Perioperative Therapy for Gastroesophageal Cancers

Dr. Elena Elimova

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Princess Margaret Cancer Centre

UHN Princess Margaret Cancer Centre

Disclosure Information

I have the following relevant financial relationships to disclose:

Consultant for:

BMS, Zymeworks, Adaptimmune, Beigene, Jazz, Astellas, Virecta Tx, Natera, Abbvie, Daiichi –Sankyo, Roche

Grant/Research support from:

BMS, Zymeworks, Astra Zeneca, Jazz, Amgen, Bold Therapeutics, Arcus Biosciences

Steering Committee Member: Jazz, Astra Zeneca

My additional financial relationship disclosures are:

Employment for: Merck (family member)

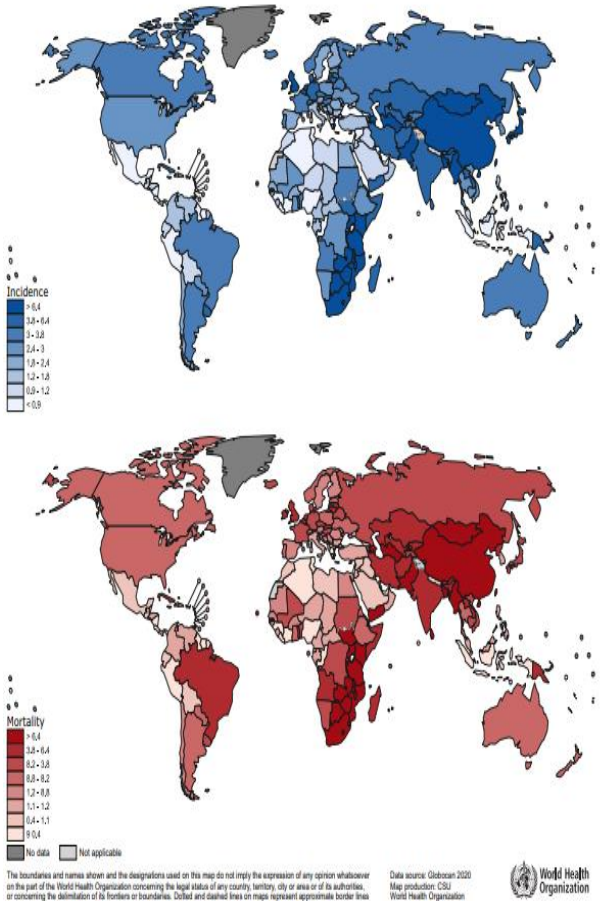
Learning Objectives

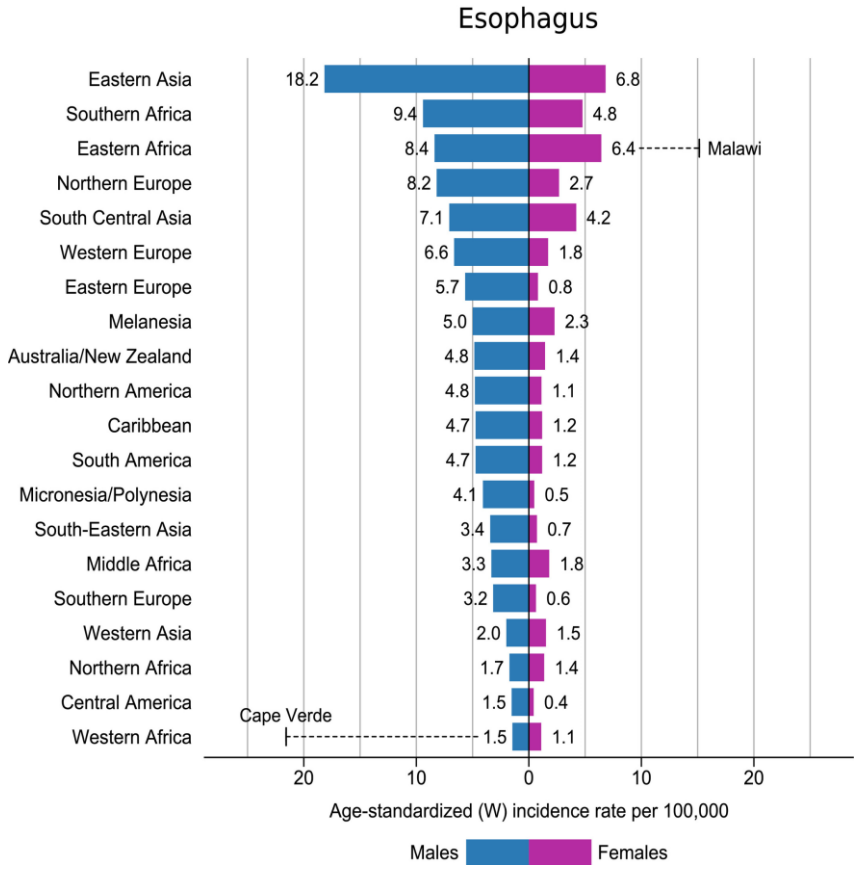
1. What is the best perioperative therapy for esophageal adenocarcinoma?

2. Predictive biomarkers in neoadjuvant gastroesophageal cancer (GEC), what have we learned?

Why Focus on GEC?

Although esophageal cancer is the 8th most commonly diagnosed cancer in the world, it is the 6th leading cause of cancer-related deaths





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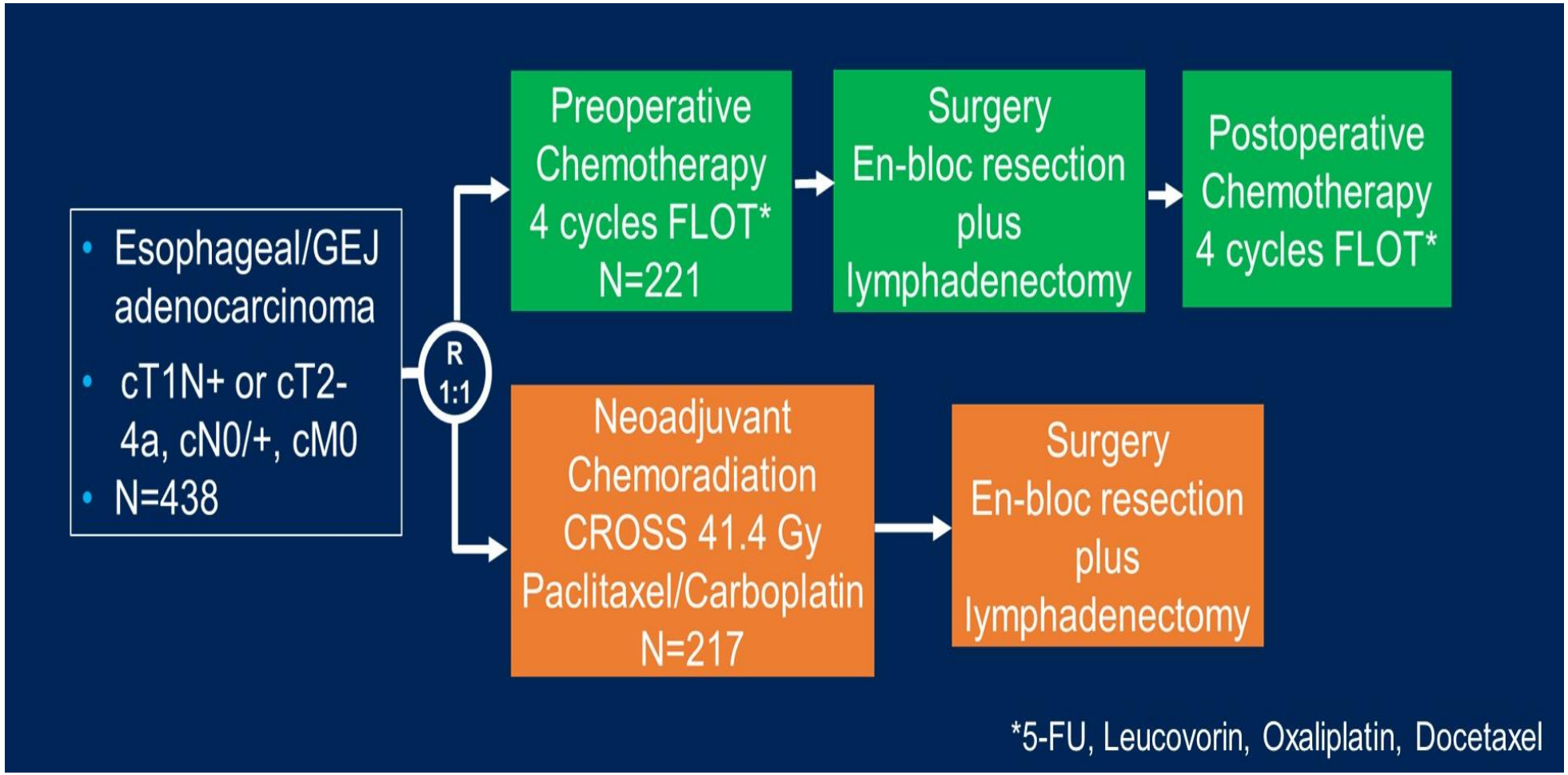
Morgan E et al, Gastroenterology, 2022

ESOPEC Trial



Hoeppner et al., ASCO Plenary 2024

Patient Characteristics

	FLOT Group	CROSS Group
N	221	217
Age mean (SD) in years	63.1 (8.6)	62.6 (9.8)
Sex male	89.1 %	89.4 %
ECOG		
> 0	26.7%	28.1%
Clinical T-stage		
cT1-2	19.5%	17.1%
cT3-4	79.1%	81.9%
Clinical N-stage		
cN0	22.2%	18.4%
cN+	77.8%	81.6%

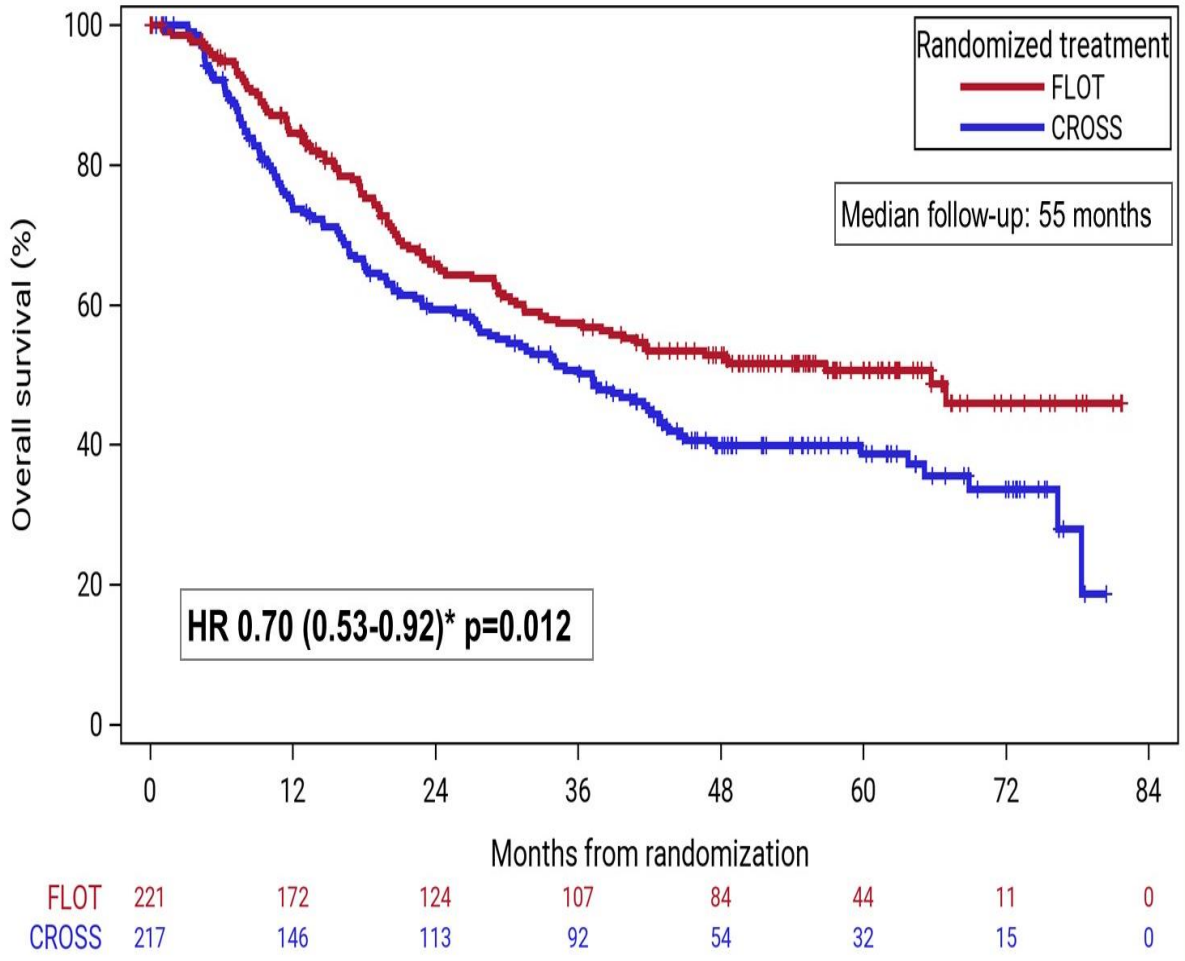
Hoeppner et al., ASCO Plenary 2024

Trial Results

	ESOPEC Trial				
	FLOT Group	CROSS Group	CROSS Trial (CRT Group - AC)	Neo-AEGIS Trial (CRT Group)	FLOT-4 (FLOT Group)
Completed **pre-op** treatment	87.3%	**67.7%**	92%	87% (RT - 99%)	90%
Completed **post-op** treatment	52.5%				46%
pCR	16.8%	**10%**	23%	12%	16%
Median OS	66 mos	**39 mos**	43 mos	49 mos	50 mos
3-year OS	57.4%	50.7%	54%	57%	57%

Hoeppner et al., ASCO Plenary 2024

Overall Survival in ITT



	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

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Hoeppner et al., ASCO Plenary 2024

Conclusion

- FLOT is better than CROSS in gastroesophageal adenocarcinoma patients
  - However CROSS really underperformed in this study and some patients were unable to finish regimen
- BUT CROSS alone is no longer standard of care
  - Adjuvant IO indicated for patients with non pCR
- Will a TOPGEAR type approach be the best - ie adding FLOT to CTRT and following with adjuvant immunotherapy?
- Can we avoid surgery altogether?

Perioperative and Adjuvant Immunotherapy of GEC

- CHECKMATE 577: adjuvant nivolumab post trimodality therapy
- PANDA trial
- DANTE/MATTEHORN/KEYNOTE585
- INFINITY/NEONIPIGA

CheckMate 577 Study Design

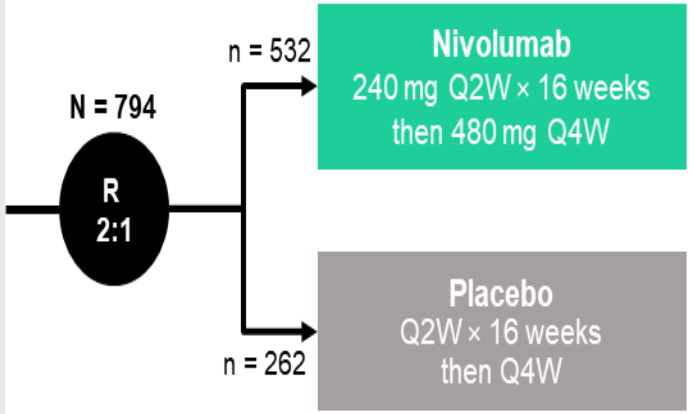
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

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 vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Primary endpoint:

- DFS[e]

Secondary endpoints:

- OS
- OS rate at 1, 2, and 3 years

Exploratory endpoints:

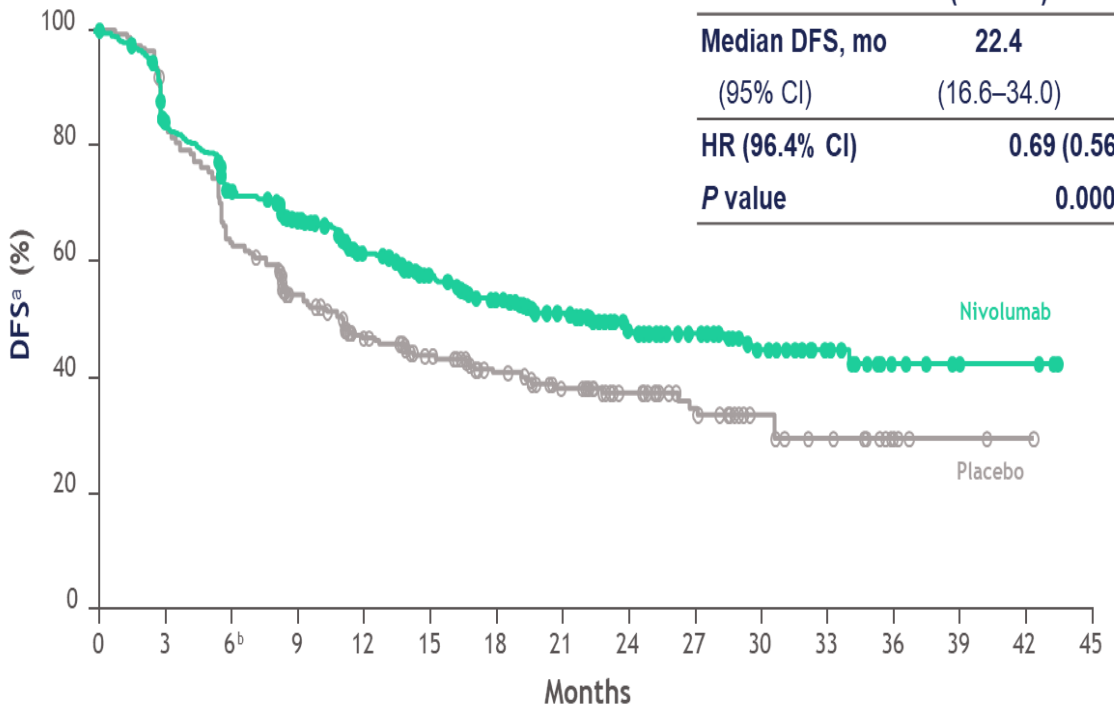
- Safety
- Biomarkers

- At the data cutoff (January 4, 2021), the median follow-up was 32.2 months (range, 14.0–52.7 months)[f]

Kelly et al, ESMO GI 2023

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]	



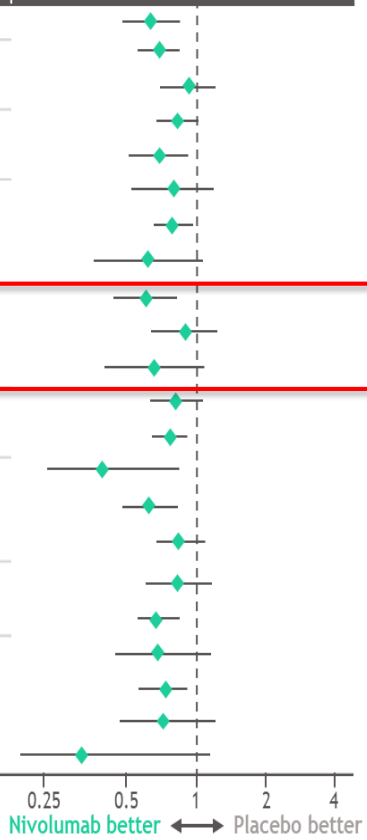
No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

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

Kelly et al, ASCO 2021

DFS Subgroup Analysis

Category	Subgroup	Median DFS, mo		Unstratified HR	Unstratified HR (95% CI)
		Nivolumab	Placebo		
Overall	N = 794	22.4	11.0	0.70	
Tumor location at initial diagnosis	Esophagus (n = 462)	24.0	8.3	0.61	
	Gastroesophageal junction (n = 332)	22.4	20.6	0.87	
Histologic type	Adenocarcinoma (n = 563)	19.4	11.1	0.75	
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61	
Tumor cell PD-L1 expression[a]	≥ 1% (n = 129)	19.7	14.1	0.75	
	< 1% (n = 570)	21.3	11.1	0.73	
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54	
PD-L1 CPS expression[a,b]	≥ 5 (n = 371)	29.4	10.2	0.62	
	< 5 (n = 295)	16.3	11.1	0.89	
	Missing/nonevaluable (n = 128)	Not reached	10.8	0.61	
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74	
	≥ ypN1 (n = 457)	14.8	7.6	0.67	
Pathological tumor status	ypT0 (n = 47)	34.0	5.2	0.35	
	ypT1 or ypT2 (n = 308)	28.3	9.3	0.60	
	ypT3 or ypT4 (n = 436)	18.9	14.1	0.84	
Time from complete resection to randomization	< 10 weeks (n = 256)	24.0	14.1	0.84	
	≥ 10 weeks (n = 538)	21.4	10.8	0.66	
Radiotherapy dosage[b,c]	< 41.4 Gray (n = 92[d])	19.7	13.8	0.69	
	41.4-50.4 Gray (n = 504)	24.0	11.1	0.73	
	> 50.4 Gray (n = 152)	21.4	8.3	0.72	
	Not reported (n = 41)	14.4	6.1	0.41	



- Disease-free survival benefit was observed with nivolumab versus placebo across multiple subgroups

Kelly et al, ASCO 2021

Post-CRT Changes in PD-L1 Expression

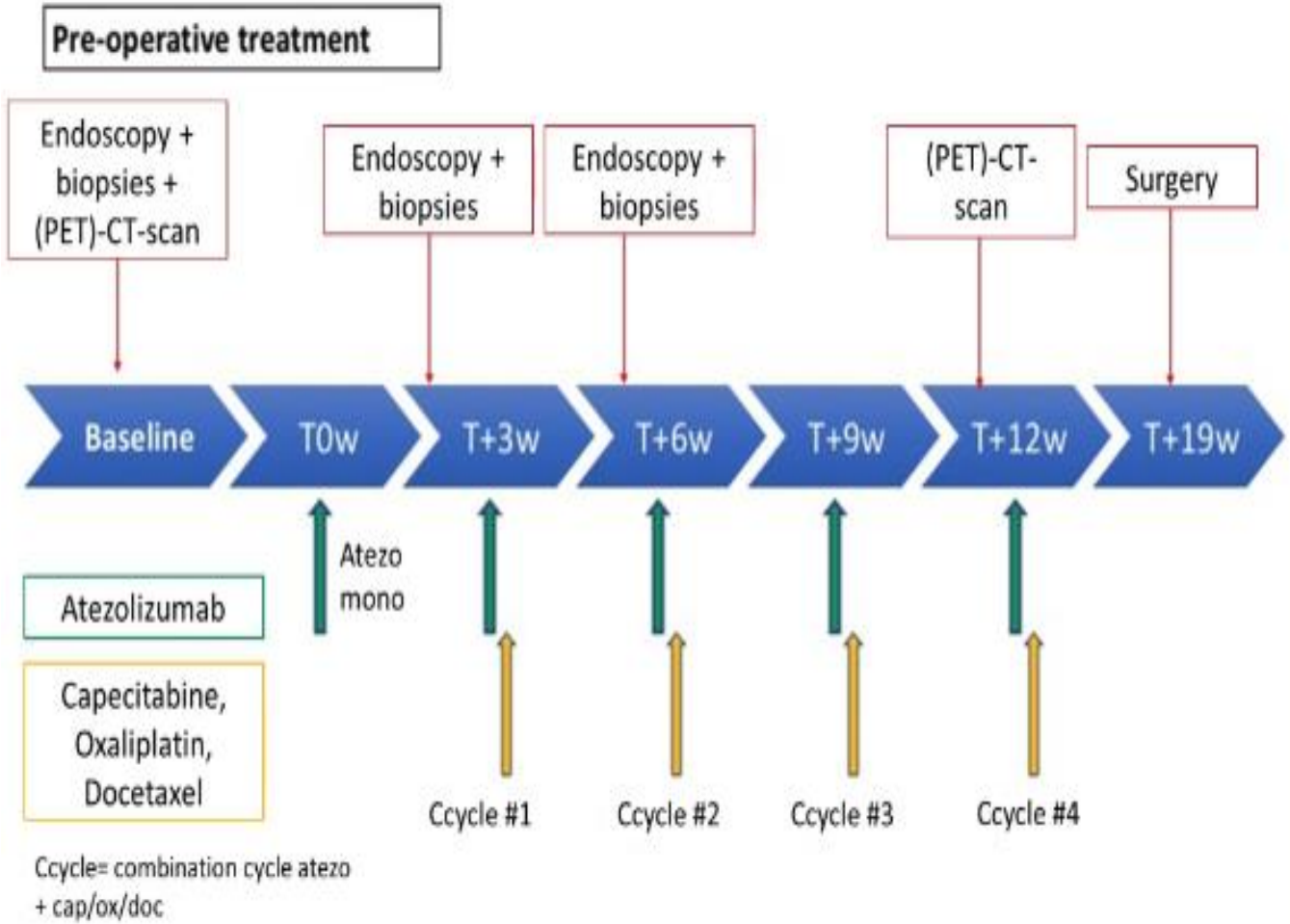
	Nivolumab	Placebo	Total
PD-L1 CPS[a] evaluable,[b] n	**51**	**29**	**80**
Median DFS (95% CI), mo	25.1 (14.5–NE)	9.3 (5.6–26.3)	–
HR (95% CI)	**0.64 (0.36–1.15)**		–
PD-L1 CPS change > 0, n (%)	23 (45)	18 (62)	41 (51)
Median DFS (95% CI), mo	NR (27.1–NE)	8.9 (5.6–NE)	–
HR (95% CI)	**0.30 (0.11–0.78)**		–
PD-L1 CPS change = 0, n (%)	7 (14)	4 (14)	11 (14)
Median DFS (95% CI), mo	16.0 (1.9–NE)	5.5 (5.4–22.8)	–
HR (95% CI)	NA[c]		–
PD-L1 CPS change < 0, n (%)	21 (41)	7 (24)	28 (35)
Median DFS (95% CI), mo	8.3 (2.8–19.4)	15.1 (2.8–NE)	–
HR (95% CI)	NA[c]		–
TC PD-L1[d] evaluable,[e] n	**65**	**33**	**98**
Median DFS (95% CI), mo	25.1 (14.5–NE)	7.1 (5.6–15.1)	–
HR (95% CI)	**0.56 (0.33–0.96)**		–
TC PD-L1 change > 0, n (%)	6 (9)	2 (6)	8 (8)
Median DFS (95% CI), mo	19.8 (2.8–NE)	NA	–
HR (95% CI)	NA[c]		–
TC PD-L1 change = 0, n (%)	49 (75)	25 (76)	74 (76)
Median DFS (95% CI), mo	23.4 (9.8–NE)	5.6 (5.4–15.1)	–
HR (95% CI)	**0.51 (0.28–0.91)**		–
TC PD-L1 change < 0, n (%)	10 (15)	6 (18)	16 (16)
Median DFS (95% CI), mo	39.2 (3.6–NE)	NR (2.9–NE)	–
HR (95% CI)	NA[c]		–

- The magnitude of DFS benefit appeared to be greater with nivolumab vs placebo in patients with an increase in PD-L1 CPS post-CRT (HR, 0.30 [95% CI, 0.11–0.78]) compared with the overall PD-L1 CPS-evaluable population[b] (HR, 0.64 [95% CI, 0.36–1.15])

Kelly et al, ESMO GI 2023

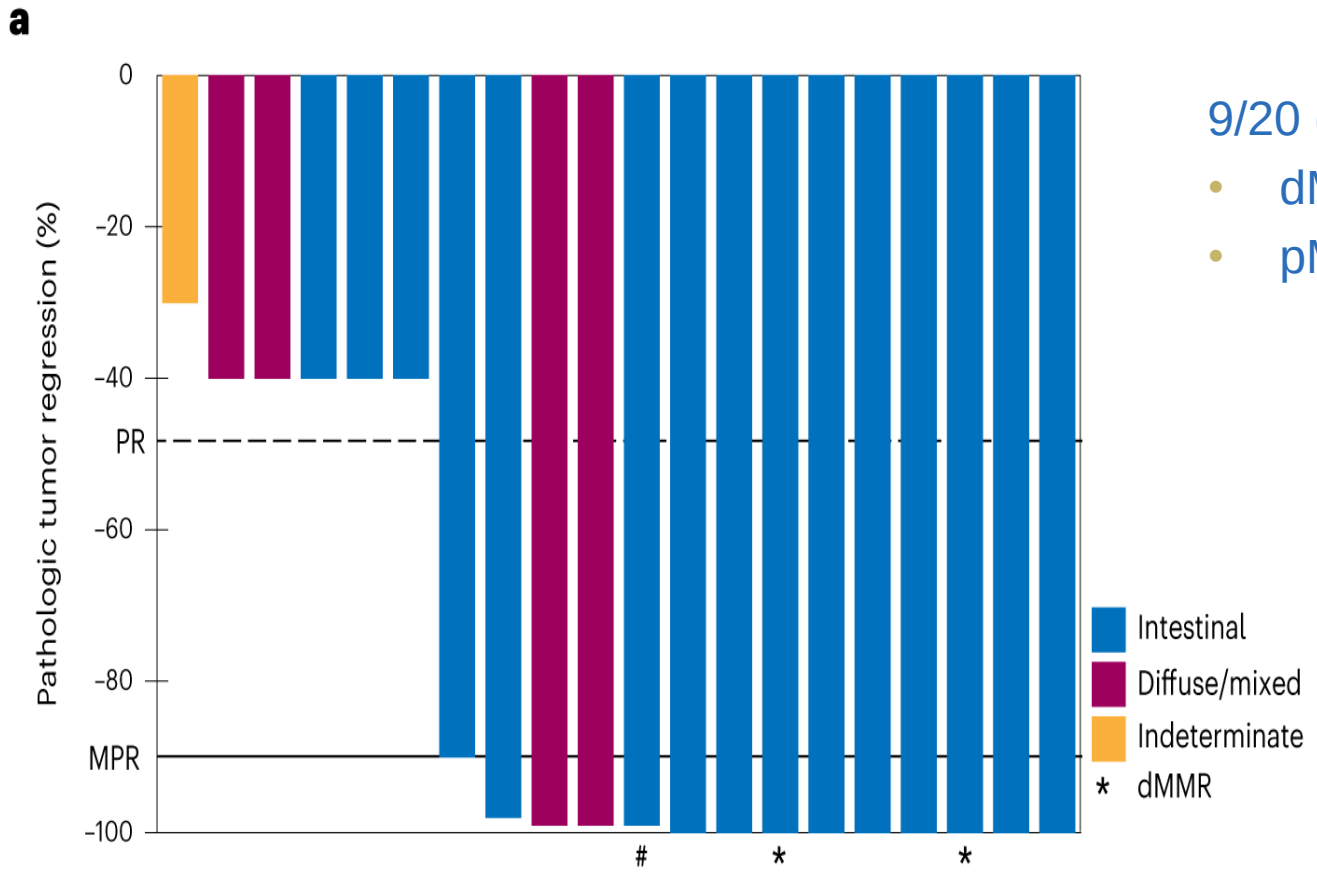
Phase 2 PANDA Trial

Neoadjuvant atezolizumab plus chemotherapy in gastric and gastroesophageal junction adenocarcinoma: the phase 2 PANDA trial



Verschoor et al, Nature Medicine 2024

Pathologic Responses



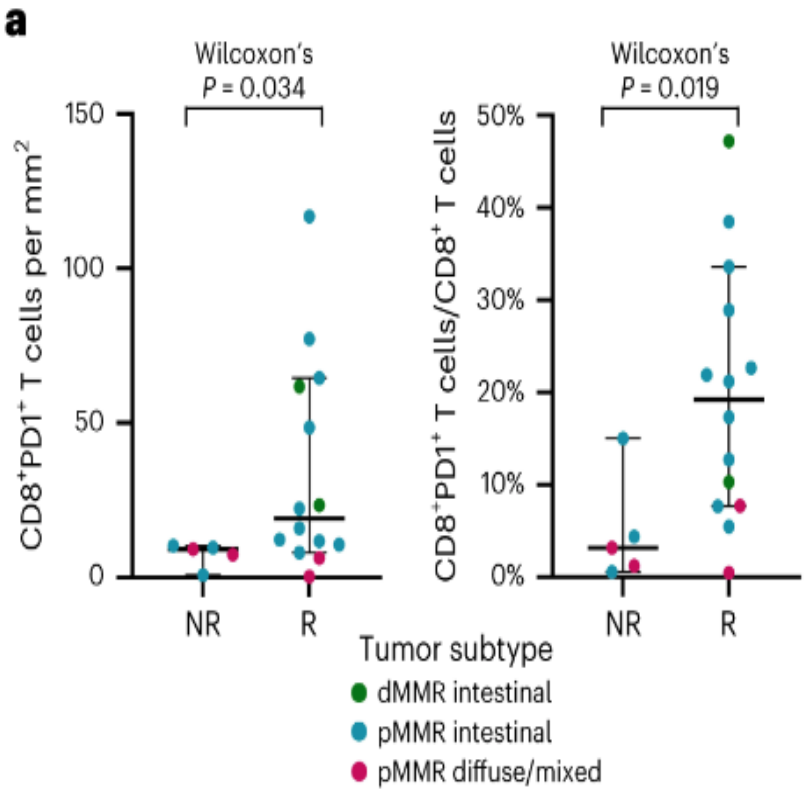
9/20 (45%) with pCR

- dMMR: 2/2 pCR
- pMMR: 7/18 (39%) pCR

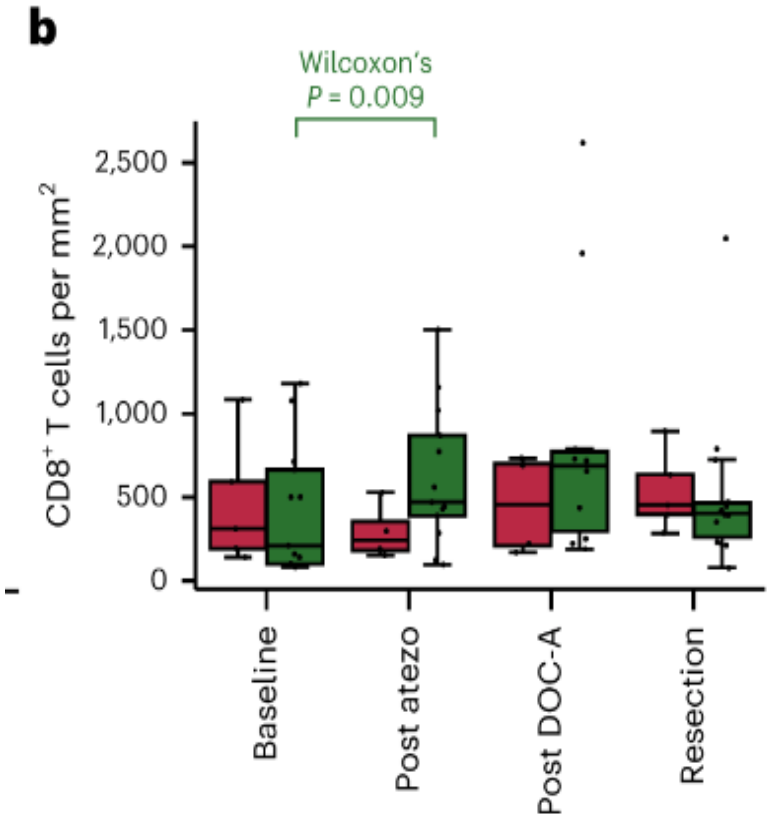
Verschoor et al, Nature Medicine 2024

CD8+ T Cells

Pre-treatment CD8+PD-1+ T cells higher in responders vs. non-responders (p=0.019)

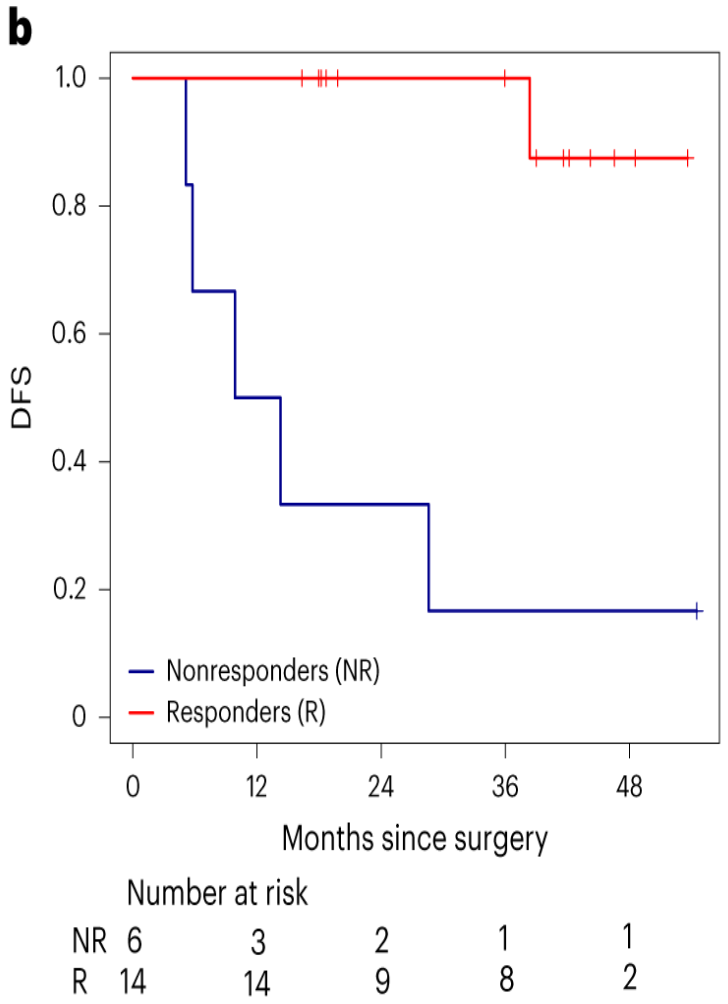


Increase in CD8+ TC infiltration in responders after one cycle of atezolizumab monotherapy (p=0.009)



Verschoor et al, Nature Medicine 2024

DFS



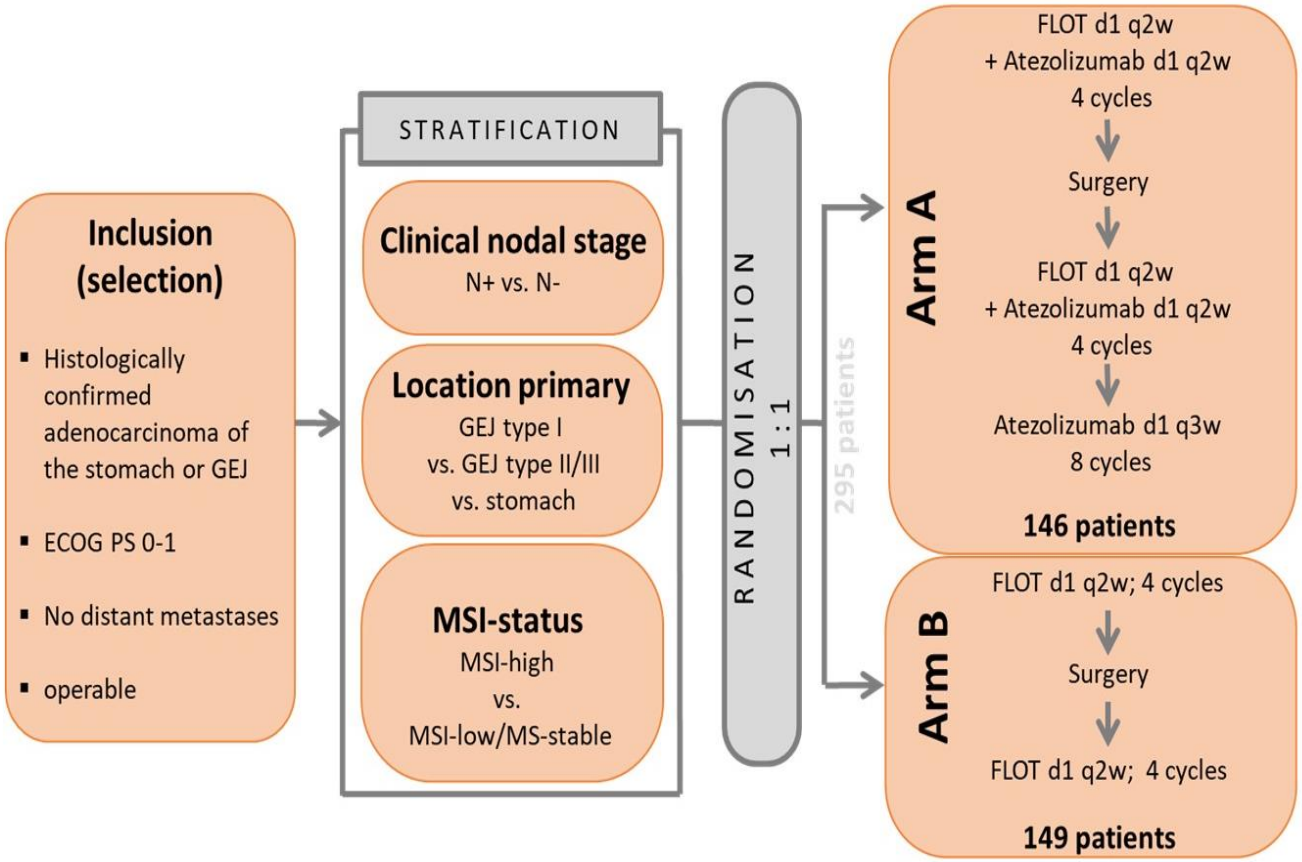
- Median follow up 47 months (range 11-59)
- 3-year DFS 73% (95% CI 55-97)
- pCR/MPR: 13/14 alive and disease-free
- Non-responders: 5/6 with recurrence

Verschoor et al, Nature Medicine 2024

Summary

- Adjuvant immunotherapy benefits patients with higher CPS
- Question remains – will addition of immunotherapy to FLOT improve outcomes in patients with gastric and GEJ cancers?
- To be answered by three trials – DANTE, MATTERHORN, and KEYNOTE 585

DANTE: Peri-operative FLOT + Atezolizumab vs FLOT



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Al Batran, ASCO 2022

Pathologic Responses (pTNM) and Regression

Tumor Response and Pathology	Arm A: FLOT + Atezolizumab (n = 146), No. (%)	Arm B: FLOT (n = 149), No. (%)
Pathologic regression		
All patients		
TRG1a[a,b]	35/146 (24)	22/149 (15)
ypT0/ypN0		
All patients	33/146 (23)	21/149 (14)

Al-Batran et al. JCO 2023

Pathologic Response/Postoperative Stage by PD-L1 CPS

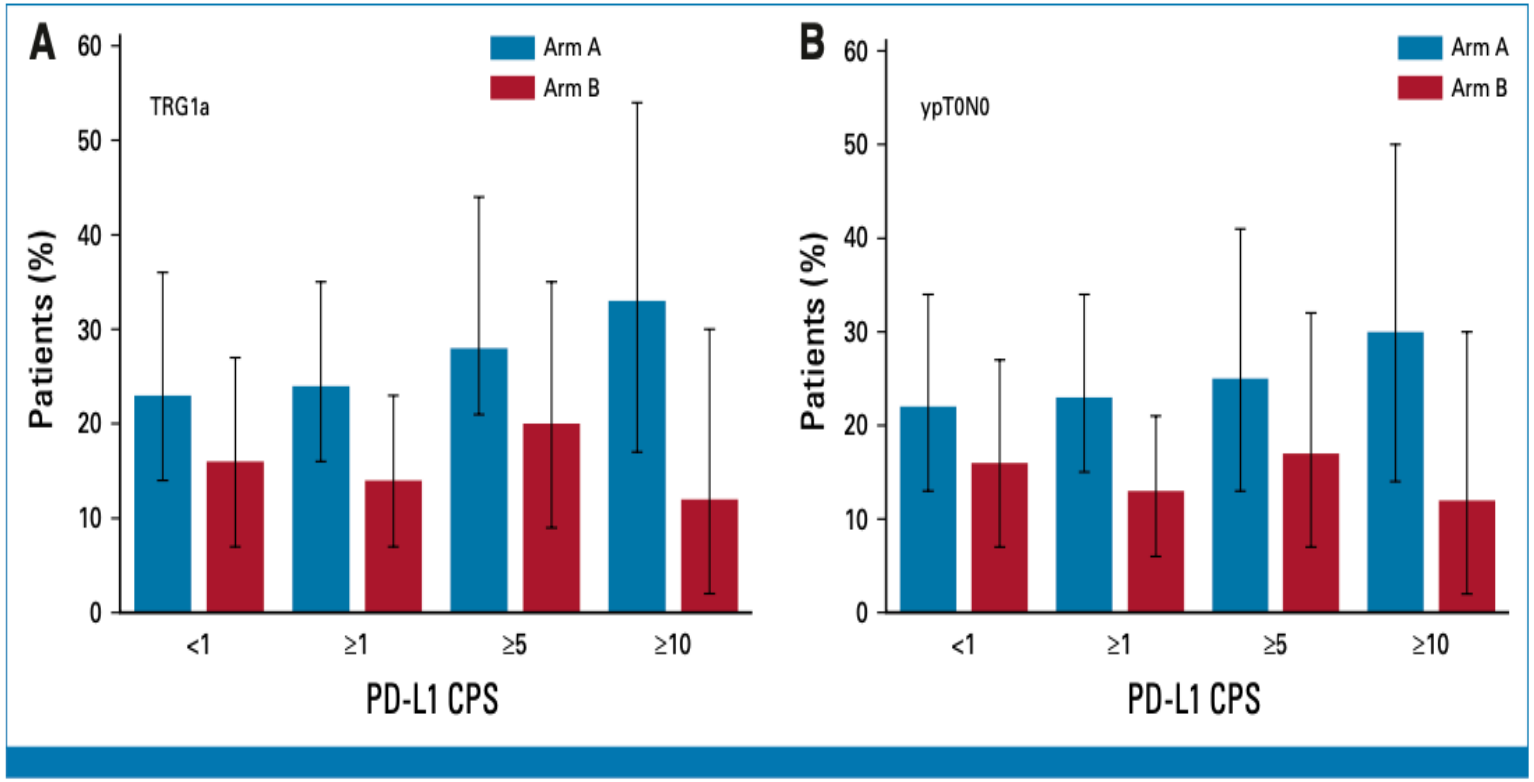
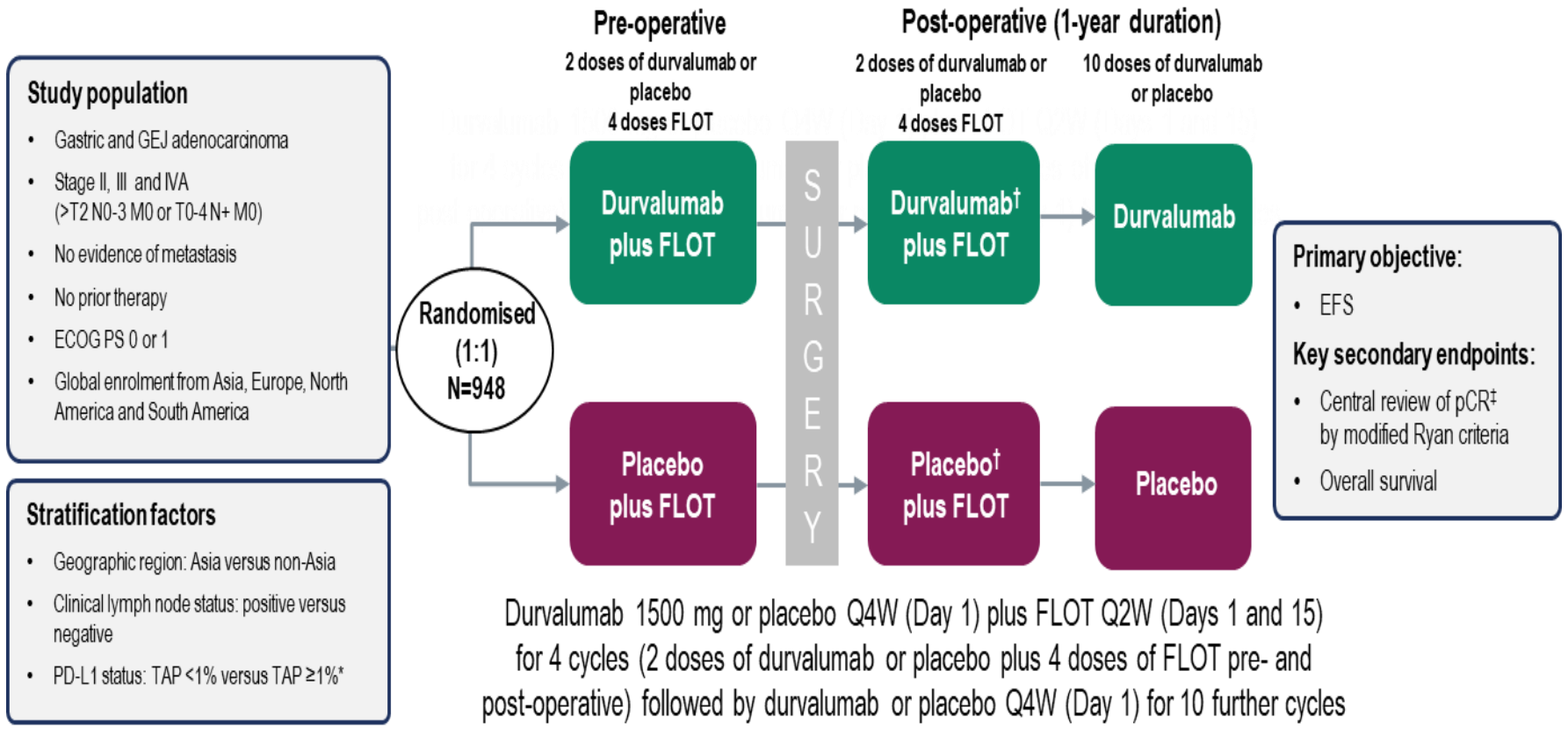


FIG 2. Outcomes by PD-L1 CPS. (A) Complete pathologic regression (TRG1a) and (B) ypT0N0 stage rates with 95% CI on the basis of PD-L1 CPS are shown for arm A and arm B. CPS, combined positive score.

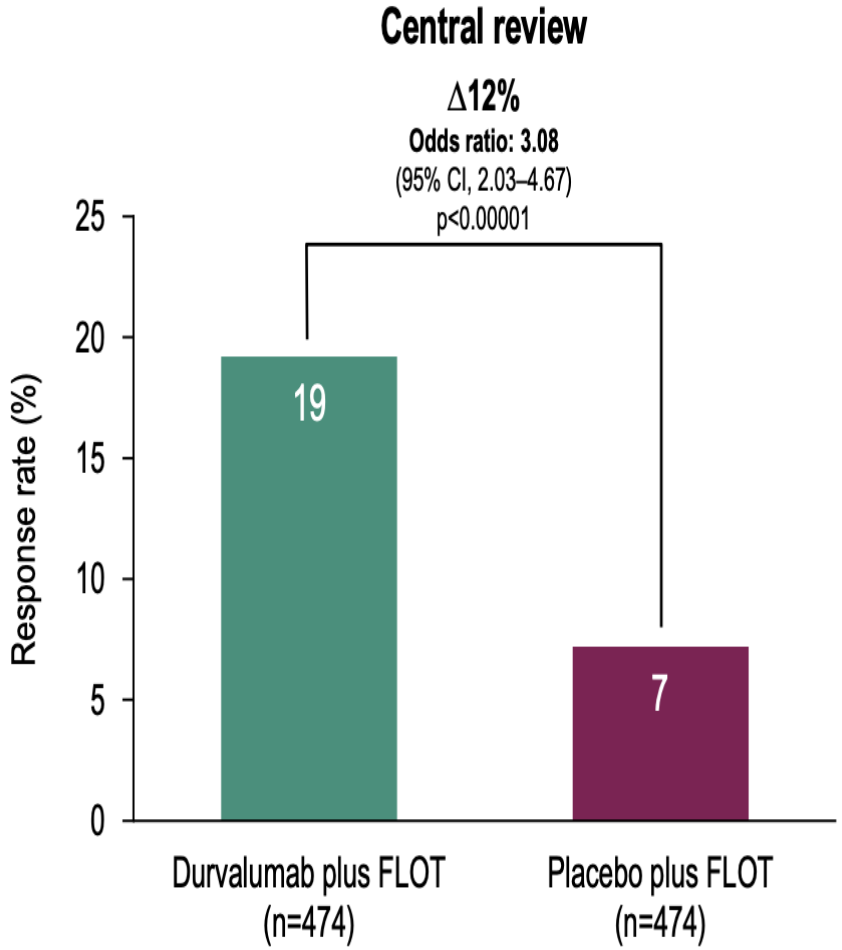
Al-Batran et al. JCO 2023

MATTERHORN: Phase 3 Randomized Double-Blind Placebo-Controlled Study



Al-Batran, ESMO 2023

Pathologic Complete Response



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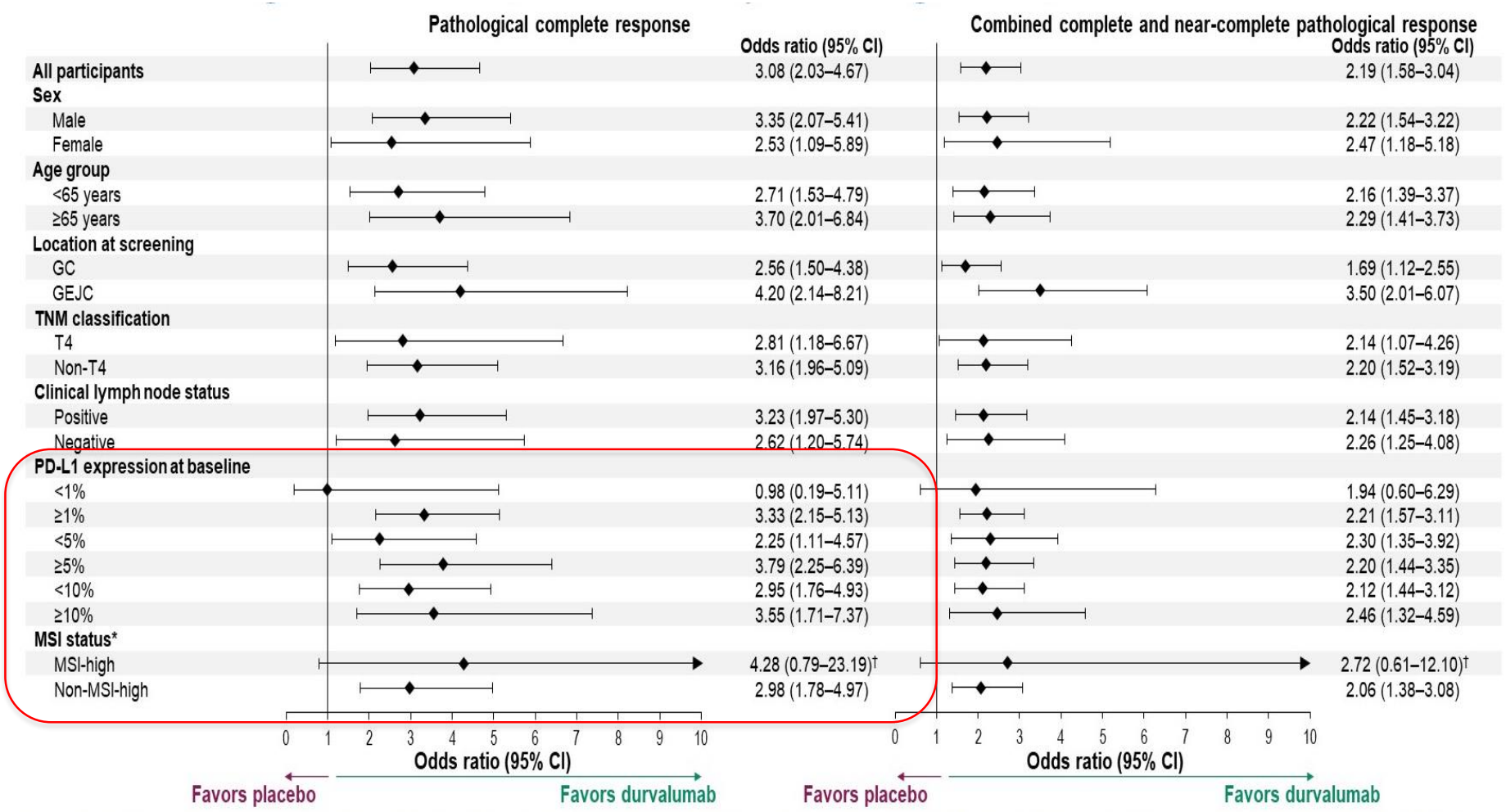
Pathologic Response by Subgroups



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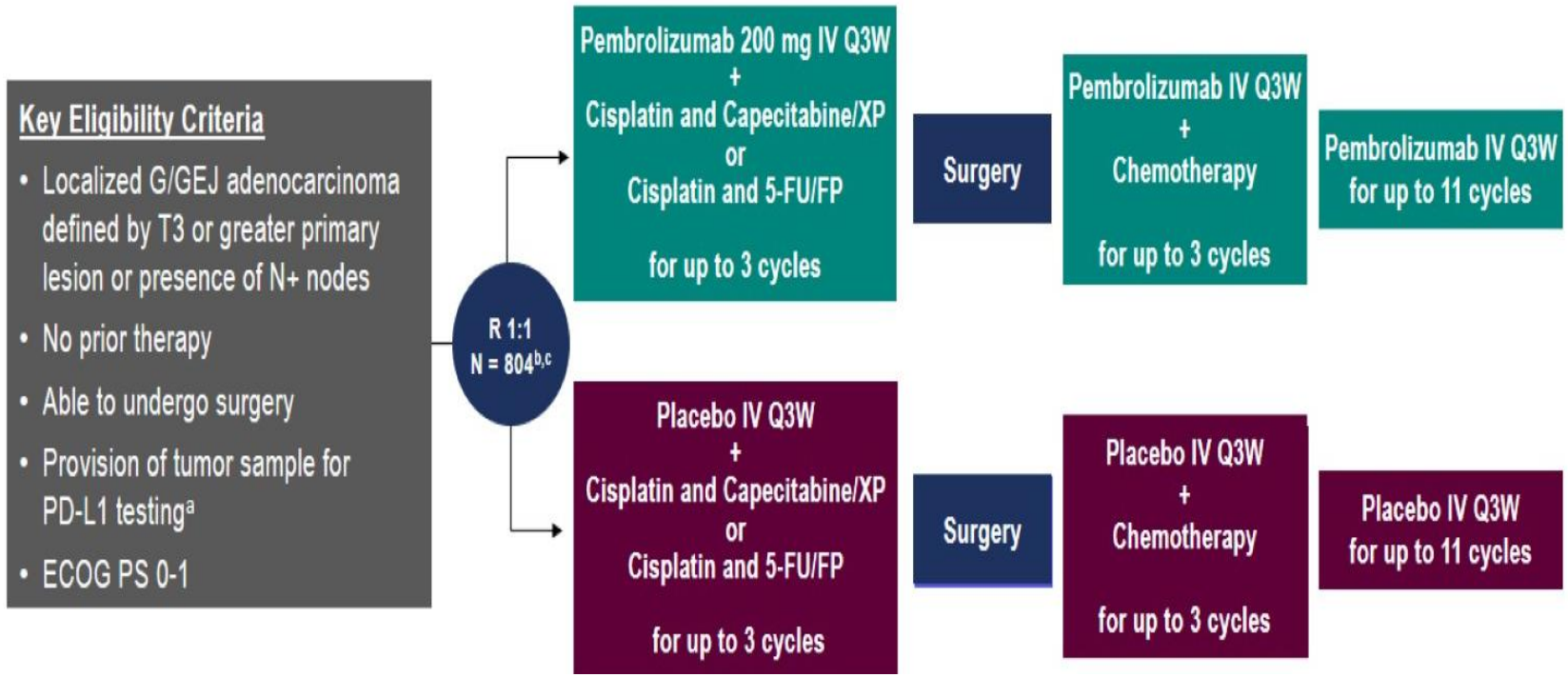
Janjigian et al. GI ASCO 2024

KEYNOTE-585

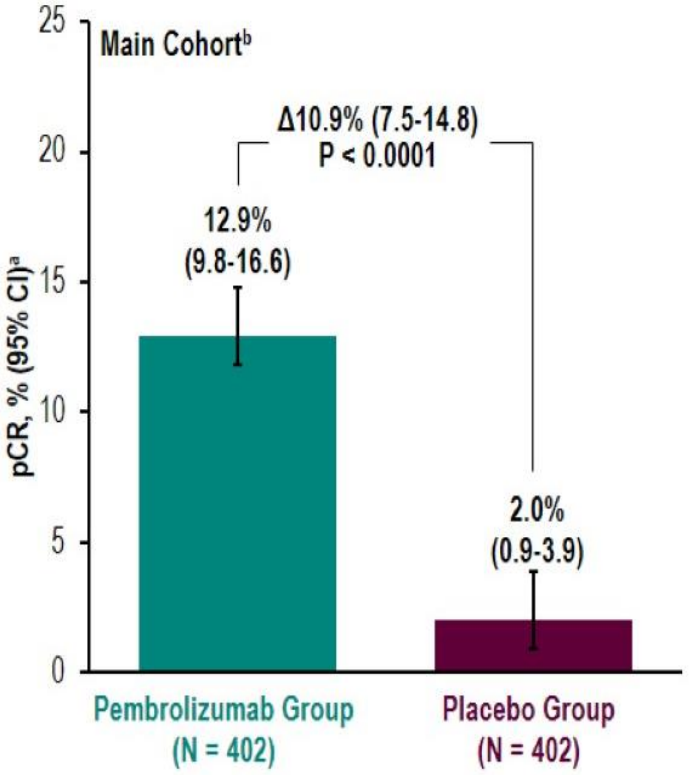
Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma (Main Cohort)

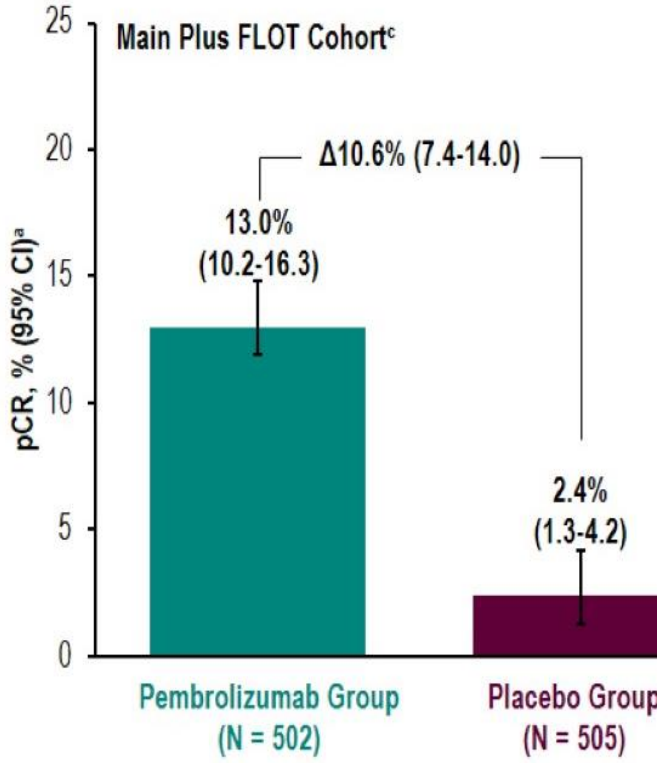


- Additional cohort of 203 patients received perioperative FLOT + pembro vs perioperative FLOT + placebo

Shitara et al, ESMO 2023

Pathologic Complete Response





Shitara et al, ESMO 2023

Event-Free and Overall Survival (Main + FLOT Cohort)

	Events	Median (95% CI), mo
Pembrolizumab group	44%	45.8 (35.9-NR)
Placebo group	52%	25.7 (21.9-33.9)

	Events	Median (95% CI), mo
Pembrolizumab group	40%	60.7 (51.5-NR)
Placebo group	43%	NR (45.7-NR)

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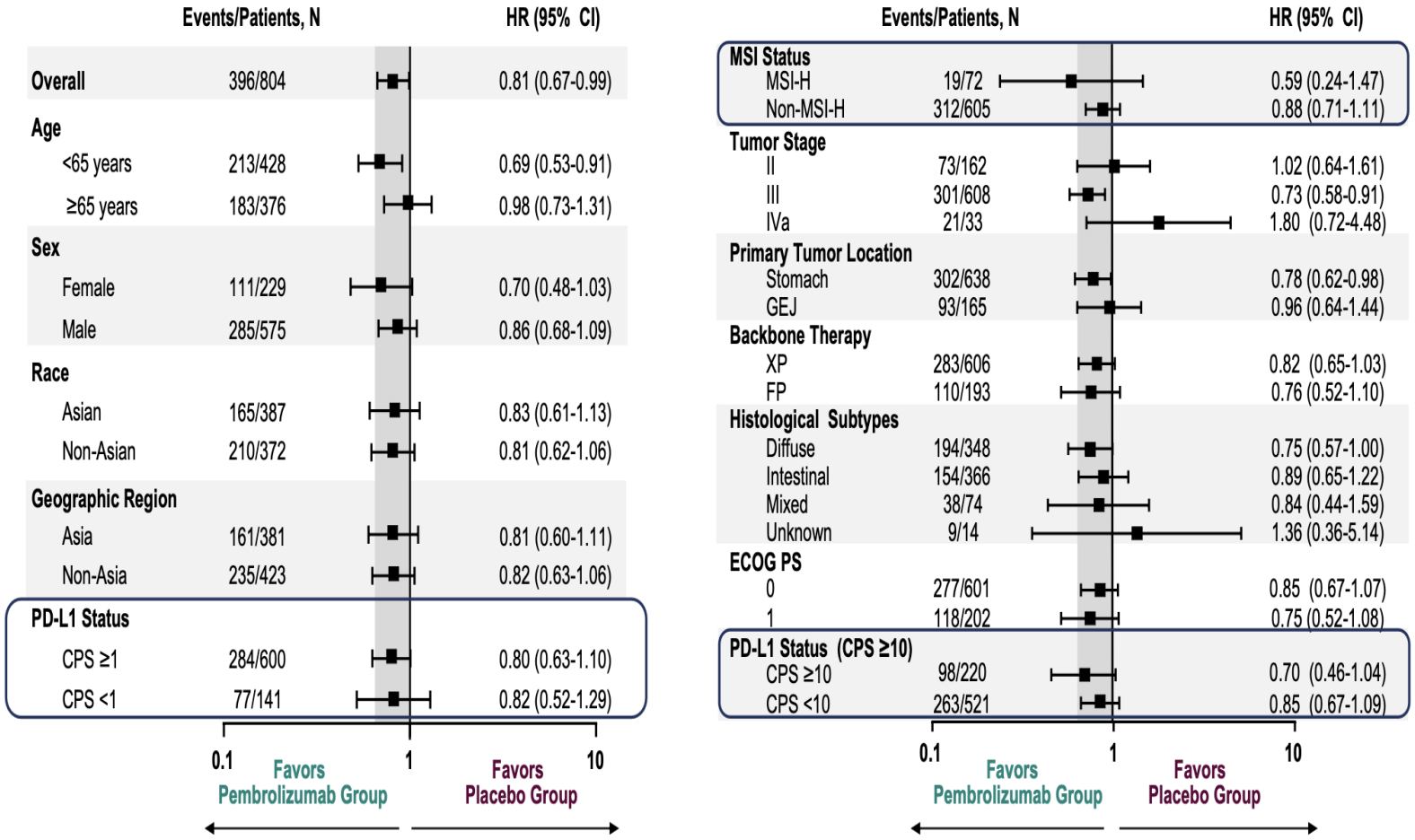
Event-Free Survival in Key Subgroups (Main Cohort)



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Shitara et al, ESMO 2023

Conclusions

- Adding IO to FLOT in locally advanced setting increases pCR rate
- But does it prolong survival?
  - KEYNOTE 585 was a negative study despite increased pCR rate
- We will have to wait for final results of ongoing studies but signal favors high PD-L1 or MSI-high tumours

Locally Advanced Disease in MSI-H Patients

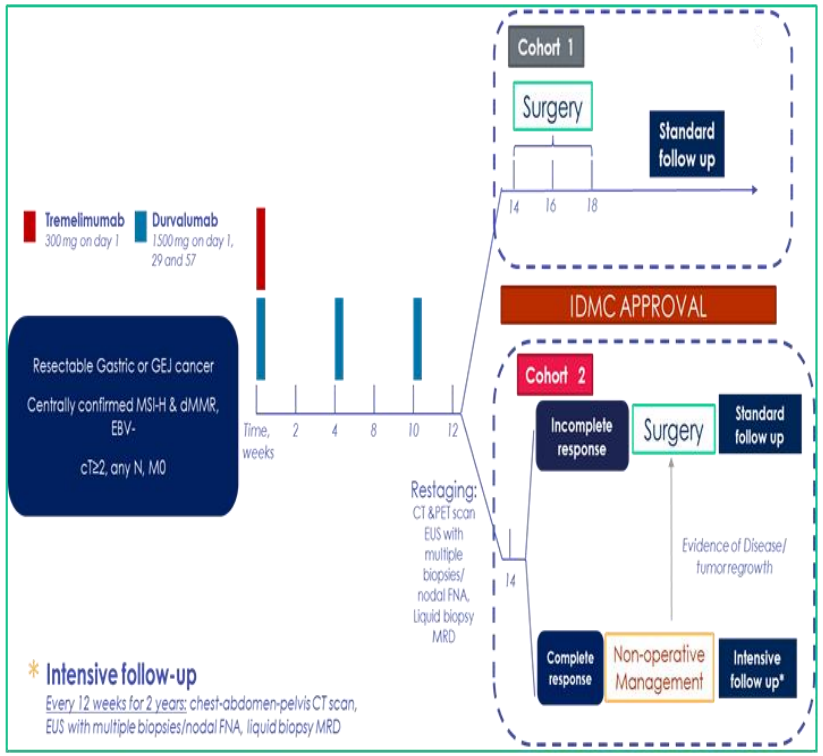
1. INFINITY
2. NEONIPIGA

- dMMR/MSI-H status is associated with better survival and potential lack of benefit from chemotherapy in resectable gastric/GEJ cancer[1]
- dMMR/MSI-H status is one of the strongest predictors of the efficacy of immunotherapy[2]
- Immunotherapy showed even higher activity in early vs advanced stage dMMR/MSI-H GI cancers and immune checkpoint inhibitors may allow omission of chemotherapy, radiotherapy, or even surgery[3-5]

1. Pietrantonio F, et al. J Clin Oncol 2019
2. Leone et al, ESMO Open 2022
3. Chalabi M, et al. ESMO 2022
4. Cercek A, et al. N Engl J Med 2022
5. André T, et al. J Clin Oncol 2022;

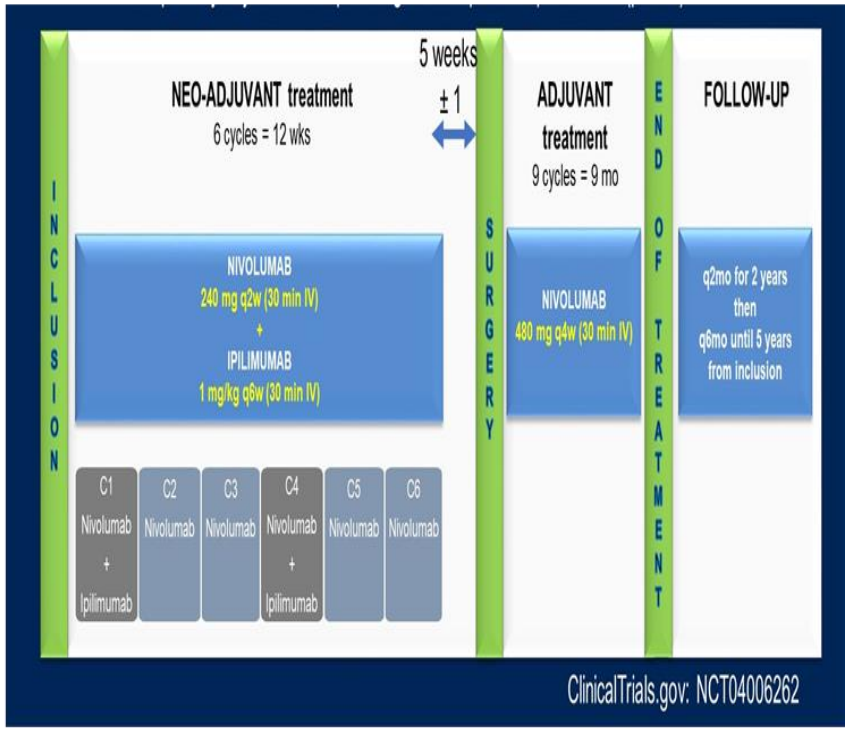
Study Designs

INFINITY: Phase II



Filippo Pietrantonio, MD

NEONIPIGA: Phase II



Andre et al, GI ASCO 2022

Primary Endpoints

INFINITY: Phase II

TRG Becker	N=15 (mITT)	%
1a	9	60%
1b	3	20%
3	2	13%

1 patient did not undergo surgery for PD

Among evaluable patients, rate of pCR was 60% and rate of major to complete pathological response (<10% viable cells) was 80%.

Filippo Pietrantonio, MD

NEONIPIGA: Phase II

TRG Becker (N=29)		
TRG 1a: complete tumor regression without residual tumor	17	58.6
TRG 1b: < 10% residual tumor per tumor bed	4	13.8
TGR 2: 10% to 50% residual tumor	2	6.9
TRG 3: > 50% residual tumor cells	6	21.7

- * 2 patients ypT0 and ypN1 (residual tumoral cells < 10% in only one node)
- ** 3 patients without surgery, 1 in metastatic PD and 2 in complete response in endoscopy with no tumoral cell on biopsy

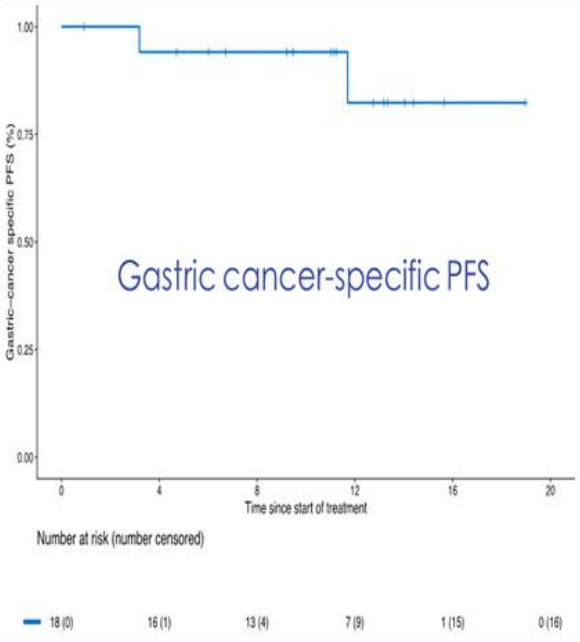
Andre et al, GI ASCO 2022

Survival Endpoints

- Immunotherapy for MSI-H patients is promising in neoadjuvant setting

INFINITY: Phase II

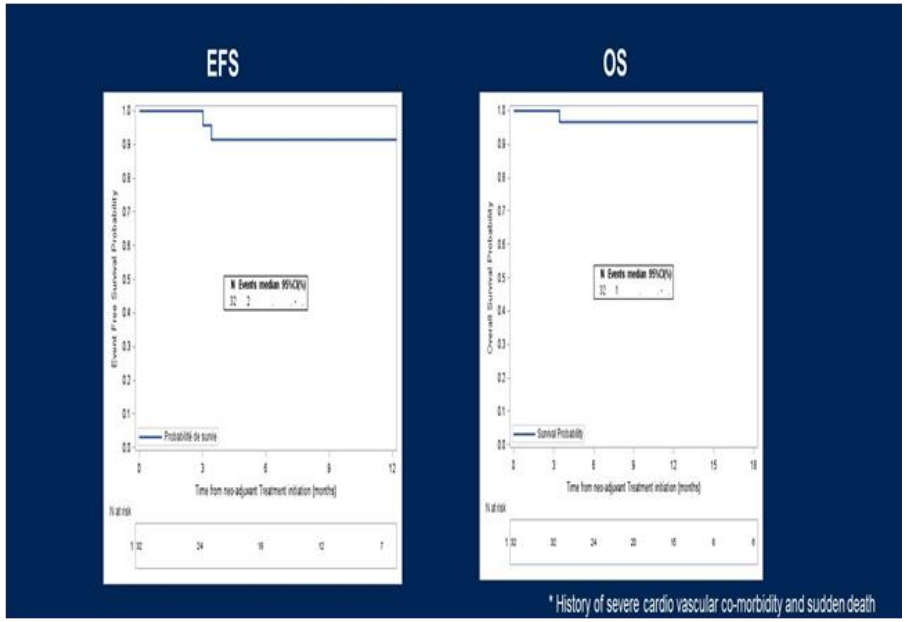
Median follow-up of 13.4 months (IQR 9.7-14.2)



Filippo Pietrantonio, MD

NEONIPIGA: Phase II

Median follow-up of 12 months (95% CI 7.8-14.2)



Andre et al, GI ASCO 2022

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Overall Conclusions

- Many biomarkers are now becoming standard of care in gastroesophageal cancers in metastatic setting and biomarkers are also important in localized setting
- At a minimum MMR has to be done prior to therapy
- We should be using a more tailored approach even in neaoadjuvant setting
- Treatment of unselected patients increases pCR but may not lead to improvement in OS

Thank you.

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