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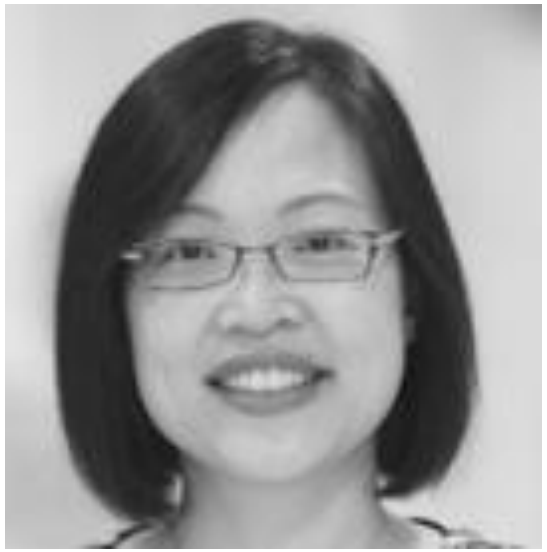

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EDUCATIONAL OBJECTIVES

- To discuss the gastric and gastroesophageal treatment landscape and disease prevalence in Asia
- To understand the current treatment options for 2L and 3L gastric and gastroesophageal cancers plus treatment selection strategies
- To learn about the latest research and clinical trials in 2L and 3L treatments for gastric and gastroesophageal cancers

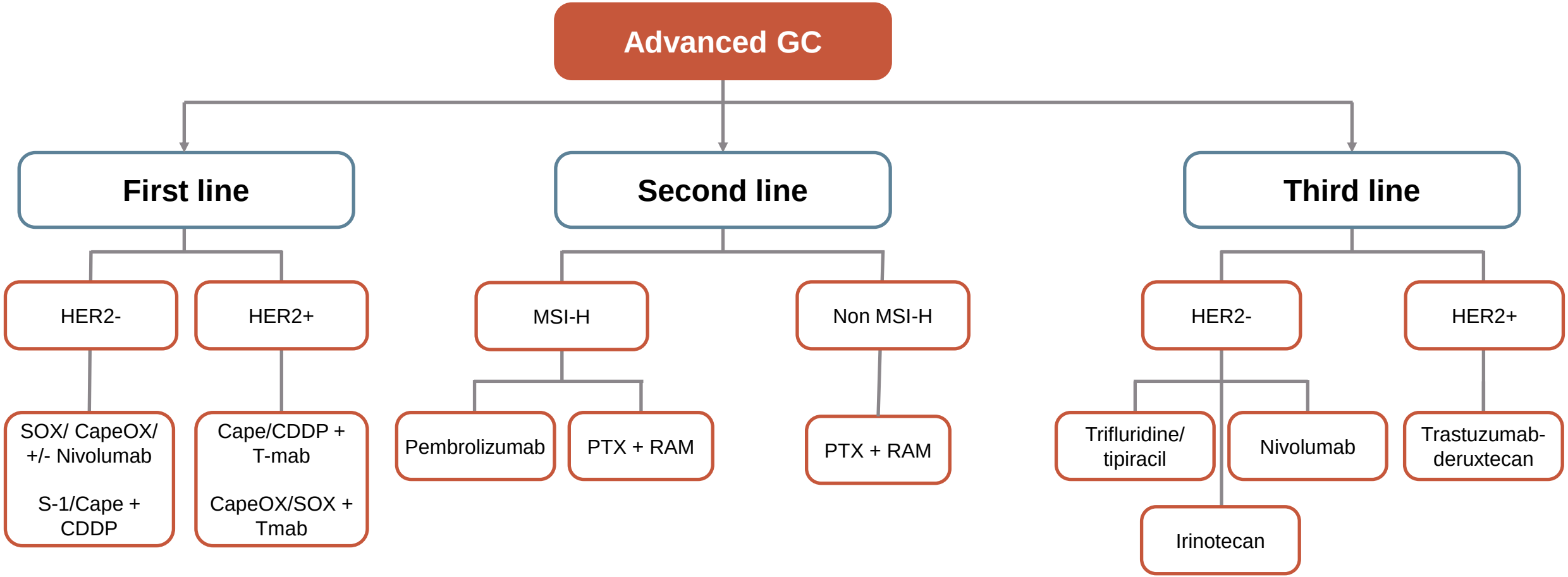
2L, second line; 3L, third line

CLINICAL TAKEAWAYS

- Overall survival in patients with advanced gastric and GE cancers has improved with more effective systemic therapy
- Current therapies in the second line and beyond setting may not be reflective of the changing landscape of first-line therapy in advanced disease but trials are ongoing.
- Factors to consider when evaluating a patient for the second line and beyond therapy include prior lines of therapy and residual toxicities, performance status and competing comorbidities
- PTX+RAM is the standard of care for second-line treatment, but there are multiple candidates for third-line treatment, which is not clearly defined
- For HER2-positive gastric cancer, T-DXd was shown to be effective after trastsuzumab failure. Currently, the development of second-line therapy after trastsuzumab failure is the focus of attention

ADVANCED GASTRIC AND GASTROESOPHAGEAL CANCERS IN ASIA: BEYOND FIRST-LINE TREATMENT

GASTRIC CANCER JAPANESE RECOMMENDED TREATMENT GUIDELINES



5-FU, fluorouracil; Cape, capecitabine; CapeOX, capecitabine and oxaliplatin; CDDP, Oxaliplatin; CPS, combined positive score; GC, gastric cancer; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability High; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PTX, paclitaxel; RAM, ramucirumab; SOX, S-1 and oxaliplatin; T-mab, trastuzumab

Japanese Gastric Cancer Association. Gastric Cancer. 2023;26:1-25

SECOND LINE TREATMENT OPTIONS IN ASIA

2L, second line

TRIALS OF SECOND LINE CHEMOTHERAPY FOR GASTRIC CANCER IN JAPAN

WJOG 4007: Study Design[1]

Phase 3

AGC Refractory to prior FP confirmed by imaging
Age 20-75 years, ECOG PS 0-2, No history of CPT-11 or taxanes

Randomisation
Stratified by
Institution, PS 0-1/2, measurable lesion -/+

- **Weekly paclitaxel** 80 mg/m² day 1, 8 & 15 q4w
- **CPT-11** 150 mg/m² day 1, 15 q4w

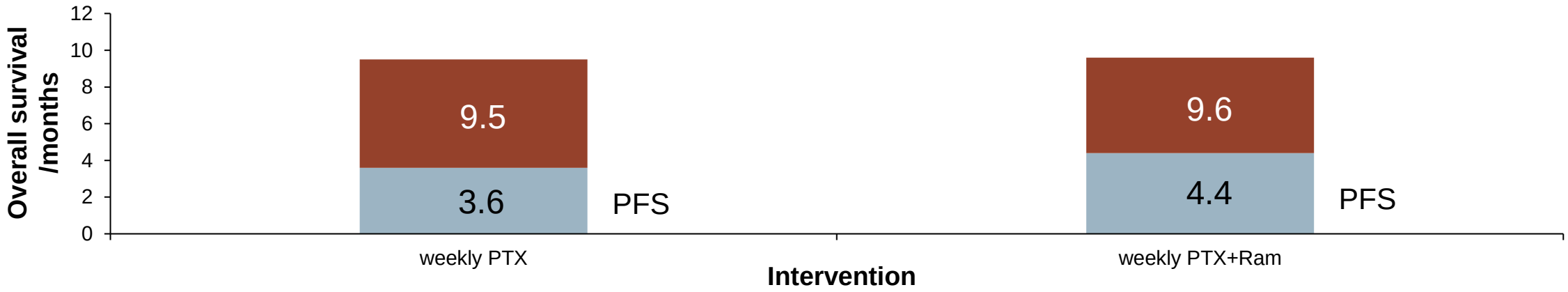
RAINBOW: Study Design[2]

Phase 3

SCREEN → **R 1:1**

- **Ramucirumab 8 mg/kg day 1 & 15 + paclitaxel 80 mg/m² day 1, 8 & 15 of a 28 day cycle** N=330
- **Placebo day 1 & 15 + paclitaxel 80 mg/m² day 1, 8 & 15** N=335

→ **Treat until disease progression or intolerable toxicity** → **Survival and safety follow-up**



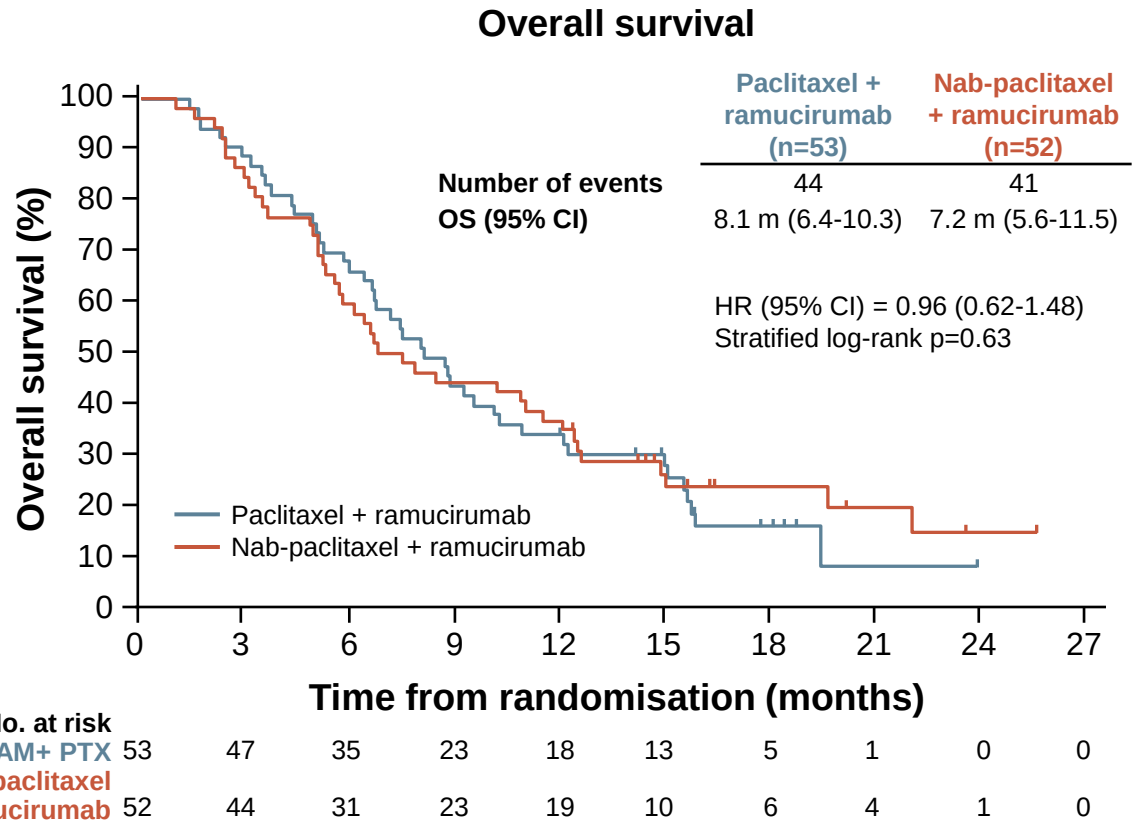
AGC, advanced gastric cancer; CPT-11, irinotecan; ECOG PS, Eastern Cooperative Oncology Group performance status; FP, fluoropyrimidine + platinum; q4w, every 4 weeks; R, randomisation; RAM, ramucirumab; WJOG, West Japan Oncology Group

1.Hironaka S, et al. J Clin Oncol. 2013;31:4438-44; 2.Wilke H, et al. Lancet Oncol. 2014;15:1224-35

SECOND-LINE CHEMOTHERAPY TRIALS' RESULT IN ASIA

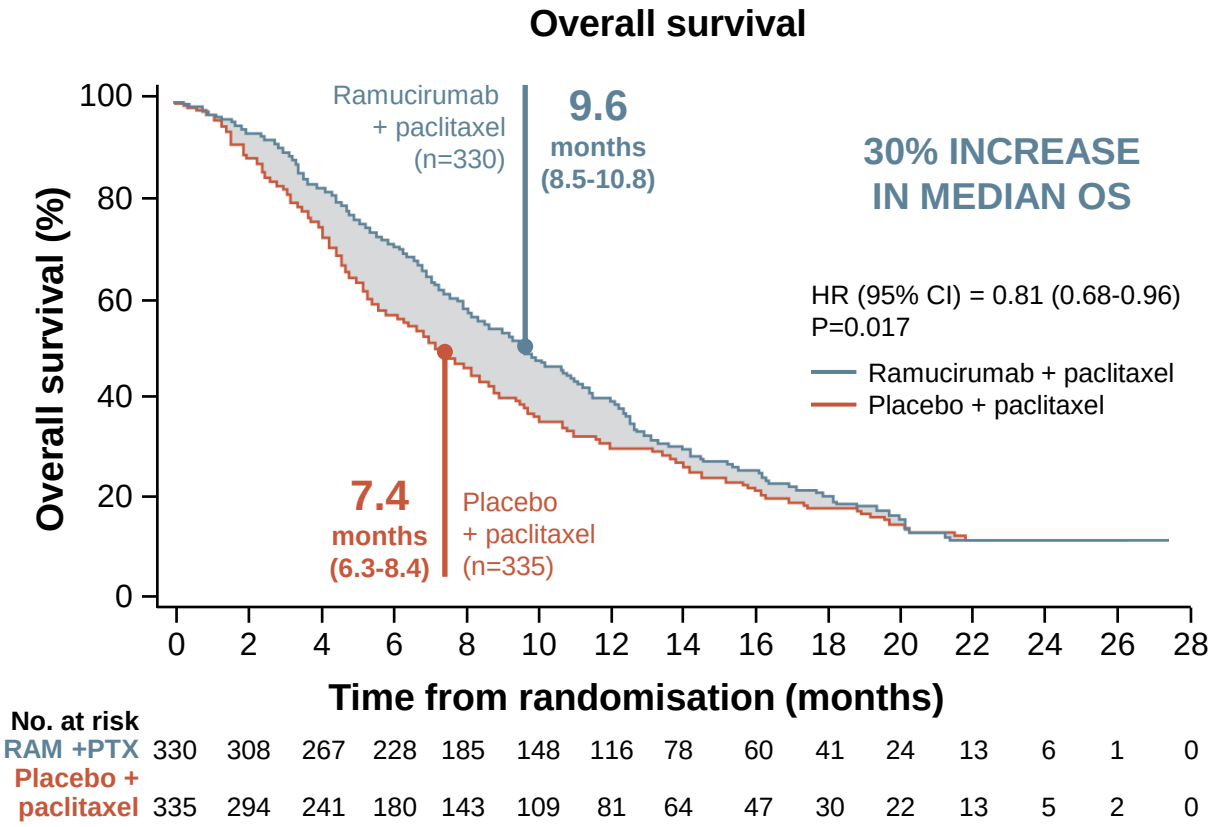
WJOG STUDY[1]

- No difference was demonstrated between nab-paclitaxel + ramucirumab and weekly paclitaxel + ramucirumab in 2L setting



RAINBOW[2]

- Demonstrated improved OS in ramucirumab + paclitaxel vs paclitaxel alone

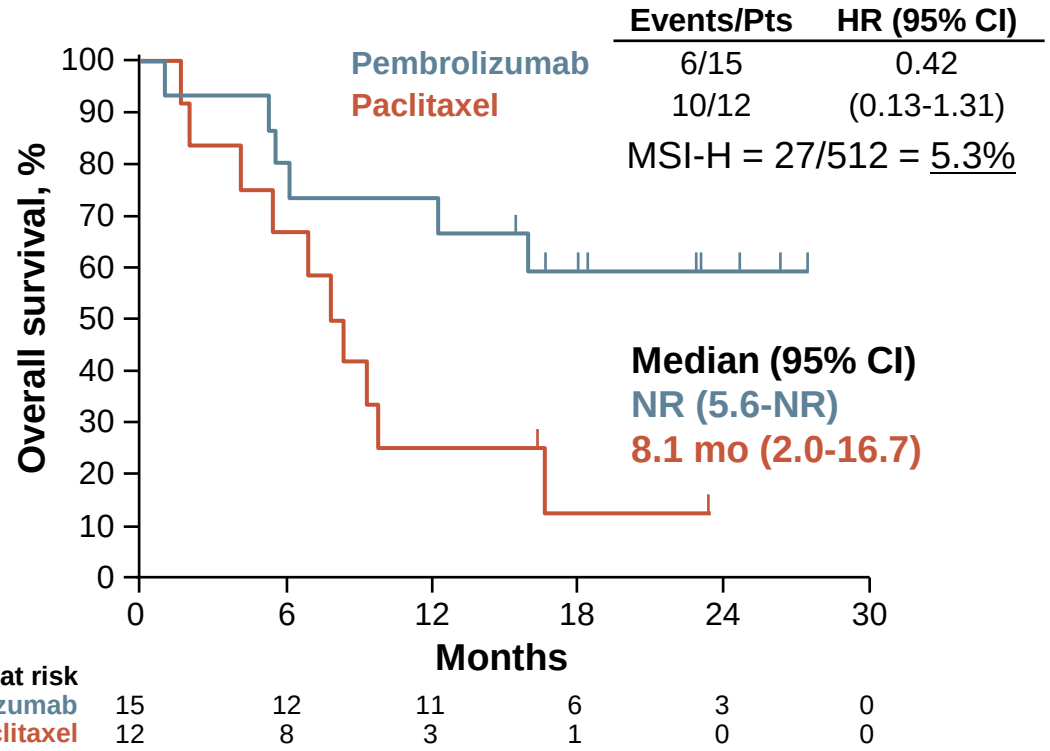


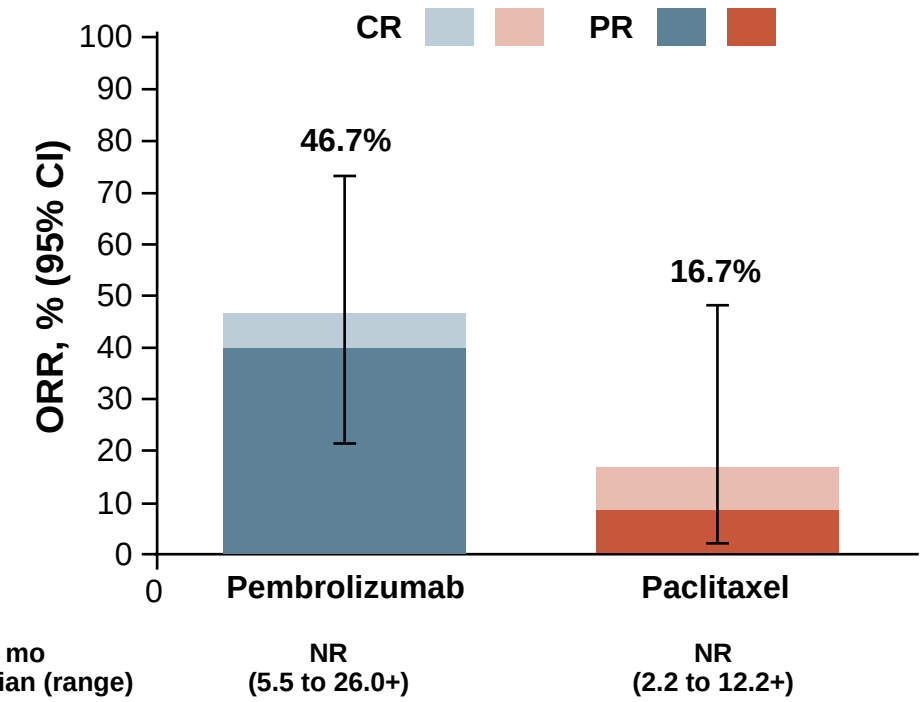
2L, second line; CI, confidence interval; HR, hazard ratio; m, months; OS, overall survival; PTX, paclitaxel; RAM, ramucirumab; WJOG, West Japan Oncology Group

1. Hirata K, et al. J Clin Oncol. 40, no. 4_suppl 280-280. ASCO GI Cancer Symposium presentation. Abstract #280; 2.Wilke H, et al. Lancet Oncol. 2014;15:1224-35

KEYNOTE-061: PEMBROLIZUMAB VS PACLITAXEL FOR PREVIOUSLY TREATED GASTRIC CANCER

OS, ORR, AND DOR FOR MSI-H TUMOURS





High efficacy of pembrolizumab in MSI-H gastric cancer was demonstrated. Paclitaxel efficacy was not different between MSI-H vs. MSS

A post-hoc subgroup analysis. Data cut-off date: Oct 26, 2017

CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; mo, months; MSI-H, microsatellite instability High; MSS, microsatellite stable; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; pt, patient

Shitara K, et al. Lancet. 2018;392:123-33

SECOND LINE ONGOING TRIALS

2L, second line

SECOND LINE FOR HER2+ METASTATIC GASTRIC CANCER

DESTINY-GC04

Failure to
- Tmab
- Fluoropyrimidine
- Platinum

Biopsy→ HER2 + per IHC/ISH required

n=490

R 1:1

- T-DXd
- Paclitaxel + RAM

Primary endpoint, Overall survival

MOUNTAINEER-02

Failure to
- Tmab
- Fluoropyrimidine
- Platinum

Multi-cohort, Open-label Phase 2

HER2+ by NGS of ctDNA or IHC/ISH of tissue

Paclitaxel Dose Optimisation
N=6-12
Pac 60 or 80 mg/m2 + TUC + Tras + Ram

Pac RD identified

- HER2+ by ctDNA → **Cohort 2A** N=24-30 TUC + Tras + Ram + Pac
- HER2- by ctDNA HER2+ by tissue → **Cohort 2A (Exploratory)** N=24-30 TUC + Tras + Ram + Pac

Double blind, placebo-controlled Phase 3

HER2+ by ctDNA → R 8:8:1

- **Arm 3A** (Test, N=235) TUC + Tmab + RAM + PAC
- **Arm 3B** (Control, N=235) TUC placebo + Tmab placebo + RAM + PAC
- **Arm 3C** (Control, N=30) TUC + Tmab placebo + RAM + PAC

Formal statistical comparisons to be made between Arms 3A and 3B

Randomisation stratified by Asia vs Rest of World, time to progression, prior gastrectomy

ctDNA, circulating tumour DNA; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in-situ hybridisation; NGS, next-generation sequencing; PAC, paclitaxel; R, randomisation; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan; Tmab, trastuzumab; TUC, tucatinib

https://clinicaltrials.gov/ct2/show/NCT04704934; https://clinicaltrials.gov/ct2/show/NCT04499924; Strickler, J.H., et al. Clin Oncol. 2021. DOI: 10.1200/JCO.2021.39.3_suppl.TPS252

THIRD LINE TREATMENTS IN JAPAN

3L, third line

THIRD LINE SYSTEMIC THERAPY TRIALS FOR GASTRIC CANCER IN JAPAN

ATTRACTION-2[1]

Eligibility
- Age ≥20 years
- Unresectable advanced or recurrent G/GEJ cancer
- Histologically confirmed adenocarcinoma
- Prior treatment with ≥2 regimens and refractory to/intolerant of standard therapy
- ECOG PS of 0 or 1

R 2:1

Nivolumab
3 mg/kg IV q2w

Placebo

Stratification based on:
- Country (Japan vs Korea vs Taiwan)
- ECOG PS (0 vs 1)
- Number of organs with metastases (<2 vs ≥2)

Primary endpoint:
- OS

Secondary endpoints:
- Efficacy (PFS, BOR, ORR, TTR, DoR, DCR)
- Safety

TAGS[2]

Patients with mGC *(including GEJ cancer)*
- ≥2 prior regimens:
  - Fluoropyrimidine
  - Platinum
  - Taxane and/or irinotecan
  - HER2 inhibitor, if available, for HER2+ disease
  - Refractory to/intolerant of last prior therapy
- ECOG PS of 0 or 1
- Age ≥18 y (≥20 y in Japan)

Target sample size: 500

R 2:1

FTD/TPI (TAS-102) + BSC (n=337)
35 mg/m² BID orally on days 1-5 and 8-12 of each 28-day cycle

Placebo

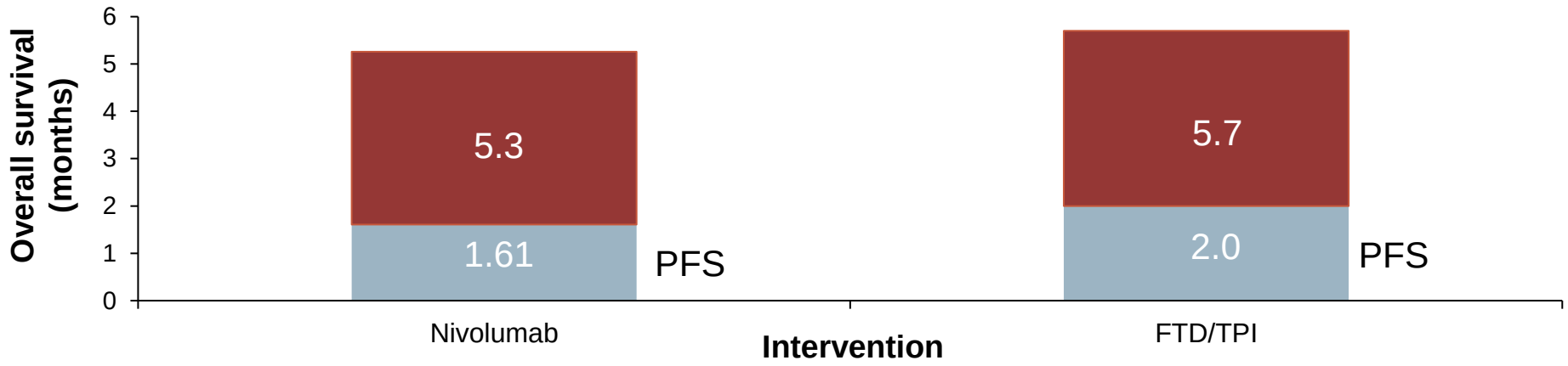
- **Stratification:** ECOG PS (0 vs 1), region (Japan vs RoW), prior ramucirumab (yes vs no)
- **Sites:** 17 countries, 110 sites; **enrolment:** February 2016 – January 2018

Primary endpoint:
- OS

Key Secondary:
- PFS, safety

Other secondary:
- ORR, DCR, QoL
- Time to ECOG PS ≥2

No prospective data available



BID, twice a day; BOR, best overall response; BSC, best supportive care; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IV, intravenous; mGC, metastatic gastric cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; QoL, quality of life; R, randomisation; RoW, rest of world; TTR, time to response; y, years

1. Kang Y-K, et al. Lancet. 2017;390:2461-71; 2. Shitara K, et al. Lancet Oncol. 2018;19:1437-48

THIRD LINE ONGOING TRIALS

3L, third line

THIRD LINE AND BEYOND: RINDBeRG STUDY IN JAPAN

- **Phase 3 study:** ramucirumab + irinotecan vs irinotecan alone

STUDY SCHEMA N=400

Patients:
- With advanced GC and EGJC
- Refractory with ramucirumab
- ECOG PS 0-1

R

1:1

Ramucirumab + Irinotecan
Ramucirumab: 8 mg/kg, day 1, q2w
Irinotecan: 150 mg/m^2, day 1, q2w

Irinotecan alone
Irinotecan: 150 mg/m^2, day 1, q2w

Primary endpoint:
- OS

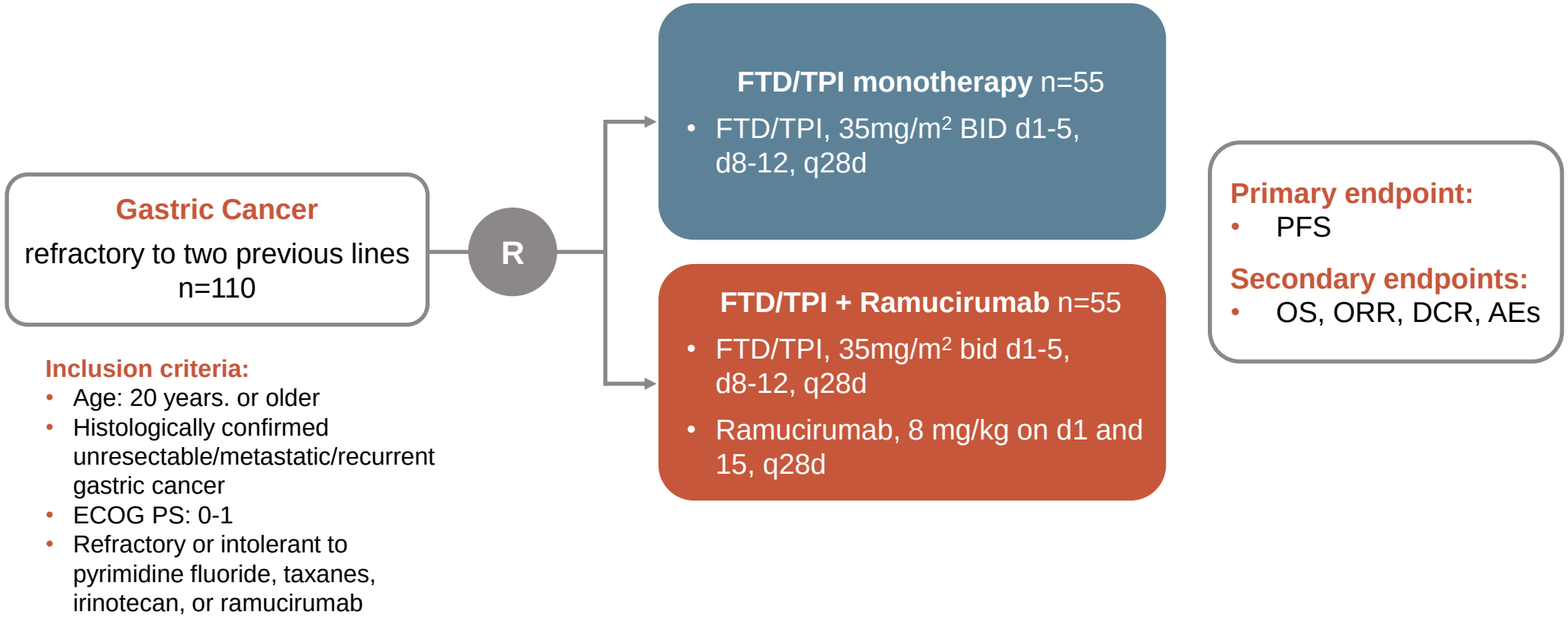
Stratified factors:
- PS: 0 vs 1
- Duration of prior chemotherapy containing ramucirumab
- Peritoneal metastasis

The results will be presented at ESMO 2023!!

ECOG PS, Eastern Cooperative Oncology performance status; EGJC, esophagogastric Junction Cancer; ESMO, European Society for Medical Oncology; GC, gastric cancer; OS, overall survival; q2w, every 2 weeks

Daisuke S, et al. J Clin Oncol. 2018. DOI: 10.1200/JCO.2018.36.15_suppl.TPS4138

BEYOND RAM WITH FTD/TPI IN THE THIRD OR LATER LINE PHASE 2 STUDY (WJOG15822G)



Inclusion criteria:

- Age: 20 years. or older
- Histologically confirmed unresectable/metastatic/recurrent gastric cancer
- ECOG PS: 0-1
- Refractory or intolerant to pyrimidine fluoride, taxanes, irinotecan, or ramucirumab

AE, adverse event; BID, twice a day; d, day; DCR, disease control rate; ECOG PS, Eastern Oncology Cooperative Group performance status; FTD/TPI, trifluridine/tipiracil; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q28d, every 28 days; RAM, ramucirumab; WJOG, West Japan Oncology Group

Takahashi N, et al. 2023. DOI: 10.21203/rs.3.rs-2796191/v1 (pre-print)

THIRD LINE AND BEYOND: INTEGRATE STUDIES

INTEGRATE IIa: regorafenib vs best supportive care

- Regorafenib improved OS:
  - After 238 events in INTEGRATE IIa, OS HR 0.68 with 12-month survival of 19% vs 6%
  - No statistically significant regional difference (Asia vs non-Asia), with benefit seen in all pre-specified sub-groups
- Regorafenib improved PFS: HR=0.53; 95% CI: 0.40-0.70; p<0.0001)
- Regorafenib toxicity profile was similar to that seen in previous reports

Endpoints

- **Primary:** OS
- **Secondary:** PFS, Objective Tumour Response Rate, QoL, EORTC (QLQ-C30 and STO22), Safety (NCI-CTCAE v 4.03)
- **Tertiary:** Pharmacokinetics, Biomarkers

INTEGRATE IIb: regorafenib + nivolumab vs investigator's choice chemotherapy

- INTEGRATE IIb is an ongoing international Phase 3 study in pre-treated patients with advanced gastric or gastroesophageal junction cancer comparing regorafenib + nivolumab to standard chemotherapy (NCT04879368)

Eligibility

- Metastatic or locally advanced gastroesophageal cancer
- Adenocarcinoma or undifferentiated carcinoma
- Failed or intolerant to at least: two lines of prior anti-cancer therapy, which must include at least a platinum agent and a fluoropyrimidine analogue as single agents or in combination

R 2:1

REGONIVO

Regorafenib 90 mg orally once daily, days 1-21 of 28 day cycle

Nivolumab 240 mg IV every 2 weeks

Endpoints:

- Overall survival (primary)

CONTROL

Investigator choice chemotherapy:

Paclitaxel, docetaxel, irinotecan or oral trifluridine/tipiracil (TAS-102)

Stratification:

- Geographic region (Asia vs rest of world)
- Prior VEGF inhibitors (Y vs N)
- Prior immunotherapy (Y vs N)

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; PFS, progression-free survival; QoL, quality of life; QLQ-C30, EORTC core quality of life questionnaire; QLQ-STO22, EORTC-QLQ-stomach module; R, randomisation; VEGF, vascular endothelial growth factor; TAS-102, trifluridine/tipiracil

Pavlakis N, et al. J Clin Oncol. 41, no. 4_suppl:LBA294-LBA294. ASCO GI Cancers Symposium presentation. Abstract #LBA294; https://clinicaltrials.gov/ct2/show/NCT02773524; https://clinicaltrials.gov/ct2/show/NCT04879368

SUMMARY

SUMMARY

- Improved overall survival: Patients with advanced gastric and GE cancers now have better survival rates due to more effective systemic therapy
- Evolving landscape of first-line therapy: Current second-line and beyond therapies may not reflect the advancements in first-line treatment for advanced disease. Ongoing trials are addressing this issue
- Factors for considering second-line and beyond therapy: Prior lines of therapy, residual toxicities, performance status, and comorbidities should be considered when evaluating patients
- Standard second-line treatment and targeted therapy: PTX+RAM is the established standard of care for second-line treatment in advanced gastric and GEJ cancers. Additionally, T-DXd has shown effectiveness as a targeted therapy after trastuzumab failure in HER2-positive populations
- Multiple options for third-line treatment: Third-line treatment for gastric and GEJ cancers lacks a clearly defined standard, with several candidates being explored

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