Poster number : 35

HGCSG1901: A Retrospective Cohort Study Evaluating the Safety and Efficacy of S-1 and Irinotecan plus Bevacizumab in Patients with Metastatic Colorectal Cancer: Analysis of first line treatment.

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Background

- TRICOLORE trial[1], which was a phase III trial, revealed the safety and efficacy of irinotecan/S-1/bevacizumab (IRIS/Bev or SIRB) for the first line treatment for metastatic colorectal cancer (mCRC) patients in Japan.

	TRICOLORE[1]	
	IRIS/Bev or SIRB (n=241)	FOLFOX/CAPOX+BV (n=243)
Progression-free survival, months (PE)	**14.0**	10.8
HR (95%C.I.)	0.84 (0.70-1.02)	
p-value (noninferiority/superiority)	**<0.0001** / 0.0815	
Overall survival, months	**34.9**	33.6
HR, p-value	0.86 (0.66-1.13), 0.2841	
Response rate, %	**66.4**	70.6
p-value	0.34	

PE : Primary endpoint, HR : Hazard ratio, BV : Bevacizumab

- Based on this result, IRIS/Bev and SIRB are one of the recommended regimens as a first line treatment for mCRC patients in Japanese Society for Cancer of the Colon and Rectum (JSCCR) guideline.
- However, there are few studies exploring the efficacy and safety of IRIS/Bev for first line setting in a real world practice.

Study Objectives

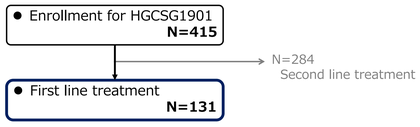
- Overall survival
- Progression-free survival
- Time to treatment failure
- Response rate
- Disease control rate
- Safety
- Drug administration
- Dose intensity

Methods

- Survival analyses were performed with Kaplan-Meier method.
  - Overall survival : Defined as the time from start date of IRIS/Bev until the date of any cause of death.
  - Progression-free survival : Defined as the time from start date of IRIS/Bev until the date of first documented disease progression or any cause of death.
  - Time to treatment failure : Defined as the time from start date of IRIS/Bev until the date of any cause of discontinuation.
- Response rate/Disease control rate : RECIST v1.1
- Adverse events : CTCAE v4.01

Analysis set

- We retrospectively analyzed the clinical data with mCRC patients who received IRIS/Bev from August 2011 to March 2018 in 24 institutes.



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[Hokkaido]
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- Keiyukai Sapporo Hospital
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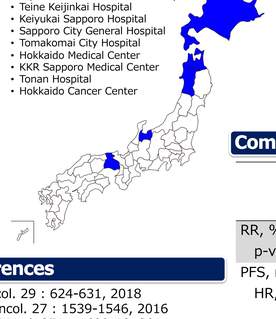
- Tomakomai City Hospital
- Hokkaido Medical Center
- KKR Sapporo Medical Center
- Tonan Hospital
- Hokkaido Cancer Center



References

1) Yamada Y, et al. Ann Oncol. 29 : 624-631, 2018
2) Yamazaki K, et al. Ann Oncol. 27 : 1539-1546, 2016
3) Loupakis F, et al. N Engl J Med. 371 : 1609-18, 2014
4) Cremolini C, et al. Lancet Oncol. 16 : 1306-15, 2015
5) Yamada Y, et al. Lancet Oncol. 14 : 1278-86, 2013
6) Heinemann V, et al. Lancet Oncol. 15 : 1065-75, 2014

Results

1. Patient's characteristics

		N (%)
Gender	Male	83 (63.4)
	Female	48 (36.6)
Age (years)	Median (range)	65 (36-83)
ECOG PS	0	107 (81.7)
	1	21 (16.0)
	2	3 (2.3)
Primary site*	Right side	43 (32.8)
	Left side	88 (67.2)
Prior colorectomy	Yes	98 (74.8)
	No	33 (25.2)
Synchronous metastases	Yes	88 (67.2)
	No	43 (32.8)
Metastatic site**	Liver	74 (56.5)
	Lung	36 (27.5)
	Lymph node	60 (45.8)
	Peritoneum	35 (26.7)
Number of metastatic organ	Median (range)	2 (1-5)
RAS status	Wild***	57 (48.3)
	Mutant	61 (51.7)
	Not tested	13
BRAF status	Wild	22 (95.7)
	V600E Mutant	1 (4.3)
	Not tested	108
MSI status	MSI-H	1 (3.7)
	Non MSI-H	26 (96.3)
	Not tested	104
UGT1A1 status	Wild	31 (54.4)
	Single Heterozygous	18 (31.6)
	Homozygous	4 (7.0)
	Double Heterozygous	4 (7.0)
	Not tested	74

* Right side(Cecum～Transverse) / Left side(Descending～Rectum)
** Some were overlapping
*** 23 patients ; *KRAS* Exon2 status was wild type, but other *RAS* status was not tested

2. Adverse events

CTCAE v4.0, grade	1	2	3	4	Any grade	≥Grade 3
White blood cell decreased	18	41	12	2	73 (55.7)	14 (10.7)
Neutrophil count decreased	29	40	25	5	99 (75.6)	30 (22.9)
Platelet count decreased	33	5	3	0	41 (31.3)	3 (2.3)
Anemia	37	26	10	2	75 (57.3)	12 (9.2)
Febrile neutropenia	-	-	4	0	4 (3.1)	4 (3.1)
Blood bilirubin increased	34	4	1	0	39 (29.8)	1 (0.8)
Aspartate aminotransferase increased	44	1	5	0	50 (38.2)	5 (3.8)
Alanine aminotransferase increased	37	6	4	0	47 (35.9)	4 (3.1)
Alkaline phosphatase increased	41	2	1	0	44 (33.6)	1 (0.8)
Creatinine increased	19	2	0	0	21 (16.0)	0 (0)
Proteinuria*	24	31	0	-	55 (47.4)	0 (0)
Epistaxis	29	0	0	0	29 (22.1)	0 (0)
Hypertension	3	15	14	0	32 (24.4)	14 (10.7)
Nausea	49	7	3	-	59 (45.0)	3 (2.3)
Vomiting	12	5	1	0	18 (13.7)	1 (0.8)
Anorexia	35	18	8	0	61 (46.6)	8 (6.1)
Fatigue	44	20	4	-	68 (51.9)	4 (3.1)
Diarrhea	40	22	10	0	72 (55.0)	10 (7.6)
Alopecia	35	20	-	-	55 (42.0)	-
Mucositis oral	31	10	3	0	44 (33.6)	3 (2.3)

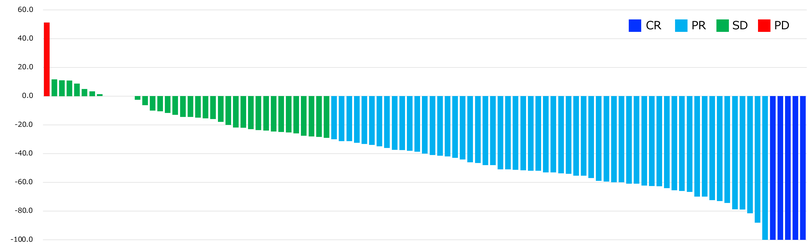
*15 patients : Urinalysis was not tested

3. Drug administration

		Irinotecan	S-1	Bevacizumab
Starting dose	Full dose	121 (92.4) [100mg/m²]	109 (83.2) [80mg/m²]	129 (98.5) [5mg/kg]
	Dose reduction	10 (7.6)	22 (16.8)	2 (1.5)
Administrated cycle	Median (range)		10 (1-59)	
	Total cycle		1657	
RDI	Median (range)	0.772 (0.190-1.000)	0.811 (0.092-1.089)	0.833 (0.291-1.000)

RDI : Relative dose intensity

4. Waterfall plot



5. Response rate (RR) / Disease control rate (DCR)

N*	CR	PR	SD	PD	NE	RR (95%C.I.)	DCR (95%C.I.)
102	5	58	36	2	1	61.8% (52.3-71.2)	97.1% (91.6-99.4)

* 29 patients : had not target lesion

6. Reason for treatment discontinuation

N=131	N (%)
On treatment	4 (3.1)
Treatment discontinuation	127 (96.9)
Progressive disease	76 (59.9)
Adverse events	21 (16.5)
Converted curative surgery	21 (16.5)
Patients withdrawn	5 (3.9)
Others	4 (3.2)

7. Post treatment

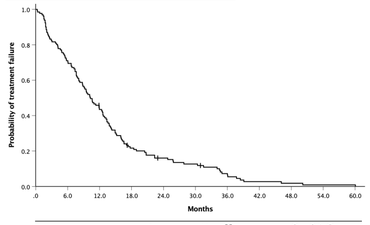
Treatment discontinuation	N=127
Post-study therapy ; Yes	108 (85.0)
Resection*	21 (16.5)
Chemotherapy*	105 (82.7)
Fluoropyrimidine	97 (92.4)
Oxaliplatin	81 (77.1)
Irinotecan	41 (39.0)
Anti-angiogenic Inhibitor	84 (80.0)
Anti-EGFR antibody**	41 (83.7)
Regorafenib	31 (29.5)
FTD/TPI	49 (46.7)
Others	2 (1.9)

* Some were overlapping
** *RAS* wild type who received chemotherapy : n=49

Comparison of adverse events in 1st line treatment with irinotecan and bevacizumab

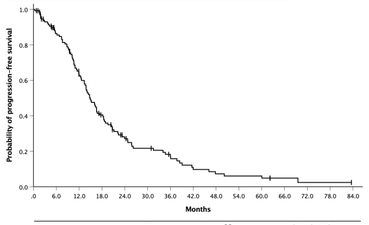
	TRICOLORE[1] [IRIS/Bev or SIRB] (n=239)		WJOG4407G[2] [FOLFIRI+BV] (n=195)		HGCSG1901 [IRIS/Bev] (n=131)	
N(%)	All Gr.	≥Gr.3	All Gr.	≥Gr.3	All Gr.	≥Gr.3
Neutrophil count decreased	172 (55.5)	52 (16.8)	172 (88.2)	89 (45.6)	99 (75.6)	30 (22.9)
White blood cell decreased	156 (50.3)	16 (5.2)	157 (80.5)	22 (11.3)	73 (55.7)	14 (10.7)
Anemia	217 (70.0)	10 (3.2)	153 (78.5)	88 (45.1)	75 (57.3)	12 (9.2)
Platelet count decreased	109 (35.2)	4 (1.3)	7 (3.6)	1 (0.5)	41 (31.3)	3 (2.3)
Febrile neutropenia	10 (3.2)	10 (3.2)	10 (5.1)	10 (5.1)	4 (3.1)	4 (3.1)
Proteinuria	113 (42.0)	16 (5.9)	77 (39.5)	0 (0)	55 (47.4)	0 (0)
Hypertension	69 (25.7)	19 (7.1)	84 (43.1)	6 (3.1)	32 (24.4)	14 (10.7)
Fatigue	132 (42.6)	10 (3.2)	146 (74.9)	11 (5.6)	68 (51.9)	4 (3.1)
Anorexia	144 (46.5)	17 (5.5)	143 (73.3)	16 (8.2)	61 (46.6)	8 (6.1)
Nausea	161 (51.9)	13 (4.2)	143 (73.3)	13 (6.7)	59 (45.0)	3 (2.3)
Diarrhea	155 (50.0)	22 (7.1)	106 (54.4)	17 (8.7)	72 (55.0)	10 (7.6)
Vomiting	85 (27.4)	6 (1.9)	82 (42.1)	9 (4.6)	18 (13.7)	1 (0.8)
Mucositis oral	83 (26.8)	5 (1.6)	109 (55.9)	5 (2.6)	44 (33.6)	3 (2.3)

8. Time to treatment failure



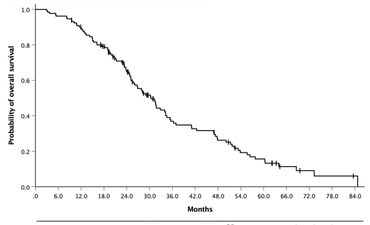
	Event	Median	95%C.I.
N=131	127/131 (96.9%)	**10.3 months**	8.2-12.4

9. Progression-free survival (PFS)



	Event	Median	95%C.I.
N=131	104/131 (79.4%)	**14.9 months**	12.9-16.9

10. Overall survival (OS)



	Event	Median	95%C.I.
N=131	97/131 (74.0%)	**30.4 months**	26.3-34.5

Conclusion

- In this retrospective analysis, IRIS/Bev in real world practice showed comparable efficacy and safety to previous report.
- IRIS/Bev is one of the standard treatment options for metastatic colorectal cancer as first-line setting.

Comparison of efficacy in 1st line treatment

	TRIBE[3][4]		SOFT[5]		FIRE-3[6] [*RAS* wild type]		WJOG4407G[2]		TRICOLORE[1]		HGCSG1901
	FOLFOXIRI+BV (n=252)	FOLFIRI+BV (n=256)	SOX+BV (n=256)	FOLFOX+BV (n=255)	FOLFIRI+Cmab (n=171)	FOLFIRI+BV (n=171)	FOLFIRI+BV (n=197)	FOLFOX+BV (n=198)	IRIS/Bev or SIRB (n=241)	FOLFOX/CAPOX+BV (n=243)	IRIS/Bev (n=131)
RR, %	65.1	53.1	62	63	65	60	64	62	66.4	70.6	**61.8**
p-value	0.006		—		0.32		0.757		0.34		
PFS, months	12.1	9.7	11.7	11.5	10.4	10.2	12.1	10.7	14.0	10.8	**14.9**
HR, p-value	0.75 (95%C.I. 0.62-0.90), 0.003		1.04 (95%C.I. 0.86-1.27), 0.014 Non-inferiority		0.93 (95%C.I. 0.74-1.17), 0.54		0.905 (95%C.I. 0.723-1.133), 0.003 Non-inferiority		0.84 (95%C.I. 0.70-1.02), <0.0001 Non-inferiority		
OS, months	29.8	25.8	29.6	30.9	33.1	25.6	31.4	30.4	34.9	33.6	**30.4**
HR, p-value	0.80 (95%C.I. 0.65-0.98), 0.03		1.05 (95%C.I. 0.80-1.38), —		0.70 (95%C.I. 0.53-0.92), 0.011		0.990 (95%C.I. 0.785-1.249), 0.730		0.86 (95%C.I. 0.66-1.13), 0.2481		

Cmab : Cetuximab

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