subtypes were half Del19 and half L858R.

Summary of response	N	%	[95%CI] * clopper-pearson
Patients with measurable lesions	26		
CR: Complete Response	1	3.8	[0.1 - 19.6]
PR: Partial Response	16	61.5	[40.6 - 79.8]
SD: Stable Disease	9	34.6	[17.2 - 55.7]
PD: Progressive Disease	0	0.0	[0.0 - 13.2]
NE: Not Evaluable	0	0.0	[0.0 - 13.2]
DCR: Disease Control Rate	26	100.0	[86.8 - 100.0]
ORR: Objective Response Rate	17	65.4	[44.3 - 82.8]

Table 2. Summary of response

DCR was 100% (26/26) with 1 confirmed CR and 16 patients confirmed PRs .

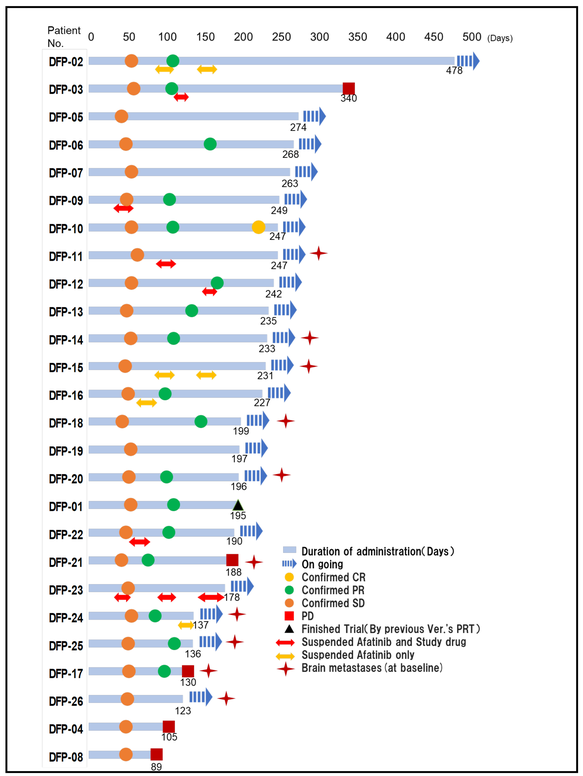


Figure 4 . Swimmer Plot

As of the end of July 2020, the longest Duration of administration is 478 days and the shortest Duration of administration is 89 days.

Adverse Event	All events				Events caused by DFP-14323				Events caused by Afatinib			
	total	Grade1	Grade2	Grade3	total	Grade1	Grade2	Grade3	total	Grade1	Grade2	Grade3
Leukopenia	1(3.8)		1(3.8)						1(3.8)		1(3.8)	
Abdominal discomfort	3(11.5)	2(7.7)	1(3.8)		1(3.8)		1(3.8)		2(7.7)	1(3.8)	1(3.8)	
Cheilitis	3(11.5)	3(11.5)			1(3.8)	1(3.8)			3(11.5)	3(11.5)		
Stomatitis	12(46.2)	10(38.5)	1(3.8)	1(3.8)	1(3.8)	1(3.8)			12(46.2)	10(38.5)	1(3.8)	1(3.8)
Diarrhoea	23(88.5)	18(69.2)	4(15.4)	1(3.8)	3(11.5)	2(7.7)	1(3.8)		22(84.6)	17(65.4)	4(15.4)	1(3.8)
Hepatic function abnormal	2(7.7)	2(7.7)			1(3.8)	1(3.8)			1(3.8)	1(3.8)		
Hepatic enzyme increased	3(11.5)	3(11.5)			1(3.8)	1(3.8)			2(7.7)	2(7.7)		
Weight decreased	6(23.1)	1(3.8)	4(15.4)	1(3.8)					3(11.5)	1(3.8)	2(7.7)	
Decreased appetite	3(11.5)	3(11.5)							3(11.5)	3(11.5)		
Dysgeusia	3(11.5)	2(7.7)	1(3.8)						3(11.5)	2(7.7)	1(3.8)	
Epistaxis	3(11.5)	3(11.5)							3(11.5)	3(11.5)		
Paronychia	17(65.4)	9(34.6)	6(23.1)	2(7.7)					17(65.4)	9(34.6)	6(23.1)	2(7.7)
Dermatitis acneiform	4(15.4)	2(7.7)	1(3.8)	1(3.8)					4(15.4)	2(7.7)	1(3.8)	1(3.8)
Dry skin	11(42.3)	9(34.6)	2(7.7)		1(3.8)	1(3.8)			11(42.3)	9(34.6)	2(7.7)	
Rash	15(57.7)	13(50.0)	2(7.7)		1(3.8)		1(3.8)		15(57.7)	13(50.0)	2(7.7)	
Pruritus	3(11.5)	2(7.7)	1(3.8)						3(11.5)	2(7.7)	1(3.8)	

Table 3. Treatment related Adverse Event

Listed with an incidence of 10% or more and important adverse events. Grade 3 adverse events were observed in 5 patients (19.2%,1 Diarrhoea, 1 Stomatitis, 2 Paronychia, and 1 Dermatitis acneiform), and all of these events were related with afatinib. No grade 4 or 5 adverse events were observed. ILD was not observed at cut-off point.

Conclusions

✓Combination of DFP-14323 and low-dose afatinib showed promising efficacy and good tolerability.

✓We are planning a phase 3 study to evaluate this combination therapy after evaluation of PFS.

Acknowledgment

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Disclosure

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