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Phase I/II clinical trial of combination of anti-PD-1 mAb, nivolumab with radiotherapy for unresectable and recurrent gastric cancer who failed to standard chemotherapy (CIRCUIT trial).

Koji Kono[1], Kosaku Mimura[1], Takashi Ogata[3], Yuya Yoshimoto[2], Daisaku Yoshida[4], Shotaro Nakajima[1], Hisashi Sato[2], Nozomu Machida[3], Takanobu Yamada[3], Yohei Watanabe[1], Tomoaki Tamaki[2], Hirohito Fujikawa[3], Yasuhiro Inokuchi[3], Hisashi Onozawa[1], Suguru Hayase[1], Hiroyuki Hanayama[1], Zenichiro Saze[1], Hiroyuki Katoh[4], Takashi Oshima[3], Yoshiyuki Suzuki[2]

[1]Department of Gastrointestinal Tract Surgery, Fukushima Medical University, [2]Department of Radiation Oncology, Fukushima Medical University,
[3]Department of Surgery, Kanagawa Cancer Center, [4]Department of Radiation, Kanagawa Cancer Center

Background:

Although basic, translational and clinical research suggest a possibility of synergistic effect of radiation-induced immunogenic cell death with immune checkpoint inhibitors, the effectiveness of concurrent therapy with radiotherapy and immunotherapy is not fully established.

Methods:

- Phase I/II, open single arm, prospective clinical trial (NCT03453164) was conducted.
- Eligible patients were unresectable advanced or recurrent gastric cancer patients (n=40) who developed progression after primary and secondary chemotherapy with more than one lesion assessable in diagnostic imaging (one lesion must be ≥2cm).
- Radiotherapy of total 22.5 Gy/5 fractions/5 days was given to the largest or symptomatic lesion and nivolumab was administered day 15-22 at a dose of 3 mg/kg or 240mg/body every 2 weeks to a total of 6 administrations.
- The primary endpoint is disease control rate of non-irradiated target lesions as an abscopal effect.
- The secondary endpoints are median survival time, safety and proportion of local control rate for irradiated lesion.
- As an ancillary analysis, immunologic parameters including CyTOF-based, high-dimensional MHC multimer analysis and TCR repertoire analysis, and ctDNA analysis are designed.

Results:

- Total 41 patients were enrolled and 40 patients were evaluated as full analysis set, since 1 patient was judged as an unmatched case to inclusion criteria.
- The clinical evaluation as an abscopal effect were CR=1 (2.5%), PR=5 (12.5%), SD=3 (7.5%), PD=15 (37.5%) and NE=16 (40%). The disease control rate (CR+PR+SD) and the response rate (CR+PR) for non-irradiated target lesions was 22.5% and 15%, respectively.
- The median survival time was 230 days (157-330 days, 95%CI) and 1-year survival rate was 28.6%.
- Any adverse event more than Grade 3 was observed in 16 cases among the 41 enrolled patients (39%). The most frequent AE more than grade 3 were anemia (19%) and appetite loss (12%).
- The local control for irradiated lesion were seen in CR=5 (12.5%), PR=6 (15%), SD=5 (12.5%), PD=4 (10%) and NE=20 (50%).
- The ancillary analysis for immunological monitoring is under investigation.

Conclusion:

- The combination of nivolumab with radiotherapy demonstrated promising anti-tumor activity with marked prolonged survival time in gastric cancer.
- No new safety issues were detected in the combination.

Figure 1. Study protocol

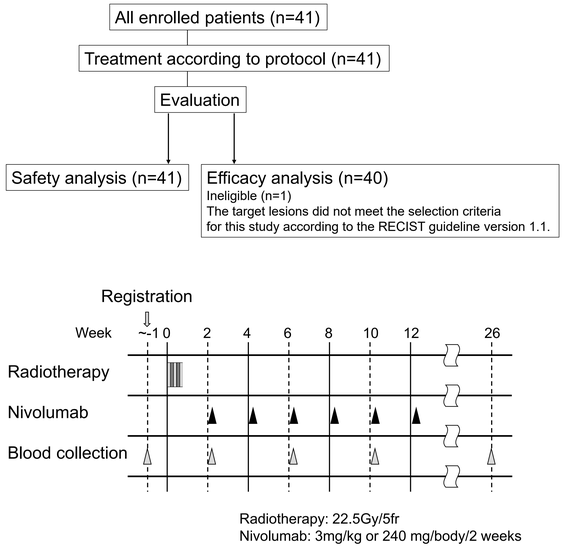


Table 1. Patient characteristics

		Safety analysis		Efficacy analysis	
n		41		40	
Sex	Male	34	(82.9%)	33	(82.5%)
	Female	7	(17.1%)	7	(17.5%)
Age	Median (range)	70 (36-86)		70 (36-86)	
Prior chemotherpy	2 regimens	24	(58.5%)	23	(57.5%)
	3 regimens	17	(41.5%)	17	(42.5%)
ECOG PS	0	30	(73.2%)	30	(75.0%)
	1	8	(19.5%)	7	(17.5%)
	2	3	(7.3%)	3	(7.5%)
Number of cancer lesions	2	1	(2.4%)	1	(2.5%)
	3	7	(17.1%)	6	(15.0%)
	4	0	(0.0%)	0	(0.0%)
	5~9	15	(36.6%)	15	(37.5%)
	≧10	18	(43.9%)	18	(45.0%)
Number of organs with cancer	1	7	(17.1%)	7	(17.5%)
	2	11	(26.8%)	10	(25.0%)
	3	20	(48.8%)	20	(50.0%)
	4	2	(4.9%)	2	(5.0%)
	5	1	(2.4%)	1	(2.5%)

Figure 2. Overall survival

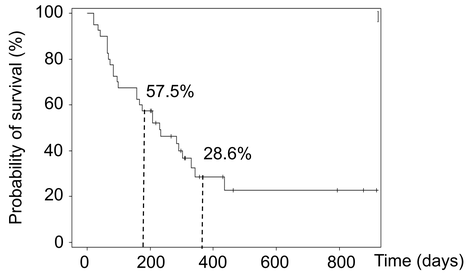
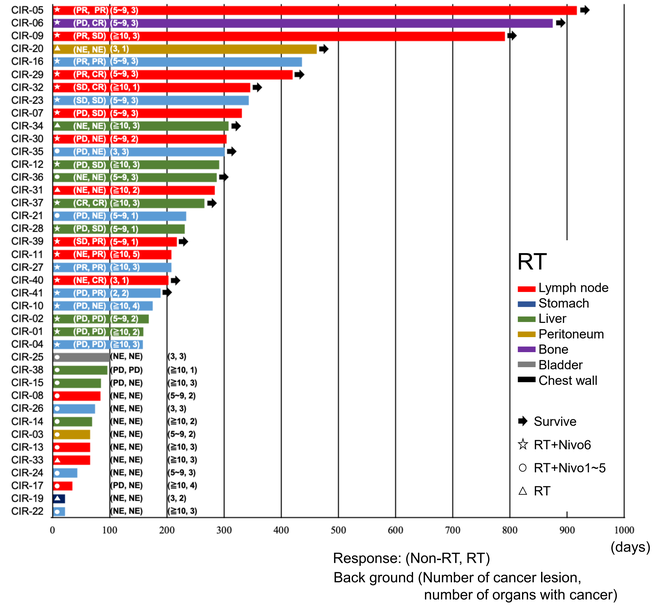


Figure 3. Swimmer plots for all enrolled patients



Response: (Non-RT, RT)
Back ground (Number of cancer lesion, number of organs with cancer)

Table 2. Efficacy of non-irradiated lesions and irradiated lesion.

	CR	PR	SD	PD	NE	CR/PR/SD rate (90%CI)
Non-irradiated lesions	1 (2.5%)	5 (12.5%)	3 (7.5%)	15 (37.5%)	16 (40%)	22.5% (12.3～ 36.0)
Irradiated lesion	5 (12.5%)	6 (15%)	5 (12.5%)	4 (10%)	20 (50%)	40.0% (26.9～ 54.2)

Table 3. Adverse events

CTCAE ver.4.0	Gr.1	Gr.2	Gr.3	Gr.4	%Gr.3-4(95%CI)
Abdominal pain	2	0	0	0	0.0 (0.0～ 8.6)
Alanine aminotransferase increased	5	0	0	0	0.0 (0.0～ 8.6)
Alkaline phosphatase increased	4	5	1	0	2.4 (0.0～ 12.8)
Anemia	5	6	6	2	19.5 (8.8～ 34.8)
Anorexia	4	4	5	0	12.1 (4.0～ 26.2)
Arthralgia	1	0	0	0	0.0 (0.0～ 8.6)
Ascites	0	2	0	0	0.0 (0.0～ 8.6)
Aspartate aminotransferase increased	7	1	0	0	0.0 (0.0～ 8.6)
Blood bilirubin increased	1	0	1	0	2.4 (0.0～ 12.8)
Cholecystitis	0	0	1	0	2.4 (0.0～ 12.8)
Constipation	3	2	0	0	0.0 (0.0～ 8.6)
Creatinine increased	3	1	0	0	0.0 (0.0～ 8.6)
Dehydration	0	0	2	0	4.8 (0.5～ 16.5)
Diarrhea	2	1	0	0	0.0 (0.0～ 8.6)
Dyspnea	0	1	1	0	2.4 (0.0～ 12.8)
Fatigue	8	1	0	0	0.0 (0.0～ 8.6)
Febrile neutropenia	0	0	1	0	2.4 (0.0～ 12.8)
Fever	4	0	1	0	2.4 (0.0～ 12.8)
Gastric hemorrhage	0	0	1	0	2.4 (0.0～ 12.8)
Gum infection	0	1	0	0	0.0 (0.0～ 8.6)
Headache	1	0	0	0	0.0 (0.0～ 8.6)
Hyperglycemia	8	7	1	0	2.4 (0.0～ 12.8)
Hyperkalemia	0	1	1	0	2.4 (0.0～ 12.8)
Hypertension	1	3	0	0	0.0 (0.0～ 8.6)
Hyperuricemia	2	0	1	0	2.4 (0.0～ 12.8)
Hypoalbuminemia	4	8	1	0	2.4 (0.0～ 12.8)
Hypocalcemia	4	4	0	0	0.0 (0.0～ 8.6)
Hypoglyemia	0	1	0	0	0.0 (0.0～ 8.6)
Hypokalemia	1	0	0	0	0.0 (0.0～ 8.6)
Hyponatremia	5	0	1	0	2.4 (0.0～ 12.8)
Hypothyroidism	0	2	0	0	0.0 (0.0～ 8.6)
Ileus	0	0	1	0	2.4 (0.0～ 12.8)
Malaise	0	2	0	0	0.0 (0.0～ 8.6)
Myalgia	1	0	0	0	0.0 (0.0～ 8.6)
Nausea	4	3	2	0	4.8 (0.5～ 16.5)
Neutrophil count decreased	1	1	0	0	0.0 (0.0～ 8.6)
Peripheral motor neuropathy	1	0	0	0	0.0 (0.0～ 8.6)
Peripheral sensory neuropathy	5	0	0	0	0.0 (0.0～ 8.6)
Platelet count decreased	2	1	1	0	2.4 (0.0～ 12.8)
Proteinuria	1	0	1	0	2.4 (0.0～ 12.8)
Pruritus	5	1	0	0	0.0 (0.0～ 8.6)
Rash maculo-papular	2	0	0	0	0.0 (0.0～ 8.6)
Small intestinal obstruction	0	1	0	0	0.0 (0.0～ 8.6)
Supraventricular tachycardia	0	0	0	1	2.4 (0.0～ 12.8)
Tumor pain	3	0	3	0	7.3 (1.5～ 19.9)
Vomiting	3	3	0	0	0.0 (0.0～ 8.6)
White blood cell decreased	1	3	1	0	2.4 (0.0～ 12.8)
Edema limbs	5	0	0	0	0.0 (0.0～ 8.6)
Lung infection	0	0	1	0	2.4 (0.0～ 12.8)
Generalized muscle weakness	1	0	0	0	0.0 (0.0～ 8.6)

COI disclosure

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