Final Overall Survival for the Phase 3 KN177 Study: Pembrolizumab Versus Chemotherapy in Microsatellite Instability-High/Mismatch Repair Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC)

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GW ONCOLOGY UPDATE

Pembrolizumab in MSI-H mCRC

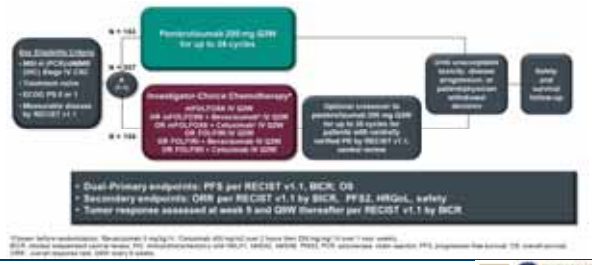
- Immune-checkpoint blockade has predicted clinical benefit in patients with mismatch-repair deficient (dMMR) or MSI-H mCRC[1-2]
- Pembrolizumab provided superior PFS versus chemotherapy in patients with MSI-H/dMMR mCRC, at interim analysis 2 (IA2) of KEYNOTE-177[3]
  - Median PFS: 16.5 vs 8.2 mo; HR 0.60; P=0.0002[3]
  - Lower incidence of grade ≥3 treatment-related events (22% vs 66%)[3] and better quality of life[4]
  - Contributed to FDA and EMA approval of pembrolizumab for the first-line treatment of patients with metastatic or unresectable (only FDA) MSI-H or dMMR CRC
- We report results of overall survival at the final analysis of the phase 3 study of pembrolizumab versus chemotherapy (± bevacizumab or cetuximab) as first-line therapy in MSI-H/dMMR mCRC

EMA, European Medicines Agency; FDA, Food and Drug Administration

1. Le et al. N Engl J Med 2015; 372:2509-20. 2. Le et al. Science 2017; 357:409-13. 3. André T et al. N Engl J Med 2020;383:2207-18. 4. André T et al. Lancet Oncol 2021.

GW ONCOLOGY UPDATE

KEYNOTE-177 Study Design
(NCT02563002)

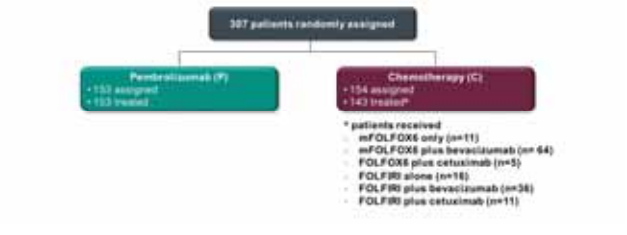


Statistical Considerations

- Efficacy: intention-to treat population of all randomized patients
- Safety: as-treated population of randomized patients with ≥1 treatment dose
- Dual-primary endpoints of PFS and OS: success if pembrolizumab superior to chemotherapy for either primary endpoint
- Final OS analysis: planned to occur at final analysis after approximately 190 OS events occurred, or 12 months after IA2, whichever occurred first
  - One-sided α of 0.0246 required for superiority of pembrolizumab versus chemotherapy in OS[a]
  - Final analysis occurred 12 months after IA2

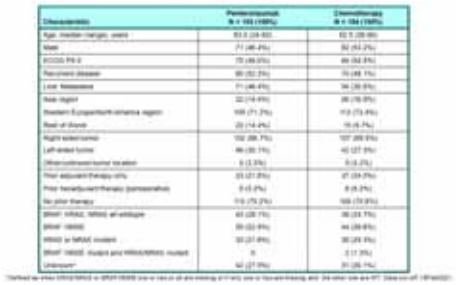
[a] At IA2, 1.25% alpha was allocated to the PFS hypothesis and 1.25% to the OS hypothesis. As PFS hypothesis was met at IA2, 98% of PFS alpha was passed to OS based on multiplicity strategy. At final analysis, per pre-defined Lan-DeMets O'Brien-Fleming spending function, OS p-value boundary was re-calculated with updated alpha and observed number of events (n=140) to 0.0246. IA2, second interim analysis. Data cut-off: 19Feb2021.

Disposition

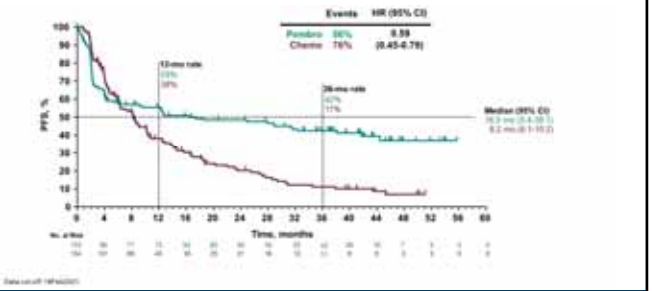


Disease progression was assessed per RECIST v1.1, BICR. Median study follow-up was 44.1 months (range, 36.5-48.3); 44.1 mo (36.5-48.3) with pembro vs 44.4 mo (36.2-48.8) with chemo. Data cut-off: 19Feb2021.

Baseline Characteristics

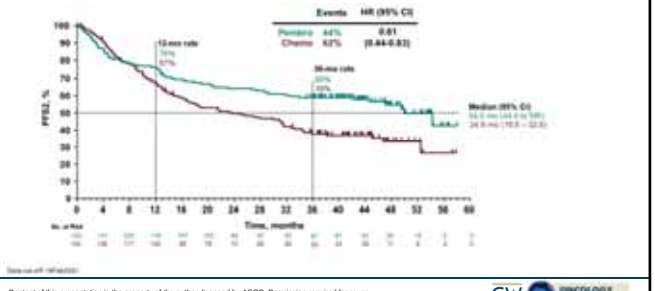


Progression-Free Survival



Progression-Free Survival

Time from randomization to progression on next line therapy or any cause death



Antitumor Response

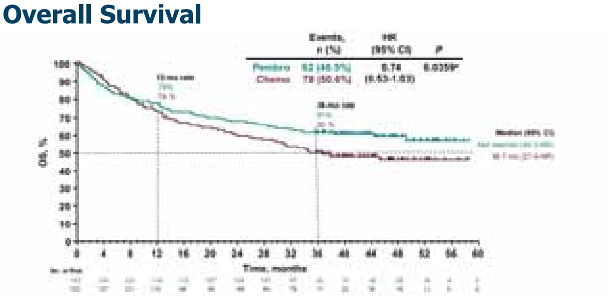
	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	69 (45.1)*	51 (33.1)
Best Overall Response, n (%)		
Complete response	20 (13.1)†	6 (3.9)
Partial response	49 (32.0)‡	45 (29.2)
Stable disease	30 (19.6)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable	3 (2.0)	2 (1.3)
No assessment	6 (3.9)	17 (11.0)
Median duration or response (range), mo	NR (2.3+ to 53.5+)	10.6 (2.8 to 48.3+)
≥ 24 months response duration, %	83.5	33.6

Cross Over and Subsequent Therapy

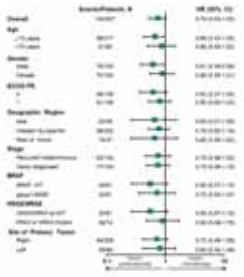
- 56 of 154 (36%) patients in the chemotherapy arm crossed over to receive pembrolizumab after confirmed disease progression
  - 37 additional patients received anti-PD-1/PD-L1 therapy outside of the study for an effective crossover rate of 60% in the ITT

	Pembrolizumab N = 153	Chemotherapy N = 154
Any anti-PD-1/PD-L1 therapy, n (%)	14 (9.2)	93 (60.4)
On protocol therapy - pembrolizumab*	8 (5.2)	56 (36.4)
Off protocol therapies	6 (3.9)	37 (24.0)
Any non-anti-PD-1/PD-L1 therapy, n (%)	38 (24.8)	28 (18.2)
Chemotherapy	35 (22.9)	21 (13.6)
VEGF inhibitor	22 (14.4)	13 (8.4)
EGFR inhibitor	6 (3.9)	5 (3.2)
Nucleoside analog/thymidine phosphorylase inhibitor	2 (1.3)	2 (1.3)
CTLA-4 inhibitor	0	5 (3.2)
ICOS agonist	1 (0.7)	1 (0.6)
LAG-3 inhibitor	1 (0.7)	0
TIM3 inhibitor	1 (0.7)	1 (0.6)
Vaccine/viral therapy	0	2 (1.3)

Overall Survival



OS in Key Subgroups



Summary of Events in All Treated Patients

Events*	Pembrolizumab N = 153	Chemotherapy N = 143
All adverse events (AEs)	149 (97.4%)	142 (99.3%)
Treatment-related	122 (79.7%)	141 (98.6%)
Grade ≥3	33 (21.6%)	85 (66.4%)
Discontinued	15 (9.8%)	10 (7.0%)
Died	0	1 (0.7%)
Immune-mediated AEs and Infusion Reactions		
All	47 (30.7%)	21 (14.7%)
Grade ≥3	14 (9.2%)	3 (2.1%)
Discontinued	10 (6.5%)	1 (0.7%)
Died	0	0

*Percentages similar to those previously published: André T et al. N Engl J Med 2020;383:2207-18. Data cut-off: 19Feb2021.

Summary and Conclusions (1)

- Pembrolizumab versus chemotherapy provided statistically superior PFS as first-line therapy for patients with MSI-H mCRC
  - Pembrolizumab versus chemotherapy met the criteria for superiority in PFS at IA2[1]
  - Superiority was not formally tested at final analysis
- Fewer treatment-related adverse events observed with pembrolizumab versus chemotherapy: grade ≥3 treatment-related events (22% vs 66%)[1]
- Schedule with 30 minutes infusion Q3W more convenient compared to chemotherapy ± cetuximab and bevacizumab Q2W (48 hours)
- Pembrolizumab monotherapy provided clinically meaningful improvements in HRQoL versus chemotherapy in this population[1]
  - Limitations include open label trial and PROs as exploratory end points
  - Results are mostly limited to treatment period in first line

1. André T et al. N Engl J Med 2020;383:2207-18.

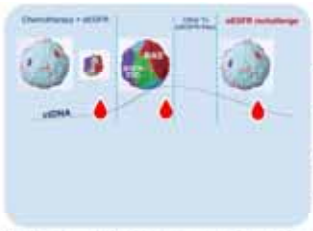
Summary and Conclusions (2)

- Treatment with pembrolizumab versus chemotherapy is associated with a non-statistically significant reduction in mortality
  - HR for OS: 0.74 (P = 0.0359; did not meet threshold for significance)
  - High crossover rate from chemotherapy to anti-PD-1/PD-L1 therapies in second line of 60%
- These data confirm pembrolizumab as standard of care in the first line for patients with MSI-H/dMMR mCRC

Background and rationale (I)

- Targeted therapeutic actionability in mCRC remains confined ERBB2, BRAF and MSI-H patients
- Most prevalent targeted Tx is driven by **negative *RAS/BRAF* selection** for EGFR-targeted moAbs
- All treated patients will eventually develop **resistance**

Background and rationale (II)



- Resistance to anti-EGFR moAbs is predominatly driven by mutant RAS and EGFR ectodomain clones[1,2]
- Resistance can be monitored by ctDNA in plasma[3]
- RAS/EGFR alleles decline upon anti-EGFR therapy withdrawal, leading the tumor to regain sensitivity[3,4]
- Clinical-based rechallenge has shown promising results[5-9]
- No data are available regarding the interventional use of ctDNA

Background and rationale (II)

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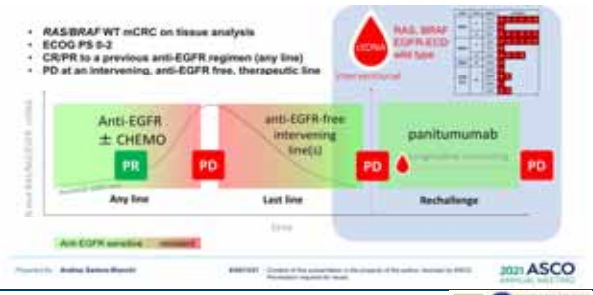
Anti-EGFR rechallenge strategies:
Clinical-based rechallenge ~ 20% ORR
Could ctDNA-driven rechallenge do better?

Trial Eligibility and Study Design

- *RAS/BRAF* WT mCRC on tissue analysis
- ECOG PS 0-2
- CR/PR to a previous anti-EGFR regimen (any line)
- PD at an intervening, anti-EGFR free, therapeutic line

Trial Eligibility and Study Design



Trial Eligibility, Objectives and Statistics

Eligibility

Main criteria:

- RAS/BRAF WT mCRC on tissue biopsy at diagnosis
- At least PR to previous anti-EGFR containing regimen
- RAS/BRAF/EGFR WT at molecular screening by ctDNA
- ECOG ≤2
- FFPE genotyping on archival solid tissue derived before anti-EGFR rechallenge

Endpoints

Primary:

- Response rate (RECIST, centrally reviewed)

Secondary:

- PFS
- OS
- Toxicity

Translational:

- ctDNA RAS/BRAF/EGFR dynamics
- ctDNA landscapes (baseline and PD)
- tDNA landscape (baseline)

Statistics

Design:
Phase II trial single-stage Fleming-A'Hern

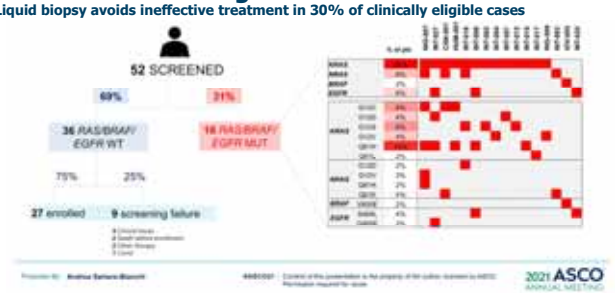
Assumption:
H_0: 10% ORR
H_1: ≥30% ORR
α=0.05; β=0.15

Sample size:
27 patients; ≥ 6 PR required to declare the study positive

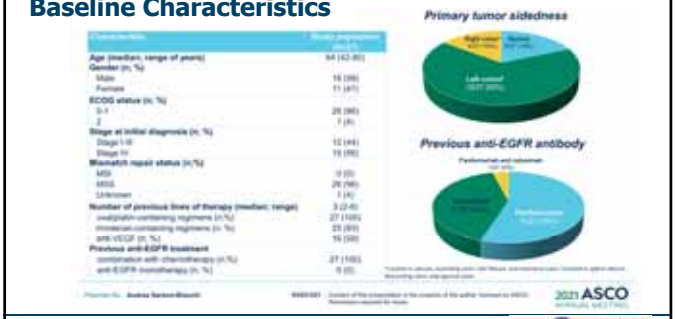
Data lock:
April 15, 2021

Molecular Screening: Results

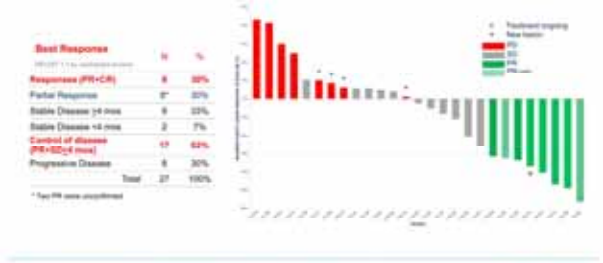
Liquid biopsy avoids ineffective treatment in 30% of clinically eligible cases



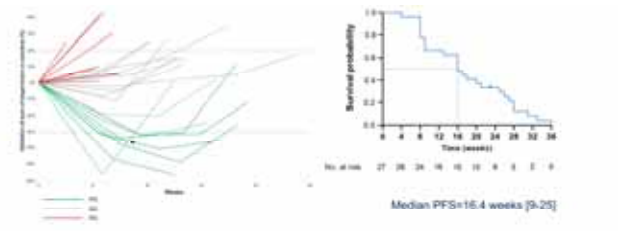
Baseline Characteristics



Objective Response Rate



Dynamics of Response and PFS



Conclusions

- CHRONOS is the first study of interventional liquid biopsy for guiding anti-EGFR therapy in mCRC
- A 30% response was achieved after ctDNA-driven rechallenge with panitumumab, meeting the primary endpoint of the trial
- ctDNA-guided rechallenge has 3 advantages over clinical-based rechallenge:
  1. Selects patients according to the actual molecular status of the tumor, independently of time intervals, previous therapies or sidedness
  2. Avoids a potentially useless treatment in approximately 30% of clinical-rechallenge eligible patients carrying resistance-conferring mutations
  3. Enhances objective response rate
- ORR favorably compares with standard of care in >2 line, making ctDNA-driven rechallenge a valid therapeutic option allowing to obtain tumor shrinkage even in pretreated mCRC

Genotyping tumor DNA in the blood to direct therapy can be effectively incorporated in the management of advanced CRCs

2021 ASCO ANNUAL MEETING

The TRUSTY study:
A randomized phase 2/3 study of trifluridine/tipiracil plus bevacizumab versus irinotecan and fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer

Yasutoshi Kuboki
National Cancer Center Hospital East, Japan
on behalf of the TRUSTY study group
Tetsuji Terazawa, Toshiki Masuishi, Masato Nakamura, Jun Watanabe, Hitoshi Ojima, Yudai Shinohara, Masahito Kotaka, Hiroki Hara, Takashi Ota, Eiji Oki, Yu Sunakawa, Soichiro Ishihara, Hiroya Taniguchi, Takako Eguchi Nakajima, Satoshi Morita, Kuniaki Shirao, Takayuki Yoshino

June 7, 2021

Background-1 (No evidence of FTD/TPI+BEV in 2nd-line setting)

- **3rd-line and subsequent treatment,**
  - ✓ Efficacy of trifluridine/tipiracil (FTD/TPI)+bevacizumab (BEV) has been demonstrated in clinical trials.[1-4]
    - ➢ mOS 9.1–11.4 months; mPFS 3.7–5.6 months; ORR 2–6.3%; DCR 61–72%
  - ✓ FTD/TPI+BEV is recommended in the NCCN guidelines.
- **1st-line treatment,**
  - ✓ FTD/TPI+BEV showed promising efficacy in patients ineligible for intensive therapy or in elderly patients.[3-6]
    - ➢ mOS 18–22.4 months; mPFS 9.2–9.4 months; ORR 34–40.5%; DCR 86–86.5%

TRUSTY Study Design

Non-inferiority

Prior to randomization, either 5-FU or S-1 was declared by each investigator when allocated FP+IRI+BEV.

mCRC in 2nd-line

- Progression on 1st-line treatment
- Fluoropyrimidine (5-FU/LV/S, Capecitabine, S-1)
- Oxaliplatin
- BEV or anti-EGFR antibody
- ECOG PS: 0 or 1
- Age: 20 years or older

R 1:1 n=524

Fluoropyrimidine+Irinotecan+BEV (FP+IRI+BEV)

FOLFIRI + BEV (q2w), S-1 + Irinotecan + BEV (q3w, p4w)

FTD/TPI+BEV

BEV: 5 mg/kg IV on d1, d15

FTD/TPI: 35 mg/m² bid orally d1-5 and d8-12, q4w

Stratification factors
- KRAS status (WGA-type vs. Mutant)
- Primary tumor location (Left-sided vs. Right-sided)
- 1st-line treatment with molecularly targeted drug (BEV vs. Anti-EGFR antibody*)

*Not included in this presentation

Primary endpoint
- Overall survival (OS)

Secondary endpoints
- Progression-free survival (PFS)
- Time to treatment failure (TTF)*
- Response rate (RR)
- Disease control rate (DCR)
- Subsequent treatment
- Time to post-study treatment failure (TTF2)
- Quality of life (QOL)*
- Adverse events (AE)

*not included in this presentation

Stratification factors

Common adverse events

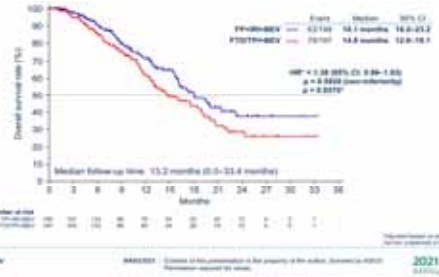
Events (CTC-AE v4.0)	FP+IRI+BEV (n = 197) All		FP+IRI+BEV (n = 197) ≥Grade 3		FTD/TPI+BEV (n = 196) All		FTD/TPI+BEV (n = 196) ≥Grade 3	
	n	(%)	n	(%)	n	(%)	n	(%)
All events	**188**	**(95.4)**	**131**	**(66.5)**	**188**	**(95.9)**	**152**	**(77.6)**
Hematological								
Leukopenia	36	(18.3)	18	(9.1)	85	(43.4)	49	(25.0)
Neutropenia	124	(62.9)	82	(41.6)	154	(78.6)	129	(65.8)
Thrombocytopenia	21	(10.7)	2	(1.0)	37	(18.9)	9	(4.6)
Anemia	20	(10.2)	6	(3.0)	44	(22.4)	12	(6.1)
Non-hematological								
Febrile neutropenia	5	(2.5)	5	(2.5)	4	(2.0)	4	(2.0)
Stomatitis	48	(24.4)	3	(1.5)	29	(14.8)	1	(0.5)
Nausea	61	(31.0)	4	(2.0)	59	(30.1)	2	(1.0)
Vomiting	20	(10.2)	2	(1.0)	20	(10.2)	0	(0.0)
Diarrhea	81	(41.1)	14	(7.1)	63	(32.1)	3	(1.5)
Anorexia	70	(35.5)	12	(6.1)	86	(43.9)	5	(2.6)
Fatigue	38	(19.3)	6	(3.0)	42	(21.4)	4	(2.0)
Alopecia*	49	(24.9)	-	-	7	(3.6)	-	-

*Grade 1-2 in each arm

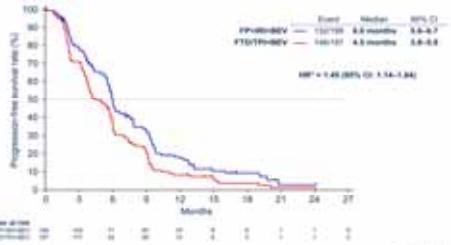
19 patients (9.5%, FP+IRI+BEV) and 17 patients (8.8%, FTD/TPI+BEV) received G-CSF

Primary endpoint

Overall survival



Progression-free survival



Best overall response

	FP+IRI+BEV (n = 184*) %		FTD/TPI+BEV (n = 183*) %		p value
CR	0.0	(n = 0)	0.0	(n = 0)	
PR	7.1	(n = 13)	3.8	(n = 7)	
SD	64.7	(n = 119)	57.4	(n = 105)	
PD	13.6	(n = 25)	24.6	(n = 45)	
NE	14.7	(n = 27)	14.2	(n = 26)	
Response rate	**7.1**	(n = 13)	**3.8**	(n = 7)	0.2438
95% CI (%)	[3.8–11.8]		[1.6–7.7]		
Disease control rate	**71.7**	(n = 132)	**61.2**	(n = 112)	0.0359
95% CI (%)	[64.6–78.1]		[53.7–68.3]		

2021 ASCO ANNUAL MEETING

DESTINY-CRC01

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-expressing Metastatic Colorectal Cancer: Final Results From a Phase 2, Multicenter, Open-label Study (DESTINY-CRC01)

Takayuki Yoshino; National Cancer Center Hospital East, Kashiwa, Japan

June 7, 2021

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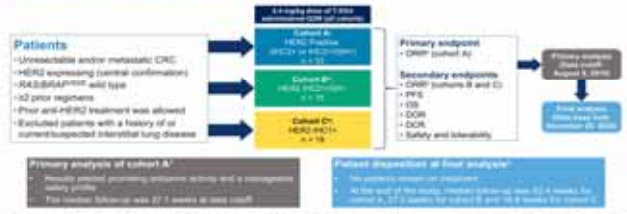
On behalf of the DESTINY-CRC01 investigators

Unmet Clinical Need for Approved Targeted Therapies in HER2-Positive Metastatic CRC

- HER2 overexpression in mCRC
  - CRC is the 3rd most common type of cancer and ~25% of patients have metastatic CRC, of which around 2-3% of patients have HER2-amplified tumors[1-3]
  - Current treatment options are fluoropyrimidine with oxaliplatin and/or irinotecan with an anti-VEGF compound or anti-EGFR monoclonal antibody (depending on the *RAS* mutational status)[4]
  - Other therapies including regorafenib and trifluridine/tipiracil are recommended in the third-line or subsequent settings[5,6]
    - Median OS was 6.4 months for regorafenib compared to 5.0 months for placebo[7] and 7.1 months for trifluridine/tipiracil compared to 5.3 months for placebo[8]
  - There are currently no approved HER2-targeted therapies for CRC[9,10]
- Trastuzumab deruxtecan
  - T-DXd is an antibody-drug conjugate[9,10] designed to deliver an optimal antitumor effect
  - Primary results of T-DXd treatment (6.4 mg/kg Q3W) in patients with HER2-overexpressing mCRC demonstrated antitumor activity[11]

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)



Baseline Characteristics

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 33)	HER2 IHC2+/ISH- Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 66)
Age, median (range), years	57.0 (27-79)	62.0 (37-78)	58.5 (43-73)	58.5 (27-79)
Female, %	52.8	33.3	38.9	46.5
Region, %				
Europe	52.8	60.0	50.0	53.5
Asia	28.3	20.0	44.4	30.2
North America	18.9	20.0	5.6	16.3
ECOG performance status, %				
0	69.8	53.3	50.0	62.8
1	30.2	46.7	44.4	36.0
2	0	0	5.6	1.2
Sum of target lesions, median, cm	8.1	8.1	10.2	9.0
Primary tumor site, %[a]				
Left	88.6	93.3	94.4	90.7
Right	11.4	6.7	5.6	9.3

Baseline Characteristics (cont)

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH- Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Microsatellite status, %[a]				
MSI-H	0	0	0	0
Microsatellite stable	81.1	93.3	66.7	80.2
Unknown	18.9	6.7	33.3	19.8
***RAS* wild type, %[a,b]**	98.1	93.3	100	97.7
***BRAF*[V600E] wild type, %[a,b]**	100	100	94.4	98.8
HER2 status, %[c]				
IHC 3+	75.5	0	0	46.5
IHC 2+	24.5	100	0	32.6
IHC 1+	0	0	100	20.9
ISH+	98.1[d]	0	22.2	65.1
ISH-	0	100	77.8	33.7

Prior Treatments

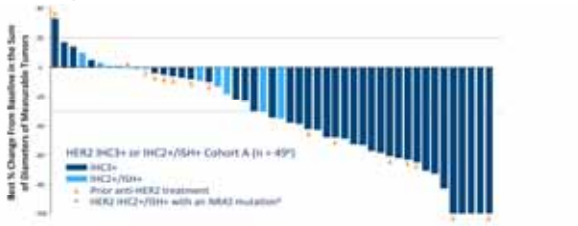
Prior Treatment, %	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH- Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Irinotecan	100	100	100	100
Fluorouracil / capecitabine	100 / 54.7	93.3 / 46.7	100 / 55.6	98.8 / 53.5
Oxaliplatin	100	93.3	100	98.8
Cetuximab or panitumumab	100	100	94.4	98.8
Bevacizumab	75.5	73.3	83.3	76.7
Prior anti-HER2 agents	30.2	0	0	18.6

- Median prior regimens for metastatic disease was 4 (range, 2–11)

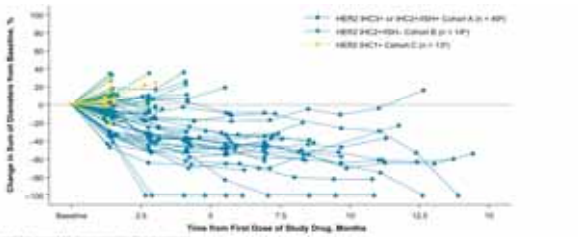
Efficacy Results

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH- Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
Confirmed ORR by ICR, n (%) [95% CI]	**24 (45.3)** [31.6-59.6]	0 [0.0-21.8]	0 [0.0-18.5]
CR	0	0	0
PR	24 (45.3)	0	0
SD	20 (37.7)	9 (60.0)	4 (22.2)
PD	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[e]	4 (7.5)	1 (6.7)	4 (22.2)
Disease control rate, % (95% CI)	83.0 (70.2-91.9)	60.0 (32.3-83.7)	22.2 (6.4-47.6)
Median duration of response, (95% CI) months	7.0 (5.5-9.5)	NE (NE-NE)	NE (NE-NE)
Median treatment duration, (95% CI) months	5.1 (3.9-7.6)	2.1 (1.4-2.6)	1.4 (1.3-1.5)

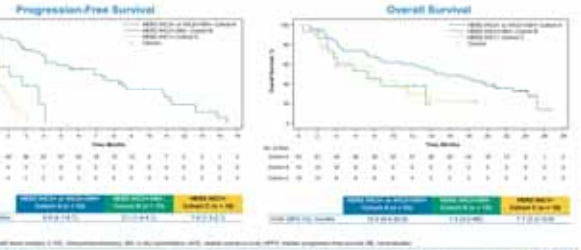
Best Change in Tumor Size in Cohort A



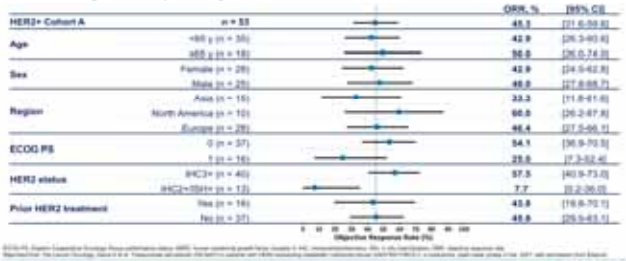
Change in Tumor Size Over Time



Progression-Free and Overall Survival



ORR by Subgroup in Cohort A



Overall Safety Summary

n (%)	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH− Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
TEAEs	53 (100)	15 (100)	18 (100)	86 (100)
Grade 3 or above	36 (68.0)	7 (46.7)	14 (77.8)	56 (65.1)
Drug-related TEAEs	51 (96.2)	15 (100)	15 (83.3)	81 (94.2)
Grade 3 or above	29 (54.7)	4 (26.7)	9 (50.0)	42 (48.8)
Serious TEAEs	20 (37.7)	0 (40.0)	9 (50.0)	35 (40.7)
Drug-related serious TEAEs	12 (22.6)	2 (13.3)	2 (11.1)	16 (18.6)
TEAEs leading to drug discontinuations	8 (15.1)	2 (13.3)	3 (16.7)	13 (15.1)
Drug-related TEAEs leading to drug discontinuations	4 (7.5)	2 (13.3)	1 (5.6)	7 (8.1)
TEAEs leading to dose reduction	11 (20.8)	0	4 (22.2)	15 (17.4)
Drug-related TEAEs leading to dose reduction	10 (18.9)	0	4 (22.2)	14 (16.3)
TEAEs leading to drug interruption	26 (49.1)	3 (20.0)	5 (27.8)	34 (39.5)
Drug-related TEAEs leading to drug interruption	19 (35.8)	1 (6.7)	3 (16.7)	23 (26.7)
TEAEs associated with death	3 (5.4)	2 (13.3)	2 (11.1)	8 (10.5)
Drug-related TEAEs associated with death*	2 (3.8)	1 (6.7)	0	3 (3.5)

TEAEs in ≥20% of Patients

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH− Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)	
n (%)	Any Grade	Any Grade	Any Grade	Any Grade	Grade ≥3
Patients with any TEAE	53 (100)	15 (100)	18 (100)	86 (100)	56 (65.1)
Nausea	37 (69.8)	9 (60.0)	7 (38.9)	53 (61.6)	5 (5.8)
Anemia	21 (39.6)	4 (26.7)	6 (33.3)	31 (36.0)	12 (14.0)
Fatigue	21 (39.6)	7 (46.7)	3 (16.7)	31 (36.0)	1 (1.2)
Decreased appetite	18 (34.0)	5 (33.3)	7 (38.9)	30 (34.9)	0
Platelet count decreased	17 (32.1)	4 (26.7)	7 (38.9)	28 (32.6)	8 (9.3)
Vomiting	23 (43.4)	3 (20.0)	1 (5.6)	27 (31.4)	1 (1.2)
Neutrophil count decreased	20 (37.7)	2 (13.3)	4 (22.2)	26 (30.2)	19 (22.1)
Diarrhea	19 (35.8)	0	4 (22.2)	23 (26.7)	1 (1.2)

AEs of Special Interest: Interstitial Lung Disease

All Patients (N=85)	n (%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)[a]
Any Grade/Total	8 (9.3)[a]

Adjudicated drug-related ILDs:
- Median time to adjudicated onset was 61.0 days (range, 9-165 days)
- 8 of 8 patients received corticosteroids
- 4 patients with grade 2 recovered and 1 patient with grade 3 did not recover (later died due to disease progression)
- Median time from adjudicated onset date to initiation of steroid treatment in the 8 ILD cases was 3.5 days, (range 0-50)

Grade 5 ILDs:
- In the 3 fatal cases adjudicated as drug-related ILD, onset was from 9 days to 120 days (median: 22 days); and death occurred 6-19 days after diagnosis (median: 6 days)

Updated ILD/pneumonitis guidelines recommend to monitor for symptoms, interrupt or discontinue T-DXd, conduct imaging (as clinically indicated), and start steroids as soon as ILD is suspected.

Conclusions

- **T-DXd monotherapy at the 6.4 mg/kg Q3W dose showed promising activity and durability with longer-term follow-up (additional 35.3 weeks from the primary analysis) in patients with HER2+ mCRC**
  - For cohort A, confirmed ORR was 45.3% (95% CI, 31.6–59.6), mDOR was 7.0 months (95% CI, 5.8–9.5), mPFS was 6.9 months (95% CI, 4.1-8.7), and mOS was 15.5 months (95% CI, 8.8–20.8)
- **No responses for ORR were observed in cohorts B and C**
- **The safety profile is consistent with the known safety profile of T-DXd**
  - Low grade gastrointestinal and hematologic AEs were most common[1]
  - ILD/pneumonitis (9.3% of patients; 3.5% grade 5) is an important risk and requires careful monitoring and prompt intervention
- **These promising results support continued exploration of T-DXd in patients with HER2+ mCRC**

2021 ASCO ANNUAL MEETING

Abstract Number for Publication: 3501

THE RANDOMIZED PHASE II STUDY OF FOLFOXIRI PLUS CETUXIMAB VERSUS FOLFOXIRI PLUS BEVACIZUMAB AS THE FIRST-LINE TREATMENT IN METASTATIC COLORECTAL CANCER WITH RAS WILD-TYPE TUMORS: THE DEEPER TRIAL (JACCRO CC-13)

Akihito TSUJI*

Hisatsugu Ohod, Tatsuro Yamaguchi, Masato Matsuura, Atsuro Nishioka, Akitaka Makiyama, Shingo Noura, Mitsugu Kochi, Tamotsu Sagawa, Masahito Kobaka, Yutaro Kubota, Yu Sunakawa, Takashi Sekikawa, Masato Nakamura, Masahito Takeuchi, Wataru Ishikawa and Masashi Fuji

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7th June, 2021

JACCRO

Japan Clinical Cancer Research Organization (JACCRO)

Backgrounds

- ✓ Triplet regimens, FOLFOXIRI, combined with bevacizumab or panitumumab have been shown to be superior in terms of early tumor shrinkage (ETS) and depth of response (DpR) compared to doublet regimen plus bevacizumab or triplet regimen in patients with *RAS* wild-type metastatic colorectal cancer (mCRC).

Study	Phase	Arm	No. of patients	ORR	PFS	OS
TRIBE trial[1]	III	FOLFIRI + Bevacizumab	256	53.1%	9.7m	25.8m
		FOLFOXIRI + Bevacizumab	252	65.1%	12.1m	31.0m
VOLFI trial[2] (AIO KRK0109)	III	FOLFOXIRI	33	60.6%	9.7m	29.8m
		mFOLFOXIRI + Panitumumab	63	87.3%	9.7m	35.7m

- ✓ There have been few studies which directly compared cetuximab with bevacizumab when combined with triplet regimen.

1 Loupakis S, et al. N Engl J Med 2014 23;371(17):1609-18
2 Modest DP, et al. J Clin Oncol 2019 10;37(35):3401-3411

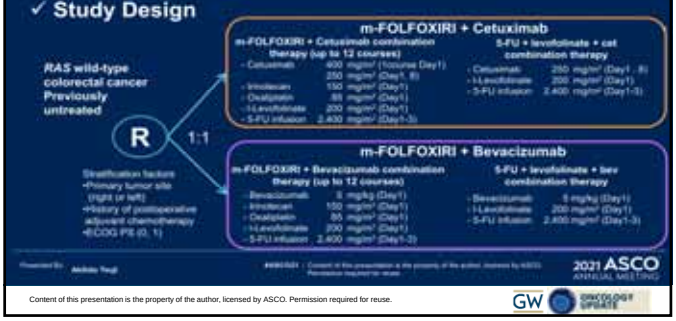
Objectives

To evaluate the efficacy and safety of modified (m)-FOLFOXIRI plus cetuximab versus bevacizumab as first-line treatment in *RAS* wild-type mCRC.

- Primary endpoint: Depth of response (DpR) during the entire course
- Secondary endpoints:
  - ✓ Early tumor shrinkage (ETS) rate at week 8
  - ✓ Overall response rate (ORR)
  - ✓ Progression-free survival (PFS) and Overall survival (OS)
  - ✓ R0 resection rate
  - ✓ Toxicity
  - ✓ DpR at month 4, Time to treatment failure, Time to tumor growth (TTG), Association between tumor shrinkage and prognosis, Association between TTG and prognosis, Secondary resection rate

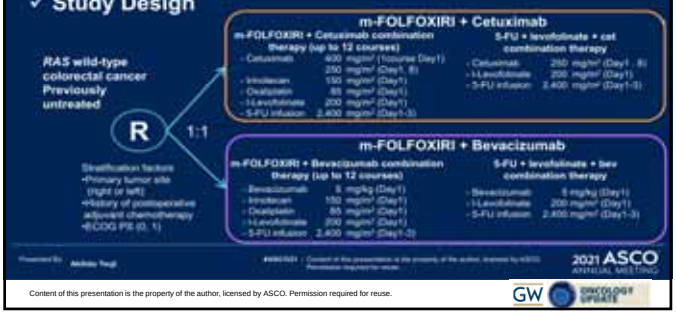
Methods

✓ Study Design



Methods

✓ Study Design



GW ONCOLOGY UPDATE

Methods

✓ Statistical considerations

- The experimental arm with cet was considered to be active if the difference of median DpR was over 12.5% compared with the bev arm, under the conditions of significance level of 0.05 and power of 0.85.
- Showing that a minimum of 338 patients were required. Thus, the nominal sample size was determined to be 360 patients considering ineligibility.
- The DpR analysis for primary endpoint was performed in the per-protocol population with cases evaluable for the DpR according to study protocol.

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Patient characteristics

	m-FOLFOXIRI + Cetuximab (n=175)	m-FOLFOXIRI + Bevacizumab (n=173)
Sex Male / Female	109 (62.3%) / 66 (37.7%)	113 (65.3%) / 60 (34.7%)
Age (years) Median (Range)	65 (26-83)	65 (29-85)
Primary tumor site Colon / Rectum	100 (57.1%) / 75 (42.9%)	100 (57.8%) / 73 (42.2%)
Site of primary tumor Right / Left	31 (17.7%) / 144 (82.3%)	30 (17.3%) / 143 (82.7%)
Adjuvant Chemotherapy None / With oxaliplatin / Without oxaliplatin	161 (92.0%) / 8 (4.6%) / 6 (3.4%)	159 (91.9%) / 9 (5.2%) / 5 (2.9%)
ECOG performance status 0 / 1	160 (91.4%) / 15 (8.6%)	157 (90.8%) / 16(9.2%)
Diagnosis Advanced / Relapse	148 (84.6%) / 27 (15.4%)	142 (82.1%) / 31 (17.8%)

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Patient characteristics (cont.)

	m-FOLFOXIRI + Cetuximab (n=175)	m-FOLFOXIRI + Bevacizumab (n=173)
Primary Lesion		
- / +	90 (51.4%) / 85 (48.6%)	95 (54.9%) / 78 (45.1%)
UGT1A1(*6, *28)		
wild/ heteral homo & double hetero	71 (40.6%) / 85 (37.1%) / 10 (5.7%)	73 (42.2%) / 52 (30.1%) / 23 (13.3%)
Metastasis		
- / +	2 (1.1%) / 173 (98.9%)	4 (2.3%) / 169 (97.7%)
Metastasis Sites		
Liver	128 (73.1%)	123 (71.1%)
Lung	46 (26.3%)	39 (22.6%)
Para-aortic lymph node	53 (30.3%)	33 (19.1%)
Regional lymph node	60 (34.3%)	54 (31.2%)
Peritoneum	38 (21.7%)	26 (15.0%)
Ascites	19 (10.9%)	8 (4.6%)
Bone	4 (2.3%)	4 (2.3%)

Depth of Response <primary endpoint>

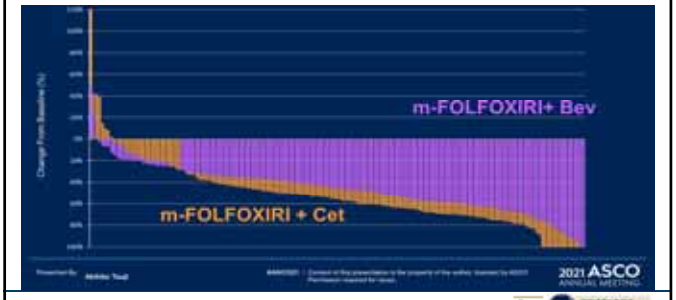
✓ By Central Review

	m-FOLFOXIRI + Cetuximab (n=158*)	m-FOLFOXIRI + Bevacizumab (n=162*)
Median (Range)	57.4% (-15.0-100)	46.0% (-0.6-100)
Mean (95%CI)	55.8% (51.9-59.7)	47.3 % (44.1-50.5)
Standard Deviation (95%CI)	25.06 (22.6-28.2)	20.53 (18.5-23.0)
t-test by welch	p=0.0010	

*DpR was analyzed in the per-protocol set population.

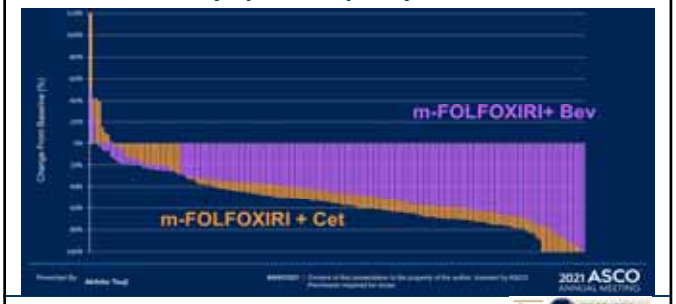
Waterfall Plot (Depth of Response)

✓ By Central Review



Waterfall Plot (Depth of Response)

✓By Central Review



Depth of Response by tumor location

Tumor location	Left		Right	
	m-FOLFOXIRI + Cetuximab (n=131)	m-FOLFOXIRI + Bevacizumab (n=137)	m-FOLFOXIRI + Cetuximab (n=27)	m-FOLFOXIRI + Bevacizumab (n=25)
Median (Range)	60.3 (-9.8-100)	45.1 (3.2-100)	50.0 (-15.0-100)	41.2 (-0.6-85.6)
Mean (95%CI)	57.5 (53.2-61.7)	48.2 (44.9-51.5)	47.7 (37.3-58.1)	42.5 (32.1-52.9)
Standard Deviation (95%CI)	24.59 (21.93-27.99)	19.55 (17.48-22.18)	26.19 (20.63-35.90)	25.17 (19.65-35.02)
t-test by welch	p<0.0001		p=0.4683	

Overall Response Rate

		m-FOLFOXIRI + Cetuximab (n=175)	m-FOLFOXIRI + Bevacizumab (n=173)
Best Response	Complete Response	11 (6.3%)	4 (2.3%)
	Partial Response	110 (62.9%)	120 (69.4%)
	Stable Disease	38 (21.7%)	41 (23.7%)
	Progressive Disease	8 (4.6%)	3 (1.7%)
	Not Evaluated	8 (4.6%)	5 (2.9%)
Overall Response Rate (95%CI)		69.1% (62.3-76.0)	71.7% (65.0-78.4)
Chi Square Test		p=0.6047	
Disease control rate (95%CI)		90.9% (86.6-95.1)	95.4% (92.2-98.5)
Chi Square Test		p=0.0963	

Early Tumor Shrinkage (ETS) Rate at week 8

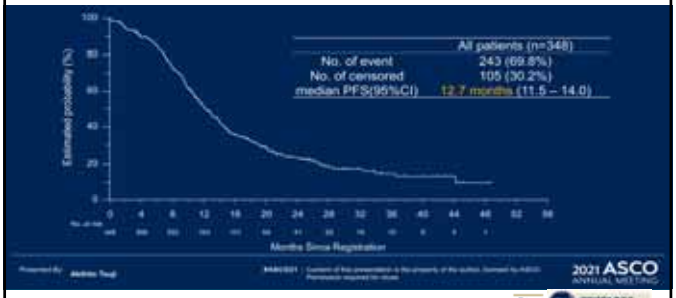
	m-FOLFOXIRI + Cetuximab (n=167*)	m-FOLFOXIRI + Bevacizumab (n=169*)
No. of ETS	130	126
ETS rate	77.8%	74.6%
Chi Square Test	p=0.4792	

*ETS rate was analyzed in the ETS evaluable population

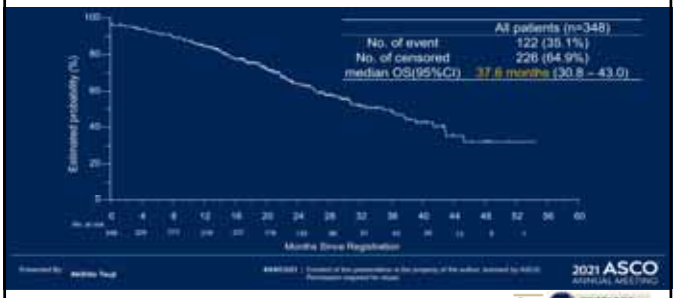
R0 Resection Rate

	m-FOLFOXIRI + Cetuximab (n=175)	m-FOLFOXIRI + Bevacizumab (n=173)
No. of Resection	50	53
R0 Resection Rate (95%CI)	28.6% (21.9-35.3)	30.6% (23.8-37.5)
Chi Square Test	p=0.6732	

Progression-Free Survival in the FAS population



Overall Survival in the FAS population



Conclusion

✓The m-FOLFOXIRI plus cetuximab has been shown to be significantly superior to the m-FOLFOXIRI plus bevacizumab in terms of DpR as the primary endpoint in first-line treatment for *RAS* wild-type mCRC.

2021 ASCO ANNUAL MEETING

RANDOMIZED STUDY TO INVESTIGATE FOLFOXIRI PLUS EITHER BEVACIZUMAB OR CETUXIMAB AS FIRST-LINE TREATMENT OF BRAF V600E-MUTANT MCRC

THE PHASE-III FIRE-4.5 STUDY (AIO KRK-0116)

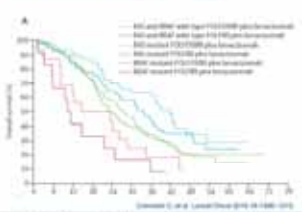
Prof. Sebastian Stintzing MD
Charité – Universitätsmedizin Berlin

June 1st 2021

Rationale of the study design

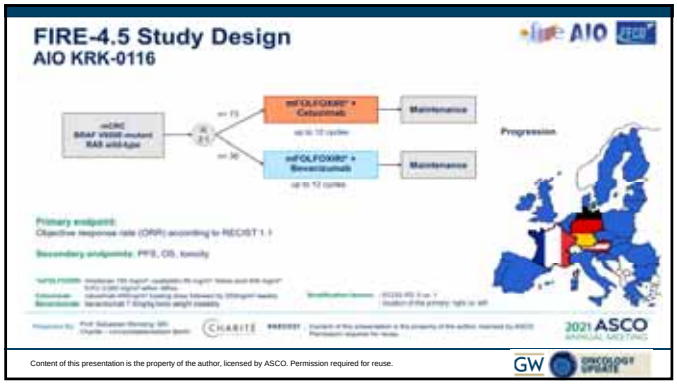
→ Prospective randomized data on BRAF V600E mutant in first-line mCRC are missing.

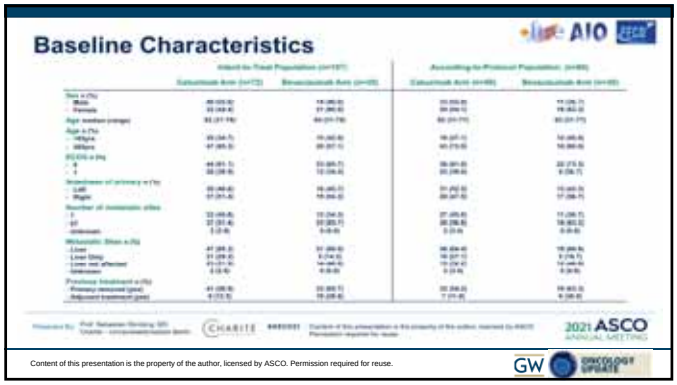
→ The use of EGFR antibodies in BRAF V600E mutant mCRC is controversial.

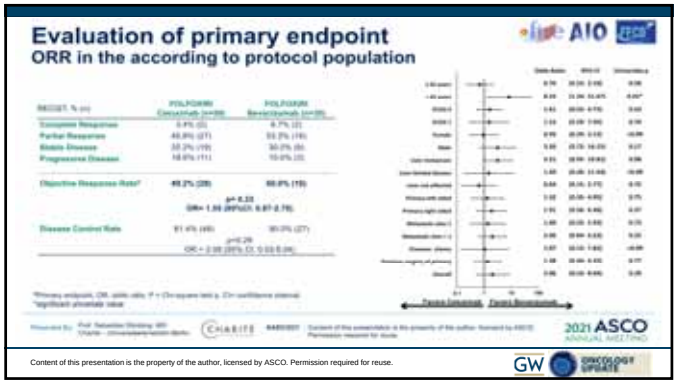


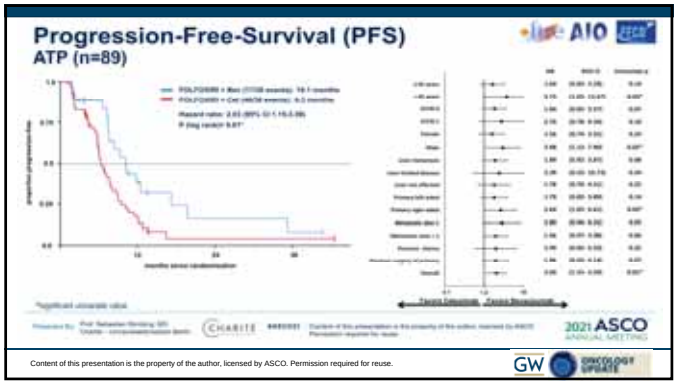
BJC

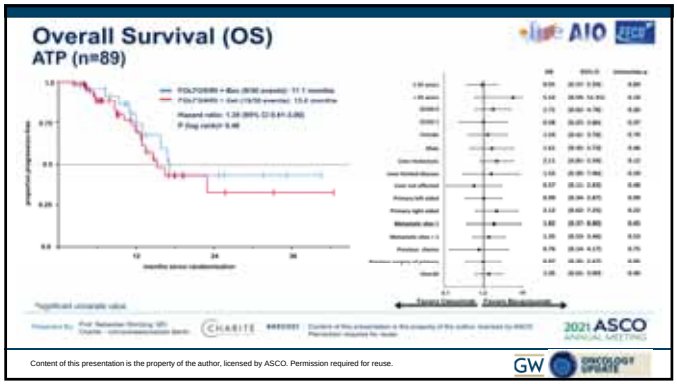
Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer

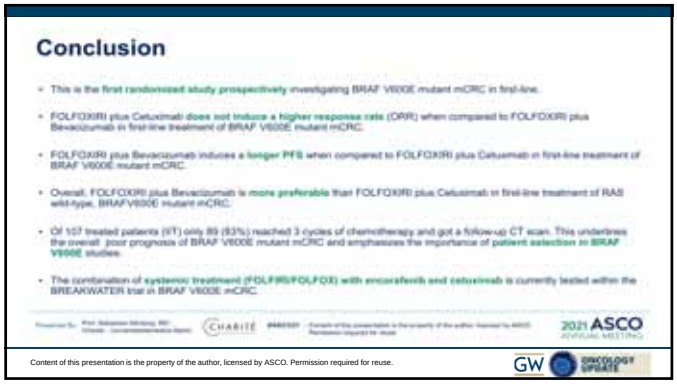












2021 ASCO ANNUAL MEETING

Nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: first results of the CheckMate 648 study

Ian Chau,[1] Yuichiro Doki,[2] Jaffer A. Ajani,[3] Jianming Xu,[4] Lucjan Wyrwicz,[5] Satoru Motoyama,[6] Takeshi Ogata,[7] Hisato Kawakami,[8] Chih-Hung Hsu,[9] Antoine Adenis,[10] Farid el Hajbi,[11] Maria Di Bartolomeo,[12] Maria Ignez Braghiroli,[13] Eva Holtved,[14] Ioannis Xynos,[15] Xuan Liu,[15] Ming Lei,[15] Kaoru Kondo,[15] Ken Kato,[16] Yuko Kitagawa[17]

Abstract Number: LBA4001

GW ONCOLOGY UPDATE

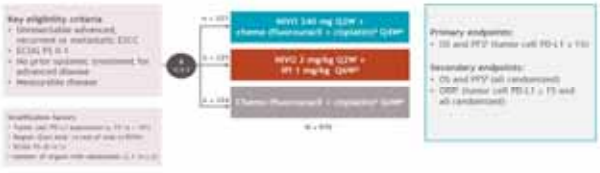
Introduction

- EC leads to over half a million deaths each year globally and ESCC accounts for ~85% of all EC cases[1,2]
- Standard 1L chemotherapy for advanced or metastatic ESCC results in poor OS (median ~ 1 year)[3-9]
- NIVO monotherapy demonstrated superior OS vs chemo in previously treated patients with advanced ESCC (ATTRACTION-3)[10]
- CheckMate 648 is the first global phase 3 study to evaluate the efficacy and safety of an I-O/I-O combination, along with an I-O/chemo combination, in advanced ESCC
- We report the first results of NIVO + chemo and NIVO + IPI vs chemo from CheckMate 648

GW ONCOLOGY UPDATE

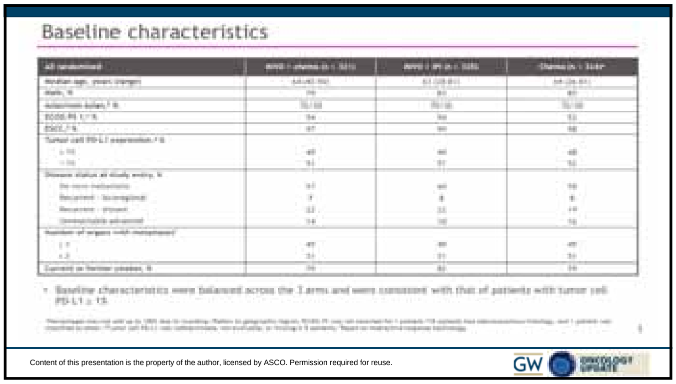
CheckMate 648 study design

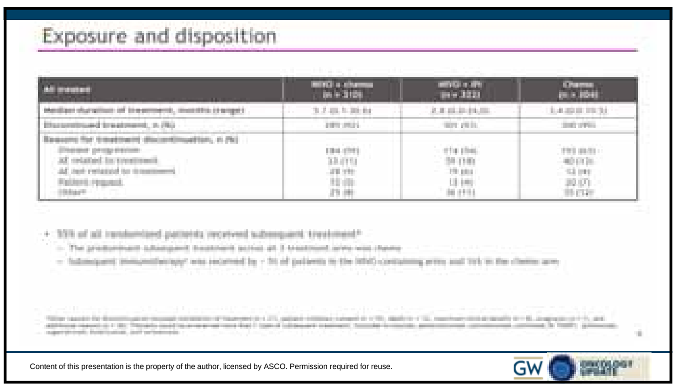
- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

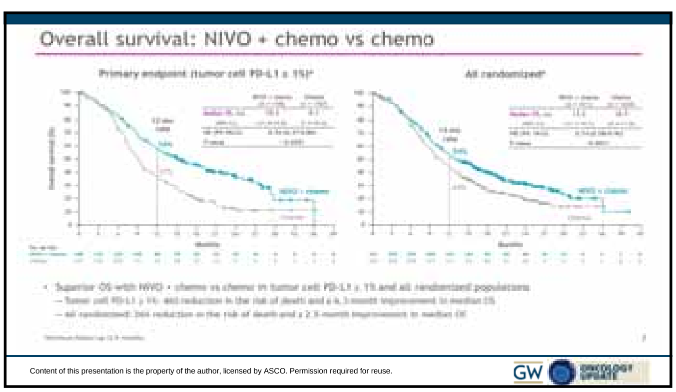


- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[a]

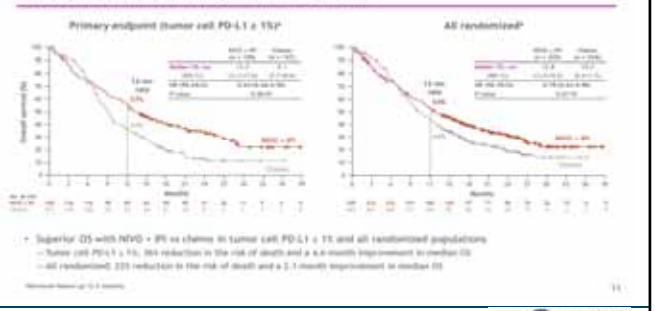
GW ONCOLOGY UPDATE





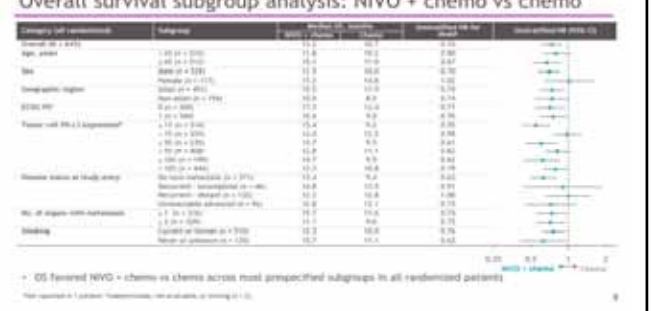


Overall survival: NIVO + IPI vs chemo



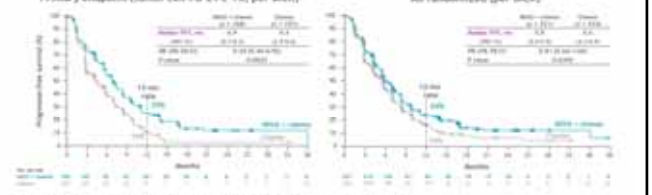
- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 6.4-month improvement in median OS
  - All randomized: 23% reduction in the risk of death and a 3.1-month improvement in median OS

Overall survival subgroup analysis: NIVO + chemo vs chemo



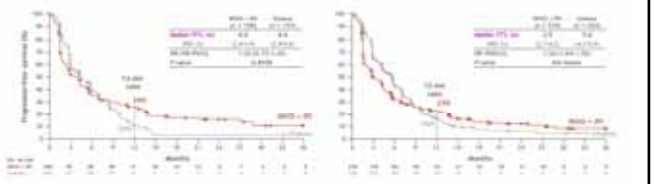
- OS favored NIVO + chemo vs chemo across most prespecified subgroups in all randomized patients

Progression-free survival: NIVO + chemo vs chemo



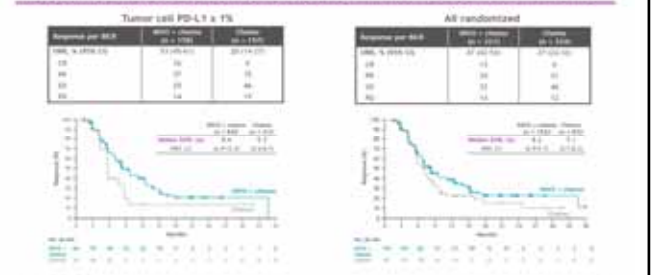
- Primary endpoint of PFS per BICR met in patients with tumor cell PD-L1 ≥ 1%
- Prespecified significance boundary for PFS per BICR not met in all randomized patients
- Improved PFS per INVP with HR of 0.53 (95% CI, 0.41-0.69) in tumor cell PD-L1 ≥ 1% and 0.69 (95% CI, 0.58-0.83) in all randomized populations

Progression-free survival: NIVO + IPI vs chemo

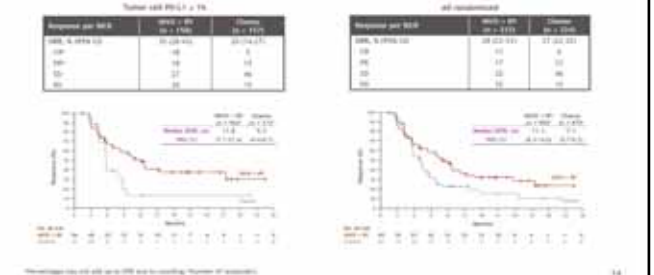


- Primary endpoint of PFS per BICR not met in patients with tumor cell PD-L1 ≥ 1%
- PFS per BICR not hierarchically tested in all randomized patients
- Directionally improved PFS per IRF* with HR of 0.83 (95% CI, 0.64-1.07) in tumor cell PD-L1 ≥ 1% and 1.01 (95% CI, 0.85-1.21) in all randomized population

Response and duration of response: NIVO + chemo vs chemo



Response and duration of response: NIVO + IPI vs chemo



TRAEs with potential immunologic etiology

Select TRAEs[a] All treated,[b] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3–4[a]	Any grade	Grade 3–4[a]	Any grade	Grade 3–4
Endocrine	36 (12)	4 (1)	88 (27)	19 (6)	1 (< 1)	0
Gastrointestinal	64 (21)	7 (2)	38 (12)	5 (2)	47 (15)	7 (2)
Hepatic	32 (10)	7 (2)	42 (13)	14 (4)	12 (4)	2 (< 1)
Pulmonary	18 (6)	2 (< 1)	26 (8)	9 (3)	2 (< 1)	0
Renal	74 (24)	7 (2)	8 (2)	2 (< 1)	57 (19)	5 (2)
Skin	54 (17)	1 (< 1)	110 (34)	13 (4)	11 (4)	0

- The majority of select TRAEs were grade 1 or 2
- Grade 3-4 events occurred in ≤ 6% of patients across organ categories

Summary

- NIVO is the first PD-1 inhibitor to demonstrate superior OS and durable responses in combination with either chemo or IPI vs chemo alone, in previously untreated patients with advanced ESCC
  - Statistically significant and clinically meaningful OS benefit with NIVO + chemo and NIVO + IPI for patients with tumor cell PD-L1 ≥ 1% and all randomized patients
  - Clinically meaningful PFS benefit and higher ORR with NIVO + chemo
  - Longer duration of response with NIVO-containing regimens
- No new safety signals were identified with NIVO + chemo or NIVO + IPI
- NIVO + chemo and NIVO + IPI each represent a new potential 1L standard of care for patients with advanced ESCC

2021 ASCO ANNUAL MEETING

First-line nivolumab plus chemotherapy vs chemotherapy in advanced gastric cancer/ gastroesophageal junction cancer/esophageal adenocarcinoma: expanded efficacy and safety data from CheckMate 649

Markus Moehler,[1] Kohei Shitara,[2] Marcelo Garrido,[3] Pamela Salman,[4] Lin Shen,[5] Lucjan Wyrwicz,[6] Kensei Yamaguchi,[7] Tomasz Skoczylas,[8] Arnoldo Campos Bragagnoli,[9] Tianshu Liu,[10] Michael Schenker,[11] Patricio Yanez,[12] Mustapha Tehfe,[13] Mengshun Li,[14] Dana Cullen,[14] Samira Soleymani,[14] Ming Lei,[14] Hong Xiao,[14] Yelena Y. Janjigian,[15] Jaffer A. Ajani[16]

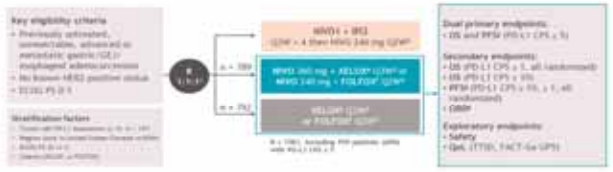
Abstract Number 4002

Introduction

- Standard 1L chemotherapy for advanced or metastatic, HER2-negative GC/GEJC results in poor OS (median ~ 1 year)[1-4]
- PD-L1 expression by CPS[a] has shown better enrichment for efficacy of checkpoint inhibitors than tumor cell PD-L1 expression in GC/GEJC/EAC[5]
- CheckMate 649 is the largest randomized, global phase 3 study of 1L PD-1 inhibitor-based therapies in advanced GC/GEJC/EAC[1]
- CheckMate 649 demonstrated superior OS, along with PFS benefit and an acceptable safety profile, with NIVO + chemo vs chemo alone in patients whose tumors expressed PD-L1 CPS ≥ 5, ≥ 1, and in all randomized patients[6]
  - Based on these results, NIVO + chemo received FDA approval as 1L treatment for GC/GEJC/EAC[7]
- We present expanded efficacy and safety analysis in all randomized patients from CheckMate 649

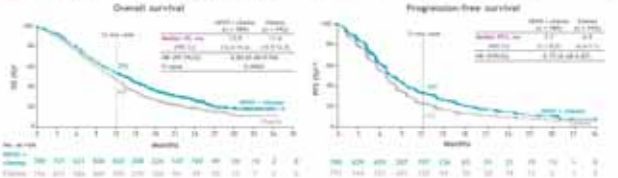
CheckMate 649 study design

- CheckMate 649 is a global, randomized, open-label, phase 3 study[a]

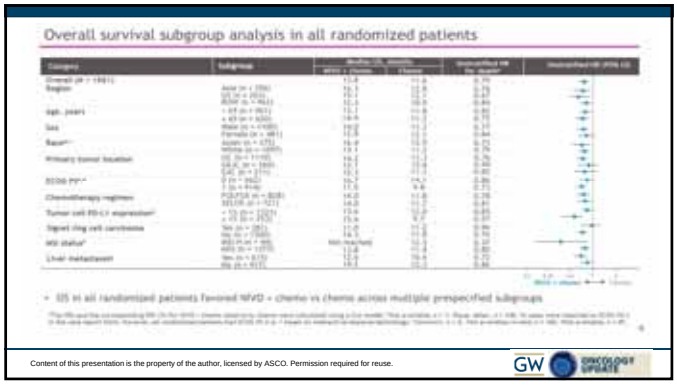


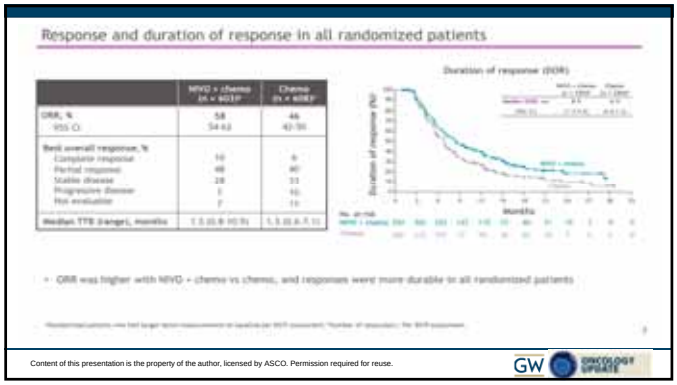
- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[6]

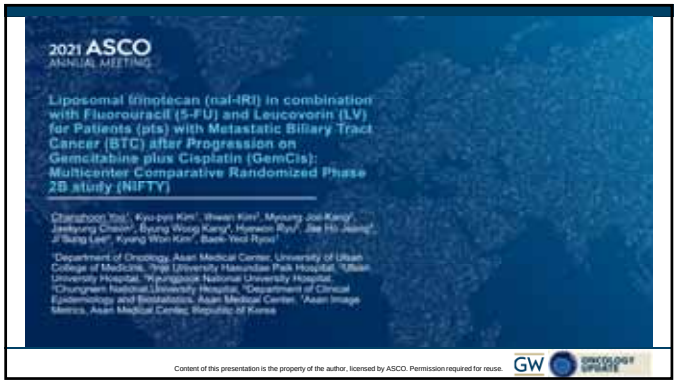
Overall survival and progression-free survival in all randomized patients



- Superior OS benefit and clinically meaningful PFS improvement in all randomized patients with NIVO + chemo vs chemo
- Median OS with NIVO + chemo vs chemo in patients with PD-L1 CPS ≥ 5 was 14.4 vs 11.1 months and median PFS was 7.7 vs 6.0 months[1]

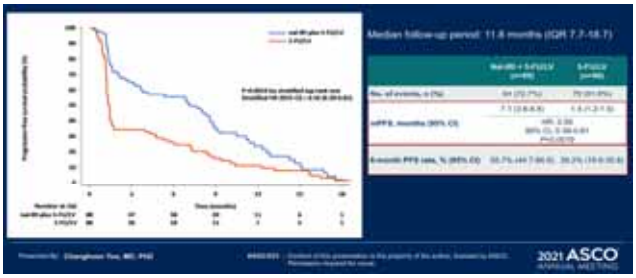




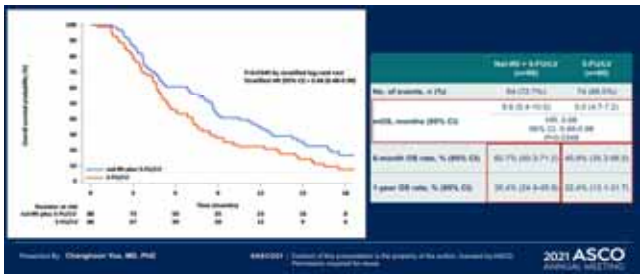


NIFTY: Multicenter, Open-label, Randomized Phase 2B Study

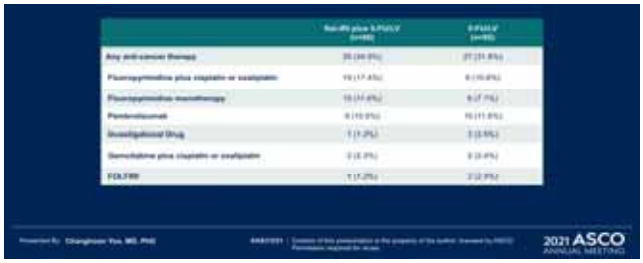
Primary Endpoint: BICR-Assessed PFS



Secondary Endpoint: Overall Survival



Post-Study Treatment



2021 ASCO ANNUAL MEETING

Neoadjuvant Hepatic Arterial Infusion Chemotherapy (HAIC) with FOLFOX Could Improve Outcomes of Resectable BCLC Stage A/B Hepatocellular Carcinoma Patients Beyond Milan Criteria: An Interim Analysis of a Multi-center, Phase 3, Randomized, Controlled Clinical Trial.

Shaohua Li, Department of Liver Surgery, Sun Yat-sen University Cancer Center, Guangzhou, P. R. China.

Jun. 5, 2021

Background

Potential neoadjuvant treatment options:

TACE, target therapy, HAIC.

Disadvantages of TACE as a neoadjuvant treatment:

Severe post-embolization syndrome;
Severe inflammation leads to adhesion;
Increasing risk and difficulty of operation.

Disadvantages of target therapy as a neoadjuvant treatment:

Low tumor response rate;
Low cost-effective.

Background

HAIC showed better survival benefits than TACE or sorafenib in advanced HCC:

	ORR			mOS			mPFS		
	HAIC	TACE	Sorafenib	HAIC	TACE	Sorafenib	HAIC	TACE	Sorafenib
Gut, 2017	40.8%	NA	NA	NA	NA	NA	8.1 mo	NA	NA
Cancer Comm, 2017	54.1%	9.8%	NA	NA	NA	NA	5.9 mo	3.6 mo	NA
J Hepatol, 2018	47.8%	NA	9.1%	14.5 mo	NA	7.0 mo	7.4 mo	NA	3.6 mo
ESMO, 2020	48.4%	32.7%	NA	NA	NA	NA	NA	NA	NA
HBSN, 2021	44.3%	7.7%	1.3%	27.8 mo	7.1 mo	7.4 mo	8.6 mo	2.8 mo	3.2 mo

2021 ASCO ANNUAL MEETING

GW ONCOLOGY UPDATE

Study Design

Overall design:

A multi-center, prospective randomized, open-label, phase 3, controlled clinical trial.

Study Objective:

To evaluate the effect of preoperative neoadjuvant HAIC on the survival of patients with BCLC stage A/B HCC beyond the Milan criteria who underwent hepatectomy.

Primary endpoint: Overall survival (OS).

Secondary endpoints: Progression free survival (PFS), recurrence free survival (RFS), and safety.

2021 ASCO ANNUAL MEETING

GW ONCOLOGY UPDATE

Treatment Plan

Candidates were randomized as 1:1;

Tumor response was evaluated following mRECIST.

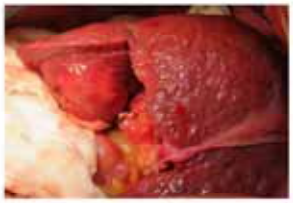
NT group, Neoadjuvant Treatment group;

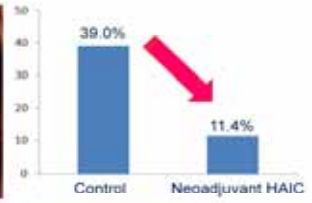
OP group, Operation group;

TAI, as known as HAIC.

GW ONCOLOGY UPDATE

Advantages of neoadjuvant HAIC





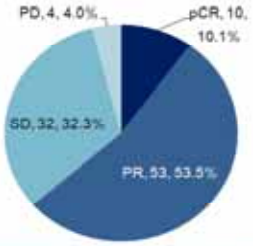
Mild inflammation and adhesion

Lower incidence of MVI

Efficacy

ORR 63.6%;
DCR 96.0%.

88 of 99 (88.9%) patients in treatment group underwent hepatectomy.

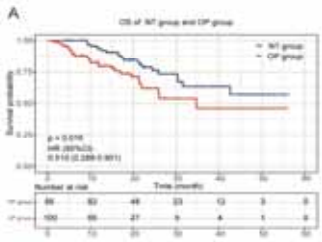


OS

OS rates of treatment and control group

1-yr	92.9%	79.5%
2-yr	78.6%	62.0%
3-yr	63.5%	46.3%

p=0.016

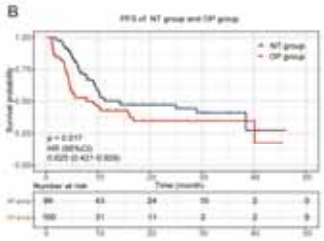


PFS

PFS rates of treatment and control group

6-mo	77.6%	52.7%
12-mo	50.4%	42.8%
18-mo	47.4%	34.8%
mPFS	14.1 mo	8.9 mo

p=0.017



Safety

59 of 99 (59.6%) and 26 of 99 (26.3%) patients in treatment group experienced grade 1 and 2 AEs, respectively;

No significant difference in operation related AEs between treatment and control groups (*p*=0.300).

Prospective

More centers, larger population, and longer follow-up;

More effective and tolerable chemotherapy regimen;

Better liver function protection;

Treatment strategy after operation;

Mechanism for lower incidence of MVI.