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**HIGHLIGHTS ON CANCERS OF THE UPPER GI TRACT**

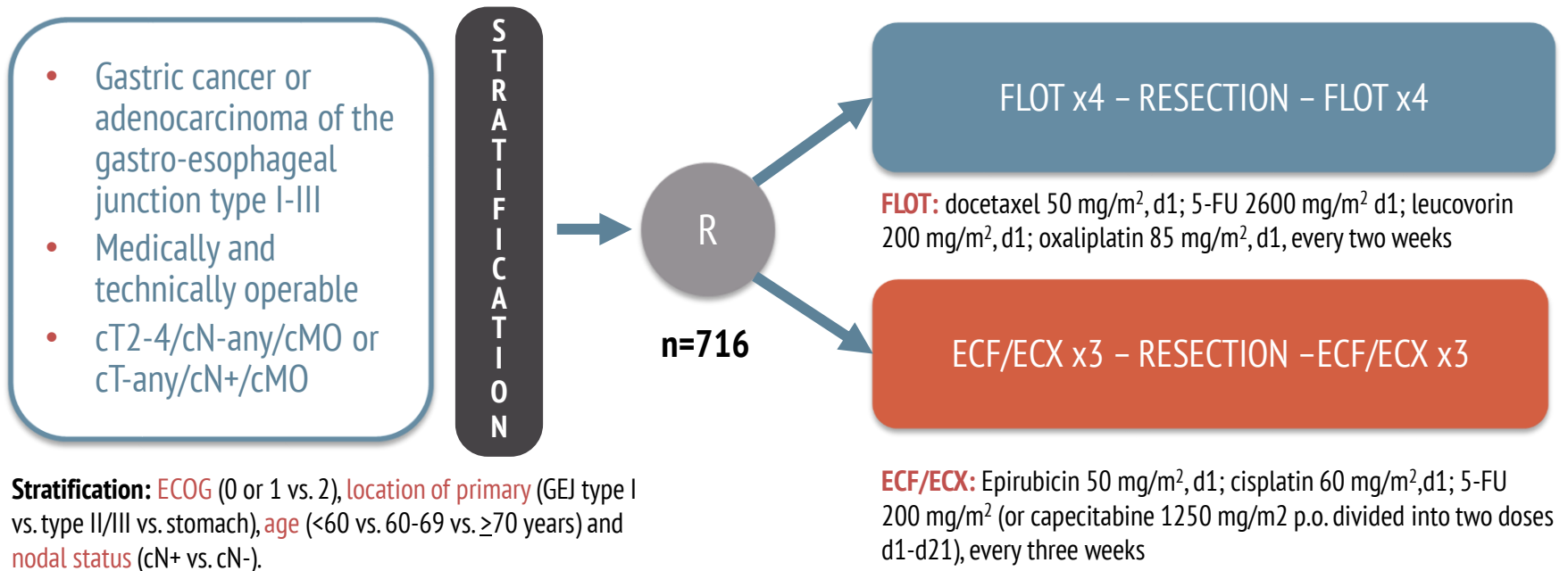
**DOCETAXEL, OXALIPLATIN AND  
FLUOROURACIL/LEUCOVORIN (FLOT) FOR  
RESECTABLE ESOPHAGOGASTRIC CANCER:  
UPDATED RESULTS FROM MULTICENTER,  
RANDOMIZED PHASE 3 FLOT4-AIO TRIAL  
(GERMAN GASTRIC GROUP AT AIO)**

**Al-Batran S et al. LBA27. ESMO Madrid 2017**

## Study Objective

- To evaluate the superiority of the FLOT scheme as compared to the standard ECF/ECX scheme in terms of OS as perioperative treatment for operable gastric and /or gastro-oesophageal cancer patients

## Randomized, multicenter, investigator-initiated, phase II/III study



# KEY RESULTS

	mPFS	mOS	Resection	R0 resection	ypT-stage <T1	ypN-stage N0
FLOT	30 months	50 months	94%	84%	25%	49%
ECX/ECF	18 months	35 months	87%	77%	15%	41%
HR	0.75 (95%CI 0.62-0.91)	0.77 (95%CI 0.63-0.94)				
P-value	0.004	0.012	0.001	0.011	0.001	0.029

# KEY RESULTS

- In a multivariate model the following characteristics were confirmed to be prognostic for worse outcome:
  - GEJ II and III, T3/4, N+, signet ring cell carcinoma, Barrett, G3/G2-3
- Despite their negative prognostic role, those groups of tumors were still benefitting from the FLOT regimen as compared to the ECX/ECF regimen

# SUMMARY

- FLOT is the new standard of care in perioperative treatment of patients with operable adenocarcinoma of the stomach and gastro-oesophageal junction
- Arms were very well balanced and there was no increase in surgical morbidity and mortality, re-surgery or hospitalization times in the FLOT arm as compared to standard regimen
- The relative effect was consistent across subgroups, even in the groups with worse prognosis
- Because the effect was observed also in early tumours, Barrett and signet ring cell carcinomas, the results of the study support the concept of perioperative treatment in debated groups like elderly, signet ring cell, Barrett and T2 or N-stage

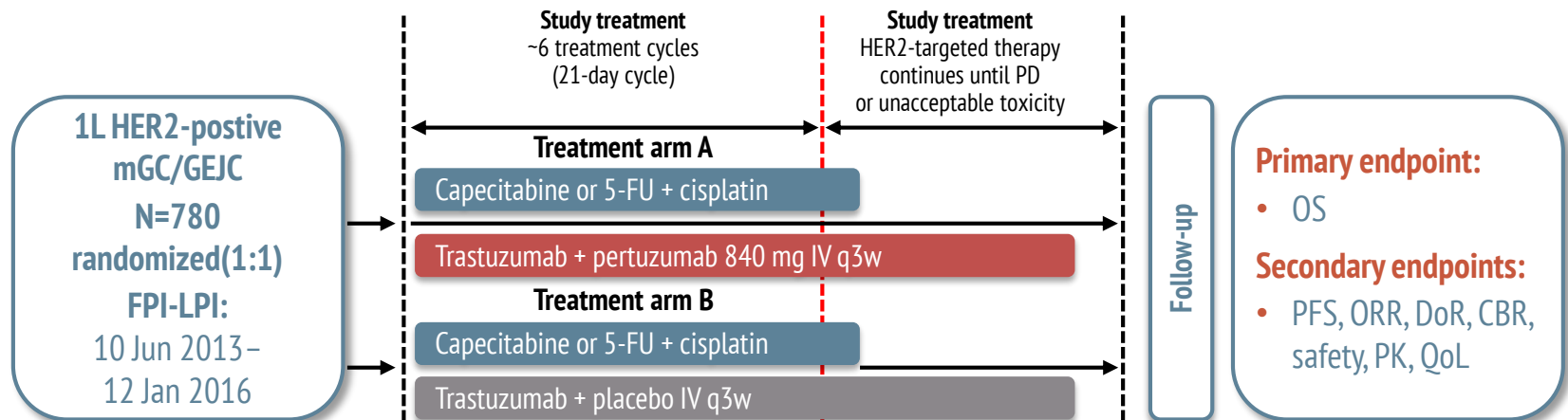
**PERTUZUMAB + TRASTUZUMAB +  
CHEMOTHERAPY FOR HER2-POSITIVE  
METASTATIC GASTRIC OR GASTRO-  
EOSOPHAGEAL JUNCTION CANCER: FINAL  
ANALYSIS OF A PHASE III STUDY (JACOB)**

**Tabernero J et al. Abstract 6160. ESMO Madrid 2017**



## Study Objective

- To evaluate the efficacy and safety of pertuzumab and trastuzumab in combination with chemotherapy as first-line treatment in HER2 positive metastatic gastric and/or gastroesophageal junction cancer patients



- Key eligibility criteria:**
- HER2-positive mGC/GEJC
  - IHC 3+ or IHC 2+ and ISH-positive (central testing required)
  - ECOG PS 0 or 1

- Stratification factors:**
- Geographical region (Asia [excluding Japan], Japan, North America/Western Europe/Australia, South America/Eastern Europe)
  - Prior gastrectomy (yes/no)
  - HER2 IHC 3+ vs IHC 2+/ISH-positive

# KEY RESULTS

- 392 patients randomized to placebo (PLA) + herceptin (H) + chemotherapy (CT)
- 388 patients randomized to pertuzumab (P) + herceptin (H) + chemotherapy (CT)
- Median follow up of approximately 2 years
- Comparable safety profile between arms except for diarrhoea (all grades: 61.6% in P + H + CT vs 35.1% in PLA + H + CT) and hypopotassiemia which did not affect the dose intensity of the regimens
- Low and similar incidence of symptomatic and asymptomatic left ventricular systolic dysfunction

# KEY RESULTS

	mOS	mPFS	Objective response %	Median duration of objective response Months (95% CI)
P + H + CT (n=388) Events, n 242	17.5 months	8.5 months	56.7	10.2 (8.4-10.7)
PLA + H + CT (n=392) Events, n 262	14.2 months	7.0 months	48.3	8.4 (6.8-8.7)
HR	0.84 (95% CI 0.71-1.00)	0.73 (95% CI 0.62-0.86)		
p-value	0.0565		*	

# SUMMARY

- Very well performed study with good statistical assumptions and design
- Patients and tumor characteristics very well balanced between arms
- Good tolerability to the combination of pertuzumab + herceptin + chemotherapy
- Control group performed similar to the ToGa trial, thus meaning that the benefit of trastuzumab in first line setting can be confirmed
- Pertuzumab showed some activity in combination with herceptin and chemotherapy in all subgroups but this was not enough to meet its primary endpoints
- **Negative trial.** Pertuzumab cannot be considered yet in combination with trastuzumab in first line setting for HER2 positive advanced gastric cancer patients

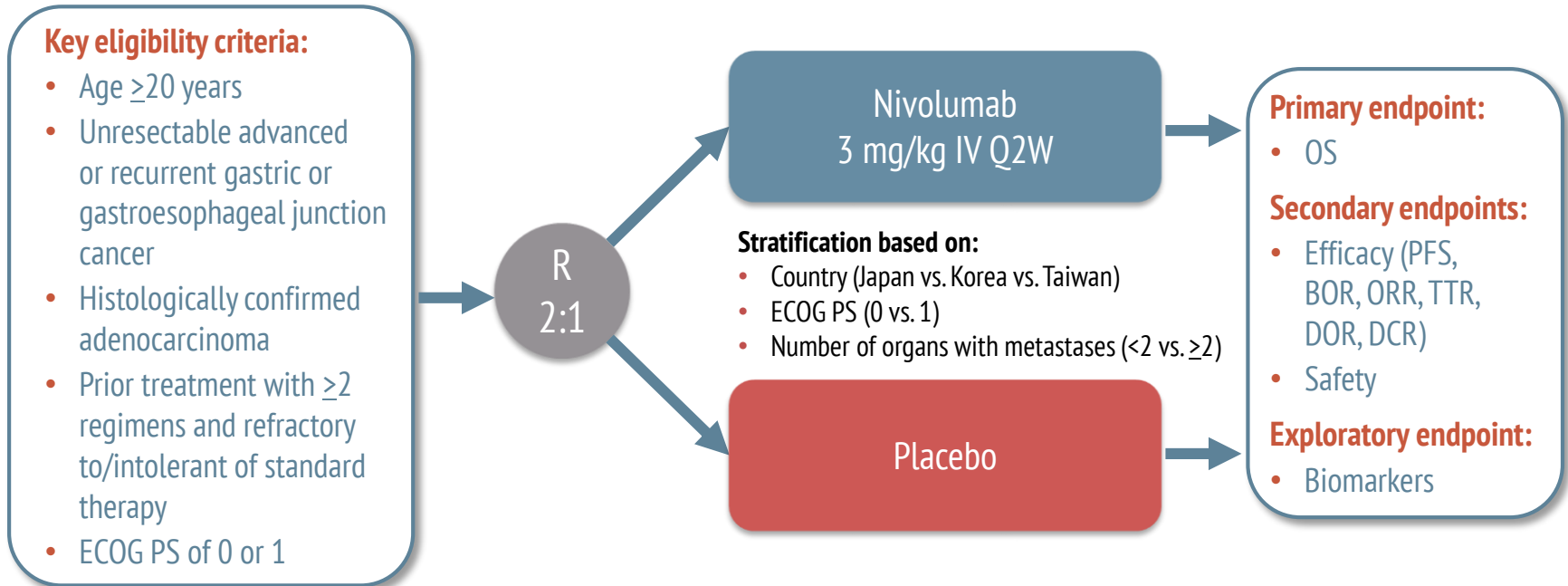
## Why?

- Is gastric cancer different to breast cancer?
- Is HER2 expression in gastric cancer more heterogeneous than in breast cancer?
- Despite the HER2 expression are HER2 positive gastric tumors heterogeneous at molecular level?
- These are points to be further investigated

**A PHASE 3 STUDY OF NIVOLUMAB IN  
PREVIOUSLY TREATED ADVANCED GASTRIC  
OR GASTROESOPHAGEAL JUNCTION  
CANCER: UPDATED RESULTS AND SUBSET  
ANALYSIS BY PD-L1 EXPRESSION  
(ATTRACTION – 02)**

**Boku N et al. Abstract 6170. ESMO Madrid 2017**

# STUDY DESIGN



Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug

# KEY RESULTS

- A total of 493 patients were randomized to a 2:1 ratio
- 330 patients received nivolumab while 163 patients received placebo
- PD-L1 expression was assessed by ICH (28-8 pharmDx assay) on pretreatment tumor biopsies of 197 patients
- Manageable safety profile with most relevant treatment related side effects (skin, gastrointestinal, hepatic and endocrine) within the first 3 months

# KEY RESULTS

	Updated mOS	OS rates at 6 months	OS rates at 12 months	mOS PD-L1 positive (expression >1%)	mOS PD-L1 negative (expression <1%)
Nivolumab (n=330)	5.32 months	46.4%	27.6%	5.2 months (16pts)	6.1 months (115 pts)
Placebo (n=163)	4.14 months	34.7%	11.6%	3.8 months (10 pts)	4.2 months (52 pts)
HR	0.61 (95%CI 0.50-0.75)	(95%CI 40.8-51.8) vs (95%CI 27.4-42.1)	(95%CI 22.8-32.6) vs (95%CI 7.2-17.1)	0.58 (95%CI 0.24-1.38)	0.71 (95%CI 0.50-1.00)
p-value	<0.0001				



# SUMMARY

- With a long term follow-up, nivolumab monotherapy confirms to give a significant survival advantage as compared to placebo in refractory gastric and gastroesophageal cancer patients
- Reduction in risk of death by 38% in the nivolumab arm
- The improvement in survival is independent from the PD-L1 status
- Manageable side effects
- The patients enrolled are all Asian. It will be interesting to test the efficacy of the drug in Caucasian refractory gastric patients
- PD-L1 expression was retrospectively performed only in 40% of patients and the antibody used is different from the one used in the Keynote 059 study, thus meaning that probably different batches of antibodies might give different results



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