

# Locally advanced resectable gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: can we do better?

Discussion of RESOLVE and DRAGON IV/CAP 05

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# DECLARATION OF INTERESTS

Hanneke van Laarhoven:

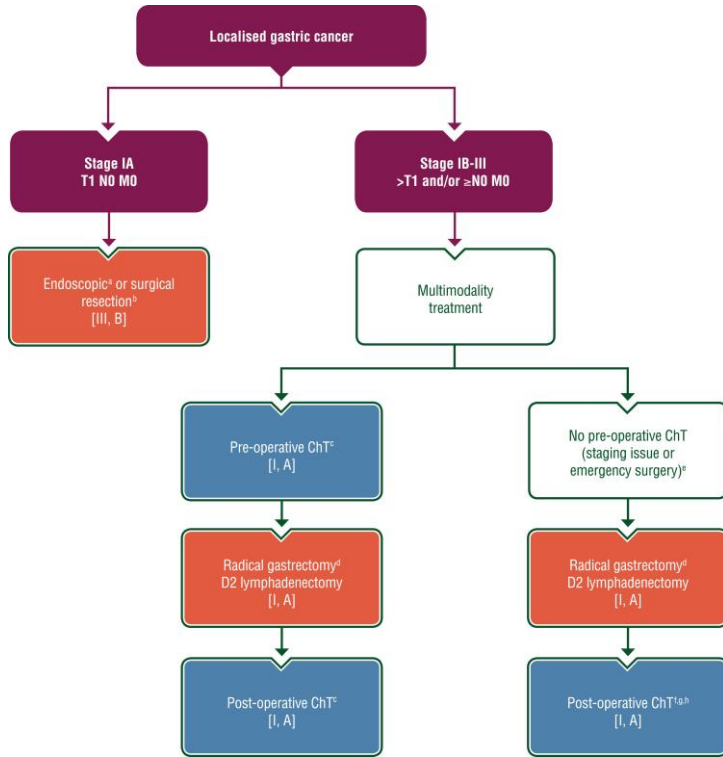
Consultant or advisory role: Amphera, Anocca, Astellas, AstraZeneca, Beigene, Boehringer, Daiichy-Sankyo, Dragonfly, MSD, Myeloid, Servier

Research funding, medication supply, and/or other research support: Auristone, Incyte, Merck, ORCA, Servier

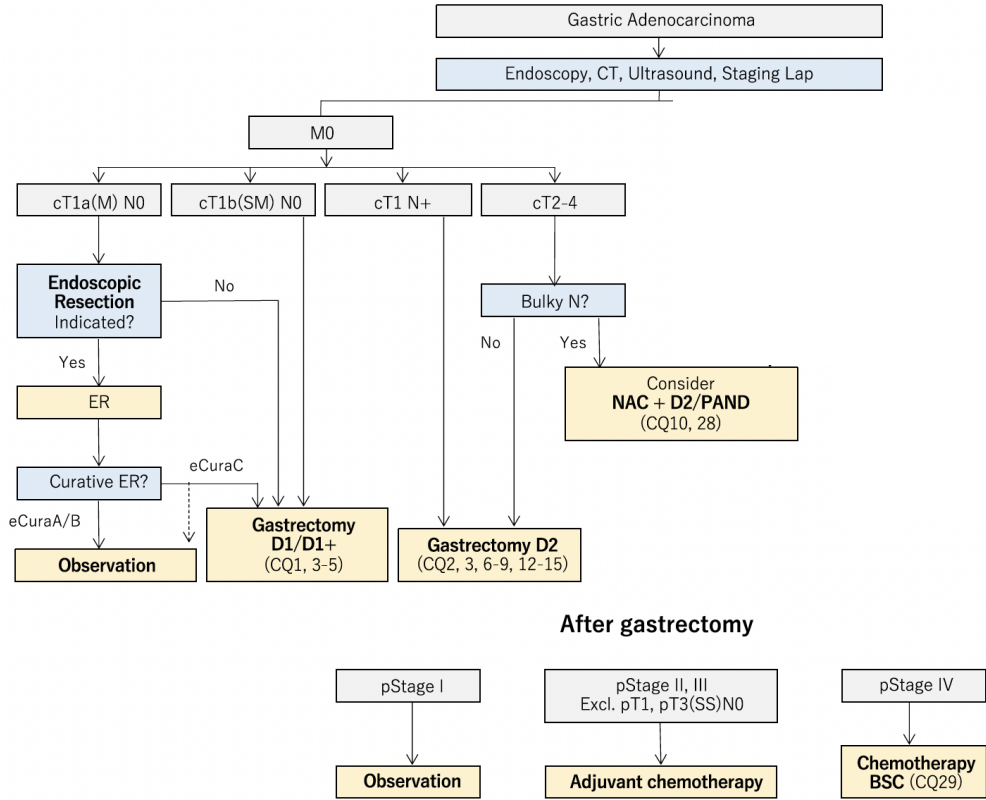
Speaker role: Astellas, Beigene, Benecke, BMS, Daiichy-Sankyo, JAAP, Medtalks, Novartis, Springer, Travel Congress Management B.V

Employment and leadership: Amsterdam UMC, the Netherlands (head of the department of medical oncology)  
Honorary: ESMO (chair upper GI faculty)

# What do we need to RESOLVE? Peri-operative versus adjuvant



Lordick et al, Ann Oncol 2022



JGCA, Gastric Cancer 2021

# Hypothesis: peri-operative/neoadjuvant treatment improves survival

Downstage the tumour

→ Increase R0 resection rate

Treat micrometastatic disease

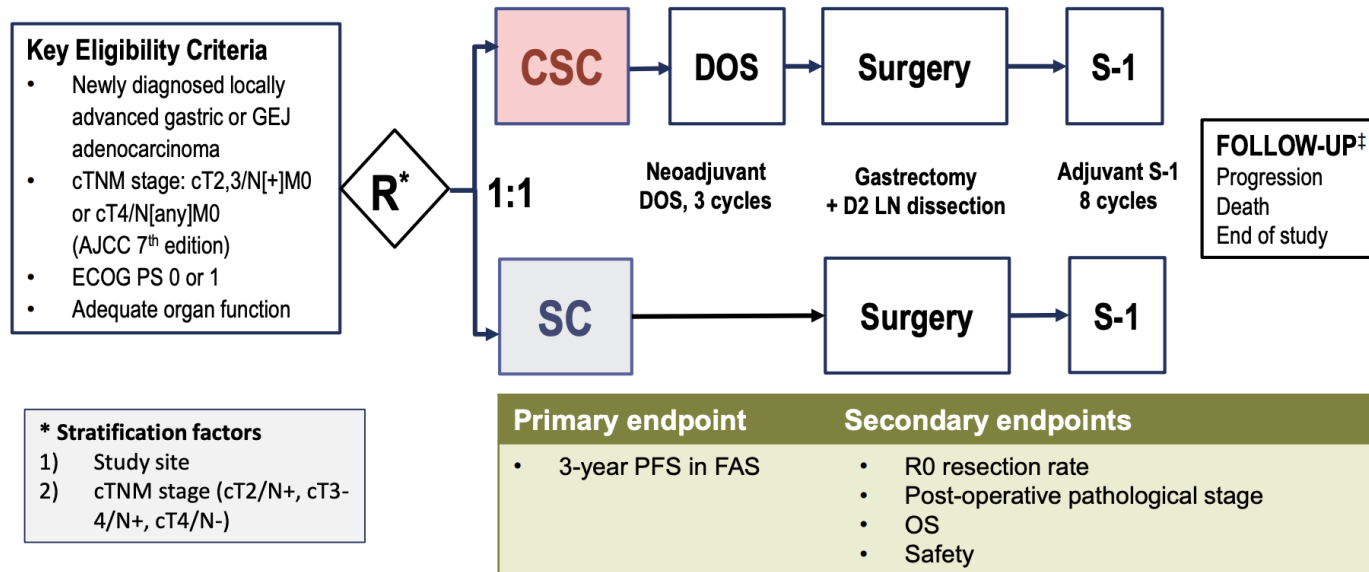
→ Improve overall survival

Better tolerability

# Peri-operative versus adjuvant: PRODIGY

**CSC arm:** Neoadjuvant Chemotherapy + Surgery + Adjuvant Chemotherapy

**SC arm:** Surgery + Adjuvant Chemotherapy

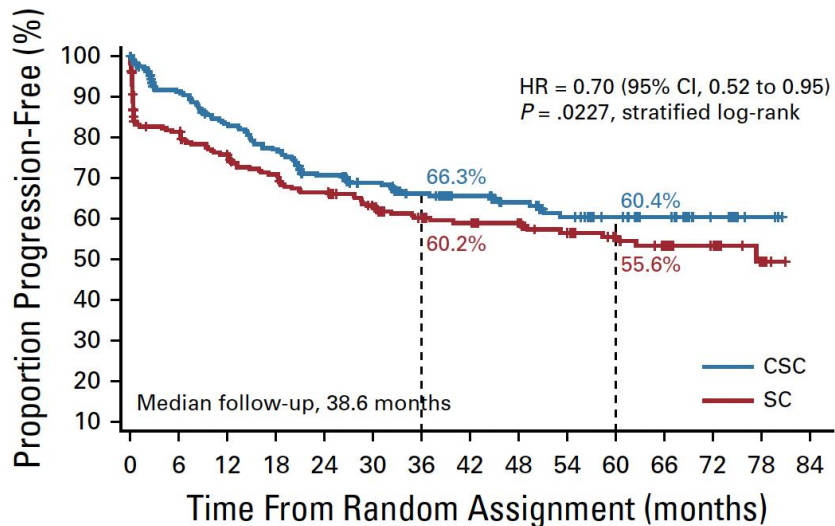


† Abdominopelvic CT every 6 months and esophagogastroduodenoscopy every 1 year after surgery

Abbreviations: FAS, Full analysis set; DOS, Docetaxel/Oxaliplatin/S-1

# Peri-operative versus adjuvant: PRODIGY

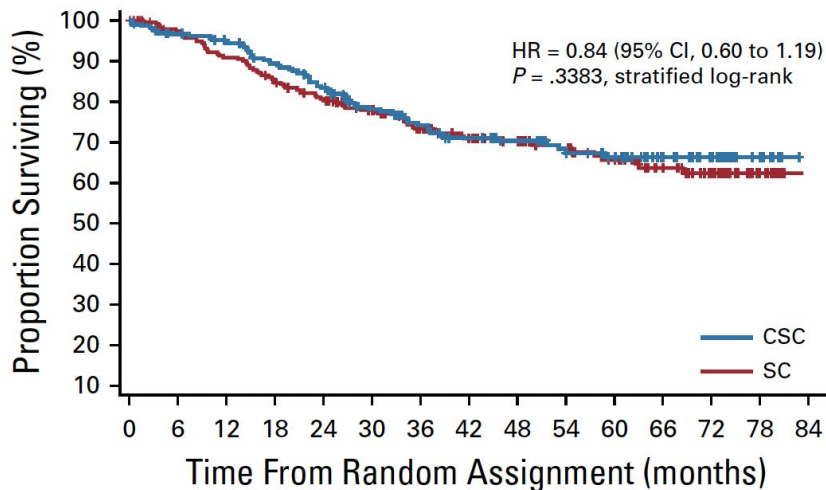
**A**



No. at risk:

CSC	238	206	186	172	155	138	110	95	78	62	51	37	17	3	0
SC	246	192	174	161	150	132	113	96	81	67	52	42	31	11	0

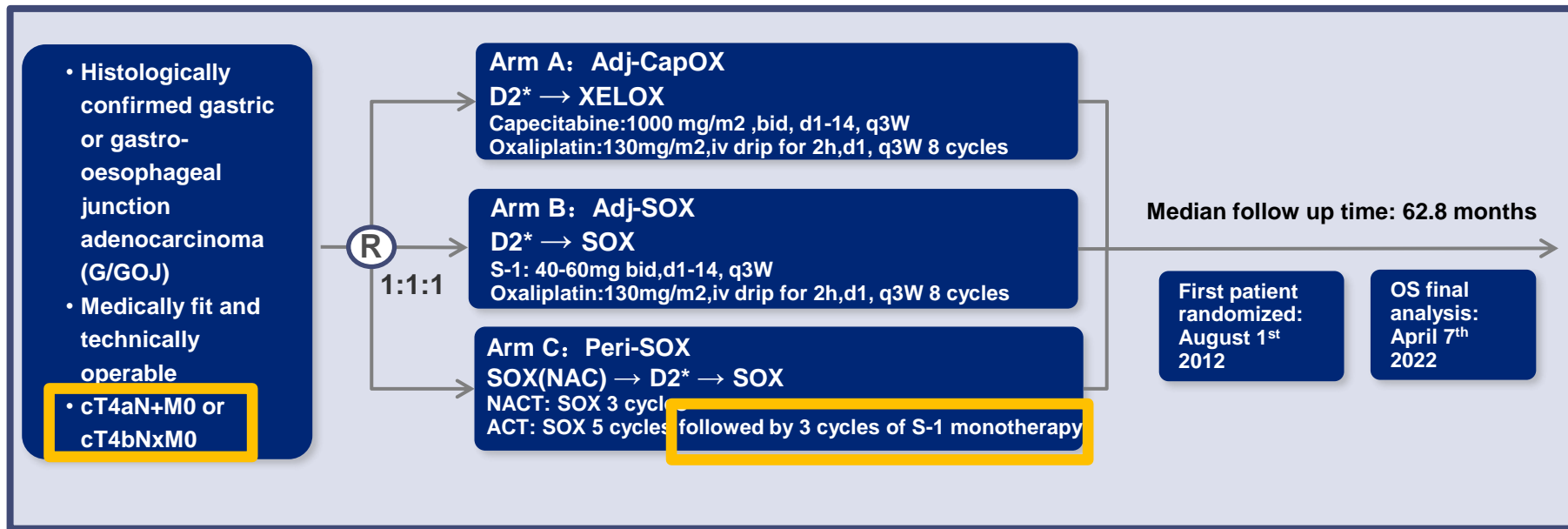
**B**



No. at risk:

CSC	238	220	212	196	182	153	123	103	86	69	64	47	33	17	0
SC	246	224	208	194	179	167	139	115	95	81	68	54	41	17	0

# Peri-operative versus adjuvant: RESOLVE



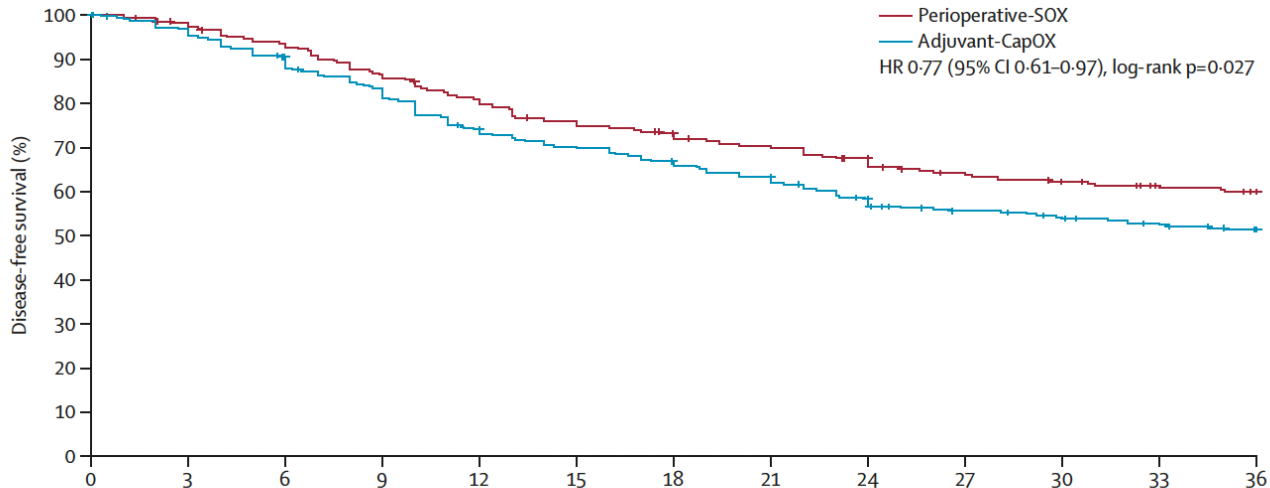
Stratified by Lauren's classification and Sites

Tumor assessment: CT/MRI of thorax/abdomen/Pelvic, endo-ultrasound (evt. diagnostic laparoscopy)

#N : mITT ; \*D2: Gastrectomy with D2 lymphadenectomy by open surgery

# Peri-operative versus adjuvant: RESOLVE - past

Three year DFS



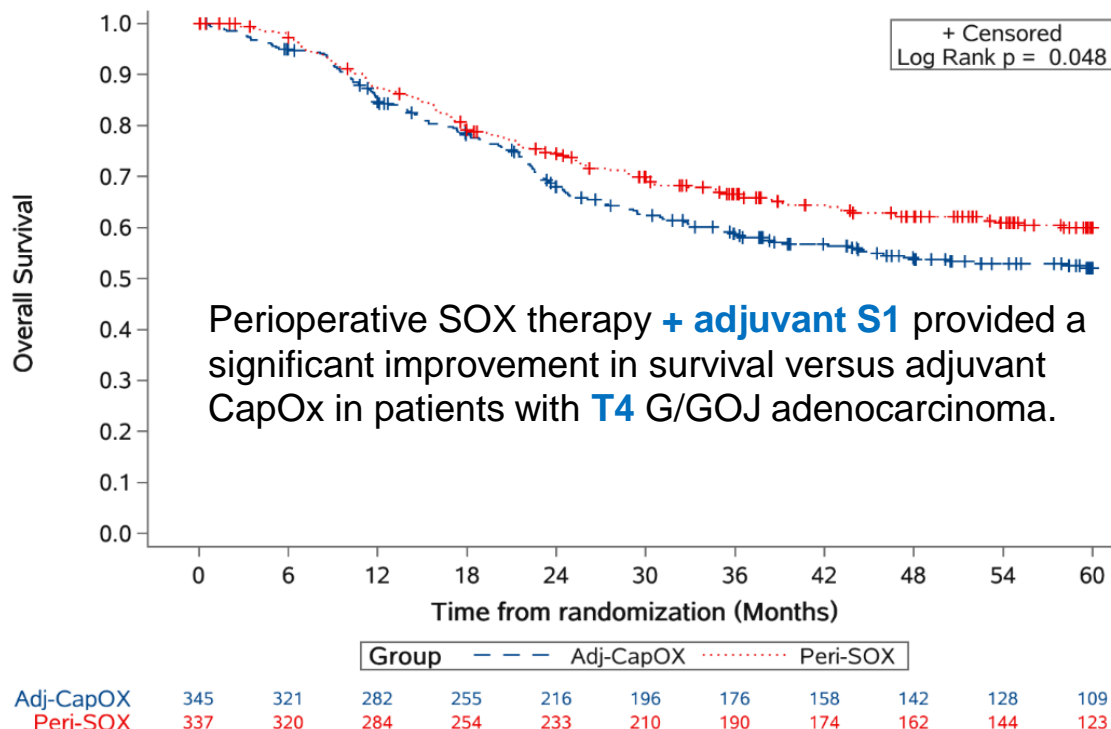
Number at risk  
(number censored)

Perioperative-SOX	345 (0)	329 (4)	304 (7)	278 (8)	245 (10)	232 (10)	220 (11)	208 (12)	188 (15)	175 (20)	169 (22)	162 (25)	153 (182)
Adjuvant-CapOX	337 (0)	322 (8)	306 (9)	281 (9)	264 (10)	248 (11)	235 (14)	220 (15)	206 (20)	193 (23)	186 (25)	179 (30)	172 (206)

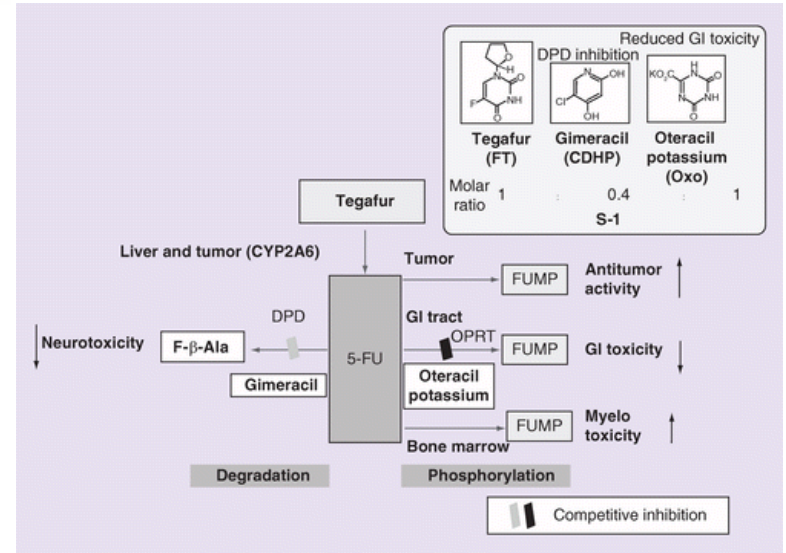
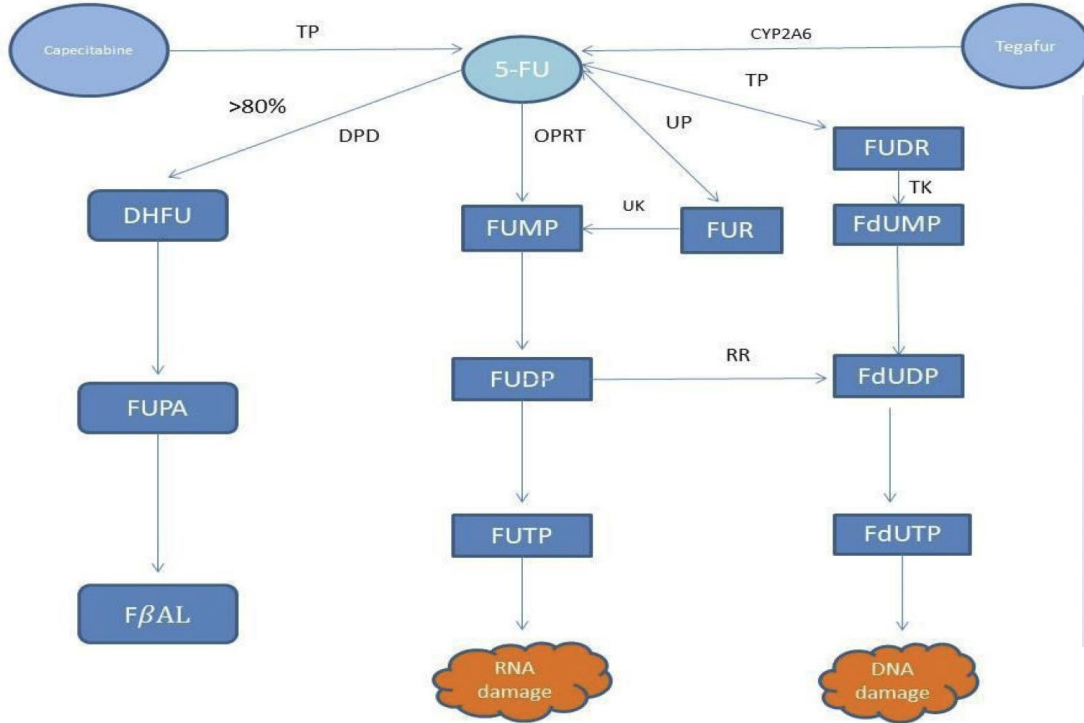


# Peri-operative versus adjuvant: RESOLVE - present

Five year OS



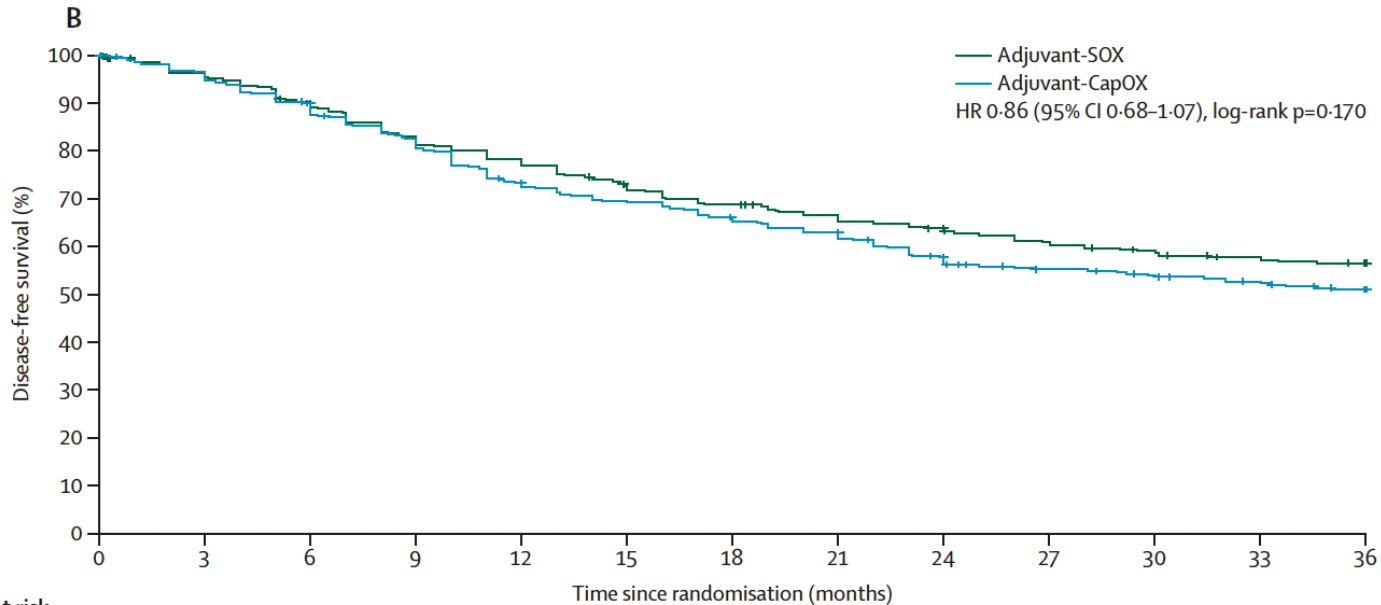
# What do we need to RESOLVE? Type of fluoropyrimidine



Nakamura et al, Future Oncology 2015

# Type of fluoropyrimidine: RESOLVE - past

Three year DFS

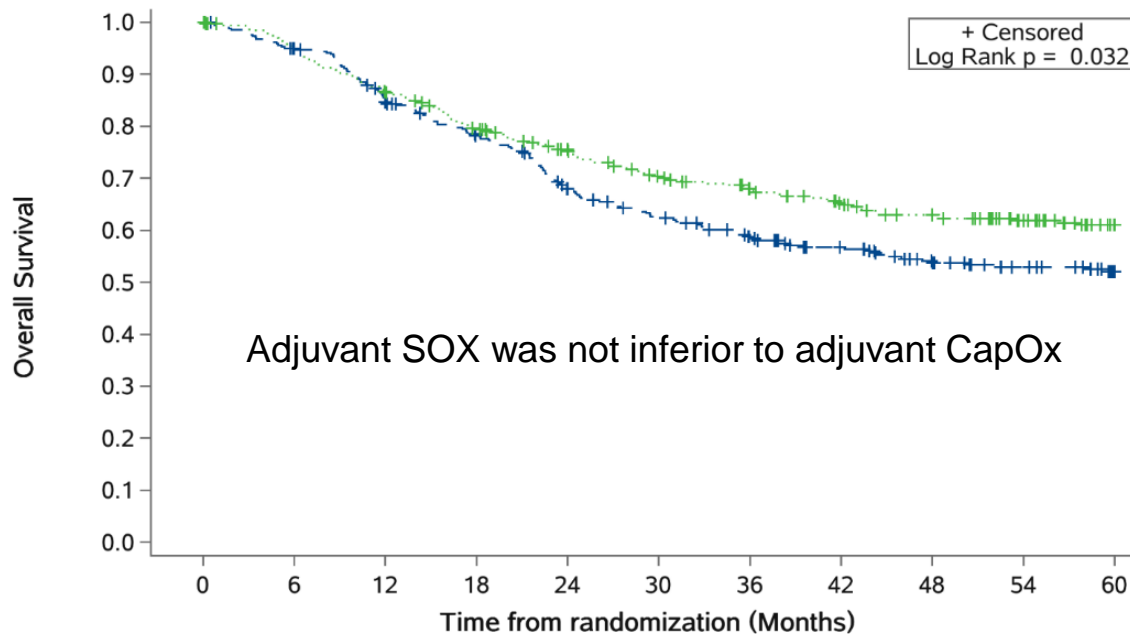


Number at risk  
(number censored)

Adjuvant-SOX	345 (0)	329 (4)	304 (7)	278 (8)	245 (10)	232 (10)	220 (11)	208 (12)	188 (15)	175 (20)	169 (22)	162 (25)	153 (182)
Adjuvant-CapOX	340 (0)	319 (9)	298 (10)	274 (10)	258 (10)	238 (12)	225 (12)	215 (15)	204 (17)	194 (18)	186 (20)	179 (23)	173 (198)

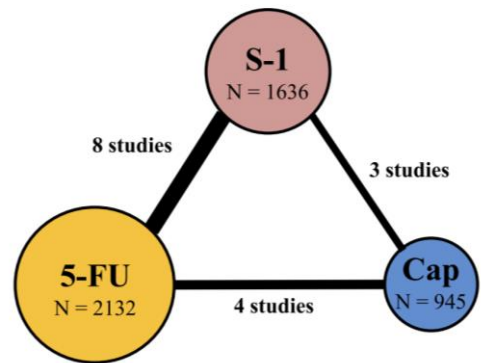
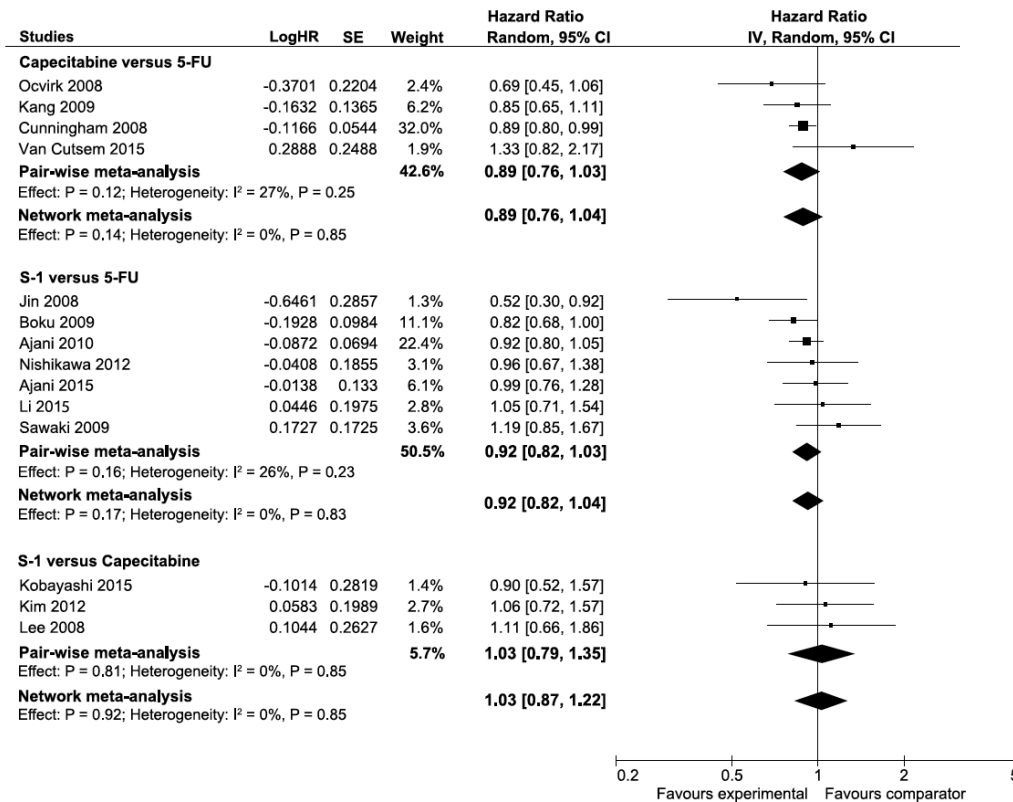
# Peri-operative versus adjuvant: RESOLVE - present

Five year OS



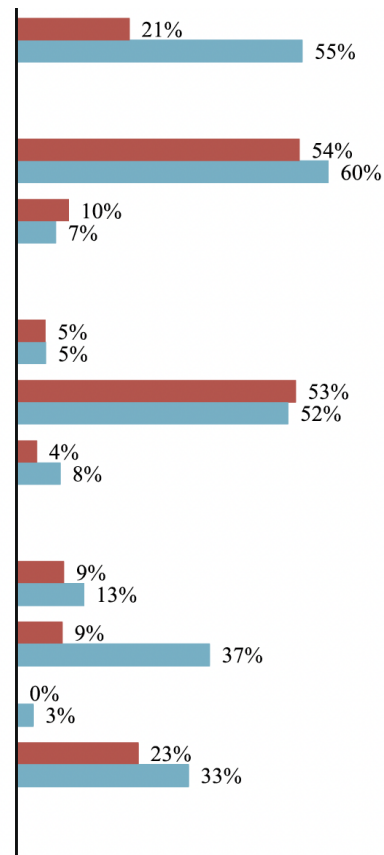
Group	Adj-CapOX	Adj-SOX
Adj-CapOX	345	340
Adj-SOX	321	315
	282	286
	255	257
	216	234
	196	212
	176	197
	158	182
	142	170
	128	153
	109	129

# Data from the metastatic setting

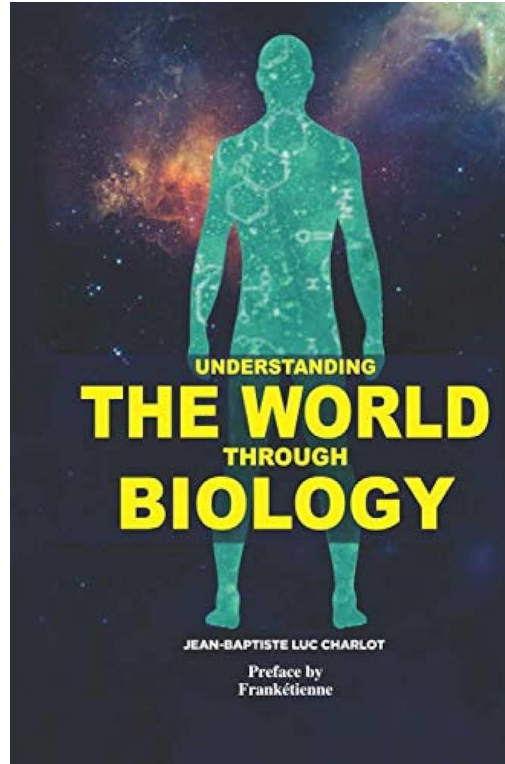


# Data from the metastatic setting

Stomatitis	1-2	S-1	9	42
		Cap	24	44
	3-4	S-1	NA	NA
		Cap	NA	NA
Anorexia	1-2	S-1	88	163
		Cap	97	163
	3-4	S-1	16	163
		Cap	12	163
Fatigue	1-2	S-1	NA	NA
		Cap	NA	NA
	3-4	S-1	3	56
		Cap	3	55
Asthenia	1-2	S-1	57	107
		Cap	57	110
	3-4	S-1	4	107
		Cap	9	110
Dehydration	1-2	S-1	NA	NA
		Cap	NA	NA
	3-4	S-1	5	56
		Cap	7	55
Hand-foot syndrome	1-2	S-1	<b>14</b>	<b>163</b>
		Cap	<b>60</b>	<b>163</b>
	3-4	S-1	0	163
		Cap	5	163
Neuropathy	1-2	S-1	28	121
		Cap	39	119
	3-4	S-1	NA	NA
		Cap	NA	NA



# How can we improve impact on survival?



# DRAGON IV/CAP05

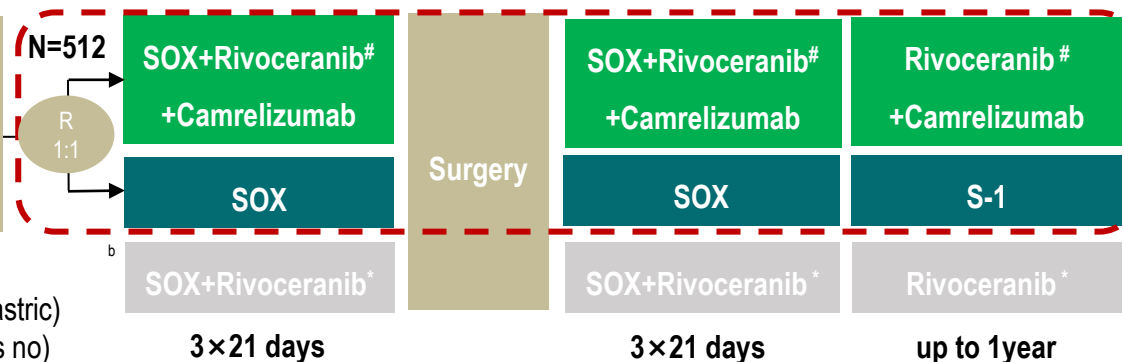
A multicenter, randomized, open-label, phase III study (NCT04208347)

## Key Eligibility Criteria

- Resectable gastric/GEJ adenocarcinoma
- Clinical stage T3-4aN+M0

## Stratification factors

- tumor location (GEJ vs gastric)
- Bulky nodal status (yes vs no)



## Primary endpoints :

- pCR(ypT0)<sup>a</sup> by BIRC
- EFS by investigators

## Secondary endpoints :

- tpCR (ypT0N0)
- MPR
- R0 resection
- ypN staging
- DFS
- OS
- Safety

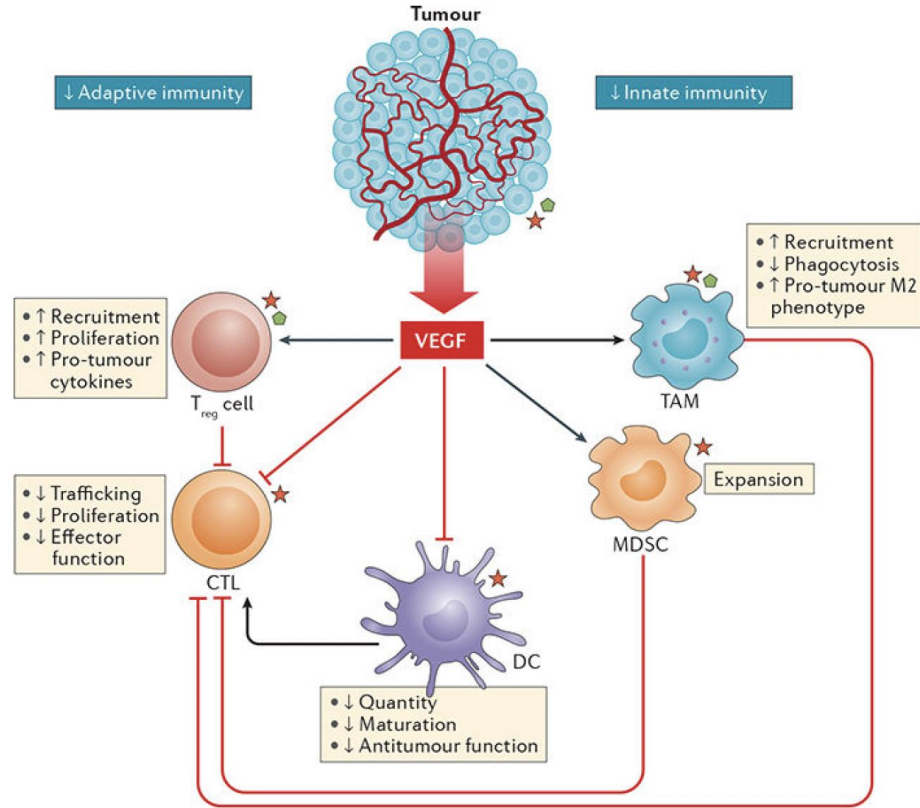
a. Grading based on Becker grading; b. Randomized controlled exploratory cohort (stopped early based on the Independent Data Monitoring Committee safety assessment)

S-1: PO BID D1-14, 40 mg (BSA < 1.25 m<sup>2</sup>), 50 mg (BSA 1.25-1.5 m<sup>2</sup>), or 60 mg (BSA ≥ 1.5 m<sup>2</sup>). Oxaliplatin: 130 mg/m<sup>2</sup> IV D1. Camrelizumab: 200 mg IV D1.

Rivoceranib: PO QD, D1-21, <sup>#</sup>250 mg, <sup>\*</sup>500 mg, for the preoperative last cycle, taken orally for 14 days only.



# VEGF and the tumor immune microenvironment



# DRAGON IV/CAP05

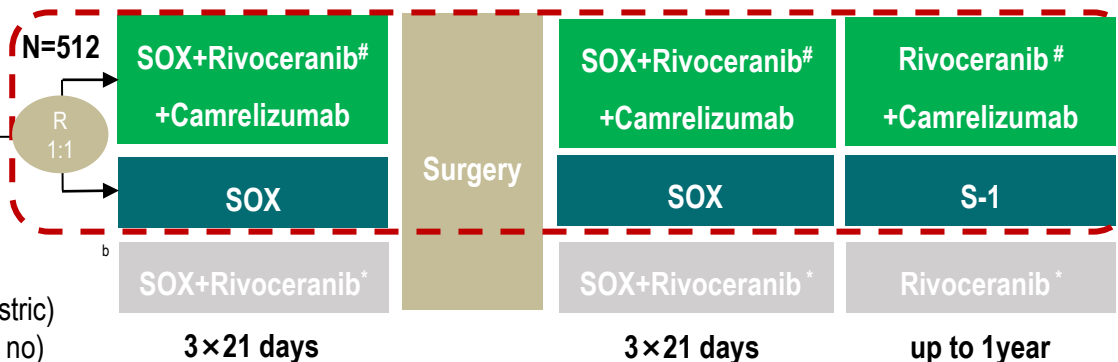
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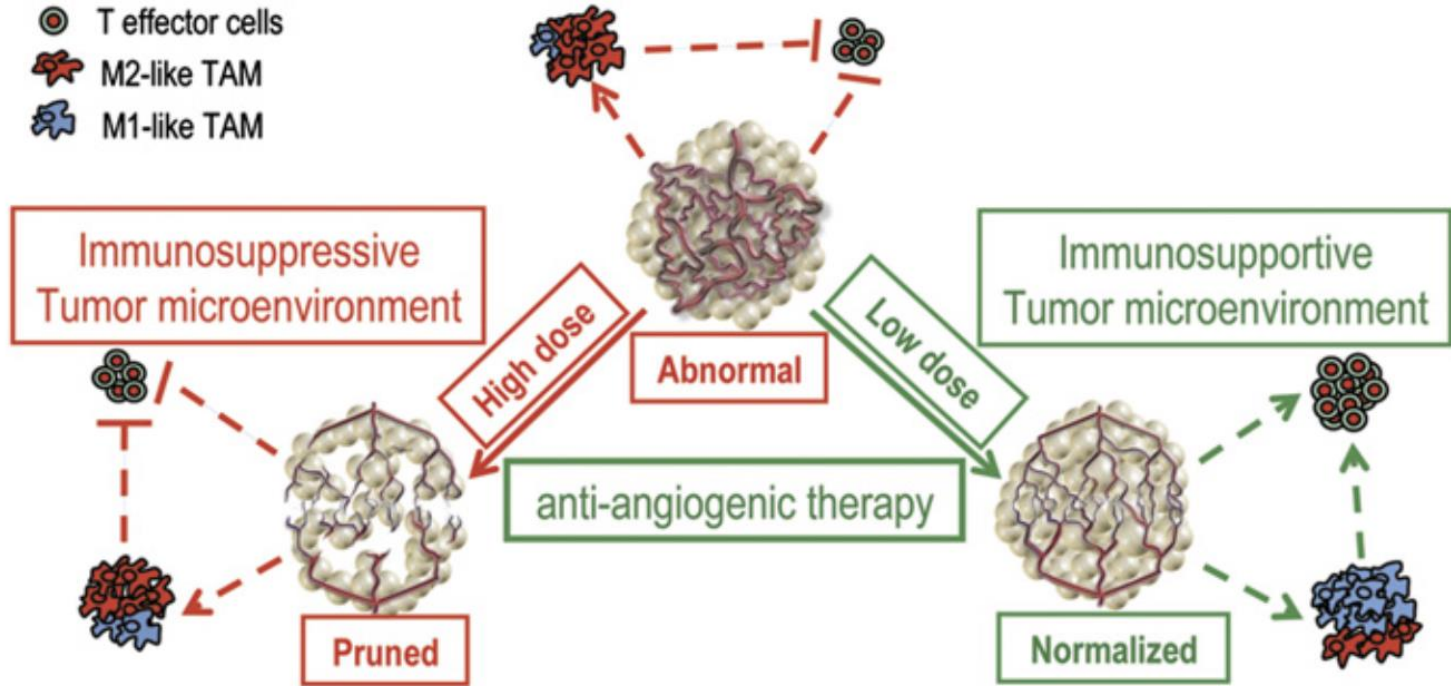
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- MPR
- R0 resection
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- DFS
- OS
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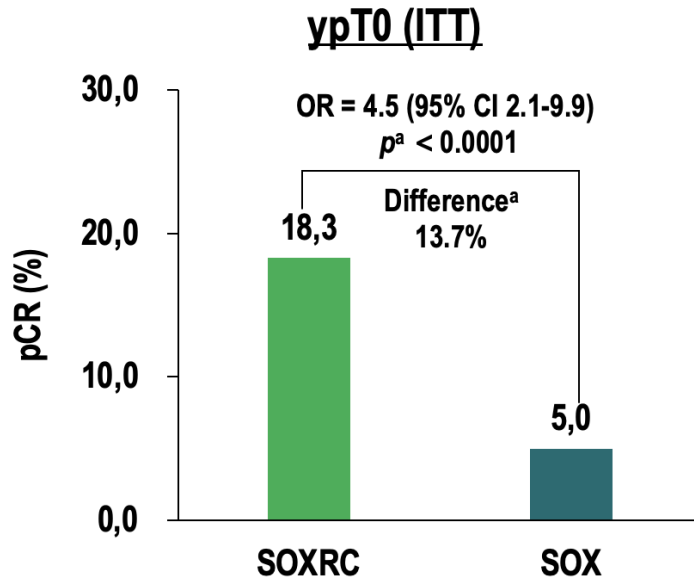
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Rivoceranib: PO QD, D1-21, **#250 mg**

# Low dose antiangiogenic treatment

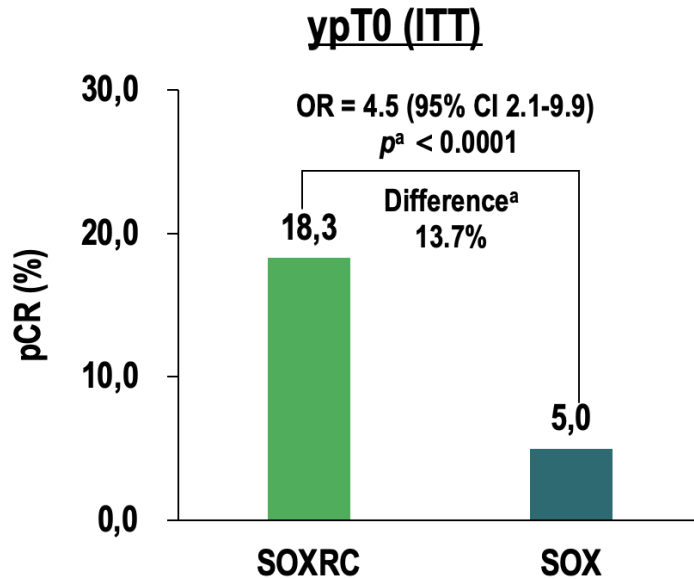


# DRAGON IV/CAP05: primary endpoint



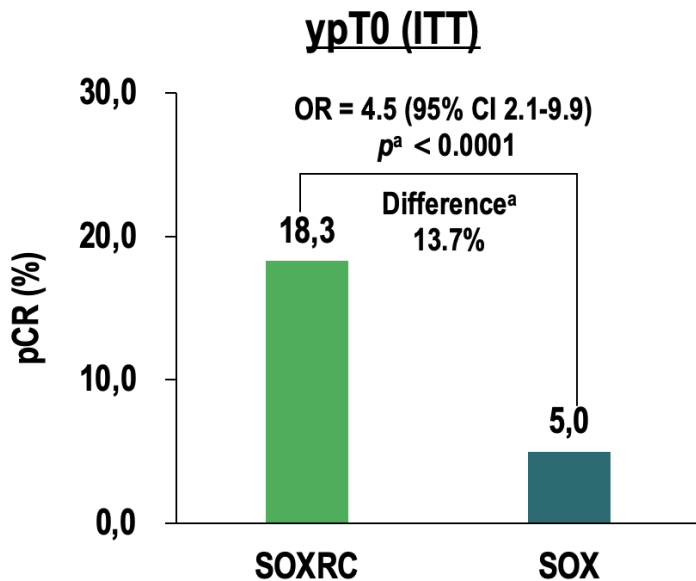
# DRAGON IV/CAP05: questions none can answer (yet)

Is this a camrelizumab effect,  
a rivoceranib effect,  
or a combination effect?

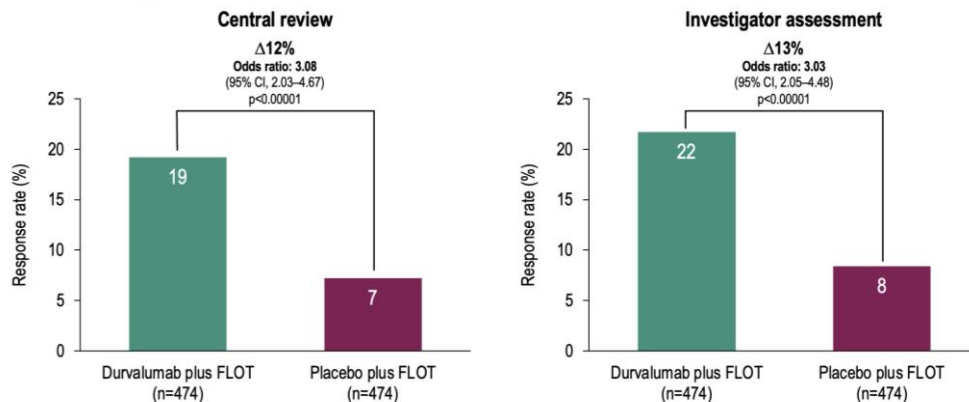


# DRAGON IV/CAP05: what agents make the difference?

Is this a **camrelizumab** effect,  
a **rivoceranib** effect,  
or a combination effect?



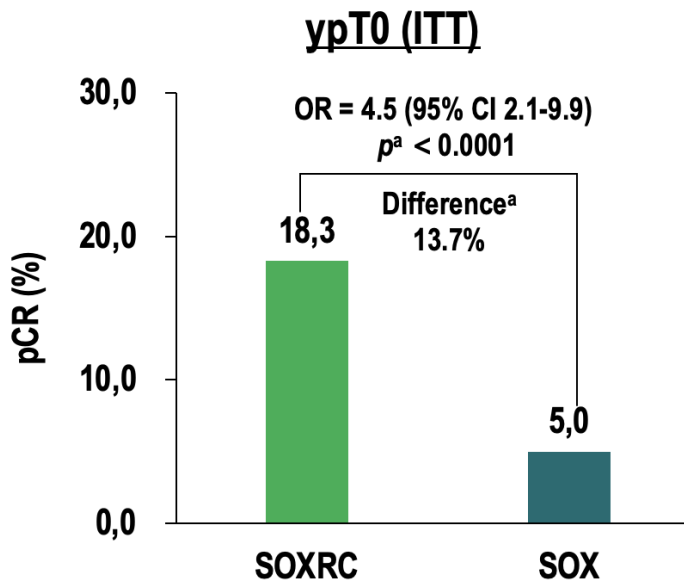
## Pathological complete response



Al-Batran et al, ESMO 2023, MATTERHORN

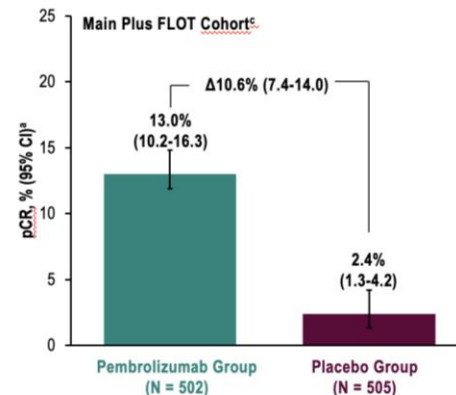
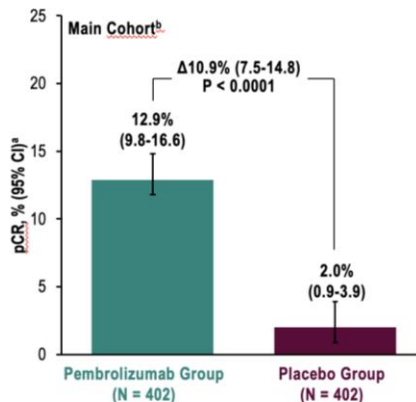
# DRAGON IV/CAP05: what about survival?

Is this pCR effect sufficient to convey survival benefit?



### Pathological Complete Response<sup>a</sup>

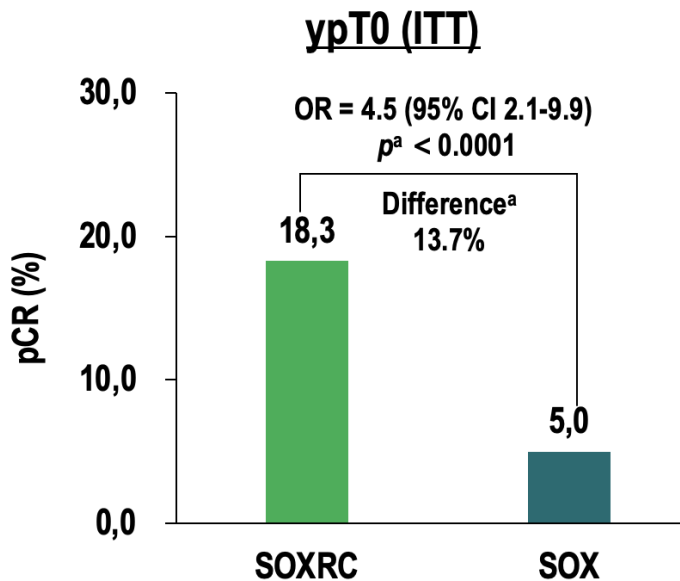
Assessed by Blinded, Independent Central Review



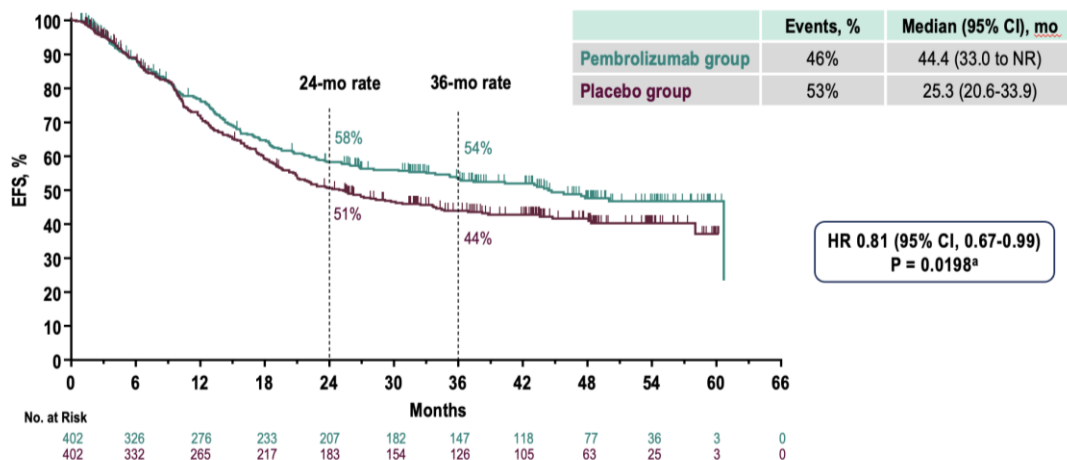
Shitara et al, ESMO 2023, Keynote-585

# DRAGON IV/CAP05: what about survival?

Is this pCR effect sufficient to convey survival benefit?



## Event-Free Survival: Main Cohort

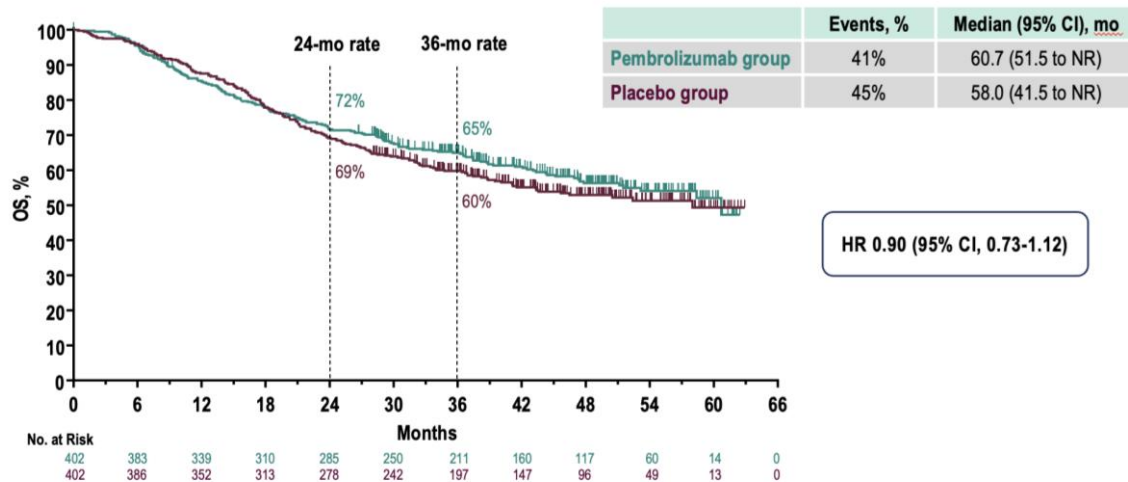
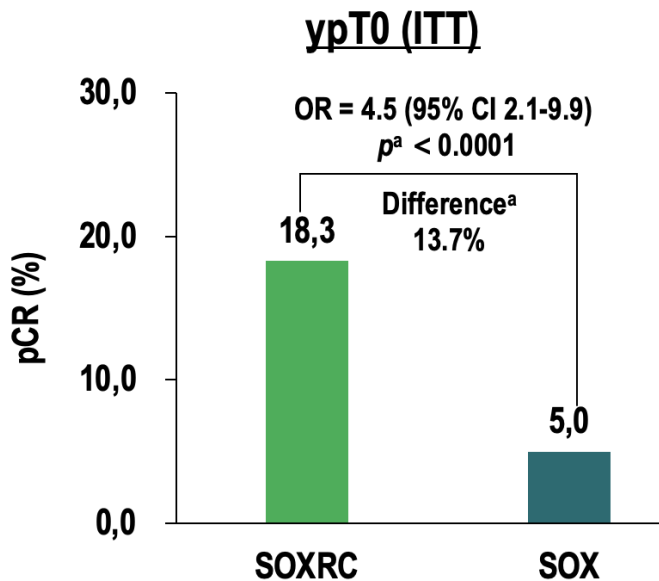


Shitara et al, ESMO 2023, Keynote-585



# DRAGON IV/CAP05: what about survival?

Is this pCR effect sufficient to convey survival benefit?



Shitara et al, ESMO 2023, Keynote-585

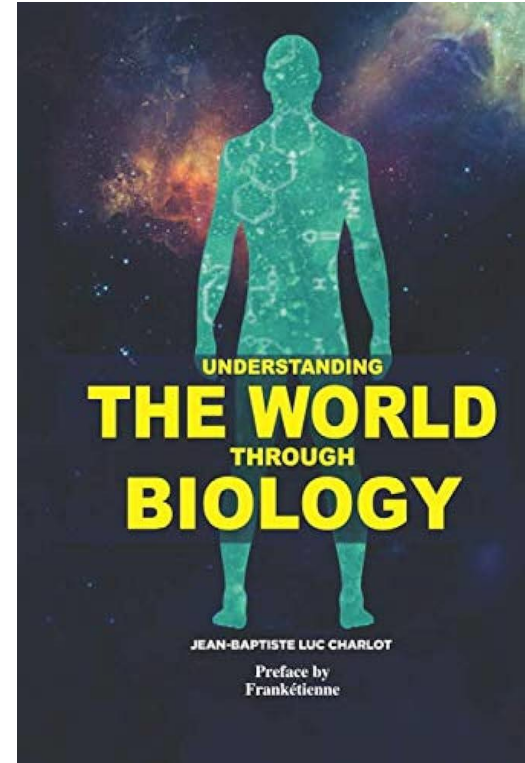
# Take home

## RESOLVE:

Peri-operative treatment preferred over adjuvant in locally advanced disease

## DRAGON IV/CAP05:

Peri-operative chemotherapy outcomes may be improved by adding IO/anti-angiogenic agents



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