Phase II Study of Cetuximab Rechallenge in Patients with *RAS* Wild-Type metastatic Colorectal Cancer: E-Rechallenge Trial

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Comprehensive Support Project For Oncological Research

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Background

Several previous reports indicated that cetuximab (Cmab) rechallenge may be efficacious in patients for whom Cmab was previously effective. On the other hand, some reports did not support this. Considering the plasticity of sensitive clone, we assumed that an anti-EGFR antibody-free interval (aEFI) and efficacy may be correlated. This current study investigates the efficacy and safety of Cmab rechallenge as a salvage chemotherapy.

Study Design

multicenter phase II study

main eligibility criteria

mCRC patients who have become refractory to fluoropyrimidines, L-OHP, CPT-11, Cmab and bevacizumab, and in whom previous treatment with Cmab was effective

- **in any earlier line** (achieving **CR, PR, or SD** that persisted for ≥6 months)
- ***RAS* wild-type**
- measurable disease
- **aEFI ≥16** weeks between the last dose of Cmab during previous treatment and the start of Cmab rechallenge

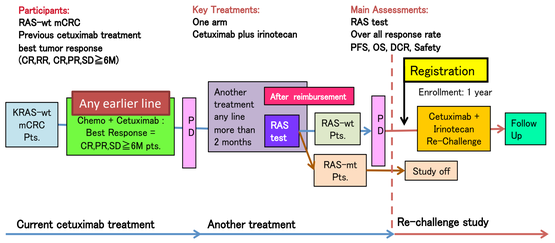
Protocol treatment: combination of weekly Cmab with biweekly CPT-11.

Primary endpoint: response rate (RR)

Secondary endpoints: progression free survival (PFS), overall survival (OS), association between the aEFI and efficacy, and safety

Statistical considerations: Using a single-stage binominal design, 45 patients were required; a RR of ≥ 20% was considered promising, and a RR of ≤ 5% unacceptable (one-sided α = 2.5%, β = 10%).

E-Rechalleng-E Trial



Clinical trial identification UMIN 000016439.
Legal entity responsible for the study
Comprehensive Support Project for Oncological Research.
Partially sponsored by Merck Serono.

Results

- **Between Dec 2014 and Oct 2017, 33 patients were enrolled. The registration of this trial was halted in Oct 2017 due to insufficient accrual.**
- **The primary endpoint; the rates of PR/SD/PD (95%CI) were PR 15.2% (5.1-31.9%)/SD 39.4% (22.9-57.9%)/ PD 42.4% (25.5-60.8%).**
- **Secondary endpoints; median PFS and OS (95%CI) were 88 days (62-113days) and 262 days (195-307days).**
- **There were no statistical significant difference of RR, PFS and OS stratified by median aEFI (311days).**
- **New safety information were not identified.**
- **Twenty four patients were enrolled the additional liquid biopsy research which was conducted optionally.**

Table1. Patients Characteristics (n=33)

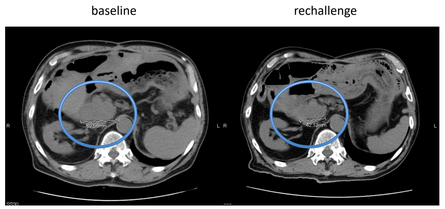
		n	%
age	average (range)	64.4 (35-78)	
sex	male	28	84.85
	female	5	15.15
pathology	well	10	30.3
	moderately	21	63.64
	poorly	2	6.06
primary site	Ascending	1	3.03
	Transverse	3	9.09
	Descending	1	3.03
	Sigomoid	16	48.48
	Rectosigmoid	4	12.12
	Rectum	2	6.06
primary site resection	yes	6	18.18
	no	7	21.21
meta site	Liver	26	78.79
	Lung	18	54.55
	Lymphnode	12	36.36
	Peritoneum	7	21.21
	Bone	1	3.03
	others	1	3.03
previous combination	none	1	3.03
	FOLFOX	9	27.27
	FOLFIRI	9	27.27
	IRIS	3	9.09
	irrinotecan	10	30.3
	others	1	3.03
best response	CR	1	3.03
	PR	26	78.79
	SD ≧6mo	6	18.18

Table2. Response Rate

	n=33	%	95%CI[a)]
PR	5	15.15	[5.11, 31.90]
SD	13	39.39	[22.91, 57.86]
PD	14	42.42	[25.48, 60.78]
NA	1		

a) Clopper–Pearson

Figure1. Representative Case of Response



The blue circle indicates the metastasis in segment 1 of the liver. Shrinkage was seen after rechallenge of CPT-11 + cetuximab.

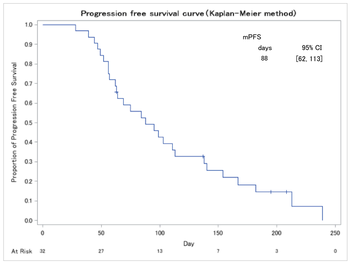
Table3. Response Rate divided by median aEFI

		PR	SD	PD	NA	
aEFI > median	N	2	8	5	1	NS
	%	12.5	50	31.3	6.25	
aEFI ≦median	N	3	5	9	0	
	%	17.7	29.4	52.9	0	

Table4. Mutation status of liquid biopsy at baseline (n=24)

Patient number	Response	EGFR S492R	KRAS G12 G13	KRAS A59 Q61	BRAF V600E	ANY MT
CRC04-01	SD	WT	WT	WT	WT	WT
CRC04-02	SD	WT	WT	WT	WT	WT
CRC04-03	PR	WT	WT	WT	WT	WT
CRC04-04	SD	WT	WT	WT	WT	WT
CRC04-05	SD	WT	WT	WT	WT	WT
CRC04-06	PD	WT	WT	MT	WT	MT
CRC04-07	PD	WT	WT	WT	WT	WT
CRC04-08	PD	WT	MT	WT	WT	MT
CRC04-11	PD	WT	MT	WT	WT	MT
CRC04-12	SD	WT	MT	MT	MT	MT
CRC04-13	PD	WT	MT	MT	WT	MT
CRC04-14	SD	WT	WT	WT	WT	WT
CRC04-15	SD	WT	WT	MT	WT	MT
CRC04-17	PD	MT	MT	WT	MT	MT
CRC04-18	PD	WT	WT	MT	MT	MT
CRC04-19	PD	WT	WT	WT	WT	WT
CRC04-20	SD	WT	WT	WT	WT	WT
CRC04-22	SD	WT	MT	MT	WT	MT
CRC04-25	SD	MT	WT	WT	WT	MT
CRC04-26	SD	MT	WT	MT	WT	MT
CRC04-27	SD	WT	MT	MT	WT	MT
CRC04-30	PR	WT	WT	WT	WT	WT
CRC04-32	PD	WT	WT	WT	WT	WT
CRC04-33	PR	WT	WT	WT	WT	WT

Figure2. Survival Curves



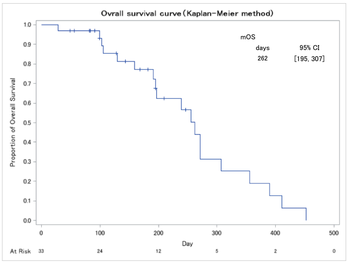
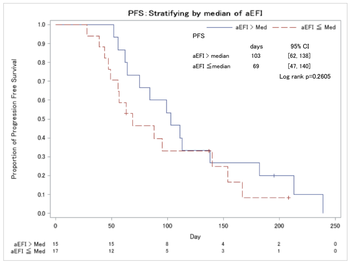
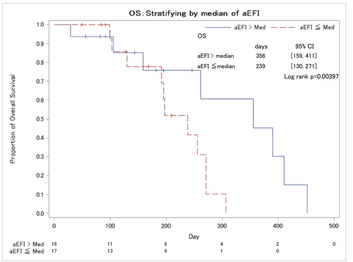


Figure3. Survival Curves divided by median aEFI





Methods

Liquid biopsy research

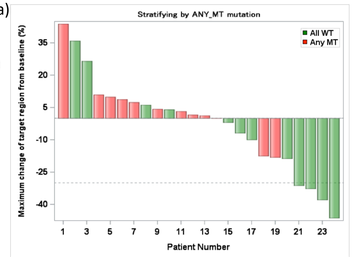
Additional research of ctDNA was conducted optionally.
Blood samples at baseline collected in STRECK BCT® tubes
DNA was extracted from plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen)
We performed ddPCR assays on a QX200 digital PCR system (BioRad laboratories) . The PCR data were quantified as copies/μL using QuantaSoft™ software (BioRad laboratories).
A mutation was considered positive with more than 0.1% fractional abundance of *KRAS* c12/c13/A59/Q61, *BRAF* (V600E) and *EGFR* S492R mutant droplets. The uniplex ddPCR method had been optimized beforehand by comparative analysis of a dilution series of synthetic copies of each indicated mutant oligonucleotide.
LBx® Probe of *KRAS* G12/G13 Screen (Riken Genesis)
LBx® Probe *KRAS* A59/Q61Screen (Riken Genesis)
LBx® Probe *BRAF* V600 Screen (Riken Genesis)
Additionally, we used ddPCR™ probe *EGFR* S492R as the detection probe for *EGFR* S492R(c.1474A>C) and S492R (c.1476C>A) (BioRad laboratories).

Results of Liquid biopsy research (Table 4 and 5, Figure 4)

Figure4. Results from ctDNA analysis(n=24)

a) Waterfall plot
b) Spider plot
c) PFS divided by any mutation of liquid biopsy

a)



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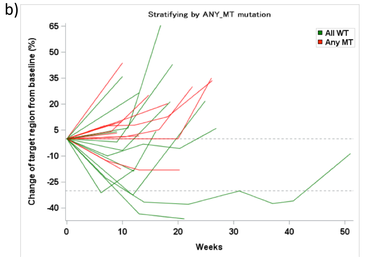

c)

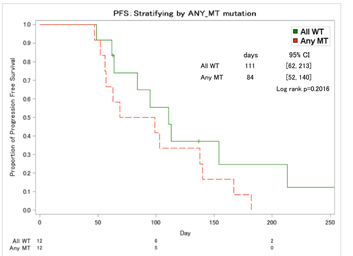

Table5. Response Rate divided by Any mutation of liquid biopsy

	ALL (n=24)	All WT (n=12)
ORR	12.50%	25%
DCR	50%	50%
PD	37.50%	25%

By narrowing down all wild type of this liquid biopsy, the response rate was increased from 12.5% to 25%.

Conclusion

Cmab rechallenge showed some activity in the salvage setting, in patients for whom Cmab was previously effective.
***KRAS* and *BRAF* screening by liquid biopsy may contribute to identify the patients with benefit from Cmab rechallenge.**