Year in Review: Gastric, Gastroesophageal Junction and Esophageal Cancer

Tuesday, February 1, 2022
5:00 PM – 6:00 PM ET

Faculty

David H Ilson, MD, PhD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2022

YiR Gastric, Gastroesophageal Junction and Esophageal Cancer Faculty

David H Ilson, MD, PhD
Attending Physician, Member
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

Zev Wainberg, MD, MSc
Co-Director, GI Oncology Program
Director of Early Phase Clinical Research
Jonsson Comprehensive Cancer Center
UCLA School of Medicine
Los Angeles, California

Commercial Support

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Dr Love — Disclosures

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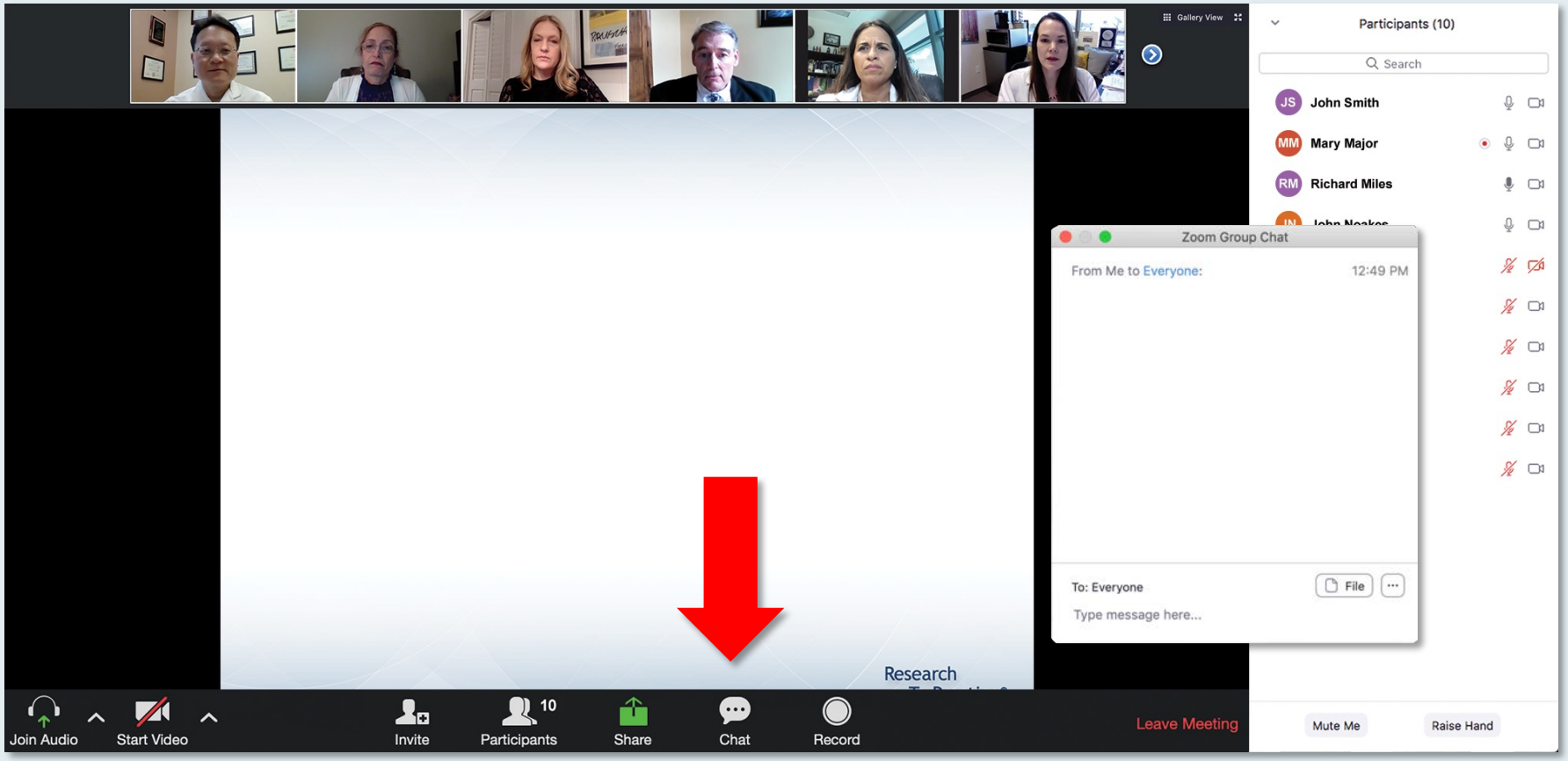
We Encourage Clinicians in Practice to Submit Questions



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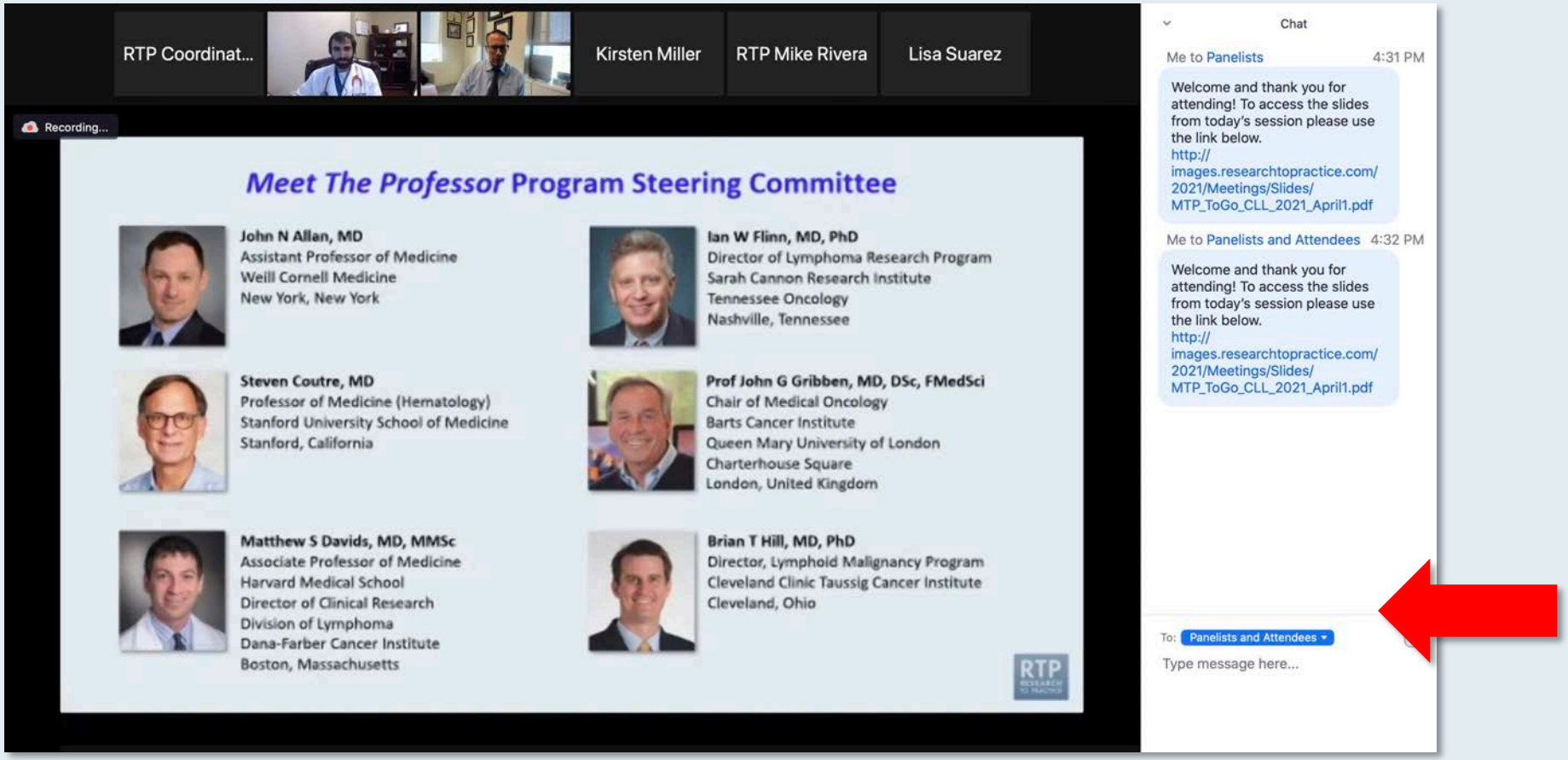

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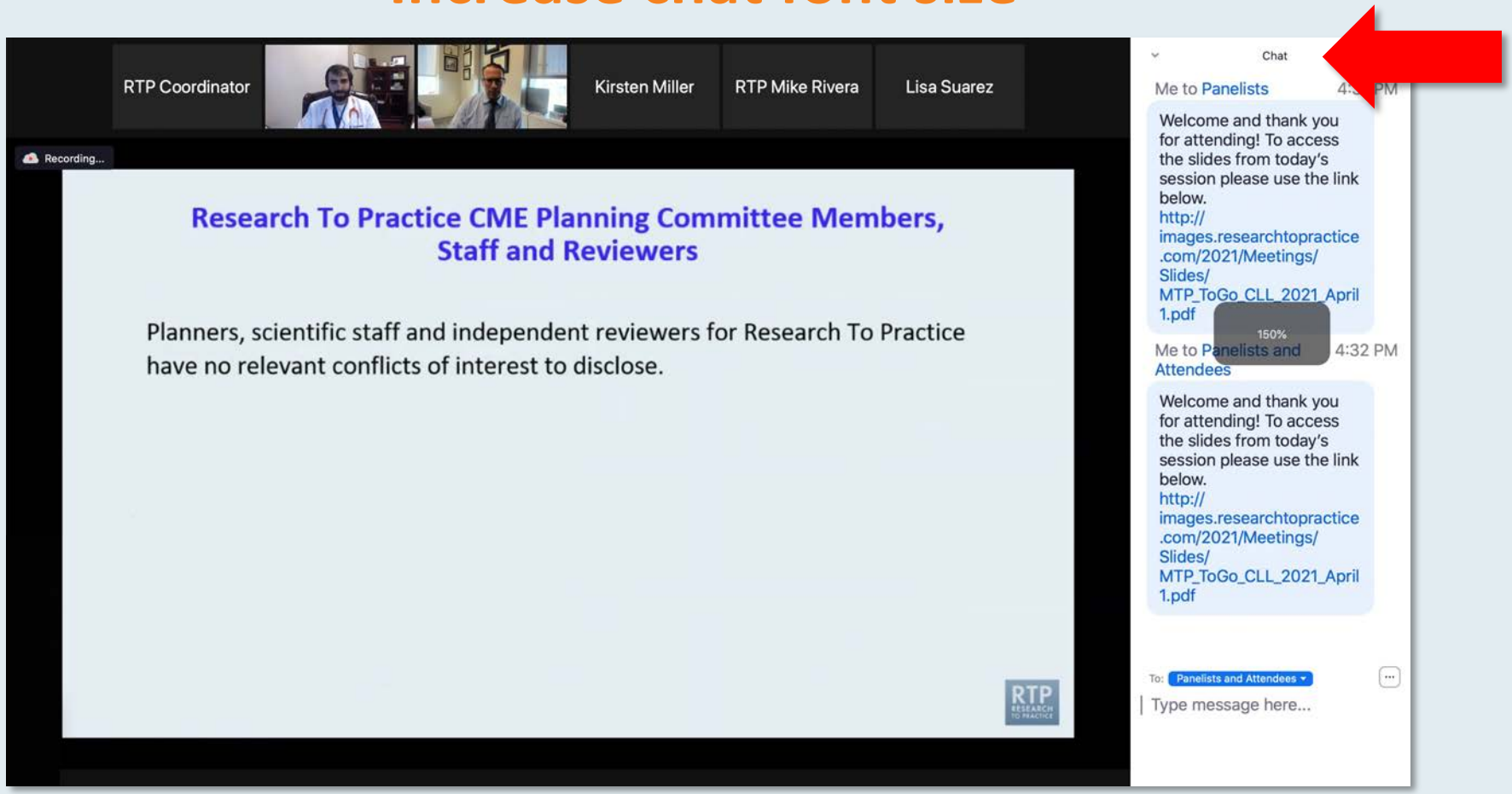

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Gastroesophageal Cancers

DR SAMUEL KLEMPNER

INSTITUTION MASSACHUSETTS GENERAL HOSPITAL

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Exploring the Current and Changing Paradigm for the Management of Newly Diagnosed Diffuse Large B-Cell Lymphoma

Wednesday, February 2, 2022
5:00 PM – 6:15 PM ET

Faculty

Christopher R Flowers, MD, MS
Neha Mehta-Shah, MD, MSCI
Grzegorz Nowakowski, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Exploring the Current and Future Role of B-Cell Maturation Antigen-Directed Therapy in the Management of Multiple Myeloma

Monday, February 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Noopur Raje, MD

Moderator

Neil Love, MD

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Key Considerations in the Optimal Clinical Care of Patients with Small Cell Lung Cancer

Wednesday, February 9, 2022
5:00 PM – 6:00 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Jared Weiss, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Recent Advances and Real-World Implications in Medical Oncology: A Daylong Multitumor Educational Symposium in Partnership with the North Carolina Oncology Association and the South Carolina Oncology Society

Saturday, February 12, 2022
8:30 AM – 4:00 PM ET

RTP
RESEARCH
TO PRACTICE

Recent Advances and Real-World Implications in Medical Oncology: Agenda

Module 1	**Chronic Lymphocytic Leukemia and Lymphomas** 8:35 AM – 9:40 AM
Module 2	**Multiple Myeloma** 9:40 AM – 10:45 AM
Module 3	**Genitourinary Cancers** 10:45 AM – 11:50 AM
Module 4	**Breast Cancer** 12:30 PM – 1:35 PM
Module 5	**Gastrointestinal Cancers** 1:35 PM – 2:40 PM
Module 6	**Lung Cancer** 2:40 PM – 3:45 PM

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RESEARCH TO PRACTICE

Meet The Professor

Current and Future Role of Immunotherapy in the Management of Lung Cancer

Tuesday, February 15, 2022
5:00 PM – 6:00 PM ET

Faculty

Charu Aggarwal, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Prostate Cancer (Part 1 of a 2-Part Series)

Thursday, February 17, 2022

7:00 PM – 9:00 PM PT

Faculty

Neeraj Agarwal, MD
Himisha Beltran, MD
Fred Saad, MD
A Oliver Sartor, MD

Moderator

Alan H Bryce, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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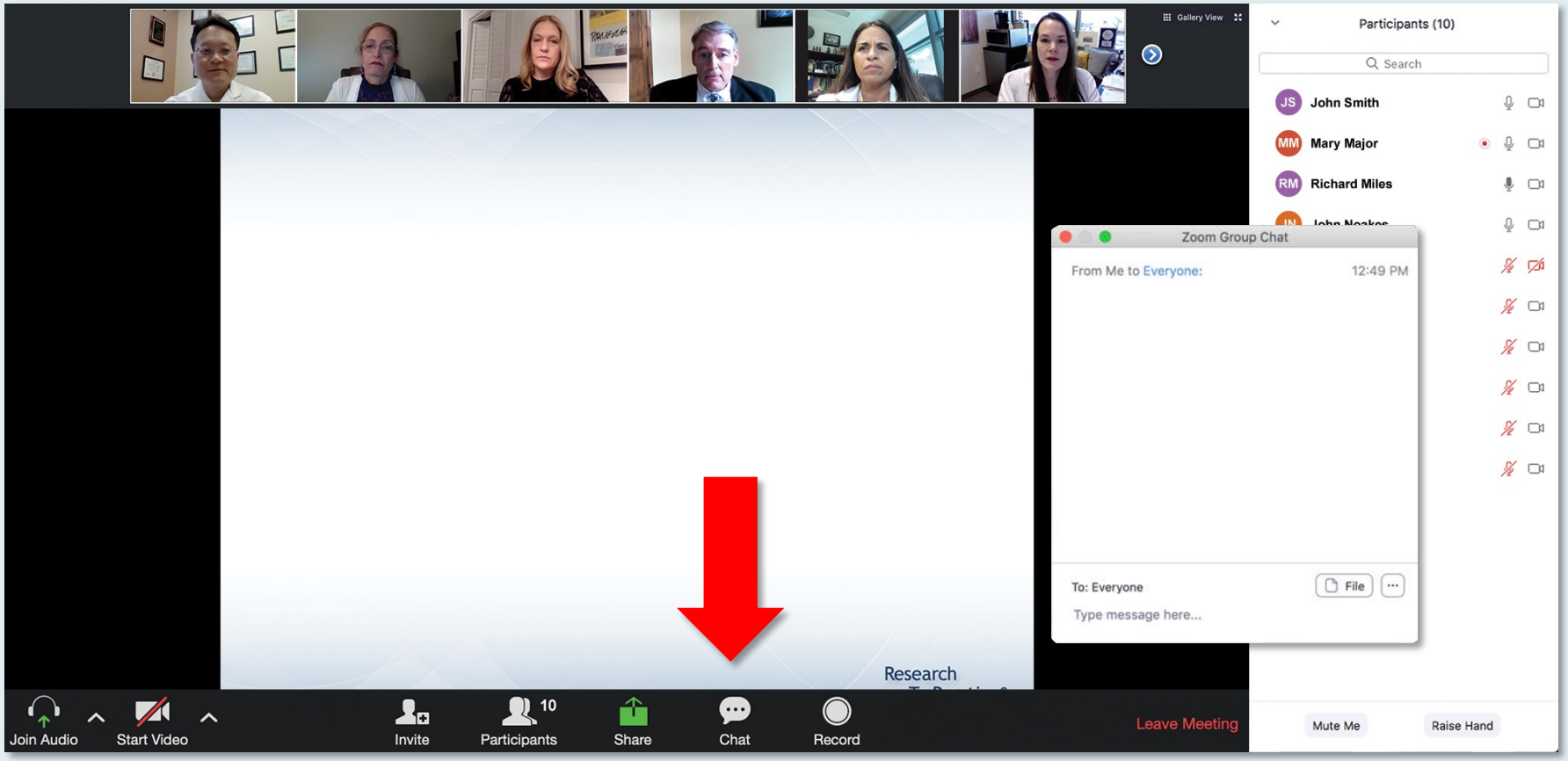

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Agenda

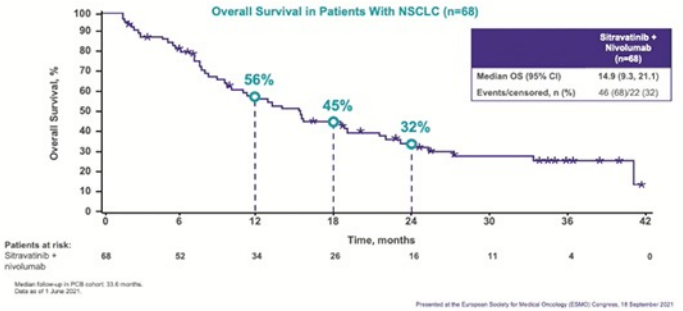
Introduction

Module 1: Localized Disease

Module 2: Metastatic Disease

Module 3: Novel Targets

Overall Survival With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy



Median follow-up in PCB cohort: 33.6 months.
Data as of 1 June 2021.

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021

24

ADVANCED

The Rams adv
team to play i

Agenda

Introduction:

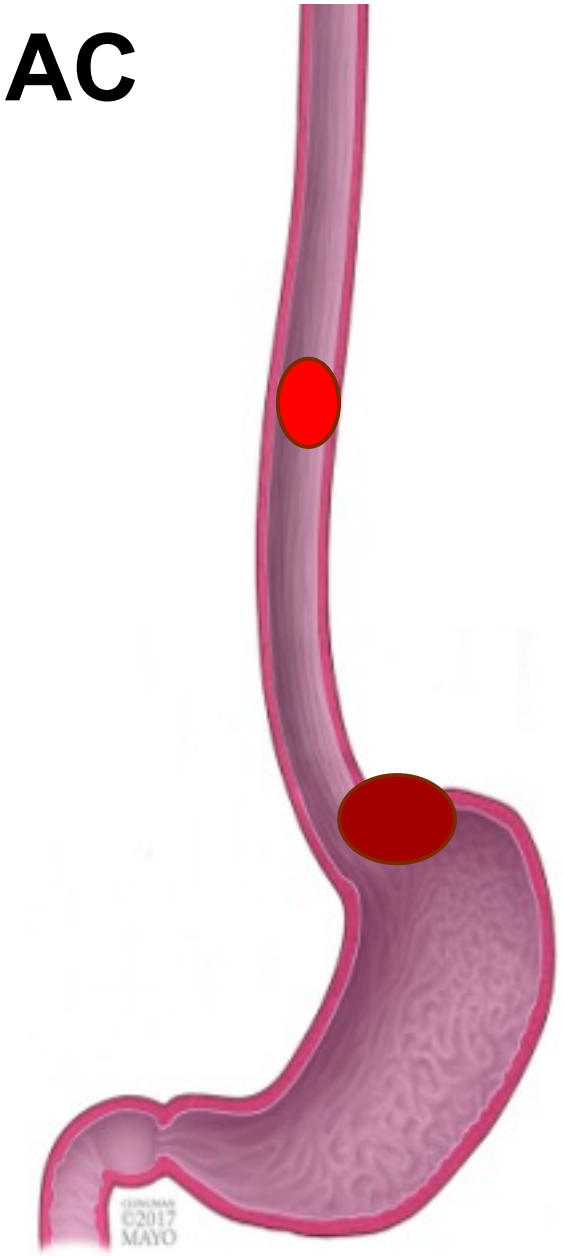
- Key Biomarkers

Module 1: Localized Disease

Module 2: Metastatic Disease

Module 3: Novel Targets

SCC vs AC



Esophageal squamous cell carcinoma (SCC)

- East/Central Asia, southeastern Africa
- Smoking & ETOH
- Proximal anatomic location
- ~ 50% of patients have tumor cell expression of PD-L1 (ie, TPS 1+) [1-7]

Adenocarcinoma (AC)

- Western
- Reflux & obesity
- Distal esophagus
- ~ 15% of patients have TPS 1+ [1, 8-12]

Courtesy of Harry H Yoon, MD, MHS

1. Salem et al. 2018. *The Oncologist.* 2. ORIENT-15. 3. ESCORT _1st. 4. ESCORT_2L. 5. CM648. 6. ATTRACTION-03. 7. CM648. 8. ATTRACTION-02. 9. CM649. 10. JAV-300. 11. ATTRACTION-04. 12. JAV100_maintenance

2021 TREATMENT LANDSCAPE FOR FIT PATIENT WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA (SCC)

Advanced, 1st-line

PD-L1-CPS ≥ 10

Pembro + platin/FP (KN590)

(NCCN 1-2A and FDA)

PD-L1-TPS ≥ 1

Consider Nivo + FOLFOX (CM648)

(Await FDA & NCCN)

PD-L1-CPS 0-9 & TPS < 1

FOLFOX

(NCCN 2A)

Pembro + platin/FP

(NCCN 2B and FDA)

After chemoradiation & surgery

SCC or AC if non-pCR

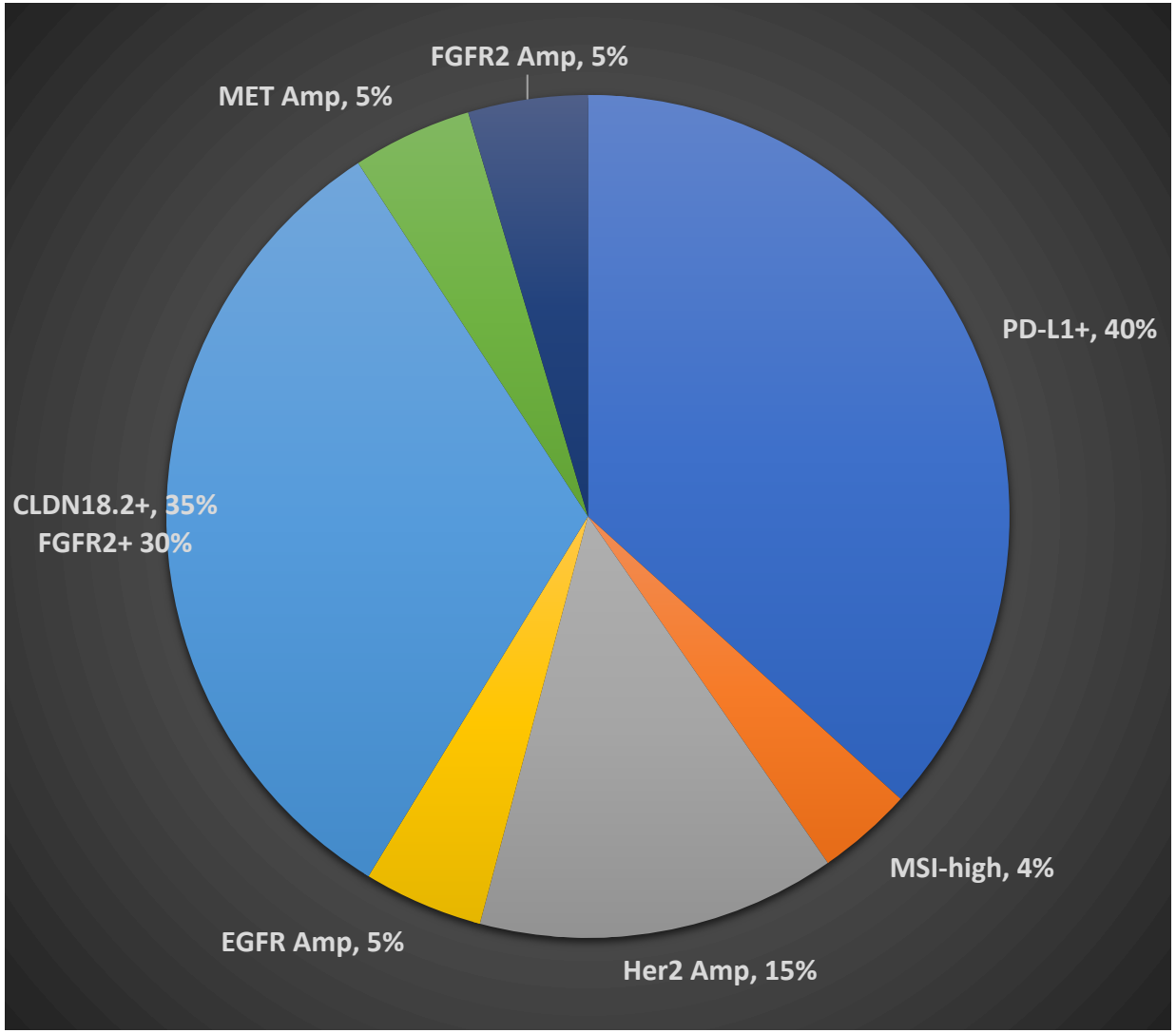
Adjuvant nivolumab x 1 yr (CM-577)

(NCCN 1-2A and FDA)

CPS, Combined positive score; **FP**, fluoropyrimidine; **nivo**, nivolumab; **pCR,** pathologic complete response; **pembro,** pembrolizumab; **TPS,** Tumor proportion score

Courtesy of Harry H Yoon, MD, MHS

Novel Biomarkers



KEY MARKERS IN ADVANCED DISEASE

- **HER2** positive – 15-20% of patients, improved survival with chemo + trastuzumab and in 2nd line with trastuzumab deruxtecan (DS8201)
- **MSI** high – 3-5% of patients, high response rates and survival with PD1 inhibitors
- **PD-L1** positive – 30-50% of patients, identifies those more likely to benefit from immune therapies, likely gradation within PD-L1+

INVESTIGATIONAL BIOMARKERS

- **CLDN18.2** high – 30-35% of patients, response predictor for zolbetuximab (FAST Trial, Sahin et al, Ann of Onc 2021)
- **FGFR2** + (IHC) 30% of patients, response predictor for bemarituzumab (FIGHT Trial, Wainberg et al, GI ASCO 2021)
- **FGFR2** amp – 5-7%, predicts response to bemarituzumab

Courtesy of Zev Wainberg, MD, MSc

Minimum testing in a newly diagnosed M1 Esophagogastric Cancer

- **1) IHC for HER2, FISH only if IHC 2+**
- **2) IHC for DNA mismatch repair protein deficiency**
  - Esophageal cancer: < 1%
  - Gastric cancer: 7%
- **3) IHC for PDL-1, Combined positive score used over Tumor Positive Score**
- **Next Generation Sequencing**
  - Covers HER2 and other gene amplification
  - Identify MSI
  - Tests for rare but targetable genes
    - NTRK gene fusion
  - Will Assess TMB
  - Blood based genomic testing if tissue unavailable

Courtesy of David H Ilson, MD, PhD

Agenda

Introduction

Module 1: Localized Disease

- CheckMate 577

Module 2: Metastatic Disease

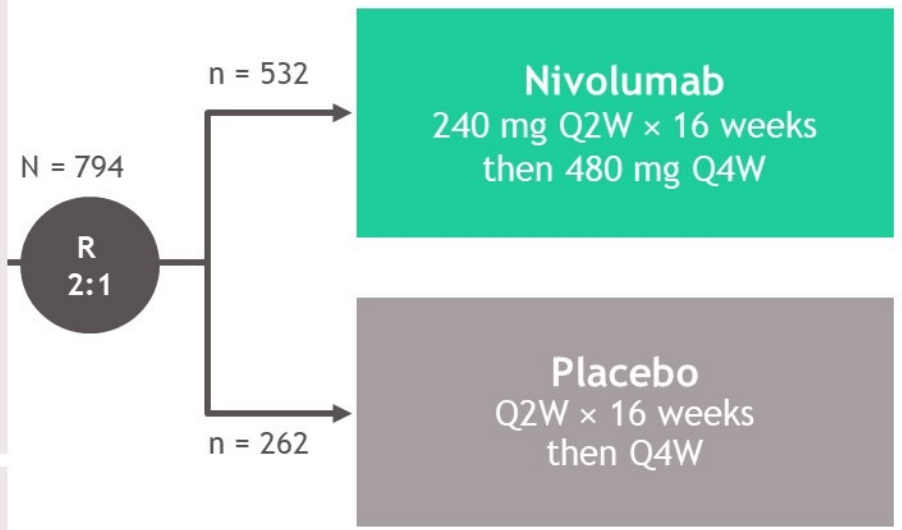
Module 3: Novel Targets

CheckMate 577 study design

- 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])



Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

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

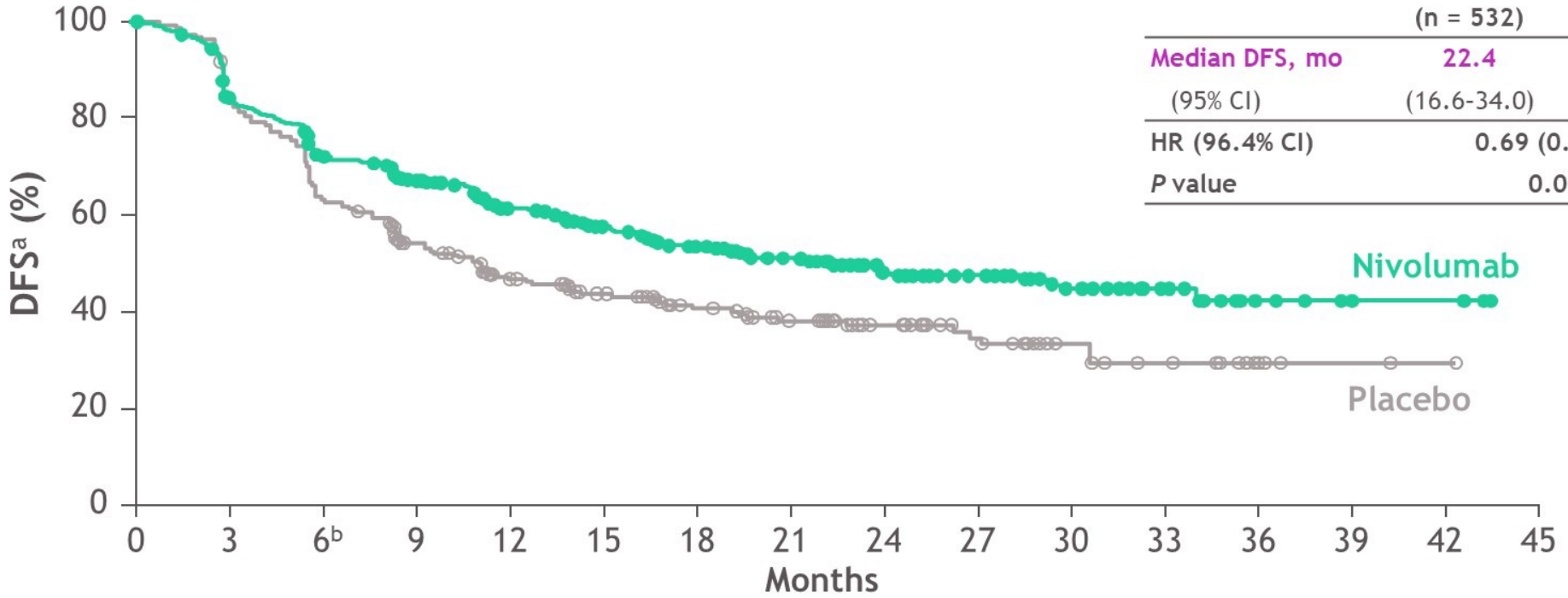
Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

- 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%)

[a]ClinicalTrials.gov. NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a prespecified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]DMFS is defined as the time between randomization and the first distant recurrence or death, whichever occurs first; [h]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; [i]Time from randomization date to clinical data cutoff (May 12, 2020).
Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Courtesy of Zev Wainberg, MD, MSc

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]	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

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

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the prespecified interim analysis required the *P* value to be less than 0.036.
Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Courtesy of Zev Wainberg, MD, MSc

Immunotherapy Neoadjuvant/Adjuvant Trials

- **Checkmate 577: + Adjuvant nivolumab**
- **KEYNOTE 975: Definitive Chemort + / - Pembro**
- **KEYNOTE 585: Perioperative Cape or 5-FU cisplatin + / - Pembro**
- **Matterhorn: Preop FLOT + / - Durvalumab**
- **ONO-4538: Adjuvant S-1 or CAPE-OX + / - Nivolumab**
- **Pilots: Combining anti PD-1 or PDL-1 agents with chemo + RT**
  - ECOG: CROSS + /- Nivolumab ➔ Surgery ➔ Nivolumab vs Ipi/Nivo

Courtesy of David H Ilson, MD, PhD

Early Stage Gastro-Esophageal

- **Clinical Implications**: Nivolumab established as the SOC for patients post-esophagectomy regardless of histology (SCC and adeno), PDL1 status, and final pathological stage
- **Questions Remain**:
  - Impact on Overall Survival
  - What about patients with complete path response?
- **Future Directions**:

  Definitive Chemoradiation: Role for Immunotherapy

  -Keynote 975 (Chemoradiation +/- Pembrolizumab), KUNLUN (chemoradiation +/- Durvalumab)
- **Early Stage Gastric Cancer?**

  -Keynote 585 (Chemo +/- Pembrolizumab), Matterhorn (FLOT +/- Durvalumab)

Courtesy of Zev Wainberg, MD, MSc

Agenda

Introduction

Module 1: Localized Disease

Module 2: Metastatic Disease

- HER2-Positive Disease
- Squamous Cell Carcinoma
- Gastric/Gastroesophageal Junction (GEJ) Adenocarcinoma

Module 3: Novel Targets

Agenda

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Module 1: Localized Disease

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- HER2-Positive Disease
  - KEYNOTE-811, DESTINY-Gastric01, DESTINY-Gastric02, DESTINY-Gastric03
- Squamous Cell Carcinoma
- Gastric/GEJ Adenocarcinoma

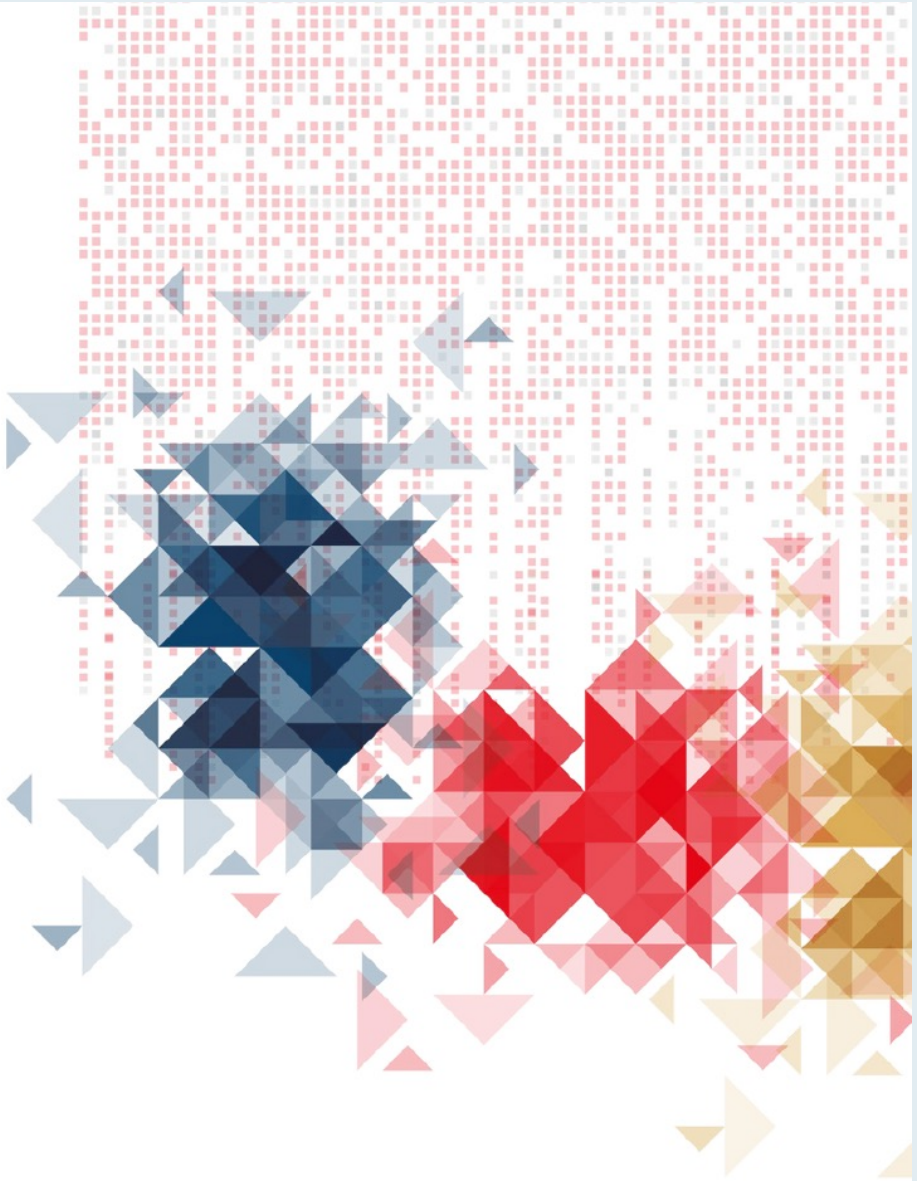
Module 3: Novel Targets

2021 ESMO congress

Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients With HER2+ Metastatic Breast Cancer: Results of the Randomized, Phase 3 Study DESTINY-Breast03

Javier Cortés, MD[a], Sung-Bae Kim, Wei-Pang Chung, Seock-Ah Im, Yeon Hee Park, Roberto Hegg, Min-Hwan Kim, Ling-Ming Tseng, Vanessa Petry, Chi-Feng Chung, Hiroji Iwata, Erika Hamilton, Giuseppe Curigliano, Binghe Xu, Caleb Lee, Yali Liu, Jillian Cathcart, Emarjola Bako, Sunil Verma, Sara Hurvitz
On behalf of the DESTINY-Breast03 investigators

[a]Medical Oncology, International Breast Cancer Center (IBCC), Quironsalud Group, and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain.



Abstract LBA1

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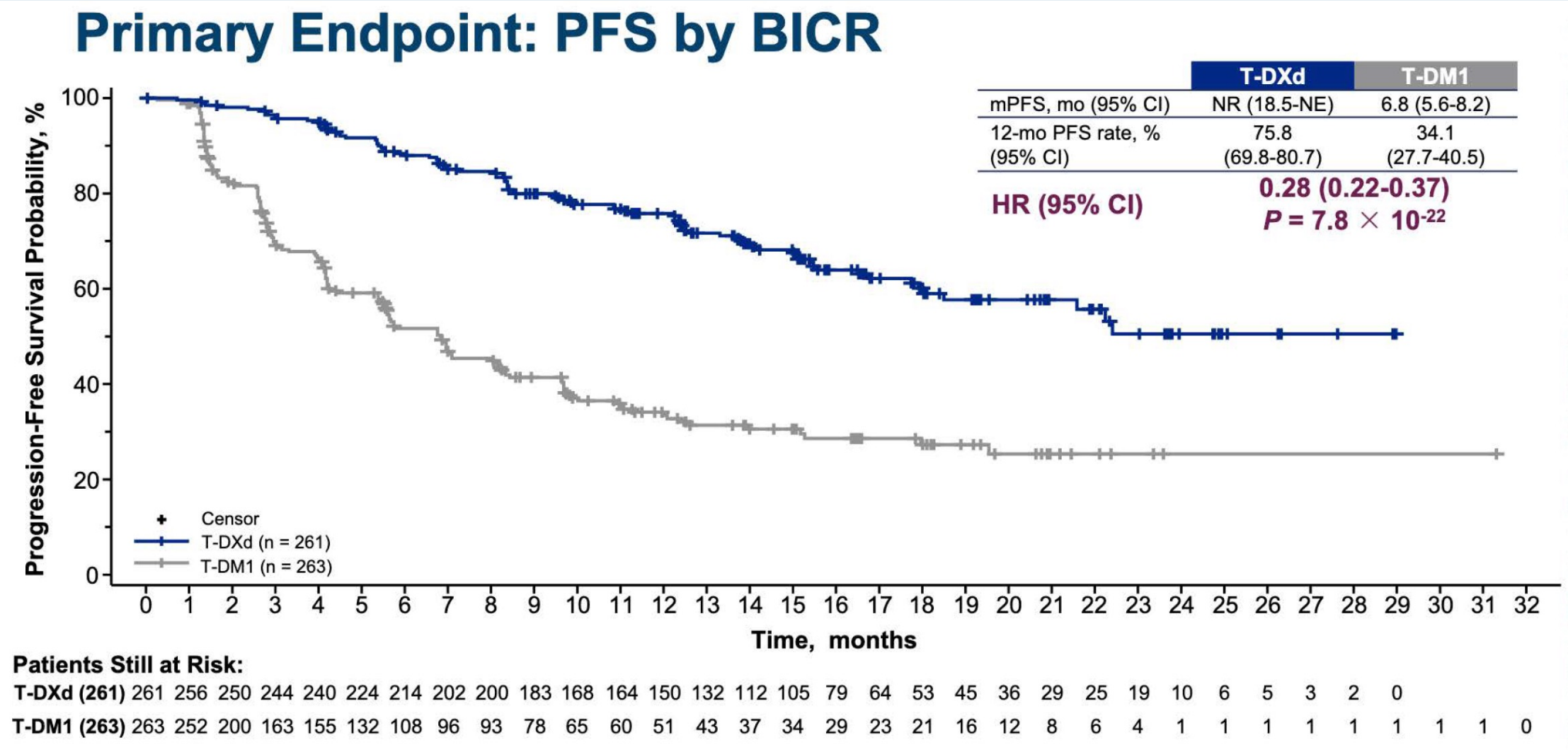
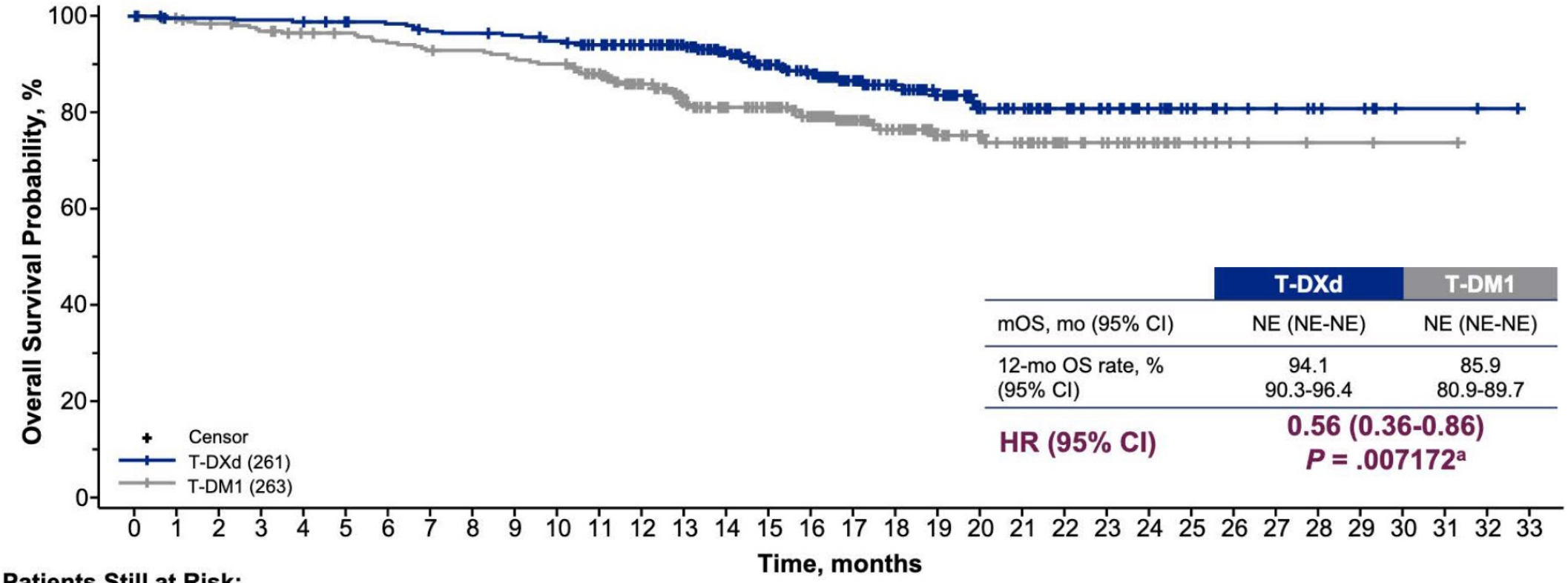
DESTINY-Breast03: Progression-Free Survival by BICR



Cortés J et al. ESMO 2021;Abstract LBA1.

DESTINY-Breast03: Overall Survival by BICR

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	**0.56 (0.36-0.86)**	
	***P* = .007172[a]**	

Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

2021 ESMO congress

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

Cortés J et al. ESMO 2021;Abstract LBA1.

RTP RESEARCH TO PRACTICE

HER2 targeted therapy and testing in first line treatment of gastric cancer

TOGA study: chemo ± trastuzumab

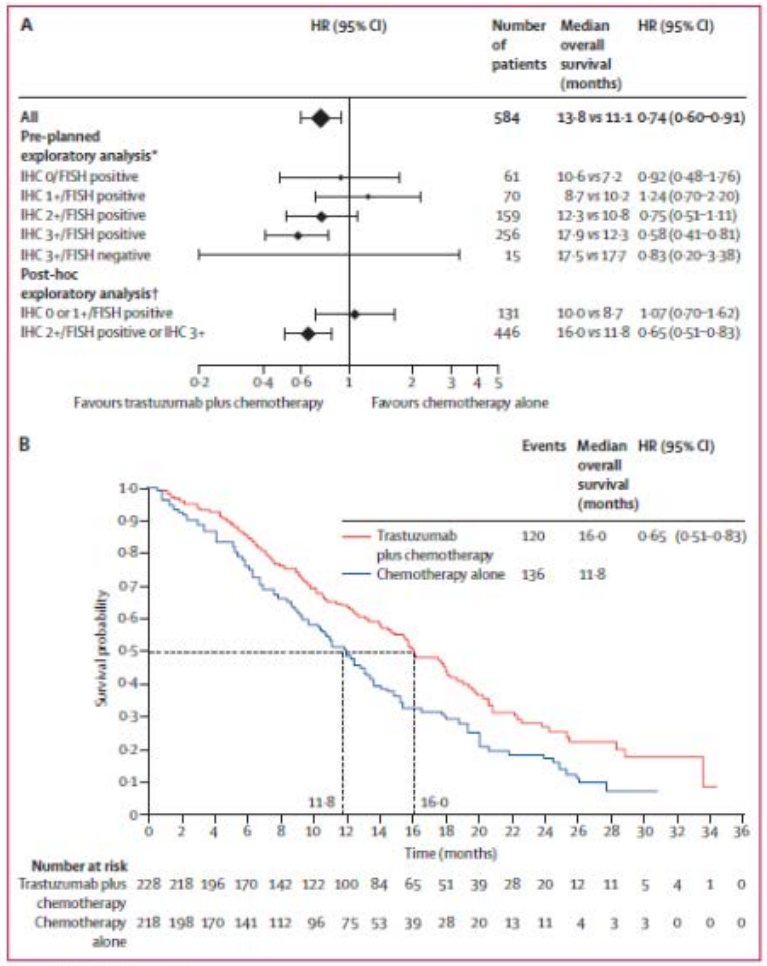


Figure 4: **Exploratory analyses**
HR=hazard ratio. (A) Pre-planned exploratory and post-hoc exploratory analyses of patients stratified by human epidermal growth factor receptor 2 (HER2) status. *n=561; patients with no immunohistochemistry (IHC) data (n=7) or IHC 3+ tumours with no fluorescence in-situ hybridisation (FISH) data (n=16) were excluded from this analysis. †n=577; patients with no IHC data (n=7) were excluded from this analysis. (B) Overall survival according to the post-hoc exploratory analysis (FISH and IHC) in patients with IHC 2+ and FISH-positive tumours or IHC 3+ tumours.

Bang Y, Van Cutsem E et al, Lancet 2010

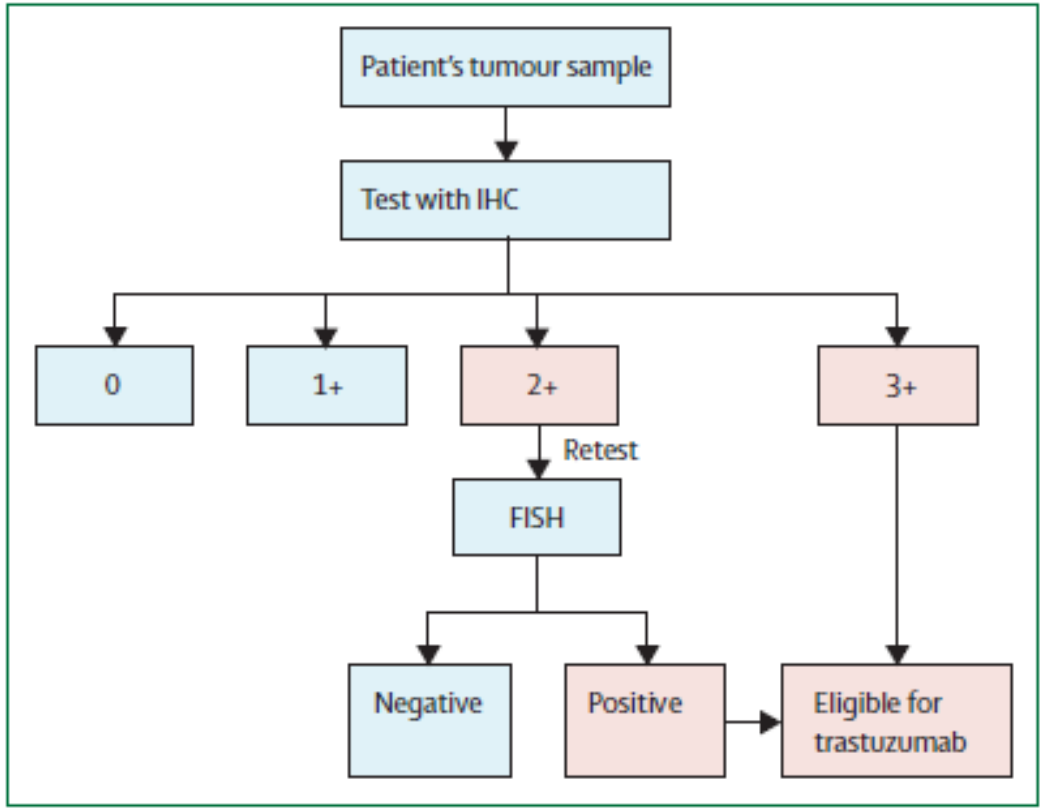
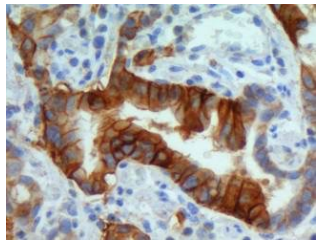
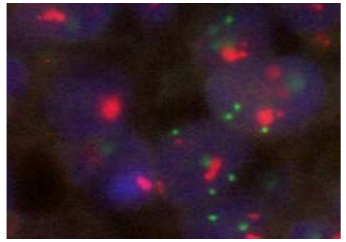


Figure 2: **Testing algorithm for *HER2* status in gastric and gastro-oesophageal-junction adenocarcinomas**
IHC–immunohistochemistry. FISH–fluorescence in-situ hybridisation.

Courtesy of Eric Van Cutsem, MD, PhD



IHC 3+



FISH +

Van Cutsem E et al, Lancet 2016

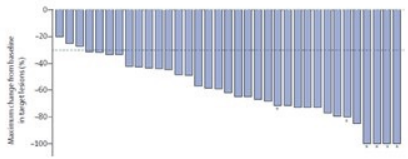
HER2+ Disease

- Clinical Implications:
  - Keynote 811: Chemo + Trastuzumab + Pembro now approved for HER2+
    - Await data on PFS, OS
  - Trastuzumab deruxtecan approved for 2nd line (and beyond) HER2+ disease
    - Await randomized Phase III data in 2nd line (Destiny Gastric 04)
    - Pneumonitis, which patients?
- Future Directions:
  - Front line therapies beyond chemo + trastuzumab/pembro
  - Other HER2 inhibitors (margetuximab, tucatinib, ZW25)

Courtesy of Zev Wainberg, MD, MSc

Background

- Standard first-line therapy for HER2-positive metastatic gastric or gastroesophageal junction (G/GEJ) cancer is trastuzumab (anti–HER2) with a fluoropyrimidine and a platinum
- Phase 2 data suggested antitumor activity and manageable safety for adding pembrolizumab (anti–PD-1) to trastuzumab and chemotherapy
  - MSKCC study (N = 37): 91% ORR, 100% DCR, 70% 6-mo PFS, 80% 12-mo OS



Janjigian YY et al. *Lancet Oncol* 2020;21:821-31.
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  - PANTHERA (N = 43): 77% ORR, 98% DCR, 77% 6-mo PFS, 77% 12-mo OS

Rha SY et al. *J Clin Oncol* 2020;38:Abstr 3081.

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)

Patients
- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- HER2-positive

Stratification Factors
- Geographic region
- PD-L1 CPS
- Chemotherapy choice

R 1:1
N ≈ 692

Pembrolizumab 200 mg IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

[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).

Courtesy of Zev Wainberg, MD, MSc

KEYNOTE-811 Global Cohort:
Phase 3 Study in HER2 pos. Gastric Adenocarcinoma

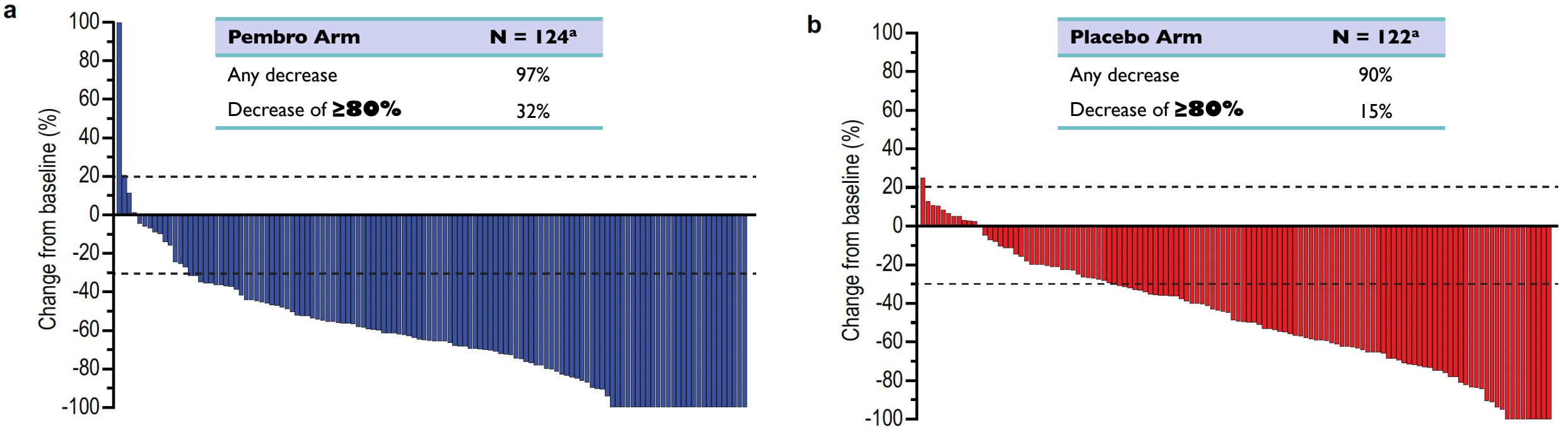


Fig. 1 | Best percentage change from baseline in the size of target lesions among participants in the efficacy population. a, Pembrolizumab group. **b**, Placebo group. Only those participants in the efficacy population who had RECIST-measurable disease at baseline and at least one evaluable post-baseline measurement are evaluable for change from baseline ($n = 124$ in the pembrolizumab group, $n = 122$ in the placebo group). The treatment regimen included trastuzumab and chemotherapy in both groups. Increases from baseline greater than 100% were truncated at 100%.

Janjigian et. al, Nature, 2021; 600(7890):727-730.

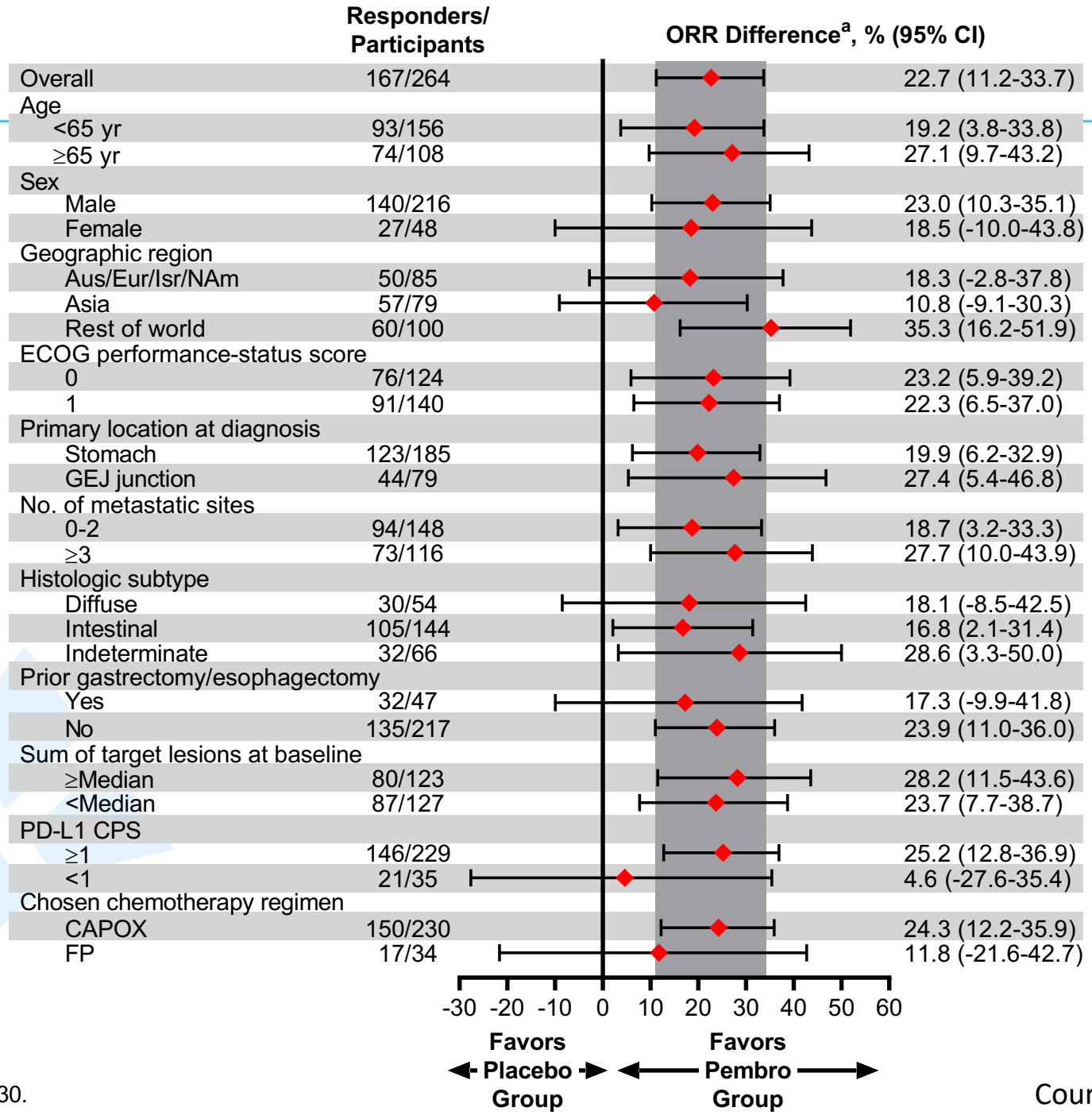
Courtesy of Eric Van Cutsem, MD, PhD

Table 1 | Summary of confirmed objective response in the efficacy population

Variable	Pembrolizumab group (*n* = 133)	Placebo group (*n* = 131)
Objective response (% (95% confidence interval))[a]	74.4 (66.2–81.6)	51.9 (43.0–60.7)
Disease control (% (95% confidence interval))[b]	96.2 (91.4–98.8)	89.3 (82.7–94.0)
Best overall response (number (%))		
Complete response	15 (11.3)	4 (3.1)
Partial response	84 (63.2)	64 (48.9)
Stable disease	29 (21.8)	49 (37.4)
Progressive disease	5 (3.8)	7 (5.3)
Not evaluable[c]	0 (0.0)	2 (1.5)
Not assessed[c]	0 (0.0)	5 (3.8)

Janjigian et. al, Nature, 2021; 600(7890):727-730.

Courtesy of Eric Van Cutsem, MD, PhD



Janjigian et. al, Nature, 2021; 600(7890):727-730.

Courtesy of Eric Van Cutsem, MD, PhD

Poster 242

ASCO Gastrointestinal Cancers Symposium

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2–Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma: Final Overall Survival (OS) Results From a Randomized, Multicenter, Open-Label, Phase 2 Study (DESTINY-Gastric01)

Kensei Yamaguchi

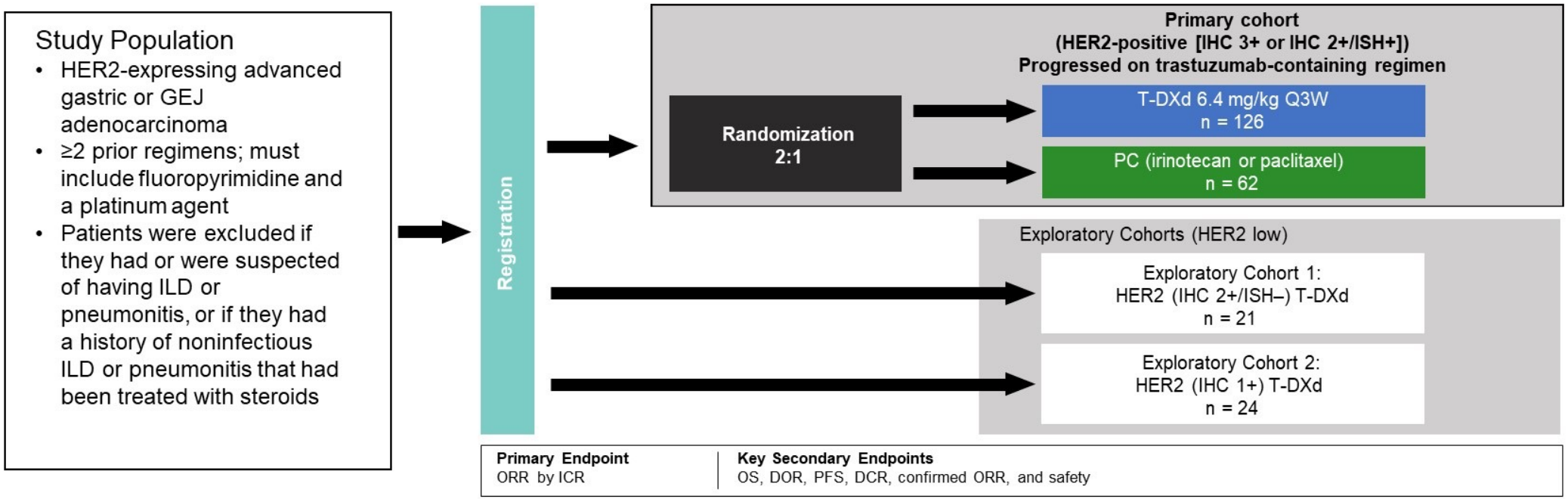
The Cancer Institute Hospital of JFCR, Tokyo, Japan

ON BEHALF OF THE DESTINY-GASTRIC01 INVESTIGATORS

Additional authors: Yung-Jue Bang, Satoru Iwasa, Naotoshi Sugimoto, Min-Hee Ryu, Daisuke Sakai, Hyun Cheol Chung, Hisato Kawakami, Hiroshi Yabusaki, Jeeyun Lee, Kaku Saito, Yoshinori Kawaguchi, Takahiro Kamio, Akihito Kojima, Masahiro Sugihara, Kohei Shitara

DESTINY-Gastric01 Study Design

An open-label, multicenter phase 2 study (NCT03329690)



- Patients were stratified by country, ECOG PS score, and HER2 status
- In the primary analysis (data cutoff: Nov 8, 2019; 101 OS events; median survival follow-up, 12.3 months), T-DXd showed statistically significant benefit vs standard chemotherapy in ORR and OS
- Key secondary endpoint of OS was to be statistically evaluated hierarchically if the primary endpoint was statistically significant
- Data cutoff: June 3, 2020 (133 OS events; median survival follow-up: 18.5 months)

DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PC, physician's choice; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Shitara K et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382:2419-2430.

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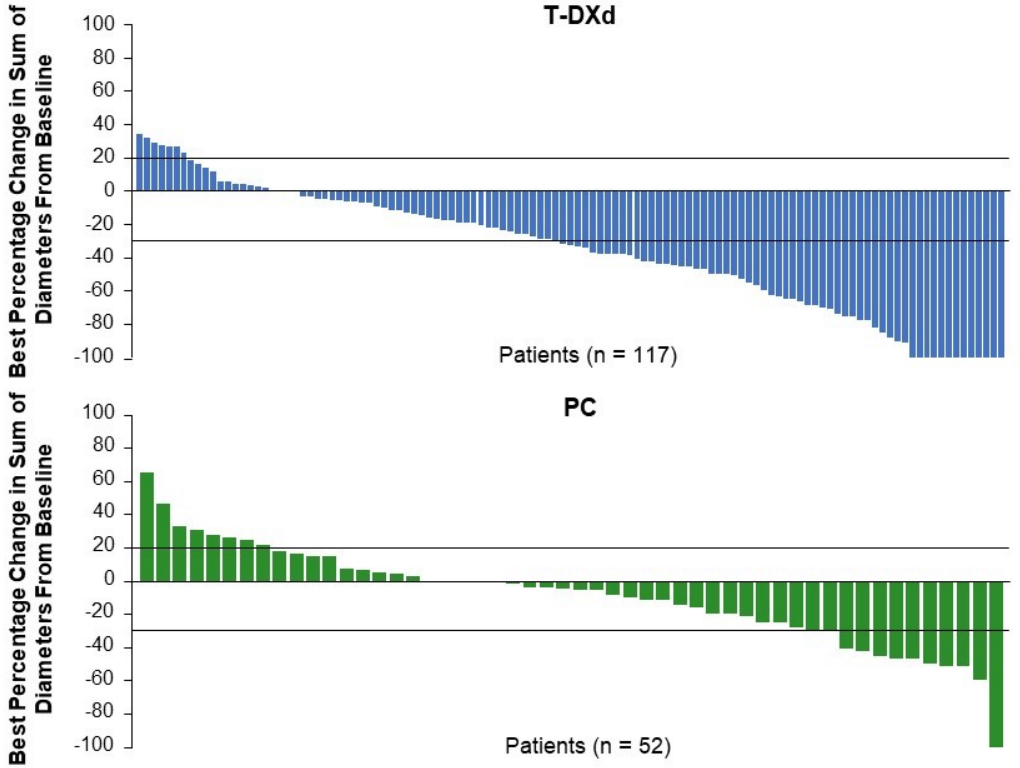
ORR and Other Efficacy Endpoints

	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	**61 (51.3) 95% CI, 41.9-60.5**	**8 (14.3) 95% CI, 6.4-26.2**
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10 (8.4)	0
PR	40[c] (33.6)	7 (12.5)
SD	52 (43.7)	28 (50.0)
PD	14 (11.8)	17 (30.4)
Not evaluable	3 (2.5)	4 (7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	102 (85.7) 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	12.5 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

Best Percentage Change from Baseline in Tumor Size for Individual Patients[d]



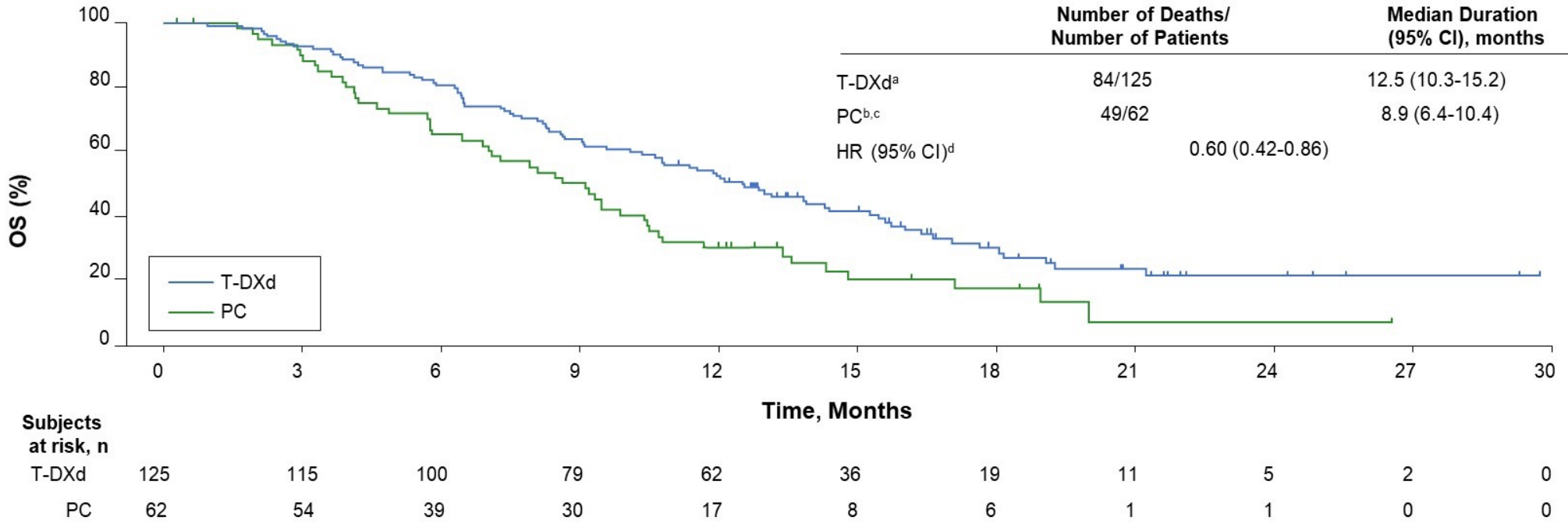
CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; NE, not estimable; ORR, objective response rate; PC, physician's choice; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTR, time to response.

Confirmed ORR: responses were confirmed by a follow-up scan ≥4 weeks after initial CR/PR. [a]Includes data for the response-evaluable set: all randomized patients who received ≥1 dose of study drug and had measurable tumors based on ICR at baseline (T-DXd, n = 119; PC overall, n = 56; irinotecan, n = 51; paclitaxel, n = 5). [b]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region. [c]According to the procedure of the ICR, the adjudicator assessment was changed from PR to SD in 1 patient at data cutoff of the final OS analysis. [d]Includes patients who had both baseline and postbaseline target lesion assessments by ICR in both treatment arms. 6 patients were excluded from this analysis because they had no postbaseline tumor assessment (T-DXd, n = 2; PC, n = 4).

Line at 20% indicates progressive disease; line at –30% indicates partial response.

Overall Survival

Kaplan-Meier Analysis of OS



	Number of Deaths/ Number of Patients	Median Duration (95% CI), months
T-DXd[a]	84/125	12.5 (10.3-15.2)
PC[b,c]	49/62	8.9 (6.4-10.4)
HR (95% CI)[d]	0.60 (0.42-0.86)	

Subjects at risk, n											
T-DXd	125	115	100	79	62	36	19	11	5	2	0
PC	62	54	39	30	17	8	6	1	1	0	0

As in the primary analysis (101 OS events; 54.0% maturity), in this updated analysis (133 OS events; 71.1% maturity), T-DXd showed superior antitumor activity compared to PC

HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.
[a]In the T-DXd arm, 41 patients (32.8%) were censored.
[b]In the PC arm, 13 patients (21.0%) were censored.
[c]1 patient in the PC arm received crossover treatment of T-DXd.
[d]HR and corresponding 95% CI were estimated using Cox proportional hazards model stratified by region.

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Overall Safety

- Grade ≥3 AEs occurred in 85.6% of T-DXd patients versus 56.5% with PC
  - The most common were decreased neutrophil count (51.2% vs 24.2%), anemia (38.4% vs 22.6%), and decreased white blood cell count (20.8% vs 11.3%)
- 16 patients (12.8%) had T-DXd–related ILD/pneumonitis, as determined by an independent adjudication committee
  - There were 13 grade 1 or 2, 2 grade 3, 1 grade 4, and no grade 5 events
  - There were 4 ILD/pneumonitis events since the primary analysis; 1 grade 1 and 3 grade 2
  - Among the 16 total ILD/pneumonitis events, the median time to first onset was 102.5 days (range, 36-638)
  - There were no ILD/pneumonitis events in the PC arm
- There was 1 T-DXd-related death from pneumonia (non-ILD), as reported in the primary analysis
- There were no AE-related deaths in the PC arm

TEAEs in ≥20% of Patients Treated with T-DXd[a]

	T-DXd n = 125			PC Overall n = 62		
		Grade			Grade	
Preferred Term, %	Any	3	4	Any	3	4
Neutrophil count decreased[b]	64.8	38.4	12.8	35.5	16.1	8.1
Nausea	63.2	5.6	0	46.8	1.6	0
Decreased appetite	60.8	16.8	0	45.2	12.9	0
Anemia[c]	57.6	38.4	0	30.6	21.0	1.6
Platelet count decreased[d]	40.0	9.6	1.6	6.5	1.6	1.6
White blood cell count decreased[e]	38.4	20.8	0	35.5	8.1	3.2
Malaise	34.4	0.8	0	16.1	0	0
Diarrhea	32.8	2.4	0	32.3	1.6	0
Vomiting	26.4	0	0	8.1	0	0
Pyrexia	24.8	0	0	16.1	0	0
Constipation	24.8	0	0	24.2	0	0
Lymphocyte count decreased[f]	23.2	7.2	4.8	3.2	0	1.6
Alopecia	22.4	0	0	14.5	0	0
Fatigue	21.6	7.2	0	24.2	3.2	0

AE, adverse event; ILD, interstitial lung disease; PC, physician's choice; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent AE.
No additional TEAEs were observed in ≥20% of patients receiving PC. [a]There were no grade 5 events. [b]Includes preferred terms "neutrophil count decreased" and "neutropenia." [c]Includes preferred terms "hemoglobin decreased," "red blood cell count decreased," "anemia," and "hematocrit decreased." [d]Includes preferred terms "platelet count decreased" and "thrombocytopenia." [e]Includes preferred terms "leukopenia" and "white blood cell count decreased." [f]Includes preferred terms "lymphocyte count decreased" and "lymphopenia."
Shitara K et al. *J Clin Oncol.* 2020;38:4513.

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Conclusions

- With continued follow-up after the primary analysis, T-DXd demonstrated clinically meaningful OS benefit (~40% reduced risk of death) and clinically relevant improvement in ORR compared with PC standard chemotherapy in HER2-positive advanced gastric or GEJ cancer
- The overall safety profile of T-DXd was manageable and consistent with that of the primary analysis
  - The most common AEs were gastrointestinal or hematologic in nature
  - 16 patients (12.8%) had T-DXd-related ILD as determined by an independent adjudication committee. Most were grade 1 or 2
- Additional follow-up provides further evidence that T-DXd is an effective treatment option for patients with HER2+ advanced gastric or GEJ adenocarcinoma who have progressed after ≥2 previous lines of therapy, including trastuzumab, fluoropyrimidine, and a platinum agent

AE, adverse event; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

Shitara K et al. *J Clin Oncol.* 2020;38:4513.

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DESTINY-Gastric01: Efficacy according to prior ICI therapy

	Prior ICI Therapy		No Prior ICI Therapy	
	T-DXd n = 44	PC Chemotherapy n = 17	T-DXd n = 81	PC Chemotherapy n = 45
ORR, %	65.9 (29/44)	25.0 (4/16)	42.7 (32/75)	10.0 (4/40)
95% CI	50.1-79.5	7.3-52.4	31.3-54.6	2.8-23.7
Confirmed ORR,[b] %	56.8 (25/44)	18.5 (3/16)	34.7 (26/75)	10.0 (4/40)
95% CI	41.0-71.7	4.0-45.6	24.0-46.5	2.8-23.7
Median OS, months	16.6	8.6	10.3	8.4
95% CI	12.1-21.2	3.6-10.7	8.1-13.0	6.9-13.6
	HR, 0.31 (95% CI, 0.15-0.63)		HR, 0.83 (95% CI, 0.50-1.35)	

Shitara K et al. Gastrointestinal Cancers Symposium 2022;Abstract 322.

2021 ESMO congress

Primary Analysis of a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients With HER2-Positive (HER2+) Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After a Trastuzumab-containing Regimen

Eric Van Cutsem, MD[a], Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A. Wainberg, Jaffer Ajani, Joseph Chao, Jabed Seraj, Yoshinori Kawaguchi, Amy Qin, Jasmeet Singh, Gerold Meinhardt, Geoffrey Ku

On behalf of the DESTINY-Gastric02 investigators

[a]University Hospital Gasthuisberg, Leuven and KU Leuven, Leuven, Belgium

Van Cutsem E et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021, Ann Oncol 2021, LBA

DESTINY-Gastric02 Study Design

An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer (NCT04014075)

Key eligibility criteria

- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Centrally confirmed HER2 positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

T-DXd
6.4 mg/kg Q3W
N = 79[a]

Primary endpoint

- Confirmed ORR by ICR

Secondary endpoints[b]

- PFS by ICR
- OS
- DOR by ICR
- Safety and tolerability

- DESTINY-Gastric02 is the first study focused only on second-line T-DXd monotherapy in Western patients with HER2+ gastric/GEJ cancer who have progressed on a trastuzumab-containing regimen
  - It is the follow-on study to DESTINY-Gastric01, which evaluated T-DXd third-line or later in Asian patients[1]
- Patients were enrolled in Europe (Belgium, Great Britain, Italy, Spain) and the United States (data cutoff: April 9, 2021)

[a]Enrollment of 80 patients was planned; actual enrollment was 79 patients.
[b]Other secondary endpoints were ORR, PFS, and DOR by investigator assessment, pharmacokinetics, anti-drug antibodies, and patient-reported outcomes.

1. Shitara K et al. *N Engl J Med*. 2020;382:2419-30.

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; Q3W, every 3 weeks.

Courtesy of Zev Wainberg, MD, MSc

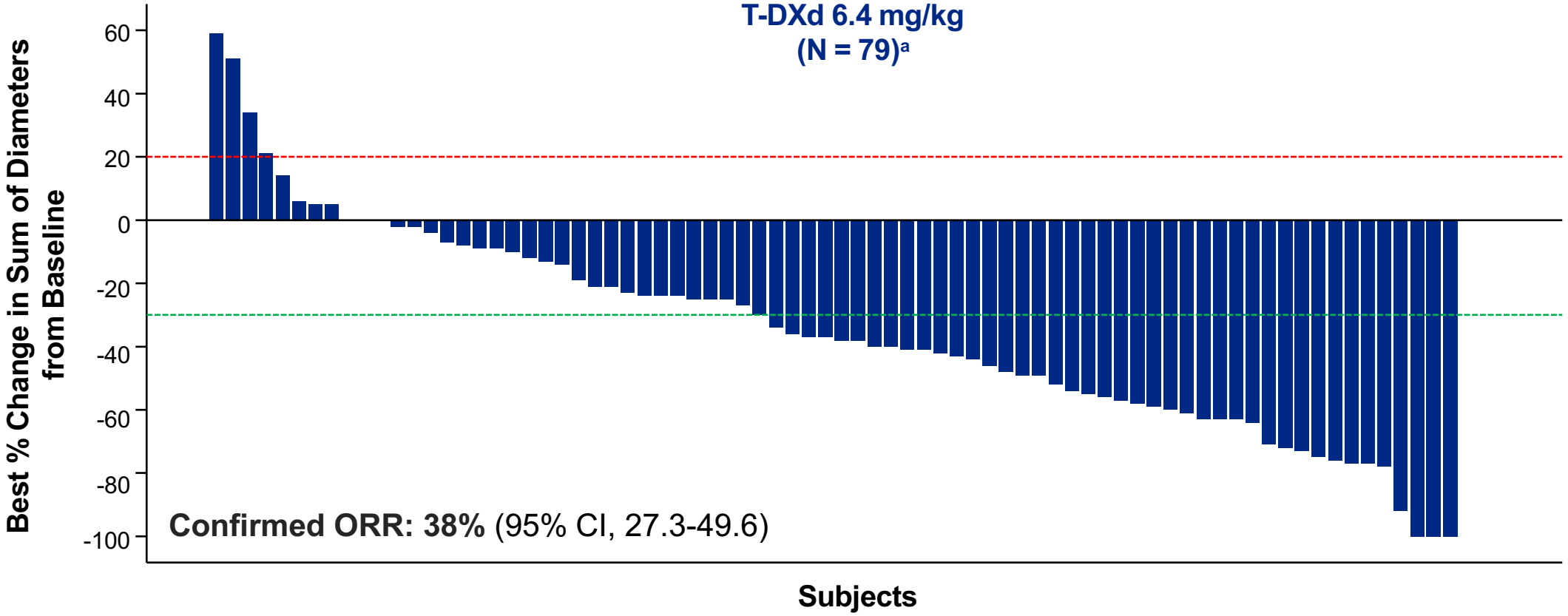
Efficacy Endpoints

	Patients (N = 79)
Confirmed ORR[a], n (%)	**30 (38)** (95% CI, 27.3-49.6)
Confirmed best overall response, n (%) CR PR SD PD Not evaluable	 **3 (3.8)** **27 (34.2)** **34 (43.0)** **13 (16.5)** **2 (2.5)**
Median DOR,[b] months	8.1 (95% CI, 4.1-NE)
Confirmed DCR[c], n (%)	64 (81.0) (95% CI, 70.6-89.0)
Median TTR, months	1.4 (95% CI, 1.4-2.6)
Median PFS,[d] months	5.5 (95% CI, 4.2-7.3)
Median follow up, months	5.7 (range, 0.7-15.2)

Cutoff date: April 9, 2021.
[a]Primary endpoint. [b]Secondary endpoint analysis based on responders (n=30); 21 patients were censored (reasons: initiating new anticancer therapy, adequate tumor assessment no longer available, and ongoing without occurrence of progressive disease or death). [c]Exploratory endpoint. [d]Secondary endpoint analysis in the full analysis set based on 42 events (36 PD, 6 deaths).
BOR, best overall response; CR, complete response; DCR, disease control rate; mo, months; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

Courtesy of Zev Wainberg, MD, MSc

Best Percentage Change of Tumor Size from Baseline



[a]3 patients were missing baseline or post-baseline target lesion assessment.
Red line at 20% indicates progressive disease; green line at -30% indicates partial response.
Analysis conducted in the full analysis set.

Courtesy of Zev Wainberg, MD, MSc

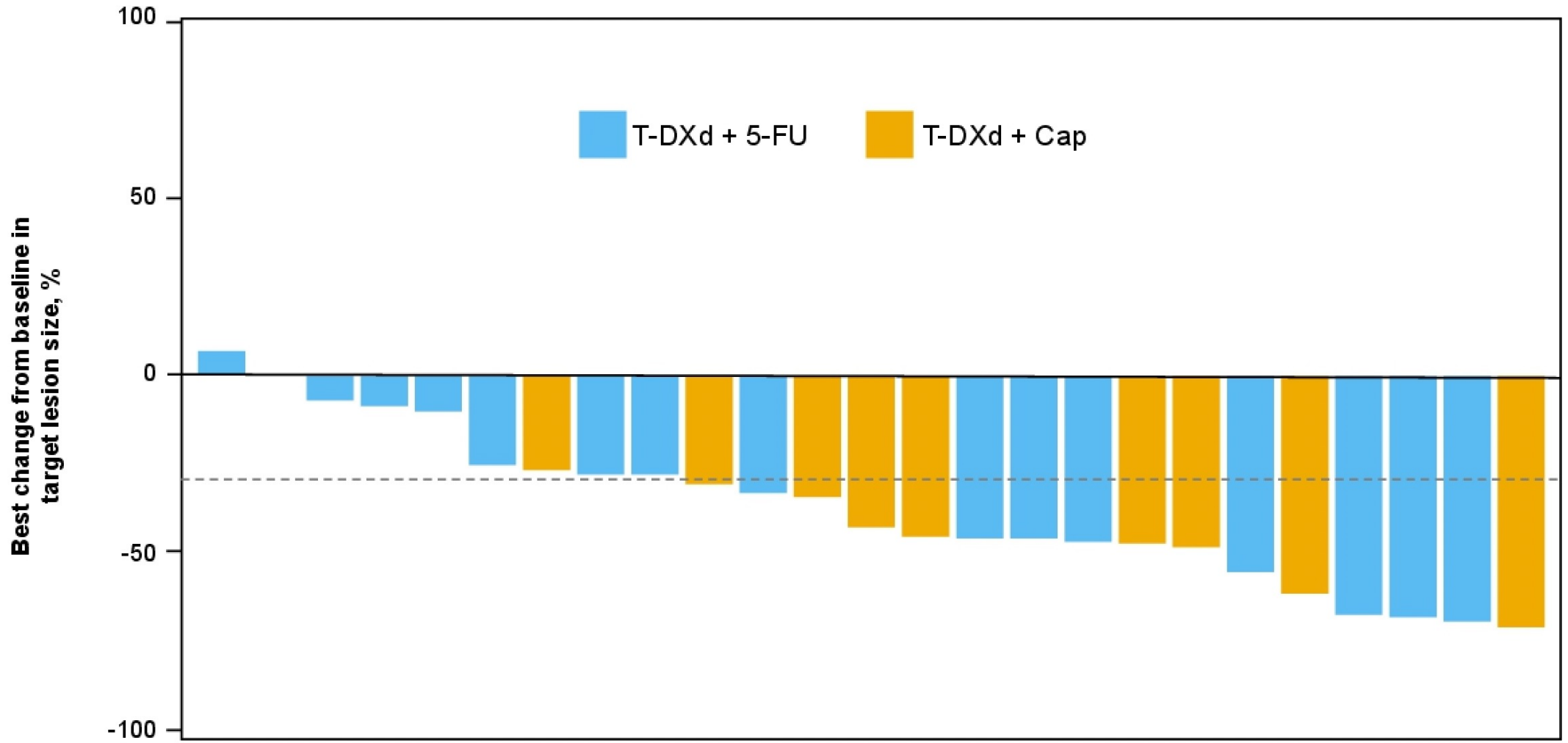
Poster 295

Dose-escalation and dose-expansion study of trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients with advanced/metastatic HER2-positive gastric cancer/gastroesophageal junction adenocarcinoma: DESTINY-Gastric03

Yelena Y. Janjigian, MD[1]; Do-Youn Oh, MD, PhD[2]; Sun Young Rha, MD, PhD[3]; Keun-Wook Lee, MD, PhD[4]; Neeltje Steeghs, MD, PhD[5]; Yee Chao, MD, PhD[6]; Maria Di Bartolomeo, MD[7]; Marc Díez García, MD[8]; Nadia Haj Mohammad, MD, PhD[9]; Alexander Stein, MD[10]; William McAdoo, PharmD[11]; Megan Winter, MSc[12]; Elizabeth Croydon, MD[12]; Jeeyun Lee, MD[13]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Seoul National University Hospital, Seoul National University College of Medicine, Jongno-gu, Seoul, Korea; [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Korea; [4]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Bundang-gu, Seongnam-si, Gyeonggi-do, Korea; [5]Netherlands Cancer Institute, Amsterdam, the Netherlands; [6]Taipei Veterans General Hospital, National Yang Ming Chiao Tung University, Beitou District, Taipei, Taiwan; [7]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [8]Vall d'Hebrón University Hospital-VHIO, Barcelona, Spain; [9]University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; [10]Hematology-Oncology Practice Eppendorf, University Cancer Center Hamburg, Hamburg, Germany; [11]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD, USA; [12]AstraZeneca Pharmaceuticals LP, Cambridge, UK; [13]Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam-gu, Seoul, Korea

Figure 2. Best percentage change in target lesion size from baseline



Janjigian YY et al. Gastrointestinal Cancers Symposium 2022;Abstract 295.

Ongoing Trastuzumab-Deruxtecan Study

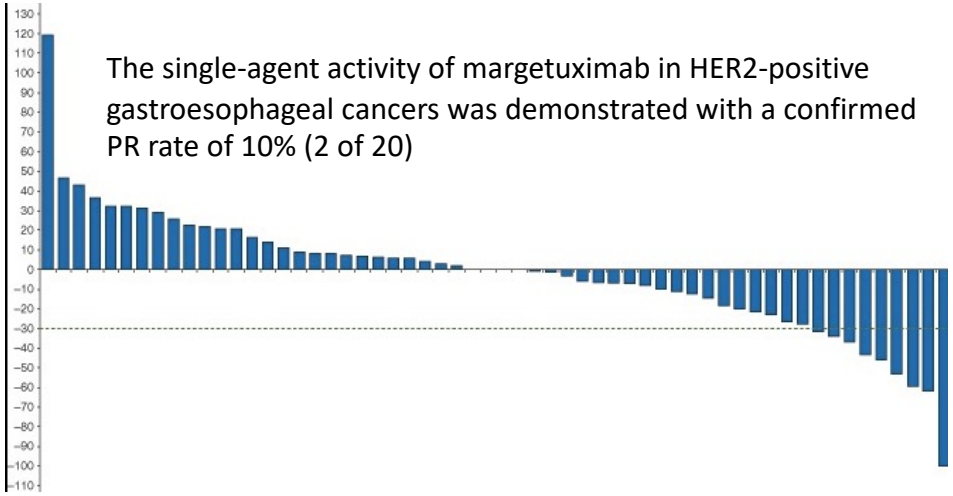
- DESTINY-Gastric04 phase III (N=490) study of 2nd-line DS8201a pending opening. [NCT04704934]

~10% pneumonitis risk → may be challenging to move this to earlier lines

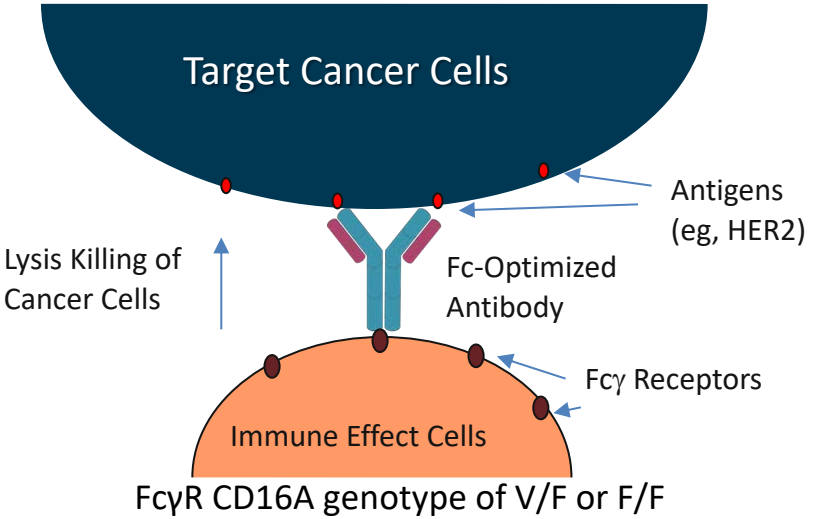
Courtesy of David H Ilson, MD, PhD

Margetuximab

- **Margetuximab had enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) compared with trastuzumab**



The single-agent activity of margetuximab in HER2-positive gastroesophageal cancers was demonstrated with a confirmed PR rate of 10% (2 of 20)



Phase 2/3 MAHOGANY: Combination margetuximab, INCMGA00012, MGD013, and chemotherapy in *HER2*+ gastric/GEJ cancer

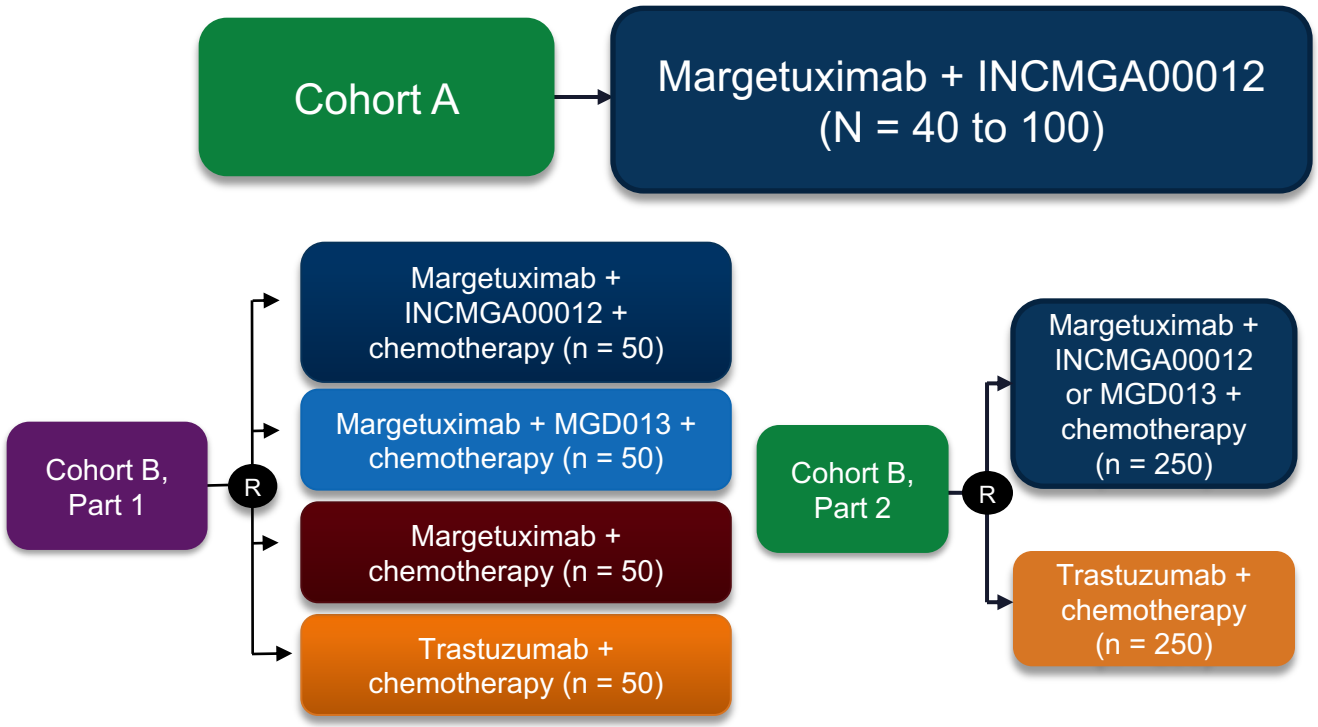
1. Bang YJ et al. Ann Oncol. 2017;
2. https://clinicaltrials.gov/ct2/show/NCT04082364

Courtesy of David H Ilson, MD, PhD

MAHOGANY Phase 2/3 Trial in HER2-Positive Gastric/GEJ Cancer[1]

Inclusion Criteria

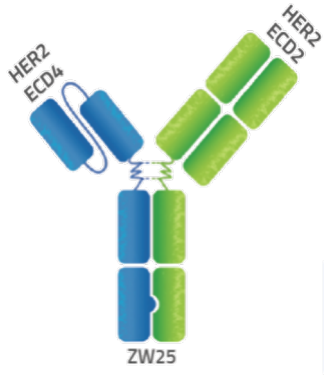
- Previously untreated advanced disease
  - Cohort A: HER2-positive (by IHC 3+) and PD-L1-positive (CPS ≥ 1%)
  - Cohort B: HER2-positive (by IHC 3+ or IHC 2+/FISH+)
- ECOG 0 or 1



- Primary outcomes: AE incidence (Cohort A), ORR (Cohorts A and B), OS (Cohort B)

Courtesy of David H Ilson, MD, PhD

Zanidatamab (ZW25), a HER2-Targeted Bispecific mAb



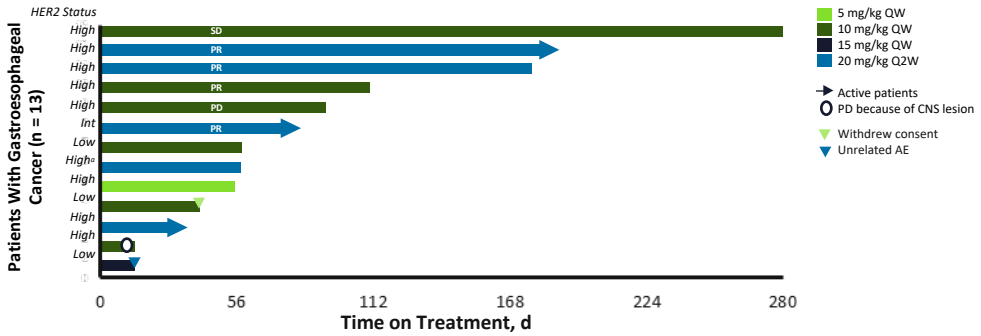
Biparatopic binding targets two distinct HER epitopes

- Same domains as trastuzumab (ECD4) and pertuzumab (ECD2)

Unique mechanisms of action designed to expand activity

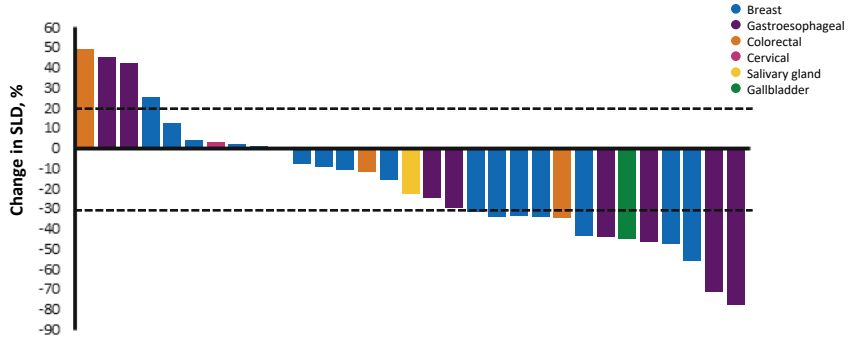
- Extended chain formation and dense HER2 receptor clustering
- Enhanced HER2 internalization and downregulation
- Increased tumor cell binding density and potent effector-mediated cytotoxicity
- Enhanced blockade of ligand-dependent and ligand-independent tumor growth

Gastroesophageal Cancer: Time on Treatment



Change in Target Lesions Across Cancer Types

Decrease in target lesions in majority of patients with measurable disease



Beeram M, et al. EORTC-NCI-AACR 2018;
Meric-Bernstam F, et al. ASCO 2018

Courtesy of David H Ilson, MD, PhD

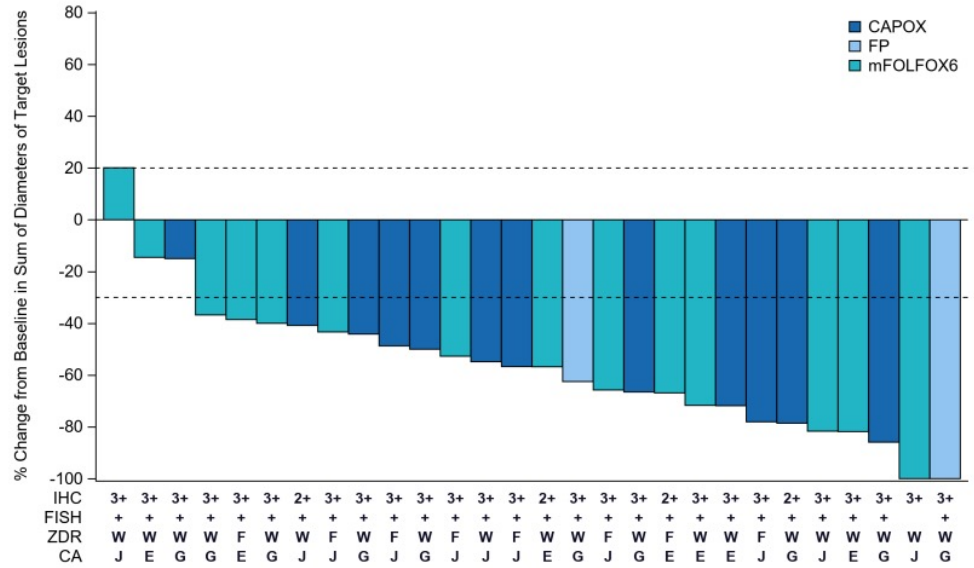
Zanidatamab (GI Symposium 2021 Abs 299): HER2 Bispecific Antibody

	Zanidatamab Single Agent (N = 36)	Zanidatamab + Paclitaxel or Capecitabine (N = 26)
Median prior systemic therapies, n (range)	3 (1–7)*	2 (1–7)
Patients with prior HER2 therapies, n (%)	34 (94)	24 (92)
Grade 3+**	4 (11)	4 (15)
Response evaluable, n	34	20
Objective response, n (%)	13 (38)	12# (60)
Disease control rate, n (%)	21 (62)	17 (85)
Median duration of response, months (95% CI)‡	6.0 (1.9, 9.2)	8.9 (3.5, Not estimable)

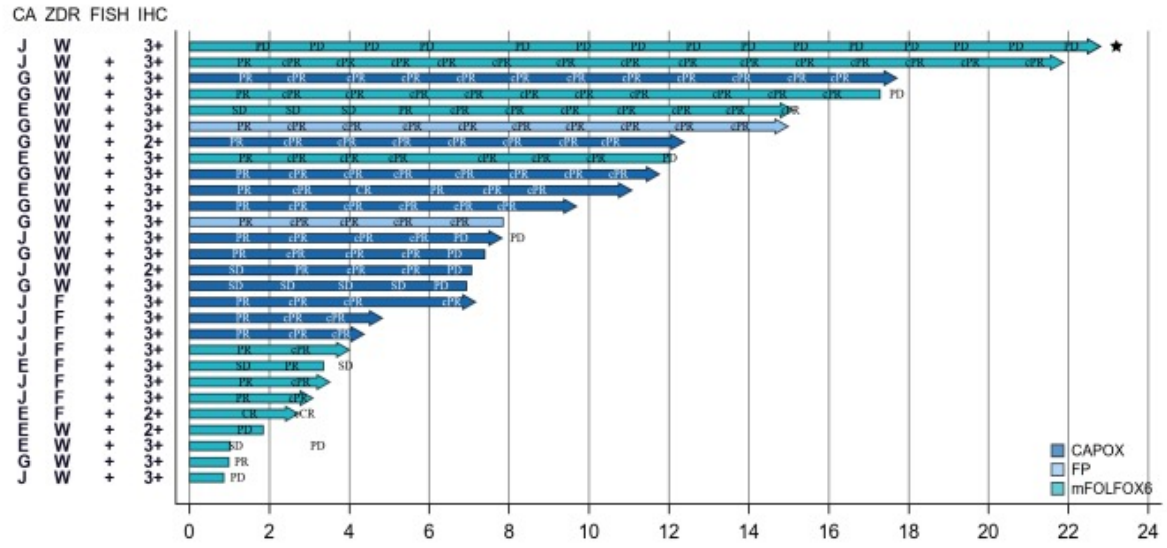
Meric Bernstam JCO 39:164; 2021

Courtesy of David H Ilson, MD, PhD

Zanidatamab+Chemo First Line



ORR 75% (21/28)
DCR 89% (25/28)



mDOR 16.4

Ku et al. Phase 2 Study of Zanidatamab + Chemotherapy in First-line HER2-expressing Gastroesophageal Adenocarcnioma. ESMO 2021

Courtesy of David H Ilson, MD, PhD

Agenda

Introduction

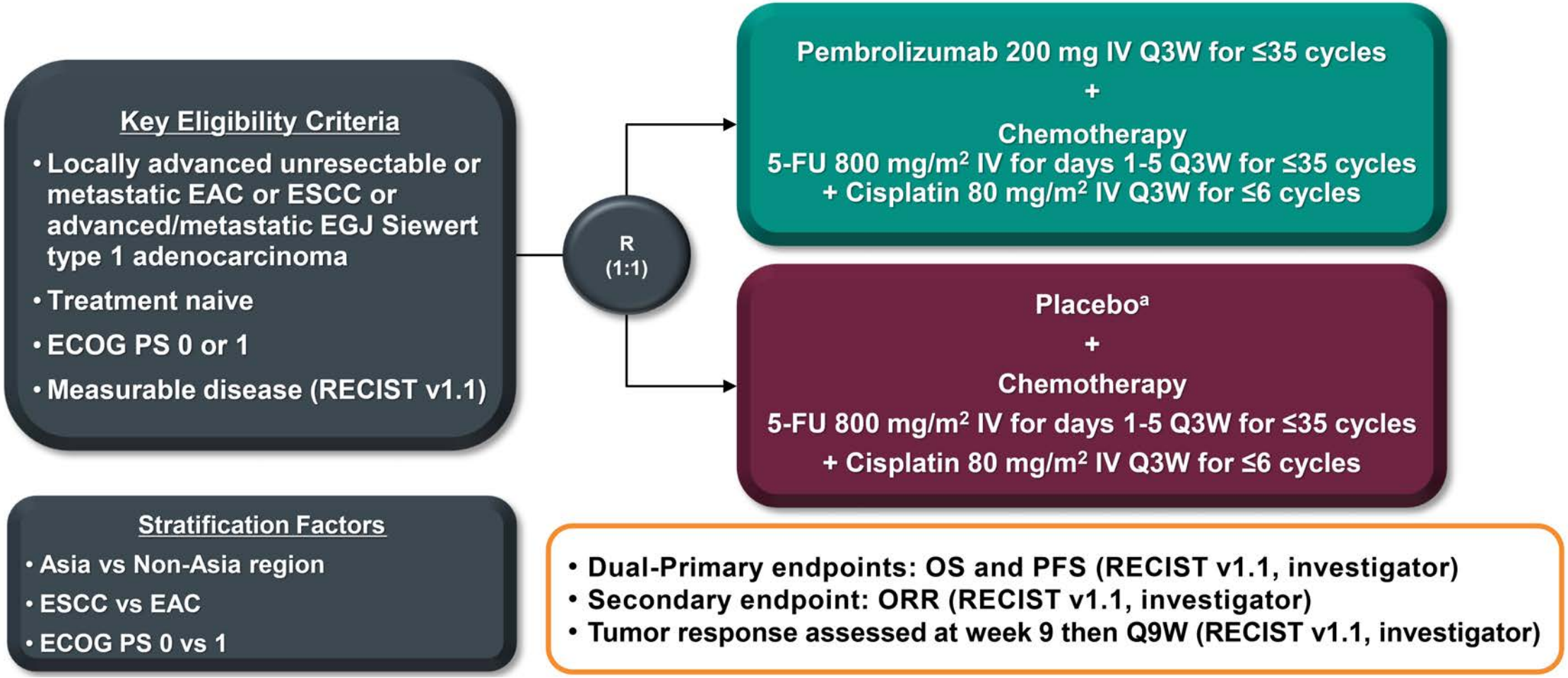
Module 1: Localized Disease

Module 2: Metastatic Disease

- HER2-Positive Disease
- Squamous Cell Carcinoma
  - KEYNOTE-590, CheckMate 648, ORIENT-15, JUPITER-06
- Gastric/GEJ Adenocarcinoma

Module 3: Novel Targets

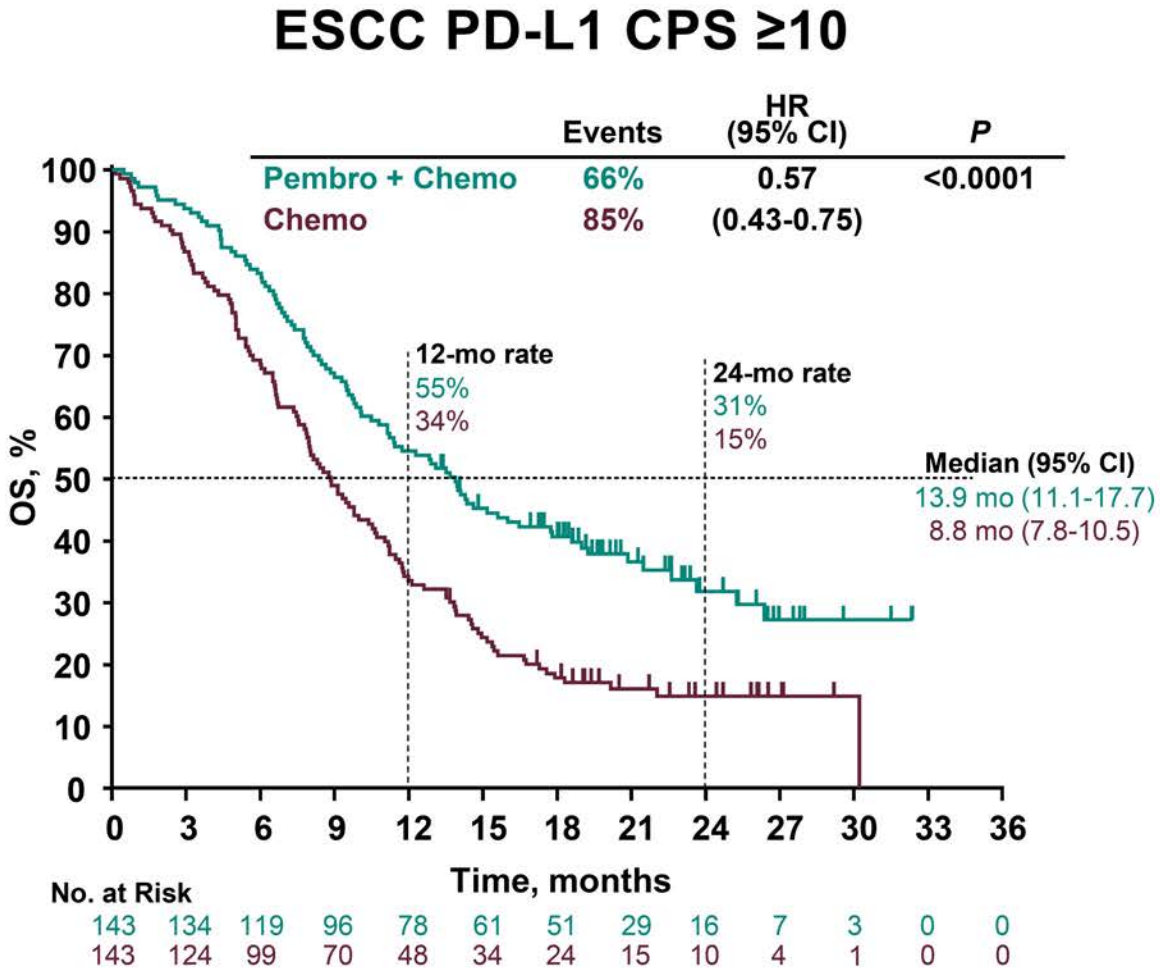
First-Line Metastatic Esophageal Cancer – KEYNOTE 590

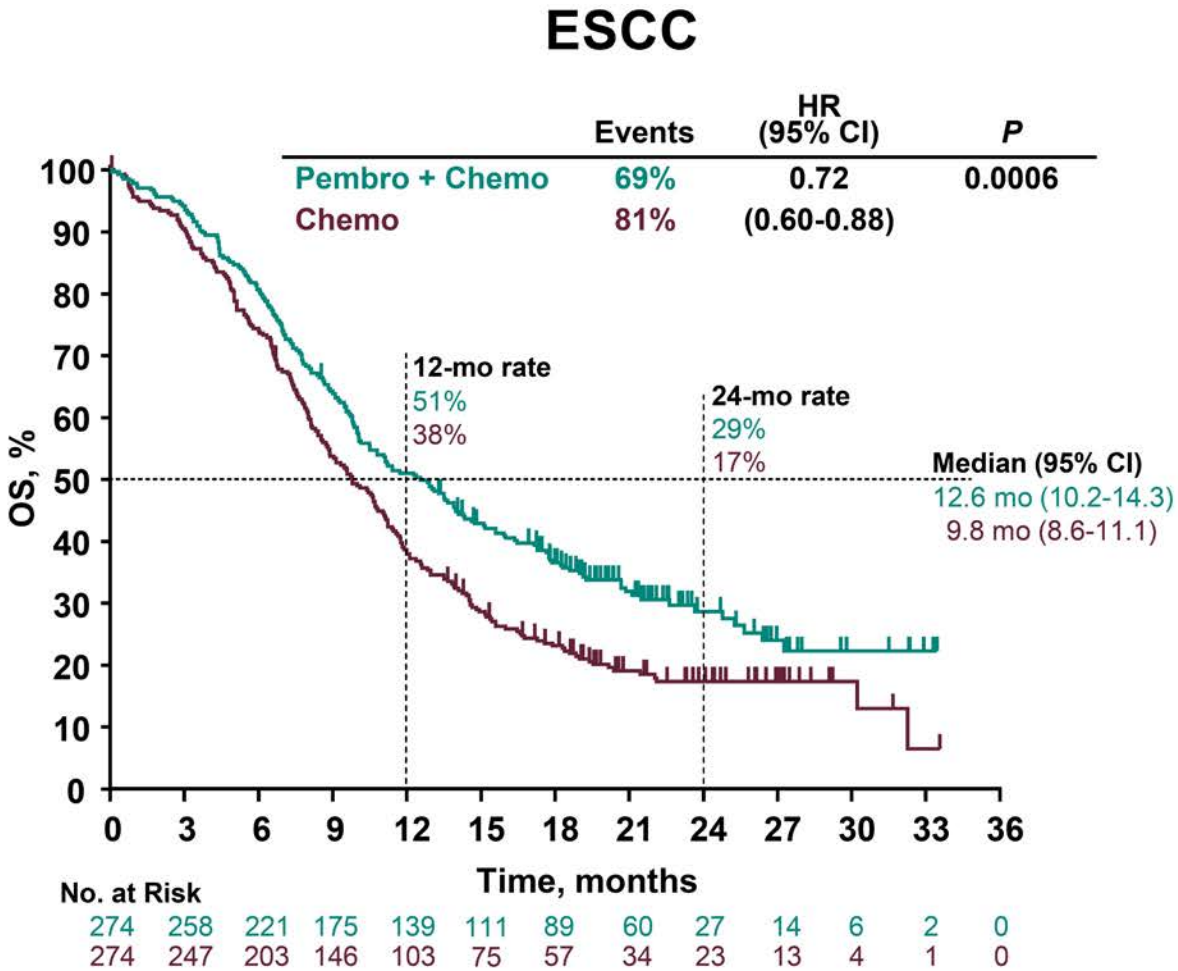


Courtesy of Zev Wainberg, MD, MSc

Kato K, et al. ESMO 2020. Abstract LBA8

KEYNOTE 590 – Overall Survival in SCC Patients





Courtesy of Zev Wainberg, MD, MSc

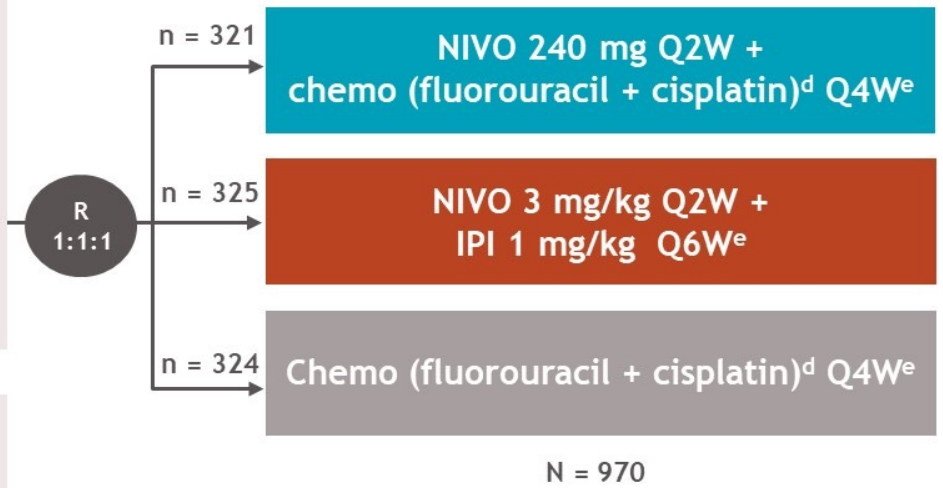
Sun et al, Lancet 2021

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]

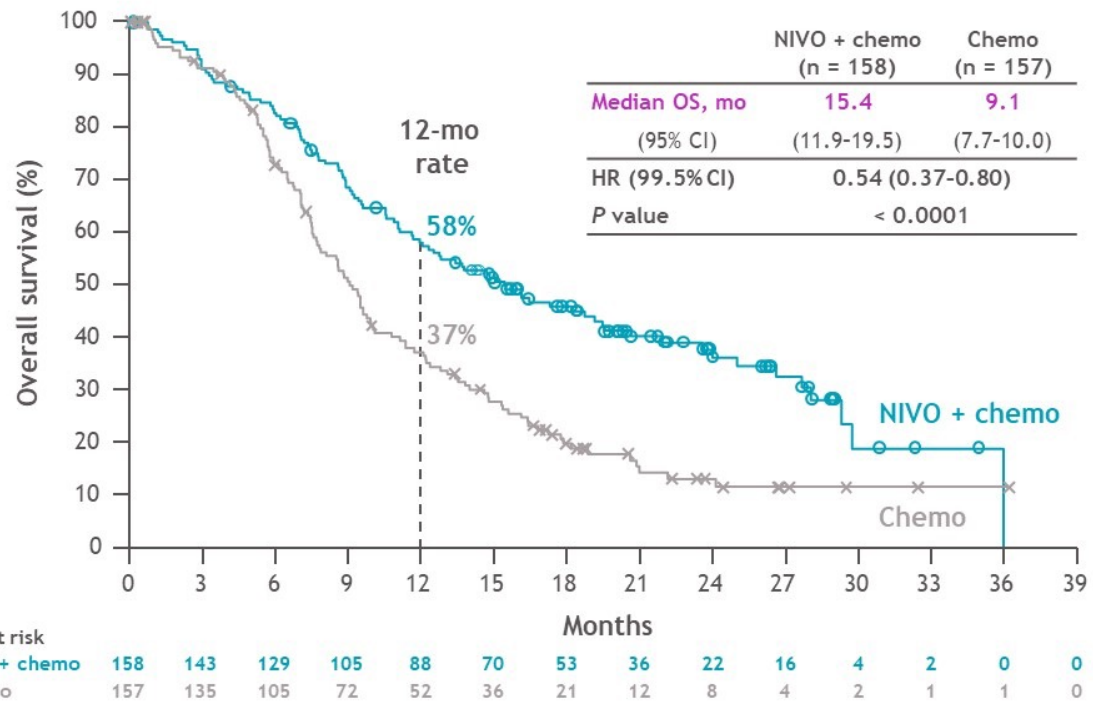
[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until 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.

Courtesy of Zev Wainberg, MD, MSc

Chau I et al, PROC ASCO 2021

Overall survival: NIVO + chemo vs chemo

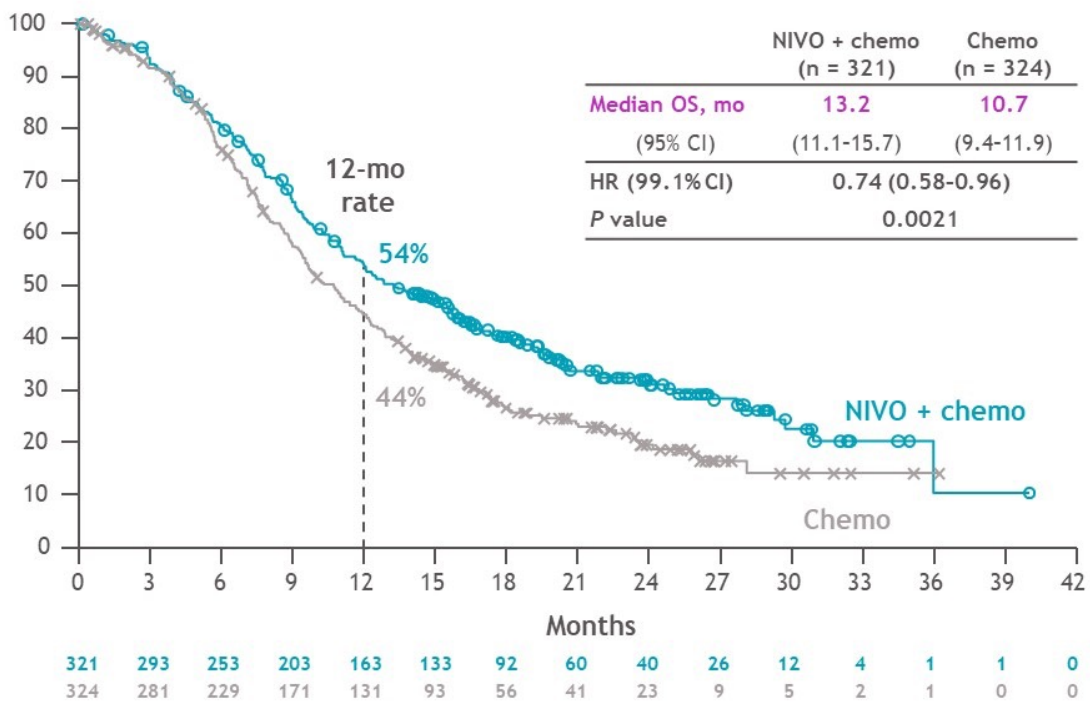
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

No. at risk														
NIVO + chemo	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

- 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

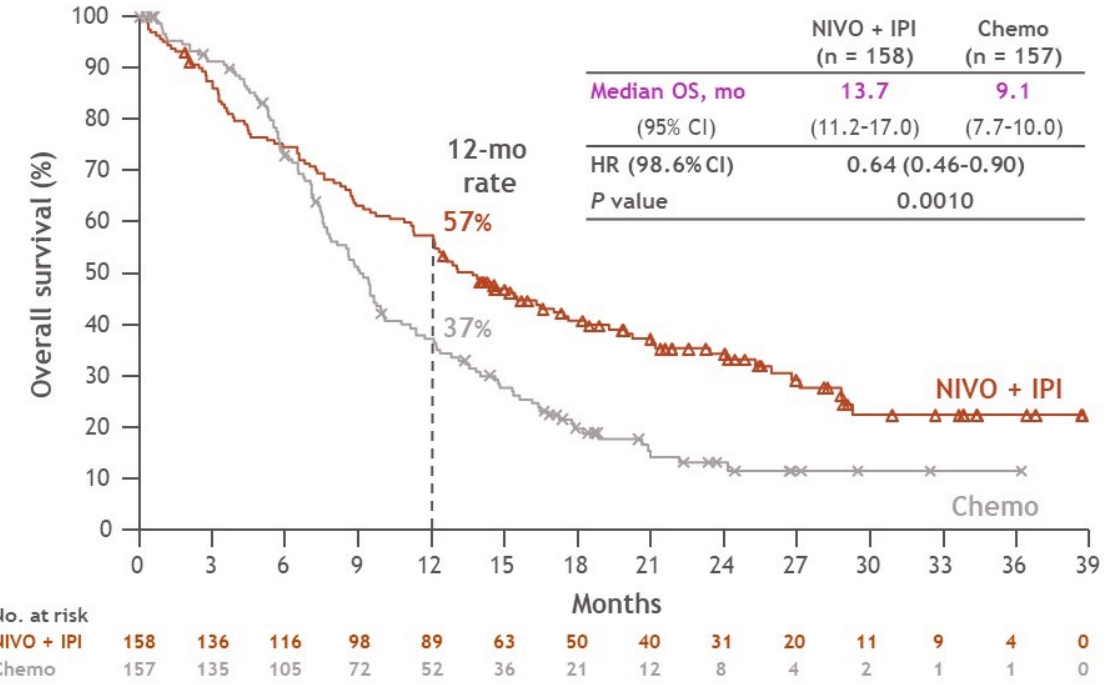
[a]Minimum follow-up 12.9 months.

Courtesy of Zev Wainberg, MD, MSc

Chau I et al Proc. ASCO 2021

Overall survival: NIVO + IPI vs chemo

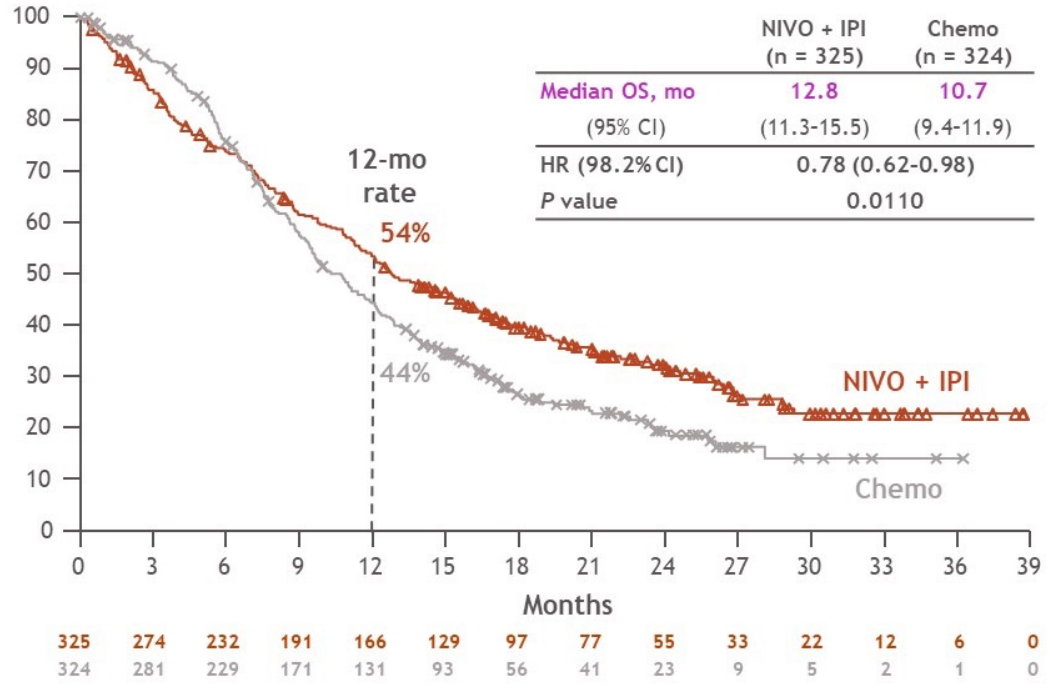
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + IPI (n = 158)	Chemo (n = 157)
Median OS, mo	13.7	9.1
(95% CI)	(11.2-17.0)	(7.7-10.0)
HR (98.6% CI)	0.64 (0.46-0.90)	
P value	0.0010	

No. at risk														
NIVO + IPI	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + IPI (n = 325)	Chemo (n = 324)
Median OS, mo	12.8	10.7
(95% CI)	(11.3-15.5)	(9.4-11.9)
HR (98.2% CI)	0.78 (0.62-0.98)	
P value	0.0110	

NIVO + IPI	325	274	232	191	166	129	97	77	55	33	22	12	6	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0

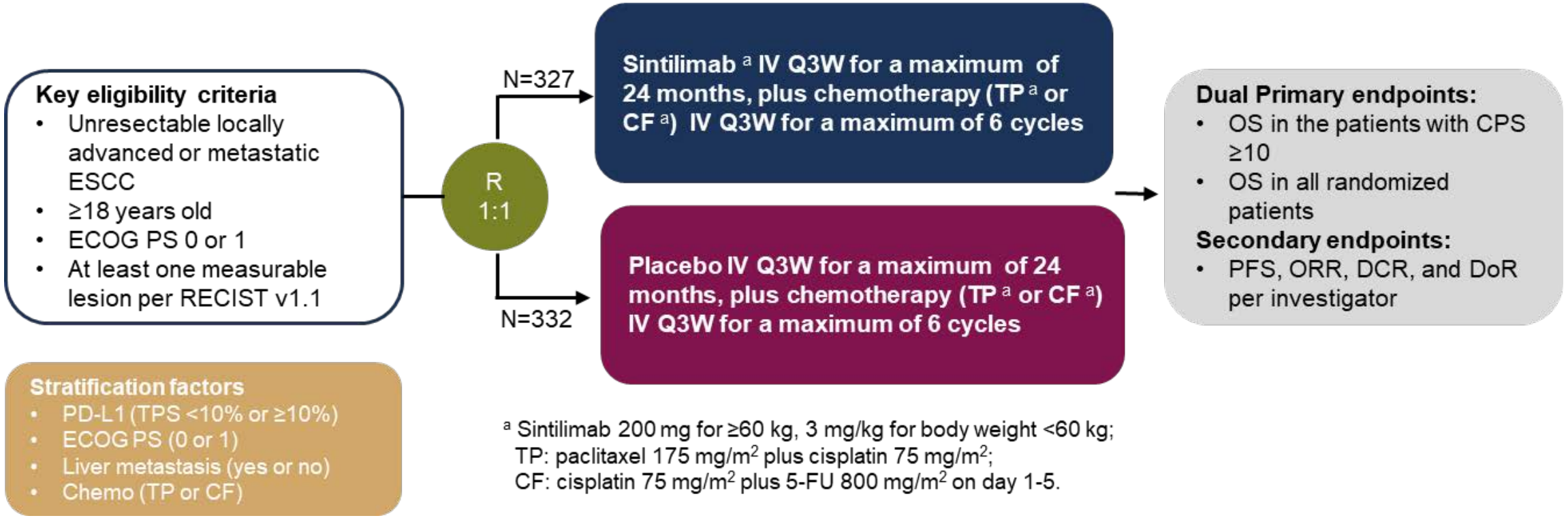
- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 4.6-month improvement in median OS
  - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

[a]Minimum follow-up 12.9 months.

Courtesy of Zev Wainberg, MD, MSc

Chau I et al Proc. ASCO 2021

ORIENT-15 Study design (NCT03748134)



[a] Sintilimab 200 mg for ≥60 kg, 3 mg/kg for body weight <60 kg;
TP: paclitaxel 175 mg/m^2 plus cisplatin 75 mg/m^2;
CF: cisplatin 75 mg/m^2 plus 5-FU 800 mg/m^2 on day 1-5.

- ORIENT-15 is a multicenter, randomized double-blind, phase 3 trial to evaluate the efficacy and safety of Sinti+Chemo vs. Chemo as the first-line treatment of advanced or metastatic ESCC
- The OS in the overall population is evaluated with an α of 0.0125 (one-sided), and OS in the PD-L1 CPS ≥10 subgroup is also evaluated with an α of 0.0125 (one-sided) to strictly control the overall type I error for the hypothesis test of OS in the two population.
- This is the interim analysis with data cut-off date on April 9, 2021.
- Median follow-up for OS was 16.0 months（IQR 12.3-19.4）in the Sinti+Chemo group and 16.9 months (IQR 11.8-20.2) in the Chemo group.

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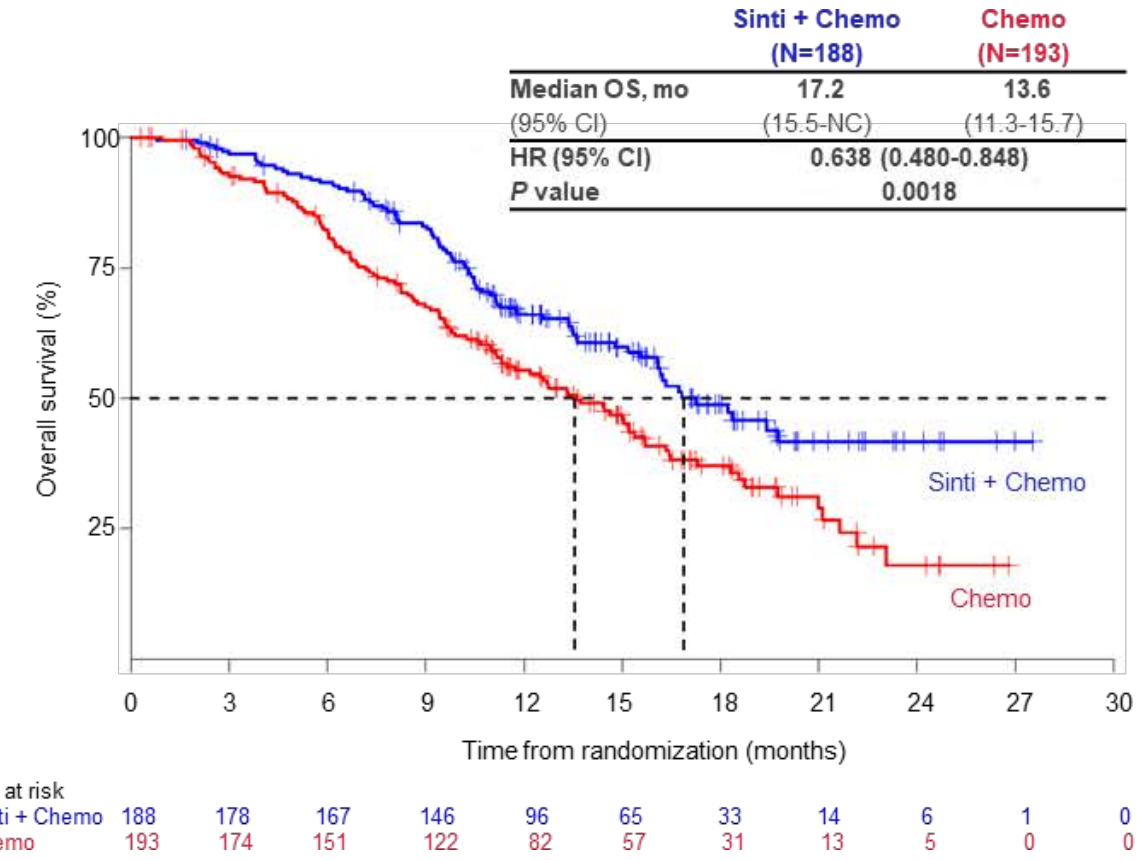
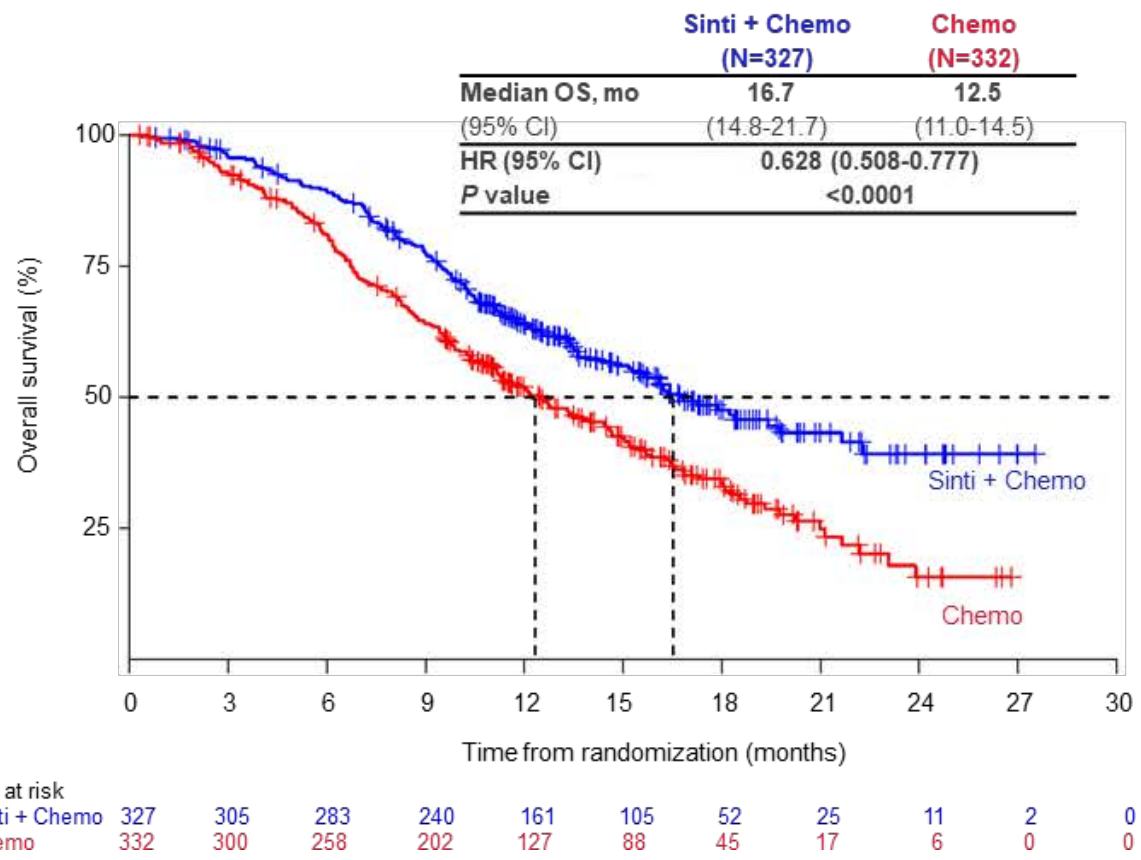
Courtesy of Zev Wainberg, MD, MSc

ORIENT-15: Overall survival

PD-L1 CPS ≥10



All patients



- Superior OS benefit with Sinti + Chemo versus Chemo in the patients with PD-L1 CPS≥10 and all randomized patients.

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Courtesy of Zev Wainberg, MD, MSc

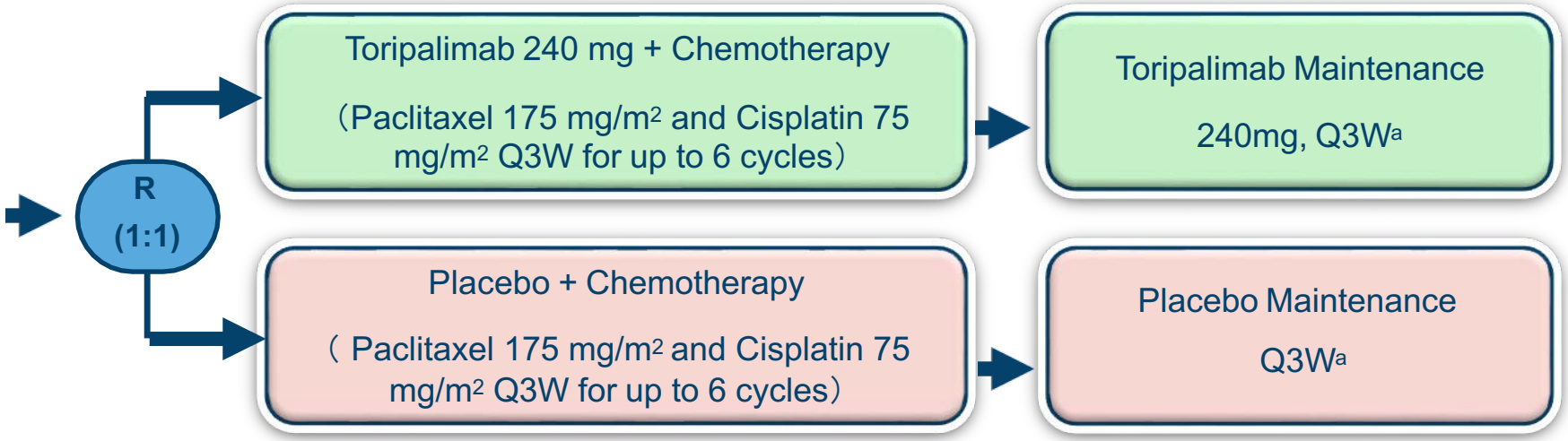
JUPITER-06: Study Design

Key Eligibility Criteria

- Histologically or cytologically confirmed advanced or metastatic ESCC
- Treatment-naïve for metastatic disease
- ECOG PS of 0 or 1
- Measurable disease per RECIST v1.1

Stratification Factors

- Prior Radiation (yes vs no)
- ECOG PS 0 vs 1



- Co-Primary endpoints: PFS by BICR per RECIST v1.1 and OS
- Secondary endpoints: PFS by the Investigator, ORR , DoR , DCR, and 1-year and 2-year PFS & OS rates, safety, and HRQoL

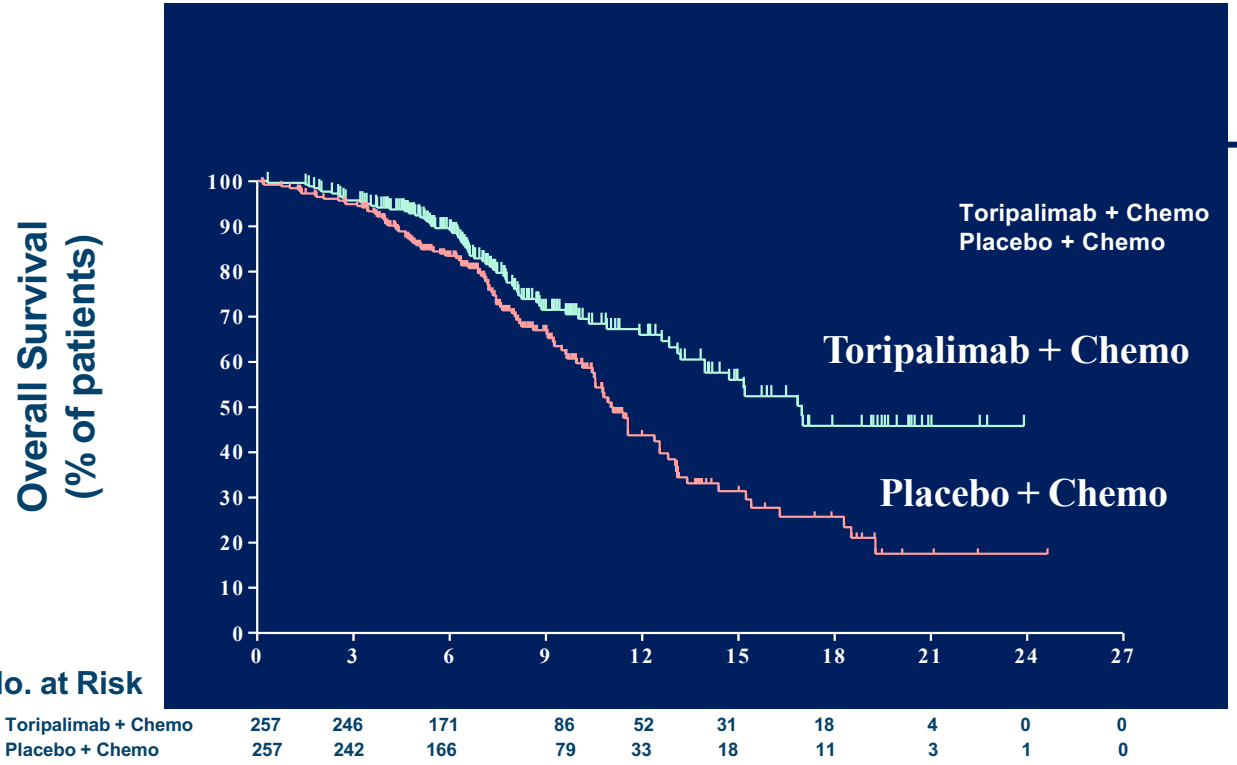
[a] Until progressive disease, intolerable toxicity, withdrawal of consent or investigator's judgement or a maximum treatment of 2 years.

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors; ECOG PS, Eastern Cooperative Oncology Group performance status score; BICR, blind independent central review ; IV, intravenously; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; DoR, duration of response; HRQoL, health-related quality of life.

Courtesy of Zev Wainberg, MD, MSc

Overall Survival

Interim OS Analysis Data cut-off Date: Mar 22, 2021



No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI) *mo*	1-Yr Overall Survival Rate % (95% CI)	2-Yr Overall Survival Rate % (95% CI)
70/257	**17.0 (14.0, NE)**	**66.0 (57.5, 73.2)**	**NE (NE, NE)**
103/257	11.0 (10.4, 12.6)	43.7 (34.4, 52.6)	17.5 (8.7, 28.9)

Stratified HR for death,

0.58 (95% CI 0.425, 0.783);
P=0.00036

PD-L1 expression subgroups:

CPS ≥ 1: 15.2 vs. 10.9 months, HR=0.61 (95%CI 0.435, 0.870)

CPS < 1: NE vs. 11.6 months, HR=0.61 (95%CI 0.297, 1.247)

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Presented by Feng Wang, MD, PhD

Courtesy of Zev Wainberg, MD, MSc

SCC-Conclusions

- Clinical Implications: Pembro/Nivo:
  - Role of PD1 plus chemo proven with Pembro (Keynote 590) and Nivo (CM 648)
  - Does PDL1 status matter in SCC?
  - What about Ipi/Nivo? Who should NOT get chemotherapy?
- Sintilimab/Toripalimab:
  - Both met primary endpoint for OS
  - Both studies exclusively in China with Cisplatin/Paclitaxel chemo

Courtesy of Zev Wainberg, MD, MSc

Agenda

Introduction

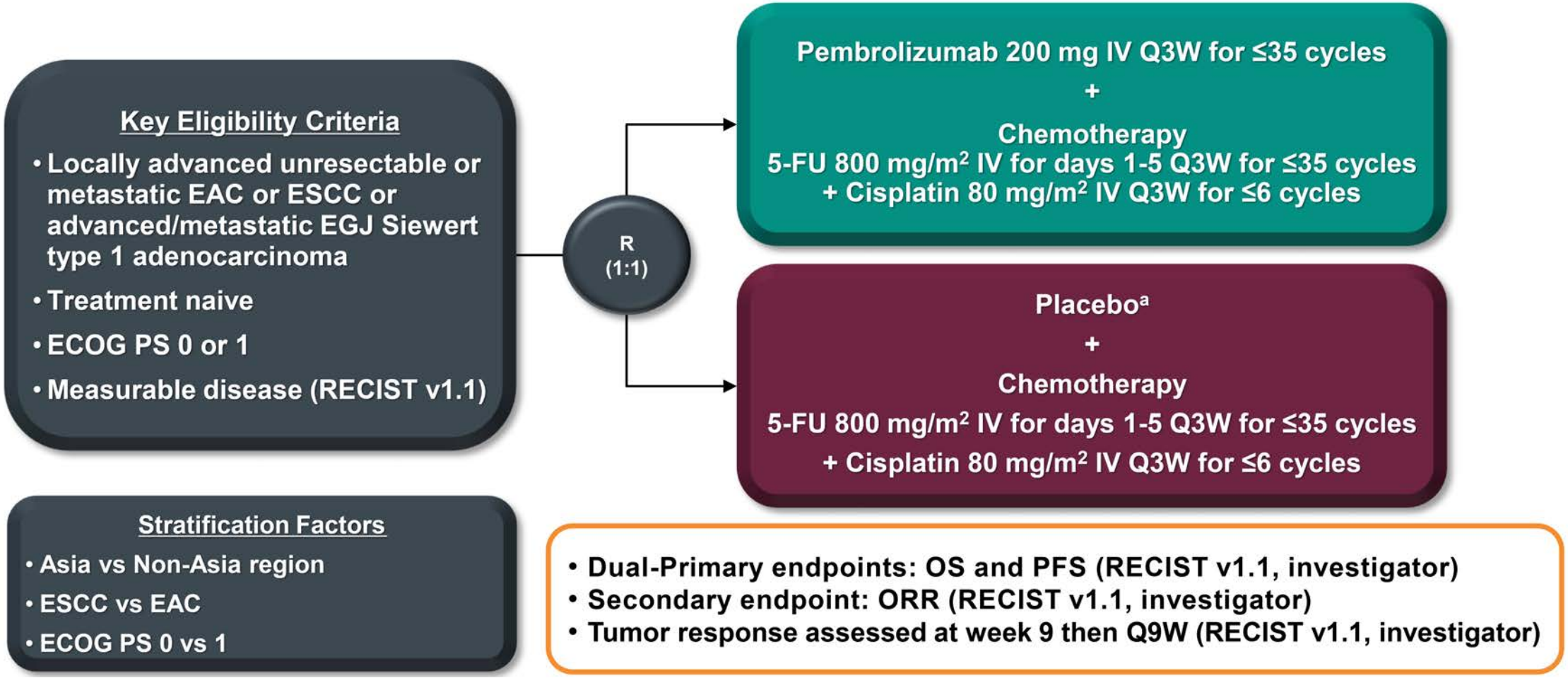
Module 1: Localized Disease

Module 2: Metastatic Disease

- HER2-Positive Disease
- Squamous Cell Carcinoma
- Gastric/GEJ Adenocarcinoma
  - KEYNOTE-590, CheckMate 649, ORIENT-16

Module 3: Novel Targets

First-Line Metastatic Esophageal Cancer – KEYNOTE-590

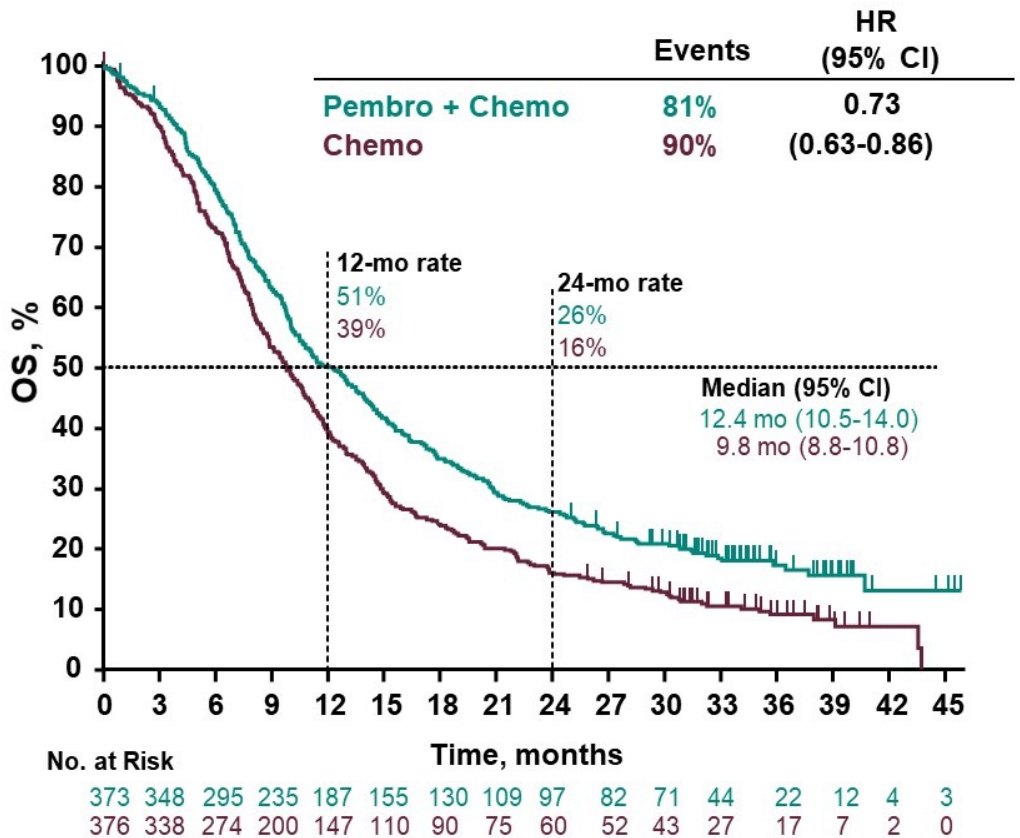


Courtesy of Zev Wainberg, MD, MSc

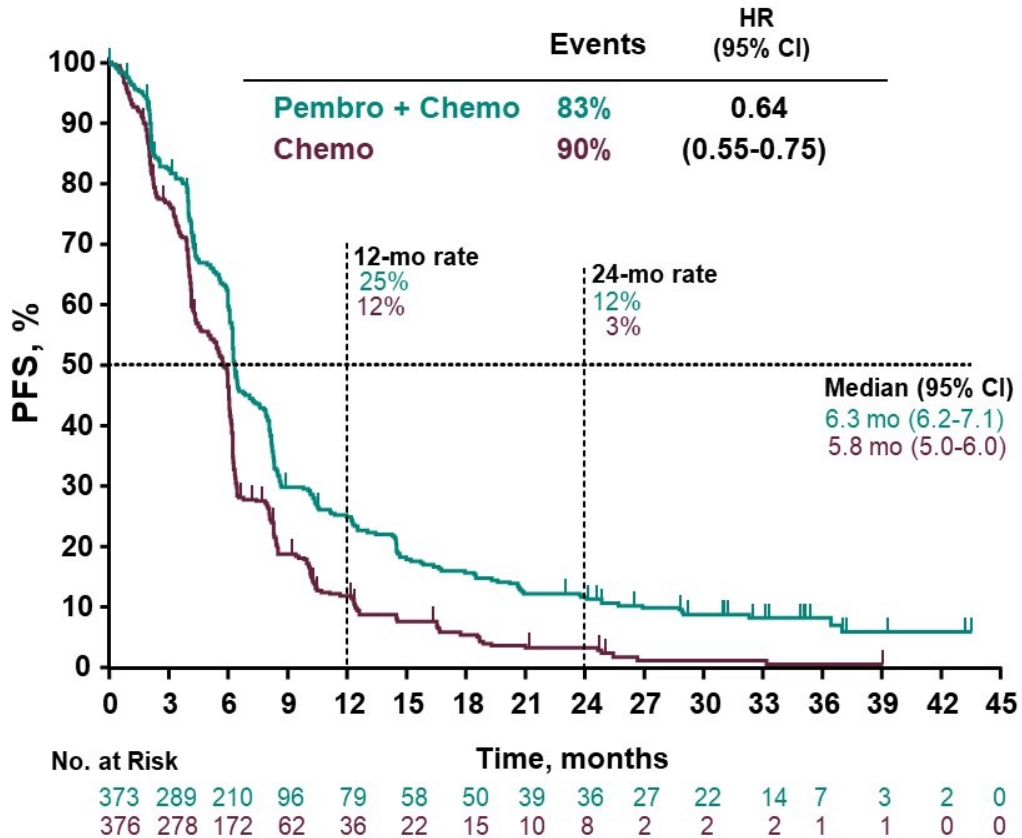
Kato K, et al. ESMO 2020. Abstract LBA8

Survival: All Patients

OS



PFS



Data cut-off: July 9, 2021.

Metges JP et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

CheckMate 649 Study Design

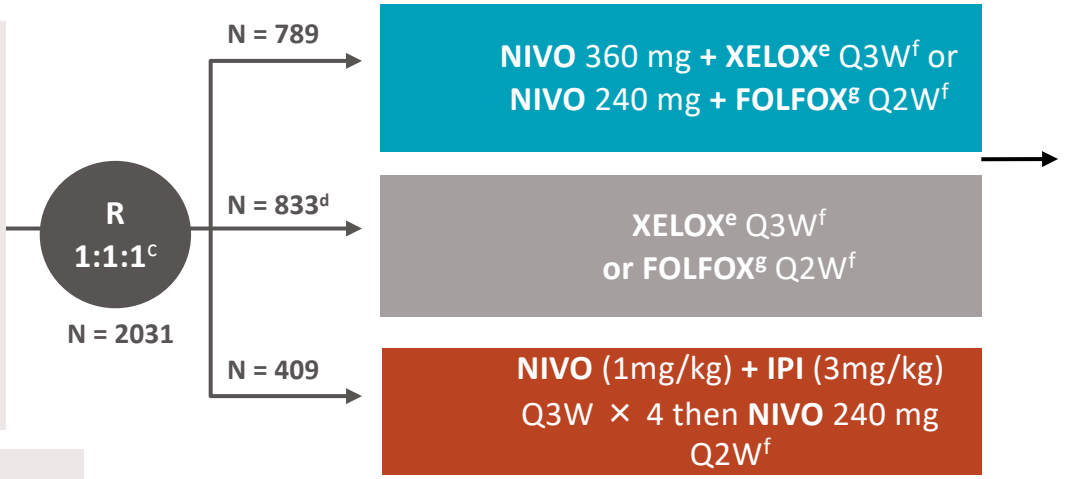
- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria

- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

Stratification factors

- Tumor cell PD-L1 expression (≥ 1% vs. < 1%[b])
- Region (Asia vs. US/Canada vs. ROW)
- ECOG PS (0 vs. 1)
- Chemo (XELOX vs. FOLFOX)



Dual primary endpoints

NIVO + chemo vs. chemo

- **OS** and **PFS**[h] (PD-L1 CPS ≥ 5)

Hierarchically tested secondary efficacy endpoints

NIVO + chemo vs. chemo

- **OS** (PD-L1 CPS ≥ 1, all randomized)

NIVO + IPI vs. chemo

- **OS** (PD-L1 CPS ≥ 5, all randomized)

PD-L1 CPS ≥ 5:

- **955/1581 (60%) patients in the NIVO + chemo vs chemo comparison**
- **473/813 (58%) patients in the NIVO+IPI vs chemo comparison**

- At data cutoff (May 27, 2021), the minimum follow-up[i] was 24.0 months in the NIVO + chemo arm and 35.7 months in the NIVO + IPI arm

[a]ClinicalTrials.gov number, NCT02872116. [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako). [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO + IPI arm was closed. Upon DMC recommendation (31-May-2018), enrollment to the NIVO + IPI arm was stopped early due to an observed increase in rates of early death and toxicity. Patients already in the NIVO+IPI arm were allowed to remain on study based on the DMC recommendation. [d]Includes patients that were concurrently randomized to receive chemo versus NIVO + IPI (October 2016–June 2018) and NIVO + chemo (June 2018-Apr 2019). [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14). [f]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years.
[g]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2). [h]BICR assessed. [i]Time from concurrent randomization of the last patient to data cutoff

1. Janjigian YY et al. *Lancet*. 2021;398:27-40. 2. Janjigian YY et al. ESMO 2021; Abstract LBA-7

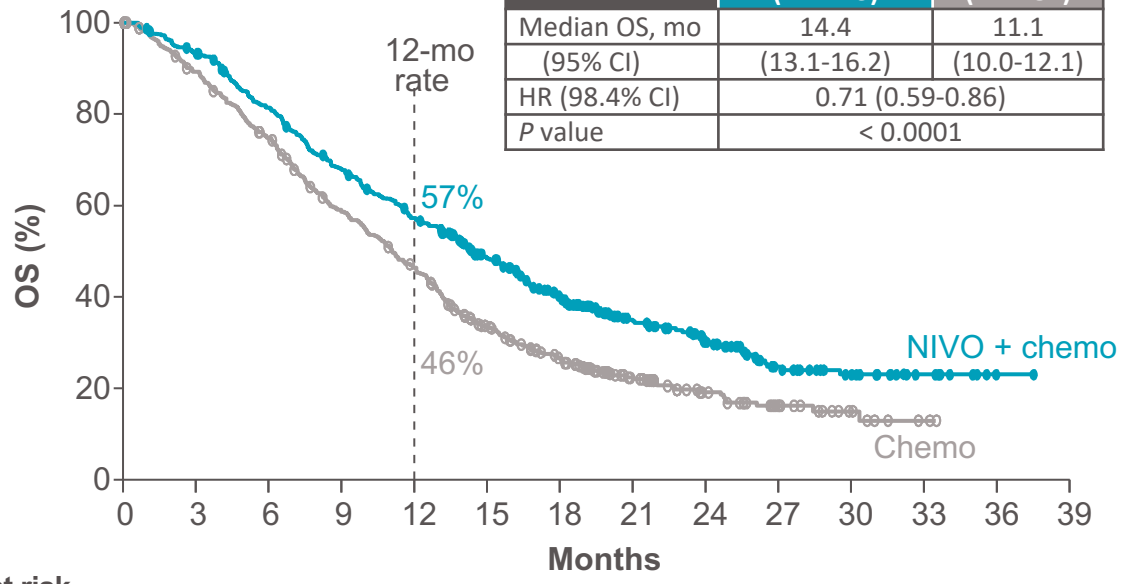
CheckMate 649: Global Phase 3 Registration Trial

NIVO + Chemo Improved Survival

FDA approved April 2021[1]

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	

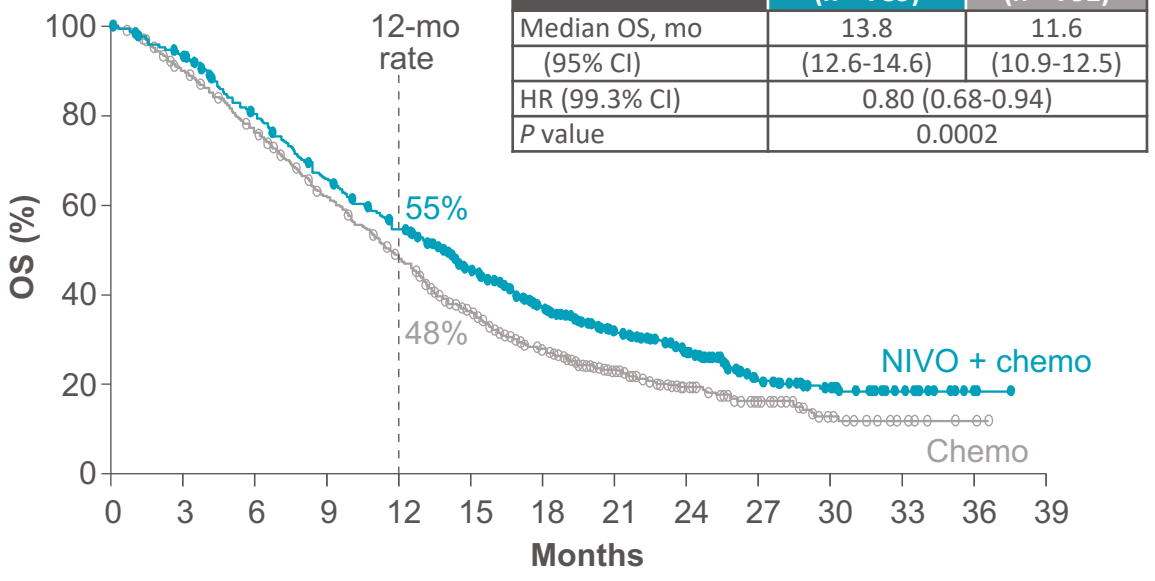


No. at risk

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

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	



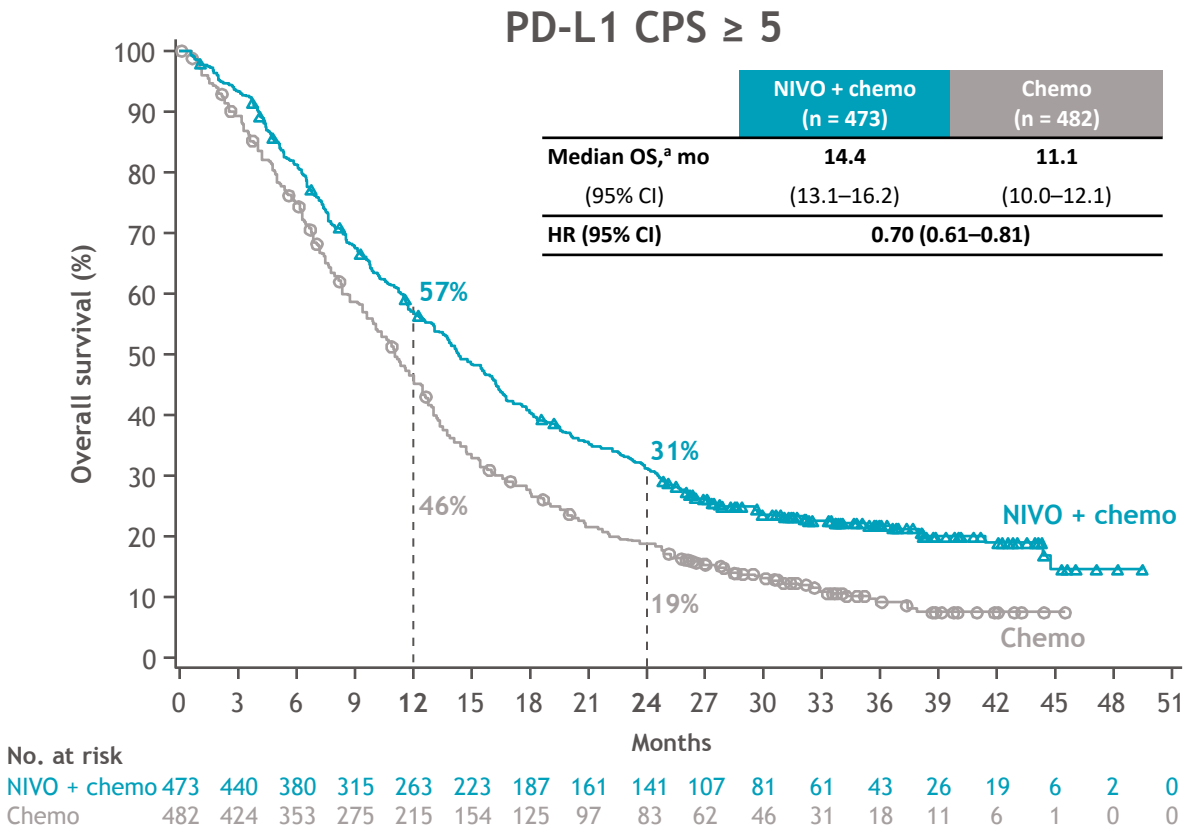
NIVO + chemo	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemo	792	697	586	469	359	239	160	94	59	35	15	7	2	0

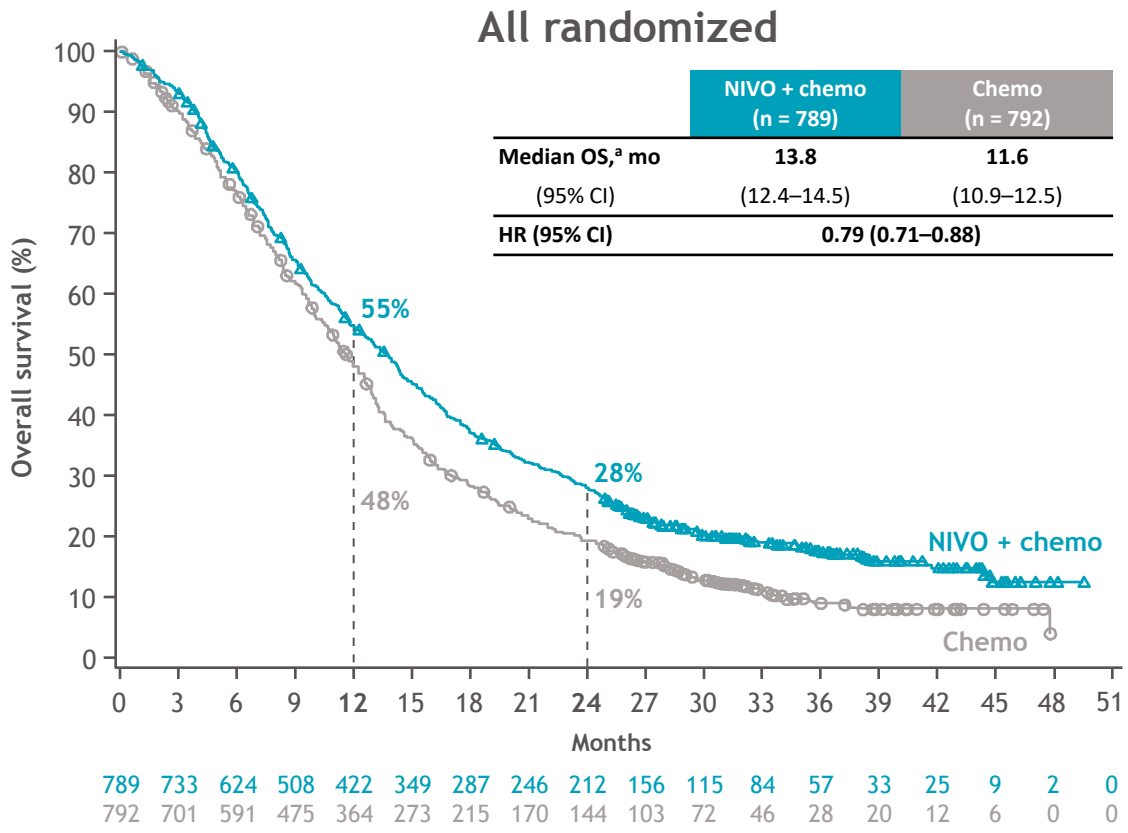
Adapted from Janjigian 2021.[2]

- Grade 3-4 treatment-related adverse events were reported in 59% of patients in the NIVO + chemo arm and 44% of patients in the chemo arm[1]
- Treatment-related deaths occurred in 16 (2%) and 4 (1%) of patients in the NIVO + chemo and chemo arms, respectively[1]

1. Package insert. 2. Janjigian YY et al. *Lancet* 2021;398:27-40.

CheckMate 649: Overall survival – NIVO + chemo vs chemo





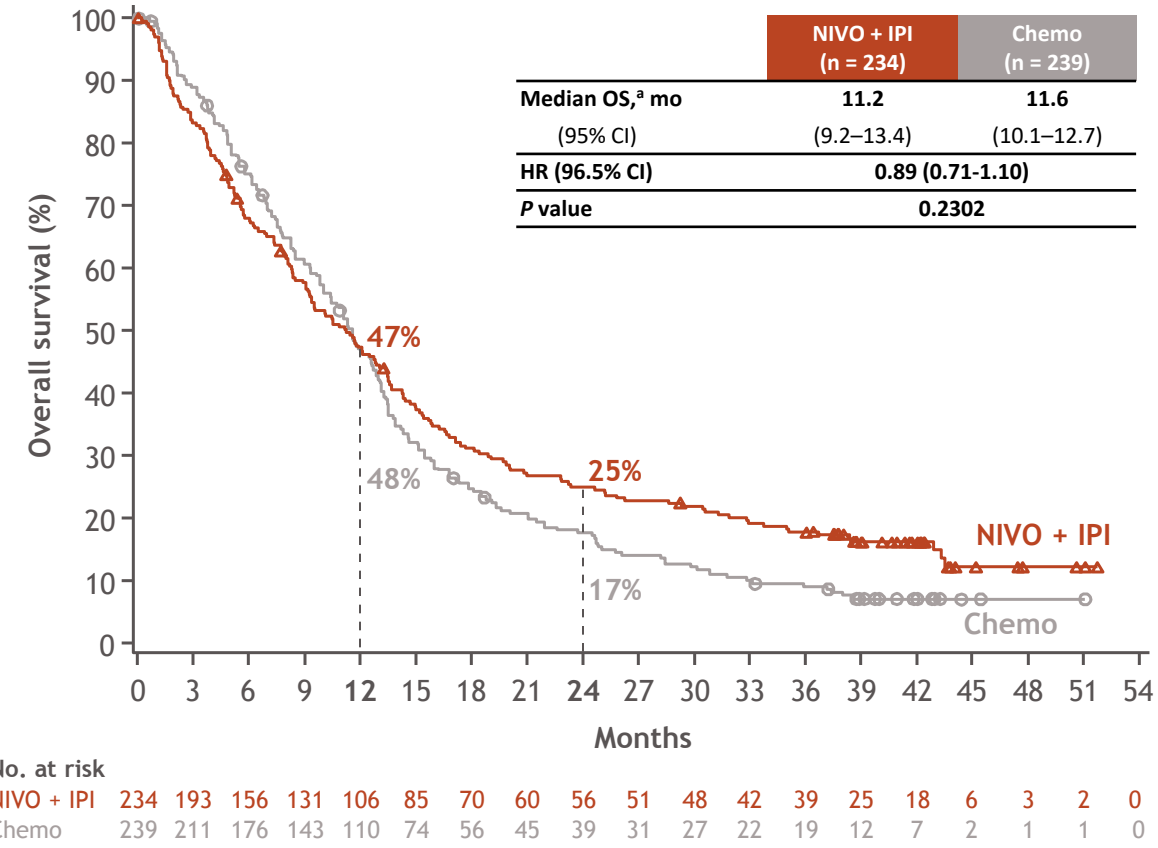
- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up
  - PD-L1 CPS ≥ 5: 30% reduction in the risk of death and 12% improvement in 24-month OS rate
  - All randomized: 21% reduction in the risk of death and 9% improvement in 24-month OS rate
  - Directionally improved HRs relative to the 12-month follow-up (PD-L1 CPS ≥ 5, 0.71 [98.4% CI, 0.59-0.86]; all randomized, 0.80 [99.3% CI, 0.68-0.94])

- [a]Minimum follow-up, 24.0 months.

Janjigian YY et al. *Lancet* 2021;398:27-40.

CheckMate 649: Overall survival – NIVO + IPI vs chemo

PD-L1 CPS ≥ 5

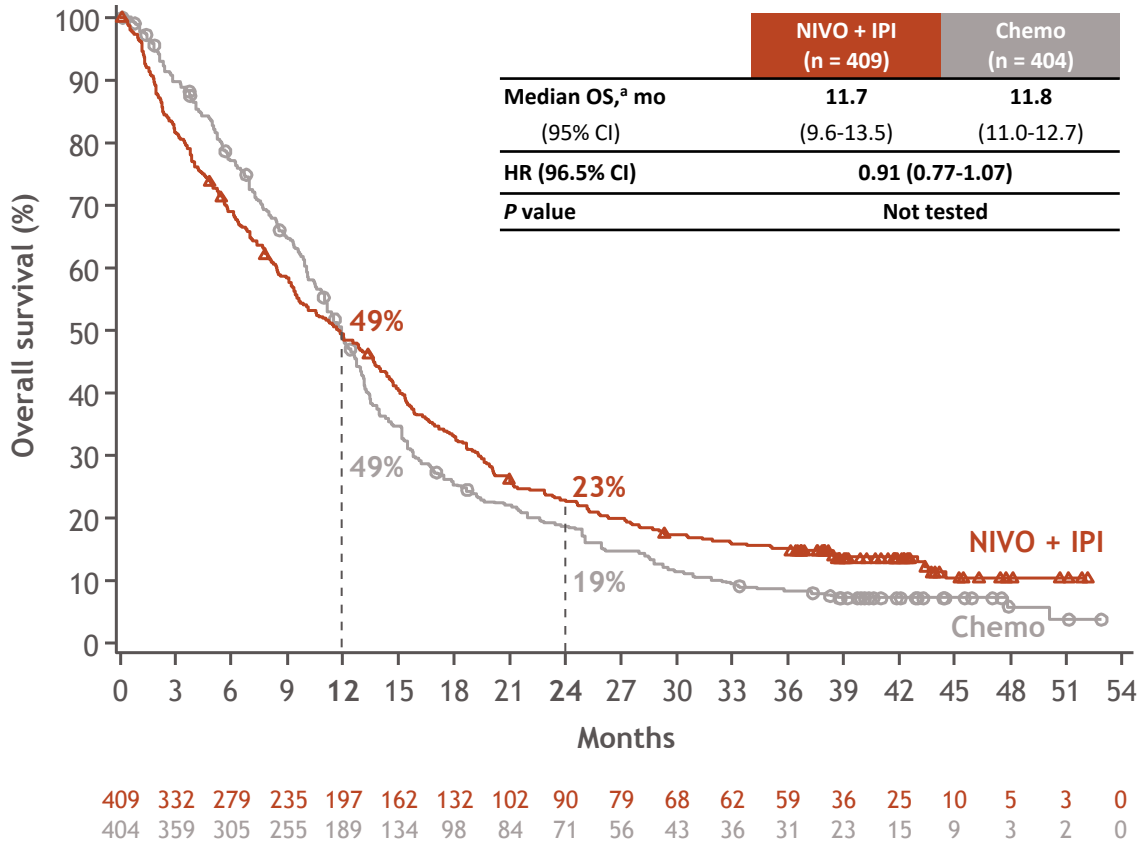


	NIVO + IPI (n = 234)	Chemo (n = 239)
Median OS,[a] mo	11.2	11.6
(95% CI)	(9.2–13.4)	(10.1–12.7)
HR (96.5% CI)	0.89 (0.71-1.10)	
P value	0.2302	

No. at risk

NIVO + IPI	234	193	156	131	106	85	70	60	56	51	48	42	39	25	18	6	3	2	0
Chemo	239	211	176	143	110	74	56	45	39	31	27	22	19	12	7	2	1	1	0

All randomized



	NIVO + IPI (n = 409)	Chemo (n = 404)
Median OS,[a] mo	11.7	11.8
(95% CI)	(9.6-13.5)	(11.0-12.7)
HR (96.5% CI)	0.91 (0.77-1.07)	
P value	Not tested	

NIVO + IPI	409	332	279	235	197	162	132	102	90	79	68	62	59	36	25	10	5	3	0
Chemo	404	359	305	255	189	134	98	84	71	56	43	36	31	23	15	9	3	2	0

- The hierarchically tested secondary endpoint of OS with NIVO + IPI vs chemo in patients with PD-L1 CPS ≥ 5 was not met; OS in all randomized patients was not statistically tested.
- Minimum follow-up, 35.7 months.

Janjigian YY et al. ESMO 2021; Abstract LBA-7

ORIENT-16: Study design

Sintilimab is a recombinant fully humanized anti-PD-1 monoclonal antibody.

Previous study has shown encouraging anti-tumor activities of Sintilimab plus chemotherapy in 1L G/GEJ cancer.

ORIENT-16[a] is a randomized, double-blind, phase 3 study

Key eligibility criteria
- Previously untreated, unresectable advanced, recurrent or metastatic G/GEJ adenocarcinoma
- ECOG PS 0 or 1
- No known Her2 positive

R 1:1

N=327 → **Sintilimab + XELOX[a] Q3W × 6 cycles, then Sintilimab + Capecitabine[a] Q3W[b]**

N=323 → **Placebo + XELOX[a] Q3W × 6 cycles, then Placebo + Capecitabine[a] Q3W[b]**

Primary endpoints:
- OS in the patients with CPS ≥5
- OS in all randomized patients

Secondary endpoints:
- PFS, ORR, DCR, and DoR
- Safety profile

Stratification factors
- ECOG PS (0 or 1)
- Liver metastasis (yes or no)
- PD-L1 (CPS <10 or ≥10)

- Data cut-off date for interim analysis was June 20, 2021
- Median follow-up: 18.8 months

Statistical considerations
- Type I error is strictly controlled using fixed sequence test. OS in CPS≥5 and all randomized are tested hierarchically
- One interim analysis is planned, and O'Brien-Fleming is used for the alpha boundary (alpha=0.0148).

[a] ClinicalTrial.gov number, NCT03745170; [b] Sintilimab 3 mg/kg for body weight <60 kg, 200 mg for ≥60 kg; Oxaliplatin 130 mg/m^2 IV; Capecitabine 1000 mg/m^2 PO Bid d1-14;
[c] Until progressive disease, intolerable toxicity, withdrawal of consent. Treatment is given for a maximum of 2 years.

2021 ESMO congress

Courtesy of Zev Wainberg, MD, MSc

Gastric/GEJ Adeno-Conclusions

- Clinical Implications:
  - FOLFOX/CapeOx + Nivo is SOC in CPS $\geq$5
  - Platinum/5-FU + Pembro also a SOC in esophageal adeno
  - No role for IPI/Nivo in gastric or GEJ adeno
  - Minimal efficacy with addition of Nivo in CPS $\leq$5
  - Sintilimab data very promising, even in CPS< 5

Courtesy of Zev Wainberg, MD, MSc

Agenda

Introduction

Module 1: Localized Disease

Module 2: Metastatic Disease

Module 3: Novel Targets

- Claudin 18.2
- FGFR2B

Gastric Cancer with CPS<5 ?

FGFRb2-Bemarituzumab

FGFR2b overexpressing mGC (30%?)

Key Eligibility Criteria
- No prior therapy for unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or *FGFR2* gene amplification by ctDNA[1]
- ECOG 0/1
- HER2 not positive
- May receive 1 dose of mFOLFOX6

Stratification Factors
- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neo-adjuvant chemotherapy

R 1:1

Double blind, placebo controlled

Bema + mFOLFOX6 (n = 77)

VS

Placebo + mFOLFOX6 (n = 78)

Treatment Q2W[2]

Primary endpoint
- Investigator-Assessed Progression-Free Survival

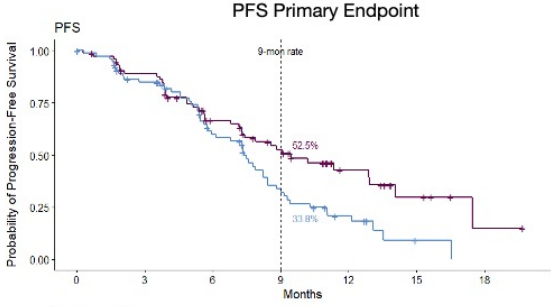
Secondary endpoints
- Overall Survival
- Response Rate

Statistical Plan

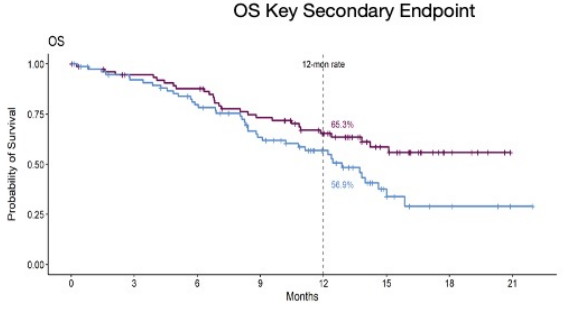
Trial initially designed as registrational Phase 3 (n=548) with 2-sided α 0.05
Amended after enrolling n = 155 to a proof-of-concept Phase 2 with pre-specified statistical assumptions of:
- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR≤0.76 for PFS at 2-sided α of 0.2

1 Central testing: Immunohistochemical stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X
2 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day 8[2]

PFS Primary Endpoint



OS Key Secondary Endpoint



Wainberg ZA, et al. *J Clin Oncol* 2021;39(suppl 3):Abstract 160.

CLDN18.2-Zolbetuximab

GLOW

Key eligibility criteria:
- Age ≥ 18 years
- Locally advanced unresectable or metastatic disease
- Gastric or gastroesophageal junction cancer
- Histologically confirmed adenocarcinoma
- prior systemic chemotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma,
- CLDN18.2 in ≥ 75% of tumor cells
- ECOGPS of 0 or 1

R 2:1

CAPOX+zolbetuximab

N = 500

CAPOX+placebo

Primary endpoint:
- PFS

2nd endpoints:
- OS
- ORR
- DOR, DCR)
- Safety

Spotlight

Key eligibility criteria:
- Age ≥ 18 years
- Locally advanced unresectable or metastatic disease
- Gastric or gastroesophageal junction cancer
- Histologically confirmed adenocarcinoma
- prior systemic chemotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma,
- CLDN18.2 in ≥ 75% of tumor cells
- ECOGPS of 0 or 1

R 2:1

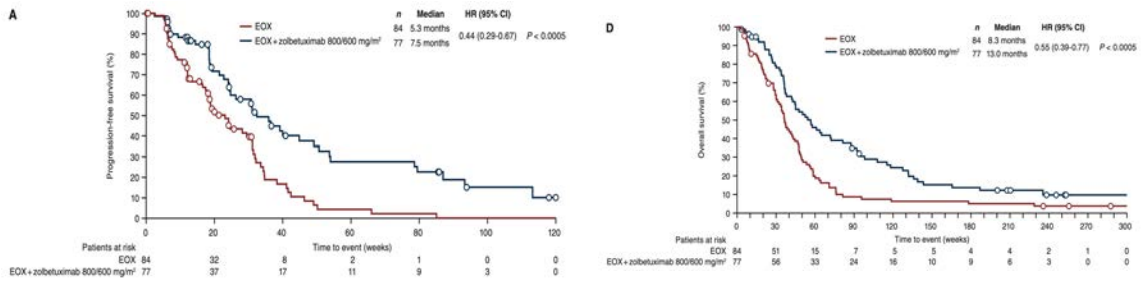
FOLFOX+zolbetuximab

N = 550

FOLFOX+placebo

Primary endpoint:
- PFS

2nd endpoints:
- OS
- ORR
- DOR, DCR)
- Safety



Sahin U, et al. *Ann Oncol* 2021;32:609–19.

Courtesy of Zev Wainberg, MD, MSc

FGFR2 Amplification: Bemarituzumab

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

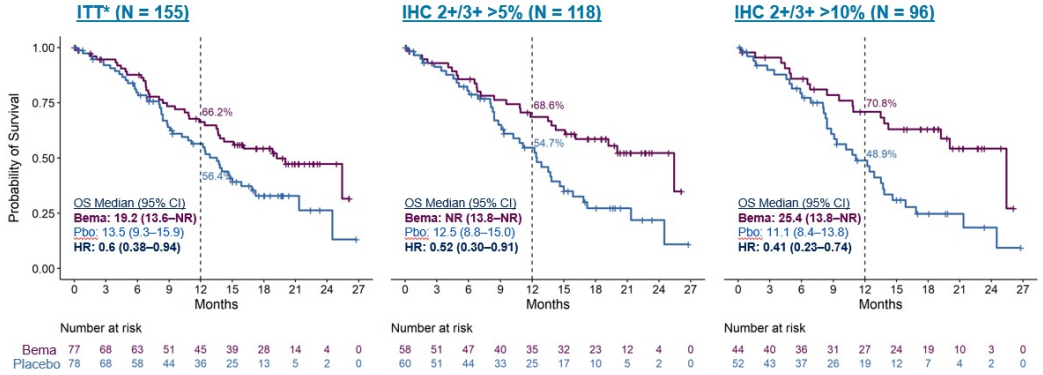
Treatment may continue until progression, unacceptable toxicity, or the patient meets other withdrawal criteria

*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.

Median OS Reached With Longer Follow-up

11

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



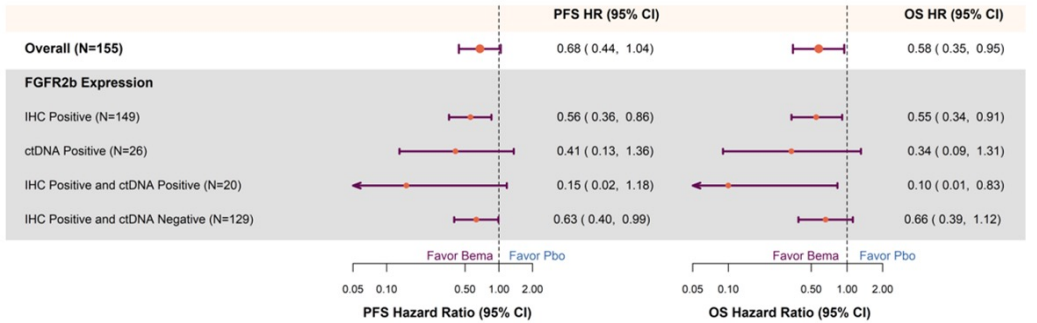
*ITT = includes 149 patients with IHC 2+/3+ and 6 with IHC <2+ or not available who were enrolled based on ctDNA alone.
NR, not reached.
Median Follow-up 12.5 months

*Based on February, 28th 2021 data cut

10

Evaluation of Efficacy by Biomarker Status

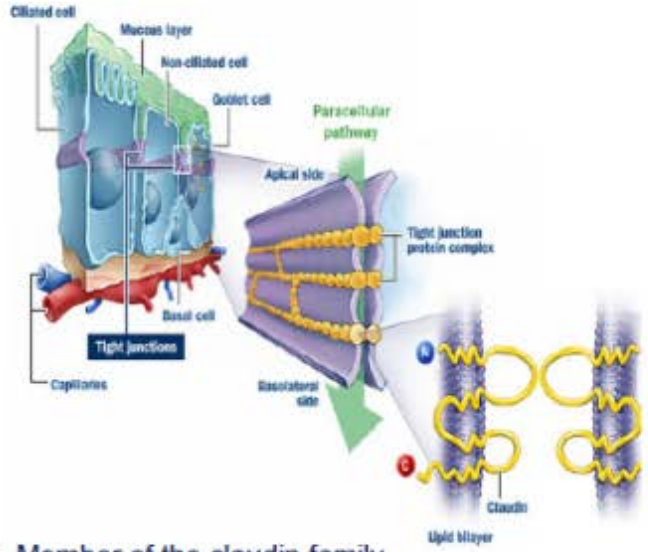
Overexpression was Sufficient, ctDNA+ with Most Pronounced Benefit



Catenacci et al. 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). ASCO abstr 2021

Courtesy of David H Ilson, MD, PhD

CLDN18.2 IS EXPRESSED IN SEVERAL CANCER TYPES



- Member of the claudin family
- Major structural component of tight junctions
  - Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except for stomach mucosa, with limited accessibility to the antibody
- Broadly expressed in various cancer types

Immunohistological CLDN18.2 Labeling		
Source of tissue	**CLDN18.2 + samples**	**[%]**
Gastric adenocarcinomas	**958/1182**	**81**
Diffuse	203/342	89
Intestinal	238/338	70
Mixed	49/63	78
Not specified	368/439	84
Gastric cancer metastases	**291/377**	**77**
Lymph node	168/219	77
Ovarian	42/48	88
Peritoneum	29/36	81
Liver	12/20	60
Other	40/54	74
Esophageal adenocarcinomas	**72/96**	**75**
Pancreatic cancers	**166/286**	**58**
Ductal adenocarcinomas	*103/174*	*59*
Neuroendocrine carcinomas	*5/25*	*20*
Acinar cell carcinoma	*1/3*	*33*
Lymph node metastasis	*34/49*	*69*
Liver metastasis	*23/35*	*66*

31

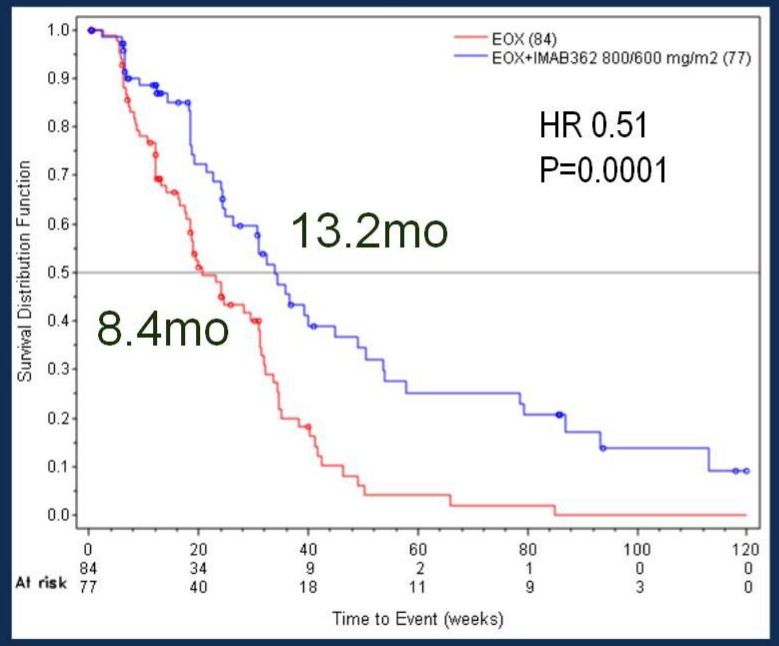
Screening by IHC

COPENHAGEN 2016 ESMO congress

Courtesy of David H Ilson, MD, PhD

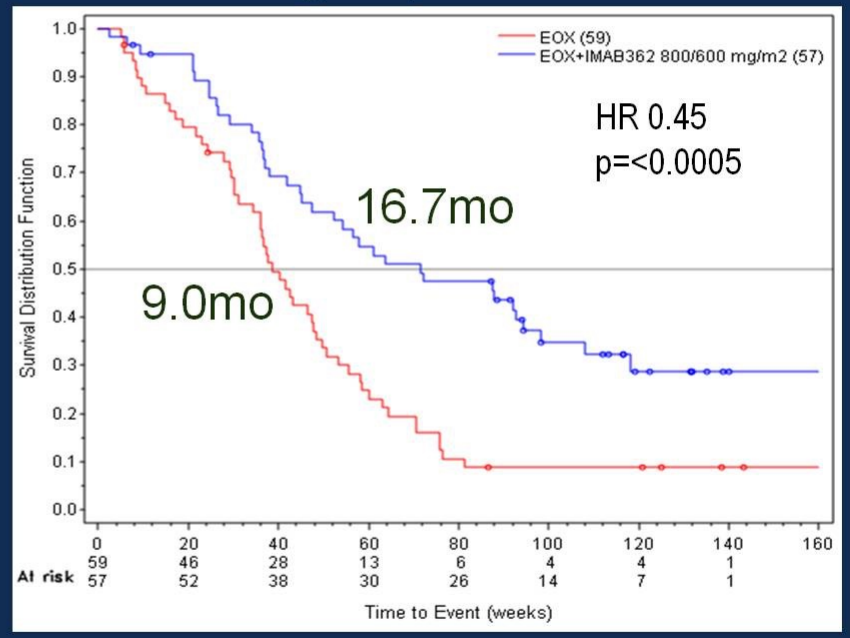
FAST - Overall Survival

Total Population*



*in patients with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells

High Expressors#



#in patients with 2+/3+ CLDN18.2 staining in ≥ 70% of tumor cells

PRESENTED AT: 2017 Gastrointestinal Cancers Symposium | #GI17

Modified from: Al-Batran SE, et al. ASCO 2016 (LBA4001):

Ongoing Trials
Spotlight: FOLFOX + / - Z
GLOW: CapeOx + / - Z

Sahin Ann Oncol 32:609; 2021

Presented By Peter Enzinger at 2017 Gastrointestinal Cancers Symposium

Courtesy of David H Ilson, MD, PhD

Conclusions

- Clinical Implications:
  - Zolbetuximab and Bemarituzumab validated in Phase II trials
  - Phase III (SPOTLIGHT-CLDN 18.2), FGFR2b (FORTITUDE)
- Future Directions:
  - Other CLDN 18.2 inhibitors (ADC's, CAR-T)
  - Other novel targets: MUC

Courtesy of Zev Wainberg, MD, MSc

Exploring the Current and Changing Paradigm for the Management of Newly Diagnosed Diffuse Large B-Cell Lymphoma

Wednesday, February 2, 2022
5:00 PM – 6:15 PM ET

Faculty

Christopher R Flowers, MD, MS
Neha Mehta-Shah, MD, MSCI
Grzegorz Nowakowski, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP Year in Review 2022