Esophageal and Gastric Cancer: New Developments

May Cho, MD

UCDAVIS

Disclosures

Consultant and honoraria - Amgen, Taiho, Astella, Ipsen and Exelixis

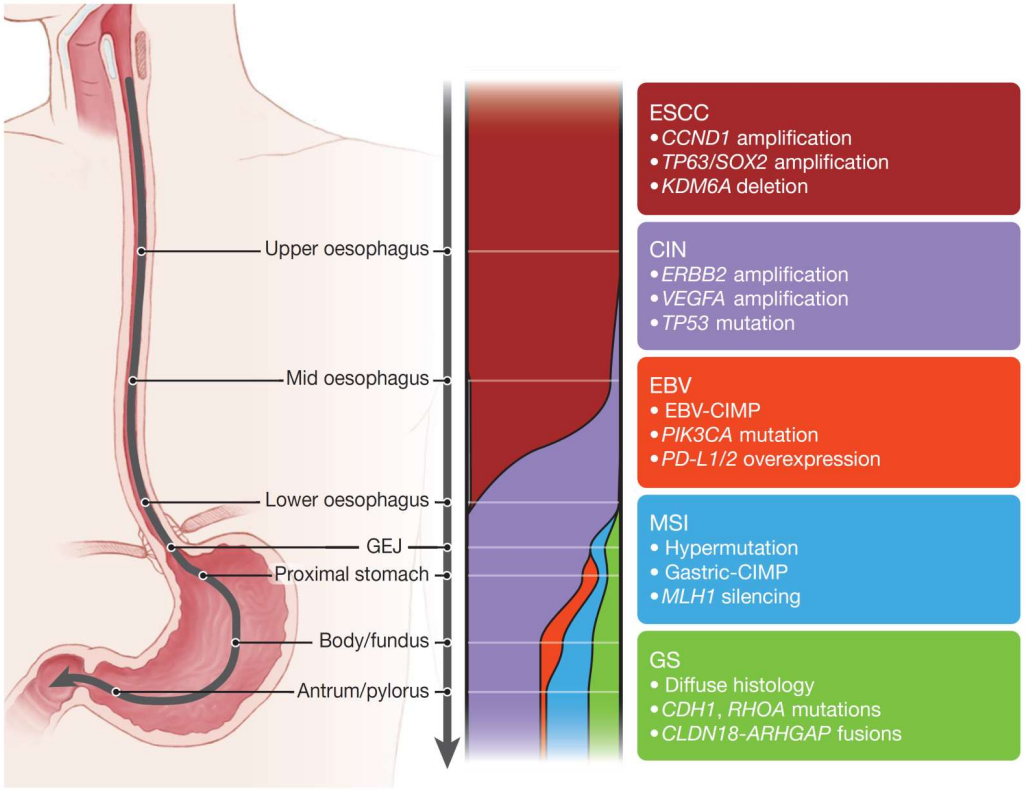
Outlines

Perioperative Therapies

Metastatic Therapies

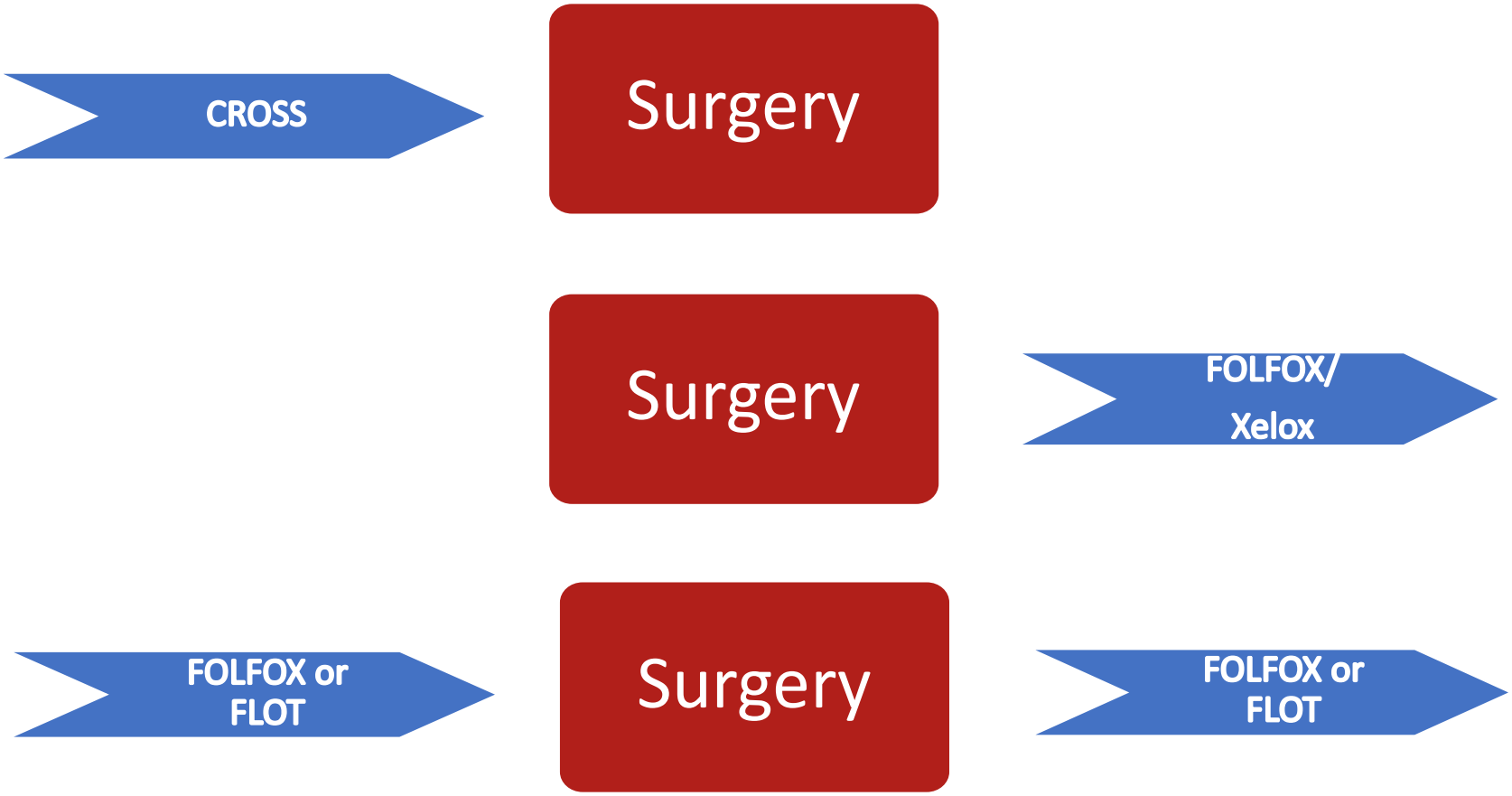
- 1st line (non-HER2 overexpression)
- 1st line (HER2 overexpression)
- 2nd line
- 3rd line

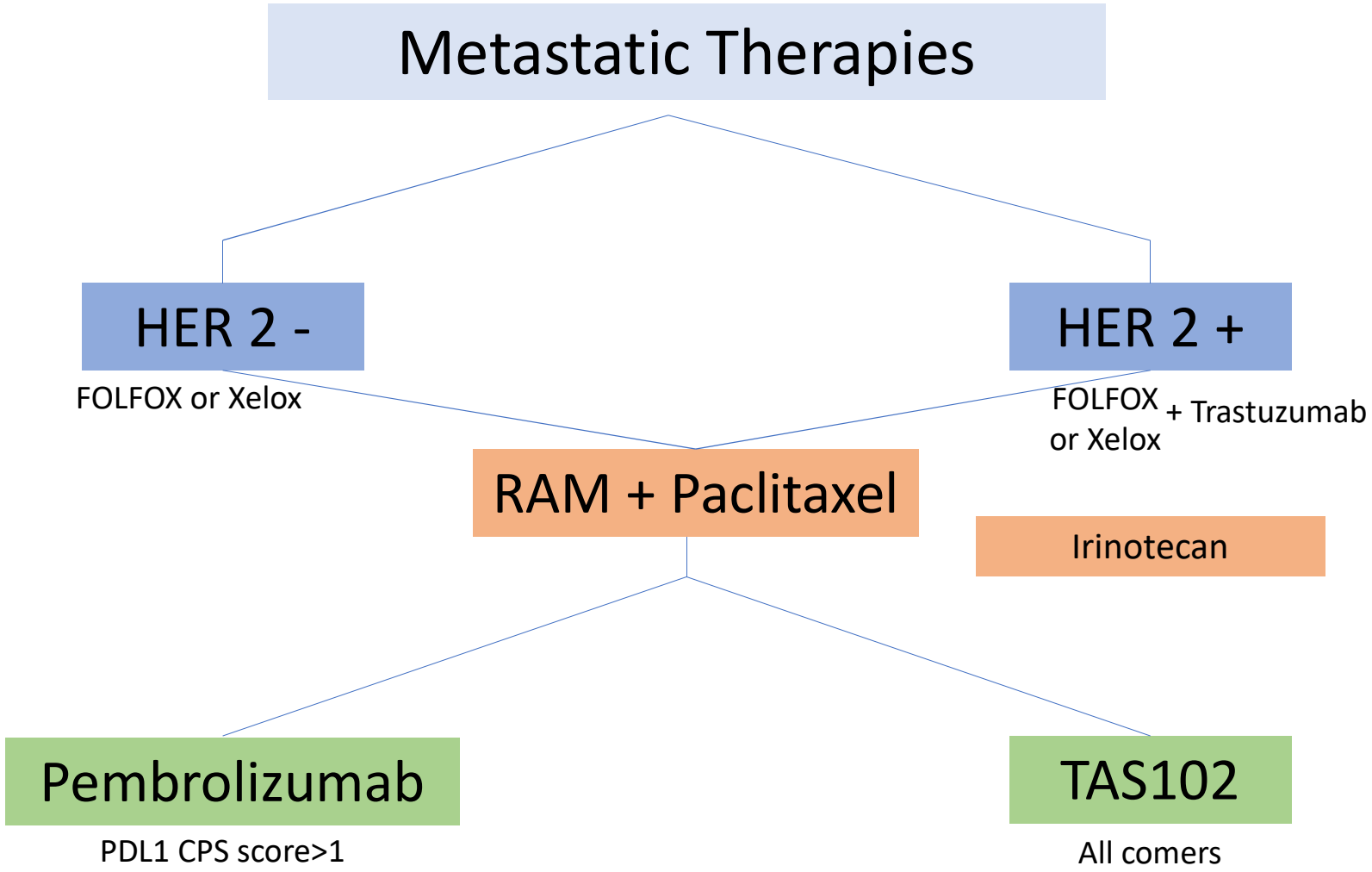
Comprehensive Molecular Characterization of Esophageal Carcinoma - The Cancer Genome Atlas (TCGA)



TCGA. Nature 2017; 541: 169-175

Perioperative Therapies




Metastatic Therapies
HER 2 -
FOLFOX or Xelox
HER 2 +
FOLFOX or Xelox + Trastuzumab
RAM + Paclitaxel
Irinotecan
Pembrolizumab
PDL1 CPS score>1
TAS102
All comers

RAMSES/FLOT7

DANTE/FLOT8

AIO

KN 062/059

PETRARCA/FLOT6

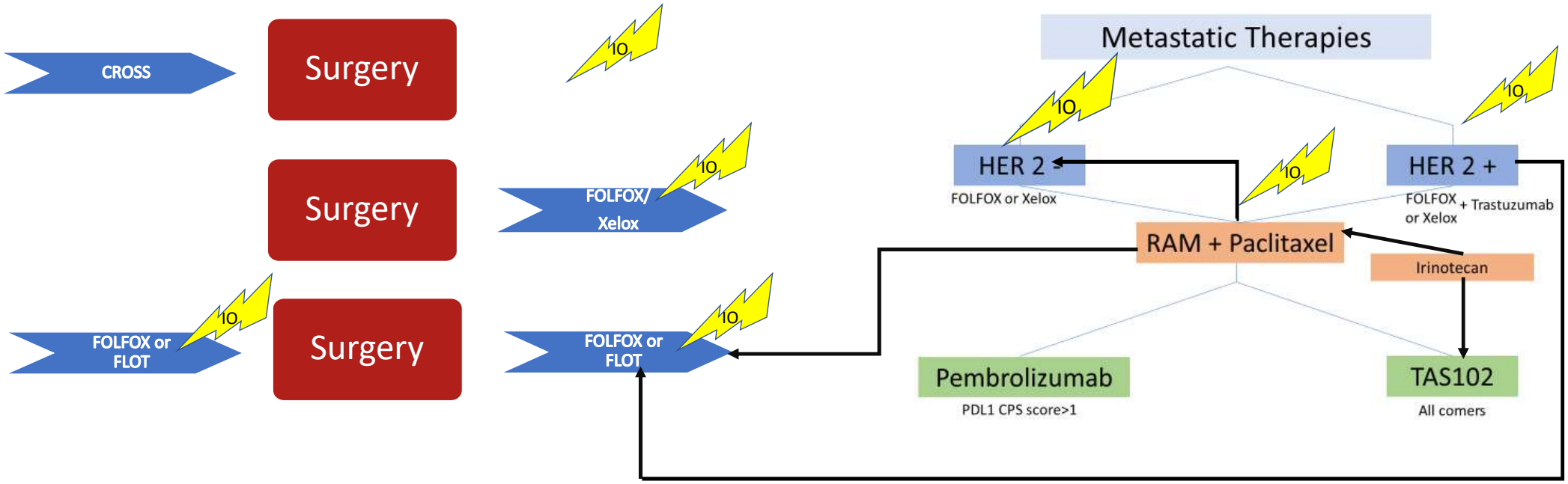
RAP

Checkmate 648/649

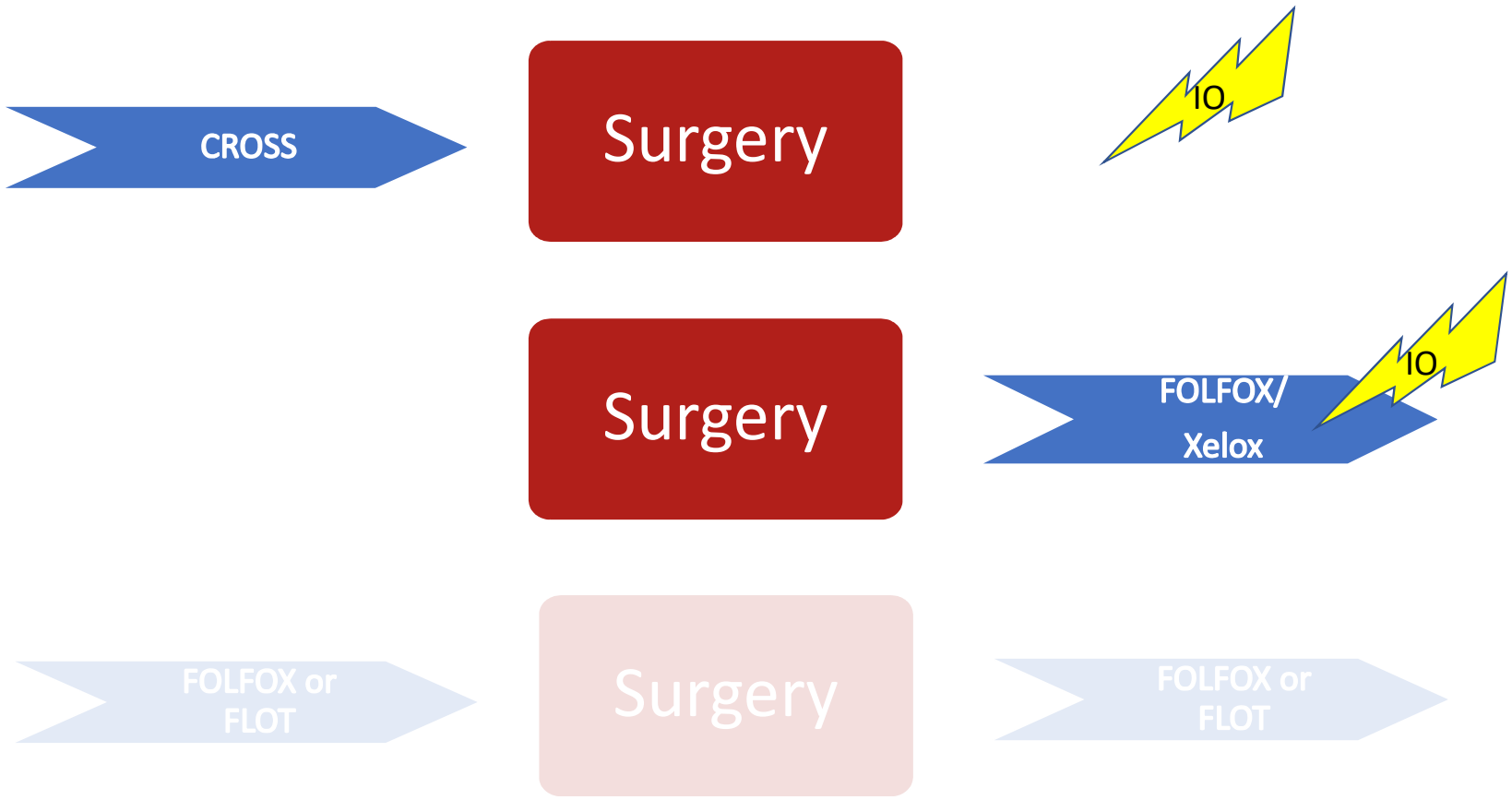
TWO RULES OF THUMB

1. Add IO to every line of therapy
2. Add later line therapies to earlier settings

Perioperative Therapies

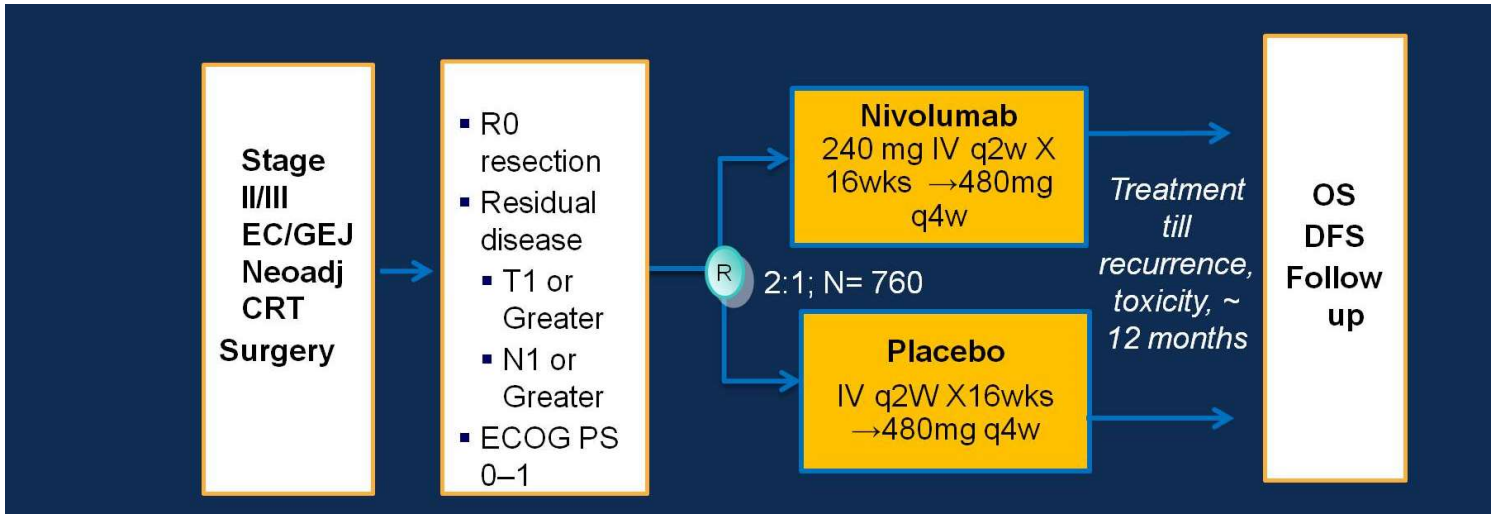


Perioperative Therapies



CHECKMATE 577

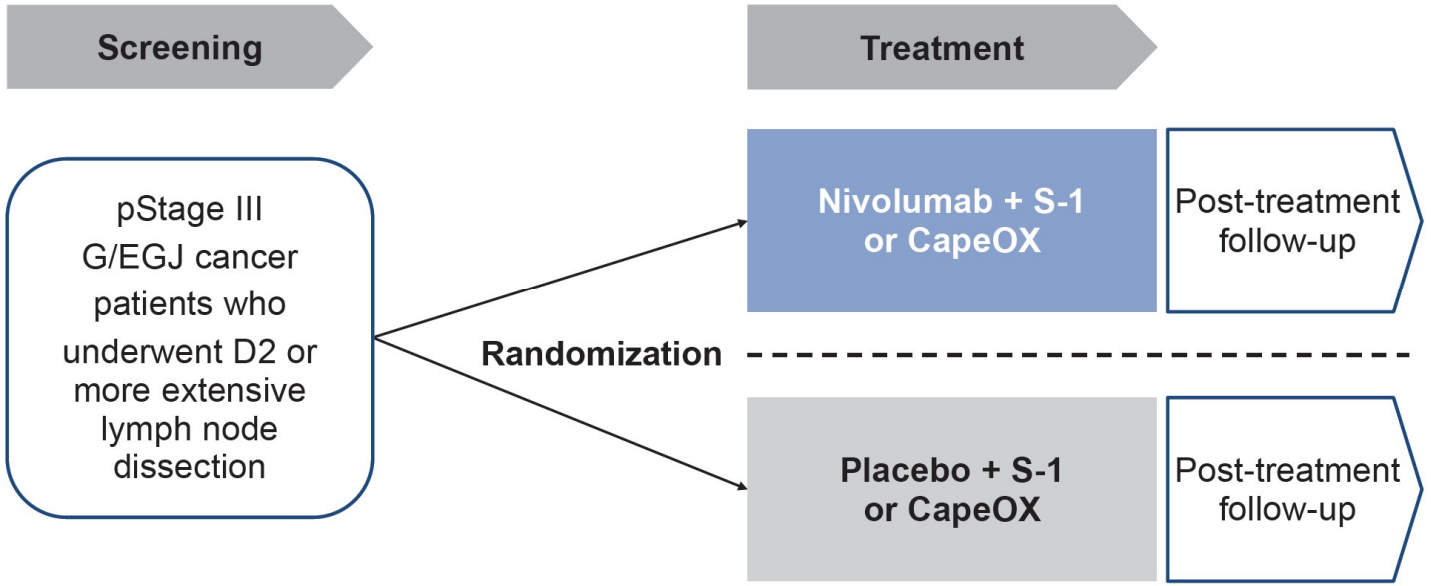
Can adjuvant PD-1 inhibition improve outcomes for esophageal/GEJ cancer patients that do not achieve a path CR after neoadjuvant chemoRT?



Kelly, R. et al., ASCO 2017

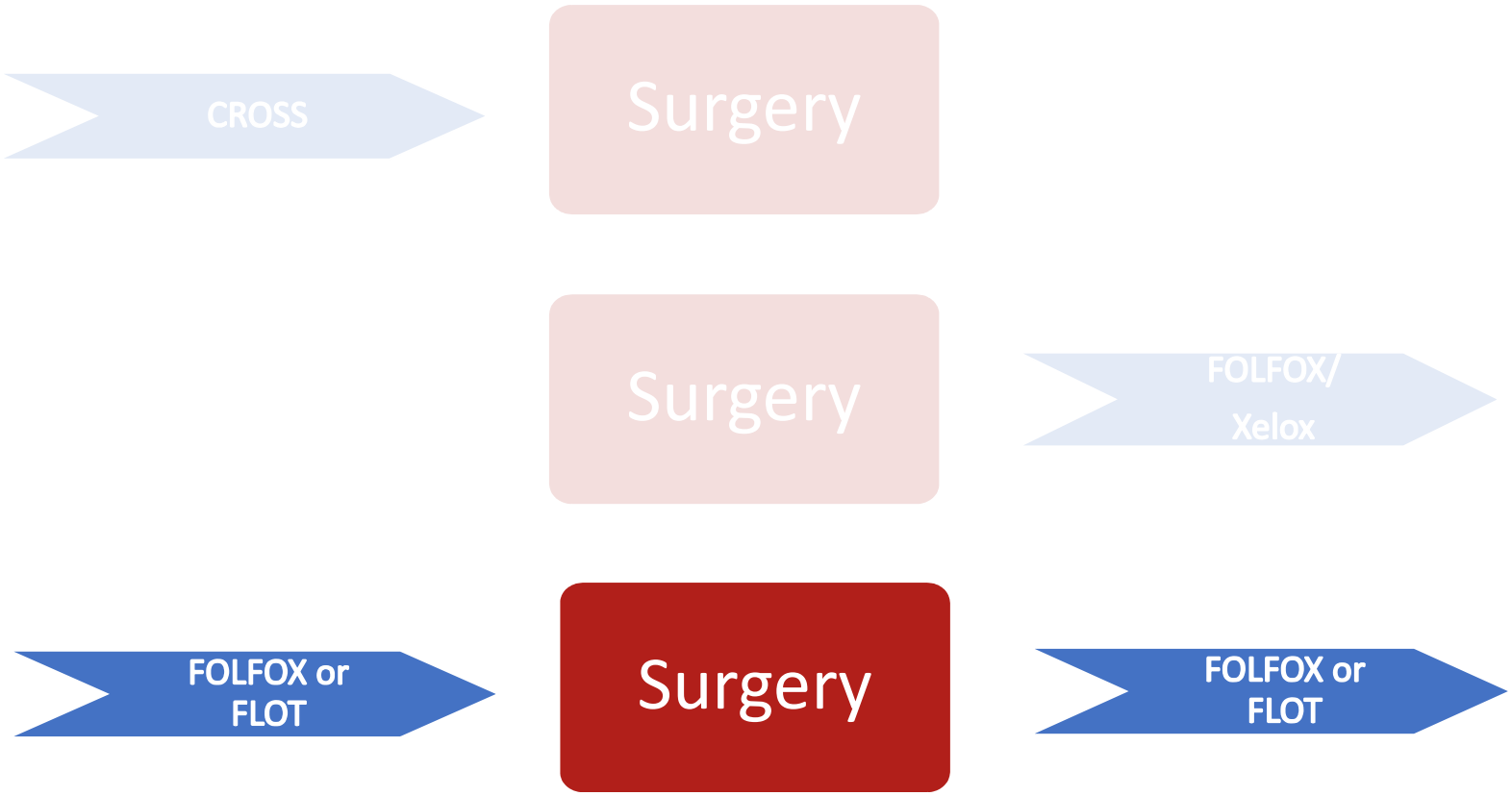
ATTRACTION-05

Can the addition of adjuvant PD-1 inhibition improve outcomes for patients treated with upfront gastrectomy and D2 lymph node dissection?



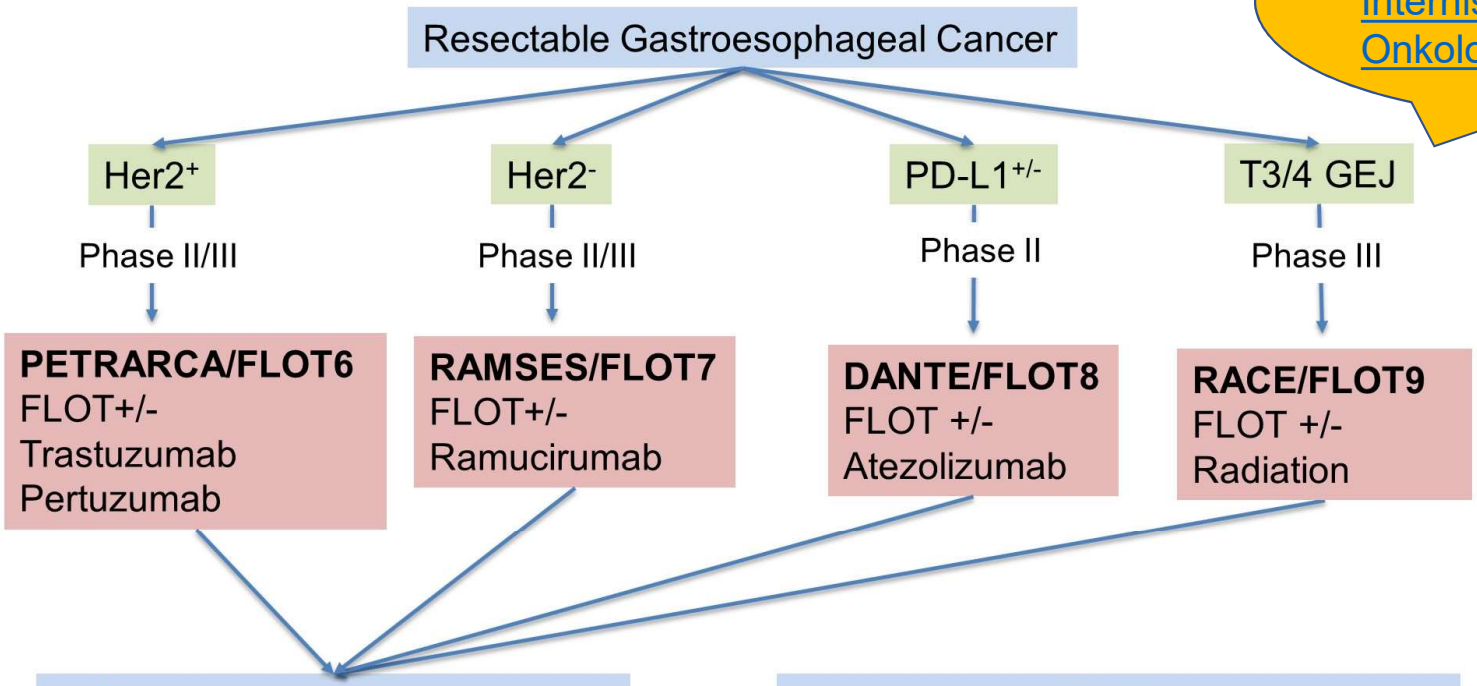
Terashima, M., ESMO 2017

Perioperative Therapies



Current AIO Gastroesophageal Cancer Research Program for Resectable Stage

Arbeitsgemeinschaft Internistische Onkologie



- Tissue sample
  → Translational research teams

Goals:

- Increase cure rates (60% cure)
- Identify genes associated with path response and resistance

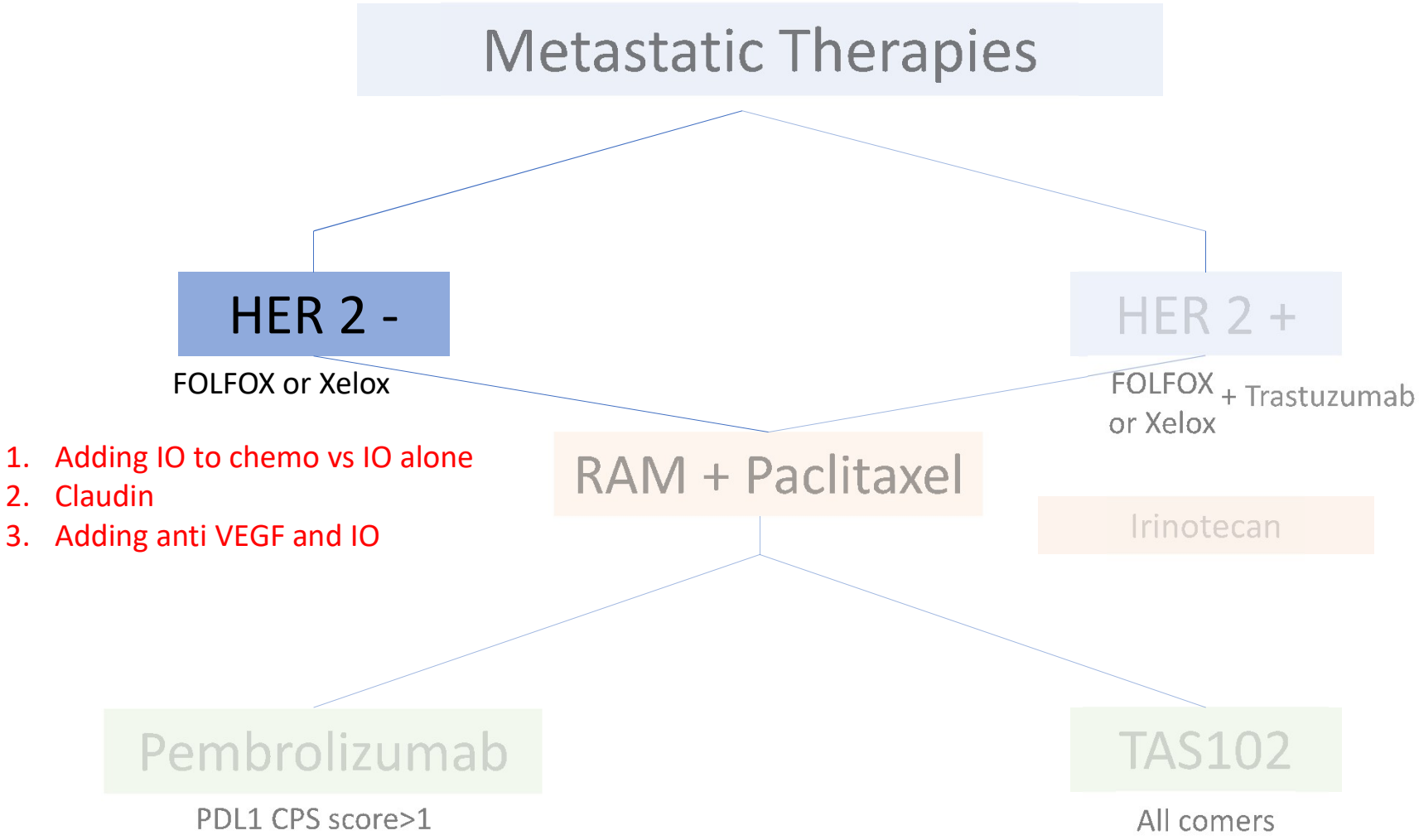
Presented By Salah-Eddin Al-Batran at 2019 ASCO Annual Meeting

A pilot study of FOLFIRINOX followed by neoadjuvant chemoradiation for gastric and gastroesophageal cancer:

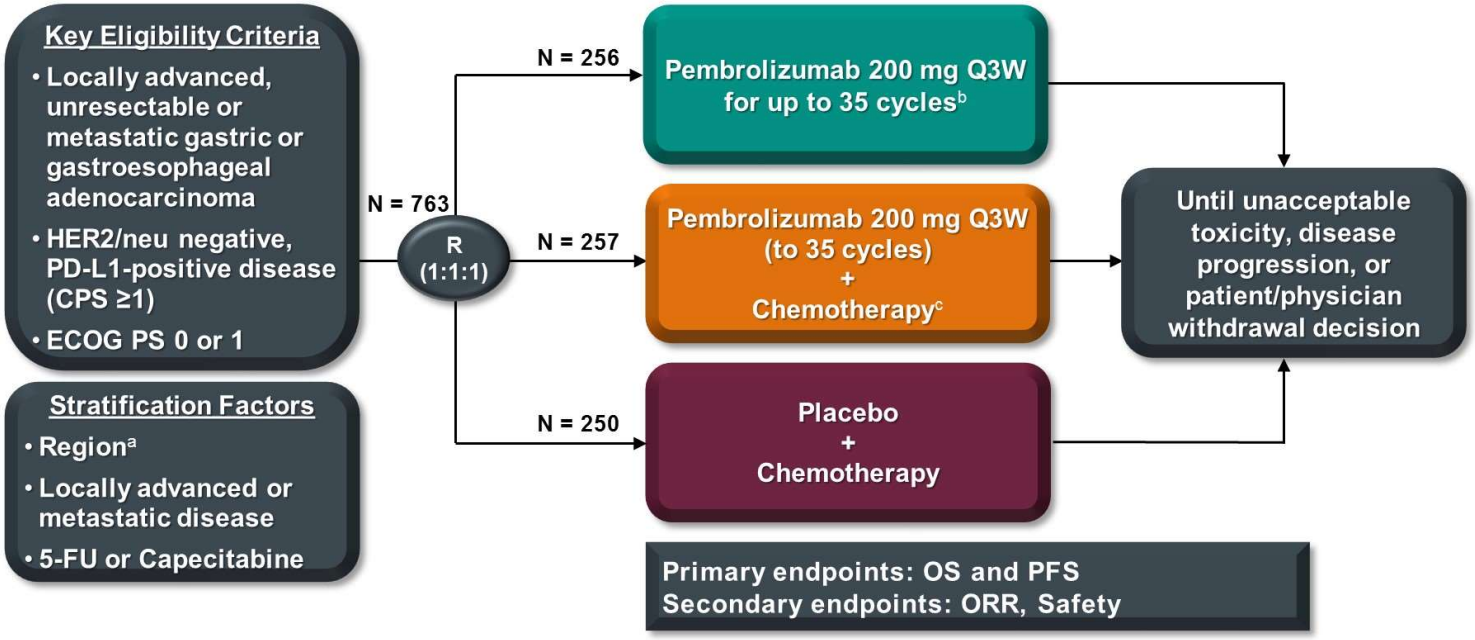
METHODS:

- Patients were enrolled on an NCI sponsored, prospective, single arm study (NCT03279237).
- Key eligibility criteria included: histologically confirmed T3/4 or lymph node (LN) positive gastric or GE junction cancer, ECOG PS ≤1, age 18+, and life expectancy > 3 months. Exclusion criteria included: visceral metastases, prior chemotherapy or RT, or prior targeted therapy. Extensive LN disease beyond the surgical field (supraclavicular or para-aortic) was permitted if deemed feasible to be encompassed within a RT field.
- Pts were treated with neoadjuvant FOLFIRINOX x 8, restaging, CRT (45 Gy for gastric, 50.4 Gy for GE junction) with concurrent C/T, restaging, followed by surgical resection. Dose reductions were at discretion of the treating physician.
- The primary objective was to determine the rate of completion of FOLFIRINOX x 8 followed by CRT delivered in the preoperative setting.
- Secondary endpoints included: 1) acute toxicity and 2) pathologic complete response (pCR).

Wo, J. et al., ASCO 2019

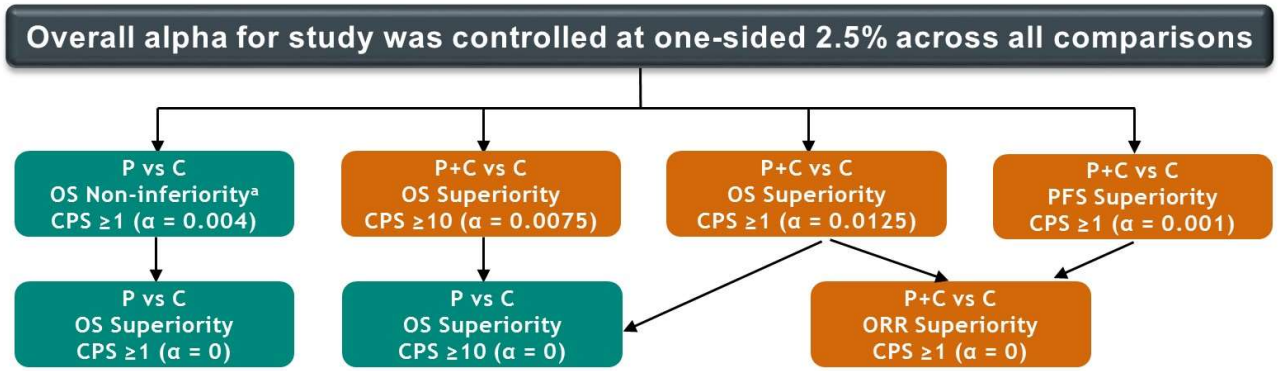

Metastatic Therapies
HER 2 -
FOLFOX or Xelox
HER 2 +
FOLFOX or Xelox + Trastuzumab
1. Adding IO to chemo vs IO alone
2. Claudin
3. Adding anti VEGF and IO
RAM + Paclitaxel
Irinotecan
Pembrolizumab
PDL1 CPS score>1
TAS102
All comers

KEYNOTE-062 Study Design (NCT02494583)



[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
[b]Administration of pembrolizumab monotherapy was not blinded.
[c]Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

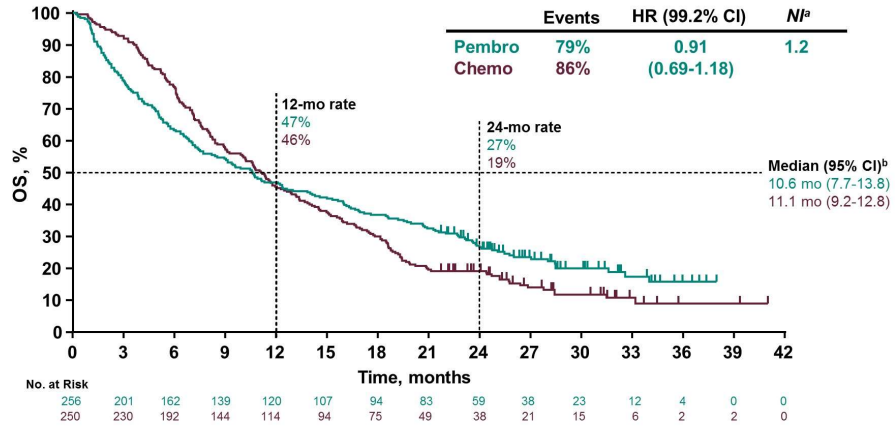
Statistical Considerations



- Hypotheses in top row tested first and in parallel
  - Remaining hypotheses tested only if preceding hypothesis was positive
  - Prespecified analysis plan allowed alpha passing from successful hypotheses
- Final analysis: planned to occur ≥22 months after last patient was randomized and ~415 OS events observed in P+C and C treatment groups in patients with PD-L1 CPS ≥1

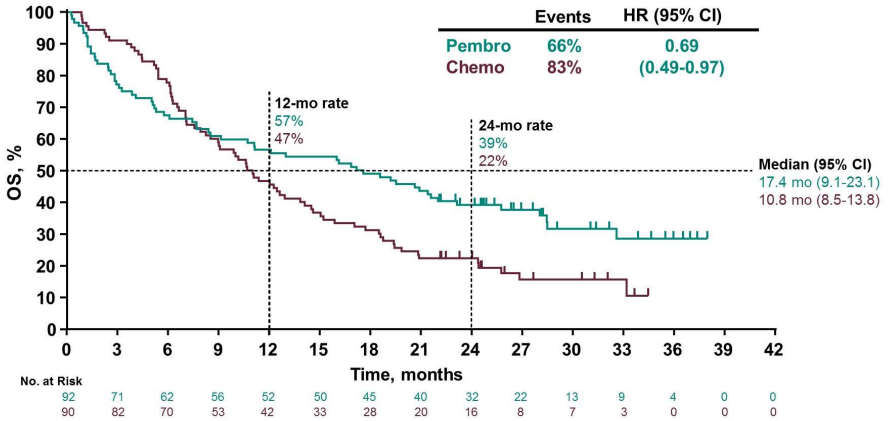
[a]Alpha passed from non-inferiority to superiority test; Median follow-up, 11.3 months (range, 0.2-41.2); Data cutoff: March 26, 2019.

Overall Survival: P vs C (CPS ≥1)



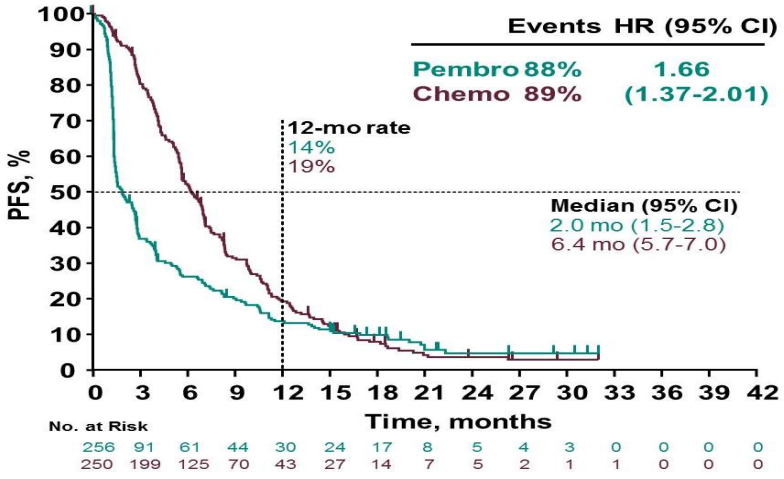
[a]NI, non-inferiority margin; [b]HR (95% CI) = 0.91 (0.74-1.10), *P* = 0.162 for superiority of P vs C; Data cutoff: March 26, 2019.

Overall Survival: P vs C (CPS ≥10)

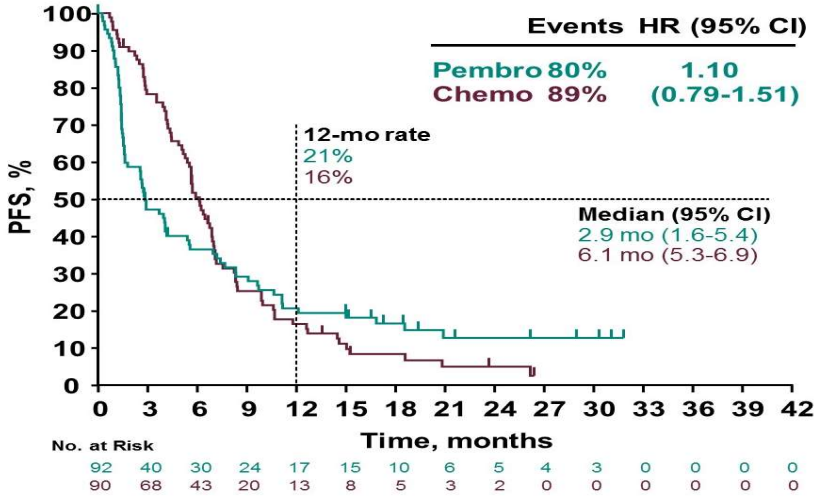


Data cutoff: March 26, 2019.

Progression-Free Survival: P vs C

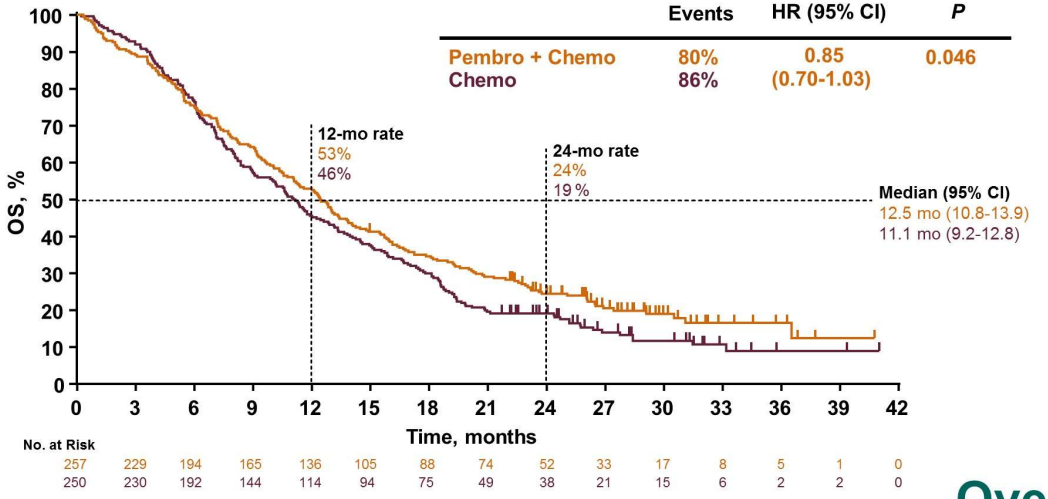


CPS ≥10



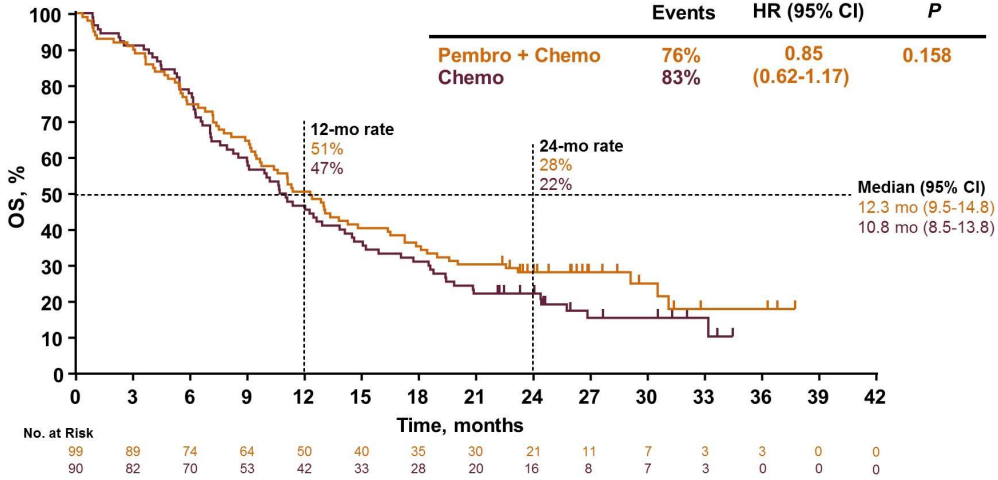
Presented By Josep Tabernero at 2019 ASCO Annual Meeting

Overall Survival: P+C vs C (CPS ≥1)



Data cutoff: March 26, 2019.

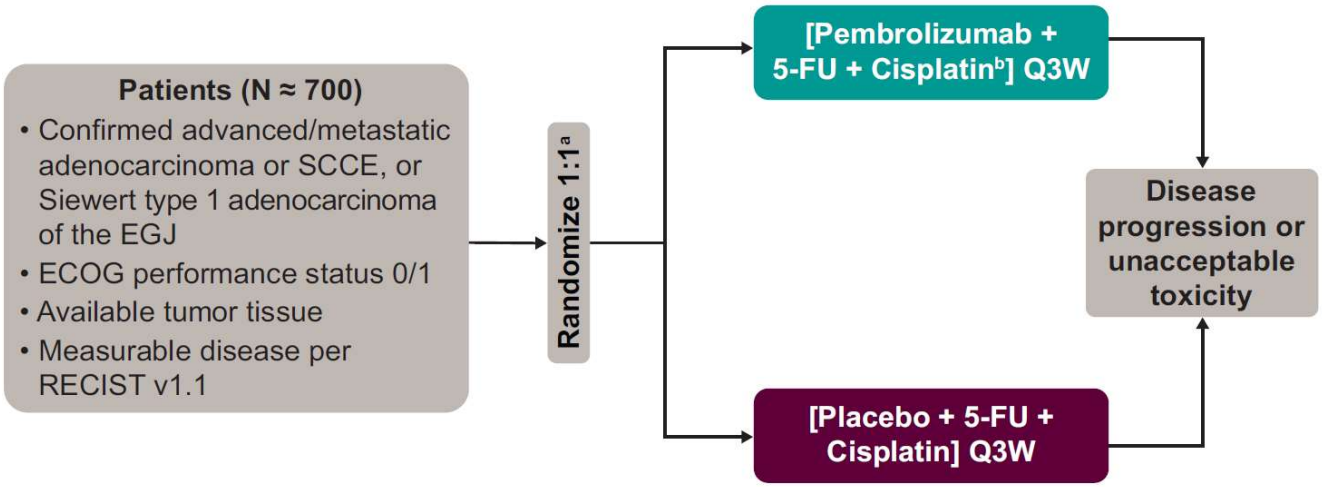
Overall Survival: P+C vs C (CPS ≥10)



Data cutoff: March 26, 2019.

Presented By Josep Tabernero at 2019 ASCO Annual Meeting

KEYNOTE-590 – Phase III Trial of Pembrolizumab in First-Line Therapy in SCC of Esophagus and Siewert type 1 adenocarcinoma of GEJ

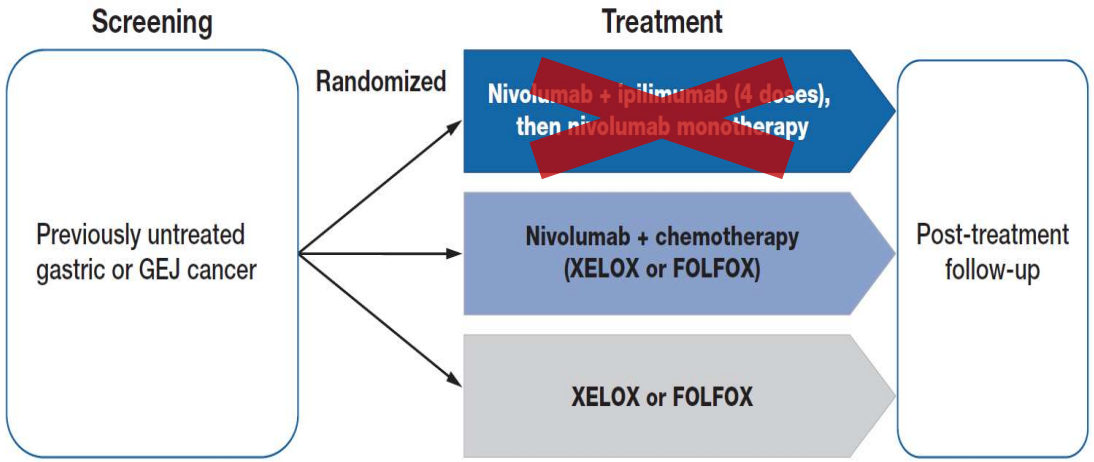


Primary

- To compare progression-free survival (PFS) per RECIST v1.1 by blinded independent central review between treatment arms in all patients and in patients with PD-L1–positive tumors (defined as combined positive score [CPS] ≥10)
- To compare overall survival (OS) between treatment arms in all patients and in patients with PD-L1 CPS ≥10

Kato K et al. World Congress on GI Cancer. 2018

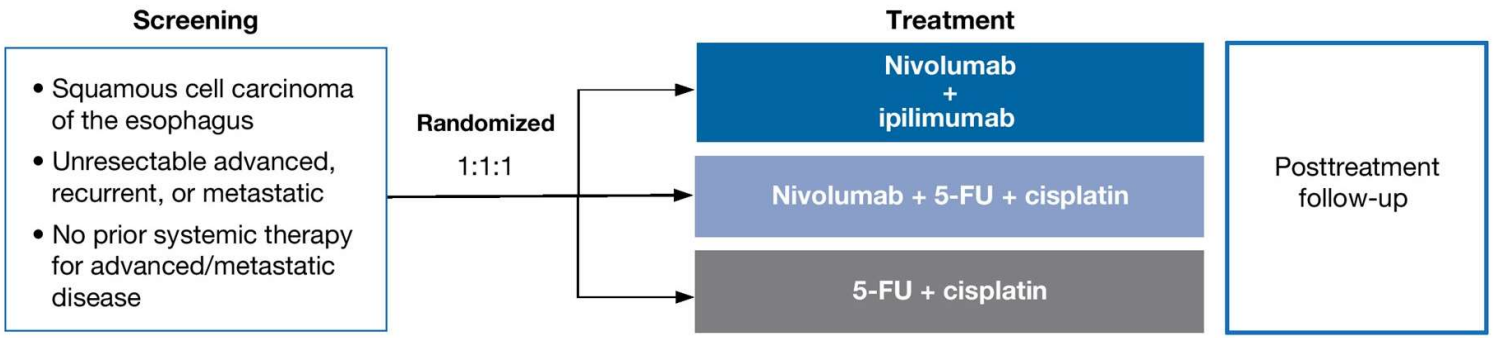
CheckMate 649- Phase III Trial of Nivolumab in First-Line Therapy (Gastric and GEJ)



Primary Endpoint	• OS in patients with PD-L1+ tumors
Secondary Endpoints	• OS in all randomized patients • PFS in patients with PD-L1+ tumors and all randomized patients • TTSD assessed via the GaCS questionnaire in patients with PD-L1+ tumors and all randomized patients

Janjigian, Y. et al., ASCO 2017

CheckMate 648 – Phase III Trial of Nivolumab/Ipilimumab in First-Line Therapy (SCC Esophagus)

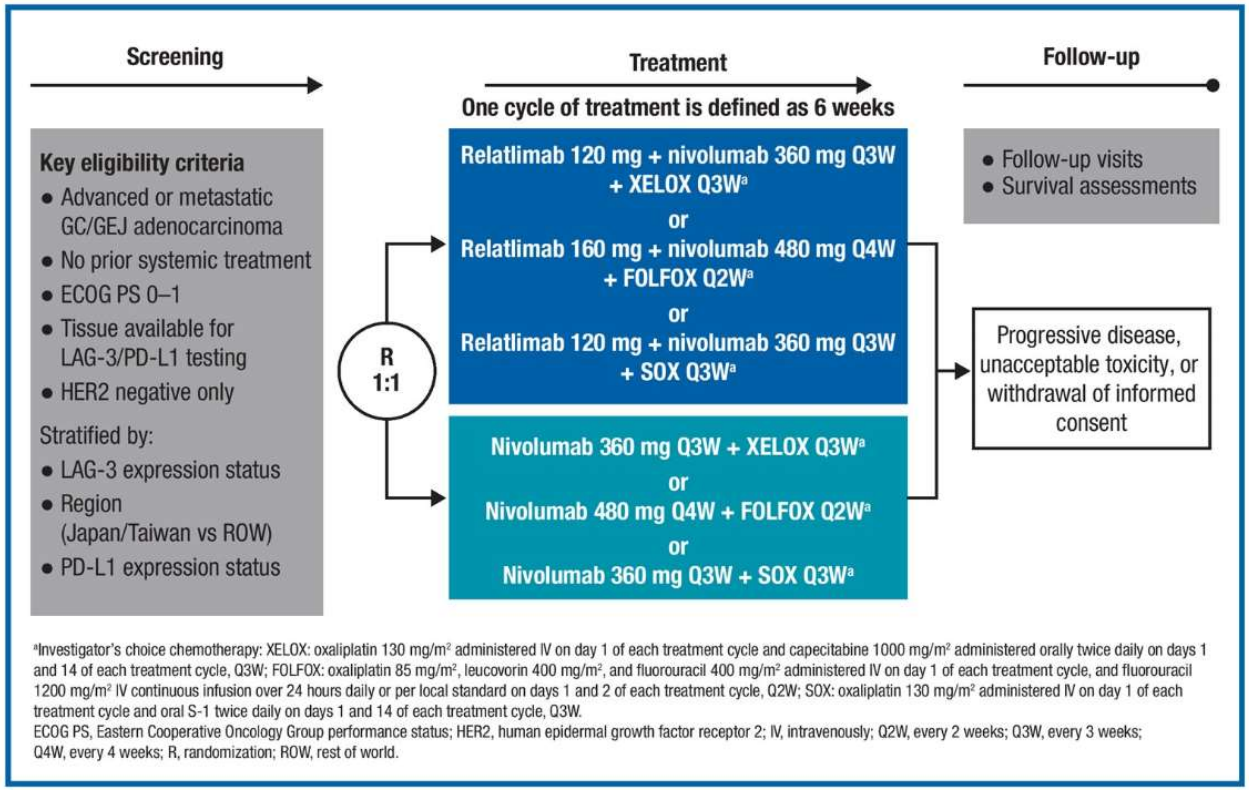


Primary endpoints	• OS and PFS[a] in patients with PD-L1+ tumors
Secondary endpoints	• ORR,[a] PFS,[a] and OS in all randomized patients • ORR[a] in patients with PD-L1+ tumors

Ajani J et al. GI ASCO. 2018

CA224-060: A randomized, Open-Label, Phase 2 Trial of Relatlimab (Anti-LAG-3) and Nivolumab With Chemotherapy vs Nivolumab with Chemotherapy as First-Line Treatment in Patients With Gastric or Gastroesophageal Junction Adenocarcinoma

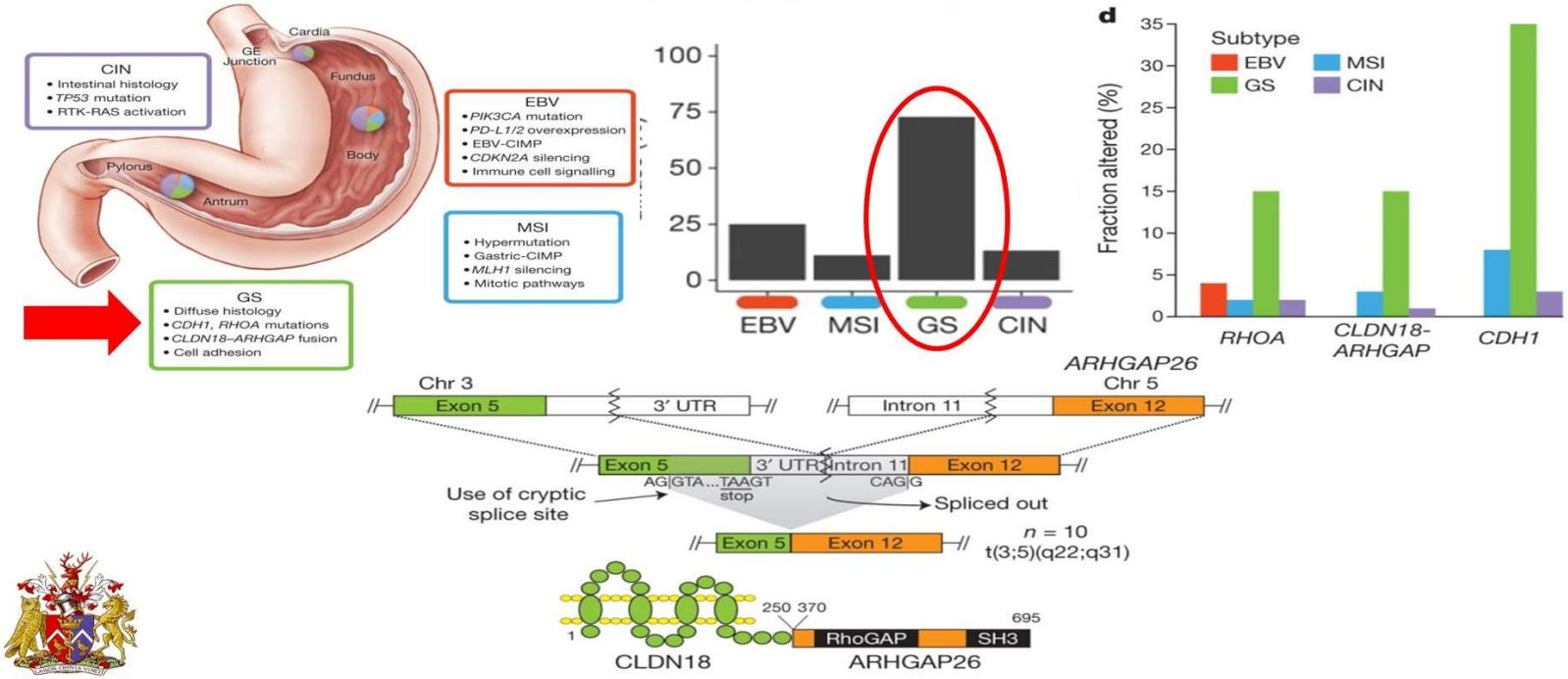
Figure 2. Study design



[a]Investigator's choice chemotherapy: XELOX: oxaliplatin 130 mg/m² administered IV on day 1 of each treatment cycle and capecitabine 1000 mg/m² administered orally twice daily on days 1 and 14 of each treatment cycle, Q3W; FOLFOX: oxaliplatin 85 mg/m², leucovorin 400 mg/m², and fluorouracil 400 mg/m² administered IV on day 1 of each treatment cycle, and fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily or per local standard on days 1 and 2 of each treatment cycle, Q2W; SOX: oxaliplatin 130 mg/m² administered IV on day 1 of each treatment cycle and oral S-1 twice daily on days 1 and 14 of each treatment cycle, Q3W.
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IV, intravenously; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomization; ROW, rest of world.

Feeney et al., ASCO 2019

Genomically stable, diffuse histology and Claudin 18

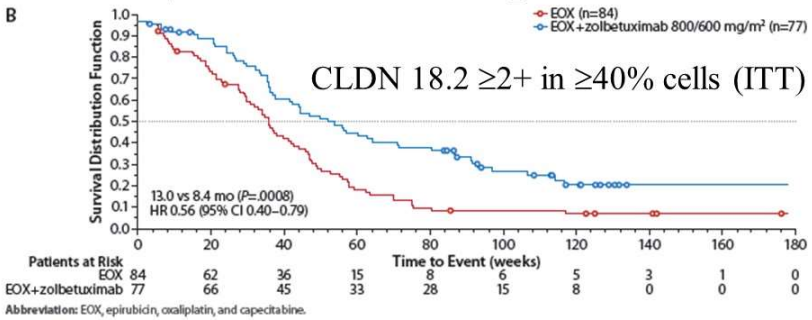


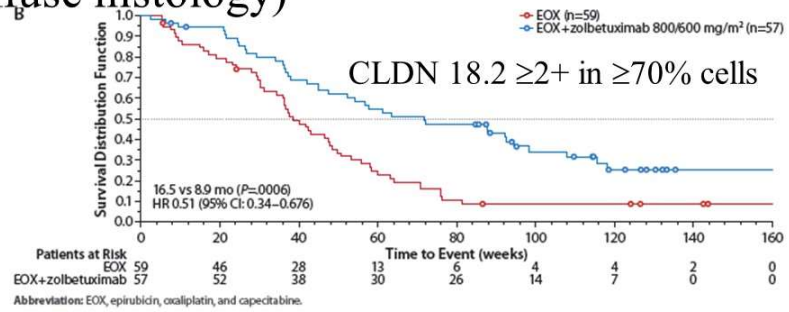
THE ROYAL MARSDEN

The Cancer Genome Atlas Research Network Nature 2014

SPOTLIGHT: 1st line FOLFOX ± Zolbetuximab (IMAB 362) study in Claudin 18.2 positive gastric and GEJ adenocarcinoma

FAST[1](45% of recruited patients were of diffuse histology)





Advanced gastric or OGJ adenocarcinoma expressing CLDN18.2 in ≥ 75% of tumour cells demonstrating (≥2+) moderate to strong membranous staining on IHC

n=550

R

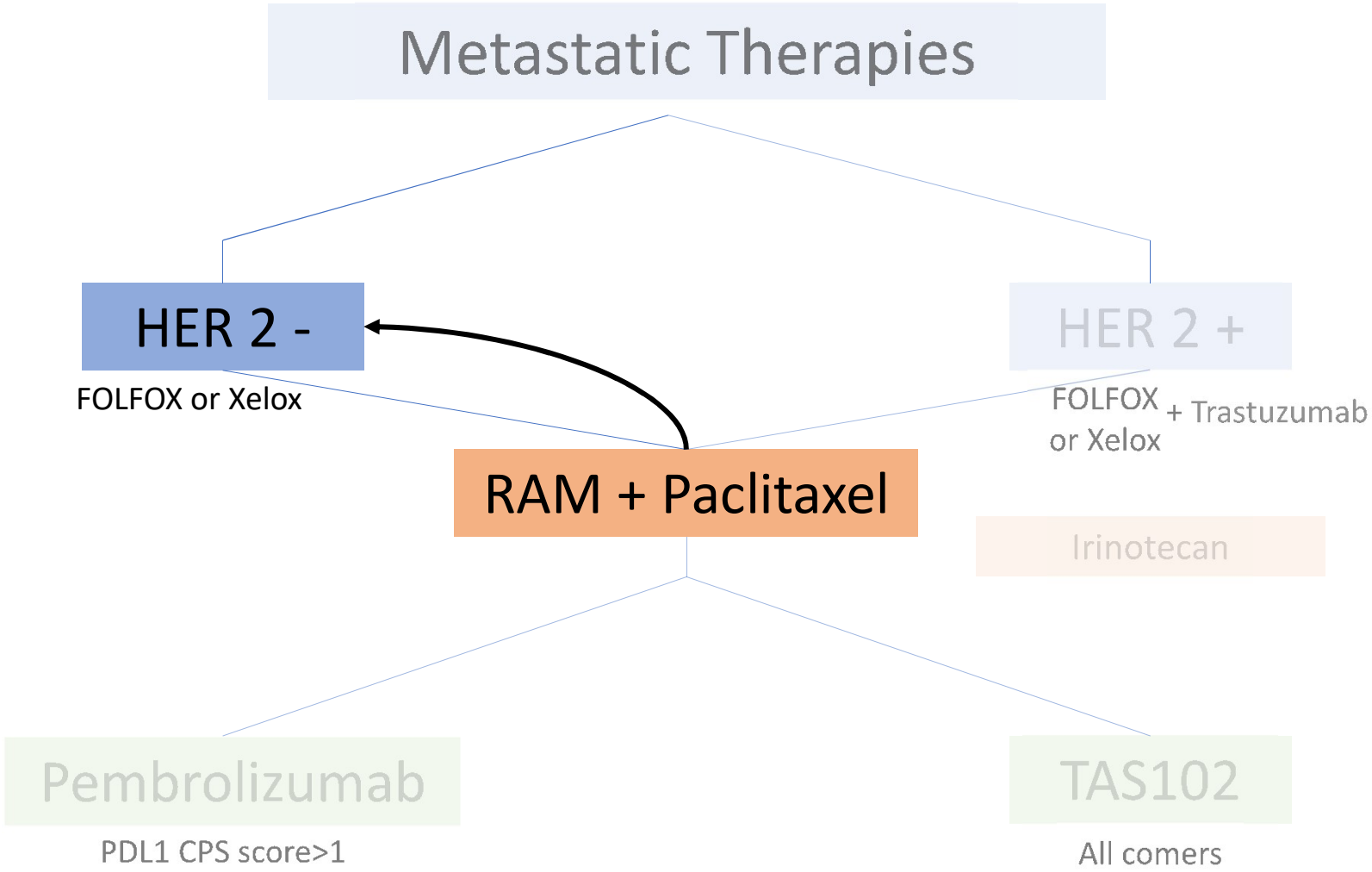
mFOLFOX 6 + placebo

mFOLFOX 6 + Zolbetuximab

1° endpoint: Progression free survival

[1]Sahin et al ASCO GI; NCT03504397

THE ROYAL MARSDEN


Metastatic Therapies
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FOLFOX or Xelox
HER 2 +
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PDL1 CPS score>1
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All comers

Camrelizumab Combined With Capecitabine And Oxaplatin Followed By Camarelizumab And Apatinib As First-line Therapy For Advanced Or Metastatic Gastric Or Gastroesophageal Junction Cancer: Updates Results From A Multicenter, Open-label Phase 2 Trial

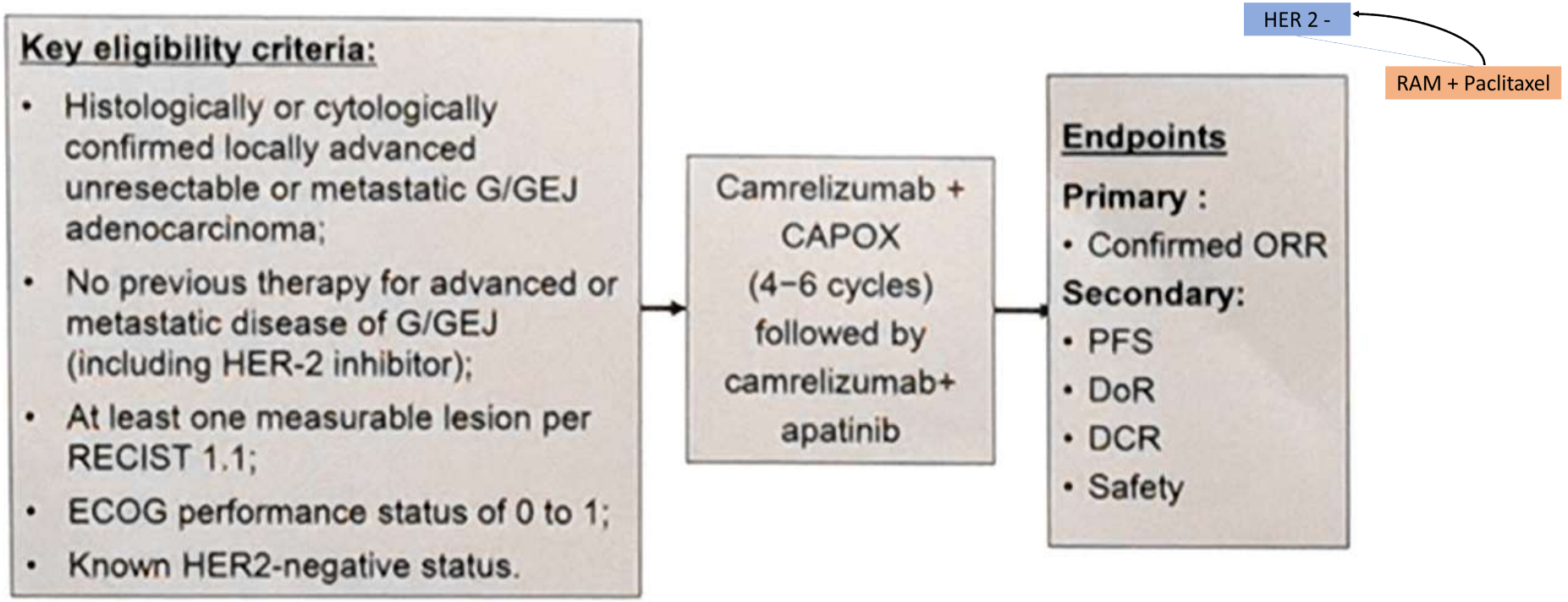


Figure 1: Study design

PFS, progression-free survival; DoR, duration of response; DCR, disease control rate.

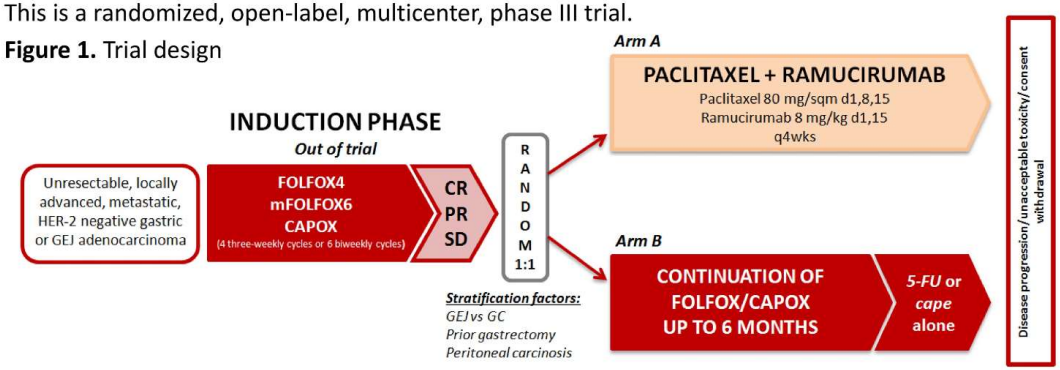
Shen, L. et al., ASCO 2019

ASSESSMENT OF RAMUCIRUMAB PLUS PACLITAXEL AS SWITCH MAINTENANCE VERSUS CONTINUATION OF FIRST-LINE CHEMOTHERAPY IN PATIENTS (PTS) WITH ADVANCED HER-2 NEGATIVE GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCERS: THE ARMANI PHASE III TRIAL

STUDY DESIGN

This is a randomized, open-label, multicenter, phase III trial.

Figure 1. Trial design



Total population: 280 pts (140 per each arm)
Start date: December 2016
Estimated end date: December 2020

NCT02934464

OBJECTIVES

PRIMARY ENDPOINT:

To compare PFS of subjects receiving maintenance with paclitaxel plus ramucirumab (arm A) versus subjects who receive continuation of first-line chemotherapy (arm B) until progressive disease/unacceptable toxicity/death.

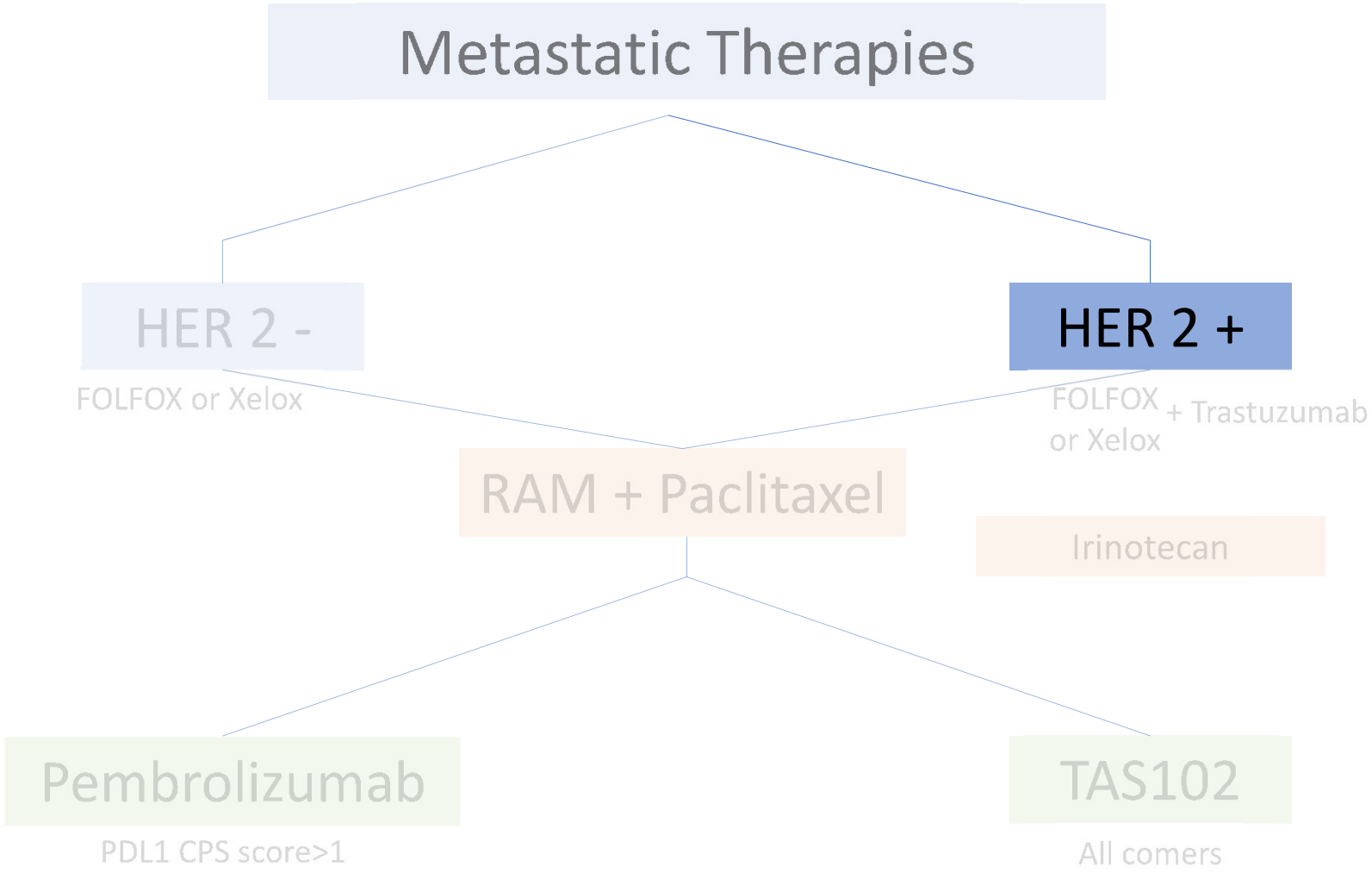
SECONDARY ENDPOINTS:

- ✓Safety
- ✓Response rate and duration of response
- ✓Overall survival
- ✓Patients reported outcomes

EXPLORATORY ENDPOINTS:

- ✓Tumor biomarkers
- ✓Blood/plasma biomarkers

Morano, J et al., ASCO 2019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Irinotecan
Pembrolizumab
PDL1 CPS score>1
TAS102
All comers

Pembrolizumab/Trastuzumab/Chemotherapy

Phase II study schema key eligibility criteria, primary and secondary endpoints and biomarker analysis

1st line Stage IV EG Cancer
HER2 IHC 3+ or IHC 2+/FISH>2.0
MSK confirmation not required prior to Rx

RECIST measurable or evaluable disease

N=37

CT Scan
cfDNA analysis

"induction"

Trastuzumab 8mg/kg
Pembrolizumab 200mg
x 1 cycle

CT Scan
cfDNA analysis
q 9 weeks

***Capecitabine 850mg/m2 bid day 1-14**
Oxaliplatin 130 mg/m2 Trastuzumab 6 mg/kg Pembrolizumab 200 mg q21 days
*** (5-FU and Cisplatin permitted)**

***Primary endpoint**: 6-months PFS*, 26 or more patients progression free at 6 months

Secondary endpoints:
- *OS*
- *ORR & DCR by RECIST 1.1*

Biomarker analysis:
- *MSK HER2 IHC/FISH*
- *PDL-1 IHC (Clone E1L3N, Cell Signaling Technology)*
- *CPS score = PDL-1-pos (tumor cells+lymphocytes +macrophages /# of tumor cells x 100)*
- *NGS by IMPACT at baseline & POD*
- cfDNA analysis

Best response to PEMBRO/TRAS/CAPEOX in RECIST 1.1measurable disease (n=35)

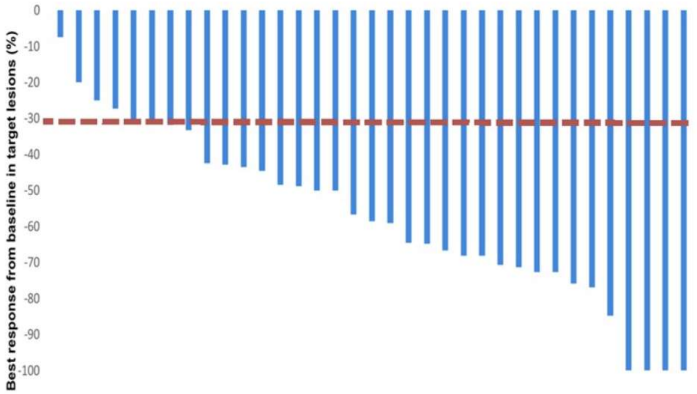


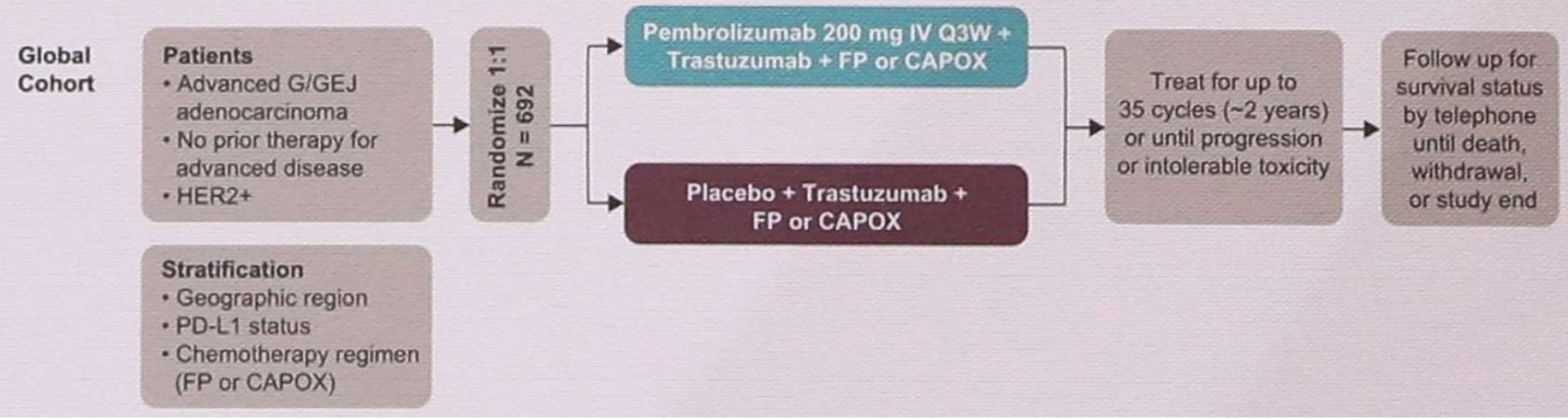
Table 4. Best Response (n=37)	Patients, n (%)
ORR, n (%)	28 (89%) 95% CI (71%; 91%)
CR PR SD PD Non-measurable	4 (11) 27 (77) 4 (11) 0 2
Disease Control Rate	100%

Janjigian Y., ASCO 2019

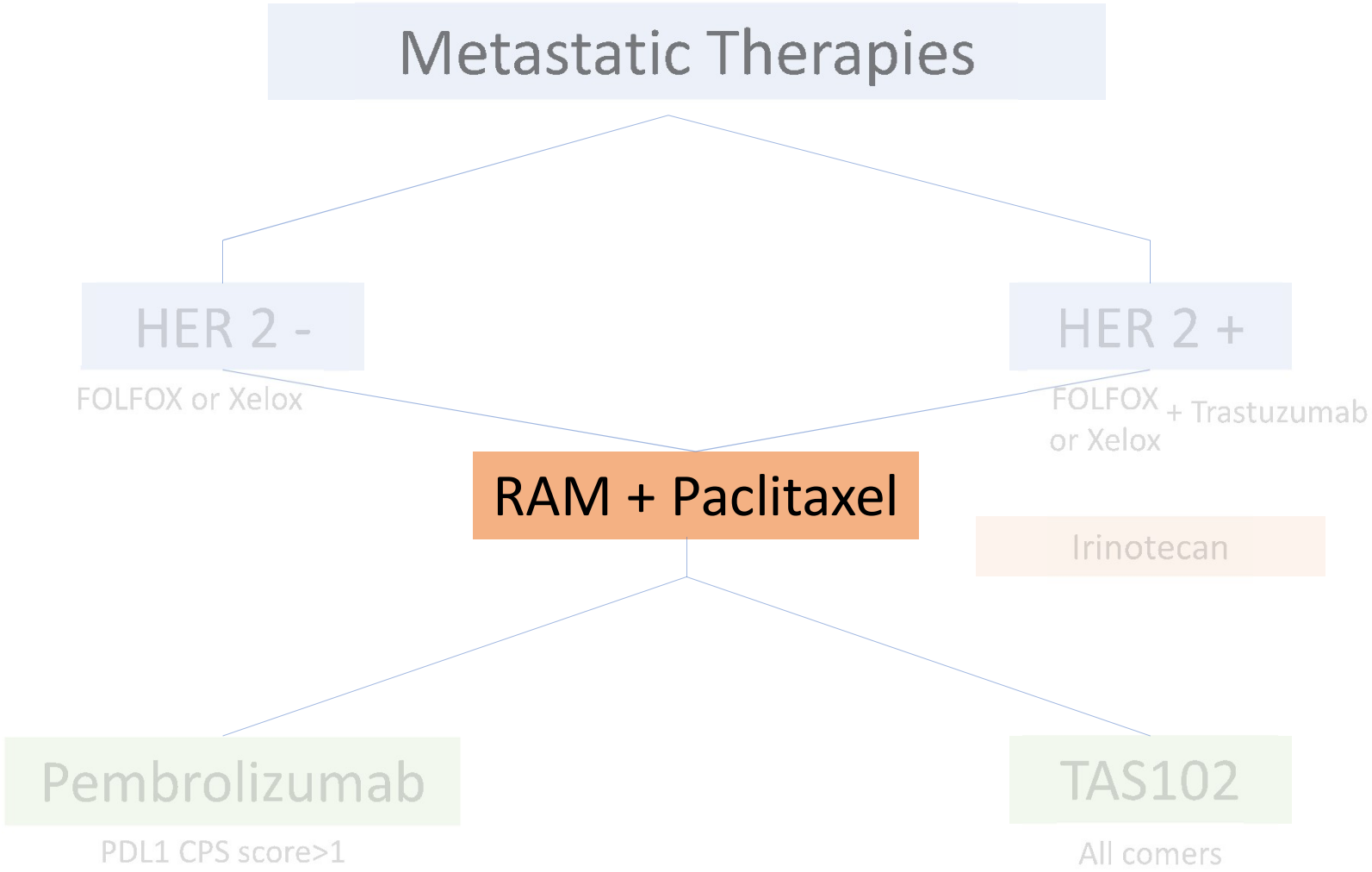
KEYNOTE-811 Phase III study of pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction cancer (mG/GEJC)

- Treatment with pembrolizumab/placebo will continue for up to 35 cycles (~2 years) or until first evidence of disease progression confirmed by blinded independent central review, clinical progression, unacceptable AEs, intercurrent illness, investigator's decision to withdraw the patient, patient withdrawal, patient pregnancy, noncompliance with trial treatment, or achievement of complete response

Figure 2. Study Design



Janjigian, Y. et al., ASCO 2019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FOLFOX or Xelox
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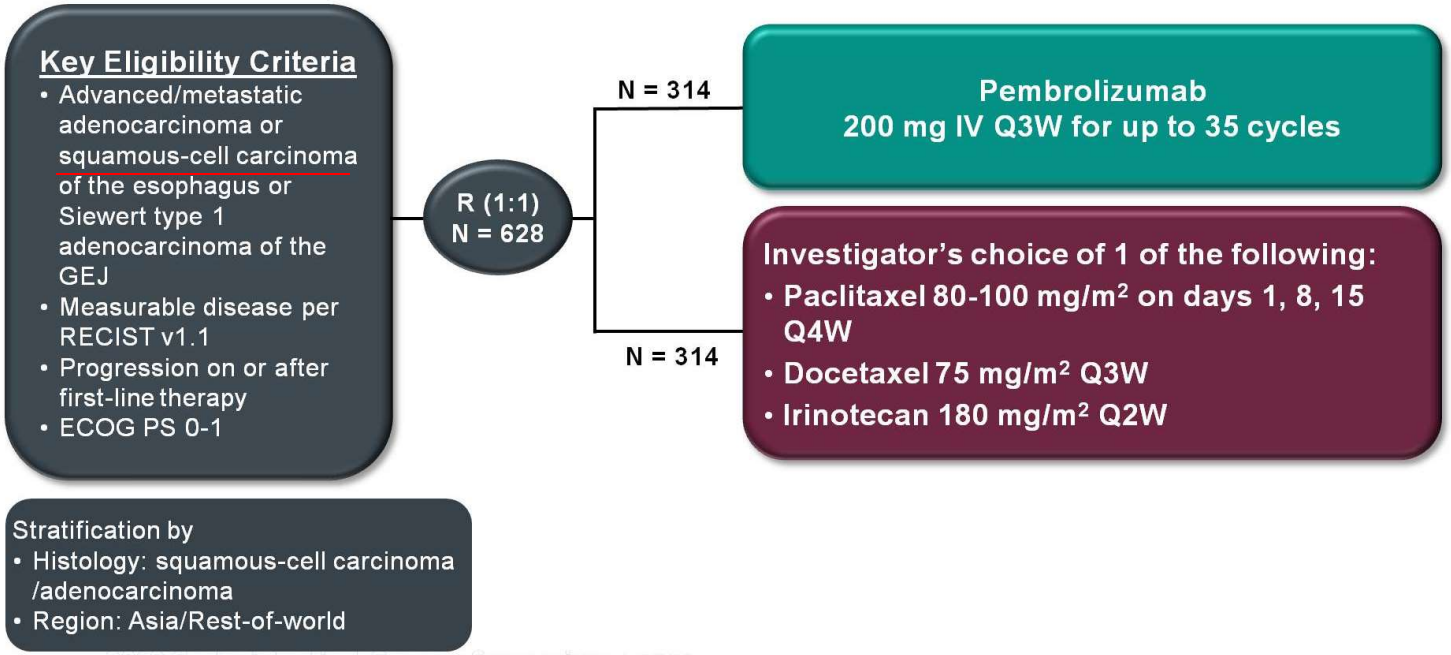
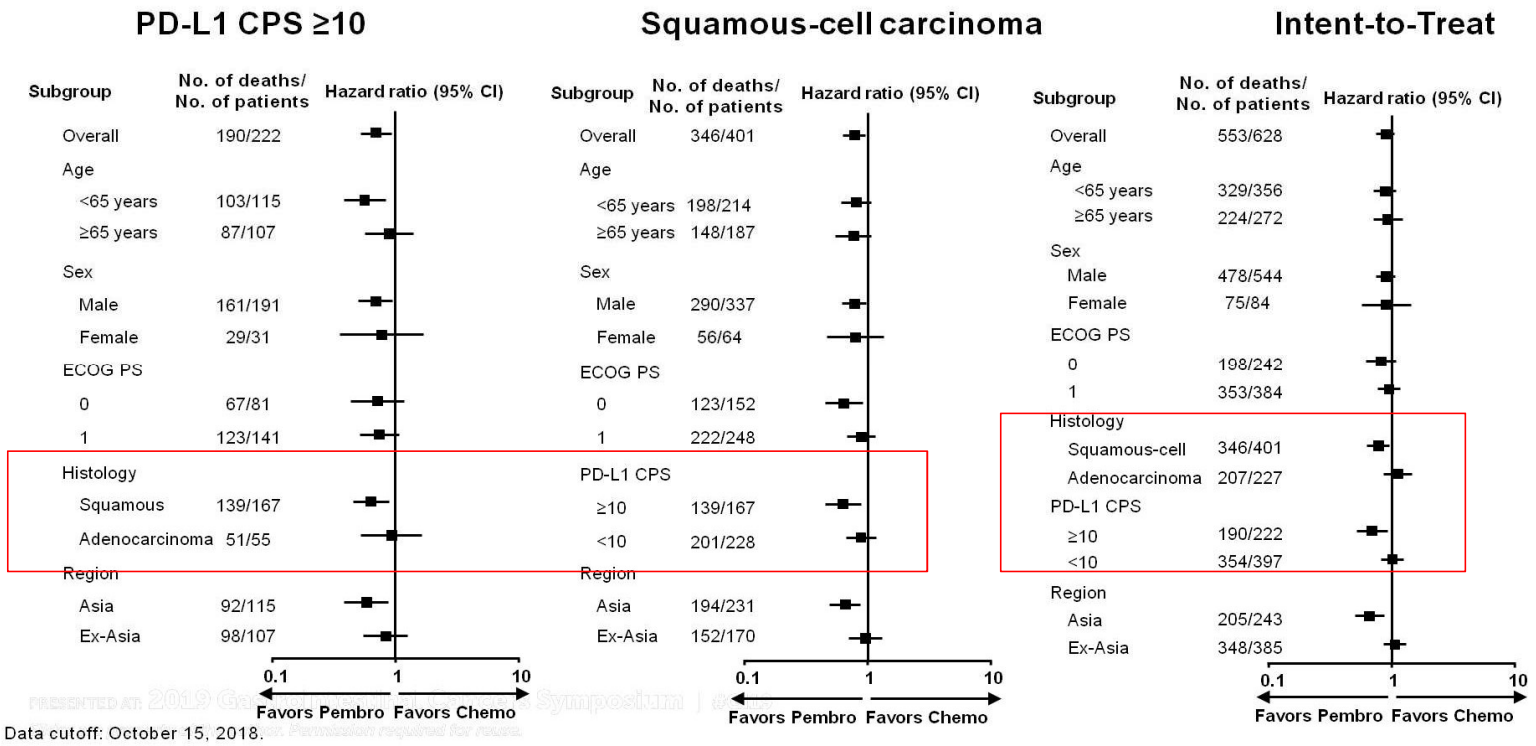
Irinotecan
Pembrolizumab
PDL1 CPS score>1
TAS102
All comers

2nd-line Pembrolizumab for Esophageal Cancer – KEYNOTE-181 Trial (SCC)



Kojima T, et al. GI ASCO. 2019

KEYNOTE 181 Trial – Overall Survival in Key Subgroups



Data cutoff: October 15, 2018.

Kojima T, et al. GI ASCO. 2019

2nd-line Pembrolizumab vs. Chemotherapy – KEYNOTE-061

Key Eligibility Criteria

- Adenocarcinoma of the stomach or GEJ that was metastatic or locally advanced but unresectable
- PD per RECIST v1.1 after first-line platinum- and fluoropyrimidine-containing therapy
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
  - First 489 patients: any PD-L1 CPS
  - Final 103 patients: PD-L1 CPS ≥1

Stratification Factors

- Region (Eur/Israel/N America/Australia vs Asia vs rest of the world)
- ECOG PS (0 vs 1)
- TTP on first-line therapy (<6 mo vs ≥6 mo)
- PD-L1 CS (<1 vs ≥1)

R
1:1

Pembrolizumab 200 mg Q3W

for 35 cycles or until confirmed PD, intolerable toxicity, patient withdrawal, or investigator decision

Paclitaxel 80 mg/m^2 on days 1, 8, and 15 of 4-week cycles

until confirmed PD, intolerable toxicity, patient withdrawal, or investigator decision

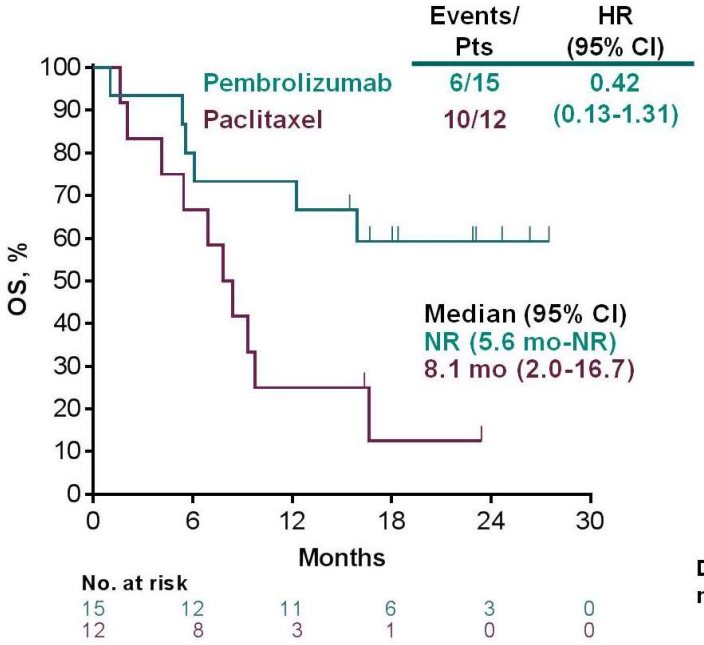
Endpoints

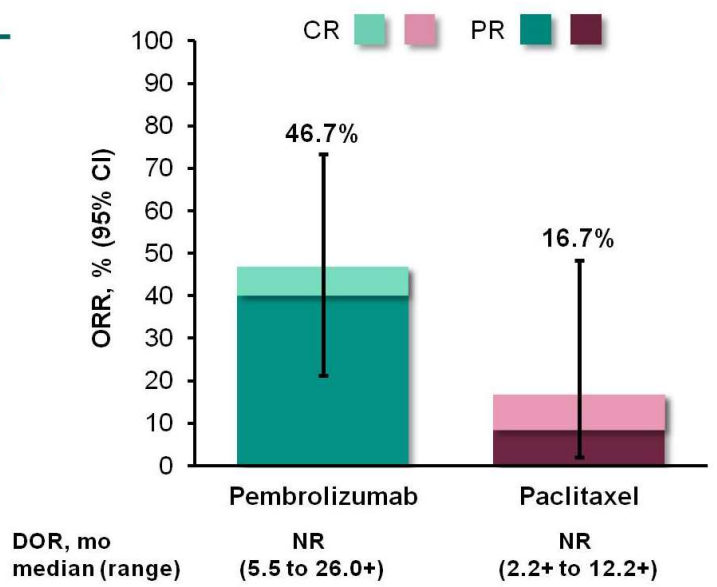
Primary: OS and PFS in the CPS ≥1 population

Secondary: ORR and DOR in the CPS ≥1 population; safety in all treated patients

Shitara K, et al. ASCO. 2018

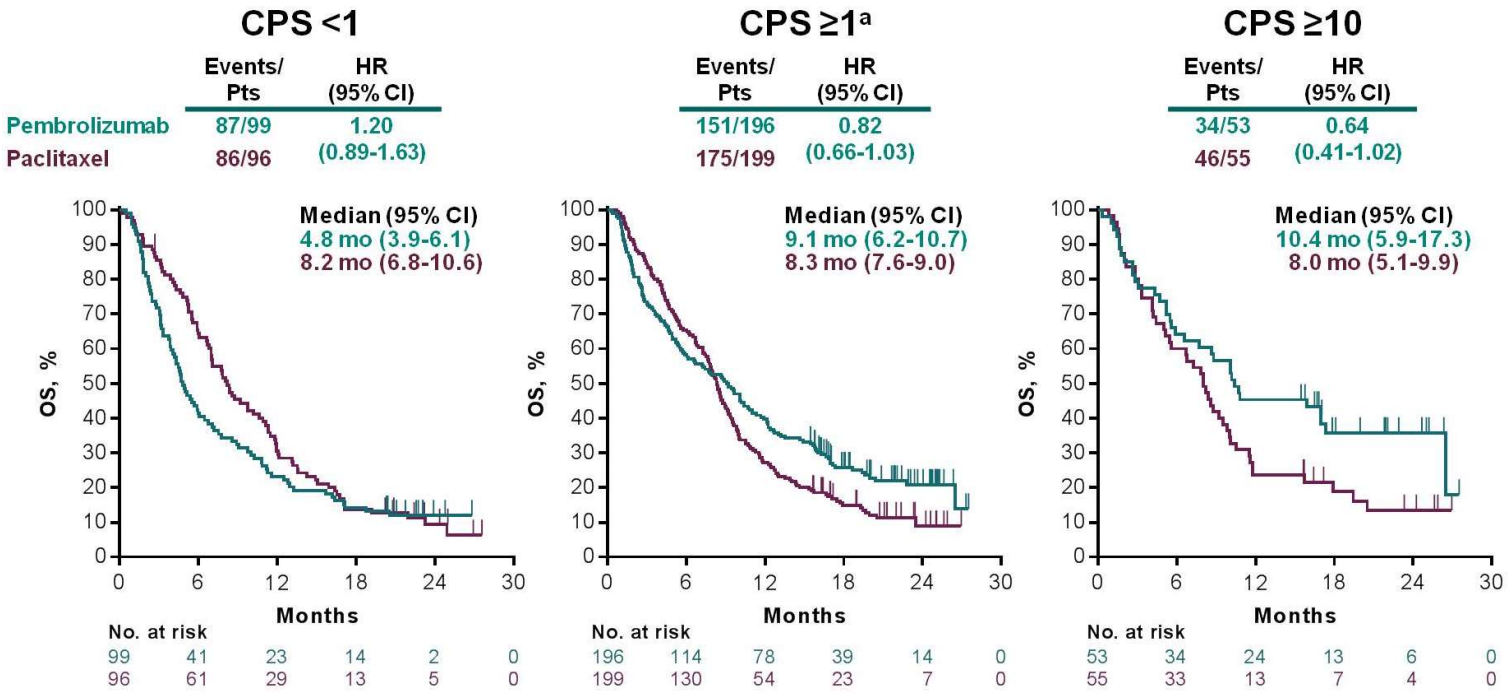
KEYNOTE-061 – Outcomes in MSI-H Subgroup





Shitara K, et al. ASCO. 2018

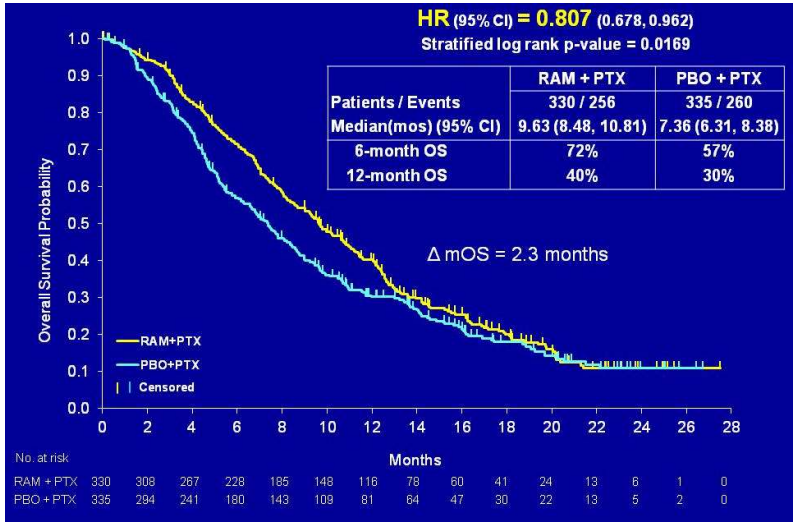
KEYNOTE-061 – Overall Survival by PD-L1 CPS



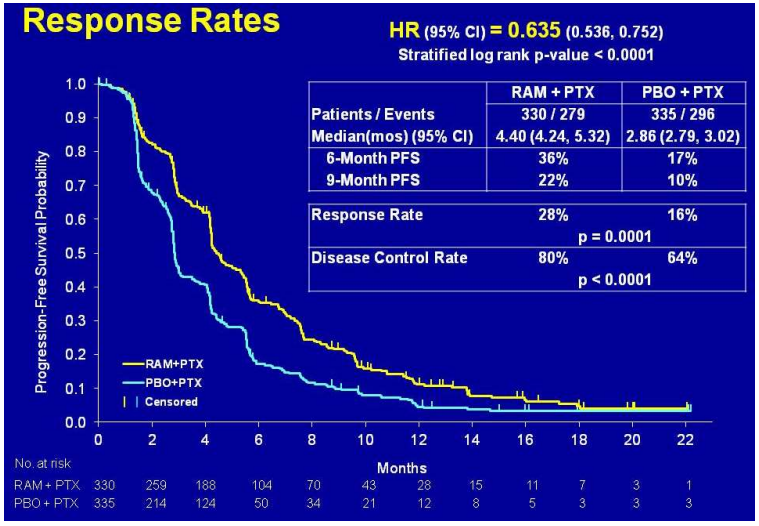
Shitara K, et al. ASCO. 2018

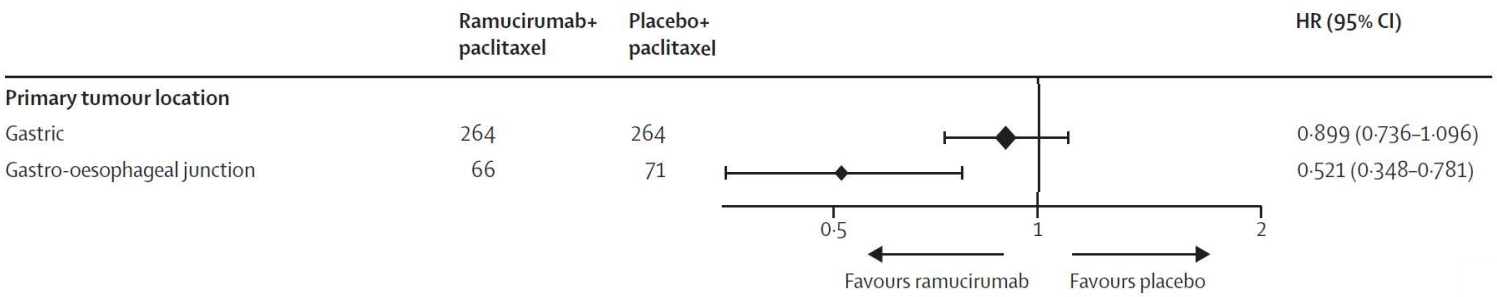
Recall the RAINBOW Trial

OS



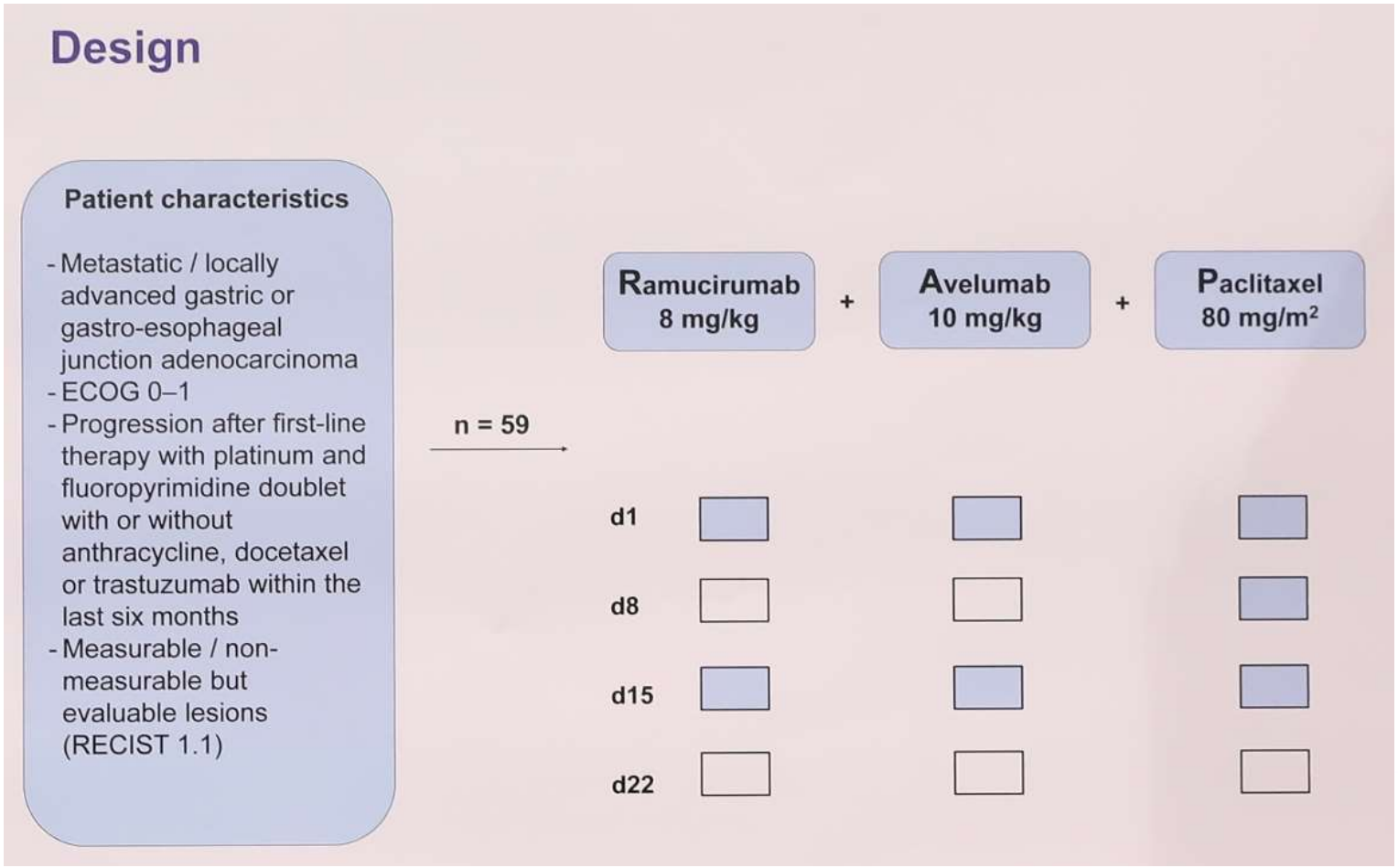
PFS



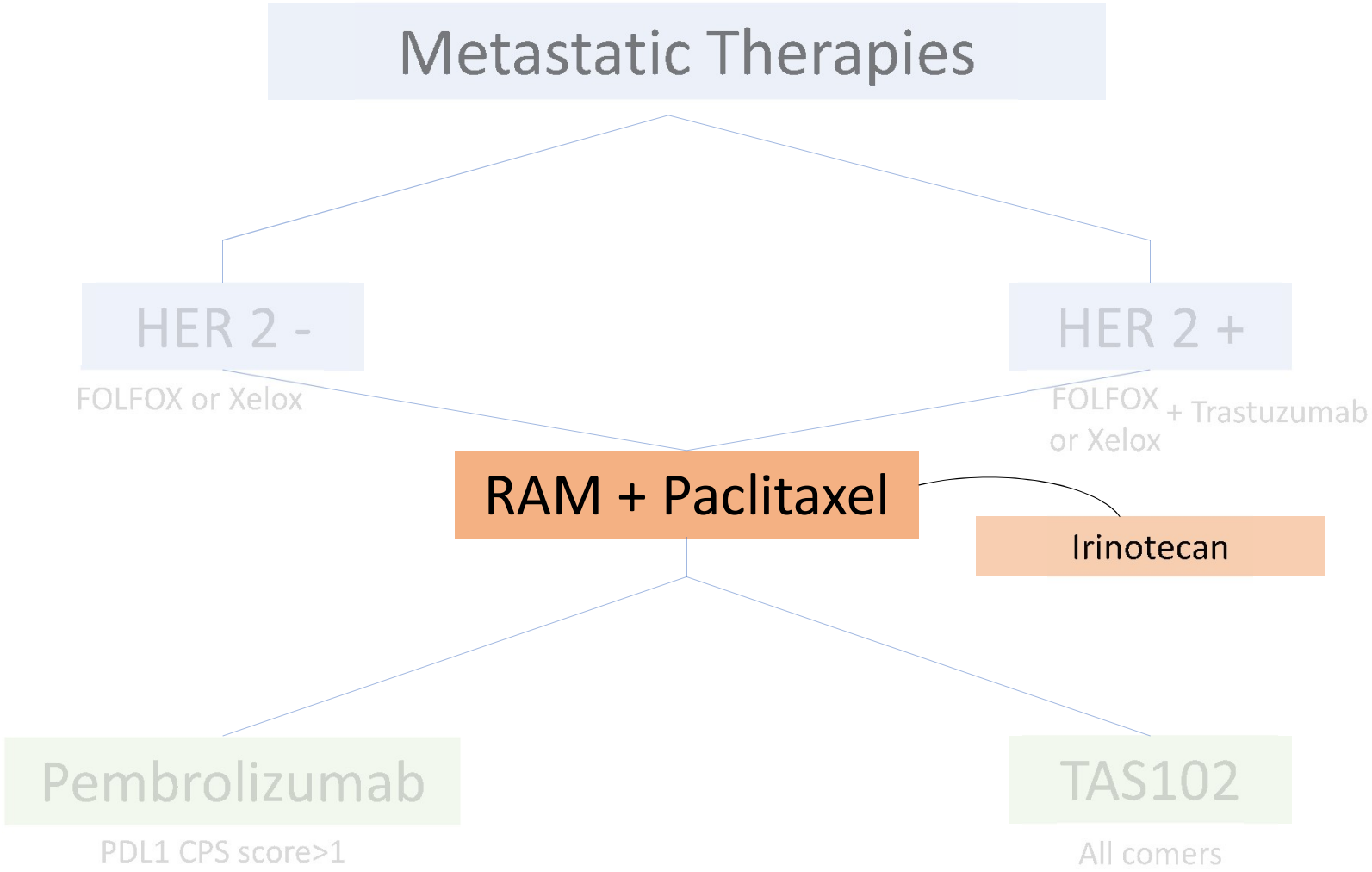


Wilke H, et al. GI ASCO. 2014

RAP: A phase II trial with Ramucirumab, Avelumab and Paclitaxel as second line treatment in gastro-esophageal adenocarcinoma of the Arbeitsgemeinschaft Internistische Onkologie (AIO)

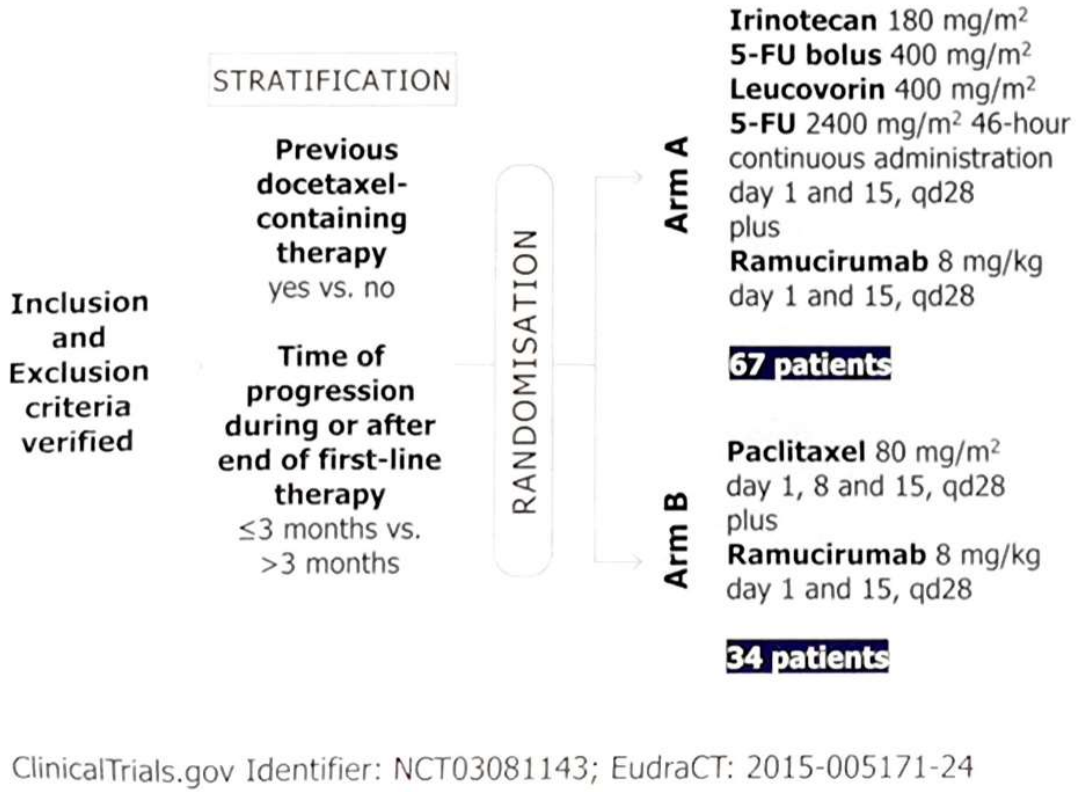


Högner, A. et al., ASCO 2019


Metastatic Therapies
HER 2 -
FOLFOX or Xelox
HER 2 +
FOLFOX or Xelox + Trastuzumab
RAM + Paclitaxel
Irinotecan
Pembrolizumab
PDL1 CPS score>1
TAS102
All comers

FOLFORI plus ramucirumab vs paclitaxel plus ramucirumab for patients with advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction as second line therapy – interim safety and efficacy results from the phase II RAMIRIS Study (AIO-STO-0415) of the German Gastric Group at AIO

Figure 1: Study Design



ClinicalTrials.gov Identifier: NCT03081143; EudraCT: 2015-005171-24

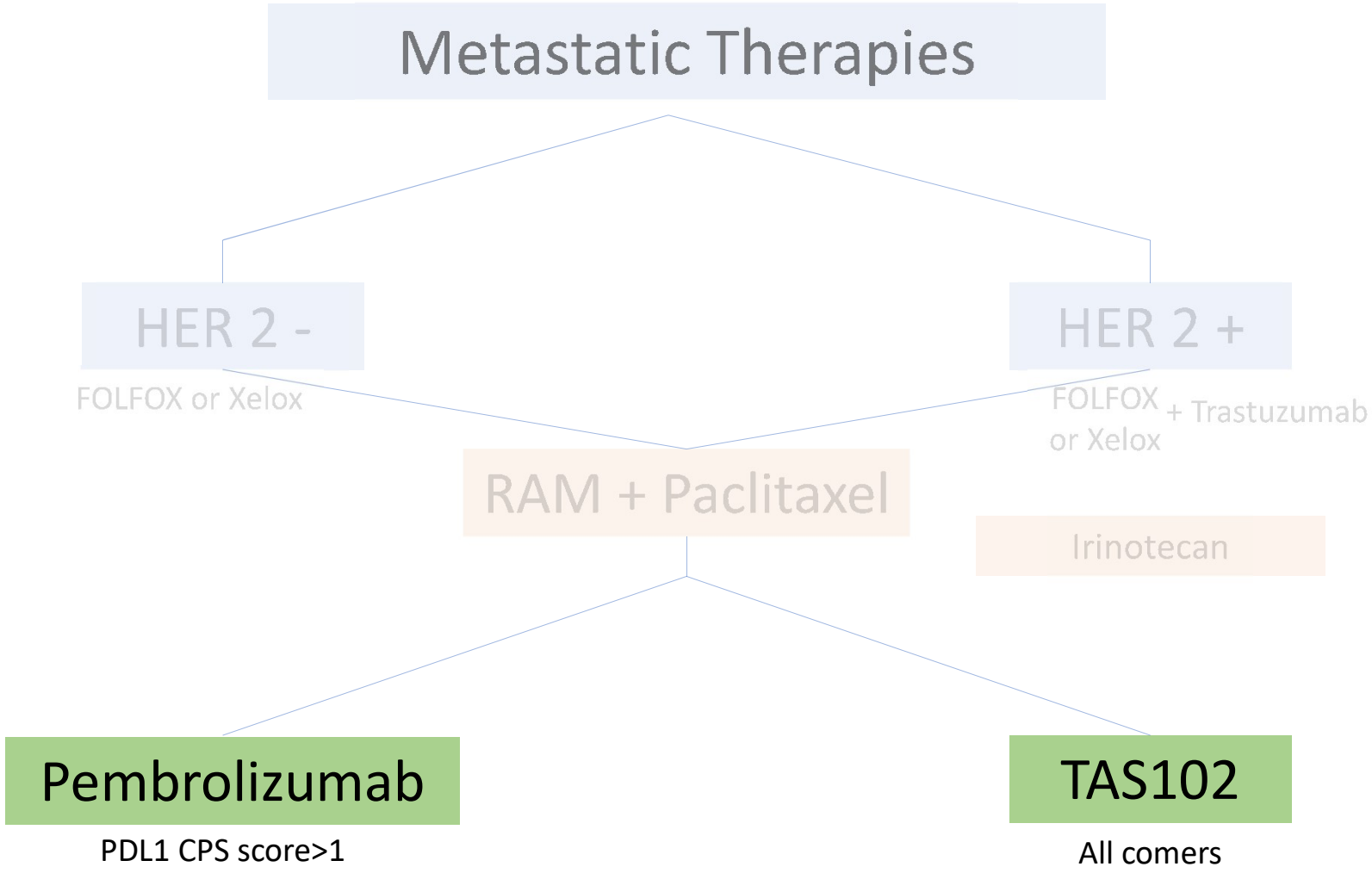
Lorenzer, P et al., ASCO 2019

Table 4: Response Rates by Taxane Pretreatment

Response Rates in 50 patients with at least one valid tumor assessment with a response categorization documented.

Stratum	Response	FOLFIRI+ Ramucirumab	Paclitaxel+ Ramucirumab
No previous docetaxel	n	14	7
	CR	--	--
	PR	1 (7%)	1 (14%)
	SD	8 (57%)	5 (71%)
	PD	5 (36%)	1 (14%)
Previous docetaxel	n	17	12
	CR	2 (12%)	1 (8%)
	PR	3 (18%)	0 (0%)
	SD	6 (35%)	5 (42%)
	PD	6 (35%)	6 (50%)

Lorenzer, P et al., ASCO 2019


Metastatic Therapies
HER 2 -
FOLFOX or Xelox
HER 2 +
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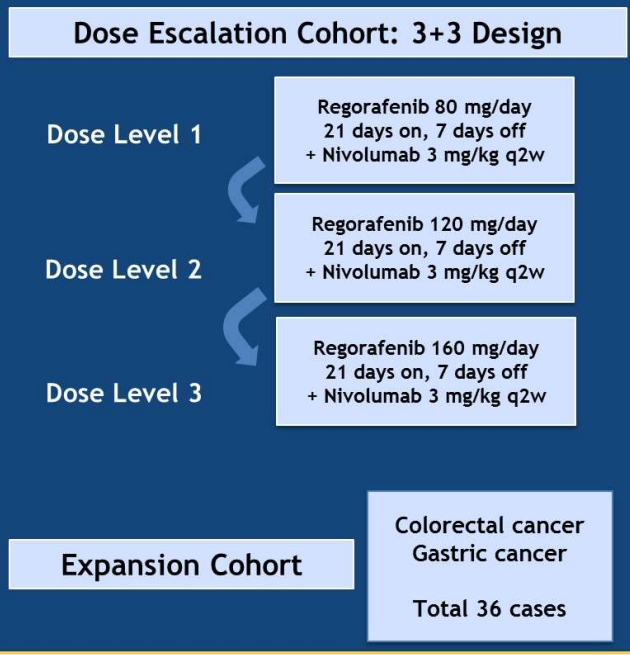
+ Trastuzumab
RAM + Paclitaxel
Irinotecan
Pembrolizumab
PDL1 CPS score>1
TAS102
All comers

Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): open-label, dose-expansion phase 1b trial (REGONIVO, EPOC1603)

Abstract 2522

- In preclinical studies, regorafenib treatment reduced TAMs in both MC38 and CT26 CRC tumors in a dose-dependent manner; regorafenib also induced M1-type macrophage conversion[1]
- Antitumor activity of both regorafenib and anti-PD-1 Ab in MC38 tumors was significantly enhanced by concomitant treatment

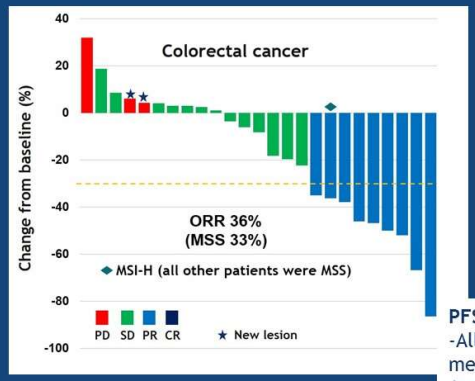


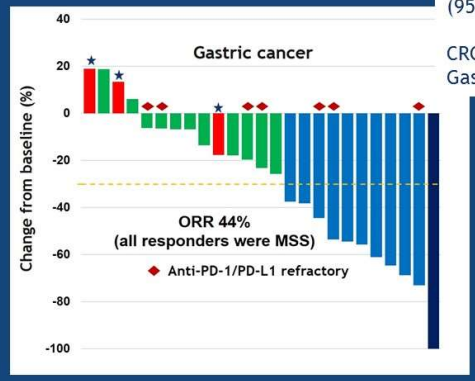
[1]Hoff, et al; ESMO 2018 7

REGONIVO: Safety and Activity

Abstract 2522

- N=50 patients enrolled:
  - Escalation n=14, expansion n=36
- 3 DLTs were observed with regorafenib 160 mg (Gr 3 rash, proteinuria, colonic perforation)
- MTD determined as 120 mg → dose decreased to 80 mg in expansion
  - Gr ≥3 adverse events rate was 27% with regorafenib 80 mg (vs 44% with 120 mg)
  - Common Gr ≥3 AEs: proteinuria (12%), rash (12%), palmar-plantar erythrodysesthesia (10%) and hypertension (4%)
- ORR 40% (95% CI:26-55); PR n=19, CR n=1
- DCR 88% (95% CI:76-96)
- Median duration of treatment was 6.1 months (range 0.7- 14.9 months)
- Suggests incremental activity considering prior reported monotherapy outcomes for either agent alone[1,2,3,4]





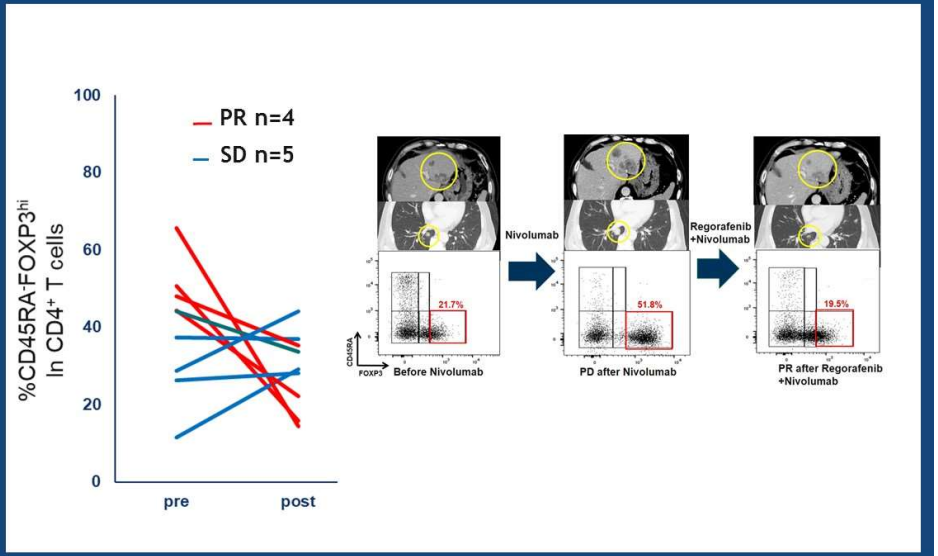
PFS:
-All patients
median 6.3 months
(95%CI 3.4-9.3)

CRC: median 6.3 months
Gastric: median 5.8 months

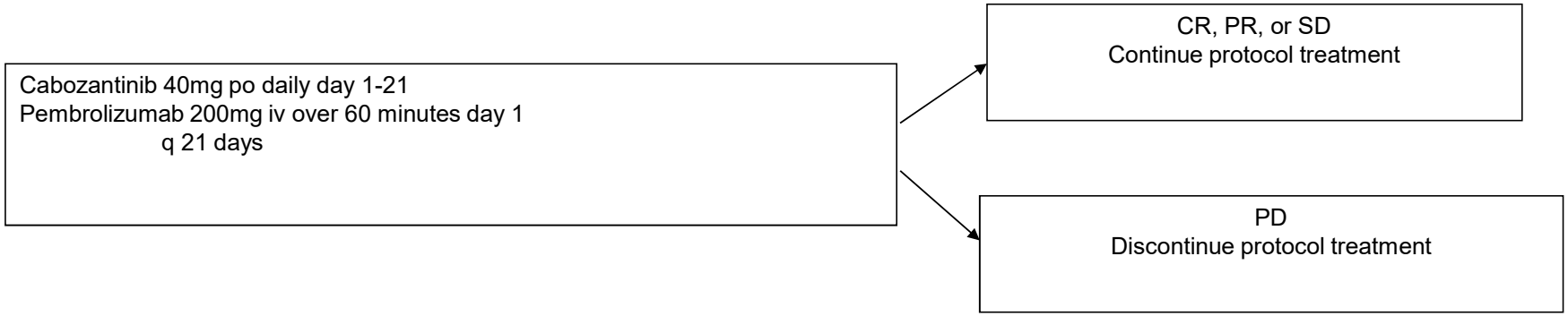
[1]Grothey, et al. *Lancet*. 2013
[2]Lee, et al. *NEJM*. 2015
[3]Pavlakis, et al. *JCO*. 2016
[4]Kang, et al. *Lancet*. 2017

REGONIVO: PD Correlatives

- Pre-and post-treatment biopsy samples in 9 gastric cancer patients were analyzed using flow cytometry
  - Post-treatment biopsy samples showed a decrease in Tregs in patients that responded to regorafenib+nivolumab



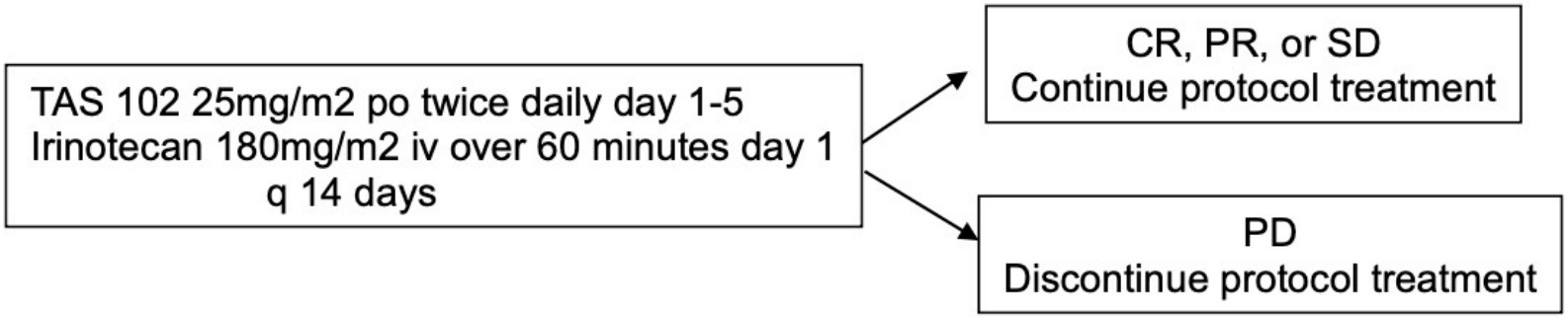
Phase 2 Study of cabozantinib combined with pembrolizumab in metastatic or recurrent gastric and gastroesophageal Adenocarcinoma



OPENING NOW at UCI and UCD

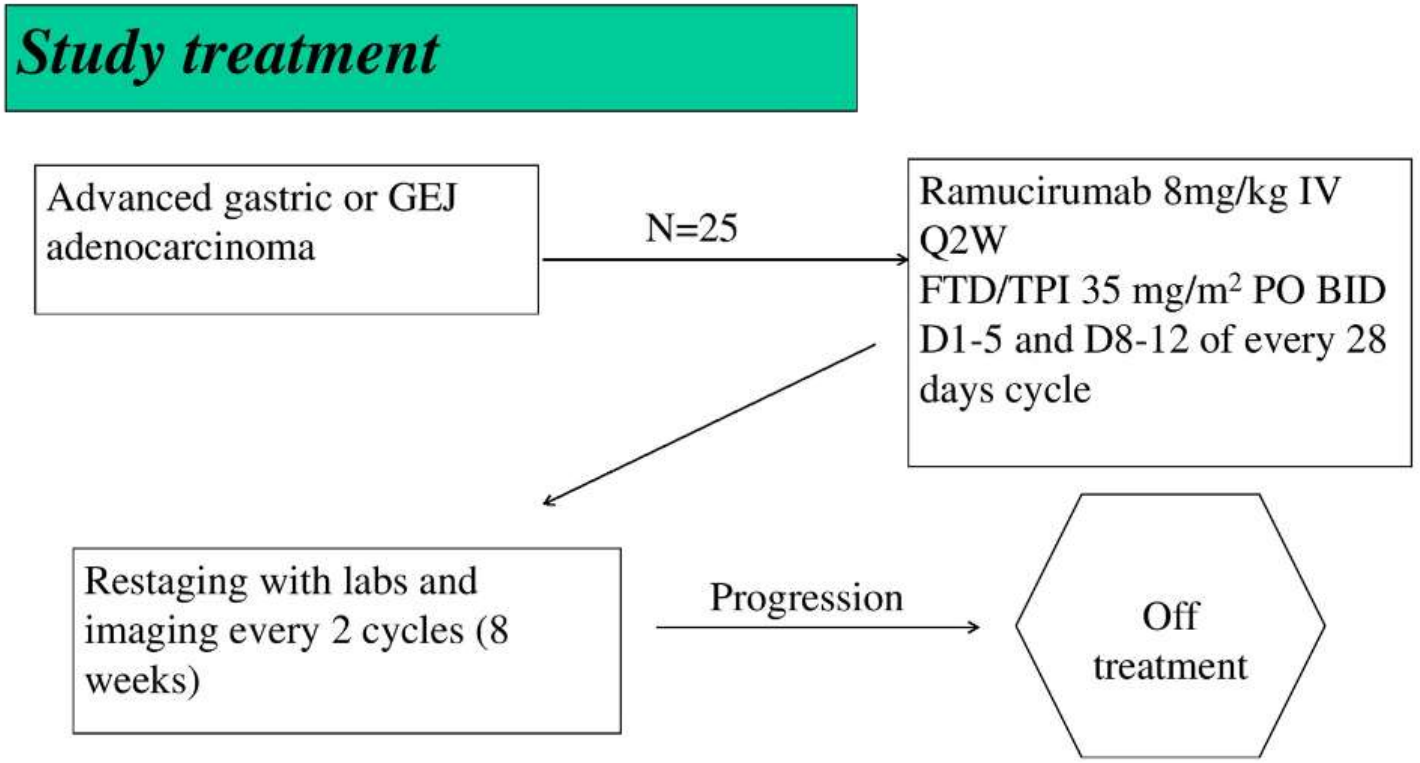
A Phase Ib study of TAS-102 (FTD/TPI) in combination with irinotecan in advanced, refractory gastric or gastroesophageal (GEJ) adenocarcinoma

STUDY SCHEMA



OPENING NOW at UCI and UCD

A Phase II study of TAS-102 (FTD/TPI) in combination with ramucirumab in advanced, refractory gastric or gastroesophageal (GEJ) adenocarcinoma



Metha, R. et al., ASCO 2019

Summary

Perioperative Therapies

Metastatic Therapies

- 1st line (non-HER2 overexpression)- 1st line IO was not impressive
- 1st line (HER2 overexpression)
- 2nd line- Pembrolizumab for 2nd SCC and CP>10
- 3rd line

Thank You

- Joseph Chao, MD and COH Heme/onc
- Edward Kim, MD, PhD, Karen Kelly, MD and UCD Heme/onc
- Farshid Dayyani, MD, PhD