

UPDATES IN GI ONCOLOGY

George Kim, MD
Associate Professor of Medicine
The George Washington University






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)

Thierry André,¹ Kai-Keen Shiu,² Tae Won Kim,³ Benny Vittrup Jensen,⁴ Lars Henrik Jensen,⁵ Cornelis Punt,⁶ Denis Smith,⁷ Rocio Garcia-Carbonero,⁸ Julia Alcaide-Garcia,⁹ Peter Gibbs,¹⁰ Christelle de la Fouchardiere,¹¹ Fernando Rivera,¹² Elena Elez,¹³ Johanna Bendell,¹⁴ Dung T. Le,¹⁵ Takayuki Yoshino,¹⁶ Wenyuan Zhong,¹⁷ David Fogelman,¹⁸ Patricia Marinello,¹⁹ Luis A. Diaz Jr.¹⁹


¹Sorbonne Université and Hôpital Saint Antoine, Paris, France; ²University College Hospital, NHS Foundation Trust, London, United Kingdom; ³Seoul Medical Center, University of Ulsan, Seoul, Republic of Korea; ⁴Herlev and Gentofte Hospital, Herlev, Denmark; ⁵University Hospital of Southern Denmark, Vejle, Denmark; ⁶Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands; ⁷Bordeaux University Hospital, Bordeaux, France; ⁸Hospital Universitario 12 de Octubre, IMA12, CNIO, UCM, Madrid, Spain; ⁹Hospital Regional Universitario de Málaga, Málaga, Spain; ¹⁰Western Health, St Albans, Australia; ¹¹Lyon Biomed Center, Lyon, France; ¹²Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain; ¹³Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA; ¹⁴Harvard Cancer Research Institute, Tennessee Oncology, Nashville, TN, USA; ¹⁵Shanghai Kailash Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; ¹⁶National Cancer Center Hospital East, Kashima, Japan; ¹⁷MSD China, Beijing, China; ¹⁸Merck & Co., Inc., Kenilworth, NJ, USA; ¹⁹National Sloan Kettering Cancer Center, New York, NY, USA.

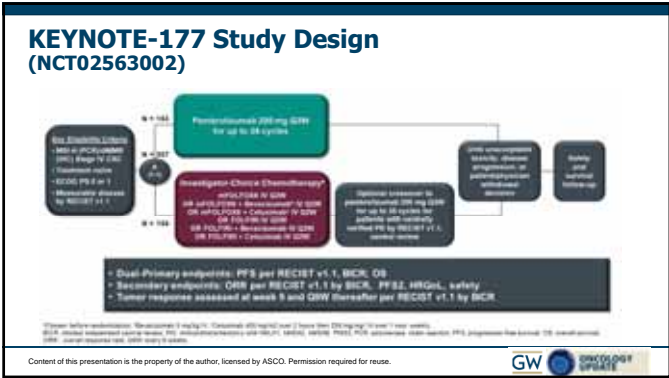


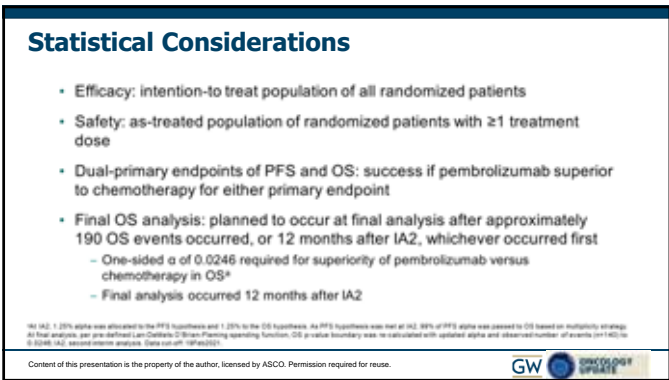
Pembrolizumab in MSI-H mCRC

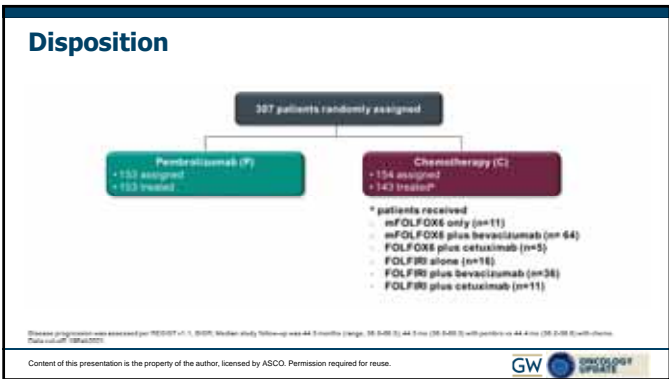
- Immune-checkpoint blockade has predicted clinical benefit in patients with mismatch-repair deficient (dMMR) or MSI-H mCRC¹⁻²
- Pembrolizumab provided superior PFS versus chemotherapy in patients with MSI-H/dMMR mCRC, at interim analysis 2 (IA2) of KEYNOTE-177³
 - Median PFS: 16.5 vs 8.2 mo; HR 0.60; P=0.0002³
 - Lower incidence of grade ≥3 treatment-related events (22% vs 66%)³ and better quality of life⁴
 - 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

9046, European Medicines Agency (EMA), Food and Drug Administration
1. Lenz H, et al. N Engl J Med 2015; 373:2028-35. 2. Lenz H, et al. Science 2017; 357:408-15. 3. André T, et al. N Engl J Med 2020; 382:2077-90. 4. André T, et al. Lancet Oncol 2021.









Baseline Characteristics

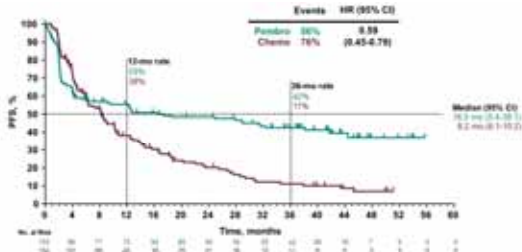
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*Actual vs. expected performance is determined as a ratio of the number of items correctly identified to the total number of items. The ratio is then multiplied by 100 to get the percentage.

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Progression-Free Survival



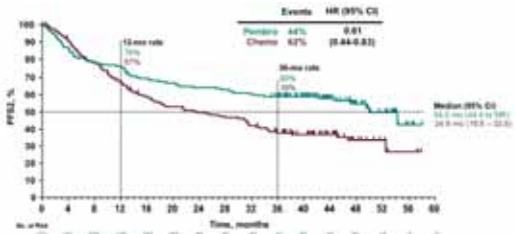
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Progression-Free Survival

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



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	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	89 (45.1)*	51 (33.1)
Best Overall Response, n (%)		
Complete response	20 (13.1) [†]	6 (3.9)
Partial response	49 (32.0) [†]	48 (29.2)
Stable disease	30 (19.6)	63 (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 of response (range), mo	NR (2.3+ to 53.5+)	10.6 (2.8 to 48.3+)
≥ 24 months response duration, %	83.5	33.6

KORR 83.8%; COR rate 91.4%; FPR rate 33.7% at 80 (data cut-off 18Feb2020).
Data cut-off: 18Feb2021.

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- 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 80% in the ITT

	Permethrin-treated N = 103	Chlorpyrifos N = 106
Any anti-IL-1/IFN-γ therapy, n (%)	19 (19.3)	37 (35.0)
On protocol therapy, "permitted"*	8 (8.3)	36 (34.4)
Off protocol therapy	11 (11.0)	17 (16.3)
Any anti-IL-1/IFN-γ therapy, n (%)	38 (37.4)	53 (50.2)
Therapies	38 (37.4)	53 (50.2)
IFN- γ monotherapy	33 (31.6)	33 (31.4)
IFN- γ + anti-IL-1	4 (3.9)	10 (9.6)
Non-monotherapy anti-IL-1/IFN- γ + other immunosuppressive agent	1 (1.0)	0 (0.0)
IFN- γ + anti-IL-1	0 (0.0)	0 (0.0)
IGRA approved	1 (0.7)	1 (0.9)
Anti-IL-1 monotherapy	1 (0.7)	0 (0.0)
IGRA disapproved	1 (0.7)	0 (0.0)
Unexplained therapy	0 (0.0)	2 (1.9)

Reusing the same 44 segments to generate different sequences will lead to an inflated

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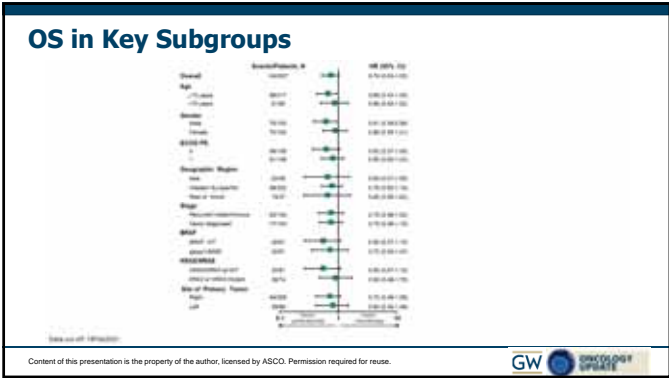
	Events, n (%)	HR (95% CI)	P
Pemetrexed	52 (50.5%)	0.74	0.0359*
Placebo	78 (50.6%)	(0.53-1.03)	

Median OS (%)
Pemetrexed (n=52): 36.1 months
Placebo (n=50): 27.4 months

*These thresholds are not adjusted for multiplicity for the 100,000 simulations. The significance threshold is subject to increased effecting (and planning) structure failure time models and overall probability of observing weighting scheme 10,000 (1), 11, 12 (1), 13 (1), 14 (1), 15 (1), 16 (1), 17 (1), 18 (1), 19 (1), 20 (1), 21 (1), 22 (1), 23 (1), 24 (1), 25 (1), 26 (1), 27 (1), 28 (1), 29 (1), 30 (1), 31 (1), 32 (1), 33 (1), 34 (1), 35 (1), 36 (1), 37 (1), 38 (1), 39 (1), 40 (1), 41 (1), 42 (1), 43 (1), 44 (1), 45 (1), 46 (1), 47 (1), 48 (1), 49 (1), 50 (1), 51 (1), 52 (1), 53 (1), 54 (1), 55 (1), 56 (1), 57 (1), 58 (1), 59 (1), 60 (1), 61 (1), 62 (1), 63 (1), 64 (1), 65 (1), 66 (1), 67 (1), 68 (1), 69 (1), 70 (1), 71 (1), 72 (1), 73 (1), 74 (1), 75 (1), 76 (1), 77 (1), 78 (1), 79 (1), 80 (1), 81 (1), 82 (1), 83 (1), 84 (1), 85 (1), 86 (1), 87 (1), 88 (1), 89 (1), 90 (1), 91 (1), 92 (1), 93 (1), 94 (1), 95 (1), 96 (1), 97 (1), 98 (1), 99 (1), 100 (1), 101 (1), 102 (1), 103 (1), 104 (1), 105 (1), 106 (1), 107 (1), 108 (1), 109 (1), 110 (1), 111 (1), 112 (1), 113 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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%)	89 (62.2%)
Discontinued	13 (8.5%)	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: Andre T et al. N Engl J Med 2020;383:2207-18. Data cut-off: 18Feb2021.

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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 IA2¹
 - 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 population¹
 - Limitations include open label trial and PROs as exploratory end points
 - Results are mostly limited to treatment period in first line

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

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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

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PHASE II STUDY OF ANTI-EGFR RECHALLENGE THERAPY WITH PANITUMUMAB DRIVEN BY CIRCULATING TUMOR DNA MOLECULAR SELECTION IN METASTATIC COLORECTAL CANCER: THE CHRONOS TRIAL

Andrea Sartore-Bianchi, Filippo Pietrantonio, Sara Lonardi, Benedetta Mussolin, Francesco Riva, Elisabetta Fenocchio, Alessio Amata, Salvatore Corallo, Chiara Manai, Federica Tosi, Paolo Manca, Francesca Daniel, Vito Torri, Angelo Vanzulli, Giovanni Cappello, Caterina Marchio, Anna Sapino, Silvia Marsoni, Salvatore Siena, Alberto Bardelli

June 7th, 2021



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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 mAbs
- All treated patients will eventually develop resistance

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Background and rationale (II)

- Resistance to anti-EGFR moAbs is predominately driven by mutant RAS and EGFR ectodomain clones^{1,2}
- Resistance can be monitored by ctDNA in plasma³
- RAS/EGFR alleles decline upon anti-EGFR therapy withdrawal, leading the tumor to regain sensitivity^{1,4}
- Clinical-based rechallenge has shown promising results^{5,6}
- No data are available regarding the interventional use of ctDNA

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

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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

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Trial Eligibility, Objectives and Statistics

Eligibility	Endpoints	Statistics
Main criteria: <ul style="list-style-type: none">RAS/BRAF WT mCRC on tissue biopsy at diagnosisAt least PR to previous anti-EGFR containing regimenRAS/BRAF/EGFR WT at molecular screening by cDNAECOG ≤2FFPE genotyping on archival solid tissue derived before anti-EGFR rechallenge	Primary: <ul style="list-style-type: none">Response rate (RECIST, centrally reviewed) Secondary: <ul style="list-style-type: none">PFSOSToxicity Translational: <ul style="list-style-type: none">cDNA RAS/BRAF/EGFR dynamicscDNA landscapes (baseline and PD)IDNA landscape (baseline)	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

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Molecular Screening: Results

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

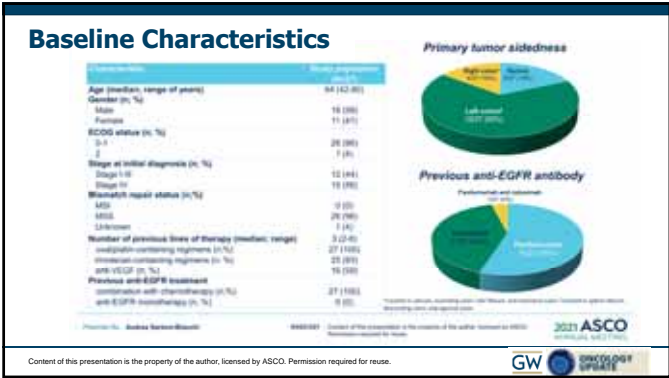
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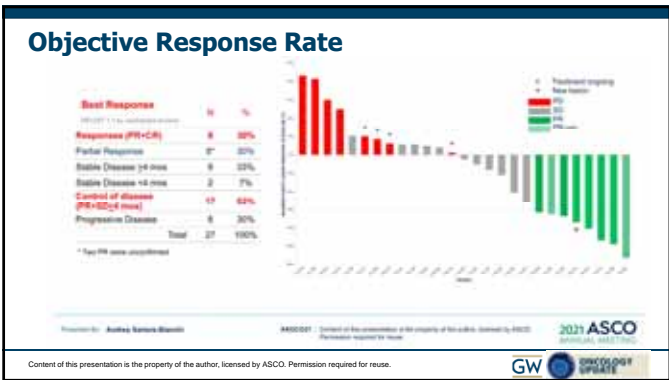
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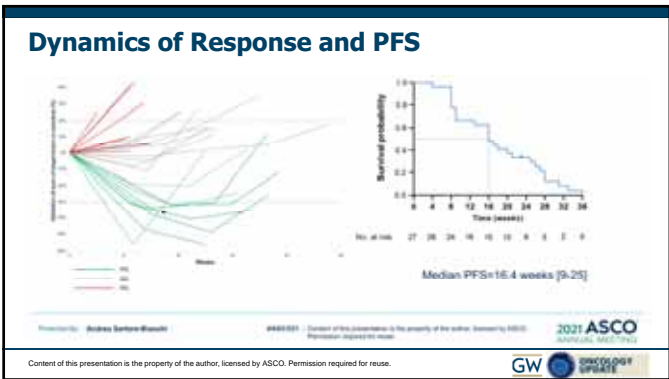
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Conclusions

- 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

Presented by: **Andrea Sartori-Ricchi**

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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, Yutai Shinohara, Masahito Kotaka, Hiroki Hara, Takashi Ota, Eiji Oki, Yu Sunakawa, Seichiro Ishihara, Hiroya Tanguchi, Takako Ejiguchi Nakajima, Satoshi Morita, Kuniaki Shirao, Takayuki Yoshino


June 7, 2021

Presented by: **Yasutoshi Kuboki**

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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.⁵⁻⁶
 - mOS 18–22.4 months; mPFS 9.2–9.4 months; ORR 34–40.5%; DCR 86–86.5%

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TRUSTY Study Design

TPUmetiracetam in Second-line mCRC

Non-intensity

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

mCRC
in 2nd-line

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

Fluoropyrimidine+irinotecan+BEV
(FP+IR+BEV)

FP+IR + BEV (cycle 1), S-F + Irinotecan + BEV (cycle 2-4)
Selected for an individual patient-based

FTD/TPH+BEV

BEV: 5 mg/kg IV on d1, d15
FTD/TPH: 10 mg/m² IV on d1, d8 and d15 (cycle 1-4)

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)

Stratification factors

• ECOG status (0/1 vs ≥2)
• Primary tumor location (Left-sided vs Right-sided)
• Up-line treatment with metastasizing (yes/no) or with EGFR antibody (yes/no)
• Race (Asian vs non-Asian)

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Common adverse events

Events (CTCAE v4.0)	FP+IR+BEV (n = 187)		FTD/TPH+BEV (n = 186)	
	All n (%)	≥Grade 3 n (%)	All n (%)	≥Grade 3 n (%)
All events	188 (95.4)	131 (69.8)	188 (95.9)	152 (77.4)
Hematological				
Leukopenia	38 (18.3)	18 (9.1)	85 (43.4)	48 (25.0)
Neutropenia	124 (52.9)	62 (41.6)	154 (79.6)	129 (65.8)
Thrombocytopenia	21 (10.7)	2 (1.0)	37 (18.3)	9 (4.6)
Anemia	29 (15.2)	8 (3.0)	44 (22.4)	12 (6.1)
Non-hematological				
Fatigue	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)	8 (3.0)	42 (21.4)	4 (2.0)
Alpecia*	49 (24.9)	-	7 (3.6)	-

19 patients (5.5%, FP+IR+BEV) and 17 patients (8.8%, FTD/TPH+BEV) received G-CSF.

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Primary endpoint

Overall survival

Event

Median

95% CI

FP+IR+BEV

42.1 (30.1-54.1)

16.1-20.2

FTD/TPH+BEV

39.1 (27.1-51.1)

14.8-19.4

HR = 1.38 (95% CI 0.89-1.93)

p = 0.0008 (post-hoc)

p = 0.0007

Median follow-up time: 13.2 months (0.0-33.4 months)

Number at risk

0 3 6 9 12 15 18 21 24 27 30 33 36

FP+IR+BEV

187 165 143 121 100 88 76 64 52 40 28 16 14 12 10 8 6 4 2 1

FTD/TPH+BEV

186 164 142 120 98 86 74 62 50 38 26 14 12 10 8 6 4 2 1

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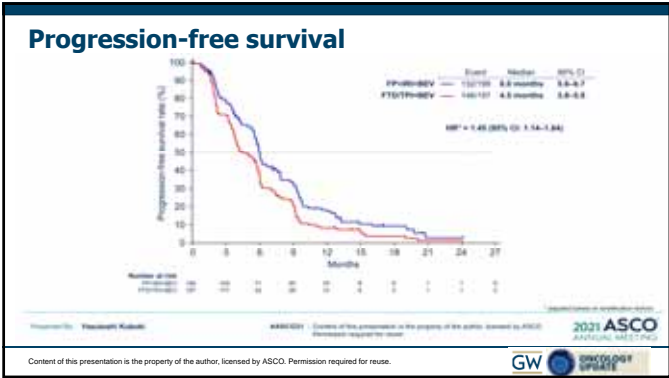
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Best overall response

	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)	0.2408
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]	

* Number of patients with measurable lesions according to RECIST version 1.1
(Based on investigator's assessment)

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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

Additional authors: Maria Di Bartholomeo, Karim Raghav, Toshiaki Masuda, Polina Lougatch, Hisaki Kawakami, Kenichi Yamaguchi, Toshihiro Nishino, Zhi Wang, Elena Elex, Javier Rodriguez, Mervan Fakh, Fortunato Ciambello, Koji Sasaki, Kyohei Kato, Emami Bak, Yasuyuki Okada, David Mannheim, Axel Grubler, Sakurako Sano

On behalf of the DESTINY-CRC01 investigators

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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 tumors¹⁻³
 - 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 placebo⁷ and 7.1 months for trifluridine/tipiracil compared to 5.3 months for placebo⁸
 - There are currently no approved HER2-targeted therapies for CRC^{2,4}
- Trastuzumab deruxtecan**
 - T-DXd is an antibody-drug conjugate⁹⁻¹¹ designed to deliver an optimal antitumor effect
 - Primary results of T-DXd treatment (8.4 mg/kg Q3W) in patients with HER2-overexpressing mCRC demonstrated antitumor activity¹¹

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DESTINY-CRC01 Study Design

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

Patients

- Unresectable and/or metastatic CRC
- HER2-expressing (central confirmation)
- RAS/BRAF/PIK3CA wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current suspected interstitial lung disease

Eligibility criteria

- HER2 IHC 3+ or IHC 2+ with ISH
- HER2 IHC 3+ or IHC 2+ with ISH
- HER2 IHC 3+ or IHC 2+ with ISH

Primary endpoint

- OS (cohort A)

Secondary endpoints

- CRP (cohorts B and C)
- PFS
- ORR
- DCR
- Safety and tolerability

Primary analysis of cohort A:

- Median overall survival (OS) and 95% CI
- Median OS and 95% CI
- Median OS and 95% CI

Post-hoc analysis of cohort A:

- Median OS and 95% CI
- Median OS and 95% CI
- Median OS and 95% CI

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Baseline Characteristics

	HER2 IHC3+ or IHC2+ with ISH Cohort A (n = 55)	HER2 IHC2+ with ISH Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 88)
Age, median (range), years	57.0 (27-79)	62.0 (37-78)	56.5 (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	69.1	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, %				
Left	69.1	93.3	94.4	90.7
Right	11.4	6.7	5.6	9.3

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	HER2 INC1+ vs INC2+HER1- Cohort A (n = 53)	HER2 INC2+HER1- Cohort B (n = 15)	HER2 INC1+ Cohort C (n = 16)	Overall (n = 84)
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
RA-S wild type, % ^{a,b}	98.1	93.3	100	97
BRCA1/2 wild type, % ^a	100	100	94.4	98.8
HERG status, % ^a				
INC 2+	75.5	0	0	48.5
INC 2+	24.5	100	0	32.6
INC 1+	0	0	100	20.9
INC 1+	98.1 ^b	0	22.2	55.1
ISH ^c	0	100	77.8	33.3

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Prior Treatment, %	HER2-POS + HER3-NEG Coherent (n = 93)	HER2-POS + HER3-NEG Incoherent (n = 15)	HER2-POS + Coherent (n = 18)	Overall (n = 126)
Investigator	100	100	100	100
Fluorouracil + capecitabine	100 / 54.7	83.3 / 40.7	100 / 55.6	98.9 / 53.5
Oxaliplatin	100	83.3	100	98.9
Cetuximab or panitumumab	100	100	94.4	98.9
Bevacizumab	75.8	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)

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UPDATE

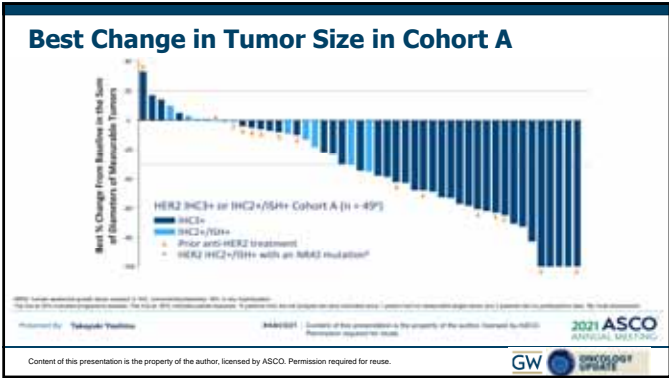
	HER2 (HC3) or Cohort A (n = 53)	HER2 (HC3) or Cohort B (n = 18)	HER2 (HC3) or Cohort C (n = 18)
Confirmed ORR by ICR, n (%) [95% CI]	24 (45.3) (31.6-69.6)	0 (0.0-21.8)	0 (0.0-18.8)
CR	6 (11.3)	0 (0.0-11.3)	0 (0.0-11.3)
PR	24 (45.3)	0 (0.0-21.8)	0 (0.0-18.8)
SD	20 (37.7)	9 (50.0)	4 (22.2)
PD	9 (16.9)	9 (50.0)	10 (55.6)
Not evaluable ^a	4 (7.5)	1 (5.6)	4 (22.2)
Disease control rate, % (95% CI)	83.0 (70.2-91.8)	66.0 (32.3-83.7)	22.0 (8.4-47.8)
Median duration of response, (95% CI) months	7.0 (5.8-8.5)	NE (NC-NE)	NE (NC-NE)
Median treatment duration, (95% CI) months	5.1 (3.3-7.6)	2.1 (1.4-6.2)	1.4 (1.1-3.3)

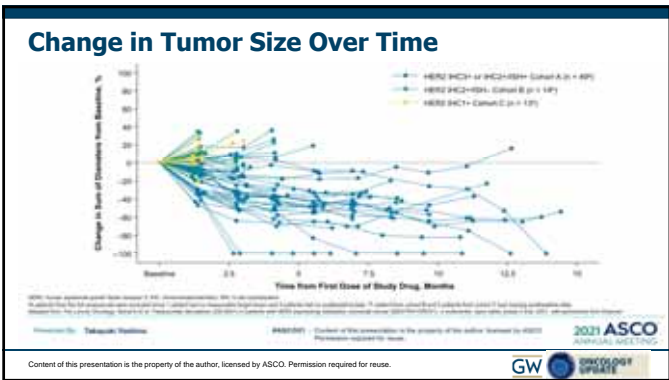
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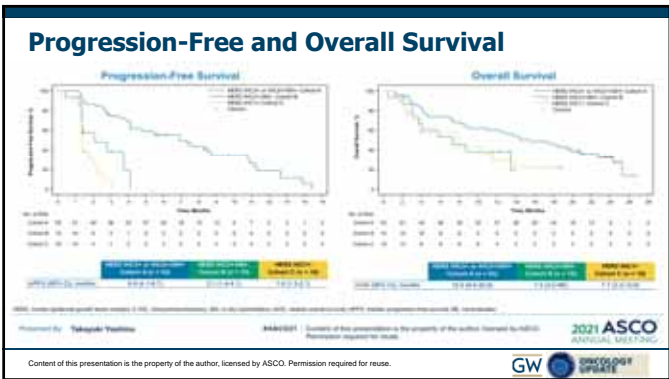
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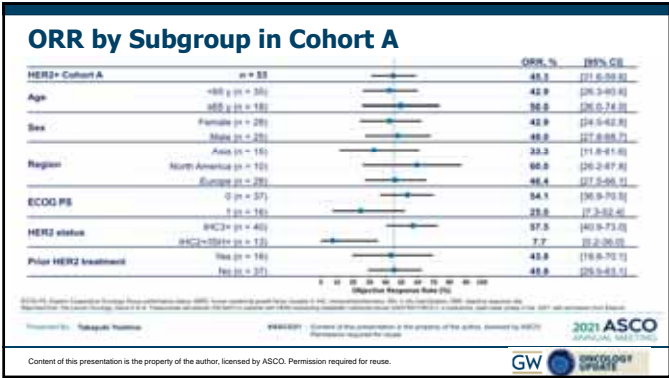
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Overall Safety Summary

n (%)	HER2 REC1+ or REC2+HER1- Cohort A (n = 53)	HER2 REC2+HER1- Cohort B (n = 15)	HER2 REC1+ Cohort C (n = 18)	Overall (n = 86)
TEAEs	83 (100)	15 (100)	18 (100)	86 (100)
Grade 3 or above	30 (56.6)	7 (46.7)	14 (77.8)	51 (59.3)
Drug-related TEAEs	81 (96.2)	15 (100)	18 (100)	81 (94.2)
Grade 3 or above	29 (54.7)	4 (26.7)	8 (50.0)	41 (47.7)
Serious TEAEs	20 (37.7)	6 (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	6 (11.3)	2 (13.3)	3 (16.7)	11 (12.8)
Drug-related TEAEs leading to drug discontinuations	4 (7.5)	2 (13.3)	1 (5.6)	7 (8.1)
TEAEs leading to dose reductions	11 (20.8)	0	4 (22.2)	15 (17.4)
Drug-related TEAEs leading to dose reductions	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	0 (0.0)	2 (13.3)	2 (11.1)	4 (4.7)
Drug-related TEAEs associated with death	0 (0.0)	1 (6.7)	0	1 (1.2)

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TEAEs in ≥20% of Patients

n (%)	HER2 REC2+ or REC2+HER1- Cohort A (n = 53)	HER2 REC2+HER1- Cohort B (n = 15)	HER2 REC1+ Cohort C (n = 18)	Overall (n = 86)
Any Grade	Any Grade	Any Grade	Any Grade	Grade 3/3
Patients with any TEAE	83 (100)	15 (100)	18 (100)	86 (100)
Nausea	37 (69.8)	9 (60.0)	7 (38.9)	53 (61.6)
Anemia	21 (39.6)	4 (26.7)	6 (33.3)	31 (36.0)
Fatigue	21 (39.6)	7 (46.7)	3 (16.7)	31 (36.0)
Decreased appetite	16 (30.2)	5 (33.3)	7 (38.9)	30 (34.9)
Weight count decreased	17 (32.1)	4 (26.7)	7 (38.9)	28 (32.6)
Swelling	23 (43.4)	3 (20.0)	1 (5.6)	27 (31.4)
Neutrophil count decreased	20 (37.7)	2 (13.3)	4 (22.2)	26 (30.2)
Diarrhea	19 (35.8)	0	4 (22.2)	23 (26.7)

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All Patients (N=88)	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 (8.3) ^a

- 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)

- In the 3 fatal cases adjudicated as drug-related ILD, onset was from 8 days to 120 days (median: 22 days); and death occurred 6–19 days after diagnosis (median: 6 days)

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2021 ASCO
Abstracts, June 1-5, 2021

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- 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

- T-DXd monotherapy: 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, 5.9–8.5), mPFS was 8.9 months (95% CI, 4.1–8.7), and MOS was 15.5 months (95% CI, 8.6–20.8)
- No responses for ER 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*
 - ILD/pneumonitis (0.3% of patients; 3.5% grade 3) 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

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GW ONCOLOGY UPDATE

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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 (JACCO CC-13)

Akiyito TSUJI*

Hatsugu Ohod, Takuhiro Yamaguchi, Masato Matsura, Atsuro Nishio, Akiyuki Makiyama, Shingo Nozaki, Mitsugu Kochi, Tamotsu Sagawa, Masahito Kobata, Yutaro Kibota, Yu Suzuki, Takashi Sekikawa, Masato Nakamura, Masahito Takachi, Wataru Ishikawa and Masashi Fuji

Department of Clinical Oncology, Faculty of Medicine, Kansas University Medical Center, Kansas City, MO

7th June, 2021



Japan Clinical Cancer Research Organization (JACCRO)

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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	266	53.1%	9.7m	26.8m
		FOLFOXIRI + Bevacizumab	252	65.1%	12.1m	31.0m
VOLFIRI trial ² (AIO KKR0109)	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 Longaticci S, et al. N Engl J Med 2014; 23:371(17):1609-18
2 Modest DP, et al. J Clin Oncol 2018; 10:3733(34):3471-3479

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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

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Methods

✓ Study Design

RAS wild-type colorectal cancer Previously untreated

R 1:1

m-FOLFOXIRI + Cetuximab combination therapy (up to 12 courses)

- Cetuximab: 400 mg/m² (course Day 1)
- Irinotecan: 250 mg/m² (Day 1, 8)
- Oxaliplatin: 150 mg/m² (Day 1)
- Oxaliplatin: 85 mg/m² (Day 1)
- Irinotecan: 200 mg/m² (Day 1)
- S-FU infusion: 2,400 mg/m² (Day 1-3)

S-FU + Irinotecan + cet combination therapy

- Cetuximab: 250 mg/m² (Day 1, 8)
- Irinotecan: 200 mg/m² (Day 1)
- S-FU infusion: 2,400 mg/m² (Day 1-3)

m-FOLFOXIRI + Bevacizumab combination therapy (up to 12 courses)

- Bevacizumab: 5 mg/kg (Day 1)
- Irinotecan: 150 mg/m² (Day 1)
- Oxaliplatin: 85 mg/m² (Day 1)
- Irinotecan: 200 mg/m² (Day 1)
- S-FU infusion: 2,400 mg/m² (Day 1-3)

S-FU + Irinotecan + bev combination therapy

- Bevacizumab: 5 mg/kg (Day 1)
- Irinotecan: 200 mg/m² (Day 1)
- S-FU infusion: 2,400 mg/m² (Day 1-3)

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GW ONCOLOGY UPDATE

Methods

Study Design

RAS wild-type colorectal cancer Previously untreated

R

1:1

Stratification factors
-Primary tumor site (right or left)
-History of preoperative adjuvant chemotherapy
-ECOG PS (0, 1)

m-FOLFOXIRI + Cetuximab combination therapy (up to 12 courses)

Cetuximab 400 mg/m² (bolus Day 1)
Irinotecan 250 mg/m² (Day 1, 8)
Oxaliplatin 85 mg/m² (Day 1)
Leucovorin 200 mg/m² (Day 1)
5-FU infusion 2,400 mg/m² (Day 1-3)

m-FOLFOXIRI + Bevacizumab combination therapy (up to 12 courses)

Bevacizumab 8 mg/kg (Day 1)
Irinotecan 150 mg/m² (Day 1)
Oxaliplatin 85 mg/m² (Day 1)
Leucovorin 200 mg/m² (Day 1)
5-FU infusion 2,400 mg/m² (Day 1-3)

m-FOLFOXIRI + Cetuximab + cet combination therapy

Cetuximab 250 mg/m² (Day 1, 8)
Leucovorin 200 mg/m² (Day 1)
5-FU infusion 2,400 mg/m² (Day 1-3)

m-FOLFOXIRI + Bevacizumab + bev combination therapy

Bevacizumab 8 mg/kg (Day 1)
Leucovorin 200 mg/m² (Day 1)
5-FU infusion 2,400 mg/m² (Day 1-3)

Presented By: **Abdalla Tughi**

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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 (29-88)
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 (17.2%) / 143 (82.7%)
Adjuvant chemotherapy		
None / With oxaliplatin / Without oxaliplatin	161 (92.0%) / 8 (4.6%) / 6 (3.4%)	109 (61.8%) / 9 (5.2%) / 5 (2.9%)
ECOG performance status		
0 / 1	160 (91.4%) / 15 (8.6%)	107 (60.8%) / 16 (9.2%)
Diagnosis		
Advanced / Relapsed	148 (84.6%) / 27 (15.4%)	142 (82.1%) / 31 (17.9%)

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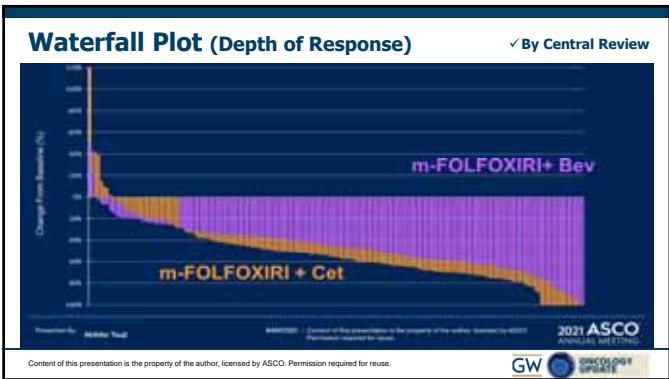
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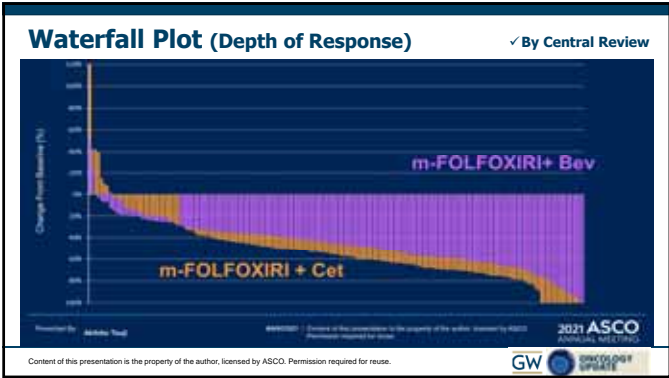
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Patient characteristics (cont.)		
	m-FOLFOXIRI + Cetuximab (n=173)	m-FOLFOXIRI + Bevacizumab (n=173)
Primary Lesion		
- / +	90 (51.4%) / 85 (48.6%)	95 (54.9%) / 78 (45.1%)
UGT1A1*6/*6		
with normal homo & double hetero	71 (40.8%) / 85 (37.1%) / 10 (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 nodes	52 (29.5%)	31 (17.8%)
Regional lymph nodes	60 (34.2%)	84 (48.2%)
Pericardium	38 (21.7%)	26 (15.0%)
Ascites	79 (45.3%)	6 (3.5%)
Bone	4 (2.3%)	6 (3.5%)

Depth of Response <primary endpoint>		
✓ By Central Review		
	m-FOLFOXIRI + Cetuximab (n=158*)	m-FOLFOXIRI + Bevacizumab (n=162*)
Median	57.4%	46.5%
(Range)	(-15.0-100)	(-0.6-100)
Mean	55.8%	47.3 %
(95%CI)	(51.9-59.7)	(44.1-50.5)
Standard Deviation	25.06	20.53
(95%CI)	(22.6-28.2)	(18.5-23.0)
t-test by welch	p=0.0010	

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





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)	40.5 (-8.8-100)	45.1 (3.3-100)	50.0 (-15.0-100)	47.2 (-0.6-85.4)
Mean (95%CI)	57.9 (33.2-81.7)	48.2 (44.9-51.5)	47.7 (37.3-58.1)	42.5 (32.1-52.8)
Standard Deviation (95%CI)	24.59 (21.63-27.98)	19.55 (17.48-22.18)	26.19 (20.62-35.90)	25.17 (19.65-35.02)
t-test by Welch	p=0.0007		p=0.4663	

Presented By: **Ashley Tsang**
ABSTRACT 1
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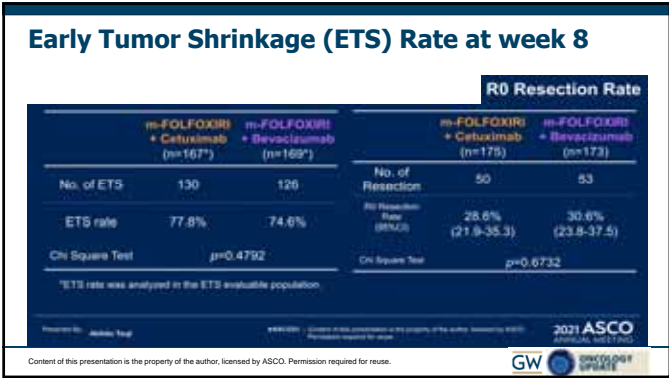
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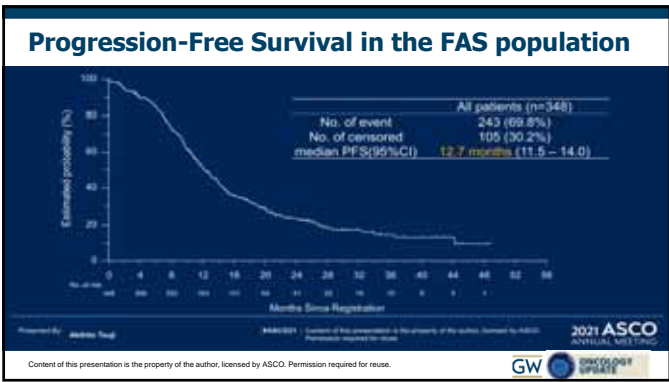
Overall Response Rate

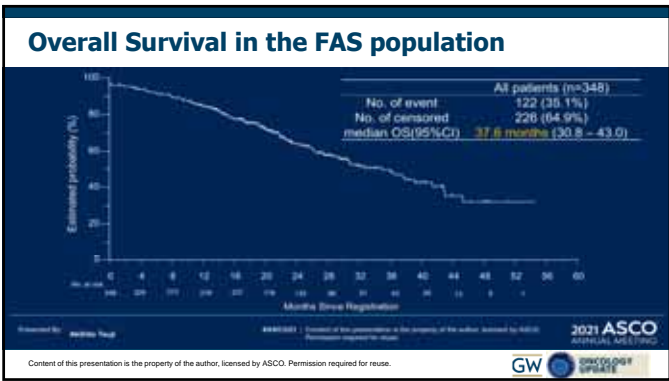
	m-FOLFOXIRI + Cetuximab (n=175)	m-FOLFOXIRI + Bevacizumab (n=173)
Complete Response	11 (6.3%)	4 (2.3%)
Partial Response	110 (62.9%)	120 (69.4%)
Best Response	38 (21.7%)	41 (23.7%)
Stable Disease	8 (4.6%)	3 (1.7%)
Progressive Disease	8 (4.6%)	5 (2.9%)
Not Evaluated	6 (3.4%)	5 (2.9%)
Overall Response Rate (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	

Presented By: **Ashley Tsang**
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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.

Presented By: **Sebastian Stenzing**

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

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

S. Stenzing, K. Heinrich, L. Tsielb, I. Schwaner, J. Eickert, R. Pihusch, M. Mauch, F. Kallies, C. Kahl, M. Karthaus, C. Müller, C. Burkart, A. Reinacher-Schick, S. Kasper-Vonckow, L. Fischer von Wilkenthal, B. Kramer-Stolten, GW Prager, D. Tougeron, V. Heinemann



Prof. Sebastian Stenzing MD
Charité – Universitätsmedizin Berlin
June 17, 2021

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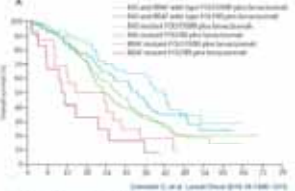
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Rationale of the study design

→ 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.



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

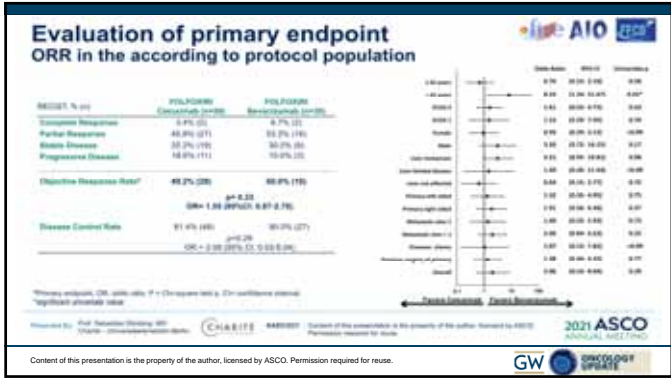
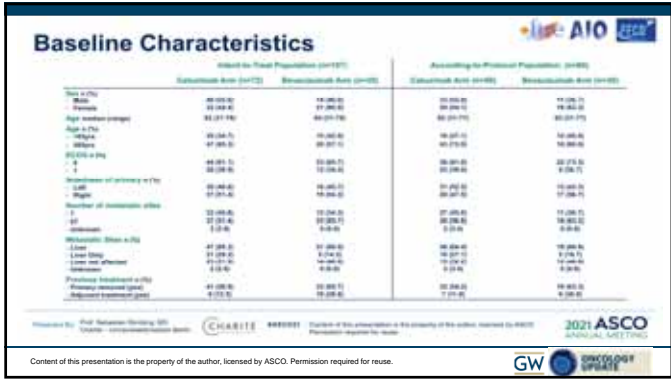
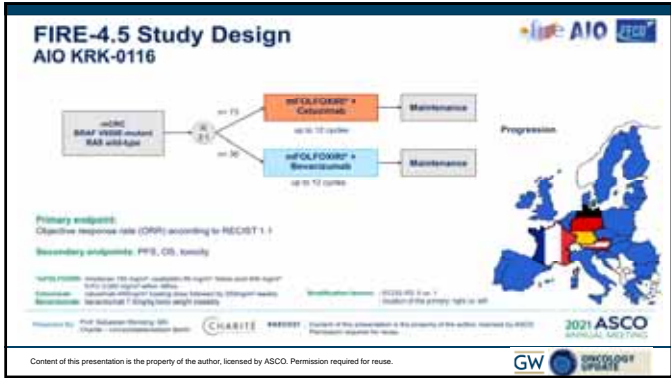
Presented By: **Prof. Sebastian Stenzing MD**

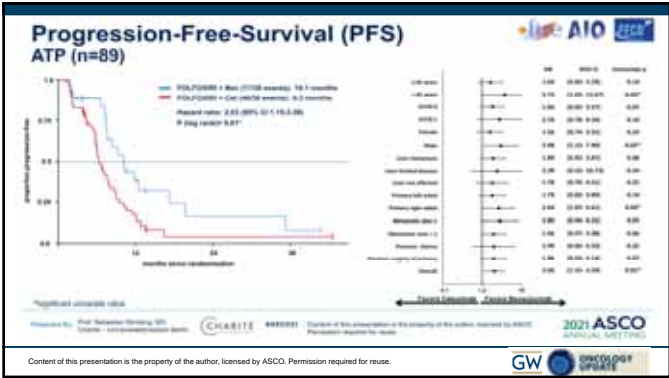
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Nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: first results of the CheckMate 648 study

Jen 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 Hajji,¹¹ Maria Di Bartolomeo,¹² Maria Inez Braghiroli,¹³ Eva Holtved,¹⁴ Ioannis Kymis,¹⁵ Xuan Liu,¹⁶ Ming Lei,¹⁷ Kaoru Kondo,¹⁸ Ken Kato,¹⁹ Yuko Kitagawa¹⁷

¹ Royal Marsden Hospital, London, UK; ² Osaka University Graduate School of Medicine, Osaka, Japan; ³ The University of Texas MD Anderson Cancer Center, Houston, TX; ⁴ Fujian Cancer Hospital, Fuzhou, China; ⁵ Institute of Military Medicine, Beijing, China; ⁶ Nippon Medical School, Tokyo, Japan; ⁷ National Cancer Center, Tokyo, Japan; ⁸ National Cancer Center, Tokyo, Japan; ⁹ National Cancer Center, Tokyo, Japan; ¹⁰ Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹¹ Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹² Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹³ Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹⁴ Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹⁵ Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹⁶ Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹⁷ Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹⁸ Centre for Cancer Research, University of Liverpool, Liverpool, UK; ¹⁹ Centre for Cancer Research, University of Liverpool, Liverpool, UK

Abstract Number: LB44001

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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)³⁻⁵
- NIVO monotherapy demonstrated superior OS vs chemo in previously treated patients with advanced ESCC (ATTRACTION-3)⁶
- 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

1. Sung H, et al. CA Cancer J Clin. 2017;67(12):1032-1058. 2. Sung H, et al. CA Cancer J Clin. 2017;67(12):1032-1058. 3. Sung H, et al. CA Cancer J Clin. 2017;67(12):1032-1058. 4. Sung H, et al. CA Cancer J Clin. 2017;67(12):1032-1058. 5. Sung H, et al. CA Cancer J Clin. 2017;67(12):1032-1058. 6. Sung H, et al. CA Cancer J Clin. 2017;67(12):1032-1058.

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UPDATE

CheckMate 648 study design

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

Key eligibility criteria

- Unresectable, advanced, recurrent or metastatic ESCC
- ECESG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors

- Region and HbA1c (median < 5.7% vs ≥ 5.7%)
- Region (East Asia vs rest of world)
- Time to first treatment (≤ 12 weeks vs > 12 weeks)

Randomized arms

- NIVO 340 mg Q2W + chemo (fluorouracil + cisplatin) Q2W
- NIVO 2 mg/kg Q2W + IPI 1 mg/kg Q2W
- Chemo (fluorouracil + cisplatin) Q2W

Primary endpoint

- OS and PFS (time to death or progression)

Secondary endpoints

- CR and PRV (rate of response)
- CRP (time to death or progression)
- CRP (time to death or progression)

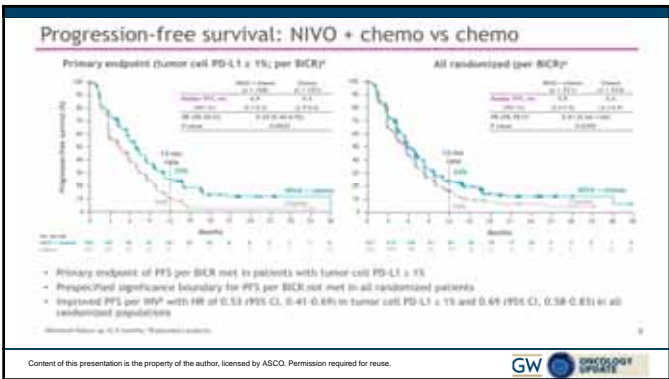
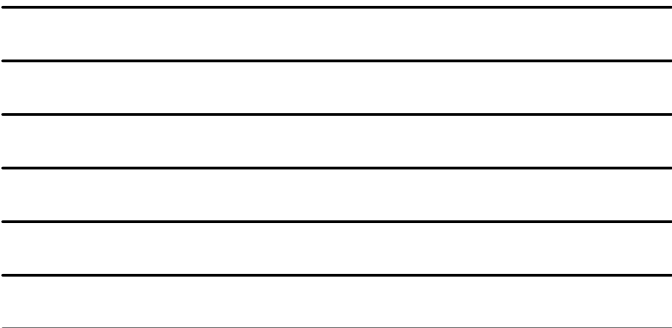
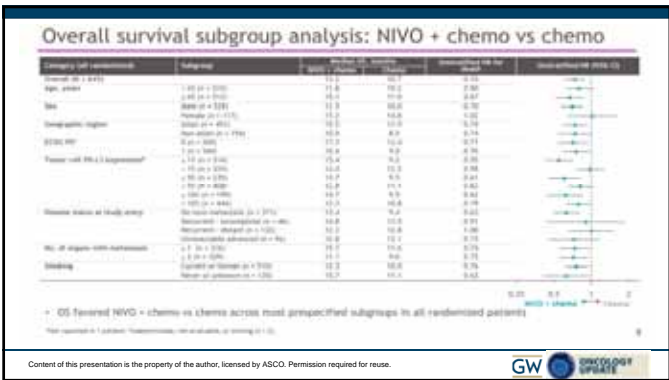
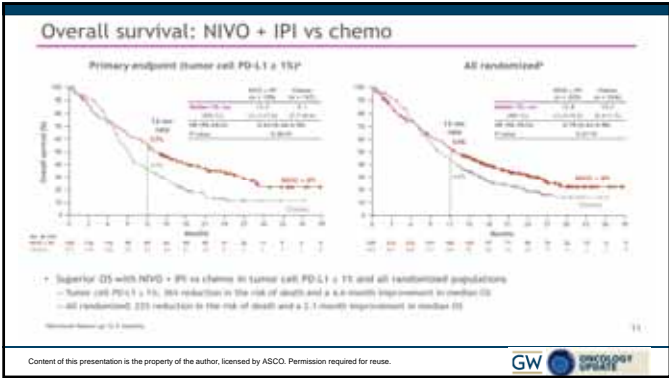
^a All data cutoff January 18, 2021; the minimum follow-up was 12.9 months

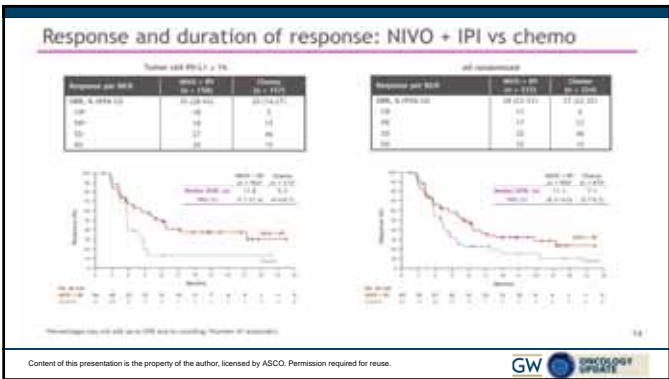
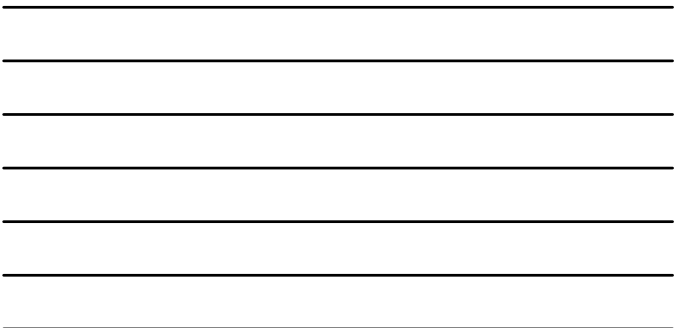
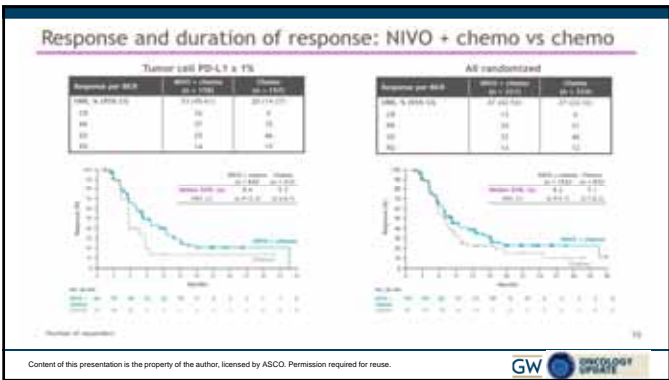
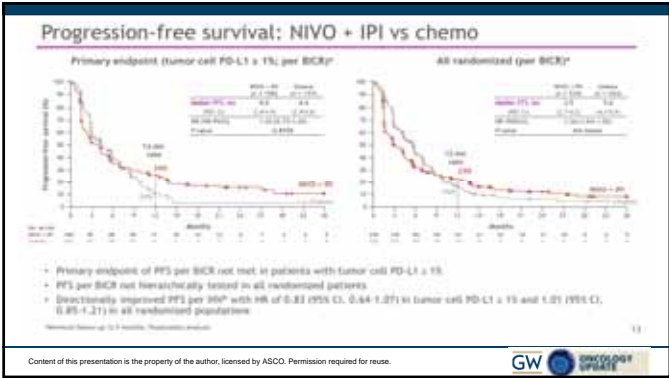
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ONCOLOGY
UPDATE







TRAEs with potential immunologic etiology

Select TRAEs* All treated, n (%)	NIVO + chemo (n = 318)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3-4†	Any grade	Grade 3-4†	Any grade	Grade 3-4
Endocrine	36 (12)	4 (1)	88 (27)	19 (6)	1 (0)	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 (0)
Pulmonary	19 (6)	2 (0)	26 (8)	9 (3)	2 (0)	0
Renal	74 (24)	7 (2)	8 (2)	2 (0)	57 (19)	5 (2)
Skin	34 (11)	1 (0)	119 (37)	13 (4)	11 (4)	0

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

*Selected TRAEs are those with potential immunologic etiology (other adverse events due to chemotherapy were excluded). †Patients who received ≥ 1 dose of study drug. Incidence in all treated patients, including those who did not receive study drug. ‡Grade 3-4 events were reported for 1 of all patients in the NIVO + chemo group, 1 of 10 patients in the NIVO + IPI group, and 1 of 10 patients in the chemo group.

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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 regimen
- 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

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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

Hansjoerg Roeloffs,¹ Kuniaki Shitara,² Marcello Garrido,³ Pamela Salmeron,⁴ Lin Shen,⁵ Lucjan Wyrwicz,⁶ Keren Yamaguchi,⁷ Thomas Skoczylas,⁸ Arnelinda Campos Bragagnoli,⁹ Tianhui Liu,¹⁰ Michael Schreiber,¹¹ Patricia Yanez,¹² Mustafa Tahir,¹³ Mengshan Li,¹⁴ Dana Culam,¹⁵ Sandra Soliman,¹⁶ Ming Lei,¹⁷ Hong Xiao,¹⁸ Helena E. Jansjagan,¹⁹ Jaffer A. Ajani²⁰

¹University of Cologne, Germany; ²Osaka University, Japan; ³University of Valencia, Spain; ⁴University of Valencia, Spain; ⁵University of Valencia, Spain; ⁶University of Valencia, Spain; ⁷University of Valencia, Spain; ⁸University of Valencia, Spain; ⁹University of Valencia, Spain; ¹⁰University of Valencia, Spain; ¹¹University of Valencia, Spain; ¹²University of Valencia, Spain; ¹³University of Valencia, Spain; ¹⁴University of Valencia, Spain; ¹⁵University of Valencia, Spain; ¹⁶University of Valencia, Spain; ¹⁷University of Valencia, Spain; ¹⁸University of Valencia, Spain; ¹⁹University of Valencia, Spain; ²⁰University of Valencia, Spain

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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 CPS⁵ has shown better enrichment for efficacy of checkpoint inhibitors than tumor cell PD-L1 expression in GC/GEJC/EAC⁶
- CheckMate 649 is the largest randomized, global phase 3 study of 1L PD-1 inhibitor-based therapies in advanced GC/GEJC/EAC⁷
- 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 patients⁸
 - Based on these results, NIVO + chemo received FDA approval as 1L treatment for GC/GEJC/EAC⁹
- We present expanded efficacy and safety analysis in all randomized patients from CheckMate 649

OS, overall survival; NIVO, nivolumab; chemo, chemotherapy; CPS, cancer program score; PD-L1, programmed death-ligand 1; EAC, esophageal adenocarcinoma; 1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; 5L, fifth-line; 6L, sixth-line; 7L, seventh-line; 8L, eighth-line; 9L, ninth-line; 10L, tenth-line; 11L, eleventh-line; 12L, twelfth-line; 13L, thirteenth-line; 14L, fourteenth-line; 15L, fifteenth-line; 16L, sixteenth-line; 17L, seventeenth-line; 18L, eighteenth-line; 19L, nineteenth-line; 20L, twentieth-line; 21L, twenty-first-line; 22L, twenty-second-line; 23L, twenty-third-line; 24L, twenty-fourth-line; 25L, twenty-fifth-line; 26L, twenty-sixth-line; 27L, twenty-seventh-line; 28L, twenty-eighth-line; 29L, twenty-ninth-line; 30L, thirtieth-line; 31L, thirty-first-line; 32L, thirty-second-line; 33L, thirty-third-line; 34L, thirty-fourth-line; 35L, thirty-fifth-line; 36L, thirty-sixth-line; 37L, thirty-seventh-line; 38L, thirty-eighth-line; 39L, thirty-ninth-line; 40L, fortieth-line; 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NIFTY: Multicenter, Open-label, Randomized Phase 2B Study

Patients with metastatic BTC

- Histologically or molecularly confirmed BTC
- All local and distant disease
- ECOG PS 0-1
- Radical surgical resection not prior to first-line systemic Tx
- No prior 5-FU-based chemotherapy
- ECOG PS 0-1
- Admissible organ function

Stratification

- Tumor site (colorectal vs. gastroesophageal)
- Performance
- Previous treatment (prior surgery)
- Participating center

Randomized

Nat-IRI plus 5-FULV

Nat-IRI 70 mg/m² (D1), 5-FU 2400 mg/m² (D1-2), LV 400 mg/m² (D1)

5-FULV

5-FU 2400 mg/m² (D1-2), LV 400 mg/m² (D1)

(Unit progression as identifiable toxicity)

Primary endpoint

BICR-assessed PFS (BICR021 +1.1)

Secondary endpoint

- Progression-free survival (PFS)
- OS
- QoL (ASCO-Q15 V1.1)
- Toxicity (NCIC CTCAE v4.03)
- QoL (EORTC QLQ-C30)

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Primary Endpoint: BICR-Assessed PFS

Median follow-up period: 11.8 months (IQR 7.7-18.7)

	Nat-IRI + 5-FULV (n=100)	5-FULV (n=100)
No. of events, n (%)	54 (52.7%)	79 (79.0%)
Median PFS, months (95% CI)	7.7 (5.8-9.6)	1.8 (1.2-2.5)
HR, 0.38 (95% CI, 0.28-0.51)		
P=0.0002		
6-month PFS rate, % (95% CI)	52.7% (44.7-60.6)	38.2% (30.0-46.4)

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Secondary Endpoint: Overall Survival

Median follow-up period: 11.8 months (IQR 7.7-18.7)

	Nat-IRI + 5-FULV (n=100)	5-FULV (n=100)
No. of events, n (%)	54 (52.7%)	79 (79.0%)
Median OS, months (95% CI)	8.6 (6.8-10.5)	5.0 (4.7-5.3)
HR, 0.48 (95% CI, 0.34-0.67)		
P=0.0002		
6-month OS rate, % (95% CI)	52.7% (44.7-60.6)	45.4% (37.0-53.8)
1-year OS rate, % (95% CI)	39.4% (30.4-48.5)	22.4% (15.4-29.5)

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Post-Study Treatment

	Receptor plus FOLFOX (n=95)	Receptor (n=95)
Any anti-cancer therapy	35 (36.8%)	27 (28.4%)
Fluoropyrimidine plus oxaliplatin or capecitabine	19 (19.9%)	9 (9.5%)
Fluoropyrimidine monotherapy	19 (19.9%)	9 (9.5%)
Pancreaticoduodenectomy	9 (9.5%)	10 (10.6%)
Investigational drug	1 (1.0%)	3 (3.2%)
Sorafenib plus capecitabine or oxaliplatin	2 (2.1%)	2 (2.1%)
FOLFIRI	1 (1.0%)	2 (2.1%)

Presented by: Shaozhong Liu, MD, PhD

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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

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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.

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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
Cui, 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

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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.

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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.

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