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Phase I study of brigatinib plus panitumumab in patients with advanced EGFR-mutated non-small cell lung cancer resistant to osimertinib (BEBOP): early termination due to severe early onset pneumonitis by brigatinib.

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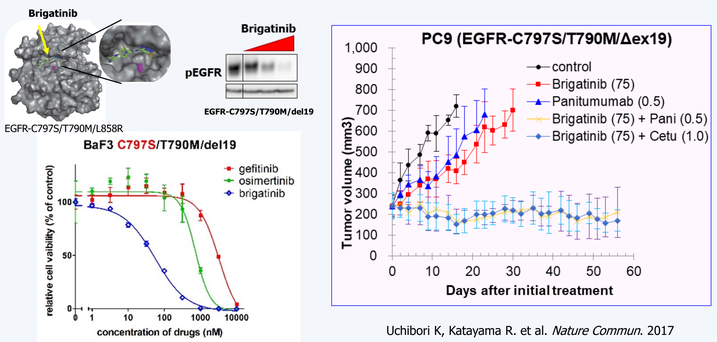
Background

Osimertinib is a standard of care for advanced EGFR-mutated non-small cell lung cancer (EGFR+NSCLC), however acquired resistance inevitably develop in 1-2 year[1-2)]. No effective targeted therapy has been established for EGFR+NSCLC after osimertinib. The EGFR C797S (CS) mutation is one of the most common resistant mechanisms to osimertinib[3)]. Brigatinib is shown to overcome CS-mediated osimertinib resistance in combination with anti-EGFR antibody in preclinical models[4)].

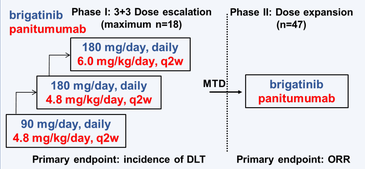


Uchibori K, Katayama R. et al. *Nature Commun.* 2017

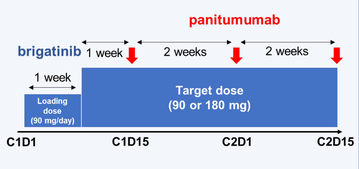
Patient and Method

We conducted a phase 1 study of brigatinib plus panitumumab in patients with advanced EGFR+NSCLC after osimertinib treatment, with 3+3 dose escalation design. Candidates were screened based on LC-SCRUM-TRY (UMIN000041957). The primary endpoint was the incidence of dose limiting toxicity (DLT) to determine recommended phase 2 dose (PR2D). The planned dose for initial cohort included brigatinib (90 mg, once daily from C1D1) and panitumumab (4.8 mg/kg, on C1D15, then every 2 weeks).

<Study schema>



<Treatment dose and schedule>



<Major eligibility criteria>
- NSCLC
- Stage III/IV or recurrent
- Common EGFR mutation (ex19del or ex21 L858R)
  *Irrespective of C797S mutation in phase I part
- Osimertinib pretreated
- Age ≥ 20
- ECOG-PS=0-2
-

<Major ineligibility criteria>
- Symptomatic CNS metastasis
- History of IP or ILD
- Chemotherapy in 2 weeks
- Immunotherapy in 1 month
- Major surgery or RT in 30 days
- EGFR-TKI in 2 weeks (Added in amended protocol ver1.4)

<Definition of dose limiting toxicity (DLT)>
Treatment-related adverse events in cycle 1 (28 days from treatment initiation)
- Grade ≥3 non-hematological adverse events
- Febrile neutropenia
- Grade 4 neutropenia persisting ≥7 days
- Grade ≥3 thrombocytopenia (symptomatic or require transfusion)
- Grade 4 thrombocytopenia persisting ≥7 days
- Recurrent Gr ≥2 pneumonitis (Added in amended protocol ver1.4)

Results

Table1. Patient characteristics

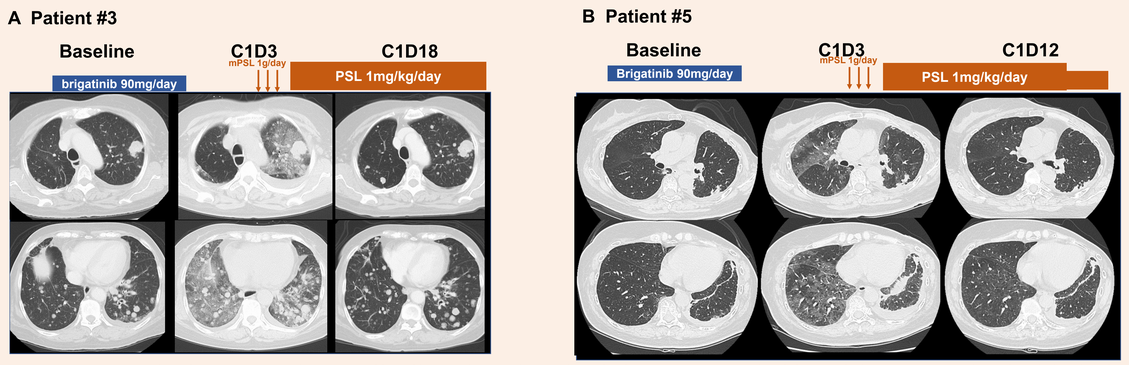
Characteristics		N=5
Age, year		
	median (range)	66 (53-75)
Sex		
	female	4
	male	1
ECOG-performance status		
	0	1
	1	4
smoking status		
	former	2
	never	3
Histology		
	adenocarcinoma	5
Stage		
	IIIB	1
	IV	1
	recurrence	3
Prior systemic treatment		
	1	1
	2	0
	3+	4
Time from last osimertinib dose to first brigatinib dose (day)		
	median (range)	11 (2-393)
Prior thoracic radiation therapy		
	Yes	1
	No	4
EGFR mutation type		
	ex19 del + T790M + C797S	2
	ex19 del + C797S	1
	ex19 del + T790M	1
	ex19 del	1

Table 2. Adverse events

Adverse events, n (%)	G1	G2	G3	Any G	G3-5
Total	0	2 (40)	3 (60)	5 (100)	3 (60)
Gastrointestinal disorder					
Diarrhea	1 (20)			1 (20)	
Nausea	1 (20)			1 (20)	
General disorders and administration site conditions					
Chest pain	1 (20)			1 (20)	
Injection site reaction		1 (20)		1 (20)	
Hepatobiliary disorders					
hepatic dysfunction		1 (20)		1 (20)	
Investigations					
Serum amylase elevation		2 (40)		2 (40)	
CPK increased	1 (20)			1 (20)	
ALP increased		1 (20)		1 (20)	
Metabolism and nutrition disorders					
Hyperkalemia			1 (20)	1 (20)	1 (20)
Musculoskeletal and connective tissue disorders					
Osteoporosis	1 (20)			1 (20)	
Respiratory, thoracic and mediastinal disorders					
Cough	1 (20)			1 (20)	
Dyspnea	1 (20)			1 (20)	
Pneumonitis		1 (20)	2 (40)	3 (60)	2 (40)
Skin ad subcutaneous tissue disorders					
Rash acneiform	1 (20)			1 (20)	

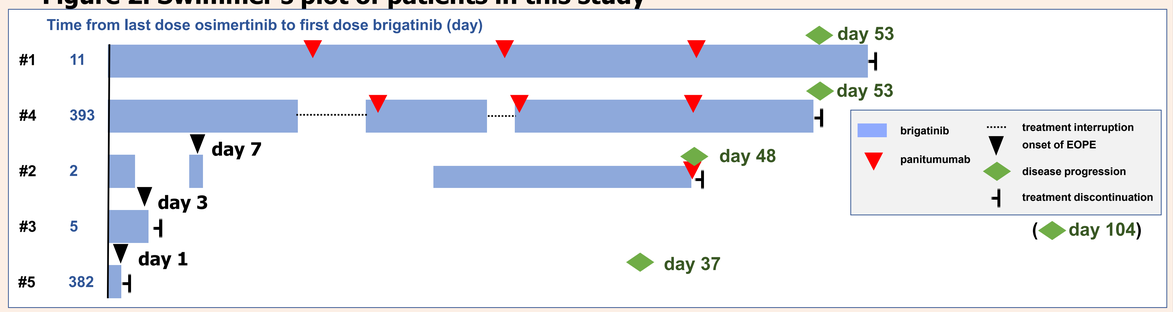
No patient experienced grade 4-5 adverse events.
Grade 3 pneumonitis in two patients were judged as treatment-related and DLT.
Grade 3 hypekalemia was not judged as treatment-related.

Figure 1. Clinical courses of patients with severe brigatinib-induced pneumonitis



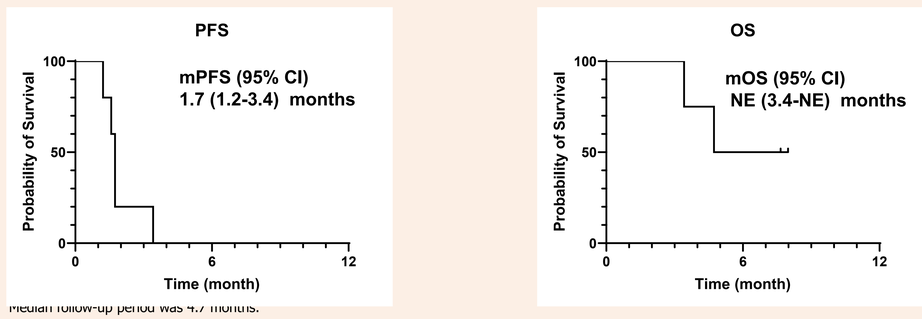
A. Patient #3 experienced grade 3 pneumonitis during 90mg/day of brigatinib monotherapy (C1D3). The patient was treated with brigatinib discontinuation and 1g of methylprednisolone (mPSL) for 3days followed by 1mg/kg of prednisolone (PSL). The pneumonitis quickly improved in 3 weeks (right panel, C1D18).
B. Patient #5 experienced grade 2 pneumonitis on C1D1, which worsened to grade 3 on C1D3. Patient discontinued brigatinib since C1D2, and then treated with 1g of mPSL for 3days followed by 1mg/kg of PSL. The pneumonitis also quickly improved in 2 weeks (right panel, C1D12).

Figure 2. Swimmer's plot of patients in this study



All of three early onset pulmonary events (EOPE) occurred during 90 mg of brigatinib monotherapy period. Three patients (#1, #2, #4) discontinued study treatment due to disease progression.

Figure 3. PFS and OS of patients in this study



Median follow-up period was 4.7 months.

Conclusion

In this study, brigatinib treatment was poorly tolerated with high incidence of early onset pneumonitis in patients with EGFR+NSCLC after osimertinib treatment, leading to early study termination.
Pretreatment with osimertinib might be related with high incidence of EOPE.
We should further investigate other strategies to overcome osimertinib resistance.

Reference

1) Mock T.S, et al. New Engl J Med. 2016, 2) Soria J.C, et al. New Engl J Med. 2017
3) Cooper A.J, et al. Nat Rev Clin Onclol. 2022, 4) Uchibori K, et al. Nature Commun. 2017

Acknowledgement

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