University of Nebraska Medical Center

Bio Ascend™

VIRTUAL CHALLENGING CASE CLINIC:

GI Cancers

Updates from ASCO and World GI

Broadcast on July 15, 2021

Presenter

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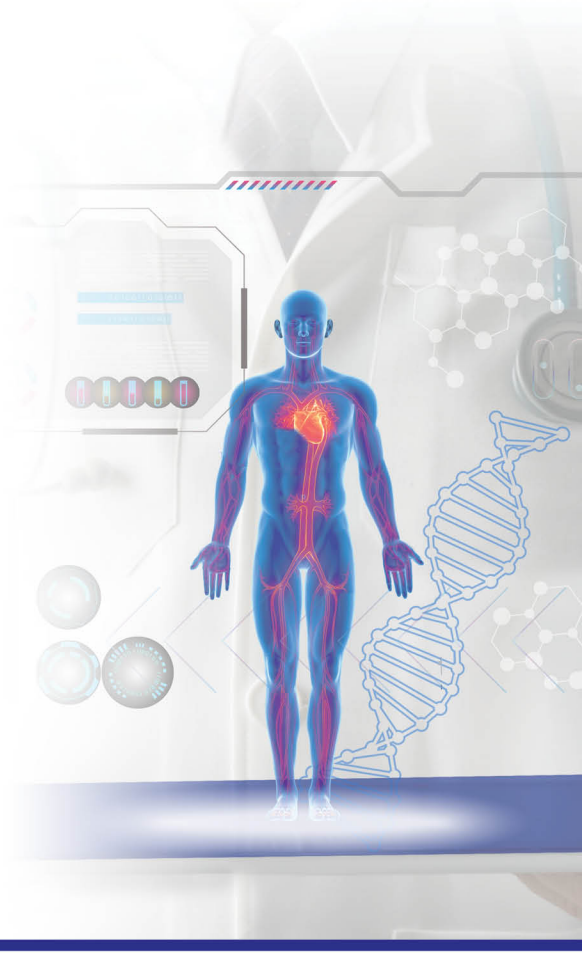
Chicago, Illinois



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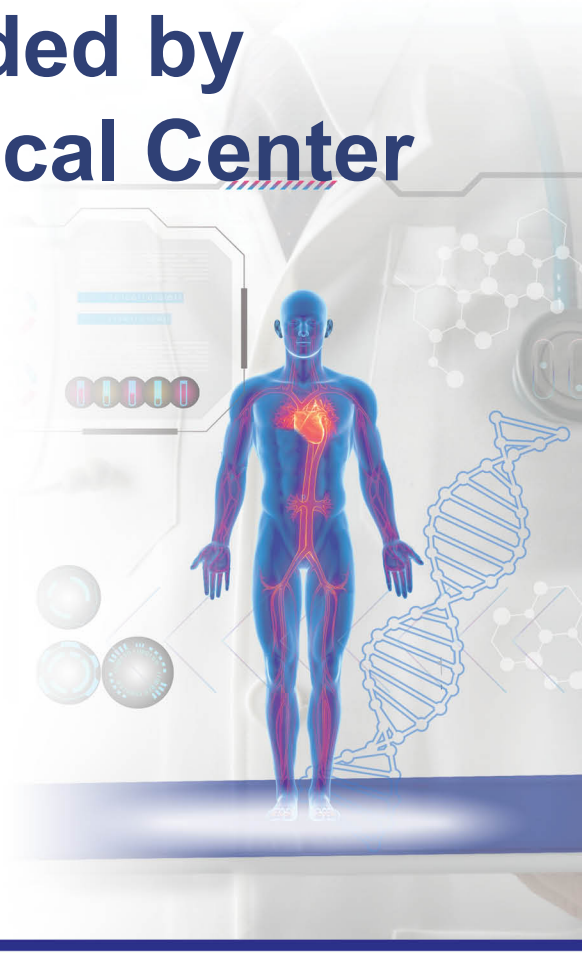

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Disclosures

Daniel Catenacci, MD

Advising/Consuting: Genentech/Roche, Eli Lilly, Merck, Daiichi Sankyo, BMS, Ono, Five Prime, Seattle Genetics, Amgen, Taiho, Astellas, Gritstone, Pieris, Zymeworks, Basilea, QED, Arcus, Foundation Medicine, Pierian, Silverback Therapeutics, Servier, Blueprint Medicines, Arcus BiosciencesTempus, Guardant Health, Archer & Natera.

Planning Committee

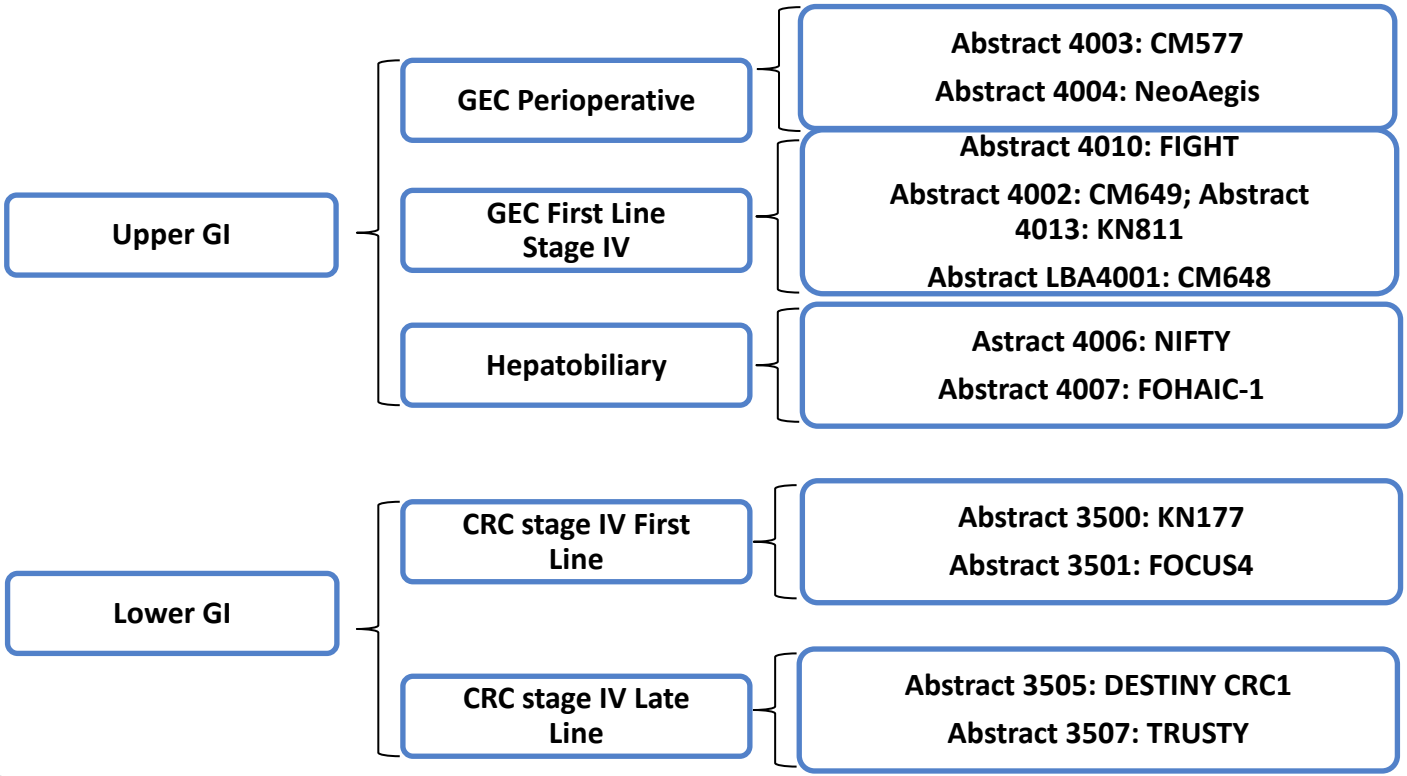
The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP

Bio Ascend: Patti Bunyasaranand, MS; Dru Dace, PhD; Lucja Grajkowska, PhD; Kraig Steubing

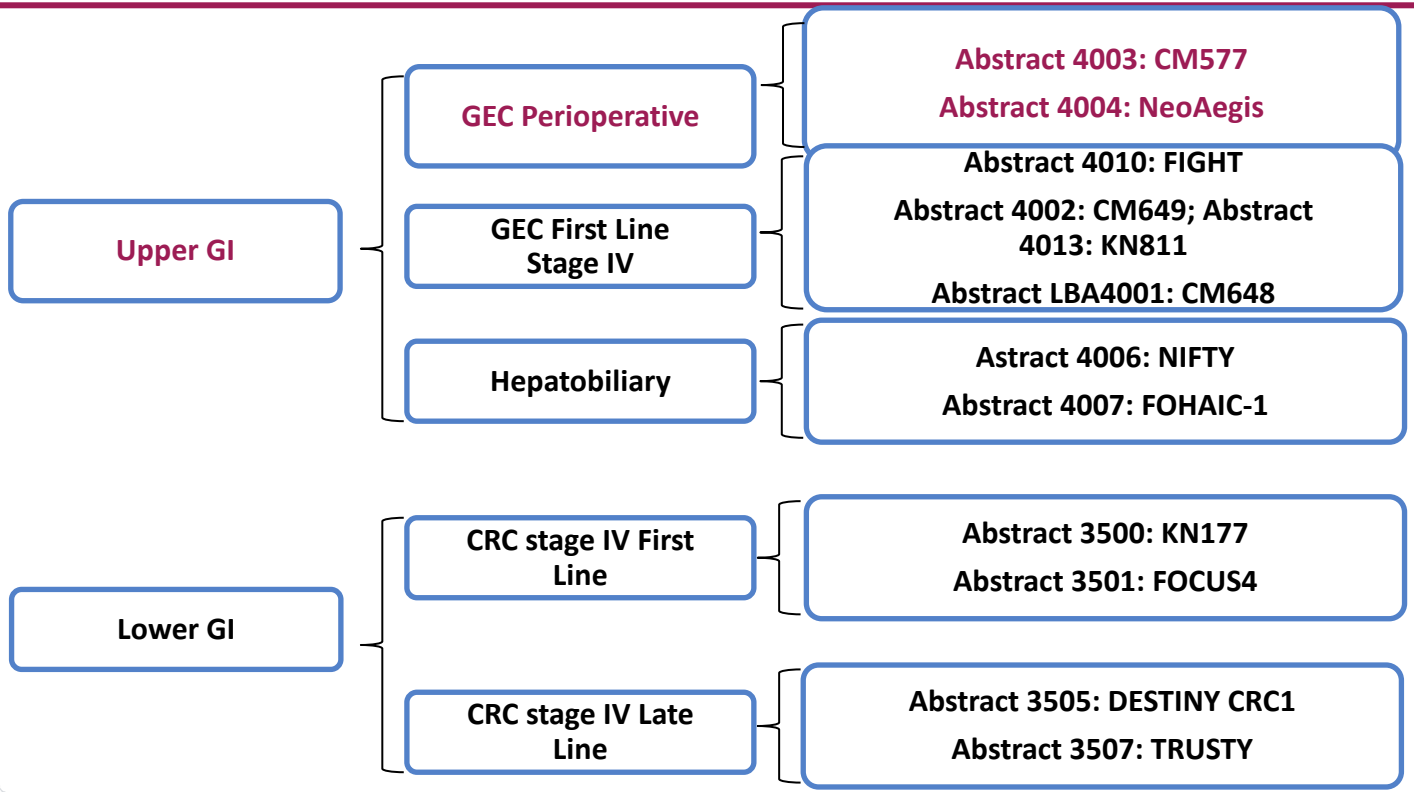
Learning Objectives

- Evaluate best available evidence regarding treatment of GI cancer
- Assess the clinical implications of emerging clinical trial data regarding treatment approaches for patients with GI cancer
- Develop strategies to address complicated GI cancer cases

ASCO 2021: Highlights in GI Malignancies



ASCO 2021: Highlights in GI Malignancies



NEO-AEGIS

(**NEO**ADJUVANT TRIAL IN **A**DENOCARCINOMA OF THE **E**SOPHAGUS AND ESOPHAGO-**G**ASTRIC JUNCTION **I**NTERNATIONAL **S**TUDY): PRELIMINARY RESULTS OF PHASE III RCT OF CROSS VS PERI-OPERATIVE CHEMOTHERAPY(MODIFIED MAGIC OR FLOT PROTOCOL) (CTRIAL-IE 10-14) (NCT01726452)

John V. Reynolds

Cancer Trials Ireland and Trinity St. James's Cancer Institute

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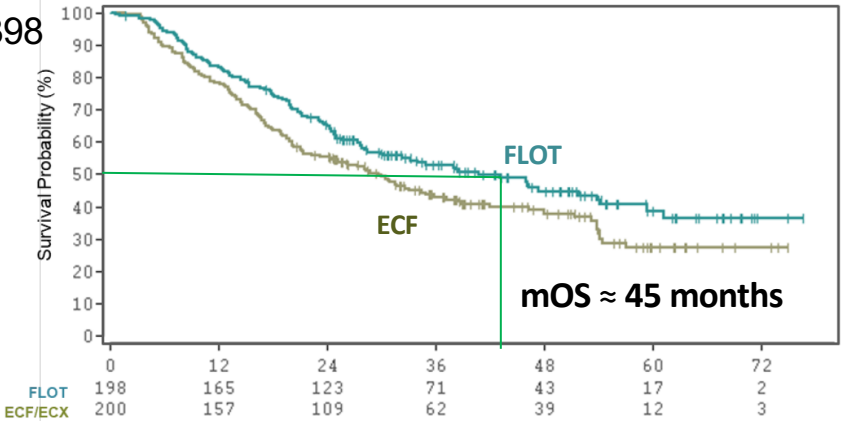
Perioperative Therapy EGJ AC: DFS, OS

LN+ disease: 78%
T4 disease: 8%

Overall survival in the gastro-esophageal (Siewert types 1-3) adenocarcinoma subgroup (intention-to-treat population)

N=398

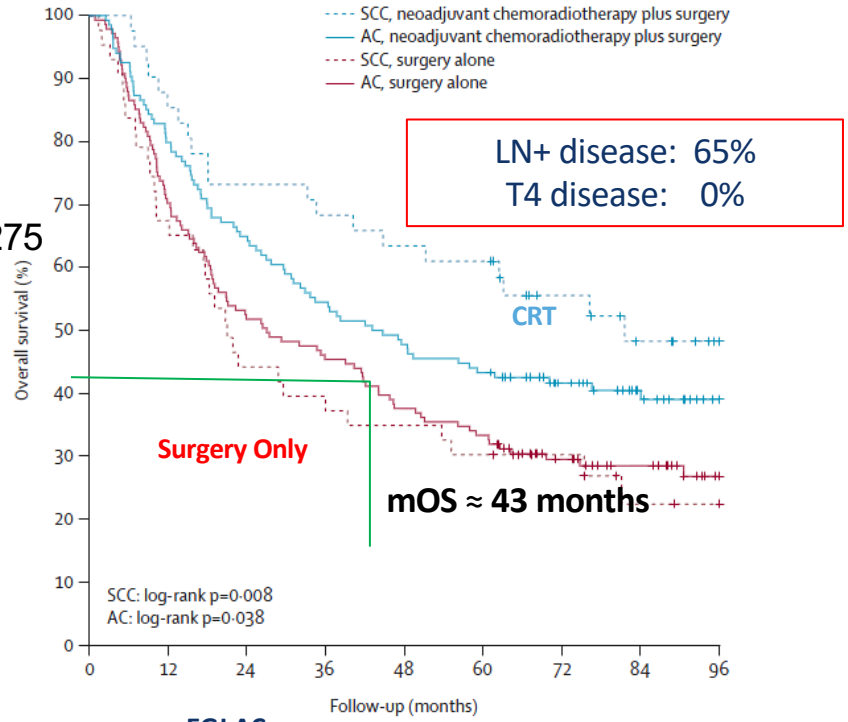


EGJ AC
FLOT > MAGIC > Surgery
HR 0.76 HR 0.74

Al-Batran et al. Phase III FLOT4. *Lancet* 2019
Cunningham et al. Phase III MAGIC. NEJM 2006

N=275

LN+ disease: 65%
T4 disease: 0%



EGJ AC
CROSS > just surg
HR 0.75

van Hagen et al. Phase III CROSS. *NEJM* 2012
Shapiro et al. Phase III CROSS. *Lancet Oncol* 2015

Forthcoming Head-to-Head Phase III studies

Neo-AEGIS

- **ECX/EOX**/FLOT vs CROSS
- Ireland, UK, Denmark
- N= 540 , EGJ (I/II) only
- HR 1.02, terminated for futility at second interim analysis
- >85% MAGIC, prior to amendment for FLOT

Reynolds et al. *BMC Cancer* 2017

TOPGEAR

- **ECX**/FLOT +/- neoCRT
- Australia, New Zealand
- N=620, **GC**/EGJ, **not type I**
- Target HR 0.76

Leong et al. *BMC Cancer* 2015

ESOPEC

- FLOT vs CROSS
- Germany
- N=438, EGJ (I/II) only
- Target HR 0.645 (!)

EGJ AC
FLOT > MAGIC > Surgery
HR 0.76 HR 0.74

716 pts

EGJ AC
CROSS > Surgery
HR 0.75

Heoppneret al. *BMC Cancer* 2016

Neo-AEGIS 2013-2018: CROSS vs (modified) MAGIC regimen

Esophageal and GEJ adenocarcinoma:
AEG I-III
cT2-3N0-3M0

Arm B 15% superior to A (n= 366)

Arm B 10% superior to A (n= 628)

R

EC(O)F(X) x 3 → Surgery → EC(O)F(X) x 3 — **Arm A**

Neo CRT (CROSS)
wCP-RT(41.4Gy)+Surgery — **Arm B**

Primary endpoint: Overall survival

Secondary end points: Disease free survival;
Time to treatment failure: TRG: R0: Toxicity: Postoperative complications; HR-QL

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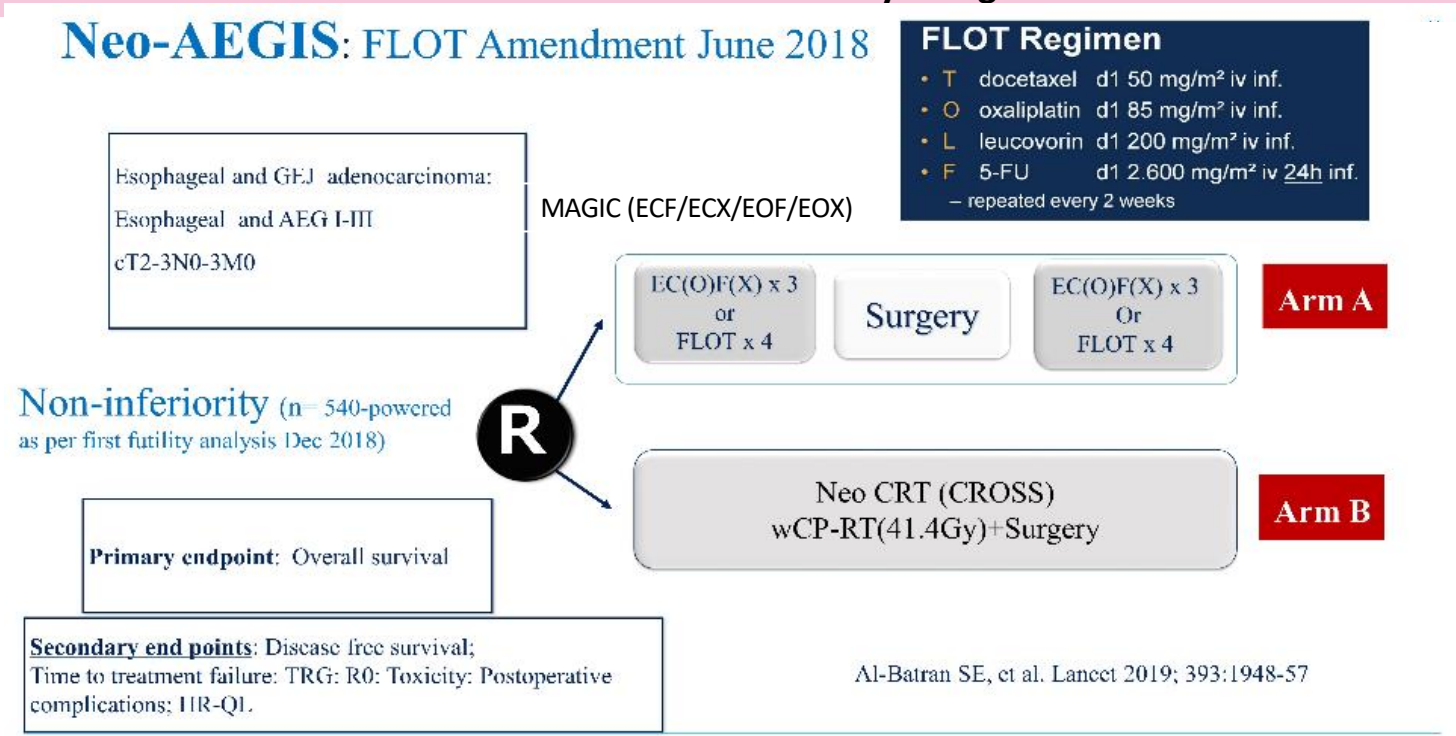
4004: Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol) in EAC and GEJ

Neo-AEGIS Amended Study Design



4004: Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol) in EAC and GEJ

International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG)

Donald E Low [1], Derek Alderson, Ivan Cecconello, Andrew C Chang, Gail E Darling, Xavier Benoit D'Journo, S Michael Griffin, Arnulf H Hölscher, Wayne L Hofstetter, Blair A Jobe, Yuko Kitagawa, John C Kucharczuk, Simon Ying Kit Law, Toni E Lerut, Nick Maynard, Manuel Pera, Jeffrey H Peters, C S Pramesh, John V Reynolds, B Mark Smithers, J Jan B van Lanschot

Results: Post operative Complications

Specific	ARM A (Chemo) N = 157	ARM B (CROSS) N = 162	
Post op mortality	N=3 (1.9%)	N=5 (3%)	p = 0.723
Anastomotic Leaks	12%	12%	
Respiratory:			
Pneumonia	19.7%	16%	
ARDS	0.6%	4.3%	p = 0.067
Respiratory Failure	7.6%	8%	
Venous Thromboembolism	3.8%	3%	
Cardiac:			
Atrial Fibrillation	12.7%	14.2	
Sepsis	5%	5%	

MAGIC = 157
FLOT = 27
Chemo 184
157/184 = 85%

Total CROSS = 178
162/178 = 91%

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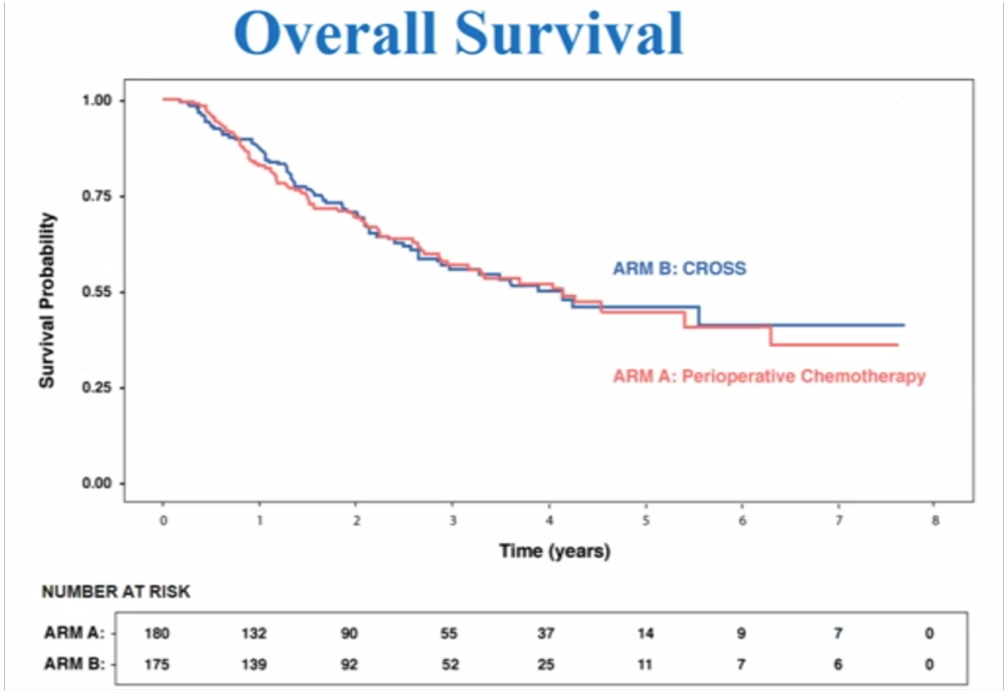
Overall Survival



HR=1.02 (ratio calculated as Arm A / Arm B) with 95% CI of 0.74 to 1.42.

4004: Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol) in EAC and GEJ

cancer trials ireland

19

2nd Futility Analysis December 2020: n= 143 deaths

- **HR=1.02 (ratio calculated as Arm A / Arm B) with 95% CI of 0.74 to 1.42.**
- No evidence that Arm A (Modified MAGIC/FLOT) is unacceptably inferior to Arm B (CROSS)
- Recruitment completed in December 2020 as per DSMB recommendation
- Final assessment in July 2022

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4004: Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol) in EAC and GEJ

MAGIC (ECF/ECX/EOF/EOX)

Peri-operative chemotherapy was not unacceptably inferior to CROSS-regimen multimodal therapy, with 3 year survival at 57% and 56%, respectively

Markers of response, including pathologic complete response, major pathologic response, R0 rate, and nodal down-staging, significantly better in CROSS Arm

No significant difference in severity of complications or specific index complication rates, or postoperative mortality, hence no negative effect of preoperative radiation therapy

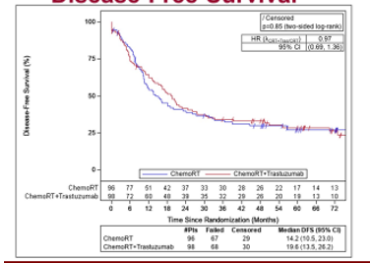
If MAGIC > Surgery (HR ~0.75) (**MAGIC** study 2006, N=503)
& CROSS > Surgery (HR ~0.74) (**CROSS** study 2012, N=368)
& MAGIC = CROSS (HR ~1.02) (**NeoAegis** study 2021, N=319)
& if FLOT > MAGIC (HR ~0.76) (**FLOT4** study 2019, N=738)

Can we solve for Y?
FLOT vs CROSS (HR Y) (**ESOPEC** study, XX, N=438)

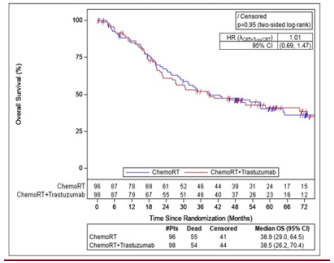
Neoadj MAGIC/FLOT +/-RT, adj MAGIC/FLOT (**TOPGEAR**, XX, N=620)

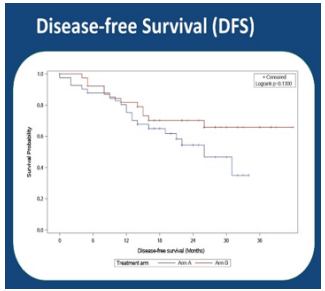
Perioperative anti-HER2 studies

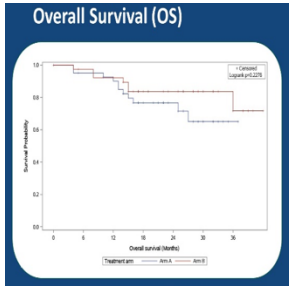
Disease-Free Survival



Overall Survival







RTOG1 010 N=194

Primary Endpoint: DFS

Surgery and Pathologic Complete Response (pCR)

	ChemoRT + Trastuzumab (n=98)	ChemoRT (n=96)	Chi-squared p-value
Surgery			
Yes	**82 (84%)**	**78 (81%)**	
No (progression, mets, death)	5 (5%)	8 (8%)	
No (other)	11 (11%)	10 (10%)	
pCR			0.71
Yes	22 (27%)	23 (29%)	
No	60 (73%)	55 (71%)	

NRG ONCOLOGY™

NRG/RTOG 1010

Safran et al. RTOG1010 Phase III. ASCO 2020

PETRARCA N=81

Primary Endpoint:

Phase 2: pCR rate

Phase 3: DFS

Histopathology & primary endpoint (pCR)

ypT-stage	FLOT N = 41	FLOT + Tras / Per N = 40	P-value
≤T1	11 (27%)	17 (43%)	
T2	9 (22%)	8 (20%)	
T3	17 (41%)	14 (35%)	
T4	3 (7%)	0 (0%)	
N0	16 (39%)	27 (68%)	
pCR	5 (12%)	14 (35%)	p = 0.02

2020 ASCO ANNUAL MEETING #ASCO20

Hofheinz et al. PETRARCA Phase II. ASCO 2020

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

Ronan J. Kelly,[1] Jaffer A. Ajani,[2] Jaroslaw Kuzdzal,[3] Thomas Zander,[4] Eric Van Cutsem,[5] Guillaume Piessen,[6] Guillermo Mendez,[7] Josephine Feliciano,[8] Satoru Motoyama,[9] Astrid Lièvre,[10] Hope Uronis,[11] Elena Elimova,[12] Cecile Grootscholten,[13] Karen Geboes,[14] Jenny Zhang,[15] Samira Soleymani,[15] Ming Lei,[15] Prianka Singh,[15] James M. Cleary,[16] Markus Moehler[17]

- [1]The Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Jagiellonian University, John Paul II Hospital, Cracow, Poland; [4]University Hospital of Cologne, Cologne, Germany; [5]University Hospitals Gasthuisberg, Leuven and KULeuven, Leuven, Belgium; [6]University of Lille, Claude Huriez University Hospital, Lille, France; [7]Fundacion Favaloro, Buenos Aires, Argentina; [8]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [9]Akita University Hospital, Akita, Japan; [10]CHU Pontchaillou, Rennes 1 University, Rennes, France; [11]Duke Cancer Institute, Durham, NC; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [14]UZ Gent, Gent, Belgium; [15]Bristol Myers Squibb, Princeton, NJ; [16]Dana Farber Cancer Institute, Boston, MA; [17]Johannes-Gutenberg University Clinic, Mainz, Germany

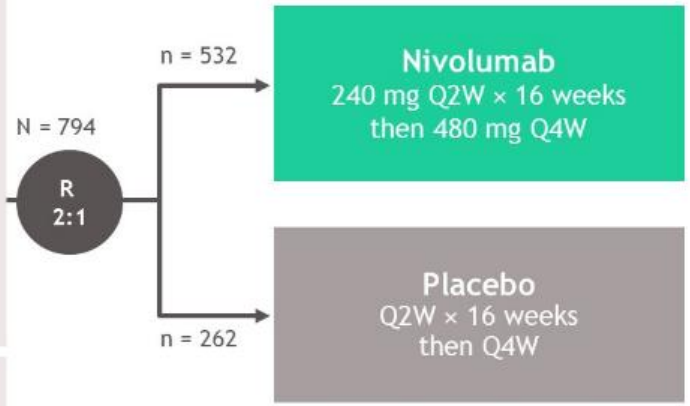
Abstract 4003

4003: Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT)

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%[c])



Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

- Median follow-up was 24.4 months (range, 6.2-44.9)[i]
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)

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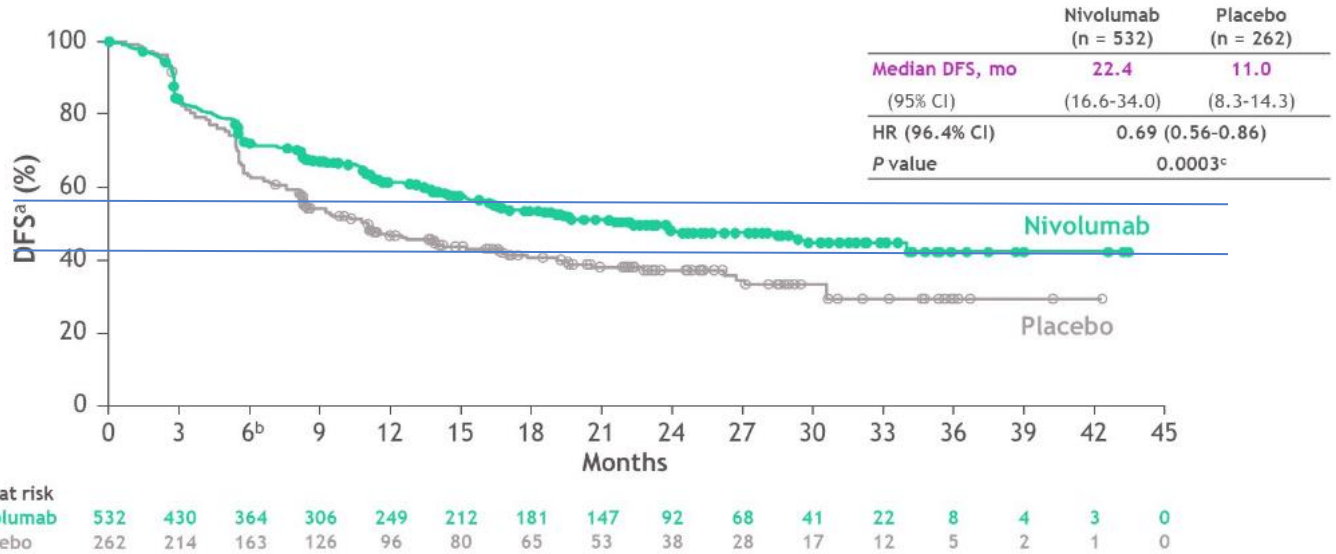
4003: Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT)

Disease-free survival (DFS)



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

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CM 577(Adj EsoSCC/EsoAC/GEJAC)

Disease-free survival by subgroups

Subgroup		Median DFS, months		Unstratified HR
		Nivolumab	Placebo	
Overall (N = 794)		22.4	11.0	0.70
Age, years	< 65 (n = 507)	24.4	10.8	0.65
	≥ 65 (n = 287)	17.0	13.9	0.80
Sex	Male (n = 671)	21.4	11.1	0.73
	Female (n = 123)	Not reached	11.0	0.59
Race	White (n = 648)	21.3	10.9	0.71
	Asian (n = 117)	24.0	10.2	0.70
ECOG PS	0 (n = 464)	29.4	11.1	0.73
	1 (n = 330)	17.0	10.9	0.66
Disease stage at initial diagnosis	II (n = 278)	34.0	13.9	0.72
	III (n = 514)	19.4	8.5	0.68
Tumor location	EC (n = 462)	24.0	8.3	0.61
	GEJC (n = 332)	22.1	20.6	0.87
Histology	Adenocarcinoma (n = 563)	19.4	11.1	0.75
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74
	≥ ypN1 (n = 457)	14.8	7.6	0.67
Tumor cell PD-L1 expression	≥ 1% (n = 129)	19.7	14.1	0.75
	< 1% (n = 570)	21.3	11.1	0.73
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54

Unstratified HR (95% CI)

TPS not CPS!!

- DFS favored nivolumab versus placebo across these pre-specified subgroups

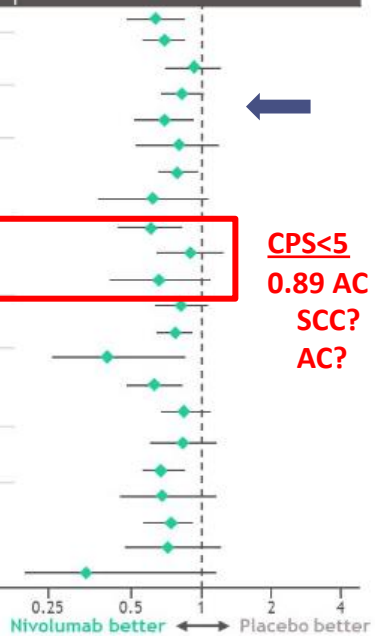
- CPS <5?
- AC?
- GEJ?

- Longer DFS/OS f/u

4003: Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT)

Disease-free survival subgroup analysis

Category	Subgroup	Median DFS, mo		Unstratified HR
		Nivolumab	Placebo	
Overall	N = 794	22.4	11.0	0.70
Tumor location at initial diagnosis	Esophagus (n = 462)	24.0	8.3	0.61
	Gastroesophageal junction (n = 332)	22.4	20.6	0.87
Histologic type	Adenocarcinoma (n = 563)	19.4	11.1	0.75
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61
Tumor cell PD-L1 expression[a]	≥ 1% (n = 129)	19.7	14.1	0.75
	< 1% (n = 570)	21.3	11.1	0.73
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54
PD-L1 CPS expression[a,b]	≥ 5 (n = 371)	29.4	10.2	0.62
	< 5 (n = 295)	16.3	11.1	0.89
	Missing/nonevaluable (n = 128)	Not reached	10.8	0.61
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74
	≥ ypN1 (n = 457)	14.8	7.6	0.67
Pathological tumor status	ypT0 (n = 47)	34.0	5.2	0.35
	ypT1 or ypT2 (n = 308)	28.3	9.3	0.60
	ypT3 or ypT4 (n = 436)	18.9	14.1	0.84
Time from complete resection to randomization	< 10 weeks (n = 256)	24.0	14.1	0.84
	≥ 10 weeks (n = 538)	21.4	10.8	0.66
Radiotherapy dosage[b,c]	< 41.4 Gray (n = 92[d])	19.7	13.8	0.69
	41.4-50.4 Gray (n = 504)	24.0	11.1	0.73
	> 50.4 Gray (n = 152)	21.4	8.3	0.72
	Not reported (n = 41)	14.4	6.1	0.41



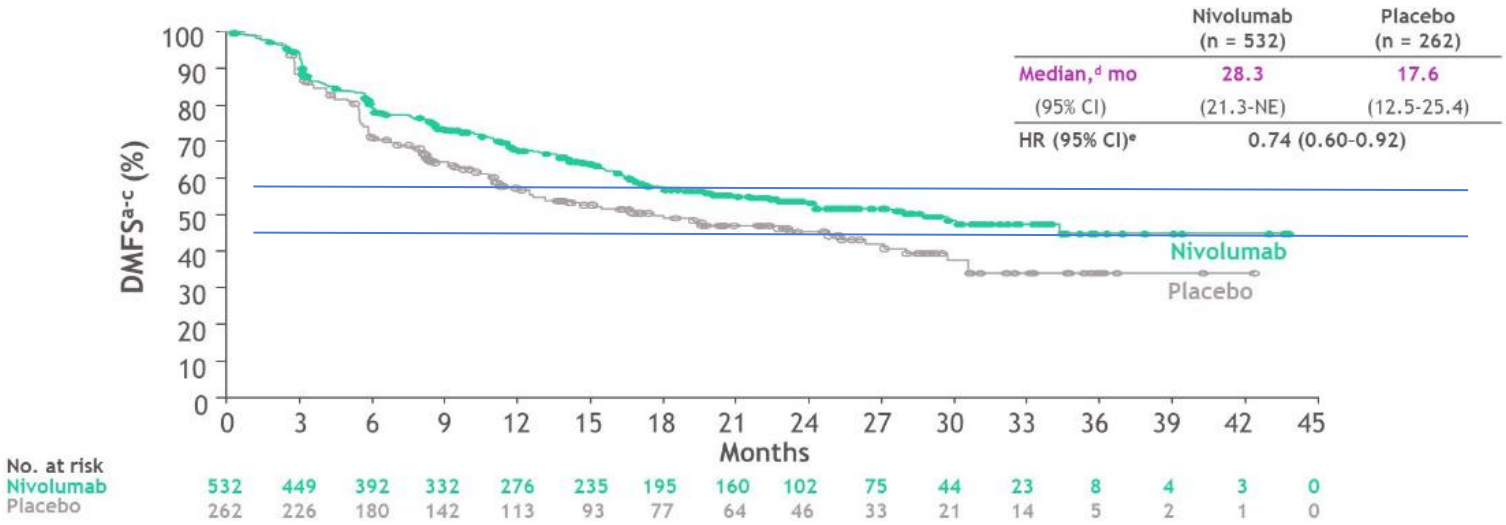
CPS<5
0.89 AC + SCC
SCC?
AC?

- Disease-free survival benefit was observed with nivolumab versus placebo across multiple subgroups

Abstract 4003

4003: Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT)

Distant metastasis-free survival (DMFS)



	Nivolumab (n = 532)	Placebo (n = 262)
Median,[d] mo	28.3	17.6
(95% CI)	(21.3-NE)	(12.5-25.4)
HR (95% CI)[e]	0.74 (0.60-0.92)	

- Nivolumab showed a 26% reduction in the risk of distant recurrence or death versus placebo
- Distant (29% versus 39%) and locoregional (12% versus 17%) recurrences were less frequent with nivolumab versus placebo, respectively

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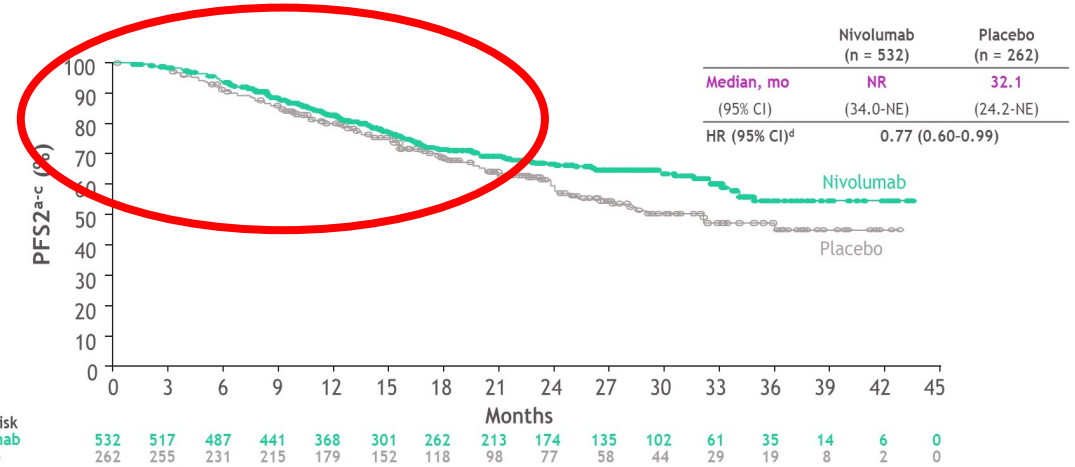
4003: Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT)

CheckMate 577

Progression-free survival 2 (PFS2)



	Nivolumab (n = 532)	Placebo (n = 262)
Median, mo	NR	32.1
(95% CI)	(34.0-NE)	(24.2-NE)
HR (95% CI)[d]	0.77 (0.60-0.99)	

- PFS2 favored nivolumab versus placebo with HR of 0.77 (95% CI: 0.60-0.99)

[a]Per investigator assessment; based on Kaplan-Meier estimates; [b]PFS2 is defined as the time from randomization to progression after the first subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever is earlier; [c]Patients without a PFS2 event were censored at the date last known alive; [d]Stratified Cox proportional-hazards model. Hazard ratio is nivolumab over placebo.

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4003: Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT)

Summary

- Adjuvant nivolumab demonstrated clinically meaningful efficacy in patients with resected EC/GEJC following neoadjuvant CRT compared to placebo
  - 31% reduction in the risk of recurrence or death and a doubling in median DFS
  - DFS benefit across multiple subgroups
  - Less frequent distant and locoregional recurrences
  - Improvement in DMFS and PFS2
- Adjuvant nivolumab demonstrated an acceptable safety profile and maintained QoL
  - TRAEs with potential immunologic etiology resolved for most patients with the use of established management algorithms
  - Similar trends in QoL improvement were observed with nivolumab and placebo during treatment and were maintained post-treatment
- These results provide further support for adjuvant nivolumab as a new standard of care for patients with resected EC/GEJC who received neoadjuvant CRT with residual pathologic disease

University of Nebraska Medical Center
Bio Ascend™

4003: Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT)

CM577

CM577 HR for DFS	
ITT	0.69
SCC	0.61
AC	0.75
CPS > 5	0.62
CPS < 5	0.89
SCC	
CPS>5	???
CPS<5	???
AC	
CPS>5	???
CPS<5	???

CM577 HR for OS	
ITT	???
SCC	???
AC	???
CPS > 5	???
CPS < 5	???
SCC	
CPS>5	???
CPS<5	???
AC	
CPS>5	???
CPS<5	???

University of Nebraska Medical Center
Bio Ascend™

FDA approves nivolumab for resected esophageal or GEJ cancer

On May 20, 2021, the Food and Drug Administration approved nivolumab (Opdivo, Bristol-Myers Squibb Company) for patients with completely resected esophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy.

If MAGIC > Surgery (HR ~0.75) (**MAGIC** study 2006, N=503)
& CROSS > Surgery (HR ~0.74) (**CROSS** study 2012, N=368)
& MAGIC = CROSS (HR ~1.02) (**NeoAegis** study 2021, N=319)
& if FLOT > MAGIC (HR ~0.76) (**FLOT4** study 2019, N=738)

Can we solve for Y?
FLOT vs CROSS (HR Y) (**ESOPEC** study, XX, N=438)

Neoadj MAGIC/FLOT +/-RT, adj MAGIC/FLOT (**TOPGEAR**, XX, N=620)

CROSS → nivo vs CROSS (HR OS?) (**CM577**, XX, N=532)
CF/FLOT-pembro vs CF/FLOT (HR OS?) (**KN585**, XX, N=1007)
FLOT-durva vs FLOT (HR OS?) (**MATTERHORN**, XX, N=900)
Adj S1/CapeOx-nivo vs Adj S1/CapeOx (HR OS?) (**ATTRACTION-05**, XX, N=700)

FLOT-atezo vs FLOT (**DANTE/FLOT8**, XX, N=295)
CROSS-nivo vs CROSS → nivo vs nivo-ipi (**EA2174**, XX, N=278)

NCCN Guidelines Version 3.2021
Esophageal and Esophagogastric Junction Cancers

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil[b] can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Definitive Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]
- Fluorouracil and cisplatin (category 1)[11]

Other Recommended Regimens
- Cisplatin with docetaxel or paclitaxel[12-14]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)

Preferred Regimens
- Fluorouracil,[b] leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)[c]
- Fluoropyrimidine and oxaliplatin[b,d]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Postoperative Therapy

Preferred Regimens
- Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)[e,15]

Other Recommended Regimens
- Capecitabine and oxaliplatin[f,16]
- Fluorouracil[b] and oxaliplatin[f]

Preoperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
- Fluorouracil and cisplatin (category 2B)[10]

Postoperative Chemoradiation
- Fluoropyrimidine (infusional fluorouracil[b] or capecitabine) before and after fluoropyrimidine-based chemoradiation[17]

[b]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[c]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[d]The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[e]See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f]Cisplatin may not be used interchangeably with oxaliplatin in this setting.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
References

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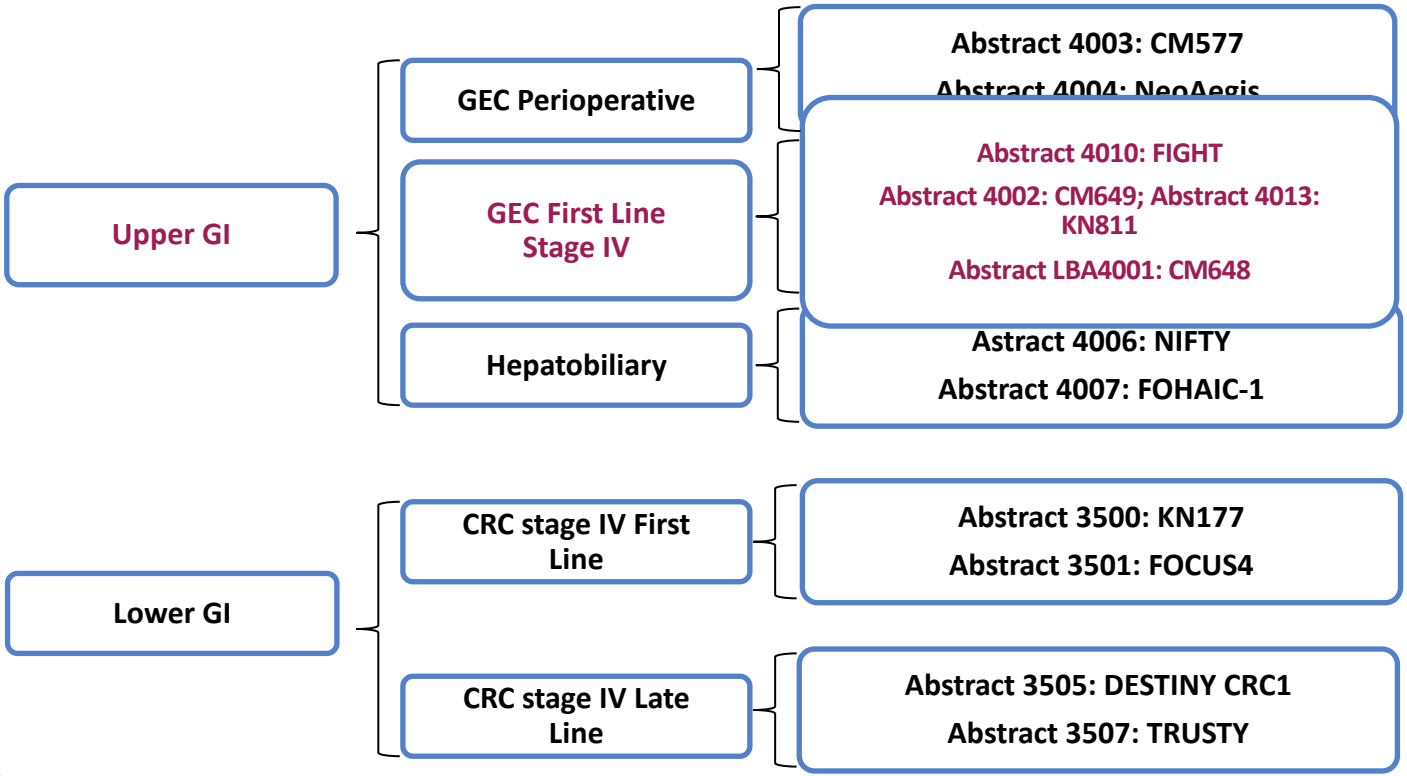
July 15, 20
June 22, 2021

ASCO 2021: Highlights in GI Malignancies



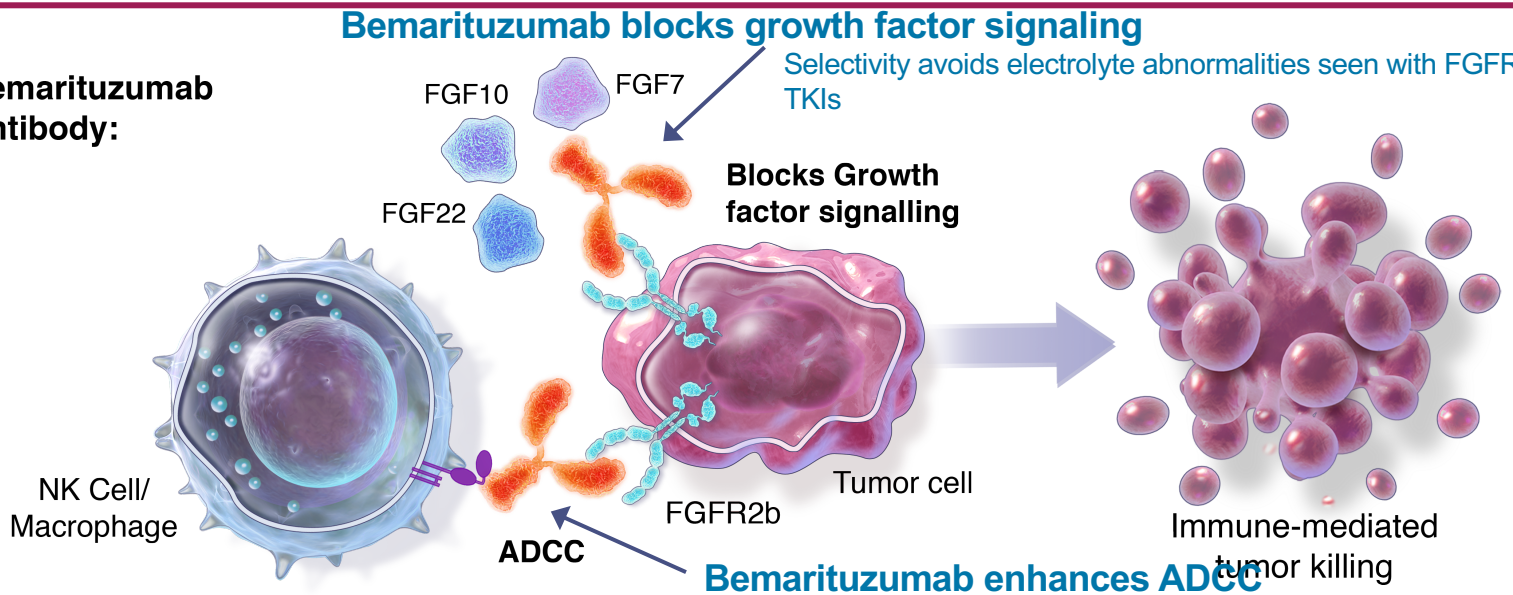
FIGHT: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY OF BEMARITUZUMAB (BEMA) COMBINED WITH MODIFIED FOLFOX6 IN 1L FGFR2B+ ADVANCED GASTRIC/GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (GC) (NCT03694522)

Presenter: Daniel Catenacci, MD
University of Chicago

Authors: Catenacci DV[1], Kang YK[2], Saeed A[3], Yamaguchi K[4], Qin S[5], Lee KW[6], Kim IH[7], Oh SC[8], Li J[9], Turk HM[10], Teixeira AC[11], Borg C[12], Hitre E[13], Udrea AA[14], Cardellino GG[15], Guardeño Sanchez R[16], Mitra S[17], Yang Y[17], Enzinger PC[18], Wainberg ZA[19]

[1]University of Chicago, Chicago, USA; [2]Asan Medical Center, Seoul, South Korea; [3]Kansas University Cancer Center, Westwood, KS, USA; [4]The Cancer Institute Hospital of JFCR, Koto-Ku , Tokyo, Japan; [5]81 Hospital Nanjing University of Chinese Medicine, Nanjing, China; [6]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Gyeonggi-do, South Korea; [7]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea; [8]Korea University Guro Hospital, Seoul, South Korea; [9]Shanghai East Hospital, Shanghai, China; [10]Department of Medical Oncology, Bezmialem Vakif University, School of Medicine, Istanbul, Turkey; [11]Hospital Senhora Da Oliveira, Guimarães, Portugal; [12]Centre Hospitalier Régional Universitaire de Besançon, Besançon France; [13]National Institute of Oncology, Budapest, Hungary; [14]SC Medisprof SRL, Cluj-Napoca, Romania; [15]Department of Oncology, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; [16]Institut Català d'Oncologia, Girona, Spain; [17]FivePrime Therapeutics, Inc., South San Francisco, USA; [18]Dana Farber Cancer Institute, Boston, USA; [19]University of California, Los Angeles, USA

Bemarituzumab: IgG1 Ab Specific to FGFR2b Receptor

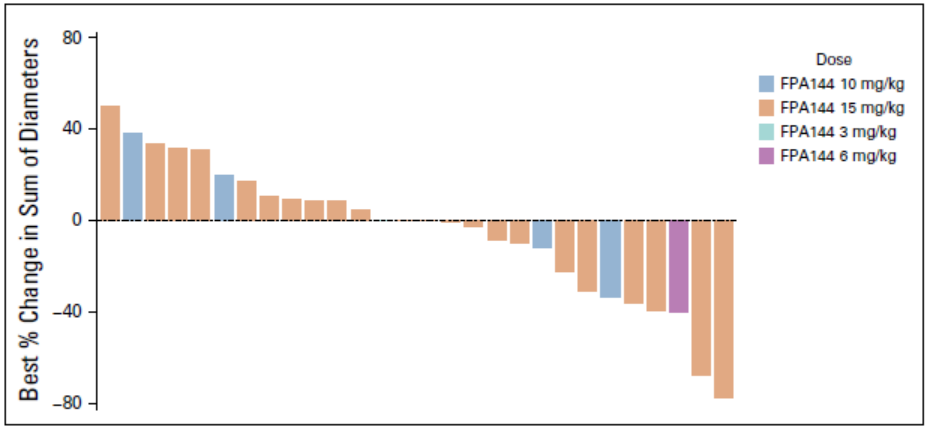


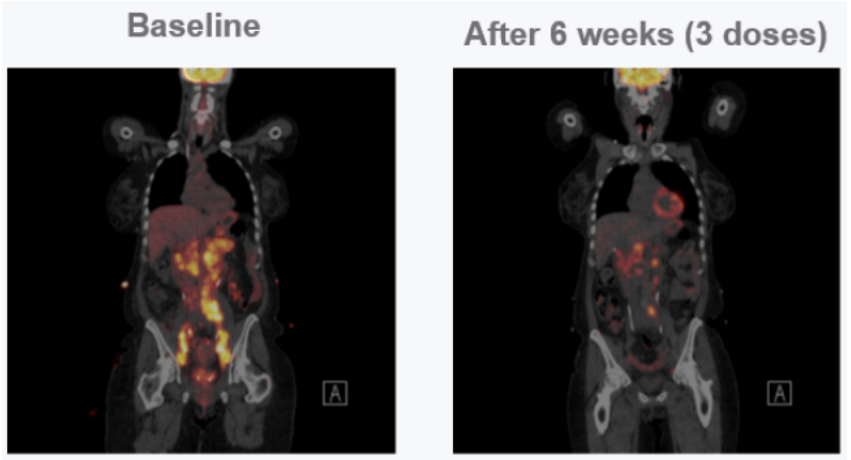
18% overall response rate in late-line FGFR2b+ gastroesophageal cancer[1]

- ADCC, antibody-dependent cell-mediated cytotoxicity; FGF, fibroblast growth factor; IgG1, immunoglobulin G1; NK, natural killer; TKIs, tyrosine kinase inhibitors.

1. Catenacci D, et al. *J Clin Oncol*. 2020.

FGFR2 Amplification: Bemarituzumab





Catenacci DVT. Phase I Escalation & Expansion Study of Bemarituzumab (FPA144) in Pts With Advanced Solid Tumors and FGFR2b-Selected Gastroesophageal Adenocarcinoma JCO 2020

Catenacci DVT. Bemarituzumab with modified FOLFOX6 for advanced FGFR2-positive gastroesophageal cancer: FIGHT Phase III study design. Future Oncol 2019

FIGHT Phase 2 Study Design

Key Eligibility Criteria

- No prior therapy for unresectable, locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression and/or *FGFR2* gene amplification
- Not HER2-positive

Stratification Factors

- Geographic region
- Single dose of FOLFOX while screening
- Prior perioperative chemotherapy

Randomization 1:1

Bemarituzumab* + mFOLFOX6 (n = 77)

VS

Placebo + mFOLFOX6 (n = 78)

Primary endpoint
- PFS

Secondary endpoints
- OS
- Response rate

Treatment may continue until progression, unacceptable toxicity, or the patient meets other withdrawal criteria

*Bemarituzumab dosing: 15 mg/kg Q2W beginning cycle 1 day 1 (plus 1 dose of 7.5 mg/kg on day 8 of cycle 1 only). FOLFOX6 dosing: standard fixed doses Q2W.

FGFR2b, fibroblast growth factor receptor 2b.

Demographics & Baseline Characteristics Well Balanced

Demographics/Characteristics n (%)	Bema + mFOLFOX6 (N = 77)	Placebo + mFOLFOX6 (N = 78)
Age, median (range), years	60.0 (23, 80)	59.5 (33, 84)
Gender, male (%)	52 (67.5%)	59 (75.6%)
Race, Asian (%)	45 (58.4%)	44 (56.4%)
Region		
US/EU	32 (41.6%)	34 (43.6%)
China	14 (18.2%)	13 (16.7%)
Rest of Asia	31 (40.3%)	31 (39.7%)
Single dose of mFOLFOX6 prior to randomization	35 (45.5%)	36 (46.2%)
Measurable disease at baseline	66 (85.7%)	60 (76.9%)
FGFR2b status		
Overexpression based on IHC	73 (94.8%)	76 (97.4%)
Amplification based on ctDNA	12 (15.6%)	14 (17.9%)
Both overexpression and amplification	8 (10.4%)	12 (15.4%)

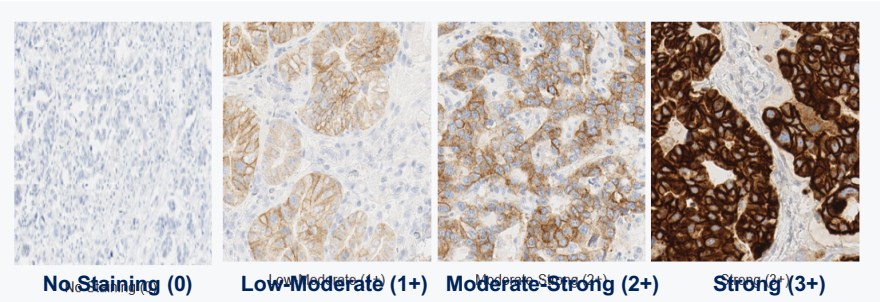
EU, European Union; US, United States.

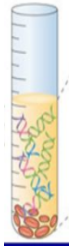
Eligibility Included FGFR2b IHC+ and/or *FGFR2* ctDNA+

30% of 910 prescreened patients were eligible

FGFR2b+ overexpression	*FGFR2* gene amplification
IHC**	ctDNA

Assays validated under design control for analysis of gastric cancer samples





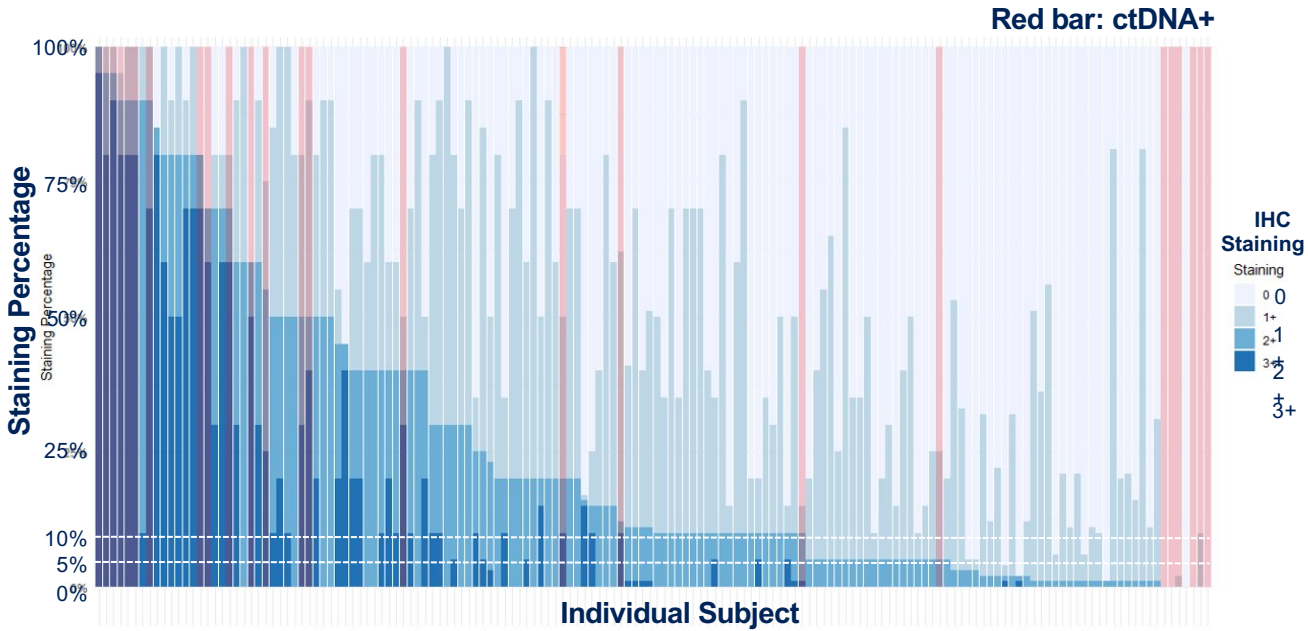
Blood or plasma containing ctDNA

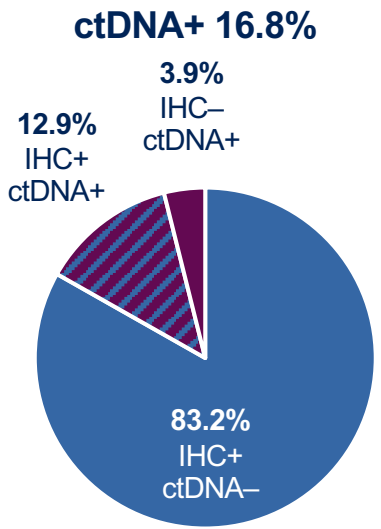
FGFR2b IHC+ defined as 2+/3+ staining

FGFR2 amplification threshold of 1.5-fold increase

** Study protocol allowed analyses on both fresh and archival samples and majority of analyses were performed on fresh samples

Most Enrolled Patients Had Tumor FGFR2b Overexpression Without Evidence of FGFR2 Amplification



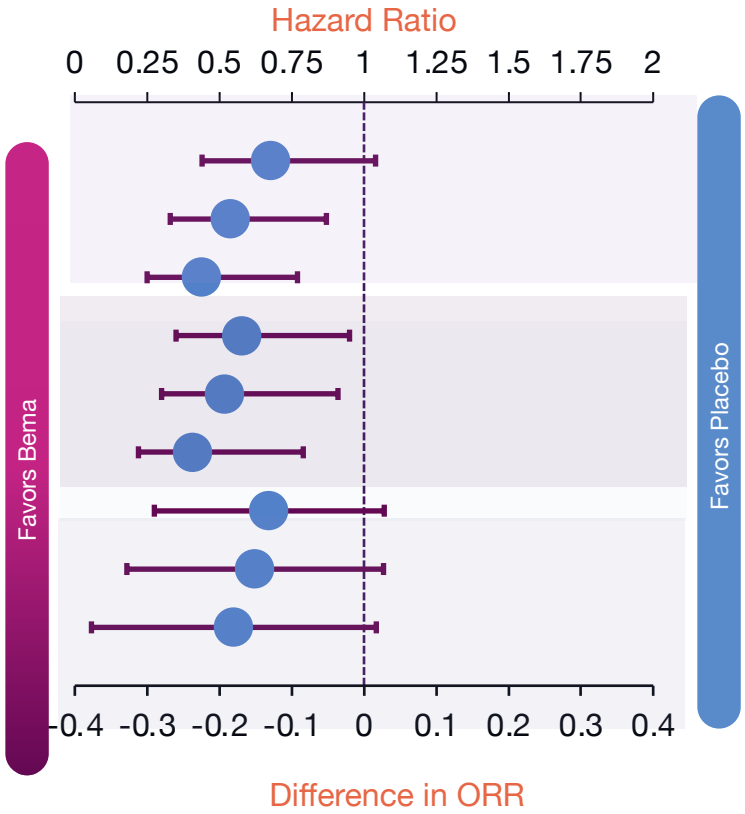


FGFR2 status of enrolled patients

ITT = any 2+/3+ staining or ctDNA+ only **N = 155**
≥ 5% tumors cells staining 2+/3+ **N = 118 (76%)**
≥10% tumors cells staining 2+/3+ **N = 96 (62%)**

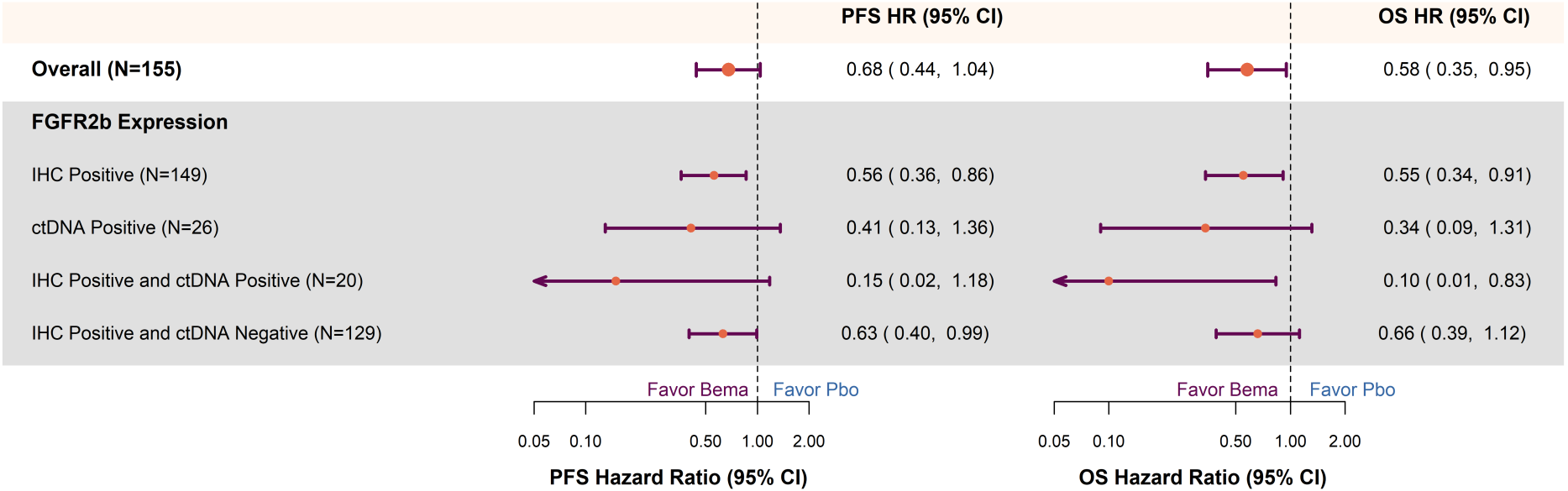
Higher Bemarituzumab Efficacy With Higher % FGFR2b+

Endpoint	Subgroup	Median PFS/OS (months) Response rate	HR (95% CI) Difference in ORR (95% CI)
PFS	Overall*	Bema: 9.5 Placebo: 7.4	0.68 (0.44, 1.04)
	IHC 2+ or 3+ ≥5%†	Bema: 10.2 Placebo: 7.3	0.54 (0.33, 0.87)
	IHC 2+ or 3+ ≥10%‡	Bema: 14.1 Placebo: 7.3	0.44 (0.25, 0.77)
OS	Overall	Bema: NR Placebo: 12.9	0.58 (0.35, 0.95)
	IHC 2+ or 3+ ≥5%	Bema: NR Placebo: 12.5	0.52 (0.30, 0.91)
	IHC 2+ or 3+ ≥10%	Bema: NR Placebo: 11.1	0.41 (0.22, 0.79)
ORR	Overall	Bema: 36 (46.8%) Placebo: 26 (33.3%)	-13.1%§ (-29.0%, 2.8%)
	IHC 2+ or 3+ ≥5%	Bema: 30 (51.7%) Placebo: 22 (36.7%)	-15.1%§ (-32.8%, 2.7%)
	IHC 2+ or 3+ ≥10%	Bema: 24 (54.5%) Placebo: 19 (36.5%)	-18.0%§ (-37.7%, 1.7%)

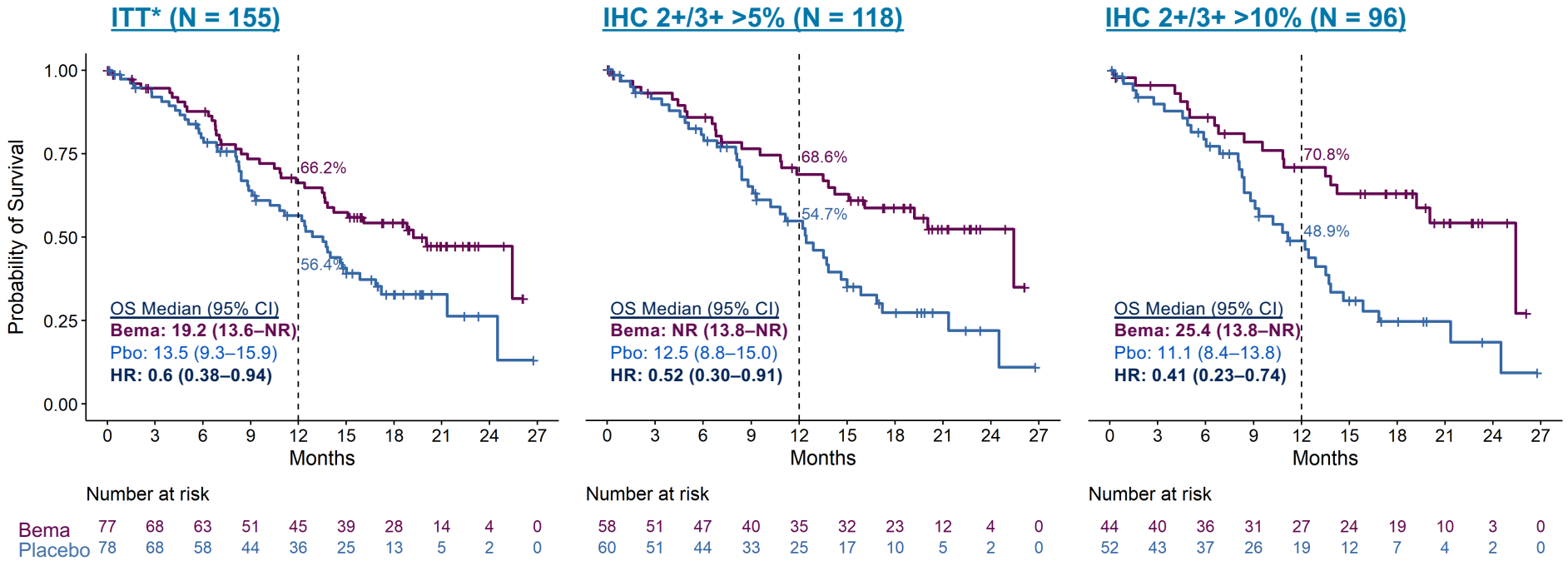


Evaluation of Efficacy by Biomarker Status

Overexpression was Sufficient, ctDNA+ with Most Pronounced Benefit



Addition of Bemarituzumab Showed a +5.7 Month Improvement in Median OS



ncludes 149 patients with IHC 2+/3+ and 6 with IHC <2+ or not available who were enrolled based on ctDNA alone.

NR, not reached.

Median Follow-up 12.5 months

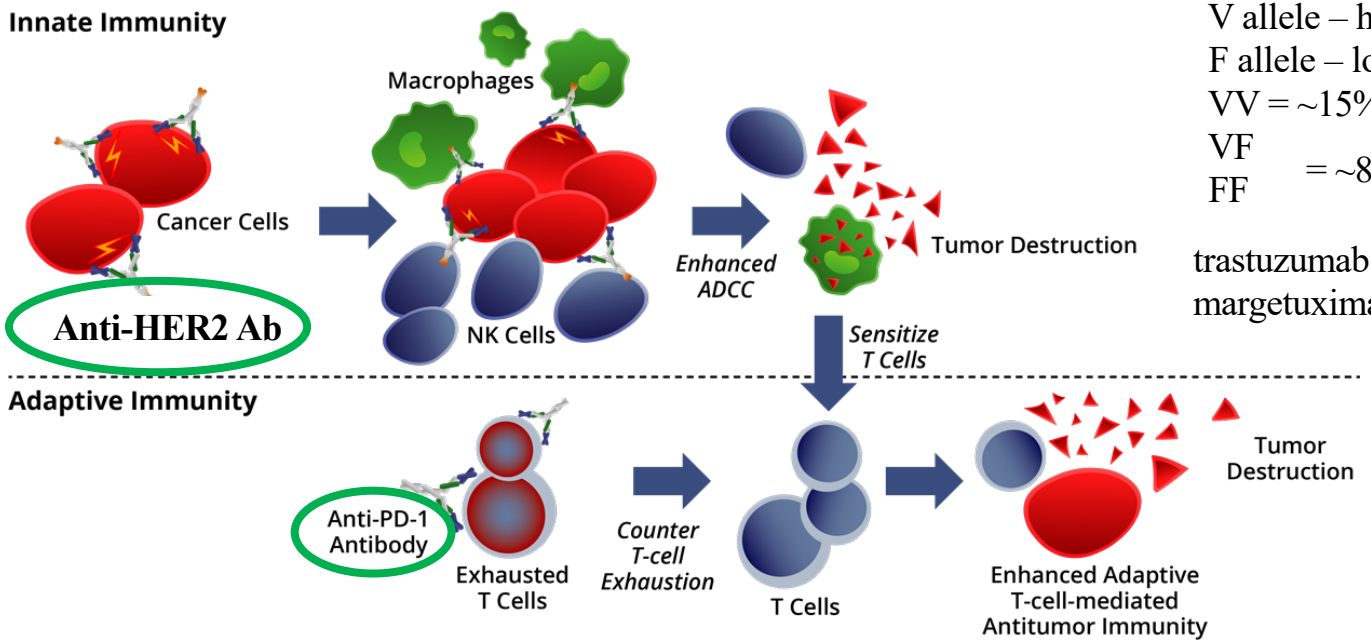
*Based on February, 28th 2021 data cut

Summary of Corneal Adverse Events

Patients with corneal AEs*	Bema (N = 76)	Placebo (N = 77)
Any corneal AE	51 (67.1%)	8 (10.4%)
Grade 1 corneal AE	16 (21.1%)	6 (7.8%)
Grade 2 corneal AE	17 (22.4%)	2 (2.6%)
Grade 3 corneal AE	18 (23.7%)	0
Grade 4 corneal AE	0	0
SAE	0	0
Time to onset (grades 2 and 3) (weeks)		
N	35	2
Median	23.7	12.8
Q1, Q3	15.9, 33.1	9.0, 16.6
Time to resolution or downgraded to grade 1 (grades 2 and 3) (weeks)		
N	21†	1
Median	19.1	2.0
Q1, Q3	9.1, 25.1	2.0, 2.0

*Duration of exposure was comparable for the two arms; †loss of follow-up of 6 patients due to death and 1 patient due to consent withdrawal.
No association with frequency or severity of corneal AE and tumor FGFR2b positivity. Corneal AEs are defined by Standardised MedDRA Queries (SMQ) of corneal disorders.

Anti-HER2 + IO Combination?



CD16A (FCGR3)

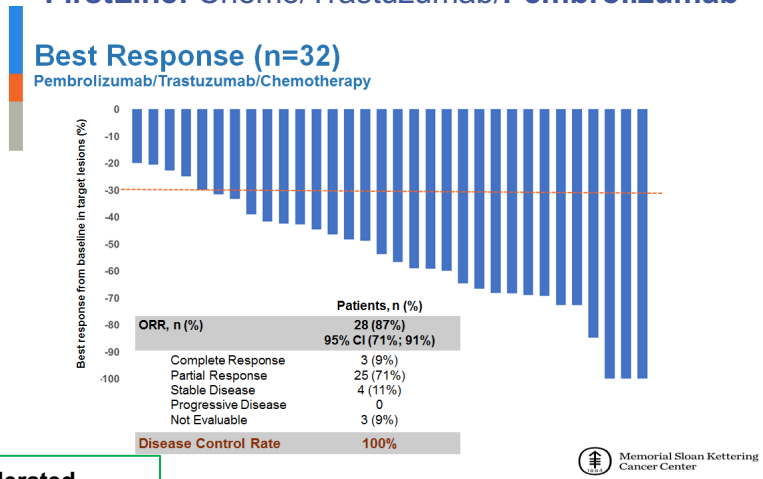
V allele – high affinity
F allele – low affinity
VV = ~15%
VF
FF = ~85%

trastuzumab vs margetuximab

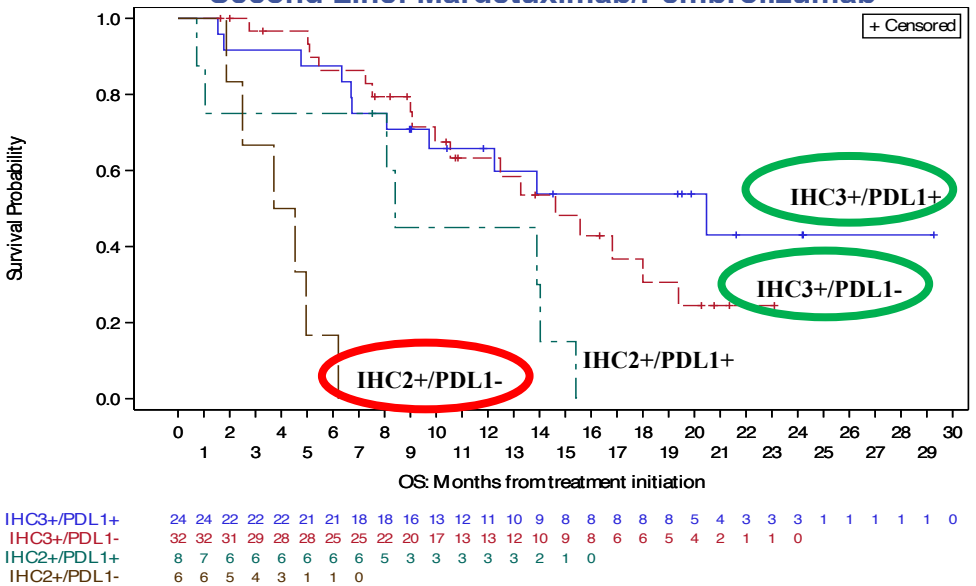
Catenacci et al. MAHOGANY: margetuximab combination in HER2+ unresectable/metastatic gastric/gastroesophageal junction adenocarcinoma. *Future Oncol* 2021

Anti-HER2 + IO Combination

FirstLine: Chemo/Trastuzumab/**Pembrolizumab**



Second Line: Margetuximab/Pembrolizumab



FDA accelerated Approval 5/2021
- **N=264**
- **52% vs 74% ORR**

Janjigian et al. *ASCO 2021 Abstr*

KN-811 1L Phase III
Chemo/trastruzumab +/- pembrolizumab

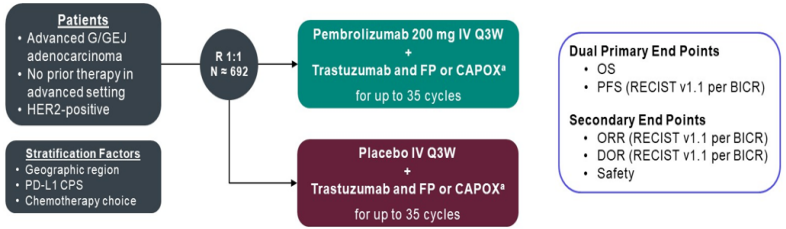
MAHOGANY 1L Phase II/III
A) margetuximab + retifanlimab (IHC3+ & PDL1 CPS>1)
B) Chemo/margetuximab +/- retifanlimab

Janjigian et al. *Lancet Oncol* 2020 Catenacci et al. *Lancet Oncol* 2020

Abstract 4013

KEYNOTE-811 Global Cohort

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)



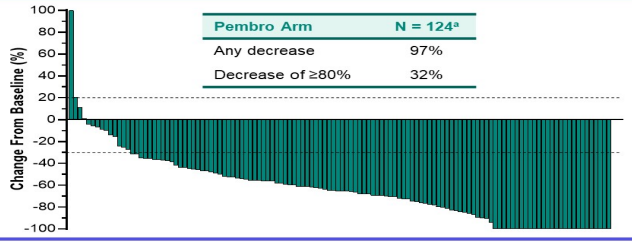
[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX dose: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

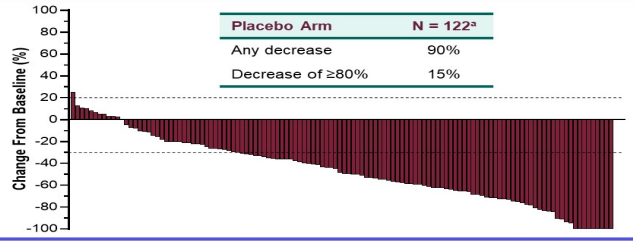
Baseline Characteristics – Efficacy Population

	Pembro Arm (N = 133)	Placebo Arm (N = 131)
PD-L1 CPS ≥1	88%	85%
HER2 status		
IHC 2+, ISH positive	18%	21%
IHC 3+	82%	79%

CPS >5 incidence? ORR > and < CPS5?
CPS >10 incidence? ORR > and < CPS10?

Confirmed Response at IA1





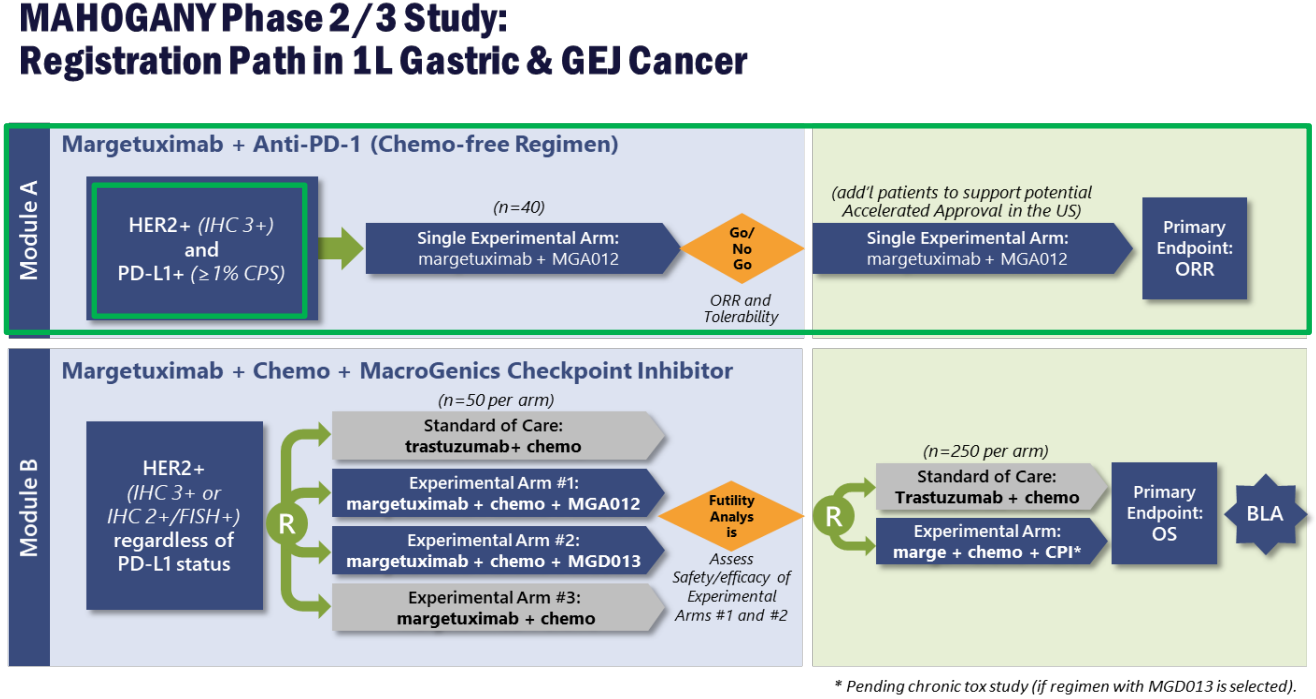
ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	74.4% (66.2-81.6)	51.9% (43.0-60.7)
ORR difference[b]	22.7% (11.2-33.7) *P* = 0.00006	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	15 (11%)	4 (3%)
PR	84 (63%)	64 (49%)
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

[a]Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Calculated in participants with best response of CR or PR. [d]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

First Line – Margetuximab/Retifanlimab



Catenacci et al. Margetuximab plus pembrolizumab for previously treated, HER2-positive GEA (CP-MGAH22–05): a single-arm, phase 1b–2 trial. *Lancet Oncology* 2020

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

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Abstract Number 4002

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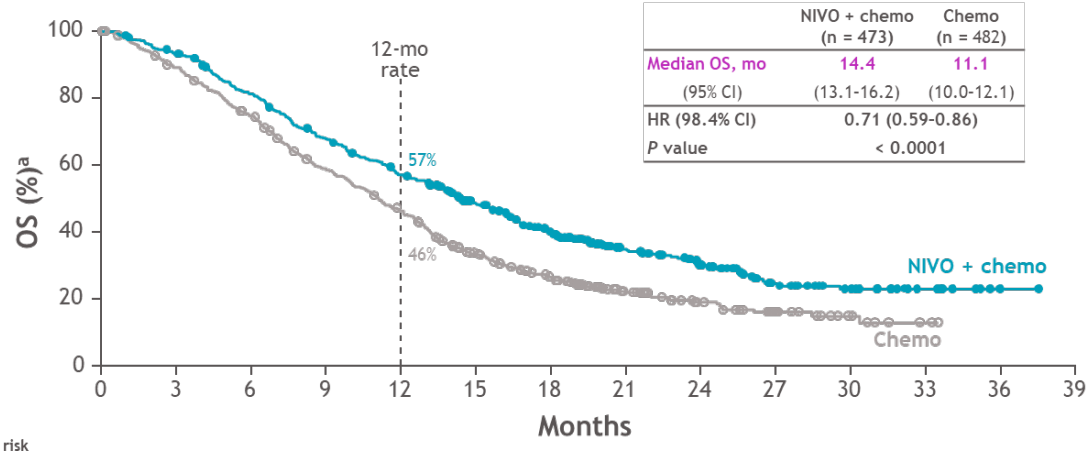
CM 649 (1L EsoAC/GEJ AC/GC AC) FOLFOX +/- Nivolumab

Overall survival

Primary endpoint (PD-L1 CPS ≥ 5)



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

No. at risk													
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

[a]Minimum follow-up 12.1 months.

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CM 649 (1L GEJ AC/GC AC)

Overall survival

CPS≥5 → CPS≥1 → All

HR 0.71 → 0.77 → 0.8

Pts# 473 → 473+168 → 641+148

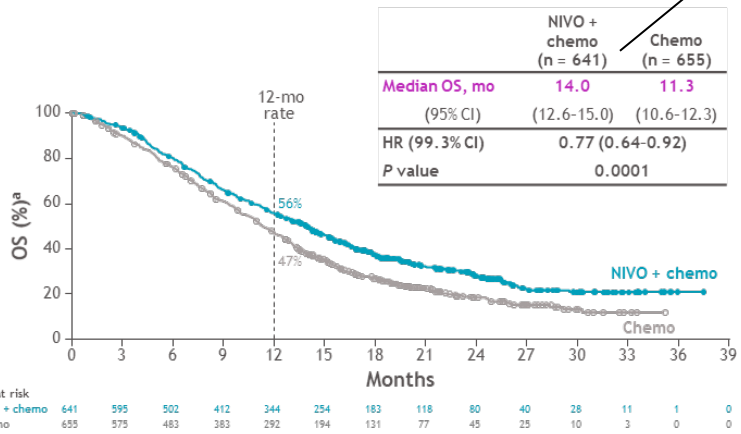
CPS 1-5 ?? 168

CPS 0 ?? 148

CPS <5 ?? 316

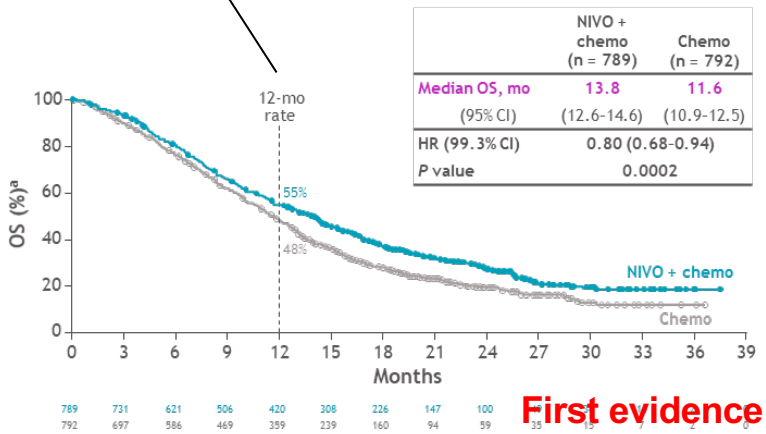
Initially Not Reported

PD-L1 CPS ≥ 1



	NIVO + chemo (n = 641)	Chemo (n = 655)
Median OS, mo	14.0	11.3
(95% CI)	(12.6-15.0)	(10.6-12.3)
HR (99.3% CI)	0.77 (0.64-0.92)	
P value	0.0001	

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P value	0.0002	

First evidence that Chemo+IO not effective in CPS <5 tumors

- Especially CPS 0

- Superior OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with NIVO + chemo versus chemo

Listed in NCCN guidelines 12/2020, CPS >5 FOLFOX+Nivo, GC, EGJ AC

FDA approved 4/16/21 for all-comers (any PDL1)

EMA no decision yet

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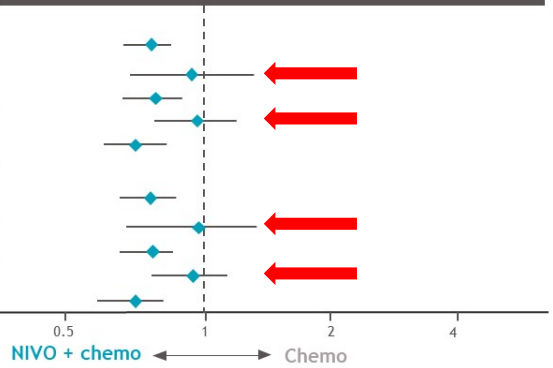
Efficacy subgroup analysis by PD-L1 CPS in all randomized patients

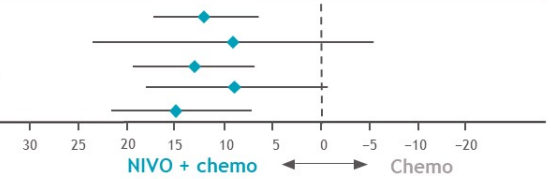
Survival

PD-L1 CPS[a]	Number of patients, n	Median, months		Unstratified HR[b]
		NIVO + chemo	Chemo	
Overall survival				
Overall (N = 1581)		13.8	11.6	0.79
< 1	265	13.1	12.5	0.92
≥ 1	1296	14.0	11.3	0.76
< 5	606	12.4	12.3	0.94
≥ 5	955	14.4	11.1	0.70
Progression-free survival				
Overall (N = 1581)		7.7	6.9	0.77
< 1	265	8.7	8.1	0.93
≥ 1	1296	7.5	6.9	0.75
< 5	606	7.5	8.2	0.93
≥ 5	955	7.7	6.1	0.69



Objective response rate

PD-L1 CPS[c]	Number of patients, n	Objective response rate, %		Unweighted ORR difference,[d] %
		NIVO + chemo	Chemo	
Overall (N = 1211)		58	46	12
< 1	178	51	41	9
≥ 1	1019	60	46	13
< 5	428	55	46	9
≥ 5	769	60	45	15



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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

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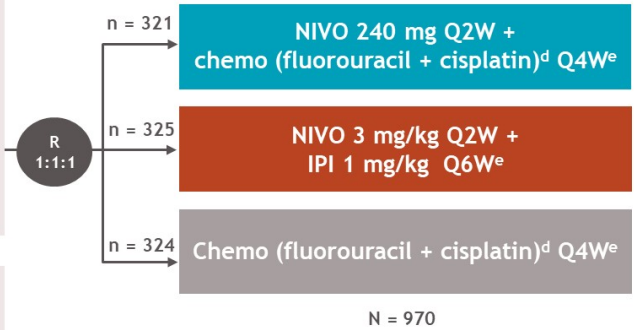
Abstract Number LBA4001

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
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

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

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

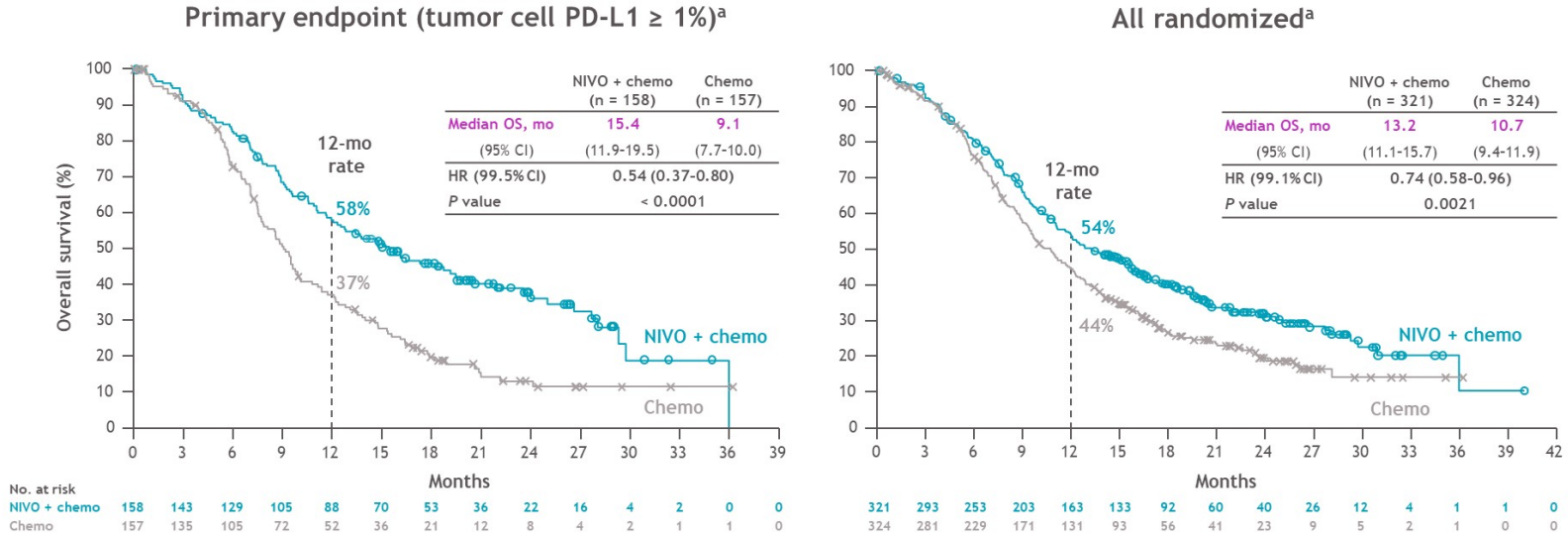
Baseline characteristics

All randomized	NIVO + chemo (n = 321)	NIVO + IPI (n = 325)	Chemo (n = 324)[a]
Median age, years (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian/non-Asian,[b] %	70/30	70/30	70/30
ECOG PS 1,[c] %	54	54	53
ESCC,[d] %	97	99	98
Tumor cell PD-L1 expression,[e] %			
≥ 1%	49	49	48
< 1%	51	51	52
Disease status at study entry, %			
De novo metastatic	57	60	58
Recurrent - locoregional	7	8	8
Recurrent - distant	22	22	19
Unresectable advanced	14	10	16
Number of organs with metastases[f]			
≤ 1	49	49	49
≥ 2	51	51	51
Current or former smoker, %	79	82	79

- Baseline characteristics were balanced across the 3 arms and were consistent with that of patients with tumor cell PD-L1 ≥ 1%

[a]Percentages may not add up to 100% due to rounding; [b]Refers to geographic region; [c]ECOG PS was not reported for 1 patient; [d]18 patients had adenosquamous histology, and 1 patient was classified as other; [e]Tumor cell PD-L1 was indeterminate, not evaluable, or missing in 5 patients; [f]Based on interactive response technology.

Overall survival: NIVO + chemo vs chemo

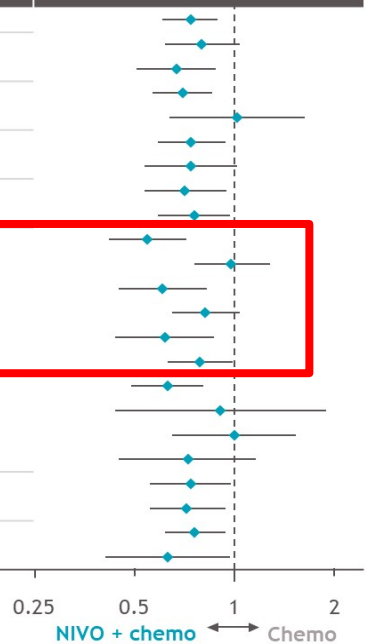


- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

[a]Minimum follow-up 12.9 months.

Overall survival subgroup analysis: NIVO + chemo vs chemo

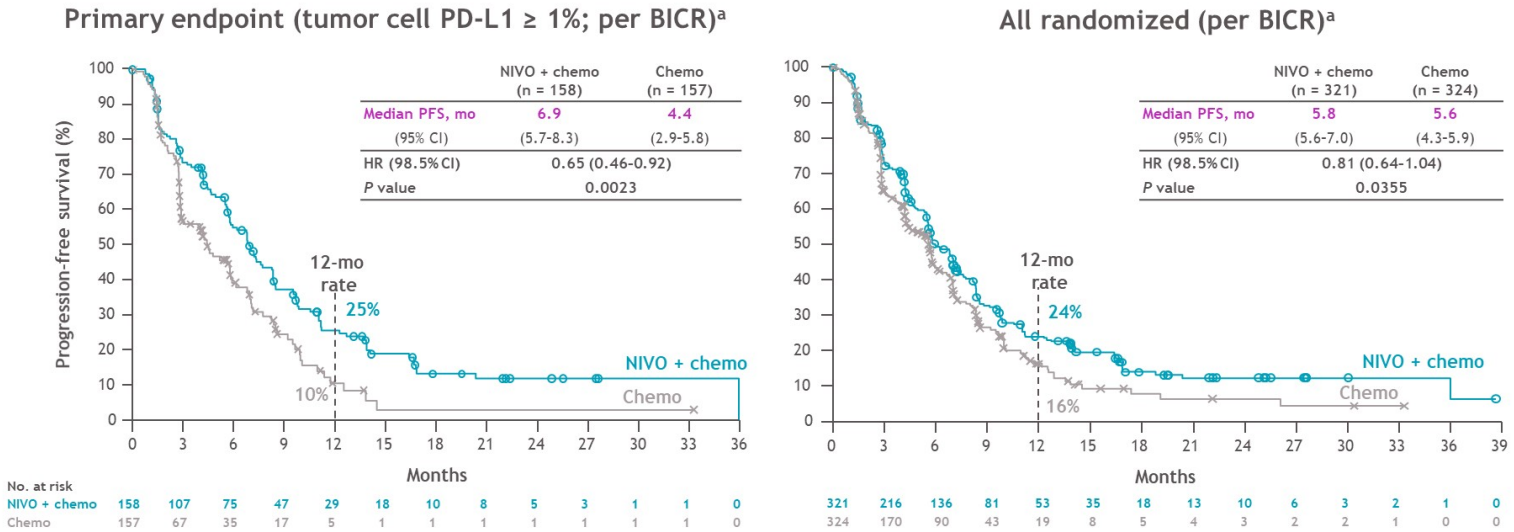
Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 645)		13.2	10.7	0.74
Age, years	< 65 (n = 333)	11.8	10.2	0.80
	≥ 65 (n = 312)	15.1	11.0	0.67
Sex	Male (n = 528)	12.5	10.0	0.70
	Female (n = 117)	15.2	14.8	1.02
Geographic region	Asian (n = 451)	15.5	11.9	0.74
	Non-Asian (n = 194)	10.5	8.5	0.74
ECOG PS[a]	0 (n = 300)	17.3	12.4	0.71
	1 (n = 344)	10.6	9.0	0.76
Tumor cell PD-L1 expression[b]	≥ 1% (n = 314)	15.4	9.2	0.55
	< 1% (n = 329)	12.0	12.2	0.98
	≥ 5% (n = 235)	13.7	9.5	0.61
	< 5% (n = 408)	12.8	11.1	0.82
	≥ 10% (n = 199)	14.7	9.5	0.62
	< 10% (n = 444)	12.3	10.8	0.79
Disease status at study entry	De novo metastatic (n = 371)	13.4	9.4	0.63
	Recurrent - locoregional (n = 46)	14.8	13.5	0.91
	Recurrent - distant (n = 132)	12.3	12.8	1.00
	Unresectable advanced (n = 96)	12.8	12.1	0.73
No. of organs with metastases	≤ 1 (n = 316)	15.7	11.6	0.74
	≥ 2 (n = 329)	11.1	9.6	0.72
Smoking	Current or former (n = 510)	12.3	10.0	0.76
	Never or unknown (n = 135)	15.7	11.1	0.63



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

[a]Not reported in 1 patient; [b]Indeterminate, not evaluable, or missing (n = 2).

Progression-free survival: NIVO + chemo vs chemo

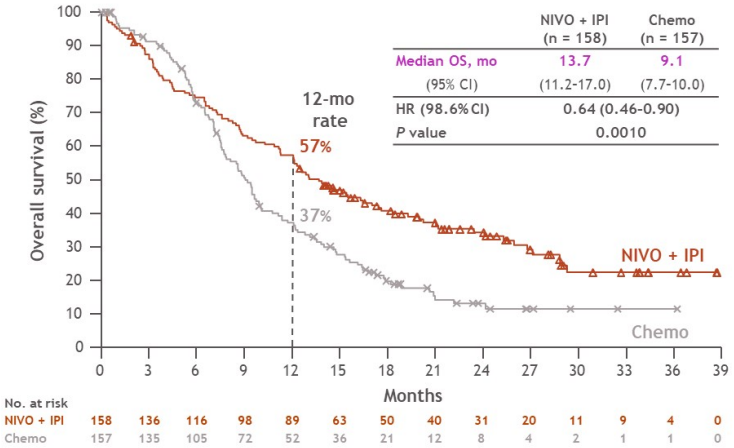


- Primary endpoint of PFS per BICR met in patients with tumor cell PD-L1 ≥ 1%
- Prespecified significance boundary for PFS per BICR not met in all randomized patients
- Improved PFS per INV[b] with HR of 0.53 (95% CI, 0.41–0.69) in tumor cell PD-L1 ≥ 1% and 0.69 (95% CI, 0.58–0.83) in all randomized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

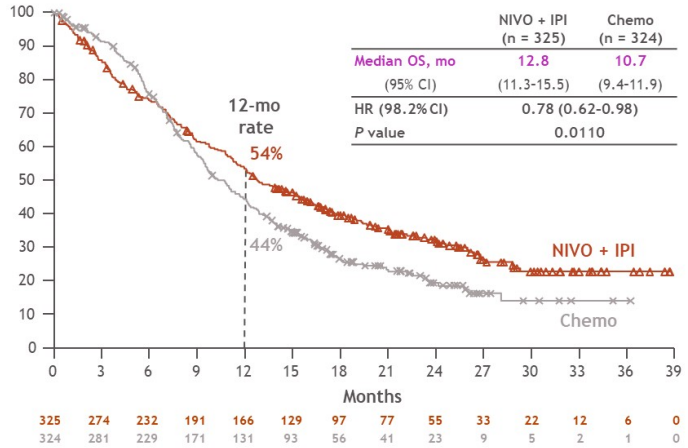
[a]Minimum follow-up 12.9 months; [b]Exploratory analysis.

Overall survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



All randomized[a]

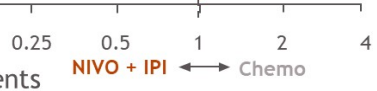


- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 4.6-month improvement in median OS
  - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

[a]Minimum follow-up 12.9 months.

Overall survival subgroup analysis: NIVO + IPI vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + IPI	Chemo	
Overall (N = 649)		12.8	10.7	0.78
Age, years	< 65 (n = 351)	12.1	10.2	0.92
	≥ 65 (n = 298)	16.0	11.0	0.63
Sex	Male (n = 544)	13.7	10.0	0.70
	Female (n = 105)	11.7	14.8	1.36
Geographic region	Asian (n = 455)	13.7	11.9	0.83
	Non-Asian (n = 194)	11.4	8.5	0.69
ECOG PS[a]	0 (n = 300)	17.0	12.4	0.73
	1 (n = 348)	9.7	9.0	0.81
Tumor cell PD-L1 expression[b]	≥ 1% (n = 314)	13.7	9.2	0.63
	< 1% (n = 330)	12.0	12.2	0.96
	≥ 5% (n = 235)	13.0	9.5	0.66
	< 5% (n = 409)	12.4	11.1	0.86
	≥ 10% (n = 200)	13.0	9.5	0.71
	< 10% (n = 444)	12.5	10.8	0.82
Disease status at study entry	De novo metastatic (n = 383)	12.1	9.4	0.75
	Recurrent - locoregional (n = 50)	13.9	13.5	1.13
	Recurrent - distant (n = 133)	15.5	12.8	0.88
	Unresectable advanced (n = 83)	17.4	12.1	0.63
No. of organs with metastases	≤ 1 (n = 318)	16.0	11.6	0.76
	≥ 2 (n = 331)	10.3	9.6	0.81
Smoking	Current or former (n = 524)	14.4	10.0	0.74
	Never or unknown (n = 125)	9.8	11.1	1.01

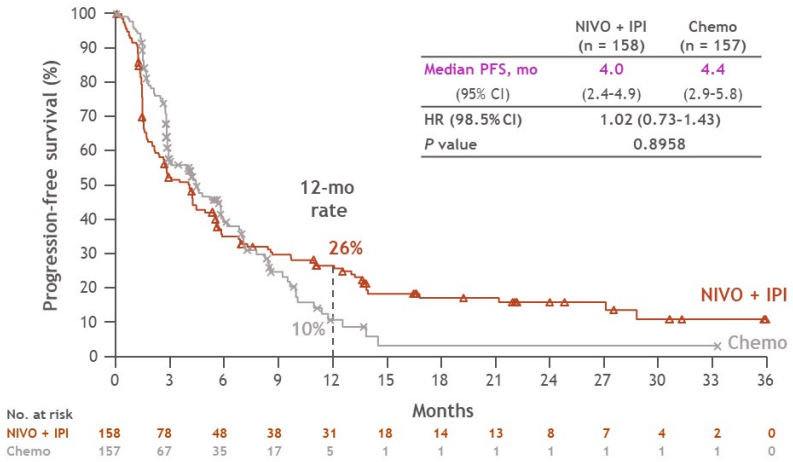


- OS favored NIVO + IPI vs chemo across most prespecified subgroups in all randomized patients

[a]Not reported in 1 patient; [b]Indeterminate, not evaluable, or missing (n = 5).

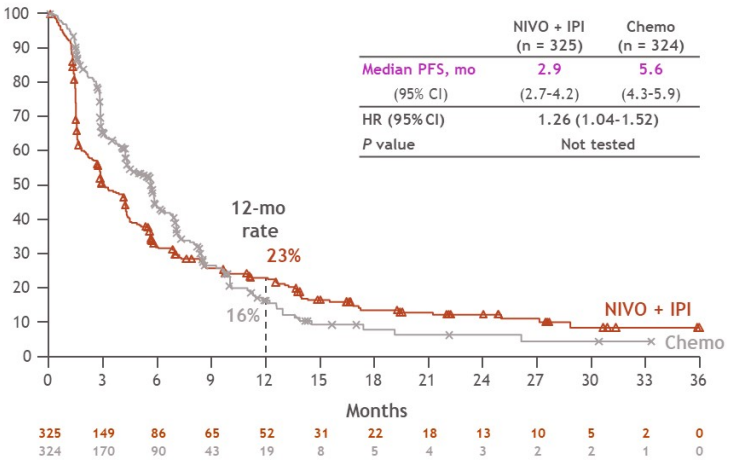
Progression-free survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%; per BICR)[a]



	NIVO + IPI (n = 158)	Chemo (n = 157)
Median PFS, mo	4.0	4.4
(95% CI)	(2.4-4.9)	(2.9-5.8)
HR (98.5% CI)	1.02 (0.73-1.43)	
P value	0.8958	

All randomized (per BICR)[a]



	NIVO + IPI (n = 325)	Chemo (n = 324)
Median PFS, mo	2.9	5.6
(95% CI)	(2.7-4.2)	(4.3-5.9)
HR (95% CI)	1.26 (1.04-1.52)	
P value	Not tested	

- 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 INV[b] 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 populations

[a]Minimum follow-up 12.9 months; [b]Exploratory analysis.

Treatment-related adverse events

All treated,[a] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs[b]	297 (96)	147 (47)	256 (80)	102 (32)	275 (90)	108 (36)
Serious TRAEs[b]	74 (24)	57 (18)	103 (32)	73 (23)	49 (16)	38 (13)
TRAEs leading to discontinuation[b,c]	106 (34)	29 (9)	57 (18)	41 (13)	59 (19)	14 (5)
Treatment-related deaths[d]	5 (2)[e]		5 (2)[f]		4 (1)[g]	

- Most common any-grade TRAEs (≥ 10%) included:
  - NIVO + chemo and chemo arms: nausea, decreased appetite, and stomatitis
  - NIVO+ IPI arm: rash, pruritus, and hypothyroidism
- The incidence of TRAEs in patients with tumor cell PD-L1 ≥ 1% was consistent with all treated patients across all arms

[a]Patients who received ≥ 1 dose of study drug; [b]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [c]TRAEs leading to discontinuation of any drug in the regimen; [d]Treatment-related deaths were reported regardless of timeframe; [e]Included 1 event each of pneumonia, pneumatosis intestinalis, acute kidney injury, pneumonitis, and pneumonitis/respiratory tract infection; [f]Included 2 events of pneumonitis and 1 event each of interstitial lung disease, acute respiratory distress syndrome, and pulmonary embolism; [g]Included 1 event each of septic shock, sepsis, acute kidney injury, and pneumonia.

Category 1
Category 2A
Category 2B

NCCN Guidelines: 6/22/21 (Version 3.2021)

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]
- HER2 overexpression negative[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥ 5) for adenocarcinoma only (category 1)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) for adenocarcinoma only (category 2B)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS ≥ 10) (category 1) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin for adenocarcinoma or squamous cell carcinoma[21-23]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin for adenocarcinoma or squamous cell carcinoma[21,24-26]

Other Recommended Regimens
- Fluorouracil[b,i] and irinotecan[j,27]
- Paclitaxel with or without cisplatin or carboplatin [j,28-32]
- Docetaxel with or without cisplatin [j,33-36]
- Fluoropyrimidine [j,25,37,38] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b, j,39,40]
- Docetaxel, carboplatin, and fluorouracil (category 2B) [j,41]

[a]An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[e]See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g]See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[h]If no prior tumor progression while on therapy with a checkpoint inhibitor.
[i]Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.
[j]Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Guidelines Version 3.2021
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11]
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,12]
  - Fluoropyrimidine (fluorouracil[b]or capecitabine) and oxaliplatin[13-15]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[13,16-18]

Other Recommended Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[g,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[g,h,19]
- Fluorouracil[b,i] and irinotecan[j,20]
- Paclitaxel with or without cisplatin or carboplatin[j,21-25]
- Docetaxel with or without cisplatin[j,26-29]
- Fluoropyrimidine[j,17,30,31] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,32,33]
- Docetaxel, carboplatin, and fluorouracil (category 2B)[j,34]

Useful in Certain Circumstances
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) (category 2B)[g,h,12]

[a]An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[f]See Principles of Pathologic Review and Biomarker Testing GAST-B).
[g]If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h]See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i]Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
[j]Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

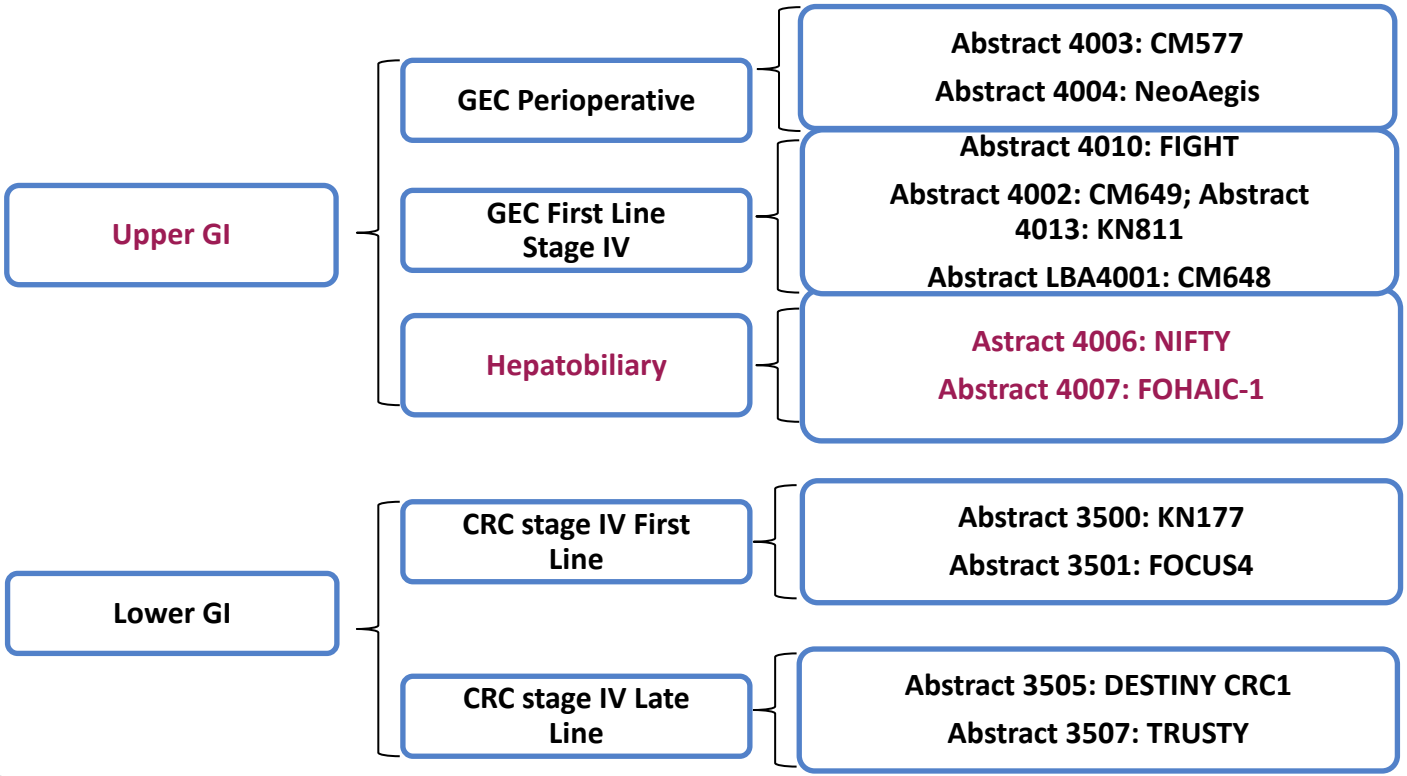
Continued
References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GAST-F
3 OF 16

PDL1 CPS 0 is not recommended to receive first-line anti-PD1 therapy for GC/GEJ/Eso for either AC or SCC!!

ASCO 2021: Highlights in GI Malignancies



Liposomal Irinotecan (nal-IRI) in combination with Fluorouracil (5-FU) and Leucovorin (LV) for Patients (pts) with Metastatic Biliary Tract Cancer (BTC) after Progression on Gemcitabine plus Cisplatin (GemCis): Multicenter Comparative Randomized Phase 2B study (NIFTY)

Changhoon Yoo[1], Kyu-pyo Kim[1], Ilhwan Kim[2], Myoung Joo Kang[2], Jaekyung Cheon[3], Byung Woog Kang[4], Hyewon Ryu[5], Jae Ho Jeong[1], Ji Sung Lee[6], Kyung Won Kim[7], Baek-Yeol Ryoo[1]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, [2]Inje University Haeundae Paik Hospital, [3]Ulsan University Hospital, [4]Kyungpook National University Hospital, [5]Chungnam National University Hospital, [6]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, [7]Asan Image Metrics, Asan Medical Center, Republic of Korea

Abstract #4003

ABC-06 | A randomised phase III, multi-centre, open-label study of Active Symptom Control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC + mFOLFOX) for patients with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy

Angela Lamarca, Daniel H Palmer, Harpreet S Wasan, Paul J Ross, Yuk Ting Ma, Arvind Arora, Stephen Falk, Roopinder Gillmore, Jonathan Wadsley, Kinnari Patel, Alan Anthoney, Anthony Maraveyas, Justin S Waters, Claire Hobbs, Safia Barber, David Ryder, John Ramage, Linda M Davies, John A Bridgewater, Juan W Valle

on behalf of the Advanced Biliary Cancer (ABC) Working Group

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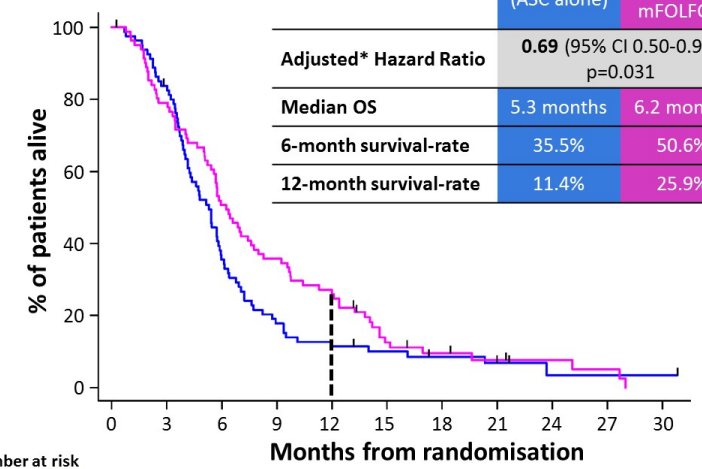
Primary end-point: Overall Survival (ITT)

- The **primary end-point was met**: adjusted* HR was 0.69 (95% CI 0.50-0.97; p=0.031) for OS in favour of ASC + mFOLFOX arm (vs ASC)

- No marked evidence was identified against the key proportional hazards assumption**; which confirmed the validity of using the Cox Regression analysis

*adjusted for platinum sensitivity, albumin and stage
**proportional hazards assumption test p-value 0.6521
ITT: intention-to-treat analysis; ASC: active symptom control

Overall survival by trial arm



	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

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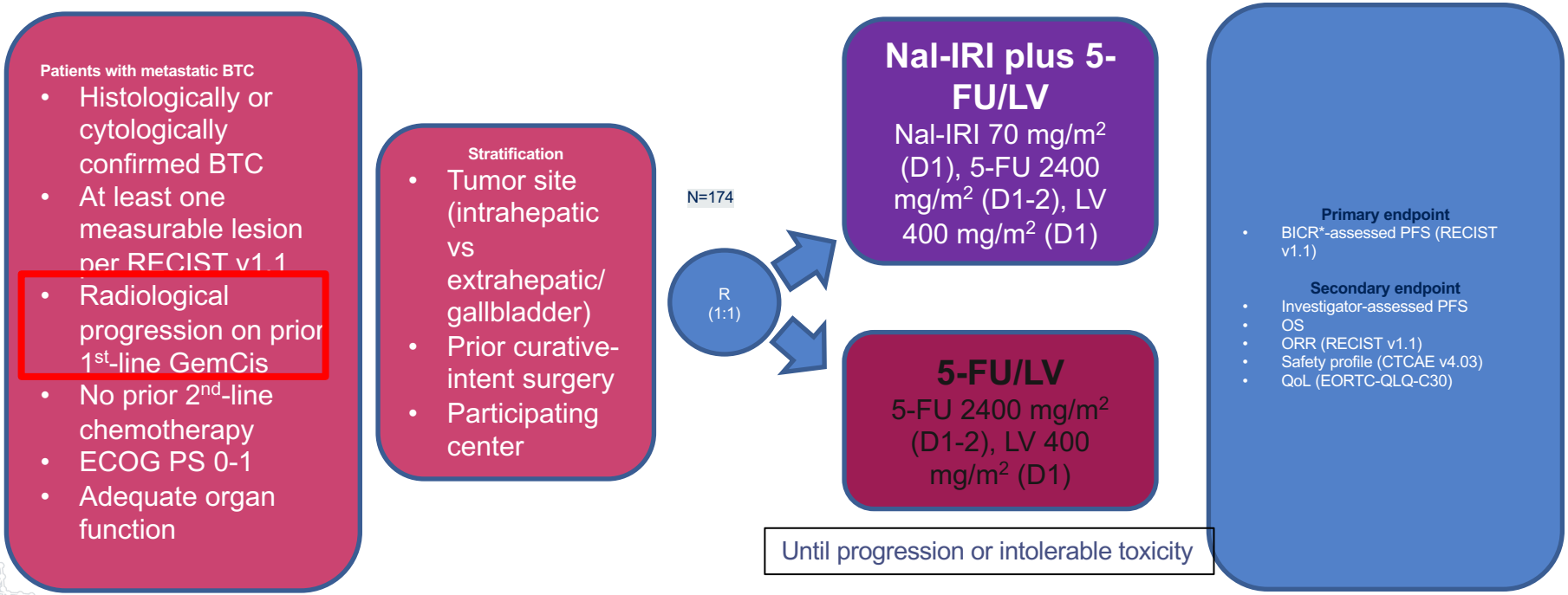
Presented By Angela Lamarca at 2019 ASCO Annual Meeting

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

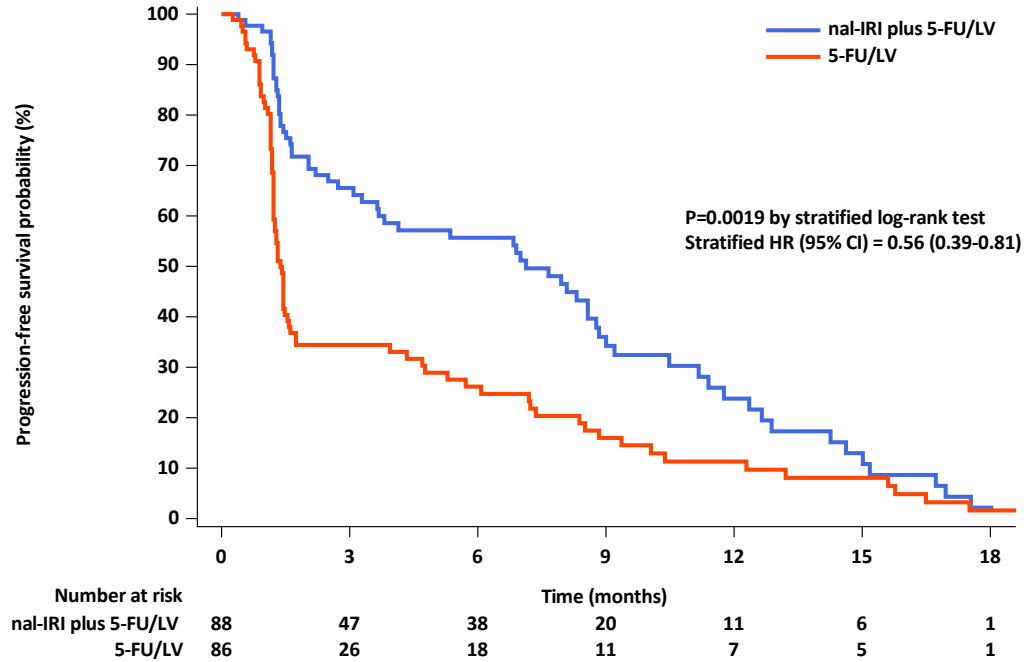


ClinicalTrials.gov identifier: NCT03524508

Patient Baseline Characteristics

	Nal-IRI plus 5-FU/LV group (n=88)	5-FU/LV group (n=86)
Age (years), median (range)	63 (38-84)	65 (37-80)
Gender, n (%)		
Male	51 (58.0%)	48 (55.8%)
Female	37 (42.0%)	38 (44.2%)
ECOG performance status, n (%)		
0	23 (26.1%)	15 (17.4%)
1	65 (73.9%)	71 (82.6%)
Primary tumor site, n (%)		
Intrahepatic	35 (39.8%)	39 (45.3%)
Extrahepatic	22 (25.0%)	25 (29.1%)
Gallbladder	31 (35.2%)	22 (25.6%)
Disease extent at screening, n (%)		
Metastatic	88 (100%)	86 (100%)
Duration of first-line GemCis, n (%)		
< Median (5.1 months)	48 (54.5%)	39 (45.3%)
≥ Median (5.1 months)	40 (45.5%)	47 (54.7%)
Prior curative-intent surgery, n (%)		
Yes	26 (29.5%)	29 (33.7%)
No	62 (70.5%)	57 (66.3%)
Serum 19-9 level, n (%)		
> Median (172 U/mL)	48 (54.5%)	39 (45.3%)
≥ Median (172 U/mL)	40 (45.5%)	47 (54.7%)

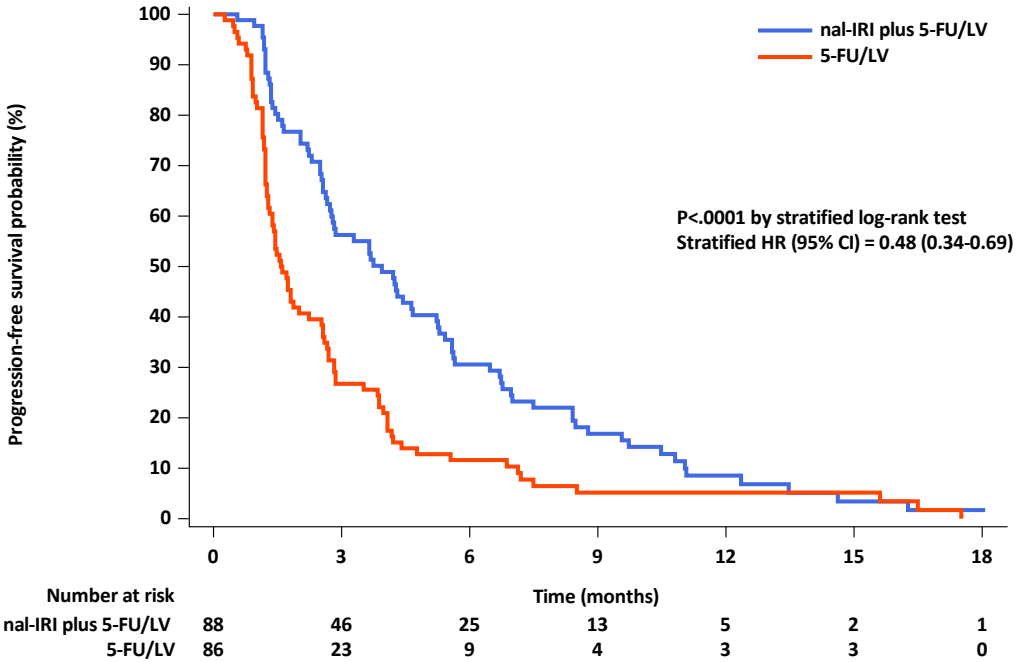
Primary Endpoint: BICR-Assessed PFS



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

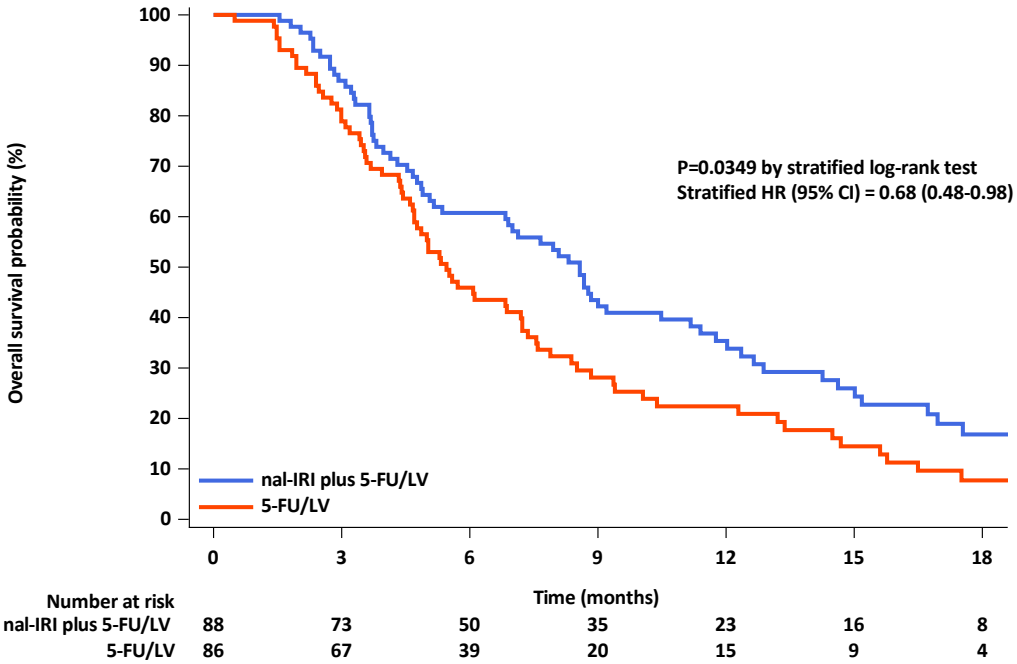
	Nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	79 (91.9%)
mPFS, months (95% CI)	7.1 (3.6-8.8)	1.4 (1.2-1.5)
	HR, 0.56 95% CI, 0.39-0.81 *P*=0.0019	
6-month PFS rate, % (95% CI)	55.7% (44.7-66.6)	26.2% (16.6-35.8)

Secondary Endpoint: Investigator Review-Assessed PFS



	Nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	79 (89.8%)	84 (97.7%)
mPFS, months (95% CI)	3.9 (2.7-5.2)	1.6 (1.3-2.2)
	HR, 0.48 95% CI, 0.34-0.69 *P*<0.0001	
6-month PFS rate, % (95% CI)	30.6% (20.6-40.5)	11.6% (4.9-18.4)

Secondary Endpoint: Overall Survival



	Nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	74 (86.0%)
mOS, months (95% CI)	8.6 (5.4-10.5)	5.5 (4.7-7.2)
	HR, 0.68 95% CI, 0.48-0.98 *P*=0.0349	
6-month OS rate, % (95% CI)	60.7% (50.3-71.2)	45.9% (35.3-56.5)
1-year OS rate, % (95% CI)	35.4% (24.9-45.9)	22.4% (13.1-31.7)

Secondary Endpoint: Overall Response Rates

Response per RECIST v1.1	BICR-assessed response		Investigator review-assessed response	
	Nal-IRI+5-FU	5-FU/LV	Nal-IRI+5-FU	5-FU/LV
Objective response	**14.8%**	**5.8%**	**19.3%**	**2.3%**
	***P*=0.0684**		***P*=0.0002**	
CR	0	0	0	0
PR	14.8%	5.8%	19.3%	2.3%
SD	50.0%	29.1%	53.4%	47.7%
PD	29.5%	64.0%	21.6%	48.8%
Not evaluable	5.7%	1.2%	5.7%	1.2%

Adverse Events Occurring in >10% of Patients

	Nal-IRI plus 5-FU/LV (n=88)		5-FU/LV (n=86)	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
With at least one AE	87 (98.9)	68 (77.3)	74 (86.0)	29 (33.7)
Hematological				
Anemia	13 (14.8)	8 (9.1)	5 (5.8)	3 (3.5)
Febrile neutropenia	2 (2.3)	2 (2.3)	0 (0)	0 (0)
Neutropenia	29 (33.0)	21 (23.9)	3 (3.5)	1 (1.2)
Thrombocytopenia	3 (3.4)	0 (0)	1 (1.2)	1 (1.2)
Non-hematological				
Nausea	22 (25.0)	5 (5.7)	14 (16.3)	1 (1.2)
Vomiting	9 (10.2)	0 (0)	4 (4.7)	1 (1.2)
Abdominal pain	22 (25.0)	4 (4.5)	14 (16.3)	3 (3.5)
Constipation	26 (29.5)	0 (0)	19 (22.1)	0 (0)
Diarrhea	20 (22.7)	4 (4.5)	9 (10.5)	0 (0)
Dyspepsia	20 (22.7)	0 (0)	12 (14.0)	0 (0)
Stomatitis	14 (15.9)	2 (2.3)	10 (11.6)	0 (0)
Fatigue/Asthenia	27 (30.7)	11 (12.5)	17 (19.8)	3 (3.5)
Pyrexia	15 (17.0)	0 (0)	8 (9.3)	1 (1.2)
Decreased appetite	24 (27.3)	1 (1.1)	16 (18.6)	0 (0)

HEPATIC ARTERIAL INFUSION CHEMOTHERAPY OF OXALIPLATIN PLUS FLUOROURACIL VERSUS SORAFENIB IN ADVANCED HEPATOCELLULAR CARCINOMA: A BIOMOLECULAR EXPLORATORY, RANDOMIZED, PHASE 3 TRIAL

THE FOHAIC-1 STUDY

- Ming Zhao 1-3
- 1 Dept. Minimally Invasive Interventional Radiology, Liver Cancer Study and Service Group, Sun Yat-sen University Cancer Center
- 2 State Key Laboratory of Oncology in South China
- 3 Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

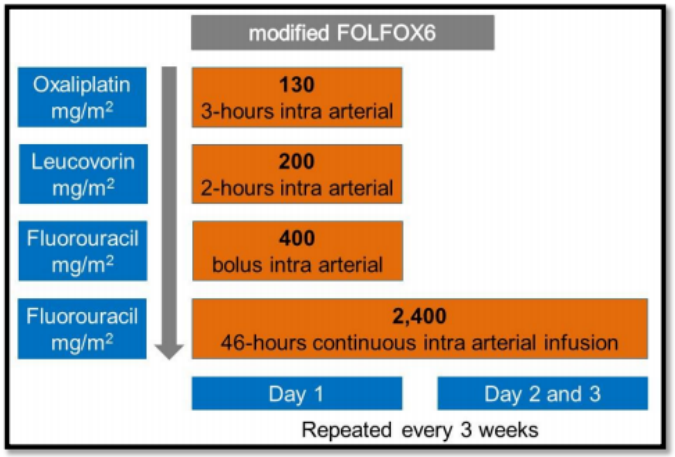
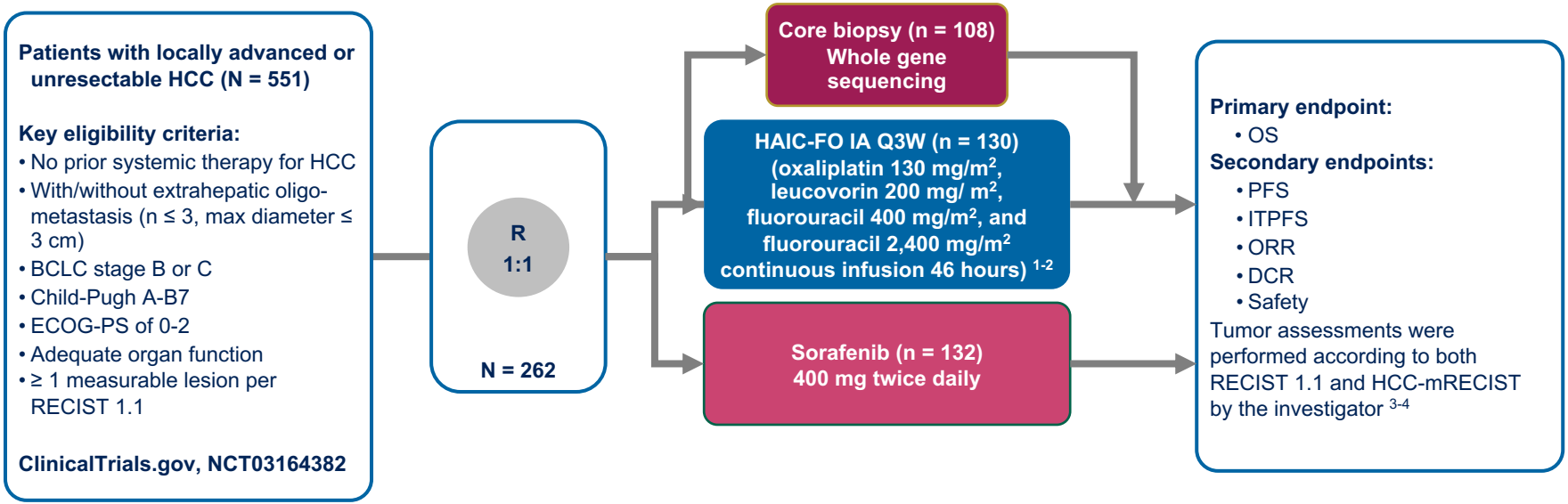


Figure S1. Treatment schedule of HAI of modified FOLFOX6.

- June 5, 2021

Trial Schema
FOHAIC-1: Randomized, head-to-head, phase 3 clinical trial



Ming Zhao
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Baseline Characteristics
Heavy Intrahepatic Tumor Burden

Characteristics	HAIC-FO (n = 130)	Sorafenib (n = 132)	P Value
Age (years) †	54 (45-61)	53 (45-62)	0.542
Sex			
Male	115 (88.5)	123 (93.2)	0.185
Female	15 (11.5)	9 (6.8)	
Etiology ‖			
Hepatitis B virus	120 (92.3)	114 (86.4)	0.295
Anti-hepatitis B virus treatment, n ‡	120	114	
Absent	6 (5.0)	10 (8.8)	0.253
Present	114 (95.0)	104 (91.2)	
Child-Pugh class			
A	88 (67.7)	93 (70.5)	0.629
B	42 (32.3)	39 (29.5)	
Performance status			
0	15 (11.5)	14 (10.6)	0.316
1	83 (63.8)	95 (72.0)	
2	32 (24.6)	23 (17.4)	
BCLC stage			
B	5 (3.8)	9 (6.8)	0.285
C	125 (96.2)	123 (93.2)	
Tumor diameter (cm)			
Mean ± SD	11.5 ± 4.5	11.0 ± 3.4	0.439
Median (IQR)	11.7 (8.3-14.0)	10.8 (8.7-13.6)	
Tumor number			
1-3	43 (33.1)	55 (41.7)	0.151
> 3	87 (66.9)	77 (58.3)	
Tumor involvement of the liver			
≤ 50%	76 (58.5)	80 (60.6)	0.724
> 50%	54 (41.5)	52 (39.4)	
Portal vein invasion			
Absent	41 (31.5)	49 (37.1)	0.341
Present	89 (68.5)	83 (62.9)	
Vp-1 and 2	21 (16.2)	26 (19.7)	
Vp-3	31 (23.8)	29 (22.0)	
Vp-4	37 (28.5)	28 (21.2)	
Tumor involvement > 50% of the liver and/or Vp-4 (High-risk)			
Absent	60 (46.2)	73 (55.3)	0.139
Present	70 (53.8)	59 (44.7)	

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Abstract 4007

Response
RECIST 1.1 & HCC-mRECIST

HAIC-FO showed a greater objective response rate than did sorafenib.

The median time to response was 9.3 weeks (IQR, 8.0 to 15.0), and the median duration of HAIC-FO was 18.0 weeks (IQR, 11.7 to 26.3).

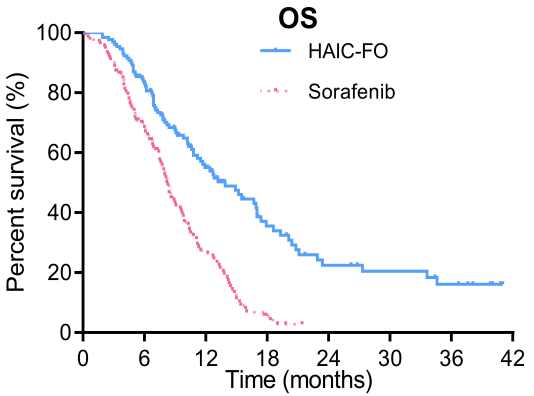
The intrahepatic disease, including tumor mass, vascular tumor thrombus, or both, was also favorable to HAIC-FO than sorafenib in objective response rate.

	Whole disease			Intrahepatic tumor		
	HAIC-FO	Sorafenib		HAIC-FO	Sorafenib	
Response (By RECIST 1.1)	(n = 130) *	(n = 132) *	P Value	(n = 130) *	(n = 132) *	P Value
Complete response	2 (1.5)	0 (0)	< 0.001	2 (1.5)	0 (0)	< 0.001
Partial response	39 (30.0)	2 (1.5)		41 (31.5)	2 (1.5)	
Stable disease	60 (46.2)	75 (56.8)		61 (46.9)	76 (57.6)	
Progressive disease	21 (16.2)	49 (37.1)		18 (13.8)	48 (36.4)	
Unknown or not evaluable	8 (6.2)	6 (4.5)		8 (6.2)	6 (4.5)	
Objective response rate †	41 (31.5)	2 (1.5)	< 0.001	43 (33.1)	2 (1.5)	< 0.001
Disease control rate ‡	101 (77.7)	77 (58.3)	0.001	104 (80.0)	78 (59.1)	< 0.001

	Whole disease			Intrahepatic tumor		
	HAIC-FO	Sorafenib		HAIC-FO	Sorafenib	
Response (By mRECIST)	(n = 130) *	(n = 132) *	P Value	(n = 130) *	(n = 132) *	P Value
Complete response	3 (2.3)	0 (0)	< 0.001	3 (2.3)	0 (0)	< 0.001
Partial response	43 (33.1)	7 (5.3)		46 (35.4)	7 (5.3)	
Stable disease	55 (42.3)	74 (56.1)		55 (42.3)	74 (56.1)	
Progressive disease	21 (16.2)	45 (34.1)		18 (13.8)	45 (34.1)	
Unknown or not evaluable	8 (6.2)	6 (4.5)		8 (6.2)	6 (4.5)	
Objective response rate †	46 (35.4)	7 (5.3)	< 0.001	49 (37.7)	7 (5.3)	< 0.001
Disease control rate ‡	101 (77.7)	81 (61.4)	0.004	104 (80.0)	81 (61.4)	0.001

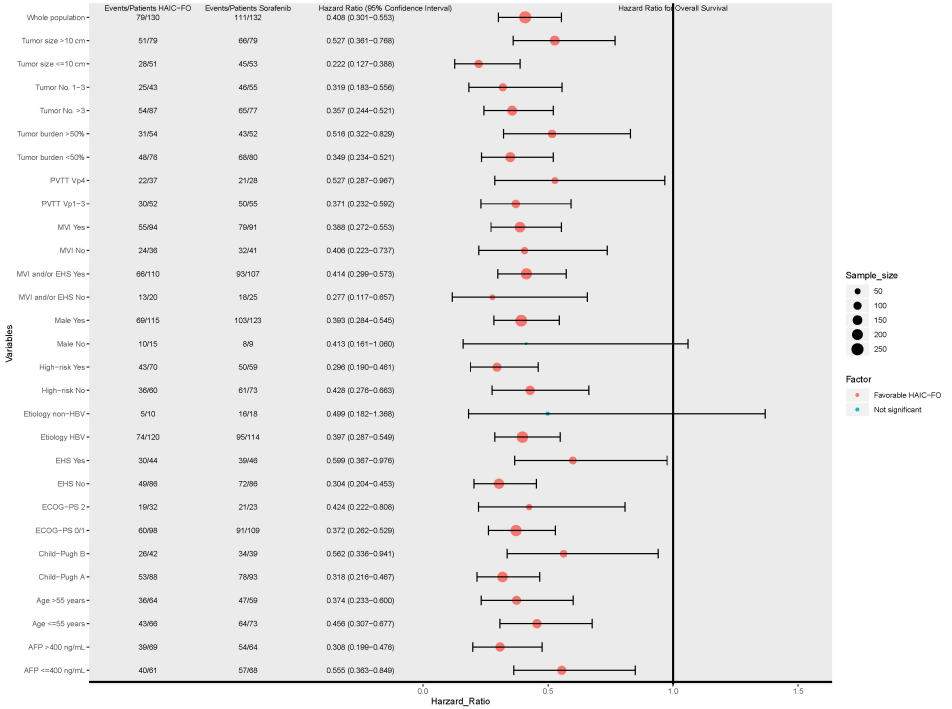
*** Data were numbers of patients, with percentages in parentheses. Statistical significance was assessed with the Chi-square test or Fisher's exact test.**
† Objective response rate = complete response + partial response.
‡ Disease control rate = complete response + partial response + stable disease.
Abbreviations: HAIC-FO, hepatic arterial infusion chemotherapy of FOLFOX regimens; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified HCC specific-RECIST criteria.

Survivals
Primary Endpoint



No. at risk								
HAIC-FO	130	107	49	23	13	10	7	0
Sorafenib	132	85	28	4	0	0	0	0

	No. of event/No. of patients (%)	Median OS (95%CI)
HAIC-FO	79/130 (60.8)	13.9 (10.6-17.2)
Sorafenib	111/132 (84.1)	8.2 (7.5-9.0)
	Hazard ratio (95%CI)	***P* value**
	0.408 (0.301-0.553)	<0.001



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Safety
Drug-related

- Grade 3 or 4 events were recorded more frequently with sorafenib (62 patients [48.1%]) than with HAIC-FO (26 [20.3%]).
- During the HAIC-FO procedure, the primary complication was acute abdomen pain occurring at the late phase of oxaliplatin infusion (52 [40.6%]).
- No patients gave up HAIC-FO therapy due to infusion-related complications.

	Grade					
	Sorafenib (n = 129)			HAIC-FO (n = 128)		
	Any	1 to 2	3 to 4	Any	1 to 2	3 to 4
Hand-foot syndrome	68 (52.7)	64 (49.6)	5 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	50 (38.8)	44 (34.1)	8 (6.2)	39 (30.5)	33 (25.8)	11 (8.6)
Diarrhea	47 (36.4)	43 (33.3)	6 (4.7)	27 (21.1)	27 (21.1)	0 (0.0)
Neutropenia	47 (36.4)	41 (31.8)	8 (6.2)	33 (25.8)	29 (22.7)	10 (7.8)
Fatigue	46 (35.7)	41 (31.8)	8 (6.2)	32 (25.0)	32 (25.0)	0 (0.0)
Elevated total bilirubin	46 (35.7)	38 (29.5)	9 (7.0)	22 (17.2)	16 (12.5)	7 (5.5)
Reduced hemoglobin	41 (31.8)	37 (28.7)	6 (4.7)	41 (32.0)	39 (30.5)	3 (2.3)
Hypoalbuminemia	38 (29.5)	34 (26.4)	4 (3.1)	36 (28.1)	36 (28.1)	1 (0.8)
Weight reduction	38 (29.5)	34 (26.4)	5 (3.9)	20 (15.6)	18 (14.1)	2 (1.6)
Elevated AST	35 (27.1)	33 (25.6)	4 (3.1)	58 (45.3)	50 (39.1)	14 (10.9)
Hypertension	35 (27.1)	25 (19.4)	13 (10.1)	1 (0.8)	1 (0.8)	0 (0.0)
Thrombocytopenia	35 (27.1)	32 (24.8)	3 (2.3)	45 (35.2)	35 (27.3)	14 (10.9)
Elevated INR	34 (26.4)	34 (26.4)	0 (0.0)	15 (11.7)	15 (11.7)	0 (0.0)
Elevated creatinine	32 (24.8)	32 (24.8)	0 (0.0)	3 (2.3)	3 (2.3)	0 (0.0)
Vomiting	29 (22.5)	27 (20.9)	2 (1.6)	21 (16.4)	21 (16.4)	1 (0.8)
Ascites	29 (22.5)	26 (20.2)	4 (3.1)	12 (9.4)	12 (9.4)	1 (0.8)
Nausea	28 (21.7)	26 (20.2)	2 (1.6)	24 (18.8)	24 (18.8)	2 (1.6)
Rash	26 (20.2)	25 (19.4)	1 (0.8)	1 (0.8)	1 (0.8)	0 (0.0)
Elevated ALT	26 (20.2)	23 (17.8)	3 (2.3)	28 (21.9)	22 (17.2)	6 (4.7)
Dizziness	22 (17.1)	22 (17.1)	0 (0.0)	6 (4.7)	6 (4.7)	0 (0.0)
Anorexia	22 (17.1)	22 (17.1)	0 (0.0)	12 (9.4)	12 (9.4)	1 (0.8)
Constipation	22 (17.1)	22 (17.1)	0 (0.0)	21 (16.4)	21 (16.4)	1 (0.8)
Alopecia	19 (14.7)	19 (14.7)	0 (0.0)	2 (1.6)	2 (1.6)	0 (0.0)
Pain not specified	19 (14.7)	18 (14.0)	2 (1.6)	5 (3.9)	5 (3.9)	0 (0.0)
Pain Abdominal	18 (14.0)	17 (13.2)	1 (0.8)	52 (40.6)	52 (40.6)	0 (0.0)
Pruritus	18 (14.0)	18 (14.0)	1 (0.8)	1 (0.8)	1 (0.8)	0 (0.0)
Abdominal distension	14 (10.9)	12 (9.3)	2 (1.6)	17 (13.3)	17 (13.3)	0 (0.0)

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspertate Aminotransferase; INR, International Normalized Ratio.

Presented By: **Ming Zhao**
SYSUCC, Guangzhou city, P.R. China

Abstract 4007

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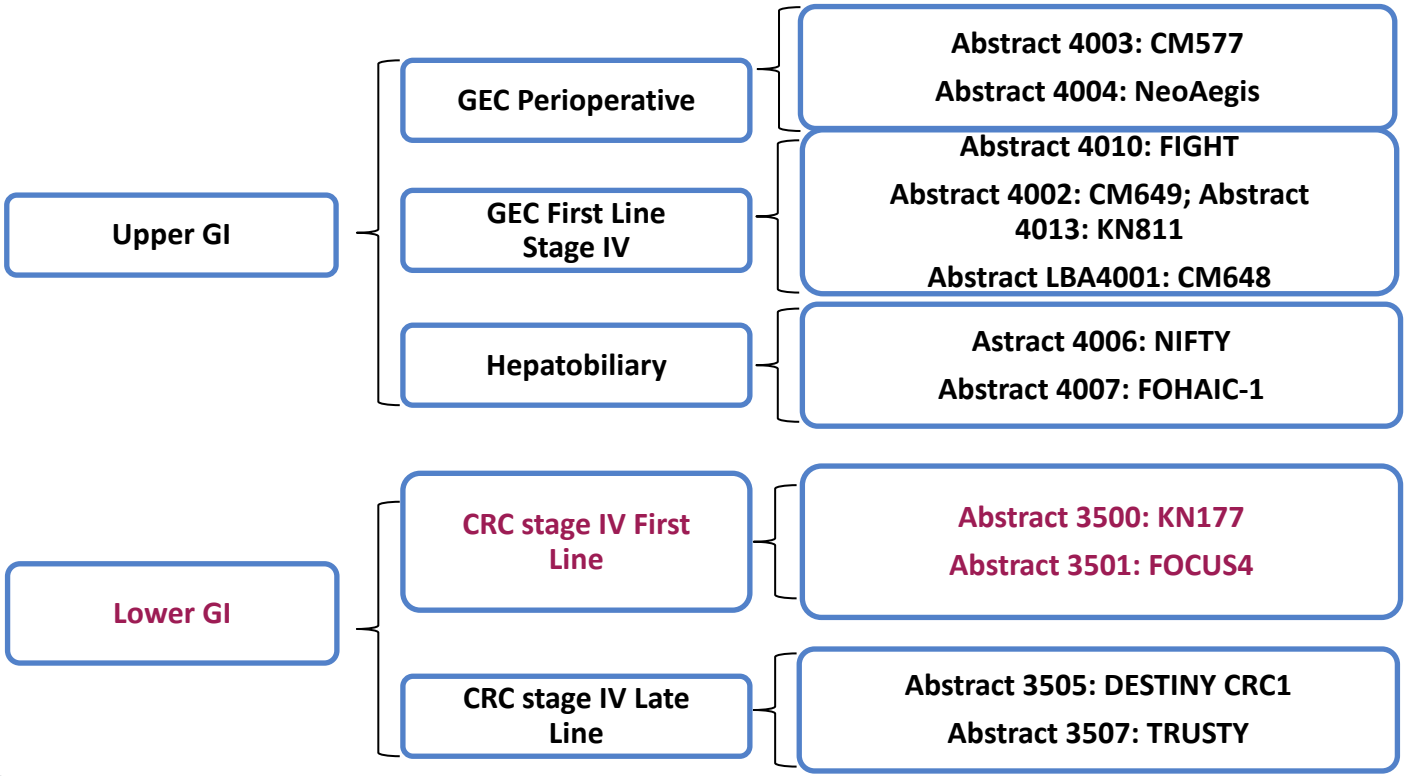
Summary and Conclusion

- The FOHAIC-1 study demonstrated that HAIC-FO had superior efficacy and survival outcome than sorafenib in the first-line treatment of advanced HCC with **a heavy intrahepatic tumor burden** (overall: 13.9 months; hazard ratio: 0.408).
- HAIC-FO has the advantage of **rapid tumor shrinkage** within a short period (median time to response 2.2 months [IQR, 1.9 to 3.5]), which has never been reported in the previous studies about standard systemic agents.
- HAIC-FO has achieved a promising rate of **tumor downstaging** (12.3%), prompting these beneficiaries to receive curable or palliative therapies and finally achieving a median overall survival (progression-free survival) of 20.8 (16.4) months (95%CI 9.1-32.5 [7.5-25.3]) with a 1-year rate of 93.8% (68.8%).
- In subgroup with high-risk factor (**Vp4-PVTT and/or tumor involvement >50% of the liver**), HAIC-FO also showed a favorable median overall survival of 10.8 months (95% CI 8.2-13.4).
- Models for predicting therapeutic effects of HAIC-FO based on genomic mutations are being developed.
- In summary, **interventional HAIC-FO therapy** might be a potential first-line option for patients with initial advanced HCC, especially for those with severe local tumors.

Ming Zhao
SYSUCC, Guangzhou city, P.R. China

ASCO 2021: Highlights in GI Malignancies



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] Wenyan Zhong,[17] David Fogelman,[18] Patricia Marinello,[18] Luis A. Diaz Jr[19]

[1]Sorbonne Université and Hôpital Saint Antoine, Paris, France; [2]University College Hospital, NHS Foundation Trust, London, United Kingdom; [3]Asan Medical Center, University of Ulsan, Seoul, Republic of Korea; [4]Herlev and Gentofte Hospital, Herlev, Denmark; [5]University Hospital of Southern Denmark, Vejle, Denmark; [6]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands; [7]Bordeaux University Hospital, Bordeaux, France; [8]Hospital Universitario 12 de Octubre, Imas12, CNIO, UCM, Madrid, Spain; [9]Hospital Regional Universitario de Malaga, Malaga, Spain; [10]Western Health, St Albans, Australia; [11]Léon Bérard Center, Lyon, France; [12]Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain; [13]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]MSD China, Beijing, China; [18]Merck & Co., Inc. Kenilworth, NJ, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

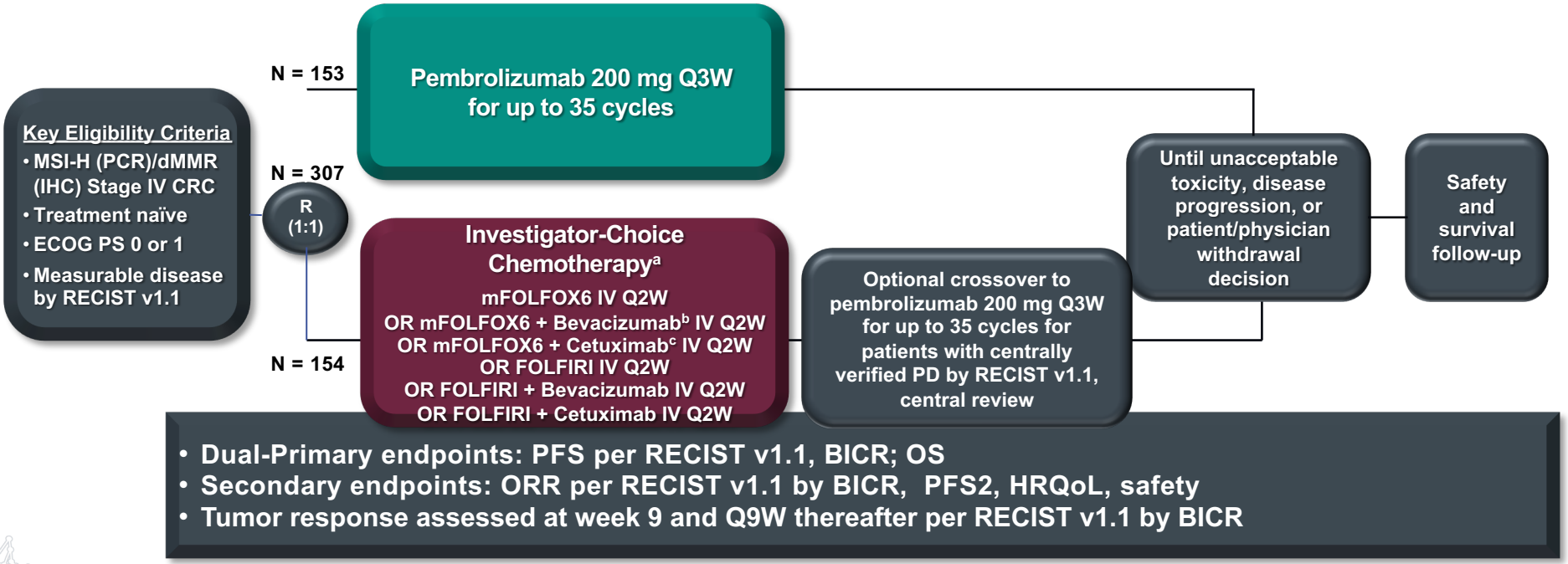
July 15, 2021

Updates from ASCO and World GI

Daniel Catenacci, MD

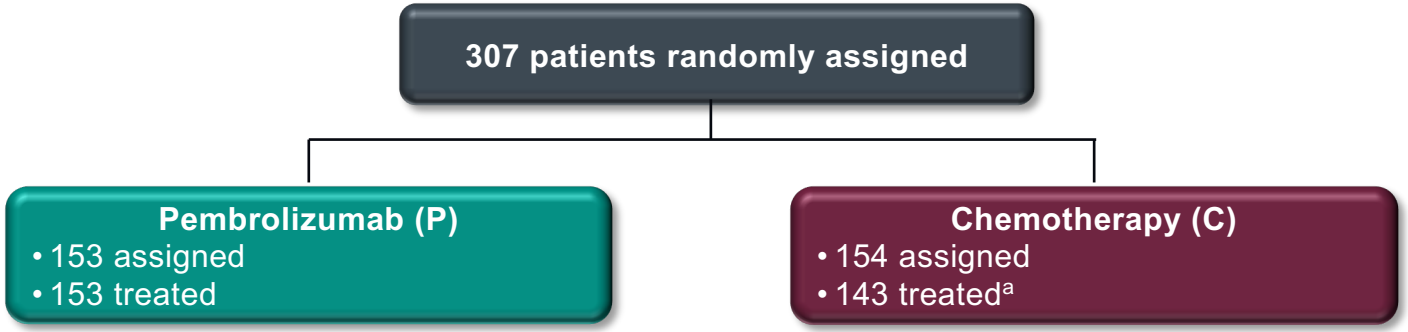
Abstract 3500

KEYNOTE-177 Study Design
(NCT02563002)



[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Disposition



[a] patients received

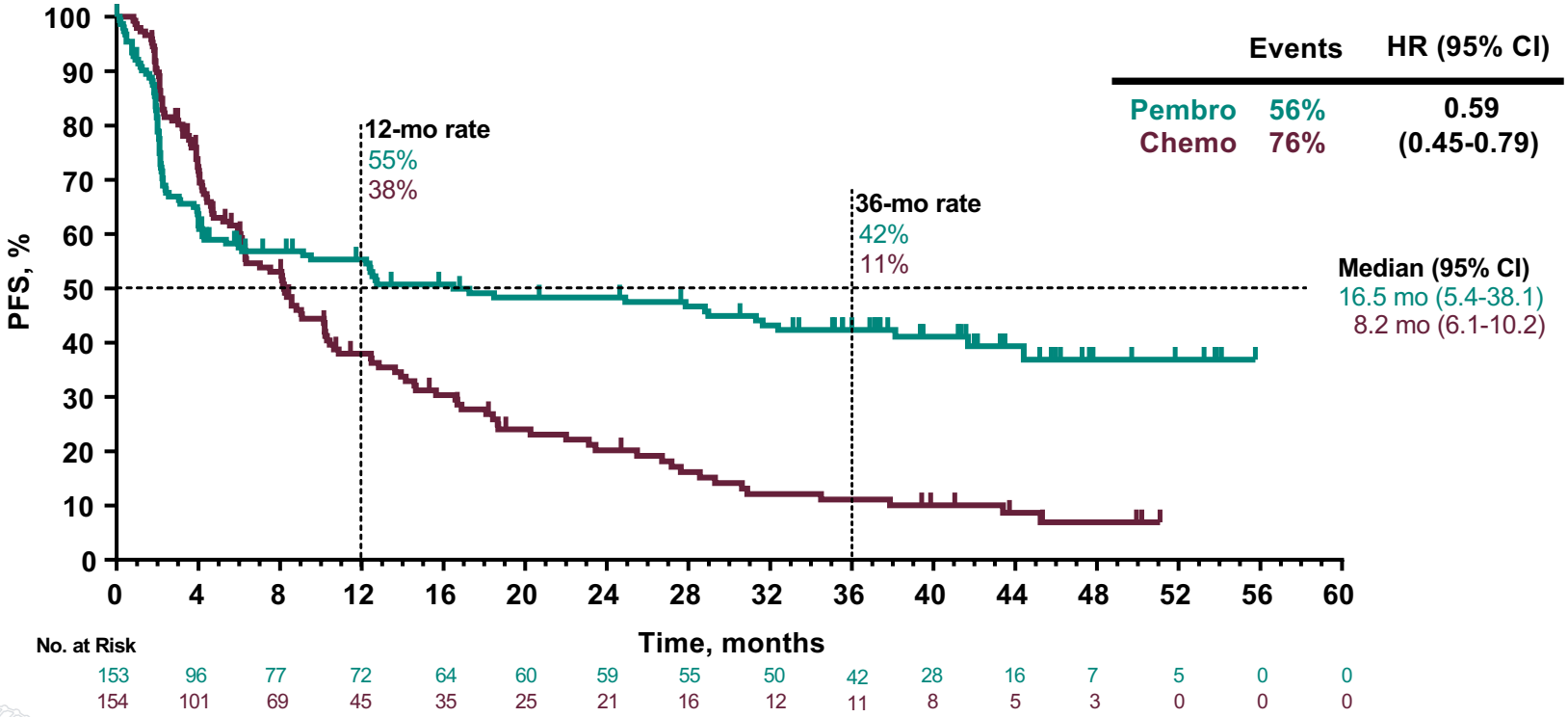
- mFOLFOX6 only (n=11)
- mFOLFOX6 plus bevacizumab (n= 64)
- FOLFOX6 plus cetuximab (n=5)
- FOLFIRI alone (n=16)
- FOLFIRI plus bevacizumab (n=36)
- FOLFIRI plus cetuximab (n=11)

Disease progression was assessed per RECIST v1.1, BICR; Median study follow-up was 44.5 months (range, 36.0-60.3); 44.5 mo (36.0-60.3) with pembro vs 44.4 mo (36.2-58.6) with chemo. Data cut-off: 19Feb2021.

Baseline Characteristics

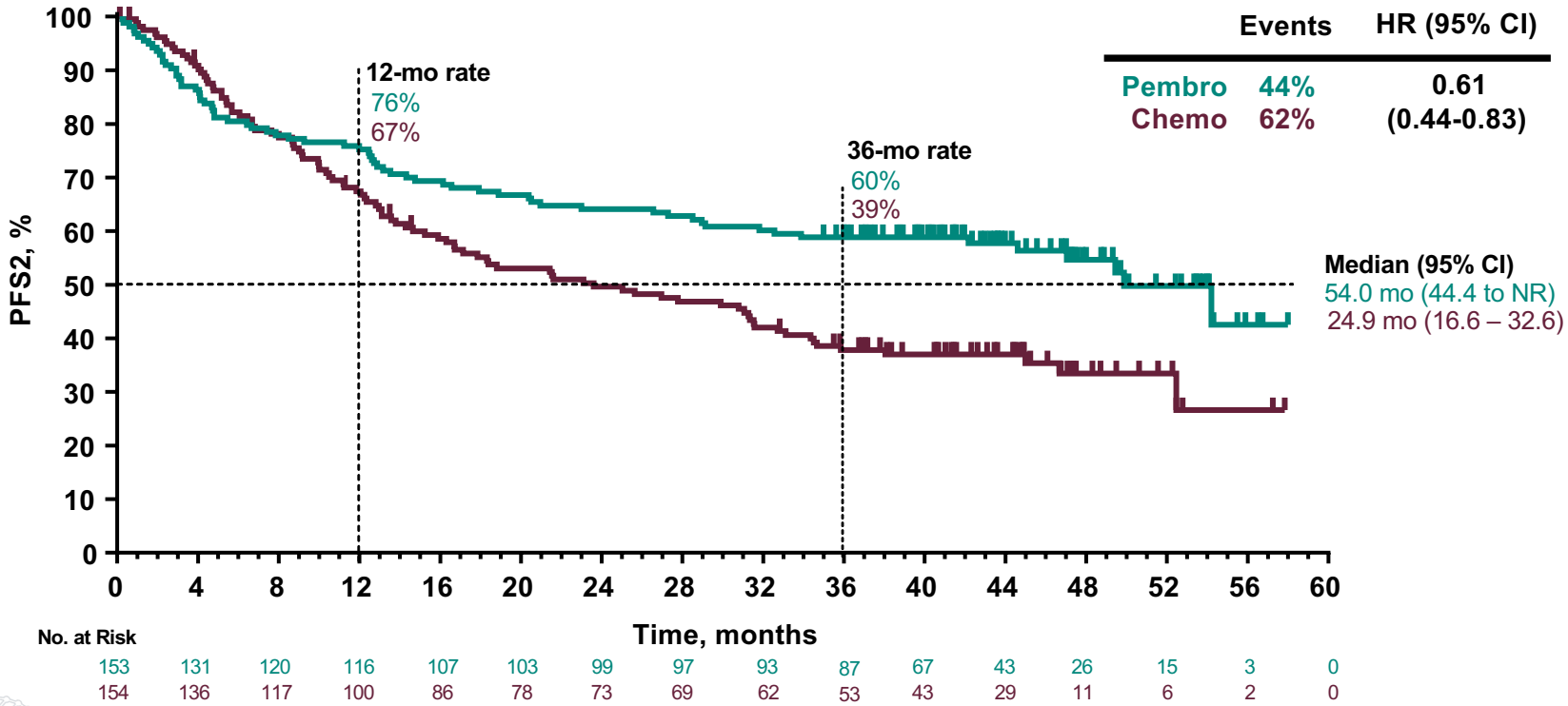
Characteristic	Pembrolizumab N = 153 (100%)	Chemotherapy N = 154 (100%)
Age, median (range), years	63.0 (24-93)	62.5 (26-90)
Male	71 (46.4%)	82 (53.2%)
ECOG PS 0	75 (49.0%)	84 (54.5%)
Recurrent disease	80 (52.3%)	74 (48.1%)
Liver Metastasis	71 (46.4%)	54 (35.0%)
Asia region	22 (14.4%)	26 (16.9%)
Western Europe/North America region	109 (71.2%)	113 (73.4%)
Rest of World	22 (14.4%)	15 (9.7%)
Right-sided tumor	102 (66.7%)	107 (69.5%)
Left-sided tumor	46 (30.1%)	42 (27.3%)
Other/unknown tumor location	5 (3.2%)	5 (3.2%)
Prior adjuvant therapy only	33 (21.6%)	37 (24.0%)
Prior neoadjuvant therapy (perioperative)	5 (3.2%)	8 (5.2%)
No prior therapy	115 (75.2%)	109 (70.8%)
BRAF, KRAS, NRAS all wildtype	43 (28.1%)	38 (24.7%)
BRAF V600E	35 (22.9%)	44 (28.6%)
KRAS or NRAS mutant	33 (21.6%)	39 (25.3%)
BRAF V600E mutant and KRAS/NRAS mutant	0	2 (1.3%)
Unknown[a]	42 (27.5%)	31 (20.1%)

Progression-Free Survival



Progression-Free Survival 2

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)[a]**	**51 (33.1)**
Best Overall Response, n (%)		
Complete response	20 (13.1)[b]	6 (3.9)
Partial response	49 (32.0)[c]	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

Andre KN177FA ASCO 2021

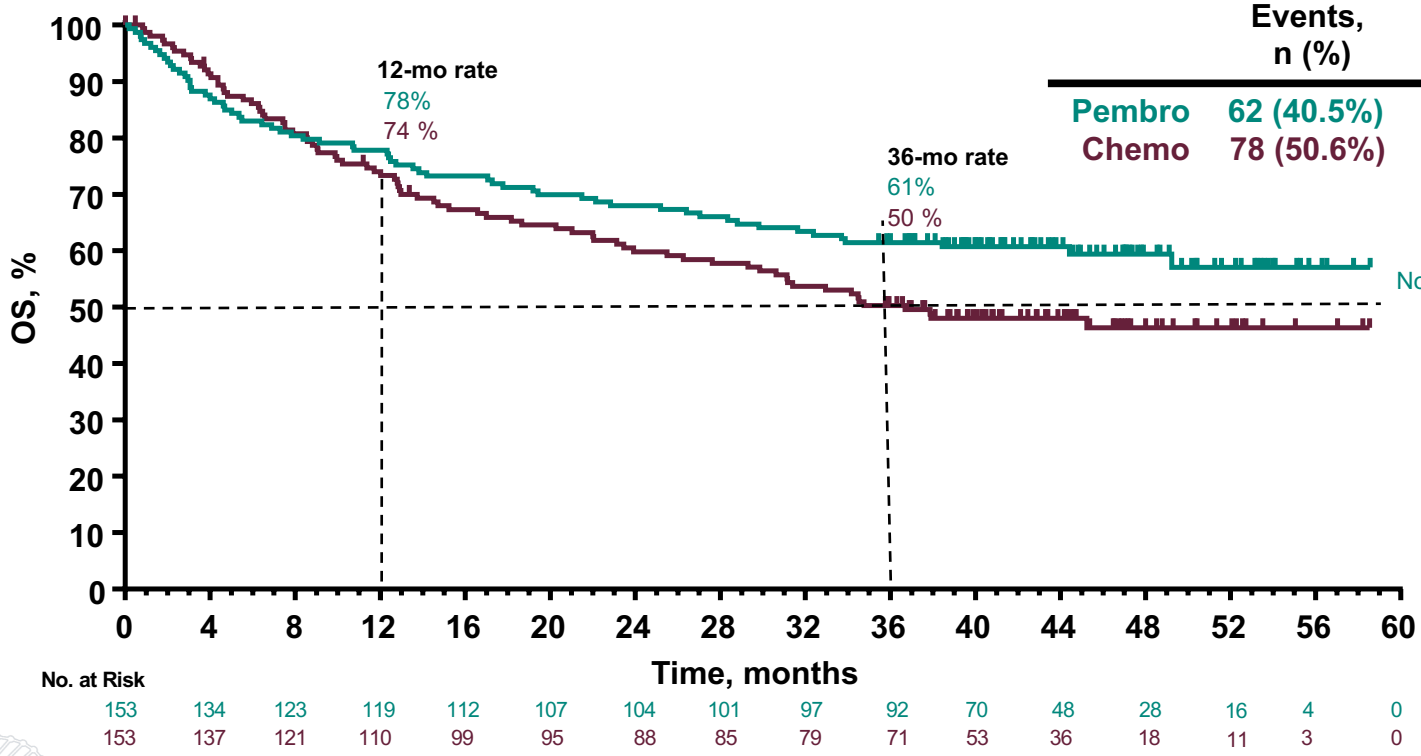
[a]ORR 43.8%; [b]CR rate 11.1%; [c]PR rate 32.7% at IA2 (data cut-off 19Feb2020).
Data cut-off: 19Feb2021.

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[a]	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)	20 (13.0)
VEGF inhibitor	22 (14.4)	13 (8.4)
EGFR inhibitor	9 (5.9)	5 (3.2)
Nucleosoide 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)

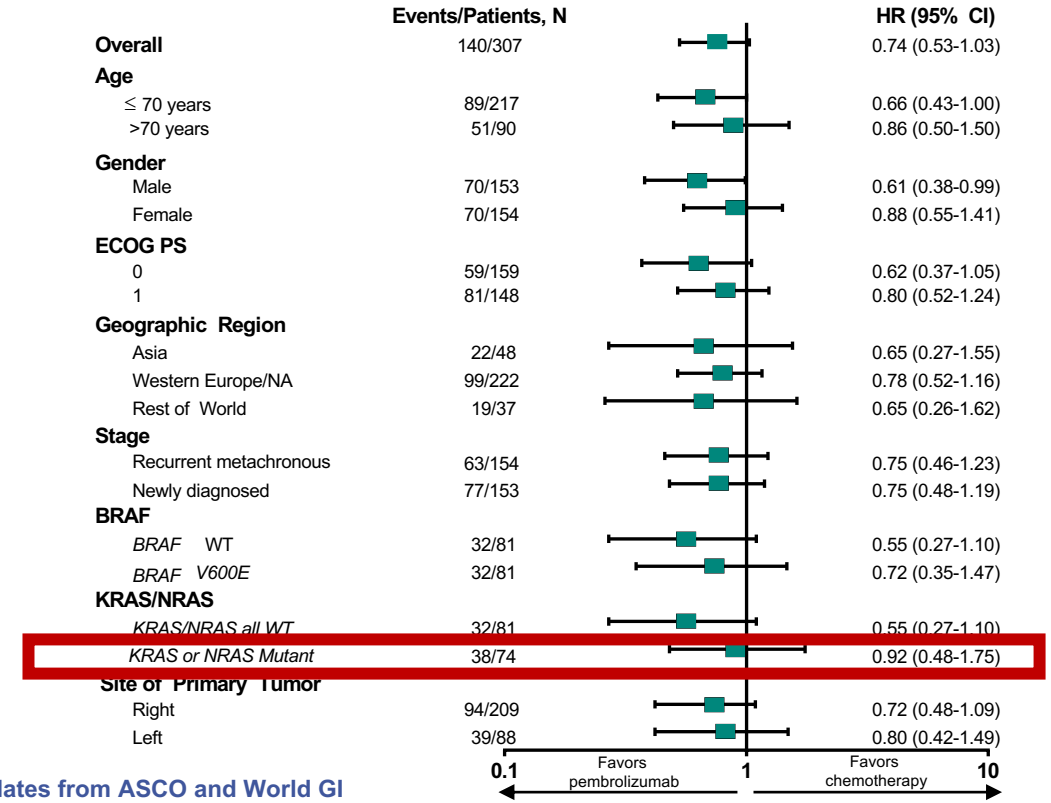
Overall Survival



	Events, n (%)	HR (95% CI)	*P*
Pembro	62 (40.5%)	0.74 (0.53-1.03)	0.0359[a]
Chemo	78 (50.6%)		

Median (95% CI)
Not reached (49.2-NR)
36.7 mo (27.6-NR)

OS in Key Subgroups



Summary of Events in All Treated Patients

Events[a]	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%)	95 (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

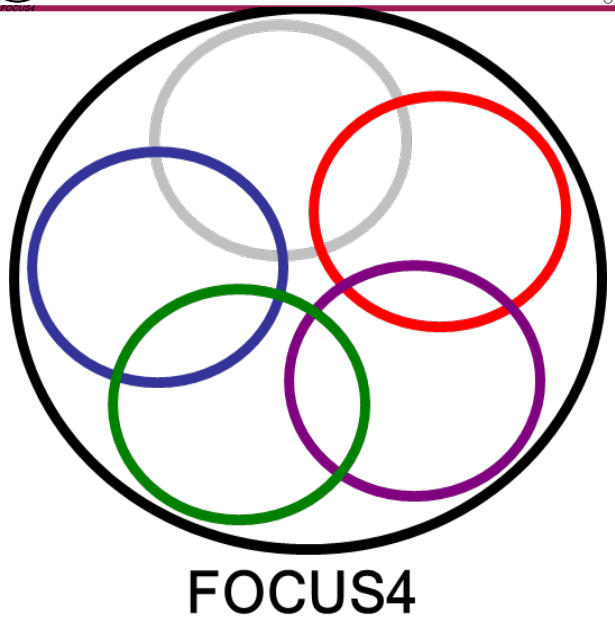
Summary and Conclusions (2)

- 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

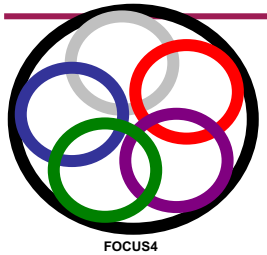
*ORAL MAINTENANCE CAPECITABINE VERSUS ACTIVE MONITORING FOR PATIENTS WITH METASTATIC COLORECTAL CANCER WHO ARE STABLE OR RESPONDING AFTER 16 WEEKS OF FIRST-LINE TREATMENT: RESULTS FROM THE RANDOMISED **FOCUS4-N** TRIAL*

Prof. Richard Adams – on behalf of FOCUS4 collaborators; Cardiff University , UK

7th June, 2021



FOCUS4: A molecularly stratified trial programme in metastatic colorectal cancer



Metastatic Colorectal cancer
First line chemo 16 wks
Stable/
responding

Diagnostic biopsy

Biomarker analysis during first 8-12 wks

On FFPE tumour block: KRAS, NRAS, BRAF, P53 mutations; PIK3CA, PTEN & MMR IHC

REGISTER

STRATIFY

RANDOMISE

FOLLOW-UP

A	B	C	D	N
BRAF mut	*PIK3CA* mut	*KRAS + p53* mut	All Wt	Non-strat
P	P	P	P	No Rx
BRAFi+MEKi+ EGFRi	Aspirin	Wee1i	Pan HERi	CAPE

Primary endpoint:
PFS in the interval

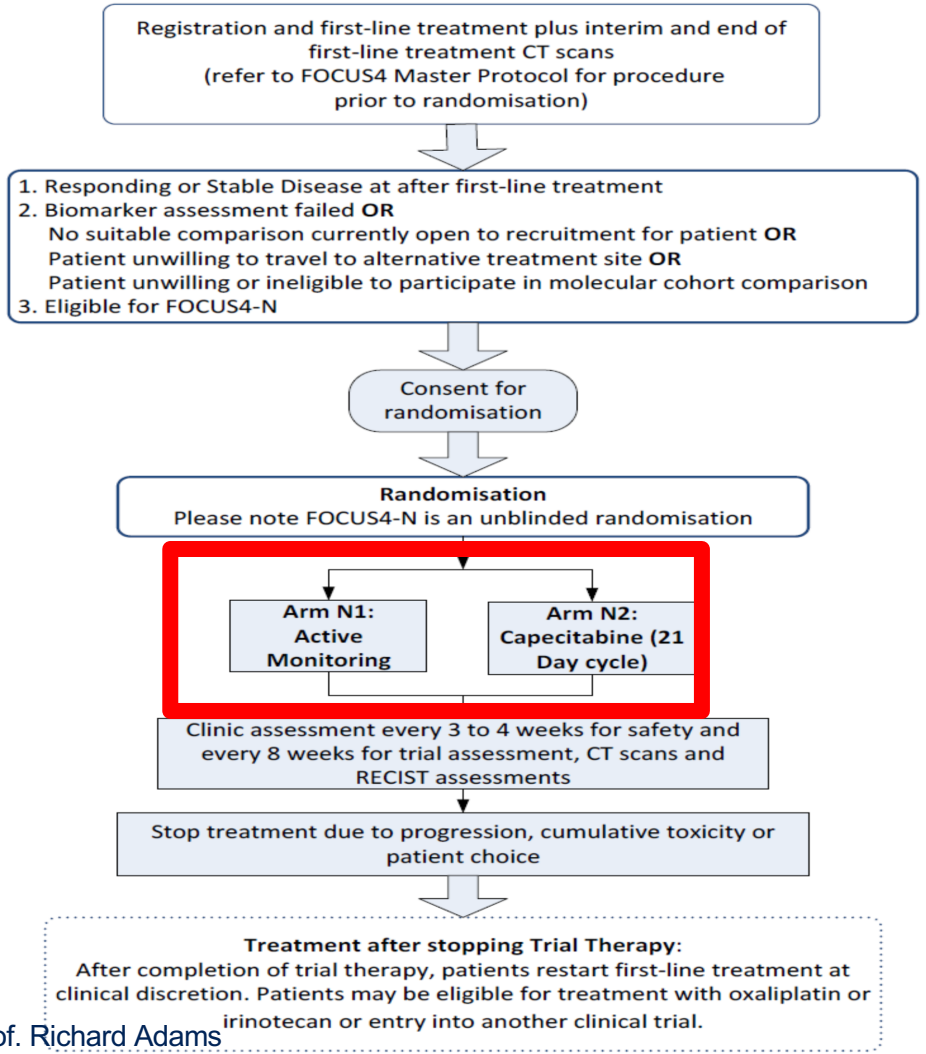
Restart first line chemo on progression

Prof. Richard Adams

FOCUS4-N: Intermittent therapy

Capecitabine: 1250mg/m^2 bd D1-14 q21 days

> 3 weeks off therapy = off trial



Prof. Richard Adams

FOCUS4-N: Intermittent therapy

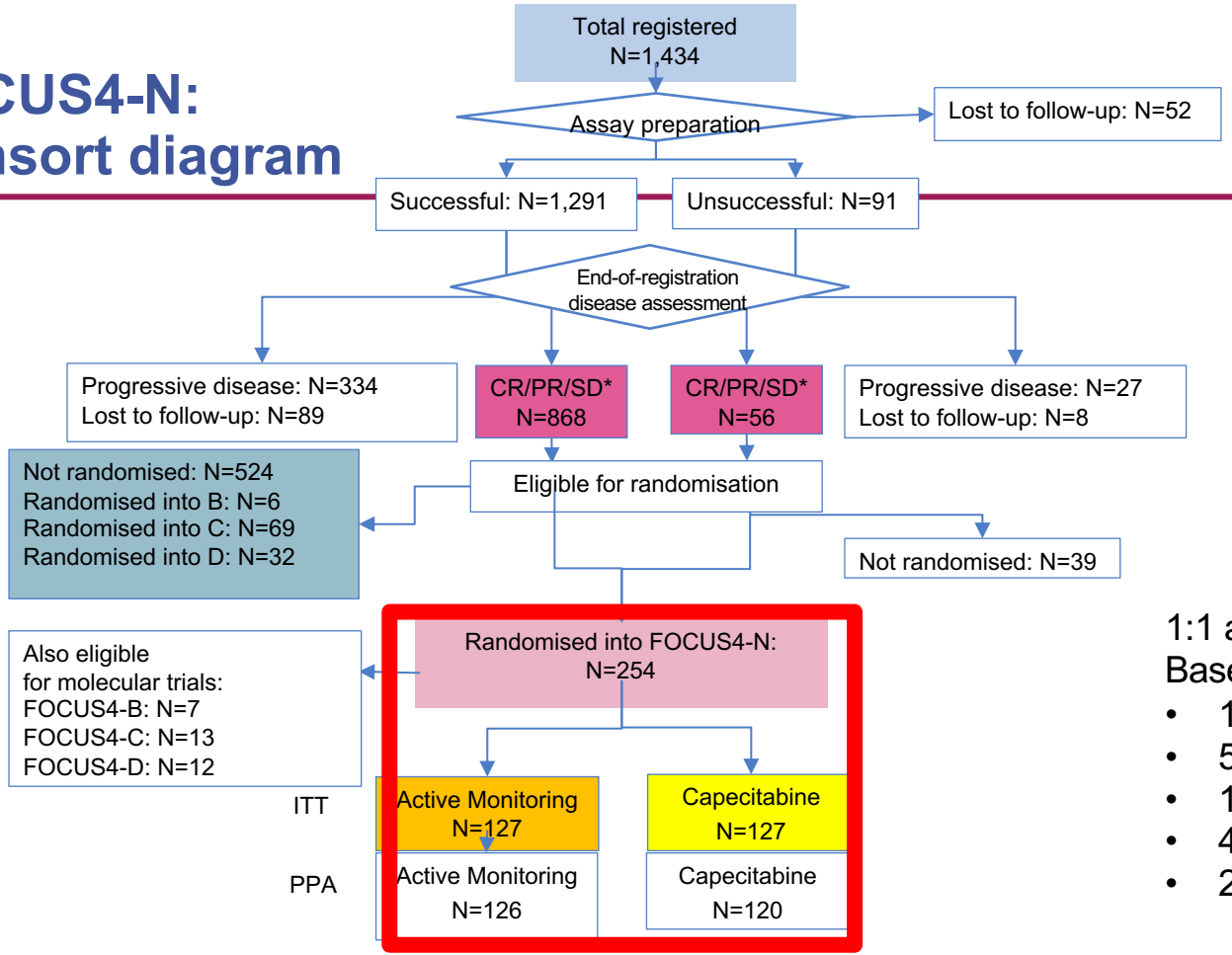
- Maintenance therapy – current SoC
  - AIO- 0207 and CAIRO3
  - Capecitabine + bevacizumab maintenance
  - Improved PFS no significant improvement in OS
  - Not cost effective

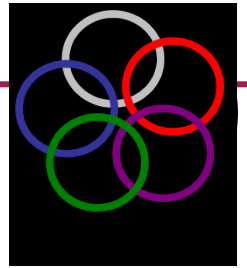
- Complete break - active monitoring (AM)
  - No toxicity, time away from hospital, improved QoL (COIN), cost effective?
  - Cancer symptoms return, return to full dose sooner?
  - ? Impact upon survival

FOCUS4-N: Endpoints

- Primary endpoint:
- PFS - defined as progression of disease according to RECIST v1.1 criteria or death from any cause.
  - Analysis timed from randomisation
  - Baseline CT scan prior to randomisation.
- Secondary endpoints:
- OS, toxicity
- QoL assessed in patients throughout (8 weekly)

FOCUS4-N: Consort diagram



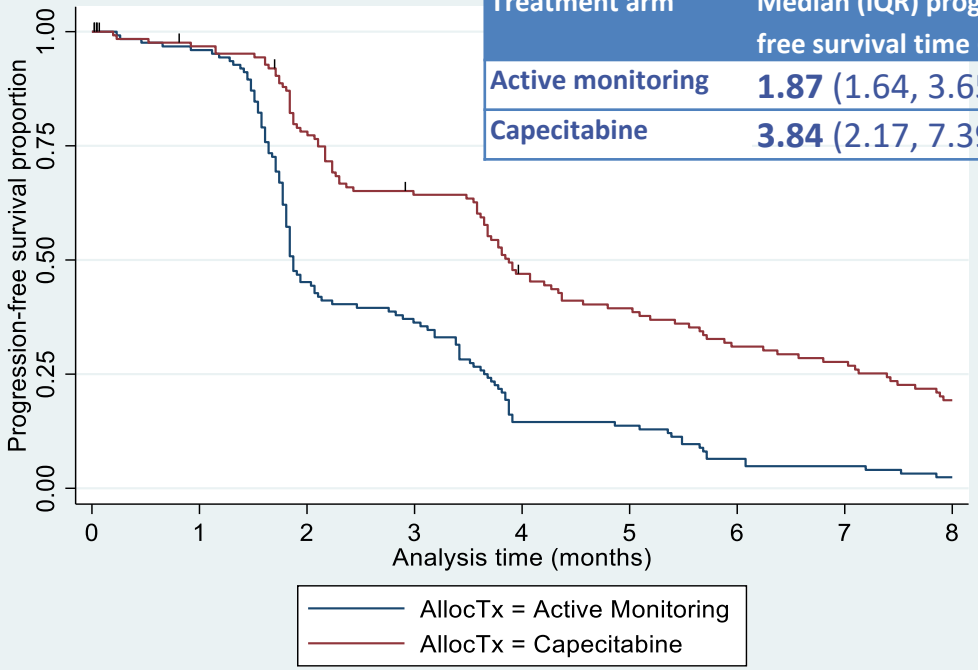


1:1 allocation ratio
Baseline factors well balanced

- 12% BRAF mut
- 54% RAS mut
- 15% PIK3CA mut
- 49% p53 mut
- 2% MSI-H

FOCUS4-N: PFS (ITT)

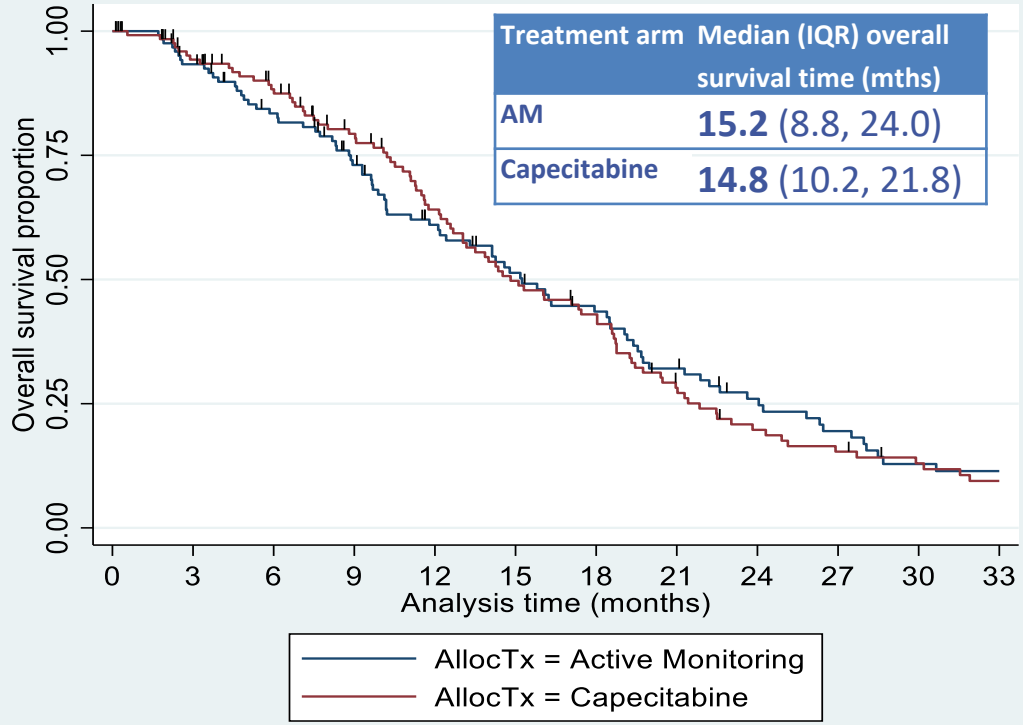
Treatment arm	Median (IQR) progression-free survival time (months)
Active monitoring	**1.87** (1.64, 3.65)
Capecitabine	**3.84** (2.17, 7.39)



Model	PFS HR (95% CI) Capecitabine vs Active Monitoring	p-value
Cox regression, unadjusted	**0.42** (0.32, 0.55)	6.9×10^{-10}
Cox regression, adjusted for minimisation factors (1) (PRIMARY MODEL)	**0.38** (0.28, 0.51)	9.5×10^{-11}
Cox regression, additional adjustment (2)	**0.38** (0.28, 0.52)	5.8×10^{-10}

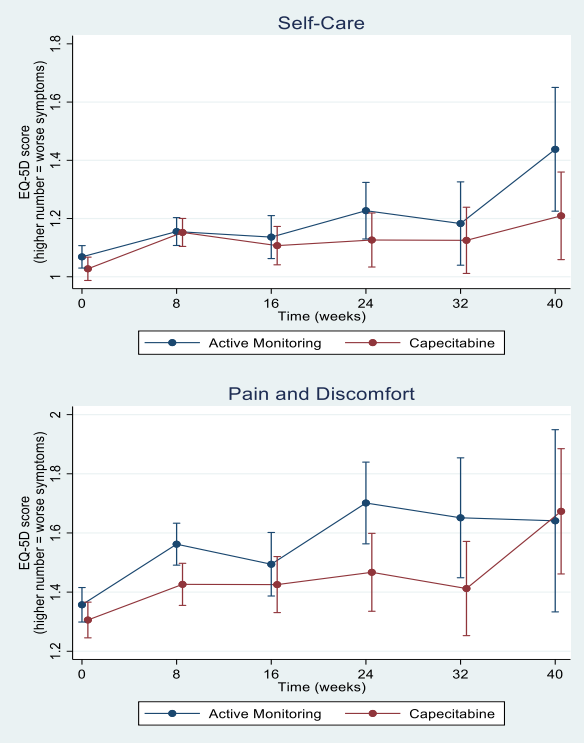
Primary Model: hospital, PTL, PS, SD/PR/CR, 1st line chemo. Mab.

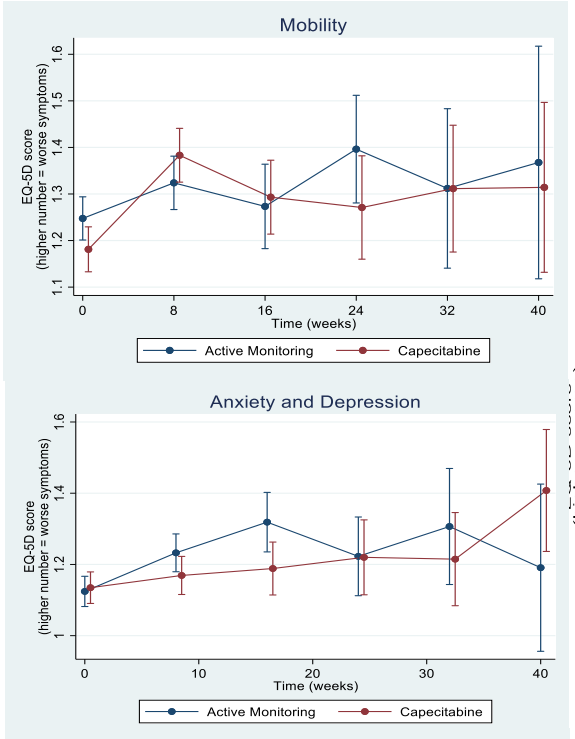
FOCUS4 N: Overall Survival (ITT)



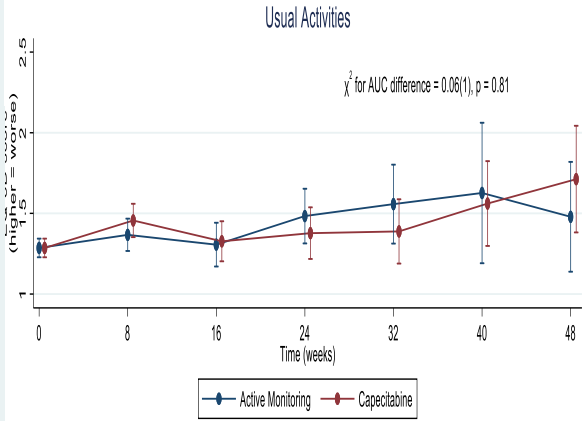
Model	OS HR (95% CI) Capecitabine vs Active Monitoring	p-value
Cox regression, unadjusted	**1.00** (0.75, 1.33)	p = 0.98
Cox regression, adjusted for minimisation factors (1)	**0.93** (0.69, 1.27)	p = 0.66
Cox regression, additional adjustment (2)	**1.07** (0.76, 1.49)	p = 0.63

FOCUS4-N: QoL





No significant differences in EQ5D QoL



Prof. Richard Adams

FOCUS4-N: Summary

- PFS: Adjusted HR= 0.38; p < 0.0001
  - CAIRO3 (Cape + Bev) HR = 0.38; p < 0.0001
- OS: Adjusted HR=0.93; p = 0.66
  - CAIRO3 HR=0.86; p = 0.1
- Trends to predict for enhanced PFS benefit from maintenance Capecitabine:
  - Left Colon PTL, PIK3CA WT, No PTEN loss, No EGFR inhibitor
- Toxicity: Capecitabine worse than AM
  - Diarrhoea, fatigue, PPE, stomatitis
- QoL: No significant differences between Capecitabine and AM

FOCUS4-N: Summary

- Capecitabine maintenance strategy is a reasonable option to discuss with patients as it doubles the time until a need to return to full dose/induction SACT
- FOCUS4-N lays out the choices between increased toxicity and PFS benefit
- No significant difference seen in OS - but our trial was underpowered to demonstrate a difference
- Improved cost effectiveness of capecitabine monotherapy over Capecitabine + bevacizumab (higher drug acquisition and administration costs)

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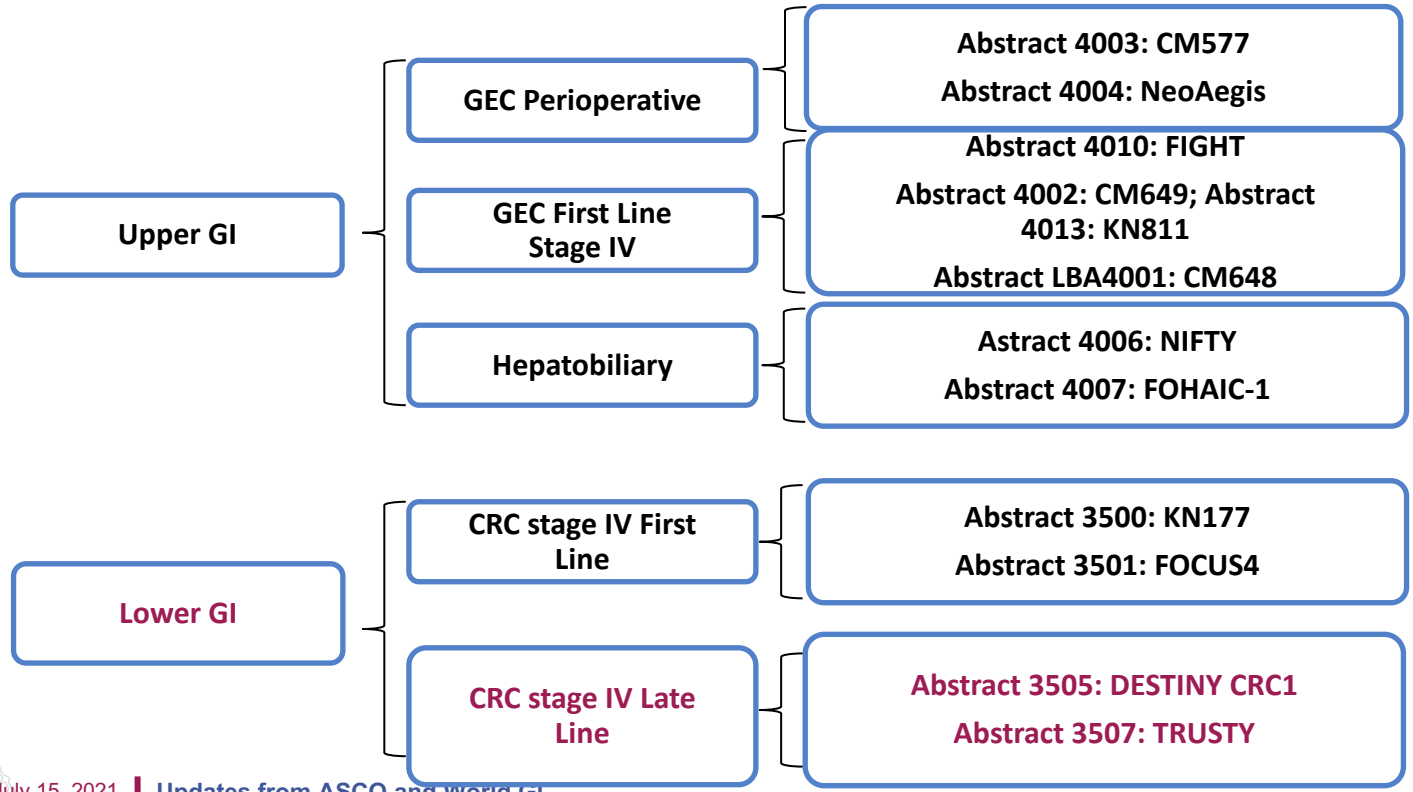


DESTINY-CRC01

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

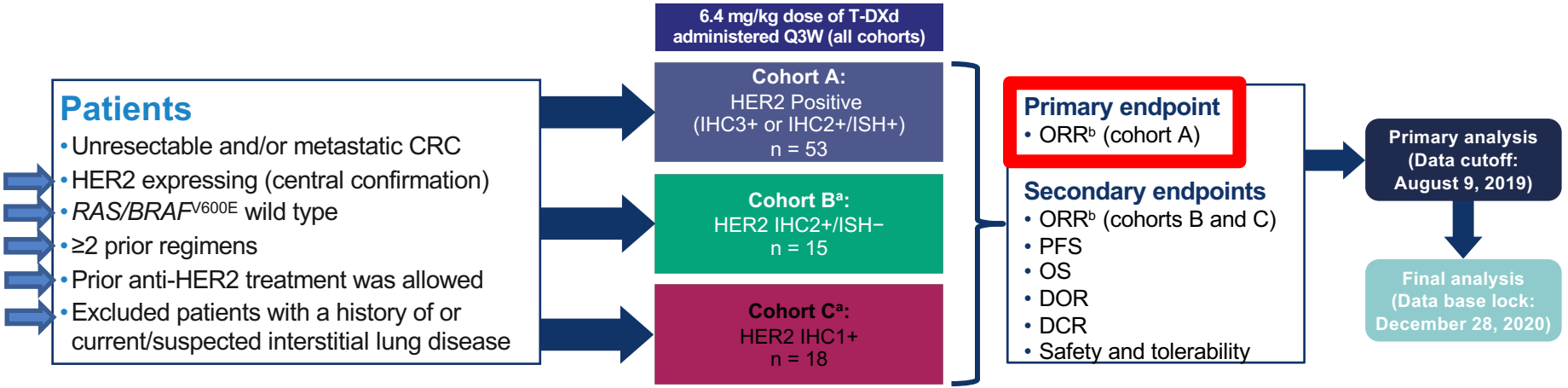
June 7, 2021

Additional authors: Maria Di Bartolomeo, Kanwal Raghav, Toshiki Masuishi, Fotios Loupakis, Hisato Kawakami, Kensei Yamaguchi, Tomohiro Nishina, Zev Wainberg, Elena Elez, Javier Rodriguez, Marwan Fakih, Fortunato Ciardiello, Kapil Saxena, Kojiro Kobayashi, Emarjola Bako, Yasuyuki Okuda, Gerold Meinhardt, Axel Grothey, Salvatore Siena

On behalf of the DESTINY-CRC01 investigators

DESTINY-CRC01 Study Design

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



Primary analysis of cohort A[1]

- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

Patient disposition at final analysis[c]

- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan.

[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST version 1.1 in all cohorts. [c]Data presented are from the full analysis set.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

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,c]**	100	100	94.4	98.8
HER2 status, %[d]				
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[e]	0	22.2	65.1
ISH–	0	100	77.8	33.7

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MSI-H, microsatellite instability status-high.
[a]By local assessment. [b]1 patient cohort A had an *NRAS* mutation; 1 patient in cohort B was not examined. [c]1 patient in cohort C was not examined. [d]By central assessment. Sums may not total 100% due to rounding. [e]1 patient was non-evaluable for ISH testing.

Prior Treatments

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

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

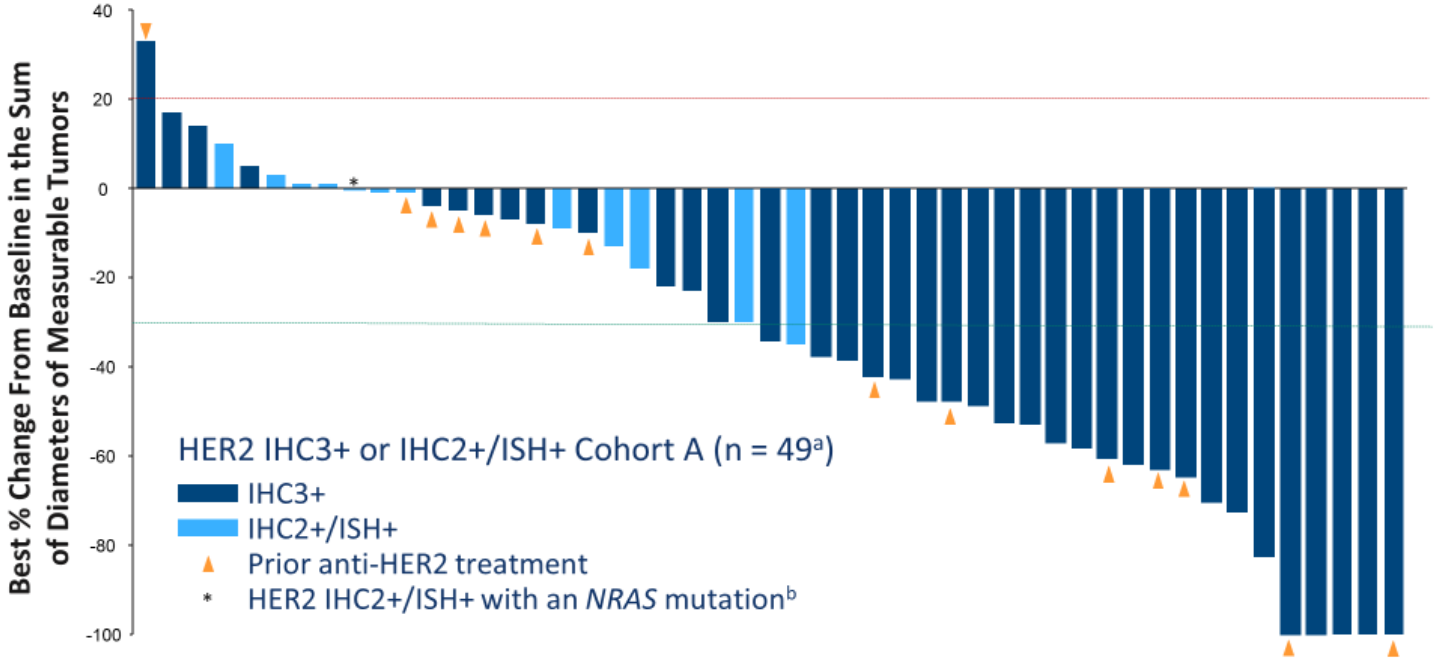
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

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[a]	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 (5.8-9.5)	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)

CR, complete response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Patients were missing postbaseline scans.

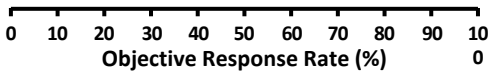
Best Change in Tumor Size in Cohort A



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
The line at 20% indicates progressive disease. The line at -30% indicates partial response. [a]4 patients from the full analysis set were excluded since 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]By local assessment.

ORR by Subgroup in Cohort A

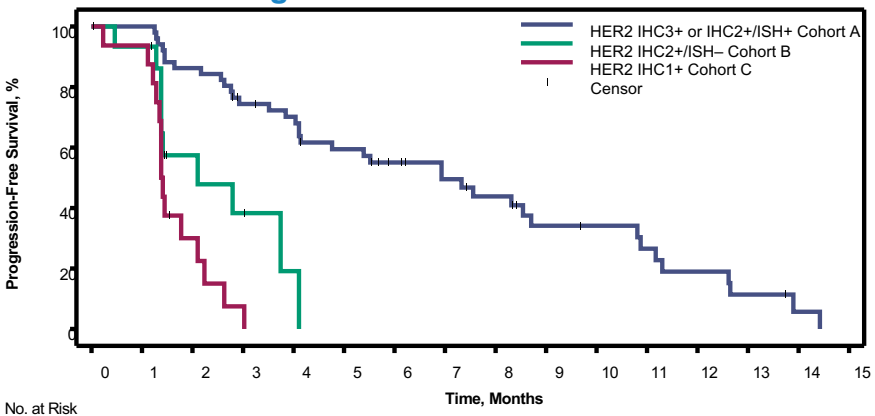
		ORR, %	[95% CI]
HER2+ Cohort A	**n = 53**	**45.3**	[31.6-59.6]
Age	<65 y (n = 35)	**42.9**	[26.3-60.6]
	≥65 y (n = 18)	**50.0**	[26.0-74.0]
Sex	Female (n = 28)	**42.9**	[24.5-62.8]
	Male (n = 25)	**48.0**	[27.8-68.7]
Region	Asia (n = 15)	**33.3**	[11.8-61.6]
	North America (n = 10)	**60.0**	[26.2-87.8]
	Europe (n = 28)	**46.4**	[27.5-66.1]
ECOG PS	0 (n = 37)	**54.1**	[36.9-70.5]
	1 (n = 16)	**25.0**	[7.3-52.4]
HER2 status	IHC3+ (n = 40)	**57.5**	[40.9-73.0]
	IHC2+/ISH+ (n = 13)	**7.7**	[0.2-36.0]
Prior HER2 treatment	Yes (n = 16)	**43.8**	[19.8-70.1]
	No (n = 37)	**45.9**	[29.5-63.1]



ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate.
Reprinted from *The Lancet Oncology*, Siena S et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. 2021, with permission from Elsevier.

Progression-Free and Overall Survival

Progression-Free Survival

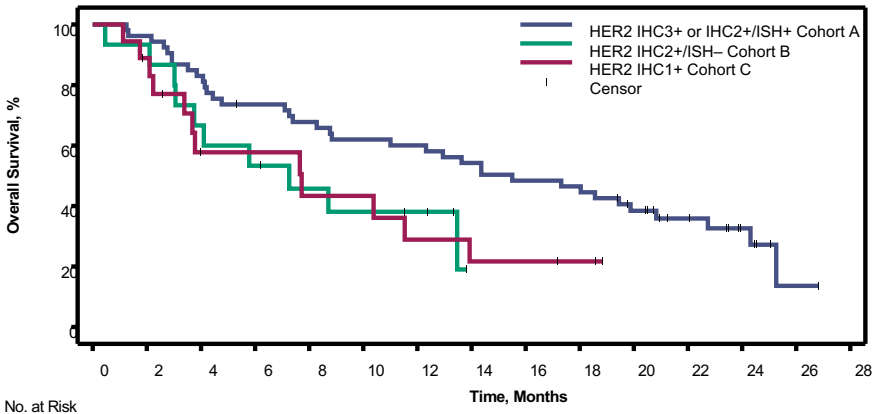


No. at Risk

Cohort A	53	51	44	36	33	27	22	18	15	10	9	7	5	3	1	0
Cohort B	15	14	6	4	1	0	0	0	0	0	0	0	0	0	0	0
Cohort C	18	15	4	1	0	0	0	0	0	0	0	0	0	0	0	0

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mPFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)

Overall Survival



No. at Risk

Cohort A	53	51	44	38	35	32	31	28	25	24	18	12	6	1	0	
Cohort B	15	14	10	8	6	5	4	0	0	0	0	0	0	0	0	
Cohort C	18	15	8	8	6	6	4	3	3	2	0	0	0	0	0	

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mOS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mOS, median overall survival; mPFS, median progression-free survival; NE, not-evaluable.

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	35 (66.0)	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)	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	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	5 (9.4)	2 (13.3)	2 (11.1)	9 (10.5)
Drug-related TEAEs associated with death[a]	2 (3.8)	1 (6.7)	0	3 (3.5)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; TEAE, treatment-emergent adverse events.
[a]3 drug-related TEAEs associated with death were 3 fatal ILDs adjudicated as drug-related.

AEs of Special Interest: Interstitial Lung Disease

All Patients (N=86)	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)[b,c]

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.

AE, adverse events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.
[a]2 patients were from cohort A, 1 from cohort B. [b]4 patients were from cohort A, 3 from cohort B and 1 from cohort C. [c]ILD grades are the highest/most severe grade recorded in a patient.

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

TRUSTY study design

TRiflUridine/tipiracil in Second-line sTudY

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/l-LV, 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, q4w*) selected on an individual patient basis

FTD/TPI+BEV

BEV: 5 mg/kg IV d1, d15
FTD/TPI : 35 mg/m^2 bid orally d1-5 and d8-12 *q4w*

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
- *RAS* status (Wild-type vs. Mutant)
- Primary tumor location (Left-sided vs. Right-sided)
- 1st-line treatment with molecularly targeted drug (BEV vs. Anti-EGFR antibody†)

†*RAS* Wild-type only

FOLFIRI+BEV irinotecan: 150 mg/m^2 IV d1, BEV: 5 mg/kg IV d1, *l*-LV: 200 mg/m^2 IV d1, 5-FU: 400 mg/m^2 bolus d1, 5-FU: 2400 mg/m^2 46 hr civ d1-2;
S-1+irinotecan+BEV (*q3w*) irinotecan: 150 mg/m^2 IV d1, BEV: 7.5 mg/kg iv d1, S-1: 40 mg/m^2 bid orally d1-14; **S-1+irinotecan+BEV (*q4w*)** irinotecan: 100 mg/m^2 VI d1, d15, BEV: 5 mg/kg VI d1,d15, S-1: 40 mg/m^2 bid orally d1-14

Statistical hypothesis

- Expected median survival time: 19.0 months (both groups)
- Hazard Ratio (HR) of non-inferiority margin: 1.33
- Alpha: 0.025 (1-sided) , Power: 80%
- Planned sample size: 524 (387 events required)
- Enrollment period: 24 months
- Follow-up period: 30 months

As a result of the first interim analysis for futility, the IDMC recommended the termination of TRUSTY study in July 2020.

- Enrollment: 397 patients from 65 institutions
- Actual enrollment period: October 1st, 2017, to July 16th, 2020
- Data cut-off: July 16th, 2020

IDMC: independent data monitoring committee

Patient characteristics

		FP+IRI+BEV (n = 199)		FTD/TPI+BEV (n = 197)	
		n	(%)	n	(%)
Gender	Male	99	(49.7)	94	(47.7)
Age	Median [range]	68.0 [32–82]		67.0 [26–80]	
	≥65	124	(62.3)	117	(59.4)
ECOG PS	0	124	(62.3)	120	(60.9)
RAS status	Wild-type	79	(39.7)	79	(40.1)
Primary tumor location*	Right-sided	50	(25.1)	47	(23.9)
Number of metastatic lesions	≥2	117	(58.8)	127	(64.5)
Time to progression	≥9 months	131	(65.8)	130	(66.0)
in 1st-line	<9 months	68	(34.2)	67	(34.0)
Biologics in 1st-line	Anti-EGFR antibody	35	(17.6)	37	(18.8)
	BEV	164	(82.4)	160	(81.2)
Intent to use†	FOLFIRI+BEV	130	(65.3)	125	(63.5)
5-FU or S-1	S-1+IRI+BEV	69	(34.7)	72	(36.5)

CAPOX, Capecitabine+Oxaliplatin; SOX, S-1+Oxaliplatin.
*Tumors located in the cecum, ascending colon, and transverse colon were considered right-sided; tumors located within the splenic flexure and beyond were considered left-sided.
† Prior to randomization, either 5-FU or S-1 was declared by each investigator when allocated FP+IRI+BEV.

Overall safety summary

	FP+IRI+BEV (n = 197)		FTD/TPI+BEV (n = 196)	
	n	(%)	n	(%)
All adverse events	**188**	**(95.4)**	**188**	**(95.9)**
≥Grade 3	131	(66.5)	152	(77.6)
All drug related adverse events	**186**	**(94.4)**	**187**	**(95.4)**
≥Grade 3	117	(59.4)	142	(72.4)
Serious adverse events	**46**	**(23.4)**	**34**	**(17.3)**
Drug-related serious adverse events	28	(14.2)	10	(5.1)
Adverse events leading to discontinuation	**19**	**(9.6)**	**18**	**(9.2)**
Drug-related adverse events leading to discontinuation	13	(6.6)	10	(5.1)
Adverse events associated with death	**3**	**(1.5)**	**1**	**(0.5)**
Drug-related adverse events associated with death	0	(0.0)	1	(0.5)

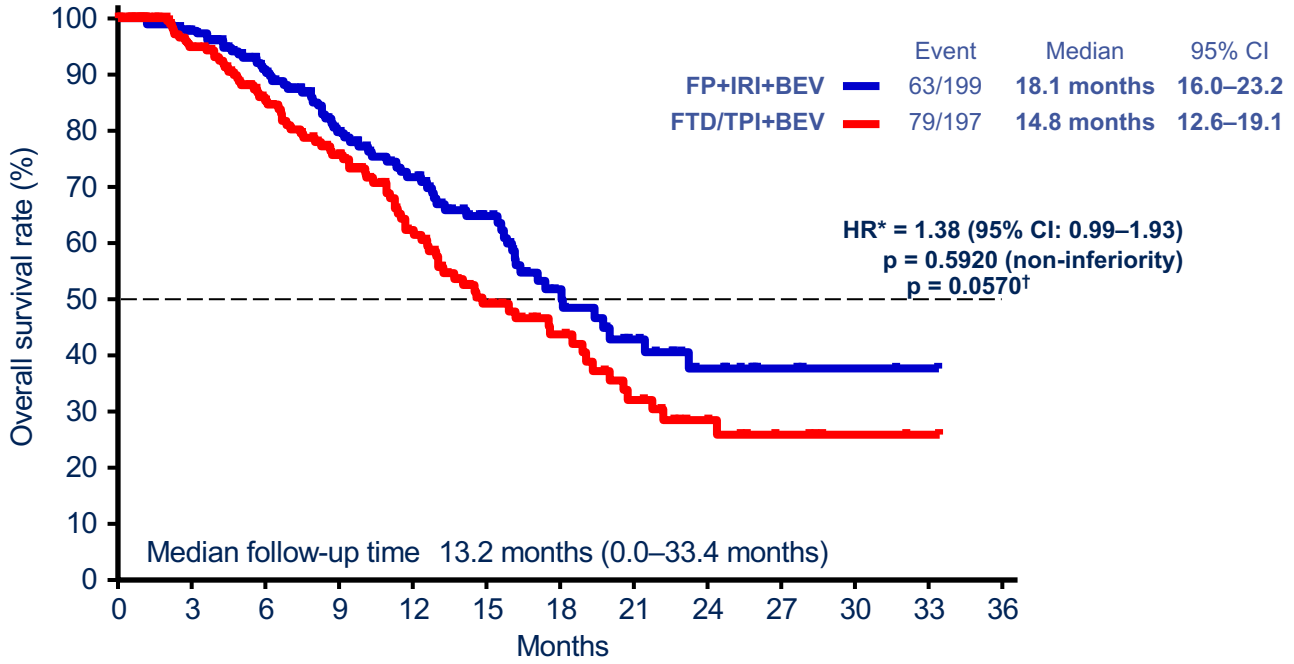
Common adverse events

Events (CTC-AE v4.0)	FP+IRI+BEV (n = 197)				FTD/TPI+BEV (n = 196)			
	All		≥Grade 3		All		≥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 3 is not applicable.

19 patients (9.5%, FP+IRI+BEV) and 17 patients (8.6%, FTD/TPI+BEV) received G-CSF.

Primary endpoint: Overall survival

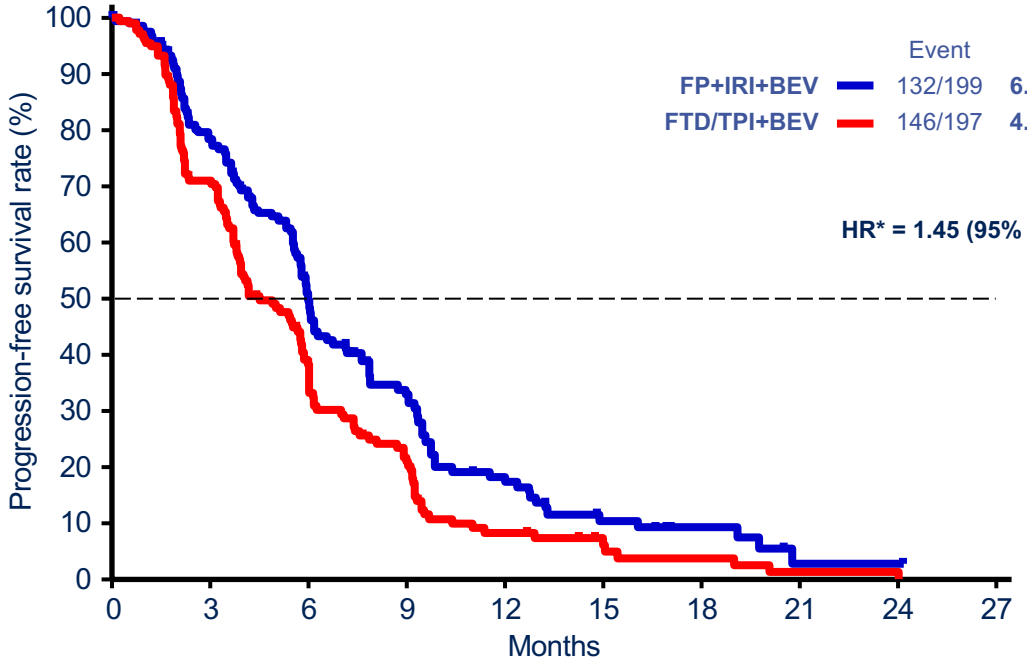


Number at risk

FP+IRI+BEV	199	167	134	98	78	54	32	20	12	4	2	1	-
FTD/TPI+BEV	197	163	122	98	66	44	28	19	12	5	2	1	-

*adjusted based on stratification factors
†*ad hoc* unplanned 2-sided superiority test

Progression-free survival



Number at risk

FP+IRI+BEV	199	129	71	40	19	9	5	1	1	0
FTD/TPI+BEV	197	117	52	28	10	6	3	1	1	0

* adjusted based on stratification factors

Best overall response

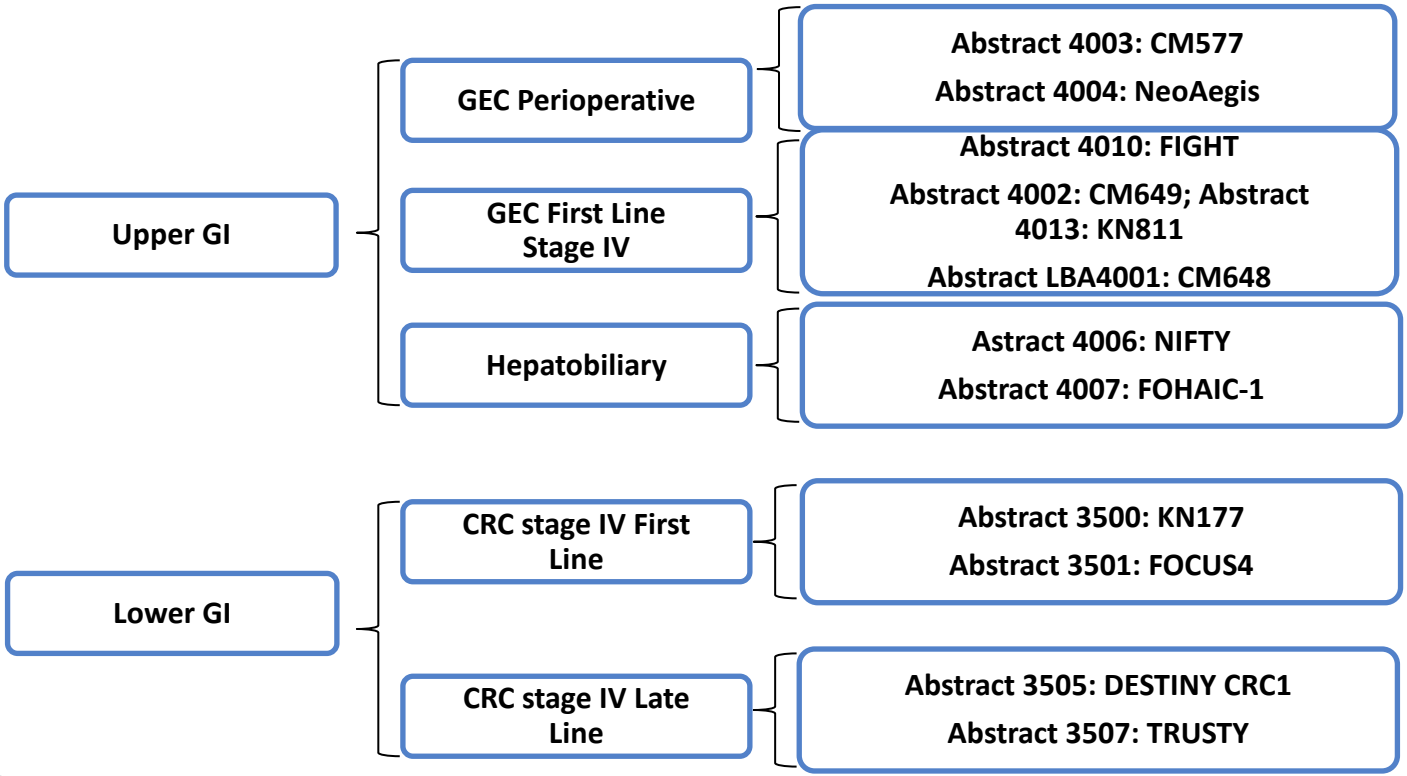
	FP+IRI+BEV (n = 184*) %		FTD/TPI+BEV (n = 183*) %		p value
CR	0.0	(n = 0)	0.0	(n = 0)	
PR	7.1	(n = 13)	3.8	(n = 7)	
SD	64.7	(n = 119)	57.4	(n = 105)	
PD	13.6	(n = 25)	24.6	(n = 45)	
NE	14.7	(n = 27)	14.2	(n = 26)	
Response rate 95% CI (%)	**7.1** [3.8–11.8]	(n = 13)	**3.8** [1.6–7.7]	(n = 7)	0.2498
Disease control rate 95% CI (%)	**71.7** [64.6–78.1]	(n = 132)	**61.2** [53.7–68.3]	(n = 112)	0.0359

* Number of patients with measurable lesions according to RECIST version1.1.
Based on investigators assessment.

Summary

- FTD/TPI+BEV did not show non-inferiority to Fluoropyrimidine+Irinotecan+BEV as a 2nd-line treatment in patients with mCRC.
  - ✓ mOS 18.1 vs 14.8 months (HR: 1.38; p = 0.5920 for non-inferiority)
  - ✓ mPFS 6.0 vs 4.5 months (HR: 1.45)
  - ✓ mTTF2 9.9 vs 8.8 months (HR: 1.12)
  - ✓ RR (DCR) 7.1 vs 3.8% (71.7 vs 61.2%)
- There were no new safety concerns in the 2nd-line setting.
  - ✓ ≥Grade 3 neutropenia 41.6 vs 65.8%, diarrhea 7.1 vs 1.5%
  - ✓ ≥Grade 3 febrile neutropenia 2.5 vs 2.0%, received G-CSF 9.5 vs 8.6%
  - ✓ Grade 1/2 alopecia 24.9 vs 3.6%
  - ✓ Drug-related serious adverse events 14.2 vs 5.1%
  - ✓ One treatment related death in FTD/TPI+BEV
- With respect to *post hoc*-adjusted OS, FTD/TPI+BEV was similar to FOLFIRI+BEV but worse than S-1+IRI+BEV.
  - ✓ mOS 17.5 vs 16.4 months (HR: 1.07; intent to use 5-FU)
  - ✓ mOS N.R. vs 13.2 months (HR: 2.14; intent to use S-1)

ASCO 2021: Highlights in GI Malignancies



Patient Case 1

56-year-old man with ECOG PS 1 presenting with newly diagnosed HER2 negative, microsatellite stable, PDL1 CPS 0 GEJ adenocarcinoma metastatic to the liver.

How would you treat this patient?

1. FOLFOX
2. ECX
3. FOLFOX-nivolumab
4. FOLFOX-trastuzumab

Patient Case 2

56-year-old man with ECOG PS 1 presenting with newly diagnosed PDL1 CPS 0 squamous cell (SCC) of the esophagus metastatic to the bone?

How would you treat this patient?

1. FLOT
2. FOLFOX
3. FOLFOX-nivolumab
4. Cisplatin/5FU-pembrolizumab

Patient Case 3

A 74-year-old male presents with dysphagia and found to have a mass at the GEJ and biopsy demonstrates a HER2+, MSS, PDL1 CPS 20 tumor. Staging shows diffuse pulmonary, bone, and liver metastases.

How would you treat this patient?

1. FOLFOX-pembrolizumab
2. FLOT
3. FOLFOX-nivolumab
4. FOLFOX-trastuzumab+pembrolizumab

Conclusions

- Upper GI Cancer
  - GEA: CM649, KN811, FIGHT
  - GEC SCC: GM648
  - Biliary: NIFTY
  - HCC: FOHAIC-1
- Lower GI Cancer
  - KNK177
  - FOCUS4
  - TRUSTY
  - DESTINY CRC-01

Thank You!

Thank you!

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